Psychological, social and biological determinants of ill health (pSoBid) in Glasgow: a cross-sectional, population-based study

FINAL STUDY REPORT

February 2013

Contents

Acknowledgements

Special thanks are due to the study team, past and present, for their enthusiasm and energy, knowledge and insight, time and dedication to the study. Thanks also to the large number of contributors and staff who shared their skills, knowledge and expertise and who supported and contributed to the preparation and publication of study manuscripts. Grateful thanks to Carol Tannahill for helpful, constructive and insightful comments on this report.

Thanks are also due to the Robertson Centre for Biostatistics, the University of Glasgow for data management, statistical support and analysis; the administrative staff in the Glasgow Centre for Population Health; the Health Information and Technology section of NHS Greater Glasgow and Clyde for sample selection and analysis; Alasdair Buchanan for GPASS data and analysis. Finally, thanks to all members of GP Practices who participated in the study and to the participants themselves.

This study was funded by the Glasgow Centre for Population Health which is a partnership between NHS Greater Glasgow and Clyde, Glasgow City Council and the University of Glasgow, supported by the Scottish Government.

Abbreviations and glossary

AVLT	Auditory Verbal Learning Test: assesses short-term auditory-verbal memory
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
cIMT	Carotid intima-media thickness: a surrogate marker of atherosclerosis
CRP	C-reactive protein: levels of this protein in the blood rise in response to inflammation
CRT	Choice reaction time: assesses reaction time in a task where the actor has to make one of two or more choices
FEC	Forced vital capacity: the maximum amount of air able to be exhaled on a single breath
FEV1	Forced expiratory volume in 1 second
GCPH	Glasgow Centre for Population Health
GM	Grey matter
GP	General Practitioner
GPASS	General Practice Administration System for Scotland: clinical record and practice administration software
ICAM	Intercellular adhesion molecule-1: associated with immune response, becomes upregulated in response to bacteria
IL-6	Interleukin-6: a cytokine with both pro-inflammatory and anti-inflammatory roles; an important mediator of fever and the acute phase response
LD	Least deprived
MD	Most deprived
MRI	Magnetic resonance imaging: used to visualise internal structures of the body
pSoBid	Psychological, Social and Biological Determinants of Ill-Health Study
RGSC	Registrar General's Social Classification
SES	Socioeconomic status
SIMD	Scottish Index of Multiple Deprivation: ranks datazones from most deprived to least deprived
TNF-α	Tumour necrosis factor alpha
VBM	Voxel based morphometry: a neuroimaging analysis technique that investigates differences in brain anatomy
vWF	von Willebrand Factor: a glycoprotein present in blood plasma; plays a major role in blood coagulation
WM	White matter

Summary

Socioeconomic inequalities in health are essentially universal: poorer health is more common among people in less advantaged circumstances. Social gradients in a range of biological and psychosocial variables exist which indicate that living in deprivation may increase the propensity to develop chronic disease, through as yet unknown mechanisms.

This study, pSoBid (pronounced 'so-bid'), sought to examine the psychological, social, behavioural and biological determinants of ill health within population groups in Glasgow that differed in socioeconomic status and in their susceptibility to develop chronic disease, especially coronary heart disease and Type 2 diabetes mellitus. The study also explored these aetiological links to try to identify potential explanatory pathways for the burden of physical and mental ill health in deprived communities.

pSoBid was established and funded by the Glasgow Centre for Population Health (GCPH). The research fieldwork was carried out from December 2005 to May 2007.

This report presents the background to the study, the full study methodology and key findings to date. It also presents the implications of these findings for future research and policy development and outlines the next steps and future direction for pSoBid.

Study design and participants

In a cross-sectional, population-based study, 666 participants took part. The sample population was selected firstly on the basis of how their area of residence ranked in the Scottish Index of Multiple Deprivation 2004. Repeated stratified random sampling was deployed to achieve approximately equal numbers of participants from the most deprived areas and the least deprived areas of Greater Glasgow, as well as approximately equal numbers of men

and women and of participants from each age group studied (35-44, 45-54 and 55-64 years).

Methods

Individuals were invited by letter to attend for assessment of their medical and early life history, lifestyle, classical and novel risk factors for chronic disease, cognitive function and psychological profile, and carotid intima-media thickness (cIMT) and plaque count as indices of atherosclerosis. A small sub-sample of male participants was also invited to attend later for MRI scanning.

Results

Study findings to date across a number of areas of interest are presented as a series of journal article abstracts across the psychological, social and biological determinants of health as investigated by the study team.

The study was successful in recruiting a sample of subjects collectively comprising a balanced sex and age profile from the most and least deprived communities of Glasgow. This study also illustrates the willingness of subjects to volunteer for a variety of investigations involving psychological, behavioural, sociological and medical questions and tests.

The depth and range of the data collected and the analyses undertaken in this study yield important information concerning the relationships between health and socioeconomic status, inflammation, atherosclerosis, mental outlook, cognitive performance and personality, early life family circumstances, genetic disposition and brain morphology. The characteristics of the least and most deprived participant groups varied, in the large majority of cases, in the expected direction across a number of indices of adult socioeconomic status, early life conditions at age 11 years, health behaviours, mental wellbeing and cognitive ability and biomarkers of systemic inflammation and carotid atherosclerosis.

Summary

The valuable and important source of information on the determinants of ill health across the socioeconomic gradient in Glasgow which pSoBid has collected places the study in a good position to provide further insight into the pathways between people's social circumstances, mental wellbeing and biological markers of disease. However, as the sample was selected from the ends of the socioeconomic gradient, subjects are not representative of the population of interest as a whole. The cross-sectional design of the study also means that it is not possible to identify causal pathways or the relationships between variables and can therefore only report associations.

Acknowledging the limitations of the study and the challenges of integrating a range of professional perspectives, the multidisciplinary approach employed in pSoBid has enabled a more holistic understanding of the diverse characteristics of individuals who reside in affluent and deprived communities and their influence on health and health inequalities. Future study analyses will continue to build an understanding of the relationships between the different types of measure, and of the pathways that link poverty, biology, behaviour and psychology and lead to health inequalities in Glasgow and beyond.

1. Introduction

Heart disease, diabetes, some cancers, rheumatoid arthritis and mental illness are examples of the burden of ill health that is carried disproportionately by those living in deprived communities (Davey Smith, 1997a; Mackenback *et al.,* 2003; Marmot, 2005). Not only is the prevalence and incidence of disease higher in areas of deprivation but also the nature of the problem appears to be qualitatively different, and treatment less successful (Ionescu *et al.,* 1998). This inequality in disease risk can partially be explained by the higher prevalence of classical risk factors in deprived areas, but this explanation fails to account for the totality of the variation (Shewry *et al.,* 1992; Tunstall-Pedoe *et al.,* 1997; Capewell *et al.,* 1999) and there is the need to uncover other potential explanatory variables.

There are social gradients in a range of biological and psychosocial variables which indicate that living in a deprived environment may increase the propensity to develop chronic disease, through as yet unknown mechanisms. A potential underlying cause of increased prevalence of disease is chronic inflammation (Steptoe *et al.,* 2002; Owen *et al.,* 2003). This has been observed to be more common in deprived than affluent populations, linked to coronary heart disease (Ross, 1999), increased risk of type 2 diabetes (Stern, 1995) and other disorders (Sattar *et al.,* 2003), as well as cognitive dysfunction and altered psychological profile (Weaver *et al.,* 2002; Yaffe *et al.,* 2003; Schram *et al.,* 2007).

These aetiological links continue to need further exploration as potential explanations of the burden of physical and mental ill health in deprived communities.

This study, pSoBid (pronounced ‘so-bid’), sought to examine the psychological, social, behavioural and biological determinants of ill health within population groups in Glasgow that differed in socioeconomic status and in their propensity to develop chronic disease, especially coronary heart disease and Type 2 diabetes mellitus.

The pSoBid study brought together expertise from social epidemiology (the study of how social interactions affect the health of populations), public health, biochemistry, psychology, neuroscience and genetics to build a better understanding of why living in poorer, more stressful circumstances results in higher levels of disease and ill-health. The study sought to relate the social conditions of the population of Glasgow to their psychological profile and their biological status.

pSoBid was established and funded by the Glasgow Centre for Population Health (GCPH). The research fieldwork was carried out from December 2005 to May 2007. The Principal Investigator and study director was Professor Chris Packard, Director of Research and Development, NHS Greater Glasgow & Clyde, and Dr Yoga Velupillai, GCPH Programme Manager, was study project manager. The study drew together academic expertise from a range of different disciplines and units from across the University of Glasgow and NHS Greater Glasgow and Clyde.

This report presents the background to the study, a review of relevant literature, the full study methodology and key findings to date as a series of abstracts from academic published papers. It also presents the public health implications of these findings for future population health research and policy development and outlines the next steps and future direction for pSoBid.

2. Review of the evidence

The psychological, social and biological determinants of health

Socioeconomic inequalities in health are essentially universal: poorer health is more common among people in disadvantaged circumstances. In all countries where data are available, mortality has been shown to be higher among those in less advantaged socioeconomic positions, regardless of whether socioeconomic position is indicated by education level, occupational social class, home ownership or income level (Adler and Ostrove, 1999; Mackenbach *et al.,* 2003; Lahelma *et al.,* 2004) and this is evident for both men and women. These variables are interrelated, but represent different dimensions of socioeconomic status (Kristenson *et al.,* 2004). Compared to present occupational status, education relates more to social status in early life, whereas income describes the availability of material resources but also a level of status. For measures of education, occupation and income, on average, the more advantaged individuals are, the better their health.

In a number of large scale studies a gradient appears across the social spectrum, rather than a threshold effect, indicating that it is the position within the social hierarchy that is important for health (Marmot and Wilkinson, 1999). Studies examining the associations of each socioeconomic indicator with mortality and morbidity have repeatedly shown consistent gradients. These gradients have been shown for all-cause mortality, but also for a wide range of diseases, especially coronary heart disease, diabetes, respiratory diseases, arthritis, poor birth outcomes, and for accidents and violent deaths (Marmot and Wilkinson, 1999).

The inverse relationship between socioeconomic position/status and health is one of the most consistent epidemiological findings. The social distribution of physiological risk is partly a reflection of the social patterning of unhealthy behaviours. Unhealthy diet, lack of exercise, tobacco and drug use have now become strongly associated with social disadvantage. Notably, material constraints, prevalent social norms and limited opportunities to make healthy

choices may act as a barrier for lower socioeconomic groups to adopt a healthy lifestyle (Wardle and Steptoe, 2003; Stringhini *et al.,* 2011).

However, an extensive volume of research identifies social and economic factors as being at the root of these inequalities in health. For example, in studies of Scottish men (MacLeod *et al.,* 2005), British civil servants in the Whitehall II study (Marmot *et al.,* 1991) and participants of the Helsinki Health Study (Lahelma *et al.,* 2004), individual social disadvantage has been consistently associated with poorer health and higher rates of mortality regardless of the measure of social position used and even after controlling for other risk factors. Area-based socioeconomic measures have also been shown to be independently associated with higher risk factors for morbidity and mortality in a number of studies (Davey Smith *et al.,* 1998a; Riva *et al.,* 2007; Vescio *et al.,* 2009). These studies have shown that there is an increased risk of mortality in deprived areas compared to more affluent ones.

The impact of socioeconomic status on health over the life-course

Socioeconomic circumstances at different stages of the life-course can influence specific adulthood health outcomes. 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. Children who experience socioeconomic disadvantage are said to be at high risk of suffering from multiple disorders by the time they reach adulthood, due to their experience of a broad range of adversities (Melchior *et al.,* 2007). It has been claimed that the risk of mortality accumulates during the life-course (Ben-Shlomo and Kuh, 2002; Power *et al.,* 2007) and that exposure to risk factors may occur many years before the development of the outcome (Davey Smith *et al.,* 1998b). 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.

A number of studies to date have emphasised the importance of childhood social circumstances for adult mortality (Davey Smith *et al.,* 1998b; Ben-Shlomo and Kuh, 2002; Galobarades *et al.,* 2006; Melchior *et al.,* 2007; Stringhini *et al.,* 2011) and recently also for general health, which has been suggested to reflect ageing processes and the chronic conditions accumulated over the life-course (Ben-Shlomo and Kuh, 2002; Osler *et al.,* 2009). To date most (Vagero and Leon, 1994; Davey Smith *et al.,* 1997b, 1998b; Brunner *et al.,* 1999; Galobardes *et al.,* 2006; Power *et al.,* 2007; Ruijsbroek *et al.,* 2011; Boardman *et al.,* 2012), but not all studies (Lynch *et al.,* 2004), suggest that childhood conditions are important predictors of risk regardless of social class destination in adulthood.

Childhood social position and coronary heart disease in adulthood

Coronary heart disease is a good example of an adult disease that develops throughout the life-course. Although coronary heart disease manifests itself in adulthood, atherosclerosis, an important underlying process leading to the disease, may begin at a much earlier age. An increasing number of studies have examined the link between childhood socioeconomic circumstances and cardiovascular disease in later life. 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 (Power *et al.,* 2007). Individuals with the most disadvantaged backgrounds had poorer health profiles across multiple measures of disease risk and health function. 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, with a general trend of deteriorating risk as quantified by participants' father's occupation, from class I (professional occupations) to V (unskilled occupations) (Power *et al.,* 2007). These findings are in line with previous studies showing associations with both child and adult socioeconomic status and position for cardio-respiratory risk in adult life. In a sample of Norwegian children followed for 30 years, childhood socioeconomic disadvantage measured by paternal education, but not maternal, has been shown to be associated with an

elevation in behavioural and physiological cardiovascular risk factors (Kvaavik *et al.,* 2011). Furthermore, similar findings have been demonstrated in a large cohort of Swedish male military service conscripts where an inverse association between childhood socioeconomic position and risk of coronary heart disease in middle age was shown (Falkstedt *et al.,* 2010). This research has however stated that social, cognitive and behavioural factors evident prior to adulthood are likely to be of major importance in explaining this association, and the importance of social position in adulthood may have been overestimated by previous studies.

Results from a small number of studies have also shown links between high levels of risk factors early in life and atherosclerosis in later life. Childhood socioeconomic position has been shown to be an important determinant of adult smoking status (Lacey *et al.,* 2010). Blood pressure, low density lipoprotein cholesterol levels, smoking and body mass index (BMI) measured between 12 to 18 years of age in the Cardiovascular Risk in Young Finns Study was associated with greater adult carotid intima-media thickness (cIMT), independent of adult levels of these risk factors (Raitakari *et al.,* 2003). Similarly, the Bogalusa Heart Study of young adults reported greater cIMT in participants who had higher levels of low-density lipoprotein cholesterol and BMI during childhood (Li *et al.,* 2003). A systematic review of forty individual level studies reported a robust inverse association between childhood circumstances and cardiovascular risk in 31 of the reviewed studies (Galobardes *et al.,* 2006). This review confirmed that the evidence supported the position that those who experienced worse socioeconomic conditions in their childhood, independent of their circumstances during adult life, generally were at greater risk of developing and dying from cardiovascular disease.

Childhood environment and adult health

It is also well recognised that early life and childhood environment and diet are important in determining rate of growth, timing of maturation, final stature and health outcomes as an adult. Low birthweight is associated with cardiovascular disease in adulthood. Short adult height is also known to be a risk for cardiovascular and cancer mortality and for poor adult health

(Wadsworth *et al.,* 2002) and leg length in childhood is a marker for cardiovascular disease and cancer (Gunnell *et al.,* 1998; Davey Smith *et al.,* 2001). Longer leg length is associated with advantaged socioeconomic circumstances in childhood. Adult leg length is a useful indicator of adverse circumstances and poor nutrition in infancy and childhood as confirmed by data from the 1946 British Birth Cohort (Gunnell *et al.,* 1998), the British Women's Heart and Health Study (Lawlor *et al.,* 2003), the Midspan Family Study (Gunnell *et al.,* 2003) and evidence from the Whitehall II study of British civil servants (Ferrie *et al.,* 2006). Studies which have investigated the association between leg length and cardiovascular disease risk and mortality have shown an increased risk of mortality with decreasing leg length measured in both childhood (Gunnell *et al.,* 1998) and adulthood (Davey Smith *et al.,* 2001). In a recent study, childhood stature was weakly inversely associated with cardiovascular mortality in the Boyd Orr cohort. Leg length was the component of stature which provided the strongest association (Whitley *et al.,* 2012). These findings suggest that adverse diet and living conditions in childhood, for which leg length seems to be a sensitive indicator, are associated with an increased risk of coronary heart disease in adulthood. This association adds additional support to the evidence that pre-adult influences are important in the aetiology of coronary heart disease.

An inverse association with coronary heart disease risk is not reported for trunk length or sitting height in adults (Wadsworth *et al.,* 2001; Davey Smith *et al.,* 2001). Dental status is affected by oral health as well as general diseases over the life course and has also been shown to be strongly related to mortality (Thompson *et al.,* 2004; Osler *et al.,* 2009).

However despite this growing evidence that early life socioeconomic position contributes to morbidity and mortality in adulthood via a number of pathways, little is known about the biological mechanisms responsible for the observed relationships and the processes responsible for the accumulation of risk. Given the evidence that both childhood and adult socioeconomic position are associated with morbidity and mortality from specific causes, it follows that

they are also likely to be associated with the biological and behavioural risk factors for those outcomes.

Coronary heart disease and socioeconomic status

Coronary heart disease (CHD) is a leading cause of mortality and morbidity in developed countries and in many populations shows an inverse social gradient as demonstrated by a higher incidence in areas of socioeconomic deprivation compared with socioeconomically advantaged areas (Davey Smith *et al.,* 1998a; Lawlor *et al.,* 2005; Singh-Manoux *et al.,* 2008a). Over the last two decades Scotland has seen a halving of mortality from coronary heart disease, although cardiovascular mortality in Scotland is still among the highest in Europe and globally (Muller-Nordhorn *et al.,* 2008). Moreover, the rate of decline appears to be slowing in young adults in deprived groups and has been attributed to poor lifestyle choices and behaviours rather than a decline in medical management of CHD (O'Flaherty *et al.,* 2009).

Traditional cardiovascular risk factors, including smoking, high blood pressure, high cholesterol and diabetes, do not fully account for or explain the excess burden of cardiovascular diseases in the population (Everson-Rose and Lewis, 2005). It is increasingly accepted that variation in the prevalence of classical risk factors only partially accounts for the gradient in CHD (Shrewy *et al.,* 1992; Tunstall-Pedoe *et al.,* 1997; Capewell *et al.,* 1999) and there is a need to uncover other potential explanatory variables.

The association of markers of inflammation with socioeconomic status

Inflammation is regarded as one of the leading hypotheses concerning how socioeconomic status exerts its effects on health. This chronic 'low grade' activation of the innate immune system may start early in life (Atabek, 2008) and be influenced by cumulative effects of socioeconomic status over the life-course (Koster *et al.,* 2006; Tabassum *et al.,* 2008). Other novel possible contributors to increased CHD risk are insulin resistance and endothelial dysfunction (Yudkin *et al.,* 1999; Pollitt *et al.,* 2008).

Low socioeconomic status has been related to higher levels of inflammatory markers. Inflammation, a biological response of the immune system, has been associated with increased morbidity and mortality across the life-course, from childhood and adolescence to old age (Pollitt *et al.,* 2008). Meta-analyses of results from prospective studies suggest that inflammatory markers such as fibrinogen, C-reactive protein (CRP) and interleukin-6 (IL-6), acute phase proteins induced as a part of the immune response to acute infection or injury, and haemostatic markers such as von Willebrand Factor (vWF) and tissue plasminogen activator antigen, are all part of the evolving understanding of cardiovascular diseases, including atherosclerosis, stroke and myocardial infarction (Fibrinogen Studies Collaboration, 2005).

Inflammation and coronary heart disease

Evidence to date supports the suggestion that inflammation plays an important part in the process of atherosclerosis and the development of CHD (Jousilahti *et al.,* 2003). It has also been suggested that atherosclerosis is primarily an inflammatory disease (Ross, 1999). CRP has been shown to bind to low density lipoprotein (LDL) (de Beer *et al.,* 1982) and is present in atherosclerotic plaques (Zhang *et al.,* 1999), indicating a potential role for CRP in CHD. CRP has been associated with the presence and severity of atherosclerosis, and has been found to predict acute cardiovascular events in middle-aged men in the Monica Study (Koening *et al.,* 1999) and older adults in the Heart and Soul Study (Lubbock *et al.,* 2005). Furthermore, in a meta-analysis of individual records of over 160,000 people without a history of vascular disease from 54 prospective studies, CRP concentration had a continuous linear association with subsequent risk of coronary heart disease, stroke, and death from several cancers and lung disease (Emerging Risk Factors Collaboration, 2010). CRP was also shown to be positively associated with several conventional risk factors (e.g. BMI, diabetes, and smoking) and inflammatory markers (e.g. IL-6) (Emerging Risk Factors Collaboration, 2010). The association between plasma fibrinogen concentration and the risk of cardiovascular disease has also been demonstrated in a number of studies (Danesh *et al.,* 2005). A review of socioeconomic status and allostatic load (the ‘wear and tear’ the body experiences when repeated inflammatory

responses are activated during stressful situations (McEwan and Stellar, 1993)) revealed an inverse relationship, with low socioeconomic status more consistently related to higher levels of allostatic load (Dowd *et al.,* 2009).

Inflammation over the life-course

The relationship between socioeconomic status throughout life and chronic inflammation was assessed in a publication by Tabassum *et al.,* (2008) who reported cumulative effects of socioeconomic status on CRP and fibrinogen. Likewise, in a large cohort of middle-aged White and African-American adults the accumulation of adverse socioeconomic conditions (at both the individual and neighbourhood level) throughout life was associated with elevated systematic inflammation in adulthood (Pollitt *et al.,* 2008). Increasing socioeconomic disadvantage over the life-course has been reported to be strongly related to allostatic load in adulthood in both men and women (Gustafsson *et al.,* 2011). A similar association was reported by Jousilahti *et al.,* (2003) in 1,500 middle-aged Finnish men, where the inverse associations between socioeconomic status and markers of inflammation were particularly strong in men below 60 years of age. In the Whitehall II study of civil servants, social position was reported to be inversely associated with IL-6 and CRP and participants who had mild depression also had impaired endothelial function (Hemingway *et al.,* 2003). In a study of over 3,000 American adults over 70 years of age, low socioeconomic status was also associated with significantly elevated levels of IL-6, CRP and tumour necrosis factor-α (TNF-α) (Koster *et al.,* 2006).

Ethnicity, socioeconomic status and inflammation

Multi-ethnic studies have also shown an association between low socioeconomic status and the incidence and prevalence of cardiovascular disease and elevated inflammatory markers but highlight significant differences between racial and ethnic groups. A systematic review of 32 relevant studies concluded that poverty and non-White race were associated with elevated CRP levels amongst adults (Nazmi and Victora, 2007). Compared to White populations, Black populations, Hispanics and South Asians had higher recorded CRP levels. The impact of socioeconomic status

on inflammation was found to be the same as in White populations (Nazmi and Victora, 2007). The Multi-Ethnic Study of Atherosclerosis, involving more than 6,000 adults aged over 45 years, reported that in multi-ethnic populations persons of lower socioeconomic position had a greater inflammatory burden than those of high socioeconomic position (Ranjit *et al.,* 2007). An analysis of the data from the US National Health and Nutrition Examination Survey of nearly 80,000 American adults reported that African-Americans, Hispanics and women were more likely to have high levels of CRP, compared to the White American population (Alley *et al.,* 2006). Socioeconomic status was related to higher CRP levels, but this effect was greatest at very high CRP levels (>10mg/L), with the authors suggesting that differences in very high CRP may be due to factors beyond acute ill health and may reflect chronic health, behavioural and disease processes associated with low socioeconomic status.

Early life socioeconomic status and inflammation

Early life socioeconomic status has also been linked with raised levels of inflammatory markers in a number of studies (Kivimaki *et al.,* 2005; Pollitt *et al.,* 2007; Miller and Chen, 2007) but not in others (Gimeno *et al.,* 2008a). Low childhood social class and education levels were associated with elevated levels of CRP, fibrinogen, white blood cell count and vWF in White children (Pollitt *et al.,* 2007). The findings were less consistent among African-American children. However in a recent study (the Cardiovascular Risk in Young Finns Study) which took a life-course perspective, the association between socioeconomic position and CRP concentrations was seen in early adulthood, 24-39 years, but not in childhood or adolescence (Gimeno *et al.,* 2008a). The authors commented that the socioeconomic differences in CRP seen in adult life do not appear to be determined at conception or to be a pathway starting early in life and tracking in adulthood. This cohort study has also reported a direct correlation between socioeconomic status, CRP levels and cIMT (Kivimaki *et al.,* 2005), a non-invasive measure of atherosclerosis and a reliable indicator of future risk of coronary heart disease. The authors reported that the observed interrelations were driven by the effects of adiposity.

The association between low level inflammation and cardiovascular risk, although quite a recent finding, is now well established. It remains to be established, however, if the risk of cardiovascular disease could be reduced by reducing levels of inflammation in individuals.

Socioeconomic status and carotid ultrasound markers of atherosclerosis

The endothelium plays a key role as the signal transducer that regulates vascular inflammation. Endothelial dysfunction and increased arterial stiffness (loss of arterial elasticity) have also been reported to be early markers of accelerated vascular ageing in young adults and in children with a family history of hypertension. Low childhood birthweight has also been associated with an increased incidence of adult cardiovascular disease, insulin resistance and high blood pressure (Barker *et al.,* 1993). In a study of 44 nine year old children, half of whom had a low birthweight, impaired endothelial function and a trend towards increased carotid stiffness was identified in the low birthweight group (Martin *et al.,* 2000).

Carotid intima-media thickness

Carotid ultrasound is an efficient validated tool for assessing the degree of atherosclerosis in an individual. Measurement of the carotid artery wall intima-media thickness (cIMT) is a commonly used marker of atherosclerosis and a valid presymptomatic predictor of coronary heart disease. The ultrasound detection of carotid plaques is also highly informative. Several studies have examined the comparative usefulness of cIMT and plaque score in predicting myocardial infarction and stroke. Plaque score has been shown to be associated with risk of myocardial infarction and stroke (van der Meer *et al.,* 2004). In the Rotterdam study of adults aged over 55 years, the non-invasive measures of atherosclerosis, carotid plaque score and cIMT, were equally strong predictors of myocardial infarction (van der Meer *et al.,* 2004). The authors concluded that the relatively crude measures directly assessing plaques in the carotid artery predicted myocardial infarction equally as well as the more precisely measured and technical cIMT. However, a number of studies have now reported plaque presence to be more strongly predictive than cIMT of future cardiovascular events (Belcaro *et al.,* 2001; Stork *et al.,*

2004). Likewise, the Tromsø Study of over 6,000 adults aged 28-84 years found the carotid plaque area to be a stronger predictor than cIMT of first myocardial infarction, particularly in women (Johnsen *et al.,* 2007).

Several studies have examined the relationship between socioeconomic status and ultrasound markers of atherosclerosis. Most studies have investigated individual level measures of socioeconomic position and their relation to cIMT (Ebrahim *et al.,* 1999; Lamont *et al.,* 2000; Kivimaki *et al.,* 2006). The Atherosclerosis Risk in Communities (AIRC) study found that cIMT fell significantly with increasing categories of income, educational attainment or occupation (Diez-Roux *et al.,* 1995). Similarly, in the Kupio Ischaemic Heart Study of Finnish men, significant inverse differences in the rate of progression of cIMT were reported in relation to income and educational attainment (Lynch *et al.,* 1997). Associations were also reported between community level socioeconomic status and cIMT and carotid plaque score in a study of hypertensive middle-aged American adults (Petersen *et al.,* 2006). This study showed community disadvantage to be associated with greater intima-media thickness irrespective of individual income or educational attainment level. Similarly, in a study of over 4,000 Swedish adults, significant associations between area level deprivation and carotid plaque score were also reported (Rosvall *et al.,* 2007). These associations were slightly reduced after adjusting for individual level markers of socioeconomic position (education, employment status and occupational social class). 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 (Kivimaki *et al.,* 2006).

Cognitive function, socioeconomic status and health

Research into cognitive function in prospective cohort studies reveals that there are likely to be multiple determinants of cognitive decline. With increasing age, the general trend is toward declines in some cognitive abilities (Deary and Gow, 2008). Some verbal and numerical abilities, and general knowledge, are well retained as people grow older. However, on average,

aspects of memory, reasoning, speed of information processing, and executive functioning decline in a fashion that is similar to the age-related changes in physical functioning (Schaie, 2005). Besides age, the other two general factors most widely implicated in this decline are biology and socioeconomic factors.

Socioeconomic status across the lifecourse and cognitive function

Growing evidence shows that low socioeconomic status is related to poor mental and physical function and that this association has a basis in both social and biological factors. Accumulating socioeconomic disadvantage from childhood to adulthood has been shown to be associated with slower walking time in old age and reduced balance ability (Birnie *et al.,* 2011). A number of studies have examined the association between educational attainment level and cognitive change (Farmer *et al.,* 1995; Lee *et al.,* 2003) and found it to be strong. However the evidence of an association between other indicators of socioeconomic status – such as occupational level, income and area of residence – and cognitive function remains limited. In a large community study of American older adults aged 70-79 years, people with low socioeconomic status had an increased risk of cognitive decline compared to people with a high socioeconomic status. This was found across a range of indicators of socioeconomic status, the strongest association being with education (Koster *et al.,* 2005). As expected, disease prevalence and risk factors were elevated in the population of low socioeconomic status. However, biomedical factors could only explain 5% of the socioeconomic differentials in cognitive decline. Neighbourhood deprivation in urban areas has also been shown to be associated with poorer cognitive function in older adults, independent of the effects of individual and household socioeconomic factors (Lang *et al.,* 2008). A similar study also reported a significantly higher prevalence of cognitive and functional impairment in elderly individuals living in socioeconomically deprived areas regardless of their own socioeconomic status (Basta *et al.,* 2007). A small number of research studies have shown that ethnic minority status is also a risk factor for poorer cognitive function in older age (Zsembik and Peek, 2001; Masel and Peek, 2009) but the impact of ethnicity on the rates of cognitive decline in old age remains unclear.

Childhood socioeconomic status is associated with cognitive ability and achievement during childhood, including IQ, literacy, achievement tests and grade retention. These associations are well established and are observed throughout development, from infancy to adolescence and into adulthood (Noble *et al.,* 2005, 2007). Cognitive function in childhood highly correlates with cognitive function in adulthood and is influenced by biological and social conditions in early life which then influence adulthood circumstances.

Socioeconomic conditions across all stages of the life-course do appear to make a unique contribution to cognitive function in later life. Evidence also suggests that in terms of cognitive function, origin is not necessarily destiny, as disadvantaged socioeconomic circumstances in childhood may be overcome to a degree by upward mobility later in life.

Heart health and cognitive function

Biomedical factors, including common diseases and their risk factors, are important mechanisms that help to explain the potential association between low socioeconomic status and cognitive decline. Evidence is now well established that vascular risk factors, such as blood pressure (Singh-Manoux and Marmot, 2005) and indicators of vascular disease are associated with cognitive impairment and dementia (Muller *et al.,* 2007). Vascular disease has been reported to be predictive of poor cognitive function in the general population. The presence of vascular disease was associated with diminished cognitive function in a large cohort of middle-aged adults (Singh-Manoux *et al.,* 2003). Poor cognitive performance was also found to be related to an increased risk of mortality from cardiovascular disease, stroke and respiratory disease in the UK Health and Lifestyle Survey (Shipley *et al.,* 2008). The common carotid artery intima-media thickness (cIMT) is one of the more recently identified vascular risk factors. As a marker of the structural and functional properties of the vessel wall and an early indicator of atherosclerosis, it has been shown to have a robust association with cardiovascular disease. An association between cIMT and cognitive impairment has also been reported in a number of studies (Breteler *et al.,* 1994; Cerhan *et al.,* 1998; Muller *et al.,* 2007). This association was reported

in analysis of the Whitehall II study which identified an overall association between cIMT and a number of measures of cognitive performance in middle-aged adults in a low socioeconomic group (Singh-Manoux *et al.,* 2008b). The authors commented that individuals with higher socioeconomic position in their study appear to have a higher cognitive reserve which is preventing functional manifestations of atherosclerosis.

Inflammation and cognitive function

Several studies have also suggested that raised levels of inflammatory markers are associated with cognitive decline in dementia and normal ageing. To date the most frequently investigated markers of systemic inflammation in relation to cognitive decline are C-reactive protein (CRP), intercellular adhesion molecule (ICAM) and interleukin-6 (IL-6). In an investigation of inflammatory marker concentrations and cognitive performance in a healthy ageing population, high concentrations of CRP were found to be indicative of impaired cognitive function (Teunissen *et al.,* 2003). Gimeno *et al.,* (2008b), in a study of middle-aged adults found that raised levels of the inflammatory marker IL-6 were moderately associated with lower cognitive performance status but there was little evidence of an association with cognitive decline in midlife. This former association was more evident in men than women. In a study of over 4,000 male Vietnam era war veterans low cognitive ability in early adulthood was related to high levels of inflammation, as indicated by ESR values (erythrocyte sedimentation rate, a stable marker of systemic inflammation) in middle age (Philips *et al.,* 2011). In the prospective Edinburgh Artery Study, Rafnsson *et al.,* (2007) found that systematic markers of inflammation (IL-6 and ICAM) were associated with progressive decline in cognitive abilities in older people.

Lifestyle behaviours and cognitive function

A growing body of evidence also supports the association between lifestyle behaviours and cognitive function. Cognition is affected by the classical lifestyle risk factors which are associated with deprivation related morbidity and which often exert their biological effects via harmful health behaviours including smoking, excessive alcohol intake and obesity (Elwood *et al.,* 1999;

Kalmijn *et al.,* 2002; Sabia *et al.,* 2008). Education, physical activity including walking, mentally demanding work and managerial positions, leisure and intellectual activities, and living with a partner have all been reported to predict a more favourable cognitive status in middle and later life (Weuve *et al.,* 2004; Hakansson *et al.,* 2009). However a study investigating the association between long working hours (more than 55 hours per week) and cognitive function identified that long working hours may be one of the risk factors having a negative effect on cognitive performance in middle age (Virtanen *et al.,* 2009). Furthermore, a recent study using data from the Whitehall II study investigating the cognitive function of over 2,000 adults in work and retirement reported that retirees showed a trend towards slowed cognitive performance compared to those still working (Roberts *et al.,* 2011).

Intelligence, mortality and health

Another novel hypothesis which has been posed as a 'fundamental cause of social inequalities in health' is intelligence, assessed by a measure of individual IQ (Gottfredson, 2004). Observations have shown that low IQ scores ascertained in childhood, mid-life and older ages are associated with elevated rates of mortality and morbidity (Hart *et al.,* 2003; Batty *et al.,* 2006, 2007). IQ scores are socially patterned and a link has also been reported between literacy and health related behaviours, injuries and the self-management of ill health (Gottfredson, 2004). In a study cohort of more than one million Swedish men followed up for more than two decades, low IQ scores in early adulthood were reported to be associated with a subsequent increased risk of non-fatal unintentional injury (poisoning, fire road traffic, medical complications and falling) (Whitley *et al.,* 2010). In a systematic review of individual level studies linking early IQ with later mortality, higher IQ in the first two decades of life was consistently related to lower rates of total mortality in middle to late adulthood (Batty *et al.,* 2007). In the West of Scotland Twenty-07 study, indices of socioeconomic position were significantly associated with health outcomes in the expected direction. Scores from a test of IQ did not explain the socioeconomic gradients in health of these participants but did lead to a reduction in the magnitude of the gradients (Batty *et al.,* 2006). Lower childhood IQ was shown to be related to

higher mortality risk for coronary heart disease in a prospective observational study linking the Midspan Studies and the Scottish Mental Survey 1932 (Hart *et al.,* 2003). In the Vietnam Experience study of male US veterans, men with higher intelligence in early adulthood were found to have a reduced risk of atherosclerosis (Gale *et al.,* 2012). However, in a population-based longitudinal study of children followed from age ten to 75 years in Sweden, mortality differences by own educational attainment in adulthood were not explained by childhood IQ (Lager *et al.,* 2009).

The link between socioeconomic status and cognitive function is well established. The impact of individual indicators of socioeconomic status, namely education and income, appear to be important. Increasing evidence also supports the biological link between impaired cognitive ability and increased levels of systemic inflammation and vascular damage. Moreover, it has been stated that not only does systemic inflammation influence cognition, but also that poor cognitive ability earlier in life is associated with inflammation later in life (Philips *et al.,* 2011). The relationship between high inflammation and impaired cognitive function appears to be reduced but not abolished by individual-level markers of low socioeconomic status. Current evidence appears to support that lower cognitive performance in deprived individuals appears to be better explained by the disadvantages of poor education and low income than by biological factors.

The impact of personality on health

Cognitive and personality traits are fundamental aspects of a person, which have relevance to life chances and life outcomes (Deary *et al.,* 2010). Personality traits are modifiable and continue to change in adulthood and these changes may be important for health and mortality (Roberts *et al.,* 2006).

The (predictive) power of personality

Associations between personality, mental wellbeing, socioeconomic status and health have been well documented (George, 1978; Chapman *et al.,* 2010). Among the psychological factors that impact on health, personality –

that is stable individual differences in thinking, feeling and behaving – plays a pivotal role. It underpins the consistency with which we think, act and feel across different situations over time. Adult personality traits are thought to be derived from early life differences in temperament which are partly genetically determined and shape exposure to social experiences (Steptoe and Molloy, 2007). These personality traits predict a range of outcomes with some consistency, including the quality of family and social relationships, marital status and satisfaction, occupational choices, political attitudes and criminality (Ozer and Benet-Martinez, 2006). Specific personality traits have also been shown to predict important life outcomes, such as mortality, divorce and success in work (Roberts *et al.,* 2007). Longitudinal studies have demonstrated that personality traits identified in childhood are able to predict health outcomes occurring in later life such as becoming overweight and obese, unintentional injuries, metabolic syndrome and longevity (Vollrath, 2006).

Personality traits and health

The association between personality factors or traits and a range of both positive and maladaptive (negative) health behaviours is now well established and known to influence morbidity and mortality. In a study of 716 men and women aged over 58 years, 'positive affect' (that is, feelings that reflect a level of pleasurable engagement with the environment, such as happiness, joy, excitement, and contentment (Cohen and Pressman, 2006)) was associated with greater social connectedness, optimism, adaptive coping responses, and lower risk of depression (Steptoe *et al.,* 2008). On the other hand, 'negative affect' (the feelings and negative mood states of anger, anxiety, contempt, fear or guilt (Cohen and Pressman, 2006)) was associated with negative relationships, greater exposure to chronic disease, depressed mood, poorer mental health and pessimism. Positive affect was related to protective social and psychological resources, but not to chronic stress exposure. Happier individuals do not experience lower levels of chronic adversity in their lives, but have greater protective resources that enable them to handle problems flexibly and effectively, together with better mental health (Steptoe *et al.,* 2008).

Personality attributes have been reported to be associated with increased risk of hypertension (Barefoot *et al.,* 1983; Carroll *et al.,* 1997), CHD and atherosclerosis (Barefoot *et al.,* 1995), myocardial infarction (Everson *et al.,* 1997) and all-cause mortality (Everson *et al.,* 1997; Nabi *et al.,* 2008a). In the Baltimore Longitudinal Study of Aging, where participants were followed for up to 50 years, longevity was associated with being conscientious, emotionally stable (low neuroticism) and active (Terracciano *et al.,* 2008). The association of personality traits with longevity was reported to be independent from the influence of smoking and obesity. Optimism (positive future expectations) was reported to be associated with a reduced incidence of CHD and total mortality in the Women's Health Initiative, a large cohort study of over 95,000 post-menopausal women in America, whereas 'cynical hostility' (pessimism) was associated with an increased risk of total mortality and cancer-related mortality across the cohort (Tindle *et al.,* 2009). These features were independently associated with these important health outcomes in Black and in White women.

Neuroticism and mortality

People who demonstrate higher levels of hostility and anger are at greater risk of heart disease and atherosclerosis (Whiteman, 2006). Neurotic characteristics have been shown to be predictive of mortality and high neuroticism is associated with poor subjective health status and also predicts clinically-defined chronic illness (Hudek-Knezević and Kardum, 2009). High levels of neuroticism have been shown to be predictive of shorter survival in an elderly North American male sample (Mroczek and Spiro, 2007), while Nabi *et al.,* (2008a) reported that the personality feature 'neurotic hostility' (traits of negativism, resentment and hostility) clearly predicted all-cause and cause-specific mortality in a large French cohort. Furthermore, in the same study CHD-prone personality types (individuals who experience anger, aggression and lack of autonomy) and antisocial personality types (individuals who exhibit psychopathic, impulsive, rebellious and hostile behaviours) were also associated with cardiovascular and external causes of mortality (accidents and suicides) respectively (Nabi *et al.,* 2008a).

Personality and health behaviours

Morbidity and subjective wellbeing are also influenced by the interactions between personality and health promoting or health-harming behaviours. A review of 194 studies by Bogg and Roberts (2004) showed that high conscientiousness was consistently related to several health-promoting behaviours (e.g. exercise, healthy diet) and also to a few health-harming ones (e.g. alcohol abuse, fast driving). Smokers have also 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 (Terracciano and Costa, 2004). The relationship between personality and the increasingly important problem of obesity is unclear. High neuroticism has been associated both with being underweight (Terracciano *et al.,* 2009) and with obesity (Chapman *et al.,* 2008) in adults. In a study of over 1,000 adolescents, dimensions of personality were associated with fruit and vegetable consumption and sports-related physical activity (de Bruijn *et al.,* 2005): adolescents with higher fruit and vegetable consumption were more agreeable and more open to experience. In the same study, extraversion was also reported to be positively associated with sport-related physical activity, a finding in line with previous studies in adults (Rhodes *et al.,* 2003). Personality's influence on health behaviours may also impact how well individuals manage health and ill health. 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 (Flynn and Smith, 2007), while high extraversion predicts a greater propensity to access health care resources, which in turn may have significant implications for morbidity and mortality (Chapman *et al.,* 2009a). In a study of patients with end-stage renal disease, high conscientiousness predicted better adherence to medication (Christensen and Smith, 1995).

Personality and inflammation

While the influence of personality in these studies is likely to be mediated by positive or maladaptive health behaviours, an intriguing explanation for some personality-based differences in health may lie in inflammatory processes.

Higher levels of markers of inflammation are often consequences of harmful health behaviours such as smoking, poor diet and lack of exercise. Positive associations have recently been reported between hostility and emotional negativity and levels of interleukin-6 (IL-6) and C-reactive protein (CRP) (Coccaro, 2006; Marsland *et al.,* 2008). Individuals high in aggression are reported to be at an increased risk of inflammatory disease, a vulnerability which appears to be evident across the socioeconomic continuum (Marsland *et al.,* 2008). Similarly, CRP has been positively associated with higher scores on 'pessimistic worry' (a feature of neuroticism) in a large sample of 42 year old females (Henningsson *et al.,* 2008). High neuroticism and low conscientiousness have also been associated with increased levels of IL-6 and CRP (Sutin *et al.,* 2009). On the other hand, Chapman *et al.,* (2009b) found no relationship between neuroticism and IL-6 in a sample of 103 primary care patients who were predominantly of low socioeconomic status. Furthermore, Jonaissant *et al.,* (2010) reported a selective ethnicity effect whereby openness to experience was associated with levels of CRP in Black, but not White, subjects in their sample of community volunteers.

Personality and socioeconomic status

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. Low socioeconomic status is associated with high levels of neuroticism (Bosma *et al.,* 1999; Jonassaint *et al.,* 2011), low levels of conscientiousness (Jonassaint *et al.,* 2011), higher hostility (Kubzansky *et al.,* 1999) and depression (Harper *et al.,* 2002), the latter disposition reflecting lower mental wellbeing. Personality factors (such as hostility) have been found to be associated with lower socioeconomic status (as assessed by indicators of occupation, education and income) among adult men and women (Carroll *et al.,* 1997; Christensen *et al.,* 2004). In a large French cohort study, personality factors explained all-cause and cardiovascular mortality gradients observed for measures of adult socioeconomic position in men, but did not explain mortality in women (Nabi *et al.,* 2008b). However, in the UK Health and Lifestyle Survey women with

both high neuroticism and low socioeconomic status were found to be at an increased risk of cardiovascular mortality compared to women of average socioeconomic status, an association not explained by health behaviours or physiological variables (Hagger-Johnson *et al.,* 2012). In this study high neuroticism was reported to be a protective factor against cardiovascular mortality in women with high socioeconomic status.

Sense of coherence and health and wellbeing

The concept of Sense of Coherence (SoC) (Antonovsky, 1993) is of particular interest in this context because of its significant association both with mental wellbeing (Pallant and Lae, 2002) and socioeconomic status (Larsson and Kallenberg, 1996). SoC does not define a personality type but is rather a disposition which characterises the individual's confidence that their internal and external environments are comprehensible, manageable and meaningful (Antonovsky, 1993). High SoC is associated with lower levels of psychological morbidity, lower trait anxiety and better self-reported health status (Larsson and Kallenberg, 1996; Pallant and Lae, 2002; Eriksson and Lindstrom, 2007). Furthermore, high SoC has also been shown to be related to a lower rating of stress for given life events (Amirkhan and Greaves, 2003), to be a predictor of onset of depression (Sairenchi *et al.,* 2011) and to be related to less emotional distress and lower levels of anxiety (Hart *et al.,* 1991).

Biological ageing, telomere length and socioeconomic status

It is generally accepted that psychological stress leads to premature ageing and the earlier onset of disease. The evidence presented here has demonstrated links between disadvantaged socioeconomic circumstances, stress and indices of poor health, including risk factors for CHD and poor cognitive function. Researchers have tried to understand how 'stress gets under the skin' to give rise to this elevated disease risk. Access to resources, health behaviours and psychological characteristics explain some, although by no means all, of the socioeconomic gradient. One further mechanistic possibility put forward is that cardiovascular disease and cancers are in part age-related diseases, whereby socioeconomic disadvantage increases mortality risk by accelerating the ageing process (Batty *et al.,* 2009).

The exact mechanisms of how such stress exerts this effect, including whether stress accelerates ageing at a cellular level and how cellular ageing translates to the ageing of the individual, is the subject of much discussion. Recent research points to the crucial role of telomeres and telomerase in cellular ageing and potentially in disease. Telomeres are DNA-protein complexes that cap chromosomal ends, promoting chromosomal stability (Epel *et al.,* 2004). Telomeres shorten with age in all replicating somatic cells; therefore telomere dynamics (length, attrition) capture biological ageing above and beyond chronological ageing, such that shorter telomeres represent increased biological senescence. In a study of 58 healthy women, mothers to either a healthy child or chronically ill child, the mothers of ill children were found to have the highest levels of perceived stress and to have telomeres shorter on average by the equivalent of at least one decade of additional ageing compared to low stress women (Epel *et al.,* 2004), implicating shorter telomeres in the adverse sequelae of prolonged psychological stress.

The impact of socioeconomic status on telomere length

To date a small number of studies have considered the impact of socioeconomic adversity or status on telomere length. The evidence at present is inconsistent. Cherkas *et al.,* (2006) showed in a large cross-sectional study of female twins that lower socioeconomic status defined by occupational class was associated with shorter telomeres independent of chronological age, body mass, smoking and physical activity. Steptoe *et al.,* (2011) researching a cohort of healthy men and women in the Whitehall II study, found that low socioeconomic status, defined in terms of educational attainment but not current socioeconomic activity (income or employment grade) was associated with shortened telomere length, where the highest levels of telomerase activity was found in those in the lowest education group. A similar association between shorter telomere length and lower educational attainment, but not social class, has also been shown by Surtees *et al*., (2012) in female participants of the EPIC-Norfolk study. Likewise, in a study of older Chinese men, an association between higher socioeconomic status and shorter telomeres was reported (Woo *et al.,* 2009).

Other studies have failed to replicate these observations. No association has been reported by Harris *et al.,* (2006) in the Scottish 1921 Lothian Birth Cohort; by Adams *et al.,* (2007) in the Newcastle Thousand Families Study; by Kananen *et al.,* (2010) in the Finland Health 2000 cohort, or by Batty *et al.,* (2009) in the West of Scotland Coronary Prevention Study. In this latter study (of over 1,500 men), the largest cross-sectional study to examine the relationship to date, there was no evidence that any of four indices of socioeconomic status (educational attainment, employment status, area-based deprivation and physical stature) was robustly related to telomere length (Batty *et al.,* 2009).

The current balance of evidence does not, at present, provide clear support for a strong and consistent socioeconomic-telomere gradient. Further large scale research is required to confirm or refute this relationship.

Brain structure and socioeconomic status

The influence of the environment on brain development is keenly debated. The brain is the central organ mediating stress reactivity, coping, and recovery processes. It determines what individuals will experience as stressful, it orchestrates how individuals will cope with stressful experiences and it changes both functionally and structurally as a result of stressful experiences (McEwan and Gianaros, 2010). Within the brain, a distributed dynamic and plastic neural circuitry co-ordinates, monitors and calibrates behavioural and psychological stress response systems to meet the demands imposed by particular stressors (McEwan and Gianaros, 2011). Low socioeconomic status is often conceptualised as a condition that engenders several forms of chronic (unpredictable) stress and adverse environmental exposures which can be construed as a state of significant, ongoing threat processed by, and ultimately affecting, the brain. This has led to a substantial body of research on recognised stress-related pathways that might explain the socioeconomic status – illness gradient (Siegrist and Marmot, 2004). An anatomical and functional network of neural circuitry including the hippocampus, amygdala and prefrontal cortex is central to the co-ordination of cognition, experience

and behaviour with neuroendocrine, immune and autonomic functions adapting to meet environmental and psychosocial challenges (McEwan and Gianaros, 2011).

The impact of socioeconomic status on brain activity

Recent neuroimaging findings on twins have shown that a high degree of variance in human brain structural anatomy is explained by unique environmental factors (Kremen *et al.,* 2010; Eyler *et al.,* 2011). Hackman and Farah (2009) propose that socioeconomic status affects different neural and cognitive systems as they mature over time and highlight the importance of studying the effect of socioeconomic status on neural systems at sensitive periods of development. There is a strong body of evidence suggesting that neurocognitive function does not appear to be consistently affected by socioeconomic status. Research investigating the effect of low socioeconomic status has shown an effect on cognitive performance – particularly language and executive function (i.e. working memory, attention, problem solving, verbal reasoning, mental flexibility and multi-tasking) (Hackman *et al.,* 2010). Furthermore, in a recent study of healthy middle-aged adults the structural integrity of white matter tracts connecting brain regions followed a socioeconomic gradient, where individuals who completed more schooling, earned higher incomes and resided in more advantaged neighbourhoods exhibited increases in white matter tract integrity and architecture, relative to disadvantaged individuals (Gianaros *et al.,* 2012).

The brain also appears to be particularly sensitive to early life stress and relative social position (Mirescu *et al.,* 2004). For example, childhood socioeconomic position is reported to influence neural development of language and executive function (Evans *et al.,* 2009), of which the latter appears especially important in achieving positive life outcomes, despite adversity, in children and adolescents of low socioeconomic position. Furthermore, the neurobiological impact of poverty appears to be greater if poverty is experienced earlier rather than later in life. This is supported by study data and by twin studies suggesting that cognitive ability is almost entirely predicted by environmental factors at lower socioeconomic status

(Hackman *et al.,* 2010). There is currently a lack of quantitative neuroimaging studies exploring the neuroanatomical structures linking socioeconomic status to health outcomes. It has however been proposed that lower socioeconomic status could have a negative effect on brain volume. In cross-sectional studies subjectively reported lower socioeconomic status and higher levels of chronic life stress (assessed by the Perceived Stress Scale) were associated with reduced grey matter volume in the rostral area of the anterior cingulate cortex (Gianaros *et al.,* 2007a) and the hippocampus (Gianaros *et al.,* 2007b) – both regions of the brain which have been associated with stress related pathology and mood disorders.

Further research is required to investigate the significance of socioeconomic status on brain morphology and plasticity, grey and white matter volumes and the impact of chronic stress.

Conclusion

In conclusion, the evidence presented here is complex, multi-disciplinary and dimensional, and rapidly expanding. Nevertheless, it strongly and repeatedly demonstrates the significant impact of socioeconomic status and area level deprivation in creating and exacerbating ill health. This review further reinforces the evidence that people in poorer communities have poorer health and outcomes compared to those who live in more affluent areas, and explores some of the pathways through which this association is expressed.

This review – carried out across population-based and community studies, national and international research and investigations from varied scientific disciplines – further highlights the complex and multifaceted nature of the interactions between the social, psychological and biological determinants of ill health. Taken together, the breadth and diversity of the research considered makes the relative consistency of the findings notable.

3. Why study the impact of socioeconomic status on health in Glasgow?

Researchers have highlighted the existence of a so-called 'Scottish effect', a term used to describe the higher levels of poor health and mortality experienced in Scotland over and above that explained by socioeconomic status and known risk factors such as smoking, alcohol consumption and lack of physical activity (Hanlon *et al.,* 2005; McCartney *et al.,* 2012). Further evidence of this 'excess' mortality being concentrated in West Central Scotland has led to the more specific 'Glasgow effect' being proposed (Walsh *et al.,* 2010a).

Glasgow, Scotland provides an ideal setting for the investigation of longstanding health inequalities in a population. The health gap in Glasgow is widely reported, but understanding of its causes remains incomplete (Hanlon *et al.,* 2006). The city has a clear socioeconomic gradient within the conurbation with 41.6% of Scotland's most deprived populations residing in the city (SIMD, 2009). The city population is large, relatively stable, exhibits marked social gradients in physical and mental health and associated variation in mortality and morbidity with the poorest health concentrated in the poorest areas (Leon *et al.,* 2003; Hanlon *et al.,* 2005). At postcode sector level (average population 3,000-5,000 individuals), the difference in male life expectancy between the most and least deprived areas is 28.7 years (Hanlon *et al.,* 2006), and in these areas there is a seven-fold variation in levels of CHD mortality, and differences of a similar magnitude in psychiatric-related hospital admission rates (NHS Health Scotland, 2004).

The extent to which the poor health profile of Glasgow can be explained solely by socioeconomic factors is unclear. A recent study by Landy *et al.,* (2012) using Scottish Health Survey data (2008/9) considered behavioural and biological factors as potential explanations of this excess risk in Glasgow as compared to the rest of Scotland. Significant differences were observed in the Glasgow population for most mental and physical health outcomes, but not for adverse health behaviours. Adjustment for area and individual level socioeconomic characteristics explained the excess risk associated with

residents of Glasgow for nearly all outcomes; however significant excess risk remained for anxiety and heart attack (Landy *et al.,* 2012).

Glasgow's health in a UK context

However, within the UK, Glasgow is not alone in experiencing relatively high levels of poor health and deprivation, with the cities of Liverpool and Manchester, for example, also standing out in this regard. A recent study comparing rates of income deprivation and mortality in Glasgow, Liverpool and Manchester reported that although the deprivation profiles for the three cities were almost identical, premature deaths in Glasgow were more than 30% higher, with all deaths approximately 15% higher (Walsh *et al.,* 2010b). This 'excess' in mortality in Glasgow is seen across the population, for all ages (except the very young), in both males and females and in deprived and affluent neighbourhoods. Furthermore, it was reported that mortality is significantly higher in Glasgow for a number of causes directly associated with adverse health behaviours. The authors concluded by stating that while deprivation is a fundamental determinant of health and therefore an important driver of mortality, it is only one part of a complex picture and additional explanations for the higher levels of mortality in Glasgow are required.

One such proposed suggestion for the poorer health in Glasgow relates to the city's history of religious sectarianism. To investigate this specific hypothesis recent research has compared deprivation and mortality between Glasgow and Belfast, a similar post-industrial city, but with a considerably more pronounced sectarian divide (Graham *et al.,* 2012). While total levels of deprivation were higher in Glasgow than in Belfast (24.8% versus 22.4%), Belfast was more unequal in terms of the distribution of deprivation across the city. All-cause mortality in Glasgow was higher for all deaths under 65 years (27%) and for death at all ages (18%), for all causes of death except 'external causes' (drug and alcohol related deaths). The authors concluded that in assessing potential additional explanations for the 'Glasgow effect', religious sectarianism seems to be an unlikely candidate (Graham *et al.,* 2012).

Glasgow's health in an international context

An international study comparing the health and wellbeing outcome data of residents in socially contrasting neighbourhoods in Glasgow and in Hamilton, Canada, reported that although both cities display a clear socioeconomic gradient with respect to various measures of health and health behaviours, the residents of Hamilton, Canada were in general healthier than residents in the Glasgow neighbourhoods investigated (Wilson *et al.,* 2010). Neighbourhoods of low socioeconomic status in both cities were associated with higher likelihoods of smoking, obesity and physical inactivity. However these results must be interpreted with caution as a neighbourhood of low socioeconomic status in one country may not mean the same for health status, health behaviours and utilisation of health services as a low socioeconomic status neighbourhood in another country.

Health behaviours and the Glasgow population

Alcohol problems occur in all social groups but there is a marked social gradient in alcohol-related morbidity and mortality. There is growing concern regarding the over-consumption of alcohol and its effect on health. In Scotland 30% of men and 20% of women reported drinking over the weekly recommended amount in 2008 (Scottish Government, 2009). The 2008 NHS Greater Glasgow and Clyde Health and Wellbeing Survey reported that 43% of respondents from Glasgow city exceeded the weekly recommended amount of alcohol. Among women in Scotland, weekly levels of consumption are highest for those in managerial or professional households; whereas in Scottish men there is no consistent pattern by socioeconomic classification (Scottish Government, 2009). However, perhaps most strikingly, people from the most deprived areas of Scotland are six times more likely to be admitted to hospital with an alcohol-related diagnosis than people from the most affluent areas (ISD, 2009).

Smoking is also socially patterned – the prevalence being much higher in lower socioeconomic groups. Although rates are declining, the prevalence of cigarette smoking in Scotland is higher than in other parts of the UK and the problem is particularly serious in Glasgow, with 34% of the adult population

smoking compared to a national average of 25% (Glasgow Community Planning Partnership, 2009). High rates have been implicated in the city's poor health record with an estimated one in five deaths attributable to the habit (Whyte *et al.,* 2007). In some of the most deprived parts of Glasgow more than 40% of adults currently smoke, compared to only 13% in the more affluent parts (Scottish Household Survey, 2007). Grey and Leyland (2009) recently confirmed the social patterning of high levels of smoking and socioeconomic position in Glasgow following an analysis of smoking status data in three consecutive cross-sectional Scottish Health Surveys.

The prevalence of obesity is increasing in industrialised countries. The prevalence of obesity and overweight in Scotland continues to rise. In 2008, 26.8% of adults in Scotland were obese and 61.5% were overweight. For children the corresponding rates were 15.1% and 31.7% respectively (Scottish Government, 2010). Obesity prevalence does not differ significantly across the socioeconomic gradient among men but rises steadily and significantly with lower socioeconomic status in women. This increasing prevalence of overweight and obesity has been linked to increasing physical inactivity and changes in eating patterns. International and UK observational studies have shown that dietary patterns and obesity rates vary between neighbourhoods, and that living in a low income or deprived area is independently associated with the prevalence of obesity and the consumption of a poor diet (Cummins and Macintyre, 2006; Macdonald *et al.,* 2007). Gray and Leyland (2008) also confirmed that the association between unhealthy eating and deprivation accounted for the tendency of people in Glasgow to have poorer diets.

Improving Glasgow's health therefore remains inextricably linked to tackling the problems associated with deprivation and poverty.

4. Study aims and hypotheses

The pSoBid study was an exploratory pilot for a larger scale investigation of the genotypic and phenotypic determinants of ill health in deprived communities. The overall study aim was to determine the extent to which the linked syndrome of central obesity/chronic inflammation explains the social gradient in vascular disease, and whether the syndrome is associated with alterations in the mental state.

The hypotheses to be tested were summarised as follows:

> *"Socioeconomic gradients in health are influenced by adverse environmental conditions, work, relationships, community, knowledge and practise of health-promoting or health-damaging behaviours. Hormonal and metabolic responses to the above stressors, while protective in the short term, in the long term causes adverse changes (e.g. hyperplasia of visceral adipose tissue and central obesity) that leads to chronic disease (e.g. atherosclerosis). Further consequences are a heightened response to stress and a tendency towards depression and altered mental function."*

The study set out to:

- examine the associations between classical and novel risk factors and health outcomes, and to further examine the interactions between these determinants
- assess the extent to which the gap in health outcomes can be explained by these factors
- yield insights into new approaches which might help address Glasgow's health record.

Research questions

The following questions were addressed through the research:

1) do deprived sections of the population display an increased prevalence of features of a condition termed metabolic syndrome (i.e. central obesity and

2) do deprived groups exhibit higher levels of serum endotoxin, revealing increased exposure to bacterial pathogens (as a result for example of damp housing) compared to affluent groups?
3) do deprived groups differ from affluent ones in psychological profile (affective state and cognition) and to what extent can this be related to the presence of the central obesity/insulin resistance/chronic inflammation syndrome?
4) is sub-clinical atherosclerosis (as detected by carotid ultrasound analysis) more prevalent in deprived groups? To what extent is the prevalence explained by classical risk factors (smoking, blood pressure, cholesterol) and to what extent is it related to the presence of metabolic syndrome?

In addition, the study sought to ascertain the feasibility of a large-scale population study by determining: the response rate, drop out rate, time taken by respondents to complete the questionnaires and the visits, any discomfort experienced by respondents in relation to the various medical assessments, numbers volunteering for Magnetic Resonance Imaging (MRI) scanning, and how the above were affected by age group, sex and deprivation category.

5. Methods

Ethical approval and confidentiality

Ethical approval for the study was obtained from Glasgow Royal Infirmary Research ethics committee. Only anonymised data were obtained from General Practice Administration System for Scotland (GPASS) records on practice computers. The Health Board's Caldicott Guardian approved the study process and, with the approval of the ethics committee, general practitioners (GPs) consented to the use of Community Health Index (CHI) and anonymised GPASS data. The Health Information and Technology (HIT) section of the Greater Glasgow Health Board (GGHB) was responsible for sample selection and assignment of a study number to each subject (from 0001 to 3,600). In all study records (electronic and paper), subjects were identified only by their study number. Information linking their identity (name, address, general practitioner) to their study number was held securely by the Glasgow Centre for Population Health.

Study population

Selection of subjects was based on the Scottish Index of Multiple Deprivation (SIMD) (SIMD, 2004) which ranks small areas of Scotland on the basis of multiple deprivation indicators (multiple indicators across six domains, namely: income (e.g. number of adults and children in Income Support households); 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 aged 16 years and over not in education); geographic access and telecommunications (e.g. drive time access to GP, supermarket and primary school); housing (e.g. number of persons in households which are overcrowded, number of persons in households which are without central heating) allowing identification of the least and most deprived areas in the Greater Glasgow Health Board area in 2005.

Five GP practices with the highest percentage of patients aged 35-64 years living in areas classified as being in the bottom 5% of SIMD (most deprived (MD)) 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 (least deprived (LD)) also agreed to participate (location of recruited GP practices shown in Appendix 1). At the time of sampling 31.4% of the Glasgow population resided in the bottom 5% of the 2004 SIMD and 6% resided in the top 20% (only 1.4% of the Glasgow population resided in the top 5% of the 2004 SIMD).

HIT generated a target population of 21,672 people from the GP lists of these ten practices. From this target population 12 groups of 300 each were selected according to strata defined by the combination of deprivation category, sex and age group (35-44, 45-54, and 55-64 years) giving a total sampling frame of 3,600 subjects. As the study progressed, over-sampling of subjects from the most deprived group was required (due to the lower response rate) and the HIT section was approached to select randomly further potential subjects from the target population. GPs were able to exclude persons from the sample who had recently died or who had a terminal illness. Due to the nature of the psychological questionnaires and cognitive assessment, only those who understood and spoke English were invited to participate in this pilot study. The eligibility of subjects was checked by GPs and Practice Managers before letters were sent.

If the participant had had an illness which was likely to increase C-reactive protein (CRP) levels acutely (e.g. urinary tract infection, upper respiratory tract infection) during the two weeks prior to his/her appointment this was recorded but assessments proceeded on the scheduled date.

Recruitment procedure

Invitation letters to selected subjects were sent in batches of 150 every two weeks from December 2005 to January 2007. 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. If there was no response after two weeks, a reminder was sent. Subjects who agreed to receive further information about the study were sent the pSoBid participant information booklet. The Research Nurse contacted those who received this booklet, and if after reading it they decided to participate in the study, they were invited to come for the first visit at their GP's clinic on a mutually agreed day and time. This process continued until approximately equal numbers were recruited for the 12 groups (see Appendix 2).

From the sampling frame of 3,600 subjects a total of 2,712 invitations were issued to recruit a cohort of 700 (25.8%) participants. Out of the 2,712 invitations sent, 812 (29.9%) people declined to participate and 1,200 (44.3%) did not respond (Appendix 3). A total of 666 subjects were recruited to the study (giving an overall response rate of 24.6%), 342 were drawn from the least deprived (LD) areas and 324 from the most deprived (MD). There were 171 male and 171 female participants in the LD group and 168 females and 156 males in the MD group. The response rate was 33.9% for LD and 19.0% for MD participants, and response rate by age group was 31.7% in 35-44 year olds, 33.3% in 45-54 year olds and 35% in 55-64 year olds.

Study protocol

The study comprised two visits, each lasting about 90 minutes to two hours. Arrangements were made for taxi transfers to and from the participants' homes. Posters advertising the study were displayed in GP clinics and also in local community centres and libraries. Two free telephone numbers were set up: one in the co-ordinating centre (GCPH) and one in the Glasgow Royal Infirmary (GRI) where the research nurses were based.

At Visit 1 the study was explained to participants and informed consent obtained. The visit involved completion of lifestyle and psychology questionnaires, assessment of health status and measurement of blood pressure, pulse rate and indices of obesity (height, weight, hip, waist and mid-thigh circumference). Lung function was measured by Forced Expiratory Volume in one second (FEV1) and Forced Vital Capacity (FVC). An

appointment was made for the second visit (to take place in a morning after a period of fasting) to be carried out at the GRI approximately two weeks later.

At Visit 2, a (10-12 hour) fasting blood sample was taken to measure cholesterol, triglycerides, very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL), markers of diabetes and obesity (glucose, insulin, leptin and adiponectin), markers of inflammation and clotting (C-reactive protein (CRP); inerleukin-6 (IL-6); fibrinogen, D dimer; tissue plasminogen activator (tPA) antigen), and markers of endothelial dysfunction (intercellular adhesion molecule (ICAM); von Willebrand Factor (vWF)). Then, after breakfast, participants completed further psychological and cognitive function tests, and underwent ultrasound assessment of their carotid intima-media thickness and plaque count. Previous research has shown an association between eating breakfast and mood and performance, with the effects due in part to experimental manipulation of the normal morning routine (Smith and Kendrick, 1992; Smith *et al.,* 1999). In this study, as far as possible breakfast was provided according to an individual's normal routine (or abstinence, if relevant), so that any effects on performance and affective state would be those observed in real life.

Before each visit the participants were contacted by telephone on the previous day to confirm their attendance and to ensure that the taxi arrangements were in place. At the end of the study all participants were sent a letter thanking them for their participation in the study. After each visit participants were asked to complete a feedback form detailing their opinion of the study and their experiences.

Lifestyle questionnaire

The lifestyle questionnaire was completed at Visit 1 and had 13 sections including basic demographic data, past and present health status, current medications, oral health, smoking history, alcohol intake, dietary intake, physical activity levels and questions relating to early life home circumstances and childhood and adult (current) socioeconomic status (see Appendix 4).

Questions about physical activity at work and in recreation were included in the lifestyle questionnaire, allowing participants to be classified as inactive, moderately inactive, moderately active or active using a previously validated protocol (Khaw *et al.,* 2006). 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 or more), what they smoked, what age they started and stopped smoking if applicable, and whether their parents smoked. Participants were also asked how often, on average, they consumed a range of food categories. 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. An overall fruit and vegetable diet score was calculated by aggregating responses to four questions from the food frequency questionnaire, relating to: fruit and vegetable intake (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.

Biochemical analysis

All blood samples were separated and frozen at -80^{o}C within one hour of venepuncture, except for samples for cholesterol, triglycerides, low density lipoprotein (LDL), high density lipoprotein (HDL), high sensitivity C-reactive protein (CRP) and glucose, which were processed immediately. Cholesterol and triglyceride were determined by enzymatic colorimetric assays on a Roche 917 analyser (Roche Diagnostics Ltd., Burgess Hill, UK). Lipid fractions were measured using ultracentrifugation and precipitation methods (National Heart and Lung Institute, 1975). Glucose was measured by hexokinase/glucose-6-phosphate dehydrogenase assay on an Abbott c8000 analyser (Abbott Diagnostics, Maidenhead, UK). Insulin was measured by a sandwich Enzyme-Linked Immunosorbent Assay (ELISA) (Mercodia AB, Uppsala, Sweden). High sensitivity C-reactive protein (CRP) was measured by an immunoturbidimetric assay (Roche Diagnostics Ltd., Burgess Hill, UK). Interleukin-6 (IL-6) and intercellular adhesion molecule-1 (ICAM) were measured by sandwich ELISA (R&D Systems Europe Ltd., Abingdon, United

Kingdom). von Willebrand Factor (vWF) was measured using an in-house ELISA, employing rabbit anti-human polyclonal antibodies (DAKO plc, High Wycombe, UK).

Psychological and cognitive assessment

Participants completed a range of psychology and cognitive questionnaires at both visits. The number and duration of the psychological and cognitive tests were constrained by the time demands that might reasonably be made upon participants.

Assessment of personality and psychological ability

A series of assessments provided indices of personality and individual differences in self-esteem. Assessment involved self-completion of the short form of the Eysenck Personality Questionnaire (EPQ:S) (Eysenck and Eysenck, 1991) and the Rosenberg Self-Esteem Scale (RSS) (Johnston *et al.,* 1995a), General Health Questionnaire-28 (GHQ-28) (Goldberg, 1972), the Generalised Self-Efficacy Scale (GSS) (Johnston *et al.,* 1995b), the Sense of Coherence Scale (SoC) (Antonovsky, 1993) and the Beck Hopelessness Scale (BHS) (Beck and Steer, 1999).

Cognitive function tests

A series of baseline tests were used to assess the principal cognitive domains of executive function, reaction and decision processing, and memory. These tests were *(a) for Executive function:* the Trail Making Test (TMT) (parts A and B), which assesses visuo-motor co-ordination and the ability to alternate responses indicative of higher-order changing of mental set (Reitan and Wolfson, 1995); and the Stroop test (Trenerry *et al.,* 1989) which assesses ability to inhibit dominant and over-learned responses; *(b) for Decision Making*: the Choice Reaction Time test (CRT) in which the response time was measured in milliseconds by a computerised system (Hope *et al.,* 1998) and which is sensitive to a range of factors affecting motor and decision speed (Deary *et al.,* 2001) and *(c) for Memory:* the Auditory Verbal Learning Test (AVLT), which assesses speed of learning, recall and recognition performance (Taylor, 1995).

Cognitive ability was estimated from the National Adult Reading Test (NART-2) (Nelson and Willison, 1991) which provides a proxy measure of 'IQ' (Crawford *et al.,* 2001).

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 included: number of siblings, whether or not their parents owned their home, father's occupational category, whether or not their parents owned a car, and household overcrowding (number of occupants in house divided by number of rooms). Father's occupational category, a measure of social class based on occupation, was classified using the Registrar General's Social Classification (RGSC). For this, participants were asked to recall what their father's occupation was when they were 11 years old. The Registrar General's social classes are described as: 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 combined and compared with merged manual social classes (IIIM, IV and V).

Participants' current (i.e. adult) socioeconomic status was assessed from self-reported information on average household income, years in education and educational achievement, and home ownership.

Carotid artery intima-media thickness (cIMT) and identification of carotid artery plaques

Measurement of the intima-media thickness (IMT) of the carotid artery by high resolution ultrasound is now a widely accepted, non-invasive, surrogate measure of atherosclerosis and a reliable indicator of future risk of a major coronary event (de Groot *et al.,* 1998; John *et al.,* 2004). Carotid intima-media thickness (cIMT) provides a suitable continuous outcome measure for atherosclerosis, enabling association studies to be performed on fewer numbers. Ultrasound examination of the carotid arteries also allows presence and number of plaques to be determined (van der Meer *et al.,* 2004; Touboul

et al., 2004). Carotid plaque count has previously been found to be a predictor of myocardial infarction (van der Meer *et al.,* 2004) and stroke (Hollander *et al.,* 2002). The carotid ultrasound examination lasted 20-30 minutes. Doppler velocity in right and left internal carotid arteries was recorded in order to identify any significant internal carotid artery stenosis. Images of the distal 1cm of the common carotid artery, the carotid bulb and the proximal internal carotid artery were recorded on the left and right side, and intima-media thickness of the far wall of the artery determined using the software package e-Track. The number of carotid plaques at each of the six sites was determined using published procedures (van der Meer *et al.,* 2004). M-mode ultrasound of the distal common carotid artery was recorded to assess arterial stiffness. Reading of the scans was performed offline by a reader who was blinded to the identity of the participants.

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). Scans were analysed using the e-Track software provided by the Department of Vascular Medicine and Physiology, Academic Medical Centre, Amsterdam, The Netherlands. cIMT was measured on the far wall of each arterial segment, averaged along a 1cm length. The number of plaques per subject was counted (Touboul *et al.,* 2007) with a plaque being defined as a focal structure encroaching into the arterial lumen of at least 0.5mm or 50% of the surrounding IMT value, or demonstrating a thickness >1.5mm as measured from media-adventitia interface to intima-lumen interface (van der Meer *et al.,* 2004). Reader reproducibility was assessed by repeat reading of a proportion of the scans, and was consistently within the predefined certification limits of a coefficient of variation (CV) of $\leq$5%.

Neuroimaging and Magnetic Resonance Imaging (MRI)

Male study participants were asked if they would be interested in participating in MRI scanning (Visit 3). From a total of 327 male participants, 140 volunteered, of which 42 were randomly selected, stratified by age group and deprivation category – 21 males from LD participant group; 21 males from MD participant group. MRI scans took place from August 2007 to December 2007.

Image acquisition

The exclusion criteria for this neuroimaging study included: history of head injury, stroke or neurological disorder; and implants contraindicated in MRI. All MRI scans were acquired using a GE Medical systems, 3T Sigma Excite HD system (Milwaukee, WI, USA). An axial 3D T1-weighted IR-FSPGR was acquired with the following imaging parameters: TR = 6.8ms; TE = 1.5ms, Inversion Preparation time = 500ms; Flip angle=12º; FOV = 26cm; Phase FOV = 70%; matrix: 320 x 320; Bandwidth 31.25kHz; Slab thickness = 1mm. The acquisition time for this scan was 8 minutes 54 seconds. This acquisition sequence with high resolution in all three imaging planes and good white matter to grey matter contrast facilitates well the tissue class segmentation that is necessary for voxel based morphometry (VBM) to be applied.

Voxel based morphometry

Preprocessing was performed to optimise the data for the subsequent analysis. The N3 inhomogeneity correction, using optimised parameters for 3T data, was applied to the T1-weighted 3D acquisition (Boyes *et al.,* 2008; Zheng *et al.,* 2009). Dartel-VBM was performed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/) and MATLAB v7.80 (Mathworks, Natick, MA, USA: http://www.mathworks.com/products/matlab/). The 3D T1-weighted MR images were segmented into the grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) tissue classes by the standard unified segmentation model within SPM5 (Ashburner and Friston, 2005). A GM study specific template was then created using a fast diffeomorphic image registration algorithm (DARTEL) (Ashburner, 2007). The templates were then affine registered to the tissue probability maps of the Montreal Neurological Institute (MNI) (http://www.mni.mcgill.ca). Non-linear warping of the GM images was then performed to the DARTEL GM template in MNI space. Subject images were modulated to preserve the relative GM volumes through the spatial normalisation procedure. Finally images were smoothed with an 8mm full width at half maximum Gaussian kernel. The normalised, modulated and smoothed GM images were added to a statistical model to assess volume differences between the LD and MD groups.

Freesurfer volume extraction

Freesurfer (FS) is a widely used MRI image analysis package (http://surfer.nmr.mgh.harvard.edu/). The component of the Freesurfer processing pipeline of most interest here was the subcortical structure segmentation (Fischl *et al.,* 2004). The aim was to independently verify any major volume differences observed using the VBM analysis. Moreover, FS quantifies the segmented volume of the grey and white matter of the cerebellum, giving the ability to measure volume differences and thus complementing the VBM results which show regions of statistically significant volume difference. The FS image processing pipeline ran automatically though it was necessary to visually inspect and correct the data at critical points in the processing pipeline in order to avoid errors permeating through the subsequent analyses.

Telomere length determination

DNA was extracted from peripheral blood leukocytes following standard procedures. Telomere lengths in the DNA samples were determined by Q-PCR, following the method of Cawthon (Cawthon, 2002; Harris *et al.,* 2006; Carrero *et al.,* 2008). Telomere length determination was performed blindly using a Roche Light Cycler LC480. Telomere length analyses were performed in triplicate for each sample, using a single-copy gene amplicon primer set (acidic ribosomal phosphoprotein, 36B4) and a telomere-specific amplicon primer set (Koppelstaetter *et al.,* 2008). Quality control parameters employed for the amplifications comprised using a cut off of 0.15 for the standard deviation (SD) of the threshold cycle (Ct) for sample replicates. At a SD above 0.15 the sample was reanalysed. The average SD across plates was 0.05.

Relative telomere length was estimated from Ct scores using the comparative Ct method after confirming that the telomere and control gene assays yielded similar amplification efficiencies. This method determines the ratio of telomere repeat copy number to single copy gene number (T/S) ratio in experimental samples relative to a control sample DNA which had mean terminal restriction fragment (TFR) lengths determined previously by standard Southern blotting procedures. This normalised T/S ratio was used as the estimate of relative

telomere length (Relative T/S). The inter-assay variation was assessed by comparing the relative telomere estimates (T/S ratio) across assays for the positive controls, which were assayed on every assay plate. The average inter assay coefficient of variance was 0.3%.

Global DNA methylation determination

DNA was extracted from peripheral blood leukocytes for 239 individuals for whom sufficient quantity and quality DNA was available for analysis, using Maxwell® 16 System and Maxwell® 16 Blood DNA Purification kit (Promega). Quantitative and qualitative DNA analyses were performed using Nanodrop. DNA was analysed for global methylation using Methylamp TM Global DNA Methylation Quantification Ultra kit (Epigentek, USA) according to the manufacturer's instructions. The capture antibody in this kit binds to 5-methylcytosine, thus measuring total DNA methylation level as a percentage of total DNA present in the sample. Hence it measures global DNA content, not specific sites, patterns or methylation types, as other systems do. Samples were run in duplicate and a standard curve was run in triplicate as were the positive and negative controls. Inter-assay precision (%CV) was <8%, intra-assay %CV was <6.5%. Briefly, the plate was coated with 200ng of DNA (100ng/ml) per well and dried at 378°C for 40 minutes followed by incubation at 608°C until the solution evaporated and wells were dried. Simultaneously, the standard curve (range 0.2-20ng of methylated DNA) and negative control DNA were prepared for each plate. The amount of methylated DNA (pg) was determined according to the manufacturer's instruction; additionally, %DNA methylation was calculated.

GPASS extraction process

GPASS was used to examine the characteristics of those who were invited to participate in the study. Eight of the ten GP practices (four in the LD area, four in the MD area) selected for the study used GPASS to record their routine data. Anonymised data were collected on smoking status and current prescription for statins, aspirin, antihypertensives, antidepressants and anti-diabetic drugs (as evidence of the prevalence of chronic disease). Data were

collected separately for those who attended visit 1 (Group 1), those who declined to attend (Group 2) and non-respondents to the invitation (Group 3). Non-participants (Group 4) were defined as the combination of groups 2 and 3.

Statistical power and analysis

Sample size in the LD and MD groups was estimated on the assumption that 90% would attend both visits and have CRP measured and that a maximum of 10% would not have good quality intima-media thickness measurements. The power calculations were based on perceived clinically meaningful differences and assumed a 1.1mg/L standard deviation for the natural logarithm of CRP measurements (Bots *et al.,* 1997) and a 0.163mm standard deviation for carotid intima-media thickness (Lawlor *et al.,* 2004). Power calculations indicated that a sample size of 350 per group would provide 84% power to detect a 30% difference in mean CRP levels and 82% power to detect a 0.04mm difference in mean carotid intima-media thickness.

Descriptive statistics are presented as mean (SD) for continuous variables and count (%) for categorical outcomes. Variables with positively skewed distributions (CRP, IL-6, ICAM, Choice Reaction Time) are described by geometric mean and log-transformation was used in regression analysis. For comparisons of population characteristics between deprivation groups, analysis of covariance is used for continuous variables and logistic regression analyses for binary responses. Absolute differences between least versus most deprived categories, point estimates, 95% confidence intervals and P-values were calculated for all variables. Analyses were conducted in SAS v9.1 and R v2.8 (The R Development Core Team, 2009).

For each area of study an appropriate approach was taken to statistical analysis. Full details are presented within each of the published journal articles.

6. Results and key published findings

This section outlines the study findings to date across a number of areas of interest. Results are presented as a series of abstracts from published journal articles across the psychological, social and biological determinants of health as investigated by the study team. The full reference (including weblink) for each article is provided here and also in Chapter 13 of this report.

Results presented herein include:

a) Presentation of the full study protocol and discussion of the study response rate and a comparison of study participants and non-participants;

b) Study investigations into *biological* determinants of health, namely differences in atherosclerosis according to area level deprivation, the associations between circulating concentrations of 25-hydroxyvitamin D and socioeconomic status, carotid artery plaques and carotid intima-media thickness, the association between household income, diet and inflammation, and telomere attrition, the associations between socioeconomic status and epigenetic differences, and the association between soluble interleukin cytokine receptors (sST2) with diabetes and cardiovascular risk factors;

c) An investigation into the *social* determinants of health, specifically the impact of early life adversity on adult health outcomes including chronic inflammation, lung function and cognitive performance; and the association between early life socioeconomic status, chronic physiological stress and concentrations of hippocampal N-acetyl aspirate (NAA).

d) Study investigations into the *psychological* determinants of health, namely interaction of personality traits with social deprivation in determining mental wellbeing and health behaviours, and the associations between personality, socioeconomic status and inflammation.

pSoBid *study protocol*

Psychological, social and biological determinants of ill health (pSoBid): Study Protocol of a population-based study

Yoga N Velupillai, Chris J Packard, G David Batty, Vladimir Bezlyak, Harry Burns, Jonathan Cavanagh, Kevin Deans, Ian Ford, Agnes McGinty, Keith Millar, Naveed Sattar, Paul Shiels, Carol Tannahill.

Abstract

Background: Disadvantaged communities suffer higher levels of physical and mental ill health than more advantaged communities. The purpose of the present study was to examine the psychosocial, behavioural and biological determinants of ill health within population groups in Glasgow that differed in socioeconomic status and in their propensity to develop chronic disease especially coronary heart disease and Type 2 diabetes mellitus.

Methods: Participants were selected at random from areas known to be at the extremes of the socioeconomic continuum in Glasgow. Within the categories of least deprived and most deprived, recruitment was stratified by sex and age to achieve an overall sample containing approximately equal numbers of males and females and an even distribution across the age categories 35-44, 45-54 and 55-64 years. Individuals were invited by letter to attend for assessment of their medical history, risk factor status, cognitive function and psychological profile, morbidity, and carotid intima-media thickness and plaque count as indices of atherosclerosis. Anonymised data on study subjects were collected from the General Practice Administration System for Scotland to analyse characteristics of participants and non-participants.

Results: 700 subjects were recruited. The response (active participants per 100 invitation letters) in the least deprived group was 35.1% and in the most deprived group was 20.3%. Lowest response was seen in young males (least deprived 22.4% and most deprived 14.1%).

Conclusions: This cross-sectional study recruited the planned sample of subjects from least deprived and most deprived areas within Glasgow. As evident in other studies response differed between the most and least deprived areas. This study brought together researchers/academics from diverse disciplines to build a more sophisticated understanding of the determinants of health inequalities than can be achieved through unidisciplinary approaches. Future analyses will enable an understanding of the relationships between the different types of measure, and of the pathways that link poverty, biology, behaviour and psychology and lead to health inequalities.

Reference:

Psychological, social and biological determinants of ill health (pSoBid): study protocol of a population-based study. Velupillai YN *et al. BMC Public Health* 2008;8:126.

Available at: www.biomedcentral.com/1471-2458/8/126

pSoBid investigations into the ***biological***

determinants of ill health

Area-based socioeconomic differentials in atherosclerosis are not explained by traditional or emerging risk factors in the Psychosocial and Biological Determinants of Ill-health (pSoBid) study – a cross-sectional, population-based study

Kevin A Deans, Vladimir Bezlyak, Ian Ford, G David Batty, Harry Burns, Jonathan Cavanagh, Eric de Groot, Agnes McGinty, Keith Millar, Paul G Shiels, Carol Tannahill, Yoga N Velupillai, Naveed Sattar, Chris J Packard.

Abstract

Objectives*:* To examine the relation between area level social deprivation and ultrasound markers of atherosclerosis (common carotid intima-media thickness and plaque score), and to determine whether any differences can be explained by "classic" (currently recognised) or "emerging" (novel) cardiovascular risk factors.

Design*:* Cross sectional, population based study.

Setting*:* Setting NHS Greater Glasgow Health Board area.

Participants: 666 participants were selected on the basis of how their area ranked in the Scottish Index of Multiple Deprivation 2004. Approximately equal numbers of participants from the most deprived areas and the least deprived areas were included, as well as equal numbers of men and women and equal numbers of participants from each age group studied (35-44, 45-54, and 55-64 years).

Main outcome measures*:* Carotid intima-media thickness and plaque score, as detected by ultrasound.

Results*:* The mean age and sex adjusted intima-media thickness was significantly higher in participants from the most deprived areas than in those from the least deprived areas (0.70 mm (standard deviation (SD) 0.16 mm) v 0.68mm (SD 0.12 mm); P=0.015). On subgroup analysis, however, this difference was only apparent in the highest age tertile in men (56.3-66.5 years). The difference in unadjusted mean plaque score between participants from the most deprived and those from the least deprived areas was more striking than the difference in intima media thickness (least deprived 1.0 (SD 1.5) v most deprived 1.7 (SD 2.0); P<0.0001). In addition, a significant difference in plaque score was apparent in the two highest age tertiles in men (46.8-56.2 years and 56.3-66.5 years; P=0.0073 and P<0.001) and the highest age tertile in women (56.3-66.5 years; P<0.001). The difference in intima-media thickness between most deprived and least deprived males remained significant after adjustment for classic risk factors, emerging risk factors, and individual level markers of socioeconomic status (P=0.010). Adjustment for classic risk factors and emerging cardiovascular risk factors, either alone or in combination, did not abolish the deprivation based difference in plaque presence (as a binary measure; adjusted odds ratio of 1.73, 95% confidence interval 1.07to 2.82). However, adjustment for classic risk factors and individual level markers of early life socioeconomic status

abolished the difference in plaque presence between the most deprived and the least deprived individuals(adjusted odds ratio 0.94, 95% CI 0.54 to 1.65; P=0.84).

***Conclusions**:* Deprivation is associated with increased carotid plaque score and carotid intima-media thickness. The association of deprivation with atherosclerosis is multifactorial and not adequately explained by classic or emerging risk factors.

***Reference**:*
Differences in atherosclerosis according to area level socioeconomic deprivation: cross sectional, population based study. Deans KA *et al., BMJ* 2009;339:b4170.
Available at: www.bmj.com/content/339/bmj.b4170

Accelerated telomere attrition is associated with relative household income, diet and inflammation in the pSoBid cohort.

Paul G Shiels, Liane M McGlynn, Alan MacIntyre, Paul CD Johnson, G David Batty, Harry Burns, Jonathan Cavanagh, Kevin A Deans, Ian Ford, Alex McConnachie, Agnes McGinty, Jennifer S McLean, Keith Millar, Naveed Sattar, Carol Tannahill, Yoga N Velupillai, Chris J Packard.

Abstract

Background*:* It has previously been hypothesized that lower socio-economic status can accelerate biological ageing, and predispose to early onset of disease. This study investigated the association of socio-economic and lifestyle factors, as well as traditional and novel risk factors, with biological-ageing, as measured by telomere length, in a Glasgow based cohort that included individuals with extreme socio-economic differences.

Methods*:* A total of 382 blood samples from the pSoBid study were available for telomere analysis. For each participant data was available for socio-economic status factors, biochemical parameters and dietary intake. Statistical analyses were undertaken to investigate the association between telomere lengths and these aforementioned parameters.

Results*:* The rate of age-related telomere attrition was significantly associated with low relative income, housing tenure and poor diet. Notably, telomere length was positively associated with LDL and total cholesterol levels, but inversely correlated to circulating IL-6.

Conclusions*:* These data suggest lower socio-economic status and poor diet are relevant to accelerated biological ageing. They also suggest potential associations between elevated circulating IL-6, a measure known to predict cardiovascular disease and diabetes, with biological ageing. These observations require further study to tease out potential mechanistic links.

Reference*:*

Accelerated telomere attrition is associated with relative household income, diet and inflammation in the pSoBid cohort. Shiels PG *et al. PLoS ONE* 2011;6(7):e22521.

Available at:

www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0022521

Socio-economic status is associated with epigenetic differences in the pSoBid cohort

Dagmara McGuinness, Liane M McGlynn, Paul CD Johnson, Alan MacIntyre, G David Batty, Harry Burns, Jonathan Cavanagh, Kevin A Deans, Ian Ford, Alex McConnachie, Agnes McGinty, Jennifer S McLean, Keith Millar, Chris J Packard, Naveed A Sattar, Carol Tannahill, Yoga N Velupillai, Paul G Shiels.

Abstract

Background*:* Epigenetic programming and epigenetic mechanisms driven by environmental factors are thought to play an important role in human health and ageing. Global DNA methylation has been postulated as an epigenetic marker for epidemiological studies as it is reflective of changes in gene expression linked to disease. How epigenetic mechanisms are affected by psychological, sociological and biological determinants of health still remains unclear. The aim of this study was to investigate the relationship between socio-economic and lifestyle factors and epigenetic status, as measured by global DNA methylation content, in the pSoBid cohort, which is characterized by an extreme socio-economic and health gradient.

Methods*:* DNA was extracted from peripheral blood leukocytes using the Maxwell_ 16 System and Maxwell_ 16 Blood DNA Purification kit (Promega, UK). Global DNA methylation was assessed using Methylamp TM Global DNA Methylation Quantification Ultra kit (Epigentek, USA). Associations between global DNA methylation and socio-economic and lifestyle factors were investigated in linear regression models.

Results*:* Global DNA hypomethylation was observed in the most socio-economically deprived subjects. Job status demonstrated a similar relationship, with manual workers having 24% lower DNA methylation content than non-manual. Additionally, associations were found between global DNA methylation content and biomarkers of cardiovascular disease (CVD) and inflammation, including fibrinogen and interleukin-6 (IL-6), after adjustment for socio-economic factors.

Conclusions*:* This study has indicated an association between epigenetic status and socio-economic status (SES). This relationship has direct implications for population health and is reflected in further associations between global DNA methylation content and emerging biomarkers of CVD.

Reference*:*

Socio-economic status is associated with epigenetic differences in the pSoBid cohort. McGuiness D *et al., International Journal of Epidemiology* 2012;41(1):151-160.
Available at: http://ije.oxfordjournals.org/cgi/content/abstract/dyr215v1

25-hydroxyvitamin D is lower in deprived groups, but is not associated with carotid intima media thickness or plaques: results from pSoBid

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Abstract

Objective*:* The association of the circulating serum vitamin D metabolite 25-hydroxyvitamin D (25OHD) with atherosclerotic burden is unclear, with previous studies reporting disparate results.

Method*:* Psychological, social and biological determinants of ill health (pSoBid) is a study of participants aged 35-64 years from Glasgow who live at extremes of the socioeconomic spectrum. Vitamin D deficiency was defined as 25OHD <25nmol/L, as per convention. Cross-sectional associations between circulating 25OHD concentrations and a range of socioeconomic, lifestyle, and biochemistry factors, as well as carotid intima media thickness (cIMT) and plaque presence were assessed in 625 participants.

Results*:* Geometric mean levels of circulating 25OHD were higher among the least deprived (45.6 nmol/L, 1-SD range 24.4-85.5) versus most deprived (34.2 nmol/L, 1-SD range 16.9-69.2; p<0.0001). In the least deprived group 15% were “deficient” in circulating 25OHD versus 30.8% in the most deprived (χ^2 p<0.0001). Log 25OHD was 27% lower among smokers (p<0.0001), 20% higher among the physically active versus inactive (p=0.01), 2% lower per 1kg/m2 increase in body mass index (BMI) (p<0.0001), and showed expected seasonal variation (χ^2 p<0.0001). Log 25OHD was 13% lower in the most versus least deprived independent of the aforementioned lifestyle confounding factors (p=0.03). Circulating 25OHD concentrations were not associated with atherosclerotic burden in univariable models; cIMT (effect estimate 0.000mm [95% CI -0.011, 0.012]); plaque presence (OR 0.88 [0.75, 1.03]), or in multivariable models.

Conclusion*:* There is no strong association of 25OHD with cIMT or plaque presence, despite strong evidence 25OHD associates with lifestyle factors and socioeconomic deprivation.

Reference*:*

25-hydroxyvitamin D is lower in deprived groups, but is not associated with carotid intima media thickness or plaques: results from pSoBid.
Knox S *et al., Atherosclerosis* 2012;223(2):437-441
Available at:
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Soluble ST2 associates with diabetes but not established cardiovascular risk factors: a new inflammatory pathway of relevance to diabetes?

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Abstract

Background*:* Preliminary data mostly from animal models suggest the sST2/IL-33 pathway may have causal relevance for vascular disease and diabetes and thus point to a potential novel inflammatory link to cardiometabolic disease. However, the characterisation of sST2 levels in terms of metabolic or vascular risk in man is completely lacking.

Methods*:* We sought to address this gap via a comprehensive analysis of risk factor and vascular correlates of sST2 in a cross-sectional study (pSoBid). We measured sST2 in plasma in 639 subjects and comprehensively related it to cardiovascular and diabetes risk factors and imaged atherosclerosis measures.

Results*:* Circulating sST2 levels increased with age, were lower in women and in highest earners. After adjusting for age and gender, sST2 levels associated strongly with markers of diabetes, including triglycerides [effect estimate (EE) per 1 standard deviation increase in sST2:1.05 [95%CI 1.01,1.10]), liver function (alanine aminotransaminase [ALT] and c-glutamyl transferase [GGT]: EE 1.05 [1.01,1.09] and 1.13 [1.07,1.19] respectively), glucose (1.02 [1.00,1.03]) and sICAM-1 (1.05 [1.02,1.07]). However, sST2 levels were not related to smoking, cholesterol, blood pressure, or atheroma (carotid intima media thickness, plaque presence).

Conclusion*:* These results suggest that sST2 levels, in individuals largely without vascular disease, are related principally to markers associated with diabetes and ectopic fat and add support for a role of sST2 in diabetes. Further mechanistic studies determining how sST2 is linked to diabetes pathways may offer new insights into the inflammatory paradigm for type 2 diabetes.

Reference*:*

Soluble ST2 associates with diabetes but not established cardiovascular risk factors: a new inflammatory pathway of relevance to diabetes? Miller AM *et al.,* PLoS ONE 2012;7(10):e47830.
Available at:
www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0047830

pSoBid investigations into the ***social*** determinants of ill health

Early life socioeconomic adversity is associated in adult life with chronic inflammation, carotid atherosclerosis, poorer lung function and decreased cognitive performance: a cross-sectional, population-based study

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Abstract

Background*:* Socioeconomic gradients in health persist despite public health campaigns and improvements in healthcare. The Psychosocial and Biological Determinants of Ill-health (pSoBid) study was designed to uncover novel biomarkers of chronic disease that may help explain pathways between socioeconomic adversity and poorer physical and mental health.

Methods*:* We examined links between indicators of early life adversity, possible intermediary phenotypes, and markers of ill health in adult subjects (n=666) recruited from affluent and deprived areas. Classical and novel risk factors for chronic disease (lung function and atherosclerosis) and for cognitive performance were assessed, and associations sought with early life variables including conditions in the parental home, family size and leg length.

Results*:* Associations were observed between father's occupation, childhood home status (owner-occupier; overcrowding) and biomarkers of chronic inflammation and endothelial activation in adults (C reactive protein, interleukin 6, intercellular adhesion molecule; $P<0.0001$) but not number of siblings and leg length. Lung function (forced expiratory volume in 1 second) and cognition (Choice Reaction Time, the Stroop test, Auditory Verbal Learning Test) were likewise related to early life conditions ($P<0.001$). In multivariate models inclusion of inflammatory variables reduced the impact and independence of early life conditions on lung function and measures of cognitive ability. Including variables of adult socioeconomic status attenuated the early life associations with disease biomarkers.

Conclusions*:* Adverse levels of biomarkers of ill health in adults appear to be influenced by father's occupation and childhood home conditions. Chronic inflammation and endothelial activation may in part act as intermediary phenotypes in this complex relationship. Reducing the 'health divide' requires that these life course determinants are taken into account.

Reference*:*
Early life socioeconomic adversity is associated in adult life with chronic inflammation, carotid atherosclerosis, poorer lung function and decreased cognitive function: a cross-sectional, population-based study. Packard CJ *et al., BMC Public Health* 2011;11:42.
Available at: www.biomedcentral.com/1471-2458/11/42

Early life socioeconomic status, chronic physiological stress and hippocampal N-acetyl aspartate concentrations.

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Abstract

Objective: Early life socioeconomic deprivation has been associated with cognitive and behavioural changes that persist through towards adulthood. In this study, we investigated whether early life socioeconomic status is associated with changes in the hippocampus N-acetyl aspartate (NAA), using the non-invasive technique of magnetic resonance spectroscopy (MRS).

Methods: We performed proton magnetic resonance spectroscopy (1H-MRS) of the hippocampus at 3 T in 30 adult males, selected from the PSOBID cohort. We conducted multiple regression analysis to examine the relationship between early socioeconomic status (SES) and concentration of N-acetyl-aspartate in the hippocampus. We also examined whether the relationship between these variables was mediated by markers of chronic physiological stress.

Results: Greater socioeconomic deprivation was associated with lower hippocampal NAA concentrations bilaterally. The relationship between early life SES and hippocampal NAA concentrations was mediated by allostatic load index – a marker of chronic physiological stress.

Conclusions: Greater early life socioeconomic deprivation was associated with lower concentrations of NAA reflecting lesser neuronal integrity. This relationship was mediated by greater physiological stress. Further work, to better understand the biological processes underlying the effects of poverty, physiological stress on hippocampal metabolites is necessary.

Reference*:*

Early life socioeconomic status, chronic physiological stress and hippocampal N-acetyl aspartate concentrations. McLean J *et al. Behavioural Brain Research* 2012;235(2):225-230.

Available at: www.sciencedirect.com/science/article/pii/S0166432812005311

pSoBid investigations into the ***psychological*** determinants of ill health

Interaction of personality traits with social deprivation in determining mental wellbeing and health behaviours

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Abstract

Background*:* Associations between personality traits, mental wellbeing and good health behaviours were examined to understand further the social and psychological context of the health divide.

Methods*:* In a cross-sectional study, 666 subjects recruited from areas of high and low socioeconomic deprivation had personality traits and mental wellbeing assessed, and lifestyle behaviours quantified. Regression models (using deprivation as a moderating variable) assessed the extent to which personality traits and mental wellbeing predicted health behaviour.

Results*:* Deprived (vs. affluent) subjects exhibited similar levels of extraversion but higher levels of neuroticism and psychoticism, more hopelessness, less sense of coherence, lower self-esteem and lower self-efficacy (all P<0.001). They ate less fruit and vegetables, smoked more, and took less aerobic exercise (all P<0.001). In the deprived group, personality traits were significantly more important predictors of mental wellbeing than in the least deprived (P<0.01 for interaction), and mental wellbeing and extraversion appeared more strongly related to good health behaviours.

Conclusions*:* Persistence of a social divide in health may be related to interactions between personality, mental wellbeing and the adoption of good health behaviours in deprived areas. Effectiveness of health messages may be enhanced by accommodating variation in the levels of extraversion, neuroticism, hopelessness and sense of coherence.

Reference*:*

Interaction of personality traits with social deprivation in determining mental wellbeing and health behaviour. Packard CJ *et al. Journal of Public Health* 2012;34(4):615-624.

Available at:

http://jpubhealth.oxfordjournals.org/content/early/2012/05/01/pubmed.fds030.full.pdf?keytype=ref&ijkey=bTHzh3nbeZpwvG8

Personality, socio-economic status and inflammation: cross sectional, population based study

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Abstract

Background: Associations between socio-economic status (SES), personality and inflammation were examined to determine whether low SES subjects scoring high on neuroticism or hostility might suffer relatively higher levels of inflammation than affluent subjects.

Methods: In a cross-sectional design, 666 subjects were recruited from areas of high (most deprived – "MD") and low (least deprived – "LD") deprivation. IL-6, ICAM-1, CRP and fibrinogen were measured along with demographic and health-behaviour variables, and personality traits of neuroticism, extraversion and psychoticism (hostility). Regression models assessed the prediction of inflammation as a function of personality, deprivation and their interaction.

Results: Levels of CRP and IL-6 were an increasing function of neuroticism and extraversion only in LD subjects: opposite trends were seen in MD subjects. The result was ascribed parsimoniously to an inflammatory ceiling effect or, more speculatively, to SES-related health-behaviour differences. Psychoticism was strongly associated with ICAM-1 in both MD and LD subjects.

Conclusions: The association between neuroticism, CRP and IL-6 may be reduced in MD subjects confirming speculation that the association differs across population sub-groups. The association between psychoticism and ICAM-1 supports evidence that hostility has adverse effects upon the endothelium, with consequences for cardiovascular health. Health interventions may be more effective by accounting for personality-related effects upon biological processes.

Reference*:*

Personality, socio-economic status and inflammation: cross sectional, population based study. Millar K *et al. PLoS ONE* 2013

Article available from March 13th 2013:

http://dx.plos.org/10.1371/journal.pone.0058256

7. Study population profile: descriptive statistics

The research reported here sought to investigate the psychological, social, behavioural and biological determinants of ill health within population groups in Glasgow that differed in socioeconomic status and in their propensity to develop chronic diseases. The research has examined the associations of social deprivation with a variety of health measures, and measured a wider range of co-factors with a view to enhancing our understanding of the relationships between social deprivation and ill health (Deans, 2011). In this section a brief overview is presented of the pSoBid study participant group characteristics.

The depth and range of the analyses performed in this study has provided important information concerning the relationships between social deprivation, obesity, inflammation, atherosclerosis and mental outlook, cognitive performance and personality, as a minimum. The characteristics of the least and most deprived participant groups varied, in the large majority of cases, in the expected direction across a number of indices of adult socioeconomic status, early life conditions at age 11 years, health behaviours, mental wellbeing, psychological ability and cognitive performance, CHD risk factors, and biomarkers of systemic inflammation and carotid atherosclerosis.

Individual level indices of socioeconomic status as an adult (household income, home ownership and years in education) varied in the expected direction between the two study groups. There were also significant differences between groups in indices of early life conditions – with participants in the most deprived group coming from larger families, as assessed by the number of siblings in the family and by a measure of habitation overcrowding at age 11 (number of occupants in house divided by the number of rooms); and their fathers being more likely to be in a manual occupational category and less likely to own the family home or a car.

Clear differences can be seen, as predicted, between the most and least deprived groups in health behaviours (cigarette smoking, exercise and diet indices). Almost half of participants (45%) in the deprived group were current smokers compared to only 6% of their more affluent counterparts. More deprived participants were also less physically active and had a poorer diet (as assessed by monthly fruit and vegetable consumption).

Biomarkers of chronic inflammation (CRP, IL-6) were higher in the more deprived group, as were markers of endothelial activation (ICAM and vWF). Participants in the deprived group also had poorer lung function (FEV1). Surprisingly total cholesterol was significantly lower in the deprived group and there was no difference in blood pressure between the two groups.

Carotid atherosclerosis (mean carotid intima-media thickness (cIMT) and the number of participants with carotid plaques present) was more extensive in the deprived than the affluent group, despite the fact that observed total cholesterol levels were higher in the latter.

From the personality trait evaluation (using the Eysenck Personality Questionnaire) it was observed that subjects from the deprived communities showed higher levels of neuroticism (reflecting negative emotions including anxiety, pessimism and guilt) and psychoticism (negative emotions and perceptions including hostility and social isolation) compared to those from affluent areas. In contrast the mean score for extraversion (sociability, optimism and impulsivity) and tendency to portray oneself favourably (lie scale) was the same in the two groups. Participants recruited from deprived areas performed less well in cognitive performance tests of short-term learning and memory recall, attention and information processing and reaction speed. Scales assessing mental wellbeing gave poorer scores for hopelessness, self-esteem and sense of coherence in participants from more deprived areas.

Participants in the deprived group were also found to have accelerated rates of telomere attrition and more rapid biological ageing compared to their more

affluent counterparts. Significant differences between groups in brain morphology were also identified, with participants in the deprived group having reduced grey and white matter volumes in the cerebellum and volume reductions in areas relating to a number of large scale cortical networks.

8. Study strengths and limitations

Several strengths of this study are worthy of comment. Participants were selected on the basis of area level deprivation, as classified by the Scottish Index of Multiple Deprivation, rather than the effects of socioeconomic status being examined *post hoc*. The setting of Glasgow, Scotland, is excellent for such a study because a wide range of deprivation and life expectancy can be found within the city, as discussed in Chapter 3. The depth and range of the analyses performed has provided important information concerning the relationships between deprivation, obesity, inflammation, atherosclerosis and mental outlook. The complete dataset, with relatively few missing results, is also a strength of the study.

There are however 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, and therefore does not represent the population of interest as a whole. Social deprivation exists as a continuum, and it could be argued that a full understanding of the effects of deprivation cannot be achieved by studying the two extremes. For practical purposes, however, and also to maximise the opportunity to identify differences between the most and least deprived populations, a study design looking at the two extremes of deprivation was pragmatic and appropriate at the time.

Another concern of this study is the question of whether study participants differed from non-participants. In particular, it was possible that the 'worried well' and the 'healthy deprived' would preferentially volunteer for this study, thus minimising potential differences between the most and least deprived groups, and affecting the representativeness of the findings. To explore the extent of any response bias, we examined the characteristics of non-respondents and found that within each age, sex and socioeconomic stratum participants were comparable to non-participants on a range of characteristics, including smoking status and current prescriptions for statins, aspirin, anti-hypertensives and antidepressants.

There is further possible response bias in the findings, particularly due to the difficulties of recruiting younger men from the most deprived areas. The response rate at about 25% is low in absolute terms, but is not unusual for population-based surveys (Cummins *et al.,* 2005; Ogilvie *et al.,* 2008). Lastly, scope for drawing conclusions for policy and practice, and for understanding causal pathways, is limited by the cross-sectional design of the study. Temporal relationships between many of the variables cannot be determined and it is therefore only possible to report associations, not causal relationships.

Study limitations have also been identified during the preparation of specific academic journal articles and areas of interest. The early life and childhood conditions of participants at age 11 years were assessed by recall, rather than by objective measures taken historically. Indicators of childhood social class, especially relating to father's occupational social class, may therefore have been wrongly reported by participants being asked to remember information up to five decades later. Furthermore, those with cognitive impairment may have been less accurate in their recall and this may have introduced confounding variation into the analysis. The use of the Eysenck three-factor measure of personality (rather than the five factor model) may be a further limitation as it does not permit the fine analysis of the facets of neuroticism and extraversion which may be critical to the expression, or inhibition, of particular health related behaviours. In the studies of brain structure only men were recruited (to avoid the potential confounds around the effects of sex hormones mediating adaptive structural plasticity in the brain, and to reduce heterogeneity). Males and females have been shown to display considerable differences in brain structure and developmental trajectory, so our conclusions cannot be generalised to the population as a whole.

While noting these limitations, the breadth and depth of the data collected, linkage to NHS records and the population-based nature of the study makes it a valuable and important resource for building an understanding about the mechanisms that help to explain deprivation-related ill health.

9. Public health implications

The implications of the pSoBid findings will be considered in terms of three sets of issues: how health inequalities are understood; implications for population health research; and implications for policy and practice.

Inequalities in health

Clear differences exist between those living in the most affluent circumstances and those in the poorest circumstances – and these differences are seen in almost all of the characteristics measured in this study. They exist in relation to health behaviours, mental wellbeing, psychological traits and cognitive performance, CHD risk factors, biomarkers of systemic inflammation, telomere length, methylation, brain morphology, carotid atherosclerosis and early years experiences. There may be medical, educational, social or environmental responses to each of these measures, but recognising that they all are associated with the common cause of socioeconomic deprivation is a clear reminder of the importance of refocusing our efforts there. pSoBid has demonstrated the considerable impact of deprivation in creating and exacerbating ill health.

Social circumstances have direct biological consequences, as well as impacting on behaviours. Moreover, traditional risk factors (whether behavioural or biological) are not sufficient to explain the differences seen in health outcomes. There is an added effect of social deprivation. Hence, all other things being equal, even if the differences were abolished between social groups in smoking rates, blood pressure, CRP and so on, differences in atherosclerosis would remain.

Alongside these direct outcome-specific inequalities in health sits the background process of accelerated ageing. The concept of poorer people having ‘more miles on the clock’ is well recognised, and results in their biological age being older than their chronological age. Our findings demonstrate that the rate of age-related telomere attrition is significantly associated with measures of lower socioeconomic status in individuals, and

also with poor diet. More tentatively, associations with measures of inflammation also seem to be present.

As well as deprivation having an impact on individuals' own health, this study has shown that socioeconomic status is also associated with epigenetic differences. DNA methylation was found to be 24% lower in manual workers than in those in non-manual jobs. Through epigenetic processes, effects of the socioeconomic environment become embedded at a biological level (within the genotype) and these changes are transmissible between generations. In short, the drivers of today's health inequalities are also laying the bedrock of health inequality in the next generation also.

Implications for population health research

pSoBid was undertaken as a pilot study, to test the feasibility of this sort of population-based research incorporating a diverse range of measures and academic perspectives. From this, much has been learnt about the practicalities of undertaking research of this type. Following considerable effort, the study was successful in recruiting subjects of the required sex and age profile from the most and least deprived areas of Glasgow. The involvement and co-operation of primary care services was crucial. Subjects were willing to volunteer for a variety of investigations involving psychological, behavioural, sociological and medical questions and tests including blood analysis. As in other studies, it was easier to enrol females than males, older compared to younger people, and the more affluent participants. Linkage to medical records allowed comparison of the health characteristics of participants and non-participants, yielding an insight into aspects of volunteer bias in studies of this type.

Building on this study, there is a clear need for longitudinal studies which similarly have a focus on health inequalities and a concern with diverse measures. These would enable conclusions to be drawn about temporal relationships – thereby elucidating pathways through which effects occur, and also highlighting measures and biomarkers of particular value for assessing the impact of health or social policy interventions. The pSoBid findings

illustrate the existence of life-course effects, and also (for example in relation to differentials in cIMT and plaque scores) the emergence of inequality in older age. These findings highlight the importance of not limiting research to a specific age group.

Also, building on pSoBid, future studies involving participants from a wider range of socioeconomic circumstances would allow hypotheses to be tested about population gradients in the distribution of the variables of interest, whether threshold effects exist, and so on.

Lastly, this study has once again highlighted the importance of including measures of socioeconomic status within health research. Measures of early life circumstances, individual socioeconomic status and area-based deprivation are all important. Just as research findings are routinely reported by gender and age, so should they routinely consider socioeconomic position.

Implications for policy and practice

Socioeconomic circumstances drive population health outcomes. Addressing poverty, deprivation and their direct consequences must therefore be a policy priority. Recognition of the impacts of deprivation also needs to be an integral part of frontline service delivery. Much more can be done in both these regards. An example where recognition has been given to the impact of deprivation is in the revision of algorithms of cardiovascular risk. Social deprivation has now been incorporated into cardiovascular risk scores, for example the ASSIGN Score, alongside classical risk factors and family history of cardiovascular disease (Woodward *et al.,* 2007). pSoBid findings support such developments: classical cardiovascular risk factors do not fully explain the differences between participants from the most and least deprived areas. In addition to differences in risk, these findings suggest that public health messages directed at classical risk factors (smoking, diet and blood pressure) will be insufficient to tackle the socioeconomic gradient in cardiovascular disease incidence and prevalence.

In line with the emphasis being placed in Scotland on the importance of supporting all children to have a good start in life, this study highlights both the fact that early years experiences continue to have an effect into adulthood (inflammation being an important mechanism) and the fact that adult circumstances will impact the next generation (through epigenetic effects). A good start in life involves attention to the parents' health and circumstances and those of the child.

Furthermore, this study has highlighted that chronic stress has a negative impact on wellbeing and cognition throughout the life-course. The current lifespan approach to research on stress and cognition emphasises the long lasting effects of exposure to early life adversity. By reducing early life adversity it may be possible to support the development of more resilient phenotypes – individuals who will be less susceptible to stress-associated cognitive disturbances/disorders in later life. This implies that efforts to reduce inequalities should continue to be broadly based, including educational opportunities and interventions directed at early life.

The relationships between socioeconomic circumstance and personality are of further interest. This study has shown that, for those in more favourable circumstances, health outcomes are better – regardless of personality characteristics. However, for those in more deprived circumstances, personality traits are significant and important predictors of mental wellbeing and health-related behaviour. To a degree, good mental wellbeing and the trait of extraversion help to protect against the consequences of poorer circumstance.

These findings also suggest that it may be appropriate to consider individual personality traits and cognition levels when developing health promotion activities, public health interventions and in the health professional-client interaction. Interventions may be more effective when they are adapted to certain personality characteristics and have a focus upon supporting and enhancing the aspects of mental wellbeing, such as SoC, which have demonstrated a positive association with health. In the development of public

health improvement activities and interventions, giving consideration to the role played by different personality traits, may improve uptake, sustainability, effectiveness and success.

Inequalities in health matter. The relationship between measures of socioeconomic position and mortality is a strikingly consistent finding. Despite the well-documented simplicity of the association between social position and health outcomes, more complex questions remain unanswered as to the mechanisms whereby such associations arise and how amenable they are to change through intervention. Future interventions need to be based on the best possible evidence about the many complex and inter-related factors that generate and maintain social and health inequalities, and the greatest gains in advancing population health will, predictably, result from investment to improve social and economic conditions in both early and later life.

10. Conclusions and next steps

The important information which pSoBid has collected on the determinants of ill health across the socioeconomic gradient in Glasgow places the study in a good position to provide further insight and understanding into the links between people's social circumstances, mental wellbeing and biological markers of disease. Acknowledging the limitations of the study and the challenges of integrating a range of professional perspectives, the multidisciplinary approach employed in pSoBid has enabled a more holistic understanding of the diverse characteristics of individuals who reside in affluent and deprived communities and their influence on health and health inequalities. The study has also allowed a biomedical perspective of population health to be obtained, by combining lifestyle and family history information with biomedical measures of health and novel scientific techniques to provide a more rounded view of health and wellbeing across the two study groups.

The study has highlighted the complex and multifactorial nature of socioeconomic inequalities in health. The relationship between social deprivation and health presents a complex interplay of early life factors, biological and psychological mediators (such as inflammatory pathways, personality and cognitive function), which in turn affect health behaviours and subsequent health outcomes. The apparently complex nature of these relationships suggest that solutions to the widening gap in health inequalities are also likely to be complex, and will need to take into account factors such as early life circumstances and personality, as well as the more the classically recognised factors such as smoking, diet, cholesterol and blood pressure if we are to stand a chance of narrowing the gap in health by improving the health of those most in need.

The growing body of evidence presented here reinforces the impact of poor early life circumstances and low socioeconomic childhood status on the accumulation and development of risk factors for poor health outcomes as an adult. It also emphasises the clear and well-established associations between

socioeconomic status and CHD and cognitive performance – and has sought to highlight some of the potential explanatory variables for these correlations. The evidence also considers the emerging fields of research which are assessing the influence of an individual's personality on their risk of disease and possible future health outcomes, the impact of accelerated biological ageing on stress and elevated disease risk and the impact of socioeconomic status and inflammation on brain morphology. These aetiological links continue to need further exploration as potential explanations of the burden of ill health in deprived communities.

Next steps

Although many public health programmes have achieved considerable success in reducing mortality and morbidity, they often fail to recognise and capitalise on interventions that address the social context and conditions in which people are born, grow, live and work, and age, all of which have a powerful influence on health.

In Scotland, extensive and far-reaching efforts to improve health and wellbeing over the last few decades have produced steady improvements in health. However, the life expectancy and healthy life expectancy of the most deprived communities continues to increase at a slower rate than in the most affluent communities (Scottish Government, 2012) so the gap is getting wider. Current approaches are not working well enough to reduce health inequalities. The effectiveness of planned interventions to change the levels of conventional risk factors and health behaviours in populations and population groups has been limited. Inequalities between groups, communities and individuals continue to persist in spite of widespread health promotion and health improvement messages and initiatives. This suggests the presence of substantial and continuing barriers to healthy change.

The research reported here has created and provided a vast range of data across the biological, psychological and social determinants of health, and in doing so it is inevitable that many new questions will also be raised.

Future analyses of the pSoBid study data will continue to build an understanding of the relationships between poverty, biology, behaviour and psychology that lead to health inequalities in Glasgow and beyond.

As discussed previously (Chapter 8), the cross-sectional design of the study means that while hypotheses can be generated about possible relationships between early life factors and adult health outcomes, a longitudinal study would be required in order to confirm temporal relationships, ideally starting at an age at which it is possible to study early life variables directly, rather than by later adult recall. Such a study would be a long-term project. Furthermore, consideration should be given to studying the effects of current or novel population health interventions (e.g. early life intervention programmes, housing interventions and so on) on lifestyle parameters, biomarkers and health outcomes.

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12. Study team

The pSoBid study team are:

University of Glasgow:

- Professor Keith Millar
- Professor Naveed Sattar
- Dr Jonathan Cavanagh
- Dr Paul Shiels

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- Vladimir Bezylak, Claudia-Martina Messow, Paul Johnson, Suzanne Lloyd

NHS Greater Glasgow and Clyde

- Professor Chris Packard (Study Principal Investigator)
- Dr Kevin Deans
- Sister Agnes McGinty

Medical Research Council, Social and Public Health Sciences Unit

- Dr G David Batty

Scottish Government

- Dr Sir Harry Burns, Chief Medical Officer

Glasgow Centre for Population Health

- Professor Carol Tannahill
- Dr Yoga Velupillai (Study Project Manager 2004-2008)
- Dr Jennifer McLean (Study Project Manager 2009-2013)

13. pSoBid published study articles (as of February 2013)

1. **Psychological, social and biological determinants of ill health (pSoBid): study protocol of a population-based study**.
Yoga N Velupillai, Chris J Packard, G David Batty, Vladimir Bezylak, Harry Burns, Jonathan Cavanagh, Kevin Deans, Ian Ford, Agnes McGinty, Keith Millar, Naveed Sattar, Paul Shiels, Carol Tannahill.
BMC Public Health 2008;8:126.
http://www.biomedcentral.com/1471-2458/8/126

2. **Differences in atherosclerosis according to area level socioeconomic deprivation: cross sectional, population based study**.
Kevin A Deans, Vladimir Bezylak, Ian Ford, G David Batty, Harry Burns, Jonathan Cavanagh, Eric De Groot, Agnes McGinty, Keith Millar, Paul G Shiels, Carol Tannahill, Yoga N Velupillai, Naveed Sattar, Chris J Packard.
British Medical Journal 2009;339:b4170
http://www.bmj.com/content/339/bmj.b4170.full

3. **Early life socioeconomic adversity is associated in adult life with chronic inflammation, carotid atherosclerosis, poorer lung function and decreased cognitive performance: a cross-sectional, population-based study.**
Chris J Packard, Vladimir Bezylak, Jennifer S McLean, G David Batty, Ian Ford, Harry Burns, Jonathan Cavanagh, Kevin A Deans, Marion Henderson, Agnes McGinty, Keith Millar, Naveed Sattar, Paul G Shiels, Yoga N Velupillai, Carol Tannahill.
BMC Public Health 2011;11:42.
http://www.biomedcentral.com/1471-2458/11/42

4. **Accelerated telomere attrition is associated with relative household income, diet and inflammation in the pSoBid cohort**.
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6. **Interaction of personality traits with social deprivation in determining mental wellbeing and health behaviours.**
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9. **Soluble ST2 associates with diabetes but not established cardiovascular risk factors: a new inflammatory pathway of relevance to diabetes?**
Ashley M Miller, David Purves, Alex McConnachie, Darren L Asquith, G David Batty, Harry Burns, Jonathan Cavanagh, Ian Ford, Jennifer S McLean, Chris J Packard, Paul G Shiels, Helen Turner, Yoga N Velupillai, Kevin A Deans, Paul Welsh, Iain B McInnes, Naveed Sattar.
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10. **Personality, socio-economic status and inflammation: cross sectional, population based study.**
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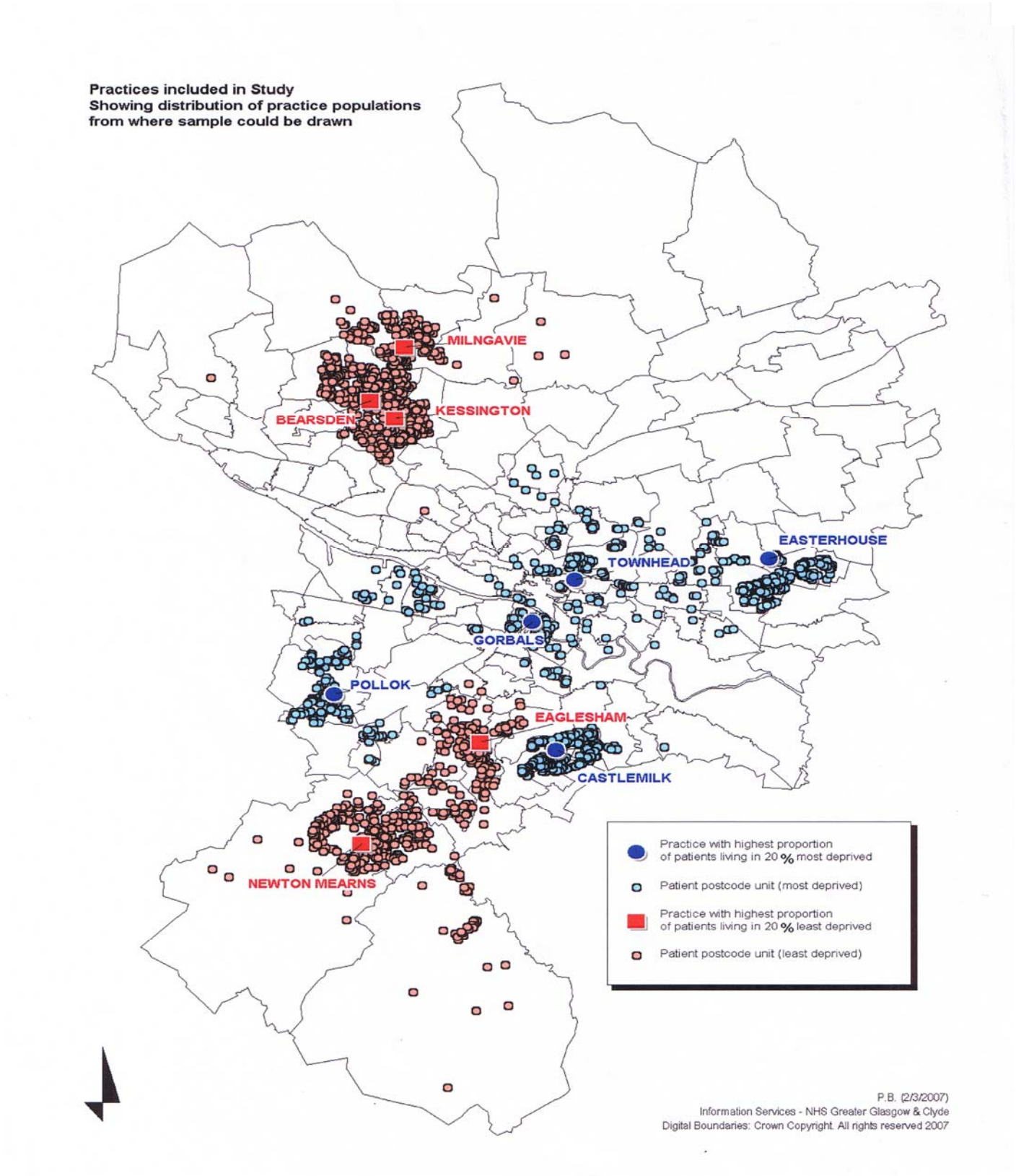
PLoS ONE 2013 Accepted for publication

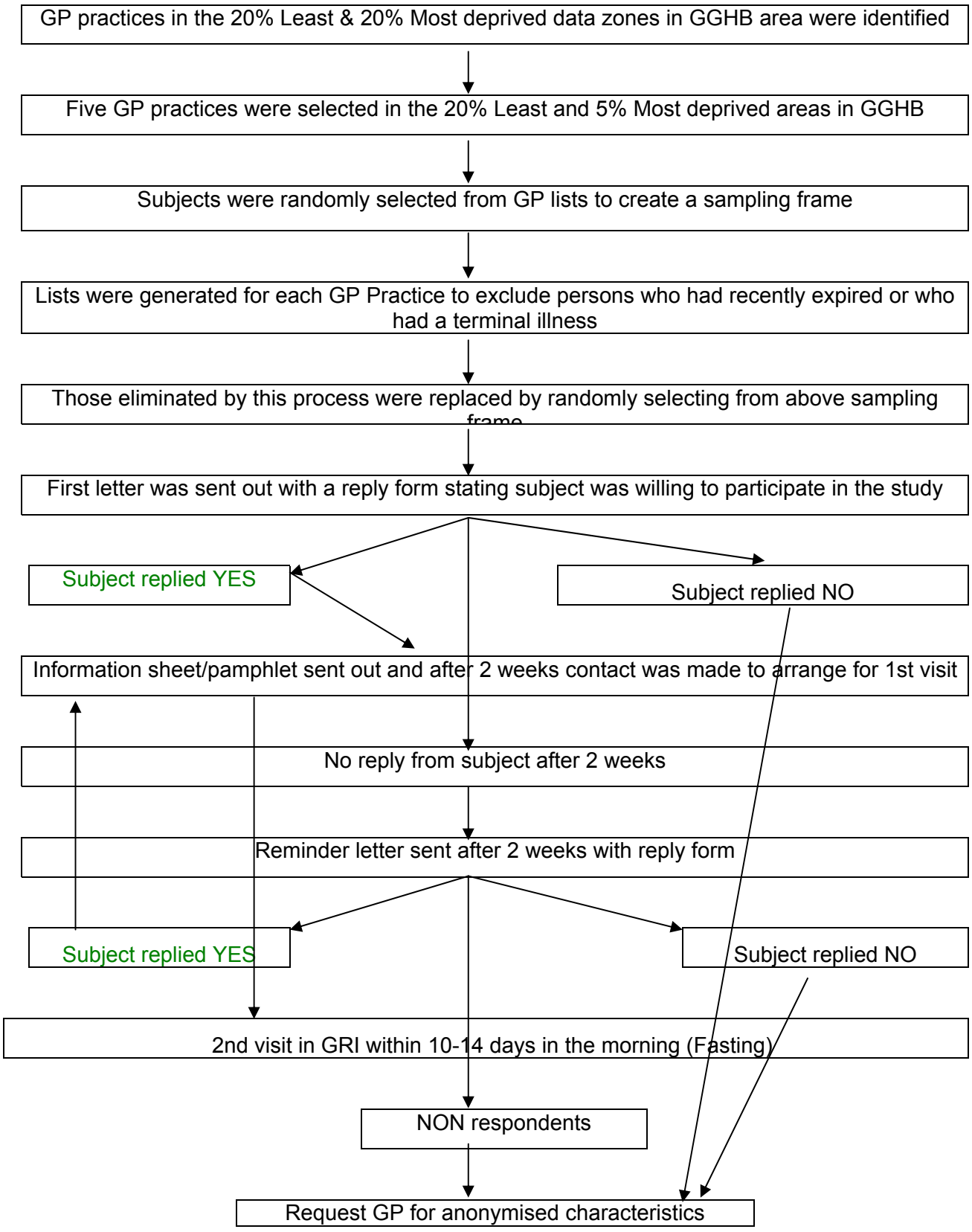
This report will be available online (www.gcph.co.uk) and in hard copy.

14. Appendices

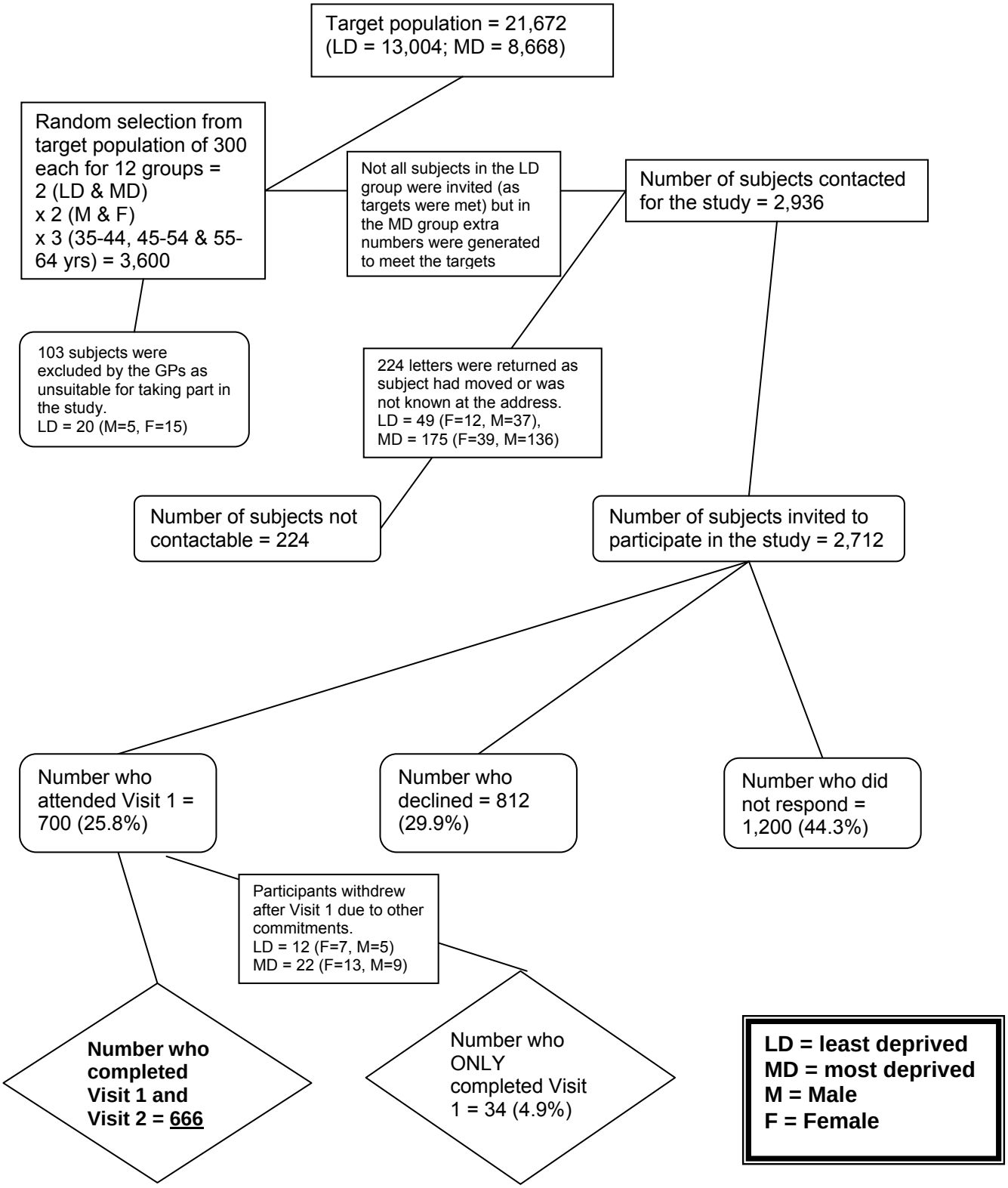
Appendix 1. Location of the recruited GP study practices and the distribution of the practice populations.



Appendix 2. Study recruitment flow chart.



Appendix 3. Study recruitment sampling framework and final recruitment numbers.



Appendix 4. Lifestyle questionnaire.

Version 3.3

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

6a. Residence ☐ Owner occupier ☐ Tenant (local authority) ☐ Tenant (private) ☐ Living with parents ☐ Other - If Other go to Q6b

6b. Please state where _____

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 _____

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	☐	☐
High cholesterol level	☐	☐	Y Y Y Y	☐	☐
High Blood Pressure	☐	☐	Y Y Y Y	☐	☐
Diabetes	☐	☐	Y Y Y Y	☐	☐
		If Yes, was your first treatment: Diet ☐ Tablets ☐ Insulin ☐			
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: _____

_____

_____

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. _____

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

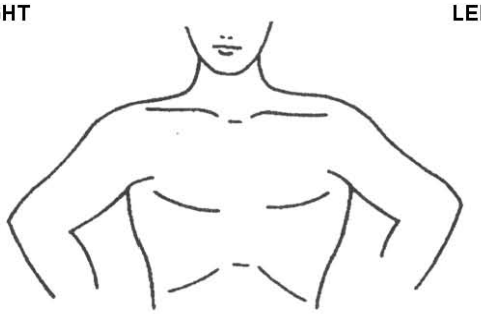
A4d. When you get pain or discomfort in your chest what do you do?
(please tick one box only) ☐ Stop ☐ Slow down ☐ Continue at the same pace

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)* ⌊Y Y Y Y⌋

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

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

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

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		NA
	6	4-5	2-3	Once	5-6	2-4	Once	1-3	< Once	
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	☐
Red 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	☐

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

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

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

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 _____

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

If self-employed/freelance with no employees, please go to Section M1 missing out question L5 below

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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