ARIC MANUSCRIPT PROPOSAL #703

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1. **Full Title**: Estimation of the causal effect of risk factor modification on mortality and incidence of CHD and stroke

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Introduction

It is well known that high blood pressure, high serum cholesterol level, cigarette smoking and increased body weight are potentially modifiable risk factors for CHD and stroke. However, less is known about the effect of modifying these risk factors on the risk of disease. One simulation study, using a model developed in part from the Framingham study, estimated gains in life expectancy (for those with the risk factor) between 0.4 years (reducing moderately high cholesterol levels) to 6.3 years (reducing high cholesterol levels), approximately 2.5 years for eliminating smoking, 5.5 years for reducing high diastolic blood pressure, and 1.3 years for reducing weight from more than 30% over the ideal to an ideal weight (Tsevat et al, 1991). However, this model assumed that all risk factors were independent, which is unlikely to be the case (see below).

One way of examining the effect of risk factor modification is to perform a randomized trial of an intervention designed to reduce the risk factor. For example, meta-analyses of randomized trials of treatments to lower blood pressure have shown lower rates of cardiovascular mortality in the treated than untreated groups (Hansson, 1997), although this may only be true in populations with high baseline risk of disease (Hoes et al, 1995). However, such a trial (if analyzed on an intention-to-treat basis) does not show the effect on an individual on modifying a particular risk factor, but merely the effect on the population of treating that risk factor. I.e. the effect is the mean difference in blood pressure between a group treated for hypertension and a group untreated for hypertension. Within the treated group, some individuals will have controlled BP, and others, uncontrolled BP. The analysis cannot differentiate between those for whom the treatment 'works' and those who still have uncontrolled BP.

An alternative is to perform an observational study, comparing outcome in an unexposed group (e.g. those with controlled hypertension) to outcome in the exposed group (e.g. those with uncontrolled hypertension). This is problematic, due to the systematic differences which often exist between the unexposed and exposed groups (those with and without the risk factor). Modification of a risk factor may also vary within individuals, over time, and thus a longitudinal study would be needed to take this into account. Statistical models relating outcome to time-varying covariates could then be used.

Another issue is that these risk factors are causally inter-related (modification of one may affect another, which may in turn influence the first, e.g. high blood pressure might cause one to stop smoking, which might result in a lower blood pressure), and any model not taking this into account, but merely adjusting for time-varying levels of the other risk factors, may produced a biased estimate of the effect of modification (Mark and Robins, 1993). Causal effect models (applied using G-estimation) have been proposed for the analysis of epidemiological data where the exposure varies over time and there are time-varying confounders which are influenced by the exposure (Witteman, 1998). Such models have been applied to the analysis of the graft-versus-leukemia effect after bone marrow transplantation (Keiding, 1999).

Causal effect models (G-estimation)

These models are applicable to the situation where there are time-varying covariates which are both confounders and intermediate variables on the causal pathway (e.g. blood pressure in the example given above). The assumption made is that, conditioning on past exposure history and covariates, outcome at current time does not depend on covariate at current time. E.g. for two individuals with identical covariates and history of hypertension (up to just before time t), decision to quit smoking at time t does not depend on blood pressure at time t. The model enables estimation of the counterfactual time to death if the subject were exposed at all time points, and the time to death if the subject were unexposed. For example, the time to death if the patient had (possibly contrary to what actually happened) given up smoking at baseline can be compared to the estimated time to death if the patient continued smoking throughout the study. Thus the fractional increase in survival if a patient stops smoking can be estimated. Knowledge of the distribution of the failure times can be used to estimate the causal rate ratio from the estimate of the fractional increase in survival due to giving up smoking.

The model is estimated by fitting models with different values for the parameter for fractional increase in survival, and estimating the parameter for dependence of outcome at a given time on the covariate at that time, given past history of both outcome and covariate. Because of the independence assumption (above), the model in which this parameter is zero provides the point estimate for the failure time parameter. The 95% confidence interval is given by the range of values for which the fitted model contained a parameter for dependence of outcome on covariate which was not significantly different from zero. Thus, multiple models are fitted in order to estimate the parameter for fractional increase in survival due to the exposure of interest.

Censoring (including by death due to other causes) can be incorporated into the model using GEE modeling techniques.

Aims

I propose to use G-estimation of causal models to identify the causal effect on mortality, CHD and stroke, of:

1) hypertension
2) high values of serum cholesterol
3) smoking
4) increased body weight

If there is adequate data, I would also like to look at the effect of stopping smoking, control of hypertension and loss of weight, for those initially at risk.

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 athersclerosis, BMI, smoking status, serum cholesterol, diabetes, use of anti-hypertensive drugs.

Outcome
Death from all causes, incidence of CHD, incidence of stroke.

Statistical analysis
Exploratory analysis using Cox proportional hazards model with time-varying covariates.
G-estimation of causal effect of risk factor modification.
Using Stata software.

Applications
Causal models of this type have only recently been developed, and their application in different fields of epidemiology needs to be explored. Many studies involve time-dependent exposures and covariates, and methodology for correctly analyzing such data is important. One result of this project would be procedures for fitting such models (using the Stata software package), which could then be used in future research.

The results would provide further knowledge in the etiology of cardiovascular risk factors, particularly the relationships between risk factors over time. They would also help in the decision-making process for individuals with high levels of risk factors. The results would enable the population impact of public health programs and health promotion interventions to be estimated with greater accuracy.

References

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