

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Social Determinants of Syphilis in South China: The Effect of Sibling Position on Syphilis and Sexual Risk Behaviors
<b>AUTHORS</b>	Tucker, Joseph; Young, Darwin; Yang, Ligang; Yang, Bin; Adimora, Adaora

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Bradley P. Stoner, MD PhD Associate Professor of Anthropology and Medicine Washington University in St. Louis St. Louis, MO USA
<b>REVIEW RETURNED</b>	26-Mar-2013

<b>THE STUDY</b>	<p>The authors report on the interesting finding that middle-born subjects attending STI clinics in China have a higher likelihood of being diagnosed with syphilis. This is an interesting finding but I have minor quibbles, such as:</p> <ul style="list-style-type: none"><li>- it seems the final-born also have a higher rate of syphilis (7.1%) compared with first-born (3.4%) but no mention is made about this increased risk. To my way of thinking, indeed middle-born is the highest risk, but shouldn't the authors really focus on the bivariate finding of first-born vs. non-first-born to show increased risk? It's not like the final-born are at low risk.</li><li>- one wonders why middle-born did not make it into the final multivariate model - doesn't that dilute the impact of the research findings somewhat? How would the multivariate model work if the input variable was first-born vs. non-first-born?</li></ul>
<b>RESULTS &amp; CONCLUSIONS</b>	it would be interesting to see whether first-born vs. non-first-born made it into the final multivariate model.
<b>GENERAL COMMENTS</b>	Well-researched and well-presented. Minor concerns as noted above.

<b>REVIEWER</b>	Gu Wei_Ming MD Shanghai Skin Disease Hospital China
<b>REVIEW RETURNED</b>	15-Apr-2013

<b>GENERAL COMMENTS</b>	<p>The authors evaluated the relationship between sibling position and sexual risk based on behavioral. This is a very interesting and special topic</p> <p>There are a few points need to be clarified :</p>
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	<p>1. line18 of page7: "Among the 1792 participants, 1280 (71.4%) had never been tested for syphilis infection in the past", and it told on line13 of page7: "721 (40.3%) of individuals reported having a history of a sexually transmitted infection". The STD surveillance files of China clearly required that HIV and syphilis serology screening should be executed in STD clinic. So far, STD control and management work have been well done in Guangdong province. But your manuscript stated that 71.4% participants had never been tested for syphilis infection in the past, why these people did not take syphilis screening. I also confused with the relationship between 71.4% and 40.3%.</p> <p>2. For each recruiter, 5 milliliters blood was collected and a questionnaire investigation was performed. I am wondering whether oral informed consent is enough for compliance with the Treaty of Helsinki.</p> <p>3. Most Chinese families only have one child. It is not clear among 842 first-born cases, how many are the only child in the family.</p> <p>4. If a given family with two children, the second child should be divided into "middle-born" or "final-born"?</p>
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<b>REVIEWER</b>	<p>Dr Tim Read sexual health physician Melbourne Sexual Health Centre Alfred Health Australia</p> <p>No conflicts of interest relevant to this article. I am or have been site principal investigator for a number of multicentre studies funded by GSK and Merck.</p>
<b>REVIEW RETURNED</b>	23-Apr-2013

<b>THE STUDY</b>	<p>This is a study of an intriguing and possibly important hypothesis that birth order may influence the risk of syphilis in China. My comments are:</p> <ol style="list-style-type: none"> <li>1. Numbers of men and women buried at end of results. Should be presented earlier and in abstract.</li> <li>2. Needs more detail in methods of exactly what is "reported STI history" eg is it any genital symptom in the past, or is it any confirmed STI?</li> <li>3. A brief comment on why Site D might be lower risk would be interesting.</li> <li>4. The term "STI patients" is confusing and could mean "patients with an STI". Suggest replace with "clinic patients" or similar.</li> </ol>
<b>RESULTS &amp; CONCLUSIONS</b>	<ol style="list-style-type: none"> <li>1. The introduction makes a case for studying sibling position as a STI risk factor, but it remains unclear how this is of benefit for health at an individual or population level. What can one do about it? I think the paper needs to explain how the final sentence could be true.</li> <li>2. The hypothesis of the study appears to be that birth order affects syphilis risk. The final multivariate model seems to disprove the hypothesis. This is an interesting and worthwhile point in itself and the paper would benefit from emphasising it. The abstract and discussion seem to obscure this and spend more time emphasising univariate associations and associations with secondary outcomes.</li> </ol>
<b>GENERAL COMMENTS</b>	Your introduction led me to expect that the comparison might be

	between first and later born individuals, and/or only children vs those from a multi-child family. Examining and reporting middle-born seems a little contrived, even if that was not intentional. The paper might read better as a confident rebuttal of the hypothesis that birth order is important as a risk factor, then mentioning that middle-birth was associated with self-reported history only.
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### VERSION 1 – AUTHOR RESPONSE

The authors report on the interesting finding that middle-born subjects attending STI clinics in China have a higher likelihood of being diagnosed with syphilis. This is an interesting finding but I have minor quibbles, such as:

- it seems the final-born also have a higher rate of syphilis (7.1%) compared with first-born (3.4%) but no mention is made about this increased risk. To my way of thinking, indeed middle-born is the highest risk, but shouldn't the authors really focus on the bivariate finding of first-born vs. non-first-born to show increased risk? It's not like the final-born are at low risk.

We agree with the reviewer that final born individuals have an increased syphilis risk in the unadjusted analysis. However, from a sociological perspective, there are unique attributes associated with middle-born and final-born individuals that lead us to these three categorizations (see references 26 and 27). We have clarified the choice of these three categories on page 6, paragraph 2. In addition, the final-born group adjusted OR for syphilis risk was only 0.99, while the middle-born adjusted OR was 1.58.

- one wonders why middle-born did not make it into the final multivariate model - doesn't that dilute the impact of the research findings somewhat?

We agree with the reviewer that middle-born not being in the final multivariate model decreases its potential importance. At the same time, middle sibling position was significantly associated with ever engaging in commercial sex which was in the final multivariate model for men. We have clarified this point in the final paragraph of page 8 and in the abstract.

See above - it would be interesting to see whether first-born vs. non-first-born made it into the final multivariate model.

The multivariate model would not change if we alter the sibling position categories to compare first-born and non first-born individuals.

Well-researched and well-presented. Minor concerns as noted above.

Reviewer:Gu Wei\_Ming  
MD  
Shanghai Skin Disease Hospital  
China

The authors evaluated the relationship between sibling position and sexual risk based on behavioral. This is a very interesting and special topic

There are a few points need to be clarified :

1. line18 of page7: "Among the 1792 participants, 1280 (71.4%) had never been tested for syphilis infection in the past", and it told on line13 of page7: "721 (40.3%) of individuals reported having a

history of a sexually transmitted infection". The STD surveillance files of China clearly required that HIV and syphilis serology screening should be executed in STD clinic. So far, STD control and management work have been well done in Guangdong province. But your manuscript stated that 71.4% participants had never been tested for syphilis infection in the past, why these people did not take syphilis screening. I also confused with the relationship between 71.4% and 40.3%.

We agree with the reviewer that syphilis screening efforts are important, but many individuals are not routinely screened for syphilis in China (see PMID 22084525, 23300709, 21660751). Reasons for not accepting STD testing in the past include stigma, poor knowledge of STDs, lack of understanding about the relationship between syphilis and HIV, and others (PMID 22337103). Among the 1792 participants, 71.4% (1280) had never been tested for syphilis in the past. Totally separate from that observation is the observation that among 1792 participants, 40.3% reported having a history of any STI. Our definition of STI has been clarified in the text (second paragraph, page 5).

2. For each recruiter, 5 milliliters blood was collected and a questionnaire investigation was performed. I am wondering whether oral informed consent is enough for compliance with the Treaty of Helsinki.

The Declaration of Helsinki indicates that oral informed consent is acceptable in certain circumstances. Our detailed procedure for obtaining consent was drafted in accordance with the principles of the Declaration of Helsinki and approved by one Chinese IRB and two US IRBs.

3. Most Chinese families only have one child. It is not clear among 842 first-born cases, how many are the only child in the family.

Among the 842 first-borns, 187 individuals were only children. This result has been added to the first paragraph on pg 7.

4. If a given family with two children, the second child should be divided into "middle-born" or "final-born"?

If a family had only two (and not three) children, then the second child would be classified as final-born.

Reviewer: Dr Tim Read  
sexual health physician  
Melbourne Sexual Health Centre  
Alfred Health  
Australia

No conflicts of interest relevant to this article. I am or have been site principal investigator for a number of multicentre studies funded by GSK and Merck.

This is a study of an intriguing and possibly important hypothesis that birth order may influence the risk of syphilis in China. My comments are:

1. Numbers of men and women buried at end of results. Should be presented earlier and in abstract.

We agree with the reviewer and have added these key numbers in the abstract and first paragraph of the results section.

2. Needs more detail in methods of exactly what is "reported STI history" eg is it any genital symptom in the past, or is it any confirmed STI?

We agree with the reviewer that the reported STI history variable is not completely explained. This was a single item that asked individuals if they had ever had any of the following infections: syphilis, gonorrhea, chlamydia, condyloma acuminata, NGU/cervicitis, genital herpes, or another STI. A yes response to any of these individual STIs was coded as having a reported STI history. This has been clarified in the second paragraph on page 5.

3. A brief comment on why Site D might be lower risk would be interesting.

Our finding that Site D had a lower burden of syphilis among men and women is striking, but the low number of sites (n=4) precluded a more formal analysis of site-level characteristics associated with syphilis infection. More comprehensive STI control services prior to this research project may have contributed to this trend. We have clarified these points on pages 8 and 9.

4. The term "STI patients" is confusing and could mean "patients with an STI". Suggest replace with "clinic patients" or similar.

We agree with the reviewer and have replaced "STI patients" with the term "clinic patients."

1. The introduction makes a case for studying sibling position as a STI risk factor, but it remains unclear how this is of benefit for health at an individual or population level. What can one do about it? I think the paper needs to explain how the final sentence could be true.

Better understanding the social context of STDs, such as family structures, can help us to inform structural interventions focused on improving sexual health. For example, the finding that later male siblings have a higher sexual risk could be used to target younger male siblings in STD control social marketing campaigns. A tailored approach to reaching most-at-risk populations has been effective in many other settings (PMID 15905741, 12206447). This point has been clarified in the final paragraph of the conclusion.

2. The hypothesis of the study appears to be that birth order affects syphilis risk. The final multivariate model seems to disprove the hypothesis. This is an interesting and worthwhile point in itself and the paper would benefit from emphasising it. The abstract and discussion seem to obscure this and spend more time emphasising univariate associations and associations with secondary outcomes. Your introduction led me to expect that the comparison might be between first and later born individuals, and/or only children vs those from a multi-child family. Examining and reporting middle-born seems a little contrived, even if that was not intentional. The paper might read better as a confident rebuttal of the hypothesis that birth order is important as a risk factor, then mentioning that middle-birth was associated with self-reported history only.

We agree with the reviewer that caution should be made about the final conclusions in this paper. We believe that this single study suggests a potential effect of birth order on syphilis risk. Based on the results of our single study, we cannot confidently rebut the entire hypothesis. We have revised the abstract and discussion sections to be more cautious in our conclusions. In addition, we have added an explanation in the methods section about why we used three categories of sibship instead of two.