Nutrition, Health Promotion, and Chronic Disease Prevention: International Perspectives

Proceedings of Joint U.S.-Hungarian Conferences
Organized by the Food and Nutrition Board,
U.S. National Academy of Sciences

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89/1423 GUTENBERG Kiadó és Nyomda Szövetkezet
Felelős vezető: Óvári László elnök

Editors:

Sushma Palmer
Frances M. Peter

Sándor Eckhardt
Zsófia Schoket

POPULATION STRATEGIES OF CVD PREVENTION: EVIDENCE FROM EPIDEMIOLOGY AND CLINICAL TRIALS

Henry Blackburn

What is the scientific base and rationale for a population strategy of CVD prevention? What have we learned about the preventability of CVDs? What are the broader implications of recommendations to change life-style to reduce risk? What are the potential benefits and adverse effects of a population strategy of prevention and health promotion?

Population surveys reveal large differences in the frequency of CVDs. This is a central and salient fact of prevention. We learn from these differences that prevention is real. It remains to find out the "why and how."

From surveillance of population trends in CVD death rates, we have learned the dynamic nature of CVDs and of the underlying processes that lead to them. Remarkable changes, upward and downward, occur in the death rates from these diseases in less than a generation, even in less than a decade. These dynamic trends emphasize the overwhelming role of environment in CVD. They tell us about lag times between major cultural changes and their public health effects. Surveillance also indicates that mortality due to CHD began to decline prior to the advent of efficient emergency medical care and prior to widespread accessibility of high-tech cardiovascular procedures, including intensive coronary care, bypass surgery, angioplasty, and thrombolytic enzymes.

Population studies of migrants emphasize the overwhelming effect of cultural change on the causes

and prevention of CVDs in a population. They reveal that risk factors change as well as disease rates, and thus, they point to different mechanisms.

Population surveys of risk factors, and of their trends over time, indicate that whole populations differ greatly from each other in the means and distributions of the major CVD risk characteristics. This difference points up the central need for a population-wide strategy of prevention. It teaches us that we are dealing with mass phenomena, "sick populations" as well as sick individuals, and the overwhelming effect of culture and social change.

Analysis of population correlations between disease rates and average risk factor levels, when measured in standard fashion within the same populations, teaches us about the necessary and sufficient causes of mass disease as distinguished from contributory causes. From these correlations we learn the important difference in the force of a risk factor as a cause of disease in the population, versus that for an individual. From such population correlations, we have learned the salience of mass hypercholesterolemia and habitual diet as essential causes of mass atherosclerosis. Population correlations thus help establish public health priorities and estimate the population effects of a prevention strategy.

Analysis of the relation between changes in population disease rates and changes in the average risk factors explains mortality trends. It teaches us a central concept in the population strategy of prevention, that is, that relatively small differences or changes in average risk characteristics for the population can be associated with large differences or changes in the population burden of disease. Such correlations contribute to the setting of public health priorities.

Longitudinal follow-up studies of cohorts of individuals suggest that changes in the incidence of CVD preceded changes in mortality. Once causation is established, we mainly learn from individual risk-disease correlations about the relative risk associated with a characteristic. This can be transformed into attributable risk and then into population-attributable risk fraction, one of the central points of evidence from which preventive potential can be estimated for societies having high CVD rates.

Randomized clinical trials contribute significantly to causal inference, although they are not essential to the establishment of cause. We learn from them the preventive effect that may be anticipated in high-risk segments of the population, the safety of preventive interventions, and the lag time between changes in risk factor and effects on disease. We also learn that change in risk is dose related, according to the degree and the duration of exposure to the lowered risk characteristic.

SMALL-SCALE CLINICAL TRIALS WITH ANGIOGRAPHIC END POINTS

An extensive experience has developed on the effects of lowering total cholesterol and LDL cholesterol by diet and drugs and the effects of ileal bypass surgery on various measures of atherosclerotic lesions of the coronaries, carotids, and other middle-sized and large peripheral arteries. The earliest randomized clinical trial (Duffield et al., 1983) showed that in patients with intermittent claudication there was less angiographic progression and more regression of plaques in the group treated with diet and drugs over a 19-month period, and it occurred in direct relation to the lowering of plasma LDL cholesterol concentration. A more recent comprehensive study (Blankenhorn et al., 1987) tested the effect of diet plus several cholesterol-lowering drugs and similarly showed less angiographic progression and more regression of plaque in coronary vessels, and in bypass graft vessels, over 2 years in the treated group. Other systemic studies are also consistent with the conclusion that reducing total cholesterol and LDL cholesterol in hypercholesterolemic persons reduces the rate of progression of atherosclerosis, according to blood lipid reduction (Arntzenius et al., 1985; Brensike et al.,1984; Cohn et al., 1975; Kuo et al., 1979; Nash et al., 1982; Nikkila et al., 1984).

LARGE-SCALE PREVENTIVE TRIALS WITH DISEASE END POINTS

As of 1988, nine major randomized clinical trials on primary prevention of coronary disease had been conducted with CHD events as end points. The composition of the study populations, design, and interventions are documented in Table 1. Five of the nine

TABLE 1 Design of Randomized Controlled Trials on Primary Prevention of Coronary Heart Disease

Study	Study Population	Double-blind	Focus of Interventions
Göteborg multifactor trial (Wilhelmsen et al., 1986)	20,015 men aged 47-55	No	Diet, cigarettes, high blood pressure
WHO multifactor trial (WHO, 1983)	66 employed groups; 49,781 men aged 40-59	No	Diet, cigarettes, high blood pressure
Multiple Risk Factor Intervention Trial Research Group (1982)	12,886 high-risk men aged 35-57	No	Diet, cigarettes, high blood pressure
LRC coronary primary prevention trial (Lipid Research Clinic Program, 1984a, 1984b)	3,806 hypercholesterolemic men aged 35-39	Yes	Cholestyramine
WHO clofibrate trial (Committee of Principal Investigators, 1978)	11,627 hypercholesterolemic men aged 30-59	Yes	Clofibrate
Los Angeles VA domiciliary study (Dayton et al., 1969)	846 men aged 55-89	Yes	Diet only
Oslo study (Hjermann et al., 1981)	1,232 hypercholesterolemic normotensive men aged 40-49	No	Diet, cigarettes
Finnish mental hospital study (Turpeinen et al., 1979)	2 mental hospitals; about 450 males aged 34-64	No	Diet only
Helsinki heart study (Frick et al., 1987)	4,081 hypercholesterolemic men aged 40-55	Yes	Diet, cigarettes, gemfibrosil

trials intervened only on plasma lipid concentration, two with diet and three with drugs. For three trials the plasma lipid effect was confounded by effects of change in cigarette smoking and blood pressure. Only one of six trials involving change of diet, the Los Angeles Veterans Administration (VA) domiciliary study, was carried out under double-blind, controlled conditions. Two studies, the WHO European multifactor prevention trial and the Finnish mental hospital study, randomized groups or institutions, whereas the others randomized individuals. None is strong evidence, in itself, for prevention. All taken together point to causation or prevention of CVD. Results of these trials are summarized in Table 2 in rank order

TABLE 2 Results of Randomized Controlled Trials on Primary Prevention of Coronary Heart Disease

Study[a]	Serum Cholesterol at Entry (mg/dl)	% Differences Experimental Serum Cholesterol	Control CHD
Göteborg multifactor trial	250	0	0
WHO multifactor trial	216	-1	-7
Multiple risk factor intervention trial	254	-2	-7
LRC coronary primary prevention trial	292	-8	-19
WHO clofibrate trial	242	-9	-20
Helsinki heart study	270	-9	-34
Los Angeles VA domiciliary study	233	-13	-24
Oslo study	329	-13	-47
Finnish mental hospital study	267	-15	-51

[a]See Table 1 for references.

of the difference in serum cholesterol concentration achieved between experimental and comparison groups. Entry values of serum cholesterol differed greatly among the studies, which were carried out over 20 years. Change in CHD incidence was proportional to the serum cholesterol difference achieved.

The duration of exposure was also strongly related to the reduction in disease risk (Table 3). A further statistical summary (R. Peto, personal communication) suggests that an index of intervention effect, in which the degree of cholesterol lowering is multiplied by the duration of the exposure, suggests a linear, graded effect according to dose. Significant differences in CHD risk were achieved in all studies that obtained an 8% or more difference in mean total cholesterol level.

TABLE 3 CHD Reduction by Duration of Difference in Total Cholesterol (TC)[a]

Trials	Duration in Those Dying of CHD	CHD Reduction from Lowering TC by 10%
13 short randomized clinical trials	1-2 years	11 ± 5
7 long randomized clinical trials	3+ years	21 ± 4
EPI cohorts	Decades	± 33

[a]R. Peto, personal communication.

From these clinical trials we have learned that lowering serum cholesterol, particularly LDL cholesterol, reduces CHD risk in middle-aged hypercholesterolemic men. Many consider it reasonable to extrapolate these results to young people, to both sexes, and to lower levels of cholesterol-associated risk because of the compatibility of the trial findings with observation studies. The Los Angeles VA study also supports an inference that the benefit of cholesterol lowering extends beyond age 65. Lowering cholesterol is generally safe, even though most of the trials show a small excess of noncardiovascular deaths in the intervention group. In no individual trial, nor in all taken together, was the excess statistically significant.

From randomized clinical trials we learn primarily that the time required for cholesterol lowering to have an effect on CHD is relatively short. A significant lowering of risk is achieved within 4 years, a one-to-one cholesterol-CHD reduction is found in shorter trials, and a one-to-two relation is found in longer trials.

From public health trials, we learn about the overall feasibility of a population strategy for prevention in which whole communities, their leadership, and their institutions participate in preventive programs. Substantial awareness and exposure of a population can be achieved. We learn about the relative effectiveness of educational, motivational, and environmental strategies to help people change in knowledge, attitudes, behavior, and risk factor. We also learn from public health trials and community prevention demonstrations about the specific impact of components of a public health program, such as the real effect of screening and education, self-help educational strategies, youth-parent programs in schools, and environmental programs in restaurants, grocery stores, and worksites. We also learn something about the cost of programs and about their permanence within the community. We learn that most communities have comparable institutions that can be involved in organizing for prevention and that educational theories and strategies, even specific programs, can be repeated and generalized.

From all these research methods, we learn that observations within and among populations are the best source for estimates of the public health impact

of disease prevention and health promotion strategies when several conditions obtain: when causation is already well established by congruence of evidence from several disciplines, when the population observations of risk and disease are made in a concurrent and systematic manner, and when the observations are sufficiently long to represent a "natural experiment" or to allow calculation of population-attributable risk.

POTENTIAL BENEFIT

The well-documented population differences in frequency of CVD, and the ecologic correlations of population risk characteristics with disease rates, suggest that CVDs are probably almost entirely preventable. Some advanced industrial nations, as well as rural societies living as humankind has lived since the beginning of agriculture, are found virtually free of CVD and its precursors, hypertension and atherosclerosis. This is the most powerful evidence available about the potential of prevention.

Individual correlations within populations having much CVD tend to underestimate the potential for prevention just as population correlations may exaggerate it. For example, the Carter Center estimates a reduction of 100,000 deaths annually based on no blood cholesterol levels greater than 220 mg/deciliter, by Framingham experience. These estimates are attenuated by individual variation and as a function of the distribution of risk. For example, cutting off values at about 220 mg/dl to estimate effects of controlling high blood cholesterol fails to redistribute the population values to give a true picture of population risk. In fact, a population in which no values for total cholesterol exceed 220 mg/dl would, by necessity, have a mean value between 170 and 180 mg/dl. And we know from studies in other populations that such a population would have little atherosclerotic disease.

POTENTIAL HARM

All this evidence indicates the real potential of prevention but gives widely varying estimates of the

effect within high-risk industrial societies. Further, the overriding issue in public health recommendations must be their safety. If most evidence points to the likelihood of benefit in the population, we must nevertheless be concerned about individuals or subgroups that might be adversely affected. This issue is most often raised by those who are simply against all change. But it is raised with better reason when intervention studies suggest possible harmful effects, such as those found in the diuretic treatment of mild hypertension among certain subgroups by the Multiple Risk Factor Intervention Trial (MRFIT) Research Group (1982).

With considerable consistency, the clinical trials of cholesterol lowering, either by diet or drugs or their combination, have failed to result in significant lowering of noncardiovascular or total deaths. In others, excessive cancer and even trauma deaths have been suggested. However, the power to detect effects on non-CVD causes of death was low in all those trials. A statistical summary by R. Peto (personal communication) of all the randomized cholesterol-lowering trials carried out to date reveals that the excess of cancer can be attributed to chance. None of the trials individually or taken together had a statistically significant excess of cancer.

But we can also learn about the benefit and adverse effects of prevention from long-term observations of the relation between noncardiovascular and cardiovascular disease rates and trends. Concordance of their death rates or of their trends over time would indicate possible common causation and, therefore, common preventives. Discordance would raise issues of the potential adverse effects of preventive strategies. Sidney and Farquhar (1983) have correlated death rates attributable to all cancer and colon cancer versus those related to CHD. Concordance is high; in countries where coronary death rates (and average blood cholesterol values) are high, colon cancer and all cancer death rates also tend to be high. This suggests that lowering serum cholesterol in the population would not adversely influence cancer risk.

F.H. Epstein and T.J. Thom (personal communication) looked at the comparability of time trends in U.S. and international mortality from CDVs and

cancer. (Cancer of the lung was treated separately because its rates are still rising in many parts of the world.) They found concordance between the change in CVD deaths and all cancer deaths other than lung. In the United States there was a consistent trend downward in both, and in all causes of death, since the 1950s. There is also a high degree of concordance between increasing or decreasing cancer and cardiovascular deaths in countries reporting their vital statistics to WHO.

In addition, correlations between population means for total cholesterol and colon cancer are positive. Sidney and Farquhar (1983) also examined correlations between data on dietary composition and cardiovascular and cancer death rates provided by the Food and Agriculture Organization. Generally, positive population correlations were found between mortality rates and fat consumption and negative correlations for carbohydrate and fiber intake. Additionally, in the community prevention demonstration of North Karelia, all cancer deaths declined in parallel with CDV deaths, during and after the intensive educational period. Finally, in the seven countries study (Farchi et al., 1987), indices of risk related to coronary disease also predict noncardiovascular and all causes of death, suggesting common factors in causation.

One relatively new issue requires further elaboration, that is, an individual correlation, found first within Japanese populations, between low serum cholesterol level and risk of stroke. With increasing diagnostic discrimination between cerebral hemorrhage and atherothrombotic disease, the picture has become clearer. It shows an inverse relation between individual blood cholesterol level and risk of cerebral hemorrhage and a positive association with atherothrombotic stroke. Similarly, in the large population (360,000) of those screened for the MFRIT program, after 6 years there was a substantial excess of deaths from cerebral hemorrhage in that small subsegment of the population having blood pressure greater than 90 mmHg diastolic and blood total cholesterol below 160 mg/dl (H. Iso et al., personal communication). However, dietary factors, alcohol intake, aspirin use, and other potential confounders were not adequately accounted for in any of the studies.

In summary, the population strategy of prevention and health promotion for CVDs is firmly based in

evidence. Preventive strategies against risk are likely to benefit the population and unlikely to harm subgroups of the population. The principal issues remaining are about the feasibility, effectiveness, and cost of preventive undertakings.

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