FETAL ORIGINS OF CORONARY HEART DISEASE AND HYPERTENSION AND ITS RELEVANCE TO INDIA: REVIEW OF EVIDENCE FROM THE MYSORE STUDIES

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ABSTRACT:

Reduced growth in utero has been associated with an increased risk of coronary heart disease and hypertension. The rising rates of coronary heart disease in India are not explained by the prevalence of risk factors such as high blood pressure, hypercholesterolaemia, smoking or obesity. The fetal origins hypothesis may therefore be particularly relevant to India. Studies conducted at the Holdsworth Memorial Hospital, Mysore show that poor fetal growth is associated with an increased risk of adult coronary heart disease. However, the association is not mediated by hypertension, left ventricular mass or arterial compliance. This suggests that the way in which the intrauterine environment influences coronary heart disease differs between Indian and Western populations. The fact that the Mysore men and women are insulin resistant, and that coronary heart disease and its risk factors have been linked to features of the insulin resistance syndrome lead to the speculation that insulin resistance may be partially responsible.

KEYWORDS : Growth in utero, fetal origins, coronary heart disease, hypertension

FETAL GROWTH AND CORONARY HEART DISEASE AND ITS RISK FACTORS

Studies in the UK, USA and Europe have shown that reduced growth in utero, as measured by small size at birth, is associated with an increased risk of morbidity and mortality from coronary heart disease (CHD) (1-5). Reduced fetal growth has also been linked with higher adult levels of known cardiovascular risk factors including hypertension, non-insulin-dependent diabetes mellitus (NIDDM), insulin resistance, raised serum lipids, increased left ventricular (LV) mass and reduced arterial compliance (6-11). These findings have led to the "fetal origins" hypothesis proposed by Barker which states that adult disease is 'programmed' in utero (12). Pathological mechanisms are initiated by fetal undernutrition during 'critical' periods of organ development which permanently alters the body's structure, physiology, and metabolism.

Barker has proposed a framework linking fetal growth to adult CHD (13). Fetal undernutrition results in altered fetal blood flow which leads to preferential perfusion of the brain at the expense of the trunk. If sustained, it may lead to reduced growth of the abdominal organs, reduced muscle mass and stunting at birth. This results in permanently altered structure and function of the liver leading to altered lipid metabolism and raised serum lipid concentrations; of the pancreas altering glucose/insulin metabolism and resulting in non-insulin dependent diabetes mellitus, and of the kidneys leading to hypertension. Reduced blood flow in the large arteries of the trunk and legs may also be associated with reduced elastin deposition, less compliant arteries and subsequent hypertension. Diversion of oxygenated blood to the brain at the expense of the trunk also increases the load on the heart and peripheral resistance, leading to left ventricular hypertrophy. Undernutrition may also reduce secretion of and sensitivity to insulin and IGF-1. It alters and results in re-setting of the IGF-growth hormone and hypothalamic-pituitary-adrenal axes, which may persist post nataly, resulting in hypertension and non-insulin diabetes mellitus. Both these mechanisms may eventually result in CHD.

CHD IN INDIANS

CHD rates in India are rising (14) and projected statistics show that CHD will be the leading cause of mortality by 2010 (15). These findings are not explained by the prevalence of classical CHD risk factors such as high total cholesterol concentrations and blood pressure, obesity, or lifestyle factors such as high saturated fat intakes and smoking (16,17), all of which tend to be lower in South Asian Indian than Western populations (18). CHD in Indian populations is, however, associated with an unfavourable metabolic profile, the Insulin ResistanceSyndrome, (consisting of impaired glucose tolerance or NIDDM, insulin resistance, raised serum triglyceride and low HDL-cholesterol

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concentrations), central obesity and abnormal plasma clotting factors (17,18). In India, CHD is more common in urban areas and among lower socio-economic groups. Although few Indian women smoke, rates of CHD are similar in men and women. People of Indian origin living outside India, also have higher rates than the indigenous populations (19). It has been suggested that Indian people have a genetically determined susceptibility to NIDDM and CHD which is enhanced on exposure to a sedentary lifestyle, high energy intake and urbanisation (20, 21). Although the genes responsible for this have not been identified, it was hypothesised that these genes confer a survival advantage in times of scarcity, but tend to cause disease in the modern times of relative affluence. The 'thrifty genotype' hypothesis implies that Indians will continue to experience high rates of CHD and NIDDM unless they return to their past way of living. This conflicts with experience elsewhere in the world, where epidemics of CHD have been followed by declining rates, even though the reasons for the decline are largely unexplained.

RELEVANCE OF THE FETAL ORIGINS HYPOTHESIS TO INDIA

The 'foetal origins' hypothesis offers an alternative explanation. Maternal nutrition is poor, and rates of fetal growth are low in India. The mean birthweight is 2.7 kg, and one third of babies are born low birthweight (<2.5 kg) (22). If low birthweight is an important risk factor for adult CHD, India will be especially vulnerable due to the vast numbers of poorly nourished infants who have been born in the past few decades. The gradual but steady decline in infant mortality and childhood mortality rates will lead to a higher proportion of such infants surviving to adult life, when their hypothesised susceptibility to CHD may become apparent. The 'fetal origins' hypothesis may therefore be particularly relevant to India. Public health strategies to arrest the 'epidemic' of CHD may require interventions to improve the growth and nutrition of girls and women. Measures to control adult risk factors may be most effectively targeted to people of low birthweight. These implications prompted a programme of research to examine the relevance of the fetal origins hypothesis in India. This paper is confined to reviewing the implications of the studies on CHD and its risk factors conducted at the Holdsworth Memorial Hospital (HMH) in Mysore, South India.

The HMH has well-maintained birth recordssince 1934, which contain the weight, length and head circumference of babies at birth. The records also contain details of parents' names, address, occupations, religion or caste and the mother's obstetric history. About 55% of the records contain maternal pelvic measurements. These were recorded for most primiparous and some multiparous women. Some mothers (roughly 40%) attended the antenatal clinic and their records also contain their weight at each antenatal visit. The records do not provide useful information on gestational age and placental weights, as there are few records with accurate measurements.

FIRST MYSORE STUDY

Subjects were traced by a door-to-door survey of a three square kilometre area around the hospital, in a central area of the city. The survey included approximately 7800 households and covered a population of over 52,000 people. For people who said they were born in HMH, the names of their parents, order of siblings, address and parents' occupation at the time of birth, date of birth and any special features of the pregnancy were obtained. 1311 people said that they were born in the hospital as singletons and were 40 years or older. The aim was to trace 500 people who were born in the hospital during a twenty-year period between 1934 and 1953. Records of all the 8,883 live births during that period were entered on a database and the people traced by survey were matched to their birth records using strict matching criteria. Matching people to their birth records was not easy, as many of the subjects did not know their correct age or date of birth. The birth records did not contain the names of the babies and therefore had to be matched on the names of both parents, address at birth, and order and sex of siblings. There were inconsistencies in spelling parental names, as names had been transcribed from Indian languages into written English. Computerised birth records were matched to parental names on the tracing form using a program devised to link names phonetically. After the computer program had identified a probable match, the original birth record was scrutinised in comparison to the information on the tracing form. Details that did not match were verified by further open-ended questioning of the prospective subjects by the field workers, who were blind to the information on the birth records. The study only included people who were matched to their birth records with certainty.

Of the 536 people matched with their birth records, 517 (96%) participated in the study (23). These subjects were invited to attend a clinic for physical examination and investigations after an overnight fast of 12 hours. Subjects underwent a standard 12-lead ECG, blood pressure recording and were administered the Rose-WHO questionnaire to

collect history of chest pain. Subjects also underwent the 75 gm, 2 hour glucose tolerance test, where blood was drawn at 0 minutes, 30 minutes and 120 minutes for measurement of plasma glucose and insulin levels. Fasting concentrations of serum total and HDL cholesterol, serum triglycerides, plasma fibrinogen and factor VII were also measured, while serum LDL cholesterol concentration was calculated. We also measured subjects' height, weight, hip and waist circumferences and four skinfolds (triceps, biceps, subscapular and suprailiac). A questionnaire was administered to collect details of current medication, previous medical history, smoking, alcohol consumption and socio-economic status. The presence of coronary heart disease was determined by the presence of one or more of the following criteria: typical angina according to the Rose/WHO chest pain questionnaire (24); ECG Minnesota codes 1-1 or 1-2 (Q and QS waves) (25); or a history of coronary artery angioplasty or bypass graft surgery.

The age range of the men and women was 38-60 years. 48% of the subjects were classified as belonging to lower social classes. The majority of the subjects were Muslims (54%), while Hindus (36%) formed the second largest religious group. 62% of the men in the study had smoked at some point, while 47% continued to do so. 21% of men reported alcohol consumption. Only one woman reported smoking and alcohol consumption. 25 (9%) men and 27 (11%) women had CHD. Subjects with CHD were older and shorter than those without the disease, and had higher systolic blood pressures, a more adverse lipid profile and higher concentrations of plasma glucose and insulin (Table 1). Insulin concentrations suggested that the Mysore subjects were insulin resistant, despite low levels of obesity.

Table 1 : Risk profile of men and women with and without CHD (Mean (SD))

	MEN				WOMEN			
	With CHD (n=25)		Without CHD (n=241)		With CHD (n=27)		Without CHD (n=224)	
General characteristics								
Age (years)	49.5	(5.5)	47.3	(4.7)	49.2	(5.0)	47.2	(4.7)
Height (cm)	164.9	(6.3)	165.9	(6.0)	151.1	(7.7)	151.5	(6.4)
Body mass index (kg/m^2)	22.5	(3.3)	22.8	(4.0)	25.1	(4.6)	24.8	(5.2)
CHD risk factors								
Systolic blood pressure (mmHg)	136	(21)	131	(16)	133	(14)	132	(19)
Diastolic blood pressure (mmHg)	82	(13)	80	(11)	76	(11)	77	(11)
Serum triglycerides (mmol/L)*	1.8	(1.8)	1.7	(1.7)	1.7	(1.6)	1.5	(1.7)
HDL-cholesterol (mmol/L)	0.9	(0.2)	0.9	(0.2)	0.9	(0.2)	1.0	(0.2)
LDL-cholesterol (mmol/L)	3.7	(1.0)	3.1	(0.8)	3.0	(0.6)	3.2	(0.8)
Total cholesterol (mmol/L)	5.3	(1.2)	4.9	(1.0)	4.7	(0.7)	4.9	(0.9)
Fasting insulin (pmol/L)*	41	(3)	48	(2)	74	(2)	54	(2)
30-min insulin (pmol/L)*	335	(2)	382	(2)	447	(2)	379	(2)
120-min insulin (pmol/L)*	342	(3)	329	(2)	464	(2)	393	(2)
Proinsulin (pmol/L)*	9.0	(2.5)	7.8	(2.4)	7.6	(2.0)	6.3	(2.1)
32-33 split proinsulin (pmol/L)*	9.2	(2.6)	8.4	(2.9)	9.3	(2.3)	8.3	(2.4)
Fasting glucose (mmol/L)*	5.5	(1.5)	5.1	(1.3)	5.7	(1.5)	5.3	(1.3)
30-min glucose (mmol/L)*	8.1	(1.4)	8.4	(1.3)	8.4	(1.4)	8.0	(1.3)
120-min glucose (mmol/L)*	6.7	(1.5)	6.4	(1.4)	7.5	(1.4)	6.9	(1.3)
Waist/hip ratio	0.91	(0.06)	0.91	(0.06)	0.85	(0.06)	0.83	(0.06)
Subscapular/triceps skinfold ratio	1.84	(0.47)	1.83	(0.48)	1.37	(0.30)	1.28	(0.32)
Plasma fibrinogen (g/L)	298	(54)	310	(80)	341	(56)	339	(60)
Factor VII (g/L)	117	(37)	112	(37)	135	(39)	124	(40)

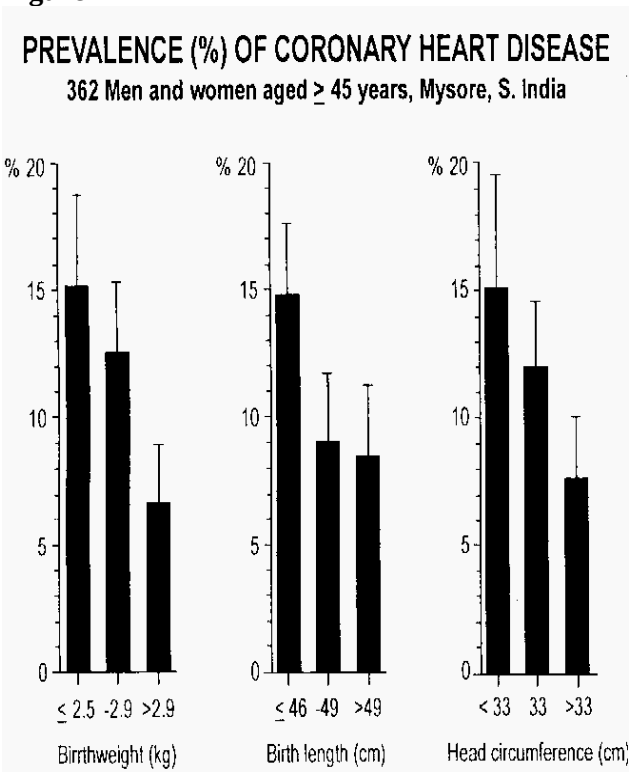
* $p<0.05$

**$p<0.01$

p values adjusted for age, sex and body size

The prevalence of CHD was higher in men and women who had lower birth weight, shorter birth length and smaller head circumference at birth. These trends were stronger among participants aged 45 years and over ($p<0.05$ for all birth measurements) (Figure 1). There was no relation with ponderal index at birth. The trends between CHD and size at birth were similar in men and women. The 30-minute plasma insulin concentration tended to be lower in subjects who had a higher birthweight and ponderal index at birth independently of age, sex and current body size (Table 2). The 120-minute insulin concentration showed a similar trend with birth weight. None of the other CHD risk factors showed any statistically significant associations with any of the birth measurements. However, systolic blood pressure tended to be higher in subjects of longer length at birth ($p=0.07$).

Figure 1



Mothers of lower weight had smaller babies, who as adults had a higher prevalence of CHD. The highest prevalence of CHD (20%) was in those who weighed less than 5.5 lbs at birth and whose mothers weighed less than 100 lbs. In contrast there were no cases of CHD in those who weighed more than 6.5 lbs at birth and whose mothers weighed more than 100 lbs. Prevalence of NIDDM was higher in people who were short at birth, with a relatively high ponderal index, and in those whose mothers had a relatively high pregnancy weight and large pelvic diameters (26). Plasma proinsulin and 32-33 split proinsulin

Table 2: Relation of birth measurements to CHD risk factors: unadjusted Pearson correlation coefficients

	Birth weight	Length	Head Circumference	Ponderal index
Blood pressure				
Systolic	0.08	0.11	-0.02	-0.04
Diastolic	0.09	0.09	<0.01	-0.02
Glucose				
Fasting	0.08	<0.01	<0.01	0.06
30 minutes	0.13	0.05	0.08	0.05
120 minutes	0.09	0.02	0.06	0.06
Insulin				
Fasting	0.03	0.01	<-0.01	<0.01
30 minutes	-0.03*	0.08	<-0.01	-0.10*
120 minutes	<-0.01*	0.05	0.05	-0.06
Proinsulin	0.09	0.06	0.04	0.01
32-33 split proinsulin	0.03	0.02	<0.01	<-0.01
Lipids				
Total cholesterol	0.05	0.06	-0.05	-0.02
LDL cholesterol	0.04	0.09	-0.07	-0.05
HDL-cholesterol	0.02	-0.02	<0.01	0.03
Triglycerides	0.01	-0.01	-0.01	0.02
Central obesity				
Waist/hip ratio	0.13	0.10	0.08	0.01
Subscapular/triceps ratio	0.01	0.07	0.06	-0.06
Clotting factors				
Fibrinogen	<-0.01	0.03	- 0.09	-0.03
Factor VII	0.03	-0.05	0.08	0.14

* $p<0.05$
**$p<0.01$
p values adjusted for age, sex and body size

concentrations were higher in subjects whose mothers were heavier during pregnancy or had larger pelvic diameters, independently of age, sex and current body size. None of the other CHD risk factors were significantly related to maternal size.

FOLLOW-UP STUDY:

In 1996-97, to elucidate mechanisms that may be responsible for the associations between fetal growth and CHD, two further cardiovascular measurements that have been shown to be linked to poor fetal growth in western populations, LV mass and arterial compliance were measured in the same cohort (27). A questionnaire was administered to obtain information on current medications. Body surface area (BSA) was calculated from weight and height using a standard formula (28). Systolic and diastolic blood pressures were recorded from the right arm, left arm and right leg, with the subject supine and rested for at least ten minutes. Arterial compliance was derived from measurement of pulse wave velocity (PWV) in 4 arterial segments (right and left aorto-radial, right aorto-femoral and aorto-posterior tibial) using a non-

invasive optical method (29). This is based on the principle that PWV is increased in stiffer (less compliant) arteries. Left ventricular mass was measured using 2D and M-mode echocardiography according to the recommendations of the American Society of Echocardiography (30).

435 (85%) of the original cohort participated in the follow-up study. There were no statistically significant differences in age, sex, adult body size and birth measurements between those who did and did not participate, or between those included and not included in the analysis. LV mass was adjusted for body size in the traditional way (30), by dividing values by BSA. People with CHD had a higher systolic blood pressure and greater LV mass than those without the disease, while arterial compliance was unrelated to CHD. Increased systolic pressure and LV mass, and decreased arterial compliance were associated with features of the insulin resistance syndrome (Table 3).

Table 3: Relation of LV mass and pulse wave velocity to risk factors for CHD: unadjusted Pearson correlation coefficients

	LV mass	LVmass/ BSA	Pulse wave velocity		
			Aorto-Radial	Aorto-femoral	Femoro-posterior tibial
Glucose					
Fasting	0.19**	0.17**	0.04	0.15*	0.15**
30 minutes	0.17**	0.08	0.16	0.15	0.15**
120 minutes	0.23**	0.13**	0.06	0.10	0.16*
Insulin					
Fasting	0.26**	0.13*	0.10	0.16	0.12
30 minutes	0.09	-0.02	0.14*	0.12	<0.01
120 minutes	0.20**	0.07	0.12*	0.11	0.15*
Proinsulin	0.37**	0.21**	0.22*	0.26*	0.15*
32-33 split proinsulin	0.27**	0.11	0.18*	0.22*	0.13
Lipids					
Total cholesterol	0.13*	0.05	0.05	0.10	0.06
LDL cholesterol	0.12*	0.05	0.02	0.05	0.02
HDL-cholesterol	-0.22**	-0.16*	-0.07	0.01	- 0.07
Triglycerides	0.29**	0.20**	0.16	0.16	0.16**
Central obesity					
Waist/hip ratio	0.47**	0.27**	0.38*	0.29**	0.09
Subscapular/ triceps ratio	0.21	0.13	0.23	0.10	0.06
Clotting factors					
Fibrinogen	-0.07	-0.06	- 0.05	0.06	<0.01
Factor VII	0.06	0.02	0.04	0.09	0.09

* p <0.05
** p <0.01
p values adjusted for age and sex; PWV values also adjusted for BSA.

There were no relations between small size at birth and systolic blood pressure, LV mass and arterial compliance. However, systolic blood pressure and LV mass were higher in those who had been longer at birth (Table 4). Systolic pressure rose by 1.64 mmHg (95% CI -0.08 to 3.37), and LV mass rose by 1.64 g/m^2 (95% CI 0.13 to 3.13) per inch increase in birth length. There were similar findings for percentages of people with hypertension and LV hypertrophy. The relationships with blood pressure persisted after allowing for adult height and were similar if subjects taking anti-hypertensive medication (n=58) were excluded from the analysis (p=0.08 for the trend with birth length, allowing for adult body mass index). Arterial compliance tended to be higher in men and women whose mothers had lower weight during pregnancy and had smaller external conjugate diameters (p<0.05).

Table 4: Relationship between cardiovascular outcome variables and length at birth

Length at Birth (cm)	Systolic Blood Pressure (mmHg)	Left Ventricular Mass Indexed by Body Surface Area (g/m^2)	Pulse Wave Velocity inthe Aorto-femoral Segment (m/s)
<45.5	124 (57)	80 (52)	3.29 (56)
45.5-	126 (135)	85 (119)	3.24 (132)
47.0-	126 (134)	85 (117)	3.31 (1320
50.0+	132 (105)	88 (87)	3.29 (104)
All	127 (431)	85.0 (375)	3.28 (424)
SD	23	18	0.5
P value	0.02	0.02	0.6
p * value	0.06		0.8
p+ value		0.03	

* = adjusted for age, sex and body size

+=adjusted for age and sex

figures in parentheses indicate number of subjects

DISCUSSION

The prevalence of CHD in Mysore was 10%, which is similar to rates elsewhere in urban India (31). The findings that CHD was associated with low birthweight, small head circumference and short body length at birth are consistent with those from studies in western countries and reflect similar associations between high rates of CHD and poor fetal growth in an Indian population. These body proportions are thought to result from fetal adaptations to undernutrition throughout gestation, with reduction in growth of the head, body length, and soft tissues. This was the first study to establish a link between CHD and low maternal weight. The finding that mothers with lowest weights had the smallest offspring, who

as adults had the highest rates of CHD, is consistent with ideas about maternal undernutrition causing impaired fetal growth leading to adult CHD. However, in contrast to findings in Western populations, there was no association between systolic blood pressure, LV mass and arterial compliance, and small size at birth. On the contrary, systolic blood pressure, LV mass and rates of hypertension and LV hypertrophy were greater in those who had been longer at birth.

This cohort was not a true 'population' sample. The study was restricted to people who were born in a single hospital in Mysore between 1934 and 1953, who were still alive, lived locally and who gave sufficient information to be able to match them to their birth records with certainty. Most deliveries at that time took place either at home or in the government hospital in the city. It is not clear what factors influenced these families to choose the HMH for delivery. The sample is therefore unrepresentative of all births in Mysore during that period. However, the analysis is based on internal comparisons and bias would be introduced only if the relationships between fetal growth and adult disease differed between those born in and outside the hospital, and between those traced and not traced. There are no reasons to suspect such differences. Their birth measurements were similar to those of all people born in the hospital during that period. Mean height and weight, and rates of CHD and NIDDM were similar to those reported in other urban Indian populations (31-33). It is not possible to compare LV mass and pulse wave velocity as there is no previously published data in healthy Indian adults.

The lack of association with small size at birth was most striking for blood pressure which, in a large number of published studies, has shown an inverse relationship to birthweight (34). There are reasons why such a relationship, if present, may have been obscured in this population. The association between low birthweight and raised blood pressure has been shown to be strongest in those born at full term (6,35). The Mysore records do not contain gestational age, and it was not possible to distinguish between low birthweight due to prematurity and that due to retarded fetal growth. This would have reduced the strength of association between low birthweight and raised systolic pressure. The records also do not contain information on placental weights. Studies in UK have suggested that the relationship between low birthweight and raised blood pressure is strongest in those born with relatively large placentae in relation to their birthweight (35). The mean birthweight in the Mysore cohort was considerably lower compared to babies born in the west; it may be that the association between small size at birth and raised systolic pressure is apparent only when there are small as well as large babies i.e., a sufficiently wide range. Many subjects were on anti-hypertensive medication, including ACE inhibitors and beta-blockers, which not only lower blood pressure but also cause regression of LV hypertrophy. This may have been another contributing factor. However the results were similar even when subjects on medication were excluded from the analysis.

It is possible that the absence of an association between high blood pressure and lower birthweight in this population is explained by different patterns of fetal growth. It has been suggested that raised blood pressure is linked to undernutrition in mid-late gestation resulting in the fetus switching down its growth (36). Indian fetuses may down-regulate growth early in gestation, remain small and either avoid adaptations or adapt differently. There is evidence that raised blood pressure is associated with small size at birth in people who become tall adults or in those who experience catch up growth postnatally (37,38). The Mysore cohort remained relatively small in adult life and this may have prevented the rise in adult blood pressure seen in western populations.

Surprisingly, mean values for systolic blood pressure and LV mass were higher in people whose length at birth was greater. Associations between blood pressure and both short and tall babies have been reported (2,39,40). These results cannot be explained.

It is thought that changes in levels of blood pressure, LV mass and arterial compliance may partly explain the relation between reduced fetal growth and increased risk of CHD. In Mysore too, risk of coronary heart disease was highest in those who were small at birth. The lack of a relation between small size at birth and blood pressure, arterial compliance or left ventricular mass, suggests that in Indian populations at least, this increased risk is mediated by other mechanisms. A study in Pune showed that poor fetal growth was associated with insulin resistance in 4-year-old children; this is the earliest age at which this relationship has been demonstrated (41). The Mysore men and women are insulin resistant. CHD and its risk factors are associated with features of insulin resistance and fetal growth in Mysore. This leads to the speculation that the mechanism linking fetal growth and CHD may be at least partially mediated by insulin resistance. Further studies may answer this hypothesis.

REFERENCES :

1. Osmond C, Barker DJP, Winter PD et al. Early growth and death from cardiovascular disease in women. BMJ 1993; 307:1519-24.

2. Barker DJP, Osmond C, Simmonds SJ et al. The relation of small head circumference and thinness at birth to death from cardiovascular disease. BMJ 1993; 306:422-6.

3. Rich-Edwards JW, Stampfer MJ, MansonJE et al. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. BMJ 1997; 315:396-400.

4. Leon DA, Lithell HO, Vagero D et al. Reduced fetal growth rate and increased risk from ischaemic heart disease: cohort study of 15,000 Swedish men and women born 1915-29. BMJ 1998; 317:241-5.

5. Forsen T, Eriksson JG, Tuomilehto J et al. Mother's weight in pregnancy and coronary heart disease in a cohort of Finnish men: follow up study. BMJ 1997; 315:837-40.

6. Law CM, de Swiet M, Osmond C et al. Initiation of hypertension in utero and its amplification throughout life. BMJ 1993; 306: 24-7.

7. Hales CN, Barker DJP, Clark PMS et al. Fetal and infant growth and impaired glucose tolerance at age 64. BMJ 1991; 303:1019-22.

8. Phillips DIW, Barker DJP, Hales CN et al. Thinness at birth and insulin resistance in adult life. Diabetologia 1994; 37:150-4.

9. Barker DJP, Martyn CN, Osmond C et al. Growth in utero and serum cholesterol concentrations in adult life. BMJ 1993; 307:1524-7.

10. Vijayakumar M, Fall CHD, Osmond C et al. Birth weight, weight at one year, and left ventricular mass in adult life. Br Heart J 1995; 73:363-7.

11. Martyn CN, Barker DJP, Jespersen S et al. Growth in utero, adult blood pressure and arterial compliance. Br Heart J 1995; 73:116-21.

12. Barker DJP. Fetal origins of coronary heart disease. BMJ 1995; 311:171-4.

13. Barker DJP. Intrauterine programming of the adult cardiovascular system. Curr Opin Nephrol Hyperten 1997; 6:106-10.

14. Gupta R, Gupta VP. Meta-analysis of coronary heart disease in India. Ind Heart J 1996; 48:241-5.

15. Bulatao RA, Stephens PW. Global estimates and projections of mortality by cause, 1970-2015. Policy research working paper 1007, Population and Human Resources Dept, The World Bank.

16. Keshavamurthy NK, Gemson K. Observations on the epidemiology of coronary heart disease from an industrial hospital. Tropical Doctor 1980; 10:103-5.

17. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. Lancet 1991; 337:382-6.

18. McKeigue PM, Ferrie JE, Pierpoint T et al. Association of early-onset coronary heart disease in South Asian men with glucose intolerance and hyperinsulinaemia. Circulation 1993; 87:152-61.

19. Balarajan R. Ethnicity and variations in mortality from coronary heart disease. Health Trends 1996; 28:45-51.

20. Neel JV. Diabetes mellitus: a 'thrifty' genotype rendered detrimental by 'progress'? Am J Human Genet 1962; 14:353-62.

21. McKeigue PM, Miller GJ, Marmot M. Coronary heart disease in South Asians overseas: a review. J Clin Epidemiol 1989; 42:597-609.

22. Gopalan C. Low Birth Weights: Significance and Implications. (from Nutrition in Children; Developing Country Concerns. eds Sachdev HPS, Chaudhary P). New Delhi: Imprint, 1994.

23. Stein CE, Fall CHD, Kumaran K et al. Fetal growth and coronary heart disease in South India. Lancet 1996; 348:1269-73.

24. Rose GA, Blackburn H. Cardiovascular Survey Methods. Geneva: World Health Organisation, 1968.

25. Prineas RJ, Crow RS, Blackburn H. The Minnesota code manual of electrocardiographic findings: standards and procedures for measurement and classification. Boston: John Wright, 1982.

26. Fall CHD, Stein CE, Kumaran K et al. Size at birth, maternal weight, and type 2 diabetes in South India. Diab Med 1998; 15:220-7.

27. Kumaran K, Fall CHD, Stein CE at al. Blood pressure, arterial compliance and left ventricular mass: no relation to small size at birth in South Indian adults. Heart 2000; 83:272-7.

28. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916; 17:863-71.

29. Greenwald SE, Denyer HT, Sobeh MS. Non invasive measurement of vascular compliance by a photoplesythmographic technique. SPIE 1997; 2970:89-97.

30. Sahn DJ, DeMaria A, Kisslo J et al. The committee on M-mode standardisation of the American Society of Echocardiography. Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. Circulation 1978; 58:1072-83.

31. Chadha SL, Radhakrishnan S, Ramachandran K et al. Epidemiological study of coronary heart disease in urban population of Delhi. Ind J Med Res 1990; 92:424-30.

32. Beegom R, Beegom R, Niaz MA et al. Diet, obesity and prevalence of hypertension in the urban population of South India. Int J Cardiol 1995;51:183-91.

33. Ramachandran A, Snehalatha C, Latha E et al. Rising prevalence of NIDDM in an urban population in India. Diabetologia 1997;40:232-7.

34. Law CM, Shiell AW. Is blood pressure inversely related to birth weight? The strength of evidence from a systematic review of the literature. J Hyperten 1996; 14:935-41.

35. Barker DJP, Bull AR, Osmond C et al. Fetal and placental size and risk of hypertension in later life. BMJ 1990; 301:259-62.

36. Barker DJP. The fetal origins of hypertension. J Hyperten 1996; 14 (Suppl 5):S117-20.

37. Leon DA, Koupilova I, Lithell HO et al. Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men. BMJ 1996; 312:401-6.

38. Ounsted MK, Cockburn JM, Moar VA et al. Factors associated with the blood pressures of children born to women who were hypertensive during pregnancy. Arch Dis Child 1985; 60:631-5.

39. Barker DJP, Godfrey KM, Osmond C et al. The relation of fetal length, ponderal index and head circumference to blood pressure and the risk of hypertension in adult life. Pediatr Perinat Epidemiol 1992; 6:35-44.

40. Law CM, Barker DJP, Bull AR et al. Maternal and fetal influences on blood pressure. Arch Dis Child 1991; 66:1291-5.

41. Yajnik CS, Fall CHD, Vaidya U et al. Fetal growth and glucose and insulin metabolism in four-year-old Indian children. Diab Med 1995; 12:330-6.