Introduction

It is well known that high blood pressure, high serum cholesterol level, cigarette smoking and increased body weight are risk factors for CHD and stroke. Less is known about the pattern of exposure to each of these risk factors which is associated with risk of each of CHD and stroke. There are many possible causal patterns. For example, the causal factor could be: one acute exposure; long-term exposure of less intensity; or there could be a time-delay between exposure and risk.

One study examined the association between risk factors in 1974, risk factors in 1987-89 and atherosclerosis (1990-92) and CHD (to 1990) (Nieto et al 1999). For CHD, the longitudinal associations were stronger than the cross sectional ones, whereas the two associations were similar when subclinical atherosclerosis was considered as the outcome. However, with only two assessments of risk factor status, there was no opportunity to examine the temporal relationship between outcome and time-varying exposure.

Another study, examining risk factors for carotid stenosis, found stronger associations with prior than current measurements of BP, similar associations with prior and current cholesterol and HDL, and higher associations with current than prior smoking status (Wilson et al 1997). However, ‘prior’ exposure was summarized by the mean exposure over all measurements taken over 34 years. Thus there was no possibility of differentiating between a long period of relatively low exposure and a short period of high exposure, which may differ in their effects. It was also assumed that the odds of carotid stenosis was linearly related to BP and cholesterol.

Statistical Methods

The effect of time-lagged exposure variables could be included in a generalized estimating equation or time-varying Cox proportional hazards model (depending on the outcome).

Models for the relationship between exposure history and outcome have recently been developed which can include relationships such as effect of long-term exposure, effect of average exposure, time-lagged effect of exposure, and threshold effects (Bandeen-Roche et al, 1999). The summary measures (e.g. average exposure over time, exposure up to one year before, etc) are chosen \textit{a priori} on scientific grounds. They are then included in generalized additive models, along with
individual covariates. In the example given, regression splines were used to allow for the extreme skewness of the data, however this is not necessary for the method to be useful.

Although covariates can be included in the model, there may still be confounding by unobserved factors. For example, there may be a personal characteristic related to both presence of hypertension and likelihood of having a stroke, in addition to the causal relationship between the two. The formulation of the model allows the longitudinal effect of exposure on outcome to be estimated without confounding by such factors, although the estimate of cross-sectional effect may be confounded. E.g. the effect of change in exposure on change in outcome from one time-point to the next is unconfounded, although the effect of exposure on outcome at a given time-point may be confounded.

The effect of exposure on outcome can be allowed to vary over time, and the assumption of a constant relationship over time can be formally examined. In the example given, GEEs were used to fit the models.

**Aims**
I propose to model the relationship between mortality, CHD and stroke, and atherosclerosis, and exposure history for:
1) hypertension
2) serum cholesterol and HDL
3) smoking
4) body weight
Different summaries of exposure history will be examined, and possible differences in effects between the different outcomes investigated.

**Patients**
All ARIC participants without evidence of CHD or stroke at baseline.

**Data needed**
Baseline: age, sex, ethnicity, social class
Each visit: BP, measure of atherosclerosis, BMI, smoking status, serum cholesterol, diabetes (glucose level?), use of anti-hypertensive drugs.

**Outcome**
Death from all causes, incidence of CHD, incidence of stroke, degree of atherosclerosis.

**Statistical analysis**
Cox proportional hazards model with time-varying covariates (mortality, CHD incidence, stroke incidence).
GEE (degree of atherosclerosis)
Exposure history model (degree of atherosclerosis).
All analyses performed using Stata software.
Applications
The results would provide further knowledge in the etiology of cardiovascular risk factors, particularly for identifying high-risk groups and targeting interventions.

References
