Understanding of cardiovascular disease has grown exponentially over the past few decades because of an intensive multidisciplinary research effort. Bench research has clarified the pathophysiology of atherosclerosis and acute vascular occlusion. Epidemiological research has identified the importance of specific independent risk factors and improved the degree to which people at increased risk of the disease can be identified. And clinical trials have conclusively shown which treatments work and which ones fall short of expectations.

The WHO-MONICA Project was started nearly 20 years ago as a multinational collaboration to examine trends in the relation between risk factors for cardiovascular disease and future cardiovascular events. This major epidemiological undertaking is now starting to bear fruit. As the two studies published in today's Lancet show, much data have been collected from over 100,000 individuals, who come from 38 populations in 21 countries. How do these data improve understanding of this complex multifactorial disease, which remains the leading cause of death worldwide?

The data presented in the two articles represent an ecological study, in which the units of analysis are populations. These data have therefore been used to compare changes in risk factors or treatments at the population level with changes in coronary events. In one of the papers, Hugh Tunstall-Pedoe and colleagues examine the effect of access to care on cardiovascular morbidity and mortality. They recognise that there is no substitute for randomised clinical trials when the aim is to show conclusively that a new treatment works as expected. Establishing cause and effect is so challenging that no other study design will do. The researchers are suitably cautious in their interpretation of the positive relations observed between the various interventions and coronary outcomes. The question that then arises is how do these data add to existing knowledge?

The companion paper, by Kari Kuulasmaa and colleagues, examines changes in classic risk factors for cardiovascular disease. Current understanding of cardiovascular risk factors is based largely on epidemiological studies such as the Framingham Heart Study or the Lipid Research Clinics Follow-Up Cohort, which used individuals as the unit of analysis. Carefully controlled systematic risk-factor measurement and comprehensive follow-up enabled the investigators in these studies to identify and quantify the relative importance of risk factors such as LDL and HDL cholesterol, systolic and diastolic blood pressure, age, sex, and the presence of glucose intolerance or smoking. The paper by Kuulasmaa and colleagues clearly shows that ecological studies are no substitute for well-performed cohort studies. The change in risk factors either individually or together was associated only weakly with the observed change in coronary event rates between populations.

The researchers offer several thoughtful explanations for this poor fit—for example, that measurements were made with varying precision and in many different settings. Other issues such as different access to new diagnostic and therapeutic interventions also conspire to increase the background noise through which attempts are made to identify important and significant correlations. Finally, data on important risk factors, such as HDL cholesterol and glucose intolerance, are missing from this dataset. Earlier studies have shown that the exclusion of even one major risk factor can seriously undermine accuracy at estimating overall cardiovascular risk. What then can be learned from these analyses?

First impressions are that the WHO-MONICA Project cannot add many new pieces to the cardiovascular puzzle. Basic science experiments, clinical trials, and large prospective cohort studies will continue to be necessary if the missing pieces are to be found. However, this major multinational collaboration does serve an important role in providing a frame on which to mount the puzzle and thereby enhancing understanding of the emerging picture.

Although clinical trials are essential for proving the efficacy of a new drug or technique, they cannot provide assurance that the findings from a carefully controlled trial will translate into real benefits in clinical practice. For instance, excellent trials of treatments for hypertension or dyslipidaemia have unequivocally established the efficacy of these interventions in reducing the risk of future cardiovascular events. However, data are emerging from community studies that indicate poor adherence by physicians and patients to treatment guidelines, which undermines the potential benefits promised by the clinical trials. It is therefore reassuring that Tunstall-Pedoe and colleagues' analyses of coronary care suggest that some of the expected benefits associated with evolving clinical care are being realised despite the inherent difficulties in
implementation and quality control. Although what has been found are associations between coronary care and a decline in occurrence of events rather than cause and effect, confirmation that these associations exist and that they are positive across a wide range of treatment settings is important. As the researchers point out, what would the implications be if the associations were in the opposite direction (ie, suggesting that evolving improvements in clinical care were not beneficial), or if clinical care seemed to do more harm than good?

The value of the ecological analyses surrounding risk factors is best summarised by figures 1–3 in the article by Kuulasmaa and colleagues. Despite a weak association between coronary events and individual risk factors or global risk scores, most of the populations with a decline in the prevalence of risk factors also experienced a reduction in events. Data from large cohort studies and randomised clinical trials suggest that community-wide risk-factor reduction should translate into lower coronary-event rates. However, this conclusion is based on the assumption that risk factors identified in one setting, such as Framingham, Massachusetts, are generalisable to other countries. Although there are data suggesting that risk factors maintain their relative importance among different western populations, there is less information from eastern European or Asian settings. Until large prospective cohort studies are completed in these countries, the WHO-MONICA results suggest that risk factors are risk factors irrespective of the community in which they occur. More importantly, modification of those amenable to change, such as blood pressure, blood lipids, and smoking, can result in risk reduction outside of clinical trials done under idealised conditions.

The main message of the WHO-MONICA Project thus seems to be one of generalisability. Despite incomplete understanding of the causes of cardiovascular disease, some modifiable risk factors that remain important irrespective of the individual’s nationality or place of residence have been identified. There also seems to be progress in efforts to prevent this disease and reduce the disability and mortality associated with it across a wide range of medical settings.

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Commentary


Towards post-genomic investigation of colorectal cancer

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Molecular markers of colorectal cancer are of potential use in classification, indication of disease spread at diagnosis, prediction of therapeutic response to therapy, population screening, and prognostic evaluation. Confusion surrounds the ability of molecular markers to establish prognosis, largely because information is based on studies most of which have been underpowered and that have yielded different findings, have assessed only one marker at a time across all stages of disease, and have used univariable statistical analysis.

Dukes’ staging has withstood the test of time, but is being supplanted by the tumour-node-metastasis (TNM) system, which will be the gold standard against which novel prognostic markers are compared. However, any new marker that is being proposed for clinical use should provide additional information, such as whether patients are in the high-risk subgroups of stage II and thus might benefit from adjuvant therapy.

A range of markers and their relation to outcome of colorectal cancer is shown in the panel. However, there is no consensus on their relevance, and the identification of a marker that provides information independent of that from TNM staging is rare. For example, although many studies suggest an association between tumour p53 mutation and poor prognosis, a recent study that confined multivariate analysis to patients with tumour-free margins at resection showed no independent effect of the p53 mutation.

In today’s Lancet, Anthony Heaney and colleagues report their results on the use of the pituitary-tumour transforming gene (PTTG) as a prognostic marker of colorectal cancer. The low expression of PTTG in normal tissue compared with its high expression in cancerous tissues prompted the researchers to wonder whether PTTG expression might correlate with invasiveness and subsequent metastasis. Studying 68 serially collected tissue samples, Heaney and co-workers found that, compared with its expression in normal tissues, PTTG was overexpressed in all 48 colorectal...