Risk of cardiovascular disease measured by carotid intima-media thickness at age 49-51: lifecourse study

Douglas Lamont, Louise Parker, Martin White, Nigel Unwin, Stuart M A Bennett, Melanie Cohen, David Richardson, Heather O Dickinson, Ashley Adamson, K G M M Alberti, Alan W Craft

Abstract

Objective To quantify the direct and indirect effects of fetal life, childhood, and adult life on risk of cardiovascular disease at age 49-51 years.

Design Follow up study of the "Newcastle thousand families" birth cohort established in 1947.

Participants 154 men and 193 women who completed a health and lifestyle questionnaire and attended for clinical examination between October 1996 and December 1998.

Main outcome measures Correlations between mean intima-media thickness of the carotid artery (carotid intima-media thickness) and family history, birth weight, and socioeconomic position around birth; socioeconomic position, growth, illness, and adverse life events in childhood; and adult socioeconomic position, lifestyle, and biological risk markers. Proportions of variance in carotid intima-media thickness that were accounted for by each stage of the lifecourse.

Results Socioeconomic position at birth and birth weight were negatively associated with carotid intima-media thickness, although only social class at birth in women was a statistically significant covariate independent of adult lifestyle. These early life variables accounted directly for 2.2% of total variance in men and 2.0% in women. More variation in carotid intima-media thickness was explained by adult socioeconomic position and lifestyle, which accounted directly and indirectly for 3.4% of variance in men (95% confidence interval 0.5% to 6.2%) and 7.6% in women (2.1% to 13.0%). Biological risk markers measured in adulthood independently accounted for a further 9.5% of variance in men (2.4% to 14.2%) and 4.9% in women (1.6% to 7.4%).

Conclusions Adult lifestyle and biological risk markers were the most important determinants of the cardiovascular health of the study members of the Newcastle thousand families cohort at age 49-51 years. The limited overall effect of early life factors may reflect the postwar birth year of this cohort.

Introduction

Risk of disease in later life may be "programmed" by impaired development in utero due to suboptimal fetal nutrition,¹ but infant and childhood experience

may also determine adult health and risk of disease independently of factors operating in fetal life or adulthood.²⁻³ The antecedents of adult disease should therefore be studied across the whole lifecourse.⁴ The "Newcastle thousand families" cohort—all 1142 children born in May and June 1947 to mothers resident in the city of Newcastle upon Tyne—provides such an opportunity. Two thirds of these children were followed to the age of 15 years, and detailed information was collected on their health, growth, and socioeconomic circumstances.⁵

We used these early life data and recent information on the health and lifestyle of the study members as adults to quantify the direct and indirect effects⁶ of characteristics of fetal life, childhood, and adult life on risk of cardiovascular disease, as measured by the intima-media thickness of the carotid artery (carotid intima-media thickness) at age 49-51 years. Carotid intima-media thickness is an established measure of preclinical atherosclerosis⁷ and a predictor of incident coronary heart disease and stroke.⁸⁻⁹

Participants and methods

Participants were cohort members who either contacted the project team in response to media publicity or were traced through the NHS central register. Data on fetal life, infancy, and childhood were abstracted from existing records. Data on adult health and lifestyle were obtained from questionnaires completed by the participants between October 1996 and December 1998. Biological risk markers were measured over the same period at the Royal Victoria Infirmary, Newcastle. Ethical approval for the study was obtained from the local research ethics committees.

Clinical examination and laboratory procedures

Carotid intima-media thickness was measured bilaterally by B mode ultrasonography (7 MHz linear array, Acuson 128/XP-10) at three locations in the common and internal carotid arteries¹⁰ and averaged over the six sites. Height, weight, and waist and hip circumferences were measured according to the protocol of the World Health Organisation monitoring trends and determinants in cardiovascular disease (MONICA) project.¹¹ Blood pressure was measured according to the guidelines of the British Hypertension Society.¹²

Department of Child Health, University of Newcastle, Sir James Spence Institute of Child Health, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP

Douglas Lamont
senior research associate in epidemiology

Louise Parker
senior lecturer in epidemiology

Melanie Cohen
research associate

Heather O Dickinson
senior research associate

Alan W Craft
professor

Department of Epidemiology and Public Health, School of Health Care Sciences, Medical School, University of Newcastle, Newcastle upon Tyne NE1 4HH

Martin White
senior lecturer in public health

Nigel Unwin
senior lecturer in epidemiology

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Additional acknowledgments and a table detailing the representativeness of the cohort by weight and social class at birth appear on the BMJ's website

www.bmj.com

Department of
Medicine, Medical
School, University
of Newcastle

Nigel Unwin
senior lecturer

Stuart M A Bennett
clinical research
associate

K G M M Alberti
professor

Department of
Radiology, Royal
Victoria Infirmary,
Newcastle

David Richardson
consultant

Human Nutrition
Research Centre,
University of
Newcastle

Ashley Adamson
lecturer

Correspondence to:
D Lamont
d.w.lamont@ncl.
ac.uk

A 12 lead electrocardiogram was recorded and Minnesota coded.¹³

The concentrations of total cholesterol, high density lipoprotein cholesterol, and triglycerides in serum were measured directly using standard enzymatic methods, and the concentration of low density lipoprotein cholesterol was calculated.¹⁴ Plasma glucose concentration after an oral glucose load of 75 g was measured immediately with an analyser (YSI 2300 Stat Plus, Yellow Springs Instruments, Farnborough, UK). Serum insulin concentration was determined by enzyme linked immunosorbent assay (ELISA). Plasma fibrinogen concentration was derived from prothrombin time using an automatic coagulator.

Measurement of early life experience

Relevant family history was defined as death from cardiovascular disease or clinically diagnosed angina, ischaemic heart disease, or stroke in a parent or sibling before the age of 55 years in men and 65 years in women.¹⁵ Socioeconomic status at birth was measured by father's occupational social class, and at ages 5 and 10 years by that of the main wage earner of the household. Housing conditions at birth and at ages 5 and 10 years were scored for the presence of up to three or more of: overcrowding; lack of hot water; shared toilet; and dampness or poor repair. Experience of adverse life events in childhood (from birth to age 15 years) was scored for the presence of up to two or more of: parental divorce or separation; death of a parent; parental incapacity through illness; serious debt; and parental criminal activity or cruelty. The number of recorded episodes of infectious illness from birth to age 15 years was calculated.

Growth data were converted to standard deviation scores comparative to contemporary growth standards.^{16 17} Birth weights were adjusted for gestational age.¹⁸ Catch up growth in childhood¹⁹ was measured as the difference in standard deviation scores for birth weight and height at age 49-51 years, adjusted for achieved adult height and birth weight.²⁰

Measurement of adult socioeconomic position and lifestyle

Occupational social class of the main wage earner in the household, the number of pack years of cigarettes smoked, and four categories²¹ of self reported alcohol consumption were derived from questionnaire data. Responses to the European prospective investigation of causes and nutrition (EPIC) food frequency questionnaire²² were analysed to provide continuous estimates of the proportion of total dietary energy accounted for by fatty acids. Classification of physical activity and exercise level was based on that used in the Medical Research Council's national survey of health and development.²³

Statistical analysis

Twins were excluded from all analyses. Measures of glucose, insulin, fibrinogen, high density lipoprotein cholesterol, and triglyceride concentration had skewed distributions and were log transformed. Values of carotid intima-media thickness for each value of all covariates were approximately normally distributed and homoscedastic and were not transformed. Physical inactivity and family history were defined as binary variables. Exercise level, alcohol consumption, adverse life events in childhood, and all measures of social class and housing conditions were defined as ordinal variables and assessed for trend. Missing values were imputed by multiple regression.²⁴

Variables were grouped within a conceptual framework²⁵ according to stage of lifecourse (figure). Associations between carotid intima-media thickness and individual explanatory variables were estimated by multiple linear regression. The percentage of total variance in carotid intima-media thickness accounted for by each group directly (pathways 1-5 on figure) was estimated by the difference in R^2 between models with and without the group of interest and including all other variables. The overall contribution of early life variables—both directly (pathways 1-3) and indirectly through adult lifestyle (pathway C)—and biological risk markers (pathway D) was estimated by R^2 from a model including these variables alone. The overall contribution

Table 1 Descriptive statistics for continuous variables

Variable	Men				Women			
	No of participants*	Range	Mean (SD)	Median (interquartile range)	No of participants*	Range	Mean (SD)	Median (interquartile range)
Carotid intima-media thickness (mm)	154	0.55-1.60	0.80 (0.17)	0.76 (0.68-0.87)	193	0.38-1.28	0.74 (0.15)	0.72 (0.65-0.80)
Cigarette smoking (pack years)	152	0.1-73†	23.7 (16.9)†	22.1 (8.3-33.5)†	193	0.1-40.5†	16.1 (10.8)†	16.6 (5.7-24.0)†
Total energy from fat (%)	149	18.7-49.4	33.8 (5.9)	34.5 (29.5-38.0)	184	18.0-50.8	32.4 (6.3)	32.6 (28.7-36.7)
Waist to hip ratio	154	0.78-1.08	0.96 (0.06)	0.95 (0.92-0.99)	193	0.68-0.97	0.80 (0.06)	0.79 (0.75-0.84)
Systolic blood pressure (mmHg)‡	139	70-185	127.0 (15.9)	125 (118-135)	170	99-186	122.5 (14.9)	120.5 (111-130)
Concentrations:								
Serum low density lipoprotein cholesterol (mmol/l)‡§	152	1.20-8.06	4.06 (1.34)	4.00 (3.20-4.89)	191	0.38-7.55	3.67 (1.24)	3.50 (2.85-4.46)
Serum high density lipoprotein cholesterol (mmol/l)‡§	152	0.47-2.10	0.96¶	0.99 (0.79-1.18)	191	0.51-2.53	1.14¶	1.18 (0.88-1.40)
Serum triglycerides (mmol/l)	152	0.31-9.64	1.23¶	1.25 (0.79-1.83)	191	0.25-3.60	0.93¶	0.88 (0.63-1.35)
Plasma fibrinogen (g/l)‡	154	1.4-5.0	2.81¶	2.75 (2.40-3.20)	189	1.3-5.0	2.95¶	2.90 (2.50-3.50)
2 Hour plasma glucose (mmol/l)§	151	2.31-13.30	5.51¶	5.54 (4.77-6.45)	189	3.23-11.50	5.54¶	5.72 (4.59-6.45)
Fasting serum insulin (mU/l)§	148	1.4-29.6	7.88¶	7.7 (5.65-12.0)	185	1.2-23.7	6.19¶	6.0 (4.5-8.6)
Birth weight (kg)	154	1.93-4.65	3.43 (0.47)	3.46 (3.12-3.74)	193	2.15-4.88	3.38 (0.52)	3.37 (3.01-3.74)
Episodes of infectious illness in childhood	131	3-50	17.1 (8.5)	15 (10-22)	162	5-47	17.1 (7.6)	16 (12-21)

*Excludes twins. †Excludes 50 men and 87 women who had never smoked.

‡Measurements of lipids, fibrinogen, and blood pressure exclude participants taking lipid lowering drugs, warfarin, or antihypertensives respectively.

§Measurements of lipids, insulin, and glucose exclude participants taking drugs for diabetes. ¶Mean of log transformed values (geometric mean of raw data).

Conceptual framework for fetal, infant, childhood, and adult influences on risk of cardiovascular disease at age 49-51 years. Pathways 1-5 are direct effects of each stage of lifecourse on carotid intima-media thickness, and pathways A-D are indirect effects mediated through later stages of lifecourse. Adult lifestyle and behaviour variables are cigarette smoking, alcohol consumption, exercise level, physical inactivity, and percentage total energy from fat. Adult biological risk markers are waist to hip ratio, systolic blood pressure, concentrations of serum low density lipoprotein cholesterol, serum high density lipoprotein cholesterol, serum triglycerides, plasma fibrinogen, 2 hour plasma glucose, and fasting insulin at time of screening

of adult lifestyle variables, both directly (pathway 4) and indirectly through biological risk markers (pathway D), was estimated by the difference in R^2 between models with and without this group and including all other variables except risk markers. Statistical analyses were carried out with STATA statistical software (release 5.0, Stata, College Station, TX).

Results

Of the original 1142 cohort members, 832 were traced (89.3% of the surviving sample of 932 children whose families remained in Newcastle for at least the first year). Of these, 574 (68.9%) completed the questionnaire and 412 (49.5%) attended for clinical examination. Ultrasound measurements of the carotid artery were available for 347 singleton study members (154 men and 193 women). This sample did not differ significantly from the original cohort in terms of birth weight ($\chi^2=5.50$ (5 df), $P=0.36$) and social class at birth ($\chi^2=7.14$ (4 df), $P=0.13$).

Mean carotid intima-media thickness was 0.77 mm (0.80 mm in men and 0.74 mm in women) (table 1).

Overall, 29 participants had electrocardiographic evidence of cardiac ischaemia (Minnesota codes 1.1-1.3, 4.1-4.3, 5.1-5.3, 7.1). Forty five participants had definite or possible angina and 27 had severe chest pain according to the Rose questionnaire.²⁶ Mean carotid intima-media thickness was 0.79 mm (95% confidence interval 0.75 to 0.83) in 35 men and 36 women with electrocardiographic evidence of ischaemia or who self reported angina or severe chest pain, or both, and 0.76 mm (0.74 to 0.78) in those who were asymptomatic (one tailed, $P=0.06$).

Fetal, infant, and childhood influences

Social class at birth in women and birth weight in men displayed the strongest associations with carotid intima-media thickness (unadjusted standardised regression coefficients $b=-0.16$, $P=0.02$ and $b=-0.17$, $P=0.03$ respectively) (tables 2 and 3). All other early life variables, including social class and

Table 2 Descriptive statistics for categorical variables

Variable	No (%) of men n=149	No (%) of women n=190
Social class at birth:		
1, 2	19 (13)	16 (8)
3	84 (56)	128 (67)
4, 5	46 (31)	46 (24)
Social class at age 5 years:		
1, 2	11 (8)	12 (7)
3N	15 (11)	21 (12)
3M	61 (44)	75 (44)
4, 5	51 (37)	62 (37)
Social class in adulthood:		
1, 2	70 (48)	94 (52)
3N	15 (10)	26 (14)
3M	45 (31)	33 (18)
4, 5	16 (11)	27 (15)
Housing conditions score at birth*:		
0	71 (47)	92 (48)
1	37 (24)	54 (28)
2	28 (18)	23 (12)
3 or more	16 (11)	24 (12)
Housing conditions score at age 5 years*:		
0	70 (50)	89 (52)
1	41 (30)	50 (29)
2	17 (12)	20 (12)
≥3	11 (8)	13 (8)
Adverse life events in childhood:		
None	82 (63)	90 (56)
1	39 (30)	51 (32)
≥2	10 (8)	21 (13)
Family history of cardiovascular disease		
	n=152	n=193
	28 (18)	47 (24)
Exercise level at age 49-51 years:		
	n=152	n=192
Most active	24 (16)	28 (15)
Less active	32 (21)	49 (26)
Least active	96 (63)	115 (60)
Physically inactive at age 49-51 years		
	n=150	n=186
	12 (8)	25 (13)
Alcohol consumption†:		
	n=152	n=191
None	11 (7)	26 (14)
Light	56 (37)	75 (39)
Moderate	57 (38)	85 (45)
Heavy	28 (18)	5 (3)

*None to three or more of: overcrowding, lack of hot water, shared toilet, and dampness or poor repair.

†Light drinking was defined as up to 5 units of alcohol per week for women (10 units for men) and moderate drinking up to 21 units for women and 28 units for men.

Table 3 Fetal, infant, and childhood influences on carotid intima-media thickness in men and women at age 49-51 years. Values are standardised regression coefficients (95% confidence intervals)

Independent variable	Unadjusted in men (n=154)	Unadjusted in women (n=193)
Fetal life		
Self reported family history of angina, heart condition, or stroke	-0.09 (-0.25 to 0.07)	-0.04 (-0.19 to 0.10)
Social class at birth†	-0.05 (-0.21 to 0.11)	-0.16 (-0.30 to -0.02)*
Poor housing conditions at birth	0.10 (-0.06 to 0.26)	0.08 (-0.07 to 0.22)
Birth weight‡	-0.17 (-0.33 to -0.02)*	-0.04 (-0.18 to 0.10)
Infancy and childhood		
Social class at age 5 years	0.02 (-0.14 to 0.18)	-0.09 (-0.24 to 0.05)
Poor housing conditions at age 5 years	-0.06 (-0.22 to 0.10)	0.02 (-0.12 to 0.17)
Adverse life events in childhood	0.06 (-0.10 to 0.22)	0.09 (-0.06 to 0.23)
Childhood infections	-0.01 (-0.17 to 0.15)	-0.08 (-0.22 to 0.07)
Catch up growth in childhood§	0.12 (-0.04 to 0.28)	0.04 (-0.11 to 0.18)

Regression coefficients expressed as standard deviation unit change in dependent variable produced by one standard deviation change in independent variable. Adjusted coefficients take account of significant and borderline significant covariates only ($P < 0.10$ to enter, $P \geq 0.10$ to remove). Adjustment for early life and adult lifestyle takes account of other variables in same group, interaction between family history, fetal and childhood components (pathways A and B on figure) and of indirect effects mediated through adult socioeconomic position and lifestyle (pathway C). Adjustment for lifecourse also takes account of indirect effects mediated through adult biological risk markers (pathway D).

* $P < 0.05$.

†In women: -0.14 (-0.28 to -0.01)* when adjusted for early life and adult lifestyle and -0.15 (-0.29 to -0.02)* when adjusted for lifecourse.

‡In men: -0.16 (-0.31 to 0.00) when adjusted for early life and adult lifestyle.

§Growth from birth to adulthood adjusted for achieved adult height and birth weight.

housing conditions at age 10 years (not shown), were unrelated to carotid intima-media thickness.

Social class at birth in women remained a statistically significant determinant of risk ($P = 0.03$) after adjustment for adult lifestyle and biological risk markers. Birth weight in men, however, although retaining borderline significance after adjustment for adult socioeconomic position and lifestyle ($P = 0.05$), was not significantly associated with carotid intima-media thickness independently of other biological risk markers ($P > 0.10$).

Socioeconomic position, lifestyle, and biological risk markers in adulthood

Waist to hip ratio and pack years of cigarette smoking in women were significant predictors of risk of cardiovascular disease (unadjusted $b = 0.24$, $P = < 0.01$ and $b = 0.20$, $P = < 0.01$ respectively) (table 4) and remained so after adjustment for other significant risk factors. Exercise level was a significant predictor overall but not after adjustment. Carotid intima-media thickness in men was significantly related to systolic blood pressure and two hour glucose concentration, and these associations changed little after adjustment. After controlling for other lifestyle variables and risk markers, however, strong associations overall with waist to hip ratio, exercise level, and insulin and triglyceride concentrations became non-significant.

Contribution of each stage of the lifecourse

A family history of cardiovascular disease independently accounted for only 0.8% of total variance in carotid intima-media thickness in men and for 0.5% in women (table 5). Socioeconomic position at birth and birth weight accounted for a further 2.2% and 2.0% of variance respectively. The direct effects of circumstances and experience in infancy and childhood contributed 3.2% of variance in men and 2.2% in women. The overall contribution of all early life variables, including indirect effects mediated through adult socioeconomic position, lifestyle, and biological risk markers, was 9.2% for men and 4.7% for women.

Most variation in carotid intima-media thickness was explained exclusively by factors operating or measured in adulthood. Biological risk markers such as hyperlipidaemia, hypertension, and impaired glucose tolerance independently accounted for 9.5% of variance in men and 4.9% in women. Adult

Table 4 Adult influences on carotid artery intima-media thickness in men and women at age 49-51 years. Values are standardised regression coefficients (95% confidence intervals)

Independent variable	Men (n=154)			Women (n=193)		
	Unadjusted	Adjusted for adulthood	Adjusted for lifecourse	Unadjusted	Adjusted for adulthood	Adjusted for lifecourse
Adult socioeconomic position and lifestyle						
Adult social class	-0.04 (-0.20 to 0.12)			-0.10 (-0.24 to 0.05)		
Cigarette smoking†	0.06 (-0.10 to 0.22)			0.20 (0.06 to 0.34)**	0.17 (0.03 to 0.31)*	0.18 (0.05 to 0.32)**
Exercise level	-0.20 (-0.35 to -0.04)*	-0.13 (-0.28 to 0.02)	-0.13 (-0.28 to 0.02)	-0.17 (-0.31 to -0.03)*	-0.13 (-0.27 to 0.01)	
Physical inactivity	0.08 (-0.08 to 0.24)			0.04 (-0.10 to 0.18)		
Alcohol consumption†	-0.04 (-0.20 to 0.12)			0.06 (-0.08 to 0.20)		
Total energy from fat (%)	0.10 (-0.06 to 0.26)			0.04 (-0.10 to 0.18)		
Adult biological risk markers						
Systolic blood pressure	0.23 (0.07 to 0.39)**	0.20 (0.05 to 0.35)*	0.20 (0.05 to 0.35)*	0.14 (-0.01 to 0.28)		
Waist to hip ratio	0.23 (0.07 to 0.38)**			0.24 (0.10 to 0.37)**	0.21 (0.07 to 0.34)**	0.22 (0.08 to 0.35)**
Concentrations:						
Serum low density lipoprotein cholesterol	0.14 (-0.02 to 0.30)			0.04 (-0.11 to 0.18)		
Serum high density lipoprotein cholesterol‡	-0.10 (-0.26 to 0.06)			-0.07 (-0.21 to 0.07)		
Serum triglycerides‡	0.16 (0.01 to 0.32)*			0.10 (-0.05 to 0.24)		
Plasma fibrinogen‡	0.15 (-0.01 to 0.31)	0.14 (-0.01 to 0.30)	0.14 (-0.01 to 0.30)	0.06 (-0.08 to 0.20)		
2 Hour plasma glucose‡	0.23 (0.07 to 0.39)**	0.19 (0.04 to 0.34)*	0.19 (0.04 to 0.34)*	-0.02 (-0.16 to 0.12)		
Fasting serum insulin‡	0.18 (0.03 to 0.34)*			0.07 (-0.08 to 0.21)		

Regression coefficients expressed as standard deviation unit change in dependent variable produced by one standard deviation change in independent variable. Adjusted coefficients take account of significant and borderline significant covariates only ($P < 0.10$ to enter, $P \geq 0.10$ to remove). Adjustment for adulthood takes account of other variables in same group and of interaction between adult lifestyle and biological risk markers (pathway D on figure). Adjustment for lifecourse also takes account of indirect effects of early life experience (pathway C).

* $P < 0.05$; ** $P < 0.01$.

†Adjusted for whether ever smoked or whether current drinker.

‡Log transformed.

Table 5 Direct and overall contributions to variance in carotid intima-media thickness in men and women at age 49-51 years from circumstances and experiences at each stage of lifecourse. Values are percentage of variance explained (95% confidence intervals)

Source	Men (n=154)	Women (n=193)
1 Self reported family history of cardiovascular disease	0.75 (0.00 to 5.87)	0.46 (0.00 to 3.14)
2 Fetal life (socioeconomic position at birth and birth weight)	2.16 (0.08 to 6.40)	2.00 (0.13 to 5.54)
3 Infancy and childhood (socioeconomic position, adverse life events, illnesses, and growth pattern)	3.20 (0.27 to 6.78)	2.22 (0.21 to 5.04)
Total early life (including indirect effects)	9.15 (2.42 to 12.26)	4.73 (2.12 to 6.68)
4 Adult socioeconomic position and lifestyle*	2.27 (0.42 to 4.04)	5.86 (0.81 to 10.90)
Total adult socioeconomic position and lifestyle (including indirect effects)	3.42 (0.51 to 6.17)	7.56 (2.08 to 12.98)
5 Adult biological risk markers† unrelated to early life experience or adult lifestyle	9.49 (2.38 to 14.21)	4.87 (1.56 to 7.39)

Confidence intervals are bias corrected and are estimated by bootstrapping R^2 statistic on 1000 repeated random samples of same size drawn with replacement from each dataset. Direct contributions from each stage of lifecourse are numbered to correspond with pathways 1-5 on figure. Overall contribution of early life variables includes indirect effects mediated through adult socioeconomic position and lifestyle (pathway C) and adult biological risk markers (pathway D). Overall contribution of adult socioeconomic position and lifestyle includes indirect effects mediated through biological risk markers (pathway D) but excludes early life influences.

*Cigarette smoking, alcohol consumption, exercise level, physical inactivity, and dietary fat intake.

†Waist to hip ratio, systolic blood pressure, concentrations of serum low density lipoprotein cholesterol, high density lipoprotein cholesterol, serum triglycerides, plasma fibrinogen, 2 hour plasma glucose, and fasting insulin at time of screening.

socioeconomic position and lifestyle accounted both directly and indirectly for 3.4% of variance in men and 7.6% in women.

Discussion

Principal finding

Adult lifestyle and biological risk markers measured in adulthood independently accounted for a greater proportion of total variance in carotid intima-media thickness at age 49-51 years than did the direct and indirect contributions of early life experience combined.

Interpretation of results and comparison with other studies

The smaller proportion of total variance accounted for by biological risk markers in women compared with men may reflect the lower risk for cardiovascular disease in this age group. The absence of significant associations with lipid, fibrinogen, glucose, and insulin concentrations in women might also be explained by the possible effects of oestrogen on lipid and glucose metabolism.²⁷ Overall, 68% (132 participants) of women in the sample were either premenopausal or had been receiving hormone replacement therapy for at least two years before screening.

Some of the variance that was independently accounted for by biological risk markers might be explained by tracking from childhood. The mediated effects of adult lifestyle, however, may be underestimated since such self reported variables are less reliably measured. The stronger association between carotid intima-media thickness and cigarette smoking in women is consistent with recent research, which has shown female smokers to be at greater risk of ischaemic heart disease.²⁸

Socioeconomic position at ages 5 and 10 years was unrelated to carotid intima-media thickness. Although there was a significant association between carotid intima-media thickness and social class at birth in women, this effect was not observed in men. Non-significant adjusted associations with birth weight also provide little evidence that suboptimal growth in utero (a marker of suboptimal fetal nutrition) leads to increased intimal thickening of the carotid artery in later life independent of adult lifestyle and risk markers. Several explanations may account for these findings, which differ from many recent reports.

Potential weaknesses of the study

A programming effect that might have been shown by alternative measures of impaired fetal growth, such as placental to fetal weight ratio or ponderal index,^{29, 30} cannot be excluded. We also cannot exclude early life effects that may have been mediated through underestimated aspects of adult lifestyle, although self reported smoking status was validated by measurement of the concentration of exhaled carbon monoxide. Overall, 109 study members (31%) reported dietary energy intakes relative to predicted basal metabolic rate³¹ of less than 1.1 (indicative of underreporting). Lack of information on families who moved out of Newcastle between 1947 and 1962 and an improvement in housing conditions over this period may also have reduced the strength of associations between socioeconomic position in childhood and adult health. Only 43% (360 participants) of those invited attended for ultrasound examination, although this proportion is only slightly lower than that achieved from other traced populations.³²

Differences in study populations

Although Martyn et al³² found a significant negative association between carotid stenosis and birth weight in a cohort born in Sheffield between 1922 and 1926,

What is already known on this topic

Numerous studies have shown statistically significant associations between low birth weight or socioeconomic disadvantage in childhood and adverse adult health outcomes

No studies, however, have quantified the proportion of variation in disease risk accounted for by factors operating in fetal life and at other stages of the lifecourse

What this paper adds

In this follow up study of a cohort of 154 men and 193 women born in Newcastle upon Tyne in 1947, early life variables such as birth weight and socioeconomic position in childhood were less strongly associated with cardiovascular disease risk at age 49-51 years than in other studies

Compared with factors operating in adulthood the independent contributions of circumstances and experiences in early life were small

Adult lifestyles and risk profiles should remain the main focus of intervention for reduction of risk of cardiovascular disease

their analysis was confined to those who remained resident in the city, whereas the Newcastle sample included 25% of the 212 study members traced to addresses outside of the north of England. The limited overall effect of early life factors may also reflect the birth year of this sample. Most cohorts that have shown significant childhood contributions to adult mortality and disease risk are at least 10 years older. They experienced childhood in the prewar rather than postwar period when the dietary and other effects of material disadvantage and unemployment may have been more prevalent and severe.³³

Conclusion

Although it is clearly important to promote good maternal and child health and to reduce the extent of socioeconomic deprivation in childhood, adult life-styles and risk profiles should remain the main focus of intervention for reduction of risk of cardiovascular disease.

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Contributors: LP, AWC, and KGMMA conceived and directed the study and participated in the study design. DL managed the project, carried out all statistical analyses, wrote the first draft of the paper, and coordinated subsequent revisions. LP, MW, NU, SMAB, MC, DR, and AA participated in the study design and contributed to the analysis. HOD provided statistical advice and assistance. MC was involved in administering the health check and questionnaire survey, undertook the tracing of study members, and organised the abstraction of data from the original study archives. SMAB participated in the supervision and execution of the health checks. All authors contributed to the drafting of the final version of the paper. DL and LP will act as guarantors for the paper.

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Retraction

First myocardial infarction in patients of Indian subcontinent and European origin: comparison of risk factors, management, and long term outcome

On 10 January 1998 we published a retraction (1998;316:116) of this paper (1997;314:550-4) requested by the authors on the grounds that examination of the data had revealed inaccuracies and that the conclusions could not be sustained. The University of Leicester, where the work was done, established an inquiry, which has now confirmed that there were significant errors in the data and that the paper's findings were unsound. The errors arose in transcribing data from paper to digital form for statistical analysis, and the individual responsible has been censured. Following this incident the university has introduced a code of practice governing the management and conduct of research.