Antenatal head circumference is associated with developmental skills in healthy twins: a study up to 24 months into infancy

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Abstract
Introduction
It is suggested that small antenatal head circumference is a predictor of developmental delays in singletons. Antenatal head circumference is known to be smaller in twins. Extrapolating from singleton data may suggest an increased risk of developmental delays, but this has not been previously investigated. We aimed to investigate the effect of antenatal head circumference size and growth on twins' development in infancy.

Materials and Methods
Developmental skills of 117 individual twins from the Birmingham Registry for Twin and Heritability Studies were assessed with the Ages and Stages Questionnaires at 3, 6, 9, 12, 18 and 24 months, for which z-scores were calculated. Head circumference was obtained from antenatal ultrasound scans. Multi-level regression analyses, adjusted for chorionicity, maternal age and gestational age at birth, were performed using head circumference at 20, 28, 33 and 36 weeks gestation, and head circumference growth between 20–27, 28–32 and 33–36 weeks gestation.

Results
A 1-mm increase above the average 36-week head circumference, and 28–32- and 33–36-week head circumference growth were associated with decreased motor and personal-social z-scores of up to −0.05 (p <0.01). Head circumference size before 36 weeks gestation was not associated with developmental skills at any follow-up age.

Conclusion
We found that antenatal head circumference size and growth in late pregnancy were associated with infant developmental skills. Furthermore, mainly motor and personal-social skills were affected by antenatal head circumference and growth. We postulate that we were able to detect negative associations in late pregnancy, whereas previous studies have found positive associations, as we had ultrasound measurements closer to birth compared with previous studies.

Introduction
Developmental skills in the field of psychology fall into four categories: cognitive, communicative, social and emotional and psychomotor skills. Children are expected to have reached developmental milestones in these categories within a certain age window. However, some children acquire these developmental skills at a slower pace. One of the potential causes of developmental and cognitive delays at older ages is low birth weight. Although these studies have approximated the relationship between antenatal growth and developmental skills by using birth weight, the actual relationship between antenatal growth and developmental skills has not been extensively investigated. Moreover, this relationship has not yet been investigated in twins, who might be at higher risk for developmental delays compared with singletons; antenatal growth of twins is known to decrease compared with that of singletons from 28 to 32 weeks onwards, which generally results in lower birth weights compared with healthy singletons.

Antenatal growth in twins is measured by ultrasound scans at regular intervals: every 2 weeks from 16 weeks onwards in monochorionic pregnancies and every 4 weeks from 20 weeks gestation onwards in dichorionic pregnancies. Standard measurements are biparietal diameter, head circumference, femur length and abdominal circumference: biparietal diameter and abdominal circumference in twin pregnancies show significant decreases in growth after about 32 weeks compared with singletons. Growth of head circumference in twins decreases from ~26 weeks onwards. Finally, femur length throughout pregnancy is similar for twins and singletons.

To our knowledge, no evidence has been previously published showing the relationship between developmental skills and femur length or abdominal circumference. Furthermore, only four studies looked...
into the relationship between antenatal growth measurements and postnatal development in singletons, with conflicting results.\textsuperscript{17-20} It remains unclear whether growth before or from mid-pregnancy onwards is more important in relation to postnatal development. In a study of healthy singletons, Walker et al.\textsuperscript{19} found a positive relationship between larger head circumference at 14 weeks and better reasoning ability at school age, while Harvey et al.\textsuperscript{18} found that decreased head growth prior to 26 weeks of gestation was related to general cognitive delays and motor impairments at 5 years. Additionally, no relationship between reasoning ability at school age with head circumference at 25 or 35 weeks of gestation\textsuperscript{17} has been found, nor a relationship between head circumference at 18 weeks gestation and intelligence at 9 years.\textsuperscript{20}

The Generation R Study, a large Dutch cohort, made a distinction between size and growth. They found that both size and growth – particularly the ratio between abdominal circumference and head circumference – from mid-pregnancy onwards were positively related to neuromotor development in the first 3 months.\textsuperscript{21} Using the same cohort, Henrichs et al.\textsuperscript{19} found that increased head growth from mid-pregnancy onwards reduces the risk of overall developmental and social delays at the age of one. The contradictory findings, namely the importance of size/growth in early pregnancy vs. after mid-gestation, in these studies may be due to the fact that (i) the age at which the children were assessed was different or (ii) the ultrasound data were only available at a few time points in the previous studies.

Because the basic developmental skills are important for later cognitive functioning,\textsuperscript{22} it is essential to better understand the effect of antenatal size and growth on developmental skills in twins from the earliest possible age onwards. Furthermore, maternal age in twin pregnancies is often older\textsuperscript{23,24} and has been associated with child development\textsuperscript{24,25} as well as antenatal growth\textsuperscript{26}, potentially increasing twins’ risks at developmental delays even further. Therefore, we aimed to describe the relationship between twins’ antenatal head size and growth and developmental skills in infancy, using ultrasound scans at more time points and developmental assessments at regular intervals.

Materials and methods
This work conforms to the values laid down in the Declaration of Helsinki (1964). The protocol of this study has been approved by the relevant ethical committee related to our institution in which it was performed. All subjects gave full informed consent to participate in this study.

Study design and participants
Participants were part of the Birmingham Registry for Twin and Heritability Studies (BiRTHS)\textsuperscript{27}, a multiple birth registry, which recruited eligible families from three large hospitals in Birmingham, UK. Twins, who were born after 22 weeks, weighed more than 500 grams at birth and did not have any congenital abnormalities, were eligible for participation in the study. Twins, for whom antenatal ultrasound details, maternal obstetric details and at least one developmental assessment were available, were included.

We approached 365 families, of which 170 (340 twin pairs) agreed to participate in the 2-year study. By the end of the study period on 15 July 2011, 11 twin pairs had not yet reached the age of 3 months and were not eligible for follow-up. Of the remaining 159 families, we did not receive any follow-up questionnaires for 36 twin pairs. Due to the relatively late introduction of the Ages and Stages Questionnaires (ASQ-3)\textsuperscript{29,30} into the study (March 2009), another 11 twin pairs were missed for the 3- or 6-month questionnaires. We were unable to complete the 24-month follow-up for all twins, because 50% of children had not yet reached the age of 18 months by the end of the study period.

Maternal and obstetric details
Details on maternal age and ethnic background were assessed by means of antenatal questionnaires. Maternal obstetric details, such as parity, gestational age at delivery (based on ultrasound) and chorionicity were extracted from maternal medical notes.

We made use of the antenatal head circumference measurements obtained from the ultrasound scans. Unfortunately, we could not include the ratio between abdominal circumference and head circumference in the current study, as the variance was extremely limited within the BiRTHS cohort and would therefore not likely be useful in statistical analyses (mean = 0.91, standard deviation (SD) = 0.04). Based on scan protocol at the participating hospitals\textsuperscript{22} and a review by Lumley\textsuperscript{29}, ultrasound data were categorised into three age windows, in which growth was likely to be most linear: 20–27, 28–32 and 33–36 weeks of gestation. Growth was defined as absolute growth in millimetres (mm) within each age window. From these age windows, we also used size at 20, 28, 33 and 36 weeks to determine their effects on developmental skills.

Developmental skills
Developmental skills at the chronological ages of 3, 6, 9, 12, 18 and 24 months were assessed with the ASQ-3. The ASQ-3 is a series of standardised parent-completed questionnaires that measure psychomotor development of children.\textsuperscript{31} One experienced researcher (C.N.) scored the questionnaires. Total scores ranged from 0 to 60 on each of the five subscales: communication, gross motor, fine motor, problem solving and personal-social skills. These scores correspond to three areas in which a child can be categorised: 'normal
development’, ‘just below normal development’ and ‘well below normal development’. Norm scores are based on healthy singleton children born at 40 weeks.

Statistical analyses
All analyses were performed in STATA 11. ASQ-3 scores on all subscales were converted into z-scores using the means and standard deviations, which were provided for the norm sample consisting of healthy singleton children born at 40 weeks. Subsequent analyses were performed using these z-scores. T-tests were performed to determine any significant difference in ASQ-3 z-scores between our sample and the norm group. Wilcoxon signed-rank tests were performed to explore any growth differences across the age windows and between chorionicity and genders.

Antenatal growth measurements were interpolated if scans were not available for the exact cut-off points for each age window. Outliers, defined as <1st centile or >99th centile for each measurement, were not included in the analyses (N = 1). Multi-level linear regression analyses were performed to study the effect of relative antenatal size at each measurement and antenatal growth in each age window on communication, motor, problem solving and personal-social skills. Although twins were considered individuals in these analyses, their relatedness was taken into account by including this in a nested level as a random effect. In the fixed part of the model, we adjusted for gestational age at birth and maternal age. Based on previous literature, we investigated the effect of adding maternal age to the regression model and found that the regression coefficient changed by >10%, justifying inclusion as a potential confounder. Following between-twin pair differences in antenatal head measurements, we performed backwards stepwise regressions, which resulted in choricity only significantly improving models for head circumference size at 20 and 36 weeks and growth in 33–36 weeks gestation. We therefore only adjusted for choricity in these models. Additionally, models for antenatal growth were also corrected for foetal size at the beginning of each age window. As we were performing up to four regression analyses per size/growth and developmental outcome pair, we applied a Bonferroni correction and results were considered statistically significant if p values were smaller than 0.0125, in order to minimise the risk of finding false positives due to multiple testing.

Results
Participants
Of the 170 families (340 individual twins) that were recruited into the BIRTHS follow-up, antenatal and follow-up data were available for 117 individual twins. Twins were born at a median age of 36 weeks (range: 28–39) with a mean birth weight of 2.4 kg (SD = 0.5). There were no significant differences in birth anthropometry between male and female infants. Mothers’ average age at delivery was 31.4 years (SD = 4.7). 93% of parents were White and 52% of twins were male. Across all follow-up time points, 47–76% of twins were conceived naturally, about a third was conceived as a twin and 56–90% were same-sex pairs (Table 1).

Antenatal growth
Table 2 provides an overview of ultrasound measurements at four gestations and antenatal growth in three age windows. Overall, head circumference growth decreased from 9.4 mm/week in 20–27 weeks...
to 8.9 mm/week in 28–32 weeks and 3.0 mm/week in 33–36 weeks. Similar to birth anthropometry, there were no significant differences between male and female infants.

**Developmental skills**

One hundred and seventeen individual twins were included, of which 52 (44%) had only one set of completed ASQ-3 questionnaires, 12 (10%) had two completed sets, 24 (21%) had three sets, nine (8%) had four sets, four (3%) had five completed sets and 16 (14%) completed all six of the ASQ-3 questionnaires. Sample size at each specific follow-up age can be found in Table 2. Mean scores and z-scores on all ASQ-3 subscales can be found in Table 3. Twins performed significantly worse than the singleton norm group on all subscales (p < 0.01). They caught up on different skills at various ages up to 24 months, except for personal-social skills, which remained worse compared with the norm group (t = −2.80; p < 0.01).

**The association of antenatal head circumference size with developmental skills**

Head circumference size before 36 weeks gestation was not associated with developmental skills at any follow-up age. Furthermore, head circumference at 36 weeks was only associated with significant changes in gross motor and personal-social z-scores (Figure 1). Larger 36-week head circumference was significantly associated with gross motor z-score decreases of −0.02 (95% confidence interval (CI): −0.03–0.00) at 12 months and −0.02 (95% CI: −0.03–0.01) at 18 months. Also, larger head circumference at 36 weeks gestation was significantly associated to a −0.04 (95% CI: −0.07–0.02) decrease in personal-social z-scores at 3 months.

**The association of antenatal head circumference growth with developmental skills**

The association of head circumference growth with gross motor and personal-social skills is graphically displayed in Figure 2. Head growth in 20–27 weeks was not significantly associated with developmental skills at any follow-up age. Increased head growth in 28–32 weeks significantly decreased fine motor z-scores at 12 months by −0.02 (95% CI: −0.03–0.00; results not shown). Finally, increased growth between 33 and 36 weeks was related to gross motor z-score decreases of −0.04 (95% CI: −0.08–0.01) at 3 months and −0.03 (95% CI: −0.05–0.01) at 18 months. Increased head circumference growth in 33–36 weeks was also associated with a personal-social...
z-score decrease of $-0.05$ (95% CI: $-0.09$–$-0.02$) at 3 months.

**Discussion**

In the current study, we aimed to investigate the relationship between twins’ antenatal head circumference size and growth and developmental skills in infancy. Findings from this study confirm that there is indeed a relationship between twins’ antenatal head size and growth and postnatal developmental skills. More specifically, it seemed that the relationship between developmental skills and antenatal head circumference (size and growth) was most evident at 36 weeks and in the age window between 33 and 36 weeks. Also, mainly gross motor skills, followed by personal-social and fine motor skills in the first 18 months seemed most affected by antenatal head measurements, while communication and problem solving skills were not. All statistically significant associations between head circumference size and growth and developmental skills were negative and occurred in late pregnancy (>33 weeks), with the exception of head circumference growth and fine motor skills (28–32 weeks). The growth analysis can be considered a valuable addition to the size analysis, because it confirmed that increased growth leads to increased size, which is related to decreased developmental skills. The correlation between growth and size at the end of each age window (results not shown) could explain the similarity in effects. However, our findings contradict previous singleton studies in which positive associations have been found. It is possible that findings in this study are different due to the use of measurements at later gestations and shorter intervals compared with previous studies. The definition of ‘late pregnancy’ in previous studies was around 30 weeks, while BiRTHS allowed for data at even later gestations (up to 36 weeks) and relatively closer to birth considering that median gestational age in the study was 36 weeks. It is possible that 30 weeks gestation was not sufficiently late in singleton pregnancy to observe any negative associations with developmental skills. Therefore, negative associations might have been observed in singleton populations if head circumference at gestations beyond 30 weeks was available.

Previous studies that have investigated the relationships between unfavourable intrauterine conditions (e.g., decreased growth) preterm delivery and subsequent cognitive delays were performed in samples of singleton children. Although twins are generally born preterm and smaller compared with singletons, they can also be perceived as a special group on their own. By doing so, the BiRTHS sample could be considered as normally
developing children compared with healthy twins. It is therefore unlikely that the ‘prematurity’ of twins in the current study can explain the negative associations between antenatal growth and developmental skills. It is also unlikely that children with small head circumferences showing the fastest growth in late pregnancy caused the negative associations, as analyses were adjusted for size at the beginning of each age window and no evidence of such antenatal catch up growth has been previously reported.

Communicative, fine motor and problem solving skills between 3 and 24 months did not seem to be affected by antenatal head size at any gestation. This finding seems to agree with previous studies, in which decreased communication, fine motor and problem solving skills are not large enough to detect in a regression analysis. A further explanation for the lack of associations with communicative skills is that it might be influenced by interactive postnatal factors that we did not investigate, such as parent-child and twin-twin interaction, and not so much by antenatal conditions. Further research is necessary to explore these options.

A possible biological explanation for our findings comes from the field of neurodevelopment, which has provided some evidence of an optimum level of head size and growth, leading to detrimental effects if this optimum is not met or is surpassed. New connections, or synapses, between brain areas that are created antenatally and in childhood, are pruned by ~50% shortly before birth and in adolescence. Bigger brain volumes in certain areas have been found in patients suffering from autism, which is characterised by cognitive and social impairments, while there is evidence of excessive synaptic pruning in cases of cognitive disorders related to schizophrenia. It is possible that negative associations between antenatal head circumference with developmental skills in this study can be explained by insufficient antenatal pruning of synapses.

The relatively small sample and incomplete postnatal follow-up may have had an impact on the interpretation of the results. For this reason, we decided to not perform a longitudinal analysis in this study. However, a larger, more complete sample would be desirable to confirm the results from this study in a longitudinal analysis, in which adjustments can be

Table 3 Means and standard deviations of raw ASQ-3 scores and their corresponding z-scores at all follow-up ages for twins included in the analyses.

<table>
<thead>
<tr>
<th>Time period</th>
<th>Communication</th>
<th>Gross motor</th>
<th>Fine motor</th>
<th>Problem solving</th>
<th>Personal social</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>z-scores (SD)</td>
<td>Mean (SD)</td>
<td>z-scores (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>3 months (N = 50)</td>
<td>40.6 (14.5)**</td>
<td>-1.3 (1.6)</td>
<td>40.5 (11.3)**</td>
<td>-1.7 (1.4)</td>
<td>27.8 (13.7)**</td>
</tr>
<tr>
<td>6 months (N = 82)</td>
<td>45.8 (11.3)*</td>
<td>-0.3 (1.2)</td>
<td>30.5 (15.1)**</td>
<td>-1.3 (1.2)</td>
<td>39.3 (17.2)**</td>
</tr>
<tr>
<td>9 months (N = 77)</td>
<td>36.3 (15.3)</td>
<td>-0.2 (1.2)</td>
<td>27.7 (16.7)**</td>
<td>-1.3 (1.2)</td>
<td>46.9 (14.9)**</td>
</tr>
<tr>
<td>12 months (N = 79)</td>
<td>43.5 (14.4)</td>
<td>0.2 (1.0)</td>
<td>36.3 (20.9)**</td>
<td>-1.0 (1.5)</td>
<td>50.7 (12.4)</td>
</tr>
<tr>
<td>18 months (N = 56)</td>
<td>38.7 (15.7)</td>
<td>-0.2 (1.1)</td>
<td>54.0 (12.8)</td>
<td>-0.2 (1.4)</td>
<td>52.4 (11.5)</td>
</tr>
<tr>
<td>24 months (N = 38)</td>
<td>48.6 (16.9)</td>
<td>-0.2 (1.3)</td>
<td>54.1 (12.2)</td>
<td>-0.1 (1.5)</td>
<td>51.3 (9.2)</td>
</tr>
</tbody>
</table>

Z-scores were calculated by using the means and standard deviations (SD) for the singleton norm group provided with the ASQ-3. Significant differences with singleton norm scores are displayed with *p < 0.01, **p <0.001.


Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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made for a child’s developmental trajectory. As mentioned earlier, we did not include ‘asymmetrical’ growth (defined as abdominal circumference/head circumference ratio) in the current study, because the range of abdominal circumference/head circumference ratios in the current study did not allow for meaningful analyses. However, previous studies have suggested it to be a good predictor of early neuromotor delays in singletons\(^1\) and could be considered in future studies. Another common foetal measure of size and growth is estimated foetal weight, which is calculated using ultrasound measurements, including antenatal head circumference. However, we decided not to use estimated foetal weight in our analyses, because we already had actual ultrasound measurements, which could be considered more accurate than an estimate. As discussed earlier, the relatively small amount of available follow-up data was in part due to the late introduction of the ASQ-3 and the inability to complete follow-up for all participants as the study period ended before some children were 24 months. Another reason was non-response to the questionnaires. However, there were no differences in demographic characteristics between responders and non-responders.

Finally, it is important to assess the relationship between a child’s postnatal growth and developmental trajectories in future studies in order to provide a complete overview of how growth affects neocognitive development, while taking into account the effect of postnatal environmental factors.

**Conclusion**

To our knowledge, no previous study has looked into antenatal growth in specific age windows up to 36 weeks, nor has there been previous research in this area with regard to twins. We found that antenatal head circumference in late pregnancy mainly seemed to have a negative influence on gross motor skills in infant twins. More research into this subject is needed, particularly with regard to postnatal covariates as children grow up. However, the current study provides promising results and should be considered a stepping-stone for further research into the effects of antenatal growth on early twin development.

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**Abbreviations**

ASQ-3, Ages and Stages Questionnaires-3; BiRTHS, Birmingham Registry for Twins and Heritability Studies; HC, Head circumference; kg, kilograms; mm, millimetres

**References**


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