



Editorial

The importance of cholesterol, blood pressure and smoking for coronary heart disease

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Worldwide cardiovascular diseases account for half of all deaths in middle age (and considerable additional disability) and one third of all deaths in old age. Most of these deaths involve ischaemic heart disease (IHD) or stroke. Epidemiological studies carried out over the last half century have shown that cigarette smoking, elevated blood pressure and dyslipidaemia increase the risk of cardiovascular diseases and randomized trials have shown that lowering blood pressure and cholesterol prevents cardiovascular disease. Nevertheless, there are popular misconceptions about the relative importance of these classical risk factors, including the widely held belief that they only account for about half of all cardiovascular diseases.¹

The underestimation of the importance of these risk factors has arisen from analyses of prospective cohort studies in which measurements of blood pressure or cholesterol recorded on enrolment to the study (the 'baseline' survey) were related to subsequent risk of developing IHD. But, due to the combined effects of measurement errors, short-term biological variability and longer-term systematic changes within individuals, baseline measurements often do not reliably indicate the long-term average, or 'usual', level of a risk factor either at around the time of the baseline measurement or during a later period of follow-up. Hence, unless some account is made for this in the analysis, the true relationship between usual levels of a risk factor in a particular period and the subsequent risk of disease during that same or some later period will be misrepresented, often by a substantial amount. Generally, the real importance of a risk factor will be systematically under-estimated unless some correction is made for this, so-called, 'regression dilution' bias.² The regression dilution bias is

directly relevant to the analysis of most observational studies, irrespective of their quality or size.

The impact of regression dilution bias on the estimated relative risk of cardiovascular associated with differences in blood pressure was first illustrated in 1990 in a meta-analysis showing that the associations between usual diastolic blood pressure, stroke and coronary heart disease were strong, positive and continuous throughout the range common in Western populations and that the strength of these relationships were about 60% stronger after taking account of regression dilution.²

In 1999 we showed that the magnitude of the regression dilution bias increases with increasing follow-up (i.e., interval between measurement of risk factor and onset of the cardiovascular events).³ Thus age-specific analyses of prospective cohort data that compare the relative risks for cardiovascular events occurring in middle and old age should take account of the generally longer follow-up for people dying in old age. Using bigger corrections for regression dilution in old age, a recent meta-analysis of individual data from 61 prospective cohort studies of blood pressure and vascular mortality from the Prospective Studies Collaboration showed that usual blood pressure is strongly associated with both IHD and stroke mortality not just in middle age but also among people in their seventies and eighties.⁴

On page 1719 of this issue of the European Heart Journal, Emberson and colleagues calculate population attributable risk fractions (PARF) of IHD for blood cholesterol, blood pressure and cigarette smoking, after accounting for regression dilution in blood pressure and cholesterol. They show that by defining the 'low-risk' group as people in the bottom fifths of total cholesterol (<5.5 mmol/l) and diastolic blood pressure (<74 mmHg) and not current smokers, the PARF estimates were 70% before correction for regression dilution and 81% after correction. Similarly, by defining the 'low-risk' group as people in the bottom tenths of total cholesterol (<5.2 mmol/l) and diastolic blood pressure (<70 mmHg) and not current smokers, the PARF estimates were 75% before correction for regression dilution and 86% after

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correction. Thus, even without taking into account error in smoking ascertainment and the underestimation caused by including ex-smokers in the 'low-risk' group, these three risk factors account for almost 90% of all IHD mortality in their cohort.

The PARF approach is a useful way of quantifying the combined impact of blood pressure, cholesterol and smoking for IHD mortality but it highlights the limitations of using threshold values to determine risk. Epidemiological studies have demonstrated log-linear associations between total cholesterol and IHD risk—so that for every unit change in cholesterol there is the same proportional change in risk, regardless of the initial level of cholesterol—with no obvious threshold value below which lower total cholesterol is not associated with a lower risk of IHD.⁵ Moreover, the Heart Protection Study demonstrated that the use of statin therapy to lower total cholesterol levels is associated with a similar proportional reduction in risk of cardiovascular disease regardless of whether the prior treatment level of total cholesterol is above or below 5.5 mmol/l.⁶ Similarly for blood pressure, the Prospective Studies meta-analysis showed that the associations of usual systolic blood pressure with stroke and IHD mortality are log-linear down to at least 115/75 mmHg.⁴ In general, a 20 mmHg difference in usual systolic blood pressure (or roughly equivalently, 10 mmHg usual diastolic) is associated with about a two-fold difference in vascular risk (slightly stronger in middle age and slightly weaker in old age and slightly stronger for stroke than for IHD). Because the associations with blood pressure and cholesterol are log-linear with no apparent thresholds (at least within the range of most Western populations) any reference category must be chosen arbitrarily. Thus, as Emberson and colleagues show, the PARF can be altered merely by changing the cut-off values. Had they chosen an even lower threshold such as 4 mmol/l for total cholesterol

(which is not uncommon in China but may be difficult to achieve on a Western diet), they would probably have found a PARF of close to 100%. Yet there is a danger that their conclusions could be misinterpreted to reinforce the importance of 5.5 mmol/l as a threshold value for total cholesterol.

An even better approach to assessing the importance of these known important risk factors, therefore, may be to calculate the impact on risk of stopping smoking and of modest and realistic reductions in blood pressure and cholesterol that could be achieved, for example, by reducing salt in processed food and encouraging the replacement of saturated fat in cooking with polyunsaturated or monounsaturated fats.⁷

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