THE FRAMINGHAM STUDY

An Epidemiological Investigation of Cardiovascular Disease

Section 34: Some Risk Factors Related to the Annual Incidence of Cardiovascular Disease and Death Using Pooled Repeated Biennial Measurements: Framingham Heart Study, 30-Year Pollowup

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Some Risk Factors Related to the Annual Incidence of Cardiovasclar Disease and Death Using Pooled Repeated Biennal Measurements: Framingham Heart Study, 30-Year follow-Up

Since 1948 the Framingham Heart Study has followed a sample of adults who in 1948 were residents of the town of Framingham, Massachusetts for development of cardiovascular disease. A standardized clinic examination was repeated at two-year intervals. By this means a wide variety of information has been collected which includes the characteristics of people in this study cohort both before and after the development of cardiovascular disease, as well as a standardized clinical evaluation of changes in their cardiovascular status. In addition, information about death and the development and course of disease has been obtained from a number of sources outside the clinic.

The design and execution of the Study were described in Sections 1 and 2 of 'this series of monographs. A complete listing of prior monographs in this series is included at the end of this section. For some characteristics, mean values are given for the first seven examinations in Sections 3 and 4, and bivariate correlations are given for the second examination in Section 5. This material is updated in Section 29. The incidence of various events is given in Sections 6, 7, and 8. Criteria for events are given in Section 8, and a description of the characteristics in Section 3. These are repeated and updated in Sections 26, 30 and in this report.

The major concern of the Study has been the evaluation of the relationship of potential risk factors-determined-in healthy individuals to the subsequent development of disease. This is done in a systematic fashion in Sections 9 through 22, using the 14 year followup. The same general material updated to include 16 years of followup is presented in Sections 26 and 27. Section 30 reports similar results for 18 years of followup. The present report is an update for 30 years of followup. Evaluation of survival following cardiovascular events has been examined in Sections 25 and 32.

Like earlier monographs in this series, this section is exclusively a display of data which provides detailed information for those who wish to interpret and use them for program planning, teaching, reviews and for comparison with their own data. The additional followup provides a more substantial body of data in the geriatric age groups, for women, and for the less common cardiovascular endpoints.

METHODOLOGY

One method of examining the relationship between potential risk factors and the development of disease is to measure the risk factors at a single moment in time and to follow

individuals in time to observe the incidence of disease. For example, in this study we could utilize the measurement of risk factors at exam 1 and report incidence over 30 years of followup according to different levels of these exam 1 measurements to ascertain whether a risk factor is associated with the subsequent development of disease. In this case, information obtained in exams 2 through 15 would be ignored. Since individuals change over time, this interim information which could influence the outcome would be lost.

The methodology in this section utilizes all measurements determined on Exams 1 through 15 for those risk factors recorded virtually every two years and relates the risk factors to the occurrence of an event within two years after the exam. Other characteristics measured. on only a few examinations are not included in -this monograph. We refer to this approach of employing the- biennial observations as the cross-sectional pooling method.

This method evaluates each two-year interval as a new short-term followup study. After being characterized at entry into the study, persons are characterized anew at each following biennial examination. Hence, a person who attended twelve of the fifteen examinations during the 30-year followup contributes the information of twelve persons who enter- the study at the beginning of a two-year cycle with the risk factors measured at the twelve examinations. More accurately, this person contributes the information of twelve person exams. To implement this approach, an observation is generated for each examination. The information obtained on the 15 two-year intervals is then pooled to obtain a file from which two-year predictions can be examined.

This method is to be distinguished from the long-term perspective described earlier in which observations only from exam 1 are employed to examine the development of disease over 30 years of followup. The cross-sectional pooling method as implemented in this section considers only the next two years of followup, given an individual's current age, sex, and risk factor status. The inherent assumption is that only the current risk factor status of an individual is needed to predict the risk of disease in the next two years.

DESCRIPTION OF TABLES

The tables in this section of the monograph series, Section 34, present data for 23 events and 19 potential risk factors. The tables are numerically sequenced according to the combination of an event and a risk factor with the numbers indexed as follows:

Numbering Scheme for Event-Risk Factor Combinations
Framingham Study Monograph 30-year Followup

EVENTS

1. Coronary Heart Disease
2. Coronary Heart Disease other than Angina Pectoris
3. Myocardial Infarction
4. Myocardial Infarction unrecognized
5. Myocardial Infarction recognized
6. Coronary Insufficiency
7. Angina Pectoris
8. Angina Pectoris uncomplicated
9. Sudden Coronary Death among persons free of CHD
10. Sudden Coronary Death among all persons
11. Coronary Heart Disease Death among persons free of CHD
12 Coronary Heart Disease Death among all persons
13. Stroke and Transient Ischemic Attack
14. Atherothrombotic Brain Infarction
15. Transient Ischemic Attack
16. Stroke Death among persons free of Stroke and TIA
17. Stroke Death among all persons
18. Intermittent Claudication
19. Congestive Heart Failure
20. Cardiovascular Disease
21. Cardiovascular Disease Death among persons free of CVD
22. Cardiovascular Disease Death among all persons
23. Death among all persons

RISK FACTORS

1. Systolic Blood Pressure, First examiner
2. Diastolic Blood Pressure, First examiner
3A. Hypertension with antihypertensive treatment
3B. Hypertension ignoring treatment
4. Serum Cholesterol
5. Hematocrit
6. Blood glucose
7. Diabetes mellitus
8. Glucose in Urine
9. Glucose intolerance
10. Metropolitan Relative Weight
11. Vital Capacity
12. Heart Rate
13. Cigarettes smoked per day
14. Albumin in Urine
15. Heart enlargement by x-ray
16. Left Ventricular Hypertrophy
17. Intraventricular conduction defect
18. Nonspecific T-wave or ST-segment abnormality by ECG

The numbering scheme on the tables indicates the number of the event first and then the number of the risk factor. For example, the table for Myocardial Infarction and Cigarettes smoked per day is numbered as 3-13.

Each **table displays** for each sex descriptive information on the relationship between the risk factor and the risk of the specified subsequent event in a two-year period. Logistic regression coefficients, for the risk factor, including univariate, bivariate with age at exam, and multivariate **analyses**, are displayed at the bottom of the table. The descriptive portion of the table displays annual rates for 6 age groups: 35-44, 45-54, 55-64, 65-74, 75-84, 85-94. Age-adjusted annual rates computed by the direct method are also given for age groups 35-64 and 65-94. Age-specific logistic regressions, using the above specified lo-year age groups, and regressions for age groups 35-64 and 65-94 are also based upon the t-do-year cross-sectional pooling method and indicate the risk of the event in the next two years of follow-up among persons free of the event at the beginning the two-year interval. However, the rates are expressed as the average annual rate per 1000.

The header of each table indicates the sex, event, risk factor, and the population at risk for each table. Each risk factor-event combination is presented on one page with the top half for males and the bottom for females.

Population at Risk

These tables report results only for persons free of cardiovascular disease at exam 1, so that any person with coronary heart disease, carebrovascular disease, intermittent claudication, or congestive heart failure is excluded from consideration. In addition, for non-fatal events the population at risk consists generally of persons free of the event under consideration at the beginning of a two-year interval. For coronary hear:: disease (CHD) events (tables 1-8), persons must be free of CHD. For cerebrovascular events (tables 13-15), persons must be free of stroke and transient ischemic attack (TIA). For intermittent claudication (IC) in table 18, congestive heart failure (CHF) in table 19, and cardiovascular disease (CVD) in table 20, persons must be free of these respective events. For fatal events, two tables are displayed, one for persons free of the disease at each exam interval and one for all persons free of cardiovascular disease at exam 1. For overall death, only the latter table is provided. tor CHD death events in tables 9 and 11 persons must be free of coronary heart disease while in tables 10 and 12 all persons free of cardiovascular disease at exam 1 are at risk including those with interim CHD events.

Risk Factor Description

The range of each risk factor, from the lowest to the highest value obsewed in the fifteen exams, is displayed in each table. The tables for hematocrit and vital capacity-height

index are the only tables which have different ranges for men and women.

Each individual is characterized by his or her value at an exam. If that value is unknown, the most recent, known value at a previous exam is used. An exception to this rule is diabetes mellitus (risk factor 7). Once a person is diagnosed as being diabetic, that person retains that diagnosis on all subsequent exams.

Results Reported

A table takes into account risk factors on all of the first fifteen examinations and the incidence of the specified event in the fifteen biennial intervals of the 30-year followup and consolidates this by the cross-sectional pooling method into an average annual incidence rate by age, sex, and level of the risk factor. The statistics shown are:

Person Exams

On each of the first fifteen examinations, persons who are free of cardiovascular disease at exam 1 and currently free of the event under consideration are considered at risk of developing the event in the next two-year interval. The person-exams column reports the number of all such exams from the persons at risk over the 30-year period. An individual who entered the study at exam 1 may contribute up to 15 observations, one for each exam at which he or she is at risk. Also, individuals can contribute to more than one age group over the 30 years of follow-up as long as that person is at risk of developing disease. Hence, the tables of this report do not yield the counts of people taking the exams. See Section 9 of the monograph series to obtain counts of persons distributed by various risk factors for the first seven exams.

# of Events

This column contains the number of subjects in the population at risk at an examination who develop a primary event in the two-year interval between that examination and the next. The numbers developing the event in a two-year interval are summed over the first fifteen examinations. The entries in this column are suppressed for an age group when fewer than five events occur in that age group.

Annual Rate

The annual rate is reported as the number of events per 1000 person years. It is obtained by dividing the number of events by twice the person exams to adjust for the two-year followup. This column is suppressed when fewer than five events occur in an age group.

Crude Annual Rate

In the middle of each page on the right, surniiary results are displayed for age groups 35-64 and 65-94. First, a column for

the sum of the events in the age group is given by level of the risk factor. Next, the crude annual rate per 1000 parson yearsis provided. It is computed by dividing the number of events by twice the population at risk (i.e. the total number of person exams). The latter can be obtained by summing the age-specific persons exams columns for the respective tan-year age groups.

Age-adiusted Annual Rate

The age-adjusted rates per 1000 person years are computed by the direct method (Fleiss, 1981) using the ten-year age group information provided. The standardizing age distribution employed for this computation is the total number of persons in each ten-year age group. Hence, each age-specific rate is weighted by the total number of persons in the age group, and the sum of the weighted products is then divided by the total number of persons in the standardizing age distribution. For example, the age-adjusted annual rate of CHD (Table 1-1) for persons 35-64 with systolic blood pressure in the range 74-119 is computed as

$$\frac{4472*(7/(2*1223)) + 7724*(21/(2*1769)) + 8049*(31/(2*1440))}{4472 + 7724 + 8049}$$

Logistic regression coefficients of the risk factor

In the bottom portion of the table, logistic regression coefficients for the risk factor, computed by the maximum likelihood method, are reported first, age-specific coefficients are given, then univariate, bivariate with age, and multivariate coefficients are reported for the 35-64 and 65-94 age groups.

The age-specific logistic regression coefficients are reported for each ten-year age group. The logistic model employed for these age-specific computations is

Pr(event in the next two years: =
p = 1/(1 + exp(-a - bX))

where a and b are the logistic parameters to be estimated and X is the value of the risk factor under consideration for a person in the population at risk. See Schlesselman (1982) for further explanation of the logistic model. According to the cross-sectional pooling approach, a person may contribute several observations to each computation as long as they remain in the .age group. The coefficient indicates the logarithm of the change in the odds of developing the event in the next two years for each unit increase in the risk factor among persons free of the event. To obtain the risk of developing disease in the next two years, the logistic model must be employed to estimate p.

Iterative maximum likelihood estimation procedures available in the "Logist" procedure of Supplemental Library of the Statistical Analysis System (SAS) were employed to obtain

estimates of the coefficients. This procedure utilizes zeros as initial values for the iterative procedure. When the procedure would not converge with these initial estimates, we employed starting values obtained from linear regression models.

when fewer than 5 events occur in an age group, the regression results are suppressed. In other situations where the regression coefficients are inestimable or nearly so, such as the case where all individuals who develop disease have the same value of the risk factor, dashes are displayed.

For continuous variables, the actual value of the risk factor is employed. The classes for categorical variables are indicated in the top portion of the table, and their coding is explained in the description of the risk factors in this report.

The univariate results report the logistic coefficients for the combined 35-64 and 65-94 age groups. Only the risk factor under consideration is included in the model in these computations.

The bivariate coefficients are computed from logistic models with age and the risk factor under consideration. These results are analogous to the age-adjusted rate computations, provided that the relationship between the risk factor and the event follows a logistic model with the log(p/(1-p)) changing in a linear fashion as the risk factor increases. The table displays only the coefficient for the risk factor under consideration and not the age coefficient.

The multivariate coefficients indicate the partial or "independent" effect of the risk factor after taking into account the risk factors known to be associated with cardiovascular disease: age, systolic blood pressure, serum cholesterol, cigarettes smoked per day, glucose intolerance, and electrocardiographic left ventricular hypertrophy. The table reports only the coefficient for the risk factor under consideration from the multiple logistic model:

$p = 1/(1 + \exp(-b_0 - b_i X_i))$

where Xi represents the risk factor under consideration and the other risk factors listed above. Generally, there are seven variables in this model. In cases where the risk factor under consideration is one of the known risk factors, there are six variables. Further, when the risk factor is highly correlated with one of the known risk factors, the model contains six variables. For example, when the risk factor is diastolic blood pressure or hypertension (tables 2, 3A and 3B), systolic blood pressure is dropped. For blood glucose, diabetes mellitus, and glucose in the urine (tables 6-8), glucose intolerance is dropped.

Standard Error of the Logistic Coefficient

The standard error of the logistic regression coefficients obtained from the second derivative of the information matrix and computed by the Logist procedure in SAS are reported in this column.

P-value

The p-value is obtained by computing the ratio of the logistic coefficient to its standard error and comparing it to the standard normal distribution.

Standardized Coefficient

The standardized logistic regression coefficient is computed as the product of the maximum likelihood coefficient obtained from the Logist procedure in SAS and the standard devjation of the risk factor in the population at risk. Standardized $b_i = b_i * SD(X_i)$ See Truett, Cornfield, Kannel (1967) and Schlesselman (1982) for a reference each standardized coefficient measures the change in the log odds or log (p/(1-p)) of risk for each change of one standard deviation of the risk variable and is often used as a measure of the importance of changes in that variable relative to changes in other risk variables. There is considerable controversy regarding the use of standardized coefficients (Greenland, Schlesselman, and Criqui (1986)) and caution is advised.

Standardized Standard Error

The standard error of the standardized logistic regression coefficient is computed by equating the ratio of the standardized coefficient to its standard error with the respective unstandardized ratio so that the two ratios have the same p-value. Hence, it is computed as
SE (standardized b_i) = (SE (b_i)/b_i) * standardized bi
Note that this is equivalent to assuming that the variance in the risk factor is estimated with high accuracy.

CRITERIA FOR EVENTS

1. Coronary Heart Disease

subjects were diagnosed as having developed coronary heart disease (CHD) if upon review of the case a Panel of three investigators agreed on one of the following definite manifestations of CHD: myocardiel infarction, coronary insufficiency, angina pectoris, sudden death from CHD, non-sudden death from CHD. Persons with pre-existing CHD at Exam 1 were excluded from the population at risk of developing CHD. Pre-existing CHD at Exam 1 was identified by any one of the following diagnoses at Exam 1: definite angina pectoris, definite history of myocardial infarction, definite myocardial infarction by electrocardiogram, doubtful myocardial infarction by electrocardiogram, definite coronary insufficiency by electrocardiogram and history.

The various manifestations of CHD are these:

Angina Dectoris

Brief recurrent chest discomfort of up to 15 minutes duration, precipitated by exertion or emotion and relieved by rest or by nitroglycerine, was regarded as angina pectoris (AP) if two physicians interviewing the subject agreed that this condition was definitely present. This diagnosis was based solely on evaluation of subjective manifestations. Abnormality of the resting or exercise electrocardiogram was not required for this diagnosis.

Angina pectoris Uncomplicated

If angina pectoris developed between two successive examinations but the person remained free of any other manifestation of coronary heart disease, the diagnosis was designated as angina pectoris uncomplicated.

Coronary heart disease other than angina pectoris (Coronary Attack)

Because an interest is often expressed in the incidence of "heart attacks," this category is established to represent the occurrence of myocardial infarction, coronary insufficiency, or death from coronary heart disease.

Myocardial infarction

pecent or acute myocardial infarction (MI) was designated when there were serial changes in the electrocardiograms indicating the evolution of an infarction, including: S-T segment elevation in the electrocardiographic tracing associated with terminal inversion of T waves and the loss of initial QRS potentials (that is, development of "pathologic" Q waves of 0.04 second duration or greater), followed by serial changes indicating reversion towards normal. An old or remote myocardial infarction was considered to be present when the

electrocardiogram showed a stable pattern including a pathologic Q wave of 0.04 second or greater or loss of initial QRS potential (R wave) in those leads in which this would not be expected to occur. Also, an interim unrecognized MI was indicated when changes from a previous tracing showed development of loss of R-wave potential or appearance of pathologic Q waves not otherwise explained, in persons in whom neither the patient nor his physician considered the possibility of MI. If the patient was asymptomatic for chest pain or upper abdominal pain during the interval at which the unrecognized MI occurred, the event was classified as silent, unrecognized. More weight was given to this finding if a T-wave abnormality was also associated with Q-wave abnormality.

Beginning in 1956, a hospital report for a subject showing a rise in the serum glutamic oxalacetic transaminase to a level of at least 60 units along with a history of prolonged ischemic chest pain was accepted as evidence of myocardial infarction. Subsequently, in 1962, pathologic elevation of another enzyme was included: lactic dehydrogenase greater than 500 units. At a later date, with a change in laboratory techniques, SGOT was abnormal at 50 and LDH at 200. CPK greater than 200 units or CPK-MB band positive was included if these tests were done.

An autopsy report showing an acute, new, or recent infarction of the myocardium was accepted as evidence of an incident myocardial infarction. Because it is not possible to date an old infarction found on autopsy such evidence was not used in the clinical diagnosis of a new event, unless there was an interim clinical event suspected of being an infarction.

Coronary insufficiency

The coronary insufficiency syndrome was designated when a history of prolonged ischemic chest pain was accompanied by transient ischemic S-T segment and T-wave abnormality in the electrocardiographic tracing but not accompanied by development of Q-wave abnormality or by serum enzyme changes characteristic of myocardial necrosis. Virtually all these subjects were hospitalized for suspected MI.

Coronary heart disease death

Death from coronary heart disease was diagnosed as either sudden or nonsudden.

Nonsudden death from CHD

If the terminal episode lasted longer than one hour, if the available information implied that the cause of death was probably CHD, and if no other cause could be ascribed, this was called nonsudden death from CHD. In making this diagnosis, the review panel used prior clinical information as well as information concerning the final illness.

Sudden death from coronary heart disease

If a subject, apparently well, was observed to have died within a few minutes (operationally documented as under one hour) from onset of symptoms and if the cause of death could not

reasonably be attributed on the basis of the full clinical information and the information concerning death to some potentially lethal disease other than coronary heart disease, this was called sudden death and was attributed to coronary heart disease.

Stroke

The diagnosis of overt vascular disease of the brain was based on the occurrence of a stroke. Minimal criteria for a stroke consisted of abrupt onset of a localizing neurologic deficit (such as hemiparesis, aphasia, homonymous hemianopia). For stroke due to intracranial hemorrhage, a change in the state of consciousness, headache, and signs of meningeal irritation in association with a bloody spinal fluid under increased pressure with or without other localizing neurological deficits. On recent examinations, CAT scan information has been used to confirm hemorrhage. A diagnosis of embolus to the brain was made if a source for embolus (that is, atria1 fibrillation, rheumatic heart disease with mitral stenosis, recent myocardial infarction, bacterial endocarditis) was present, the clinical course consistent (that is, rapid onset and clearing, slightly bloody spinal fluid, a more localized deficit), or the occurrence of associated peripheral emboli elsewhere noted. A consultant neurologist and the clinical staff of the study reviewed hospital and clinic protocols. Starting with Exam 8 neurologists have examined patients suspected of stroke in the hospital.

Atherothrombotic brain infarction

Specifically, thrombotic brain infarction was defined as the sudden onset of a localizing neurologic deficit (for example, aphasia, homonymous hemianopia, a central type of facial weakness, hemiparesis) documented by a physician, lasting longer than 24 hours, in the absence of: 1) known source of embolism (atria1 fibrillation, rheumatic heart disease with mitral stenosis, myocardial infarction within preceding six months, bacterial endocarditis), 2) intracranial hemorrhage (intracerebral, subarachnoid), 3) known hypercoagulable states (for example, erythremia) 4) other disease processes causing focal brain deficits (brain tumor, subdural hematoma, hypoglycemia). All stroke data were evaluated by a neurologist. On recent examinations CAT-scan information has been used to exclude intracranial hemmorrhage.

Transient Ischemic Attack

A transient ischemic attack was designated when a history of a focal neurologic deficit was documented which lasted less than 24 hours in duration.

Stroke Death

Death attributed to stroke was designated when a documented focal neurologic deficit of greater than 24 hours duration preceeded death and was responsible for the fatality.

Intermittent claudication

Minimum criteria for the subjective diagnosis of intermittent claudication consisted of a cramping discomfort in the calf clearly provoked by walking some distance with the pain appearing sooner when walking quickly or uphill and being relieved within a few minutes by rest. Interviews for symptoms of claudication were conducted by the physician using structured forms for uniformity of the assessment. In addition, a second physician confirmed all cases suspected of claudication at time of examination.

Congestive heart failure

A definite diagnosis of congestive heart failure required that a minimum of two major or one major and two minor criteria present concurrently. The presence of other conditions capable of producing the symptoms and signs was considered in evaluating the findings.

Major criteria:

1) Paroxysmal nocturnal dyspnea.
2) Distended neck veins (in other than the supine position).
3) Rales.
4) Increasing heart size by X-ray
5) Acute pulmonary edema described in hospital record.
6) Ventricular S(3) gallop.
7) Increased venous pressure (greater than 16 cm H_2O from right atrium).
8) Circulation time (greater than 24 seconds, arm to tongue).
9) Hepatojugular reflux.
10) Pulmonary edema, visceral congestion, cardiomegaly shown on autopsy.

Minor criteria:

1) Bilateral ankle edema.
2) Night cough.
3) Dyspnea on ordinary exertion.
4) Hepatomegaly.
5) Pleural effusion.
6) Decrease in vital capacity by one-third from maximum record.
7) Tachycardia (120 beats per minute or more).

Arbitrary major or minor criterion:

Weight loss (ten pounds or more in five days) while on therapy for congestive heart failure.

Cardiovascular disease

Cardiovascular disease is considered to have developed if there is a definite manifestation of coronary heart disease, intermittent claudication, congestive heart failure, stroke or transient ischemic attack in the absence of a previous manifestation of any of these diseases or rheumatic heart disease. Criteria for all these events have been given. A person having more than one cardiovascular manifestation within the followup period is counted as a case only at the time of the first event.

Death from cardiovascular disease

This cause of death was designated when any disease of the heart or blood vessels was considered responsible.

Death

The fact of death was supported by a death certificate. Additional information was obtained from records supplied by hospital, attending physician, pathologist, medical examiner, or family. A panel of staff physicians reviewed all evidence to arrive at the cause of death.

DESCRIPTION OF CHARACTERISTICS

1. Blood pressure, first examiner, systolic (mm Hg)

2. Blood pressure, first examiner, diastolic (mm Hg)

Systolic and diastolic readings in the left arm of the subject were taken with a mercurial sphygmomanometer and a 14-cm cuff long enough to fit the most obese arm. The recommendations of the American and British Heart Associations were followed for reading the pressure (see Standardization of Blood Pressure Readings, American Heart Journal, July 1939, 18:95). Palpatory method was used to check auscultatory systolic readings. Measurement was expressed in millimeters of mercury on the scale of the manometer. Although the original protocol did not specify the accuracy of the measurement to be employed most readings were made to the nearest even number. After Exam 5 this became the standard practice.

At the beginning of the Study two readings were taken on each subject: 1) admission blood pressure taken by the nurse and 2) final blood pressure taken by the examining physician. Beginning in April 1950 three readings were taken on each subject: 1) admission blood pressure taken by the nurse, 2) blood pressure taken by the first examining physician at the start of his interview, and 3) another blood pressure taken at the end of the examination by a second physician after drawing blood. All of these pressures were taken on the left arm with the subject seated and the arm at heart level. In coding blood pressure at Exam 1 for subjects through Record Number 2938, the nurse's blood pressure is used as the reading by the first examining physician.

Minor changes in procedure have occurred in some earlier exams. A second blood pressure reading by the same examining physician has been substituted for a reading by a second examiner when a second observer was not present.

3. Hvuertension

At examination, a subject had two blood pressure readings taken by the examining physician(s). If both readings were "abnormal" the subject had definite hypertension; if both readings were "normal" the subject had normotension; with any other combination of readings the subject had borderline hypertension.

A blood pressure reading was "abnormal" if either the systolic or the diastolic component was "abnormal". The reading was "normal" if both systolic and diastolic parts were "normal". A systolic pressure was called "normal" when under 140 mm Hg, "abnormal" when 160 or greater. A diastolic pressure was called "normal" when under 90 mm Eg, "abnormal" when 95 or greater. Thus, a person was a definite hypertensive if both of the following conditions held:

1. the first systolic pressure was 160 or greater or the first diastolic pressure was 95 or greater.

and

2. the second systolic pressure was 160 or greater or the second diastolic pressure was 95 or greater.

When on rare occasion a subject had only one blood pressure reading taken by the examining physician, hypertensive status was determined on the basis of this one reading.

For purposes of analysis in this monograph, hypertension was evaluated in two fashions: (1) one utilizing only blood pressure readings as described above and (2) one in which individuals not treated with anti-hypertensive medication were classified on the basis of blood pressure while persons treated with anti-hypertensive medication were considered as definite hypertensives.

4. Serum cholesterol (mg/100 ml)

At the beginning of the Study, serum cholesterol concentrations were determined by the coiorimetric method of Sperry (Schoenheimer and Sperry: J. Biol. Chem. 106, 745, 1934. Sperry: Am. J. Clin. Path. & Tech. Supplement 2, 91, 1938). On December 12, 1952 after the start of Exam 2, the method of Abell-Kendall was adopted (Abell, L.L., Levy, B.B., Brodie, B.B., and Kendall, F.F.,J. Biol. Chem. 195, 357-366, 1952).

5. Hematocrit

Blood was collected in a balanced oxalate tube and spun at 5000 rpm for 20 minutes. Hematocrit was read in the tube against a special scale constructed for this purpose. This method proved more reliable than the standard capillary method. On exams 1 to 3, hemoglobin was measured instead of hematocrit. These measurements were converted into hematocrit by dividing by 3.129.

6. Blood glucose (mg/100 ml)

The amount of glucose present in a casual specimen of the subject's whole blood (collected in a solution of potassium oxalate and sodium flouride) was determined using the method of Nelson (Nelson, B., J. Biol.Chem. 153, 375, 1944; Somogyi, M., J. Biol. Chem. 160, 61, 1945; Somogyi, M., J. Biol. Chem. 160, 69, 1945). Blood glucose was measured on Exams 1 to 4, 6, 8, 9, and 10, 12-15 (not on Exams 5, 7 and 11).

Diabetes mellitus

A subject was diagnosed as having diabetes if he or she was under treatment by a private physician for diabetes or the subject had a record of an abnormal glucose tolerance test or had on at least two exams a casual blood glucose determination of 150 mg/100 ml or more.

Treatment by private physician meant that the subject was taking insulin or oral hypoglycemic agents. In addition, if the subject was taking oral agents, the diagnosis of diabetes was made only if records from the Framingham Study, private physician, or hospital showed several elevated blood glucose determinations before treatment started. For this purpose an elevated blood glucose meant a value of 150 mg/100 ml or higher.

The study did not give subjects glucose tolerance tests; therefore the record of such tests had to be obtained from a private physician or hospital. The standard glucose tolerance test was taken as the ingestion of 100 grams of glucose after a 12-hour fast. The test was considered abnormal if the blood glucose concentration was 160 mg/100 ml or more at one hour after challenge, 140 or more at two hours, and was still higher at three hours than when the test began.

8. Glucose in urine, definite or trace

Procedure for testing the presence of glucose in a subject's freshly voided urine was as follows:

To five drops of urine in test tube add 10 drops of water and one Clinitest tablet. Allow to stand 15 seconds after boiling has ceased and then read promptly. Compare color to chart provided with tablets. Read as: negative, 1+, 2+, 3+, or 4+.

In coding the result of the color comparison, definite urine glucose is 2+, 3+, or 4+; trace urine glucose is 1+.

After exam 11, the Ames Combustix (Labstix) method was employed.

9. Glucose intolerance

A subject was said to demonstrate glucose intolerance at examination if any one of the following conditions obtained:

a) A diagnosis of diabetes mellitus at that examination or any preceding examination;

b) A determination of glucose in the urine sample, either definite or trace by Clinitest or Combustix, at that examination;

c) 'A measurement of the amount of glucose present in a casual specimen of whole blood equal to 120 milligrams or more per 100 milliliters at that examination.

10. Metropolitan relative weight(percent)

This relative weight at exam was computed for a subject by forming the ratio of his body weight at that exam to the desirable weight for his particular sex-height group according to standards set by the Metropolitan Life Insurance Company.

The ratio is expressed as a whole number in percent. The reference weight, for a given sex-height group, is the midpoint of the range for medium frame shown in the table of desirable weights' on page 12 of "Four Steps to Weight Control" (1969), distributed by the Metropolitan Life Insurance Company. By linear extrapolation, reference weights were assigned to those sex-height groups not covered by the Metropolitan table, women 55 inches and men 60 inches tall. since the desirable weights are shown for persons with their clothes and shoes on, adjustments are made to apply the reference weight to the subjects in the Framingham study, who were weighed without clothes and measured for height without shoes: five pounds are subtracted from the weight for men, four pounds for women; one inch was subtracted from the-height for men, two inches for women. The resulting set of reference weights is:

Height (inches)	Weight (pounds) Men	Women	Height (inches'	Weight (pounds) Men	Women
55		94	65	131	128
56		97	66	135	132
57		100	67	140	136
58		103	68	144	140
59		106	69	148	

Height (inches)	Weight (pounds) Men	Women	Height (inches'	Weight (pounds) Men	Women
60	116	109	70	152	
61	119	112	71	157	
62	122	116	72	161	
6 3	125	120	73	166	
64	128	124	74	170	

11. Vital caoacitv-heiqht index (ml/inch)

A nurse or technician instructed the subj ect to take the deepest breath possible and exhale to the fullest extent into the tube of a water-sealed spirometer (Collins Vitalometer) Three trials were made for each subject; the highest reading was recorded. This measurement of vital capacity was read to the next lower 0.1 liter on the scale of the spirometer. The vital capacity in milliliters was divided by the subject's height in inches to get the vital capacity-height index.

12. Heart rate (per minute)

The heart rate is the ventricular rate as determined by the physician from the electrocardiogram made with the subject in the recumbent position. Electrocardiograms were made at each exam and the ventricular rate was coded for data processing for all exams except 2 and 3.

13. Cigarettes smoked (number per day)

Histories of cigarette smoking were obtained on every exam except Exam 6. However, information fron the first three exams was coded to represent usage at Exam 1, leaving Exams 2 and 3

uncoded. On the initial examinations there was no fixed rule for deciding whether a person was an ex-cigarette smoker, but persons who 'had only recently stopped were always considered still smoking. On later examinations anyone smoking cigarettes within a year was considered a current smoker. For current smoker, the number of cigarettes usually smoked each day was recorded. Additional details are given in Sections 3 and 26 of the monograph series.

14. Albumin in urine, definite

Procedure for testing for *the* presence of albumin in a subject's freshly voided urine was as follows:

To 10 cc of urine in test tube add 2 cc reagent (Quantitest reagents: beta naphthalene sulphonic acid and glacial acetic acid). Allow to stand. Result is read in milligrams of albumin per 100 milliliters by comparing turbidity with standards in lighted rack. In coding the result of the turbidity comparison, definite urine albumin is 20 mg/100 ml or higher; trace urine albumin is 10 mg/ 100 ml.

This method was employed for examinations 1 to 8, though the results were not coded on Exam 4. Since Exam 9, the Combustix (Labstix) method has been utilized to determine urine albumin.

15. Heart enlarsement by x-ray

Roentgenograms were taken at each exam with a Westinghouse Autoflex 300-milliampere X-ray unit and with a Machlett superdynamax tube. The subject was positioned erect in max-respiration phase with full anterior chest against the film cassette. The X-ray tube was placed at level of seventh thoracic vertebra, a distance of two meters from anode to film. The film size was 14 x 17 inches. Beginning *in* Exam 4 the machine was actuated by a device attached to the subject through electrodes applied to the left and right axillary margin at level of the seventh rib, to take the X-ray at-the moment of full diastole. (Peak of R wave plus 0.008 second to termination of exposure insured the shadow of the cardiac silhouette in full systole.) The transthoracic Lead I electrocardiographic tracing showing the point of X-ray exposure was printed at the top of the exposed X-ray film before development.

All films were interpreted by a roentgenology consultant who did not have access to clinical data on the subject before viewing his films. Beginning in early 1952 one consultant, *Dr.* Lloyd E. Hawes, viewed all films taken at the Framingham Heart Clinic and made the X-ray interpretations.

The diagnosis of left ventricular hypertrophy signified that this chamber was enlarged as shown by an *extension* of the left apex of the heart towards the left, an elevation of the apex and a squaring of the apex. The transverse diameter of the heart was usually more than half the transverse width of the chest.

However, in a subject with a large chest the square prominent shape of the left apex of the heart may have signified left ventricular hypertrophy even with transverse diameter of the heart less than half the width of the chest. The diagnosis of left ventricular hypertrophy could be made with normal measurement of the transverse diameter of the heart.

The diagnosis of generalized cardiac enlargement was made when the heart shadow was rounded and expanded both to the right and the left, giving an appearance not of left ventricular hypertrophy alone but of either a dilatation of all chambers or a dilatation of the atria and right ventricle as in mitral heart disease.

A diagnosis of generalized cardiac enlargement and left ventricular hypertrophy was made if the heart was rounded overall and enlarged, and the apex projected further out and was square and prominent.

A subject with heart enlargement had either generalized cardiac enlargement or left ventricular hypertrophy or both.

16. Left ventricular hypertrophy by electrocardiogram

Electrocardiograms were taken at each exam with a Sanborn Visocardiette. The subject was in the recumbent position. Thirteen leads were used, three standard, three augmented unipolar limb leads, and seven precordial leads of Wilson. See description of technique, pages 31 to 44, Katz, Electrocardiography, Lee and Febiger, Philadelphia, 1947.

Left ventricular hypertrophy consisted of a tracing exhibiting a slight prolongation of "ventricular activation time" (at least 0.05 second on the left) associated with R-wave potentials of at least 20 mm in standard leads, at least 11 mm in augmented unipolar leads, at least 25 mm in any deflection in precordial leads or at least 35 mm combining any V (1), V (2) S-wave deflection with R-wave deflections from V (5) or V (6). This had to be accompanied by depressed S-T segments or flattened to inverted T waves reflecting potentials from left precordial leads.

A category of possible left ventricular hypertrophy was designated when tracings exhibited characteristics similar to those above except in less striking degree or when not all were present. Increased R-wave potential without associated S-T and T-wave abnormality was included in this category.

17. Intraventricular conduction defect with QRS interval more than 0.11 second

Complete right intraventricular heart block was diagnosed when QRS duration exceeded 0.11 second and an R-R' wave was noted in any one or more right precordial leads, with a delayed peak of R' wave (equal to 0.03 second or greater) after onset of QRS complex, accompanied by broad S waves in left precordial

leads and a corresponding broad S wave in Lead I. Complete left intraventricular heart block was designated when the QRS interval exceeded 0.11 second and tall slurred R waves were observed along with absent Q waves in any of the left precordial leads and a reciprocal deep S wave in the right precordial leads. The peak of the notched R' wave occurred at greater than 0.06 second after the onset of the QRS complex in one or more left precordial leads. Complete indeterminate intraventricular heart block was designated when the QRS interval was prolonged beyond 0.11 second and the characteristic changes indicative of either right or left intraventricular heart block were absent, but the lengthened QRS interval was not obtained at the expense of a shortened P-R interval (as in the Wolff-Parkinson-White syndrome). No hemiblock or bifascicular block designations were distinguished.

18. Definite Nonspecific T-wave or ST-segment abnormality by electrocardiogram

Nonspecific abnormality was designated in the absence of a prominent R wave when there was ST-segment depression (exceeding one millimeter below the base line) and/or primary T-wave inversion or flattening. This diagnosis was not made if a more specific explanation could be made for these changes (such as intraventricular block, myocardial infarction, or left ventricular hypertrophy) or if the changes occurred in those leads where such variation is acceptable.

Glucose Intolerance:

1= glucose intolerant
0= no glucose intolerance

Left Ventricular Hypertrophy:
1=no
2=borderline
3=definite

Hypertension ignoring antihypertensive treatment

1=none
2=borderline
3=definite

Hypertension with antihypertensive treatment:

1=none
2=borderline (not treated)
3=definite (not treated)
4=treated

In the logistic regressions treated persons are coded as 3, definite hypertensives.

Diabetes:
1=diabetes previously diagnosed
0=nondiabetic

Glucose in Urine:

0=negative
1=positive, trace or doubtful, light, medium, *or* dark

Albuminim Urine:

0=negative or trace
1=positive

Heart Enlargement by X-ray:

1-none
2=possible GCE or definite LVH without definite GCE
3=definite GCE

Nonspecific T-wave or ST-segment abnormality:

0=none or doubtful
1=definite on either T-wave or ST-segment

Intraventricular conduction defect:

l=no IV Block, either complete or incomplete on left or right
2=incomplete on left,right, or indeterminate and not complete on any
3=complete on left or right or indeterminate

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