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Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth

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Summary. Two follow-up studies were carried out to determine whether lower birthweight is related to the occurrence of syndrome X – Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia. The first study included 407 men born in Hertfordshire, England between 1920 and 1930 whose weights at birth and at 1 year of age had been recorded by health visitors. The second study included 266 men and women born in Preston, UK, between 1935 and 1943 whose size at birth had been measured in detail. The prevalence of syndrome X fell progressively in both men and women, from those who had the lowest to those who had the highest birthweights. Of 64-year-old men whose birthweights were 2.95 kg (6.5 pounds) or less, 22% had syndrome X. Their risk of developing syndrome X was more than 10 times greater than that of men whose birthweights were more than 4.31 kg (9.5 pounds). The association between syndrome X and low birthweight was independent of duration of gestation and of possible confounding variables including cigarette smoking, alcohol consumption and social class currently or at birth. In addition to low birthweight, subjects with syndrome X had small head circumference and low ponderal index at birth, and low weight and below-average dental eruption at 1 year of age. It is concluded that Type 2 diabetes and hypertension have a common origin in sub-optimal development in utero, and that syndrome X should perhaps be re-named "the small-baby syndrome".

Key words: Type 2 (non-insulin-dependent) diabetes mellitus, hypertension, hyperlipidaemia, syndrome X, reduced fetal growth.

A recent study showed that lower birthweight and weight at 1 year of age are associated with the subsequent development of Type 2 (non-insulin-dependent) diabetes mellitus in adult life [1]. Among 370 men aged 64 years living in the county of Hertfordshire, UK, the percentage who had either Type 2 diabetes or impaired glucose tolerance fell progressively from 40% in those whose birthweight was 2.5 kg (5.5 pounds) or less, to 14% in those whose birthweight was 4.31 kg (9.5 pounds) or more. There were similar strong trends with weight at 1 year of age. These trends are interpreted as the long-term effects of nutritional and other factors which reduce fetal and infant growth and impair the development of the endocrine pancreas. This conclusion was strengthened by the recent finding that 30-min plasma glucose concentrations were inversely related to birthweight in 21-year-old men [2].

Hypertension is also associated with reduced fetal growth. Studies of men and women aged 36, 50 and 64 years have shown that systolic and diastolic pressures are lower in people who had higher birthweight [3–5]. These associations are independent of duration of gestation. Blood pressure is not, however, related to weight at 1 year of age independent of birthweight [5]. These trends are interpreted as the long-term effects of intra-uterine changes in blood vessel development.

Type 2 diabetes and hypertension tend to occur in the same patients [6–10]. Patients with both disorders often have other abnormalities, including high plasma insulin concentrations, high serum triglyceride concentrations, low serum HDL concentrations and high body mass indices and waist to hip ratios. This combination of abnormalities has been called syndrome X [8] and is associated with increased mortality from ischaemic heart disease [11]. The suggested explanation for syndrome X is that the primary defect is insulin resistance and consequent hyperinsulinaemia [7–9, 12]. The association of both Type 2 diabetes and hypertension with reduced fetal growth has, however, raised the possibility that these and other components of syndrome X may have a common origin in sub-optimal development at a particular stage of intra-uterine life [1, 13].

We have analysed the occurrence of syndrome X in men aged 64 years living in Hertfordshire to determine its relation to birthweight and weight at 1 year of age. We

have also carried out glucose tolerance tests on a sample of men and women aged 50 years living in Preston (Lancashire, UK). Measurements recorded at birth in Preston were more detailed than those in Hertfordshire where only birthweight was measured. The Preston data include duration of gestation and therefore allow the effects of reduced fetal growth and premature birth to be distinguished. They also include head size and length at birth, which give an insight into the timing of fetal growth retardation during gestation.

Subjects and methods

Hertfordshire

In Hertfordshire from 1911 onwards, each birth was recorded by the attending midwife. A health visitor saw the child at home periodically throughout infancy. She recorded birthweight, weight at 1 year of age and number of teeth at 1 year of age. Weights were measured in pounds (1 pound = 0.45 kg) and were often rounded to the nearest half pound or pound. We have traced singleton boys born in East Hertfordshire between 1920 and 1930, for whom both birthweight and weight at 1 year of age were recorded. We were able to establish that 1157 of the men still lived there. Of these, 845 agreed to be interviewed at home and were visited by one of four trained fieldworkers [14]. The fieldworker had not seen the subject's birth data. Height was measured with a portable stadiometer and weight with a portable Seca scale. The waist circumference and hip girth were measured. Blood pressure was measured with an automated recorder (Dinamap Model 18465X; Critikon, Tampa, Fla., USA) with the subject seated. Readings were taken on the left arm using the cuff size recommended for the arm circumference. Two readings were taken and the average used in the analysis. The subject was asked about his social history, smoking and drinking habits. Alcohol consumption was converted to the total number of units each week (1 unit = 10 ml ethanol). The father's occupation was used to define social class at birth and current social class was derived from the subject's occupation. Before starting the study the procedures for the measurements were standardised.

After the interview the subjects were asked to come to a local clinic, following an overnight fast, to have a blood sample taken. Of the 468 subjects who complied, 408 agreed to have a 75-g oral glucose tolerance test. Subjects who stated at interview that they had diabetes were not included in the study. Measurements on the blood samples included plasma glucose and insulin concentrations at 0, 30 and 120 min and proinsulin and 32–33 split proinsulin concentrations at baseline. Our previous report was based on the 370 men who had complete measurements on all samples. This report is based on 408 men who had a glucose tolerance test but incomplete measurements on some samples. All had their 2-h plasma glucose concentrations measured. Plasma glucose was measured by a hexokinase method [15]. Plasma insulin, proinsulin and 32–33 split proinsulin concentrations were determined by two-site immunometric assays with either ^{125}I or alkaline phosphatase as labels [16, 17]. The insulin assay was standardised against the first International Reference Preparation coded 66/304 and the intact and 32–33 split proinsulin assays against standards obtained from Lilly Research Laboratories (Indianapolis, Ind., USA).

The fasting blood samples were also analysed for serum triglycerides, total cholesterol, HDL-cholesterol, apolipoproteins A1 and B, plasminogen activator inhibitor antigen, fibrinogen and factor VII. Serum triglycerides, total cholesterol and HDL-cholesterol were measured on the RA 1000 (Bayer Diagnostics, Basingstoke, UK), using standard enzymatic methods [18–21]. Interassay coefficients of variation for these assays were in the range 1.7% to 2.7%. LDL-cholesterol was derived using the Friedwald-Fredrickson formula [22]. Apolipoproteins A1 and B were measured by immunoturbidimetric assays on the RA 1000, with interassay coefficients of variation of less than 5% [23]. Plasma plasminogen activator inhibitor antigen was measured by an enzyme immunoassay (Immulyse; Porton Products, Cambridge, UK). Plasma plasminogen activator inhibitor activity was measured by a two-stage indirect enzymatic assay (Spectrolyse; Porton Products). Thrombin-clottable fibrinogen was measured by the Clauss method, using an electrical impedance end-point [24]. Factor VII was measured by a one-stage assay using a bovine deficient plasma and rabbit brain thromboplastin [25]. The fasting lipids of one subject were not analysed and results are therefore presented for 407 subjects.

Preston

In Preston a standardised record form was kept for each woman admitted to the maternity ward at Sharoe Green Hospital between 1935 and 1943. The record included the date of the mother's last menstrual period and the baby's birthweight, placental weight, length from crown to heel, and head circumference. Weights were measured in pounds (1 pound = 0.45 kg) and lengths and head circumferences in inches (1 inch = 2.54 cm).

Of the singleton infants born during the period 1935–1943, 503 still live in Lancashire. In a previous study 449 of them were interviewed at home by one of three fieldworkers. Height, weight, waist circumference, hip girth and blood pressure were recorded as in the Hertfordshire study, and the results have been previously reported [4]. Social class was defined in the same way as in the Hertfordshire study.

After the interview the 393 men and women who lived in or close to Preston were asked to come to Sharoe Green Hospital in the morning following an overnight fast and to have a blood sample taken. Of those asked 281 complied, and 266 (68%) agreed to have a 75-g oral glucose tolerance test. Samples were analysed using the same methods as in the Hertfordshire study.

Statistical analysis

The measurements of glucose, insulin, proinsulin, 32–33 split proinsulin, triglycerides, apolipoproteins A1 and B, plasminogen activator inhibitor, fibrinogen and factor VII have skewed distributions, and we therefore transformed them in the analysis by using logarithms. Multiple linear and logistic regression were used to analyse the data and to make adjustments for sex in the Preston data.

Results

Hertfordshire

The ages of the 407 men in Hertfordshire ranged from 59 to 70 years, with a mean of 64 years. As reported previously, those with higher birthweights had lower 2-h plasma glucose and insulin concentrations, and lower systolic and diastolic pressures [1, 5]. Syndrome X was identified in 56 of the men using the following criteria: a 2-h plasma glucose concentration of 7.8 mmol/l or more, a systolic blood pressure of 160 mmHg or more (or, for five subjects, current antihypertensive treatment), and a fasting serum triglyceride concentration equal to or above the median value of 1.4 mmol/l. We compared mean body size, currently, at birth and at 1 year of age, with that of the other men in this study (Table 1). Men with syndrome X were of similar height but were heavier and had a higher BMI and waist to hip ratio. In contrast their birthweights

Table 1. Mean body size, currently, at birth and at 1 year of age in men with syndrome X and the other men in the Hertfordshire study

	Syndrome X ($n = 56$)	Other men ($n = 351$)	Difference (95% confidence interval)	p-value
Height (m)	1.71	1.72	−0.01 (−0.03 to 0.01)	0.22
Weight (kg)	84	78	5.9 (2.7 to 9.1)	0.0004
BMI (kg/m^2)	28.9	26.5	2.3 (1.4 to 3.3)	< 0.0001
Waist to hip ratio (%)	95.7	93.3	2.4 (0.9 to 3.9)	0.002
Birthweight (kg)	3.4	3.6	−0.2 (−0.4 to −0.1)	0.004
Weight at 1 year of age (kg)	9.9	10.3	−0.4 (−0.7 to −0.1)	0.02
Number of teeth at 1 year of age	6.0	6.9	−0.9 (−1.6 to −0.1)	0.02

Table 2. Percentages of men in the Hertfordshire study with syndrome X according to birthweight

Birthweight (kg)	Total number of men	Number (%) with syndrome X	Odds ratio[a] (95% confidence interval)
≤ 2.50	20	6 (30)	18 (2.6 to 118)
− 2.95	54	10 (19)	8.4 (1.5 to 49)
− 3.41	114	19 (17)	8.5 (1.5 to 46)
− 3.86	123	15 (12)	4.9 (0.9 to 27)
− 4.31	64	4 (6)	2.2 (0.3 to 14)
> 4.31	32	2 (6)	1.0
Total	407	56 (14)	

[a] Odds ratio adjusted for BMI (χ^2 for trend = 16.0, $p < 0.001$)

Table 3. Mean values of plasma insulin, proinsulin, serum lipids, plasminogen activator inhibitor, fibrinogen and factor VII in men in Hertfordshire with syndrome X

	Syndrome X ($n = 56$)	Other men ($n = 351$)	p-value[a]
2-h insulin (pmol/l)	331	136	< 0.0001
Fasting proinsulin (pmol/l)	5.1	2.7	< 0.0001
Fasting 32–33 split proinsulin (pmol/l)	5.5	2.8	< 0.0001
Cholesterol (mmol/l)	6.9	6.6	0.09
LDL-cholesterol (mmol/l)	4.8	4.7	0.52
HDL-cholesterol (mmol/l)	1.08	1.24	0.004
Apolipoprotein A1 (g/l)	1.26	1.30	0.35
Apolipoprotein B (g/l)	1.25	1.07	0.0003
Plasminogen activator inhibitor antigen (ng/ml)	41	22	< 0.0001
Plasminogen activator inhibitor activity (au/ml)	15	8.3	0.0001
Fibrinogen (g/l)	3.19	3.03	0.11
Factor VII (% standard)	116	107	0.08

[a] Adjusted for BMI

and weights at one year were lower, and they had fewer erupted teeth at 1 year of age.

Table 2 shows that the percentage of men with syndrome X fell progressively from 30% in those whose birthweight was 2.5 kg (5.5 pounds) or less, to 6% in those whose birthweight was more than 4.31 kg (9.5 pounds). The corresponding odds ratios, adjusted for BMI, fell from 18 to 1. The odds ratio for the two lowest birthweight groups combined, that is all men who weighed 2.95 kg (6.5 pounds) or less, was 10.5 (95% confidence interval 1.9 to 58).

Table 3 shows that biochemical measurements of the 56 men corresponded to those described for syndrome X [8]. When compared with the other men they had higher 2-h plasma insulin concentrations and lower HDL-cholesterol concentrations. They also had raised fasting proinsulin and 32–33 split proinsulin concentrations, and raised apolipoprotein B and plasminogen activator inhibitor concentrations.

Preston

The ages of the 266 men and women in the Preston study ranged from 46 to 54 years, with a mean of 50 years. Using the same criteria for definition of syndrome X as in Hertfordshire, 10 cases were identified in the Preston sample. The percentage of men and women with the syndrome fell progressively from 10 in those whose birthweight was 2.5 kg (5.5 pounds) or less, to 1 in those whose birthweight was more than 3.41 kg (7.5 pounds). Because the subjects studied in Preston are younger than those in Hertfordshire, and because blood pressure increases with age, we lowered the defining level of systolic blood pressure from 160 to 150 mm Hg. This defined a group of 17 people, 10 men and 7 women, who had impaired glucose tolerance or diabetes, hypertension and a serum triglyceride concentration equal to or above the median value of 1.0 mmol/l for men and 1.3 mmol/l for women. Table 4 shows their biochemical measurements.

In order to compare this group's body size, currently and at birth, with that of the other men and women in the study, it was necessary to adjust for the unequal numbers of men and women. Table 5 shows the adjusted differences between their measurements and those of the other subjects. Men and women with syndrome X were shorter in stature but had higher BMI and waist to hip ratios. This was found when each sex was separately analysed. Men and women also had lower birthweights. Their duration of gestation was 9.7 days less, but even allowing for this their birthweight remained significantly lower ($p = 0.03$). They had smaller head circumferences and lower ponderal indices at birth. There was no difference in their mean placental weight or length at birth. A lower birthweight, head circumference and ponderal index at birth was found in both men and women with syndrome X.

Table 6 shows that the percentage of men and women with syndrome X fell progressively from 13% in those

Table 4. Mean values of plasma insulin, proinsulin, serum lipids, plasminogen activator inhibitor, fibrinogen and factor VII in men and women with syndrome X in the Preston study

	Syndrome X ($n = 17$)	Other subjects ($n = 249$)	p-value[a]
2-h insulin (pmol/l)	354	152	< 0.001
Fasting proinsulin (pmol/l)	5.5	3.1	0.005
Fasting 32–33 split proinsulin (pmol/l)	2.4	1.5	0.01
Cholesterol (mmol/l)	6.9	6.5	0.21
LDL-cholesterol (mmol/l)	4.7	4.4	0.33
HDL-cholesterol (mmol/l)	1.2	1.4	0.11
Apolipoprotein A1 (g/l)	1.3	1.3	0.8
Apolipoprotein B (g/l)	1.3	1.0	0.02
Plasminogen activator inhibitor antigen (ng/ml)	26	15	0.07
Plasminogen activator inhibitor activity (au/ml)	17	12	0.19
Fibrinogen (g/l)	3.12	2.91	0.4
Factor VII (% standard)	122	111	0.3

[a] Adjusted for sex and BMI

Table 5. Difference in mean body size, currently and at birth, between men and women with syndrome X and all other men and women in the Preston study

	Difference (95% confidence interval)	p-value[a]
Height (m)	−0.05 (−0.08 to −0.02)	0.002
Weight (kg)	4.0 (−1.7 to 9.7)	0.17
BMI (kg/m^2)	3.1 (1.2 to 5.1)	0.002
Waist to hip ratio (%)	5.9 (2.6 to 9.3)	0.0007
Birthweight (kg)	−0.4 (−0.7 to −0.1)	0.003
Placental weight (kg)	−0.03 (−0.11 to 0.04)	0.4
Head circumference at birth (cm)	−1.5 (−2.4 to −0.6)	0.001
Length at birth (cm)	−0.8 (−2.1 to 0.6)	0.3
Ponderal index at birth $\left\{\frac{1000 \times \text{birthweight in g}}{[\text{length in cm}]^3}\right\}$	−2.0 (−3.5 to −0.5)	0.01

[a] Adjusted for sex

Table 6. Percentages of men and women in the Preston study with syndrome X according to birthweight

Birthweight (kg)	Total number of men and women	Number (%) with syndrome X	Odds ratio[a] (95% confidence interval)
≤2.50	30	4 (13)	13.5 (1.4–129)
−2.95	55	6 (11)	9.0 (1.0–79)
−3.41	99	6 (6)	5.2 (0.6–44)
>3.41	82	1 (1)	1.0
Total	266	17 (6)	

[a] Odds ratio adjusted for sex and BMI (χ^2 for trend = 7.4, $p = 0.006$)

whose birthweight was 2.5 kg (5.5 pounds) or less, to 1 in those whose birthweight was more than 3.4 kg (7.5 pounds). The corresponding odds ratio, adjusted for BMI, fell from 13 to 1.

Table 7. Percentage of men in the Hertfordshire study and men and women in the Preston study with syndrome X according to social class at birth, current social class, smoking history and alcohol consumption

	Hertfordshire	Preston	
		Men	Women
Social class at birth			
I, II, III Non-manual	18 (9)	6 (2)	8 (3)
III Manual	12 (15)	8 (5)	7 (3)
IV, V	14 (28)	9 (3)	0 (0)
Current social class			
I, II, III Non-manual	11 (13)	8 (4)	4 (3)
III Manual	15 (28)	5 (3)	25 (1)
IV, V	14 (14)	11 (3)	7 (3)
Smoking history			
Never smoked	13 (9)	7 (2)	5 (3)
Ex-smoker	14 (32)	9 (5)	5 (1)
Current smoker	14 (15)	6 (3)	8 (3)
Alcohol consumption[a]			
Low	16 (17)	12 (4)	5 (2)
Moderate	12 (20)	4 (1)	6 (4)
High	15 (19)	6 (5)	5 (1)

[a] Low = 0 units/week; Moderate = 1–7 units/week; High = >7 units/week, 1 unit = 10 ml ethanol.
Figures in parentheses are number of people with syndrome X

Confounding variables

In Hertfordshire and Preston the prevalence of syndrome X did not vary with cigarette smoking, alcohol consumption, or with social class at birth (Table 7). In Hertfordshire a higher percentage of men with syndrome X were currently of low social class but this was a weak association and adjustment for it had little effect on the trends in Table 2. The relation between syndrome X and birthweight is present in each social class, defined currently or at birth, in Hertfordshire and Preston.

Discussion

We have identified men and women who have impaired glucose tolerance or Type 2 diabetes, together with hypertension and raised fasting serum triglyceride concentrations. We defined elevated triglyceride concentrations as those above the median. Notwithstanding this relatively low cut-off point the men and women thus defined as having syndrome X have the other characteristics, elevated plasma insulin and decreased HDL-cholesterol concentrations, which together comprise syndrome X [8]. Consistent with findings in other studies they also have high BMI and waist to hip ratios and high serum apolipoprotein B and plasminogen activator inhibitor concentrations [9, 26].

The prevalence of syndrome X was strongly related to birthweight. It fell progressively in both men and women from those who had the lowest to those who had the highest birthweights. Of the 64-year-old men whose birthweights were 2.95 kg (6.5 pounds) or less, 22% had the syndrome. Their risk of developing the syndrome was more than 10 times greater than that of men whose birth-

weights were more than 4.31 kg (9.5 pounds). The association of syndrome X and low birthweight was independent of possible confounding variables including cigarette smoking, alcohol consumption and social class currently or at birth. In Hertfordshire, a rural area, birthweight is unrelated to social class [27]. It is unlikely that an unknown confounding variable related to adult lifestyle would produce the large and graded relation between relative risk of syndrome X and birthweight. Such a confounding variable would have a stronger effect on the risk of syndrome X than any variable hitherto identified and its existence is likely to have been known already, or at least suspected.

The study was based on samples of people who still lived in the area where they were born. They may have differed from those who moved to other places. However, our analysis was based on internal comparisons and selection bias would be introduced only if the relationship between fetal growth and syndrome X differed in the two groups; this is unlikely. The same arguments apply to possible selection bias due to unwillingness to participate in the studies. The study samples also represent people who survive into middle-age. It seems likely that people who survive will have a lower incidence of hypertension, diabetes and other disorders than people who die prematurely. Our findings might therefore underestimate the strength of associations with fetal growth.

The men in Hertfordshire with syndrome X were characterised by low birthweight, low weight at 1 year of age and delayed dental eruption at 1 year of age. The mean and women in Preston with syndrome X were characterised by low birthweight, which was not due to shortened gestation, and by small head circumference and low ponderal index at birth. In a previous analysis of data from Preston, we have shown that there are two groups of babies who develop high blood pressure as adults [28]. One group is those who have below-average birthweight and head circumference and are thin at birth as measured by a low ponderal index. We have now shown that these babies are also liable to develop syndrome X. The other group is those who have above-average birthweight and head circumference but below-average length at birth. These babies do not appear to develop syndrome X although they may develop other abnormalities, including raised plasma fibrinogen concentrations [4].

Insulin resistance has been proposed as the abnormality which underlies syndrome X. It is suggested that hyperinsulinaemia may not only lead to obesity and abnormal plasma lipid and plasminogen activator inhibitor concentrations but could raise blood pressure through a number of mechanisms, including renal sodium retention and altered sodium handling by the arterial smooth muscle cells [10]. However, this view is not consistent with a number of observations as a recent paper by Jarrett [29] points out. Our findings indicate that Type 2 diabetes and hypertension have a common origin in sub-optimal development *in utero*. We have previously suggested that an association between reduced fetal growth and Type 2 diabetes reflects impaired development of the endocrine pancreas during a critical early period with consequent reduced ability to secrete insulin [1]. Similarly the association between reduced fetal growth and later hypertension may reflect an early change in blood vessel development [4]. In a hypothesis which attempts to unify these observations, we proposed that a variety of long-term changes in organ function may arise from different types and time-scales of poor fetal and infant growth and development [13, 27]. Thus the variable components of syndrome X, including defective beta-cell function, hypertension, hyperlipidaemia and insulin resistance may be programmed [30] by changes in the intrauterine and early infant environment. The relative contributions of insulin deficiency and insulin resistance to the production of Type 2 diabetes may also vary according to the spectrum of changes in the environment in early life.

The observation that syndrome X is associated with small head circumference as well as below-average birthweight suggests that the influences which programme syndrome X may act early in gestation. Little is known about the nature of these influences, although we suspect that nutrition is important [27]. Nor do we know whether they programme the disorder by modifying gene expression, cell numbers or organ structure. They produce, however, a marked reduction in fetal and infant growth. A consistent feature of the studies which have linked fetal and infant growth to adult cardiovascular disease and diabetes, is that the relationships between early growth and adult disease are continuous [27]. In keeping with this the risk of syndrome X falls progressively up to the highest values of birthweight. The influences which programme syndrome X must therefore act across the whole range of fetal growth. If the criteria for successful fetal growth include adult health and longevity, we may no longer be entitled to assume that a baby of average birthweight has achieved optimal growth.

In conclusion, we suggest that syndrome X should be re-named "the small-baby syndrome".

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References

1. Hales CN, Barker DJP, Clark PMS et al. (1991) Fetal and infant growth and impaired glucose tolerance at age 64 years. BMJ 303: 1019–1022

2. Robinson S, Walton RJ, Clark PM, Barker DJP, Hales CN, Osmond C (1992) The relation of fetal growth to plasma glucose in young men. Diabetologia 35: 444–446
3. Barker DJP, Osmond C, Golding J, Kuh D, Wadsworth MEJ (1989) Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ 298: 564–567
4. Barker DJP, Bull AR, Osmond C, Simmonds SJ (1990) Fetal and placental size and risk of hypertension in adult life. BMJ 301: 259–262
5. Barker DJP, Meade TW, Fall CHD et al. (1992) Relation of fetal and infant growth to plasma fibrinogen and factor VII concentrations in adult life. BMJ 304: 148–152
6. Stamler J, Rhomberg P, Schroenberger JA et al. (1975) Multivariate analysis of the relationship of seven variables to blood pressure: findings of the Chicago Heart Association detection project in industry. 1967–72. J Chron Dis 28: 527–548
7. Modan M, Halkin H, Almog S et al. (1985) Hyperinsulinaemia: a link between hypertension obesity and glucose intolerance. J Clin Invest 75: 809–817
8. Reaven GM (1988) Role of insulin resistance in human disease. Diabetes 37: 1595–1607
9. Ferrannini E, Haffner SM, Mitchell BD, Stern MP (1991) Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome. Diabetologia 34: 416–422
10. Yudkin J (1991) Hypertension and non-insulin dependent diabetes. BMJ 303: 730–731
11. Fontbonne A, Charles MA, Thibult N et al. (1991) Hyperinsulinaemia as a predictor of coronary heart disease mortality in a healthy population: the Paris Prospective Study, 15-year follow-up. Diabetologia 34: 356–361
12. Foster DW (1989) Insulin resistance, a secret killer? N Engl J Med 320: 733–734
13. Hales CN, Barker DJP (1992) Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 35: 595–601
14. Barker DJP, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO (1991) The relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. BMJ 303: 671–675
15. Kunst A, Draeger B, Ziegenhorn J (1983) UV-methods with hexokinase and glucose-6-phosphate dehydrogenase. In: Bergmeyer HU (ed) Methods of enzymatic analysis, Vol VI. Weinheim Verlag Chemie, Deerfield, pp 163–172
16. Sobey WJ, Beer SF, Carrington CA, Gray IP et al. (1989) Sensitive and specific two-site immuno-radiometric assays for human insulin, proinsulin, 65–66 split and 32–33 split proinsulins. Biochem J 260: 535–541
17. Alpha B, Cox L, Crowther N, Clark PMS, Hales CN (1992) Sensitive amplified immunoenzymometric assays (IEMA) for human insulin and intact proinsulin. Eur J Clin Chem Biochem 30: 27–32
18. Allain CC, Poon LS, Chan CSG, Richmond W, Fu PC (1974) Enzymatic determination of serum total cholesterol. Clin Chem 20: 470–475
19. Lie AF, Schmitz JM, Pierre KJ, Gochman N (1976) Cholesterol oxidase-based determination by continuous flow analysis of total and free cholesterol in serum. Clin Chem 22: 1627–1630
20. Lopes-Virella MF, Stone P, Ellis S, Colwell JA (1977) Cholesterol determination in high density lipoproteins separated by three different methods. Clin Chem 23: 882–884
21. Fossati P, Prencipe L (1982) Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. Clin Chem 28: 2077–2080
22. Friedwald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 18: 499–502
23. Bhatnagar D, Durrington PN (1991) Clinical value of apolipoprotein measurement. Ann Clin Biochem 28: 427–437
24. Clauss A (1957) Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. Acta Haematol (Basel) 17: 237–246
25. Brozovic M, Stirling Y, Harricks C, North WRS, Meade TW (1974) Factor VII in an industrial population. Br J Haematol 28: 381–391
26. Sundell IB, Nilsson TK, Hallmans G, Hellsten G, Dahlen GH (1989) Interrelationships between plasma levels of plasminogen activator inhibitor, tissue plasminogen activator, lipoprotein (a), and established cardiovascular risk factors in a North Swedish population. Atherosclerosis 80: 9–16
27. Barker DJP (ed) (1992) Fetal and infant origins of adult disease, 1st edn. British Medical Journal, London
28. Barker DJP, Godfrey KM, Osmond C, Bull A (1992) The relation of fetal length, ponderal index and head circumference to blood pressure and the risk of hypertension in adult life. Paediatr Perinat Epidemiol 6: 35–44
29. Jarrett RJ (1992) In defence of insulin; a critique of syndrome X. Lancet 340: 469–471
30. Lucas A (1991) Programming by early nutrition in man. In: Bock GR, Whelan J (eds) The childhood environment and adult disease. Ciba Foundation Symposium 156. John Wiley, Chichester pp 38–55

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