Pediatrics. Author manuscript; available in PMC 2009 November 23.

Published in final edited form as:
Pediatrics. 2007 November ; 120(5): e1225–e1228. doi:10.1542/peds.2006-2951.

Impact of Size at Birth on the Microvasculature: The Avon Longitudinal Study of Parents and Children

Robyn J. Tapp, PhD[a,b], **Cathy Williams, PhD**[c], **Nicholas Witt, MSc**[a], **Nish Chaturvedi, MD**[a], **Richard Evans, BA**[a], **Simon A. McG Thom, MD**[a], **Alun D. Hughes, MD**[a], and **Andrew Ness, PhD**[c]

[a]International Centre for Circulatory Health, National Heart and Lung Institute, St Mary's Hospital and Imperial College London, United Kingdom

[b]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

[c]Department of Social Medicine, University of Bristol, United Kingdom

Abstract

BACKGROUND—The impact of early life factors on the microvasculature is relatively unknown.

OBJECTIVES—We hypothesized that small birth size may be associated with structural variations in the retinal vasculature in children.

METHODS—The Avon Longitudinal Study of Parents and Children followed a cohort of children born in 1991-1992 from birth. The current study included the first 263 children who were systematically screened in the year-12 follow-up. Complete data were available for 166 children with a gestation of ≥37 weeks. Retinal circulatory measures were evaluated, including retinal microvascular tortuosity and bifurcation optimality deviance, an indicator of abnormal endothelial function.

RESULTS—Optimality deviance and retinal tortuosity were higher among those with lower birth weight. Linear regression modeling was used to assess the association of retinal microvascular measures with birth weight. The standardized β coefficient between optimality deviance and birth weight was −.182 adjusted for gender and age in weeks; additional adjustment for systolic blood pressure and heart rate had little impact on the β coefficient. A similar association was observed for retinal tortuosity.

CONCLUSION—The findings of this study suggest that early life factors may have an important impact on retinal vascular structure, possibly through an adverse effect on endothelial function.

Keywords

ALSPAC; retinal vascular geometry; birth weight

The role of the microcirculation in the pathogenesis of cardiovascular disease (CVD) is being increasingly recognized.1 Retinal microvascular abnormalities have been associated with an increased risk of stroke,2 ischemic heart disease,3,4 and diabetes,5 independent of other well-established risk factors in adults. These are important observations that could

Address correspondence to Robyn J. Tapp, PhD, International Centre for Circulatory Health, NHLI, Imperial College London, St Mary's Campus, London W2 1LA, United Kingdom. rtapp@imperial.ac.uk.

The authors have indicated they have no financial relationships relevant to this article to disclose.

Europe PMC Funders Author Manuscripts

further our understanding of mechanisms linking the long-observed association among low birth weight and CVD,6 hypertension,7 and diabetes8 in adults. Determining whether these associations represent cause or effect has been difficult in adult populations where these conditions are common. A population of children where the frequency of hypertension and other metabolic disorders is low provides the ideal setting to determine whether retinal microvascular abnormalities are associated with early life factors. We hypothesized that small birth size may be associated with structural variations in the retinal vasculature in children.

METHODS

The population, methods, and response rate for the Avon Longitudinal Study of Parents and Children (ALSPAC) are described in detail elsewhere.9 In brief, ALSPAC researchers enrolled pregnant women living in 3 health districts centered in Bristol, England, who had an expected date of delivery between the start of April 1991 and the end of December 1992. Of these, 11 211 had a white singleton live-born child. The current study includes the first 263 children systematically screened in the ALSPAC year-12 follow-up. The children were aged 12 years at this follow-up. Complete data were available for 166 children with a gestation of ≥37 weeks. There were no significant differences in the ages ($P = .269$) or genders ($P = .628$) of the youth with complete and incomplete data.

The date of the last menstrual period as reported by the mother at enrollment and the date of delivery were used to estimate gestation. Term birth was defined as birth on or after 37 completed weeks of gestation. Infant gender and birth weight were recorded in the delivery room and abstracted from obstetric records and/or birth notifications. Measures of childhood weight, height, heart rate, and blood pressure (BP) used in the present study were taken at age 9 years. Height was measured with shoes and socks removed using a Harpenden stadiometer (Holtain Ltd, Crymych, Pembs, United Kingdom) to the nearest 0.1 cm, and weight was measured by using a Tanita TBF 305 body-fat analyzer and weighing scales (Tanita UK Ltd, Yewsley, Middlesex, United Kingdom). BMI was calculated as weight (kilograms)/height (meters squared). Systolic and diastolic BP were recorded on the right arm while the subject was seated using a Dinamap 9301 vital signs monitor (Critikon, Tampa, FL).

We took 45° digital retinal images of the macular center of each retina using a Topcon nonmydriatic retinal camera (Topcon TRC-NW6s, Topcon Technologies, Paramus, NJ) fitted with a Nikon D1X (Nikon, Tokyo, Japan). Images were graded by 2 observers who were blinded to subject data using a semiautomated system that captures a wide range of retinal geometric parameters, and reproducibility of this technique has been reported previously.4,10-14 Measured parameters included the (1) arteriolar diameters, (2) arteriolar bifurcation angles, (3) length/diameter ratios of arteriolar segments and arteriolar/venular diameter ratios (these parameters provide measures of arteriolar narrowing that are relatively unaffected by differences in optical refraction), (4) arteriolar tortuosity (estimated as the actual length of the vessel divided by the straight line distance between bifurcations minus 1), and (5) arteriolar optimality ratio and optimality deviance. Optimality ratio is the ratio of sum of “daughter” arteriolar diameters divided by the “parent” arteriolar diameter corrected for asymmetry.4 For a theoretically optimal bifurcation, the optimality ratio should be 0.79, and the optimality deviance was calculated as the absolute value of the optimality ratio minus 0.79.

Ethical approval of the study was obtained from the ALSPAC Law and Ethics Committee. Written informed consent for the study was obtained.

Statistical Methods

The data analysis was performed with SPSS 14.0 for Windows (SPSS Inc, Chicago, IL). Descriptive information for each of the variables was derived, and the distribution was assessed. Baseline data are presented as mean ± SE or percentages. Linear regression was used to assess the association of birth weight with measures of the retinal microcirculation. Standardized β coefficients were used, because they allow for direct comparison of the strength of associations between risk factors and disease.

RESULTS

The characteristics of the population are shown in Table 1. Optimality deviance and retinal tortuosity were higher among those with lower birth weight (birth weight groups: <3.2, 3.2-3.6, and >3.6 kg).

Linear regression modeling was used to assess the association of retinal vascular measures with birth weight (Table 2). Linear regression identified lower birth weight as an independent factor associated with increased optimality deviance after adjustment for age (in weeks), gender, and systolic BP. The standardized β coefficient between optimality deviance and birth weight was −.208 ($P = .007$); adjustment for gender, age in weeks, systolic BP, and heart rate had little impact on the β coefficient ($\beta = -.184$; $P = .021$). Further adjustment for BMI at age 9 years had little impact on the association with birth weight. A similar association was observed for retinal tortuosity (Table 2).

DISCUSSION

To our knowledge, this is one of the first studies to assess the relationship between birth weight and the retinal microvasculature in children. We have shown that low birth weight is strongly associated with increased optimality deviance and retinal tortuosity, findings that fit well with the known association among low birth weight, stroke, and CVD in adults6,15 and we have provided some insights into possible mechanisms underlying these associations.

The present study suggests that early life factors may have an important impact on microvascular structure and function in children. Optimality deviance is an indicator of endothelial dysfunction,16 and this may imply that a primary disorder of the endothelium in early life is the mechanistic link between birth weight and CVD. This is consistent with previous findings of impaired endothelial function in large conduit arteries in children and young adults of low birth weight17,18 and decreased capillary recruitment and reduced vasodilator responses to acetylcholine in the skin of children of low birth weight.19 Although this question has not been examined previously in the retinal microvasculature of children, Chapman et al12 observed that adult men of low birth weight had narrower bifurcation angles compared with normal birth weight control subjects, indicative of retinal arteriolar rarefaction. Similarly, in a study by Kistner et al20 of women born preterm, the researchers observed a higher length index for arterioles and a decreased number of vascular branching points compared with women born at term. Both of these studies concluded that the observed architectural changes in the retinal microvasculature might be related to impaired fetal growth. The present study was small and underpowered to detect some associations. Further investigation is warranted in a well-documented large prospective study of children at risk of future vascular disease.

CONCLUSION

The findings of this study suggest that early life factors may have an important impact on vascular structure, possibly through an adverse effect on endothelial function.

Europe PMC Funders Author Manuscripts

Acknowledgments

The United Kingdom Medical Research Council, the Wellcome Trust, and the University of Bristol provide core support for the ALSPAC. Dr Tapp is supported by a Sidney Sax Fellowship from the National Health and Medical Research Council of Australia (grant 334173). Dr Witt is supported by a fellowship from the Foundation for Circulatory Health.

We are extremely grateful to all of the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses.

Abbreviations

CVD	cardiovascular disease
ALSPAC	Avon Longitudinal Study of Parents and Children
BP	blood pressure

REFERENCES

1. Zeiher AM, Drexler H, Wollschlager H, Just H. Endothelial dysfunction of the coronary microvasculature is associated with coronary blood flow regulation in patients with early atherosclerosis. Circulation. 1991; 84:1984–1992. [PubMed: 1934373]
2. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. Lancet. 2001; 358:1134–1140. [PubMed: 11597667]
3. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women: the Atherosclerosis Risk in Communities Study. JAMA. 2002; 287:1153–1159. [PubMed: 11879113]
4. Witt N, Wong TY, Hughes AD, et al. Abnormalities of retinal microvascular structure and risk of mortality from ischemic heart disease and stroke. Hypertension. 2006; 47:975–981. [PubMed: 16585415]
5. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of diabetes mellitus in middle-aged persons. JAMA. 2002; 287:2528–2533. [PubMed: 12020333]
6. Lawlor DA, Ronalds G, Clark H, Smith GD, Leon DA. Birth weight is inversely associated with incident coronary heart disease and stroke among individuals born in the 1950s: findings from the Aberdeen Children of the 1950s prospective cohort study. Circulation. 2005; 112:1414–1418. [PubMed: 16129799]
7. Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. J Hypertens. 2000; 18:815–831. [PubMed: 10930178]
8. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ. Early adiposity rebound in childhood and risk of type 2 diabetes in adult life. Diabetologia. 2003; 46:190–194. [PubMed: 12627317]
9. Golding J, Pembrey M, Jones R. ALSPAC: the Avon Longitudinal Study of Parents and Children. I. Study methodology. Paediatr Perinat Epidemiol. 2001; 15:74–87. [PubMed: 11237119]
10. Stanton AV, Wasan B, Cerutti A, et al. Vascular network changes in the retina with age and hypertension. J Hypertens. 1995; 13:1724–1728. [PubMed: 8903640]
11. King LA, Stanton AV, Sever PS, Thom SA, Hughes AD. Arteriolar length-diameter (L:D) ratio: a geometric parameter of the retinal vasculature diagnostic of hypertension. J Hum Hypertens. 1996; 10:417–418. [PubMed: 8872809]
12. Chapman N, Mohamudally A, Cerutti A, et al. Retinal vascular network architecture in low-birth-weight men. J Hypertens. 1997; 15:1449–1453. [PubMed: 9431851]
13. Chapman N, Haimes G, Stanton AV, Thom SA, Hughes AD. Acute effects of oxygen and carbon dioxide on retinal vascular network geometry in hypertensive and normotensive subjects. Clin Sci (Lond). 2000; 99:483–488. [PubMed: 11099390]

14. Chapman N, Witt N, Gao X, et al. Computer algorithms for the automated measurement of retinal arteriolar diameters. Br J Ophthalmol. 2001; 85:74–79. [PubMed: 11133716]
15. Barker DJ. Fetal programming of coronary heart disease. Trends Endocrinol Metab. 2002; 13:364–368. [PubMed: 12367816]
16. Griffith TM, Edwards DH, Davies RL, Harrison TJ, Evans KT. EDRF coordinates the behaviour of vascular resistance vessels. Nature. 1987; 329:442–445. [PubMed: 3498901]
17. Leeson CP, Whincup PH, Cook DG, et al. Flow-mediated dilation in 9- to 11-year-old children: the influence of intrauterine and childhood factors. Circulation. 1997; 96:2233–2238. [PubMed: 9337195]
18. Goodfellow J, Bellamy MF, Gorman ST, et al. Endothelial function is impaired in fit young adults of low birth weight. Cardiovasc Res. 1998; 40:600–606. [PubMed: 10070502]
19. Serne EH, Stehouwer CD, ter Maaten JC, ter Wee PM, Donker AJ, Gans RO. Birth weight relates to blood pressure and microvascular function in normal subjects. J Hypertens. 2000; 18:1421–1427. [PubMed: 11057429]
20. Kistner A, Jacobson L, Jacobson SH, Svensson E, Hellstrom A. Low gestational age associated with abnormal retinal vascularization and increased blood pressure in adult women. Pediatr Res. 2002; 51:675–680. [PubMed: 12032260]

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

TABLE 1

Characteristics of the Population at Age 9 Years According to Birth Weight Group

Characteristic	Birth Weight < 3.2 kg	Birth Weight 3.2-3.6 kg	Birth Weight > 3.6 kg	*P*
N	50	69	47	
Female, %	35	46	19	.004
BMI, mean ± SE, kg/m^2	16.8 ± 0.4	17.4 ± 0.3	18.1 ± 0.2	.084
Height, mean ± SE, cm	137.8 ± 0.9	140.4 ± 0.8	141.2 ± 0.9	.020
Weight, mean ± SE, kg	32.1 ± 0.9	34.5 ± 0.9	36.3 ± 1.2	.021
Systolic BP, mean ± SE, mm Hg	103.6 ± 1.3	105.5 ± 1.2	104.6 ± 1.6	.581
Diastolic BP, mean ± SE, mm Hg	58.9 ± 0.9	58.7 ± 0.7	58.7 ± 0.9	.984
Heart rate, mean ± SE, bpm	80.2 ± 1.4	78.2 ± 1.2	79.6 ± 1.4	.552
Arteriolar optimality deviance, mean ± SE	0.094 ± 0.011	0.076 ± 0.007	0.070 ± 0.007	.132
Arteriolar bifurcation angle, mean ± SE	80.0 ± 1.9	79.6 ± 1.7	76.3 ± 12.1	.375
Arteriolar simple tortuosity, mean ± SE	0.031 ± 0.004	0.025 ± 0.003	0.018 ± 0.002	.031
Arteriolar LDR, mean ± SE	13.1 ± 0.5	13.5 ± 0.4	12.7 ± 0.5	.470
Arteriolar diameter, mean ± SE, pixels	15.7 ± 1.5	15.7 ± 1.4	15.8 ± 1.5	.873
Venular diameter, mean ± SE, pixels	20.1 ± 3.7	19.5 ± 3.3	19.1 ± 3.2	.310
AVR, mean ± SE	0.90 ± 0.02	0.91 ± 0.02	0.91 ± 0.01	.584

LDR indicates length/diameter ratio; AVR, arteriolar/venular diameter ratio; bpm, beats per minute.

Europe PMC Funders Author Manuscripts

TABLE 2

Standardized *β* Coefficients and *P* Values for Measures of the Retinal Vasculature With Population Characteristics at Age 9 Years

Variable	Arteriolar Optimality Deviance		Arteriolar Simple Tortuosity		Arteriolar Bifurcation Angle		Arteriolar LDR	
	β	P	*β*	P	*β*	P	*β*	P
Model 1								
Birth weight, kg	−.182	.023	−.198	.013	−.071	.378	−.016	.841
Gender	.064	.424	.050	.524	.063	.433	−.073	.366
Age, wk	−.001	.989	.087	.258	.121	.120	−.035	.654
Model 2								
Birth weight, kg	−.184	.021	−.193	.014	−.068	.393	−.016	.840
Gender	.050	.539	.087	.273	.083	.308	.072	.387
Age, wk	−.011	.892	.068	.374	.093	.236	.042	.597
Systolic BP, mm Hg	.089	.273	.056	.480	.153	.059	−.045	.588
Heart rate, bpm	.040	.629	−.193	.017	−.138	.091	.019	.820
Model 3								
Birth weight, kg	−.190	.021	−.179	.026	−.094	.244	−.015	.858
Gender	.048	.554	.091	.255	.075	.352	.072	.387
Age, wk	−.018	.823	.085	.288	.060	.459	.044	.597
Systolic BP, mm Hg	.074	.418	.088	.325	.089	.324	−.041	.658
Heart rate, bpm	.038	.639	−.190	.019	−.144	.077	.019	.818
BMI, kg/m^2	.033	.728	−.072	.437	.144	.126	.008	.937

bpm indicates beats per minute.