No association between age at menarche and sex of offspring

Sir,

We read with interest the article by Fukuda et al. (2011). The title ‘The sex ratio of offspring is associated with the mothers’ age at menarche’ suggests a direct connection between age at menarche and sex of offspring. We consider this interpretation a stretch of the presented data and want to comment on some issues in their study. Additionally, results from our substantially larger Danish cohort are presented.

We would like to start with raising some points in the analysis by Fukuda et al. (2011) that make their results look more extreme than they actually are:

(i) The results were based on a comparison of the sex ratio for age at menarche 14 years with the sex ratios at other ages at menarche. The fact that the category 14 years showed the highest sex ratio implies odds ratios (ORs) below 1 for all other age categories and made it easier to achieve nominal significance. We cannot see any arguments for an a priori choice (before actually looking at the data) of this reference category. A more sensible choice would have been the category with the largest number of observations or maybe the one closest to the overall mean age at menarche; these criteria would have lead to the selection of an age at menarche of 12 or 13 years, respectively. Hence, the deviations from the reference group would have been more modest.

(ii) Large parts of the discussion were based on the results for the 9-year category, which only comprised 14 women and 18 offspring and thus had a very broad confidence interval spanning over an OR of 1.

(iii) The selected age cut-off of 31/32 years in the age at birth analysis was not motivated and could be based on a favourable split of the data.

Furthermore, we think that the non-significant heterogeneity test based on the whole sex × age at menarche table (P = 0.11) was the analysis relevant for an association between maternal age at menarche and sex of offspring and should have been in the focus of the article. The additional results should have been considered hypothesis-generating, therefore requiring replication in other studies.

To follow up on the study by Fukuda et al. (2011), we investigated the potential association between maternal age at menarche and sex of offspring based on a total of 177,599 live born singleton infants delivered by 75,803 women enrolled as mothers in the Danish National Birth Cohort (DNBC, Olsen et al., 2001). Age at menarche information was available from a questionnaire asked at Week 12 of gestation. Table I shows the same analyses as Table I in Fukuda et al. (2011). The overall sex ratio is 1.056, well in line with the ratio of 1.055 reported for Denmark by The World Fact Book (2011).

The number of life-born infants per mother is relatively high, but understandable, given that (i) these mothers were recruited in the context of being pregnant during the study period from 1996 to 2002 and (ii) all children born to these mothers in the period from 1973 to 2010 could be retrieved from the Danish Medical

Table I

<table>
<thead>
<tr>
<th>Age at menarche</th>
<th>Women</th>
<th>Male offspring</th>
<th>Female offspring</th>
<th>Sex ratio</th>
<th>Sex ratio (95%CI) (ref. 13 years)</th>
<th>Sex ratio (95%-CI) (ref. 10 years)</th>
<th>No. of infants per woman (SD)</th>
<th>Age at birth (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>276</td>
<td>334</td>
<td>328</td>
<td>1.018</td>
<td>0.963 (0.826–1.123)</td>
<td>0.923 (0.776–1.098)</td>
<td>2.92 (1.37)</td>
<td>27.80 (5.17)</td>
</tr>
<tr>
<td>10</td>
<td>975</td>
<td>1180</td>
<td>1070</td>
<td>1.103</td>
<td>1.043 (0.959–1.135)</td>
<td>ref.</td>
<td>2.69 (0.99)</td>
<td>29.02 (4.85)</td>
</tr>
<tr>
<td>11</td>
<td>5234</td>
<td>6287</td>
<td>6055</td>
<td>1.038</td>
<td>0.982 (0.945–1.021)</td>
<td>0.942 (0.861–1.030)</td>
<td>2.71 (0.96)</td>
<td>29.57 (4.76)</td>
</tr>
<tr>
<td>12</td>
<td>13107</td>
<td>15740</td>
<td>15017</td>
<td>1.048</td>
<td>0.991 (0.964–1.019)</td>
<td>0.950 (0.872–1.036)</td>
<td>2.67 (0.90)</td>
<td>29.66 (4.63)</td>
</tr>
<tr>
<td>13</td>
<td>24507</td>
<td>29500</td>
<td>27904</td>
<td>1.057</td>
<td>ref.</td>
<td>0.959 (0.881–1.043)</td>
<td>2.66 (0.88)</td>
<td>29.96 (4.52)</td>
</tr>
<tr>
<td>14</td>
<td>19318</td>
<td>23293</td>
<td>21788</td>
<td>1.069</td>
<td>1.011 (0.987–1.037)</td>
<td>0.969 (0.891–1.055)</td>
<td>2.66 (0.91)</td>
<td>30.07 (4.51)</td>
</tr>
<tr>
<td>15</td>
<td>7852</td>
<td>9425</td>
<td>9040</td>
<td>1.043</td>
<td>0.986 (0.954–1.019)</td>
<td>0.945 (0.866–1.032)</td>
<td>2.68 (0.97)</td>
<td>30.43 (4.54)</td>
</tr>
<tr>
<td>16</td>
<td>3182</td>
<td>3912</td>
<td>3608</td>
<td>1.084</td>
<td>1.026 (0.977–1.076)</td>
<td>0.983 (0.895–1.080)</td>
<td>2.68 (0.91)</td>
<td>30.65 (4.53)</td>
</tr>
<tr>
<td>17</td>
<td>1041</td>
<td>1186</td>
<td>1203</td>
<td>0.986</td>
<td>0.933 (0.859–1.012)</td>
<td>0.894 (0.797–1.003)</td>
<td>2.57 (0.83)</td>
<td>30.95 (4.39)</td>
</tr>
<tr>
<td>18</td>
<td>311</td>
<td>379</td>
<td>350</td>
<td>1.083</td>
<td>1.024 (0.885–1.186)</td>
<td>0.982 (0.831–1.161)</td>
<td>2.69 (0.95)</td>
<td>31.10 (4.37)</td>
</tr>
<tr>
<td>Overall</td>
<td>75803</td>
<td>91236</td>
<td>86363</td>
<td>1.056</td>
<td></td>
<td></td>
<td>2.67 (0.91)</td>
<td>29.99 (4.57)</td>
</tr>
</tbody>
</table>

Mean age at menarche (SD) 13.30 (1.38)
Birth Registry. The number of life-born infants per woman is relatively stable over age at menarche, i.e. woman with lower age at menarche do not have fewer children as suggested earlier (Fukuda et al., 2011). The mean age at menarche is the same with 13.30 ± 1.38 years for male and female offspring. The highest sex ratio is observed for age at menarche 10 years (1.103), which contradicts the previous study, where the lowest sex ratios were observed in the younger age at menarche categories. However, choosing an age at menarche of 13 years as reference category, there is no nominally significant (P < 0.05) increased or decreased sex ratio in any age category. Thus, the differences in sex ratios are most likely due to random variation. To illustrate the importance of an appropriate reference category, we present the same data with age at menarche 10 years as reference, leading to the impression that categories with higher ages show somewhat lower sex ratios. Finally, we also performed a χ² test of heterogeneity for the whole sex × age at menarche table, which shows no deviation from the null hypothesis (P = 0.41), underlining that there is no association between maternal age at menarche and sex of offspring in this comprehensive study group.

In conclusion, our results prove at least that the suggested association between maternal age at menarche and sex ratio of offspring does not hold on a worldwide level. We acknowledge that Fukuda et al. (2011) stated in the conclusions and the final paragraph that their results were only suggestive, but their title remains misleading and would only be justified by a solid association finding.

References


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Advanced Access publication on September 9, 2011

Reply: No association between age at menarche and sex of offspring

Sir,

We thank Dr Geller et al. for their interest in our work. It is difficult to argue against their substantially much larger data on a Danish cohort of 177 599 live born singleton infants delivered by 75 803 women where there is no trend towards the age at menarche and the sex ratio of the offspring. Although our study from women in Japan (Fukuda et al., 2011a) is smaller in size, the different results may point to an effect of other differences between the two cohorts. One such factor could potentially be parental smoking during or around the time of the pregnancy. It has been reported that when the mother and the father smoked during pregnancy, daughters experience an earlier menarche (Windham et al., 2004; Shrestha et al., 2011), although reports also suggest that prenatal exposure to cigarette smoke causes delayed menarche (Ferris et al., 2010) or did not affect menarche at all (Fukuda et al., 2011b). Perhaps, the smoking habits of parents during pregnancy are different in Denmark and Japan. It is well known that the smoking habits around the time of conception affect the sex ratio of the offspring (Tidswell, 1912; Fukuda et al., 2002; Koshy et al., 2010) and possible long-term effects of smoking at this juncture might impact on the sex ratio in relation to menarche. In addition, there may be environmental factors, demographical factors, ethnic factors or other unknown factors which may also affect age at menarche and offspring sex ratio.

Currently, there is a trend for menarche to occur at an earlier age in females. In our study, we found no women in the older age group (i.e. those who had entered menopause) who had reached menarcheal age of 9 years, whereas in the younger age group (i.e. those who were premenopausal), 14 women had entered menarche at the age of 9 years. We have recently experienced some young teenagers who entered menarche at the age of 8 years. One of the questions of interest in our study was to evaluate what potential impact this trend towards an early menarche might have. It has been recently reported that the median age at menarche tends to increase with each increasing number of siblings up to three or more, suggesting that menarcheal age comes earlier in a one-daughter families (Hinobayashi et al., 2008). Such a trend was also seen in Australia (Milne and Judge, 2011) and we wonder whether a similar trend exists in Denmark, whether there in the Danish material is any information of young girls entering menarche at the age of 7 or 8 years and whether the sex ratio of children from women entering menarche at this young age may potentially be affected.

References


