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Are rates of ageing determined *in utero*?

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Abstract

Background: epidemiological studies have shown that poor early growth is associated with cardiovascular and other degenerative diseases. This has been explained by programming, whereby undernutrition and other influences which restrict early growth permanently change the structure and physiology of the body. The long-term effects of poor early nutrition on ageing have been demonstrated in animals but not studied in man.
Objectives: to determine if poor early growth was associated with increased markers of ageing in later life.
Methods: we traced 1428 men and women, born in Hertfordshire between 1920 and 1930, for whom records of early weight were available. 824 (58%) were interviewed at home and 717 (50%) attended clinic for eye examination, audiometry, grip strength measurement, skin thickness ultrasound and anthropometry.
Results: lower weight at 1 year was associated with increased lens opacity score, higher hearing threshold, reduced grip strength and thinner skin. Visual acuity, macular degeneration and intraocular pressure were not related to early growth.
Conclusions: the associations between early growth and markers of ageing suggest that in some systems, ageing may be programmed by events in early life. A potential mechanism is the impaired development of repair systems.

Keywords: *ageing, prenatal growth, programming, repair*

Introduction

"We have a winding sheet in our mother's womb that grows with us from our conception and we come into the world wound up in that winding sheet for we come to seek a grave" wrote John Donne. It seems that he may have been right, for there is now evidence that events before birth that are linked to fetal growth may influence lifespan.

People who are small at birth and during infancy are destined to live shorter lives. For example, among 10 000 British men, those who had below average birth weight and weighed less than 8.2 kg (18 pounds) at 1 year had 4 years less expectation of life than those with above average birth weight who reached 12.25 kg (27 pounds) at 1 year [1]. This was mostly due to higher rates of cardiovascular disease and chronic obstructive lung disease [2]. The association between these diseases and low rates of early growth is thought to result from programming—the process whereby undernutrition and other influences which restrict early growth permanently change the structure and physiology of the body [3].

Animal studies give numerous examples of nutritional programming and demonstrate that the effects of undernutrition *in utero* include raised blood pressure [4] and altered glucose and lipid metabolism [5, 6], which are associated with cardiovascular disease. Undernutrition of animals *in utero* or in the early postnatal period before weaning also accelerates age-related changes such as reduced immune response, slower learning and decline in serum haemoglobin concentration [7, 8].

Since the nutritional programming of ageing processes has not been investigated in humans, we have measured a number of structural and functional markers of ageing in a group of elderly men and women whose birth weight and weight in infancy had been recorded.

Methods

From 1911 to 1948, each birth in Hertfordshire, England was notified by the attending midwife and the birth weight of the baby was recorded [9]. Health

visitors also saw each child routinely during infancy, recorded the method of feeding and the weight at the age of 1 year. There were 6803 live singletons born in North Hertfordshire between 1920 and 1930; with the help of the National Health Service central registry, we traced 1428 who still lived there. Only women born between 1923 and 1930 were included in the study because those born earlier had often changed their name through marriage and were therefore impossible to trace. This reduced the number of women available for inclusion.

Eight hundred and twenty-four (58%) of the traced people agreed to home interview from one of four nurses who had not seen the infant data. Information on medical and social history, including smoking and drinking habits, was obtained. Social class was defined from occupation (husband's occupation for married women) [10].

After interview, 717 attended a local clinic for measurement of grip strength and skin thickness, eye examination and a hearing test. Grip strength was measureed with a Harpenden handgrip dynamometer [11]. Skin thickness was measured with a Dermotronics DM70 A-scan ultrasound system [12]. The eye examination included measurement of visual acuity, intraocular pressure (with a Perkins hand-held applanation tonometer after insertion of local anaesthetic drops) [13] and slit lamp examination after pupil dilatation with 1% tropicamide. Lens opacity was graded by the LOCS III system [14]. Clinical classification of macular degeneration was followed by macular photography using the Canon CR4 camera to allow subsequent validation of the clinical assessment by a second observer. Hearing was assessed by pure-tone manual audiometry using the Hughson-Westlake method [15].

Current body size was characterized by measurement of height, weight and waist and hip circumference. Blood tests for haematological indices, erythrocyte sedimentation rate (ESR) and renal function were used to help exclude major disease and anthropometry was performed [13] to determine current body size and proportions as a marker of previous growth.

Subjects who initially declined a home interview or clinic visit were invited to complete a short postal questionnaire at the end of the study.

Statistical analyses were used to quantify the relationship between birth weight and weight at 1 year (converted to metric units) and each of the ageing measures. Lens opacity score and hearing threshold had skewed distributions and were therefore logarithmically transformed to normality. We used multiple regression analysis and tabulations of means against birth weight and weight at 1 year divided into six groups. *P* values refer to analyses using continuously distributed variables.

Results

There were 6803 live singletons born in North Hertfordshire between 1920 and 1930 of which 1428 (21%) were found to be still living in the area. A home interview was obtained in 824 (57.7%) of the traced people and of these 717 (50.2%) also came to clinic. A further 286 (20%) completed the short postal questionnaire at the end of the study. The reasons for non-participation included an incorrect trace, death, change of address and refusal by the subject or their general practitioner.

In total, 411 men and 306 women attended clinic (Table 1). The average age of the participants was 67.5 years. The mean birth weights were 3526 g for the men and 3409 g for the women. The corresponding weights at 1 year were 10.26 kg and 9.74 kg. The men were on average taller and heavier than the women taking part; 21.9% of the men and 23.2% of the women were in social class IV or V but more men than women smoked or drank alcohol.

Table 1. Characteristics of study group

	Mean (SD)	
	Men	Women
Mean birth weight (g)	3526 (504)	3409 (467)
Mean weight at 1 year (kg)	10.26 (1.19)	9.74 (0.99)
Percent breast fed	64.5	63.1
Percent breast + bottle fed	29.7	31.0
Percent bottle fed	5.8	5.9
Mean age (years)	67.5 (2.4)	67.5 (2.2)
Mean height (cm)	172.1 (6.6)	159.4 (5.7)
Mean weight (kg)	80.1 (12.7)	68.8 (11.8)
Percent social class IV or V	21.9	23.2
Percent ever smoked	75.4	52.6
Percent ever drink alcohol	85.6	67.9

The mean birth weights for subjects who did not attend the clinic were 3510 g for men and 3345 g for women. Their weights at 1 year were 10.20 kg (men) and 9.59 kg (women). The non-participants responding only to the postal questionnaire were of similar weight in infancy, adult size, social class and smoking and alcohol habits as those attending clinic.

Our clinic attenders were taller and heavier than a national sample of people aged 65-74 selected randomly for a Department of Health and Social Security survey of nutrition but had very similar social class distribution and smoking habits [16].

Table 2 shows the relationship between early growth and four of the seven markers of ageing. The p values have been adjusted for age, sex, social class and height because these were independent predictors of the ageing outcomes. After allowing for these variables, decreasing weight at 1 year was statistically significantly associated with increasing lens opacity score ($P = 0.003$), such that those in the lowest infant weight category had scores 16% greater than those in the highest group. The relationship persisted when men and women were analysed separately. There was no relationship between opacity score and birth weight in either sex. Visual acuity, macular degeneration and intraocular pressure were not related to either measure of early growth.

Decreasing weight at 1 year was also associated with lower hearing acuity ($P = 0.008$), such that those who were lightest at 1 year had a 32% higher hearing threshold than those who were heaviest. Again, this relationship was similar in men and women considered separately and was not apparent for birth weight. Lower weight at 1 year was associated with reduced grip strength ($P = 0.02$) and thinner skin ($P = 0.19$). The relationship for grip strength was more pronounced among men than among women, while that for skin thickness only attained statistical significance in women ($P = 0.04$). Grip strength was the only physiological measure which correlated significantly with birthweight ($P = 0.01$).

There was no relationship between number of teeth, haematological indices, ESR or renal function and either of the measures of early growth.

Four hundred and fifty-eight subjects (63.9%) were exclusively breast fed, 42 (5.9%) were exclusively bottle fed and the remaining 217 (30.2%) had a mixed feeding pattern. There was no statistically significant relation between the pattern of infant feeding and lens opacity score, hearing acuity, grip strength or skin thickness. The associations of these markers of ageing with infant weight were also unaffected by adjusting for gestational age and social class at birth.

Discussion

We have found in this cross-sectional analysis that

Table 2. The association between early weights and age-related outcomes adjusted for age and sex

	Mean ageing outcome (and no. of subjects)			
Early weight, kg (and pounds)	LOCS III lens opacity[a]	Hearing threshold (dBA)[a]	Grip strength (kg)	Skin thickness (mm)
At birth				
≤2.50 (≤5.5)	2.27 (16)	24.4 (16)	28.5 (16)	1.19 (16)
2.50-2.95 (5.5-6.5)	2.36 (94)	29.3 (93)	30.3 (95)	1.27 (95)
2.95-3.4 (6.5-7.5)	2.38 (224)	29.2 (231)	31.0 (231)	1.24 (231)
3.4-3.86 (7.5-8.5)	2.38 (205)	28.7 (217)	32.2 (217)	1.24 (217)
3.86-4.31 (8.5-9.5)	2.29 (84)	28.4 (89)	32.5 (89)	1.22 (89)
>4.31 (>9.5)	2.36 (32)	28.8 (35)	32.4 (35)	1.25 (35)
Multiple regression[b]	$P = 0.71$	$P = 0.97$	$P = 0.01$	$P = 0.32$
At 1 year				
≤8.16 (≤18)	2.67 (26)	33.6 (26)	29.8 (26)	1.20 (26)
8.16-9.07 (18-20)	2.40 (133)	29.4 (134)	30.7 (134)	1.22 (134)
9.07-9.98 (20-22)	2.33 (198)	29.3 (209)	31.1 (211)	1.24 (211)
9.98 -10.89 (22-24)	2.37 (187)	29.1 (194)	31.6 (194)	1.25 (194)
10.89 -11.79 (24-26)	2.33 (70)	26.5 (77)	32.6 (77)	1.25 (77)
>11.79 (>26)	2.24 (41)	24.8 (41)	34.2 (41)	1.25 (41)
Multiple regression[b]	$P = 0.003$	$P = 0.008$	$P = 0.02$	$P = 0.19$
All	2.36 (655)	28.8 (681)	31.5 (683)	1.24 (683)
Standard deviation	1.21	1.6	10.1	0.18

[a]Logarithms used in analysis therefore means geometric.
[b]Adjusted for age, sex, current social class, social class at birth and height.

people who had had lower weight at 1 year showed increased ageing in some systems as characterised by more lens opacity, higher hearing threshold, lower grip strength and thinner skin.

These associations could be explained in a number of ways. First, it could be argued that children born into an adverse environment in which they do not gain weight in infancy remain there and that it is the poor adult environment which leads to more rapid ageing. The effects of ageing determined here, however, were independent of adult social class. Secondly, they might have arisen through selection bias. The study group represented 50% of the people invited and 10% of all babies born in the area. However the findings were based on internal comparisons and unless the associations between measurements of early growth and ageing markers differed in non-responders or in people who have died or moved away, no bias should have been introduced. They are also consistent with our previous observations that weight in infancy is a predictor of earlier cardiovascular death.

We therefore suggest that the associations between early growth and markers of ageing are causal and that the rate of ageing at least in some systems may be programmed by events in early life. This hypothesis will be tested by revisiting the subjects 5 years after the initial examination to measure the rate of change in the ageing markers.

The relationships are predominantly with weight at 1 year rather than birth weight but are not explained by method of infant feeding. However, infant growth is also related to prenatal growth and while growth failure in early gestation reduces birth weight, growth failure in late gestation affects body proportions at birth and subsequent infant growth [17]. Late gestation may be the critical phase for programming of ageing processes in these systems.

One process underlying ageing is thought to be imperfect molecular repair and the consequent accumulation of molecular damage [18]. This may be of particular relevance to long-lived molecules where turnover is minimal [19]. Molecular damage may result from intrinsic as well as extrinsic exposures. For example, high circulating concentrations of blood glucose cause modification of both proteins and nucleic acids in a process called nonenzymatic glycosylation and this has been linked to ageing changes [20]. One explanation for the findings in this study therefore is that early undernutrition influences ageing by permanently resetting glucose metabolism

Recent support for a central role of repair systems in ageing came from isolation of the gene for Werner's syndrome, a rare condition associated with premature ageing [21]. The syndrome is associated with a mutation identified in the gene coding for helicase, an enzyme required for DNA repair. Our observations point to environmental rather than genetic effects on ageing since early growth is essentially regulated by nutrient supply rather than by the genome [22, 23]. Our findings could therefore also be explained by a detrimental effect of undernutrition during gestation, especially late gestation, on the development of repair systems as well as growth.

The associations that we have found between early growth and markers of ageing in the lens, ear, muscle and skin suggest that undernutrition at this stage may particularly affect those tissues containing a large proportion of long-lived molecules such as lens crystallins, collagen and elastin. Here, in the relative absence of regeneration, molecular repair processes may be most critical. Perhaps the winding sheet that we bring into this world is our programmed capacity for repair.

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Key points

- Epidemiological studies have demonstrated that poor early growth is associated with cardiovascular and other degenerative diseases. However its relationship with ageing has not been directly studied before in man.
- In this retrospective cohort study, lower weight at 1 year was associated with a number of ageing markers including increased lens opacity score, higher hearing threshold, reduced grip strength and thinner skin.
- The association between poor early growth and increased markers of ageing suggests that ageing may be programmed by events in early life. A potential mechanism is the impaired development of repair systems by inadequate early nutrition.

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