



## Epidemiology in History

# The Origins and Early Evolution of Epidemiologic Research in Cardiovascular Diseases: A Tabular Record of Cohort and Case-Control Studies and Preventive Trials Initiated From 1946 to 1976

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This article serves as a ready reference guide to the pioneering formal studies in cardiovascular disease (CVD) epidemiology initiated during 3 decades of the subject's evolution into an established academic field that contributed to the public health. The article is not intended to be a history of CVD epidemiology or an editorial about its significance. The appended tables include the titles and starting dates of the early studies, the names of their principal investigators, and references to a single defining article from each. The early observational studies of CVD epidemiology provided a widely useful CVD risk-factor paradigm. The early clinical trials justified the more definitive preventive trials of the 1980s and beyond. This early research in populations, along with others in clinics and laboratories, led to greater understanding of the causes of CVD, to a vigorous practice of preventive cardiology, and to national policy and programs of health promotion, all of which were coincident with a 50-year decline in CVD mortality rates.

cardiovascular disease; case-control studies; cohort studies; trials

Abbreviation: CVD, cardiovascular disease.

*The great and wonderful success story—not to say—saga—of CVD epidemiology—is rooted in the accumulated knowledge gained over a remarkably short space of time in a number of countries from an even larger number of studies. The wonder and fascination lies in having been able to build a solid, coherent, and powerful theory of causation as a starting point for preventive action.*

—Frederick Epstein (1)

In a pioneering period of chronic disease epidemiologic research—from Gertler and White's (2) 1946 Harvard study of risk characteristics among 100 young coronary patients versus controls to cohort studies of varied groups in the United States, Britain, the European Continent, and Japan—a wave of cardiovascular disease (CVD) preventive research swept the world. These studies among populations, along with prevention research conducted in clinics and laboratories, were an enthusiastic and rapid response of the scientific community—mainly nonepidemiologists—to the epidemic of heart attacks that was recognized soon after World War II.

Absent an authoritative academic text on the history of CVD epidemiology, some documentation of the origins and early evolution of this new science, as well as of the community of investigators and institutions that nurtured it, may be found in modern literature (3–6). That history is also accessible from a dedicated archive and website of the University of Minnesota School of Public Health (7).

The tabular presentation herein is not, in itself, a history of CVD epidemiology; rather, it is a ready reference to the early literature that comprises that history. The tables ignore less formal but nonetheless influential historical elements upon which formal CVD epidemiology was built. The sources tabulated here exclude the following:

- Accounts of informal observations by medical “Marco Polos,” that is, astute travelers who encountered people having apparently few CVD events in one place and populations with an apparently great CVD burden in another. Voyagers returned from foreign lands with new and researchable ideas about possible causes of the apparent cultural differences. A critical

**Table 1.** Cohort Studies Initiated From 1946 to 1976

| Defining Publication of the Study <sup>a</sup> | Common Name of the Study                                | Principal Investigator              | Start Date |
|------------------------------------------------|---------------------------------------------------------|-------------------------------------|------------|
| Gertler and White, 1954 (2) <sup>b</sup>       | Coronary Heart Disease in Young Adults                  | P. D. White                         | 1946       |
| Keys et al., 1963 (16)                         | Minnesota Business and Professional Men Study           | A. Keys                             | 1947       |
| Dawber et al., 1957 (17)                       | Framingham Heart Study                                  | T. R. Dawber                        | 1948       |
| Thomas, 1951 (18)                              | Johns Hopkins Precursors Study                          | C. B. Thomas                        | 1948       |
| Chapman et al., 1957 (19)                      | Los Angeles Civil Servants Study                        | J. Chapman                          | 1949       |
| Morris et al., 1953 (20)                       | London Transport and Postal Workers Studies             | J. Morris                           | 1949       |
| Paffenbarger et al., 1970 (21)                 | California Longshoremen Study                           | R. Paffenbarger                     | 1951       |
| Doll and Hill, 1954 (22)                       | British Doctors Study                                   | R. Doll and B. Hill                 | 1951       |
| Cooperative Lipoprotein Study Group, 1956 (23) | Cooperative Lipoprotein Study                           | Cooperative Lipoprotein Study Group | 1952       |
| Doyle et al., 1957 (24)                        | Albany Civil Servants Study                             | J. Doyle                            | 1953       |
| Pell and D'Alonzo, 1961 (25)                   | Dupont Company Study                                    | S. Pell and C. A. D'Alonzo          | 1956       |
| Keys, 1980 (26)                                | Seven Countries Study                                   | A. Keys                             | 1957       |
| Paul et al., 1963 (27)                         | Chicago Western Electric Study                          | O. Paul                             | 1957       |
| Taylor et al., 1970 (28)                       | US Railway Study                                        | H. L. Taylor                        | 1957       |
| Stamler et al., 1960 (29)                      | Chicago Peoples Gas Company Study                       | J. Stamler                          | 1958       |
| Epstein et al., 1965 (30)                      | Tecumseh Community Health Study                         | T. Francis, Jr.                     | 1959       |
| Keil et al., 1977 (31)                         | Charleston Heart Study                                  | E. Boyle                            | 1960       |
| Rosenman et al., 1966 (32)                     | Western Collaborative Group Study                       | R. H. Rosenman                      | 1960       |
| Hames, 1971 (33)                               | Evans County Heart Study                                | C. Hames                            | 1960       |
| Carlson and Lindstedt, 1968 (34)               | Stockholm Study                                         | L. A. Carlson                       | 1961       |
| Sadoshima et al., 1980 (35)                    | Hisayama Study                                          | S. Sadoshima                        | 1961       |
| Paffenbarger et al., 1978 (36)                 | Harvard Alumni Study                                    | R. Paffenbarger                     | 1962       |
| Komachi et al., 1971 (37)                      | Osaka Study                                             | Y. Komachi                          | 1963       |
| Medalie et al., 1973 (38)                      | Israel Ischemic Heart Disease Study                     | J. H. Medalie                       | 1963       |
| Tibblin et al., 1975 (39)                      | Göteborg Study of Men Born in 1913                      | G. Tibblin                          | 1963       |
| Marmot et al., 1975 (40)                       | Ni-Hon-San Study                                        | Ni-Hon-San Study Group              | 1963       |
| Breslow and Breslow, 1993 (41)                 | Alameda County Study                                    | L. Breslow                          | 1964       |
| Cutler, 1967 (42)                              | Seal Beach Study                                        | R. A. Stallones                     | 1964       |
| Hagerup, 1974 (43)                             | Glostrup Study                                          | L. M. Hagerup                       | 1964       |
| Trombold et al., 1966 (44)                     | Honolulu Heart Study                                    | A. Kagan                            | 1964       |
| Kornitzer et al., 1993 (45)                    | Belgian Bank Study                                      | M. Kornitzer                        | 1964       |
| Kozarevic et al., 1981 (46)                    | Yugoslavia Cardiovascular Disease Study                 | D. Kozarevic                        | 1964       |
| Connolly et al., 1981 (47)                     | Olmsted County Study                                    | D. C. Connolly                      | 1965       |
| García-Palmieri et al., 1978 (48)              | Puerto Rico Cardiovascular Disease Study                | R. Garcia-Palmieri                  | 1965       |
| Reunanen et al., 1983. (49)                    | Finnish Social Insurance Institution Study              | A. Aromaa                           | 1966       |
| Pyörälä et al., 1979 (50)                      | Helsinki Policemen Study                                | K. Pyörälä                          | 1966       |
| Welborn et al., 1969 (51)                      | Busselton Health Study                                  | T. A. Welborn                       | 1966       |
| Marmot et al., 1984 (52)                       | Whitehall I Study                                       | M. Marmot                           | 1967       |
| Stamler et al., 1975 (53)                      | Chicago Heart Association Detection Project in Industry | J. Stamler                          | 1967       |
| Jouven et al., 1998 (54)                       | Paris Prospective Study                                 | J. Richard                          | 1967       |
| Bengtsson, 1973 (55)                           | Prospective Study of Swedish Women                      | C. Bengtsson                        | 1968       |

Table continues

Table 1. Continued

| Defining Publication of the Study <sup>a</sup>                       | Common Name of the Study                | Principal Investigator                                    | Start Date |
|----------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------|------------|
| Lannerstad et al., 1977 (56)                                         | Malmö Study of Men Born in 1914         | O. Lannerstad                                             | 1970       |
| The Lipid Research Clinics Program Epidemiology Committee, 1979 (57) | Lipid Research Clinics Population Study | The Lipid Research Clinics Program Epidemiology Committee | 1971       |
| Lauer et al., 1975 (58)                                              | Muscantine Iowa Study                   | R. M. Lauer                                               | 1971       |
| Berenson et al., 1978 (59)                                           | Bogalusa Heart Study                    | G. Berenson                                               | 1972       |
| Hawthorne et al., 1995 (60)                                          | Paisley-Renfrew Study                   | V. M. Hawthorne                                           | 1972       |
| Holme et al., 1980 (61)                                              | Oslo Study (Cohort)                     | P. Leren                                                  | 1972       |
| Schnohr et al., 1977 (62)                                            | Copenhagen City Heart Study             | P. Schnohr                                                | 1976       |

Abbreviation: Ni-Hon-San, Nippon, Honolulu, San Francisco.

<sup>a</sup> The references are those that either defined the particular study and called international attention to it or presented the first substantive results. They are usually neither the very first nor the summative or final study reports.

<sup>b</sup> This study in young coronary patients began in 1946 as a case-control study and is included here because it was later converted into a prospective study of the cohort that was followed for 25 years with pair-matched and unmatched controls.

few among these travelers recognized that such widely contrasting “natural experiments” indicated powerful environmental and behavioral influences on CVD and thus the potential for prevention (8).

- Salient clinical studies, such as a large case-series of coronary disease in the US armed forces by Yater et al. (9), and systematic comparisons of arterial pathology across cultures, such as the International Geopathological Study by Strong et al. (10) from New Orleans.
- Cross-sectional surveys of CVD risk factors and prevalence, either single or serial, in which individuals were not subsequently followed (and thus were not cohort studies).

This tabulation of articles from CVD epidemiologic studies initiated between 1946 and 1976 includes the following:

- Formal prospective studies among varied cohorts (Table 1) and experiments as prevention trials (Table 2). Case-control comparisons, so fruitful in cancer epidemiology, were uniquely uncommon in early CVD epidemiology and played no role in construction of the popular CVD risk profile. Here, for the sake of completeness and consistency, the entirety of early case-control literature for CVD is included in Table 3, comprising 3 articles, 2 of which were analyses from the Framingham Study. (Nested case-control comparisons have since come into substantial use in post hoc analyses, often of newer ideas about risk, carried out in long-term data bases of large cohort studies.)

## THE TABULATIONS

Publications from early population studies and trials of CVD prevention initiated between 1946 and 1976 are catalogued here to facilitate pursuit of the historic beginnings of CVD epidemiology. “Initiation” refers to the approximate start of data collection in each study, which usually followed extensive planning, collaboration, and pilot studies. The tables are intended for use by students and scholars of CVD, public health, and the history

of science. The publications chosen (1 per study) are those that either defined the particular study and called international attention to it or that presented the first substantive results. Therefore, the articles are often neither the very first nor the summative or final report from a given study.

A few of the earliest diet trials are labeled with a note indicating the studies were inadequately controlled, and thus their conclusions about diet effects were questionable. Those articles are included in this collection because of their impact at the time: They were led by noted investigators, they were published after review by prestigious journals, and their conclusions were widely, if erroneously, accepted.

## CONTEXT

A remarkable element of this array of historical observational studies (Tables 1 and 3) is the overwhelming early adoption of cohort design, that is, a baseline survey to establish personal characteristics and CVD prevalence at entry, with follow-up observations of varied duration for rates of CVD events and deaths. This more expensive and “patient” cohort strategy was chosen over case-control design because of its strength and for its simplicity: It was a straightforward design readily understood by CVD investigators who had insufficient training or understanding of the complexities of case-control comparisons.

An additional strong feature of these early epidemiologic studies was the prominent use of whole or healthy population cohorts, thus providing greatest relevance to primary prevention. Another was the great variety of populations recruited. Study initiators used whatever population was at hand: an accessible organization, industry, school, or community. This variety of samples had positive implications for the generalizability of the several CVD risk characteristics that were consistently found.

## EVOLUTION

Despite stumbling performance—frequently by the pioneering CVD experts who were untrained in epidemiology or trial

**Table 2.** Prevention Trials Initiated From 1946 to 1976

| Defining Publication of the Trial <sup>a</sup>                            | Common Name of the Trial                                     | Diet, Drug, or Lifestyle Advice               | Principal Investigator                                         | Start Date |
|---------------------------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------|------------|
| <i>Diet</i>                                                               |                                                              |                                               |                                                                |            |
| Morrison, 1951 <sup>b</sup> (63)                                          | Morrison Diet-Heart Study                                    | Diet <sup>c</sup>                             | L. M. Morrison                                                 | 1946       |
| Christakis et al., 1966 <sup>b</sup> (64)                                 | Anti-Coronary Club Trial                                     | Diet <sup>d</sup>                             | G. Christakis                                                  | 1957       |
| Leren, 1966 (65)                                                          | Oslo Diet-Heart Study                                        | Diet <sup>c</sup>                             | P. Leren                                                       | 1957       |
| Turpeinen et al., 1968 (66)                                               | Finnish Mental Hospital Study                                | Diet <sup>d</sup>                             | O. Turpeinen                                                   | 1958       |
| Dayton et al., 1968 (67)                                                  | Wadsworth Veterans Administration Domiciliary Hospital Study | Diet <sup>d</sup>                             | S. Dayton                                                      | 1959       |
| Bierenbaum et al., 1967 <sup>b</sup> (68)                                 | Bierenbaum-St. Vincent's Hospital Study                      | Diet <sup>c</sup>                             | M. L. Bierenbaum                                               | 1959       |
| British Medical Research Council, 1968 (69)                               | British MRC Soya-Bean Oil Trial                              | Diet <sup>c</sup>                             | British Medical Research Council                               | 1960       |
| National Diet-Heart Research Group, 1968 (70)                             | National Diet Heart Pilot Trial                              | Diet <sup>d</sup> (pilot)                     | National Diet-Heart Research Group                             | 1962       |
| <i>Drugs: Cholesterol Lowering</i>                                        |                                                              |                                               |                                                                |            |
| Committee of Principal Investigators, 1984 (71)                           | WHO Cooperative (Clofibrate) Trial                           | Drugs <sup>d</sup>                            | Committee of Principal Investigators (M. Oliver, chairman)     | 1962       |
| Research Committee of the Scottish Society of Physicians, 1971 (72)       | Scottish Society of Physicians Clofibrate Trial              | Drug <sup>c</sup>                             | Research Committee of the Scottish Society of Physicians       | 1964       |
| Krasno and Kidera, 1972 (73)                                              | United Airlines Study                                        | Drug <sup>c</sup> and drug <sup>d</sup>       | L. R. Krasno                                                   | 1966       |
| Coronary Drug Project Research Group, 1977 (74)                           | Coronary Drug Project                                        | Diet <sup>c</sup>                             | Coronary Drug Project Research Group (J. Stamler, chairman)    | 1966       |
| Carlson and Rosenhamer, 1988 (75)                                         | Stockholm Prevention Trial with Clofibrate and Niacin        | Drug <sup>c</sup>                             | L. A. Carlson                                                  | 1972       |
| The Lipid Research Clinics Program Group, 1984 (76)                       | Lipid Research Clinics Coronary Primary Prevention Trial     | Drug <sup>d</sup>                             | Lipid Research Clinics Program Group                           | 1973       |
| <i>Hypertension</i>                                                       |                                                              |                                               |                                                                |            |
| VA Cooperative Study on Hypertension, 1967 (77)                           | VA Cooperative Study on Hypertension                         | Drug <sup>d</sup>                             | E. D. Freis (chair)                                            | 1962       |
| VA Cooperative Study on Hypertension, 1970 (78)                           | VA Cooperative Study on Hypertension                         | Drug <sup>d</sup>                             | E. D. Freis (chair)                                            | 1962       |
| Smith, 1977 (79)                                                          | US Public Health Service Hospitals Cooperative Study         | Drug <sup>d</sup>                             | W. McFate Smith                                                | 1966       |
| Hypertension Detection and Follow-up Program Cooperative Group, 1979 (80) | Hypertension Detection and Follow-up Program                 | Diet and drug <sup>d</sup>                    | Hypertension Detection and Follow-up Program Cooperative Group | 1971       |
| Helgeland (81)                                                            | The Oslo Study on Mild Hypertension I                        | Drug <sup>d</sup>                             | A. Helgeland                                                   | 1972       |
| Amery et al., 1985 (82)                                                   | European Working Party on High Blood Pressure in the Elderly | Drug <sup>d</sup>                             | A. Amery                                                       | 1972       |
| Parry, 1980 (83)                                                          | Australian National Blood Pressure Study                     | Drug <sup>d</sup>                             | Management Committee                                           | 1973       |
| <i>Smoking</i>                                                            |                                                              |                                               |                                                                |            |
| Rose et al., 1982 (84)                                                    | Whitehall Anti-Smoking Trial                                 | Lifestyle and antismoking advice <sup>d</sup> | G. Rose                                                        | 1972       |
| <i>Multifactorial</i>                                                     |                                                              |                                               |                                                                |            |
| University Group Diabetes Program Group, 1970 (85)                        | University Group Diabetes Program                            | Drug and diet <sup>d</sup>                    | University Group Diabetes Program Group                        | 1960       |

Table continues

**Table 2.** Continued

| Defining Publication of the Trial <sup>a</sup>           | Common Name of the Trial                                                                | Diet, Drug, or Lifestyle Advice                             | Principal Investigator                        | Start Date |
|----------------------------------------------------------|-----------------------------------------------------------------------------------------|-------------------------------------------------------------|-----------------------------------------------|------------|
| Wilhelmsen et al., 1986 (86)                             | Göteborg Multifactorial Primary Prevention Trial                                        | Diet and drug <sup>d</sup>                                  | L. Wilhelmsen                                 | 1970       |
| Rose et al., 1983 (87)                                   | WHO European Collaborative Trial of Multifactorial Prevention of Coronary Heart Disease | Lifestyle advice and treatment of hypertension <sup>d</sup> | WHO Collaborative Group (G. Rose, chair)      | 1971       |
| Multiple Risk Factor Intervention Trial Group, 1976 (88) | Multiple Risk Factor Intervention Trial                                                 | Diet and drug <sup>d</sup>                                  | Multiple Risk Factor Intervention Trial Group | 1971       |
| Hjermann, 1980 (89)                                      | Oslo Study of Diet and Anti-Smoking Advice                                              | Diet and antismoking advice <sup>d</sup>                    | I. Hjermann                                   | 1972       |
| Miettinen et al., 1985 (90)                              | Multifactorial Cardiovascular Disease Prevention Trial in Helsinki Businessmen          | Diet, antismoking advice, and drugs <sup>d</sup>            | T. A. Miettinen                               | 1974       |

<sup>a</sup> The references are those that either defined the particular study and called international attention to it or presented the first substantive results. They are usually neither the very first nor the summative or final study reports.

<sup>b</sup> Nonrandomized controls.

<sup>c</sup> Secondary prevention.

<sup>d</sup> Primary prevention.

design—the magnitude, sophistication, and fruits of research on population rates and on risk of CVD advanced rapidly after World War II. The curiosity of the early investigators and the intense postwar period of prospective studies, particularly among healthy cohorts, established by the mid-1970s a risk-factor paradigm for CVD that proved universally useful in the research, practice, and policy of prevention. During 3 decades of combined, focused clinical, laboratory, and epidemiologic research from the mid-1940s to the mid-‘70s, sufficient evidence was brought forward to provoke the greater systemic efforts required to better understand and modify the underlying disease processes of atherosclerosis and hypertension.

The combined enterprise of this early period led to greater acceptance, support, and research volume in CVD epidemiology, a prime stimulus for which was the advent of new policy at the US National Institutes of Health that soon followed by measures from the World Health Organization and various national heart foundations. Under pressure from and the guidance of expert recommendations from the science community (11–13), Theodore Cooper, Director of the National Heart and Lung Institute (now the National Heart, Lung, and Blood Institute), announced a broad US policy and program of CVD prevention at the 1971

Annual Scientific Sessions of the American Heart Association (14). This was promptly translated into new prospective studies, trials, and community education programs (on tobacco use, hypertension control, and diet and blood lipids), as well as a proliferation in teaching and practice of CVD epidemiology and preventive cardiology. The ultimate mission was to prevent CVD in the individual and among the population at large.

Beginning in the late 1960s and continuing today, CVD death rates have declined in many industrial countries; there have also been favorable trends in health knowledge and behavior and in cardiac care (3). The average decline in age-adjusted CVD mortality rate from its US peak in 1968 was 3% per year for the decades 1968–1997 and 5% per year from 1998 to 2008 (15). Similar rates of decline occurred in other industrial countries, with wide variations among the regions and ethnic groups of those countries.

Nevertheless, today much of the world is experiencing rapid socioeconomic development, with new exposures and behaviors accompanied by a scourge of mass obesity and metabolic diseases. Concerned scholars of this new epidemic should profit from the lessons of history reflected in these early reports, as well as from today’s improved epidemiologic skills.

**Table 3.** Case-Control Studies Initiated From 1946 to 1976

| Defining Publication of the Study <sup>a</sup> | Common Name of the Study                                    | Principal Investigator | Dates of the Study |
|------------------------------------------------|-------------------------------------------------------------|------------------------|--------------------|
| Gertler and White, 1954 (2) <sup>b</sup>       | Coronary Heart Disease in Young Adults                      | P.D. White             | 1946–1954          |
| Friedman et al., 1966 (91)                     | Case-control versus cohort analysis in the Framingham Study | G. D. Friedman         | 1964               |
| Friedman et al., 1974 (92)                     | Case-Control Study of Standard Risk Factors                 | G. D. Friedman         | 1972–1973          |

<sup>a</sup> The references are those that either defined the particular study and called international attention to it or presented the first substantive results. They are usually neither the very first nor the summative or final study reports.

<sup>b</sup> This study was converted to a prospective study of the cohort with both pair-matched and unmatched controls, then followed for 25 years.



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