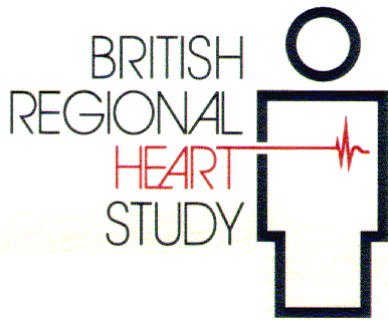## British Regional Heart Study Newsletter 2005 / 2006

Welcome to our first Annual Newsletter! We have decided to condense our usual twice-yearly newsletters into one comprehensive overview of the achievements of the year, and will produce this each December. We are pleased to report that 2005 has been a very successful year for the British Regional Heart Study, with some 24 papers published or accepted for publication. Dr Goya Wannamethee (Co-Director of the BRHS) has recently received a promotion to Reader in Epidemiology. Two new members joined the BRHS Research Group: **Julia Tchernova** (BHF funded Research Fellow) has been working closely with Dr Wannamethee and Professor Naveed Sattar from Glasgow on analysing the adiponectin and leptin data. **Dr Sheena Ramsay** (DoH funded Research Fellow) has been working with Professor Whincup, Dr Richard Morris and Olia Papacosta on the secondary prevention of cardiovascular disease and is now beginning to investigate evidence of social inequalities. Mary Thomas (DoH funded Clerical Assistant P/T) is now in the final year of the MSc Demography & Health at the London School of Hygiene & Tropical Medicine. Andy Thomson, Mary Thomas and Lucy Lennon continue to keep the BRHS database up to date. Some aspects of our work, for example recent studies of diabetes prevalence and coronary heart disease (CHD) prevention, have been carried out jointly with the British Women's Heart and Health Study (Directed by Professor Shah Ebrahim). We look forward to continuing collaboration with BWHHS.

Activities over the last year

A postal questionnaire was sent out to the 4478 surviving BRHS men in April 2005, which was completed by 80% of participants. In this survey we collected new information on lifestyle and health-related behaviours (including diet), social circumstances, ill-health and disability, and investigations and treatment for cardiovascular disease. The information obtained will be important for the study of the determinants of cardiovascular disease and other chronic diseases later in life, providing 5-7 years of follow-up since the re-examination in 1998-2000. These data are currently being entered and will be available for analysis from January 2006. We are planning our next Record Review for June 2006, and will be approaching our colleagues in General Practice to seek their consent to carry out the customary review of participant records. We remain indebted to both the members of the cohort and staff in the General Practices for their continuing co-operation in this research study.

Overview of recent publications and papers in press

The BRHS has continued to yield important new findings in several areas. A new analysis of time trends in CHD has shown that the large decline in major CHD (particularly myocardial infarction and CHD death) has been substantially offset by a rise in the prevalence of angina[4]. Two recent reports have reassessed the contribution of lifestyle factors to cardiovascular disease risk, taking account of imprecision in the measurement of these factors[1,3]. These reports emphasized the enormous potential for prevention of cardiovascular disease through lifestyle changes (66% of all CVD events could have been prevented if all men had been non-smokers, moderately active and had a BMI under 25 kg/m^2 in middle age). Taking account of imprecision in risk factor measurement also affected the relationship between alcohol intake and cardiovascular disease, suggesting that the adverse cardiovascular effects of heavy drinking had been underestimated while the apparent protective effect of light alcohol intake had been overestimated[1].

Other reports have emphasized the importance of overweight on a variety of risk factors for vascular disease, including metabolic risk factors and lung function[10,13,23]. In addition, an important recent paper has shown that intentional weight loss (as opposed to unintentional weight loss) is associated with a reduction in all-cause mortality[12]. The rising prevalence of type 2 diabetes has been a source of national concern. We have reported on the prevalence of type 2 diabetes in the BRHS population, showing that the prevalence of undiagnosed diabetes (6.7%) is similar to that of diagnosed diabetes. This report also quantifies the prevalence of impaired fasting glucose among older men[8]. We have also shown that hepatic enzymes gamma-glutamyl transferase and alanine aminotransferase are useful measures in identifying subjects at high risk of diabetes[22].

The metabolic syndrome has been widely promoted as a means of identifying patients for lifestyle intervention to reduce risk factors and CVD disease. Our recent report comparing the metabolic syndrome and the Framingham risk score (FRS) in the prediction of coronary heart disease, stroke and type 2 diabetes confirmed that the metabolic syndrome is a significant predictor of CHD, stroke and diabetes but is inferior to the FRS in predicting CHD [23].

Our successful collaboration with Professor Lowe examining inflammatory and haemostatic markers in the BRHS population has shown that obesity, the metabolic syndrome and cigarette smoking all have appreciable adverse effects on inflammatory markers, haemostasis and endothelial function[5,11,14]. Finally, a series of recent reports suggest that, although considerable progress has been made in the treatment of CHD, there is still scope for improvement in secondary prevention[20]. We have also identified marked inequalities in treatment by age (applies both to secondary prevention and revascularization) and by social class (for revascularization)[7,19,21].

Still in the news…

Smoking in public places remains is a hot topic in the media and in political debate. Earlier studies examining the influence of passive smoking on CHD risk have for the most part focussed on the effects of partner smoking. A report from the BRHS has examined the relation between overall passive smoking exposure (assessed through measurement of serum cotinine) and CHD risk. The results suggested that the full effects of passive smoking have been underestimated, and that the increased risk for passive smokers could be considerably more than the earlier estimate of 25%. *(BMJ. 2004;329:200-205)*. This study adds to the weight of evidence that passive smoking is harmful to health and strengthens the case for minimizing exposure to it.

LATEST RESULTS FROM PAPERS SUBMITTED FOR PUBLICATION

Extent of and inequalities in secondary prevention of CHD since the NSF implementation

We have examined the extent to which the use of secondary prevention had changed since the publication of the National Service Framework (NSF) for CHD in 2000. Our results showed that there were improvements in the use of key secondary prevention medication since the introduction of the NSF. By 2003, antiplatelet drugs were used in over 80% of CHD patients and the use of statins had almost doubled (from 34% to 65%). However, large numbers of patients who could benefit from these medications were still not receiving them. Moreover, the prevalences of ACE inhibitor and beta-blocker use were low (44%). In our collaborative work with the British Women's Heart and Health Study, we were able to extend these analyses to compare medication use in women. Although medication use in women had also increased between 2000 and 2003, the prevalence of medication use was lower in women compared to men. Fewer patients with uncomplicated angina received secondary prevention compared to those with myocardial infarction both in men and women. This report thus highlights the continuing scope for improving the use of secondary prevention medication in older CHD patients.

We also investigated the extent of inequalities by age, social class or region in the use of medication for CHD. We found strong evidence of age inequalities, with older CHD patients being less likely to receive secondary prevention, though there was little social class or geographic difference. The age difference was most obvious in the use of statins. In 2000, older subjects (74-85 years) were 60% less likely to take statins compared with younger subjects (62-73 years); this pattern changed very little between 2000 and 2003. We also found that the prevalence of use of all medication decreased with increasing time since diagnosis. Patients who were diagnosed more than 10 years ago were less likely to receive secondary prevention compared to those who were diagnosed within the last 5 years. Further action is needed to reduce these inequalities, particularly those related to age, since older patients are at particularly high risk of recurrent and fatal CHD.

Influence of obesity on ill health & disability

There has been concern about the role of obesity as a cause of ill-health and disability in later life. Although body mass index (BMI) is often used as a marker of obesity, this is problematic in later life, when changes in BMI (particularly declines) may reflect changes in lean mass rather than obesity. We are currently investigating how body composition measures (fat mass and lean mass) are associated with ill health and disability in older age We found that BMI, waist circumference and fat mass are associated with cardiovascular disease, reporting of fair/poor health and physical disability.

In contrast, lean mass was only associated with having poor respiratory function. BMI and waist circumference are adequate markers of morbidity and disability in the elderly and though lean mass plays an important role it may be mainly with relation to respiratory function.

Geographic associations between inflammatory, haemostatic and rheological factors and CHD in older British men; ecological analysis

In collaboration with Professor Gordon Lowe we are examining the role of inflammatory, haemostatic and rheological variables in geographic variation in CHD within the UK, taking account of behavioural and socio-demographic influences. Levels of C-Reactive Protein, an inflammatory marker which has been implicated in the aetiology of coronary heart disease, were strongly associated with CHD mortality, but this difference was much diminished after adjustment for body mass index, physical activity and smoking status. Levels of plasma viscosity were also related to CHD mortality rates; this association persisted after adjustment for behavioural and socio-demographic factors. The influence of plasma viscosity will be explored further in the next prospective phase of BRHS analyses.

Carboxyhaemoglobin levels in older men

During the 20 year follow-up examination we measured carboxyhaemoglobin (COHb) levels (a marker of carbon monoxide exposure) in BRHS participants. Although we have already reported the findings to the Department of Health, we are now completing a report for publication. The COHb distribution was positively skewed. Geometric mean COHb level was 0.46% and the median 0.50%; 9.2% of men had a COHb level of 2.5% or more and 0.1% of subjects had a level of 7.5% or more. Factors that were independently related to mean COHb level included season (highest in autumn and winter), region (highest in Northern England), gas cooking (slight increase) and central heating (slight decrease). The strongest determinant was current smoking. Mean COHb levels were more than ten times greater in men smoking more than 20 cigarettes a day (3.08%) compared with non-smokers (0.32%); almost all subjects with COHb levels of 2.5% and above were smokers (93%). Pipe and cigar smoking was associated with more modest increases in COHb level. Passive cigarette smoking exposure had no independent association with COHb after adjustment for other factors. Active smoking accounted for 41% of variance in COHB level and all factors together for 47%.

The metabolic syndrome in older men: effects of lifestyle changes.

The term `metabolic syndrome' refers to the clustering of risk factors including particularly abdominal obesity, dyslipidemia, hypertension and insulin resistance in individuals. We have examined the influence of lifestyle factors (and changes in these factors) on risk of having the metabolic syndrome in 3051 BRHS men aged 60-79 years and with no diagnosis of diabetes or coronary heart disease. After adjustment for each of the other modifiable lifestyle factors, overweight/obesity and physical inactivity were associated with a significant increased risk of the metabolic syndrome as were cigarette smoking and high carbohydrate diet. Alcohol intake and dietary fat were unrelated to the metabolic syndrome. Particularly important was the finding that taking up physical activity and weight loss in the previous three years were associated with a reduction in risk of the metabolic syndrome. We conclude from these findings that lifestyle modification, even in older age, has considerable potential for prevention of the metabolic syndrome.

Associations of adiponectin with metabolic and vascular risk parameters in the BRHS reveal stronger links to insulin resistance-related than to CHD risk-related parameters

Adiponectin is considered by many to be part of the "common soil" linking type 2 diabetes and coronary heart disease (CHD). Working in collaboration with Professor Naveed Sattar we have examined the relationship between adiponectin and insulin resistance, metabolic, inflammatory and haemostatic risk factors and hepatic function in 3640 non-diabetic men aged 60-79 years who were not taking warfarin. Adiponectin was associated with waist circumference and physical activity (inversely), and alcohol intake (positively); no association was seen with cigarette smoking, prevalent CHD or stroke. After adjustment for these factors, adiponectin was significantly inversely associated with insulin resistance, triglyceride, C-reactive protein (but not interleukin 6), tissue plasminogen activator (a marker of endothelial dysfunction), alanine aminotransferase and positively associated with HDL-Cholesterol and factor VIII, factors known to be associated with diabetes. No association was seen with cholesterol, smoking, systolic blood pressure or coagulation factors. Risk of the metabolic syndrome decreased significantly with increasing adiponectin. In summary, adiponectin was found to be inversely associated with factors strongly associated with the development of diabetes. Limited associations with the major risk factors more specific to CHD suggest adiponectin may be a stronger marker of risk for diabetes than for CHD.

Plasma leptin: associations with metabolic, inflammatory and haemostatic risk factors for cardiovascular disease

Leptin, an adipocyte-derived protein, which regulates food intake and metabolism, has been implicated in the development of coronary heart disease. We have examined the relationship between leptin and vascular risk factors including insulin resistance, metabolic, inflammatory and haemostatic risk factors in 3640 non-diabetic men aged 60-79 years who were not taking warfarin. Leptin was strongly positively correlated with waist circumference (r=0.58;p<0.0001). Leptin concentrations decreased significantly with increasing physical activity, were lower in cigarette smokers and were elevated in men with pre-existing coronary heart disease and stroke; no association was seen with alcohol intake. After adjustment for waist circumference and lifestyle factors, increased leptin was independently associated with significant increases in insulin resistance, triglyceride, inflammatory markers (interleukin- 6, C-reactive protein, fibrinogen), plasma viscosity, coagulation factor VIII, endothelial markers (von Willebrand factor, tissue plasminogen activator), and fibrin D-dimer levels; and a decrease in HDL-cholesterol. No association was seen between leptin and blood pressure, total cholesterol, glucose or white cell count. The findings indicate that plasma leptin is independently associated with insulin resistance, inflammation and disturbances in haemostasis suggesting possible pathways by which leptin may influence risk of cardiovascular disease.

RELATED CHILDREN STUDIES

Earlier observations made in the BRHS gave rise to a series of studies investigating the development of cardiovascular risk among children and adolescents in towns across Britain. These studies (the Ten Towns Heart Health Studies) initiated in 5-7 year-old children, are still continuing and have themselves given rise to a new large-scale investigation into the health of children from different ethnic groups. During the last year reports from the Ten Towns Studies have highlighted the early emergence of ethnic differences in the development of insulin resistance and hyperglycaemia[25], and the importance of obesity and the metabolic syndrome in emerging vascular disease in young people[26]. Most recently the studies have drawn attention to the fact that, despite the enormous attention given to school meals recently, children eating packed lunches have similar or less favourable cardiovascular risk profiles[27].

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With all good wishes on behalf of the BRHS research group

Professor Peter Whincup   Dr Richard Morris   Dr Goya Wannamethee

Co-Directors of the BRHS Research Group