Author's response to reviews

Title: Association between adolescent idiopathic scoliosis prevalence and age at menarche in different geographic latitudes

Authors:

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Version: 2 Date: 8 May 2006

Author's response to reviews: see over
Reviewer's report

Title: Association between adolescent idiopathic scoliosis prevalence and age at menarche in different geographic latitudes

Version: 1 Date: 1 April 2006

Reviewer: Toru Maruyama

Reviewer's report:

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1: The authors conducted two linear regression procedures, one between the prevalence of idiopathic scoliosis and the geographic latitude, and the other between the age at menarche and the geographic latitude. Why didn’t the authors directly inspect the correlation between the prevalence of idiopathic scoliosis and the age at menarche? Otherwise, they can not conclude that late age at menarche is parallel with higher prevalence of AIS.

Authors’ response: Due to the study design, our data were collected from two different groups of publications. The first group consisted of publications regarding the prevalence of scoliosis whereas the publications of the second group described the different age at menarche in various geographic latitudes. As a result, we worked with two different samples. Since the data for the prevalence of IS and the age at menarche referred to different latitudes, a direct correlation could not be carried out. Moreover, no articles which had data for age at menarche and the prevalence of IS for a specific latitude could be found. At long last the results of our study suggest a possible correlation between age at menarche and prevalence of IS based on statistical analysis. This statement is added in the discussion of the revised paper.

2: Table 2 showed the results of linear regression between the prevalence of idiopathic scoliosis and the geographic latitude, if I understood correctly. What has become of the results of linear regression between the age at menarche and the geographic latitude?

Authors response: The results of linear regression between the age at menarche and the geographic latitude are shown in the following table 4 which has been added in the revised paper:

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of obs</td>
<td>68763</td>
<td>R-squared</td>
<td>0.342</td>
</tr>
<tr>
<td>$F$ (2,288036)</td>
<td>17855.41</td>
<td>Adj R-squared</td>
<td>0.342</td>
</tr>
<tr>
<td>(Prob &gt; $F$)</td>
<td>&lt;0.001</td>
<td>Root MSE</td>
<td>0.409</td>
</tr>
<tr>
<td>Age at menarche</td>
<td>Unstandardized coefficient (B)</td>
<td>P&gt;</td>
<td>t</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------</td>
<td>--------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Latitude</td>
<td>-0.1123787</td>
<td>&lt;0.001</td>
<td>-0.1135448 -0.1112126</td>
</tr>
<tr>
<td>Latitude^2</td>
<td>0.0018579</td>
<td>&lt;0.001</td>
<td>0.0018381 0.0018776</td>
</tr>
<tr>
<td>Constant (Intercept)</td>
<td>14.07617</td>
<td>&lt;0.001</td>
<td>14.06203 14.09031</td>
</tr>
</tbody>
</table>

The table 2 needs to be replaced with the following modified one:

<table>
<thead>
<tr>
<th>Number of obs=</th>
<th>287939</th>
<th>R-squared=</th>
<th>0.509</th>
</tr>
</thead>
<tbody>
<tr>
<td>F (2,288036)=</td>
<td>149257.39</td>
<td>Adj R-squared=</td>
<td>0.509</td>
</tr>
<tr>
<td>(Prob &gt; F)</td>
<td>&lt;0.001</td>
<td>Root MSE=</td>
<td>0.7122</td>
</tr>
</tbody>
</table>

| Prevalence | Unstandardized coefficient (B) | P>|t| | 95% Conf. Interval |
|------------|--------------------------------|--------|-----------------|
| Latitude   | 0.024758                       | <0.001 | 0.024045 0.0254713 |
| Latitude^2 | 0.000484                       | <0.001 | 0.000472 0.0004965 |
| Constant (Intercept) | 0.712796                  | <0.001 | 0.703129 0.7224631 |

3: In figure 1, fitted curve seems to be linear, not curvilinear.  
Authors’ response: We agree that the fitted curve seems to be linear but is really not. The effect of the quadratic term is present but is very slight to make the fitted curve seem curvilinear even if it really is.

4: In figure 2, there does not seem to be a linear correlation between age at menarche and the geographic latitude.  
Authors’ response: The linear correlation between age at menarche and geographic latitude is better shown in the following figure where all observations below latitude of 25 degrees are not described. This is also added in the results of the revised paper.
5: The results that the AIS prevalence decreases as the geographic latitude approaches the equator is interesting. Patients with idiopathic scoliosis are known to have delayed menarche in comparison with normal girls. Delayed menarche may be one of the risk factors of AIS. The authors hypothesized that delayed age at menarche was caused by high levels of melatonin due to light insufficiency and that melatonin is pathogenetic factor of AIS. Their opinion is opposite to some researchers who attributed progression of idiopathic scoliosis to melatonin insufficiency. Is there any evidence that melatonin level of the people living in northern country is elevated?

**Authors’ response:** Under the subtitle “A hypothesis” it is written that …. “A possible preservation of high levels of melatonin secretion during the pre-menarcheal period in scoliotic girls due to light insufficiency in northern countries is associated with delay of the age at menarche. These high levels of melatonin are possibly identifiable before presentation of AIS, but would not be apparent at the time of clinical presentation of AIS in the vast majority of cases. The pre-menarcheal elevated levels of melatonin could be considered as a possible initiating factor of idiopathic scoliosis and it does not correlate with the severity and the site of the curve. It is lengthening the period of spine vulnerability while other pre-existing or aetiological factors are contributing to the development of AIS. ….

It is clearly then implicated that in our study melatonin is not considered a pathogenetic factor “per se”. In the pre-menarchal age in northern countries, melatonin by its association with delay of the age at menarche lengthens the period of spine vulnerability while other pre-existing or aetiological factors are contributing to the development of AIS.
This is why we consider high levels of melatonin secretion as a possible initiating factor of idiopathic scoliosis.

As far as we know there is no published paper reporting in general that melatonin level of the people living in northern countries is elevated, but it is well established that darkness is stimulating melatonin secretion and that there is increased rates of melatonin in normal women during night-time. Also Melatonin acts on the gonads indirectly, reducing the secretion of gonadotropines and mainly that of LH. The inhibition of ovulation in the Eskimos during the months of winter night period is associated with the above-described mechanism.

Dr Maruyama is stating “Their opinion is opposite to some researchers who attributed progression of idiopathic scoliosis to melatonin insufficiency”.

Yes, our opinion is opposite to some researchers who attributed progression of idiopathic scoliosis to melatonin insufficiency.

There is a lot of discussion on the issue, mentioned also in this paper, but some critical papers that are incorporated in the final version of our study, reversing totally the above theory that progression of idiopathic scoliosis is attributed to melatonin insufficiency are the following:

And

where it is reported that an increased incidence of scoliosis has not been observed in children after pinealectomy or pineal irradiation because of pineal neoplasias, although they have a lack of serum melatonin.

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Reviewer’s report
Title: Association between adolescent idiopathic scoliosis prevalence and age at menarche in different geographic latitudes
Version: 1
Date: 9 April 2006
Reviewer: Anastasios Christodoulou

Reviewer’s report:
I think this paper does merit to be published but needs to be mentioned the clinical relevance. Has the age of menarche changed over the years?

Answer to Dr A. Christodoulou comments
Dr A. Christodoulou is asking about
a) the clinical relevance of the study and
b) he is also querying whether the age of menarche has changed over the years.

a) It is indeed a critical point of our hypothesis the clinical relevance and the therapeutic implication that in northern latitudes, in girls with anticipated progressive scoliosis with no menarche, hormonal treatment in order to commence the menarche might be of potential value to stop progression. This therapeutic implication derived from our study is also included in our revised paper.

* There are reports on the age at menarche from the same country indicating small changes in the age at menarche between the two recent centuries!

Discretionary Revisions (which the author can choose to ignore)

**What next?:** Accept after minor essential revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.