Does raised intraocular pressure begin in utero?

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Abstract

***Aim*—To determine whether fetal and infant growth, as assessed by weight at birth and weight at 1 year, are related to intraocular pressure.**

***Methods*—717 men and women born in Hertfordshire between 1920 and 1930, for whom records of birth weight and weight at 1 year were available, were examined. Visual fields were assessed using the Takagi central 25 degree 75 point static threshold screening program. Tonometry was performed using the Perkin's tonometer. The disc was assessed by direct ophthalmoscopy through dilated pupils.**

***Results*—A significant inverse relation was found between systolic blood pressure and birth weight. However, no association was found between birth weight or weight at 1 year and intraocular pressure, cup/disc ratio, or visual field defects.**

***Conclusions*—There was no evidence to support fetal or infant growth as being important factors for the subsequent development of raised intraocular pressure.**

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The programming hypothesis proposes that events that take place in utero or in early infant life can profoundly affect the structure and function of the body.[1] Evidence for this has been collected for hypertension,[2 3] diabetes mellitus,[4] chronic obstructive pulmonary disease,[5] osteoporosis,[6] and coronary heart disease.[2 7 8] Some of these diseases, notably diabetes and coronary heart disease, are relatively new, suggesting incomplete adaptation to recent environmental changes, such as the "Western diet". A conceptual model for this can be readily constructed. It takes 47 cycles of cell division to generate an adult and of these, the first 42 take place in utero. Events occurring during these first 42 cell divisions could affect the "reserve" of any particular system and this would be most pronounced for those system(s) for which there is least spare capacity. An attraction of this model is that it could explain some associations between diseases as casual, rather than causal, if the systems affected are formed at a similar developmental stage.

Intraocular pressure (IOP) is an attractive candidate for the programming hypothesis for the following reasons. There is a positive association between blood pressure and IOP[9 10] and several investigators have reported that the IOP, like blood pressure, shows a gradual rise with age[11–15] as a result of increased resistance to aqueous outflow,[16] though it should be noted that the rise of IOP with age has not been a universal finding.[9] Primates are unusual in having aqueous drained via the canal of Schlem, whereas in most mammals, aqueous outflow is via the ciliary sulcus. The ciliary sulcus is obliterated in primates owing to the enlargement of the ciliary muscle and the development of the ability to accommodate. Thus, the canal of Schlem is an example of a recently evolved human structure which is susceptible to "premature degeneration". Season of birth has been reported to be a risk factor for progressive open angle glaucoma (POAG)[17] suggesting that pre- or perinatal factors may be important in its aetiology.

We therefore decided to look for an association between IOP, optic disc cupping, visual field changes, and POAG with birth weight and weight at 1 year, using data from a study designed to examine the relation between early growth and markers of aging.[18]

Subjects and methods

SUBJECTS

Following the Boer war, there was great concern about the physical state of army recruits. As a consequence, Margaret Burnside, who was the chief health visitor and lady inspector of midwives for the county of Hertfordshire in England, set up an "army" of trained midwives. From 1911 onwards, all women giving birth in Hertfordshire were attended by midwives and their babies inspected by health visitors. Detailed records were kept of these infants during their first year of life and this information was recorded in ledgers.[19] The birth weight and weight at 1 year were obtained on men and women who were born in Hertfordshire between the years 1920 and 1930 and still lived there. Seven hundred and seventeen attended for examination (50.2%) (see Table 1).

METHODS

The intraocular pressure was measured using the hand held Perkin's tonometer. The individual was deemed to have glaucoma if one eye had glaucoma. Therefore it was decided to select the worse measurement from either eye for further analysis. For all analyses of IOP the

Table 1 Composition of the study group

	Total (%)	*Men (%)*	*Women (%)*
Traced	1428 (100)	777 (100)	651 (100)
Interview	824 (58)	459 (59)	365 (56)
Interview and clinic	717 (50)	411 (53)	306 (47)
Postal questionnaire	286 (20)	140 (18)	146 (22)
Incorrect trace	12 (1)	7 (1)	5 (1)
Died	37 (3)	25 (3)	12 (2)
Moved	44 (3)	24 (3)	20 (3)
GP refusal	17 (1)	9 (1)	8 (1)
Subject refusal	208 (15)	113 (15)	95 (15)

Table 2 Summary of the measurements recorded on the patients

	Number with data	Mean	Median	SD	Range
Age (years)	717	67.5	67.2	2.3	63.4–73.6
Average pulse (beats/min)	714	66	66	11.2	38–112
Average blood pressure (BP)	714	107	107	14.4	74–161
Average systolic BP	714	155	154	22.6	133–228
Average diastolic BP	714	83	83	12.3	52–137
Body mass index (kg/m^2)	714	27.0	26.5	4.0	17.4–43.1
Birth weight (ounces*)	717	122	120	18	64–180
Weight at 1 year (ounces*)	717	353	352	40	176–480
Maximum IOP	716	17.9	18.0	2.88	12–34
Maximum C/D ratio	711	0.23	0.20	0.16	0–1
Random blood glucose (mmol/l)	711	6.3	5.7	2.5	3.4–31
Packed cell volume	711	0.425	0.424	0.035	0.30–0.54

*1ounce = 28.38 g.

Table 3 Correlations between the extracted data from the visual fields (see text) and the four factors extracted by principal components analysis

	Factor 1	Factor 2	Factor 3	Factor 4
Number of points missed in left Bjerrum field	0.922	0.22	0.10	0.05
Largest number of left contiguously missed points	0.91	0.17	0.17	0.02
Number of left points of reduced sensitivity	0.86	0.22	−0.11	0.12
Number of left points missed contiguous with the blind spot	0.65	0.08	0.01	−0.31
Number of left points missed at maximum brightness	0.59	0.21	0.54	−0.06
Number of points missed in right Bjerrum field	0.25	0.91	0.17	−0.03
Largest number of right contiguously missed points	0.18	0.90	0.19	−0.06
Number of right points of reduced sensitivity	0.22	0.86	−0.07	0.04
Number of right points missed contiguous with the blind spot	0.02	0.64	−0.25	−0.26
Number of right points missed at maximum brightness	0.25	0.55	0.49	−0.08
Left foveal sensitivity	0.06	−0.04	−0.62	−0.08
Right foveal sensitivity	−0.08	0.04	−0.56	0.04
Left fixation ratio	−0.06	−0.02	−0.04	0.80
Right fixation ratio	0.03	−0.10	0.04	0.75

greater pressure from the two eyes was used. Strong correlation was noted between average and maximum IOP with a Pearson correlation coefficient of 0.98.

The pupils were dilated using tropicamide 1% eye drops and optic nerve head assessment was made by direct ophthalmoscopy by a single observer. In addition to recording the cup to disc ratio, a relative measure was obtained of the absolute disc size by projecting a slit, of 3 mm height, with the Haag-Streit slit lamp on to the disc and recording the ratio of the disc height to this slit. As for IOP, the greater cup/disc ratio was used for subsequent analysis

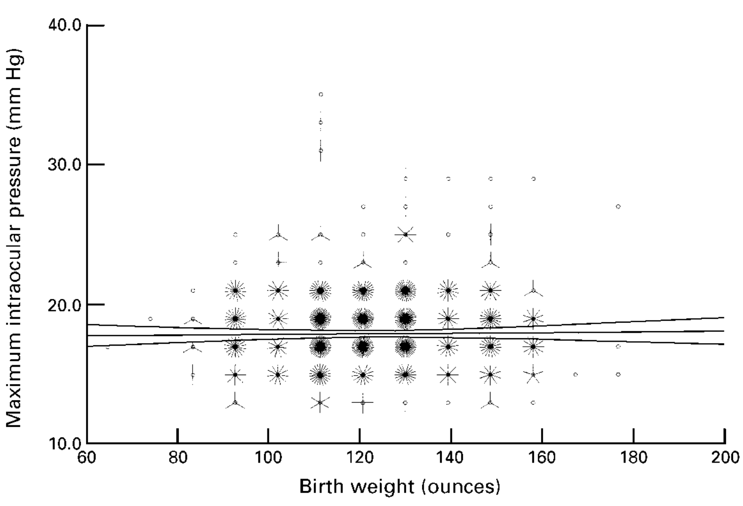

Figure 1 Scatter plot (using sunflowers) of the maximum of the intraocular pressure from the two eyes against birth weight. The regression line of maximum intraocular pressure at birth weight and the 95% confidence intervals for the mean are shown on the scatter plot.

Visual field assessment was performed by an automated perimeter using the Takagi central 25 degree 75 point static threshold screening program on 539 patients—the first 178 did not have fields performed (as the machine was not available from the outset of the study).

Cases of POAG were diagnosed as all cases on treatment, or had had surgery for this.

Systolic blood pressure, diastolic blood pressure, and pulse rate were measured using a Dinamapp automated blood pressure recorder cuff and the readings recorded directly onto computer as previously described.[3] An average of two readings of pulse and blood pressure were taken and used for all subsequent analyses.

In addition to the above, information was also recorded as to smoking status (recorded as ever smoked and never smoked), number of units of alcohol consumed per week, use of antihypertensive and antiglaucoma medication, previous ocular surgery, and social class of patient and spouse (and was analysed on the basis of the higher social class of the pair), social class at birth (taken as social class of father), weight, and height (from which the body mass index was calculated—weight (kg)/height (m)^2), packed cell volume, and random blood glucose.

Analyses were performed using SPSS for Windows version 6.0 and missing data were handled in a pairwise manner.

Results

The study population comprised 411 men and 306 women and their ages ranged from 63 to 74 years. Two hundred and eleven were taking antihypertensive medication and 11 were taking antiglaucoma medication. Three had had previous glaucoma surgery. Two hundred and fifty eight had never smoked and 457 had smoked at some time in their lives, while 253 did not drink alcohol, 402 drank 21 units or less per week, and 45 drank more than 21 units week (no data on 19). The interval and ratio variables are summarised in Table 2.

Birth weight, weight at 1 year, and the body mass index were normally distributed. The distribution of IOP followed its known pattern. The majority of values were normally distributed. The observed mean of 17.8 is close to its normally accepted value of 16 mm Hg and the observed SD of 2.88 is close to its normally accepted value of 3.[20] Under 3% of observations do show a positive skew and this data set was no exception. The number of non-normally distributed cases was small and not improved by standard data transformations (the standard transformation for positively skewed data is the square root transformation).

Maximum cup-disc ratio had a mean value of 2.3 and was positively skewed with skewness and kurtosis of 1.35 and 1.99 respectively. The degree of skewness and kurtosis was reduced to 0.35 and 0.44 respectively with the square root transformation. The transformed maximum cup-disc ratio was used for all analyses.

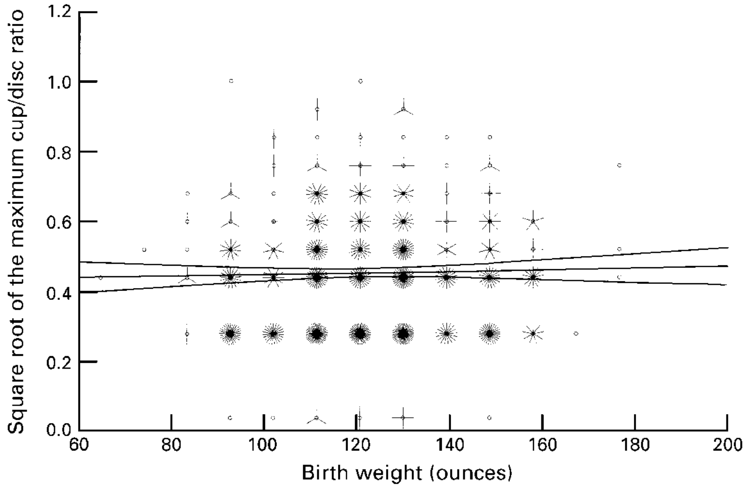

Figure 2 Scatter plot (using sunflowers) of the square root transformed maximum of the cup/disc ratio from the two eyes against birth weight. The regression line of the transformed maximum cup/disc ratio at birth weight and the 95% confidence intervals for the mean are shown on the scatter plot.

Table 4 Results of maximum intraocular pressure and the transformed maximum cup/disc ratio for mean, range, and standard error of the mean (SEM) according to birth weight

*Birth weight (lb)**	*Number*	*Mean*	*Range*	*SD*	*SEM*
Maximum intraocular pressure:					
≤5.5	22	17.1	12–20	1.86	0.40
5.5 <−6.5	108	17.9	12–25	2.59	0.25
6.5 < −7.5	238	17.9	12–34	3.07	0.20
7.5 < −8.5	225	18.1	12–28	2.86	0.19
8.5 < −9.5	90	17.9	12–28	2.87	0.30
>9.5	36	17.4	12–29	3.12	0.52
Transformed maximum cup/disc ratio:					
≤5.5	22	0.41	0.0–0.71	0.19	0.04
5.5 <−6.5	108	0.44	0.0–1.0	0.15	0.01
6.5 < −7.5	238	0.46	0.0–1.0	0.17	0.01
7.5 < −8.5	225	0.46	0.0–0.89	0.16	0.01
8.5 < −9.5	90	0.44	0.0–0.84	0.15	0.02
>9.5	36	0.46	0.32–0.77	0.12	0.02

*1lb = 454 g.

Table 5 Results of univariate linear regression with birth weight as a predictor for IOP, optic nerve head cupping, and visual field defects

Dependent variable	*B*	*SE B*	*95% Confidence interval for β*	*β*	*p Value*
Average IOP	0.0023	0.0058	−0.0091 to 0.0137	0.0148	0.69
Maximum IOP	0.0019	0.0060	−0.010 to 0.014	0.0138	0.75
Average cup/disc ratio	<0.0001	0.0003	−0.0005 to 0.0007	0.008	0.82
Square root of the maximum cup/disc ratio	0.0002	0.0003	−0.0005 to 0.0007	0.0009	0.54
Fields					
factor 1	0.0044	0.0025	−0.0004 to 0.0093	0.0779	0.07
factor 2	−0.0014	0.0025	−0.0063 to 0.0034	−0.0258	0.55
factor 3	−0.0009	0.0025	−0.0058 to 0.0039	−0.016	0.71
factor 4	−0.0016	0.0025	−0.0065 to 0.0033	−0.028	0.51

Table 6 Results of univariate linear regression with weight at 1 year as a predictor for IOP, optic nerve head cupping, and visual field defects

Dependent variable	*B*	*SE B*	*95% Confidence interval for β*	*β*	*p Value*
Average IOP	0.0001	0.0026	−0.0050 to 0.0052	0.0015	0.97
Maximum IOP	0.00002	0.0027	−0.0053 to 0.0053	0.0003	0.99
Average cup/disc ratio	0.0002	0.0001	−0.0001 to 0.0005	0.060	0.11
Square root of the maximum cup/disc ratio	0.00024	0.0002	−0.0002 to 0.0005	0.0589	0.12
Fields					
factor 1	0.0003	0.0011	−0.0018 to 0.0025	0.0129	0.77
factor 2	0.0010	0.0010	−0.0011 to 0.0003	0.0405	0.35
factor 3	0.0009	0.0011	−0.0010 to 0.0030	0.0363	0.41
factor 4	0.0012	0.0011	−0.0009 to 0.0034	0.0512	0.24

ANALYSIS OF FIELD DATA

There is no simple way to analyse visual field data and we elected to analyse the visual fields as follows. Firstly, a number of points were excluded as being unreliable (the points on the outside perimeter, the top two rows as being potentially due to upper lid induced defects and the point opposite the blind spot across the central meridian). From the remainder of the points, five summary statistics were recorded for each field (the total number of relative points missed, the total number of absolute points missed, the number of relative and absolute points on the 10 and 15 degree perimeters, the number of contiguous relative and absolute points missed, and the number of relative and absolute points adjacent to the blind spot missed). In addition, the foveal threshold (in decibels) was recorded and the ratio of fixation of losses for each eye. Thus, 14 summary statistics were generated for each eye. These variables showed a considerable amount of co-correlation (Kaiser–Meyer–Olkin measure of sampling adequacy = 0.71 and the Bartlett test of sphericity = 5277, p <0.00005). They were handled by transforming the variables into standardised form followed by simplification by principal components analysis followed by varimax rotation to provide a final solution. This generated four factors (called factors 1 to 4) with eigenvalues of 5.0, 1.9, 1.4, and 1.2 which were used for subsequent analyses. Table 3 summarises the results of the factor analysis. Factor 1 can be identified with loss of points in the left visual field, factor 2 in the right visual field, factor 3 with the foveal sensitivity of both eyes, and factor 4 with fixation with both eyes. These four factors were used for the subsequent analyses.

ASSOCIATION OF IOP, DISC, AND FIELD CHANGES WITH BIRTH WEIGHT AND WEIGHT AT 1 YEAR

Univariate analyses showed that birth weight, or weight at 1 year, had no predictive value for adult IOP, optic nerve head appearance, or field defects. The results are summarised in Figures 1 and 2 and Tables 4–6.

A total of 13 cases of POAG were identified. Not all cases had visual fields performed. There were seven cases out of 520 (1.3%) who had visual fields performed and was six out of 199 (3.0%) who did not have fields performed. This difference was not significant.

The visual field indices did not correlate with either optic nerve head appearances or IOP. It is well recognised that there is a marked learning curve by patients in performing automated perimetry and this variation in performance may have masked detection of underlying pathology. No further analysis of visual field data was performed.

Multivariate models were constructed using linear regression in a forward stepwise manner (probability for entry into the model of 0.5 or less and value of 0.1 or more for removal and missing data handled in a pairwise manner) for maximum IOP and for maximum cup/disc ratio. The predictor variables used for the model were body mass index, birth weight, weight at 1 year, age, sex, maximum social class (on the basis of occupation and taken as the higher class of individual and his/her spouse), father's social class (as an indicator of social

Table 7 Results of the model predicting the maximum IOP using linear regression in a forward stepwise manner with missing values handled in a pairwise manner

Variable	B	SE B	95% Confidence intervals of β	β	p Value
Average diastolic blood pressure	0.032	0.009	0.014 to 0.050	0.137	0.0004
Use of antiglaucoma medication	−3.397	0.904	−5.17 to −1.62	−0.14	0.0002
Constant	22.0	1.95	18.1 to 25.8		<0.00005

Table 8 Results of the model predicting the maximum cup/disc ratio using linear regression in a forward stepwise manner

Variable	B	SE B	95% Confidence intervals of β	β	p Value
Average systolic blood pressure	−0.005	0.0002	−0.001 to −0.00004	−0.07	0.03
Maximum disc size	0.856	0.066	0.725 to 0.986	0.44	<0.00005
Maximum IOP	0.007	0.002	0.003 to 0.010	0.119	0.0006
Sex	0.046	0.011	0.024 to 0.068	0.142	<0.00005
Constant	−0.084	0.061	−0.204 to 0.035		0.17

Table 9 Results of the model predicting the maximum cup/disc ratio using linear regression in a forward stepwise manner, including the variable disc size and excluding the 13 patients thought to have POAG

Variable	B	SE B	95% Confidence intervals of β	β	p Value
Average diastolic blood pressure	−0.0001	0.0004	−0.002 to −0.0006	-0.07	0.04
Maximum disc size	0.8213	0.0659	0.692 to 0.950	0.439	<0.00005
Maximum IOP	0.006	0.002	0.0012 to 0.089	0.912	0.0087
Sex	0.039	0.011	0.016 to 0.061	0.122	0.0006
Constant	−0.035	0.062	−0.158 to 0.089		0.58

Table 10 Results of univariate linear regression with systolic blood pressure being the dependent variable and the predictor variable for each analysis being one of the variables that was a measure of weight

	B	SEB	95% Confidence intervals of β	β	Significance
Birth weight	−0.119	0.044	−0.21 to -0.032	−0.094	0.007
Weight at 1 year	−0.059	0.020	−0.01 to -0.012	−0.102	0.003
Percentage weight gain in first year	0.571	1.754	−2.87 to 4.01	0.011	0.75
Adult weight	−0.066	0.062	−0.189 to 0.056	−0.040	0.28
Body mass index (kg/m^2)	0.421	0.2110	0.006 to 0.835	0.0746	0.047

Table 11 Month of birth as a predictor for birth weight, weight at 1 year, systolic and diastolic blood pressure, IOP, optic nerve head cupping, and visual field defects using one way ANOVA

Dependent variable	Between groups mean squares	Within groups mean squares	F ratio	p Value
Average IOP	8.89	7.68	1.16	0.31
Maximum IOP	9.949	8.267	1.20	0.28
Average cup/disc ratio	0.0213	0.0219	0.97	0.47
Maximum cup/disc ratio	0.019	0.026	0.74	0.70
Fields				
factor 1	1.84	0.98	1.88	0.04
factor 2	1.12	0.997	1.13	0.34
factor 3	0.463	1.01	0.458	0.93
factor 4	1.51	0.989	1.53	0.12
Birth weight	234	320	0.73	0.70
Weight at 1 year	1707	1599	1.07	0.39
Diastolic blood pressure	83.8	151.7	0.55	0.87
Systolic blood pressure	234.0	517.1	0.45	0.93

class status at birth), systolic blood pressure, diastolic blood pressure, pulse rate, blood glucose, haematocrit, use of tobacco (coded as either ever used or never used), alcohol consumption, use of antihypertensive medication (coded as yes/no), and the use of antiglaucoma medication (coded as yes/no). The results are summarised in Table 7 for the maximum IOP and Table 8 for the maximum cup/disc ratio. The only differences between the two models were that maximum IOP and maximum disc size were included in the list of independent variables for predicting the maximum cup/disc ratio and the variable for use of antiglaucoma medication was deleted.

For the multivariate models, co-correlation and autocorrelation were also checked in addition to the checks on variable distribution and heteroscedasity. The largest single bivariate co-correlation was noted between systolic and diastolic blood pressure with r=0.68 and the next largest had r=0.43. The tolerances of the predictor variables exceeded 0.9 for all variables with the exception of systolic and diastolic blood pressure whose tolerances exceeded 0.5. Autocorrelation was checked using the Durbin–Watson statistic whose values varied from 2.03 to 2.13 (values of 2 have no autocorrelation and the range is from 0 to 4) for all the models presented in this paper.

Interestingly, the maximum IOP was a predictor of the maximum cup/disc ratio even though most of the patients were “normal”. The model was rerun without the 13 known cases of glaucoma and the relation persisted (see Table 9).

ASSOCIATION OF BLOOD PRESSURE WITH IOP

An association with both systolic and diastolic blood pressure was found (both significant at the 0.001 level). The association was stronger for diastolic blood pressure and in a stepwise regression model, systolic blood pressure added no extra information after allowance had been made for diastolic blood pressure. However, the correlation between diastolic blood pressure and IOP was weak (r = 0.15).

ASSOCIATION OF BLOOD PRESSURE WITH BIRTH WEIGHT AND WEIGHT AT 1 YEAR

Table 10 shows the results of univariate analysis of systolic blood pressure against birth weight, weight at 1 year, percentage weight gain ((weight at 1 year − birth weight)/birth weight) and weight at time of examination (adult weight). Similar analyses were performed for diastolic blood pressure, which showed similar, but weaker, correlations that failed to reach significance at the 0.05 level. These data confirm the previous observations of the association between birth weight and blood pressure in adults.

ASSOCIATION OF IOP, DISC, AND FIELD CHANGES WITH MONTH OF BIRTH

The presence of an association between month of birth and birth weight, weight at 1 year, systolic and diastolic blood pressure, IOP, disc cupping, and visual field defects was tested for by one way ANOVA. The results are summarised in Table 11. Only one association showed significance and that was factor 1 from the field data and this may be spurious. No other significant association was found.

The season of birth was calculated (December to February was winter, March to May was spring, June to August was summer, and September to November was autumn). In all, 174 were born in summer, 281 in autumn, 67 in winter, and 197 in spring. There was no significant association between season of birth

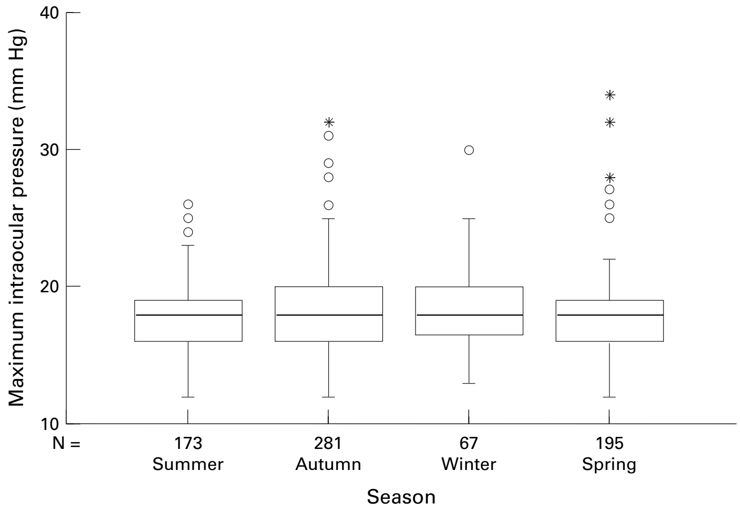

Figure 3 A box plot of maximum intraocular pressure against season of birth. The central line, in a box plot, is the median, the boxes represent the interquartile range, and the whiskers represent the range of values that are not outliers. "○" marks cases which are more than 1.5 box lengths from the 75th percentile and "" marks cases that are three box lengths from the 75th percentile.*

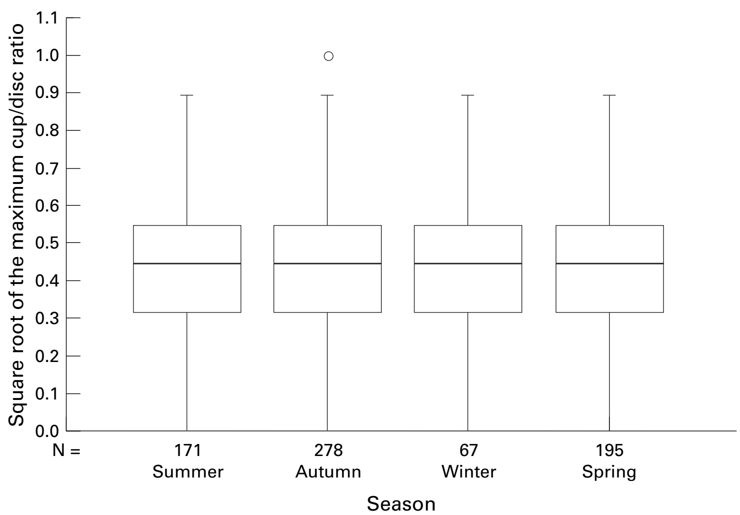

Figure 4 A box plot of the transformed maximum cup/disc ratio against season of birth.

and any of the above (see Figures 3 and 4), with the exception of a weak association with factor 1 (p=0.046).

Discussion

This study confirmed the previously reported inverse relation between adult blood pressure and birth weight. It also confirmed the previously reported association between blood pressure and IOP.[9 10 21] Birth weight and weight at 1 year best predicted systolic blood pressure, whereas IOP most closely follows diastolic blood pressure. There was no association found between either birth weight or weight at 1 year and IOP.

There is no easy definition of POAG. A definition is a progressive loss of neurons in the optic nerve head in a pressure dependent manner. Measurement of IOP is straightforward and accurate. The two best measures of loss of neurons in the optic nerve are its appearance (the cup/disc ratio) and psychophysical testing by measuring the visual fields. It is not clear what weight should be given to each component and each ophthalmologist does it differently. For this reason, we elected to analyse the data for each separate component, the IOP, the disc appearance, and the visual field data. The difficulty of diagnosing POAG on a single examination is such that we only labelled patients as having glaucoma if they were already on, or had had, treatment for it.

No relation between birth weight and weight at 1 year was found for POAG or any of the associated features of raised IOP, cup to disc ratio, or field defects. The prevalence of POAG was 1.8% which accords well with other estimates from population surveys for this age range of 0.9–2.7%,[9 13 22–24] but this resulted in very few cases in our sample and no association was found between them and birth weight and weight at 1 year. Because of the low numbers, this study had very low power in detecting an association between glaucoma and birth weight or weight at 1 year, even if such an association exists. This is one of the major limitations of this study.

Despite the few cases of glaucoma, there was an association between the disc/cup ratio and the maximum IOP. This relation persisted unaltered, even if these 13 cases were excluded from the analysis and allowance was made for total disc size. This suggests that there is pressure dependent loss of optic nerve head tissue even in the normal population. Airaksinen and colleagues[25] used surface planimetry and found that the average yearly loss of neuroretinal rim area was 0.23% in normals, 0.47% in stable patients with ocular hypertension, and 2.75% in those with POAG. These data suggest that even in those with "normal" eyes that there is pressure dependent neuroretinal rim loss and what characterises the glaucomatous patient from normals is the rate of the pressure dependent field loss. Although the study was underpowered for detection an association between POAG and birth weight, it did detect the appropriate associations between IOP and optic nerve head appearances and this, combined with a failure to demonstrate any equivalent associations with birth weight and weight at 1 year, does suggest that the programming hypothesis may not apply to POAG.

A second limitation of this study is that only 50% of successfully traced people were examined. Selection bias therefore has to be considered. However, the findings are based on internal comparisons and unless the associations between measurements of early growth and IOP differed in non-responders, no bias should have been introduced.

It has been previously reported that the season of birth is a risk factor for the subsequent development of POAG.[17] We were unable to observe any effect of either month of birth or season of birth with either cup/disc ratio or the IOP (see Table 11). There was a weak association with one of the visual field variables called factor 1. With multiple statistical testing, the occasional weak association is an expected chance finding. Factor 1 was a measure of field loss in the left eye, and if the association had been genuine, then one would have expected an equivalent association with factor 2 which is a measure of field loss in the right eye. Furthermore, it is estimated that one has to lose around 80% of one's retinal ganglion cells before a field defect becomes apparent and therefore one would expect the optic nerve appearance to be a more sensitive indicator of optic nerve fibre loss. The absence of such an association also argues against this being important.

The study reporting an association between POAG and season of birth was very different from this one. This was a population based survey while the previous study was based on one hospital's outpatients with an established diagnosis of open angle glaucoma.

The absence of any effect of in utero or early infancy on IOP is in contrast with several other diseases including cardiovascular disease,[2 7 8] chronic obstructive pulmonary disease,[5] osteoporosis,[6] and diabetes mellitus.[4] It is known that the brain is relatively protected against environmental stress both in utero and during infancy and this may help explain the lack of relation of optic nerve head damage or IOP with birth weight or weight at 1 year.

One postulated aetiology for POAG is that the optic nerve damage is by a microvascular process. The absence of associations between the maximum cup/disc ratio and systemic hypertension, random blood glucose, and packed cell volume argue against this.

The results from this study suggest that the programming hypothesis does not apply to IOP or to the maximum disc/cup ratio.

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