

THE SEVEN COUNTRIES STUDY.

OBJECTIVES AND HISTORY*

*Henry Blackburn***

SUMMARY

The Seven Countries Study is a prototypical comparison of populations made across a wide range of diet, life style, risk, and disease experience. It was the first to explore associations among diet, life style, risk, and disease in contrasting populations (ecologic correlations). There were, of course, limitations: the relatively small number of units for ecological correlations; the selection of the samples in the different geographic areas in part for reasons of convenience; the technical challenges of conducting surveys across cultures by national teams, often working under difficult field conditions. But the study was unique for its time in standardisation of measurements for diet, risk factors, and disease, in training its survey teams, for its high response rates, and for the central, blind-fold coding and analysis of the data. It produced in the end powerful evidence for the causes of population differences in rates of the common cardiovascular diseases and thus a sound base for prevention policy and program.

INTRODUCTION

The Seven Countries Study was the first to examine systematically the relation among diet, lifestyle, risk factors and the rates of coronary heart disease and stroke in contrasting populations.¹⁻⁶ The idea of the study arose in various forms in the minds of individuals capable of integrating clinical, laboratory, and population evidence and curious about the origins and possible prevention of these diseases. Ancel Keys, the leader of the study, gave the concept its scope, design, impetus, and direction. He coordinated the program in seven countries, Yugoslavia, Greece, Italy, Netherlands, Finland, Japan and the United States, working from the Labo-

ratory of Physiological Hygiene, School of Public Health, University of Minnesota, Stadium Gate 27, in Minneapolis.

In the mid-1950s, when the Seven Countries Study (SCS) was mounted, there was no “big science” and nothing like a Program Project existed in the agenda of the new National Institutes of Health of the USA. So there was neither precedent nor support for an optimally organised, rigorously and centrally directed, adequately funded, multi-center epidemiological undertaking. The Seven Countries Study was, nevertheless, pioneering and forward-looking for its day. It developed methods and tested major hypotheses of diet, lifestyle, and disease. It measured

* Extracto do artigo publicado em “Prevention of Coronary Heart Disease. Diet, lifestyle and risk factors in the Seven Countries Study”, D. Kromhout, A. Menotti, H. Blackburn (eds), The Netherlands, Kluwer Academic Publishers, 2002, pps. 267. Publicação autorizada pelo autor.

** Professor, MD, Division of Epidemiology, School of Public Health, University of Minnesota, MN 55454, USA

prevalence, incidence, risk characteristics, and rates of major cardiovascular diseases, both for individuals and among contrasting populations.

HYPOTHESES

Keys and colleagues posed the hypothesis that differences among populations in the frequency of coronary disease and stroke would occur in some orderly relation to physical characteristics and lifestyle, particularly composition of the diet, and especially of fatty acids in the diet, and to levels of serum cholesterol.

BACKGROUND AND PILOT STUDIES

The background of the study lies in Keys's application to health of physiological principles and knowledge in a quantitative human biology that he called physiological hygiene. The war-time observations and experiments of Keys and colleagues at Minnesota profoundly changed their thinking about the modifiability, by diet composition, calorie restriction, exercise, and bed rest, of such presumably immutable attributes as body build and type, circulatory responses, and blood pressure and cholesterol levels. Moreover, Keys facility with computation, including regression equations, extended their thinking to correlations among individual levels, and then among population levels, of risk attributes, diet, behaviour, and disease rates. Keys was also particularly impressed at the time with news reports of an apparent epidemic of heart attacks among executives in the U.S. and with reports in the medical literature of a dra-

matic fall and subsequent rise of cardiac deaths, especially in northern Europe, during and after World War II. He set about to study the characteristics of executives in health with the intent to follow them for the risk of later disease. Inadequate in numbers and ranges of variables, the Minnesota Business and Professional Men's Study became, nevertheless, a pioneer longitudinal epidemiological study of cardiovascular diseases and a crucial predecessor to the Seven Countries Study.

But it was Keys's Sabbatical year at Oxford and related world travels in 1951-1952, which opened the larger issues of cultural differences in diet, behaviour, cholesterol levels and disease risk. It led to discussions with nutritional and clinical scientists such as Hugh Sinclair, Flaminio Fidanza, John Brock and others already beginning to ponder such population differences. The contrasts they explored together in the course of a few years of the early 1950s, in eating patterns, nutrient intake, blood cholesterol levels (and vital statistics on heart attack rates) by social or occupational class, in Italy, Spain, Yugoslavia, South Africa, and Japan, set off Keys's wider questioning. This led, in turn, to his conceptual formulations about the relation of mass cultural phenomena to the population burden of major heart diseases. This rich preparation and experience led Keys and colleagues in the mid 1950s to a broad view of human biology and health. At the same historical moment, opportunities for research grew from expansion in the USA of the review and support role of the National Institutes of Health and its new National Heart Institute. At this time also, Keys's match-up with great clinicians

completed the picture: he sought out, or they sought him, such leaders as Paul Dudley White of Boston (then the first Executive Director of the new National Heart Institute), Christ Aravanis of Athens, John Brock of Capetown, Martti Karvonen of Helsinki, Noboru Kimura of Japan, and Vittorio Puddu of Rome. All these remarkable physicians saw beyond the clinic and beyond the individual patient to the origins of common heart attacks in the population, its environment and culture. Distinguished nutritionists were soon brought into the picture: Cees den Hartog in the Netherlands, Paavo Roine in Finland, Flaminio Fidanza in Italy, and Ratko Buzina in Yugoslavia. Keys formulated all the ideas into grant proposals, and over the years of the study, into syntheses of the study's major monographs. But first, there were field methods to develop and pilot studies to carry out to provide evidence sufficient to back the assumptions of the central proposal and grant application to NIH. Keys, Anderson, and Grande in Minnesota pioneered modifications of chemical measurement of blood lipids and diet analyses, including measured serum samples dried on filter paper. Taylor developed sampling and recruitment and scheduling strategies for the field surveys; Brozek established standard anthropometric measures related to body mass, body configuration, and body fat distribution, while Blackburn, Rautaharju, Rose and colleagues developed protocols for medical history and physical examinations, blood pressure, electrocardiography and stress testing, and diagnosis-related classifications including the Minnesota Code.⁷

Keys then enlisted the collaboration of enthusiastic colleagues in Finland (Karvonen), the Netherlands (Dalderup), Italy (Fidanza and Puddu), former Yugoslavia (Buzina and Djordjevic), Greece (Aravanis and Dontas), Japan (Kimura), and the USA (Taylor and Blackburn), and launched pilot surveys in fall of 1956 in Finland and in 1957 in Italy and Crete. There the feasibility was tested of recruitment and survey examinations among total samples of rural populations of men in the target ages, 40-59. This pilot experience was conveyed in a formal application to NIH for central coordination of the study at Minnesota and for conduct of field surveys in selected regions. Henry Taylor's NIH-funded study among U.S. railworkers was treated at the outset as a non-comparable industrial U.S. population; its counterpart in Italy, the Rome Railway Study, was added in 1963. Ancel Keys recruited the core of investigator teams and coordinated the study from the Laboratory of Physiological Hygiene located in offices under Memorial Stadium, Gate 27, at the University of Minnesota. Henry Blackburn served as Project Officer in the early years and in 1972, central coordination of follow-up and field clinical data was shifted to Alessandro Menotti at the University of Rome. All field studies were carried out under the aegis of a National Heart Institute grant (#HE04697). Local support was substantial throughout, however, in that the central grant averaged only about \$25,000 a year per collaborating center. Both public and private sources, as well as the American Heart Association and World Health Organization, provided either direct or logistic support.

SEVEN COUNTRIES STUDY SURVEYS BEGIN

The baseline round of formal Seven Countries surveys was carried out from 1958 to 1964 in total populations of men ages 40-59, in 16 areas of the seven countries. The second and third rounds were carried out in the same season of the year, 5 and 10 years later. Follow-up for deaths in the cohorts continues to the present day. Most of the areas were stable and rural and had large and obvious contrasts in habitual diet. Central chemical analysis of foods consumed among randomly selected families in each area, plus diet recall measures in some areas, allowed an effective test of the dietary hypothesis. Little more than hearsay and crude vital statistics were then available about comparative coronary or stroke death rates in those regions. At the time, women were not considered for study because of the apparent great rarity of cardiac events among them and the invasiveness of the field examinations.

PUBLICATIONS OF THE SEVEN COUNTRIES STUDY

The methods, baseline findings, and the first 5 and 10-years' observations of the Seven Countries Study were published in major monographs referenced below in 1967, 1968, 1970, and 1980.¹⁻⁴ Since that time, emphasis has shifted to individual presentations in the world literature.

BOOKS AND MONOGRAPHS

1. Keys A, Aravanis C, Blackburn HW, Van Buchem FSP, Buzina R, Djordjevic BS, Dontas AS, Fidanza F, Karvonen MJ, Kimura N, Lekos D, Monti M, Puddu V, Taylor HL. Epidemiological studies related to coronary heart disease. Characteristics of men aged 40-59 in Seven Countries. *Acta Med Scand* 1967;460 (Suppl.180):392 pp.
2. Den Hartog C, Buzina R, Fidanza F, Keys A, Roine P. Dietary studies and epidemiology of heart diseases. Stichting tot wetenschappelijke Voorlichting op Voedingsgebied, The Hague, The Netherlands 1968. 157 pp.
3. Keys A (Ed). Coronary heart disease in seven countries. *Circulation* 1970;41(Suppl.1):211 pp.
4. Keys A, Aravanis C, Blackburn H, Buzina R, Djordjevic BS, Dontas AS, Fidanza F, Karvonen MJ, Kimura N, Menotti A, Mohacek I, Nedeljkovi S, Puddu V, Punsar S, Taylor HL, Van Buchem FSP. Seven Countries. A multivariate analysis of death and coronary heart disease. Cambridge, MA; Harvard University Press, ISBN: 0-674-80237-3, 1980. 381 pp.
5. Kromhout D, Menotti A, Blackburn H (Eds). The Seven Countries Study: A scientific adventure in cardiovascular disease epidemiology. Brouwer Offset b.v., Utrecht, ISBN 90-6960-048-x, 1994. 219 pp.
6. Toshima H, Koga Y, Blackburn H, Keys A (Eds). Lessons for science from the Seven Countries Study. Springer Verlag, Berlin, Heidelberg, New York, Tokyo. ISBN 3-540-70140-0, 1994. 243 pp.
7. Rose G, Blackburn H. Cardiovascular Survey Methods. World Health Organization, Geneva. 1968. 188 pp.



Henry Blackburn. (Crédito fotográfico ao próprio)