PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Differentiating the cognitive development of early term births in infants and toddlers: a cross-sectional study in China
AUTHORS	Hua, Jing; Sun, Jie; Cao, Zhijuan; Dai, Xiaotian; Lin, Senran; Guo, Jialin; Gu, Guixiong; Du, Wenchong

VERSION 1 - REVIEW

REVIEWER	Elaine Boyle University of Leicester, UK
REVIEW RETURNED	24-Aug-2018

GENERAL COMMENTS	This paper looks at the cognitive development of babies and children born at late preterm gestation compared with those born at full term. This is an important question and an area of research that is still in its infancy. I am not aware of any similar reports from China. Methods: The sample size is large (n=1444), but the group chosen is from a very wide age range (16 days to 42 months). All children were assessed using the Bayley III Scales of Infant development. Although this variation in age at assessment in a study is somewhat unusual, the scales are developed to be able to assess children across this range of ages. The cohort was also split for analysis into toddlers and infants.This was also a relatively healthy group of children, as entry criteria excluded those with significant medical complications. Multiple births were also excluded - this is appropriate, as outcomes for twins and higher order multiples may be different. Results The results are in line with other studies from the USA and Europe in this population, in showing a significant difference in cognition between the early term and full term groups, although this study reported the difference only in children born at 37 weeks, whereas those at 38 weeks did not seem to be disadvantaged. However, all scores were within the normal range. Interestingly, an effect of breastfeeding duration was seen was seen, with those receiving less breast milk doing less well than breast fed babies. This is also in line with findings of other studies. Comments The major weaknesses of this study are the relatively small numbers, the variation in age of children assessed and the lack of any details about obstetric complications during pregnancy. I think it might be helpful to show the distribution of ages at which

	children were assessed. The exclusion of any children with complications may lead to underestimation of problems associated with birth at this gestation. However, it might also suggest that those with the greatest problems post-natally might be those whose mothers had complications - this is an interesting point for speculation, as, having delineated the extent of problems in this population, it will now be important for further research to tease out which groups are at greatest risk of adverse outcomes. Despite limitations, this paper adds something to the small body of literature about early term birth. Minor comments In general the paper is well written. However, there are a few terms that might benefit from being changed: 1. Abstract, page 2, line 45 and throughout the manuscript - the meaning of the word "clues" is not clear. Would "evidence" be better? 2. Introduction, page 9, line 6 - what is meant by the word "sober" - to me this has connotations of alcohol, but I am sure this is not the case, and I am not sure the word is needed. 3. I don't think I saw a specific statement in the manuscript confirming that ethics approval was sought/obtained. 4. there is duplication of a reference - Quigley et al Arch Dis Child Fetal Neonatal Ed 2012

REVIEWER	Carolyn Drews-Botsch Emory University, USA
REVIEW RETURNED	19-Nov-2018

GENERAL COMMENTS	This paper addresses an important and evolving concern regarding whether early term birth is associated with increased risks of adverse developmental outcomes. The study shows that, among infants (ages 16 days to 17 months only), delivery at 37 weeks is associated with reduced cognitive development as measured by an adapted, Chinese version of the Bayley Scales of Infant Development. Overall the results are interesting and add to the body of literature regarding early term births. However, there are a number of concerns. 1. The focus appears to be on statistical testing, rather than on estimation of the effect size. 2. The sample size, particularly among those born at 37 weeks is small (only 87) and then is split into those tested in infancy or later. Thus, I anticipate that the main findings are based only on a group of about 43 children. Thus, the authors may wish to provide further details about their sample and the age at testing. Further, the specific ages at testing is not provided. This is particularly important since at the earliest ages (16 days) an infant born at 37 weeks would not have even reached his/her expected date of delivery. 3. Although it is not typical to adjust for gestational age among those born at term, given the focus of this research question such adjustment may be warranted, particularly at the earliest gestational ages, especially since rapid brain development may be occurring at this age. Additionally, and relatedly, this, rather than or in addition to the greater impact of postnatal and family life on development, may be the reason that the findings are limited to

	the earliest period. Further, if, in truth, only early development is affected by early term birth, the public health importance of this effect may be limited. 4. Adjustment for confounding appears to minimize the observed findings. Therefore, the authors should consider in detail whether they have adjusted for all appropriate confounders and considered whether there might be misclassification of the confounders that would tend to result in residual confounding that negates the observed results. 5. Although it is clear from the remainder of the paper that the focus is on "early term births", the first sentence in the abstracts suggests that the focus is on "preterm births at 37 and 38 weeks of gestation". Clearly the usual convention is to consider all of these to be term births and the focus on early term delivery.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Elaine Boyle

Institution and Country: University of Leicester, UK

Please state any competing interests or state ‘None declared’: None declared

Many thanks for the reviewer’s suggestion. We have presented the competing interests: ‘None declared’ at the end of the manuscript.

Please leave your comments for the authors below

This paper looks at the cognitive development of babies and children born at late preterm gestation compared with those born at full term. This is an important question and an area of research that is still in its infancy. I am not aware of any similar reports from China.

Methods:

The sample size is large (n=1444), but the group chosen is from a very wide age range (16 days to 42 months). All children were assessed using the Bayley III Scales of Infant development. Although this variation in age at assessment in a study is somewhat unusual, the scales are developed to be able to assess children across this range of ages. The cohort was also split for analysis into toddlers and infants. This was also a relatively healthy group of children, as entry criteria excluded those with significant medical complications. Multiple births were also excluded - this is appropriate, as outcomes for twins and higher order multiples may be different.

Results

The results are in line with other studies from the USA and Europe in this population, in showing a significant difference in cognition between the early term and full term groups, although this study reported the difference only in children born at 37 weeks, whereas those at 38 weeks did not seem to be disadvantaged. However, all scores were within the normal range. Interestingly, an effect of breastfeeding duration was seen was seen, with those receiving less breast milk doing less well than breast fed babies. This is also in line with findings of other studies.

Comments

The major weaknesses of this study are the relatively small numbers, the variation in age of children assessed and the lack of any details about obstetric complications during pregnancy. I think it might be helpful to show the distribution of ages at which children were assessed. The exclusion of any children with complications may lead to underestimation of problems associated with birth at this gestation. However, it might also suggest that those with the greatest problems post-natally might be those whose mothers had complications - this is an interesting point for speculation, as, having delineated the extent of problems in this population, it will now be important for further research to tease out which groups are at greatest risk of adverse outcomes. Despite limitations, this paper adds something to the small body of literature about early term birth.

Response: Many thanks for the reviewer's positive comments. The major weakness of this study has been presented in the section of conclusion. The reviewer's suggestions also provide us important evidences for our further study.

Minor comments

In general the paper is well written. However, there are a few terms that might benefit from being changed:

1.Abstract, page 2, line 45 and throughout the manuscript - the meaning of the word "clues" is not clear. Would "evidence" be better?

Response: Many thanks for the reviewer's suggestion. We have changed the word 'clues' into 'evidence'.

2. Introduction, page 9, line 6 - what is meant by the word "sober" - to me this has connotations of alcohol, but I am sure this is not the case, and I am not sure the word is needed.

Response: Many thanks for the reviewer's suggestion. We have changed the word 'sober' into 'calm'.

3.I don't think I saw a specific statement in the manuscript confirming that ethics approval was sought/obtained.

Response: Many thanks for the reviewer's suggestion. The study received ethical approval from the Local Committee of Soochow University, China (201101). Written informed consent was obtained from the parents or legal guardians of the participants prior to the questionnaire survey. The ethic approval appeared at the end of the manuscript in the revised manuscript.

4. There is duplication of a reference - Quigley et al Arch Dis Child Fetal Neonatal Ed 2012

Response: Many thanks for the finding the error. We have deleted the repeated reference.

Reviewer: 2

Reviewer Name: Carolyn Drews-Botsch

Institution and Country: Emory University, USA

Please state any competing interests or state 'None declared': None declared

Response: Many thanks for the reviewer's suggestion. We have added the statement of 'None declared'. The statement appeared at the end of the manuscript in the revised manuscript.

Please leave your comments for the authors below

This paper addresses an important and evolving concern regarding whether early term birth is associated with increased risks of adverse developmental outcomes. The study shows that, among infants (ages 16 days to 17 months only), delivery at 37 weeks is associated with reduced cognitive development as measured by an adapted, Chinese version of the Bayley Scales of Infant Development. Overall the results are interesting and add to the body of literature regarding early term births. However, there are a number of concerns.

1. The focus appears to be on statistical testing, rather than on estimation of the effect size.

Response: Many thanks for the reviewer's suggestion. According to your comments, we have revised the explanation of the results, and focused more on the estimation of the effect size.(see the section of results)

2. The sample size, particularly among those born at 37 weeks is small (only 87) and then is split into those tested in infancy or later. Thus, I anticipate that the main findings are based only on a group of about 43 children. Thus, the authors may wish to provide further details about their sample and the age at testing. Further, the specific ages at testing is not provided. This is particularly important since at the earliest ages (16 days) an infant born at 37 weeks would not have even reached his/her expected date of delivery.

Response: Many thanks for the reviewer's suggestion. According to the reviewer's comments, we have provided the sample size of early term (37 and 39 gestational age respectively) and full term births in infants and toddlers (see the revised table 2). Further, we also added a table (as supplementary material), providing the information of the sample size of the specific ages at testing. The sample size of the earliest ages (16 days to 25 days after birth) in infants born at 37 gestational age were very small (n=2)(see the supplementary material).

3. Although it is not typical to adjust for gestational age among those born at term, given the focus of this research question such adjustment may be warranted, particularly at the earliest gestational ages, especially since rapid brain development may be occurring at this age. Additionally, and relatedly, this, rather than or in addition to the greater impact of postnatal and family life on development, may be the reason that the findings are limited to the earliest period. Further, if, in truth, only early development is affected by early term birth, the public health importance of this effect may be limited.

Response: Many thanks for the reviewer's suggestion. We agree with the reviewer's opinion that the public health importance of the effect may be relatively limited, because the effects of postnatal environment may play important roles on children's cognitive effects. The results will be confirmed by our recent national survey (2017-2018), and also providing us the evidence to conduct a further intervention study to explore the effects of postnatal environment on children's cognition under Chinese context. We have added the limitation and explained the necessary for further study in the section of conclusion. Additionally, according to the literature, there was difference of the brain development in different gestational age among those born at 'full' term (children born at 39-41gestational weeks). For instance, S Yang, et al reported that children's born at 40 gestational age have higher IQ score than those born at any other gestational weeks (American Journal of Epidemiology, 2010). This is very interesting point to explore the development of children born at different gestational weeks among term children. However, the main purpose of our study is to differentiate the cognitive development of early term births, so we explore effects of 37 and 38 of gestational births respectively when compared with full term children. Moreover, due to the relative small sample size in our study, adjusting more factors may minimize the observed findings. We will consider adjusting the gestational age in our further study (a national survey in China with larger sample size).

4. Adjustment for confounding appears to minimize the observed findings. Therefore, the authors should consider in detail whether they have adjusted for all appropriate confounders and considered whether there might be misclassification of the confounders that would tend to result in residual confounding that negates the observed results.

Response: Many thanks for the reviewer's comments. We agree with the reviewer's opinion that the adjustment for confounding may minimize the observed findings especially when the sample size of the study was not very large. In our study, the low-risk infants and toddlers were included in our study, as entry criteria excluded those with significant medical complications. Therefore, there were relatively limited confounders (children's and maternal characteristics, and socio-economic factors) should be considered. We try to appear the observed findings when the confounders were controlled (adjusted OR) or not controlled (crude OR). However, several other potential confounding factors were not measured (such as maternal and obstetric factors) in our study. We have presented the limitation in the section of 'Strengths and limitations of this study'. In the revised manuscript, we have also added the maternal and obstetric factors which were also potential confounders in more detail way (such as fetal distress, hypertensive disorder complicating pregnancy, and gestational diabetes mellitus which may affect offspring's cognitive development according to the literature.), and these factors will be considered in our recent study (a national survey in China) to further study the associations between early term and neurobehavioral outcomes(see the section of conclusions).

5. Although it is clear from the remainder of the paper that the focus is on "early term births", the first sentence in the abstracts suggests that the focus is on "preterm births at 37 and 38 weeks of gestation". Clearly the usual convention is to consider all of these to be term births and the focus on early term delivery.

Response: Many thanks for finding the error. We have revised the sentence into '"early term births at 37 and 38 weeks of gestation"(see the section of abstract).