PSYCHOSOCIAL AND BIOLOGICAL DETERMINANTS OF ILL HEALTH IN RELATION TO DEPRIVATION

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ABSTRACT

Background

Despite public health campaigns and improvements in healthcare, socioeconomic gradients in health and life expectancy persist, and in many cases are becoming more marked – the gradient in coronary heart disease being a prime example. Classic cardiovascular risk factors (e.g. smoking, cholesterol and blood pressure) only partially explain the deprivation effect, and attempts to narrow the health gap by focussing on such risk factors do not appear to be succeeding. There also appear to be socioeconomic differences in uptake of healthy lifestyle advice. The work described in this thesis aimed to expand current understanding of the deprivation-based gap in health and life expectancy, focussing particularly on the socioeconomic gradient in cardiovascular risk.

Methods

Using a cross-sectional, population-based study design based in the Greater Glasgow area, 666 participants were selected on the basis of area-level social deprivation (Scottish Index for Multiple Deprivation ranking). The study was designed to include approximately equal numbers from most deprived and least deprived areas; equal numbers of male and female participants and equal numbers of participants from each age group studied (35-44; 45-54 and 55-64 years). Participants completed an extensive questionnaire on health, lifestyle and early life experiences. Anthropometric measures (height, leg length, weight, waist, hip and thigh circumferences) were recorded. Blood pressure, heart rate and parameters of lung function (Forced Expiratory Volume in 1 second [FEV1] and Forced Vital Capacity [FVC]) were recorded. Psychological assessments (General Health Questionnaire-28, Generalised Self-Efficacy Scale, Sense of Coherence Scale, Beck Hopelessness Scale, Eysenck Personality Scale and Rosenberg Self-Esteem Scale) and assessments of cognitive function (Auditory Verbal Learning Test, Choice Reaction Time and Stroop Test) were undertaken. Fasting blood samples were obtained for classic and emerging cardiovascular risk factors including lipid profile, glucose, insulin, leptin, adiponectin, C-reactive protein, interleukin-6, soluble intercellular adhesion molecule-1, von Willebrand Factor, fibrinogen, D-dimer and tissue plasminogen activator antigen. Carotid ultrasound assessment of intima-media thickness (cIMT), plaque score and arterial stiffness was performed.

Results

Total and low density lipoprotein cholesterol were significantly higher in the least deprived group (both $p<0.0001$). Triglycerides were higher and high density lipoprotein cholesterol lower in the most deprived group (both $p<0.0001$). Fasting glucose, insulin and leptin were higher in the most deprived group. C-reactive protein, interleukin-6 and soluble intercellular adhesion molecule-1 were higher in the most deprived group (all $p<0.0001$). Von Willebrand factor, fibrinogen and D-dimer were higher in the most deprived group. Age- and sex-adjusted cIMT was significantly higher in the most deprived group, but on subgroup analysis this difference was only apparent in the highest age tertile in males ($\geq$56.3 years). Plaque score showed a much more highly significant deprivation difference in the group as a whole ($p<0.0001$). No differences in parameters of arterial stiffness were found between the most deprived and least deprived groups. Neither adjustment for classic nor emerging cardiovascular risk factors, either alone or in combination, abolished the area-level deprivation-based difference in plaque presence or cIMT. Adjustment for early life markers of socioeconomic status in addition to classic cardiovascular risk factors abolished the deprivation-based difference in plaque presence. Further associations between early life factors and health outcomes were noted: lung function (FEV1) and cognitive performance appeared to be influenced by father's occupation, whether the parents/guardians were owner-occupiers or tenants, and by degree of overcrowding; cIMT was modestly related to father's occupation and carotid plaque was related strongly to father's occupation and parental home status. Socioeconomic differences were noted in the impact of personality in determining mental wellbeing, and also in relation to the health behaviours of fruit and vegetable consumption and smoking cessation.

Conclusions

The relationship between social deprivation and health is complex and multifactorial and appears to involve the interplay of early life factors, biological mediators, psychological parameters such as personality and cognitive function, health behaviours and outcomes such as atherosclerosis. Approaches aiming to narrow the deprivation gap in health will need to be designed to take into account this complexity, addressing factors such as early life experiences and personality, as well as the more classically recognised factors such as smoking, cholesterol and blood pressure, if they are to have a chance of succeeding in improving the health of those most in need.

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LIST OF RELEVANT PUBLICATIONS

Deans KA, Bezlyak V, Ford I, Batty GD, Burns H, Cavanagh J, de Groot E, McGinty A, Millar K, Shiels PG, Tannahill C, Velupillai YN, Sattar N and Packard CJ. Differences in atherosclerosis according to area level socioeconomic deprivation: cross sectional, population based study. *BMJ* 2009;339:b4170 doi:10.1136/bmj.b4170

Velupillai YN, Packard CJ, Batty GD, Bezlyak V, Burns H, Cavanagh J, Deans KA, Ford I, McGinty A, Millar K, Sattar N, Shiels P and Tannahill C. Psychological, social and biological determinants of ill health (pSoBid): Study protocol of a population-based study. *BMC Public Health* 2008;8:126

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The pSoBid study was funded by the Glasgow Centre for Population Health, a partnership between NHS Greater Glasgow and Clyde, Glasgow City Council and the University of Glasgow, supported by the Scottish Government. Additional biochemical analyses were funded by Glasgow Royal Infirmary Research Endowment Fund.

DECLARATION

I declare that I am the author of this thesis, and that no part of it has been reported in another thesis. I was involved in the work described in this thesis from the earliest planning stages, and contributed to overall design of the Psychological, Social and Biological Determinants of Ill Health (pSoBid) study, in collaboration with the other members of the pSoBid study group. I was responsible for writing the protocol for carotid ultrasound analysis, and also arranged the repertoire of blood samples to be collected and the protocol for specimen collection, processing and storage. Biochemical analyses were carried out by staff in the Departments of Vascular Biochemistry and Vascular Medicine, University of Glasgow, and the Department of Clinical Biochemistry, Glasgow Royal Infirmary, co-ordinated by myself. I was responsible for training and day-to-day supervision of the research nurses. The majority of the carotid ultrasound scans were performed by one research nurse (Sister Agnes McGinty) with some scans performed by myself. I analysed all ultrasound scans. Statistical analysis was in some cases carried out by me, with some more complex analyses being performed by colleagues in the Robertson Centre for Biostatistics after discussion with myself regarding the statistical approach to be taken. The work reported in this thesis is entirely my own, with the caveat that the work reported in Chapter 8 was led by Professor Chris Packard (Research and Development Director, NHS Greater Glasgow and Clyde) and Professor Keith Millar (Professor of Medical Psychology, University of Glasgow). I collaborated in the work reported in Chapter 8, and it is reported in this thesis by kind permission of Professors Packard and Millar, in order to set the scene of the wider picture surrounding my own work.

Kevin A Deans

ABBREVIATIONS

25-OHD	25-hydroxy vitamin D
AAA	Aspirin for Asymptomatic Atherosclerosis
ACE	Angiotensin converting enzyme
ADMA	Asymmetric dimethylarginine
ALT	Alanine aminotransferase
ARIC	Atherosclerosis Risk in Communities
ASE	American Society of Echocardiography
ASSIGN	Assessing cardiovascular risk using SIGN
AST	Aspartate aminotransferase
AVLT	Auditory verbal learning test
BHS	Beck Hopelessness Scale
BMI	Body mass index
B-mode	Brightness mode
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence intervals
cIMT	Carotid intima-media thickness
CRP	C-reactive protein
CRT	Choice reaction time
CV	Coefficient of variation
CVD	Cardiovascular disease
DICOM	Digital Imaging and Communications in Medicine
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EPIC-Norfolk	European Prospective Investigation of Cancer and Nutrition in Norfolk
EPR	Eysenck Personality Scale
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GHQ-28	General Health Questionnaire-28
GPASS	General Practice Administration System for Scotland
GROS	General Register Office for Scotland
GSS	Generalised Self-Efficacy Scale
HDL	High density lipoprotein
HMW	High molecular weight
HOMA-IR	Homeostasis Model Assessment - Insulin Resistance
HPLC	High performance liquid chromatography
IL-6	Interleukin-6
IMT	Intima-media thickness
IQ	Intelligence quotient
IQR	Interquartile range
ISD Scotland	Information Services Division Scotland

JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
LCCA	Left common carotid artery
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LD	Least deprived
LDL	Low density lipoprotein
LE	Life expectancy
MD	Most deprived
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
M-mode	Movement mode
MONICA	Monitoring of Trends and Determinants in Cardiovascular Disease
MRFIT	Multiple Risk Factor Intervention Trial
NAFLD	Non-alcoholic fatty liver disease
NHS	National Health Service
NHSHS	National Health Service Health Scotland
NICE	National Institute for Health and Clinical Excellence
PAI-1	Plasminogen activator inhibitor-1
pSoBid	Psychological, Social and Biological Determinants of Ill Health Study
PWV	Pulse Wave Velocity
QOF	Quality and Outcomes Framework
RCCA	Right common carotid artery
RR	Relative risk
RSES	Rosenberg Self-Esteem Scale
SD	Standard deviation
SDMA	Symmetric dimethylarginine
SES	Socioeconomic status
sICAM-1	Soluble intercellular adhesion molecule-1
SIGN	Scottish Intercollegiate Guidelines Network
SIMD	Scottish Index of Multiple Deprivation
SoC	Sense of Coherence
SPE	Solid-phase extraction
tPA	Tissue plasminogen activator
VDR	Vitamin D receptor
VLDL	Very low density lipoprotein
vWF	Von Willebrand factor
WOSCOPS	West of Scotland Coronary Prevention Study

CHAPTER 1 – INTRODUCTION

1.1 Introduction – the relationship between social deprivation and ill health

1.1.1 The relationship between social deprivation and life expectancy – a historical perspective

The inverse relationship between social deprivation and life expectancy has long been recognised. A paper published in the Lancet in 1843 observed that there was a strong association between occupation and life expectancy (**Table 1.1)**. The paper concluded by calling for legislation to, "compel the corporations and ground-landlords to make alterations for the comfort and health of those comparatively helpless classes of the community, the artisans and labourers."[1] In more recent times, Watt in 1992 compared mortality in Glasgow with that in Edinburgh. He predicted that in 1989-93 Glasgow men would have a mortality rate equivalent to that of Edinburgh men who were 5.1 years older, with the figure for women being 3.9 years. Commenting that it was unlikely that differences in smoking and diet explained all of these differences, he suggested that the explanation was likely to lie in differences in levels of socioeconomic deprivation between Glasgow and Edinburgh.[2]

1.1.2 The Greater Glasgow story

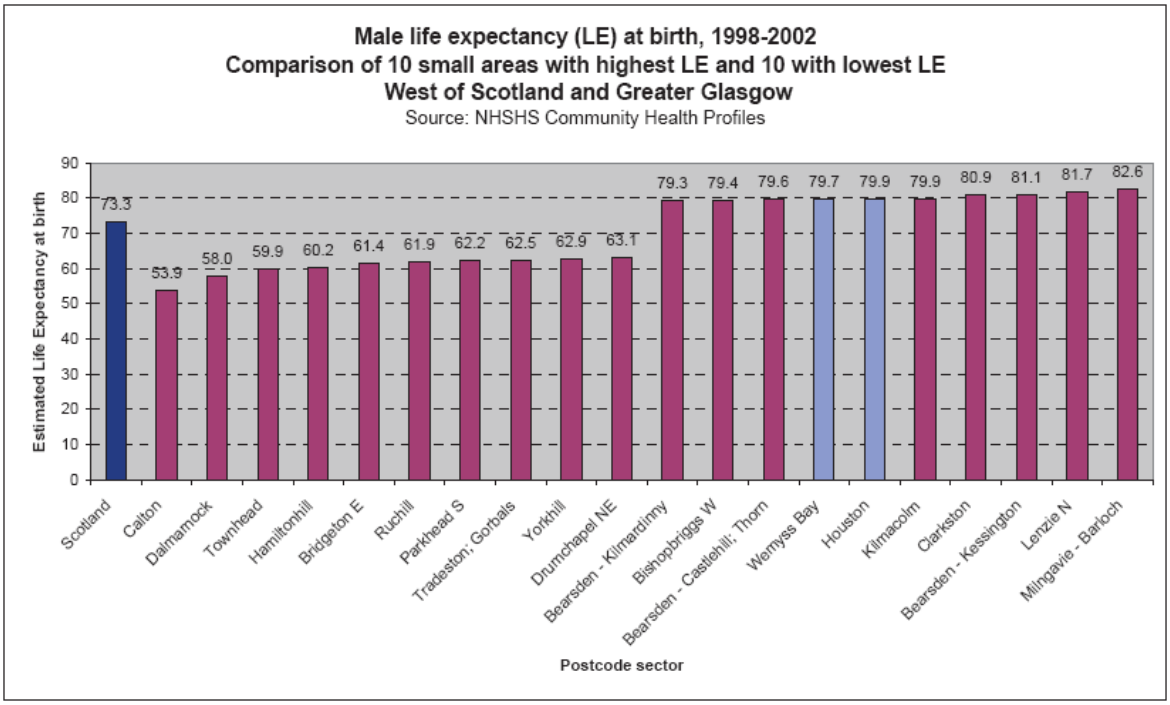
The relationship between social deprivation and life expectancy is most strikingly demonstrated in the Greater Glasgow area of Scotland. At a community level (average population of 70 000 people) male life expectancy at birth varies from 63.5 to 78.7 years. When these areas are further broken down to postcode level areas (average population of 3000 to 5000 people) these differences become even more marked, with male life expectancy varying across Greater Glasgow from 53.9 to 82.6 years **(Figure 1.1)**.[3] Female life expectancy shows similar trends, although with less extreme absolute differences between areas, with life expectancy at birth varying at community level from 74.1 to 82.2 years, and at postcode sector level from 68.8 to 84.4 years.[3]

Table 1.1 Life expectancy by occupation in selected districts and towns, 1843

Districts and towns	Gentry/professional	Farmers/tradesmen	Labourers/artisans
1. Rural and suburban districts			
Rutland	52	41	38
Wiltshire	50	48	33
Kendal Union	45	39	34
Kensington Union	44	29	26
2. Towns			
Bath	55	37	25
Truro	41	33	28
Leeds	44	27	19
Bethnal Green (London)	45	26	16
Manchester	38	20	17
Liverpool	35	22	15

Life expectancy is given in years. Table reconstructed with data from reference [1].

Figure 1.1 Male life expectancy at birth, 1998-2002. Comparison of 10 postcode sectors with highest life expectancy with those with lowest life expectancy in the West of Scotland and Greater Glasgow



Life expectancy is given in years. Areas in dark red are within Greater Glasgow; areas in light blue are other West of Scotland council areas.

From reference [3], reproduced by kind permission of Glasgow Centre for Population Health.

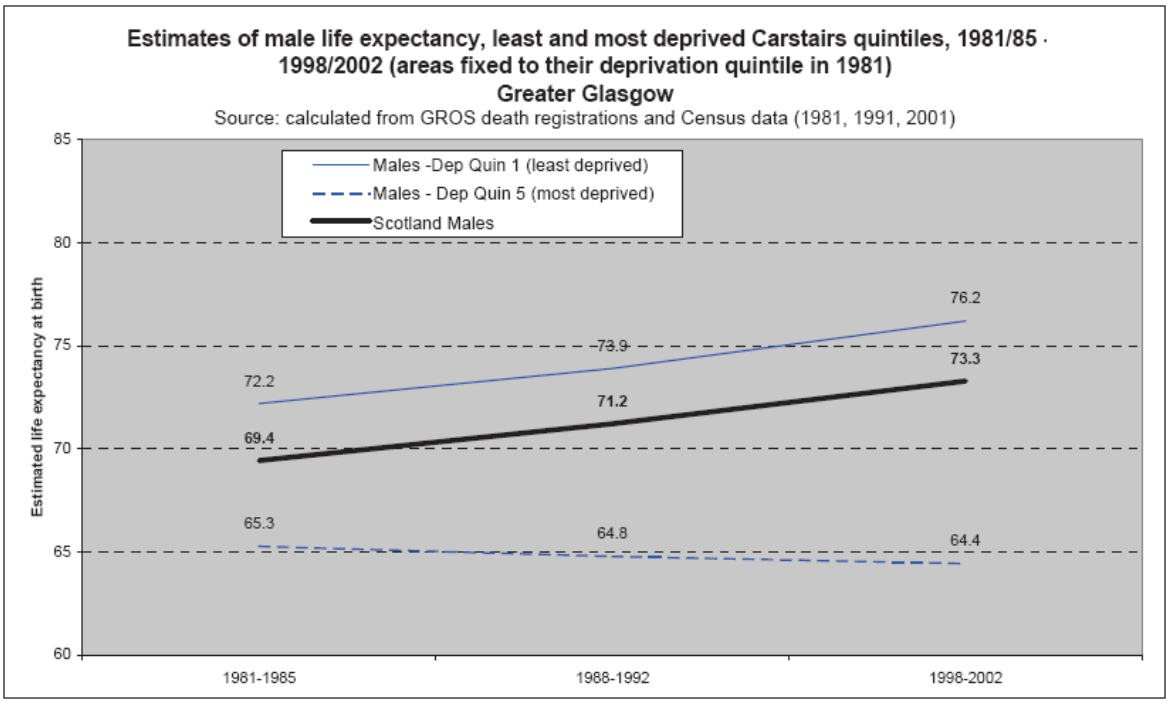
1.1.3 Trends with time

An examination of trends in life expectancy over recent years gives further cause for concern. In Scotland as a whole, from 1981 to 2002 male life expectancy increased from 69.4 years to 73.3 years. However, when the most and least deprived communities in Greater Glasgow (as defined by the Carstairs score)[4] are examined, it can be seen that while male life expectancy in the least deprived areas of Greater Glasgow has been consistently above the Scottish average, and has risen in parallel with the Scottish average, life expectancy in the most deprived areas has fallen over this time period. This has resulted in a significant widening of the difference in life expectancy between most and least deprived areas from 6.9 to 11.8 years **(Figure 1.2)**.[3] A similar, though less pronounced, pattern is seen in females, with the gap in life expectancy having risen from 5.4 to 7.5 years.[3]

1.1.4 Cardiovascular disease as a major cause of death, and its associations with social deprivation

While in Victorian times, epidemics of infectious disease were a common cause of death,[5] in Scotland in 2008 the three most common causes of death were cancer (27% of all deaths), ischaemic (coronary) heart disease (16%) and cerebrovascular disease (stroke) (10%).[6] Although death rates from ischaemic heart disease and stroke have fallen in recent years,[6] cardiovascular disease remains a significant cause of mortality and morbidity. **Figure 1.3** demonstrates that although mortality from heart disease has decreased across all Greater Glasgow communities, there remains significant variation in heart disease mortality across the Greater Glasgow area, with the difference between the highest and lowest death rates (Bridgeton/Dennistoun, areas of high social deprivation versus Anniesland/Bearsden/Milngavie, areas of low deprivation) having increased slightly over the past ten years.[3]

Figure 1.2 Male life expectancy in the least deprived and most deprived quintiles in Greater Glasgow from 1981 to 2002

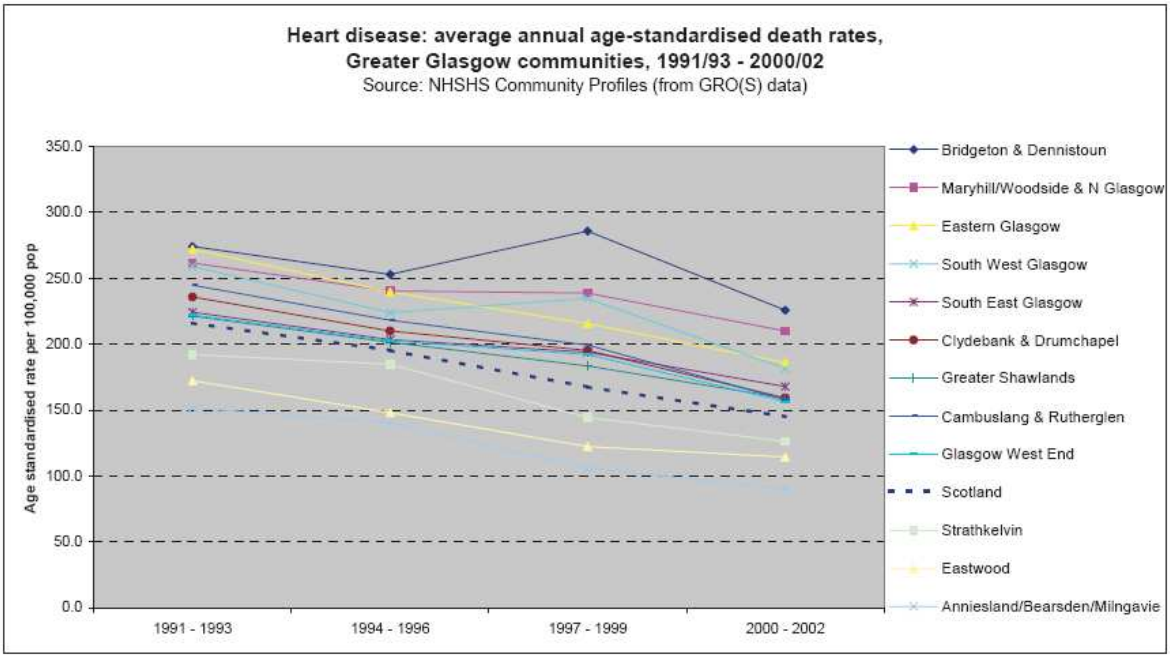


Life expectancy is given in years.

GROS – General Register Office for Scotland

From reference [3]. Reproduced by kind permission of Glasgow Centre for Population Health.

Figure 1.3 Heart disease: average annual age-standardised death rates, Greater Glasgow communities, 1991/93 – 2000/02



The highest death rate from heart disease in Greater Glasgow is seen in Bridgeton and Dennistoun, areas of high social deprivation. Anniesland, Bearsden and Milngavie (areas of low social deprivation) have the lowest heart disease death rates.

NHSHS – National Health Service Health Scotland

GRO(S) – General Register Office for Scotland

From reference [3]. Reproduced by kind permission of Glasgow Centre for Population Health.

The association between social deprivation and coronary heart disease has been well documented.[7] The Whitehall study, which studied 17 530 male civil servants aged between 40 and 64 years, reported in 1981 a rate of angina that was 53% higher in the lowest employment grade compared with the highest. This difference was only partly explained by currently recognised cardiovascular risk factors.[8] Furthermore, the British Women's Heart and Health Study found, in a study involving individuals living in 23 different British towns, an increasing prevalence of coronary heart disease with increasing socioeconomic deprivation, based on the Carstairs score of area-level deprivation. This association between area-level deprivation and coronary heart disease persisted after adjustment for ten indicators of individual life-course socioeconomic status.[9]

Given the socioeconomic gradient in prevalence of coronary heart disease, and the widening gap in life expectancy between those at the two extremes of the deprivation continuum, the next logical question to ask is to what extent coronary heart disease contributes to the deprivation gap in life expectancy. In Scotland as a whole, the three most common causes of "premature death" (death before the age of 65 years) between 2001 and 2003 were acute myocardial infarction (8.5% of all deaths before the age of 65 years), malignant neoplasm of bronchus or lung (7.9%) and chronic ischaemic heart disease (6.6%). In Greater Glasgow, however, alcoholic liver disease was the commonest cause of premature death (9.0%), followed by malignant neoplasm of bronchus or lung (8.1%). Acute myocardial infarction (7.8%) and chronic ischaemic heart disease (6.9%) were the third and fourth most common causes. In Bridgeton and Dennistoun (areas of high social deprivation within Greater Glasgow), alcoholic liver disease was clearly the most common cause of death (13.6%), followed by acute myocardial infarction (7.7%) and chronic ischaemic heart disease (7.1%). These figures indicate the emerging importance of alcohol (and in particular alcoholic liver disease) as a cause of premature death, especially in more deprived areas, and, therefore, as a likely contributor to the widening socioeconomic gap in life expectancy. However, even in Bridgeton and Dennistoun (where alcoholic liver disease made a particularly marked contribution to premature mortality), coronary heart disease caused 14.8% of premature deaths (the combined total of deaths from acute myocardial infarction and chronic ischaemic heart disease)[3] so it appears highly likely that coronary heart disease is a significant (although by no means unique) contributor to the socioeconomic gradient in life expectancy.

1.2 Cardiovascular risk factors

The currently recognised classic cardiovascular risk factors include the nonmodifiable risk factors of age and male sex and the modifiable risk factors of lipids (especially low density lipoprotein cholesterol), cigarette smoking, hypertension, diabetes mellitus, obesity and physical inactivity.[10] In recent years, additional possible risk factors have been identified; these "emerging" risk factors include markers of insulin resistance, inflammation, endothelial dysfunction and haemostasis.[10]

1.2.1 Smoking

1.2.1.1 Association of smoking with cardiovascular risk

Ever since Doll's observations on mortality in British doctors in relation to smoking,[11] the associations of cigarette smoking with cardiovascular risk have been well documented. The relationship between cigarette smoking and ischaemic heart disease is dose dependent,[11] is demonstrable in both males and females[12] and has been confirmed in subsequent studies, including the Framingham study[13] and the Multiple Risk Factor Intervention Trial (MRFIT).[14]

1.2.1.2 Association of smoking with social deprivation

The association of cigarette smoking with social deprivation is now well recognised. Lyratzopoulos and co-workers studied cigarette smoking in a UK context in a primary care-based cardiovascular risk factor screening programme involving 33 977 men and 37 161 women aged between 35 and 60 years. Social deprivation was assessed using the Townsend deprivation score, which determines area-level deprivation based on unemployment, overcrowding, non-car ownership and non-home ownership. They found that for any ordinal increase in deprivation group, odds ratio for current smoking increased by 1.24 (95% CI 1.22 to 1.26) in men and 1.26 (95% CI 1.24 to 1.28) in women. At the start of their study in 1989, current smoking in the most affluent group was 43.0% for men, falling to 24.7% in 1999, a fall of 42.6%. By contrast, in the most deprived group, smoking prevalence fell from 65.8% to 59.7% over the same time period, a fall of 9.3%. Similar trends were seen in women, with a fall of 60.8% in the most affluent group and 15.6% in the most deprived group. Thus, although percentage of current smokers is decreasing generally with time, the gap between most and least deprived areas is also widening.[15]

Similar associations between social deprivation and cigarette smoking have been observed when individual markers of socioeconomic status such as education,[16] occupation[17] or income[18] are used.

In Greater Glasgow, a similar picture is seen, with smoking prevalence in 2001 varying from 16% in areas of low social deprivation to 63% in areas of high social deprivation.[3] Subsequent to this, in March 2006 a ban on smoking in enclosed public places was introduced in Scotland.[19] In an analysis of the ongoing Aspirin for Asymptomatic Atherosclerosis (AAA) Trial, an increase was noted in the proportion of smokers stopping smoking in the three months prior to the introduction of this legislation. In this study, no association was noted between area-level social deprivation and likelihood of stopping smoking,[20] although it remains to be seen whether a socioeconomic differential in likelihood of smoking cessation at the time of introduction of the legislation will be seen when statistics from the wider population are analysed.

1.2.2 Lipids

1.2.2.1 Association of lipids with cardiovascular risk

The relationship between serum cholesterol concentration and risk of coronary heart disease is well documented. The Multiple Risk Factor Intervention Trial (MRFIT) demonstrated, in 356 222 men aged between 35 and 57 years, a continuous and graded relationship between serum cholesterol concentration and risk of death from coronary heart disease.[21] This finding was consistent with findings from the Framingham study, in which total[22] and low density lipoprotein (LDL)[23] cholesterol were found to be associated with risk of coronary heart disease. The inverse relationship between high density lipoprotein (HDL) cholesterol and coronary heart disease risk is also well documented, with an analysis of four prospective studies (Framingham Heart Study, Lipid Research Clinics Prevalence Mortality Follow-up Study, Coronary Primary Prevention Trial and Multiple Risk Factor Intervention Trial) finding that an increase in HDL cholesterol of 0.026mmol/L was associated with a 2% decrease in coronary heart disease risk in men and 3% in women.[24]

1.2.2.2 Association of lipids with social deprivation

Previous studies examining the relationship between total cholesterol and social deprivation have yielded varied results. The Whitehall II study, which studied 10 308 civil servants (6895 male and 3413 female) between the ages of 35 and 55 years at baseline, found no association between socioeconomic status (assessed by occupation) and percentage of subjects having serum cholesterol concentration $\geq$6.2mmol/L.[25] Similarly, the European Prospective Investigation of Cancer and Nutrition in Norfolk (EPIC-Norfolk) study, which included 22 478 (10 150 male and 12 328 female) participants aged 39 to 79 years, found no consistent associations between occupational social class (Registrar General's classification) and total serum cholesterol.[26] Contrasting findings were reported in a study of 2063 individuals aged 23 to 25 years in Brazil, in which lower total and LDL cholesterol concentrations were found in more deprived individuals.[27]

Given the recognised associations between social deprivation and both diabetes mellitus (discussed in section 1.2.5) and insulin resistance (see section 1.3.1.1) it would not be unexpected for higher concentrations of triglycerides and lower concentrations of high density lipoprotein (HDL) cholesterol (both characteristic of insulin resistance) to be found in more deprived populations. The English Longitudinal Study of Ageing examined concentrations of HDL cholesterol and triglycerides in 4774 participants age 50 years and over living in England, relating these to area-level social deprivation. In 52-65 year old participants, no associations were observed between deprivation and HDL cholesterol concentration, but a significant gradient ($p=0.01$) was noted in triglyceride concentration, with higher concentrations in more deprived groups. In participants over 65 years of age, significant associations (both $p<0.001$) were evident for HDL cholesterol (lower in more deprived participants) and triglycerides (higher in more deprived groups). All of the above significant associations persisted after additional adjustment for the individual socioeconomic indicators of occupational social class, educational attainment and wealth.[28] These findings were broadly consistent with previous findings from the Whitehall II study of civil servants, in which significant associations ($p=0.0001$for the trend in both cases) were found between employment grade and both HDL cholesterol (higher concentrations in participants of higher employment grade) and triglycerides (higher concentrations in participants of lower employment grade). Consistent with these findings, there was a strong inverse relationship between employment grade and prevalence of metabolic syndrome (defined in this study as having three or more of the following variables in the top quintile: 2 hour glucose in oral glucose tolerance test, systolic blood pressure, fasting

triglyceride concentration, HDL cholesterol [lowest quintile] and waist: hip ratio).[29] The findings of the Whitehall II study were, in turn, consistent with earlier findings from the Lipid Research Clinics Program, in which HDL cholesterol concentrations were measured in 2182 white females and 2368 white males aged 20 to 59 years in nine North American populations. When examining HDL cholesterol concentration in relation to educational attainment as an individual-level marker of socioeconomic status, HDL cholesterol concentration was positively associated with educational attainment in both males and females. When genders were analysed separately, the association between educational attainment and HDL cholesterol was stronger in females than in males.[30] The published literature is, therefore, generally consistent in reporting higher triglyceride concentrations and lower HDL cholesterol concentrations in more deprived populations.

1.2.3 Physical activity

1.2.3.1 Association of physical activity with cardiovascular risk

It is widely accepted that physical inactivity increases risk of coronary heart disease and that, conversely, regular physical activity reduces coronary heart disease risk.[10] It is likely that this effect is mediated through several mechanisms, with beneficial effects of regular physical activity having been demonstrated on HDL cholesterol,[31] reduction of insulin resistance and risk of developing type 2 diabetes mellitus,[32] and lowering of blood pressure.[33]

1.2.3.2 Association of physical activity with social deprivation

An analysis of the 2003 Scottish Health Survey, involving 2346 men and 2941 women aged 25 to 64 years, studied the association between lifecourse socioeconomic status (indicated by parental occupational social class, participant's education and occupational social class and housing tenure) and physical activity (indicated by occupational activity, walking, sport and exercise, housework and manual leisure). In both males and females, a significantly higher percentage of most deprived participants were classed as having low or no physical activity, compared to least deprived participants.[34] These findings are in contrast to those reported in the 2002 NHS Greater Glasgow Health/Well-Being Survey, in which 53% of least deprived subjects were found to take at least 20 minutes of vigorous exercise at least 3 times per week or 30 minutes of moderate exercise at least 5 times per week, compared with 59% of most deprived subjects.[3] However, this survey mainly

focused on leisure time physical activity, and it is known that there are significant associations between balance of work and leisure time physical activity and socioeconomic status.[35] It is likely, therefore, that an assessment which includes work and leisure physical activity will give a fuller picture of physical activity than one which assesses only leisure time physical activity.

1.2.4 Hypertension

1.2.4.1 Association of blood pressure with cardiovascular risk

Epidemiological studies have consistently shown a continuous association between blood pressure and risk of coronary heart disease, with no lower threshold level below which the relationship does not hold.[36] This association exists in men and women,[37] and has been demonstrated to exist in various different parts of the world.[38]

1.2.4.2 Association of blood pressure with social deprivation

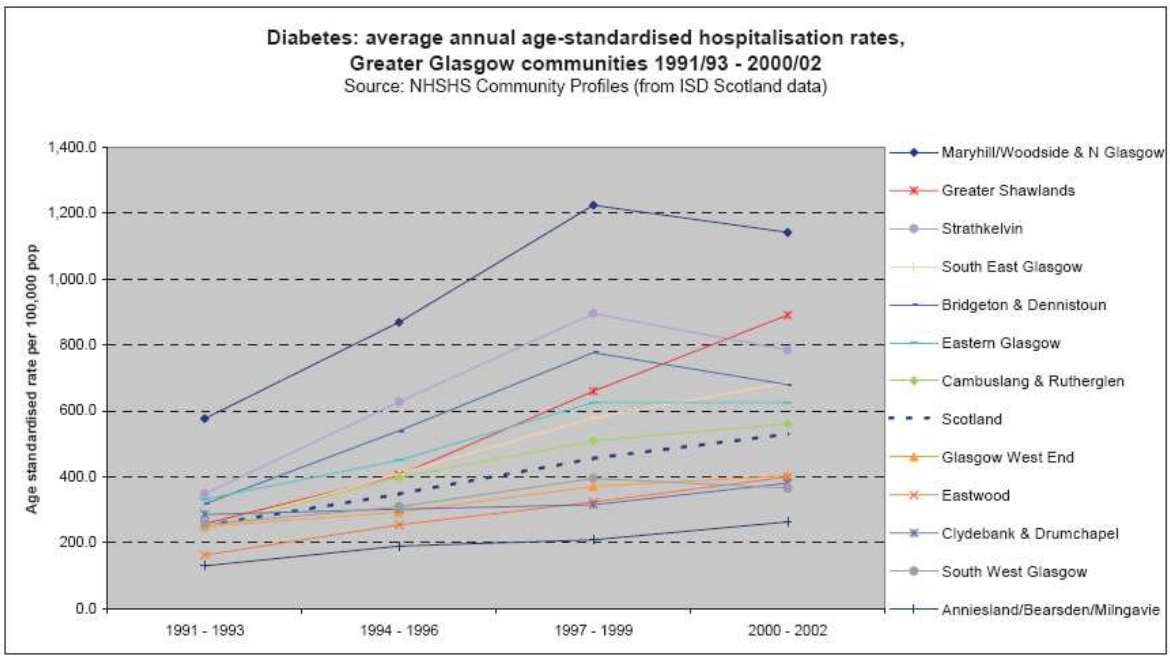
Studies examining the relationship between social deprivation and blood pressure have yielded fairly consistent results. The Scottish Heart Health study, involving 5123 men and 5236 women aged between 40 and 59 years, found associations in men between diastolic blood pressure and both housing tenure and employment status, and in women with occupational social class, housing tenure and level of education.[39] Similarly, the Stockport Cardiovascular Disease Risk Factor Screening Programme, which studied 33 977 men and 37 161 women aged between 35 to 60 years, found that for every incremental increase in the Townsend area-level deprivation score, systolic blood pressure increased by 0.47 mmHg in men and 0.56 mmHg in women, and diastolic blood pressure increased by 0.33 mmHg in men and 0.37 mmHg in women (all $p < 0.001$).[15] Consistent with this, an analysis of the Whitehall II prospective cohort study, involving 5363 male civil servants aged 40 to 62 years at baseline, found a significantly higher prevalence of hypertension in men of low socioeconomic status, compared with those of intermediate or high socioeconomic status, with hypertension being defined as >140/90 mmHg or on antihypertensive medication, and socioeconomic status classified according to employment grade.[25]

1.2.5 Association of diabetes mellitus with social deprivation

The relationship between diabetes mellitus and risk of coronary heart disease or stroke has been well recognised for many years.[40 41] The association between social deprivation and diabetes mellitus is also well recognised. Within Greater Glasgow, diabetes prevalence rates show significant geographical variation.[3] Consistent with this, annual age standardised hospitalisation rates for diabetes vary from around 260 per 100 000 population in the more affluent Anniesland/Bearsden/Milngavie area to 1150 per 100 000 population in the more deprived Maryhill/Woodside and North Glasgow areas.[3] An examination of **Figure 1.4** also reveals that although hospitalisation rates for diabetes have risen in all areas over the period from 1991 to 2002, the rates have risen fastest and to the greatest degree in the most deprived areas, leading to a significant widening of the gap between the Maryhill/Woodside/North Glasgow and Anniesland/Bearsden/Milngavie areas.

Findings from other geographical areas have been consistent with the findings in Greater Glasgow. The Whitehall II study found an incidence of diabetes of 6% in participants with a high occupational socioeconomic status; 7% in those of intermediate socioeconomic status and 11% in those of low socioeconomic status (although diabetes was diagnosed for the purposes of this study as fasting glucose $\geq$6.1 mmol/L or taking antidiabetic medication,[25] thus including those who, by World Health Organisation diagnostic criteria, had either diabetes or impaired fasting glycaemia).[42] Similar findings emerged from a study of 13 European countries, with significant inverse associations being found between educational attainment and both prevalence of diabetes mellitus and diabetes-related mortality.[43] Consistent with this, low childhood socioeconomic status has been shown to be associated with risk of developing type 2 diabetes in adulthood, especially in females.[44]

Figure 1.4 Average annual age-standardised hospitalisation rates for diabetes mellitus in Greater Glasgow from 1991 to 2002



Maryhill, Woodside and North Glasgow, with the highest hospitalisation rate for diabetes mellitus, are areas of relatively high social deprivation; Anniesland, Bearsden and Milngavie, with the lowest hospitalisation rate, are areas of low social deprivation.
NHSHS – National Health Service Health Scotland
ISD Scotland – Information Services Division Scotland
From reference [3]. Reproduced by kind permission of Glasgow Centre for Population Health.

1.2.6 Anthropometry

1.2.6.1 Weight / Body Mass Index (BMI)

Body mass index (defined as weight [kg] divided by the square of height [m]) has, for many years, been the recognised way of relating an individual's weight to healthy target values.[10] The associations of obesity with coronary heart disease and associated factors such as dyslipidaemia, hypertension, insulin resistance, endothelial dysfunction, inflammation and a prothrombotic state are well recognised.[45]

1.2.6.2 Waist circumference and waist / hip ratio

It has been recognised for some time that distribution of body fat is associated with coronary heart disease risk, with visceral adiposity being particularly indicative of an unfavourable risk profile. Insulin resistance, hypertension and dyslipidaemia have all been implicated as potential mechanistic links between abdominal obesity and increased cardiovascular risk.[46] The European Prospective Investigation into Cancer and Nutrition in Norfolk (EPIC-Norfolk) cohort study, which included 24 508 participants aged 45 to 79 years who were followed up for over 9 years, found that in a multivariate model adjusted for age, waist circumference, hip circumference and body mass index, a 1SD increase in waist circumference or body mass index was associated with an increased risk of coronary heart disease, while a 1SD increase in hip circumference was inversely associated with coronary heart disease risk **(Table 1.2)**.[47] Consistent with this, after adjusting for BMI, age, systolic blood pressure, total cholesterol, cigarette smoking, physical activity and alcohol intake, it was found that the association with coronary heart disease risk was stronger for waist-hip ratio than for waist circumference alone. Men in the top fifth of waist-hip distribution had 50% excess risk compared to those in the bottom fifth, compared to 20% for waist circumference alone. Women in the top fifth of waist-hip distribution had 90% excess coronary heart disease risk compared to those in the bottom fifth, compared to 80% for waist circumference.[48]

Table 1.2 Risk for coronary heart disease per 1 SD increase in waist and hip circumference and body mass index in men and women 45 to 79 years of age in the EPIC-Norfolk study

Parameter	Hazard ratio for CHD (95% CI)	
	Males (n=11 117)	**Females (n=13 391)**
Waist circumference	1.21 (1.10 to 1.33)	1.41 (1.25 to 1.59)
Hip circumference	0.78 (0.72 to 0.84)	0.74 (0.64 to 0.85)
Body mass index	1.29 (1.18 to 1.42)	1.27 (1.09 to 1.48)

CHD – Coronary heart disease

Table adapted from reference [47].

Given the above evidence, it is logical that waist circumference and waist/hip ratio have been incorporated into relevant clinical guidelines. The National Institute for Health and Clinical Excellence (NICE) has advised that people with a waist circumference of ≥94cm (males) or ≥80cm (females) are at increased risk of health problems, and those with a waist circumference of ≥102cm (males) or ≥88cm (females) are at yet higher risk, even if body mass index is within the normal range of 18.5 to 25kg/m^2. NICE further advises that waist/hip ratio is a useful measure of central adiposity in adults, but is more difficult to measure than waist circumference alone.[49] Similarly, the National Cholesterol Education Program defines abdominal obesity as a waist circumference of greater than 102cm in men or 88cm in women.[10]

1.2.6.3 Association between obesity and social deprivation

The association between area-level social deprivation and obesity was examined in the Stockport Cardiovascular Disease Risk Factor Screening Programme. For every incremental increase in Townsend deprivation score, Body Mass Index (BMI) increased by 0.11kg/m^2 (95% CI 0.08 to 0.14) in men and by 0.39kg/m^2 (95% CI 0.36 to 0.43) in women. Between 1989 and 1999, there was a slight reduction in the deprivation inequality in BMI in both men and women.[15]

The finding of higher BMI in individuals from more deprived areas is broadly consistent with findings from the Scottish Heart Health Study which examined BMI in relation to various markers of individual-level socioeconomic status. Consistent inverse associations were noted between BMI and socioeconomic status using occupational, housing tenure or educational markers of social class.[39]

1.2.7 To what extent do classic risk markers explain the deprivation gap in cardiovascular risk?

Given the associations detailed above between socioeconomic status and many classic cardiovascular risk factors (in particular cigarette smoking, hypertension, diabetes mellitus, physical activity and obesity) the next logical question to address is whether these differences in risk factors explain the socioeconomic inequality in cardiovascular risk. This question was addressed in the EPIC-Norfolk cohort study. Occupational class was determined using Registrar General's social class. When comparing those in the unskilled group with those in the professional group, age-adjusted relative risk for cardiovascular

disease hospital admissions in the 8902 men studied was 1.90 (95% CI 1.47 to 2.47; p<0.001). This relative risk fell to 1.76 (95% CI 1.35 to 2.28; p<0.001) on adjusting for smoking, but was essentially unchanged on adjusting in addition for the classic cardiovascular risk factors of BMI, systolic blood pressure, total cholesterol and history of diabetes (relative risk 1.75; 95% CI 1.34 to 2.27; p<0.001). Furthermore, additional adjustment for physical activity, weekly alcohol intake and plasma vitamin C concentration had no significant impact (relative risk 1.70; 95% CI 1.31 to 2.22; p<0.001). A similar pattern was seen in the 10 652 women studied.[26]

The Whitehall II study reported similar findings. Assessing socioeconomic status by employment grade, the contribution of smoking, hypertension (blood pressure >140/90mmHg or on antihypertensive medication), hypercholesterolaemia (total cholesterol ≥6.2mmol/L) and diabetes (defined in this study as fasting glucose ≥6.1mmol/L or on antidiabetic medication) to the socioeconomic gradient in coronary heart disease incidence was studied. Compared to the high socioeconomic status group, the low socioeconomic status group had a relative risk for coronary heart disease of 1.66 (95% CI 1.20 to 2.29). Smoking accounted for 18% of this excess risk; hypertension accounted for 14%; hypercholesterolaemia contributed 3% and diabetes 6%. Taking all four risk factors together, only 38% of the excess coronary heart disease risk was explained.[25]

Findings from the British Regional Heart Study were also similar. In this study of 5628 British men between the ages of 40 and 59 years, the relative hazard for coronary heart disease for manual compared to non-manual occupational social class was 1.50 (95% CI 1.25 to 1.79). Adjustment for cigarette smoking, systolic blood pressure, total cholesterol, BMI, physical activity, alcohol intake and Forced Expiratory Volume in 1 second (FEV1) explained 39% of this excess risk.[50] Similarly, the US-based Cancer Prevention Studies I and II found that the inverse association between educational attainment and coronary heart disease risk was only partly explained by adjusting for smoking, BMI, diet, alcohol intake, hypertension and menopausal status in women.[51] Similar findings had been previously reported in the Western Collaborative Group Study.[52]

1.3 Emerging cardiovascular risk markers

Given the fact that classic cardiovascular risk factors only partially explain the socioeconomic inequality in cardiovascular risk, the search for explanatory risk factors then turns to the more recently identified emerging risk factors.[10] Many of these can be classified as markers of insulin resistance/adiposity, inflammation, endothelial dysfunction or haemostasis. The associations of these emerging risk factors with cardiovascular disease and with social deprivation will now be examined.

1.3.1 Markers of insulin resistance/adiposity

The associations of type 2 diabetes mellitus (Section 1.2.5) and obesity (Section 1.2.6) with cardiovascular disease and with social deprivation are discussed above. Specific novel markers of insulin resistance and/or adiposity will now be examined.

1.3.1.1 Insulin and Homeostasis Model Assessment – Insulin Resistance (HOMA-IR)

The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is calculated from fasting plasma glucose and insulin concentrations, using the formula: HOMA-IR = Glucose (mmol/L) x Insulin (mU/L) / 22.5, and has been shown to correlate well with assessment of insulin resistance by the euglycaemic clamp procedure.[53] In view of the known associations between social deprivation and type 2 diabetes mellitus, it is not surprising that those studies which have specifically studied the association between indices of insulin resistance and social deprivation have also reported significant associations.

The British Women's Heart and Health Study examined 4286 women between the ages of 60 and 79 years. After adjustment for age, HOMA-IR was found to increase by 3.75% per quintile increase in Carstairs area-level deprivation score. After additional adjustment for individual life-course socioeconomic status, this figure fell to 1.90%, remaining statistically significant.[54] This study had previously reported associations between adverse social circumstances in childhood and later risk of insulin resistance.[55]

1.3.1.2 Adiponectin

Adiponectin, a protein secreted exclusively by adipocytes, is known to have insulin-sensitising, anti-inflammatory and anti-atherosclerotic effects. Several different multimeric forms exist, including homotrimers, hexamers and higher molecular weight forms. Adiponectin increases insulin-responsive glucose transport in adipocytes, thus enhancing insulin sensitivity. In addition, adiponectin inhibits secretion of several inflammatory mediators including interleukins-6 and -8. Low adiponectin concentrations are known to predict independently the development of insulin resistance and type 2 diabetes mellitus. Recently, evidence has emerged that it is the high molecular weight (HMW) multimeric forms of adiponectin that are specifically associated with favourable metabolic effects, with the ratio of HMW to total adiponectin correlating with insulin sensitivity in humans.[56] Although the associations between adiponectin and insulin resistance, dyslipidaemia and atherosclerosis have been previously studied,[57] no studies have been identified that examined the association between socioeconomic status and the various forms of adiponectin.

1.3.1.3 Leptin

Leptin is a protein secreted by white adipose tissue, and circulating concentrations correlate with adiposity. Binding of leptin to its receptor in the hypothalamus activates pathways involved in regulation of energy homeostasis, glucose homeostasis and food intake. Rare cases of congenital leptin deficiency have been described in humans, with resulting marked hyperphagia and obesity, but the vast majority of obese humans have elevated leptin concentrations and are relatively resistant to leptin, with the result that administration of leptin in pharmacological doses to obese humans does not lead to significant weight loss.[58]

Leptin concentrations were measured in the British Women's Heart and Health Study and related to adult and childhood occupational social class. In this study (somewhat surprisingly in view of the known associations between social deprivation and obesity) no significant association was found between either childhood or adult social class and leptin concentration.[59]

1.3.2 Markers of inflammation

1.3.2.1 C-reactive protein (CRP)

It is now generally accepted that inflammatory pathways have a significant role in the process of atherogenesis.[60] C-reactive protein, an acute-phase protein released by the liver in response to stimulation by interleukin-6 (IL-6), is an easily measured inflammatory marker. The Women's Health Study of 27 939 American women measured both LDL cholesterol and CRP. For each increasing quintile of LDL cholesterol concentration, relative risks for first cardiovascular event (compared to those in the lowest quintile) were 0.9, 1.1, 1.3 and 1.5 ($p<0.001$). However, the relative risks for each increasing quintile of CRP were 1.4, 1.6, 2.0 and 2.3 ($p<0.001$), suggesting that CRP is a stronger predictor of cardiovascular risk than LDL cholesterol.[61] The Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Augsburg study of men in southern Germany found that in men determined by the Framingham risk score to have a 10 year coronary event risk of between 10 and 20%, measurement of CRP improved risk prediction.[62] Subsequently, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study tested the hypothesis that people with elevated CRP but without elevated LDL cholesterol would benefit from statin treatment. JUPITER randomised 17 802 healthy men and women with LDL cholesterol concentrations of less than 3.4 mmol/L and CRP concentrations of $\geq$2.0 mg/L to either rosuvastatin 20mg daily or placebo. The trial was stopped early, with the hazard ratio for first major cardiovascular event in the rosuvastatin group being 0.56 compared to the placebo group ($p<0.00001$).

The association of CRP with social deprivation has been studied in samples from the West of Scotland Coronary Prevention Study (WOSCOPS) and the Midspan family study. In both studies, a correlation was noted between Carstairs deprivation category and CRP concentration ($p<0.0001$). This association was independent of age, BMI, smoking status and prescriptions for angiotensin converting enzyme (ACE) inhibitors, statins and aspirin. In the WOSCOPS study, each unit increase in Carstairs deprivation category was associated with a 5.4% increase in CRP after adjustment for age, BMI, smoking and the above medications.[63]

1.3.2.2 Interleukin-6 (IL-6)

As the main cytokine responsible for stimulating the hepatic acute phase response, the role of IL-6 in atherosclerosis is worthy of study. In the Iowa 65+ Rural Health Study, elevated IL-6 concentrations were more strongly associated with mortality than were elevated CRP concentrations, with the associations of IL-6 and CRP being additive.[64] Several mechanisms have been suggested by which IL-6 may increase risk of atherosclerosis – these include effects on insulin sensitivity; release of adhesion molecules from endothelial cells; release of fibrinogen by the liver and procoagulant effects on platelets.[65]

The association between IL-6 concentrations and social deprivation was studied in a US-based study of 851 men and women between the ages of 30 and 54 years. Individual-level socioeconomic status (measured by income and educational attainment) was inversely associated with IL-6 concentrations, as was area-level socioeconomic status. After adjustment for lifestyle factors (smoking, alcohol consumption, sleep, exercise, BMI) and individual socioeconomic status, the inverse relationship between area-level socioeconomic status and IL-6 concentrations persisted. This suggests an effect of area-level social deprivation on inflammation beyond that captured by the individual-level markers of income and educational attainment (although early life markers such as childhood overcrowding were not examined). However, the association between individual-level socioeconomic status and IL-6 was abolished after adjusting for lifestyle factors.[66] Similarly, the British Regional Heart Study found a significant inverse relationship between occupational social class and IL-6 concentration, with this association being reduced (although still statistically significant) after adjusting for age, body mass index, smoking, alcohol consumption and physical activity.[67] In the Whitehall II Study, the longitudinal association between occupational social class and IL-6 concentration was examined, with the conclusion that a steep socioeconomic gradient in IL-6 persisted over the 12 year study period, with no strong evidence of an interaction between socioeconomic status and rate of increase in IL-6 concentrations over this time period.[68]

1.3.3 Markers of endothelial dysfunction

1.3.3.1 Soluble intercellular adhesion molecule-1 (sICAM-1)

The role of endothelial dysfunction in atherosclerosis is now well recognised.[69] Soluble intercellular adhesion molecule-1 (sICAM-1) is a circulating form of ICAM-1. ICAM-1 is present on endothelial cells, and is involved in facilitating leukocyte adhesion and migration across the endothelium. Release of sICAM-1 is stimulated by several mediators, including IL-6. sICAM-1 concentrations are elevated in association with hypertension, with insulin resistance and with cigarette smoking, and have been found to be higher in people with unstable angina pectoris when compared to people with stable angina and healthy controls. Furthermore, elevated sICAM-1 is predictive of risk of developing myocardial infarction, leading to recognition of sICAM-1 as an emerging cardiovascular risk factor.[70]

The association between socioeconomic status and sICAM-1 concentration was examined in the US-based Women's Health Study. In this study, sICAM-1 concentrations decreased progressively with increasing categories of education and income.[71] Similarly, the Framingham Offspring Study found a significant inverse association between educational attainment and sICAM-1 concentration ($p<0.0001$), with the association persisting after adjusting for age, sex, smoking, blood pressure, total to high density lipoprotein cholesterol ratio, BMI, lipid-lowering and antihypertensive medication, prevalent cardiovascular disease and depression.[72]

1.3.4 Markers of haemostasis

1.3.4.1 Von Willebrand factor (vWF)

Von Willebrand factor (vWF), produced by endothelial cells, has a role in platelet adhesion and aggregation, and also functions as a carrier protein and stabiliser for clotting factor VIII. Given its production by endothelial cells and its functions in haemostasis, it can legitimately be viewed as both a marker of endothelial dysfunction and of haemostasis. The ability of vWF concentrations to predict risk of future coronary heart disease has been examined in several studies, with odds ratio for coronary heart disease in highest versus lowest quartile of vWF ranging from 1.23 to 3. The consensus is that vWF is at best

weakly predictive of future coronary heart disease in initially healthy people, although it becomes a much stronger predictor in patients with existing vascular disease.[73]

1.3.4.2 Fibrinogen

Fibrinogen, the most abundant coagulation protein in blood, has major effects on coagulation, blood viscosity and platelet aggregation. A meta-analysis of 31 prospective studies involving 154 211 participants found an approximately log-linear association between fibrinogen concentration and coronary heart disease risk. Per 1g/L increase in fibrinogen concentration, age- and sex- adjusted hazard ratio for coronary heart disease was 2.42 (95% CI 2.24 to 2.60), falling to 1.93 (95% CI 1.79 to 2.08) after adjustment for smoking, total cholesterol, systolic blood pressure and BMI. In a subset of participants with available C-reactive protein results, further adjustment for C-reactive protein had no significant impact on the results.[74]

1.3.4.3 Fibrin D-dimer

Fibrin D-dimer is a marker of fibrin turnover, being present in several fibrin degradation products. The association between D-dimer concentrations and coronary heart disease risk was studied prospectively in the British Regional Heart Study. Men in the top third of D-dimer concentrations had an odds ratio for coronary heart disease of 1.67 (95% CI 1.31 to 2.13) after adjusting for age and town of residence. Further adjustment for smoking, blood pressure, total and HDL cholesterol, triglycerides, BMI and individual socioeconomic status had no significant impact (adjusted odds ratio 1.79 [95% CI 1.36 to 2.36]). A meta-analysis of six previous population-based prospective studies yielded a very similar odds ratio of 1.7 (95% CI 1.3 to 2.2).[75]

1.3.4.4 Tissue plasminogen activator (tPA)

Tissue plasminogen activator (tPA) is responsible for activating clot dissolution, and is produced by vascular endothelial cells. tPA antigen is more easily measured in plasma than free active tPA, and is a marker of complex formation between tPA and its inhibitor, plasminogen activator inhibitor-1 (PAI-1). tPA antigen was measured in the British Regional Heart Study. The odds ratio for coronary heart disease in top versus bottom third of tPA antigen concentrations was 2.20 (95% CI 1.70 to 2.85) after adjusting for age and town of residence. After further adjustment for smoking, total and HDL cholesterol,

triglycerides, BMI, blood pressure and physical activity, this odds ratio fell to 1.60 (95% CI 1.20 to 2.13). A meta-analysis of 12 prospective studies revealed similar results, with an odds ratio of 2.18 (95% CI 1.77 to 2.69) after adjusting for age and sex, falling to 1.47 (95% CI 1.19 to 1.81) after additional adjustment for classic cardiovascular risk factors.[76]

1.3.4.5 Association of markers of haemostasis with socioeconomic status

The associations between social deprivation and markers of haemostasis have previously been investigated. An analysis of the 1958 British Birth Cohort found higher concentrations of fibrinogen, von Willebrand factor antigen and tissue plasminogen activator antigen in individuals with higher cumulative lifecourse levels of social deprivation. After adjustment for body mass index, smoking and physical activity, the trend for fibrinogen remained significant.[77] Similarly, the British Regional Heart Study found that in British men aged 60 to 79 years with no diagnosis of cardiovascular disease, diabetes or musculoskeletal disease requiring anti-inflammatory medication, occupational social class was inversely associated with fibrinogen, von Willebrand factor and fibrin D-dimer, but not tPA antigen. The association with von Willebrand factor persisted after adjustment for age, BMI, smoking, alcohol consumption and physical activity.[67]

1.3.5 To what extent do emerging risk markers explain the deprivation gap in cardiovascular risk?

Given the associations between socioeconomic status and many emerging cardiovascular risk markers, and given the failure of differences in classic cardiovascular risk factors to explain the totality of the socioeconomic gradient in cardiovascular risk, it is logical to ask if these emerging risk markers can contribute anything to the explanation. This question was addressed to some extent in the US-based Women's Health Study. Using the individual-level socioeconomic indicators of education and income, emerging biomarkers examined included C-reactive protein, sICAM-1 and fibrinogen. The primary outcome was a combined endpoint including non-fatal myocardial infarction, non-fatal ischaemic stroke, cardiovascular death and coronary revascularisation procedures. For increasing education categories, age- and ethnicity-adjusted relative risks for the primary cardiovascular endpoint were 1.0, 0.7, 0.5, 0.4 and 0.5. Adjusting for classical cardiovascular risk factors reduced the differences to some extent (without loss of statistical significance). Further adjustment for emerging risk markers had no significant impact. Use of household income

instead of education as the marker of socioeconomic status yielded very similar results **(Table 1.3)**.[71] This study indicates that CRP, sICAM-1 and fibrinogen – despite their associations with cardiovascular risk and with social deprivation – do not contribute significantly to the explanation of the socioeconomic gradient in cardiovascular risk. As discussed above, however, many other biomarkers have now emerged whose contribution to the explanation could be tested in a similar way.

Table 1.3 Contribution of classic and emerging cardiovascular risk factors to the socioeconomic gradient in cardiovascular risk

Category	n	RR (age and ethnicity adjusted)	RR (classic risk factor adjusted)	RR (classic and emerging risk factor adjusted)
Education				
<2 y health professional education	2771	1.0	1.0	1.0
2-<4 y health professional education	9726	0.7 (0.5-0.8)	0.8 (0.7-1.0)	0.8 (0.7-1.0)
Bachelor's degree	5422	0.5 (0.4-0.7)	0.7 (0.5-0.9)	0.7 (0.5-0.9)
Master's degree	3502	0.4 (0.3-0.6)	0.6 (0.5-0.9)	0.6 (0.5-0.9)
PhD/MD	1267	0.5 (0.3-0.7)	0.8 (0.5-1.2)	0.8 (0.5-1.2)
P for trend		<0.001	0.006	0.006
Annual household income (US $)				
<19 999	1143	1.0	1.0	1.0
20 000-29 999	2184	1.0 (0.8-1.4)	1.2 (0.9-1.7)	1.2 (0.9-1.7)
30 000-39 999	3139	0.9 (0.6-1.2)	1.1 (0.8-1.5)	1.1 (0.8-1.5)
40 000-49 999	3753	0.7 (0.5-0.9)	0.9 (0.7-1.3)	0.9 (0.7-1.3)
50 000-99 999	9426	0.7 (0.5-0.9)	1.0 (0.7-1.3)	1.0 (0.7-1.3)
>100 000	3043	0.4 (0.3-0.7)	0.8 (0.5-1.2)	0.8 (0.5-1.2)
P for trend		<0.001	0.09	0.08

From reference [71].

RR: relative risk (with 95% confidence intervals)

Classic risk factor adjustment: adjusted for age, ethnicity, BMI, smoking, hypertension, diabetes, LDL and HDL cholesterol, triglycerides, hormone use, family history of myocardial infarction before 60 years of age, alcohol intake and physical activity

Classic and emerging risk factor adjustment: as classic risk factor adjustment + CRP, sICAM-1, fibrinogen and homocysteine

1.4 Carotid ultrasound markers of atherosclerosis

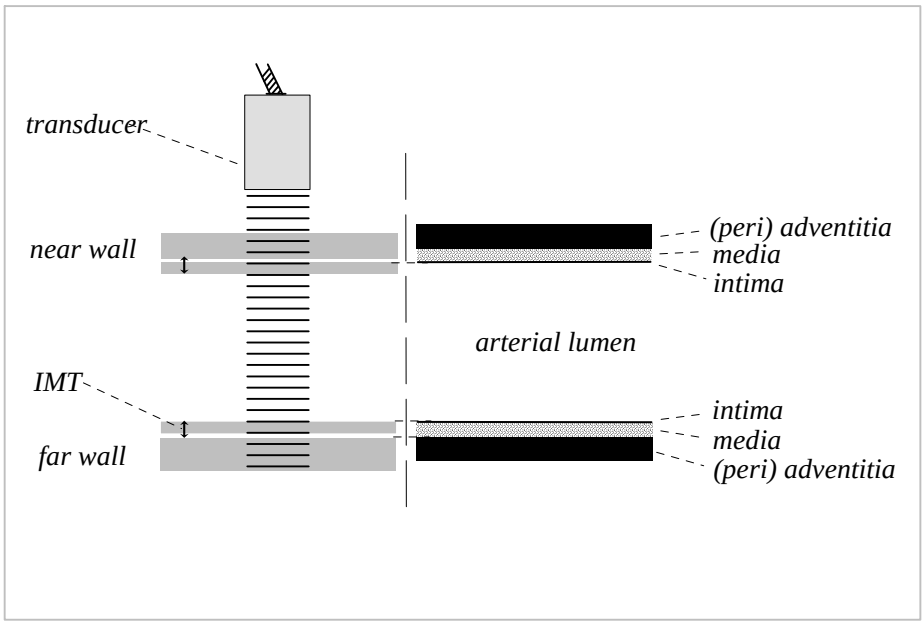
1.4.1 Carotid intima-media thickness (cIMT) – association with risk of MI/stroke

In recent years, carotid ultrasound has emerged as an efficient and validated surrogate marker for assessing the degree of atherosclerosis in an individual. Measurement of the distal common carotid artery intima-media thickness (cIMT) is a commonly employed index **(Figure 1.5)**. The American Society of Echocardiography (ASE) has recognised a clinical role for cIMT measurement and plaque detection in refining cardiovascular risk assessment in asymptomatic patients assessed as being at intermediate risk of coronary heart disease, defined as 6-20% 10 year risk of myocardial infarction or coronary heart disease death. The ASE recommendation is that people with carotid plaque, or with cIMT greater than or equal to the 75th centile for an age, sex and ethnicity matched population should be considered to be at increased risk, and may warrant more aggressive treatment of risk factors.[78]

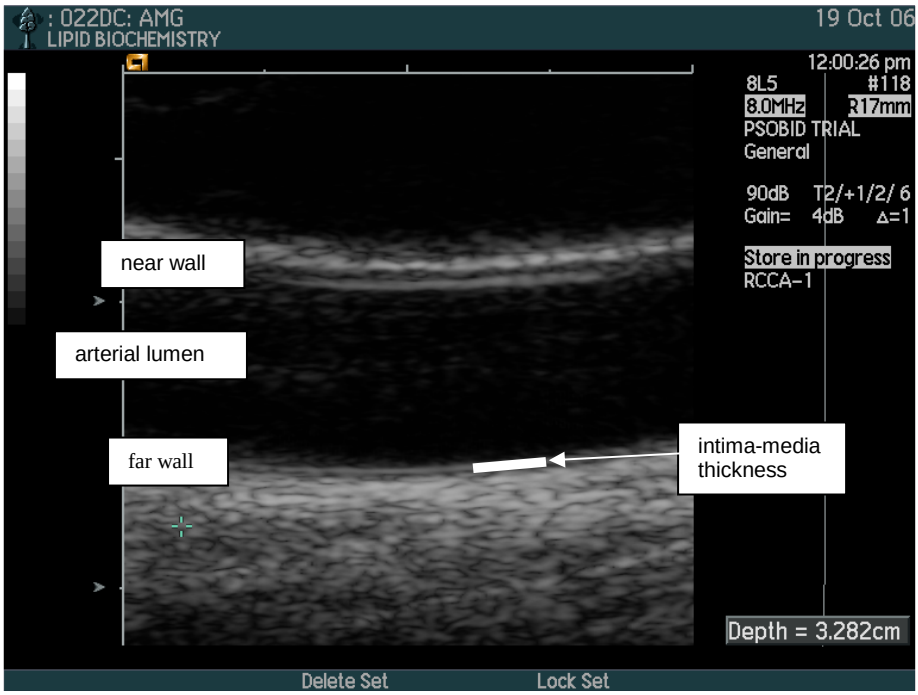
The utility of cIMT in predicting risk of myocardial infarction and stroke was assessed in a recent meta-analysis. Based on 8 prospective observational studies involving 37 197 subjects with ages ranging from 19 to 90 years, the age-and-sex-adjusted relative risk for myocardial infarction was found to be 1.26 (95% confidence intervals 1.21 to 1.30) for every 1 standard deviation increase in cIMT and 1.15 (95% confidence intervals 1.12 to 1.17) for every 0.10mm increase in cIMT. For stroke, the age-and-sex-adjusted relative risk was 1.32 (95% confidence intervals 1.27 to 1.38) per 1 standard deviation increase in cIMT and 1.18 (95% confidence intervals 1.16 to 1.21) for every 0.10mm increase in cIMT.[79]

Figure 1.5 Ultrasound assessment of common carotid intima-media thickness

A. Schematic diagram of distal common carotid artery



B. Ultrasound image of distal common carotid artery



1.4.2 Carotid plaque - association with risk of MI/stroke

As well as allowing measurement of cIMT, carotid ultrasound can be used to identify carotid plaque[80] – indeed given current understanding of the process of atherogenesis, plaque presence is a more mechanistically plausible marker of atherosclerosis than is cIMT. Plaque score has been shown to be associated with risk of myocardial infarction[81-83] and stroke.[84] In the Rotterdam study, hazard ratio for myocardial infarction was 1.83 (95% confidence intervals 1.27 to 2.62) for plaque score of $\geq$3 versus 0[81] and age-and-sex-adjusted relative risk for stroke was 1.61 (95% confidence interval 1.16–2.23) for highest to lowest tertile of plaque score.[84]

Several studies have examined the comparative usefulness of cIMT and plaque score in predicting myocardial infarction and stroke. The Rotterdam study found carotid plaque score and cIMT to be equally strong predictors of myocardial infarction. The hazard ratio for myocardial infarction was 1.95 (95% CI 1.19 to 3.19) for highest to lowest quartile of cIMT and 1.83 (95% CI 1.27 to 2.62) for highest to lowest category of plaque score.[81] Interestingly, cIMT was a stronger predictor of stroke than was presence of plaque (age- and sex-adjusted relative risk of stroke for highest to lowest tertile of cIMT 2.23 [95% CI 1.48 to 3.36]; for highest to lowest tertile of plaque score 1.61 [1.16 to 2.23]),[84] although in elderly males, plaque burden has been found to be a more consistently strong predictor than cIMT of cardiovascular and all-cause mortality.[85] Similarly, a study of 13 221 low risk, healthy individuals in Italy found plaque presence to be more strongly predictive than cIMT of future cardiovascular events.[86] Plaque presence was also found in the Kuopio Ischaemic Heart Disease Risk Factor Study to be a stronger predictor than cIMT of acute myocardial infarction.[87] Similarly, the Tromso Study found carotid plaque area to be a stronger predictor than cIMT of first myocardial infarction, particularly in women.[82]

1.4.3 Association between social deprivation and cIMT/carotid plaque

Several studies have examined the relationship between socioeconomic status and ultrasound markers of atherosclerosis. Most have examined individual-level measures of socioeconomic position in relation to carotid intima-media thickness (cIMT). The Atherosclerosis Risk in Communities (ARIC) study found that cIMT fell significantly with increasing categories of income, educational attainment or occupation.[88] Very similar results were obtained in the Kuopio Ischaemic Heart Disease study of Finnish men aged 42 to 60 years,[89] in which significant inverse differences in rate of progression of cIMT were also noted in relation to both income and educational attainment.[90] The effect of childhood socioeconomic status (assessed by parental occupational social class) on cIMT was studied in the Young Finns study, with no association being found between childhood socioeconomic status and cIMT after adjusting for adult socioeconomic status.[91]

Rosvall *et al* studied a population-based sample of 4033 individuals, finding significant associations between area-based indicators of social deprivation and carotid plaque score, with these associations only slightly reduced on adjusting for the individual level markers of education, employment status and occupational social class.[92] Similarly, a study of untreated hypertensive men in Pittsburgh, USA, found inverse associations between community socioeconomic status and both cIMT and carotid plaque occurrence. The association with plaque occurrence persisted after adjusting for the individual-level markers of education and annual income.[93]

1.5 Carotid ultrasound markers of arterial stiffness

Traditionally, systolic and diastolic blood pressure have been the main targets for blood pressure control in clinical practice. However, in an analysis of data from the Framingham Heart Study, pulse pressure was found, in subjects between 50 and 79 years of age, to be a stronger predictor of coronary heart disease than either systolic or diastolic blood pressure.[94] The significance of this finding is that, in people within this age bracket and older, the major determinant of pulse pressure is large artery stiffness, suggesting possible benefit in measuring arterial stiffness.[95] Several non-invasive methods of assessing arterial stiffness have been developed, of which the most commonly used are assessment of pulse wave velocity, M-mode ultrasound assessment of changes in artery diameter which can then be related to pulse pressure, and pulse waveform analysis.

1.5.1 Pulse wave velocity

Arterial pulse wave velocity (PWV) increases with increasing arterial stiffness, and is an independent predictor of cardiovascular events. PWV is measured by recording an arterial pulse wave at a proximal artery such as the common carotid, and at a more distal artery such as the femoral. The time delay between the arrival of a predefined part of the pulse wave at the two selected points is measured, and PWV is calculated as distance travelled / time.[95] Raised PWV has been noted to be associated with a range of recognised cardiovascular risk factors[96] including age,[97] hypercholesterolaemia,[98] type 2 diabetes mellitus[99] and sedentary lifestyle.[97]

1.5.2 M-mode ultrasound assessment

Parameters of arterial stiffness can be assessed using measurements obtained by M-(movement) mode ultrasound. Changes in arterial wall diameter are related to pulse pressure, allowing calculation of a range of parameters of arterial stiffness, including compliance, distensibility, Petersen elasticity modulus and stiffness.[95] In the Rotterdam Study, ultrasound was used to assess common carotid artery distensibility. An inverse association was found between distensibility and atherosclerosis as assessed by carotid intima-media thickness, severity of carotid artery plaques and severity of aortic plaques.[100]

1.5.3 Pulse waveform analysis

Radial artery waveforms can be analysed non-invasively by applanation tonometry, with the waveform being calibrated to conventionally measured brachial blood pressure. Central aortic waveforms can be derived from the peripheral waveforms, and from the central aortic waveform an augmentation index can be calculated. The augmentation index is the proportion of central pulse pressure that results from arterial wave reflection, and gives a measure of arterial stiffness.[95] The augmentation index has been found to increase with age[101] and is also higher in patients with type 1 diabetes[102] and in hypercholesterolaemia.[103]

1.5.4 Associations between markers of arterial stiffness and risk of myocardial infarction (MI)/stroke

The Rotterdam population-based study related carotid-femoral PWV and common carotid artery distensibility to ultrasound indicators of atherosclerosis (cIMT, carotid artery plaque and abdominal aorta calcified plaques). Significant increases in PWV were noted with increasing quartiles of cIMT and with increasing categories of carotid or aortic plaque. Similarly, common carotid distensibility decreased with increasing quartiles of cIMT and with increasing categories of carotid or aortic plaque. These associations persisted after adjustment for age, sex, mean arterial pressure, heart rate, total and HDL cholesterol, glucose, smoking, BMI and presence of diabetes mellitus. The authors suggested possible explanations for these associations, including the possibility that atherosclerosis leads to arterial stiffening, or that increased arterial stiffness leads to vessel wall damage and atherosclerosis, or indeed that arterial stiffness and atherosclerosis are independent processes that frequently occur at similar sites without a causal relationship existing between the two processes.[100] The relationships between arterial stiffness and cardiovascular and all-cause mortality have also been investigated, with carotid-femoral PWV being an independent predictor of cardiovascular and all-cause mortality in hypertensive patients; aortic PWV and carotid artery stiffness being predictive of mortality in patients with end-stage renal failure and lower carotid artery distensibility being predictive of cardiovascular events after renal transplantation.[95]

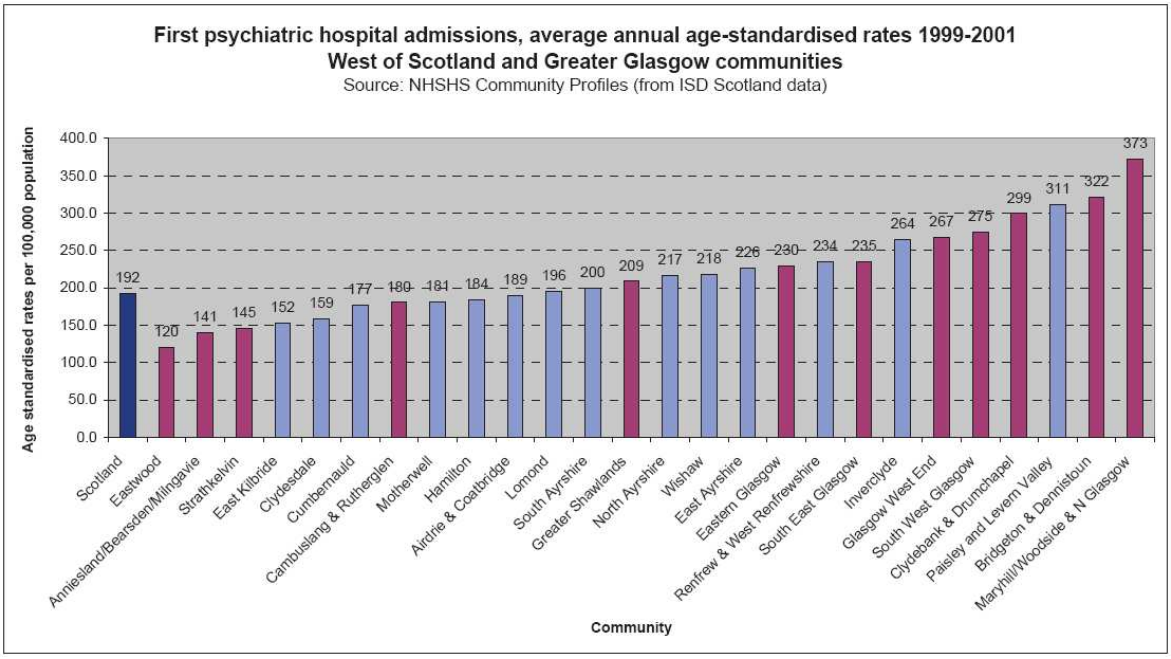
1.5.5 Associations between social deprivation and markers of arterial stiffness

The association between educational attainment and arterial stiffness (assessed by pulsatile arterial diameter change) was examined in 10 091 participants aged 45 to 64 years in the Atherosclerosis Risk in Communities study. A direct association was observed between educational attainment and arterial diameter change, i.e. lower educational attainment was associated with stiffer arteries. This association persisted after adjusting for age, height, diastolic diameter, systolic blood pressure, pulse pressure, ethnicity, gender and smoking status.[104] More recently, a study of Japanese civil servants found significant inverse associations in men between brachial-ankle PWV and both educational attainment and employment grade, with these associations persisting after adjusting for age, BMI, smoking, alcohol consumption, exercise, medication for hypertension, hyperlipidaemia and diabetes, heart rate, systolic blood pressure, total and HDL cholesterol, triglycerides and CRP.[105] Interestingly, a recently published study in adolescents living in the USA found associations between PWV and both parental educational attainment and family income, despite no associations being found between these markers of socioeconomic status and cIMT.[106] It is clearly interesting to find differences in arterial stiffness emerging at such a young age (mean age was 17.8 years) and before differences can be identified in cIMT. This finding may lend support to the hypothesis that changes in arterial stiffness precede development of atherosclerosis in individuals.

1.6 Mental wellbeing, social deprivation and associations with cardiovascular risk

The detrimental effects of social deprivation on physical health have been extensively described, with the discussion above focussing on the effects on cardiovascular disease. However, it is increasingly being recognised that deprivation has associations also with psychological wellbeing. If psychiatric hospital admission is taken as a crude indicator of lack of mental wellbeing, the relationship between social deprivation and psychiatric illness is demonstrated in **Figure 1.6**, which shows that the rate of first psychiatric hospital admissions in Maryhill/Woodside and North Glasgow is over three times that in Eastwood, both areas being part of the Greater Glasgow area.[3]

Figure 1.6 First psychiatric hospital admissions in relation to social deprivation in West of Scotland and Greater Glasgow communities



Areas in dark red are within Greater Glasgow; areas in light blue are other West of Scotland council areas. Within Greater Glasgow, rate of first psychiatric hospital admissions is lowest in Eastwood (an area of low social deprivation) and highest in Maryhill, Woodside and North Glasgow (areas of high social deprivation).
From reference [3], reproduced by kind permission of Glasgow Centre for Population Health.

1.6.1 Associations between psychological parameters, social deprivation and cardiovascular risk

There are recognised associations between lower socioeconomic status and work stress, and between work stress and coronary heart disease, with the majority of studies in the field showing an independent association between work stress and coronary heart disease, suggesting the possibility of a causal relationship. Similarly, the majority of prospective studies have found an association between depression and risk of coronary heart disease, with depression overall conveying an approximately twofold increased risk of developing coronary heart disease, and a dose-effect relationship existing. Suggested mechanisms include depression promoting an inflammatory state, which in turn promotes atherosclerosis; both depression and coronary heart disease being products of widespread atherosclerosis; both depression and coronary heart disease arising from chronic environmental stress or depression leading to the adoption of harmful behaviours such as smoking, poor diet and lack of exercise, which in turn lead to atherosclerosis. Other potential mechanistic links between psychological parameters and coronary heart disease include: cortisol excess, which has been demonstrated in depression, work stress and hostility, and also in men of lower socioeconomic status; endothelial dysfunction, as brachial flow-mediated dilatation is impaired in depression, and sICAM-1 is higher; and platelet activation, which is increased in depression and in men of lower socioeconomic status. Hopelessness, anxiety and anger have also been linked to coronary heart disease.[107]

The associations between these psychological parameters, deprivation and risk of coronary heart disease have potential implications for public health programmes aiming to narrow the deprivation gap in health and life expectancy. There is a clear socioeconomic differential in acceptance of many aspects of health promotion advice, with those in areas of high deprivation being less likely to accept such advice. It is quite plausible that features such as depression and hopelessness may affect an individual's ability to respond to public health messages advising them to modify aspects of their lifestyle, which may partly explain why current attempts to narrow the deprivation gap are not being successful – in fact, as discussed above, the gap is widening.

1.6.2 Associations between cognitive function, social deprivation and cardiovascular risk

The associations between socioeconomic status and cognitive function were investigated in 10,308 civil servants aged 35 to 55 years in the Whitehall II study. Verbal memory, inductive reasoning, vocabulary and verbal fluency were assessed and related to lifecourse socioeconomic status. The findings suggested that while childhood socioeconomic status did not have a direct effect on cognitive function, there was evidence of a substantial indirect effect mediated through education and adult socioeconomic status.[108]

Hart *et al* linked data from the Midspan studies with the Scottish Mental Survey and found that childhood intelligence quotient (IQ) was inversely associated with all-cause and coronary heart disease mortality, both with and without adjustment for area-level deprivation, with the association between childhood IQ and all-cause mortality also remaining after adjusting for occupational social class.[109] The hypothesis that differences in IQ explain the deprivation gradient in ill health was further explored in the west of Scotland twenty-07 study. Coronary heart disease mortality was examined in relation to individual and area markers of social deprivation. Significant associations with coronary heart disease mortality were noted for childhood social class, income and Carstairs deprivation score. Adjustment for IQ reduced but did not abolish these associations, suggesting that IQ does not fully explain the socioeconomic gradient in coronary heart disease risk.[110]

1.7 Methods of assessing social deprivation

From the literature discussed above, it is clear that there are many different parameters by which social deprivation can be assessed and described. These parameters can be divided into area-based indicators of deprivation and individual-level indicators of socioeconomic status. These indicators will now be described in more detail. It is necessary first of all to define what is meant by deprivation. Townsend has defined deprivation as follows:

> "People are relatively deprived if they cannot obtain, at all or sufficiently, the conditions of life – that is, the diets, amenities, standards and services – which allow them to play the roles, participate in the relationships and follow the customary behaviour which is expected of them by virtue of their membership of society. If they lack or are denied resources to obtain access to these conditions of life and so fulfil membership of society, they may be said to be in poverty."[111]

The emphasis of deprivation as a relative concept, in which individuals may be described as deprived if they lack the resources needed for them to function according to the norms of the society in which they live, is also a feature of the definition used in a report to the Scottish Executive by Bailey *et al* in 2003, in which the term 'deprivation' is noted for its focus on:

> "…the lack of goods, services or social relations or inadequate physical or social environment which results from a lack of financial resources. It is a relative measure where standards are defined in relation to social norms or expectations."[112]

1.7.1 Area-based measures of deprivation

Area-level indicators of socioeconomic status generally take into account a variety of parameters by which the relative deprivation of a community can be described. The Scottish Index of Multiple Deprivation (SIMD) 2009 uses 38 indicators in seven domains: current income; employment; health; education, skills and training; geographic access to services; housing and crime.[113] Areas are divided into data zones, which are small areas with a population of 500 to 1000 household residents. The data zones (6505 in total) are then ranked according to relative deprivation.[114]

1.7.2 Individual-level measures of deprivation

Individual measures of deprivation capture a range of information about each individual's material and social circumstances – e.g. household income or occupational social class, with the information largely being derived from household surveys. The extent to which such measures can be obtained is, therefore, limited by the practicalities of surveying large numbers of people, a potentially time-consuming and labour-intensive process.[112]

It is generally accepted that area-based and individual-level measures of deprivation serve different purposes, yielding different, but complementary, information. Individual-level measures provide a direct indication of the living standards experienced by each person living in an area, thus providing an indication of the number of people within an area who are living in conditions of deprivation. It is, therefore, possible to track changes in levels of deprivation over time. By contrast, area-based measures of deprivation give an indication of the characteristics of the area, and thus cannot be used to determine the number of individuals in a given area who are living in conditions of deprivation. Furthermore, as

area-based measures rank areas in terms of deprivation in relation to each other, it is not possible to use such measures to compare absolute changes in levels of deprivation over time.[112]

1.8 Aims of thesis

The overall aim of the work described in this thesis was to enhance current understanding of the factors underlying the socioeconomic gradient in ill health. In particular, this thesis focuses on the association between social deprivation and risk of coronary heart disease. Building on the observations that classic cardiovascular risk factors explain only part of the socioeconomic gradient in coronary heart disease risk, a key aim of the work described here was to determine the extent to which emerging cardiovascular risk factors contribute to the explanation of the socioeconomic gradient in coronary heart disease. Given the known involvement of inflammatory pathways in atherosclerosis and the known associations between deprivation and markers of inflammation, a prespecified hypothesis was that inflammation would explain the deprivation-based gap in coronary heart disease risk (as indicated by the surrogate ultrasound markers of intima-media thickness and plaque score).

As discussed above, it is now being recognised that the effects of inflammation may extend to effects on cognition and personality, and that there are recognised associations between some of these psychological parameters and coronary heart disease risk. A further aim of this work was, therefore, to further understanding of the associations between social deprivation and markers of cognition and personality.

In summary, therefore, the research questions addressed were:
1) Do deprived sections of the community display increased prevalence of central obesity, insulin resistance and chronic inflammation compared to affluent sections?
2) Is sub-clinical atherosclerosis (as detected by carotid ultrasound) more prevalent in deprived groups? To what extent is the prevalence explained by classic risk factors (smoking, blood pressure, cholesterol) and to what extent is it related to emerging risk factors?
3) Do deprived groups differ from affluent ones in psychological profile (affective state and cognition)? What are the implications of any such differences for public health strategies aiming to narrow the deprivation gap in health?

CHAPTER 2 – METHODS

2.1 Identification of potential participants

Potential subjects for the Psychological, Social and Biological Determinants of Ill Health (pSoBid) study were identified on the basis of the Scottish Index for Multiple Deprivation (SIMD) 2004,[115] which ranks small areas on the basis of multiple deprivation indicators. The six domains of multiple deprivation indicators used in SIMD 2004 were: income (e.g. number of adults and children in households receiving Income Support); employment (e.g. unemployment claimant count average over 12 months, number of working age Incapacity Benefit recipients); health (e.g. number of hospital episodes related to alcohol use and drug use, number of hospital emergency admissions); education, skills and training (e.g. number of working age people with no qualifications, number of school leavers age 16 years and over not in education); geographic access and telecommunications (e.g. drive time access to General Practitioner, supermarket and primary school) and housing (e.g. number of persons in households which are overcrowded, number of persons in households which are without central heating). Using SIMD 2004, the least and most deprived areas in the Greater Glasgow Health Board area were identified. At the start of the study, 31.4% of the Glasgow population were in the bottom 5% of the SIMD classification and 6% were in the top 20% of the SIMD classification. In order for the population composition of Greater Glasgow to be reflected in the study population, and to provide sufficient numbers of participants from each end of the deprivation continuum for valid comparisons to be made, the decision was made to study participants living in areas classified as being in the bottom 5% (most deprived) of SIMD areas, and in the top 20% (least deprived).

Five general practices with the highest percentage of patients aged 35-64 years living in areas classified as being in the bottom 5% of SIMD were approached and all agreed to participate in the recruitment process. A further five practices with the highest percentage of patients aged 35-64 years living in areas classified as being in the top 20% of SIMD also agreed to participate. The Health Information and Technology section of Greater Glasgow Health Board generated a target population of 21 672 people from the practice lists of these ten practices. From this target population, 12 groups of 300 participants were selected according to strata defined by the combination of home address SIMD classification, gender and age group (35 to 44, 45 to 54 and 55 to 64 years), giving a total sampling frame of 3600 subjects. As the sampling frame was constructed from general practice lists, this

included individuals regardless of whether or not they actually visited their general practitioner.

2.2 Power calculation

Sample size in the least deprived and most deprived groups was estimated on the assumption that 90% of participants would attend both study visits and have C-reactive protein measured and that a maximum of 10% would not have a carotid ultrasound scan of satisfactory quality for measurement of carotid intima-media thickness. The power calculations were based on perceived clinically meaningful differences and assumed a 1.1mg/L standard deviation for the natural logarithm of C-reactive protein measurements[116] and a 0.163mm standard deviation for carotid intima-media thickness.[117] Power calculations indicated that a sample size of 350 per group (most deprived and least deprived) would provide 84% power to detect a 30% difference in mean C-reactive protein concentration and 82% power to detect a 0.04mm difference in mean carotid intima-media thickness.

2.3 Ethical approval

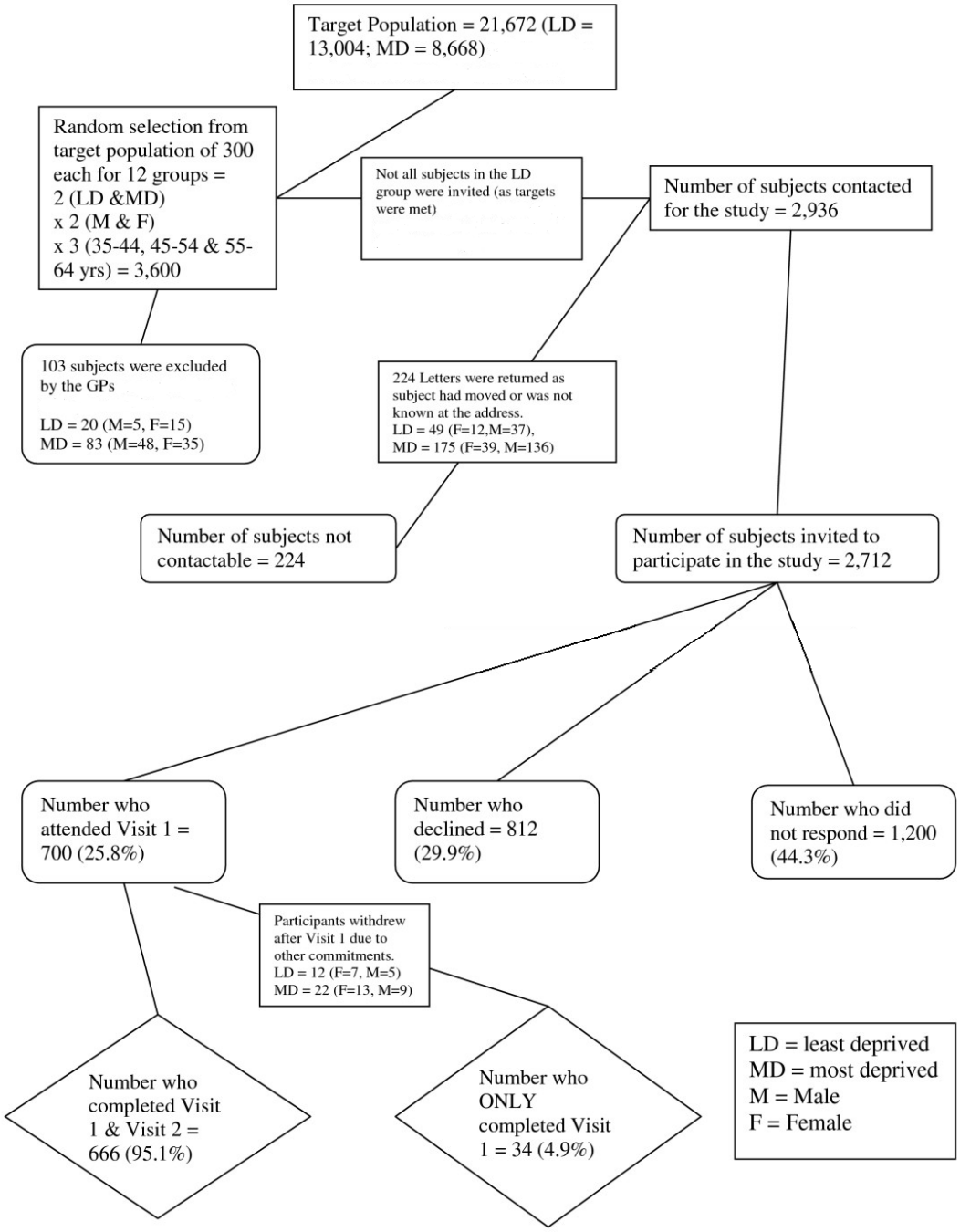
The study was approved by the Glasgow Royal Infirmary Research Ethics committee. All participants gave written informed consent.

2.4 Recruitment and response rates

Letters inviting potential subjects to participate were sent in batches of 150 every two weeks. Accompanying the letter was a form for the subject to return (in a reply paid envelope) recording their contact details and indicating their willingness to consider participation. Subjects who agreed to receive further information about the study were sent the pSoBid participant information booklet (Appendix 1). If there was no response after two weeks, a reminder was sent. The Research Nurse contacted those who received the participant information booklet, and if after reading the information booklet they decided to participate in the study, they were invited to come for the first visit at their General Practitioner's premises on a mutually agreed day and time. This process continued until approximately equal numbers for the 12 groups were recruited.

Figure 2.1 shows the recruitment flowchart for the study. Of the original sampling frame of 3600 potential subjects (1800 least deprived and 1800 most deprived), 1008 least deprived were invited to participate. (Not all of the 1800 subjects were contacted as recruitment targets had been met.) By contrast, 1704 most deprived subjects were invited to participate in order to meet recruitment targets. The only exclusion criteria for the study were having a terminal illness or an inability to understand the English language (due to the nature of the psychological questionnaires and cognitive assessments). General Practitioners were able to exclude subjects from the sample who were recently deceased or had a terminal illness.

Figure 2.1 Recruitment flowchart for the pSoBid study



Overall, 2712 invitations to participate were issued, with 700 participants completing study visit 1, giving an overall response rate of 25.8%. The response rates of different groups are shown in **Table 2.1**. This shows that the least deprived group (those who attended at least study visit 1) comprised 176 males and 178 females, while the most deprived group consisted of 165 males and 181 females. For the least deprived group as a whole, response rate was 35.1%, and for the most deprived group 20.3%. When examining each of the 12 groups stratified by deprivation (most/least deprived), gender and age (35-44 years, 45-54 years and 55-64 years), response rate varied from 14.1% in most deprived males age 35-44 years, to 52.9% in least deprived males age 55-64 years. In general, response rates were higher in older age groups, and in the least deprived group. The vast majority of participants were born in the United Kingdom or Republic of Ireland, with only 19 participants (2.7%) being born outside of these countries (14 from the least deprived group and 5 from the most deprived group).

Table 2.1 Response rates in the groups invited to participate in the pSoBid study

Sex/Depcat	Age Group	Completed Visit 1 & 2	Withdrew after Visit 1	Replied 'No'	Non-Respondents	Sent Letters
LD Female	**35–44**	55 (30.4%)	2 (1%)	66 (36.5%)	58 (32.1%)	181 (100%)
LD Female	**45–54**	56 (31.5%)	4 (2.2%)	74 (41.6%)	44 (24.7%)	178 (100%)
LD Female	**55–64**	60 (49.2%)	1 (0.8%)	46 (37.7%)	15 (12.3%)	122 (100%)
LD Female	**Total**	**171 (35.6%)**	**7 (1.4%)**	**186 (38.7%)**	**117 (24.3%)**	**481 (100%)**
LD Male	**35–44**	52 (21.6%)	2 (0.8%)	74 (30.7%)	113 (46.9%)	241 (100%)
LD Male	**45–54**	58 (34.7%)	1 (0.6%)	51 (30.6%)	57 (34.1%)	167 (100%)
LD Male	**55–64**	61 (51.2%)	2 (1.7%)	31 (26.1%)	25 (21.0%)	119 (100%)
LD Male	**Total**	**171 (32.4%)**	**5 (1%)**	**156 (29.6%)**	**195 (37.0%)**	**527 (100%)**
LD Participants		***342 (33.9%)***	***12 (1.2%)***	***342 (33.9%)***	***312 (31%)***	***1008 (100%)***
MD Female	**35–44**	55 (17.3%)	6 (1.9%)	70 (22.0%)	187 (58.8%)	318 (100%)
MD Female	**45–54**	55 (26%)	5 (2.4%)	69 (32.7%)	82 (38.9%)	211 (100%)
MD Female	**55–64**	58 (27.2%)	2 (1%)	81 (38.0%)	72 (33.8%)	213 (100%)
MD Female	**Total**	**168 (22.6%)**	**13 (1.8%)**	**220 (29.6%)**	**341 (46.0%)**	**742 (100%)**
MD Male	**35–44**	49 (13.6%)	2 (0.5%)	56 (15.5%)	254 (70.4%)	361 (100%)
MD Male	**45–54**	53 (16.5%)	4 (1.3%)	79 (24.6%)	185 (57.6%)	321 (100%)
MD Male	**55–64**	54 (19.3%)	3 (1.1%)	115 (41.0%)	108 (38.6%)	280 (100%)
MD Male	**Total**	**156 (16.2%)**	**9 (0.9%)**	**250 (26.0%)**	**547 (56.9%)**	**962 (100%)**
MD Participants		***324 (19.0%)***	***22 (1.3%)***	***470 (27.6%)***	***888 (52.1%)***	***1704 (100%)***
GRAND	**TOTAL**	**666 (24.6%)**	**34 (1.3%)**	**812 (29.9%)**	**1,200 (44.2%)**	**2712 (100%)**

LD = Least Deprived.
MD = Most Deprived
The total response rates were calculated by combining those who completed Visit 1 & 2 (column 3) with those who withdrew after Visit 1 (column 4).

2.5 Study protocol

Participant visits were conducted between December 2005 and May 2007, with participants attending for two visits, generally around two weeks apart. In visit 1, subjects completed lifestyle and psychology questionnaires, and underwent measurement of blood pressure, heart rate, hip, waist and mid-thigh circumference and assessment of lung function (Forced Expiratory Volume in 1 second [FEV1] and Forced Vital Capacity [FVC]. For visit 2, participants attended fasting for blood to be taken for biochemical analyses. Height and weight were measured. After being provided with breakfast, subjects completed psychological and cognitive tests. Finally, carotid ultrasound assessment of cIMT, plaque score and arterial stiffness was performed.

2.5.1 Lifestyle questionnaire

At visit 1, participants completed an extensive lifestyle and health questionnaire, with a study nurse asking the questions and directly recording the participants' answers onto an electronic proforma on a laptop. Questions addressed the following areas:

- Residence (owner-occupier/tenant/living with parents/other)
- Dependents; marital status
- Self-rating of health (very good/good/fair/bad/very bad)
- Past and present health
- Prescribed and over-the-counter medication
- Chest pain
- Periodontal disease
- Smoking
- Alcohol consumption
- Diet
- Physical activity
- Childhood circumstances
- Birth weight and place of birth
- Parental history
- Education
- Employment
- Income

Appendix 2 contains a paper version of the full lifestyle questionnaire.

2.5.2 Psychology questionnaires

In order to assess psychological parameters in relation to social deprivation and cardiovascular risk, participants next completed a series of psychology questionnaires. In visit 1, the General Health Questionnaire-28 (GHQ-28) was used to detect psychological distress by assessing the participant's current state and asking if it differed from their usual state.[118] Self-efficacy was assessed by the Generalised Self-Efficacy Scale (GSS);[119] sense of coherence by the Sense of Coherence Scale (SoC)[120] and hopelessness by the Beck Hopelessness Scale (BHS).[121] In visit 2, after being provided with breakfast, participants completed the Eysenck Personality Scale (EPR), which assesses the personality traits of neuroticism (the tendency to experience negative emotions including anxiety, anger and guilt), psychoticism (the predisposition to become sociopathic and tendency to be hostile, manipulative and impulsive) and extraversion (the tendency to enjoy positive events and human interaction).[122] Self-esteem was then assessed using the Rosenberg Self-Esteem Scale (RSES).[123]

2.5.3 Measurement of blood pressure and heart rate

In visit 1, after completion of the lifestyle questionnaire, blood pressure and heart rate were measured. The Standard Operating Procedure for study visits stipulated that the participant should remain seated for at least 10 minutes prior to measurement of blood pressure and heart rate, although in practice participants were seated for much longer than this, as the lifestyle questionnaire took around an hour to complete. Blood pressure and heart rate were measured on the participant's left arm using an Omron electronic sphygmomanometer (Omron Healthcare UK Ltd., Milton Keynes, United Kingdom).

2.5.4 Anthropometric measurements

In visit 1, after measurement of blood pressure and heart rate, participants' waist, hip and mid-thigh circumferences were measured using a standardised protocol. Waist circumference was measured with the participant standing, with the measurement being made at the level of the highest point of the iliac crest. Hip circumference was measured with a measuring tape placed around the buttocks at the maximum extension of the buttocks, encircling the hips in a horizontal plane. Mid-thigh circumference was measured on the right leg, with the participant sitting with legs straight and feet resting flat on the

ground. The mid-thigh location was defined as the point midway between the outer edge of the inguinal crease and the mid-point of the patella. Height, sitting height (to allow calculation of leg length) and weight were measured in visit 2.

2.5.5 Lung function

Forced Expiratory Volume in 1 second (FEV1) and Forced Vital Capacity (FVC) were measured at the end of visit 1 using a Vitalograph compact II spirometer (CareFusion 232 Ltd., Chatham Maritime, United Kingdom).

2.5.6 Biochemical analysis

Participants attended visit 2 having fasted for 12 hours in order for fasting blood samples to be taken for biochemical analysis of classic and emerging cardiovascular risk markers. All blood samples were separated and frozen at -80ºC within 1 hour of venepuncture, except for samples for cholesterol, triglycerides, Low Density Lipoprotein (LDL) cholesterol, High Density Lipoprotein (HDL) cholesterol, C-reactive protein (CRP) and glucose, which were analysed on fresh plasma.

2.5.6.1 Classic risk factors

Lipid profile: Cholesterol was determined by an enzymatic colorimetric assay on a Roche 917 analyser (Roche Diagnostics Ltd., Burgess Hill, United Kingdom). Triglyceride was determined by an enzymatic colorimetric assay on a Roche 917 analyser (Roche Diagnostics Ltd., Burgess Hill, United Kingdom). Lipid fractions were measured using ultracentrifugation at 105 000g at 4ºC for 16 hours, producing an upper fraction containing Very Low Density Lipoprotein (VLDL) and a lower fraction containing HDL and LDL. The LDL component was precipitated using a solution of heparin and manganous chloride, leaving the HDL in solution.[124] All of these lipid analyses had a between batch coefficient of variation (CV) of less than 3%.

Glucose: Glucose was measured by hexokinase/glucose-6-phosphate dehydrogenase assay on an Abbott c8000 analyser (Abbott Diagnostics, Maidenhead, United Kingdom). Between batch CVs ranged (on the different Abbott c8000 analysers used) from 1.13 to

1.89% at a glucose concentration of 3.23mmol/L; from 1.10 to 1.45% at 6.42mmol/L and from 0.83 to 1.83% at 20.4mmol/L.

2.5.6.2 Emerging risk factors

Insulin resistance/adiposity: Insulin was measured by a sandwich Enzyme-Linked Immunosorbent Assay (ELISA) (Mercodia AB, Uppsala, Sweden). Between batch analytical CV was 7.26% at 6.04mU/L and 7.85% at 11.2mU/L. Homeostasis Model Assessment – Insulin Resistance (HOMA-IR) was calculated as: Glucose (mmol/L) x Insulin (mU/L) / 22.5.[53] Leptin was measured by an in-house radioimmunoassay validated against a commercially available assay.[125] Between batch CVs for the leptin assay were 8.5% at 33ng/mL, 4.4% at 11.7ng/mL and 5.7% at 1.4ng/mL. Adiponectin was measured by sandwich ELISA (ALPCO Diagnostics, Salem, USA), and had a between batch CV of 8.9% for the total adiponectin assay and 15.1% for the high molecular weight assay. The higher CV for the high molecular weight assay was due to the fact that this assay has a number of pre-treatment steps before the samples are applied to the plate.

Inflammation/endothelial dysfunction: C-reactive protein (CRP) was measured by an immunoturbidimetric assay (Roche Diagnostics Ltd., Burgess Hill, United Kingdom), and had a CV of less than 3%. Interleukin-6 (IL-6) and soluble Intercellular Adhesion Molecule-1 (sICAM-1) were measured by sandwich ELISA (R&D Systems Europe Ltd., Abingdon, United Kingdom). The between batch CV for IL-6 was 8.3% at a concentration of 2.84pg/mL and 10.0% at 5.38pg/mL. The between batch CV for sICAM-1 was 5.5% at an analyte concentration of 190ng/mL and 8.1% at 240ng/mL.

Haemostasis: Von Willebrand Factor (vWF) was measured using an in-house ELISA, employing rabbit anti-human polyclonal antibodies (DAKO plc, High Wycombe, United Kingdom) and had a between batch CV of 3.4% at 128IU/dL. Fibrinogen was measured on an automated coagulometer (MDA-180, Organon Teknika, Cambridge, United Kingdom) with a between batch CV of 3.7% at a fibrinogen concentration of 2.89g/L. D-dimer and tissue Plasminogen Activator (tPA) antigen were measured by ELISA (Hyphen, Neuville-sur-Oise, France). The between batch CV for D-dimer was 5.3% at a concentration of 109ng/mL, and for tPA antigen was 6.5% at an analyte concentration of 4.42ng/mL.

2.5.7 Assessment of cognitive function

In visit 2, after venepuncture, consumption of breakfast (or abstinence, according to each participant's usual habit) and completion of the Eysenck Personality Scale and Rosenberg Self-Esteem Scale as detailed in Section **2.5.2**, participants underwent a series of psychometric assessments of cognitive function. The test battery was designed to assess the principal cognitive domains of memory, reaction and decision processes and executive function. The number and duration of the tests was constrained by the time demands that might reasonably be made upon participants who were required to attend two separate study visits. Memory was assessed by the Auditory Verbal Learning Test, which assesses the rate of learning, recall and recognition performance.[126] Five-choice reaction time was measured in milliseconds by the computerised system due to Hope *et al*[127] and sensitive to a range of factors affecting motor and decision speed. Executive function was assessed by means of the Stroop test, which assesses the ability to inhibit dominant and over-learned responses.[128]

2.5.8 Carotid ultrasound

The last part of study visit 2 involved a carotid ultrasound assessment of intima-media thickness, plaque score and arterial stiffness. All scans were performed on a Siemens Acuson Sequoia 512 scanner with an L7 5-12MHz linear array broadband transducer (Siemens Medical Solutions, Erlangen, Germany). The majority of the scans were performed by the same research nurse, who had prior training in ultrasound techniques as detailed in Chapter 3.

Carotid arteries were assessed bilaterally. The first stage of the protocol involved measuring Doppler velocity in the internal carotid artery to exclude significant internal carotid artery stenosis **(Figure 2.2)**. A protocol for action to be taken on finding a raised internal carotid artery Doppler velocity had previously been agreed with the vascular surgeons of Glasgow Royal Infirmary. Briefly, this protocol involved no action being required in the case of asymptomatic participants with a Doppler velocity of less than 1.2m/s. For asymptomatic individuals with a Doppler velocity of 1.2 to 2.3m/s (approximately corresponding to a 50-70% stenosis), the participant's General Practitioner was advised to commence the individual on appropriate secondary cardiovascular prevention. Where the velocity was greater than 2.3m/s (corresponding to greater than 70% stenosis) a recommendation was made to the General Practitioner that secondary

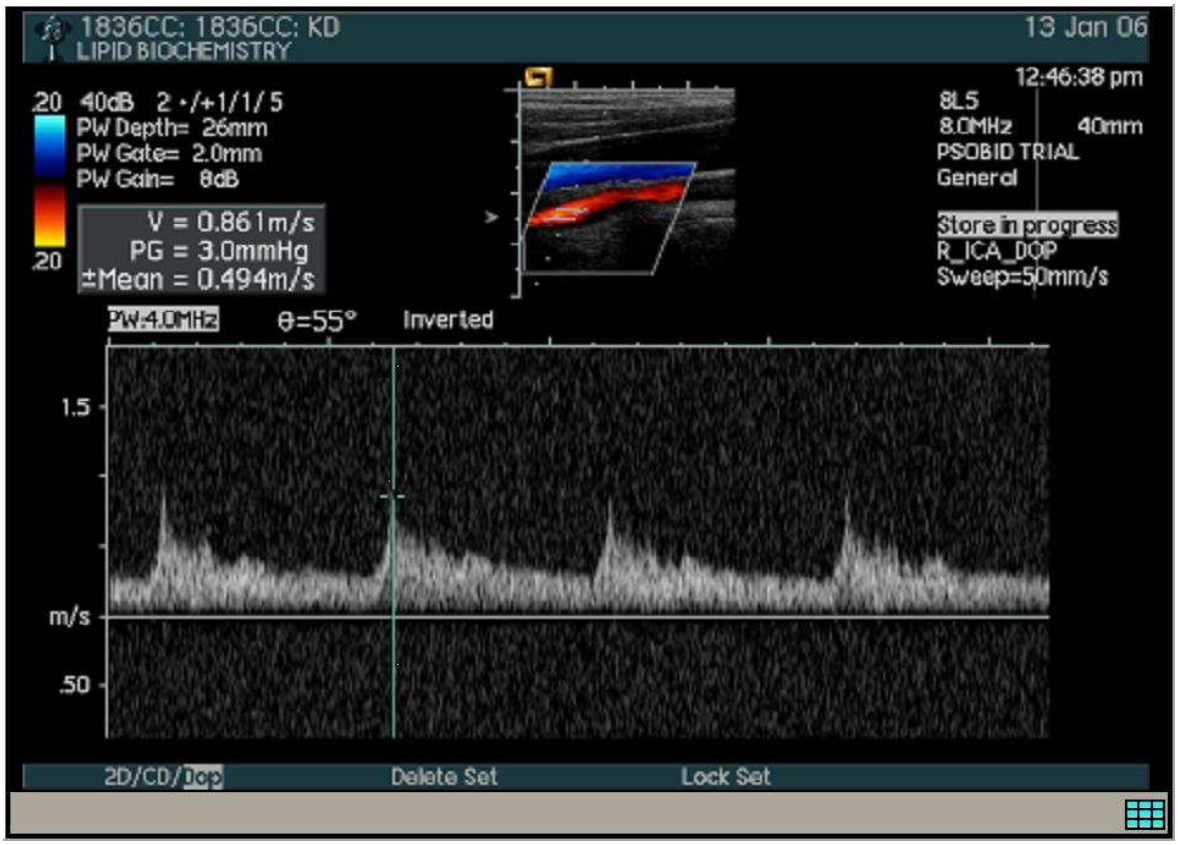
cardiovascular prevention therapy be instituted, and in addition it was suggested that the General Practitioner discuss with the individual whether he or she would like to be referred to the vascular surgeons for discussion of the possibility of surgical treatment. For symptomatic individuals (i.e. those experiencing recurrent transient ischaemic attacks) referral to the Stroke Service was recommended. A Doppler trace from a participant found to have a 50-70% right carotid artery stenosis and an image of the underlying stenosing plaque are shown in **Figure 2.3**.

B (brightness)-mode still images and dynamic clips were then recorded of the distal 1cm of the common carotid artery, the carotid bulb and the proximal internal carotid artery **(Figure 2.4)**. Care was taken to keep the images horizontal, and to maximise the length of far arterial wall over which the double-line pattern representing the combined thickness of the tunica intima and tunica media was visualised.

Finally, an M (movement)-mode image of the movement of the walls of the distal 1cm of the common carotid artery was recorded over at least two cardiac cycles, to allow assessment of parameters of arterial stiffness **(Figure 2.5)**. Blood pressure was measured using an Omron electronic sphygmomanometer (Omron Healthcare UK Ltd., Milton Keynes, United Kingdom) immediately before and after capturing each M-mode image in order to allow the parameters of arterial stiffness to be calculated.

Each scan was saved as a DICOM (Digital Imaging and Communications in Medicine) database.

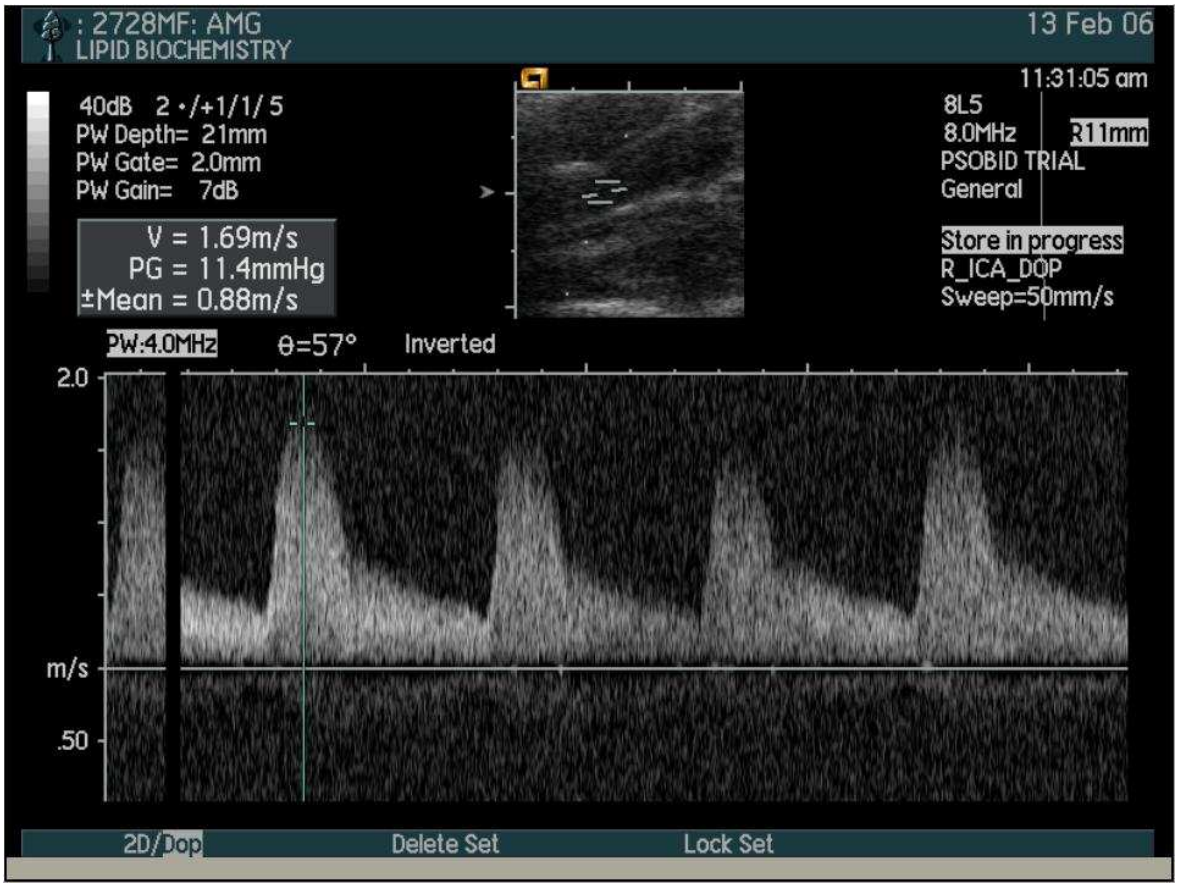
Figure 2.2 Internal carotid artery Doppler trace



Right internal carotid artery Doppler trace showing a Doppler velocity of 0.861m/s.

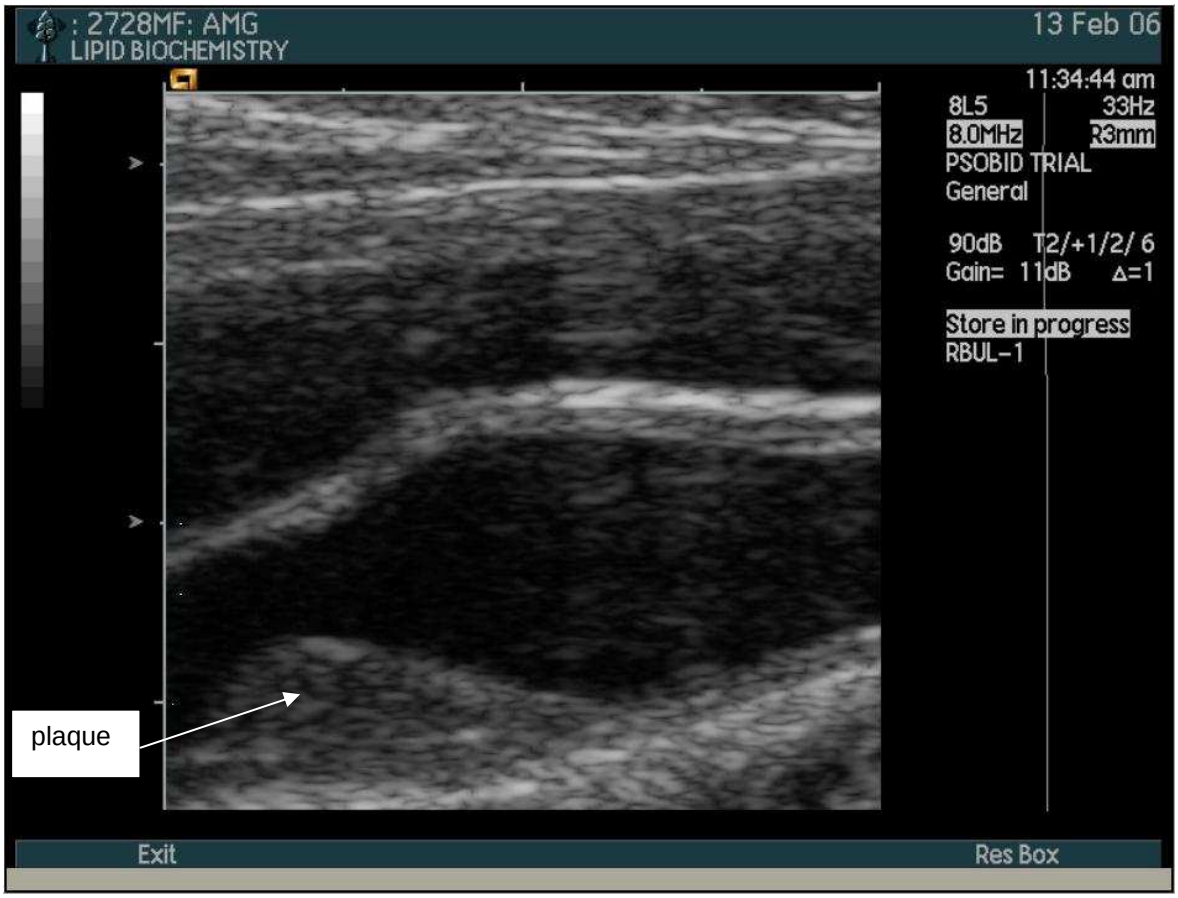
Figure 2.3 Internal carotid artery Doppler trace and B-mode ultrasound image from an individual with a 50-70% right carotid artery stenosis

A. Doppler trace



The right internal carotid artery Doppler velocity of 1.69m/s is consistent with a 50-70% carotid stenosis.

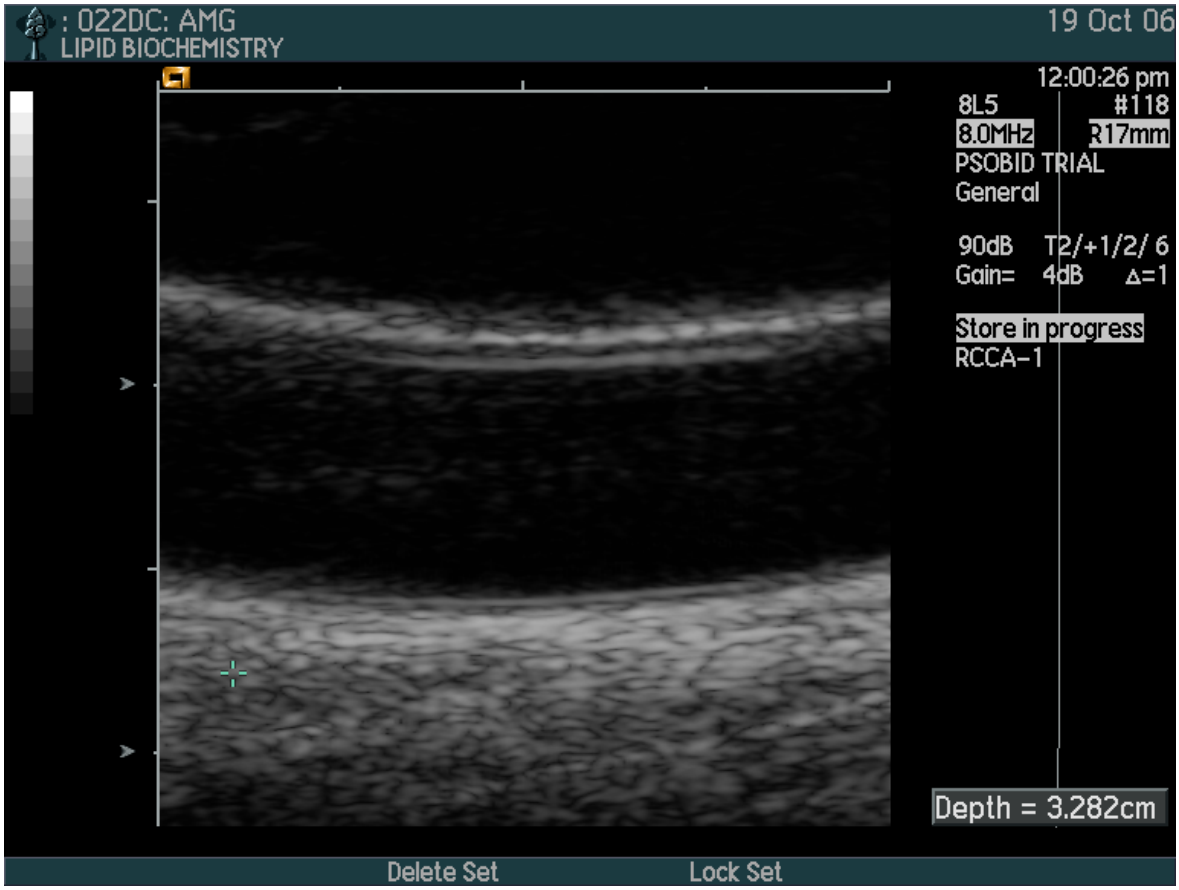
B. B-mode image of right carotid bulb



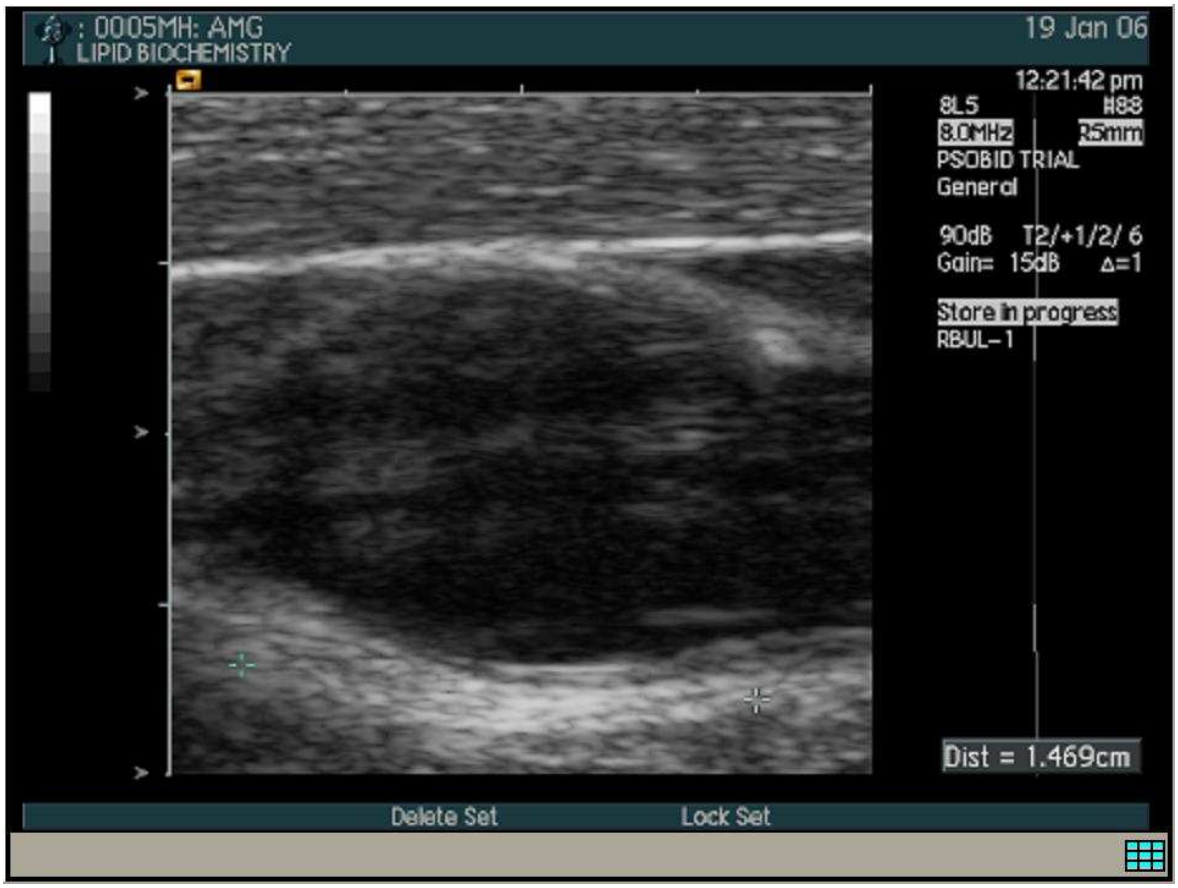
The plaque causing the 50-70% stenosis can be seen clearly on this B-mode ultrasound image.

Figure 2.4 B-mode still images of distal common carotid artery, carotid bulb and proximal internal carotid artery

A. Common carotid artery



B. Carotid bulb



C. Internal carotid artery

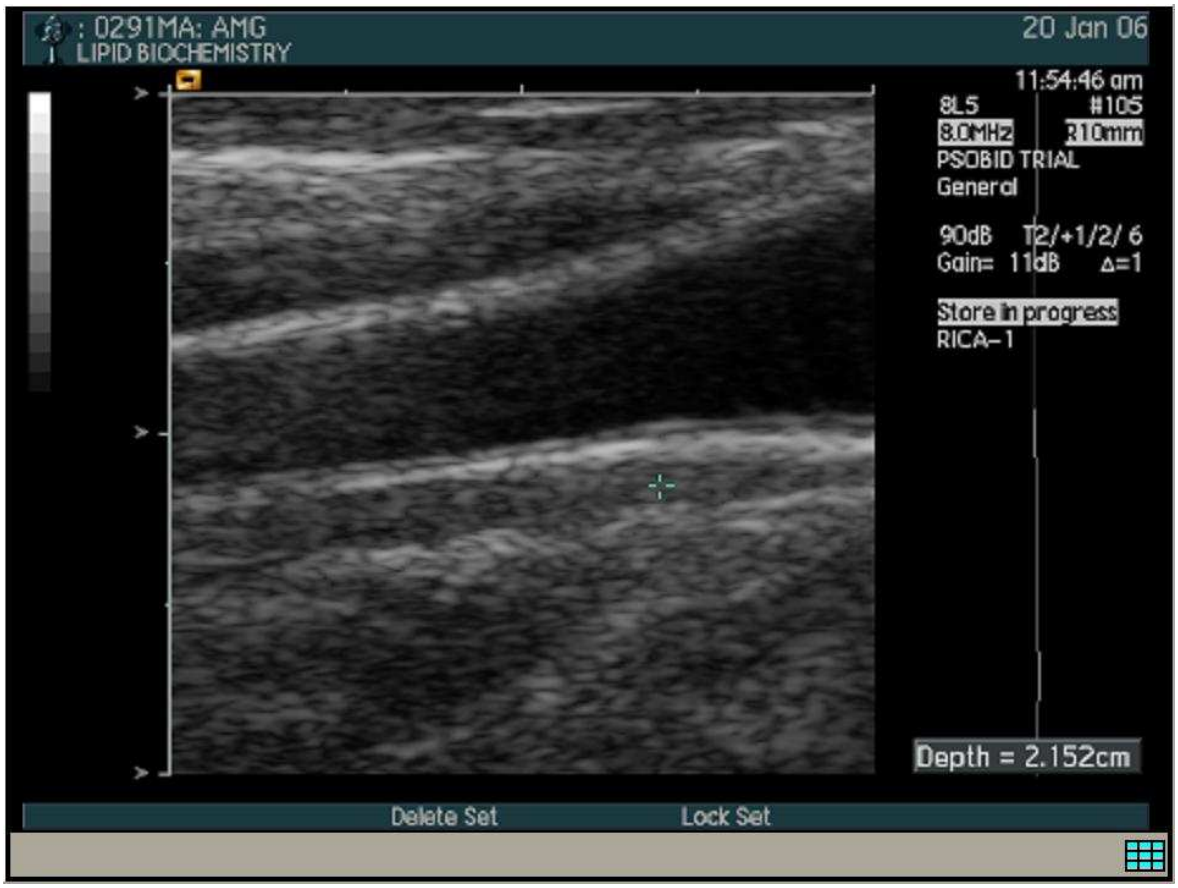
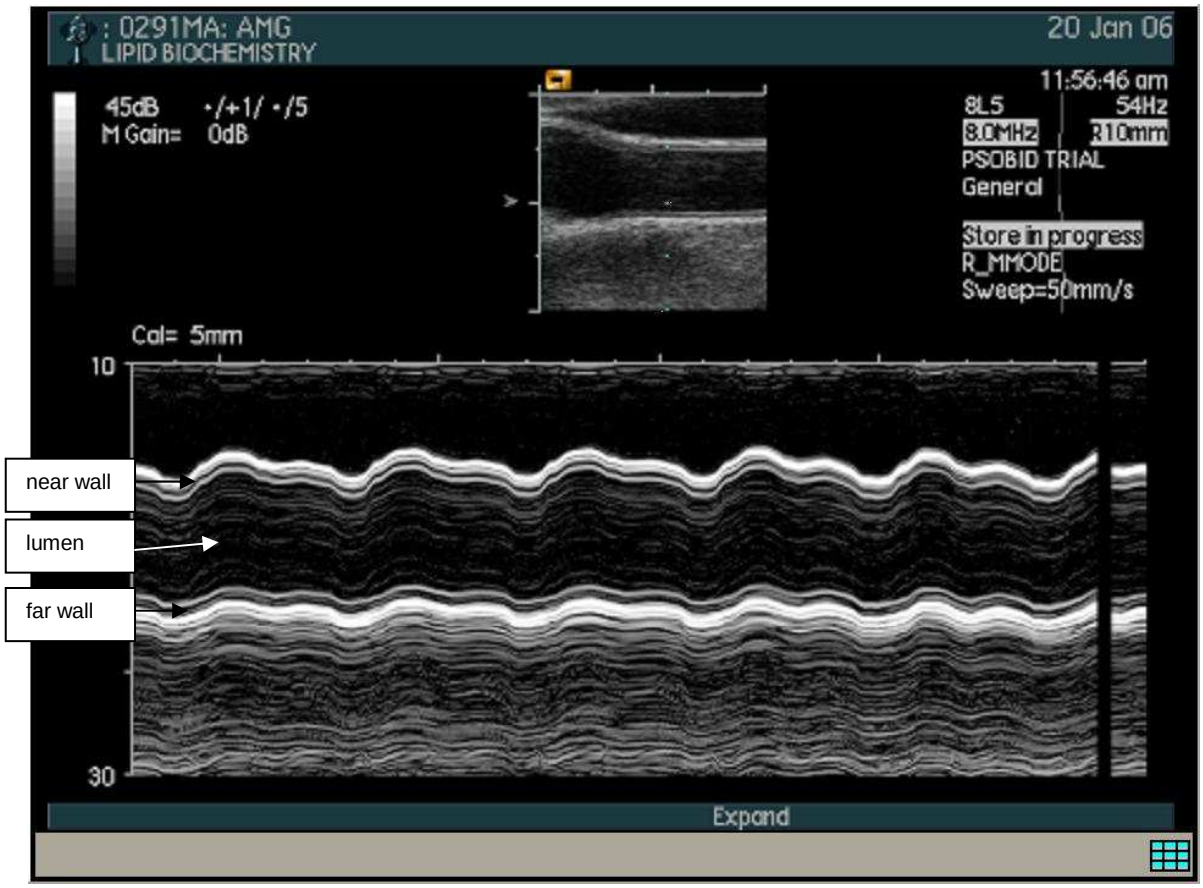


Figure 2.5 M-mode image of right distal common carotid artery



The small upper image shows a B-mode image of the distal common carotid artery, showing the region through which the cross-sectional M-mode image (lower image) was taken.

Scans were analysed using the eTrack software provided by the Department of Vascular Medicine and Physiology, Academic Medical Centre, Amsterdam, The Netherlands. All scans were analysed by myself, blinded to the identities of the participants. Carotid intima-media thickness (cIMT) was measured on the far wall of each arterial segment, averaged along a 1cm length, or as much of this as was able to be read **(Figure 2.6)**.

Plaque score was also calculated.[81] This was determined by counting the number of plaques, with plaque being defined as a focal structure encroaching into the arterial lumen of at least 0.5mm or 50% of the surrounding carotid intima-media thickness (cIMT) value, or demonstrating a thickness >1.5mm as measured from media-adventitia interface to intima-lumen interface.[80] This plaque count was then converted to plaque score by dividing by the number of readable images present and multiplying by 6 (the maximum possible number of images per subject),[81] thus adjusting for unreadable images.

Calculation of parameters of arterial stiffness was also carried out using the eTrack software to analyse the M-mode images of right and left common carotid arteries as shown in **Figure 2.7**. The algorithms used to derive the parameters of arterial stiffness are as follows:[129]

ΔP = systolic blood pressure – diastolic blood pressure
Δdiameter = change in lumen diameter between systole and diastole
strain = Δdiameter / diastolic diameter

distensibility = 2 x strain / ΔP

compliance = ($\prod$ x diastolic diameter x Δdiameter) / (2 x ΔP)

Petersen elasticity modulus = (ΔP/strain)

Stiffness(ß) = [ln(systolic blood pressure/diastolic blood pressure)] / Strain

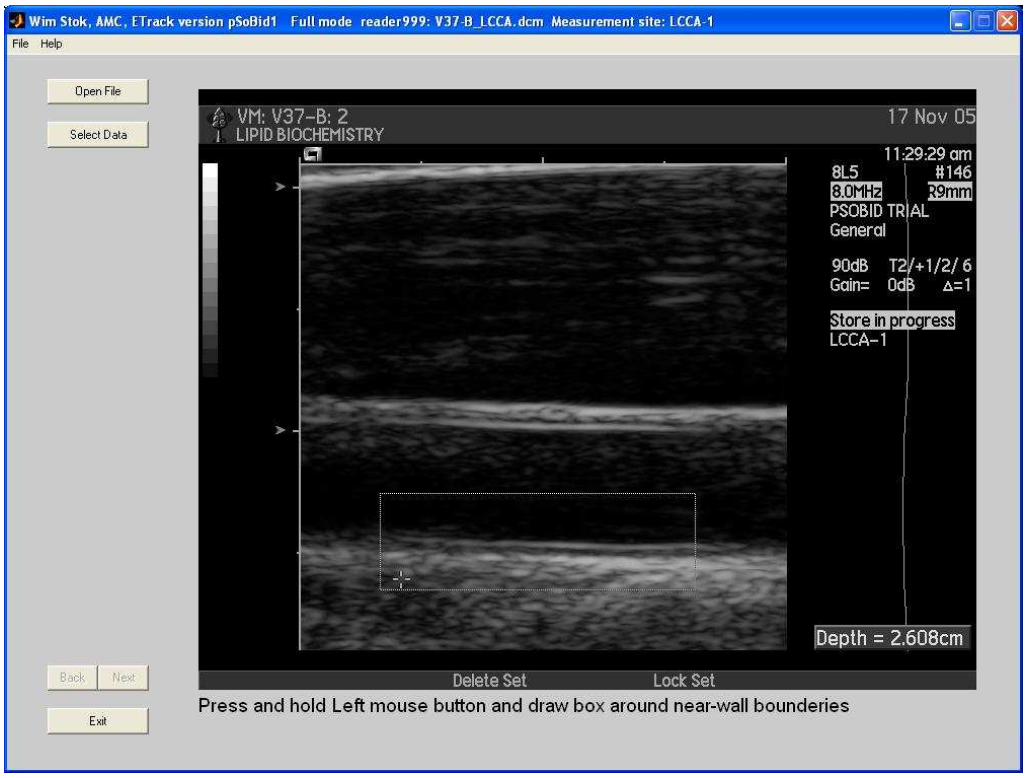
Modified formulae according to Heijden-Spek[130] were also used in order to account for non-negligible area changes over one heart beat in the large arteries:

$$distensibility\_Tf = (2 \times \Delta diameter \times diastolic\ diameter + \Delta diameter^2) / (\Delta P \times diastolic\ diameter^2)$$

$$compliance\_Tf = (\prod \times [2 \times \Delta diameter \times diastolic\ diameter + \Delta diameter^2]) / (4 \times \Delta P)$$

Figure 2.6 Analysis of common carotid artery intima-media thickness

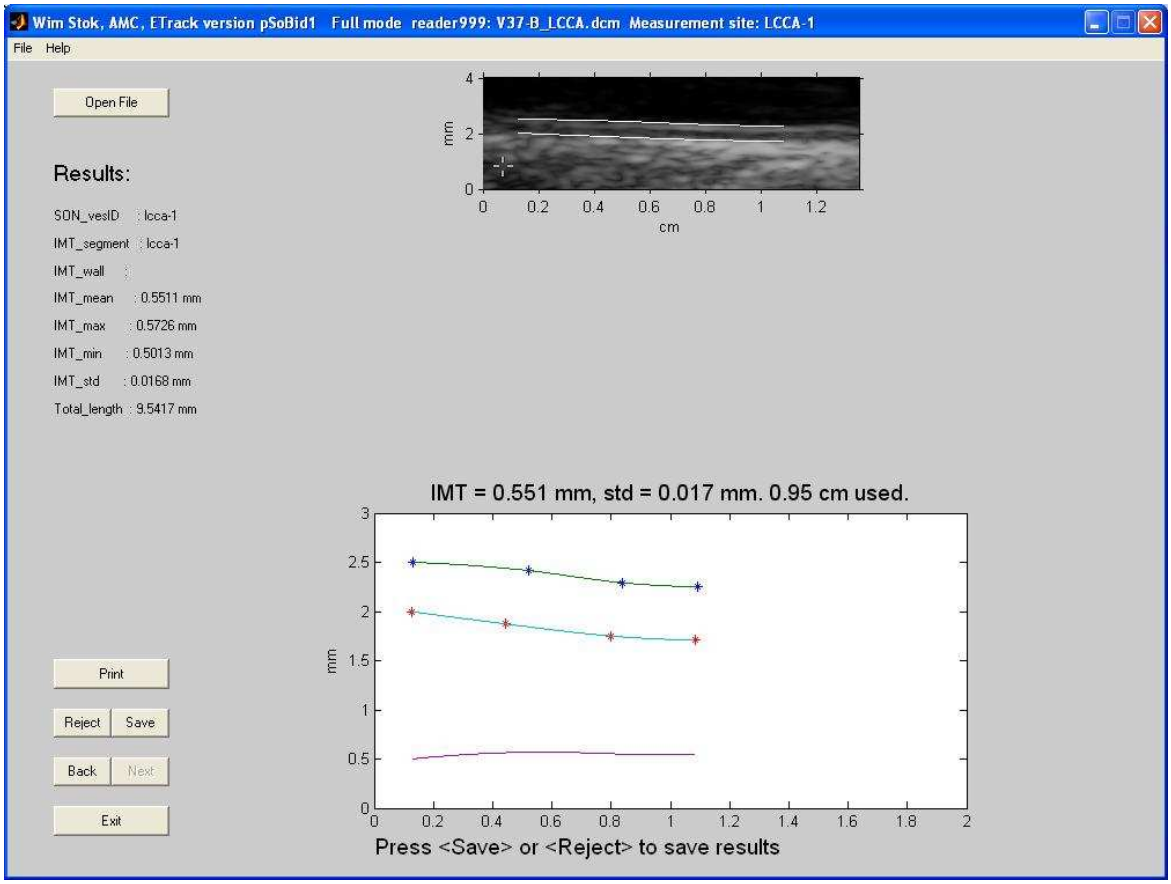
A. Selection of region of interest (distal 1cm of far wall of common carotid artery)



B. Identification of lumen-intima and media-adventitia borders on far wall

The analyst manually places the markers on the lumen-intima and media-adventitia borders.

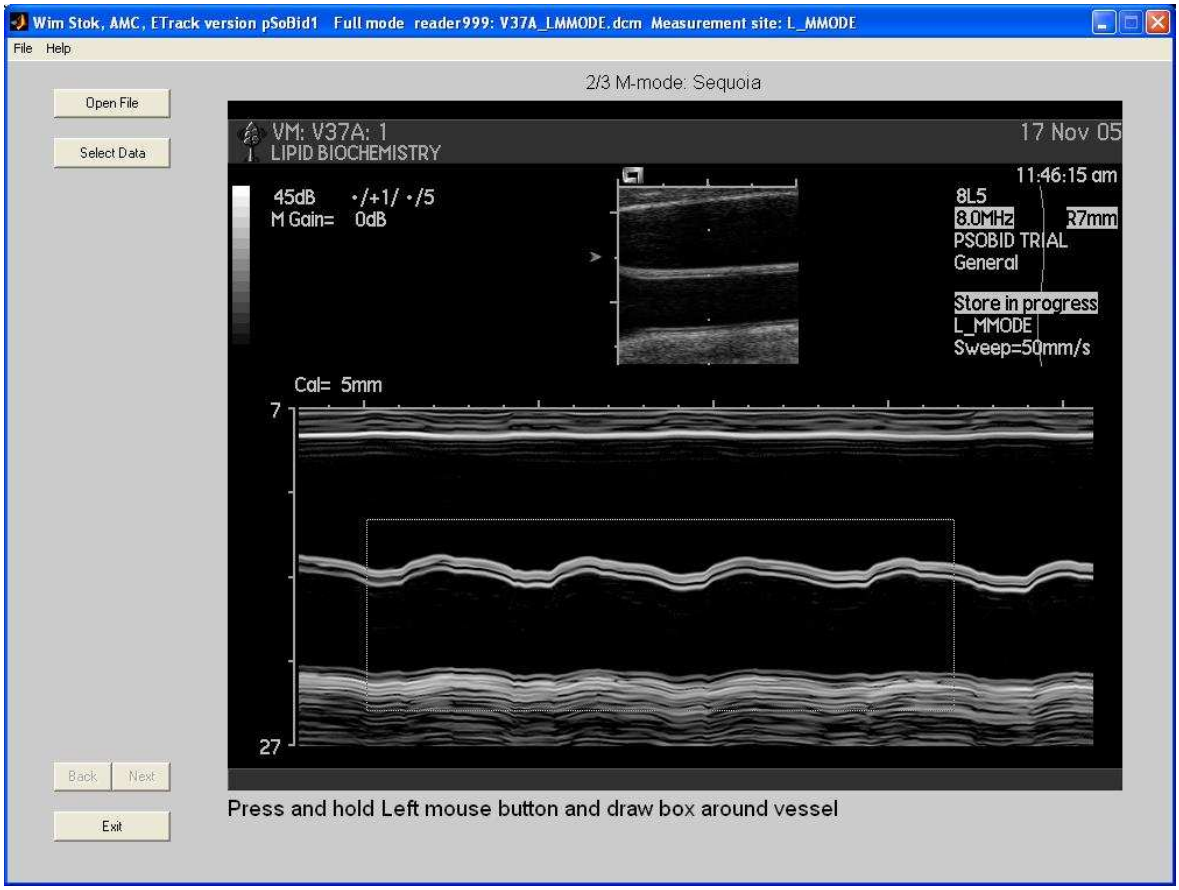
C. Automated calculation of intima-media thickness



Intima-media thickness is then automatically calculated. The value used is the mean intima-media thickness along the length of artery wall selected.

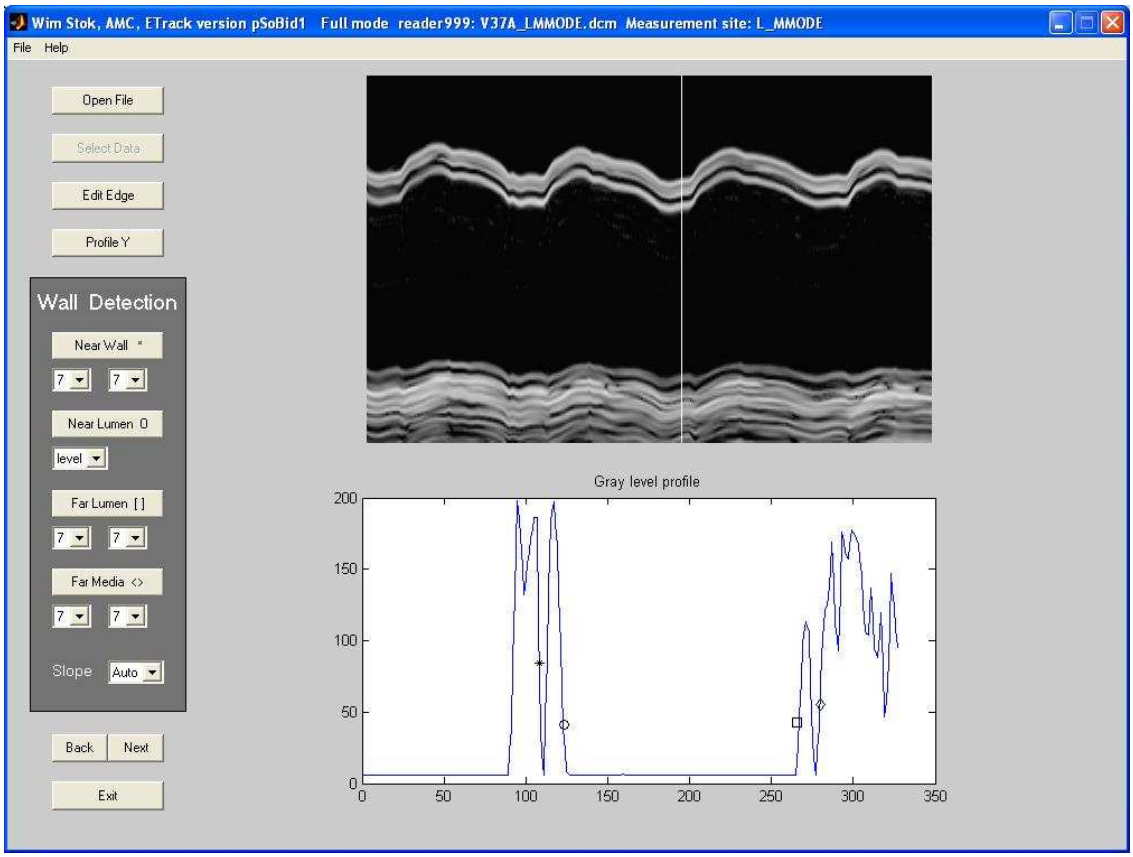
Figure 2.7 Calculation of parameters of arterial stiffness from M-mode image of distal common carotid artery

A. Selection of region of interest

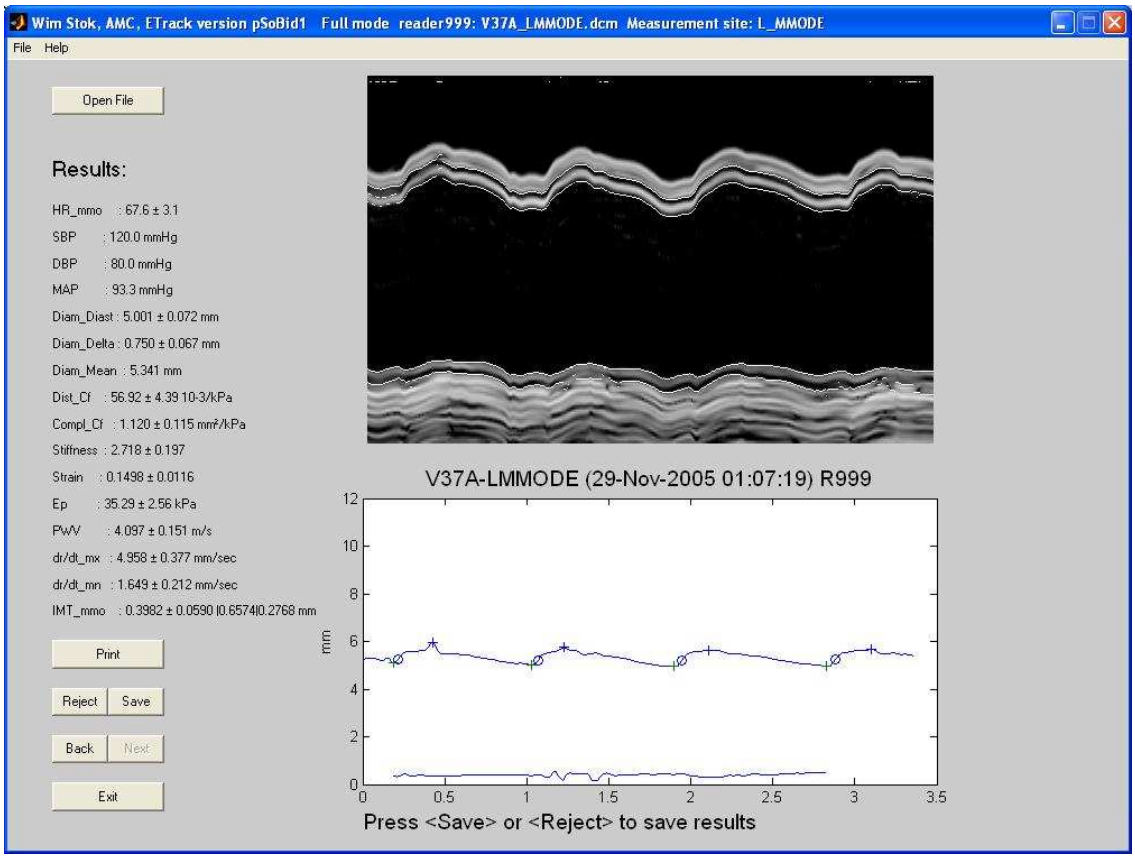


A region of the M-mode image encompassing near and far artery walls over at least two cardiac cycles is selected.

B. Identification of near and far walls



C. Automated identification of near and far walls and calculation of parameters of arterial stiffness



2.6 Descriptive statistics of study participants (Markers of individual-level socioeconomic status)

The characteristics of study participants in terms of markers of individual-level socioeconomic status are shown in **Table 2.2**.

2.6.1 Early life markers of socioeconomic status

The first striking feature of note **(Table 2.2)** is that height differed by 6cm and leg length by over 3cm between most and deprived participants (both $p<0.0001$). Leg length is recognised as a marker of nutritional status during the years of growth,[131] hence its inclusion as an early life marker of socioeconomic status. Number of people per room at age 11 years (as a marker of overcrowding in childhood) was significantly higher in the most deprived group. As expected, highly statistically significant differences in father's occupation and total years of education were observed between the most deprived and least deprived groups.

2.6.2 Other markers of individual-level socioeconomic status

As can be seen from **Table 2.2**, participant's occupation and annual income were significantly different ($p<0.0001$) in participants from most deprived areas compared to least deprived. A word of explanation is needed regarding the classification of participant's occupation by Registrar General's Social Class, and the apparently surprisingly low percentage of unemployed participants (0.6%) in the most deprived group. Registrar General Social Class was determined by each participant's current or most recent paid job – thus those not currently working were classified according to their last paid employment. Consequently, only those who were unemployed and had never been in paid employment were classified as unemployed in this analysis.

Table 2.2 Markers of individual-level socioeconomic status

Variable	Least deprived (n=342)	Most deprived (n=324)	p
(a) Early life markers of individual-level socioeconomic status			
Height (cm)	171.0 (9.4)	165.0 (8.7)	<0.0001
Data missing	2	1	
Leg length (cm)	81.9 (6.0)	78.7 (5.4)	<0.0001
Data missing	41	21	
People/room at age 11 yrs	1.2 (0.5)	1.8 (0.9)	<0.0001
Data missing	0	2	
Father's occupation:			<0.0001
0 Data not classifiable	15 (4%)	17 (5%)	
I Professional	30 (9%)	1 (0.3%)	
II Managerial & technical	130 (38%)	27 (8%)	
IIIN Skilled non-manual	30 (9%)	13 (4%)	
IIIM Skilled manual	98 (29%)	155 (48%)	
IV Partly skilled	22 (7%)	43 (13%)	
V Unskilled	10 (3%)	42 (13%)	
Unknown to participant	4 (1%)	16 (5%)	
Unemployed	1 (0.3%)	10 (3%)	
Data missing	2	0	
Total Education (years)	16.1 (3.6)	11.8 (2.5)	<0.0001
Data missing	0	0	
(b) Other markers of individual-level socioeconomic status			
Participant's occupation:			<0.0001
0 Data not classifiable	1 (0.3%)	16 (5%)	
I Professional	58 (17%)	5 (2%)	
II Managerial & technical	193 (57%)	57 (18%)	
IIIN Skilled non-manual	59 (17%)	52 (16%)	
IIIM Skilled manual	16 (5%)	87 (27%)	
IV Partly skilled	10 (3%)	70 (22%)	
V Unskilled	2 (0.6%)	35 (11%)	
Unemployed	1 (0.3%)	2 (0.6%)	
Data missing	2	0	
Annual Income:			<0.0001
<£15 000	12 (4%)	186 (57%)	
£16-25 000	29 (9%)	78 (24%)	
£26-35 000	40 (12%)	21 (7%)	
£36-45 000	44 (13%)	13 (4%)	
>£45 000	187 (55%)	10 (3%)	
Data missing	30	16	

Values are mean (SD), except for categorical variables for which percentages are shown. P values refer to difference between most deprived and least deprived, using analysis of covariance, adjusting for age and sex.

2.7 Comparison of participants and non-participants

In a population-based study such as this, it is clearly vital that the study group is as closely representative as possible of the population from which the subjects are drawn. On planning this study, a source of concern was the possibility that those volunteering to participate in the study would not be typical of the majority of the population from which the subjects were drawn – in particular that the "worried well" and "healthy deprived" would preferentially volunteer for the study, thus minimising the differences between the most deprived and least deprived groups being studied. To address this concern, and with the agreement of the Local Research Ethics Committee and the Greater Glasgow Health Board Caldicott Guardian, the characteristics of participants and non-participants were compared using anonymised data extracted from the General Practice Administration System for Scotland (GPASS),[132] which was used by 8 out of 10 of the practices from which participants were drawn (4 in the least deprived and 4 in the most deprived areas). Data were obtained on smoking status and current prescriptions for statins, aspirin, antihypertensives, antidepressants and antidiabetic drugs. Data were collected separately for those who attended visit 1 (Group 1, n=700), those who declined to attend (Group 2, n=812) and non-respondents to the invitation (Group 3, n=1200). Non-participants (Group 4, n=2012) were defined as the combination of groups 2 and 3.

In the least deprived group, a higher percentage of non-participants were current smokers (11.5%) compared to participants (6.3%); p=0.017, although no such difference was observed in the most deprived group (non-participants who were current smokers 50.5%; participants who were current smokers 48.8%; p=0.6). Both least and most deprived participants were more likely than non-participants to be on statins (least deprived participants 8.8%; least deprived non-participants 5.0%; p=0.03; most deprived participants 29.7%; most deprived non-participants 15.5%; p<0.0001), antihypertensives (least deprived participants 18.2%; least deprived non-participants 13.3%; p=0.05; most deprived participants 34.8%; most deprived non-participants 24.5%; p=0.0004), and antidiabetic medication (least deprived participants 2.8%; least deprived non-participants 0.9%; p=0.03; most deprived participants 8.5%; most deprived non-participants 5.0%; p=0.02).

Although these data demonstrate differences between participants and non-participants, it is plausible that the higher levels of prescriptions for statins, antihypertensives and antidiabetic drugs in participants compared to non-participants, especially in the most

deprived group, is that those in the most deprived group who participated had a higher level of recognised morbidity than those who did not participate, and probably were more concerned with their health, or were more used to visiting their General Practitioner. Thus, the initial concerns that the “healthy deprived” would preferentially volunteer from the most deprived group, do not appear to have materialised.

CHAPTER 3 – DEVELOPMENT AND VALIDATION OF CAROTID ULTRASOUND PROTOCOL

3.1 Initial training in carotid ultrasound

Carotid ultrasound assessment of intima-media thickness and plaque score had not previously been undertaken by the University Department of Vascular Biochemistry at Glasgow Royal Infirmary. For the purposes of obtaining the necessary training and expertise in carotid ultrasound techniques, I therefore arranged to collaborate with Professor John Kastelein, Dr Eric de Groot and colleagues in the Department of Vascular Medicine, Academic Medical Centre, Amsterdam, The Netherlands. For the carotid ultrasound work, it was preferable that the scans would be analysed by a different person to the sonographer, so that the analyst could read the scans blinded to the identity of the study participants. It was, therefore, planned that I would be responsible for analysing the ultrasound scans, with a research nurse carrying out the ultrasonography. However, it was prudent for me to be proficient in carrying out ultrasonography also, so that I could oversee training of the research nurse, and also so that I could scan participants if required to provide cover for the research nurse on rare occasions. I therefore received training in both ultrasonography and carotid ultrasound scan analysis from Dr Eric de Groot – this was undertaken at the Lipidklinikken, Rikshospitalet, Oslo, Norway, where Dr de Groot was training some research nurses in carotid ultrasound for another study.

3.2 Development of pSoBid carotid ultrasound protocol

Having become competent in carotid ultrasonography and analysis of scans, it was necessary to develop a carotid ultrasound protocol which would be suitable for the purposes of the pSoBid study. The protocol used is detailed in Chapter 2. The rationale behind each component of the protocol is as follows:

Common carotid artery intima-media thickness: One of the sources of difficulty in comparing the results of different carotid ultrasound studies is that different studies have used a variety of methods to measure intima-media thickness. In this study, mean common carotid intima-media thickness measured over as much of the far wall of the distal 1cm of the common carotid artery as possible, was the primary outcome; this was consistent both with the standards set out in the Mannheim Carotid Intima-Media Thickness consensus,[80] and also with accepted practice in the Department of Vascular Medicine, Academic

Medical Centre, Amsterdam, which is an internationally recognised authority on carotid intima-media thickness assessment.

Carotid bulb and internal carotid artery intima-media thicknesses: On a practical level, it was necessary to image the carotid bulbs and internal carotid arteries for assessment of plaque score (discussed in section 3.6, below) in any case. Furthermore, early atherosclerotic changes may be seen more commonly in the carotid bulbs and proximal internal carotid arteries than in the common carotid artery, so it was appropriate also to measure cIMT at these sites.

3.3 Training of research nurse

The vast majority of the carotid ultrasound scans were performed by the same research nurse, who had no previous experience of carotid ultrasound. Before the study commenced, therefore, she underwent a period of intensive training in carotid ultrasound scanning, with assessment of proficiency before the study commenced. Training was provided by myself in conjunction with Dr Eric de Groot and Mr Johan Gort of the Department of Vascular Medicine, Academic Medical Centre, Amsterdam, The Netherlands, and took place in part at Glasgow Royal Infirmary and in part at Academic Medical Centre, Amsterdam. Throughout this period, the research nurse performed practice scans on staff volunteers, leading up to an assessment of her precision as described in section 3.4, below.

3.4 Assessment of reproducibility of replicate scans

Towards the end of the period of intensive training in carotid ultrasound described in section 3.3, the research nurse performed duplicate carotid ultrasound scans on 10 staff volunteers, with the replicate scans being performed on separate days. This allowed assessment of the mean absolute difference for mean common carotid artery intima-media thickness, as prespecified in the ultrasound training plan for the pSoBid study. The results of these replicate scans are shown in **Table 3.1**, which shows that the mean absolute difference for mean common carotid artery IMT was 0.0542mm. This was well within the predefined performance requirement for sonographer certification, with the requirement having been determined by the Department of Vascular Medicine, Academic Medical Centre, Amsterdam, to be a mean absolute difference of $\leq$0.15mm, and was also within the

more stringent requirements suggested by the American Society of Echocardiography, who suggest a certification requirement of a mean absolute difference of $\leq$0.055mm.[78]

Approximately 1 year after commencement of the pSoBid study, assessment of reproducibility was repeated using the same procedure as detailed above, except that 5 staff volunteers had duplicate scans on separate days on this occasion. Again, reproducibility was within acceptable limits using either the Academic Medical Centre or American Society of Echocardiography criteria.

Table 3.1 Assessment of sonographer reproducibility of common carotid artery intima-media thickness measurement

Volunteer	RCCA IMT (mm) – 1st scan	LCCA IMT (mm) – 1st scan	Mean cIMT (mm) – 1st scan	RCCA IMT (mm) – 2nd scan	LCCA IMT (mm) – 2nd scan	Mean cIMT (mm) – 2nd scan	Absolute Difference in cIMT (mm)
1	0.5848	0.4293	**0.5071**	0.4867	0.4461	**0.4664**	**0.0407**
2	0.5342	0.5983	**0.5663**	0.4856	0.5028	**0.4942**	**0.0721**
3	U	0.4751	**0.4751**	0.5324	0.4947	**0.5136**	**0.0385**
4	0.4554	0.4291	**0.4423**	0.3656	0.3543	**0.3600**	**0.0823**
5	0.4873	0.4896	**0.4885**	0.6410	0.5199	**0.5805**	**0.0920**
6	0.4255	0.4430	**0.4343**	0.4189	0.4632	**0.4411**	**0.0068**
7	0.5064	0.4757	**0.4911**	0.5454	0.5948	**0.5701**	**0.0790**
8	0.6537	U	**0.6537**	0.6183	0.7803	**0.6993**	**0.0456**
9	0.4225	0.4703	**0.4464**	0.3548	0.4296	**0.3922**	**0.0542**
10	0.4056	0.4056	**0.4056**	0.4111	0.4616	**0.4364**	**0.0308**
Mean absolute difference for mean common carotid IMT (mm)							**0.0542**

RCCA: right common carotid artery

LCCA: left common carotid artery

U: scan unable to be analysed

3.5 Assessment of reproducibility of cIMT analysis

In a similar way to assessment of sonographer precision, scan analyst reproducibility was also assessed by repeat reading of 5% (n=33) of the pSoBid study scans. Results are shown in **Table 3.2**. The mean absolute difference in cIMT for my reproducibility as a scan analyst was 0.0362mm, which is within the predefined limit of satisfactory performance which was set by the Department of Vascular Medicine, Academic Medical Centre, Amsterdam, as a mean absolute difference $\leq$0.05mm, and also within the American Society of Echocardiography recommended limit of $\leq$0.055mm.[78]

Table 3.2 Assessment of reader reproducibility of common carotid artery intima-media thickness analysis

Participant ID	RCCA IMT (mm) – 1st reading	LCCA IMT (mm) – 1st reading	Mean cIMT (mm) – 1st reading	RCCA IMT (mm) – 2nd reading	LCCA IMT (mm) – 2nd reading	Mean cIMT (mm) – 2nd reading	Absolute Difference in cIMT (mm)
0002WL	0.6265	0.7403	**0.6834**	0.6287	0.7890	**0.7089**	**0.0255**
0188MN	0.5380	0.5333	**0.5357**	0.5051	0.5761	**0.5406**	**0.0050**
0277JM	1.1563	0.8671	**1.0117**	1.0228	0.8522	**0.9375**	**0.0742**
0367SK	0.5810	0.5940	**0.5875**	0.5982	0.5419	**0.5701**	**0.0175**
0492TH	0.7415	0.8142	**0.7779**	0.7220	0.7393	**0.7307**	**0.0472**
0611MD	0.5894	0.5809	**0.5852**	0.6676	0.5742	**0.6209**	**0.0358**
0704MM	0.7734	0.9227	**0.8481**	0.8240	0.9619	**0.8930**	**0.0449**
0809PI	0.6436	0.6359	**0.6398**	0.6173	0.6375	**0.6274**	**0.0124**
0910CC	0.6319	0.6649	**0.6484**	0.5946	0.7073	**0.6510**	**0.0026**
1064KJ	0.5960	0.6260	**0.6110**	0.6577	0.5601	**0.6089**	**0.0021**
1222VC	0.5763	0.5840	**0.5802**	0.5885	0.7863	**0.6874**	**0.1073**
1297AC	U	U	**U**	U	U	**U**	**U**
1407CB	0.6563	0.5098	**0.5831**	0.5573	0.5597	**0.5585**	**0.0246**
1524CL	0.5590	0.7883	**0.6737**	0.4923	0.7037	**0.5980**	**0.0757**
1613DD	0.6421	0.4232	**0.5327**	0.6502	0.4331	**0.5417**	**0.0090**
1761JC	0.5053	0.5582	**0.5318**	0.5611	0.5073	**0.5342**	**0.0025**
1842JW	0.9560	0.9937	**0.9749**	0.9764	1.0736	**1.0250**	**0.0502**
1996JH	0.8124	0.7240	**0.7682**	0.7940	0.6934	**0.7437**	**0.0245**
2135HC	0.7454	1.0696	**0.9075**	0.8250	1.0868	**0.9559**	**0.0484**
2233MM	0.5883	0.4983	**0.5433**	0.5464	0.5954	**0.5709**	**0.0276**
2403AD	0.7348	0.7850	**0.7599**	0.7308	0.8113	**0.7711**	**0.0112**
2630VK	0.8539	0.8793	**0.8666**	0.8651	0.7849	**0.8250**	**0.0416**
2744MC	0.7225	0.7787	**0.7506**	0.7224	0.7132	**0.7178**	**0.0328**
2859HW	0.7006	0.7344	**0.7175**	0.6198	0.5959	**0.6079**	**0.1097**
2984RB	0.6486	0.7586	**0.7036**	0.5779	0.7709	**0.6744**	**0.0292**
3100JS	0.7194	0.5593	**0.6394**	0.5965	0.4356	**0.5161**	**0.1233**
3225EB	0.4775	U	**0.4775**	0.4738	U	**0.4738**	**0.0037**
3349DA	U	U	**U**	U	U	**U**	**U**
3493NM	0.7973	0.7939	**0.7956**	0.7625	0.7573	**0.7599**	**0.0357**
3610JS	0.8847	0.5468	**0.7158**	1.0392	0.5072	**0.7732**	**0.0575**
3853WT	0.6900	0.6373	**0.6637**	0.7467	0.6274	**0.6871**	**0.0234**
4129EM	0.6105	0.5385	**0.5745**	0.5618	0.5647	**0.5633**	**0.0113**
4450SL	0.5900	0.8186	**0.7043**	0.5783	0.8180	**0.6982**	**0.0062**
Mean absolute difference (mm)							**0.0362**

RCCA: right common carotid artery

LCCA: left common carotid artery

U: scan unable to be analysed

3.6 Plaque score

In order for determination of plaque score to be as objective and reproducible as possible, it was necessary to define plaque using objective criteria. The most widely accepted definition of plaque is as set out in the Mannheim Carotid Intima-Media Consensus (2004-2006),[80] which defines plaque as:

> "a focal structure encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value, or demonstrating a thickness >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface."

A very similar definition of plaque has been recommended by the American Society of Echocardiography.[78]

Using the above definition of plaque, the six movie images per subject (common carotid artery, carotid bulb and internal carotid artery on each side) were examined offline and the total number of plaques for each subject was recorded. The movie images were used as it was much easier on these images to differentiate plaque from image artefact, which could occasionally be difficult to differentiate in some subjects who had been difficult to scan. I analysed all scans for plaque number, blinded to the identity of the participants. I did not have facilities to assess plaque cross-sectional area, or plaque volume (the assessment of which is still very much an emerging technique).[133]

It was then necessary to adjust plaque count to take account of missing or unreadable images, in order to avoid biasing the results by attributing to all unreadable images an assumed plaque count of zero. In order to do this, an approach akin to that used in the Rotterdam study was derived.[81] The plaque number, derived as detailed above, was divided by the number of readable image segments for that subject, then multiplied by 6 (the maximum number of readable image segments per subject), thus adjusting for any unreadable images.

CHAPTER 4 – SOCIAL DEPRIVATION AND CARDIOVASCULAR RISK MARKERS

4.1 Introduction

As discussed in detail in chapter 1, the currently recognised (classic) cardiovascular risk factors include smoking, physical activity, hypercholesterolaemia, diabetes mellitus, obesity and hypertension. Although clear socioeconomic gradients exist for many of these risk factors, differences in classic risk factors typically explain only part of the excess coronary heart disease risk associated with social deprivation (38% of the excess risk in the Whitehall II study[25] and 39% in the British Regional Heart Study).[50] Attention must therefore turn to emerging risk factors in an attempt to explain the remainder of the excess coronary heart disease risk associated with social deprivation.

Such emerging risk factors include markers of insulin resistance and adiposity (fasting insulin, Homeostasis Model Assessment – Insulin Resistance [HOMA-IR], adiponectin and leptin), inflammation (e.g. CRP and IL-6), endothelial dysfunction (e.g. sICAM-1) and haemostasis (vWF, fibrinogen, D-dimer and tPA antigen). The associations of these factors with coronary heart disease risk and with social deprivation have been discussed in chapter 1. The contribution of these emerging risk factors to the explanation of the socioeconomic gradient in coronary heart disease risk has been less extensively studied than that of the classic risk factors. However, the Women's Health Study found that adjusting for CRP, sICAM-1, fibrinogen and homocysteine had no impact on the socioeconomic gradient in cardiovascular events.[71]

Other potential risk factors are, of course, constantly emerging, and asymmetric dimethylarginine (ADMA) is one of those. ADMA is an inhibitor of nitric oxide synthase, the enzyme which synthesises nitric oxide, the major endothelium-derived relaxing factor. Nitric oxide also has a number of antiatherogenic properties. Intravenous infusion of ADMA raises systemic vascular resistance, impairs the cardiac response to exercise and has adverse effects on renal perfusion and sodium excretion. Associations have been noted between ADMA concentration and hypercholesterolaemia, insulin resistance, chronic kidney disease and hypertension. ADMA concentration is higher in people with coronary heart disease than in controls; is associated with severity of lesions at angiography in people with established CHD; correlates with cIMT and independently predicts cIMT progression. In prospective studies, ADMA has been shown to predict acute coronary

events, cardiovascular mortality and all-cause mortality, independent of classic cardiovascular risk factors.[134] No studies have been identified to date that examined ADMA concentrations in relation to social deprivation.

In recent years, much attention has been focussed on associations between low concentrations of vitamin D and cardiovascular risk.[135] Vitamin D receptors (VDRs) have recently been shown to be expressed in various tissues which are aetiologically important in the progress of cardiovascular disease, including vascular smooth muscle cells, vascular endothelium, cardiomyocytes, and in T-cells, B-cells and dendritic cells.[136] Observational studies have found low circulating concentrations of 25-hydroxy vitamin D to be prevalent in cardiovascular diseases such as coronary heart disease, heart failure and stroke.[137-139] Prospectively, a link between low 25-hydroxy vitamin D concentrations and higher risk for incident cardiovascular disease (CVD) events was recently reported, with a hazard ratio of 1.80 (1.05-3.08) at <10ng/ml in fully adjusted models.[140] A similar finding was reported in the Health Professionals Study.[141] By contrast, a randomised intervention trial of vitamin D and calcium supplementation in >36 000 women[142] showed no difference in a post hoc analysis of risk for incident CVD with combined intakes of vitamin D and calcium versus placebo. A possible explanation for this discrepancy is confounding of circulating vitamin concentrations by socioeconomic status, which is often inadequately adjusted for in epidemiological studies.[143] Further data relating vitamin D levels to vascular markers of CVD are required, in particular with better assessment of potential confounding factors, including social deprivation.

Cortisol has been identified as a potential mediator between chronic stress and CHD risk. The Caerphilly study of 2512 men aged 45 to 59 years found a prospective association between morning serum cortisol to testosterone ratio and incident ischaemic heart disease (age-adjusted odds ratio of 1.22 per z score change in cortisol:testosterone ratio, p=0.003). Adjusting for markers of insulin resistance (fasting glucose, insulin and HOMA-IR) markedly attenuated this association (adjusted odds ratio 1.10 per z score change in cortisol:testosterone ratio, p=0.18). These findings suggested that the association between cortisol:testosterone ratio, as a marker of chronic stress, and CHD risk may be mediated through insulin resistance.[144] Despite the associations between chronic stress and serum cortisol, a recent review of the literature found no consistent evidence for an association between serum cortisol and socioeconomic status. Although some studies included in the review had reported an association between lower socioeconomic status and higher

concentrations of cortisol, many studies had found no association, and some had reported the opposite relationship.[145]

Non-alcoholic fatty liver disease (NAFLD), typically (but non-specifically) characterised by an elevated alanine aminotransferase (ALT) concentration,[146] is now recognised to be strongly associated with obesity, insulin resistance, dyslipidaemia and type 2 diabetes mellitus, and to be an independent cardiovascular risk factor.[147]

Chronic kidney disease is now well recognised as being indicative of increased cardiovascular risk.[148] In routine clinical practice, glomerular filtration rate (GFR) is often estimated using the four variable Modification of Diet in Renal Disease (MDRD) equation, which uses serum creatinine concentration, age, sex and ethnicity to estimate GFR.[149] Cystatin C, a protein synthesised at a constant rate in all nucleated cells, freely filtered in the glomerulus and completely reabsorbed and catabolised in the proximal tubule, has been proposed as a more ideal marker of GFR – although it is also influenced by age, BMI, sex and smoking status. Importantly, cystatin C concentration has been found to be predictive in elderly patients of cardiovascular death from all causes, MI, stroke, incident heart failure and death from all causes. In patients with existing CHD, cystatin C is predictive of all-cause mortality and MI, and in patients with established chronic kidney disease, cystatin C predicts all cause mortality. In patients without chronic kidney disease, cystatin C predicts hypertension, death (both cardiovascular and non-cardiovascular), heart failure, stroke and MI. Furthermore, cystatin C appears to improve identification of individuals at high risk of cardiovascular events compared to models which use creatinine or estimated GFR values, possibly because of the ability of cystatin C to identify earlier stages of deteriorating renal function.[150] The association of cystatin C with social deprivation has been examined in a study of 736 African Americans aged over 65 years. Renal dysfunction was found to be strongly associated with low income (<$8000/year) when renal dysfunction was classified by either cystatin C or estimated GFR.[151]

The aim of the work detailed in this chapter was to enhance current knowledge of the associations between social deprivation and the cardiovascular risk markers detailed above. Primarily, this was in order to identify potential mediators of the associations between social deprivation and cardiovascular risk, with differences in the measured biomarkers being analysed to determine if they contribute to the explanation of any differences in ultrasound markers of subclinical atherosclerosis – this aspect of the work is detailed in chapter 5.

4.2 Methods

4.2.1 Biochemical methods

The plasma samples used for the work described in this chapter were obtained in the pSoBid study as detailed in chapter 2. Biochemical methods for lipids, glucose, insulin, adiponectin, leptin, CRP, IL-6, sICAM-1, vWF, fibrinogen, D-dimer and tPA antigen are described in chapter 2. In addition, the following biochemical analyses were carried out: ADMA was measured by High Performance Liquid Chromatography (HPLC) after cation exchange extraction and derivatisation.[152] 25-hydroxy vitamin D was measured using an automated solid-phase extraction (SPE) procedure with liquid chromatography-tandem mass spectrometry (LC-MS/MS).[153] Cortisol was measured by immunoassay on an Abbott c8000 analyser (Abbott Diagnostics, Maidenhead, United Kingdom). Creatinine, cystatin C, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyl transferase (GGT) were measured on an ILAB 600 clinical chemistry analyser (Instrumentation Laboratory UK Ltd., Warrington, United Kingdom). Creatinine was measured by kinetic Jaffe reaction (Randox Laboratories, Crumlin, United Kingdom). Estimated Glomerular Filtration Rate (eGFR) was calculated by the 4-variable Modified Diet in Renal Disease (MDRD) equation.[149] Cystatin C was measured immunoturbidimetrically (Dako UK Ltd., Ely, United Kingdom). Alanine aminotransferase (ALT) was measured by enzymatic reaction with lactate dehydrogenase (Instrumentation Laboratory UK Ltd., Warrington, United Kingdom). Aspartate aminotransferase (AST) was measured by enzymatic reaction with malate dehydrogenase (Instrumentation Laboratory UK Ltd., Warrington, United Kingdom). Gamma glutamyl transferase (GGT) was measured enzymatically (Instrumentation Laboratory UK Ltd., Warrington, United Kingdom).

4.2.2 Statistical methods

Descriptive statistics are presented as mean (SD) for continuous variables and count (%) for categorical outcomes. Variables with positively skewed distributions (triglyceride, CRP, IL6 and sICAM-1) are described by geometric means and log-transformation was used for regression analysis. For comparisons of population characteristics between deprivation groups, analysis of covariance was used for continuous variables, and logistic regression analyses for binary responses, with the results presented as p values comparing adjusted ‘least’ minus ‘most’ deprived means and odds ratio for least versus most deprived

categories respectively, adjusting for age and sex. Alcohol consumption, arginine, homoarginine, ADMA, symmetric dimethylarginine (SDMA), ALT, AST, creatinine, cystatin C and GGT showed non-parametric distribution and are described as median (interquartile range) and comparison of most versus least deprived is by Mann-Whitney test. Cortisol was normally distributed and so is described as mean (SD) and comparison between most and least deprived is by Student's T test. Normality of distribution was assessed by the Anderson-Darling test. Analyses were conducted in R v2.8 and Minitab Release 13.1.

4.3 Results

Differences in classic and emerging cardiovascular risk factors between most and least deprived participants are shown in **Table 4.1.**

4.3.1 Classic risk factors

4.3.1.1 Behavioural risk factors

As expected, there was a highly significant difference in number of participants who had ever smoked regularly, and also in percentage of current cigarette smokers, between most affluent and most deprived areas. Physical activity was significantly different between least and most deprived, with almost half of those in the most deprived areas being physically inactive, compared with just under a quarter of those in the least deprived areas ($p<0.0001$ for trend).

The findings on alcohol consumption at first seem surprising, with self-reported weekly alcohol consumption being significantly higher in the least deprived group ($p<0.0001$). **Figure 4.1** gives further detail about the distribution of alcohol consumption in least versus most deprived groups. Although the median weekly alcohol consumption was higher in the least deprived group, there were a number of outliers in the most deprived group with very high weekly alcohol consumption.

4.3.1.2 Physiological risk factors

Total and Low Density Lipoprotein (LDL) cholesterol were significantly different between least and most deprived participants, with the difference being the opposite of what might

intuitively be expected, in that total cholesterol and LDL were higher in the least deprived group. These differences persisted after adjusting for statin use: 69 (21.3%) of the most deprived and 18 (5.3%) of the least deprived participants were on statin therapy. If participants on statin therapy were excluded, mean (SD) total cholesterol was 5.36 (0.98) mmol/L in the least deprived group and 5.13 (1.00) mmol/L in the most deprived; adjusted p value=0.049 after adjusting for age, sex and statin use (data not shown). The differences in triglycerides and High Density Lipoprotein (HDL) were in the expected directions (higher HDL and lower triglycerides in the least deprived group). LDL/HDL ratio did not differ between least and most deprived (mean of 2.37 in both; p=0.91).

Fasting glucose was higher in the most deprived group, as was waist/hip ratio. Weight did not differ between the two groups, but by virtue of the differences in height, body mass index (BMI) was significantly higher in the most deprived group. Blood pressure did not differ between the two groups.

4.3.2 Emerging risk factors

4.3.2.1 Markers of insulin resistance / adiposity

Fasting insulin was significantly higher in the most deprived group. As a consequence of this and the higher fasting glucose concentration in the most deprived group, Homeostasis Model Assessment – Insulin Resistance (HOMA-IR) was higher in the most deprived group. Adiponectin did not differ between the two groups. Consistent with the higher body mass index and waist/hip ratio, leptin (a marker of adiposity) was higher in the most deprived group.

4.3.2.2 Markers of inflammation/endothelial dysfunction

Higher levels of inflammation in the most deprived group are demonstrated by the higher concentrations of CRP and IL-6 in this group. Higher levels of endothelial dysfunction in the most deprived group are demonstrated by the higher concentrations of sICAM-1.

4.3.2.3 Markers of haemostasis

vWF, fibrinogen and D-dimer were all significantly higher in the most deprived group. tPA antigen did not differ between the two groups.

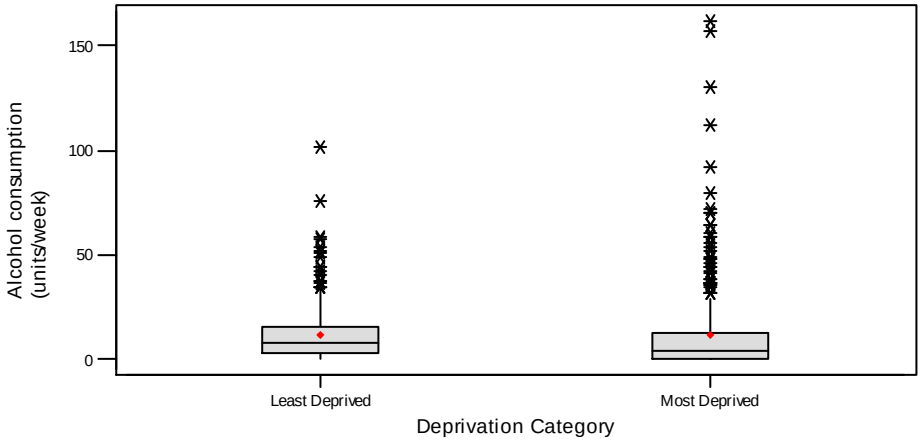
Table 4.1 Differences in classic and emerging cardiovascular risk factors between most and least deprived participants

Variable	Least deprived (n=342)	Most deprived (n=324)	p
Classical risk factors (behavioural):			
Smoking:			
Ever smoked regularly	121 (35.4%)	241 (74.4%)	<0.0001
Current cigarette smoker	21 (6.1%)	131 (40.4%)	
Data missing	0	0	
Physical activity:			<0.0001
Inactive	82 (24%)	160 (49%)	
Moderately inactive	84 (25%)	37 (11%)	
Moderately active	87 (25%)	71 (22%)	
Active	89 (26%)	56 (17%)	
Data missing	0	0	
Alcohol consumption (units/week) [a]	7.8 (2.4, 15.0)	3.5 (0.0, 12.0)	<0.0001
Data missing	0	0	
Classical risk factors (physiological):			
Cholesterol (mmol/L)	5.29 (1.03)	4.95 (1.05)	<0.0001
Data missing	7	14	
Triglycerides (mmol/L) [b]	1.19	1.44	<0.0001
Data missing	7	14	
LDL cholesterol (mmol/L)	3.16 (0.87)	2.86 (0.88)	<0.0001
Data missing	7	18	
HDL cholesterol (mmol/L)	1.43 (0.38)	1.30 (0.39)	<0.0001
Data missing	7	14	
Glucose (mmol/L)	5.15 (0.69)	5.42 (1.90)	0.0088
Data missing	19	35	
Weight (kg)	78.7 (15.3)	78.2 (18.4)	0.78
Data missing	1	1	
Waist/hip ratio	0.88 (0.08)	0.92 (0.09)	<0.0001
Data missing	3	4	
Body mass index (kg/m^2)	26.9 (4.49)	28.7 (6.34)	<0.0001
Data missing	2	2	
Blood pressure (mmHg)	135 (17.8)/81.4(10.3)	136 (20.0)/81.1(11.6)	0.58/0.74
Data missing	2	2	
Emerging risk factors: Insulin resistance / adiposity:			
Insulin (mU/L)	6.62 (4.91)	7.72 (5.97)	0.011
Data missing	18	41	
HOMA-IR	1.52 (1.22)	1.81 (1.60)	0.015
Data missing	24	49	
Total adiponectin (μg/mL)	5.81 (3.02)	5.54 (3.21)	0.12
Data missing	10	15	
HMW adiponectin (μg/mL)	3.02 (2.18)	2.88 (2.27)	0.22
Data missing	10	15	
Leptin (ng/mL)	18.7 (16.8)	23.7 (24.0)	0.0017
Data missing	14	20	
Emerging risk factors: Inflammation / endothelial dysfunction:			
CRP (mg/L) [b]	1.16	2.07	<0.0001
Data missing	11	19	
IL-6 (pg/mL) [b]	1.36	2.08	<0.0001
Data missing	13	24	
sICAM-1 (ng/mL) [b]	235.8	302.4	<0.0001
Data missing	10	20	
Emerging risk factors: Haemostasis:			
vWF (IU/dL)	129 (39)	155 (47)	<0.0001
Data missing	8	23	
Fibrinogen (g/L)	3.23 (0.60)	3.50 (0.80)	<0.0001
Data missing	10	23	
D-dimer (ng/mL)	130 (97)	155 (102)	0.0018
Data missing	8	23	
tPA antigen (ng/mL)	4.89 (4.12)	5.30 (4.32)	0.18
Data missing	8	23	

[a] results presented as median (IQR)

[b] indicates use of geometric means

Figure 4.1 Self-reported weekly alcohol consumption in relation to social deprivation



Means are indicated by solid circles. Grey boxes represent interquartile ranges, with horizontal lines showing medians.

4.3.3 Additional biomarkers measured

Differences between most and least deprived groups in additional biomarkers measured are shown in **Table 4.2**.

4.3.3.1 Asymmetric dimethylarginine and associated variables

Asymmetric dimethylarginine was significantly higher in the most deprived group compared to the least deprived ($p<0.0001$). Arginine did not differ between the two groups. As a result of the differences in ADMA, Arginine/ADMA ratio was higher in the least deprived group. Symmetric dimethylarginine, which is renally excreted, did not differ between the two groups. Homoarginine was higher in the least deprived group.

4.3.3.2 Liver “function” tests

Neither ALT nor AST differed between most and least deprived groups. Despite weekly alcohol consumption being higher in the least deprived group, GGT was significantly higher in the most deprived group ($p<0.0001$). In order to explore this finding further, multivariate models were constructed to examine the ability of deprivation to predict ALT, AST and GGT after adjusting for alcohol consumption, age and sex. The results are shown in **Tables 4.3, 4.4 and 4.5.** In the case of ALT **(Table 4.3)**, age, male sex and alcohol consumption predicted ALT, but deprivation did not predict ALT in either the model which included alcohol consumption or the model in which alcohol consumption was not included. The association of age with ALT in both models was an inverse association. For AST, only male sex and alcohol consumption predicted AST. There was a non-significant trend towards higher AST in the most deprived group in the model including age, sex and deprivation and the model including age, sex, deprivation and alcohol consumption. In the case of GGT, alcohol consumption, male sex and being in the most deprived group all predicted having a higher GGT. For GGT, a further model was constructed to include BMI as a covariate in addition to deprivation, age, sex and alcohol consumption **(Table 4.6)**. In this model, higher BMI was predictive of higher GGT, but inclusion of BMI in the model did not abolish the significance of deprivation as a predictor of GGT.

Table 4.2 Differences between most and least deprived participants in additional biomarkers measured

Variable	Least deprived	Most deprived	p
	Asymmetric dimethylarginine and associated variables:		
	(n=329)	**(n=306)**	
ADMA (umol/L)	0.44 (0.40, 0.50)	0.47 (0.42, 0.52)	<0.0001
SDMA (umol/L)	0.38 (0.34, 0.43)	0.38 (0.33, 0.44)	0.344
Arginine (umol/L)	65.6 (58.3, 75.9)	66.3 (58.3, 77.6)	0.3701
Homoarginine (umol/L)	1.67 (1.30, 2.14)	1.57 (1.17, 2.02)	0.0089
Arginine/ADMA	150.7 (127.5, 171,3)	143.2 (125.1, 165.0)	0.0151
	Liver "function" tests:		
	(n=330)	**(n=308)**	
ALT (IU/L)	22.0 (18.0. 31.0)	22.0 (17.0, 31.0)	0.4653
AST (IU/L)	22.0 (19.0, 27.0)	22.0 (18.0, 28.0)	0.667
GGT (IU/L)	24.0 (17.0, 35.3)	29.0 (21.0, 49.8)	<0.0001
	Markers of renal function:		
	(n=330)	**(n=308)**	
Creatinine (umol/L)	83.0 (75.2, 91.4)	80.1 (72.4, 87.8)	0.0023
MDRD-4 eGFR (mL/min/1.73m2)	82.9 (76.8, 92.5)	88.7 (76.4, 99.6)	0.0007
Cystatin C (mg/L)	0.92 (0.86, 1.00)	0.96 (0.89, 1.07)	<0.0001
	Other biomarkers:		
	(n=318)	**(n=298)**	
Cortisol (nmol/L) [a]	347 (120)	361 (131)	0.183
25-hydroxy vitamin D (nmol/L) [b]	45.7 (1.87)	34.2 (2.02)	p<0.0001

Values shown are median (IQR) except:

[a] mean (SD)

[b] geometric mean

Table 4.3 Prediction of ALT from deprivation, age, sex and self-reported weekly alcohol consumption

	Model not including alcohol consumption			Model including alcohol consumption		
	Estimated effect	95% confidence interval	p	Estimated effect	95% confidence interval	p
Deprivation (most deprived)	-0.024	(-2.227, 2.179)	0.983	-0.051	(-2.247, 2.145)	0.964
Age	-0.185	(-0.318, -0.051)	0.007	-0.181	(-0.314, -0.048)	0.008
Sex (male)	10.558	(8.356, 12.760)	<0.001	9.699	(7.384, 12.013)	0.001
Alcohol	-	-	-	0.078	(0.011, 0.145)	0.022

Table 4.4 Prediction of AST from deprivation, age, sex and self-reported weekly alcohol consumption

	Model not including alcohol consumption			Model including alcohol consumption		
	Estimated effect	95% confidence interval	p	Estimated effect	95% confidence interval	p
Deprivation (most deprived)	1.373	(-0.115, 2.861)	0.071	1.329	(-0.124, 2.781)	0.073
Age	-0.019	(-0.109, 0.072)	0.685	-0.012	(-0.101, 0.076)	0.781
Sex (male)	5.776	(4.288, 7.263)	<0.001	4.365	(2.834, 5.896)	<0.001
Alcohol	-	-	-	0.129	(0.084, 0.173)	<0.001

Table 4.5 Prediction of GGT from deprivation, age, sex and self-reported weekly alcohol consumption

	Model not including alcohol consumption			Model including alcohol consumption		
	Estimated effect	95% confidence interval	p	Estimated effect	95% confidence interval	p
Deprivation (most deprived)	18.024	(10.076, 25.971)	<0.001	17.748	(10.062, 25.435)	<0.001
Age	0.204	(-0.277, 0.686)	0.405	0.242	(-0.224, 0.708)	0.308
Sex (male)	20.057	(12.113, 28.001)	<0.001	11.278	(3.175, 19.380)	0.006
Alcohol	-	-	-	0.801	(0.566, 1.035)	<0.001

Table 4.6 Prediction of GGT from deprivation, age, sex, self-reported weekly alcohol consumption and Body Mass Index (BMI)

	Estimated effect	95% confidence interval	p
Deprivation (most deprived)	15.691	(7.765, 23.617	<0.001
Age	0.1729	(-0.2889, 0.6347)	0.454
Sex (male)	11.080	(2.838, 19.322)	0.007
Alcohol	0.8578	(0.6168, 1.0988)	<0.001
Body Mass Index (BMI)	1.1512	(0.4232, 1.8792)	0.002

4.3.3.3 Markers of renal function

There was a significant difference in plasma creatinine and consequently in eGFR, with higher creatinine in the least deprived group. This is further discussed in Section 4.4, in which it is recognised that this finding must be interpreted in the context of a 6cm difference in muscle mass. Cystatin C was higher in the most deprived group ($p<0.0001$), suggesting poorer renal function in that group.

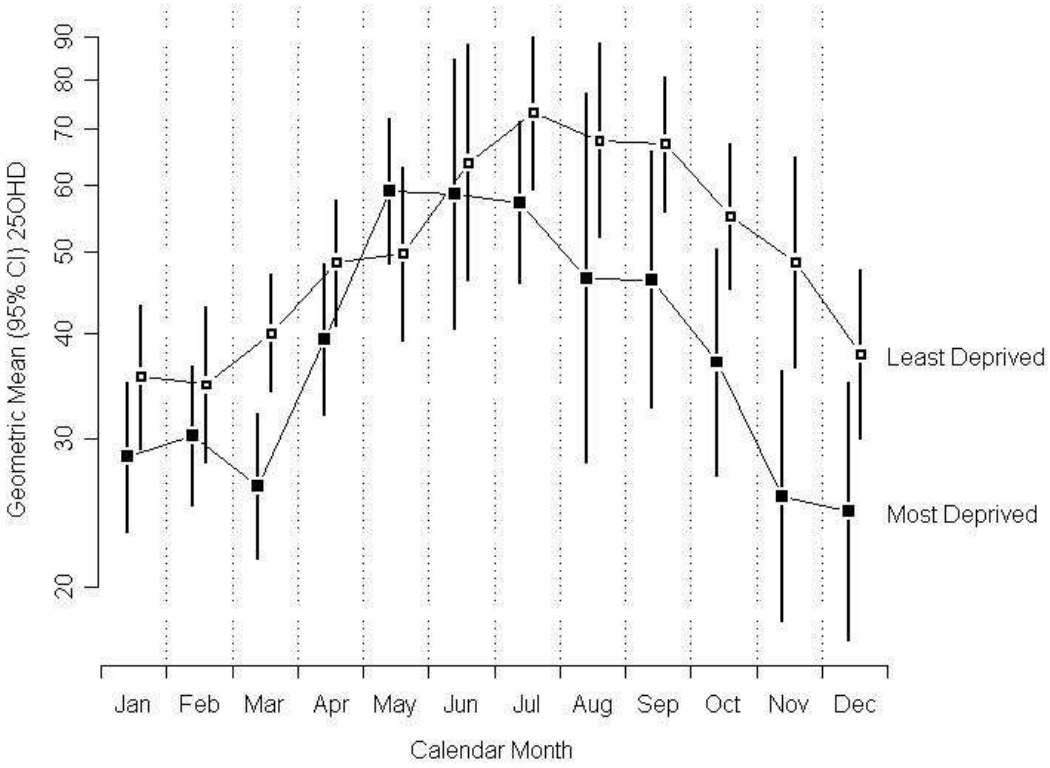
4.3.3.4 Cortisol

There was no difference in plasma cortisol concentrations between the most and least deprived groups. Importantly, all specimens were taken in the morning (between 8am and 11am). Analysis of cortisol results was repeated excluding participants who were on exogenous corticosteroid therapy, whether oral, inhaled or topical. A total of 284 least deprived and 263 most deprived participants remained. Mean (SD) plasma cortisol in the least deprived group was 350 (119) nmol/L, and in the most deprived group was 366 (127) nmol/L; $p=0.133$ for most versus least deprived (data not shown).

4.3.3.5 Vitamin D

Geometric mean concentrations of 25-hydroxy vitamin D (25-OHD) were higher among the least deprived (45.7±1.87 nmol/L) compared to the most deprived (34.2±2.02 nmol/L); $p<0.0001$. A total of 141 participants (22.6%) could be defined as being deficient in circulating 25-OHD (<25nmol/L), 49 in the least deprived group and 92 in the most deprived group (χ^2 $p<0.0001$). Circulating 25-OHD concentrations were strongly associated with month of participation (blood sampling) across all participants; χ^2 $p<0.0001$. Median 25-OHD concentrations were lowest in February (33.1nmol/L; IQR 22.0-49.9nmol/L, n=103) and highest in June (70.8nmol/L; IQR 44.7-103.5nmol/L, n=40). When examining seasonal effects on 25-OHD concentrations by deprivation status (**Figure 4.2**), there was some evidence that the least deprived group had higher 25-OHD than the most deprived group at the onset of winter (Oct-Dec, $p<0.05$ in comparison of levels). Least deprived groups appeared to have higher 25-OHD concentrations for much of the year. There was no evidence of a trend towards month of participation in the study being different by deprivation group (χ^2 $p=0.69$).

Figure 4.2 Variation in 25-OHD concentrations by month of participation in the two deprivation groups



Point estimates are geometric means; error bars are 95% CI. Difference in 25-OHD between the least and most deprived groups is seen in March ($p<0.01$), October ($p<0.05$), November ($p<0.01$), and December ($p<0.05$).

4.4 Discussion

4.4.1 Differences in cardiovascular risk factors between most and least deprived

The finding that a significantly higher proportion of most deprived participants are current smokers compared to most affluent participants is entirely consistent with what would be expected from previously published statistics.[3] In this current study, proportion of current cigarette smokers varied from 6.1% to 40.4%. The Let Glasgow Flourish report[3] cites smoking prevalence varying from 16% in the least deprived areas to 63% in the most deprived areas. Although the ages of the survey populations are not directly comparable (16-74 years in Let Glasgow Flourish compared with 35 to 64 years in this study) the most striking difference is the date of sampling: 2001 in the case of Let Glasgow Flourish, and December 2005 to May 2007 in the case of this study. In March 2006, a ban on smoking in enclosed public places was introduced in Scotland, so the majority of participant visits in this study were conducted once the ban was in place. Previous data have shown an association between introduction of the public smoking ban and an increase in the rate of smoking cessation.[20]

In this study, there was a significant difference in physical activity between least and most deprived participants, with just under half of most deprived participants being classed as inactive, compared with a quarter of least deprived participants. This classification is based on an assessment of both work and leisure time activity.[154] This finding is in contrast to data from the NHS Greater Glasgow Health/Well-Being Survey 2002, which found that 53% of most affluent subjects took at least 20 minutes of vigorous exercise at least 3 times per week or 30 minutes of moderate exercise at least 5 times per week, compared with 59% of most deprived subjects.[3] The differences between the findings of these two studies may be because of different methods of assessing physical activity, with the assessment in this study being more extensive, and including assessment of occupational and leisure activity. Another study which used similar methodology in assessing physical activity yielded similar results to this study.[34]

The figures for self-reported alcohol consumption (7.8 units/week in the least deprived group; 3.5 units/week in most deprived) seem, at first glance, surprisingly low. As a point of comparison, the 2003 Scottish Health Survey found that in adults (age 16 years or older) living in Greater Glasgow, 32% of males and 17% of females were exceeding

recommended safe weekly limits of alcohol consumption (21 units for males and 14 units for females).[3] Using these cut-offs, 26% of males and 10% of females in the pSoBid study were exceeding recommended limits (data not shown). Given the different ages of the two study populations (all aged 16 years or over in the case of the Scottish Health Survey and 35 to 64 year olds in the pSoBid study) it is reasonable to expect a lower proportion of people to exceed recommended limits in the pSoBid study. While acknowledging the difficulties in obtaining accurate data on alcohol consumption, and the inherent potential inaccuracies when using self-reported alcohol consumption, the figures obtained in the pSoBid study therefore appear plausible.

The results of the lipid analyses were very interesting. Total and LDL cholesterol were higher in the least deprived group. Findings from previous studies are conflicting. The Whitehall II study (which studied civil servants based in London)[25] and the European Prospective Investigation of Cancer and Nutrition in Norfolk (EPIC-Norfolk)[26] found no consistent associations between socioeconomic status and total cholesterol concentration. In contrast, a study of 2063 adults aged 23 to 25 years in Brazil yielded similar results to this study, with lower total and LDL cholesterol concentrations being found in more deprived individuals.[27] One message that can be taken from this finding is that if LDL/HDL ratio is used as an indicator of the contribution to cardiovascular risk from lipid parameters, this is unlikely to explain the deprivation-based difference in cardiovascular risk, as the LDL/HDL ratio was identical in the least and most deprived groups in this study (2.37 in both groups, p=0.91; data not shown).

The observations of higher serum triglyceride concentration, lower HDL cholesterol concentration, higher fasting glucose and insulin concentrations, higher HOMA-IR index and higher waist/hip ratio in the most deprived group are easier to explain. There is a well documented higher risk of developing type 2 diabetes mellitus [3 25 43 44 155] and metabolic syndrome[156 157] in more deprived individuals when compared with more affluent individuals. Abdominal obesity, fasting serum triglycerides $\geq$1.7mmol/L, HDL cholesterol <1.04mmol/L in men or <1.30mmol/L in women and fasting plasma glucose $\geq$6.1mmol/L are, of course, four of the five components used to diagnose metabolic syndrome (with blood pressure $\geq$130/85mmHg being the fifth component, and three or more providing a diagnosis of metabolic syndrome).[10] Adiponectin concentrations are also known to be reduced in obesity and insulin resistance,[158] so lower concentrations might have been expected in more deprived subjects, although this was not observed in this study. Leptin concentration is known to show a significant correlation with percentage fat mass,[125] so it

is not surprising to find higher leptin concentrations in the most deprived group which had higher waist/hip ratio and, by virtue of having smaller height, a higher Body Mass Index (BMI). The height difference between the most deprived and most affluent group (a difference of 6cm) is, in itself, striking, and presumably related to significant differences in childhood nutrition.[159]

The finding of higher levels of inflammation in the most deprived group, as demonstrated by higher CRP and IL-6 concentrations, is in keeping with previous data from the West of Scotland Coronary Prevention Study (WOSCOPS) and the Midspan Study, in which associations noted between CRP and social deprivation were not fully explained by smoking and body mass index.[63] Soluble intercellular adhesion molecule (sICAM-1) has been implicated in inflammatory processes and in endothelial dysfunction.[70] Associations have been noted between increasing concentrations of sICAM-1 and risk of future myocardial infarction[160] so the finding of increased concentrations of sICAM-1 in the most deprived group is of interest, although not unexpected.

The associations between social deprivation and markers of haemostasis have previously been investigated. An analysis of the 1958 British Birth Cohort found higher concentrations of fibrinogen, von Willebrand Factor antigen and tissue Plasminogen Activator antigen in individuals with higher cumulative levels of social deprivation. After adjustment for body mass index, smoking and physical activity, the trend for fibrinogen remained significant.[77] Similarly, the British Regional Heart Study found that in British men aged 60 to 79 years with no diagnosis of cardiovascular disease, diabetes or musculoskeletal disease requiring anti-inflammatory medication, social deprivation was associated with higher concentrations of fibrinogen, von Willebrand Factor and fibrin D-dimer, but not tissue Plasminogen Activator antigen. The association with von Willebrand Factor persisted after adjustment for behavioural risk factors.[67] Remarkably similar findings are demonstrated in this study which involved males and females in a younger age group, but again demonstrated a socioeconomic gradient in vWF, fibrinogen and D-dimer, but not tPA antigen.

The finding of higher concentrations of ADMA in the most deprived group is interesting, and – to the best of my knowledge – novel. This finding is not surprising, though, in view of the known associations of ADMA with insulin resistance, and the evidence of higher levels of insulin resistance in the most deprived group in this study. ADMA is a biomarker around which there is considerable current interest, and there is significant potential for

further work exploring the extent to which ADMA is a mediator, as opposed to simply a marker, of processes leading to atherosclerosis. Similarly, the finding of higher homoarginine concentrations in the least deprived group is novel. Homoarginine has been less extensively studied than ADMA. However, it is known that homoarginine competes with arginine for binding sites on nitric oxide synthase. Unlike ADMA, which directly inhibits nitric oxide synthase, homoarginine is simply a less efficient substrate than arginine for nitric oxide synthase.[161] Interestingly, homoarginine is increased during the second and third trimesters of pregnancy, and it has been suggested that this may contribute to the enhanced endothelial function seen in pregnancy.[162] Thus, the finding of higher concentrations of homoarginine in the least deprived may be suggestive of superior endothelial function in this group, which is in turn consistent with lower concentrations of sICAM-1 being found in the least deprived group.

Of the three markers of liver damage measured, only GGT differed between the most and least deprived groups. It is striking that this difference (higher GGT in the most deprived group) was seen despite weekly self-reported alcohol consumption being higher in the least deprived group, and the effect of deprivation in predicting GGT being independent of age, sex and alcohol consumption. Although ALT is the most commonly recognised marker of non-alcoholic fatty liver disease, GGT is also elevated in many cases of fatty liver, and its elevation is indicative of increased mortality in men, especially those with ultrasound evidence of hepatic steatosis.[163] It is, therefore, unsurprising that higher BMI was significantly associated with higher GGT in a model adjusted for age, sex, deprivation and self-reported alcohol intake **(Table 4.6)**. However, deprivation remained a significant predictor of GGT, even after this additional adjustment for BMI.

The finding of higher creatinine concentrations in the least deprived group might at first seem surprising. However, there was a difference of 6cm in height between the most and least deprived groups, so it is likely that the differences in creatinine concentration are a result of differences in muscle mass. Furthermore, MDRD 4 variable eGFR uses creatinine, age, sex and ethnicity to estimate GFR. Since the participants were selected in a way to include approximately equal numbers of males and females in each group, and equal numbers from each age tertile, it is not surprising that eGFR has been estimated to be higher in the most deprived group: again, this is likely to be a consequence of lower creatinine in this group as a results of lower muscle mass. Cystatin C, whose concentration is not specifically related to muscle mass, is likely to be a more appropriate marker of renal function in this context. The finding of higher cystatin C concentration, i.e. lower GFR, in

the most deprived group, is consistent with previous findings in an African American population,[151] and may be indicative of higher cardiovascular risk in the most deprived group.[150]

No difference was noted in plasma cortisol concentrations between the most and least deprived groups. This is in contrast to the findings from the Caerphilly study, although that study examined cortisol to testosterone ratios on the basis that the response to stress in males involves a rise in cortisol concentrations and a fall in testosterone, the ratio therefore incorporating both of these features. In addition, the pSoBid study had some variation in time of sampling between 8 and 11am, although all samples were still morning plasma samples, and the timing was less variable than in the Caerphilly study, in which samples were taken between 3 and 11am, although the majority were between 7 and 8am.[144]

Circulating 25-hydroxy vitamin D concentrations were “suboptimal” in a sizeable proportion (22.6%) of the urban population of Glasgow, particularly in socially deprived communities. The observation that social deprivation is an important determinant of 25-OHD status significantly extends a prior study suggesting 25-OHD concentrations are lower among UK state benefit recipients.[164] Association of 25-OHD with social deprivation may be one explanation for the discrepancy between epidemiological findings of associations between 25OHD and CVD risk, and lack of efficacy of vitamin D supplementation in randomised controlled trials,[143] although of course, dose of supplementation may be relevant.

In summary, the work described in this chapter has shown deprivation-based differences in cigarette smoking, physical activity, self-reported alcohol consumption (higher in least deprived), total and LDL cholesterol (higher in least deprived), markers of insulin resistance/adiposity, inflammation, endothelial dysfunction, haemostasis, renal function and vitamin D status. The next question to be addressed, therefore, is which – if any – of these factors contribute to the deprivation-based difference in cardiovascular risk, and this issue is addressed in Chapter 5.

CHAPTER 5 – SOCIAL DEPRIVATION AND ULTRASOUND MARKERS OF ATHEROSCLEROSIS

5.1 Introduction

As discussed in Chapter 1, the socioeconomic gradient in coronary heart disease is only partly explained by classic cardiovascular risk factors[39 165] and it remains to be seen to what extent emerging risk factors contribute to this gradient.

Carotid ultrasound is recognised as an efficient and validated tool for assessing the degree of atherosclerosis in an individual. Measurement of the artery wall intima-media thickness (cIMT) is a commonly employed index. As discussed in Chapter 1, the age-and-sex-adjusted relative risk for myocardial infarction is 1.15 (95% confidence intervals 1.12 to 1.17) for every 0.10mm increase in cIMT. For stroke, the age-and-sex-adjusted relative risk is 1.18 (95% confidence intervals 1.16 to 1.21) for every 0.10mm increase in cIMT.[79] Ultrasound detection of carotid plaque is also highly informative,[80] plaque score having been shown to be associated with risk of myocardial infarction[81-83] and stroke.[84] In the Rotterdam study, hazard ratio for myocardial infarction was 1.83 (95% confidence intervals 1.27 to 2.62) for plaque score of $\geq$3 versus 0[81] and age-and-sex-adjusted relative risk for stroke was 1.61 (95% confidence interval 1.16–2.23) for highest to lowest tertile of plaque score.[84] The American Society of Echocardiography has recognised a clinical role for carotid intima-media thickness (cIMT) measurement and plaque detection in refining cardiovascular risk assessment in asymptomatic patients assessed as being at intermediate cardiovascular risk.[78] Previous studies have found associations between area-based indicators of social deprivation and both cIMT and plaque presence.[92 93]

The aim of the work described in this chapter was to enhance current understanding of the factors underlying associations between deprivation and atherosclerosis. The hypothesis was that social deprivation would be associated with higher cIMT and / or plaque score but that adjustment for emerging risk factors, especially inflammatory markers, would account for such differences.

5.2 Methods

5.2.1 Carotid ultrasound

Carotid ultrasound was performed during the second study visit as described in Chapter 2. The pre-specified primary outcome was mean common carotid intima-media thickness, measured on the far wall of each arterial segment, averaged along a 1cm length, or as much of this as was able to be read. The secondary outcome was plaque score,[81] determined by counting the number of plaques, dividing by the number of readable images present and multiplying by 6 (the maximum possible number of images per subject),[81] thus adjusting for unreadable images.

5.2.2 Statistical analysis

For cIMT an analysis was performed of thickness versus age for males and females in each deprivation category. Since the slopes and intercepts differed in least versus most deprived groups a 2-degree of freedom test was employed. For analysis of plaque score, negative binomial regression was carried out with additional adjustment for the number of missing scans. For multivariate models involving plaque, plaque presence was used as the dependent variable and logistic regression was used for modelling. In multivariate analyses, missing values were removed from the relevant analyses.

Carotid intima-media thickness data are presented in tertile of age for each deprivation group using "box-and-whisker" plots. Plaque score in age tertiles and deprivation groups is presented as a bar plot.

5.3 Results

Differences in ultrasound markers of atherosclerosis are shown in **Table 5.1.** For mean cIMT, the age and sex-adjusted difference for most versus least deprived was +0.02mm (p=0.015). When analysing males and females separately, mean cIMT showed a statistically significant difference between most and least deprived for males (p=0.044) but not for females (p=0.77) (data not shown). **Figure 5.1** shows the differences in cIMT and plaque score for each gender, separately split by age tertile. The ages stated for each age tertile are the ages of the participants at the time of carotid ultrasound scan, by which point the participants were slightly older than they were at the time of original selection for the study. The expected increase in cIMT with age was observed and the difference in cIMT between most and least deprived only reached statistical significance in the highest age tertile (56.3-66.5 years) in males and did not achieve statistical significance in females at any age. By contrast, plaque score showed highly significant differences (all $p<0.01$) in males in the two highest age tertiles (46.8-56.2 years and 56.3-66.5 years) and in females in the highest age tertile (56.3-66.5 years).

5.3.1 Area-level deprivation difference in cIMT: potential explanatory variables

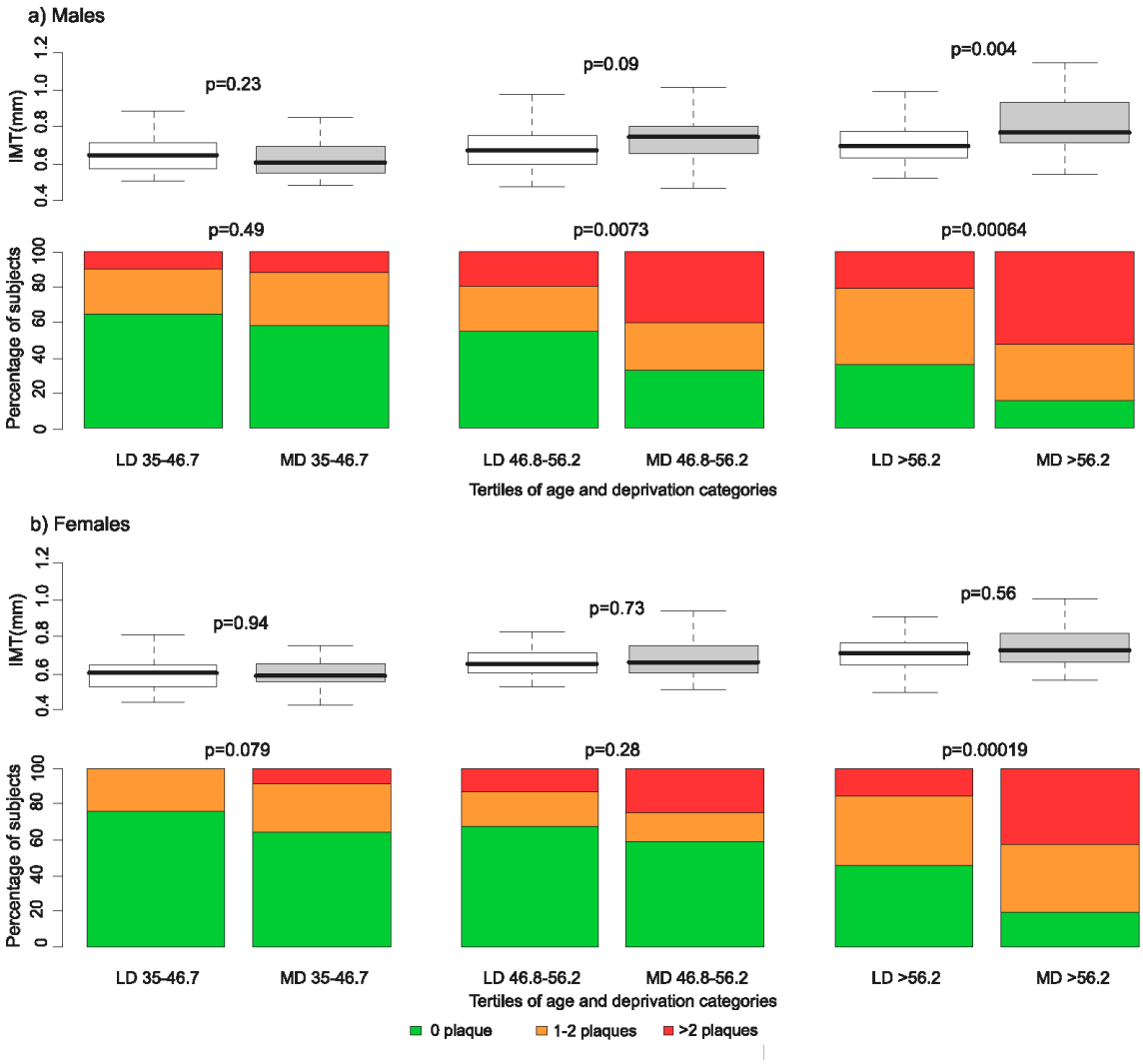
As planned in the study protocol,[166] analyses were carried out to uncover potential explanations for the area-level deprivation difference in cIMT. Since this difference was significant only in males when analysing the genders separately, only males were included in these analyses. For age-adjusted carotid intima-media thickness cIMT, the following variables of the list in **Table 4.1** were significant correlates: log triglycerides showed a positive association (p=0.0092); HDL cholesterol was negatively associated (p=0.044) and systolic blood pressure was positively associated (p=0.028). Of note, 25-hydroxy vitamin D concentration was not associated with cIMT (p=0.99). A number of multivariate models were then constructed, with potential explanatory variables grouped according to category of risk marker (e.g. classical risk factors; markers of insulin resistance; inflammatory markers; markers of haemostasis). On plotting cIMT versus age, both gradients and intercepts differed between most and least deprived males. **Table 5.2** shows the mean difference in gradient between most and least deprived males, adjusted as described for each model. Model 2, which included classic risk factors (age, triglycerides, low density lipoprotein cholesterol, high density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, history of regular smoking and history of hypertension)

Table 5.1 Differences in ultrasound markers of atherosclerosis between most and least deprived groups

Variable	Least deprived (n=342)	Most deprived (n=324)	p
Mean carotid intima-media thickness (cIMT) (mm)	0.68 (0.12)	0.70 (0.16)	0.015[a]
Data missing	23	29	
Plaque score:			
0 plaques	193 (56.9%)	130 (41.7%)	
1-2 plaques	101 (29.8%)	89 (28.5%)	<0.0001 for trend
>2 plaques	45 (13.3%)	93 (29.8%)	
Data missing	3	12	

[a] difference between least deprived and most deprived after adjusting for age and sex

Figure 5.1 Severity of atherosclerosis by tertile of age and deprivation category



LD: Least Deprived; MD: Most Deprived. Numbers refer to tertiles of age in years – e.g. "LD 35-46.7" refers to the Least Deprived youngest age tertile (35 to 46.7 years old). Grey and white box-and-whisker plots show cIMT in mm; coloured (red, amber and green) bars indicate the percentage of subjects in each group with 0 (green), 1-2 (amber) or more than 2 (red) plaques.

Table 5.2 Difference between men from the least deprived areas and those from the most deprived areas in gradient of mean common carotid intima-media thickness (cIMT) plotted against age

	Mean difference (95% CI)	F-test p value
Model 1	-0.07 (-0.11 to -0.02), p=0.0059	0.0011
Model 2 (classic)	-0.06 (-0.11 to -0.01), p=0.021	0.031
Model 3 (classic+insulin resistance)	-0.07 (-0.12 to -0.02), p=0.008	0.017
Model 4 (classic+inflammatory)	-0.06 (-0.11 to -0.01), p=0.021	0.018
Model 5 (classic+haemostasis)	-0.06 (-0.11 to -0.01), p=0.02	0.037
Model 6 (classic+physical activity)	-0.06 (-0.11 to -0.01), p=0.018	0.026
Model 7 (classic+all emerging+ physical activity)	-0.08 (-0.13 to -0.02), p=0.0075	0.010
Model 8 (classic+individual socioeconomic status – early life)	-0.06 (-0.11 to -0.01), p=0.024	0.053
Model 9 (classic+individual socioeconomic status – all factors)	-0.07 (-0.12 to -0.02), p=0.01	0.03
Model 10 (classic+all)	-0.1 (-0.16 to -0.03), p=0.0025	0.010

Model 1 – not adjusted for other factors
Model 2 (classic markers) – adjusted for: triglycerides, LDL cholesterol, HDL cholesterol, systolic blood pressure, diastolic blood pressure, smoking, history of hypertension
Model 3 (classic+insulin resistance markers) – as Model 2+waist circumference, glucose, HOMA-IR, adiponectin, leptin, history of diabetes
Model 4 (classic+inflammatory) - as Model 2+CRP, IL-6, sICAM-1
Model 5 (classic+haemostasis) - as Model 2+fibrinogen, D-dimer, vWF
Model 6 (classic+physical activity) – as Model 2+physical activity
Model 7 (classic+all emerging + physical activity) – as Model 2+ waist circumference, glucose, HOMA-IR, adiponectin, leptin, history of diabetes, CRP, IL-6, sICAM-1, fibrinogen, D-dimer, vWF, physical activity
Model 8 (classic+individual socioeconomic status – early life) – as Model 2+height, leg length, people/room at age 11 years, father's Registrar General Social Class, total years of education
Model 9 (classic+individual socioeconomic status – all factors) – as Model 8+participant's Registrar General Social Class, annual household income
Model 10 (classic+all) – as Model 2+waist circumference, glucose, HOMA-IR, adiponectin, leptin, history of diabetes, CRP, IL-6, sICAM-1, fibrinogen, D-dimer, vWF, physical activity, height, leg length, people/room at age 11 years, father's Registrar General social class, participant's Registrar General social class, annual household income, total years of education

failed to attenuate the cIMT difference in most versus least deprived men. In further models, emerging risk markers were added in groups representing insulin resistance, inflammatory factors and haemostasis. Further models incorporating physical activity and individual-level markers of socioeconomic status were constructed. Finally, all variables were added simultaneously to the model. With all classic and emerging risk factors added, and individual level markers of socioeconomic status included, the difference in cIMT between most and least deprived males remained significant (Model 10).

5.3.2 Area-level deprivation difference in plaque score: potential explanatory variables

On age and sex adjusted analyses, the following were significant predictors of plaque presence: log triglycerides (p=0.0016), systolic blood pressure (p=0.0079), diastolic blood pressure (p=0.049), current smoking (p<0.0001), log sICAM-1 (p=0.00028) and fibrinogen (p=0.023). Height (p=0.00013) and hip circumference (p=0.00014) were negatively associated with plaque presence. 25-hydroxy vitamin D concentration was not associated with plaque presence (p=0.36).

Similar models to those used for cIMT were constructed using presence of plaque as the dependent variable, with the analyses being run in all subjects (as plaque score demonstrated significant differences between most and least deprived in both males and females). Plaque presence was used as the dependent variable in these analyses (rather than plaque score) because plaque score did not fit conventional distributions that might be used for regression analyses and it was decided that the binary approach transformation would contain most of the information in the data. The results are shown in **Table 5.3**. With all classic and emerging risk factors and physical activity included in a model predicting plaque presence (Model 7), the area-level deprivation-based differences in plaque presence remained significant (adjusted odds ratio of 1.73 [95% confidence intervals 1.07 to 2.82] for plaque presence in most deprived versus least; p=0.026). In general terms, individuals from most deprived areas had around a 1.6 to 2-fold higher risk for presence of carotid plaque compared to those from least deprived areas.

In contrast to the effect on cIMT, however, inclusion of early life individual markers of socioeconomic status (height, leg length, people/room at age 11 years, father's Registrar General Social Class and total years of education) in an age-and sex-adjusted model (Model 8) abolished the area-level deprivation-based difference in plaque presence

(adjusted odds ratio for plaque presence = 0.94 [0.54 to 1.65]; p=0.84). When the individual level markers of socioeconomic status (height, leg length, people/room at age 11 years, father's Registrar General Social Class, participant's Registrar General Social Class, annual income, total years of education) were each added in turn to an age-and-sex adjusted model, none of the individual-level markers of socioeconomic status on their own abolished the area-level deprivation-based difference in plaque presence (data not shown).

Table 5.3 Odds ratio for presence of plaque in most deprived versus least deprived individuals with adjustment for classic risk factors without and with addition of emerging risk factors

	Odds ratio for plaque presence (95% CI)
Model 1	2.05 (1.45 to 2.89) p<0.0001
Model 2 (classic)	1.71 (1.14 to 2.55) p=0.009
Model 3 (classic+insulin resistance)	1.82 (1.18 to 2.80) p=0.0066
Model 4 (classic+inflammatory)	1.71 (1.11 to 2.65) p=0.015
Model 5 (classic+haemostasis)	1.77 (1.16 to 2.69) p=0.0075
Model 6 (classic+physical activity)	1.60 (1.05 to 2.41) p=0.027
Model 7 (classic+all emerging+ physical activity)	1.73 (1.07 to 2.82) p=0.026
Model 8 (classic+individual socioeconomic status – early life)	0.94 (0.54 to 1.65) p=0.84
Model 9 (classic+individual socioeconomic status – all factors)	1.12 (0.53 to 2.37) p=0.76
Model 10 (classic+all)	1.05 (0.45 to 2.44) p=0.91

Model 1 – adjusted for age, sex and scans present
Model 2 (classic markers) – adjusted for: age, sex, scans present, triglycerides, LDL cholesterol, HDL cholesterol, systolic blood pressure, diastolic blood pressure, smoking, history of hypertension
Model 3 (classic+insulin resistance markers) – as Model 2+waist circumference, glucose, HOMA-IR, adiponectin, leptin, history of diabetes
Model 4 (classic+inflammatory) - as Model 2+ CRP, IL-6, sICAM-1
Model 5 (classic+haemostasis) - as Model 2+fibrinogen, D-dimer, vWF
Model 6 (classic+physical activity) – as Model 2+physical activity
Model 7 (classic+all emerging + physical activity) – as Model 2+ waist circumference, glucose, HOMA-IR, adiponectin, leptin, history of diabetes, CRP, IL-6, sICAM-1, fibrinogen, D-dimer, vWF, physical activity
Model 8 (classic+individual socioeconomic status – early life) – as Model 2+height, leg length, people/room at age 11 years, father's Registrar General social class, total years of education
Model 9 (classic+individual socioeconomic status – all factors) – as Model 8+participant's Registrar General social class, annual household income
Model 10 (classic+all) – as Model 2+waist circumference, glucose, HOMA-IR, adiponectin, leptin, history of diabetes, CRP, IL-6, sICAM-1, fibrinogen, D-dimer, vWF, physical activity, height, leg length, people/room at age 11 years, father's Registrar General social class, participant's Registrar General social class, annual household income, total years of education

5.4 Discussion

The work described in this chapter examined prevalence of carotid atherosclerosis in subjects at extremes of the socio-economic gradient in Glasgow, a city with well documented health issues associated with social deprivation. Plaque score and cIMT were significantly worse in the more deprived group. Although there were clear differences in biomarkers of chronic inflammation between most and least deprived groups (see Chapter 4), neither these nor classic risk factors satisfactorily explained the increased atherosclerosis burden in the lower socio-economic group. Only adjusting for individual-level markers of socioeconomic status explained the area-level difference in carotid plaque presence, and even this adjustment did not explain the area-level difference in cIMT.

A striking finding is that plaque score showed differences between the two groups at an earlier age than cIMT, although the trends in cIMT are in the expected direction (rising with age; greater in males). It is not surprising that the difference in cIMT between least and most deprived did not reach statistical significance in females in any age tertile studied given that the difference in males only reached statistical significance in the highest age tertile, and the fact that atherosclerosis tends to develop around a decade later in females. In contrast to cIMT, differences in plaque score were highly statistically significant, reaching significance in the two highest age tertiles in males, and the highest age tertile in females. This observation suggests that plaque score measured in a standardised, objective and blinded way could be more useful than cIMT when studying differences in severity of atherosclerosis as in this study.

5.4.1 Factors underlying the area-level deprivation difference in atherosclerosis

On multivariate analysis, classic risk factors reduced but did not abolish the area-level deprivation difference in plaque presence and cIMT, strongly suggesting that classic risk factors do not fully explain the difference in ultrasound markers of atherosclerosis between most and least deprived subjects. Given the involvement of inflammatory pathways in atherosclerosis,[167] and the significant differences in inflammatory markers noted between deprivation categories in this and other studies,[63] it might have been expected that inclusion of markers of inflammation and/or endothelial dysfunction would have reduced or abolished the significant difference in plaque score, and this was indeed my hypothesis. However, none of the measured markers of inflammation, insulin resistance or haemostasis

had a significant impact on the ability of area-level deprivation to predict plaque presence, with area-level deprivation remaining a significant predictor even once all classic and emerging risk factors were included in the model. These findings are consistent with those from the Women's Health Study, in which the inverse association between educational attainment and risk of cardiovascular events was not reduced by adjusting for CRP, sICAM-1, fibrinogen or homocysteine.[71] Only by adjusting for individual-level early life markers of socioeconomic status was the area-level deprivation-based difference in plaque presence abolished, and it is of interest that even this adjustment did not explain the area-level deprivation-based difference in cIMT in males. Given the fact that area-level and individual-level markers of socioeconomic status are likely to be highly correlated, it is clearly highly plausible that the abolition of the area-level deprivation difference in plaque presence on adjusting for individual-level markers of socioeconomic status may be due to overadjustment. It would have been of further interest to know if assessment of plaque volume would have yielded further useful information,[133] although the technology allowing such assessment is not yet widely available.

This work demonstrates the great significance of area level deprivation as a predictor of atherosclerosis. Classic cardiovascular risk factors did not fully explain the difference in plaque presence between most and least deprived participants, suggesting that current public health messages directed at classic risk factors (diet, blood pressure, smoking) may not adequately address the problem of the continuing socioeconomic gradient in cardiovascular disease. The findings add weight to the case for inclusion of social deprivation in cardiovascular risk assessment, as has been done in the ASSIGN (ASSessing cardiovascular risk using SIGN) scoring system.[168]

Although the deprivation-based difference in atherosclerosis was not explained by the classic risk factors examined, neither (and somewhat surprisingly) was it explained by the range of emerging markers measured in this study. Health status is a reflection not only of features of the individual but also of wider social and economic influences, health and social services, early life experience and environmental factors. The analyses reported in this chapter have focused on biological pathways. Further analyses focusing on the relative strengths of different pathways in explaining the health gap seen between the most and least deprived groups may help in unravelling the multifactorial nature of health inequalities.

CHAPTER 6 – RELATIONSHIP BETWEEN CARDIOVASCULAR RISK MARKERS AND ULTRASOUND MARKERS OF ATHEROSCLEROSIS

6.1 Introduction

In Chapter 5, differences were observed between the information that could be gleaned from cIMT and that obtainable from plaque score. More marked differences between the deprivation groups were noted for plaque score than for cIMT, and the differences became significant at a younger age for plaque score than for cIMT. Furthermore, while individual-level early life markers of socioeconomic status explained the deprivation-based difference in plaque score, adjustment for individual-level markers of socioeconomic status did not explain the differences in cIMT. These observations prompt a closer examination of the relationship between the measured cardiovascular risk markers and cIMT and plaque.

cIMT is thought to represent hypertrophy of intimal and medial cells in response to lipid infiltration or hypertension, while plaque formation is thought to represent a later stage of atherogenesis involving inflammation, oxidation, endothelial dysfunction and/or smooth muscle cell proliferation.[169] The Cardiovascular Health Study of 5201 men and women aged 65 years and older found that increasing age, male sex, systolic blood pressure, LDL cholesterol concentration, history of smoking, hypertension, diabetes mellitus and presence of any major ECG abnormality were associated with increased cIMT. HDL cholesterol and diastolic blood pressure were negatively associated with cIMT.[170] A study by Spence and Hegele found age, male sex, smoking, diabetes mellitus, systolic blood pressure, total cholesterol, plasma homocysteine and treatment with lipid-lowering or antihypertensive therapy to be associated with total carotid plaque area.[169] A more recent study involving the same investigators found that cIMT was significantly associated with hypertension, total plaque area with smoking and plasma cholesterol and total plaque volume with diabetes mellitus.[171]

The wide range of biomarkers analysed in the pSoBid study provides an ideal opportunity for further investigation of the biomarkers associated with cIMT and those associated with plaque score. The aim of the work described in this chapter was to further understanding of the biomarkers associated with variation in cIMT and those associated with plaque score. Emerging biomarkers have been much less extensively studied than classic risk factors, so a particular aim was to expand knowledge of the role of emerging biomarkers. The hypothesis was that hypertension and cholesterol would explain much of the variation in

cIMT, while emerging biomarkers, especially markers of inflammation, would contribute to the explanation of variation in plaque score.

6.2 Methods

The cIMT and plaque results used for the analysis described in this chapter are those detailed in Chapter 5. The biomarkers used as covariates are those detailed in **Table 4.1**.

Multivariate models were constructed using log transformed cIMT as the dependent variable. For these analyses, all participants were included (i.e. the analysis was not restricted to males only as it had been in Chapter 5). An initial model (Model 1) was adjusted for age, sex and deprivation. In subsequent models, covariates were added in groups representing: classic risk factors (Model 2), inflammation (Model 3), insulin resistance (Model 4), haemostasis (Model 5) and early life socioeconomic factors (Model 6). In each case, after construction of the full model, a backward selected model was used to identify those variables retaining a significant association with cIMT. Finally (Model 7) bootstrap variable selection was used. A sample of the data (of the same size, where individuals can appear more than once in the sample) was taken and variables identified which had a significant association with cIMT, from those variables identified in the individual backward selected models (Models 1 to 6). This was repeated 1000 times and the confidence interval and p-value derived from these 1000 values. A forward stepwise selection was then carried out on those variables that had been selected in at least 50% of the models in order to identify those variables retaining a significant association with cIMT. This bootstrap model selection was then repeated in only those subjects with no history of CVD, in those not on statin therapy, in those not on antihypertensive treatment and in those not on statin or antihypertensive treatment.

This procedure was repeated with plaque presence (as a binary variable) as the dependent variable, using logistic regression analysis.

6.3 Results

6.3.1 Predictors of cIMT

Table 6.1 shows the effect of age, male sex and being in the most deprived group on cIMT. As expected (and as observed in Chapter 5), cIMT increased with age, and was higher in males than in females. The effect on cIMT of being in the most versus least deprived group has already been extensively discussed in Chapter 5. The purpose of Model 1 was to provide an age, sex and deprivation-adjusted baseline model to which classic and emerging cardiovascular risk factors could be added in groups, in order to identify which factors were associated with and might underlie increases in cIMT.

The associations of classic risk factors with cIMT are shown in **Table 6.2**. Of the classic risk factors, HDL cholesterol had a negative association with cIMT ($p<0.001$ in backward selected model). Systolic blood pressure was positively associated with cIMT ($p<0.001$) and diastolic blood pressure had an inverse association ($p = 0.014$).

The associations of inflammatory markers with cIMT are shown in **Table 6.3**. In the full model, CRP was positively associated with cIMT. However, none of the markers of inflammation were associated with cIMT in the backward selected model.

The associations with cIMT of markers associated with insulin resistance are shown in **Table 6.4**. The only significant association was a negative effect of adiponectin on cIMT. Lower concentrations of adiponectin indicate a higher degree of insulin resistance, so this finding is consistent with higher levels of insulin resistance being associated with thicker cIMT. None of the markers of haemostasis were associated with cIMT **(Table 6.5)**.

In **Table 6.6**, the associations of early life individual-level markers of socioeconomic status with cIMT are shown. Leg length, a marker of childhood nutrition, showed a negative association with cIMT, i.e. shorter leg length (and, by association, poorer childhood nutritional status) was associated with thicker cIMT. Paradoxically, the association of height with cIMT was positive: taller height was associated (albeit less strongly than leg length) with thicker cIMT.

Table 6.1 Effect of age, sex and deprivation on cIMT (Model 1)

Variable	Effect	95% confidence interval	p
Age	0.010	(0.009, 0.012)	<0.001
Sex (male)	0.059	(0.033, 0.085)	<0.001
Deprivation (most deprived)	0.029	(0.003, 0.055)	0.028

Table 6.2 Associations of classic cardiovascular risk factors with cIMT (Model 2)

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.008	(0.006, 0.010)	<0.001	0.009	(0.007, 0.011)	<0.001
Sex (male)	0.019	(-0.011, 0.048)	0.210	0.027	(-0.001, 0.055)	0.062
Deprivation (most deprived)	0.001	(-0.030, 0.032)	0.947	0.013	(-0.013, 0.040)	0.321
Triglycerides *	0.011	(-0.019, 0.042)	0.458	-	-	-
LDL cholesterol	0.016	(0.000, 0.032)	0.055	-	-	-
HDL cholesterol	-0.071	(-0.113, -0.030)	0.001	-0.066	(-0.103, -0.030)	<0.001
Systolic blood pressure	0.003	(0.002, 0.004)	<0.001	0.003	(0.002, 0.004)	<0.001
Diastolic blood pressure	-0.003	(-0.004, -0.001)	0.005	-0.002	(-0.004, 0.000)	0.014
Smoking (current)	0.031	(-0.005, 0.066)	0.088	-	-	-
History of hypertension	-0.001	(-0.038, 0.036)	0.958	-	-	-

* log-transformed

Table 6.3 Associations of inflammatory markers with cIMT (Model 3)

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.010	(0.009, 0.012)	<0.001	0.010	(0.009, 0.012)	<0.001
Sex (male)	0.063	(0.036, 0.090)	<0.001	0.059	(0.033, 0.085)	<0.001
Deprivation (most deprived)	0.027	(-0.003, 0.058)	0.081	0.029	(0.003, 0.055)	0.028
CRP *	0.020	(0.005, 0.035)	0.009	-	-	-
IL-6	-0.010	(-0.021, 0.002)	0.091	-	-	-
sICAM-1 *	0.001	(-0.058, 0.059)	0.978	-	-	-

* log-transformed

Table 6.4 Associations of markers of insulin resistance with cIMT (Model 4)

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.011	(0.009, 0.013)	<0.001	0.011	(0.009, 0.012)	<0.001
Sex (male)	0.042	(-0.009, 0.092)	0.104	0.037	(0.008, 0.066)	0.012
Deprivation (most deprived)	0.025	(-0.003, 0.053)	0.075	0.023	(-0.004, 0.050)	0.093
Waist circumference	0.000	(-0.001, 0.002)	0.684	-	-	-
Glucose	-0.011	(-0.033, 0.011)	0.313	-	-	-
HOMA-IR *	0.001	(-0.026, 0.028)	0.941	-	-	-
Adiponectin *	-0.055	(-0.087, -0.023)	0.001	-0.051	(-0.079, -0.022)	0.001
Leptin *	0.007	(-0.023, 0.037)	0.651	-	-	-
Diabetes	-0.059	(-0.250, 0.132)	0.543	-	-	-

* log-transformed

Table 6.5 Associations of markers of haemostasis with cIMT (Model 5)

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.011	(0.009, 0.012)	<0.001	0.010	(0.009, 0.012)	<0.001
Sex (male)	0.058	(0.030, 0.085)	<0.001	0.059	(0.033, 0.085)	<0.001
Deprivation (most deprived)	0.032	(0.004, 0.061)	0.026	0.029	(0.003, 0.055)	0.028
Fibrinogen	0.015	(-0.007, 0.038)	0.173	-	-	-
D-dimer *	-0.018	(-0.045, 0.008)	0.176	-	-	-
von Willebrand factor	0.000	(-0.001, 0.000)	0.367	-	-	-

* log-transformed

Table 6.6 Associations of early life socioeconomic factors with cIMT (Model 6)

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.010	(0.008, 0.012)	<0.001	0.010	(0.009, 0.012)	<0.001
Sex (male)	0.061	(0.016, 0.105)	0.007	0.061	(0.019, 0.104)	0.005
Deprivation (most deprived)	0.011	(-0.031, 0.054)	0.597	0.026	(-0.005, 0.057)	0.104
Height	0.004	(0.000, 0.008)	0.029	0.004	(0.000, 0.007)	0.046
Leg length	-0.008	(-0.013, -0.003)	0.002	-0.008	(-0.012, -0.003)	0.002
People per room at age 11 years *	-0.002	(-0.040, 0.036)	0.923	-	-	-
Father's social class (Non-manual)	-0.019	(-0.054, 0.016)	0.287	-	-	-
Years of education *	-0.038	(-0.112, 0.036)	0.310	-	-	-

* log-transformed

As described in Section 6.2, bootstrap variable selection was then used to identify, from all variables identified in the previous backward selected models (Models 1 to 6), those associated with cIMT. The results are shown in **Table 6.7**. HDL cholesterol had a negative association with cIMT; systolic blood pressure had a positive association, and diastolic blood pressure had a negative association. Leg length had a negative association with cIMT.

In order to determine if the associations identified in Model 7 were consistent throughout the study subjects, the same procedure of bootstrap variable selection was used: in only those subjects with no history of CVD **(Table 6.8)**; in only those subjects not on statin therapy **(Table 6.9)**; in only those subjects not on antihypertensive therapy **(Table 6.10)** and in only those subjects on neither statin nor antihypertensive therapy **(Table 6.11)**. The findings in each subgroup were generally consistent: in subjects with no history of cardiovascular disease **(Table 6.8)**, significant associations with cIMT were found for HDL cholesterol (negative association), systolic blood pressure (positive association) and diastolic blood pressure (negative association). Adiponectin showed a negative association with cIMT, i.e. lower adiponectin concentrations (associated with higher levels of insulin resistance) were associated with thicker cIMT.

When the same analyses were run only in subjects not on: statin therapy **(Table 6.9)**; antihypertensive therapy **(Table 6.10)** or either statin or antihypertensive therapy **(Table 6.11)**, the associations of systolic blood pressure, diastolic blood pressure (negative association), leg length (negative association) and HDL cholesterol (negative association) with cIMT were again present.

Table 6.7 Associations of co-factor variables with cIMT (Model 7)

	Estimated effect	95% confidence interval	p
Age	0.009	(0.007, 0.010)	<0.001
Sex (male)	0.050	(0.014, 0.087)	0.007
Deprivation (most deprived)	-0.002	(-0.032, 0.028)	0.895
HDL cholesterol	-0.071	(-0.110, -0.032)	<0.001
Systolic Blood Pressure	0.003	(0.002, 0.004)	<0.001
Diastolic Blood Pressure	-0.003	(-0.005, -0.001)	0.002
Leg length	-0.004	(-0.007, -0.001)	0.014

Variables were selected by bootstrap selection from all variables selected in the previous backward selected models (Models 1 to 6).

Table 6.8 Associations of co-factor variables with cIMT – only subjects without history of CVD

	Estimated effect	95% confidence interval	p
Age	0.009	(0.007, 0.011)	<0.001
Sex (male)	0.007	(-0.024, 0.039)	0.649
Deprivation (most deprived)	0.010	(-0.018, 0.038)	0.492
HDL cholesterol	-0.057	(-0.100, -0.014)	0.009
Systolic Blood Pressure	0.003	(0.002, 0.004)	<0.001
Diastolic Blood Pressure	-0.002	(-0.004, 0.000)	0.025
Adiponectin *	-0.049	(-0.082, -0.016)	0.004

* log-transformed

Table 6.9 Associations of co-factor variables with cIMT – only subjects not on statin therapy

	Estimated effect	95% confidence interval	p
Age	0.009	(0.007, 0.010)	<0.001
Sex (male)	0.044	(0.006, 0.082)	0.025
Deprivation (most deprived)	-0.005	(-0.035, 0.026)	0.763
HDL cholesterol	-0.070	(-0.111, -0.029)	0.001
Systolic Blood Pressure	0.003	(0.002, 0.005)	<0.001
Diastolic Blood Pressure	-0.003	(-0.005, -0.001)	0.002
Leg length	-0.004	(-0.007, -0.001)	0.014

Table 6.10 Associations of co-factor variables with cIMT – only subjects not on antihypertensive therapy

	Estimated effect	95% confidence interval	p
Age	0.009	(0.007, 0.011)	<0.001
Sex (male)	0.045	(0.006, 0.085)	0.025
Deprivation (most deprived)	-0.007	(-0.039, 0.025)	0.668
HDL cholesterol	-0.071	(-0.114, -0.028)	0.001
Systolic Blood Pressure	0.003	(0.002, 0.005)	<0.001
Diastolic Blood Pressure	-0.003	(-0.005, -0.001)	0.005
Leg length	-0.004	(-0.008, -0.001)	0.011

Table 6.11 Associations of co-factor variables with cIMT – only subjects not on statin or antihypertensive therapy

	Estimated effect	95% confidence interval	p
Age	0.009	(0.007, 0.011)	<0.001
Sex (male)	0.054	(0.014, 0.094)	0.008
Deprivation (most deprived)	-0.011	(-0.043, 0.021)	0.509
HDL cholesterol	-0.064	(-0.107, -0.020)	0.004
Systolic Blood Pressure	0.003	(0.002, 0.005)	<0.001
Diastolic Blood Pressure	-0.003	(-0.005, -0.001)	0.007
Leg length	-0.005	(-0.008, -0.001)	0.007

6.3.2 Predictors of plaque score

As described in Section 6.2, similar models to those reported in Section 6.3.1 for cIMT were run with plaque presence (as a binary variable) being the dependent variable. **Table 6.12** shows the contribution of age, sex and deprivation to plaque presence. Consistent with the findings reported in detail in Chapter 5, increasing age, male sex and being in the most deprived group were associated with greater risk of having one or more carotid plaques.

The associations of classic cardiovascular risk factors with plaque presence are shown in **Table 6.13**. When all classic risk factors were included in the model, only current smoking was associated with plaque presence.

Table 6.14 shows a model containing markers of inflammation/endothelial dysfunction along with age, sex and deprivation. None of the markers measured (CRP, IL-6 and sICAM-1) were associated with plaque presence.

Of the markers of insulin resistance / adiposity (**Table 6.15**), only waist circumference predicted plaque presence – although paradoxically, the association was negative, i.e. greater waist circumference was associated with lower likelihood of plaque presence. In order to explore this finding further, the contribution of waist circumference to the deprivation effect on plaque presence was assessed by determining the difference in deprivation effect between Model 4 (which included markers of insulin resistance/adiposity) and Model 1 (which included only age, sex and deprivation). In Model 4, the deprivation effect was actually strengthened (estimated difference -0.093; 95% bootstrap confidence interval -0.195 to -0.024; p=0.006, data not shown). This indicates that, consistent with the findings reported in Chapter 5, waist circumference did not contribute to the explanation of the difference in plaque presence, and suggests that once deprivation was adjusted for, there was an apparent negative association between waist circumference and plaque presence.

The associations of markers of haemostasis with plaque presence are shown in **Table 6.16**. There were no associations between plaque presence and any of the markers of haemostasis (fibrinogen, D-dimer and vWF).

Table 6.12 Associations of age, sex and area-level deprivation with plaque presence (Model 1)

	Effect	95% confidence interval	p
Age	0.084	(0.063, 0.105)	<0.001
Sex (male)	0.523	(0.194, 0.857)	0.002
Deprivation (most deprived)	0.743	(0.411, 1.079)	<0.001

Table 6.13 Associations of classic cardiovascular risk factors with plaque presence (Model 2)

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.073	(0.048, 0.098)	<0.001	0.082	(0.061, 0.105)	<0.001
Sex (male)	0.535	(0.147, 0.928)	0.007	0.516	(0.175, 0.861)	0.003
Deprivation (most deprived)	0.483	(0.076, 0.891)	0.020	0.459	(0.079, 0.840)	0.018
Triglycerides *	0.335	(-0.065, 0.739)	0.102	-	-	-
LDL cholesterol	0.156	(-0.052, 0.366)	0.143	-	-	-
HDL cholesterol	0.348	(-0.208, 0.915)	0.223	-	-	-
Systolic blood pressure	0.003	(-0.012, 0.018)	0.675	-	-	-
Diastolic blood pressure	-0.006	(-0.030, 0.019)	0.643	-	-	-
Smoking (current)	0.738	(0.273, 1.213)	0.002	0.727	(0.280, 1.182)	0.002
History of hypertension	0.231	(-0.259, 0.725)	0.357	-	-	-

* log-transformed

Table 6.14 Associations of markers of inflammation/endothelial dysfunction with plaque presence (Model 3)

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p-value
Age	0.081	(0.059, 0.104)	<0.001	0.084	(0.063, 0.105)	<0.001
Sex (male)	0.584	(0.239, 0.933)	0.001	0.084	(0.063, 0.105)	<0.001
Deprivation (most deprived)	0.736	(0.351, 1.128)	<0.001	0.743	(0.411, 1.079)	<0.001
CRP *	-0.047	(-0.237, 0.142)	0.626	-	-	-
IL-6	-0.011	(-0.156, 0.135)	0.883	-	-	-
sICAM-1 *	0.366	(-0.373, 1.110)	0.332	-	-	-

* log-transformed

Table 6.15 Associations of markers of insulin resistance/adiposity with plaque presence (Model 4)

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.083	(0.059, 0.108)	<0.001	0.087	(0.065, 0.109)	<0.001
Sex (male)	0.575	(-0.081, 1.238)	0.087	0.669	(0.321, 1.022)	<0.001
Deprivation (most deprived)	0.843	(0.475, 1.218)	<0.001	0.838	(0.498, 1.185)	<0.001
Waist circumference	-0.027	(-0.049, -0.006)	0.014	-0.018	(-0.031, -0.005)	0.005
Glucose	0.092	(-0.207, 0.435)	0.573	-	-	-
HOMA-IR *	0.011	(-0.345, 0.365)	0.953	-	-	-
Adiponectin *	-0.403	(-0.829, 0.017)	0.061	-	-	-
Leptin *	-0.036	(-0.422, 0.350)	0.854	-	-	-
Diabetes	13.572	(-52.146, NA)	0.979	-	-	-

* log-transformed

Table 6.16 Associations of markers of haemostasis with plaque presence (Model 5)

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.083	(0.060, 0.107)	<0.001	0.084	(0.063, 0.105)	<0.001
Sex (male)	0.511	(0.167, 0.858)	0.004	0.523	(0.194, 0.857)	0.002
Deprivation (most deprived)	0.841	(0.482, 1.207)	<0.001	0.743	(0.411, 1.079)	<0.001
Fibrinogen	0.028	(-0.252, 0.308)	0.845	-	-	-
D-dimer *	-0.120	(-0.459, 0.217)	0.485	-	-	-
von Willebrand factor	-0.001	(-0.006, 0.003)	0.586	-	-	-

* log-transformed

Of the early life individual-level markers of socioeconomic status, father's social class was associated with plaque presence, with participants whose father was in the non-manual social classes being less likely to have a plaque than those whose father had a manual social class **(Table 6.17)**.

Using similar bootstrap selection procedures to those used for cIMT, variables were selected from those identified on backward selection in Models 1 to 6. The results are shown in **Table 6.18**. The variables associated with plaque presence using these procedures were current smoking, waist circumference (negative association as previously observed) and father's social class, with non-manual father's social class being identified with less likelihood of plaque presence than manual father's social class.

When carrying out the above model selection process in only those subjects with no history of CVD **(Table 6.19)**, the negative association of waist circumference with plaque presence was again present, as was the association of father's social class with plaque presence. Smoking was not associated with plaque presence when only those subjects with no history of CVD were included – this may be because smoking and CVD are strongly associated.

When including only subjects not on statin therapy **(Table 6.20)**, smoking, waist circumference (negative association) and father's social class were the significant associations with plaque presence as in the analysis of the whole study population.

In subjects not on antihypertensive treatment **(Table 6.21)** and in subjects on neither antihypertensive nor statin therapy **(Table 6.22)**, the associations with plaque presence were waist circumference and father's social class.

Table 6.17 Associations of early life socioeconomic factors with plaque presence (Model 6)

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.083	(0.058, 0.109)	<0.001	0.089	(0.066, 0.112)	<0.001
Sex (male)	1.051	(0.467, 1.647)	<0.001	0.640	(0.288, 0.995)	<0.001
Deprivation (most deprived)	0.074	(-0.474, 0.617)	0.790	0.573	(0.181, 0.969)	0.004
Height	-0.030	(-0.080, 0.020)	0.245	-	-	-
Leg length	0.017	(-0.049, 0.083)	0.611	-	-	-
People per room at age 11 years *	0.099	(-0.399, 0.600)	0.697	-	-	-
Father's social class (Non-manual)	-0.451	(-0.905, 0.000)	0.050	-0.443	(-0.844, -0.044)	0.030
Years of education *	-1.062	(-2.045, -0.102)	0.032	-	-	-

* log-transformed

Table 6.18 Associations of co-factor variables with plaque presence

	Estimated effect	95% confidence interval	p
Age	0.089	(0.066, 0.114)	<0.001
Sex (male)	0.738	(0.356, 1.128)	<0.001
Deprivation (most deprived)	0.445	(-0.016, 0.908)	0.059
Current smoking	0.554	(0.065, 1.050)	0.027
Waist circumference	-0.015	(-0.030, -0.001)	0.033
Father's social class (non-manual)	-0.464	(-0.876, -0.055)	0.027

Table 6.19 Associations of co-factor variables with plaque presence – only subjects with no history of CVD

	Estimated effect	95% confidence interval	p
Age	0.084	(0.060, 0.109)	<0.001
Sex (male)	0.834	(0.440, 1.235)	<0.001
Deprivation (most deprived)	0.565	(0.135, 1.000)	0.010
Waist circumference	-0.020	(-0.035, -0.006)	0.007
Father's social class (non-manual)	-0.451	(-0.877, -0.028)	0.037

Table 6.20 Associations of co-factor variables with plaque presence – only subjects not on statin therapy

	Estimated effect	95% confidence interval	p
Age	0.080	(0.055, 0.106)	<0.001
Sex (male)	0.794	(0.391, 1.205)	<0.001
Deprivation (most deprived)	0.295	(-0.197, 0.787)	0.239
Current smoking	0.595	(0.071, 1.125)	0.026
Waist circumference	-0.021	(-0.036, -0.006)	0.007
Father's social class (non-manual)	-0.444	(-0.881, -0.010)	0.046

Table 6.21 Associations of co-factor variables with plaque presence – only subjects not on antihypertensive treatment

	Estimated effect	95% confidence interval	p
Age	0.083	(0.057, 0.111)	<0.001
Sex (male)	0.819	(0.409, 1.238)	<0.001
Deprivation (most deprived)	0.511	(0.061, 0.966)	0.027
Waist circumference	-0.021	(-0.037, -0.005)	0.010
Father's social class (non-manual)	-0.626	(-1.077, -0.179)	0.006

Table 6.22 Associations of variables with plaque presence – only subjects not on antihypertensive or statin therapy

	Estimated effect	95% confidence interval	p
Age	0.081	(0.054, 0.108)	<0.001
Sex (male)	0.847	(0.432, 1.271)	<0.001
Deprivation (most deprived)	0.433	(-0.028, 0.897)	0.066
Waist circumference	-0.022	(-0.039, -0.006)	0.008
Father's social class (non-manual)	-0.583	(-1.043, -0.129)	0.012

6.4 Discussion

The aim of the work described in this chapter was to examine the co-factors associated with cIMT and those associated with plaque, with the hypothesis that lipid parameters and blood pressure would explain much of the variability in cIMT, while plaque would be explained by other variables – possibly some of the lesser studied emerging biomarkers, and specifically markers of inflammation.

In the case of cIMT, the consistent associations noted were a negative association with HDL cholesterol, a positive association with systolic blood pressure and a negative association with diastolic blood pressure. A negative association between adiponectin and cIMT was seen in the model incorporating markers of insulin resistance/adiposity (Model 4), which may imply an association between insulin resistance and cIMT, but no significant association between adiponectin and cIMT was identified once other variables were included **(Table 6.7)**. The early life socioeconomic factors analysed as covariates are clearly much more 'upstream' markers than the biomarkers analysed. Leg length, a marker of nutritional status during the years of growth,[131] was inversely associated with cIMT. The possible significance of early life factors in influencing health outcomes in later life is further explored in Chapter 8. The positive association between height and cIMT appears at first unexpected, and is the opposite of what would be expected from previous studies in which height and leg length were found to be inversely associated with CHD.[172] However, in the model reported here **(Table 6.6)**, height and leg length were both included in the model, and it is in the context of a highly significant inverse association between leg length and cIMT that a weaker positive association was seen between height and cIMT. If the association between cIMT and height *per se* were to be assessed, a model would need to be constructed in which height was included without leg length, given the obvious co-linearity between height and leg length.

The inverse association between HDL cholesterol and cIMT, and the direct association between systolic blood pressure and cIMT are consistent with findings from previous work. Given that IMT is thought to represent hypertrophy of intimal and medial cells in response to lipid infiltration or hypertension,[169] and given that previous work has shown associations between cIMT and both lipid parameters and hypertension,[170] the findings reported here are consistent with previous findings. The negative association between diastolic blood pressure and cIMT (after adjusting for systolic blood pressure) might at first seem counter-intuitive, in view of the positive association between systolic blood

pressure and cIMT. However, a similar finding was reported in the Cardiovascular Health Study, and the investigators in that study hypothesised that this might be due to the fact that lower diastolic blood pressure may reflect decreased arterial compliance leading to increased pulse pressure.[170]

In contrast to cIMT, in the case of plaque presence the consistent associations were with current cigarette smoking, waist circumference (negative association) and father's social class. Contrary to my prior hypothesis, no associations were demonstrated between any emerging biomarkers and plaque presence. This was particularly surprising in the case of markers of inflammation/endothelial dysfunction, with no associations noted between CRP, IL-6 or sICAM-1 and plaque presence. Given the growing body of evidence for the role of inflammation in atherogenesis,[60] a worthy area for future extension of this work would be to expand the repertoire of inflammatory markers measured on stored plasma from the pSoBid study.

The association between cigarette smoking and plaque presence is, of course, unsurprising, given the overwhelming body of evidence for the relationship between smoking and atherosclerosis.[13] Model 2, which examined the associations between classic risk factors and plaque presence **(Table 6.13)** powerfully demonstrates that when smoking is in the model predicting plaque presence, no other classic risk factor (other than age and sex) adds to the ability to predict plaque presence.

Father's social class, which was also associated with plaque presence, is a much more 'upstream' marker than the biomarkers measured in this study. It is likely that there is a degree of co-linearity between father's social class and area-level deprivation (which was demonstrated in Chapter 5 to be strongly associated with carotid plaque). However, the demonstration of the association between father's social class and carotid plaque presence may suggest a role for early life socioeconomic factors. The role of early life factors in general is explored more fully in Chapter 8.

The negative association between waist circumference and plaque presence is interesting, and at first glance surprising. However, it must be remembered that this effect was seen in models which already adjusted for age, sex and deprivation. This might suggest a differential effect of abdominal obesity on plaque presence in the two deprivation groups, although such a suggestion can only be speculative. In any case, the fact that the deprivation effect on plaque presence was strengthened rather than weakened after

adjusting for waist circumference indicates that, whatever the relationship between waist circumference and plaque presence, differences in waist circumference do not contribute to the explanation of the difference in plaque presence between the most and least deprived groups.

In summary, the work described in this chapter shows clearly differential associations of risk factors with cIMT compared to plaque. The main associations for cIMT are HDL cholesterol (negative association), systolic blood pressure and leg length (negative association). In the case of plaque presence, the main predictors are cigarette smoking, father's social class and the paradoxical inverse association with waist circumference.

CHAPTER 7 – SOCIAL DEPRIVATION AND ARTERIAL STIFFNESS

7.1 Introduction

As discussed in Chapter 1, carotid ultrasound also allows for assessment to be made of parameters of arterial stiffness, using M-(movement) mode. Associations have been reported between ultrasound-derived parameters of arterial stiffness and cIMT and carotid plaque severity.[100] Furthermore, arterial stiffness parameters have been shown to be predictive of mortality in patients with end-stage renal failure and of cardiovascular events after renal transplantation.[95]

Some previous studies have examined associations between parameters of arterial stiffness and some individual-level markers of social deprivation. Associations between educational attainment and lower arterial stiffness were reported in 45-64 year-old men in the Atherosclerosis Risk in Communities study.[104] A study of adolescents living in the USA found inverse associations between PWV and both parental educational attainment and family income, despite no associations being found between these markers of socioeconomic status and cIMT,[106] leading some to suggest that changes in arterial stiffness might precede development of atherosclerosis in individuals.

The work described in this chapter had three aims. The first aim was to expand on previous work by others who have examined the association between individual-level markers of socioeconomic status and parameters of arterial stiffness, by assessing whether differences can be identified in parameters of arterial stiffness between participants selected from the two extremes of social deprivation as determined by area-level markers of deprivation. The second aim was to identify which classic and emerging cardiovascular risk factors are associated with parameters of arterial stiffness. Finally, I sought to identify any associations between ultrasound parameters of arterial stiffness and ultrasound markers of atherosclerosis, namely cIMT and carotid plaque.

7.2 Methods

At the same time as participants in the pSoBid study were having carotid ultrasound assessment of cIMT and plaque presence, M-mode ultrasound analysis of parameters of arterial stiffness was undertaken as detailed in Section 2.5.8, with blood pressure being recorded immediately before and after acquisition of the M-mode image. Calculation of parameters of arterial stiffness was carried out offline later by myself, blinded to the identities of the participants. The details of the semi-automated procedure for analysis of M-mode images, and the algorithms used by the eTrack reader software to calculate the parameters of arterial stiffness are to be found in Section 2.5.8.

Statistical analysis was performed using Minitab release 13.1 and R version 2.9. Normality of distribution was assessed by the Anderson-Darling test. All of the arterial stiffness parameters were non-parametrically distributed, and so are described as median (interquartile range). P values for differences in parameters of arterial stiffness between most and least deprived groups are shown adjusted for age and sex.

For assessment of associations between cardiovascular risk factors and parameters of arterial stiffness (only stiffness and distensibility were used as dependent variables in this analysis), multivariate models were constructed using log transformed stiffness or log transformed distensibility as the dependent variable. Similar models to those used in chapter 6 for cIMT were then constructed. An initial model (Model 1) was adjusted for age, sex and deprivation. In subsequent models, covariates were added in groups representing: classic risk factors (Model 2), inflammation (Model 3), insulin resistance (Model 4), haemostasis (Model 5) and early life socioeconomic factors (Model 6). In each case, after construction of the full model, a backward selected model was used to identify those variables retaining a significant association with the dependent variable. Finally (Model 7) bootstrap variable selection was used. A sample of the data (of the same size, where individuals can appear more than once in the sample) was taken and variables identified (from those which were significant on backward selection in Models 1 to 6) which had a significant association with the dependent variable. This was repeated 1000 times and the confidence interval and p-value derived from these 1000 values. A forward stepwise selection was then carried out on those variables that had been selected in at least 50% of the models in order to identify those variables retaining a significant association with the dependent variable. This bootstrap model selection was then repeated in only

those subjects with no history of CVD, in those not on statin therapy, in those not on antihypertensive treatment and in those not on statin or antihypertensive treatment.

For the analysis of associations of stiffness and distensibility with cIMT and plaque presence, similar models were constructed to those described in Chapter 6, with cIMT or plaque as the dependent variable, and the parameters of arterial stiffness as covariates.

7.3 Results

7.3.1 Comparison of parameters of arterial stiffness between most and least deprived groups

The distribution of parameters of arterial stiffness in most and least deprived groups is shown in **Table 7.1**, demonstrating that there were no differences in any of the arterial stiffness variables between most and least deprived groups.

7.3.2 Association of stiffness (β) with classic and emerging cardiovascular risk factors

Table 7.2 shows the effect of age, sex and deprivation on stiffness. As expected, stiffness increased with age and was higher in males than females. To this age, sex and deprivation-adjusted model, co-factor variables were then added in groups as described in Section 7.2 in order to examine the associations of these co-factors with stiffness (β).

When classic risk factors were added to the age, sex and deprivation adjusted model **(Table 7.3)**, significant associations were observed for systolic blood pressure and current smoking – although the effect of smoking was a negative effect.

When the associations of markers of inflammation/endothelial dysfunction with stiffness were modelled **(Table 7.4)**, there was a significant association between CRP and stiffness – although paradoxically the association was in a negative direction.

No significant associations were evident with stiffness for markers of insulin resistance/adiposity **(Table 7.5)**, haemostasis **(Table 7.6)** or early life socioeconomic factors **(Table 7.7)**.

Table 7.1 Comparison of parameters of arterial stiffness between most and least deprived groups

Parameter	Least deprived (n=325)	Most deprived (n=293)	p *
Distensibility (10^{-3}/kPa)	32.4 (25.0, 39.8)	34.2 (26.5, 44.0)	0.067
Distensibility_Tf (10^{-3}/kPa)	34.5 (26.4, 43.2)	36.7 (28.0, 47.5)	0.062
Compliance (mm^2/kPa)	0.82 (0.65, 1.00)	0.89 (0.68, 1.04)	0.060
Compliance_Tf (mm^2/kPa)	0.87 (0.69, 1.07)	0.94 (0.71, 1.13)	0.051
Stiffness (β)	4.58 (3.68, 5.61)	4.53 (3.47, 5.65)	0.12
Elasticity (Petersen) (kPa)	60.7 (47.4, 78.3)	59.5 (45.8, 77.5)	0.73

* p value refers to difference between most and least deprived groups, adjusted for age and sex.

Table 7.2 Association of age, sex and deprivation with stiffness (β) (Model 1)

	Effect	95% confidence interval	p
Age	0.014	(0.011, 0.017)	<0.001
Sex (male)	0.123	(0.078, 0.169)	<0.001
Deprivation (most deprived)	-0.037	(-0.082, 0.009)	0.116

Table 7.3 Association of classic cardiovascular risk factors with stiffness (β) (Model 2)

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.013	(0.009, 0.016)	<0.001	0.013	(0.010, 0.016)	<0.001
Sex (male)	0.115	(0.062, 0.168)	<0.001	0.110	(0.062, 0.159)	<0.001
Deprivation (most deprived)	-0.021	(-0.077, 0.035)	0.460	-0.016	(-0.069, 0.036)	0.544
Triglycerides *	-0.004	(-0.058, 0.051)	0.898	-	-	-
LDL cholesterol	0.005	(-0.024, 0.034)	0.727	-	-	-
HDL cholesterol	0.027	(-0.048, 0.102)	0.480	-	-	-
Systolic blood pressure	0.002	(0.000, 0.004)	0.057	0.002	(0.000, 0.003)	0.009
Diastolic blood pressure	-0.001	(-0.004, 0.002)	0.559	-	-	-
Smoking (current)	-0.062	(-0.125, 0.001)	0.055	-0.068	(-0.130, -0.007)	0.030
History of hypertension	0.028	(-0.041, 0.096)	0.429	-	-	-

* log-transformed

Table 7.4 Association of markers of inflammation/endothelial dysfunction with stiffness (β) (Model 3)

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.015	(0.012, 0.018)	<0.001	0.015	(0.012, 0.018)	<0.001
Sex (male)	0.116	(0.069, 0.164)	<0.001	0.119	(0.073, 0.165)	<0.001
Deprivation (most deprived)	-0.022	(-0.075, 0.031)	0.412	-0.026	(-0.073, 0.022)	0.293
CRP *	-0.025	(-0.051, 0.001)	0.057	-0.023	(-0.044, -0.001)	0.040
IL-6	0.011	(-0.010, 0.032)	0.303	-	-	-
sICAM-1 *	-0.057	(-0.160, 0.045)	0.273	-	-	-

* log-transformed

Table 7.5 Association of markers of insulin resistance/adiposity with stiffness (β) (Model 4)

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.014	(0.011, 0.017)	<0.001	0.014	(0.011, 0.017)	<0.001
Sex (male)	0.071	(-0.019, 0.161)	0.121	0.123	(0.078, 0.169)	<0.001
Deprivation (most deprived)	-0.047	(-0.096, 0.003)	0.064	-0.037	(-0.082, 0.009)	0.116
Waist	0.000	(-0.003, 0.003)	0.832	-	-	-
Glucose	0.012	(-0.027, 0.052)	0.541	-	-	-
HOMA-IR *	0.009	(-0.038, 0.057)	0.696	-	-	-
Adiponectin *	-0.045	(-0.102, 0.012)	0.125	-	-	-
Leptin *	-0.030	(-0.082, 0.022)	0.258	-	-	-
Diabetes	0.199	(-0.140, 0.538)	0.249	-	-	-

* log-transformed

Table 7.6 Association of markers of haemostasis with stiffness (β) (Model 5)

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.015	(0.012, 0.018)	<0.001	0.014	(0.011, 0.017)	<0.001
Sex (male)	0.120	(0.072, 0.168)	<0.001	0.123	(0.078, 0.169)	<0.001
Deprivation (most deprived)	-0.028	(-0.077, 0.021)	0.267	-0.037	(-0.082, 0.009)	0.116
Fibrinogen	-0.016	(-0.055, 0.023)	0.412	-	-	-
D-dimer *	0.024	(-0.023, 0.070)	0.315	-	-	-
von Willebrand factor	0.000	(-0.001, 0.000)	0.172	-	-	-

* log-transformed

Table 7.7 Association of early life socioeconomic factors with stiffness (β) (Model 6)

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.016	(0.012, 0.019)	<0.001	0.014	(0.011, 0.017)	<0.001
Sex	0.121	(0.045, 0.197)	0.002	0.123	(0.078, 0.169)	<0.001
Deprivation (deprived)	-0.008	(-0.080, 0.064)	0.826	-0.037	(-0.082, 0.009)	0.116
Height	0.004	(-0.002, 0.011)	0.188	-	-	-
Leg length	-0.007	(-0.015, 0.002)	0.133	-	-	-
People per room at age 11 *	-0.020	(-0.085, 0.045)	0.537	-	-	-
Father's social class (Non-manual)	-0.019	(-0.080, 0.042)	0.547	-	-	-
Years of education *	0.094	(-0.035, 0.223)	0.154	-	-	-

* log-transformed

Table 7.8 Association of co-factor variables with stiffness (β)

	Estimated effect	95% confidence interval	p
Age	0.014	(0.011, 0.017)	<0.001
Sex (male)	0.108	(0.059, 0.157)	<0.001
Deprivation (most deprived)	-0.003	(-0.057, 0.052)	0.923
Systolic blood pressure	0.002	(0.001, 0.003)	0.007
Current smoking	-0.065	(-0.127, -0.002)	0.043
CRP *	-0.026	(-0.049, -0.004)	0.022

* log-transformed

On carrying out bootstrap selection from the variables that were significant in Models 1 to 6, the same variables were significantly associated with stiffness as had been identified in the individual models, namely systolic blood pressure, CRP (negative association) and smoking (negative association) **(Table 7.8)**.

When only subjects with no history of cardiovascular disease were included in the analysis, the associations with systolic blood pressure and CRP remained, although the inverse association of smoking with arterial stiffness was no longer present, most likely because of the strong association of smoking with CVD meaning that relatively few smokers remained in this analysis **(Table 7.9)**. Including only subjects not on statin or antihypertensive therapy did not significantly change the results (data not shown).

Table 7.9 Association of co-factor variables with stiffness (β) – only subjects with no history of CVD

	Estimated effect	95% confidence interval	p
Age	0.013	(0.010, 0.016)	<0.001
Sex (male)	0.106	(0.055, 0.156)	<0.001
Deprivation (most deprived)	-0.039	(-0.090, 0.012)	0.131
Systolic blood pressure	0.002	(0.001, 0.004)	0.004
CRP *	-0.025	(-0.048, -0.002)	0.033

* log-transformed

Table 7.10 Association of co-factor variables with distensibility

	Estimated effect	95% confidence interval	p
Age	-0.014	(-0.017, -0.011)	<0.001
Sex (male)	-0.143	(-0.193, -0.093)	<0.001
Deprivation (most deprived)	0.046	(-0.003, 0.095)	0.068
Systolic blood pressure	-0.004	(-0.006, -0.002)	<0.001
Diastolic blood pressure	-0.004	(-0.007, 0.000)	0.035

The same set of models was then constructed with distensibility as the dependent variable. Of the classic risk factors, both systolic blood pressure (effect estimate -0.004; 95% CI -0.006 to -0.002; p<0.001) and diastolic blood pressure (effect estimate -0.004; 95% CI -0.007 to 0.000; p=0.035) were inversely associated with distensibility, i.e. lower blood pressure was associated with higher distensibility (data not shown). None of the markers of inflammation/endothelial dysfunction showed significant association with distensibility. In the model which included markers of insulin resistance/adiposity, HOMA-IR was inversely associated with distensibility (effect estimate -0.056; 95% CI -0.094 to -0.018; p=0.004), i.e. lower levels of insulin resistance were associated with higher distensibility. No markers of haemostasis or early life socioeconomic status were associated with distensibility. On bootstrap variable selection, significant negative associations were observed for systolic and diastolic blood pressure **(Table 7.10)**, and this was also the case when only participants with no history of CVD, those not on statin therapy, or those not on antihypertensive therapy were included in the analysis (data not shown).

7.3.3 Associations of parameters of arterial stiffness with cIMT and plaque

In order to identify any associations of arterial stiffness or distensibility with cIMT, an age, sex and deprivation-adjusted model was constructed with cIMT as the dependent variable and stiffness and distensibility as covariates. Neither stiffness nor distensibility was associated with cIMT in this model **(Table 7.11)**. Similarly, when plaque presence was the dependent variable in a similar model, there were no associations between stiffness or distensibility and plaque presence **(Table 7.12)**

Table 7.11 Association of parameters of arterial stiffness with cIMT

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.011	(0.009, 0.013)	<0.001	0.010	(0.009, 0.012)	<0.001
Sex	0.066	(0.039, 0.093)	<0.001	0.059	(0.033, 0.085)	<0.001
Deprivation (most deprived)	0.023	(-0.003, 0.049)	0.081	0.029	(0.003, 0.055)	0.028
Stiffness *	-0.050	(-0.127, 0.027)	0.206	-	-	-
Distensibility *	-0.007	(-0.075, 0.061)	0.841	-	-	-

* log-transformed

Table 7.12 Association of parameters of arterial stiffness with carotid plaque presence

	Full model			Backward selected model		
	Effect	95% confidence interval	p	Effect	95% confidence interval	p
Age	0.082	(0.058, 0.106)	<0.001	0.084	(0.063, 0.105)	<0.001
Sex	0.589	(0.236, 0.946)	0.001	0.084	(0.063, 0.105)	<0.001
Deprivation (most deprived)	0.763	(0.422, 1.110)	<0.001	0.743	(0.411, 1.079)	<0.001
Stiffness *	-0.556	(-1.583, 0.443)	0.280	-	-	-
Distensibility *	-0.436	(-1.349, 0.451)	0.341	-	-	-

* log-transformed

7.4 Discussion

Of the three aims of the work described in this chapter, the first was to determine if any parameters of arterial stiffness were different in the two area-level deprivation groups. It is quite clear that no deprivation-based differences in arterial stiffness parameters were evident in the pSoBid study population. This is in contrast to the findings in some previous studies, the Atherosclerosis Risk in Communities Study having reported in 45 to 64 year olds an association between educational attainment and arterial diameter change,[104] and a study in adolescents having found associations between pulse wave velocity and both parental educational attainment and family income.[106] However, both of these studies were examining associations between arterial stiffness and individual-level markers of socioeconomic status, so the finding reported in this chapter of no associations between arterial stiffness and area-level deprivation is not in direct conflict with the above findings. Furthermore, the methods used in the various studies differ, making the results not directly comparable. In the Atherosclerosis Risk in Communities study, the parameter used was B-mode ultrasound echo-tracked pulsatile arterial diameter change,[104] which does not involve derivation of the range of parameters of arterial stiffness examined in this study. Thurston *et al*'s study of adolescents used carotid-femoral pulse wave velocity,[106] rather than M-mode carotid ultrasound as was done in this study. The findings in this study indicate that, in this study population, B-mode ultrasound assessment of cIMT and plaque score is a more useful tool for studying differences between the deprivation groups than is M-mode ultrasound assessment of arterial stiffness.

The second aim of this part of the work was to determine which cardiovascular risk factors are associated with parameters of arterial stiffness. Not surprisingly, the most consistent associations were for blood pressure (systolic blood pressure in the case of stiffness, and both systolic and diastolic blood pressure in the case of distensibility). The fact that associations with cardiovascular risk factors were very similar for both stiffness and distensibility is not surprising, given that stiffness and distensibility are essentially variations on a theme, both being calculated from systolic and diastolic blood pressure and strain.

Of the other associations identified, the association of smoking with stiffness is certainly counterintuitive, in that it was a negative association. However, in the set of models constructed, smoking was only analysed in models which also contained blood pressure, which is clearly the main determinant of arterial stiffness. If the effect of smoking on

arterial stiffness were to be explored further, models would be required which do not include blood pressure. The fact that no association was observed between smoking and stiffness when only subjects with no history of CVD were analysed is probably due to the strong association between CVD and smoking, meaning that relatively few smokers remained in the analysis after removing those with CVD. A recent systematic review found that acute smoking causes an acute increase in arterial stiffness, passive smoking increases arterial stiffness acutely and chronically and most studies have found chronic smoking to be a risk factor for increased arterial stiffness.[173]

The negative association of CRP with arterial stiffness is also surprising. A possible explanation is that all the models reported in this chapter were already adjusted for deprivation. Although arterial stiffness was not associated with deprivation in this study, CRP was significantly associated with deprivation, so by adjusting for deprivation and CRP simultaneously, there may be the possibility of overadjustment. In general, studies which have set out to investigate the association of inflammation with arterial stiffness *a priori* have found a positive association of inflammation with arterial stiffness, with some evidence that even acute systemic inflammation leads to increased arterial stiffness.[174]

The inverse relationship between HOMA-IR and distensibility is interesting – although this association was only significant in the model containing markers of insulin resistance, and not in the full model containing all significant variables **(Table 7.10)**. This may be because the full model also adjusted for blood pressure, with the strong associations of blood pressure with distensibility masking any other associations present. The observation of higher HOMA-IR (i.e. higher levels of insulin resistance) being associated with lower distensibility is consistent with recent findings by Webb *et al*, in which HOMA-IR was found to be a powerful predictor of arterial stiffness.[175]

In this study population, no evidence was found of any associations between parameters of arterial stiffness and either cIMT **(Table 7.11)** or plaque **(Table 7.12)**. This is in contrast to findings from the Rotterdam study, in which significant increases in carotid-femoral PWV were noted with increasing quartiles of cIMT and with increasing categories of carotid or aortic plaque, and common carotid distensibility decreased with increasing quartiles of cIMT and with increasing categories of carotid or aortic plaque – although the Rotterdam study population was significantly older (age 60 to 101 years) than this study population.[100]

In conclusion, the work described in this chapter has shown carotid ultrasound-derived parameters of arterial stiffness to be no different between those in most versus least deprived areas. Consequently, of the ultrasound markers assessed in this study, carotid plaque score has been shown to be the most discriminant marker, followed by mean common carotid intima-media thickness.

CHAPTER 8 – SOCIAL DEPRIVATION AND EARLY LIFE, BIOLOGICAL FACTORS AND PSYCHOLOGY

8.1 Introduction

The work described so far in this thesis has focused on the associations of social deprivation with classic and emerging cardiovascular risk factors and ultrasound markers of atherosclerosis and arterial stiffness, these being the areas of the pSoBid study for which I was responsible. However, the pSoBid study was a collaborative study, involving investigators from many fields such as epidemiology, public health, psychology and biostatistics. This chapter, therefore, seeks to set in context the work described in the preceding chapters, by giving a brief overview of some of the other aspects of the pSoBid study – work which I undertook in collaboration with other members of the pSoBid study team. This chapter will principally explore the relevance of early life experiences, and the role of personality, in the relationships between social deprivation and ill health.

8.2 Associations between early life socioeconomic adversity and chronic inflammation, carotid atherosclerosis, lung function and cognitive performance in adult life

8.2.1 Introduction

Increasing evidence indicates that socioeconomic circumstances during the early years of life are important determinants of later health outcomes and disease risk in adult and older life, with the propensity for poor health in adulthood being greatest among those from disadvantaged backgrounds. Risk of mortality accumulates during the life course[176 177] with exposure to risk factors occurring many years before the development of an outcome.[178] Adverse childhood socioeconomic position has been reported to be associated with a poorer health profile in mid adulthood (45 years of age), independent of adult social position and across diverse measures of disease risk and physical and mental functioning.[176] At mid adulthood associations with childhood social class were identified for blood pressure, body mass index, high density lipoprotein, triglycerides, lung function, depressive symptoms and chronic widespread pain. Increased risk of ill-health was related to participants' father's occupation i.e. from class I (professional occupations) to V (unskilled occupations).

Whether increased morbidity and mortality in adulthood are the result of biological programming due to critical events *in utero*, the accumulation and interaction of harmful exposures along the pathway between infancy and adulthood, or a combination of both remains unclear for most diseases. It follows that better understanding of the antecedents of the greater burden of chronic disease and disability in relatively deprived populations gained from an exploration of life course effects from pre-birth[179] through childhood[131 178 180] to adult life is essential to tackle the growing "health divide."

The research question investigated in this section was whether adverse early life conditions give rise to intermediary phenotypes such as a persistent chronic inflammatory state, increased insulin resistance and endothelial activation (possibly as a response to repeated infection or poor nutrition), and whether these in turn are associated with adverse effects on a range of health outcomes in adulthood (atherosclerosis, lung function and cognitive impairment), which may share common aetiological determinants.[181-183]

8.2.2 Methods

8.2.2.1 Early life and adult individual level socioeconomic status

A number of indices based on participant recall were used to assess childhood conditions at age 11 years. These were number of siblings, whether or not their parents owned their home, father's occupational category, whether or not they reported being bullied as a child, whether or not their parents owned a car, overcrowding (number of occupants in house divided by number of rooms), leg length and trunk length. Father's occupational category was classified using the Registrar General's Social Classification (that is: I – professional occupations; II – managerial and technical occupations; IIINM – skilled occupations (non-manual); IIIM – skilled occupations (manual); IV – partly skilled occupations; and V – unskilled occupations). For the purposes of analysis, non-manual social classes (I, II and IIINM) were merged and compared with merged manual social classes (IIIM, IV and V). Current (i.e. adult) socioeconomic status was assessed from income (average household income in GB Pounds Sterling), educational achievement (years in education), and home ownership (owner occupier, tenant – local authority, tenant – private, living with parents, other).

Methods for analysis of biomarkers, carotid ultrasound and assessment of cognitive function are detailed in Chapter 2.

8.2.2.2 Statistical methods

For comparisons of population characteristics between deprivation groups, linear regression was used for continuous variables and logistic regression for binary responses, from which p-values for differences or odds ratios between deprivation groups were calculated for all variables with adjustment for age and sex. Analyses were conducted in SAS v9.1 and R v2.8.

A multivariate model (Model 1) was used to investigate the impact of adverse early life conditions on *(a)* biomarkers of chronic inflammation and endothelial dysfunction and *(b)* adult lung function, cognitive performance and carotid atherosclerosis. A second model (Model 2) explored the extent to which variables reflecting chronic inflammation/endothelial activation explained the associations. The values provided in **Table 8.3** are regression (beta) coefficients with associated significance levels.

8.2.3 Results

Table 8.1 provides summary statistics by area level deprivation for variables related to early life conditions and individual socioeconomic status (SES) as adults, lung function and cognitive performance. There were significant differences between groups in early life variables, i.e. the number of siblings in the family, a measure of habitation overcrowding at age 11 years (number of occupants in house divided by the number of rooms), father's occupational category, and whether or not parents owned the family home or a car. There was no significant difference between groups in relation to being bullied as a child. Individual level indices of socioeconomic status as an adult (household income, home ownership and years in education) varied as expected.

Subjects recruited from deprived areas performed less well in tests of memory recall (Auditory Verbal Learning Test [AVLT]) and executive cognitive function (Stroop test; Choice Reaction Time thinking time [CRT]). Their lung function (FEV1) was also poorer.

Table 8.1 Early life conditions, biomarkers of chronic disease and cognitive function by area level deprivation

	Least Deprived (n=342)	Most Deprived (n=324)	p [a]
Early life conditions			
Number of siblings	2.6 (1.2) [b]	3.6 (1.8)	<0.0001
People/room	1.2 (0.5)	1.8 (0.9)	<0.0001
Parents owned home	49.4%	5.9%	<0.0001
Parents owned car	57.6%	19.6%	<0.0001
Reported being bullied	24.6%	28.7%	0.24
Father's occupational category [c] (non-manual/manual)	55.8% / 38.2%	12.6% / 74.1%	<0.0001
Adult socioeconomic status			
Average household income	£41,699	£16,461	<0.0001
Age left school (years)	16.6 (1.0)	15.5 (0.9)	<0.0001
Current home status (owner-occupier/tenant)	97.7% / 2.3%	29.9% / 70.1%	<0.0001
Cognitive Function			
Stroop test (s)	8.3 (12.6)	18.7 (19.1)	<0.0001
Choice Reaction Time (ms) [d]	531 (101) [e]	630 (185)	<0.0001
AVLT (words recalled)	12.4 (1.9)	10.9 (2.4)	<0.0001
Lung Function			
FEV1 (L)	3.2 (0.8)	2.7 (0.7)	<0.0001

[a] p-values from linear or logistic regression models, adjusted for age and sex;
[b] Values given are mean with 1 Standard Deviation in parenthesis for continuous variables;
[c] Father's occupational category for Least Deprived was unemployed for n=1 (0.3%) and unknown/unclassifiable for n=19 (5.6%); Father's occupational category for Most Deprived was unemployed for n=10 (3.1%) and unknown/unclassifiable for n=33 (10.1%); P value derived by Chi squared across the distribution;
[d] Choice Reaction Time (CRT), data for the thinking time element of test presented; Auditory Verbal Learning Test (AVLT); Forced Expiratory Volume (FEV1).
[e] Indicates use of geometric means

8.2.3.1 Early life conditions and biomarkers of chronic disease

The possibility was explored that variation in inflammatory status, endothelial activation and insulin resistance in adults was related to early life conditions. Thereafter, associations were sought between the selected health outcomes and early life adversity, and putative intermediary phenotypes (increased chronic inflammation, enhanced endothelial activation and increased insulin resistance) identified.

Relationships (adjusted only for age and sex) between childhood conditions and indicators of potential ill health in adulthood were explored by examining the statistical associations of leg length, number of siblings, people/room in the parental home, parental home status and father's occupational category (grouped as non-manual or manual) with phenotypes of increased chronic inflammation, poorer cognitive performance, decreased lung function, prevalence of classical CHD risk factors and carotid atherosclerosis **(Table 8.2)**. Biomarkers of inflammation and endothelial activation appeared to be influenced little by the number of siblings, moderately by leg length and strongly by early life home conditions and father's occupational category. Likewise, lung function and cognitive performance in adults also appeared to be influenced significantly by father's occupation, whether the parents/guardians were owner-occupiers or tenants, and by degree of overcrowding. Cognitive performance was associated also with the number of siblings. Insulin resistance was linked to father's occupational category and whether the participant's parents owned their own home. cIMT was modestly related to father's occupation but not to home conditions or number of siblings whereas the presence of carotid plaque was related strongly to father's occupation and parental home status, and moderately to the number of people per room and the number of siblings.

Table 8.2 Association of early life conditions with biomarkers of intermediary phenotypes and health outcomes in adulthood

	Quartile of leg length[c] (shortest to longest)	Number of siblings[d] ≤1, >1 to 2, >2 to 3, ≥4	People/room[e] ≤1, >1 to 2, >2	Parents owned home[f] Yes/No	Fathers occupation[g] Non-manual/Manual
A. Inflammatory & CHD Biomarkers					
CRP (mg/L)[b]	**2.03, 1.61, 1.30, 1.28****	1.52, 1.32, 1.56, 1.70	**1.23 , 1.63, 2.30*****	**1.13/1.73*****	**1.14/1.88*****
IL-6 (pg/ml)[b]	1.78, 1.72, 1.67, 1.49	1.91, 1.55, 1.59, 1.71	**1.46, 1.72, 2.11***	**1.32/1.82*****	**1.35/1.87*****
ICAM (ng/ml)[b]	**269, 269, 258, 254***	**260, 249, 261, 274****	**247, 266, 292*****	**239/272*****	**245/273*****
vWF (IU/dl)[a]	**143, 139, 146, 138***	140, 135, 143, 145	**132, 145, 141****	**129/146*****	**131/148*****
LDL Cholesterol (mmol/l)[a]	2.97, 3.05, 3.01, 3.00	3.00, 3.04, 3.10, 2.94	**3.09, 3.00, 2.86 ***	**3.13/2.97***	3.08/3.02
BP systolic (mmHg)[a,h]	**136, 134, 135, 138***	139, 136, 135, 135	135, 136, 137	**132/137***	134/136
HOMA-IR[a,h]	1.54, 1.63, 1.72, 1.71	1.79, 1.63, 1.60, 1.69	1.63, 1.68, 1.70	**1.45/1.76***	**1.48/1.79***
B. Adult Health Outcomes					
Stroop test (s)[a]	14.5, 14.3, 11.7, 13.2	**12.1, 10.8, 12.9. 16.3****	**9.4, 14.4, 20.9*****	**7.7/15.7*****	**8.6/15.6*****
Choice Reaction Time (ms)[b]	584, 572, 561, 554	**569, 530, 569, 582*****	**523, 572, 562*****	**518/582*****	**529/583*****
AVLT (words recalled)[a,h]	**11.7, 11.8,11.5, 11.8***	**11.7, 12.1, 11.5, 11.4****	**12.3, 11.4, 11.2*****	**12.3/11.4*****	**12.3/11.2*****
FEV1 (L)[a,h]	**2.36, 2.75, 3.04, 3.52***	**2.90, 3.03, 2.98, 2.81***	**3.14, 2.89, 2.43*****	**3.28/2.7*****	**3.18/2.78***
Carotid IMT (mm)[a]	**0.69, 0.69,0.72, 0.69***	0.70, 0.68, 0.38, 0.70	0.68, 0.69, 0.74	0.67/0.70	**0.68/0.70***
Plaque present (%)[a]	45.3, 45.1, 54.7, 48.1	**47.9, 42.6, 48.5, 55.5***	**43.6, 49.7, 64.2***	**38.3/49.2****	**40.7/55.4****

Table 8.2 (continued)

[a] Mean values for continuous variables adjusted for age and sex;
[b] Geometric means adjusted for age and sex;
[c] Entire group of 666 subjects was divided by quartile of leg length (mean length in quartiles 1 through to 4 was 66.1, 76.0, 84.5, to 97.4 cm respectively);
[d] In a similar manner the entire population were divided by number of siblings, for category ≤1 n=94; for >1 to 2 n= 123, for >2 to 3, n=223 and for >4 n=227;
[e] Number of people per room was calculated by dividing the total number of people in the house (adults and children) by the number of rooms; 241 subjects were in the category people/room ≤1, 337 in the 1 to 2 category, and 81 were in the category people/room >2;
[f] The number of participants at age 11 whose parents who owned their own home was 188, the number of participants at age 11 whose parents who rented or were tenants was 476;
[g] The number of participants whose fathers had a non-manual occupation was 231; the number of participants whose fathers had a manual occupation was n=381; the number of participants whose father was unemployed was n=11; the number of participants whose father's occupation was unclassifiable or unknown was n=43;
[h] Auditory Verbal Learning Test (AVLT); Forced Expiratory Volume in 1 second (FEV1); Homeostasis Model Assessment of Insulin Resistance (HOMA-IR); Blood Pressure (BP)
$^{*}, ^{**}, ^{***}$ *P* value relates to the significance of the trend for the variable's association on early life conditions in the range of * <0.05 – 0.01; ** 0.01- 0.001; *** <0.0001.

Figure 8.1 presents the association of overcrowding in the childhood home with biomarkers of chronic disease in adult life. It can be seen that indices of inflammation and endothelial activation (CRP, sICAM-1) in adulthood were related significantly in an apparently linear fashion to overcrowding in childhood, as were lung function (FEV1) and cognitive function (as assessed by Choice Reaction Time). LDL cholesterol, insulin resistance and blood pressure (data not shown) on the other hand were not.

Table 8.3 explores in multivariate models the independent associations of early life variables with a range of health outcomes related to lung function, cognitive performance and carotid atherosclerosis. It can be seen that father's occupational category and overcrowding were related in Model 1 to FEV1, and overcrowding to Choice Reaction Time. Father's occupational category was also related to Stroop and AVLT. Trunk length was related independently to FEV1 and measures of cognitive performance. In these age and sex adjusted models early life variables explained 13% to 65% of the variation in the health outcomes. Again, in models where father's occupational category was omitted parental home status became a significant predicator of FEV1 and cognitive function.

Model 2 in **Table 8.3** included key biomarkers of the putative intermediary phenotypes (sICAM-1 and IL-6) in the 'early life model' and it can be seen that for FEV1, Choice Reaction Time and AVLT, early life variables were no longer independent predictors of performance. Father's occupational category continued to be a predictor of Stroop test performance.

Figure 8.1 Influence of early life overcrowding on inflammation, lung function and cognitive performance in adulthood

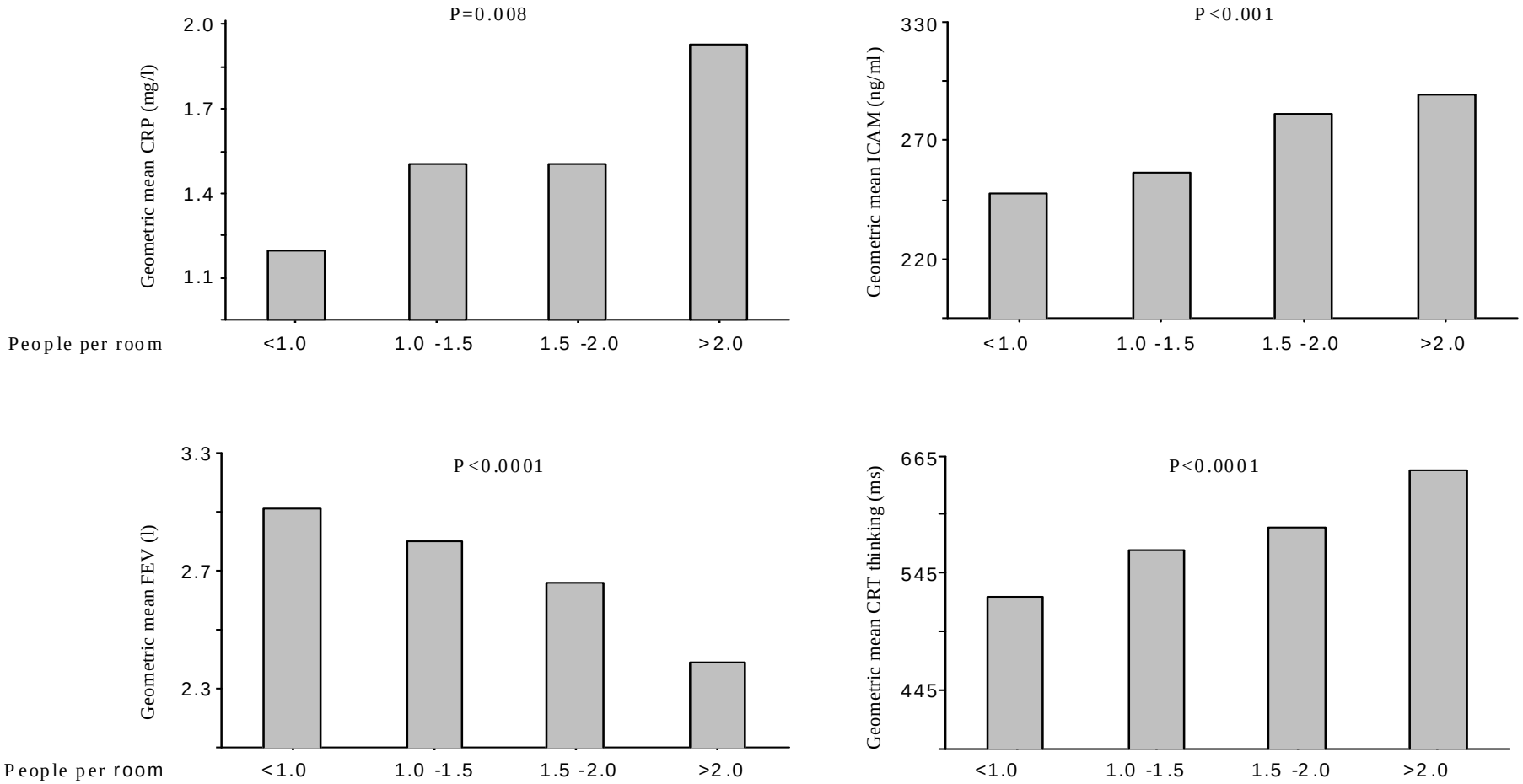


Figure 8.1 Influence of early life overcrowding on inflammation, lung function and cognitive performance in adulthood (continued)

The entire group of 666 participants was divided into categories dependent on the number of people (adults and children) in the home when the subject was aged 11 years divided by the number of rooms in the home. 241 participants were in the category people/room <1, 205 participants were in the category people/room 1.0-1.5, 137 participants were in the category people/room 1.5-2.0, and 81 participants were in the category people/room >2. 2 participants did not report the number of rooms in the childhood home. P value is the significance of number of people per room as a predictor of CRP, sICAM-1, FEV1 and Choice Reaction Time in age and sex adjusted regression models. The height of the bar represents the geometric mean within each category of people/room.

Table 8.3 Multivariate analyses of early life determinants of lung function, cognitive performance and atherosclerosis

	FEV1 β-coefficient	Choice Reaction Time β-coefficient	Stroop test β-coefficient	AVLT β-coefficient	Plaque present β-coefficient
Model 1					
Age[a]	**-0.153*****	**0.047*****	**2.70*****	**-0.207*****	**1.46*****
Sex	**-0.268*****	-0.040	-3.16	**1.24*****	**0.391*****
Parental home status	-0.094	0.033	2.10	-0.254	1.21
Father's occupational category	**0.160*****	-0.042	**-4.75****	**0.614****	0.650
People/room	**-0.065***	**0.027***	0.162	-0.106	1.05
Number of siblings	-0.015	0.003	0.967	-0.070	1.09
Leg length	**0.034*****	-0.001	0.178	0.025	0.995
Trunk length	**0.058*****	**-0.007****	**-0.608****	**0.072****	0.964
Overall R^2	*65%*	*21%*	*16%*	*13%*	*19%*
Model 2					
Age	**-0.140*****	**0.048*****	**2.77*****	**-0.213*****	**1.43*****
Sex	-0.314	-0.021	-3.73	**1.21*****	**0.368*****
Parental home status	-0.040	0.024	2.20	-0.204	1.12
Father's occupational category	0.118	-0.028	**-4.12***	0.446	**0.623***
People/room	-0.063	0.013	-0.994	0.002	1.20
Number of siblings	0.012	0.005	0.878	-0.051	1.06
Leg length	0.033	0.000	0.195	0.024	0.990
Trunk length	0.055	**-0.006****	**-0.665*****	**0.069****	0.960
sICAM-1	**-0.292*****	0.075	**7.82***	**-1.28****	1.51
IL-6	**-0.092*****	0.030	-0.131	-0.013	0.823
Overall R^2	*68%*	*25%*	*18%*	*15%*	*19%*

Table 8.3 Multivariate analyses of early life determinants of lung function, cognitive performance and atherosclerosis (continued)

Model 1 examined the influence of the early life variables identified as most strongly linked to inflammation and tested their independence;
Model 2 included not only early life variables but also markers of inflammation (IL-6 and sICAM-1);
[a] Regression coefficient calculated as per 5 years for age;
[*,**,***] Relate to the significance of the *P* value associated with the regression coefficient in the range of [*] <0.05-0.001; [**] 0.001-0.0001; [***] <0.0001.

8.2.4 Discussion

Chronic inflammation is considered to be a 'common soil' in the aetiology of a number of diseases and disorders including cardiovascular disease and type 2 diabetes.[184] It also appears to be related to cognitive decline in older people.[183] This work explored possible links between early life adversity, intermediary phenotypes, and a range of poorer health outcomes in deprived communities. By examining the statistical associations between variables, evidence emerged that childhood living conditions may impact on the state of activation of the innate immune system and on endothelial activation in adult life. Notably, father's occupational category, whether or not the subject's parents owned the family home, and a measure of overcrowding in the home (number of occupants divided by number of rooms) showed significant associations with biomarkers of inflammation and endothelial dysfunction. These findings add weight to the postulate that the social and family environment in early life influences through biological pathways the propensity to develop common, chronic diseases in later life. Emerging data also suggest that the duration of childhood spent in poverty or in a household of low socioeconomic status accumulates over time to affect adversely morbidity and mortality in later adulthood.[185 186]

Indices of lung function, cognitive performance and carotid artery plaque presence appear to be likewise affected by adverse early life conditions. This finding is in line with earlier work showing a prospective association between the duration of childhood poverty and adult working memory, an association which in part appears to be explained by elevated chronic stress during childhood.[187] The observation that inclusion of IL-6 and sICAM-1 in multivariate models (Model 2) reduced the importance of father's occupation/parental home conditions (owner-occupier status and overcrowding) as potential predictors suggests that chronic inflammation and endothelial activation may be intermediary phenotypes in the relationship between adverse childhood home conditions and poorer lung function and cognitive performance. The results of the present analysis are in line with a recent report of associations between socioeconomic status, inflammatory markers and psychometric performance.[188] Early life socioeconomic status has also been shown recently to be significantly associated with CRP levels, independent of later life socioeconomic status, with adiposity accounting for the majority of this association between life-course socioeconomic indicators and CRP levels.[189] Similarly, it has been reported that adolescent females who spent their early life in a family owned, as opposed to a rented, home had lower levels of expression of specific inflammatory genes in peripheral blood monocytes.[190] In a systematic review of population based studies examining CRP levels

and indicators of socioeconomic position, race and ethnicity, elevated CRP levels were associated with increasing poverty and non-white race.[189] Similarly, an investigation of the life course association between childhood maltreatment and adult inflammation in a birth cohort as part of the Dunedin Multidisciplinary Health and Development Study, maltreated children showed a significant and graded increase in CRP levels in adulthood,[191] providing evidence of a causal association between childhood maltreatment and adult inflammation and evidence of a dose-response relation between severity of maltreatment and inflammation. Low birth weight and infection in childhood are also related to endothelial dysfunction[192] and these may be additional mechanisms by which childhood socioeconomic circumstances relate to these adult biomarkers of chronic disease. However, these association studies cannot eliminate the impact of unmeasured potential confounders on the outcome of interest. Thus, while chronic inflammation is plausible as a mechanistic application, further work needs to be done to establish cause and effect.

The influence of early life conditions on cognitive executive function is consistent with earlier reports of executive dysfunction in children living in deprived circumstances.[193 194] The aetiological links underlying these associations are likely to be complex and include the increased likelihood of childhood illness (and missed education) in overcrowded homes, as well as an increased risk of compromised lung function.

8.3 Interaction of personality traits with social deprivation in determining mental well-being and health behaviours

8.3.1 Introduction

The association between personality factors and a range of both positive and maladaptive health behaviours is now well established, and is known to influence morbidity and mortality. The work described in this section addresses the question as to whether these relationships between personality and behaviour differ according to socioeconomic status.

Extraverted and neurotic characteristics have both been shown to be associated with mortality. In a large longitudinal study (N = 2359) involving 50-year follow-up, those participants who scored 1 SD above the mean on characteristics of emotional stability (low neuroticism), general activity (a sub-trait of extraversion) and conscientiousness survived some 2 to 3 years longer than did those who scored 1 SD below the mean. The effect was independent of smoking and obesity.[195] Higher levels of neuroticism have also been shown to be predictive of shorter survival in an elderly North American male sample,[196] while neurotic hostility, allied to Coronary Heart Disease (CHD)-prone personality features and anti-social personality, have predicted mortality in a large French cohort (N = 14,445).[197] Personality is linked also to subjective and objective morbidity. For example, high neuroticism is associated with poor subjective health status and also predicts clinically-defined chronic illness.[198]

Interactions between personality and health behaviours are seen to influence morbidity and subjective well-being. Smokers have been shown to score more highly on the personality factor of neuroticism, and lower on characteristics of agreeableness and conscientiousness than those who have never smoked.[199] Openness to experience (a facet of extraversion) and low neuroticism have been associated with a more active decision-making style with respect to self-health care,[200] while high extraversion predicts a greater propensity to access health care resources which in turn may have significant implications for morbidity, mortality and health costs.[201]

The evidence that personality factors are associated with health-related behaviours that influence health status may have important implications for understanding why certain sub-groups within the population experience significantly better, or worse, health than others. The marked gradient in health as a function of socio-economic status is a case in

point: people living in deprived circumstances are significantly more prone than their affluent peers to health conditions that are often a product of maladaptive and harmful health behaviours. Given the evidence above that neuroticism is associated with harmful health behaviours, it would be important to establish whether neuroticism tends to exacerbate the health problems of those living in deprivation while extraversion may offer a protective function. Moreover, given the greater prevalence of affective disorder in socially-disadvantaged groups, and the association between affective disorder and neurotic traits, it would be important to consider whether the latter traits are also more prevalent in deprived groups.

The work reported in this section examines the association between socioeconomic status, personality, mental well-being and health behaviours. The research question posed was whether personality traits interacted with measures of social deprivation in determining a subject's mental wellbeing and the ability to adopt healthy living advice.

8.3.2 Methods

8.3.2.1 Indices of health behaviours

A score for the consumption of fruit and vegetables was calculated from self-reported food frequency questionnaire participant responses. Participants were asked on average how often they consumed of a range of food categories (20 food categories listed). Responses for each question ranged from daily consumption (number of portions per day) to weekly and monthly consumption. Participants selected one response per food category. For the purposes of the present analysis responses to four questions from the food frequency questionnaire relating to fruit and vegetable intake were aggregated to give an overall indicative diet score (i.e. frequency of intake of fresh fruit, cooked green vegetables (fresh or frozen), cooked root vegetables (fresh or frozen) and raw vegetables or salad (including tomatoes)). Monthly diet scores were calculated on the basis of a 28 day month.

The number of hours per month each study participant undertook vigorous exercise was also calculated. In the participant lifestyle questionnaire 'vigorous physical activity' was defined as the undertaking of activities vigorously enough to cause sweating or a faster heartbeat. The number of hours of activity per month was based on a 28 day month.

Participants' smoking behaviours were also assessed. As part of the participant lifestyle questionnaire, participants were asked whether they ever smoked regularly (at least one

cigarette a day for 12 months of more), what they smoked, what age they started and stopped smoking if applicable, and if their parents smoked.

Details of the assessments of psychological profile and mental wellbeing can be found in Chapter 2.

8.3.2.2 Statistical analysis

Analysis of covariance (Rosenberg Self-Esteem Scale, Sense of Coherence, Generalised Self-Efficacy Scale) and ordinal logistic regression (Beck Hopelessness Scale, Eysenck Personality Questionnaire) analyses were used, with the results presented as point estimates, 95% confidence intervals and p-values. Binary logistic regression was used for the components of the Eysenck Personality Questionnaire. Quality of the models was compared by R^2. Analyses were conducted in SAS v9.1 and R v2.8.

8.3.3 Results

Table 8.4 provides summary statistics by area level deprivation (as defined by SIMD) for variables related to health behaviours, psychological profile and mental wellbeing as assessed by a panel of validated questionnaires. Clear differences can be seen, as predicted, between the most and least deprived groups in health behaviours (cigarette smoking, exercise and diet indices), and in indicators of mental well-being (Sense of Coherence, Self Esteem, Hopelessness and Self-Efficacy, General Health Questionnaire-28). (Due to the design of the Rosenberg Self-Esteem Scale, a higher score on this scale indicates a lower degree of self-esteem.) From the personality trait evaluation it was observed that subjects from the deprived communities showed higher levels of neuroticism (the tendency to experience negative emotions including anxiety, anger and guilt) and psychoticism (the predisposition to become sociopathic and tendency to be hostile, manipulative and impulsive) compared to those from affluent areas. In contrast the mean score for extraversion (the tendency to enjoy positive events and human interaction) and tendency to portray themselves favourably (lie scale) was the same in the two groups.

Table 8.4 Mean differences by area deprivation category of indices of health behaviour, personality and mental wellbeing

	Least Deprived (n=342, all ages)	Most Deprived (n=324, all ages)	*P*
Indices of Health Behaviour			
Cigarette smoker (never/former/current)	64.6%/29.3%/6.1%	25.6%/34.0%/40.4%	<0.0001
Regular aerobics physical activity (inactive/mod inactive/mod active/active)	23.9%/24.6%/25.4%/26%	49.4%/11.4%/21.9%/17.3%	<0.0001
Fruit & vegetable diet score (portions per month)	95.7(51.5)	59.9(50.4)	<0.0001
Eysenck Personality Trait (EPR)			
Neuroticism	4.06(3.19)	5.96(3.79)	<0.0001
Extraversion	7.49(3.41)	7.34(3.61)	0.58
Psychoticism	1.26(1.30)	2.58(2.02)	<0.0001
Lie	5.35(2.68)	5.34(2.78)	0.95
Mental Wellbeing Scores			
Beck Hopelessness (Missing data n=38)	2.82(3.24)	5.12(4.81)	<0.0001
Sense of Coherence (Missing data n=12)	70.31(11.34)	59.63(15.33)	<0.0001
Rosenberg Self-Esteem (Missing data n=17)	17.49(4.48)	20.78(5.32)	<0.0001
Generalised Self-Efficacy (Missing data n=7)	32.74(4.42)	30.08(6.14)	<0.0001
GHQ Total (Missing data n=27)	2.53(4.06)	5.19(6.87)	<0.0001

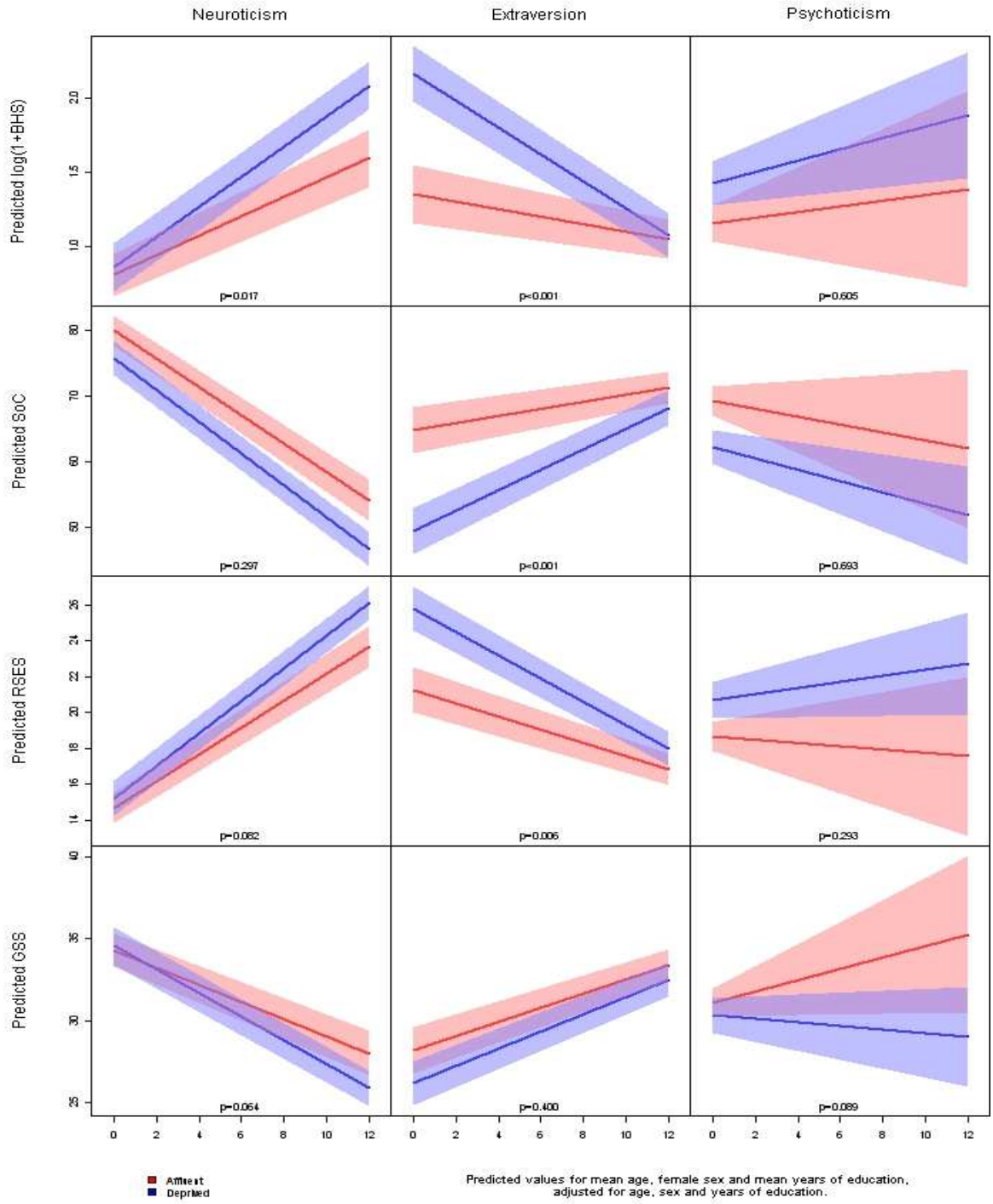
Values are presented as Mean (SD) for all participants; or as percentages for categorical variables

8.3.3.1 Personality, deprivation and mental well-being

Personality traits are expected to influence mental wellbeing. However the question asked was whether this association was the same in those who lived in least versus most deprived areas. **Figure 8.2** models the impact of neuroticism, extraversion and psychoticism on mental wellbeing. Increased levels of neuroticism were linked strongly to hopelessness, a reduced sense of coherence, reduced self-esteem and generalised self-efficacy in a similar manner in the 2 groups.

Variation in the personality trait of extraversion appeared to have a different impact in the 2 groups. Subjects exhibiting a higher degree of extraversion had similar low levels of hopelessness, a high sense of coherence and high levels of self-esteem and self-efficacy, regardless of socioeconomic status. However, lower scores for extraversion had a significantly greater impact on mental wellbeing in the deprived versus affluent group. The models of psychoticism gave broader confidence ranges and similar ranges and similar trends with mental wellbeing in the two groups.

Figure 8.2 Interaction of personality traits with deprivation in determining mental wellbeing



P value refers to interaction effect.

8.3.3.2 Mental well-being, deprivation and uptake of health advice

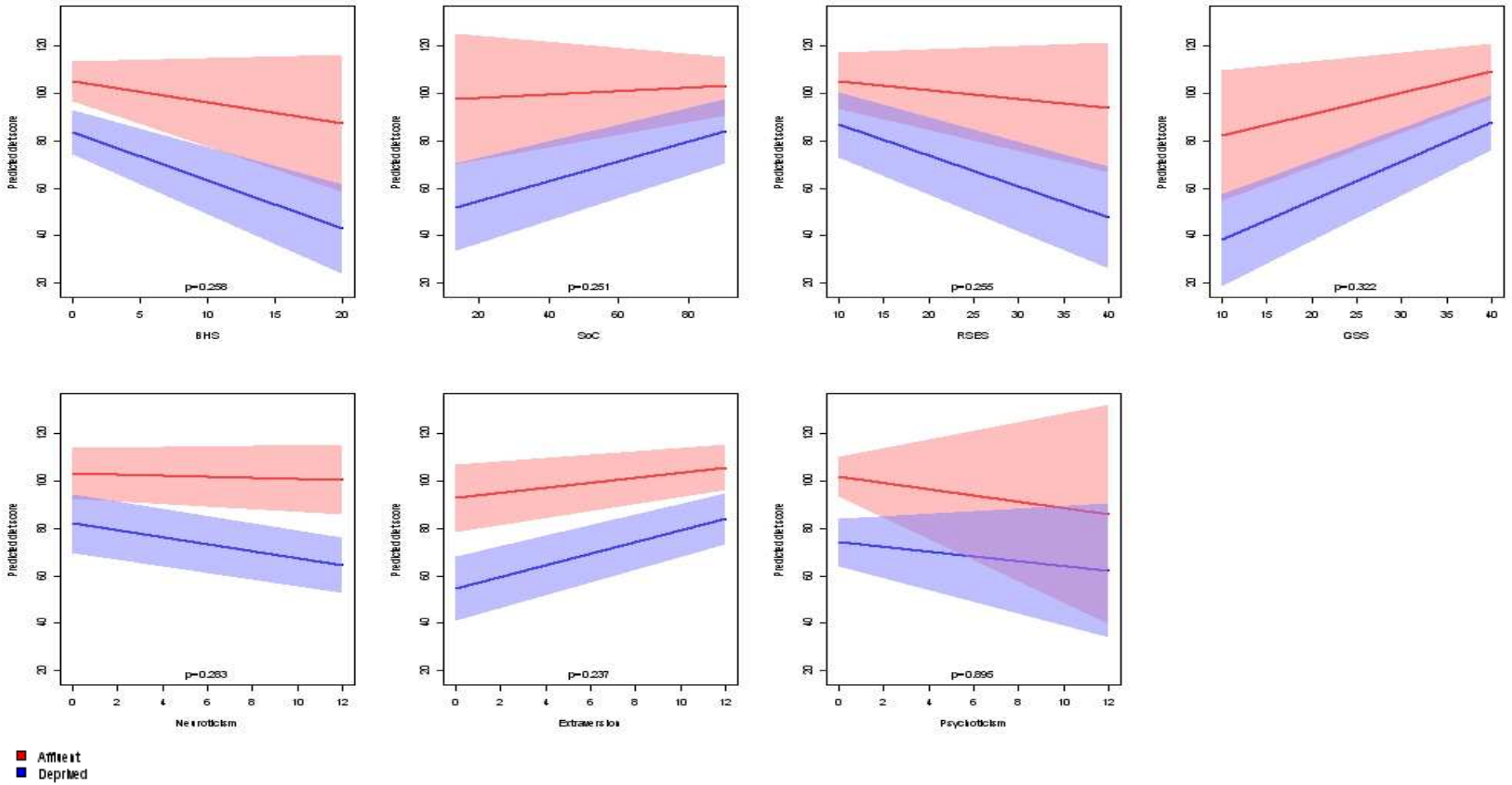
In an attempt to understand the potential impact of personality and mental well-being on the physical health of deprived populations, an analysis was undertaken of the association between parameters of mental well-being and responses to current public health messages, that is the consumption of fruit and vegetables in the diet and giving up smoking.

Subjects in the most deprived group ate on average about a third fewer portions of fruit and vegetables on a monthly basis compared to those in the least deprived **(Table 8.4)**.

Figure 8.3 shows the relationship between mental wellbeing and monthly fruit and vegetable consumption in the two groups. It can be seen that the number of portions of fruit and vegetables consumed in a month decreased with increasing hopelessness and decreasing self-esteem (higher RSES score) and increased with higher degrees of sense of coherence and self-efficacy.

Extraversion was related significantly to fruit and vegetable consumption in the Most deprived group ($p=0.002$) but not in the Least Deprived group, although the p value for the interaction was not significant ($p=0.237$).

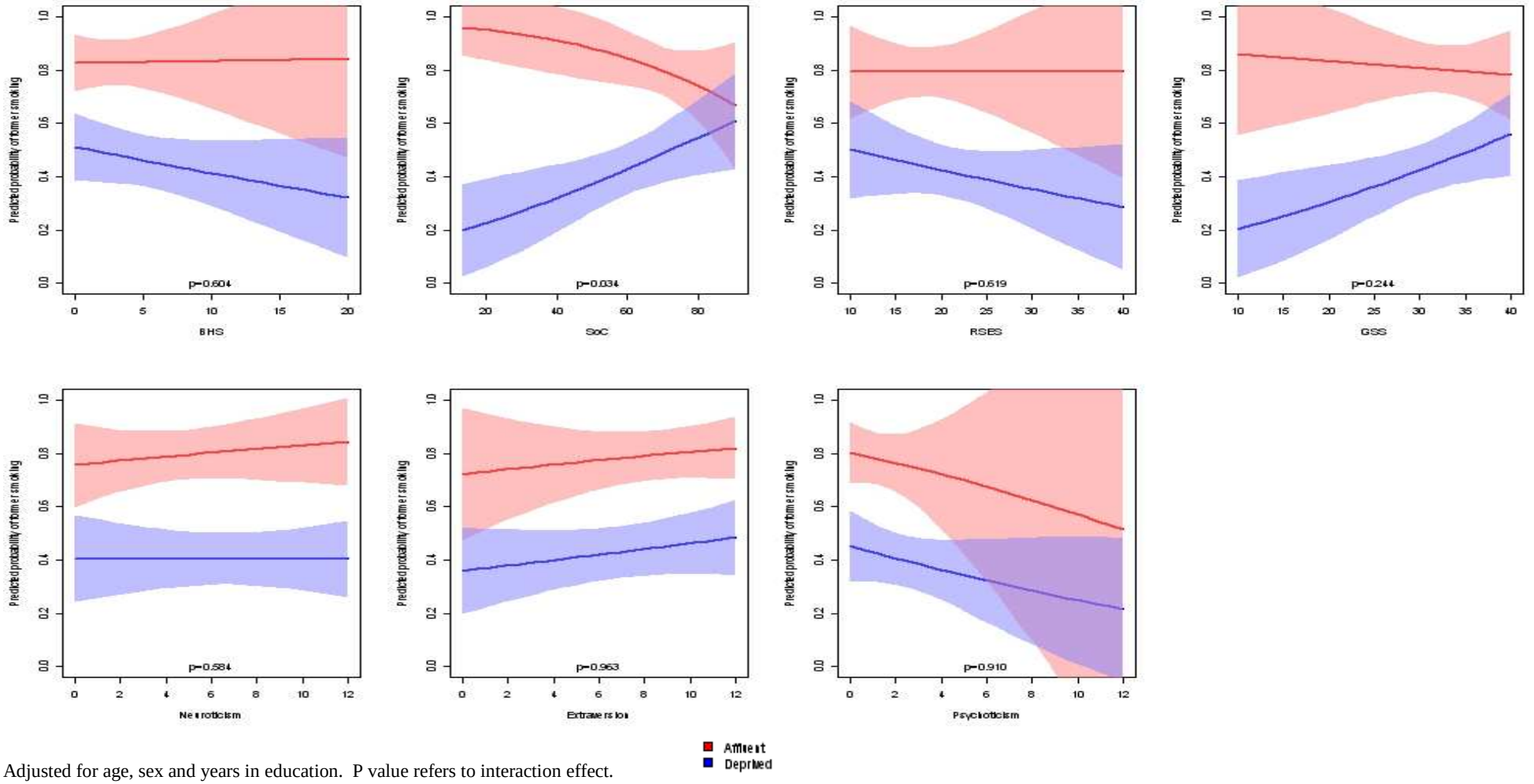
Figure 8.3 Relationship between mental wellbeing, personality and monthly consumption of fruit and vegetables



Adjusted for age, sex and years in education. P value refers to interaction effect.

Smoking differed markedly between the least and most deprived groups **(Table 8.4)**. The former was characterised by a high number of ‘never smokers’ (64.6%) while 74.4% of subjects in the latter had smoked at some time and 40.4% were current smokers. The relationship between personality, mental wellbeing and smoking cessation was examined **(Figure 8.4)**. Sense of coherence and self-efficacy had an impact on smoking cessation, and for the former there was a significant interaction (p=0.034) with deprivation category.

Figure 8.4 Relationship between mental wellbeing, personality and probability of being a former smoker (smoking cessation)



Adjusted for age, sex and years in education. P value refers to interaction effect.

8.3.4 Discussion

The work reported in this section demonstrates that not only are there differences in health behaviours and mental wellbeing between the most deprived and least deprived groups, but also the impact of personality on mental wellbeing is significantly greater in the most deprived group, especially in the case of extraversion. Uptake of good health behaviours (high fruit and vegetable consumption, stopping smoking and participation in aerobic exercise) was higher in the least deprived group and there was evidence that mental wellbeing and personality traits had an impact on the uptake of good health behaviours in the most deprived but not least deprived group. A possible limitation of this study is the possibility that participants might over-report desirable health behaviours, and it was not possible to explore whether this was the case and if so, whether there was any difference between most deprived and least deprived groups in such over-reporting.

However, these findings suggest that in order to address deprivation-based differences in uptake of health promotion messages, more attention should be paid to the effects of personality traits and parameters of mental wellbeing in determining the uptake of health promoting advice. Those who are of high extraversion, low neuroticism and high sense of coherence appear to adopt a healthier lifestyle, but this outcome may be more difficult to achieve in deprived populations where low extraversion, high hopelessness and a low sense of coherence are more common personality traits. Health messages designed to reduce the socioeconomic gradient in health may need to be tailored to personality type and address mental wellbeing as well as the adoption of good health behaviours.

CHAPTER 9 – DISCUSSION

The work reported in this thesis has examined the associations of social deprivation with a variety of health measures, and measured a wide range of co-factors with a view to enhancing our understanding of the relationships between social deprivation and ill health. In this chapter, the most significant findings will be drawn together in order to build up a picture of the factors mediating the socioeconomic gradient in ill health. Thereafter, the 'bigger picture' will be discussed: what implications do the findings from this work have for public policy in terms of attempts to improve the health of the whole population while narrowing the gap in health between most and least deprived? Suggestions for future research will be considered, before finally drawing some conclusions.

The stated aims of this study were: to enhance understanding of the factors underlying the socioeconomic gradient in ill health, focussing especially on the association between social deprivation and risk of coronary heart disease; to determine the extent to which emerging cardiovascular risk factors – especially markers of inflammation – contribute to the explanation of the socioeconomic gradient in coronary heart disease, and to further current understanding of the associations between social deprivation and markers of cognitive function and personality. The main findings from this work will now be drawn together to demonstrate the extent to which these aims have been achieved.

9.1 Principal findings and their significance

Comparison of classic and emerging cardiovascular risk factors between the most and least deprived groups (Chapter 4) revealed clear differences between the two groups in: cigarette smoking, physical activity, BMI (by virtue of differences in height), waist/hip ratio, triglyceride concentration, HDL concentration and fasting plasma glucose concentration (all $p<0.01$). Total and LDL cholesterol concentrations were higher in the least deprived group ($p<0.0001$) and this difference persisted after adjusting for statin therapy (adjusted p value = 0.049). Self-reported weekly alcohol consumption was higher in the least deprived group ($p<0.0001$). Of the emerging risk factors, there were significant differences between most deprived and least deprived groups in markers of: insulin resistance/adiposity (fasting insulin, HOMA-IR, leptin concentration); inflammation/endothelial dysfunction (CRP, IL-6 and sICAM-1) and haemostasis (vWF, fibrinogen and D-dimer). Of additional biomarkers measured, deprivation-based differences were evident in ADMA (a marker associated with insulin resistance) and GGT (but not ALT or AST). The deprivation difference in GGT persisted after adjusting for age, sex and alcohol consumption, suggesting that the deprivation difference in GGT may reflect an alternative aetiology such as non-alcoholic fatty liver disease. Of the markers of renal function analysed, plasma creatinine was higher in the least deprived group, and consequently MDRD-4 eGFR was lower in this group. However, cystatin C was higher in the most deprived group, indicative of poorer renal function in the most deprived group. It is likely that the higher serum creatinine concentrations in the least deprived group were due to the 6cm height difference between least and most deprived, and consequently differences in muscle mass. There was a significant difference between most and least deprived groups in vitamin D status as assessed by 25-hydroxy vitamin D concentration ($p<0.0001$).

Having identified significant differences in many classic and novel cardiovascular markers, the next question to address was to what extent these markers explain the deprivation gap in cardiovascular risk. There were significant differences between most deprived and least deprived groups in both cIMT and plaque score. Plaque score was the more discriminant marker, with more highly statistically significant differences between the deprivation groups as a whole, and on age tertile subgroup analysis, differences between most and least deprived being evident at a younger age for plaque score than for cIMT. Classic cardiovascular risk factors explained around 30% of the difference in plaque presence between most and least deprived – this was broadly consistent with what would be expected from previous studies exploring aspects of cardiovascular risk in relation to social

deprivation.[25 26 50-52] Surprisingly, none of the emerging risk factors included in the multivariate models for plaque presence added anything further to the explanation of the deprivation-based difference in plaque presence – this included markers of inflammation and endothelial function (CRP, IL-6 and sICAM-1). The range of emerging risk factors examined in this study is much more extensive than that examined in the earlier Women's Health Study, in which CRP, sICAM-1 and fibrinogen failed to add to the ability to predict cardiovascular events based on classic risk factors alone.[71] Given current understanding of the role of inflammatory pathways in atherosclerosis,[60] a prespecified hypothesis at the outset of my work was that inflammatory markers would contribute to the explanation of the deprivation-based difference in plaque presence. It was also surprising that when the associations of co-factors with plaque presence were modelled after adjusting for age, sex and deprivation, no associations were evident for CRP, IL-6 or sICAM-1 with plaque presence. A worthy extension to this work would be to expand the repertoire of inflammatory markers analysed in order to determine if there is, indeed, evidence of genuine associations of inflammation with plaque presence once a fuller assessment of inflammatory pathways is undertaken.

As it stands, it was only when early life individual-level markers of socioeconomic status were added as covariates in multivariate models of the area-level deprivation effect on plaque presence that the deprivation difference in plaque presence was abolished. When the role of early life factors was further studied in relation to selected health outcomes (cIMT and plaque presence), FEV1 and parameters of cognitive function (Chapter 8), lung function and cognitive performance appeared to be influenced by father's occupation, whether the parents/guardians were owner-occupiers or tenants, and by degree of overcrowding; cIMT was modestly related to father's occupation but not to home conditions or number of siblings, and carotid plaque was related strongly to father's occupation and parental home status, and moderately to number of people per room and number of siblings. Interestingly, when sICAM and IL-6 were incorporated into early life models, in the case of FEV1, Choice Reaction Time and AVLT early life variables were no longer independent predictors of outcome (although father's occupational category remained a predictor of Stroop test performance). These findings suggest a possible role for inflammation as an intermediary phenotype in the relationship between early life variables and adult health outcomes, and provide valuable information about possible mechanisms by which previously observed associations between early life adversity and adult morbidity and mortality may be mediated.[185 190] As this was a cross-sectional study, caution must be exerted in drawing firm conclusions about lifecourse effects such as these,

but the findings are certainly hypothesis-generating and worthy of further study in a longitudinal study.

Finally, the associations of deprivation, mental wellbeing and health behaviours were examined. As expected, there were clear differences in indices of health behaviour (cigarette smoking, physical activity and fruit and vegetable consumption) between the most deprived and least deprived groups (all $p<0.0001$), as well as differences in the personality traits of neuroticism and psychoticism, and indices of mental wellbeing (Beck Hopelessness, Sense of Coherence, Rosenberg Self-Esteem, Generalised Self-Efficacy and General Health Questionnaire) (all $p<0.0001$). The most interesting findings, however, were in relation to deprivation-based differences in the mediating effect of extraversion on mental wellbeing. Lower scores for extraversion had a significantly greater impact on mental wellbeing (higher levels of hopelessness and lower sense of coherence, self-esteem and self-efficacy) in the most deprived group than in the least deprived group. Furthermore, extraversion was related significantly to fruit and vegetable consumption in the most deprived group but not in the least deprived group. Similarly, sense of coherence and self-efficacy had an impact on smoking cessation, and there was a significant interaction with deprivation in the case of the association between sense of coherence and smoking cessation. These findings may help to explain differential uptake of health promotion messages by different sections of the population, and why despite sustained efforts to provide healthy living advice, the deprivation gap in health is widening. The potential implications of these observations for public policy are discussed further in Section 9.3.

9.2 Generalisability of study findings to the Greater Glasgow population as a whole, and to populations beyond Glasgow

A concern from the planning stages of this study onwards was whether the recruited participants would be typical of the population of Greater Glasgow as a whole. Clearly, participants would be those who volunteered to participate (after receiving a letter of invitation to participate via the General Practice with which they were registered). In particular, there was the concern that from the most deprived group, those who volunteered would be those most motivated to pay attention to their health, and that from the least deprived group, those most concerned about their health would volunteer, resulting in the "healthy deprived" and "worried well" participating, with the potential that differences between the two groups would be minimised. One step that was taken in order to make the study group as representative as possible of the population as a whole was to identify potential participants from the practice lists of the ten General Practices through which participants were recruited, thus ensuring that potential participants would be invited regardless of whether or not they actually visited their General Practitioner. Thereafter, it was invaluable to be able to compare anonymised data on drug prescriptions and smoking habit for participants and non-participants. As detailed in Section 2.7, there were differences between participants and non-participants in levels of prescriptions, with higher levels of prescriptions for statins, antihypertensives and antidiabetic drugs in participants compared to non-participants, especially in the most deprived group. This may suggest that those in the most deprived group who participated had a higher level of recognised morbidity than those who did not participate, and do not appear to represent the "healthy deprived."

Having taken steps to ensure that the study population was as representative as possible of the general population of Greater Glasgow, the next question is whether the Greater Glasgow story is unique, or to what extent the findings from this study are generalisable to other cities in the United Kingdom and beyond. Certainly, as detailed in Section 1.1.2, the two extremes of deprivation and associated health outcomes are seen in Glasgow. However, ongoing work by the Glasgow Centre for Population Health suggests that current levels (and distributions) of socioeconomic deprivation in Glasgow are almost identical to those seen in Liverpool and in Manchester (when based on up-to-date and spatially sensitive measures of deprivation) (Glasgow Centre for Population Health, unpublished observations). Thus, the deprivation profile of Glasgow is not unique in the context of

other UK post-industrial cities. It is reasonable, therefore, to expect that the findings from this study are applicable to other similar (post-industrial) cities in the UK.

9.3 Implications for public policy

The work reported in this thesis has provided significant insights into the interplay between early life, classic and emerging biomarkers, cardiovascular risk, personality, cognitive function and health behaviour. How can these findings be used in attempts to reverse the ongoing widening of the deprivation gap in health and life expectancy? These questions were discussed in session 9 of Glasgow's Healthier Future Forum, an event on 25 February 2010 at which the initial findings of the pSoBid study were presented to an audience composed of approximately 120 representatives from universities, the NHS, Public Health, local councils, Scottish Government, voluntary sector organisations and other groups. After the main study findings were presented, a panel discussion was convened, during which a number of themes emerged. One was the recognition of the complex nature of the issue of social deprivation and health outcomes, and the fact that there is no 'easy answer' to these issues. Tackling these problems requires a multidisciplinary approach, in which the interplay of biological and sociological factors is recognised. The importance of early life experiences in determining health in later life was a recurring theme.

Looking beyond the UK, the American Heart Association has recently produced a report setting out their "Strategic Impact Goal Through 2020 and Beyond," in which they detail their goal of improving the cardiovascular health of all Americans by 20% by 2020 while reducing deaths from cardiovascular diseases and stroke by 20%. In order to achieve this goal, they introduce the concept of "cardiovascular health," defined by the presence of both ideal health behaviours (non-smoking, BMI<25 kg/m^2, physical activity at goal levels, and pursuit of a diet consistent with current guideline recommendations) and ideal health factors (untreated total cholesterol <200mg/dL [5.18mmol/L], untreated blood pressure <120/80mmHg, and fasting plasma glucose <100 mg/dL [5.55mmol/L]). In considering how to achieve this, they consider the issue of primordial prevention, i.e. preventing the development of risk factors in the first place (as opposed to primary prevention, in which individuals with adverse risk factors are treated with a view to preventing the first occurrence of a clinical event). They then discuss the high-risk (focussing interventions on individuals at highest risk) and population-wide (addressing the distribution of risk in the whole population) approaches to prevention, noting that as the majority of CVD and stroke events occur in individuals without markedly elevated levels

of risk factors, that if the entire distribution of cardiovascular risk is to be shifted, population strategies are required in addition to the high-risk approach that addresses risk reduction for those individuals with markedly elevated levels of risk factors. They propose that to achieve improvements in cardiovascular health across the entire population, the seven parameters listed above (smoking, BMI, physical activity, healthy diet score, total cholesterol, blood pressure and fasting plasma glucose) are monitored across the population and classified as ideal, intermediate or poor. In their Impact Goal statement, they highlight the fact that attention should be focussed on underserved minority populations in order to achieve the 2020 Impact Goal in these groups as well.[202]

What principles can we take from the American Heart Association Strategic Impact Goal that could be applied in the UK? One of the founding principles of the UK National Health Service is that of universal access for all, which should place the UK in a strong position to address the health of the whole population. The Quality and Outcomes Framework (QOF) for General Practice provides a framework within which practices are rewarded for providing good quality care to their patients, and has indicators in areas such as, for patients with coronary heart disease, the percentage of patients whose last measured total cholesterol is 5 mmol/L or less, or for smoking, the percentage of patients with coronary heart disease, stroke or transient ischaemic attack, hypertension, diabetes, chronic obstructive pulmonary disease or asthma who smoke whose notes contain a record that smoking cessation advice or referral to a specialist service, where available, has been offered within the previous 15 months.[203] While this approach provides a framework for addressing reduction of risk factors in those in whom those factors have been identified (mainly in a secondary prevention context), it remains likely that the socioeconomic differential in uptake of healthy lifestyle advice will remain unless strategies are developed which recognise the interaction of deprivation and personality in likelihood of adopting healthier behaviour. Furthermore, the concept of primordial prevention raised by the American Heart Association echoes the findings presented in this thesis regarding the importance of early life experiences in influencing adult health. Further work is needed to delineate further which early life factors influence which adult health outcomes, so that strategies can be developed to address these factors.

9.4 Limitations of this study

There are limitations inherent in the design of this study. First the sample was selected from the ends of the Scottish Index of Multiple Deprivation (SIMD) gradient. In 2004 at the time of sampling, 31.4% of the population of Glasgow fell into the bottom of the SIMD classification, while only 6% fell into the top 20% of the SIMD. Thus the study reflects the particular socioeconomic make up of the city at the start of the study but does not provide information on the nature of the gradient of outcome indicators across all SIMD categories, nor is it representative of the Scottish population as a whole. Furthermore, the cross-sectional design of this study means that it is not possible to identify temporal relationships between variables (although these are of course inherent in the relationship between early life and adulthood) and only associations can be reported.

9.5 Future work

The work reported in this thesis has provided a vast range of data, but it is inevitable that in so doing, many new questions will also be raised, and so there is significant potential for further work to be done in this subject area. There is potential for further analysis of the existing dataset. For example, the associations of further biomarkers (e.g. ADMA, liver 'function' tests and markers of renal function) could be examined in relation to the deprivation-based differences in cIMT and plaque score to determine if any such markers help to explain the difference in subclinical atherosclerosis between the most and least deprived groups. Furthermore, there remains a significant biobank of frozen plasma from study participants, and work is already planned to extend the repertoire of biomarkers measured on these samples, focussing particularly on a fuller assessment of mediators of inflammatory pathways, and also on some other recently emerging cardiovascular risk markers. As discussed in Section 9.4, the cross-sectional design of this study means that while hypotheses can be generated about possible relationships between early life factors and adult health outcomes, and suggestions made about putative intermediary phenotypes, a longitudinal study would be required in order to confirm temporal relationships – preferably starting at a stage at which it is possible to study early life variables directly, rather than by later adult recall. Such a study would clearly be a long-term project. Finally, thought should be given to studying the effect of current or novel population health interventions (e.g. housing interventions or early life intervention programmes) on lifestyle parameters, biomarkers and health outcomes.

9.6 Conclusions

The work reported in this thesis has underlined the complex and multifactorial nature of socioeconomic inequalities in health. It would appear that the relationship between social deprivation and health represents the interplay of, in many cases, early life factors, mediators such as inflammatory pathways, psychological parameters such as personality and cognitive function, affecting health behaviours and subsequently outcomes such as atherosclerosis. The apparently complex nature of these relationships suggests that answers to the problem of the widening deprivation gap in health are also likely to be complex, and will have to take into account factors such as early life experiences and personality, as well as the more classically recognised factors such as smoking, cholesterol and blood pressure, if they are to stand a chance of succeeding in narrowing the health gap by improving the health of those most in need.

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Appendix 1 pSoBid Study Participant Information Booklet

pSoBid1

You are being invited to take part in a research study.

Before you decide it is important for you to understand why the research is being done and what it will involve.

Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

UNIVERSITY of GLASGOW

Glasgow Centre for Population Health

NHS Greater Glasgow

PARTICIPANT INFORMATION

Study Title

Factors determining physical and mental well being in affluent and deprived communities in Glasgow - psychosocial and biological determinants of disease (pSoBid1) study.

What is the purpose of the study?

Glasgow is well known around the world for its poor health record. While we understand about the effects of smoking, bad diet and the lack of exercise on the diseases that affect the people in the city, there is a great deal that we don't yet know about how a person's situation - where he / she lives, whether or not they have a job, and life events - affects their health. The study we would like you to participate in is looking at how a person's social circumstances and physical well-being affects their mental wellbeing and their risk of heart disease.

Technically speaking, we are trying to relate the social conditions of the population of Glasgow to their psychological profile and their biological status (hence the title 'pSoBid' study). By looking at people in this complete way, we hope to build up a much better picture than has been possible previously to understand how health inequalities arise between those living in well off, as compared to those living in not so well off areas of Greater Glasgow.

This study is being carried out by the Glasgow Centre for Population Health (GCPH), which is a partnership between NHS Greater Glasgow, Glasgow City Council and the University of Glasgow, supported by the Scottish Executive.

UNIVERSITY of GLASGOW

Why have I been chosen?

To include everybody living in Glasgow would take too long and cost too much money. Instead we are selecting people at random to represent those living in different areas of the city. The areas have been chosen by postcode and people's names have been taken from the register held by the NHS Board on behalf of GPs. So you have been chosen to represent people in a similar situation to yourself.

Do I have to take part?

The study is entirely voluntary and so, while we would like you to take part, if for any reason you feel you cannot then that is fine. Also if you decide to participate and then change your mind you are free to withdraw at any time. If there is any part of the testing or questions that you would rather not complete please say so, and we will miss you out for that part. However, it is the case that the more selected people who participate the more useful the overall findings will be at the end of the study.

If you choose not to participate this will in no way affect the care you receive now or in the future.

Initial approach:

If, after reading this information leaflet, you are happy to participate in the study then our nurse will contact you and arrange for you to come for the first visit at your GP clinic. The nurse, or one of the other study staff, will telephone to arrange a suitable time, usually about 10-14 days after you receive this leaflet.

When you attend for the visit the nurse will go over the information sheet with you, answer any questions you have and ask you to sign a consent form if you are happy to proceed.

Visit 1:

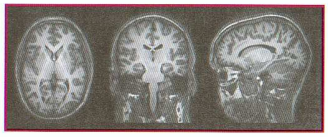
Visit 1 will take about one and a half hours and will be in the afternoon. The nurse will measure your waist and hip size (totals 5 minutes). The nurse will also check your blood pressure and lung function using simple tests (totals 15 minutes). You will be asked questions about your lifestyle (diet, exercise, smoking and drinking habits) and we will record some basic information such as your age, sex, marital status, employment, education, and a brief medical history (total 20 minutes). The information will be entered onto a computer by the research nurse. You will then be asked to complete a set of questionnaires that ask about how you are coping with life and how you feel generally (total 25 minutes).

At the end of this visit the nurse will arrange for a suitable time for you to attend the second visit which uses special equipment and needs to be conducted at a hospital (Glasgow Royal Infirmary).

NHS Greater Glasgow

Visit 3:

A few subjects (about 30) will be asked to volunteer for an extra test which uses a Magnetic Resonance Imaging (MRI) scanner to take pictures of the brain (one hour). We will ask you questions to see if you are suitable for this test since some people (for example those who don't like enclosed spaces or have metal implants e.g. pacemakers) may prefer not to take part. The result of this scan will be related to questionnaire results.



This MRI scan is designed to answer research questions, not examine your brain medically. It is not a substitute for one a doctor would request. It may not show problems that would be picked up by a full medical MRI scan. However, your scan will be reviewed by a specialist radiologist, and if we believe that an abnormality may be present we will contact you and your health team and help you get a more detailed assessment and medical follow-up where necessary. There is a small possibility that detection of an abnormality may be a false alarm that might cause you unnecessary concern. The report on the scan will become part of your hospital record.

Please note: At the end of each visit we will ask you to fill in a comment sheet telling us how you enjoyed taking part and what we can do better (10 minutes). For each visit, arrangements will be made for a taxi to pick you up from your home and to take you back. There will be no cost to you.

Visit 2:

Visit 2 will be in the morning. It is normally 10-14 days after visit 1 and will take about two hours. The first thing that the nurse will do is to take a sample of blood (about two tablespoonfuls, which takes about 10 minutes). The sample will be used to test cholesterol levels, clotting factors and other blood constituents that we know predict risk of heart disease. Some of the sample will be stored frozen and will be used for future tests when new factors are discovered. Also, we will prepare some of your DNA from the blood and analyse it for specific genetic features that we believe are linked to risk of disease. Again in the future, with new discoveries, we may repeat the genetic testing. The future measurements on blood and DNA will only be made with the approval of the ethics committee that reviewed this study (a group of experts and members of the public who oversee all medical research locally).

We ask you to fast overnight before attending the second visit since eating food or drinking liquids that contain calories will affect the results of our tests. Once the sample is taken we will provide you with breakfast and ask you to complete some more questionnaires. This time the questions will test your memory and speed of thinking (like an IQ test at school – total of 25 minutes). Then your height and weight will be measured.

In the final part of this visit we would like to try a new, simple test that uses an ultrasound machine to test the health of the arteries in your neck (this is the same machine as is used for examining women during pregnancy – total 30 minutes). A probe (similar to a stethoscope) is placed on the skin of your neck behind your ear and the sound wave helps us to take a picture of the blood vessels that are there. In particular we can measure the thickness and stiffness of the arteries.

The results of the test give us an idea as to whether there is "hardening" of your arteries and give an indication of your future risk of heart problems.

In a similar way we will use ultrasound to test the blood supply in your neck and wrist (total 15 minutes). These are very safe procedures and are used every day in

What do I have to do?

For Visit 1:

For about **30 minutes before you arrive** please:

- do not eat

- do not smoke

- do not drink alcohol

- avoid vigorous exercise

as any of these could affect your blood pressure readings.

Please do not wear clothing which is tight (e.g. lycra, tight jeans) or has a thick belt, otherwise your waist and hip measurements will not be accurate. It would also be very helpful if you could wear light clothing.

The nurse needs to record the prescribed medicines that you may be taking as some of these may affect the measurements. If you are taking any prescribed medicines it would be very helpful if you could bring the containers along with you. Also before you come please think about your place of birth and your birth weight, where you went to primary school and your circumstances when you were 11 years old. Also think about your parents' date of birth and their present age.

For Visit 2:

Before you arrive **please fast from 10pm the night before** (no food or drinks with calories. Water is ok as is tea or coffee without milk or sugar).

It would also be very helpful if you could, again, wear light clothing.

What are the possible benefits of taking part?

The main reason for taking part in this study is to help us get a more complete picture of the mental and physical health of the population living in different parts of Glasgow. This will help us in our work to improve the health of the population.

You will learn a lot about the state of your health and the risk of heart disease in the future. If we detect any particular problems then, with your permission, we will send your results to your GP and he / she will arrange for further treatment.

What are the possible disadvantages and risks of taking part?

The study will generate a lot of information about you and your future risk of heart problems. Your GP will be told that you have volunteered for the study. If you give agreement in writing, we will send results of the usual tests that are done to test the risk of heart disease (blood pressure, cholesterol, etc.) to your GP. Your GP will not receive the results of the questionnaires. These will be confidential to the study.

If you agree to the results being sent to the GP then if he or she is asked for a medical report about you (for example if you apply for a new life insurance or a new job) then your results have to be included in this report. If you choose not to have the results sent to your GP then they will be retained as confidential by the research team.

Glasgow Centre for Population Health

You should note that your GP cannot issue a medical report without your permission and that you have the right to see it before it is sent off. If we report abnormal test results to your GP (for example high cholesterol) then these may affect your eligibility for medical or life insurance or lead to a higher premium being charged. They may also affect your employment prospects.

We will not test for any virus (including the AIDS / HIV virus).

During the taking of the blood sample you may experience some discomfort from the needle and a little local bruising may occur.

If you are one of the few people asked to participate in the MRI scan (Visit 3) then you may experience claustrophobia (dislike of enclosed space) and should tell us if this is likely to be the case.

Some of the questionnaires ask personal questions about your current mental wellbeing and your situation as a child at 11 years old. This information is important to get the best picture of the lifetime experiences of the population of Glasgow, but if you feel any particular questions are upsetting or too difficult to complete then you just have to say so and we will omit them.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

Will my taking part in this study be kept confidential?

Yes. We take very great care to protect the confidentiality of the information we are given. The study results, when published, will not be in a form which can reveal your identity; this will only be known to the chief investigator and the research team. If you were to tell us at a later date that you no longer wanted the information collected about you to be used in the study then it will be deleted.

However, if you agree and give us your written permission, the information you provide in this study may be put together with other parts of your medical records held by the NHS in Scotland, for example the results of future in-patient and out-patient hospitalisation. This increases the value of the information you provide and is again done in a completely confidential way.

What will happen to the results of the research study?

The overall results of the study will be used to prepare a report which will be published in the scientific press and will be made available to NHS Board planners. No individual will be identified in the report.

Who is organising and funding the research?

This study is being carried out by the Glasgow Centre for Population Health (GCPH), which is a partnership between NHS Greater Glasgow, Glasgow City Council and the University of Glasgow, supported by the Scottish Executive.

Glasgow Centre for Population Health

NHS Greater Glasgow

Glasgow City Council

University of Glasgow

SCOTTISH EXECUTIVE

Who has reviewed the study?

The Glasgow Royal Infirmary Local Research Ethics Committee reviewed the study.

Contact for Further Information

We hope this leaflet answers the questions you may have, and that it shows the importance of the study. If you have any other questions, please do not hesitate to ring one of the contacts listed below.

Thank you very much for your help with this important study.

Shoshana Morecroft and Agnes McGinty
Research Nurses
Glasgow Royal Infirmary
Freephone: 0800 015 9313

Dr Yoga Velupillai
pSoBid1 Manager
Glasgow Centre for Population Health
Freephone: 0800 027 0508

The pSoBid1 study team

THANK YOU FOR CONSENTING TO TAKE PART IN THIS STUDY.

You will be given a copy of the information sheet and a signed consent form to keep.

Appendix 2 Paper version of lifestyle questionnaire

Glasgow Centre for Population Health

NHS Greater Glasgow

UNIVERSITY of GLASGOW

Version 3.1

Lifestyle Questionnaire

A. ENROLMENT

1. Time started ⌊_⌋⌊_⌋:⌊_⌋⌊_⌋

2. pSoBid1 Id: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (01 02)

3. Post Code ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ ⌊_⌋

4. Participant Initials ⌊_⌋⌊_⌋⌊_⌋

5. Date of Birth ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (D D M M Y Y Y Y)

6. Residence ☐ Owner occupier ☐ Tenant (local authority) ☐ Tenant (private) ☐ Living with parents ☐ Other _____

7. Dependents ☐ None ☐ Dependent children under 16 ☐ Dependent relatives ☐ Both dependent children and relatives

Total Dependents ⌊_⌋⌊_⌋

8. Sex ☐ Male ☐ Female

9. Marital Status ☐ Married ☐ Single ☐ Divorced ☐ Separated ☐ Widowed ☐ Co-habiting

10. Date of interview ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋ (D D M M Y Y Y Y)

11. Interviewer _____

pSoBid1

Version 3.1

A1. ABOUT YOUR HEALTH

A1a. Over the last 12 months how would you say your health in general has been?
(please tick one box only)

☐ Very Good ☐ Good ☐ Fair ☐ Bad ☐ Very Bad

A2. ABOUT YOUR PAST AND PRESENT HEALTH

A2a. Have you ever been told by a doctor that you have, or have had, any of the following conditions? If a medical condition applies to you please select 'yes' and give the year when it was diagnosed, otherwise select 'no'.

Condition	No	Yes	If Yes, when was it first diagnosed?	Were you hospitalised?	Ongoing
Heart Attack (Myocardial Infarction)	☐	☐	Y Y Y Y	☐	☐
Coronary Thrombosis	☐	☐	Y Y Y Y	☐	☐
Other heart trouble	☐	☐	Y Y Y Y	☐	☐
Stroke	☐	☐	Y Y Y Y	☐	☐
Peptic Ulcer	☐	☐	Y Y Y Y	☐	☐
Gout	☐	☐	Y Y Y Y	☐	☐
Gall bladder disease	☐	☐	Y Y Y Y	☐	☐
Thyroid disease	☐	☐	Y Y Y Y	☐	☐
Arthritis	☐	☐	Y Y Y Y	☐	☐
Bronchitis	☐	☐	Y Y Y Y	☐	☐
Asthma	☐	☐	Y Y Y Y	☐	☐
Emphysema	☐	☐	Y Y Y Y	☐	☐
Diabetes	☐	☐	Y Y Y Y	☐	☐
		If Yes, was your first treatment: Diet ☐ Tablets ☐ Insulin ☐			
High Blood Pressure	☐	☐	Y Y Y Y	☐	☐
High cholesterol level	☐	☐	Y Y Y Y	☐	☐
Cancer	☐	☐	Y Y Y Y	☐	☐
(a) Other *specify* _____	☐	☐	Y Y Y Y	☐	☐
(b) Other *specify* _____	☐	☐	Y Y Y Y	☐	☐

A2b. If you have had cancer, which part of the body did it affect? Please give details:_____

_____

_____

Version 3.1

A3. DRUG HISTORY

A3a. Please mention all the "prescribed" drugs you are taking now?

Medication

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____

A3b. Please mention all the "over-the-counter" drugs you are taking now?

Medication

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____

Version 3.1

A4. CHEST PAIN

A4a. Have you ever had a pain or discomfort in your chest? ☐ No ☐ Yes

If No, go to Question B1
If Yes, continue

A4b. Do you get this pain or discomfort when you walk uphill or hurry? ☐ No ☐ Yes

A4c. Do you get this pain or discomfort when you walk at an ordinary pace on the level? ☐ No ☐ Yes

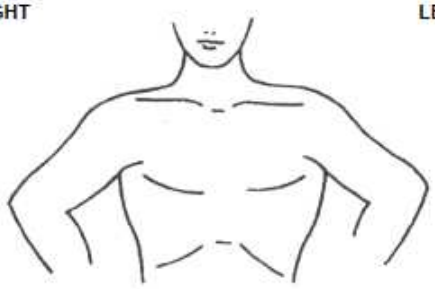
A4d. When you get pain or discomfort in your chest what do you do?
(please tick one box only) ☐ Stop ☐ Slow down ☐ Continue at the same pace

A4e. Does the pain or discomfort go away when you stand still? ☐ No ☐ Yes

A4f. How soon before the pain or discomfort goes away? ☐ 10 minutes or less ☐ More than 10 minutes

A4g. Where do you get this pain or discomfort? *(Mark the place(s) with an 'X' on the diagram below)*

RIGHT **LEFT**



A4h. Have you ever had a severe pain across the front of your chest last for half an hour or more? ☐ No ☐ Yes

If No, go to Question B1
If Yes, continue

A4i. Did you talk to a doctor about it? ☐ No ☐ Yes

If No, go to Question A4k
If Yes, continue

A4j. What did the doctor say it was? _____

_____

A4k. How many of these attacks have you had? ⌊__⌋

A4l. Have you ever had heart trouble suspected or confirmed? ☐ No ☐ Yes

If No, go to Question B1
If Yes, continue

A4m. When was the first time? *(Give year)* ⌊__⌋⌊__⌋⌊__⌋⌊__⌋

A4f. Have you ever had either of the following operations to improve the circulation to your heart? (tick all that apply)

☐ Coronary artery bypass surgery ☐ Balloon angioplasty

Version 3.1

B. DENTAL QUESTIONS (Periodontal disease)

B1a. Have you seen a dentist? ☐ No ☐ Yes

B1b. What year did you last visit your dentist? ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ Y Y Y Y

B2. Has your dentist ever told you that you have gum disease or "periodontal disease"? ☐ No ☐ Yes

B3. Do your gums bleed when you brush them? ☐ No ☐ Yes

B4. Do you still have some of your own teeth in your mouth? ☐ No ☐ Yes

C. QUESTIONS ABOUT SMOKING

C1. Have you ever smoked regularly? ☐ No **If No, go to C8**
☐ Yes If Yes, continue

C2. What did/do you smoke? ☐ Cigarettes ☐ Other

If Other, specify_____

C3. Have you ever smoked cigarettes regularly? (by regularly we mean at least one cigarette a day for 12 months or more.) ☐ No ☐ Yes, current smoker ☐ Yes, ex-smoker

C4. If Yes, current smoker, about how many cigarettes a day do you usually smoke? ⌊_⌋⌊_⌋⌊_⌋

C5. If you are an ex-smoker, about how many cigarettes a day did you usually smoke? ⌊_⌋⌊_⌋⌊_⌋

C6. How old were you when you stopped smoking cigarettes regularly? ⌊_⌋⌊_⌋ years

C7. How old were you when you started smoking cigarettes regularly? ⌊_⌋⌊_⌋ years

C8. Did either of your parents or guardians smoke regularly when you lived with them?

☐ No, neither parent smoked ☐ Yes, mother smoked
☐ Yes, father smoked ☐ Yes, both parents smoked ☐ Don't know

D. QUESTIONS ABOUT DRINKING

D1. Thinking of the last 7 days, how much of each of the following did you drink? (If it helps, think back over each day to this time last week)

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	NA
Beer, lager, cider:	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋ pints	☐
Wine:	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋ glasses	☐
Martini, sherry, port:	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋ glasses	☐
Spirits:	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋ measures	☐
Other alcoholic drinks:	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋ glasses	☐

D2. In the last year how often have you had a hangover from drinking alcohol? (Select one only)

☐ At least once a week
☐ 2-3 times a month
☐ Once a month
☐ Less than once a month
☐ Not at all in the last year

Version 3.1

E. QUESTIONS ON EATING HABITS

E1. What kind of bread do you usually eat? (Select one only)

- ☐ White
- ☐ Brown, granary, wheatmeal
- ☐ Wholemeal
- ☐ Do not have usual type
- ☐ Do Not Know
- ☐ Do not eat any type of bread
- ☐ Other kind

E2. What do you usually spread on your bread? (Select one)

- ☐ Butter
- ☐ Margarine
- ☐ Low fat spread
- ☐ Do not have usual type
- ☐ Don't know
- ☐ Do not use fat spread on bread

E3. a. What kind of milk do you usually use for drinks, in tea or coffee and on cereals etc? (Select one)

- ☐ Whole milk
- ☐ Semi-skimmed
- ☐ Skimmed
- ☐ Do not have usual type
- ☐ Dont Know
- ☐ Do not drink milk
- ☐ Other Kind

If Other, specify _____

E4. a. Do you drink tea or coffee? ☐ No ☐ Yes

If yes, do you usually take sugar in: (Do not include sweeteners)

b. Tea ☐ No ☐ Yes

c. Coffee ☐ No ☐ Yes

E5. At the table do you usually add salt to your food.. (Select one)

- ☐ Without tasting it first
- ☐ Generally After tasting
- ☐ Occasionally after tasting
- ☐ Rarely or never

Version 3.1

E6. Which type of breakfast cereal do you normally eat? (Select one)

- ☐ High fibre (eg All bran, Branflakes, Shredded Wheat, Muesli, Porridge, Weetabix)
- ☐ Others (eg, Cornflakes, Rice Krispies, Special K, Sugar Puffs, honey Smacks)
- ☐ Do not have a usual type
- ☐ Do not eat breakfast cereal

E7. At around 11 years of age in school, what did you usually do for lunch? Did you:-

- ☐ Eat a packed lunch
- ☐ Eat a school meal
- ☐ Other (this might include eating at home, at a cafe etc)

E7b. Please give details: _____

E8. On average, how often do you eat each of these foods. (Please only select one for each category of food)

Food	Per Day				Per Week			Per Month		
	6	4-5	2-3	Once	5-6	2-4	Once	1-3	< Once	NA
Breakfast cereal	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Fresh fruit	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Cooked green vegetables (fresh or frozen)	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Cooked root vegetables (fresh or frozen)	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Raw vegetables or salad (including tomatoes)	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Chips	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Potatoes, pasta, rice	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Meat	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Meat products (e.g. haggis, pâté)	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Poultry	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
White fish	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Other types of fish	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Cheese	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Beans or pulses	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Sweets, chocolate	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Ice cream	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Crisps, savoury snacks	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Soft-fizzy drinks	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Cakes, scones, sweet pies or pastries	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐
Biscuits	☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐

Version 3.1

F. ABOUT YOUR PHYSICAL ACTIVITY

F1. Are you at present in any type of work (including self-employed)? ☐ No, not working ☐ Yes, currently working

F2. We would like to know about your level of physical activity and the type and amount of physical activity involved in your work. Please tick one box that best corresponds to your present activities from the following four possibilities:

☐ Sedentary occupation: You spend most of your time sitting (such as in an office) or standing

☐ You spend most of your time standing or walking. However, your work does not require intense physical effort (eg shop assistant, hairdresser, guard, etc) or physical work

☐ This involves some physical effort, including handling of very heavy objects (eg plumber, cleaner, nurse, sports instructor, electrician, carpenter, etc) or Heavy manual work

☐ This involves very vigorous physical activity including handling of very heavy objects (eg docker, miner, bricklayer, construction worker, etc)

F3. Leisure activity: In a typical week during the past 12 months, how many hours did you spend on each of the following activities? (Put 0 if none)

F3. a. Walking, including walking to work, shopping and leisure:

1. in summer ⌊_,_⌋ hours per week ☐ NA
2. in winter ⌊_,_⌋ hours per week ☐ NA

F3. b. Cycling, including cycling to work and during leisure time:

1. in summer ⌊_,_⌋ hours per week ☐ NA
2. in winter ⌊_,_⌋ hours per week ☐ NA

F3. c. Gardening:

1. in summer ⌊_,_⌋ hours per week ☐ NA
2. in winter ⌊_,_⌋ hours per week ☐ NA

F3. d. Housework such as cleaning, washing, cooking, childcare: ⌊_,_⌋ hours per week ☐ NA

F3. e. Do-it-yourself: ⌊_,_⌋ hours per week ☐ NA

F3. f. Other physical exercise such as keep fit, aerobics, swimming, jogging:

1. in summer ⌊_,_⌋ hours per week ☐ NA
2. in winter ⌊_,_⌋ hours per week ☐ NA

F4. a. Vigorous exercise: In a typical week, during the past year did you practise any of these activities vigorously enough to cause sweating or a faster heartbeat? ☐ No ☐ Yes ☐ Don't Know

b. If yes, for how many hours per week in total did you practise such vigorous physical activity? (Put 0 if none) ⌊_,_⌋ hours per week

F5. Other Activity: In a typical day during the past 12 months, how many floors of stairs did you climb up?(Put 0 if none) ⌊_,_⌋ flights per day

Version 3.1

G. ABOUT YOUR CHILDHOOD

A person's experiences in childhood may affect their health in later life so we would like to ask you questions about your own childhood.

G1. Up to the age of 11 years who brought you up? (Select all that apply)

- ☐ Both my natural (biological) parents
- ☐ At least one of my natural (biological) parents
- ☐ Brought up by other relatives
- ☐ Brought up by adoptive parents
- ☐ Lived in children's home or was fostered

G2. At the time you were 11 years old, was your family home:

- ☐ Owned by your family (with or without a mortgage)
- ☐ Rented from the local council
- ☐ Rented from private land lord
- ☐ NV
- ☐ Other

If Other, specify _____

G3. At the time you were 11 years old, did your family own a car? ☐ No ☐ Yes

G4. At the time you were 11 years old, how many living rooms and bedrooms did the family home have?

Number of living rooms (include the kitchen if it was used as a living room): ⌊__⌋

Number of bedrooms: ⌊__⌋

G5. When you were aged 11 years old, how many children and adults lived in your family home?

Number of adults (aged 18 or over): ⌊__⌋

Number of children (aged under 18 including yourself): ⌊__⌋

G6. Have you moved out of the family home? ☐ No ☐ Yes

G6a. What age were you when you finally moved out of your family home? ⌊__⌋ years

G7. How many friends did you have in primary school compared to other children?

- ☐ More friends than other children
- ☐ About the same number of friends as other children
- ☐ Fewer friends than other children

G8. Did you ever experience being bullied by your class mates in primary school?

- ☐ Yes, very often
- ☐ Yes, sometimes
- ☐ No

G9. Since you were 11 years old, have you moved away to anywhere other than Glasgow for more than a year? ☐ No ☐ Yes

G9a. If Yes, what age were you when you first moved away from Glasgow for more than a year? ⌊__⌋ years

Version 3.1

H. ABOUT YOUR BIRTH WEIGHT AND PLACE OF BIRTH

H1. In which city/town or village were you born? ☐ NV

City _____ Town _____ Village _____

H2. Where did the birth take place?

☐ Home
☐ Hospital
☐ Don't Know
☐ Other specify _____
☐ NV

H3. If Hospital, what was the name of the hospital where you were born? _____

H4. Do you know your birth weight? ☐ No ☐ Yes ☐ NV

H5. If yes, what was your birth weight?
(Birth weight in pounds and ounces) ___ pounds ___ ounces ☐ NV

H6. Please say where you obtained the information about your birth weight.

☐ Mother
☐ Other family member
☐ Don't Know
☐ Other specify _____
☐ NV

J. QUESTIONS ABOUT YOUR PARENTS

Your health may be related to the health of your parents. We would therefore like to ask you about them. If you were adopted, please answer the questions in this section with respect to your adoptive parents.

J1. Is your father still alive? ☐ No ☐ Yes ☐ Don't know, Go to J4

J2. If Yes, how old is your father? (please write age in years) ___ years ☐ Don't know, Go to J4 ☐ NV

J3. If No, how old was your father when he died?
(please write age in years) ___ years ☐ Don't know, Go to J4 ☐ NV

J4. Is your mother still alive? ☐ No ☐ Yes ☐ Don't know, Go to J7

J5. If Yes, how old is your mother? (please write age in years) ___ years ☐ Don't know, Go to J7 ☐ NV

J6. If No, how old was your mother when she died?
(please write age in years) ___ years ☐ Don't know, Go to J7 ☐ NV

J7. Please give the title of your father's job at the time you were 11 years old (or his last job if he died or retired before this time), and describe what he actually did.

J7. a. Job Title: _____ ☐ NV

b. Job Description: _____

_____ ☐ NV

c. ☐ Don't know

J8. In that job, was your father...

☐ Manager
☐ A foreman or supervisor
☐ An employee (other than manager or foreman)
☐ Self-employed with employees
☐ Self-employed/freelance without employees
☐ Don't know
☐ NV

Version 3.1

K. QUESTIONS ABOUT YOUR EDUCATION

K1. What secondary school did you go to when you left primary school?

School _____ Town/City _____

K2. At what age did you leave secondary school? ☐☐ years

K3. Have you been in further or higher education since you left school? ☐ No ☐ Yes

K4. For how many years in total were you in full or part-time further or highter education? If less than 1 year write 0.

Full-time ☐☐ years

Part-time ☐☐ years

K5. Which of the following qualifications do you have? Select all that apply.

K5. a. No formal qualifications ☐

K5. b. Degree or degree level qualification (including a higher degree) ☐

K5. c. Teaching qualification, HNC/HND, BECT/TECT higher, BTEC (higher) City and Guilds Full Technological Certificate, Nursing Qualification ☐

K5. d. Certificate in Sixth Year Studies, Highers, A-levels, ONC? OND? VEC? TEC (not higher), City and Guilds Advanced/Final Level ☐

K5. e. 'O' Grade Passes, 'O'Level passes, CSE grade 1, School certificate or matric, City and Guild Craft/Ordinary level ☐

K5. f. CSE grades 2-5, Clerical/commercial qualifications ☐

K5. g. CSE ungraded ☐

K5. h. Other ☐

If Other, specify _____

L. EMPLOYMENT QUESTIONS

L1. Which of these best describes your current situation? (Select one)

Go to question L3
- ☐ In paid work(including self-employed)
- ☐ Unemployed

Go to question L2
- ☐ Permanently sick or disabled
- ☐ Retired from paid work
- ☐ Looking after the home or family
- ☐ A full-time student
- ☐ Other

If Other, specify _____

L2. Have you ever been in paid employment or been self-employed?
- ☐ No, Go to M1
- ☐ Yes, Go to L3

L3. Please give the title of your present or most recent paid job (or period of self-employment), and describe what you actually do/did?

Title _____

Description _____

_____

_____

Version 3.1

L. EMPLOYMENT QUESTIONS continued...

L4. In that job, are you or were you... (Select one)

- ☐ a manager
- ☐ a foreman or supervisor
- ☐ an employee (other than manager or foreman)
- ☐ self-employed with employees
- ☐ self-employed/freelance without employees

L5. How many people work(ed) for your employer at the place where you work(ed)? (Select one)

- ☐ 1-9 persons
- ☐ 10-24 persons
- ☐ 25-499 persons
- ☐ 500 or more persons

M. INCOME QUESTIONS

M1. There has been a lot of talk about health and income. I would like to get some idea of your household's income. Can you please tell me which kind of income you (and your husband/wife/partner) receive?

- ☐ Earnings from employment or self-employment
- ☐ State retirement pension
- ☐ Pension from former employer
- ☐ Personal pension
- ☐ Child Benefit
- ☐ Job-Seekers Allowance
- ☐ Income Support
- ☐ Working families tax credit, Child tax credit or working tax credit
- ☐ Housing benefit
- ☐ Other state benefits
- ☐ Interest from savings and investments (eg stocks and shares)
- ☐ other kinds of regular allowance from outside your household (eg maintenance, student's grants, rent)
- ☐ No source of income
- ☐ Does not want to answer

M2. What is your total income in a year?

- 1 ☐ Less than £15,000
- 2 ☐ £16,000 to £25,000
- 3 ☐ £26,000 to £35,000
- 4 ☐ £36,000 to £45,000
- 5 ☐ £45,000 or more
- ☐ RTA

N. END OF VISIT

N1. Time completed ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋

N2. Date of 2nd interview ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋
D D M M Y Y Y Y

N3. Time of 2nd visit ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋

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