

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Adverse Childhood Experiences, the Risk of Pregnancy Complications and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis
<b>AUTHORS</b>	Mamun, Abdullah; Biswas, Tuhin; Scott, James; Sly, P.D.; McIntyre, David; Thorpe, Karen; Boyle, Frances; Dekker, N; Doi, Suhail; Mitchell, Murray; McNeil, Keith; Kothari, Alka; Hardiman, Leah; Callaway, Leonie Kaye

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Seabrook, Jamie Western University, London, Canada, Paediatrics
<b>REVIEW RETURNED</b>	02-May-2022

<b>GENERAL COMMENTS</b>	<p>This systematic review and meta-analysis evaluates the strength of the correlation between adverse childhood experiences (ACEs) and pregnancy complications and adverse birth outcomes. The review is important and novel. However, I have some comments that will require change to enhance the quality of the paper.</p> <p>Abstract</p> <p>Line 48, Spell out ACE before abbreviating. Line 52, It is noted that a comprehensive search was conducted on Google Scholar in the Abstract, but this is not mentioned in the text of the article. Lines 54-56 are choppy and should be rephrased. Line 59, Only I-squared is mentioned in the statistical analysis subsection of the manuscript, not Cochran's Q. Lines 62-66, Be consistent in rounding. Some odds ratios are rounded to 1 decimal place, others to 2 decimal places. All should round to 2 decimal places. Also, the authors claim that maternal ACEs were associated with gestational diabetes mellitus, but the 95% confidence interval shows that the odds ratio is not statistically significant.</p> <p>Methods</p> <p>Lines 200-202, state “ACE scores were considered on the continuous scale (for each unit change) and three categories: i) none versus at least one ACEs; ii) one to three as low ACEs; and (iii) four or more as high ACEs.” So, if they had exactly 1 ACE were they in category (i) or (ii)?</p> <p>Results</p> <p>The results section is all single-spaced. Perhaps this occurred when</p>
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	<p>the manuscript was converted to PDF. Please ensure the same line spacing throughout. In addition, the references in the Results section are no longer superscripted, which makes them difficult to follow when reading sentences.</p> <p>Lines 220-223, state “32 studies met our inclusion criteria for full text review, and 20 were included in meta-analysis (Figure 1). 75% of the studies (n =24) were cohort studies and the remainder were either cross sectional or case-control studies.” These sentences are confusing and appear inaccurate. Figure 1 shows that 72 articles received a full text review and that 31 studies met your inclusion criteria for the systematic review. Tables 1-2 also show 31 studies.</p> <p>Lines 227-228 are poorly worded and need to be rephrased due to grammatical errors and typos. Table 1 title – either capitalize or not. Figure 1 needs to be bigger.</p> <p>Page 14, lines 47-50, state “In risk factor-specific sub-analysis, five studies (7116 participants) were available for meta-analysis, which produced a moderate association between maternal ACEs and risk of GDM (OR=1.2, 95% CI: 0.9-1.5).” Why discuss a moderate association when the results are not statistically significant? The 95% confidence interval overlaps 1.</p> <p>Page 14, line 54, should read “were associated with any pregnancy complications”, not “were associated with and any pregnancy complications”</p> <p>Page 14, lines 56-58, state “For every single unit increase of ACEs, the odds of pregnancy complications increased 1.12 times (OR=1.1, 95% CI: 0.9-1.3) (supplementary figure- 1.3). Again, this odds ratio is not statistically significant.</p> <p>Page 15, line 5, - To be consistent with previous and subsequent reporting, start "Out of 31 students" on the next line.</p> <p>Page 15, lines 12-13 are unclear and need to re-phrased.</p> <p>Page 15, lines 20-21, state “A study by Gillespie et al reported that maternal childhood abuse was associated with birth timing.” Be more specific. What about birth timing?</p> <p>Discussion</p> <p>The authors cast a wide net with ACEs and more attention should be given to other fundamental causes of health disparities in adulthood, particularly socioeconomic status. The following reference would be useful here to expand your argument and to provide more theory underlying the association between ACEs and pregnancy complications and adverse birth outcomes:</p> <p>Seabrook JA, Avison WR. Socioeconomic status and cumulative disadvantage processes across the life course: implications for health outcomes. <i>Can Rev Sociol.</i> 2012; 49(1):50-68</p>
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<b>REVIEWER</b>	Condon, Eileen M University of Connecticut, Nursing
<b>REVIEW RETURNED</b>	27-May-2022

<b>GENERAL COMMENTS</b>	Thank you for the opportunity to review this manuscript. ACEs are an important public health issue, and this systematic review and meta analysis makes a significant contribution to the literature by examining the relationship between ACEs and pregnancy outcomes. The authors use rigorous methodologies at each stage of the systematic review process. I have a few suggestions that I feel will
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help strengthen an already strong and compelling manuscript.

**Methods:**

Given that almost a year has passed since July 2021 and given the increasing attention towards ACEs in the scientific literature, I think this review should be updated to capture any additional studies that were published from July 2021 to the present. I recognize that this is a potentially time-consuming suggestion, but since many outcomes included in the meta-analysis were based on a small number of studies, even adding just a few additional studies from the past year may have a significant influence on the review results.

It would be helpful to briefly describe the process for screening at the title/abstract and full text level. This is mentioned under Data Extraction (“A similar approach was used for full text reviews”), but I think this deserves its own subsection, or at least a separate description.

What was the process for quality appraisal? Were there two reviewers for this as well?

**Results:**

The references in the results section are not in superscript, at least in my version. There are also a few typos (e.g. “sued” instead of “used”, line 227).

In the PRISMA diagram, I believe that reasons for exclusion at the full text level are typically included as bullet points. Please describe the reasons for exclusion for these 41 studies in the appropriate box.

**Discussion:**

The authors list a number of potential physiologic, health, and behavioral pathways that may explain the relationship between ACEs and pregnancy/birth outcomes. I appreciate that the authors address these extensive possibilities, but the current presentation of the information in the first two paragraphs is somewhat hard to follow. For example, the first paragraph jumps from the HPA axis to neurodevelopment and then back to ANS and “stress regulatory pathways.” These are all certainly interconnected, but I suggest that the others reorganize and synthesize this information so it’s clearer and more succinct. An explanation of the relationship between stress physiology and inflammation may also be useful.

Similarly, I don’t think it’s safe to assume that all readers will understand terms like “allostatic load.” Again, a restructuring of this section to clearly describe the relationship between chronic stress, physiology, and health/behavior (with appropriate definitions as needed) will be helpful.

I agree that there is a critical need for trauma informed care in maternal and child health. However, there is some controversy about whether screening for ACEs is a safe and ethical practice, especially if the consequences of discussing ACEs (e.g. effects on mental health) cannot be readily addressed. Therefore, I think this discussion section would be strengthened by addressing both the potential benefits and harms of ACEs screening. The following references may be helpful for incorporating these perspectives: Campbell, T. L. (2020). Screening for adverse childhood experiences (ACEs) in primary care: A cautionary note. *JAMA*, 323(23), 2379-2380.

	<p>Gillespie, R. J. (2019). Screening for adverse childhood experiences in pediatric primary care: Pitfalls and possibilities. <i>Pediatric Annals</i>, 48(7), e257-e261.</p> <p>I think the implications of this review are multi-level, and the authors might consider taking a broader/more upstream approach in their recommendations. For example, beyond screening for ACEs, what might be done to reduce childhood adversity and poor pregnancy outcomes from a policy or community perspective? How can we prevent the issue of intergenerational transmission that is described in the introduction?</p>
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### VERSION 1 – AUTHOR RESPONSE

#### Reviewer 1:

Comment	Response
<p>Abstract Line 48, Spell out ACE before abbreviating. Line 52, It is noted that a comprehensive search was conducted on Google Scholar in the Abstract, but this is not mentioned in the text of the article.</p>	<p>Thank you for your suggestion. We have now spelled it out. Please see page number 3, line number 53.</p>
<p>Lines 54-56 are choppy and should be rephrased.</p>	<p>Thank you for your suggestion. Now it reads: “A comprehensive search was conducted using PubMed, EMBASE, CINAHL, PsycINFO, ClinicalTrials.gov and Google scholar up to July 2022 ”</p> <p>Please see page number 3, line number 60-61.</p>
<p>Line 59, Only I-squared is mentioned in the statistical analysis subsection of the manuscript, not Cochran's Q.</p>	<p>Revised it. Now it reads: “Two reviewers independently conducted the screening and quality appraisal using a validated tool. Meta-analysis using the quality-effects model on the reported odds ratio (OR) was conducted. Heterogeneity and inconsistency were examined using the I<sup>2</sup> statistics”.</p> <p>Please see page number 3, line number 63-65.</p>
<p>Lines 62-66, Be consistent in rounding. Some odds ratios are rounded to 1 decimal place, others to 2 decimal places. All should round to 2 decimal places. Also, the authors claim that maternal ACEs were associated with gestational diabetes mellitus, but the 95% confidence interval shows that the odds ratio is not statistically significant.</p>	<p>Thank you for your suggestion. Now we have consistently reported 2 decimal places throughout of the manuscript. We have now updated our search up to June 2022. According to updated result, maternal ACEs were associated with gestational diabetes mellitus. Now it reads:</p> <p>“Pooled analyses showed that exposure to ACEs increased the risk of pregnancy complications (odds ratio, OR=1.37, 95% CI: 1.20-1.56) and adverse pregnancy outcomes (OR=1.31, 95% CI: 1.16-1.48). In sub-group analysis, maternal ACEs were associated with gestational diabetes mellitus (OR=1.39, 95% CI: 1.11-1.74), antenatal depression (OR=1.59, 95% CI: 1.15-2.20), low offspring birth weight (OR=1.27, 95% CI: 1.02-1.59), and preterm delivery (OR=1.41, 95% CI: 1.16-1.71)”.</p> <p>Please see the revised result in abstract and as well as result section.</p>

<p>Methods</p> <p>Lines 200-202, state “ACE scores were considered on the continuous scale (for each unit change) and three categories: i) none versus at least one ACEs; ii) one to three as low ACEs; and (iii) four or more as high ACEs.” So, if they had exactly 1 ACE were they in category (i) or (ii)?</p>	<p>This was unclear. We have revised and clarified this in the revised manuscript . Now it reads: ACE scores were considered on the continuous scale (for each unit change) and three categories: i) none versus one ACEs; ii) two to three ACEs ( low ACEs); and (iii) four or more ACEs (high ACEs). Please see page number 10, line number 268-270.</p>
<p>Results</p> <p>The results section is all single-spaced. Perhaps this occurred when the manuscript was converted to PDF. Please ensure the same line spacing throughout. In addition, the references in the Results section are no longer superscripted, which makes them difficult to follow when reading sentences.</p>	<p>Formatted as per journal requirement</p>
<p>Lines 220-223, state “32 studies met our inclusion criteria for full text review, and 20 were included in meta-analysis (Figure 1). 75% of the studies (n =24) were cohort studies and the remainder were either cross sectional or case-control studies.” These sentences are confusing and appear inaccurate. Figure 1 shows that 72 articles received a full text review and that 31 studies met your inclusion criteria for the systematic review. Tables 1-2 also show 31 studies.</p>	<p>We have now revised it. Now it reads: “The literature search resulted in 1,508 records, which were screened for duplication (n=398), review of titles (n=1,086) and further abstract evaluation (n=485). Finally, 32 studies met our inclusion criteria for systematic review, and 21 were included in meta-analysis (<b>Figure 1</b>)”.</p> <p>Please see page number 11, line number 287-289.</p>
<p>Lines 227-228 are poorly worded and need to be rephrased due to grammatical errors and typos.</p>	<p>Revised it. Now it reads: There is little information about ACEs and the associated risk of pregnancy complications and adverse birth outcomes.”</p> <p>Please see page number 6, line number 190-191.</p>
<p>Table 1 title – either capitalize or not.</p>	<p>Revised it</p>
<p>Figure 1 needs to be bigger.</p>	<p>Revised it</p>
<p>Page 14, lines 47-50, state “In risk factor-specific sub-analysis, five studies (7116 participants) were available for meta-analysis, which produced a moderate association between maternal ACEs and risk of GDM (OR=1.2, 95% CI: 0.9-1.5).” Why discuss a moderate association when the results are not statistically significant? The 95% confidence interval overlaps 1.</p>	<p>We have now updated our search up to July 2022. According to current result maternal ACEs were associated with gestational diabetes mellitus. Now it reads: “Pooled analyses showed that exposure to ACEs increased the risk of pregnancy complications (odds ratio, OR=1.37, 95% CI: 1.20-1.56) and adverse pregnancy outcomes (OR=1.31, 95% CI: 1.16-1.48). In sub-group analysis, maternal ACEs were associated with gestational diabetes mellitus (OR=1.39, 95% CI: 1.11-1.74), antenatal depression (OR=1.59, 95% CI: 1.15-2.20), low offspring birth weight (OR=1.27, 95% CI: 1.02-1.59), and preterm delivery (OR=1.41, 95% CI: 1.16-1.71)”.</p> <p>Please see the revised result in abstract and as well as result section.</p>
<p>Page 14, line 54, should read “were associated with any pregnancy complications”, not “were associated with and any pregnancy complications”</p>	<p>Revised it</p>
<p>Page 14, lines 56-58, state “For every single unit increase of ACEs, the odds of pregnancy complications increased 1.12 times (OR=1.1, 95% CI:</p>	<p>We have excluded this text from the revised manuscript.</p>

0-9-1-3) (supplementary figure- 1.3). Again, this odds ratio is not statistically significant.	
<p>Page 15, line 5, - To be consistent with previous and subsequent reporting, start "Out of 31 students" on the next line.</p> <p>Page 15, lines 12-13 are unclear and need to be re-phrased.</p> <p>Page 15, lines 20-21, state "A study by Gillespie et al reported that maternal childhood abuse was associated with birth timing." Be more specific. What about birth timing?</p>	Revised and clarified
<p>Discussion</p> <p>The authors cast a wide net with ACEs and more attention should be given to other fundamental causes of health disparities in adulthood, particularly socioeconomic status. The following reference would be useful here to expand your argument and to provide more theory underlying the association between ACEs and pregnancy complications and adverse birth outcomes:</p> <p>Seabrook JA, Avison WR. Socioeconomic status and cumulative disadvantage processes across the life course: implications for health outcomes. <i>Can Rev Sociol.</i> 2012; 49(1):50-68.</p>	<p>Thank you for your suggestion. We have now discussed it in discussion section. Now it reads:</p> <p>"According to our findings and other systematic review evidence, it may be valuable to assess the role of routine ACE screening during pregnancy to improve maternal and child health. Trauma informed care is not well incorporated into clinical practice guidelines. Much of the emphasis in maternity care is on individual behaviour change, including advice about diet, exercise, smoking cessation and uptake of clinical care. Approaches that do not incorporate the personal experiences of trauma by women attending antenatal services may inadvertently cause iatrogenic harm. For many years, there has been an interest in improving pregnancy outcomes by focusing on a limited set of physical parameters that can easily be measured such as gestational weight gain, without attention to the underlying mechanisms.<sup>74,75</sup> Overall, studies of diet and exercise in pregnancy to reduce GDM, HDP and other adverse pregnancy outcomes have been disappointing.<sup>76</sup> A recent scoping review by Mishra et al<sup>77</sup> found that ACEs screening does not excessively disrupt clinic workflow. In addition, it is also established that the effects of socioeconomic status and cumulative disadvantage on producing health disparities across the life course<sup>78</sup>".</p> <p>Please see page number 17, line number 517-527.</p>

**Reviewer 2:**

<b>Comment</b>	<b>Response</b>
<p>Methods:</p> <p>Given that almost a year has passed since July 2021 and given the increasing attention towards ACEs in the scientific literature, I think this review should be updated to capture any additional studies that were published from July 2021 to the present. I recognize that this is a potentially time-consuming suggestion, but since many outcomes included in the meta-analysis were based on a small number of studies, even adding just a few additional studies from the past year may have a significant influence on the review results.</p>	<p>We have now updated our search up to July 2022. We found one article according to our inclusion criteria.</p>
<p>It would be helpful to briefly describe the process for screening at the title/abstract and full text level. This is</p>	<p>Thank you for your suggestion, we have now revised it. Please see page number 8, line number 243-249.</p>

<p>mentioned under Data Extraction (“A similar approach was used for full text reviews”), but I think this deserves its own subsection, or at least a separate description. What was the process for quality appraisal? Were there two reviewers for this as well?</p>	
<p>Results: The references in the results section are not in superscript, at least in my version. There are also a few typos (e.g. “sued” instead of “used”, line 227).</p>	<p>Corrected.</p>
<p>In the PRISMA diagram, I believe that reasons for exclusion at the full text level are typically included as bullet points. Please describe the reasons for exclusion for these 41 studies in the appropriate box.</p>	<p>Thank you for your suggestion. We revised the PRISMA diagram.</p>
<p>Discussion: The authors list a number of potential physiologic, health, and behavioral pathways that may explain the relationship between ACEs and pregnancy/birth outcomes. I appreciate that the authors address these extensive possibilities, but the current presentation of the information in the first two paragraphs is somewhat hard to follow. For example, the first paragraph jumps from the HPA axis to neurodevelopment and then back to ANS and “stress regulatory pathways.” These are all certainly interconnected, but I suggest that the others reorganize and synthesize this information so it’s clearer and more succinct. An explanation of the relationship between stress physiology and inflammation may also be useful.</p>	<p>We have made a substantial revision of the discussion addressing these concerns.</p>
<p>Similarly, I don’t think it’s safe to assume that all readers will understand terms like “allostatic load.” Again, a restructuring of this section to clearly describe the relationship between chronic stress, physiology, and health/behavior (with appropriate definitions as needed) will be helpful.</p>	<p>We have made a substantial revision of the discussion addressing these concerns.</p>
<p>I agree that there is a critical need for trauma informed care in maternal and child health. However, there is some controversy about whether screening for ACEs is a safe and ethical practice, especially if the consequences of discussing ACEs (e.g. effects on mental health) cannot be readily addressed. Therefore, I think this discussion section would be strengthened by addressing both the potential benefits and harms of ACEs screening. The following references may be helpful for incorporating these perspectives: Campbell, T. L. (2020). Screening for adverse childhood experiences (ACEs) in primary care: A cautionary note. <i>JAMA</i>, 323(23), 2379-2380. Gillespie, R. J. (2019). Screening for adverse childhood experiences in pediatric primary care: Pitfalls and possibilities. <i>Pediatric Annals</i>, 48(7), e257-e261.</p>	
<p>I think the implications of this review are multi-level, and the authors might consider taking a broader/more upstream approach in their recommendations. For example, beyond screening for ACEs, what might be done to reduce childhood adversity and poor</p>	<p>We have made a substantial revision of the discussion. We agree that this is an important implication of the findings and that multi-level and upstream approaches are essential. We have now highlighted this point in the discussion but further</p>

pregnancy outcomes from a policy or community perspective? How can we prevent the issue of intergenerational transmission that is described in the introduction?	more detailed exploration of the specific steps that an upstream approach might entail is beyond the scope of this review.
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**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Seabrook, Jamie Western University, London, Canada, Paediatrics
<b>REVIEW RETURNED</b>	09-Dec-2022
<b>GENERAL COMMENTS</b>	The authors have done a good job addressing all of my previous concerns. I have no further issues with this manuscript.