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Title	Variations in male to female ratios among births to Canadian-born and Indian immigrants to Canada, 1990-2011. A population-based register study
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Reviewer 1	Jennifer Hutcheon
Institution	University of British Columbia, Department of Obstetrics & Gynaecology
General comments (author response in bold)	1. Although the general topic of fetal sex selection among Canadian parents is highly important, the gain in knowledge on the topic from this specific research study seemed relatively modest. As discussed by the authors, they have previously demonstrated a distorted male to female ratio in third-order livebirths to Indian-born mothers in Ontario, and these patterns have been confirmed at the national level using national census data. While there are certainly new findings in the paper (paternal place of birth, comparisons between provinces), the extent to which these findings will move our understanding of this public health problem forward seems fairly minor forward compared with other major research gaps such as using pregnancy termination data to better understand how the sex selection is occurring or examining the patterns using data on ethnicity rather than place of birth to examine the extent to which sex-selection is occurring in second generation Canadians. **In a companion paper (submitted to CMAJ) we are filling the gap regarding the link between pregnancy terminations and sex ratios.** 2. Anecdotally, ethnic fetal sex selection also occurs in decisions to terminate following identification of abnormalities on ultrasound. Since many pregnancy terminations for anomalies happen in the weeks shortly after 20 weeks in Canada (following the 18-22 week anomalies scan), they must be registered as stillbirths; data from British Columbia show that at 20,21,22 and 23 weeks, ~ 75% of "stillbirths" are pregnancy terminations (CMAJ 2013;185:E345). Rather than excluding fetal deaths from the study, did the authors consider examining the presence of distorted M:F ratio in the 20-23 weeks fetal death data? Ideally, such analyses could be restricted to stillbirths with a documented anomaly, in which group the fraction of pregnancy terminations is likely even higher. Given the administrative burden likely associated with linking pregnancy termination and parental ethnicity data, such analyses might be a way to begin to provide new insights into the use of pregnancy termination in distorted fetal sex ratios. **We did not have access to stillbirth data. The database only included livebirths, so there is nothing we could do about it. Prenatal sex determination by ultrasonography is accurate from 13 weeks of gestation; therefore, the approach suggested by the reviewer, although it may detect a gender bias at 20-23 weeks gestation, will result in severe under-ascertainment of pregnancy terminations at 13-19 weeks gestation. Our companion paper submitted to CMAJ provides a more powerful approach.** 3. A reference or a more thorough explanation of the approach to calculate the number of "missing" girls would be helpful. The number of missing girls was calculated for each strata with an odds ratios >1.07 (the limit of biologic variation); it would be helpful to outline why this was restricted to those estimates where the lower limit of the 95% CI was >1.07, rather than all point estimates >1.07 where the confidence interval excluded the null (i.e., an OR of 1.19 [95% CI 1.05, 1.33] is not included). The approach used seems overly conservative. Using all strata with a statistically significant OR >1.07 might provide a more accurate estimate, and an approach such as repeated sampling from the probability distributions obtained from the OR with 95% CIs could be used to account for statistical uncertainty by providing a confidence interval around the estimated number of missing girls. It would also be helpful to confirm that the crude rather than adjusted OR was used. **We agree that more details regarding the calculation of missing girls would help the reader, as the reviewer seemed to have problems in understanding what we did. The reviewer interpreted that we used each stratum with an Odds Ratio > 1.07. This is not correct. We used each stratum with a M:F Ratio significantly > 1.07, which is the upper limit of the documented normal variability and we provided supporting references. An M:F Ratio is an Odds and an Odds Ratio is a ratio of two Odds (a ratio of two M:F ratios). The reviewer seemed to have mixed these two metrics since the OR of 1.19 [95% CI 1.05, 1.33] that he/she points out is actually a M:F ratio.** **In any case, we agree with the reviewer's suggestions of i) providing less conservative estimates, ii) providing a confidence interval around the estimates using bootstrap techniques, and iii) confirming we used the crude M:F ratios.** **The new estimate we report is 4472 (95% CI: 3211, 5921) compared to the previous estimate of 4210. The difference is not large and mainly reflects the addition of a few strata that were not included before. For a few strata with relatively small number of births, the lower 95% CI was negative and therefore we set them to zero. The estimate including the negative counts is 4472 (3017, 5921), that is, a small difference of 194. We do not have a strong preference, as the difference between the two approaches is negligible. If the reviewer or editors feel we should use the second approach; that is fine with us.** **"The number of missing girls was calculated using M/(F+x)=1.07 where x is the number of missing girls. The 95% CI was calculated using bootstrap with 10000 replications. The lower bound was set to be 0 when negative."**
Reviewer 2	Meghan Azad

Institution	University of Alberta, Pediatrics
General comments (author response in bold)	1. As someone unfamiliar with this topic, I am curious why the "normal" M:F ratio is significantly greater than 1. Other readers may also be curious. Is there a known biological reason for this? **The biological reasons of this robust observation are not established. There are many speculations based on inconsistent evidence. We provided an additional reference in the intro summarizing the most common hypotheses.** 2. Please briefly describe the CVSBD. Eg. Does it capture ALL births in Canada? Are these data reported by the vital statistics bureaus of each province? How is this database better or worse than Cenusus data for addressing your research question? **We provided more background on the CVSBD. (pages 3,4)** **The CVSBD has advantages and disadvantages with respect to census data. The main advantage is the direct and (virtually) complete ascertainment of births (the birth is the unit of analysis) vs. 20% sample of households, which results in much larger sample sizes; and annual coverage. The main disadvantage is the lack of information on socio-demographic characteristics, such as sex of previous siblings, religion, etc.** 3. Births outside of Canada were excluded. Were they incorporated in the calculation of birth order? Please clarify. **Yes, birth order counts the total number of livebirths women ever had by the time of the current birth, irrespective of the place of delivery of the previous livebirths. We added this explanation.** 4. Fig 1 – Please specify if these are crude or adjusted ratios. You could improve readability by simplifying the years on the x-axis. **Yes, crude ratios. We have simplified the years in the x-axis and provided the original excel file so the editorial team can further edit, if needed.** 5. Page 7, line 21 – sentence is repeated. **Thanks. Removed. (page 5)** 6. The tables are quite dense. Could you display some of these results graphically? **We agree, but do not see how we can replace the tables with graphs without losing information. To simplify, we have removed odds ratios from Table 3, which also created some confusion between the sex ratios and the odds ratios (ratio of two sex ratios).** 7. In your analysis of maternal and paternal nativity (Table 3) how did you treat data from single mothers? Were they excluded? Please explain. **No, they were not excluded. Marital status is another variable in the dataset. Single mothers are asked to report the characteristics of the fathers as well, irrespective of their marital status.** 8. You have noted in the discussion that M:F ratios for Indian-born mothers were somewhat higher in BC and Manitoba-Saskatchewan. Can you elaborate / speculate on this? Eg. are there differences across provinces in policy or practice related to prenatal ultrasound (revealing sex?) or IVF (sex selection permitted?) that might contribute to these differences? Or, differences in the predominant religious groups of Indian immigrants in these provinces (since one of the studies you have cited found differences according to nativity and religion)? **Good point. Unfortunately, we do not have data to elaborate on these differences. We therefore highlighted this as a focus for further research." Although the M:F ratio at the fourth birth was somewhat higher in British Columbia and Manitoba and Saskatchewan compared to Ontario, something worthy of further exploration, it was higher than expected in all Canadian provinces." (page 8)** 9. The finding that M:F ratios are higher among Indian-born mothers confirms results from previous studies. A novel aspect of this study is the assessment of fathers' nativity as a contributing factor to M:F ratios and (presumably) prenatal sex-selection practices. This has been briefly mentioned in the discussion but could be emphasized more. It is quite striking that 4+ order M:F ratios are consistently elevated for all scenarios where the father is Indian-born (1.37 with Canadian mother, 1.62 with Indian mother, 1.22 with Other mother), while an elevated ratio is only seen for Indian-born mothers partnered with non-Canadian fathers (1.01 with Canadian father, 1.62 with Indian father, 1.32 with Other father). Does this suggest that fathers have more influence on prenatal sex-selection practices than mothers? If so, this is an important finding that could help inform future studies and strategies to reduce prenatal sex selection. **Good point. We are not confident to say that fathers are more influential than mothers on the sex ratios, as India-born mothers without an India-born father also were associated with higher than expected sex ratios. However, fathers are undoubtedly important. We have slightly re-written the discussion section to highlight the importance of fathers for further research and potential interventions (2nd last paragraph).** 10. In the abstract, consider omitting the time trend findings since it seems confusing that the 3rd and 4th order birth M:F ratios changed in opposite directions over time. (As discussed in the main text, this likely reflects a parallel trend towards smaller family sizes; this requires explanation and does not come across in the abstract). Instead, you could state the M:F ratios for each order of birth among Indian-born women, demonstrating that it increases with birth order. **Ok, done.** 11. A limitation that is mentioned but not explicitly listed in the "Limitations" section is that grandparent birth place was not captured, so second-generation immigrants could not be identified. Some of the studies you have cited found sex-ratio differences among infants born to second generation immigrants. **We added this as a limitation (page 7, 1st paragraph). "Finally, grandparents' birthplace was not captured, so second-generation immigrants could not be identified."**