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# Neonatal circumcision and prematurity are associated with sudden infant death syndrome (SIDS)

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Dear authors,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you resubmit your work.

Your revision is due by Sep 08, 2018.

To submit a revision, go to https://jctres.editorialmanager.com/ and log in as an Author. You will see a menu item called Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger

Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: This is a highly original study that will certainly be of use to researchers studying both SIDS and circumcision, and it provides some nice data in support of the allostatic load hypothesis that distinguishes it from competing accounts. It is well written and nicely acknowledges the limitations inherent to the subject matter. Hopefully it will inspire prospective studies as the authors suggest. I recommend that the paper be published upon minor revision, and, to aid with this, I have given very specific comments below that the authors should implement in revising their manuscript.

Page 2 Line 9: it should be "cumulative perinatal" not the other way around

Page 2 Line 13: seems strange to describe prematurity as a "stressor" … being born early may well make one more stressed by various stimuli (stressors), but the state of prematurity, just conceptually, feels different from the concept of being a stressor

Page 2 Line 23: I would delete "reminiscent of the Jewish myth of Lillith, killer of infant males." It feels out of place in the scientific abstract

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Page 2 Line 33: Re: "Preterm birth and neonatal circumcision increase the risk for SIDS and should be avoided." Presumably it should said that those variables are "associated with a greater risk" rather than that they "increase the risk" as that implies causal evidence. Also, what would it mean to say "Preterm birth … should be avoided" … ? Presumably if someone has a child pre-term, this is not intentional, and all measures are already taken to avoid pre-term birth that is not necessary. The "should be avoided," then, is probably supposed to refer just to neonatal circumcision (since that's intentional), but then the whole sentence is confusing. Saying that both pre-term birth and MNC are 'risk facors' and that further research should be done to try to assess the evidence in a more causal/prospective way would be appropriate, but saying, on the basis of correlational evidence, that (on that basis alone) MNC should be avoided feels too much like a command or bald assertion rather than something that follows from the finding in a logical way.

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Page 3 Line 30. "Both stressor" should be "Both stressors"

Page 3 Line 35. Re: complications, Krill et al. should also be cited: Krill, A. J., Palmer, L. S., & Palmer, J. S. (2011). Complications of circumcision. The Scientific World Journal, 11, 2458-2468. Re: deaths, Earp et al. should be cited: Earp, B. D., Allareddy, V., Allareddy, V., & Rotta, A. T. (2018). Factors associated with early deaths following neonatal male circumcision in the United States, 2001-2010. Clinical Pediatrics, in press. Online version ahead of print at https://www.researchgate.net/publication/326040454_Factors_associated_with_early_deaths_following_neonatal_male_circumcision_in_the_United_States_2001-2010.

Page Page 3 Line 38/39. The references regarding pain, trauma, and potential long term psychological effects are not as strong as they could be (or at least, are liable to seen as controversial), and the phrasing in this sentence needs improvement and greater specificity. For example, "severe and long-lasting pain" is confusing—certainly, severe pain can occur, especially when anesthesia is not used, but "long-lasting pain" is less clear because, what counts as long-lasting? I would rewrite this section to make the precise empirical findings more carefully stated, as well as update the references as follows:

MC can cause clinically significant pain despite the use of analgesia and severe pain when no analgesia is used [1-3]. The procedure has been associated with "strikingly significant changes in physiological, hormonal and behavioral parameters, and adverse events such as choking and apnea" [4]. Common expressions of extreme distress in response to circumcision include "very strained and labored upper limb movements, high-pitched screeches, bilateral arm raising and widening, breath holding, abrupt and intentional arm movements, and frantic upper limb movements" [5]. Pain during wound-healing for newborn circumcision has been observed up to 6 weeks following the surgery [6], as the exposed glans may come into contact with urine and feces. Circumcision involves maternal separation and restraint to a board, with removal of highly sensitive penile tissues, which may increase the risk of long-term adverse psychosexual sequelae [7-10]. Research suggests that procedures that are far milder than MC, such as routine heel punctures, can have persistent negative effects, with changes to immune, endocrine, and behavioral reactions to stressful events continuing into childhood or even adulthood [11, 12].

1. Banieghbal, B. (2009). Optimal time for neonatal circumcision: An observation-based study. Journal of Pediatric Urology, 5, 359-362. doi:10.1016/j.jpurol.2009.01.002

2. Bellieni, C. V., Alagna, M. G., & Buonocore, G. (2013). Analgesia for infants' circumcision. Italian Journal of Pediatrics, 39(38), 1-7.

3. Howard, C. R., Weitzman, M. L., & Howard, F. M. (1994). Acetaminophen analgesia in neonatal circumcision: the effect on pain. Pediatrics, 93(4), 641-646.

4. Taddio, A. (2001). Pain management for neonatal circumcision. Paediatric drugs, 3(2), 101-111.

5. Warnock, F., & Sandrin, D. (2004). Comprehensive description of newborn distress behavior in response to acute pain (newborn male circumcision). Pain, 107(3), 242-255.

6. Freeman, J. J., Spencer, A. U., Drongowski, R. A., Vandeven, C. J., Apgar, B., & Teitelbaum, D. H. (2014). Newborn circumcision outcomes: Are parents satisfied with the results? Pediatric Surgery International, 30, 333-338. doi:10.1007/s00383-013-3430-5

7. Bossio, J. A., Pukall, C. F., & Steele, S. S. (2016). Examining penile sensitivity in neonatally circumcised and intact men using quantitative sensory testing. The Journal of urology, 195(6), 1848-1853.

8. Earp, B. D. (2016). Infant circumcision and adult penile sensitivity: implications for sexual experience. Trends in Urology & Men's Health, 7(4), 17-21.

9. Boyle, G. J., Goldman, R., Svoboda, J. S., & Fernandez, E. (2002). Male circumcision: pain, trauma and psychosexual sequelae. Journal of Health Psychology, 7(3), 329-343.
10. Hammond, T., & Carmack, A. (2017). Long-term adverse outcomes from neonatal circumcision reported in a survey of 1,008 men: an overview of health and human rights implications. The International Journal of Human Rights, 21(2), 189-218.

11. Anand, K. J. (1998). Clinical importance of pain and stress in preterm neonates. Neonatology, 73(1), 1-9.

12. AAP Committee on Fetus and Newborn (2016). Prevention and management of procedural pain in the neonate: an update. Pediatrics, 137(2), e20154271.

Page 7 Line 26. It should be "time consuming investigations" not "a time consuming investigations."

Page 7 Line 42. The references on circumcision and breastfeeding may not be the best available. I cannot seem to access the Caplan "Response to Nikki Lee" so cannot check its quality, but a letter and a response to a letter are not typically the strongest sources. A better citation might be: Howard, C. R., Weitzman, M. L., & Howard, F. M. (1994). Acetaminophen analgesia in neonatal circumcision: the effect on pain. Pediatrics, 93(4), 641-646. However, I am not sure raising the "disrupts breastfeeding" possibility is really the most sensible choice, as more recent studies seem to converge on a null effect for circumcision disrupting breastfeeding:

Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2008). Neonatal circumcision: effects on breastfeeding and outcomes associated with breastfeeding. Journal of paediatrics and child health, 44(1-2), 44-49.

Gattari, T. B., Bedway, A. R., Drongowski, R., Wright, K., Keefer, P., & Mychaliska, K. P. (2013). Neonatal circumcision: is feeding behavior altered?. Hospital pediatrics, 3(4), 362-365.

Mondzelewski, L., Gahagan, S., Johnson, C., Madanat, H., & Rhee, K. (2016). Timing of circumcision and breastfeeding initiation among newborn boys. Hospital pediatrics, hpeds-2015.

Page 9 Line 12/13. It is probably imprudent to refer to female genital 'mutilation' as equivalent to male circumcision, because the latter term encompasses more than a dozen different procedures, and not all can be compared along certain dimensions. It would be much better to say "parallel" or "analogous" procedure; and "female genital mutilation" (which is a politicized term used by activists, not scholars) should be changed to "non-therapeutic female genital cutting" or something like that. The reference to the Matthews piece is okay, but since a direct comparison is being made between male and female genital cutting it would probably be more appropriate and useful to cite work that directly discusses the physical and symbolic overlaps between the two procedures while highlighting their different treatment in law, such as:

Earp, B. D. (2015). Female genital mutilation and male circumcision: Toward an autonomy-based ethical framework. Medicolegal and Bioethics, 5(1), 89-104.

Shahvisi, A., & Earp, B. D. (in press). The law and ethics of female genital cutting. In S. Creighton & L.-M. Liao (Eds.) Female Genital Cosmetic Surgery: Solution to What Problem. Cambridge: Cambridge University Press.

Page 9 Line 19. The word "decimate" is too specific since it means divide by 10. Why not just say "reduce" the bias?

Page 9 Line 48. I think "deadly practice" should be "potentially deadly practice" as it is mostly NOT deadly.

Pag 10 Lines 11/12. To say that sudden death is "highly prevalent" seems too strong. Better would be "sudden death following circumcision was and is a non-trivial risk"

Page 11 Lines 4/5. The phrase "the most common unnecessary surgery in the world" should perhaps be rephrased to "the most common pediatric surgery performed on healthy children without a valid medical indication"

Page 11 Line 10. The 'financial motives' argument is very contentious and not necessary here; the Margulis and Hill references will also be seen as controversial. I would re-write this sentence to say: "While the risks of pre-term births are well-recognized, the debate concerning MNC is polarized between ethical concerns [99] and advocacy with respect to contested health benefits [100-101], with few resources devoted to investigating potential long-term risks to infants." And I would cite 100 and 101 as follows:

100. Frisch, M., Aigrain, Y., Barauskas, V., Bjarnason, R., Boddy, S. A., Czauderna, P., ... & Gahr, M. (2013). Cultural bias in the AAP's 2012 Technical Report and Policy Statement on male circumcision. Pediatrics, 131(4), 796-800.

101. Dave, S., Afshar, K., Braga, L. H., & Anderson, P. (2018). Canadian Urological Association guideline on the care of the normal foreskin and neonatal circumcision in Canadian infants (full version). Canadian Urological Association Journal, 12(2), E76.

Page 12 Line 6: "a carefully constructed cohort studies" is ungrammatical

Page 16 Line 33. I would not cite statistics from the MGM bill as that is a political advocacy group, such that, even if the statistics may be reliable, it will attract criticism and suspicion.

Page 16 Line 28. Reference 30 "Born Too Soon" - what is this referring to/ where is the rest of the information?

Page 20 Line 42. Stang and Stellman reference is referred to only as "Stang" in the main text.

Reviewer #2: General Comments: Very interesting premise for a study. A ecological or geological study is a good place to start for testing hypothesis. This study makes a good start, but there are several weaknesses of this study that need to be addressed before it can be considered for publication.

First, I would recommend dropping the analysis of from the various countries from around the world. The data is weak and unreliable. Only a few countries are included in the analysis and the definition of SIDS is more likely to vary between these countries than would vary between States within the United States. From reviewing the data used in the calculations, it appears that circumcision prevalence in the various countries was used rather than rates of neonatal circumcision. Circumcision prevalence, which in many of the countries included is the result of circumcisions performed after the newborn period, would not be temporally related to SIDS mortality if circumcisions are performed after the age at which SIDS is likely to occur. It may be worth mentioning in passing that similar results to those garnered in the United States was found in a cursory survey of the handful of countries for which data are available.

Second, the State by State data needs to be weighted by the number of live-births in each State each year. If this is not done, then Wyoming has as much influence on analyses as California. Weighted and unweighed calculations can be both be undertaken and compared. I used 2015 data [Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Matthews TJ. Births: Final Data for 2015. National Vital Statistics Reports 2015; 66(1): Table 10 page 38. Available at https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_01.pdf] on number of live births in each State and performed weighted calculations on SAS. I have included these in the text below.

Third, the discussion of Lilith, while interesting, should be dropped.

Fourth, clearly explained multifactorial regression analysis should be performed and reported. An example of this would be a model of that evaluates the impact on SIDS mortality rate by prematurity, circumcision rate, and region of the country. I have used the authors' unweighted data and performed this analysis.

| | Beta | SE | t | p | Beta 95%CI |
|---|---|---|---|---|---|
| preterm | -0.04561 | 0.50535 | -0.90 | 0.3733 | -0.148422 to +0.057206 |
| circ | 0.0080082 | 0.002685 | 2.98 | 0.0053 | +0.0025455 to +0.01347 |
| region | 0.0005 | | | | |
| Weighted for population | | | | | |
| preterm | 0.059441 | 0.0616280 | 0.960 | 0.3418 | -0.0659415 to +0.18482 |
| circ | 0.0076430 | 0.00273755 | 2.79 | 0.0086 | +0.002073 to +0.013212 |
| region | 0.0130 | | | | |

Specific comments:

There is no "prevalence of SIDS." SIDS has mortality rate per live-births.

Abstract: Page 2 line 18: Drop the statistics listed and replace with : Increase of 0.0967 (95%CI=0.0040-0.1534) per 1000 live-births SIDS mortality per 10% increase in circumcision rate; US: Unweighted: Increase of 0.0509 (95%CI=0.0.085376-0.0932) per 1000 live-births SIDS mortality per 10% increase in circumcision rate; Weighted: 0.0508 (95%CI=0.0125-0.0891, t=2.69, p=.0107))

Need to replace the results with change in SIDS incidence per percentage change (1% or 10%) with 95% confidence intervals. Unclear what these CIs are referring to. r-values, t-tests and p-values are reflected in the slope value and this confidence intervals of this value, and by themselves are not informative.

For prematurity: When I ran the data provided for Global data there was no correlation (r=0.21282, p=.4287)]; For US replace statistics with: Unweighted: Increase of 0.12439 (95%CI=0.03569-0.21309) per 1000 live-births SIDS mortality per 1% increase in preterm rate; Weighted: 0.18325 (95%CI=0.11439-0.25210, t=5.35, p<.0001.

Page 2 line 32-33: Last sentence of abstract. This sounds clunky. Perhaps changed to "and efforts should be focused on reducing the rates of both."

page 3 line 45: The comparison of SIDS rates in Anglophone versus other countries using a t-test is somewhat unstable because the standard deviations between the two groups of countries are disparate. The difference (32.1%, 95%CI=7.8% to 56.5%) is statistically significant when a pooled t-test is used (t=2.83(df=14), p=.0133) but not when the more accurate Satterwaite method is used (t=2.34 (df=6.09), p=.0572). This provides more reason to relegate the Global data to the backseat.

Some of the abbreviations (NWH and others) appear in the manuscript but not in the abbreviation list.

Page 4, line 12: referring to the SIDS rate as "alarmingly high" is hyperbolic. Better to note the percentage drop following BTS and that there remains room for improvement.

Page 4, line 23: avoid stark referral to reference numbers. Instead use "Similarly to the methods employed by Bauer and Kriebel [29] …"

Page 4, line 28-29: It appears that circumcision prevalence in adults may be confused with the incidence of neonatal circumcision. Given that many Muslims are circumcised by the time they reach adulthood, but are not circumcised as neonates, this might undermine attempts to estimate the association between MNC and SIDS if those circumcised after the neonatal period are included. For this reason Global analysis should be only mentioned peripherally.

Page 5, lines 24-27: This is confusing. Were analyses performed separately for the year 2000, 2010, and 2015? These should be reported as differences and the 95%CI of the differences rather than p-values. Were state data weighted for state population? Consider using a marginal mixed model in which multiple values (from different years) for each state can be imputed into a single model that can provide an overall summary result. Consider presenting as a Table. Alternatively, a summary statistic may all that is needed as this a tangential finding rather than the focus of the analysis.

Page 5, line 32: Once again, is this three analyses? These data can be combined in a marginal mixed model. This is a linear regression and the results should be reported as the slope (ß) and the 95%CI of the slope. Reporting r-values and p-values is much less informative.

Page 5, line 37: Avoid describing an association as "strongly" or "marginally" significant. Something is either significant or it is not. Replace statistics with results of linear regression:

Increase of 0.0967 (95%CI=0.0040-0.1534) per 1000 live-births SIDS mortality per 10% increase in circumcision rate, t=3.66, p=.0026).

Page 5, lines 38-41: The sensitivity analysis of halving or doubling is not necessary and should be deleted. Delete this. The 95%CIs of the slope will tell the same story.

Page 5, line 46: Replaced analysis with linear regression: Controlling for being an Anglophone nation the SIDS rate (per 1000 live-births) was not significantly impacted by prematurity rates (p=.6021), but was impacted by circumcision (increase of 0.07444 (95%CI=0.002534-0.1463) per 10% increase in circumcision, t=2.24, p=.0435).

Page 5, lines 48-49: Replace statistics with regression results: Unweighted:Increase of 0.0509 (95%CI=0.0.085376-0.0932) per 1000 live-births SIDS mortality per 10% increase in circumcision rate, t=2.44, p=.0198Weighted: 0.0508 (95%CI=0.0125-0.0891, t=2.69, p=.0107.

Page 5, lines 55-56. Things are not "marginally" significant. This finding is not statistically significant, so need to call it a non-significant trend.

Page 5, lines 57-58. The correlation between SIDS and circumcision was impacted by the region of the country (F=8.68, p=.0002). When adjusted for region the association remained statistically significant (0.083237, 95%CI=0.02954-0.136935, t=3.15, p=.0034 WEIGHTED).

Page 6, line 8: Instead of these statistics needs a linear regression. I did not have time to run this regression, but the results should be reported as slope (ß) and 95%CIs.

Page 6, lines 8-10: Accounting for 14% of the variability is one of the study's most important findings. More attention needs to be paid to this. Explain how this was determined.

Page 6, lines 10-16: Instead give difference and its 95%CIs. Also make it more clear which populations are being compared here. I did not have time to run the analysis.

Page 6, lines 25-27: Not sure what the intervals represent. I ran the data provided by the authors and found different numbers r=0.21282, p=.4287. The numbers listed here by the authors are what came up for a correlation between circumcision and SIDS, r=0.69925, p=.0026. My calculation for slope was also different: I calculated the slope to be 0.180 (95%CI=-0.264 to +0.6537, t=0.81, p=.4287.

Page 6, lines 30-33: replace prematurity statistics with regression results: Unweighted: Increase of 0.12439 (95%CI=0.03569-0.21309, t=2.84, p=.0073) per 1000 live-births SIDS mortality per 1% increase in preterm rate; Weighted: 0.18325 (95%CI=0.11439-0.25210, t=5.35, p<.0001.

Page 6, lines 34-38: Drop the comparison between Southern states as it is cherry-picking comparisons. Instead state: The correlation between SIDS and prematurity was not found on regression analysis to have regional differences (F=1.77, p=.1661).

Page 6, line 51: Work in: A weighted multivariate model of SIDS deaths that include circumcision, prematurity, and region of the country found that circumcision (ß=0.07643, 95%CI=0.020734-0.13212, t=2.79, p=.0086) and geographic region (F=4.18, p=.0130) were significant factors, while prematurity was not statistically significant (ß=0.059441, 95%CI=-0.06594 to +0.1848, t=0.96, p=.3418).

Page 6, lines 58-59: Not clear which test was used. May need to only report results of multivariate regression and whether interaction terms are statistically significant. Test for interaction between circumcision and region was not significant (p=.1219 Weighted model) and interaction between circumcision and prematurity was also negative (p=.1338 Weighted model).

Page 7, line 4: Discussion section should begin with a summary of the findings.

Page 7, line 9: "pertain" should be "pertains"

Page 7, lines 11-15: Change sentence to: "Therefore, SIDS can be expected to decrease over time as parental education and diagnostic methods improve. Indeed, the rate of SIDS has been declining worldwide since the 1980s [45] …"

Page 7, line 20: Has the success of the BTS campaign been limited, or has it achieved it's maximal potential?

Page 8, lines 4-8: Ambiguous. Is it being asserted that infants with all three risk factors will all die of SIDS? Or is it being asserted that for those who have the risk factors who die of SIDS, there was nothing that could have been done to prevent the death?

Page 8, 45-46: This is a rather broad claim. There are many who would not agree that there are no congenital or genetic risk factors for SIDS. Instead soften the language to state that given the lack of clear genetic or congenital risks factors.

Page 9, line 19: "decimate" is too strong a term to the point of being hyperbolic. Consider "ameliorate."

Page 9, 28-30: This is confusing. It is well documented that during the procedure that blood pressure, heart rate, respiratory rate all increase, while oxygen levels decrease. Is it being asserted that after the procedure the heart rate, blood pressure, and oxygen perfusion are decreased? If so, that needs to clarified.

Page 9, lines 39-42: The NHS had excluded coverage of circumcision prior to the publication of Gairdner's report.

Page 9, line 44 through page 10, line 19: While a very interesting diversion, this entire paragraph can be easily be deleted. It adds little to the thrust of the study.

Page 10, line 42: Analysis found no interaction between circumcision and prematurity, so prematurity was not an effect modifier and only has an additive effect, that in the model was not statistically significant.

Page 11, line 4: Not sure if circumcision is the most common in the world and whether it is unnecessary is hotly contested and does not need to be litigated in this venue.

Page 11, line 6: add "accounting for 14% of an infant's risk of dying from SIDS." to the end of the sentence. This finding needs more emphasis than it is currently given.

Reference 38: Needs more details than "Born Too Soon."

Not sure if all of the Tables and Figures are needed in the final version.

Overall, a very interesting study. When published it will come under blistering, unscientific scrutiny by circumcision advocates, so the analysis needs to be as solid as possible.

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Author's rebuttal

**Response to reviewers**
We first wish to thank Dr. Heger for allowing resubmission of our manuscript. We also wish to express our deepest gratitude to the two anonymous reviewers for their extremely thorough and enlightening review, which no doubt took many efforts. We appreciate that all the reviewers acknowledged the importance of the problem we tackle and contributed to improving our work. The reviewers have also raised important issued that we have now addressed. We also simplified the terminology, added new analyses, added new references, and revised the manuscript to increase quality and clarity. One comments, which was critical to the success of the paper, was to use circumcision data from an official source rather than from http://www.cirp.org/. It took much time (and a small fortune) to receive the new data. We found that the cirp data were wrong and that the official sources had fewer data, which reduced the power of a few of our analyses. We added new analyses to compensate and reported this limitation in the analyses where the power was reduced. We believe that these revisions significantly improved quality of the manuscript and express our willingness to carry out further improvements if necessary. Please see below our detailed answers to the reviewers.

**Reviewer #1**: This is a highly original study that will certainly be of use to researchers studying both SIDS and circumcision, and it provides some nice data in support of the allostatic load hypothesis that distinguishes it from competing accounts. It is well written and nicely acknowledges the limitations inherent to the subject matter. Hopefully it will inspire prospective studies as the authors suggest. I recommend that the paper be published upon minor revision, and, to aid with this, I have given very specific comments below that the authors should implement in revising their manuscript.
We thank the reviewer for the recommendations and detailed comments. We accepted all the comments and revised the manuscript accordingly.

Page 2 Line 9: it should be "cumulative perinatal" not the other way around
OK

Page 2 Line 13: seems strange to describe prematurity as a "stressor" … being born early may well make one more stressed by various stimuli (stressors), but the state of prematurity, just conceptually, feels different from the concept of being a stressor  We replaced this term with "phenotype"

Page 2 Line 23: I would delete "reminiscent of the Jewish myth of Lillith, killer of infant males." It feels out of place in the scientific abstract

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Page 2 Line 33: Re: "Preterm birth and neonatal circumcision increase the risk for SIDS and should be avoided." Presumably it should said that those variables are "associated with a greater risk" rather than that they "increase the risk" as that implies causal evidence. Also, what would it mean to say "Preterm birth … should be avoided" … ? Presumably if someone has a child preterm, this is not intentional, and all measures are already taken to avoid pre-term birth that is not necessary. The "should be avoided," then, is probably supposed to refer just to neonatal circumcision (since that's intentional), but then the whole sentence is confusing. Saying that both pre-term birth and MNC are 'risk facors' and that further research should be done to try to assess the evidence in a more causal/prospective way would be appropriate, but saying, on the basis of correlational evidence, that (on that basis alone) MNC should be avoided feels too much like a command or bald assertion rather than something that follows from the finding in a logical way.
We revised to read: "Preterm birth and neonatal circumcision are associated with a greater risk of SIDS and efforts should be focused on reducing their rates."

Page 3 Line 22. Male predominance is mentioned in the US, but is there a similar male predominance in other countries (in particular those that do not circumcise)? That should be stated if so. The focus on US only here is confusing.
We removed the reference to the US.

Page 3 Line 30. "Both stressor" should be "Both stressors"
OK, we now use "phenotypes"

Page 3 Line 35. Re: complications, Krill et al. should also be cited: Krill, A. J., Palmer, L. S., &
Palmer, J. S. (2011). Complications of circumcision. The Scientific World Journal, 11, 24582468. Re: deaths, Earp et al. should be cited: Earp, B. D., Allareddy, V., Allareddy, V., & Rotta,
A. T. (2018). Factors associated with early deaths following neonatal male circumcision in the United States, 2001-2010. Clinical Pediatrics, in press. Online version ahead of print at https://www.researchgate.net/publication/326040454_Factors_associated_with_early_deaths_foll owing_neonatal_male_circumcision_in_the_United_States_2001-2010. These and other references were added to make this passage more comprehensive.

Page 3 Line 38/39. The references regarding pain, trauma, and potential long term psychological effects are not as strong as they could be (or at least, are liable to seen as controversial), and the phrasing in this sentence needs improvement and greater specificity. For example, "severe and long-lasting pain" is confusing—certainly, severe pain can occur, especially when anesthesia is not used, but "long-lasting pain" is less clear because, what counts as long-lasting? I would rewrite this section to make the precise empirical findings more carefully stated, as well as update the references as follows:

MC can cause clinically significant pain despite the use of analgesia and severe pain when no analgesia is used [1-3]. The procedure has been associated with "strikingly significant changes in physiological, hormonal and behavioral parameters, and adverse events such as choking and apnea" [4]. Common expressions of extreme distress in response to circumcision include "very strained and labored upper limb movements, high-pitched screeches, bilateral arm raising and widening, breath holding, abrupt and intentional arm movements, and frantic upper limb movements" [5]. Pain during wound-healing for newborn circumcision has been observed up to 6 weeks following the surgery [6], as the exposed glans may come into contact with urine and feces. Circumcision involves maternal separation and restraint to a board, with removal of highly sensitive penile tissues, which may increase the risk of long-term adverse psychosexual sequelae [7-10]. Research suggests that procedures that are far milder than MC, such as routine heel punctures, can have persistent negative effects, with changes to immune, endocrine, and behavioral reactions to stressful events continuing into childhood or even adulthood [11, 12].

1. Banieghbal, B. (2009). Optimal time for neonatal circumcision: An observation-based study. Journal of Pediatric Urology, 5, 359-362. doi:10.1016/j.jpurol.2009.01.002

2. Bellieni, C. V., Alagna, M. G., & Buonocore, G. (2013). Analgesia for infants' circumcision. Italian Journal of Pediatrics, 39(38), 1-7.

3. Howard, C. R., Weitzman, M. L., & Howard, F. M. (1994). Acetaminophen analgesia in neonatal circumcision: the effect on pain. Pediatrics, 93(4), 641-646.

4. Taddio, A. (2001). Pain management for neonatal circumcision. Paediatric drugs, 3(2), 101111.

5. Warnock, F., & Sandrin, D. (2004). Comprehensive description of newborn distress behavior in response to acute pain (newborn male circumcision). Pain, 107(3), 242-255.

6. Freeman, J. J., Spencer, A. U., Drongowski, R. A., Vandeven, C. J., Apgar, B., & Teitelbaum, D. H. (2014). Newborn circumcision outcomes: Are parents satisfied with the results? Pediatric Surgery International, 30, 333-338. doi:10.1007/s00383-013-3430-5

7. Bossio, J. A., Pukall, C. F., & Steele, S. S. (2016). Examining penile sensitivity in neonatally circumcised and intact men using quantitative sensory testing. The Journal of urology, 195(6), 1848-1853.

8. Earp, B. D. (2016). Infant circumcision and adult penile sensitivity: implications for sexual experience. Trends in Urology & Men's Health, 7(4), 17-21.

9. Boyle, G. J., Goldman, R., Svoboda, J. S., & Fernandez, E. (2002). Male circumcision: pain, trauma and psychosexual sequelae. Journal of Health Psychology, 7(3), 329-343.

10. Hammond, T., & Carmack, A. (2017). Long-term adverse outcomes from neonatal circumcision reported in a survey of 1,008 men: an overview of health and human rights implications. The International Journal of Human Rights, 21(2), 189-218.

11. Anand, K. J. (1998). Clinical importance of pain and stress in preterm neonates. Neonatology, 73(1), 1-9.

12. AAP Committee on Fetus and Newborn (2016). Prevention and management of procedural pain in the neonate: an update. Pediatrics, 137(2), e20154271.

Thank you, we embedded the suggested paragraph in the text.

Page 7 Line 26. It should be "time consuming investigations" not "a time consuming investigations."
OK

Page 7 Line 42. The references on circumcision and breastfeeding may not be the best available. I cannot seem to access the Caplan "Response to Nikki Lee" so cannot check its quality, but a letter and a response to a letter are not typically the strongest sources. A better citation might be: Howard, C. R., Weitzman, M. L., & Howard, F. M. (1994). Acetaminophen analgesia in neonatal circumcision: the effect on pain. Pediatrics, 93(4), 641-646. However, I am not sure raising the "disrupts breastfeeding" possibility is really the most sensible choice, as more recent studies seem to converge on a null effect for circumcision disrupting breastfeeding:

Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2008). Neonatal circumcision: effects on breastfeeding and outcomes associated with breastfeeding. Journal of paediatrics and child health, 44(1-2), 44-49.

Gattari, T. B., Bedway, A. R., Drongowski, R., Wright, K., Keefer, P., & Mychaliska, K. P. (2013). Neonatal circumcision: is feeding behavior altered?. Hospital pediatrics, 3(4), 362-365.

Mondzelewski, L., Gahagan, S., Johnson, C., Madanat, H., & Rhee, K. (2016). Timing of circumcision and breastfeeding initiation among newborn boys. Hospital pediatrics, hpeds-2015. Thank you, we updated the references.

Page 9 Line 12/13. It is probably imprudent to refer to female genital 'mutilation' as equivalent to male circumcision, because the latter term encompasses more than a dozen different procedures, and not all can be compared along certain dimensions. It would be much better to say "parallel" or "analogous" procedure; and "female genital mutilation" (which is a politicized term used by activists, not scholars) should be changed to "non-therapeutic female genital cutting" or something like that. The reference to the Matthews piece is okay, but since a direct comparison is being made between male and female genital cutting it would probably be more appropriate and useful to cite work that directly discusses the physical and symbolic overlaps between the two procedures while highlighting their different treatment in law, such as:

Earp, B. D. (2015). Female genital mutilation and male circumcision: Toward an autonomybased ethical framework. Medicolegal and Bioethics, 5(1), 89-104.

Shahvisi, A., & Earp, B. D. (in press). The law and ethics of female genital cutting. In S.

Creighton & L.-M. Liao (Eds.) Female Genital Cosmetic Surgery: Solution to What Problem.
Cambridge: Cambridge University Press.
Thank you, we updated the references.

Page 9 Line 19. The word "decimate" is too specific since it means divide by 10. Why not just say "reduce" the bias?
This was the old meaning of the term, but not anymore https://en.oxforddictionaries.com/definition/us/decimate. Nonetheless, we revised to avoid confusion.

Page 9 Line 48. I think "deadly practice" should be "potentially deadly practice" as it is mostly NOT deadly.
OK

Pag 10 Lines 11/12. To say that sudden death is "highly prevalent" seems too strong. Better would be "sudden death following circumcision was and is a non-trivial risk"
OK

Page 11 Lines 4/5. The phrase "the most common unnecessary surgery in the world" should perhaps be rephrased to "the most common pediatric surgery performed on healthy children without a valid medical indication"
OK

Page 11 Line 10. The 'financial motives' argument is very contentious and not necessary here; the Margulis and Hill references will also be seen as controversial. I would re-write this sentence to say: "While the risks of pre-term births are well-recognized, the debate concerning MNC is polarized between ethical concerns [99] and advocacy with respect to contested health benefits [100-101], with few resources devoted to investigating potential long-term risks to infants." And I would cite 100 and 101 as follows:

100. Frisch, M., Aigrain, Y., Barauskas, V., Bjarnason, R., Boddy, S. A., Czauderna, P., ... & Gahr, M. (2013). Cultural bias in the AAP's 2012 Technical Report and Policy Statement on male circumcision. Pediatrics, 131(4), 796-800.

101. Dave, S., Afshar, K., Braga, L. H., & Anderson, P. (2018). Canadian Urological Association guideline on the care of the normal foreskin and neonatal circumcision in Canadian infants (full version). Canadian Urological Association Journal, 12(2), E76.

OK

Page 12 Line 6: "a carefully constructed cohort studies" is ungrammatical
Thank you, the sentence now reads: “Some of the remaining limitations may be addressed in future cohort studies, but…”

Page 16 Line 33. I would not cite statistics from the MGM bill as that is a political advocacy group, such that, even if the statistics may be reliable, it will attract criticism and suspicion. We replaced this references with a references to the HCUPnet and KID databases. The MGM data were partially wrong. Thank you for this excellent comment.

Page 16 Line 28. Reference 30 "Born Too Soon" - what is this referring to/ where is the rest of the information?
The full references has been updated. It now reads:
March of Dimes: **Born Too Soon**. In. http://www.marchofdimes.org/mission/globalpreterm.aspx# (Last access August 12th 2018); 2010.

Page 20 Line 42. Stang and Stellman reference is referred to only as "Stang" in the main text.
Corrected, thank you.

**Reviewer #2**: General Comments: Very interesting premise for a study. A ecological or geological study is a good place to start for testing hypothesis. This study makes a good start, but there are several weaknesses of this study that need to be addressed before it can be considered for publication.
We thank the reviewer for all the comments and corrections and revised the manuscript accordingly. There was some confusion about the calculation. Please note, that now there is a single script for all the analyses and calculations in the paper. The script is very well annotated so that you can produce all our results (calculations + figures). The script is available at https://github.com/eelhaik/SIDS_eco_study.

First, I would recommend dropping the analysis of from the various countries from around the world. The data is weak and unreliable. Only a few countries are included in the analysis and the definition of SIDS is more likely to vary between these countries than would vary between States within the United States.
The reviewer is correct that reliable SIDS data are very hard to collect due to the strict definition of SIDS. For this reason, we analyzed only SIDS data collected by the *International Society for the Study and Prevention of Perinatal and Infant Death* using the same methodology (https://www.ispid.org/infantdeath/id-statistics/). We have also consulted with the PI Fern Hauck regarding these data. We, thereby, believe that these data are reliable, and albeit limited in size, provide a true representation of the international SIDS rates in the respective countries. This information is both valuable in our study as a replication cohort and for follow up studies.

From reviewing the data used in the calculations, it appears that circumcision prevalence in the various countries was used rather than rates of neonatal circumcision. Circumcision prevalence, which in many of the countries included is the result of circumcisions performed after the newborn period, would not be temporally related to SIDS mortality if circumcisions are performed after the age at which SIDS is likely to occur. It may be worth mentioning in passing that similar results to those garnered in the United States was found in a cursory survey of the handful of countries for which data are available.
Looking at Table S1, which summarizes all the MNC data, there are 5 countries for which we were able to obtain MNC data. For the remaining countries, MNC was estimated from the population of Jews and Muslims, following [1]. While there is no doubt when Jews circumcise, the question when Muslim circumcise is of relevant to our assumption. The rate of MNC among Muslims vary based on numerous factors, but nonetheless exists. We did a sensitivity analysis to confirm this result. We added the following paragraph in the method section:

Unlike Jewish traditions where ritualistic circumcision is performed on the eight day after birth, Islamic traditions do not provide a specific recommendation and the age of circumcision varies according to family, parents' education, Islamic branch, country of origin [2], MNC costs, and the contemporary country's norms and legislation [3]. Nonetheless, a sizeable proportion of circumcisions are done neonatally in Iraq [4] (18% were circumcised in the first 180 days), Norway [5] (20% were circumcised in their first year), Pakistan [6] (44% were circumcised in the first 60 days within two months), and Turkey [7, 8] (14.8% were circumcised in their first year, half of them within the first 30 days). In Belgium the circumcision age decreases with time [9]. These variations will have minimal effect on our analyses, provided the average low MNC rates in the countries where they were estimated from the Muslim and Jewish populations.

The most important concern for our calculations is the last line. Our correlation analysis also includes both half and twice the estimates in Table S1. Finally, we noted that as a limitation of our study (we well as any other study that evaluated the rate of out-of-the-hospital circumcision rates, as in [10]).

Second, the State by State data needs to be weighted by the number of live-births in each State each year. If this is not done, then Wyoming has as much influence on analyses as California. Weighted and unweighed calculations can be both be undertaken and compared. I used 2015 data
[Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Matthews TJ. Births: Final Data for 2015. National Vital Statistics Reports 2015; 66(1): Table 10 page 38. Available at https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_01.pdf] on number of live births in each State and performed weighted calculations on SAS. I have included these in the text below. We completely agree with the reviewer. Weighted analyses have been added to all the analyses. We also revised some of the figures to be weighted.

Third, the discussion of Lilith, while interesting, should be dropped. We believe that there are several reasons to include this paragraph:

First, in epidemiology we always seek the historical perspective that would help us understand the genetic-environmental relationships and answer the ultimate question: "Is this diagnosis changes over time [environment] or is steady [genetic]." Fortunately, although we lack the historical perspectives in SIDS, mainly because it is a very young concept, we can make careful inferences from historical documents describing deaths of unknown reasons. The major challenge is to identify which of the past deaths fits our definition of SIDS. We believe that the Lilith myth allows us to do so through the connection with MNC, which strongly supports our hypotheses.

Second, since our study deals with MNC, a non-clinical religious practice that is passed as a clinical practice, a multi-disciplinary approach is necessary in understanding its origin and to properly discuss its advantages and disadvantages. In that respect, since MNC was not practiced in Europe prior to the 19$^{th}$ century and as the only population who practice solely MNC, it makes sense to study the history of MNC and SIDS among Jews. This also addresses a very obvious question that arises from our study: What are the SIDS rates among Jews? Do they experience more SIDS then others? If they do not, our thesis is problematic. If Jews have been experienced SIDS for centuries, why this 2018 study is the first to notice it? Moreover, in his book, David Gollaher [11] reviewed the reasons for MNC in the US. His final conclusion is that it is done for religious reasons, i.e., for Americans to feel a little bit closer to Jews. So again the question is, to what extent has MNC risked the Jewish community? This question is also important to the Jewish community itself. They deserve an answer.

As you know, we do not have SIDS data for Jews. By definition, the SIDS rates in Israel are NIL
(no postmortems) and SIDS data elsewhere do not record religion. Our study shows that Jews were so well aware of the MNC-SIDS connection (SIDS - as we understand it today!) that they embedded it into their beliefs and behavior and that it survived to the present day among both religious and secular Jews.

Third, we added a following paragraph about Hispanics, who exhibit opposite trends both in MNC and SIDS.

Fourth, we understand that this is a clinical journal, however it is also about translation. There is a very large Jewish population who are committed to circumcision but also still fear of Lilith.
This is evidenced by the hundreds of thousands of Jews who do not cur their boys' hairs. This paragraph would help this people better understand their fears and make a more educated decision about MNC. A population-wise approach, of course, is a major part of clinical analyses and, historically, observations that Jews "benefit" from MNC more than non-Jews prompted the medicalization of this practice. It is only fair to address the aspect of mortality due to MNC among Jews, which has been pushed under the rag for centuries.

Finally, we feel that the "Lilith paragraph," which is quite brief, provides an important basis to understand the history of SIDS – thousands of years before it was formally defined and its effect on the Jewish community, not to mention that it addresses several open and important anthropological questions.

To satisfy the reviewer, we omitted the Lilith part from the abstract and revised the paragraph be better embedded in the paper – alongside the above explanation.

Fourth, clearly explained multifactorial regression analysis should be performed and reported. An example of this would be a model of that evaluates the impact on SIDS mortality rate by prematurity, circumcision rate, and region of the country. I have used the authors' unweighted data and performed this analysis.

| | Beta | SE | t | p | Beta 95%CI |
|---|---|---|---|---|---|
| preterm | -0.04561 | 0.50535 | -0.90 | 0.3733 | -0.148422 to +0.057206 |
| circ | 0.0080082 | 0.002685 | 2.98 | 0.0053 | +0.0025455 to +0.01347 |
| region | | | | 0.0005 | |
| Weighted for population | | | | | |
| preterm | 0.059441 | 0.0616280 | 0.960 | 0.3418 | -0.0659415 to +0.18482 |

| | | | | | |
|---|---|---|---|---|---|
| circ | 0.0076430 | 0.00273755 | 2.79 | 0.0086 | +0.002073 to +0.013212 |
| region | | | | 0.0130 | |

Thank you, we included this analysis as suggested by the reviewer, using our updated numbers.

Specific comments:
There is no "prevalence of SIDS." SIDS has mortality rate per live-births. Corrected, thank you.

Abstract: Page 2 line 18: Drop the statistics listed and replace with : Increase of 0.0967 (95%CI=0.0040-0.1534) per 1000 live-births SIDS mortality per 10% increase in circumcision rate; US: Unweighted: Increase of 0.0509 (95%CI=0.0.085376-0.0932) per 1000 live-births
SIDS mortality per 10% increase in circumcision rate; Weighted: 0.0508 (95%CI=0.0125-0.0891, t=2.69, p=.0107))
OK

Need to replace the results with change in SIDS incidence per percentage change (1% or 10%) with 95% confidence intervals. Unclear what these CIs are referring to. r-values, t-tests and pvalues are reflected in the slope value and this confidence intervals of this value, and by themselves are not informative. OK, the CI now is for the slope.

For prematurity: When I ran the data provided for Global data there was no correlation (r=0.21282, p=.4287)]; For US replace statistics with: Unweighted: Increase of 0.12439 (95%CI=0.03569-0.21309) per 1000 live-births SIDS mortality per 1% increase in preterm rate; Weighted: 0.18325 (95%CI=0.11439-0.25210, t=5.35, p<.0001.

Page 2 line 32-33: Last sentence of abstract. This sounds clunky. Perhaps changed to "and efforts should be focused on reducing the rates of both."
OK

page 3 line 45: The comparison of SIDS rates in Anglophone versus other countries using a t-test is somewhat unstable because the standard deviations between the two groups of countries are disparate. The difference (32.1%, 95%CI=7.8% to 56.5%) is statistically significant when a pooled t-test is used (t=2.83(df=14), p=.0133) but not when the more accurate Satterwaite method is used (t=2.34 (df=6.09), p=.0572). This provides more reason to relegate the Global data to the backseat.
We used the default t-test in R, which is the Welch test that is equal to the Satterwaite method and the p-value was significant on both cases.

Some of the abbreviations (NWH and others) appear in the manuscript but not in the abbreviation list.
Thank you, we updated the abbreviation list.

Page 4, line 12: referring to the SIDS rate as "alarmingly high" is hyperbolic. Better to note the percentage drop following BTS and that there remains room for improvement.

Thank you, we replaced “alarmingly” with “relatively”. The percentage of drop in SIDS after the BTS is a complicated issue which is discussed at length in the discussion.

Page 4, line 23: avoid stark referral to reference numbers. Instead use "Similarly to the methods employed by Bauer and Kriebel [29] …" Thank you

Page 4, line 28-29: It appears that circumcision prevalence in adults may be confused with the incidence of neonatal circumcision. Given that many Muslims are circumcised by the time they reach adulthood, but are not circumcised as neonates, this might undermine attempts to estimate the association between MNC and SIDS if those circumcised after the neonatal period are included. For this reason Global analysis should be only mentioned peripherally. This comment is a similar to the second comment of this reviewer. We agree that it is a problem and addressed it, but the solution is in cautious assumptions and analysis or otherwise no investigations of MNC in Europeans (and perhaps elsewhere) will be unfeasible since MNCs are done outside of hospital setting.

Our answer to this question was:
*Looking at Table S1, which summarizes all the MNC data, there are 5 countries for which we were able to obtain MNC data. For the remaining countries, MNC was estimated from the population of Jews and Muslims, following [1]. While there is no doubt when Jews circumcise, the question when Muslim circumcise is of relevant to our assumption. The rate of MNC among Muslims vary based on numerous factors, but nonetheless exists. We did a sensitivity analysis to confirm this result. We added the following paragraph in the method section:*

*Unlike Jewish traditions where ritualistic circumcision is performed on the eight day after birth, Islamic traditions do not provide a specific recommendation and the age of circumcision varies according to family, parents' education, Islamic branch, country of origin [2], MNC costs, and the contemporary country's norms and legislation [3]. Nonetheless, a sizeable proportion of circumcisions are done neonatally in Iraq [4] (18% were circumcised in the first 180 days), Norway [5] (20% were circumcised in their first year), Pakistan [6] (44% were circumcised in the first 60 days within two months), and Turkey [7, 8] (14.8% were circumcised in their first year, half of them within the first 30 days). In Belgium the circumcision age decreases with time [9]. These variations will have minimal effect on our analyses, provided the average low MNC rates in the countries where they were estimated from the Muslim and Jewish populations.*

*The most important concern for our calculations is the last line. Our correlation analysis also includes both half and twice the estimates in Table S1. Finally, we noted that as a limitation of our study (we well as any other study that evaluated the rate of out-of-the-hospital circumcision rates, as in [10]).*

Page 5, lines 24-27: This is confusing. Were analyses performed separately for the year 2000, 2010, and 2015? These should be reported as differences and the 95%CI of the differences rather than p-values. Were state data weighted for state population? Consider using a marginal mixed model in which multiple values (from different years) for each state can be imputed into a single model that can provide an overall summary result. Consider presenting as a Table. Alternatively, a summary statistic may all that is needed as this a tangential finding rather than the focus of the analysis.

OK. Analyses were done separately for each year. Analyses were weighted by the state population. We now report the *t*-statistic and 95%CI of the differences, instead of the p-value. Table S4 has all the data. We also added a mixed effect model, which yielded similar results.

Page 5, line 32: Once again, is this three analyses? These data can be combined in a marginal mixed model. This is a linear regression and the results should be reported as the slope (ß) and the 95%CI of the slope. Reporting r-values and p-values is much less informative.
OK. These are all separate analyses. We now report the slope and the 95% of the slope.
Page 5, line 37: Avoid describing an association as "strongly" or "marginally" significant. Something is either significant or it is not. Replace statistics with results of linear regression: Increase of 0.0967 (95%CI=0.0040-0.1534) per 1000 live-births SIDS mortality per 10% increase in circumcision rate, t=3.66, p=.0026).
OK. "Strongly" and "marginally" were removed. Results are now reported as requested.

Page 5, lines 38-41: The sensitivity analysis of halving or doubling is not necessary and should be deleted. Delete this. The 95%CIs of the slope will tell the same story.
This comment conflicts with a comment made by reviewer #1. We feel that these are necessary due to the uncertainty of the MNC estimates using the proportion of Jews and Muslims in the population. This is because definitions of Jews\Muslims can vary by how religious they are, the existence of mixed couples, the existence of non-Jews/Muslims who perform MNC, and many other factors.

Page 5, line 46: Replaced analysis with linear regression: Controlling for being an Anglophone nation the SIDS rate (per 1000 live-births) was not significantly impacted by prematurity rates (p=.6021), but was impacted by circumcision (increase of 0.07444 (95%CI=0.002534-0.1463) per 10% increase in circumcision, t=2.24, p=.0435).

Page 5, lines 48-49: Replace statistics with regression results:  Unweighted:Increase of 0.0509 (95%CI=0.0.085376-0.0932) per 1000 live-births SIDS mortality per 10% increase in circumcision rate, t=2.44, p=.0198Weighted: 0.0508 (95%CI=0.0125-0.0891, t=2.69, p=.0107.

Page 5, lines 55-56. Things are not "marginally" significant. This finding is not statistically significant, so need to call it a non-significant trend.

Page 5, lines 57-58. The correlation between SIDS and circumcision was impacted by the region of the country (F=8.68, p=.0002). When adjusted for region the association remained statistically significant (0.083237, 95%CI=0.02954-0.136935, t=3.15, p=.0034 WEIGHTED).

Page 6, line 8: Instead of these statistics needs a linear regression. I did not have time to run this regression, but the results should be reported as slope (ß) and 95%CIs. OK, these statistics were added.

Page 6, lines 8-10: Accounting for 14% of the variability is one of the study's most important findings. More attention needs to be paid to this. Explain how this was determined.
Unfortunately, limiting ourselves to the official data reduced the power of this analysis and the pvalue is now 0.1. The explained variation is still very high (16%). We added a few more

analyses to demonstrate that MNC is associated with the gender bias in unexplained death. Answering the reviewer's question, we wrote:

Male predominance is one of the hallmark of SIDS. In 21 out of 40 US states where Medicaid, the most common US health insurance, covers MNC (Table S2), the average MNC rate is nearly 1.5 fold higher than the MNC rate in other states ( $\bar{x}$ =72% vs 49%, Welch two-sided *t*-test, $t$=2.7, $p$=0.01) (Figure 6a), in agreement with Leibowitz et al. [12] (69.6% and 31.2%, respectively). The unexplained mortality rate is higher ( $\bar{x}$ =0.79 vs 0.69, Welch two-sided *t*-test, $t$=0.21, $p$=0.82), although not statistically significant, and the SIDS male gender bias is significantly higher ($\bar{x}$=1.48 vs 1.125, Welch two-sided *t*-test, $t$=2.6, $p$=0.02) (Figure 6b).
There is a high positive correlation between the MNC rate and SIDS gender ratio per state (Unweighted: $N$=18, $r$=0.38, $\beta$=0.67 95% CI: -0.18–1.52, *t*-test, $t$=1.66, $p$=0.11; Weighted: $N$=18, $r$=0.38, $\beta$=0.63 95% CI: -0.13–1.4, *t*-test, t=1.74, $p$=0.1) (Figure 7a). It is likely that the results were insignificant due to insufficient data, however the $r^2$ inferred in the regression analysis suggests that MNC may explain 16% of the variability in male SIDS deaths in the US. Grouping the results by population, US states with high population of Hispanic Whites (>12.5%) had significantly lower SIDS gender bias compared to NHW (Welch two-sided *t*-test, $t$=-2.78, $p$=0.008), which also have the highest MNC rates. NHB, who have intermediate MNC rates also show lower SIDS gender bias compared to NHW (Welch two-sided *t*-test, $t$=-2.64, $p$=0.0002) between 1999 and 2016 (Figure 7b, Table S3). Interestingly, the SIDS gender bias was closer to 1 in half of the states with low SIDS rates compared to the remaining states ($N_{High}$=9, $N_{Low}$=9, M/F $\text{ratio}_{\text{High}}$=1.55, M/F $\text{ratio}_{\text{Low}}$ 1.23, Welch two-sided *t*-test, $t$=-1.72, $p$=0.1), in contrary to reports associating SIDS with male bias. These results imply the existence of a common covariate to both SIDS and male bias. In other words, higher male mortality is not a characteristic of SIDS, but rather of high SIDS rates that rise due to the existence of one or more risk factors that affect males more strongly than females.

Page 6, lines 10-16: Instead give difference and its 95%CIs. Also make it more clear which populations are being compared here. I did not have time to run the analysis. OK.

Page 6, lines 25-27: Not sure what the intervals represent. I ran the data provided by the authors and found different numbers r=0.21282, p=.4287. The numbers listed here by the authors are what came up for a correlation between circumcision and SIDS, r=0.69925, p=.0026. My calculation for slope was also different: I calculated the slope to be 0.180 (95%CI=-0.264 to +0.6537, t=0.81, p=.4287.
OK. We corrected the 95% CI throughout the paper. We provide the code with detailed headlines. The reviewer will have no problem replicating our results.

Page 6, lines 30-33: replace prematurity statistics with regression results: Unweighted: Increase of 0.12439 (95%CI=0.03569-0.21309, t=2.84, p=.0073) per 1000 live-births SIDS mortality per 1% increase in preterm rate; Weighted: 0.18325 (95%CI=0.11439-0.25210, t=5.35, p<.0001.
OK

Page 6, lines 34-38: Drop the comparison between Southern states as it is cherry-picking comparisons. Instead state: The correlation between SIDS and prematurity was not found on regression analysis to have regional differences (F=1.77, p=.1661).
OK

Page 6, line 51: Work in: A weighted multivariate model of SIDS deaths that include circumcision, prematurity, and region of the country found that circumcision (ß=0.07643, 95%CI=0.020734-0.13212, t=2.79, p=.0086) and geographic region (F=4.18, p=.0130) were significant factors, while prematurity was not statistically significant (ß=0.059441, 95%CI=0.06594 to +0.1848, t=0.96, p=.3418).
Thank you.

Page 6, lines 58-59: Not clear which test was used. May need to only report results of multivariate regression and whether interaction terms are statistically significant. Test for interaction between circumcision and region was not significant (p=.1219 Weighted model) and interaction between circumcision and prematurity was also negative (p=.1338 Weighted model). We tried interactions between all the terms and only MNC was significant. It shows in the R code.

Page 7, line 4: Discussion section should begin with a summary of the findings. A summary was added.

Page 7, line 9: "pertain" should be "pertains"
Thank you

Page 7, lines 11-15: Change sentence to: "Therefore, SIDS can be expected to decrease over time as parental education and diagnostic methods improve. Indeed, the rate of SIDS has been declining worldwide since the 1980s [45] …"
OK

Page 7, line 20: Has the success of the BTS campaign been limited, or has it achieved it's maximal potential?
First, we revised the paragraph to improve clarity. It now reads:
*Interestingly, much of the decline in SIDS rates following the BTS campaign has been due to an increase in SUID deaths and other death classification [13] attesting to the limited success of the BTS campaign in preventing "true" deaths [14].*

Second, we refer the reviewer to the excellent Hauck and Tanabe [14] paper that reviews this subject.

Third, in answering the question, we note that it is extremely difficult to assess the success of the BTS campaign, particularly in relation to SIDS. This is because prone sleeping, in itself, is not a cause of death. It is actually the preferred position for infants. It is a risk factor only due to suffocation, etc. but these should not have been classified as SIDS, unless they were misclassified (which is probably what happened before the BTS campaign). By contrast, infants are very uncomfortable in the supine position. Their sleep is inconsistent and they wake up more often (does it protect them from death or disrupt their brain development?). However, it reduces the chances of suffocation. Following the BTS campaign there was an increased awareness that prone=suffocation, so infants that still slept in prone position and died were no longer classified as SIDS but as SUID (which is what [13] argued – that there was no true reduction in deaths, just relabeling). Deaths in the supine position were still classified as SIDS and again, [13] claimed that there was only a little reduction in that group, whereas Hauck and Tanabe [14] agree but were more cautious in completely dismissing the decrease in death rates. Our opinion is that the supine position saves the lives of those who could have died of suffocation, but it does not reduce SIDS.

We added figure 10 to illustrates all of the above in relation to the actual
decrease of unexplained mortality since 1979 and the rates of each unexplained death code. We did not wish to delve into the debate concerning the nature of the decline as it was not the purpose of the paper, just highlight the difficulties in studying SIDS in light of the trends and changes in death
classification.

Page 8, lines 4-8: Ambiguous. Is it being asserted that infants with all three risk factors will all die of SIDS? Or is it being asserted that for those who have the risk factors who die of SIDS, there was nothing that could have been done to prevent the death?
Thank you, we revised the two paragraphs to focus on the different models to reduce overlap and improve clarity. It now reads:

The misunderstanding of SIDS is best demonstrated by the popular *triple risk hypothesis* devised in 1972 by Wedgwood [15], revised in 1994 by Filiano and Kinney [16], and then continuously modified by different authors. This hypothesis proposes that factors which increase the risk of sudden death include a critical development period, exogenous stressors, and a vulnerable infant [17]. Filiano and Kinney [16] stated that “an infant will die of SIDS only if he/she possesses all three factors” and emphasized the potential existence of “brain abnormalities.” A later report, found enrichment of focal granule cell bilamination in SIDS victims [18], but did not establish causation and due to the choice of controls the commonality of these abnormalities in the general population remained unclear. A comprehensive SIDS investigation sequenced the full exons of 64 genes associated with SIDS in 351 infant and young sudden death decedents [19] found that less than 4% of unexpected deaths were associated with a pathogenic genetic variant. Therefore, the *triple risk hypothesis* not only fails to explain the main characteristics of SIDS, but its central argument remains unsupported by the genetic data.
The *allostatic load hypothesis*, initially proposed to explain how stress influences the pathogenesis of diseases [20] and later applied to specific disorders [e.g., 21], proposes that prolonged and repetitive stressful, painful, and traumatic experiences during the peri- and pre-natal developmental periods lead to the accumulation of allostatic load that may be lethal [22]. Thereby, both hypotheses consider genetic vulnerabilities and external stressors but disagree on the definition of at-risk infants and the sequence of events that lead to SIDS. The *allostatic load hypothesis* considers any infant to be at risk of sudden death in a direct proportion to their genetic vulnerabilities and the cumulative stress that they have experienced (a “wear and tear” process) [22], rather than the “intersection” moment of three different risk factors.

Page 8, 45-46: This is a rather broad claim. There are many who would not agree that there are no congenital or genetic risk factors for SIDS. Instead soften the language to state that given the lack of clear genetic or congenital risks factors.
OK.

Page 9, line 19: "decimate" is too strong a term to the point of being hyperbolic. Consider "ameliorate."
Corrected, thank you.

Page 9, 28-30: This is confusing. It is well documented that during the procedure that blood pressure, heart rate, respiratory rate all increase, while oxygen levels decrease. Is it being

asserted that after the procedure the heart rate, blood pressure, and oxygen perfusion are decreased? If so, that needs to clarified. Thank you, we revised the sentence to read:
*For instance, during circumcision there is an increase in the blood pressure, breathing rate, and heart rate [23, 24]. Even with the most advanced techniques, bleeding occurs in over 15% of the cases [25], in which case there is a danger that a lower blood volume would result in low blood pressure and reduced amount of oxygen that reaches the tissues*

Page 9, lines 39-42: The NHS had excluded coverage of circumcision prior to the publication of Gairdner's report.
Thank you, we removed this statement.

Page 9, line 44 through page 10, line 19: While a very interesting diversion, this entire paragraph can be easily be deleted. It adds little to the thrust of the study.
As explained above, we revised the justification to the paragraph to be a better fit to the discussion. Moreover, anticipating the objection to the study from a population that culturally sees itself associated with MNC, although it is nearly an all-American practice, we believe that this paragraph addresses the MNC-SIDS question as direct data do not exist (and likely never will).

Page 10, line 42: Analysis found no interaction between circumcision and prematurity, so prematurity was not an effect modifier and only has an additive effect, that in the model was not statistically significant.
We added that to the end of the sentence.

Page 11, line 4: Not sure if circumcision is the most common in the world and whether it is unnecessary is hotly contested and does not need to be litigated in this venue. We revised this statement to read:

*Our findings suggest that MNC, the most common pediatric surgery performed on healthy children without a valid medical indication, is a major risk-factor for SIDS.*

Page 11, line 6: add "accounting for 14% of an infant's risk of dying from SIDS." to the end of the sentence. This finding needs more emphasis than it is currently given.
OK

Reference 38: Needs more details than "Born Too Soon." Corrected, thank you.

Not sure if all of the Tables and Figures are needed in the final version.
OK

Overall, a very interesting study. When published it will come under blistering, unscientific scrutiny by circumcision advocates, so the analysis needs to be as solid as possible.
We agree and are grateful to the reviewer for going above and beyond the call of duty.

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2nd editorial response:

Date: 12-Dec-2018

Ref.: Ms. No. JCTRes-D-18-00017R1
Neonatal circumcision and prematurity are associated with Sudden Infant Death Syndrome (SIDS)
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers:

Reviewer #1: The author has very thoroughly addressed my concerns, so, with respect to the aspects of the manuscript I am competent to evaluate, I think it is ready to be published (after minor copy editing for language issues). However, the other reviewer would certainly need to take another thorough look at the statistical analyses, which are outside of my expertise.

Reviewer #2: My concerns have been addressed. The manuscript is much stronger after what are obviously intense efforts on the part of the author. Good job!