DIFFERENCES IN CORONARY HEART DISEASE IN FRAMINGHAM, HONOLULU AND PUERTO RICO

TAVIA GORDON*, MARIO R. GARCIA-PALMIERI†, ABRAHAM KAGAN‡, WILLIAM B. KANNEL§ and JOYCE SCHIFFMAN*

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INTRODUCTION

Large variations in the incidence of Coronary Heart Disease (CHD) have been claimed to exist around the world [1, 2]. It is important to establish the validity of geographic variation in CHD incidence as it provides clues to the causes and prevention of this disease.

Vital statistics have shown a lower death rate from CHD among middle aged men in Puerto Rico and in the Honolulu Japanese than in the United States white population [3, 4]. To investigate this finding prospective studies were begun in 1965 in Honolulu and Puerto Rico, and the results are compared here with those from the older Framingham Study. An effort is made to evaluate geographic differences with a uniformity of methodology and diagnostic criteria in representative samples of the three populations. An attempt is also made to determine if the CHD differences observed are explained by differences in some uniformly measured risk factors in the three population samples.

MATERIAL AND METHODS

The designs of the three studies are described elsewhere [5, 7]. A description of those aspects relevant to this paper will be given here.

Only men age 45–64 are considered (Table 1). The Framingham Study population is a probability sample of residents in Framingham, Massachusetts in 1949–50, born between 1890 and 1920. The Honolulu Study cohort are all men of Japanese ancestry, resident on the Island of Oahu, Hawaii, who were born between 1900 and 1919. The Puerto Rico Study is targeted at all men born between 1900 and 1919 who were living in 4 urban and 3 rural districts of and adjacent to San Juan. Framingham provided 1079 men within the specified age group at entry. To increase this number and take advantage of a greater length of follow-up experience, men 45–64 at each of the first 7 examinations (1949–64) were considered independent populations and grouped together to obtain a nominal prevalence population of 8486 men. This meant that the

*National Heart and Lung Institute.
†Puerto Rico Heart Health Program.
‡Honolulu Heart Study.
§Framingham Heart Disease Epidemiology Study.
TABLE 1. NUMBER OF MEN BY AGE

<table>
<thead>
<tr>
<th>Age (entry)</th>
<th>Framingham</th>
<th>Honolulu†</th>
<th>Puerto Rico‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>8,486*</td>
<td>7,555</td>
<td>8,751</td>
</tr>
<tr>
<td>45-49</td>
<td>2,583</td>
<td>1,832</td>
<td>2,237</td>
</tr>
<tr>
<td>50-54</td>
<td>2,361</td>
<td>2,792</td>
<td>2,669</td>
</tr>
<tr>
<td>55-59</td>
<td>2,044</td>
<td>1,593</td>
<td>2,107</td>
</tr>
<tr>
<td>60-64</td>
<td>1,498</td>
<td>1,338</td>
<td>1,738</td>
</tr>
</tbody>
</table>

*Exams 1-7.
†Exams 1-6.
‡At entry.

experience of men who became 45 at a later examination was added in but it also meant that the same man might be counted several times so long as his age at examination was within the 45-64 range. In Honolulu and Puerto Rico, men appearing at the initial examination (1965-68) were considered only once, providing prevalence populations of 7,555 and 8,751 respectively. Examination rates for the three populations at Exam 1 were 69 per cent in Framingham, 81 per cent in Honolulu, and 81 per cent in Puerto Rico [8-10].

In order to avoid possible differences in case-finding owing to different hospital admission practices and different interpretations of subjective symptoms, prevalence estimates in this report are based exclusively on the initial electrocardiogram (ECG) at Honolulu and Puerto Rico and on ECG tracings obtained in the first seven examinations at Framingham. The electrocardiograms read by the individual studies in patients with a diagnosis of any manifestation of CHD were exchanged among all three studies without any accompanying information and read independently for definite, possible or no myocardial infarction (MI). When two studies agreed that definite MI was present, the subject was considered a prevalence case of MI. As a methodological backup and to obtain a uniform reading from one source, all these ECGs were also sent to the laboratory of Dr. Henry Blackburn for readings according to the Minnesota criteria.

The readings by the individual studies were given scores of 2 for definite MI, 1 for possible MI and 0 for no MI. If the sum of the 3 readings was 3 or more, the subject was excluded from the population at risk for CHD incidence. Otherwise he was considered at risk of CHD even if the study itself had made a diagnosis of definite CHD at entry.

For incidence readings, the ECGs exchanged were those of two consecutive examinations. Readers were asked to evaluate the latter tracing with the previous one. A reading of a serial change consistent with the development of definite MI by at least two of the three studies defined an incidence case of MI by ECG.
The end points used for CHD incidence were definite MI by ECG and CHD death. Death was attributed to CHD if it was sudden (within 1 hr after onset of illness), and without another disease to account for it, or if it was non-sudden with course and evidence consistent with CHD. Special efforts were made in the three studies to evaluate deaths that occurred both in the hospital and out-of-hospital. Autopsy information was obtained in all cases where an autopsy was performed. Angina pectoris and coronary insufficiency diagnoses, although available, were not used for incidence purposes, as it was difficult to standardize their criteria.

Incidence rates were calculated on the basis of person-yr experience. Men at risk in Puerto Rico were given 2.5 yr and those at Framingham and Honolulu 2 yr, since these were the respective average re-examination intervals. At Framingham, where some men were considered at risk on more than one examination, each man was reclassified each examination he appeared at risk, using his age and other characteristics at that examination, including an independent re-assessment of his ECG status. This yielded 14,054 person-yr experience or a nominal baseline population of 7027, derived from the first 6 examinations.

Many characteristics considered likely to explain interstudy differences were explored. Chief among these were serum cholesterol, blood pressure, and cigarette smoking, but information on other variables was also considered.

Serum cholesterol determinations at Framingham were done by the Abell-Kendall method [11], in Honolulu by a modification of the colorimetric procedure of Block, Jarret and Levine [6], and in Puerto Rico by a modification of the method of Huang et al. [12]. Only casual specimens were taken. Interstudy comparisons of cholesterol measurements were made from June 1968 to May 1970 using a common set of serum pools supplied by the Communicable Disease Center in Atlanta, Georgia. Taking these calibration results in consideration, as well as known intralaboratory shifts, the apparent Framingham–Honolulu differences can be accepted as given but the Framingham–Puerto Rico difference should be diminished by 6.9 mg/100 ml.

Blood pressure determinations were made on the left arm by the cuff method and the systolic value recorded at the point of appearance of Korotkoff sounds. In each study blood pressures were obtained with the subject seated. In all three studies the number of cigarettes smoked per day was recorded in a similar manner by an interview. Methods for determining other characteristics are available in the study protocols, which are partly described in published sources [6, 7, 13].

Standards for relative weight in Framingham and Puerto Rico are derived from 'desirable weights' by height published by the Metropolitan Life Insurance Company. Standards for Honolulu Japanese derive from a special methodological study and were estimated so as to be comparable to the Metropolitan Life tables for Caucasians. They are roughly 5 per cent less at any height than those for Caucasians.

The information on incidence by levels of various characteristics was supplemented with an examination of age-adjusted mean differences between cases and non-cases and by a series of bivariate regression analyses by the method of Walker–Duncan [14] in which age was one variable. Based on the regression analysis, smoothed CHD incidence curves by level of characteristic were prepared for selected variables.

Two different multivariate logistic functions were computed by the method of Walker–Duncan, first including and then excluding from the population at risk those men with prior clinical evidence of CHD (not confirmed by inter-study ECG readings).
One function included age, serum cholesterol, systolic blood pressure and cigarette smoking. The other included age, serum cholesterol and systolic blood pressure only. Each of these was computed separately for each study. At fixed levels of each of the variables at 5 specified ages (45, 50, 55, 60 and 64 yr) a smoothed estimate of the probability of CHD was obtained separately for each study group. The variance of the logistic exponent was computed, to obtain confidence intervals for the exponent. These could then be used to compute non-central confidence intervals for the estimated conditional probabilities and for the ratios of the odds for each pair of studies.

**RESULTS**

**Population characteristics**

The Honolulu Japanese and Puerto Ricans differ in many respects from the Framingham population (Table 2). The Puerto Rican and Japanese men average, respectively, 2 and 3 in. shorter than the men in the Framingham cohort and weigh 17 and 28 lb less. If the standards used for desirable weight in the different populations are really comparable, the Framingham men are fatter than the men in the other two groups.

**Table 2. Some characteristics of the populations at risk**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Framingham</th>
<th>Honolulu</th>
<th>Puerto Rico</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (in.)</td>
<td>67.02</td>
<td>64.17</td>
<td>64.91</td>
</tr>
<tr>
<td>Weight (lb)</td>
<td>168.54</td>
<td>140.10</td>
<td>151.27</td>
</tr>
<tr>
<td>Weight at age 25 (lb)</td>
<td>149.95</td>
<td>129.10</td>
<td>133.43</td>
</tr>
<tr>
<td>Weight change since age 25 (lb)</td>
<td>18.59</td>
<td>11.00</td>
<td>17.84</td>
</tr>
<tr>
<td>Relative weight (%)</td>
<td>120.04</td>
<td>113.25</td>
<td>112.50</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>136.41</td>
<td>136.37</td>
<td>130.35</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>85.07</td>
<td>82.68</td>
<td>82.19</td>
</tr>
<tr>
<td>Serum cholesterol (mg %)</td>
<td>233.96</td>
<td>218.55</td>
<td>202.45</td>
</tr>
<tr>
<td>Blood glucose (mg %)</td>
<td>83.55</td>
<td>*</td>
<td>96.28</td>
</tr>
<tr>
<td>No. of cigarettes smoked</td>
<td>12.26</td>
<td>10.52</td>
<td>7.63</td>
</tr>
<tr>
<td>Total vital capacity (deciliters)</td>
<td>3.53</td>
<td>3.25</td>
<td>3.12</td>
</tr>
<tr>
<td>Physical activity index</td>
<td>33.40</td>
<td>32.85</td>
<td>33.28</td>
</tr>
<tr>
<td><strong>Percent of subjects with attribute</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine glucose</td>
<td>2.2</td>
<td>5.8†</td>
<td>2.8</td>
</tr>
<tr>
<td>Diabetes by history</td>
<td>3.7</td>
<td>9.2</td>
<td>5.3</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>6.3</td>
<td>14.8</td>
<td>8.4</td>
</tr>
<tr>
<td>LVH-ECG</td>
<td>2.3</td>
<td>0.7</td>
<td>1.5</td>
</tr>
<tr>
<td>IV Block</td>
<td>2.0</td>
<td>2.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Non-spec. T-wave abnormality</td>
<td>5.0</td>
<td>5.9</td>
<td>4.8</td>
</tr>
<tr>
<td>Smoking</td>
<td>57.7</td>
<td>44.1</td>
<td>44.4</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>3.8</td>
<td>1.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Coronary insufficiency</td>
<td>0.5</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.2</td>
<td>1.0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*Blood glucose taken 1 hr after a 50 g glucose challenge.
†Honolulu specimen taken before glucose challenge.

Systolic blood pressures are about the same in Framingham and Honolulu but lower in Puerto Rico. Compared to Framingham, serum cholesterol levels were roughly 15 mg per cent lower in Honolulu and, if allowance is made for known laboratory differences, 25 mg per cent lower in Puerto Rico. There were fewer cigarette smokers in Honolulu and Puerto Rico than Framingham. However, in Honolulu those who
smoked consumed more cigarettes (on the average) than their counterparts in Framingham, whereas in Puerto Rico average consumption by smokers was less than in Framingham. On the balance the average cigarette consumption is slightly less in Honolulu than in Framingham and less in Puerto Rico than in Honolulu.

A history of diabetes was slightly more common in Puerto Rico than in Framingham and much more common in Honolulu. The presence of glucose in casual urine specimens showed similar differences. Mean casual blood glucose levels were also higher in Puerto Rico than Framingham. In Honolulu blood glucose levels were measured one hour after a 50 g glucose challenge, so these cannot be directly compared with either those in Puerto Rico or Framingham.

Modest differences in mean total vital capacities were noted among the three studies but these were not adjusted for differences in stature. Crude estimates of physical activity levels differed little among the three populations.

ECG findings other than MI differed somewhat. Framingham had the highest prevalence of ECG-LVH, Honolulu the lowest. Puerto Rico was intermediate. There were only slight differences in the prevalence of intraventricular block or ST- and T-wave abnormalities. Considering the similarity in blood pressures in Honolulu and Framingham, the marked difference in prevalence of ECG-LVH is curious. These readings were not standardized.

General mortality

There were 155 deaths in the Framingham cohort, 71 in the Honolulu cohort and 166 in the Puerto Rico cohort (Table 3). Of these 140, 69, and 154, respectively, occurred in the population free of definite or possible MI by ECG yielding annual death rates of 464/1000 in Honolulu, 7.12/1000 in Puerto Rico and 9.96/1000 in Framingham (Table 4).

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Framingham</th>
<th>Honolulu</th>
<th>Puerto Rico</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total at risk</td>
<td>155</td>
<td>140</td>
<td>71</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>73</td>
<td>58</td>
<td>17</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>10</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Other cardiovascular</td>
<td>15</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Cancer</td>
<td>31</td>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>Trauma</td>
<td>3</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>19</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

*Free of MI by ECG at entry. Follow-up was 2 yr at Framingham and Honolulu, 2.5 yr at Puerto Rico.

In Puerto Rico 48.7 per cent of the deaths in the population at risk occurred in the hospital. The comparable percentages in Framingham and Honolulu were 52.6 and 62.3 per cent, respectively. Autopsy rates for out-of-hospital deaths were relatively high in Puerto Rico (40.5 per cent) and Honolulu (50.0 per cent) but only 10.8 per cent in Framingham. The majority of hospital deaths were autopsied in all three studies (Table 5).
CHD accounted for less than a fourth of all deaths in Honolulu and Puerto Rico. In Framingham it accounted for over 40 per cent. CHD death rates were much higher in Framingham than in the other two groups—4.13 per 1000 per yr as against 1.01 in Honolulu and 1.66 in Puerto Rico. Nearly half of the CHD deaths were autopsied in Honolulu and Puerto Rico whereas only a fourth of the CHD deaths were autopsied in Framingham. Similarly, in Honolulu and Puerto Rico nearly half of the CHD deaths occurred in the hospital whereas the comparable percentage was 32.8 in Framingham. This is explained by the greater proportion of sudden CHD deaths in Framingham.

In summary, then, the overall level of mortality, as well as mortality from CHD was substantially higher in the Framingham cohort than in Honolulu and Puerto Rico. As will appear later, the difference in CHD mortality was more striking than differences noted in morbidity suggesting that not only is CHD more common, but that it is also more lethal in Framingham.

**MI prevalence and incidence**

Table 6 gives the prevalence of MI by ECG at entry. Except in the age group 60–64 the prevalence rate was lowest in Puerto Rico. Framingham had rates consistently higher than those for either the Honolulu Japanese or the Puerto Ricans. Overall, the prevalence rate for this finding in Framingham was double that in Honolulu or Puerto Rico, with an even greater ratio at age 60–64.

Persons who gave a history of definite angina pectoris at entry are retained at risk unless their ECG findings exclude them. This history finding was twice as common in the population at risk in Framingham as in Honolulu or Puerto Rico. Also, after excluding men with definite or possible MI by standardized ECG readings, some persons with clinical findings of myocardial infarction or coronary insufficiency (CI) remained at risk. These residuals were more common in Framingham than Honolulu. In Puerto Rico clinical MI is almost absent from the population at risk, reflecting the exclusive dependence of their diagnosis on the clinic ECG, whereas CI was about as prevalent as in Framingham.

The incidence rate for MI by ECG was also highest in Framingham (Table 7). Overall, the incidence rate for Framingham was double that for the Honolulu Japanese and for Puerto Ricans. The CHD death rate in Framingham was also more than double that for Puerto Rico and 4 times that for Honolulu Japanese.

Not only was CHD mortality in the population at risk lowest in the Hawaii Japanese, but their CHD case-fatality rate was the lowest of the three studies: Less than a third of the incidence in Honolulu presented as CHD death. The comparable
<table>
<thead>
<tr>
<th>Deaths by cause</th>
<th>Framingham Total</th>
<th>Framingham No autopsy</th>
<th>Honolulu Total</th>
<th>Honolulu No autopsy</th>
<th>Puerto Rico Total</th>
<th>Puerto Rico No autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With autopsy</td>
<td></td>
<td>With autopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cases</td>
<td>75</td>
<td>40</td>
<td>35</td>
<td>43</td>
<td>30</td>
<td>13</td>
</tr>
<tr>
<td>CHD, sudden</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>CHD, non-sudden</td>
<td>18</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>CVA</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
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<td>6</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Cancer</td>
<td>24</td>
<td>10</td>
<td>14</td>
<td>14</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Trauma</td>
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<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
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<td>4</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Out of hospital</td>
<td>65</td>
<td>7</td>
<td>58</td>
<td>26</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>All cases</td>
<td>34</td>
<td>3</td>
<td>31</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>CHD, sudden</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>CHD, non-sudden</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
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<tr>
<td>Trauma</td>
<td>7</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
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<td>2</td>
<td>3</td>
<td>8</td>
<td>8</td>
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<tr>
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</tr>
</tbody>
</table>
ratios for Framingham and Puerto Rico were 49.2 and 47.4 per cent, respectively. The proportion of CHD deaths that were sudden was highest in Framingham (35/58). In Puerto Rico and Honolulu it was somewhat lower—14/36 and 6/15, respectively.

The total incidence of MI or CHD death was about the same in Puerto Rico and Honolulu but more than twice as great in Framingham. The excess Framingham incidence was relatively small at age 45-49 but very large at age 60-64 (Table 7).

**Table 6. Prevalence of Myocardial Infarction by ECG at Entry by Age**

<table>
<thead>
<tr>
<th>Age (entry)</th>
<th>Framingham Clinical</th>
<th>Framingham Minnesota</th>
<th>Honolulu Clinical</th>
<th>Honolulu Minnesota</th>
<th>Puerto Rico Clinical</th>
<th>Puerto Rico Minnesota</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>192</td>
<td>58</td>
<td>108</td>
<td>51</td>
<td>115</td>
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<tr>
<td>45-49</td>
<td>25</td>
<td>38</td>
<td>10</td>
<td>17</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>50-54</td>
<td>24</td>
<td>37</td>
<td>22</td>
<td>38</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>55-59</td>
<td>33</td>
<td>61</td>
<td>13</td>
<td>27</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>60-64</td>
<td>42</td>
<td>56</td>
<td>13</td>
<td>26</td>
<td>20</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Rate/1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>14.6</td>
<td>22.6</td>
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<td>14.3</td>
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<tr>
<td>45-49</td>
<td>9.7</td>
<td>14.7</td>
<td>5.5</td>
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</tr>
<tr>
<td>50-54</td>
<td>10.2</td>
<td>15.7</td>
<td>7.9</td>
<td>13.6</td>
<td>2.3</td>
<td>6.0</td>
</tr>
<tr>
<td>55-59</td>
<td>16.2</td>
<td>29.8</td>
<td>8.2</td>
<td>16.9</td>
<td>8.1</td>
<td>16.4</td>
</tr>
<tr>
<td>60-64</td>
<td>28.1</td>
<td>37.4</td>
<td>9.7</td>
<td>19.4</td>
<td>11.5</td>
<td>27.0</td>
</tr>
</tbody>
</table>

*Note. Minnesota criteria are any Q and QS patterns, codes 1. Clinical are described in the text.*

**Table 7. Incidence of MI by ECG or CHD Death by Age**

<table>
<thead>
<tr>
<th>Age (entry)</th>
<th>Framingham MI-ECG CHD death</th>
<th>Framingham CHD</th>
<th>Honolulu MI-ECG CHD death</th>
<th>Honolulu CHD</th>
<th>Puerto Rico MI-ECG CHD death</th>
<th>Puerto Rico CHD death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of cases</td>
<td>Rate/1000/yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>118</td>
<td>8.40</td>
<td>42.7</td>
<td>4.13</td>
<td>2.32</td>
<td>2.22</td>
</tr>
<tr>
<td>45-49</td>
<td>11</td>
<td>2.57</td>
<td>1.40</td>
<td>1.17</td>
<td>1.93</td>
<td>1.66</td>
</tr>
<tr>
<td>50-54</td>
<td>33</td>
<td>8.23</td>
<td>4.49</td>
<td>3.74</td>
<td>3.09</td>
<td>2.00</td>
</tr>
<tr>
<td>55-59</td>
<td>37</td>
<td>10.99</td>
<td>5.34</td>
<td>5.64</td>
<td>3.51</td>
<td>1.92</td>
</tr>
<tr>
<td>60-64</td>
<td>37</td>
<td>15.44</td>
<td>7.51</td>
<td>7.93</td>
<td>4.99</td>
<td>3.84</td>
</tr>
</tbody>
</table>

*Note. Cases with MI by ECG at entry excluded. Parenthetical entries for CHD deaths are the number of sudden deaths.*

**Relation of entry characteristics to CHD incidence**

In general the personal attributes associated with a higher subsequent incidence of MI or CHD death were the same in all three studies. This is summarized in Table 8, which gives the average difference between cases and non-cases. Regression analyses (not included) were also undertaken and lead to identical conclusions. For selected variables these logistic regressions have been transformed into smooth incidence curves (Figs. 1–3).
TABLE 8. RELATION OF SOME CHARACTERISTICS AT ENTRY TO THE INCIDENCE OF MI–ECG OR CHD DEATH

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age-adjusted mean differences†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Framingham</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Relative weight (%)**</td>
<td>1.67</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)**</td>
<td>13.00**</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)**</td>
<td>5.50**</td>
</tr>
<tr>
<td>Serum cholesterol (mg%)**</td>
<td>10.67**</td>
</tr>
<tr>
<td>Blood glucose (mg%)</td>
<td>0.80</td>
</tr>
<tr>
<td>No. of cigarettes/day**</td>
<td>4.17**</td>
</tr>
<tr>
<td>Total vital capacity (deciliters)**</td>
<td>-0.12*</td>
</tr>
<tr>
<td>Physical activity index**</td>
<td>-0.92</td>
</tr>
<tr>
<td>Urine glucose</td>
<td>0.018</td>
</tr>
<tr>
<td>Diabetes by history</td>
<td>0.009</td>
</tr>
<tr>
<td>Glucose intolerance*</td>
<td>0.04</td>
</tr>
<tr>
<td>LVH–ECG**</td>
<td>0.09**</td>
</tr>
<tr>
<td>IV block*</td>
<td>0.04**</td>
</tr>
<tr>
<td>Non-specific T wave**</td>
<td>0.04</td>
</tr>
<tr>
<td>Angina pectoris**</td>
<td>0.16**</td>
</tr>
<tr>
<td>MI or CI**</td>
<td>0.064**</td>
</tr>
</tbody>
</table>

†If \( n_i \) is the number of cases in the \( i \)th age group (45–49, 50–54 . . . ) and \( d_i \) is the difference in means for a given characteristic (case—non-cases), then \( \Sigma n_i d_i / \Sigma n_i \) is the age-adjusted mean difference.

Note. *means significant at a level of \( p < 0.05 \). **means significant at a level of \( p < 0.01 \). Where it appears alongside the characteristic it means that the combined probabilities for all 3 studies (by method of R. A. Fisher) are statistically significant at the specified level.

A considerable number of the variables considered appear to be related to the incidence of MI or CHD death in all three studies. These are: systolic and diastolic blood pressure, angina pectoris and clinical evidence of MI or CI (not validated by standardized readings of the entry ECG). Serum cholesterol also seems related to CHD in all studies but this relationship is strongest in Puerto Rico and weakest (indeed not statistically significant) in Honolulu. Vital capacity is related to incidence in all three studies, although only for Puerto Rico is this statistically significant in both forms of analysis. In addition, lower physical activity seems related to higher incidence in all studies. Although the relationship always falls short of statistical significance, combining probabilities for all three studies (by the method of R. A. Fisher) [15] gives a statistically significant result. Among the variables considered, only relative weight has a significant association with incidence in Honolulu and Puerto Rico but not a statistically significant association in Framingham. However, more extensive data from Framingham have shown a significant relationship of relative weight to CHD [16]. The various ECG findings considered in relation to incidence, none of them based on standardized readings, yield somewhat inconsistent results among the studies. The studies agree in finding no statistically significant relationship between any of their measures of glucose intolerance and the incidence of MI or CHD death.

The one striking exception to this general agreement is the finding that cigarette smoking in Puerto Rico is unrelated to the incidence of MI or CHD death, despite the fact that it is among the most powerful precursors of these events in Framingham and Honolulu. This remarkable finding is quite rare in epidemiological studies but not unprecedented [1].
In order for a characteristic to 'account for' a population difference in incidence the level of the characteristic must differ substantially from one population to the other and it must be related to incidence in both populations. The weaker the relationship the larger the necessary difference in characteristics. For all practical purposes the only characteristic of those listed in Tables 2 and 8 that appear to satisfy these conditions when all three studies are compared is serum cholesterol. Between Honolulu and Framingham cigarette smoking is another such factor. Since blood pressure is a strong risk factor in all three studies and is slightly lower in Puerto Rico than Framingham or Honolulu, it is also included. Prior clinical evidence of CHD not validated by the ECG also falls into this category but it seemed more reasonable to treat this as a possible exclusion rather than another risk factor. The only other factor that might warrant consideration is relative weight but uncertainty that the standards used are truly comparable must leave that comparison moot.

![Graph](image_url)

**Fig. 1.** Probability at age 55 yr, of CHD occurring in 2 yr according to systolic blood pressure.

A direct comparison of incidence rates at fixed levels of each variable (not included in this report but available on request) showed that, except for that variation which would be expected at random, incidence rates at any level were roughly twice as great in Framingham as the other studies. This is true for every variable found to be related to incidence in the 3 studies. The smoothed comparisons for selected variables shown in Figs. 1–3 are consistent with the direct comparisons.

Even among men crudely characterized as low risk on several variables the incidence in Framingham is at least twice that for the other studies. For example, in men free of angina pectoris at entry, without glycosuria, hypertension (≥140/90) or hypercholesterolemia (≥300), the annual incidence of CHD per 1000 was 3.83 in Framingham, 2.21 in Honolulu and 1.89 in Puerto Rico. If, in addition, smokers are omitted, the Framingham rate drops to 2.25 while the rate in Honolulu becomes 0.90. Since cigarette smoking is not a risk factor in Puerto Rico, omitting smokers would alter the rate only trivially there.
Multivariate comparisons are more difficult to make as well as to explain. Selected results are given in Tables 9 and 10 and Fig. 4. The detailed analyses (available on request) are too extensive to include here but they may be summarized as follows: At every age and at every combination of levels within the usual range of systolic blood pressure, serum cholesterol and cigarette smoking, the probability of CHD is greater in Framingham than Honolulu. There is a clear suggestion that the difference is greater in older men than younger.
It is difficult to make one overall statement of statistical significance covering all comparisons between Honolulu and Framingham. For values of the risk factor within the usual range, the ratio of odds (Framingham to Honolulu) is always greater than one; that is, the chances of MI or CHD death appearing are always greater in Framingham than at Honolulu, no matter what age or what levels of these characteristics are present. However, at age 45 these ratios are never statistically significant (that is, their 95 per cent confidence interval always includes one) no matter what values of the independent variables are considered. Similarly, in high risk individuals (here taken as men with a serum cholesterol level of 300 mg per cent, a systolic blood pressure of 190 mm Hg and smoking 45 cigarettes a day) the ratios tend to be small and are not statistically significant at any age. At moderate and low values the ratios are larger and, above age 50, statistically significant. At the average values of these characteristics for Honolulu the odds of CHD are more than twice as great in Framingham as in Honolulu whether or not the population at risk includes persons whom the individual studies found to have clinical evidence of pre-existing CHD but who were retained by the inter-study rules in the population at risk. Impressions left by univariate and multivariate analysis are, therefore, in accord.

![Fig. 4. Probability of CHD developing in 2 yr at average levels of specific characteristics.](image)

Note. The fixed levels are: age 54, serum cholesterol—219, systolic blood pressure—15, cigarettes/day —10.

Multivariate comparisons between Puerto Rico and Framingham yield similar conclusions. At the mean levels of age, serum cholesterol and systolic blood pressure in Puerto Rico, the Framingham odds for CHD are 2.02 times those in Puerto Rico. The contrast between Puerto Rico and Honolulu, on the other hand, is trivial. At the mean levels for these characteristics in Honolulu the Puerto Rico odds are 1.21 times those in Honolulu. Allowance for the known laboratory differences in measuring serum cholesterol would shift these ratios by a trivial amount to 1.90 (Framingham–Puerto Rico) and 1.29 (Puerto Rico – Honolulu). Only the first ratio is significantly different from 1.00 at a 5 per cent level. Thus, the incidence of MI or CHD death is significantly greater in Framingham than Puerto Rico even after considering risk characteristics in these two populations whereas Puerto Rico and Honolulu incidence are not significantly different.

Again there is a clear impression that differences in incidence between Framingham and Puerto Rico are greater in older men than younger. In fact, at age 45 the ratio of odds does not differ from 1.0 at a 5 per cent level no matter what configuration of risk
factors is considered. None of the Honolulu–Puerto Rico contrasts yield statistically significant differences in the multivariate analysis, although some of the nominal differences are quite large.

<table>
<thead>
<tr>
<th>TABLE 9. PROBABILITY OF CHD DEVELOPING IN 2 YR AT AVERAGE LEVELS OF SPECIFIED CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
</tr>
<tr>
<td>Probability in populations at risk</td>
</tr>
<tr>
<td>Framingham</td>
</tr>
<tr>
<td>Puerto Rico</td>
</tr>
<tr>
<td>Honolulu</td>
</tr>
<tr>
<td>Probability in populations at risk excluding persons with other clinical evidence of CHD at entry*</td>
</tr>
<tr>
<td>Framingham</td>
</tr>
<tr>
<td>Puerto Rico</td>
</tr>
<tr>
<td>Honolulu</td>
</tr>
</tbody>
</table>

*Other clinical evidence of CHD* is definite AP, clinically defined MI or CI.
†The average values used were:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Puerto Rico</th>
<th>Honolulu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol</td>
<td>202</td>
<td>219</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>130</td>
<td>136</td>
</tr>
<tr>
<td>Age</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>—</td>
<td>10</td>
</tr>
</tbody>
</table>

Note. Parenthetical values are 95 per cent confidence intervals.

<table>
<thead>
<tr>
<th>TABLE 10. RELATIVE ODDS OF CHD DEVELOPING IN 2 YR AT AVERAGE LEVELS OF SPECIFIED CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative odds in populations at risk</td>
</tr>
<tr>
<td>Framingham/Puerto Rico*</td>
</tr>
<tr>
<td>Puerto Rico/Honolulu*</td>
</tr>
<tr>
<td>Framingham/Honolulu*</td>
</tr>
<tr>
<td>Framingham/Honolulu†</td>
</tr>
<tr>
<td>Relative odds in populations at risk excluding men with other clinical evidence of CHD at entry</td>
</tr>
<tr>
<td>Framingham/Puerto Rico*</td>
</tr>
<tr>
<td>Puerto Rico/Honolulu†</td>
</tr>
<tr>
<td>Framingham/Honolulu*</td>
</tr>
<tr>
<td>Framingham/Honolulu†</td>
</tr>
</tbody>
</table>

*Based on 3-variable function.
†Based on 4-variable function.

Note. In each case the relative odds were computed at the level of the denominator population. Parenthetical values are 95 per cent confidence intervals.
DISCUSSION

When examining data from different studies it is a matter of concern to determine to what extent these are actually comparable. The prevalence data for the examined cohorts of Framingham, Honolulu and Puerto Rico are comparable, as the figures were based upon replicated unbiased clinical readings of ECGs by the different studies and by a central reading according to the Minnesota criteria.

The degree to which the examined cohorts represent the populations sampled is another area of importance. The lower response rate in Framingham than in Honolulu and Puerto Rico probably tends to bias CHD prevalence downward relative to the other studies, since ill persons may be less likely to appear for examination; but by the same token, the much higher prevalence of the illness encountered in Framingham than in the other studies probably understates a greater difference.

The comparability of incidence is more difficult to assess. Fortunately, the reliance on independent, blind readings of the ECGs by the three studies give a strong support for comparison. Hopefully, whatever bias might arise from those that did not return for examination was equivalent in the three studies. The high percentage of reappearance for examination in all three studies provides some reassurance in this respect.

Death from CHD is a more difficult problem. Even though the rules for collecting and assessing death data were practically the same in the three studies, the differences in medical practice and autopsy rates cannot be erased. As the senior investigator in Honolulu worked for many years at Framingham, and the senior investigator at Framingham reviewed documentation for a large sample of cardiovascular deaths in the Puerto Rico study, it is our judgment that the collection and evaluation of CHD mortality data are reasonably comparable. The fact that overall death rates are in line with the observed coronary mortality adds to our assurance that the data themselves are reasonably comparable.

The incidence comparison could have been obscured by the inability to eliminate angina pectoris from the populations at risk due to the lack of a standardized diagnosis. However, even if subjects with an unstandardized diagnosis of angina pectoris are excluded from the population at risk in each study, there remains the same statistically significant higher incidence of CHD in Framingham than in Honolulu and Puerto Rico at fixed levels of age, serum cholesterol and blood pressure. Furthermore, the incidence of MI or CHD death in men entering with angina was twice as great in Framingham as Honolulu or Puerto Rico (Fig. 5). Apparently the prognosis of angina is less favorable in Framingham or the diagnosis of angina is more conservative there.

Although the lifetime levels of serum cholesterol, blood pressure and cigarette smoking in the three populations are not known, it is unlikely that former larger differences in these risk attributes provide a full explanation for the differences in CHD incidence between populations.

Differences in CHD incidence are greater in the older men, suggesting that the incidence diverges as the populations get older or that the younger men have a more similar coronary background or predisposition. This is consistent with the idea that there are substantial cohort differences in Honolulu and Puerto Rico, men in the cohort born at the beginning of this century being at less risk of developing CHD than men born later. In Honolulu, informal historical evidence suggests a substantially different (more Japanese) way of life among Japanese living there before World War II.
In Puerto Rico there has been a substantial urbanization and upgrading of the standard of living since World War II. Hence it is reasonable to expect cohort differences of the kind suggested by the data. The immunity of the Honolulu and Puerto Rico populations may be disappearing.

**Fig. 5.** Probability at age 55 yr, of CHD occurring in 2 yr by presence or absence of angina pectoris at entry.

**SUMMARY**

An effort to evaluate geographic differences in prevalence and incidence of coronary heart disease in men from Framingham, Japanese from Honolulu, and residents of Puerto Rico was made, using comparable methodology and criteria.

The prevalence of CHD was twice as great in Framingham as in Honolulu and Puerto Rico. CHD incidence by ECG alone, by CHD death, or by both was from 2 to 4 times as high in Framingham as in Honolulu and Puerto Rico.

There was a striking agreement among the studies with respect to the relationship of baseline characteristics to subsequent incidence of CHD. In particular, all three studies found a positive association of serum cholesterol and blood pressure to subsequent CHD incidence. A similar relationship was encountered with cigarette smoking in Framingham and Honolulu but not in Puerto Rico. All three found little or no relationship to the various measures of clinical and subclinical diabetes. A number of other variables showed relationships that were similar in all three studies. On the other hand, relative weight was a much weaker risk factor in Framingham than in Honolulu or Puerto Rico.

Since serum cholesterol levels and the amount of cigarette smoking differ in the three populations it is logical to inquire whether this could account for the differences in CHD incidence. The answer is clear that the average Honolulu Japanese and Puerto Rican has a lower CHD incidence than his counterpart in Framingham. Even after
allowing for differences in population characteristics, the difference is statistically significant and about 2.1 in magnitude.

This suggests that new factors or explanations should be sought in order to clarify the additional protection against coronary heart disease found in some populations.

Acknowledgements—While it is impossible to give full credit to all persons assisting in preparing this paper, special acknowledgement must be made to Drs. Raul Costas, Jr., Mercedes Cruz-Vidal and Marcelino Cortis-Alicea in Puerto Rico, Dr. William P. Castelli and Patricia M. McNamara in Framingham, and Drs. George G. Rhoads, Peter D. Zeegen, Steven M. Peskoe and Joseph Moore in Honolulu for their help.

REFERENCES