Relation between Size at Birth and Risk of Age-Related Macular Degeneration

Nigel F. Hall, Catharine R. Gale, Holly Syddall, Christopher N. Martyn, and David I. W. Phillips

PURPOSE. To determine whether poor fetal growth, as determined by size at birth, is associated with increased risk of age-related macular degeneration.

METHODS. A total of 660 men and women born in Sheffield, United Kingdom, between 1922 and 1930 and whose size at birth was available were traced and invited to take part in the study. Of these, 392 attended for ophthalmic examination. Age-related macular degeneration in these volunteers was determined by the Wisconsin Age-Related Maculopathy Grading System.

RESULTS. The mean birth weight of subjects with macular degeneration (early or late) was heavier than that of those without (7.6 lb vs. 7.3 lb, respectively; P = 0.03). After adjustment for age, gender, and risk factors for macular degeneration, a significantly increased risk of macular degeneration was found in subjects with higher birth weight (odds ratio [OR] 1.5, 95% confidence interval [CI] 1.1–2.0 for each SD [1 lb, 5 oz] increase in birth weight). Other parameters describing size at birth showed a weaker relation or no relation with macular degeneration. (head circumference-to-birth weight ratio) was significantly associated with risk of macular degeneration. Subjects with macular degeneration had a significantly lower head circumference-to-birth weight ratio than did those without (11.2 vs. 12.0 respectively; P = 0.01).

CONCLUSIONS. The finding that age-related macular degeneration was associated with increased rather than decreased birth weight was unexpected. Failure of the developing fetus’s normal brain-sparing mechanism is a possible explanation for our finding of a lower head circumference-to-birth weight ratio among subjects with macular degeneration. (Invest Ophthalmol Vis Sci. 2002;43:3641–3645)

Age-related macular degeneration, the leading cause of blindness in economically developed Western countries, is thought to be a multifactorial disease in which both genetic and environmental factors play a part. Genetic factors may account for up to half of the variability in risk,\(^1,2\) although the genetic defects so far identified account for only a small proportion of cases.\(^3\) Oxidative stress such as cigarette smoking appears to increase risk,\(^4-7\) and dietary antioxidants, especially carotenoid xanthophyll pigments, may confer protection,\(^8-11\) but current understanding of the causes of macular degeneration is very incomplete.

A further mechanism to be considered is fetal programming caused by interruptions in growth during fetal or infant development. The macula appears by approximately 11 to 13 weeks of gestation and by 13 weeks contains highly differentiated cone and retinal pigment epithelial cells. The pigment epithelium is a nondividing system, and, with increasing age, there is a net loss of cells with a resultant increase in size of those remaining.\(^12\) An insult that occurs during this critical stage of development may thus become apparent with increasing age when the epithelial cells fail to maintain their lytic and voiding capacity with respect to engulfed photoreceptor discs, hence increasing susceptibility to macular degeneration.

Another way in which influences acting in early life may alter risk of age-related macular degeneration is the effect of cardiovascular disease, which has been linked with both small size at birth\(^13\) and macular degeneration.\(^14\) There is now substantial evidence that poor growth in early life increases blood pressure,\(^16\) impairs glucose tolerance,\(^19\) and is associated with increased rates of coronary artery disease and stroke.\(^20\)

We therefore investigated whether small size at birth is associated with increased risk of macular degeneration by examining a sample of older adults living in Sheffield, United Kingdom, whose size at birth was known.

METHODS

All women admitted for childbirth to the Jessop Hospital for Women, Sheffield, had details of their confinement recorded on standard forms. Details included date of their last menstrual period, placental weight, and the infant’s birth weight, head and abdominal circumferences, and crown-heel length. We asked the Office of National Statistics to trace all 4793 people whose births were recorded between 1922 and 1930, by using the National Health Service (NHS) Central Register. We traced individuals still living in the Sheffield area. A stratified sample of 746 men and women comprising all 159 subjects from the highest (>8.5 lb) and all 77 subjects from the lowest (5.5 lb or less) fifths of birth weight and 85 randomly chosen subjects of each sex from each of the three intervening fifths of birth weight (>5.5 to 6.5 lb, >6.5 to 7.5 lb, and >7.5 to 8.5 lb) was selected. Having obtained permission from Sheffield Health and the general practitioners, we wrote to 660 men and women asking whether we could interview them at home. Of those, 412 (62%) agreed and were interviewed by a field worker. Six subjects were excluded because of an incorrect trace (incorrect identification of participant by the NHS Central Register).

The participants were then invited to attend a clinic at the Northern General Hospital, Sheffield. Of those interviewed, 392 (95%) agreed to attend. At the clinic, we measured participants’ height with a portable stadiometer and weight with a Seca scale. We determined plasma levels of carotenoids by high-performance liquid chromatography. We determined the refractive error by measuring subjects’ usual distance glasses (Lensmeter LM-350; Nidek Co. Ltd., Aichi, Japan) after first assessing visual acuity in each eye (at 4 m) with a Baillie-Lovie log

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of the minimum angle of resolution (logMAR) chart (Lighthouse Enterprises, Long Island City, NY). Retinoscopy and subjective refraction was performed on all eyes failing to read logMAR 1.2 or better. Subjects who did not habitually wear distance glasses were assumed to be emmetropes if their unaided visual acuity was logMAR 1.2 or better. We calculated the spherical equivalent for each eye by adding the spherical error to half the cylindrical component. We calculated the spherical equivalent for each eye by adding the spherical error to half the cylindrical component.

The participants’ pupils were dilated with 1% tropicamide and 2.5% phenylephrine, and two pairs of stereoscopic fundus photographs were taken of each eye on transparency film (E1008; Eastman Kodak, Rochester, NY), with a fundus camera (Carl Zeiss, Jena, Germany) equipped with an Allen stereo separator. The stereo pairs were centered on the optic disc and on the center of the macula, according to the recommendations of the Wisconsin Age-Related Maculopathy Grading System (WARMGS). One observer (NH), masked to the identity of the participants and hence to their sizes at birth, graded each eye for the presence or absence of macular degeneration and known risk factors for macular degeneration. We used logistic regression to analyze the relation between early life measurements and macular degeneration, with adjustment for potential confounding variables. The odds ratios (with 95% confidence intervals) for presence of macular degeneration according to approximate thirds of the distribution of the early life variables are presented, together with probabilities for the trend in the odds ratios across the groups. Numbers within groupings of early life variables differ because of rounding of the original birth measurements. Standardized residuals from a regression of head circumference on birth weight were calculated after adjustment for gender.

**RESULTS**

Of the 380 subjects (207 male and 173 female) included in the analysis, 78 (20.5%; 45 male and 33 female) had signs of either early or late age-related macular degeneration in the worse eye. This comprised 64 (16.8%) subjects with early macular degeneration, and 14 (3.7%) with signs of late macular degeneration. Because of the small number of subjects with late macular degeneration, those with early and late onset were combined for the analysis.

Table 1 summarizes the age, gender, plasma carotenoid xanthophyll pigment levels and other suspected risk factors for macular degeneration of our study sample, according to the presence or absence of macular degeneration. Subjects with macular degeneration were significantly older than those without, but there were no significant gender differences. The plasma concentration of the xanthophyll pigment zeaxanthin was significantly lower in those subjects with age-related macular degeneration than in those without. The plasma concentration of the other ocular xanthophyll pigment lutein was also lower in those subjects with macular degeneration, but the difference was not significant. Participants with macular degeneration had smoked more cigarettes than those without, although the difference was not statistically significant. Total alcohol consumption was no different among participants with and without macular degeneration, but a significantly greater proportion of participants with macular degeneration reported drinking beer once a week or more compared with those without. By contrast, wine consumption was greater among the participants without macular degeneration, though the difference was nonsignificant. Twenty-two (6%) subjects had undergone coronary artery bypass grafting or angioplasty. A
history of having had either of these two procedures performed was reported significantly more frequently among those subjects with macular degeneration than in those without (12% vs. 4% respectively; \(P = 0.02\)). Subjects with age-related macular degeneration tended to be more hypermetropic than those without, though the difference was not statistically significant. There were no significant differences in the proportions of participants from social classes I-IIIa (non-manual) among the groups with and without macular degeneration; however, there was a small (nonsignificant) difference in level of education between the groups with and without macular degeneration. Those without macular degeneration had a significantly lower head circumference-to-birth weight ratio \(P < 0.001\)—that is, infants whose head circumference was small in relation to their birth weight were at increased risk. We explored this further in a multivariate model, adjusting simultaneously for both birth weight and head circumference and for age, sex, and other risk factors for macular degeneration. Both increased birth weight and decreased head circumference were significantly associated with increased risk of age-related macular degeneration. In this model, the odds ratio for macular degeneration was 2.0 (95% CI 1.3–3.0; \(P = 0.001\)) for each standard deviation increase in birth weight, and 0.6 (95% CI 0.4–0.9; \(P = 0.008\)) for each standard deviation increase in head circumference. As expected, birth weight and head circumference are correlated \((r = 0.7; P < 0.001)\), raising the possibility in this model of colinearity’s causing unstable estimates of effect. We therefore derived standardized residuals from a linear regression of head circumference on birth weight and used these in a further logistic regression model. Table 5 shows that the residuals of head circumference on birth weight affect risk of age-related macular degeneration.

### Table 2. Measures of Early Growth According to the Presence of Age-Related Macular Degeneration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Absent ((n = 302))</th>
<th>Present ((n = 78))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (lb)</td>
<td>7.3 ± 1.3</td>
<td>7.6 ± 1.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Length at birth (in.)(\dagger)</td>
<td>20.1 ± 1.1</td>
<td>20.3 ± 1.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Head circumference at birth (in.)</td>
<td>13.6 ± 0.7</td>
<td>13.6 ± 0.7</td>
<td>0.99</td>
</tr>
<tr>
<td>Placental weight (oz)(\ddagger)</td>
<td>22.3 ± 4.8</td>
<td>21.5 ± 5.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Gestational age (weeks)(\dagger)</td>
<td>39.6 ± 2.5</td>
<td>39.8 ± 2.0</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Data are the mean ± SD.

\(\dagger\) Data on length at birth was missing for 31 subjects.

\(\ddagger\) Data on placental weight was missing for 60 subjects.

\(\dagger\) Data on gestational age was missing for 15 subjects.

### Table 3. Risk of Age-Related Macular Degeneration According to Measures of Early Growth with Adjustment for Risk Factors for Macular Degeneration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio (95% CI) for Risk of Age-Related Macular Degeneration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Early or Late)</td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>1.3 (1.0–1.7)</td>
</tr>
<tr>
<td>Multivariate adjusted</td>
<td>1.4 (1.0–1.8)</td>
</tr>
<tr>
<td>Multivariate adjusted (excluding pre-term births)</td>
<td>1.5 (1.1–2.0)</td>
</tr>
<tr>
<td>Birth length</td>
<td></td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>1.2 (0.9–1.6)</td>
</tr>
<tr>
<td>Multivariate adjusted</td>
<td>1.3 (1.0–1.8)</td>
</tr>
<tr>
<td>Multivariate adjusted (excluding pre-term births)</td>
<td>1.3 (0.9–1.7)</td>
</tr>
<tr>
<td>Head circumference</td>
<td></td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>1.0 (0.8–1.5)</td>
</tr>
<tr>
<td>Multivariate adjusted</td>
<td>0.9 (0.7–1.2)</td>
</tr>
<tr>
<td>Multivariate adjusted (excluding pre-term)</td>
<td>1.1 (0.8–1.4)</td>
</tr>
</tbody>
</table>

Odds ratios quantifying the effect of a standard deviation increase in birth measurement on risk of age-related macular degeneration with adjustment for age, sex, gestation, plasma zeaxanthin, cigarette smoking, beer consumption, hypermetropic refractive error, and educational attainment.
macular degeneration. In each of the models (age- and sex-adjusted, multivariate-adjusted, and multivariate-adjusted) excluding preterm births, an increase in the residual—that is, larger head circumference in relation to birth weight—was associated with a significantly decreased risk of age-related macular degeneration. In other words, larger head circumference was associated with lower risk of macular degeneration, once an allowance was been made for birth weight.

### DISCUSSION

In this group of men and women aged 66 to 75 years, we found a relationship between indicators of early growth and age-related macular degeneration. Although we hypothesized that macular degeneration would be associated with reduced fetal growth, we found, contrary to our expectation, increased risk of macular degeneration to be associated with higher birth weight but decreased ratio of head circumference to birth weight.

In this study we used the Wisconsin Age-Related Macular Degeneration Grading System. It has been validated and widely used in both clinical and epidemiologic surveys of the same age group. The prevalence of macular degeneration was similar to that in previous surveys. For example, in the Beaver Dam Eye study, the prevalence of early macular degeneration is 18.0% and of late macular degeneration 1.4% in the 65 to 74 age group. Given that several exploratory analyses were performed in the examination of these data, some statistically significant findings may have occurred by chance. However, the relationships we found between macular degeneration and other risk factors were consistent with the results of other studies. These included increased age, cardiovascular disease, cigarette smoking, educational attainment, low levels of the carotenoid pigments lutein and zeaxanthin, hypermetropic refractive error, and beer consumption.

Our study was based on 392 participants who agreed to attend the hospital clinic—53% of the 741 people selected to take part in the study. The people in our study were not a representative sample of all people born in Sheffield at the time, because they were born in hospitals at a time when most births took place at home and because they continued to live in the city in which they were born. However, in the statistical analysis, all comparisons were made within the group who participated. Selection bias could explain our findings, either if subjects with higher birth weight and macular degeneration were more likely to take part, or if subjects with lower birth weight and macular degeneration were less likely to take part or were excluded from the study. As shown previously, however, there were no significant differences in birth weight between the 380 subjects finally included in the analysis and that of those who were not included. Therefore, we do not think that nonresponse or our inability to follow up all members of the original cohort resulted in bias sufficient to cause a substantive change in the relationship between birth weight and later risk of macular degeneration.

Because poor early growth is associated with cardiovascular disease and accelerated aging, which are both known to be risk factors for macular degeneration, we had hypothesized that macular degeneration would be associated with low birth weight. Rather, we found that it was associated with high birth weight. A possible explanation for this trend is suggested by our finding that infants in whom head circumferences was small in proportion to birth weight were at increased risk of macular degeneration. Normally, when a growing fetus encounters a limitation of nutrient supply, it maintains growth of the brain at the expense of growth of the trunk and abdominal viscera. A small head circumference in relation to birth weight suggests a failure of the normal brain-sparing mechanism, and could be an indication that growth and development of the eye was interrupted at a critical phase, increasing the subsequent risk of age-related macular degeneration.

There have been reports of associations between growth early in life and parameters of the aging eye, such as cataract, visual acuity, and intraocular pressure. A relation between early growth and macular degeneration, has not previously been reported. Whether this relation is simply a chance association that is not causal, a direct effect of early development on the long-term viability of the macula, or whether an intermediary link such as cardiovascular disease is involved is a matter for speculation. Our findings, however, highlight the need to continue looking for causes of macular degeneration.

### Table 4. Fetal Proportion at Birth According to Presence of Macular Degeneration

<table>
<thead>
<tr>
<th>Measure of Fetal Proportion</th>
<th>Age-Related Macular Degeneration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
</tr>
<tr>
<td>Ponderal index (oz/in.$^3 \times 100$)</td>
<td>14.0 (12.9–15.5)</td>
</tr>
<tr>
<td>Head circumference-to-length ratio $\times 100$</td>
<td>67.5 (65.8–70.0)</td>
</tr>
<tr>
<td>Head circumference-to-birth weight ratio $\times 100$</td>
<td>12.0 (10.7–13.1)</td>
</tr>
</tbody>
</table>

Data are median with interquartile range in parentheses. Probabilities are by the Wilcoxon rank-sum test.

### Table 5. Risk of Age-Related Macular Degeneration, Early or Late, According to the Residuals of Head Circumference on Birth Weight

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residuals of head circumference on birth weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>0.8 (0.6–1.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Multivariate adjusted</td>
<td>0.7 (0.5–0.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Age and sex adjusted (excluding pre-term births)</td>
<td>0.7 (0.5–1.0)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Odds ratios quantifying the effect of a standard deviation (1.0) increase in the residual of head circumference on birth weight on risk of age-related macular degeneration, with adjustment for age, sex, gestation, plasma zeaxanthin, cigarette smoking, beer consumption, hypermetropic refractive error, and educational attainment.
throughout the life course, and not just among adult risk factors.

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References


