Clustering of Metabolic Factors and Coronary Heart Disease

Peter W. F. Wilson, MD; William B. Kannel, MD; Halit Silbershatz, PhD; Ralph B. D’Agostino, PhD

**Background:** The degree of clustering for common metabolic coronary disease risk factors is not well known, the antecedents of clustering are not well studied, and the impact of such clusters on coronary risk has not been assessed systematically.

**Methods:** Prospective community sample of 2406 men and 2569 women aged 18 to 74 years at baseline. The 6 metabolically linked risk factors considered were the lowest sex-specific quintile of high-density lipoprotein cholesterol and the highest quintiles of body mass index, systolic blood pressure, triglycerides, glucose, and serum total cholesterol.

**Results:** At baseline the risk factor sum, represented as integer values, ranged from 0 to 6, and clusters of 3 or more risk factors occurred at twice the rate predicted by chance. After adjustment for age and obesity level, a 2.25-kg (5-lb) weight increase over 16 years was associated with an increased risk factor sum in men (+20%; \( P = .002 \)) and women (+37%; \( P < .001 \)), and a 2.25-kg weight loss was associated with a decreased risk factor sum in men (−48%; \( P < .001 \)) and women (−40%; \( P < .001 \)). Clusters of 3 or more risk factors were associated with a 2.39 (95% confidence interval, 1.56-3.36) and 5.90 (95% confidence interval, 2.54-13.73) times greater risk of coronary heart disease in men and women, respectively (both \( P < .001 \)).

**Conclusions:** Atherogenic risk factor clustering is common in both sexes, worsens with weight gain, and is associated with greatly increased risk of coronary disease risk in both sexes.

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**Persons Who Develop Coronary Heart Disease (CHD)** typically have more than 1 risk factor. This tendency to cluster is part of the foundation for expert panel recommendations concerning cholesterol and blood pressure interventions that emphasize the treatment of several factors at a time to reduce coronary risk.\(^1,2\) While this approach has been taken clinically, the extent of metabolic risk factor clustering, the impact of initial weight and weight change on the extent of risk factor clustering over time, and the association of clustering with CHD incidence have not been well documented.\(^3\)

Previous reports on risk factor clustering have often used commonly accepted cutoff levels and assessed the impact of extreme risk factor levels on vascular disease incidence.\(^4\) Such an approach has its merits, but clinically derived criteria weight the impact of each factor differently, as the prevalence of each abnormality varies greatly.

This investigation examined population aspects of metabolic risk factor clustering in a community-based sample of adult men and women, after initially defining metabolic cardiovascular risk factors based on quintiles of their population distributions. Using sex-specific quintiles derived from the study sample for each risk factor allowed us to compare the degree of observed clustering and the amount expected on the basis of chance from the binomial distribution. The analysis used 16 years of follow-up to estimate the degree of change in clustering over time in relation to obesity and weight change, and estimated the impact of clustering on the incidence of CHD.

**RESULTS**

Mean levels and criteria for the metabolic risk factors considered are shown in Table 1 for men and women. Risk factor definitions were based on the quintiles of the distributions for measurements made in 2406 men and 2569 women aged 18-74 years at the time of the first Framingham Offspring Study examination in 1971-1974. The risk factor sums ranged from 0 to 6,
METHODS

This investigation was based on the experience of the Framingham Offspring Study, a population-based sample of 2406 men and 2569 women aged 18-74 years at the time of their first clinic examination in 1971-1974. The baseline evaluation included a cardiovascular history, physical examination, and blood chemistry determinations. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. Blood pressure determinations were made in the left arm with a mercury sphygmomanometer in subjects who had been seated for at least 5 minutes. A large cuff was used when required and readings were recorded to the nearest even number. At the baseline and follow-up examinations, plasma total cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) levels were determined after a 12-hour fast, using methods promulgated by the Lipid Research Clinics Program.5 A total of 1872 men and 2024 women returned for the fourth examination of the Offspring sample in 1987-1990. The same clinical methods were used for measurement of blood pressure and BMI at the follow-up visit. Lipoprotein cholesterol and triglyceride levels at the follow-up examination were measured enzymatically, using Abbot A-gent reagents.6 In crossover laboratory analyses that were undertaken in 1983 the mean cholesterol levels were approximately 1% lower at the later examination and HDL-C levels were approximately 2% lower at the later examination.

Six factors were considered in this analysis, including the lowest quintile for HDL-C and highest quintile for cholesterol, BMI, systolic pressure, triglycerides, and glucose. Sex-specific levels were defined from the study population sample as risk factors to allow estimation of the expected extent of clustering from the binomial formula. The cutoff values corresponding to these various extreme quintiles are presented in Table 1. The expected degree of risk factor clustering was estimated, calculating the probability of d occurrences for n factors where the probability of each occurrence was 0.20. Individual probabilities were calculated from the binomial formula:

\[
\binom{n}{d} (0.8)^{-d} (0.2)^d
\]

but a sum of 4 or greater was very uncommon, and comparisons are shown for the frequencies of 0, 1, 2, or 3 or more risk factors among the clinic attendees (Figure 1). Accompanying the data for men and women are the estimated frequencies of the risk factor sum from the binomial equation. The relative odds for a risk factor sum of 3 or more was 1.86 (95% CI, 1.57-2.21) for men and an identical 1.86 for women (95% CI, 1.63-2.14).

Table 1. Risk Factor Quintile Criteria: Framingham Offspring Examination 1, Ages 18 to 74 Years, 1971-1974

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Mean ± SD</th>
<th>Cutoff</th>
<th>Mean ± SD</th>
<th>Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n = 2406)</td>
<td></td>
<td></td>
<td>Women (n = 2569)</td>
<td></td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mmol/L (mg/dL)</td>
<td>1.15 ± 0.29 (44.2 ± 11.1)</td>
<td>&lt;0.91 (35)</td>
<td>1.47 ± 0.38 (6.6 ± 14.6)</td>
<td>&lt;1.14 (44)</td>
</tr>
<tr>
<td>Cholesterol, mmol/L (mg/dL)</td>
<td>5.23 ± 1.04 (202 ± 40)</td>
<td>≥5.98 (≥231)</td>
<td>4.97 ± 0.98 (192 ± 38)</td>
<td>≥5.75 (≥222)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.8 ± 3.6</td>
<td>≥29.5</td>
<td>24.2 ± 4.7</td>
<td>≥26.8</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>127 ± 16</td>
<td>≥138</td>
<td>118 ± 17</td>
<td>≥130</td>
</tr>
<tr>
<td>Triglycerides, mmol/L (mg/dL)</td>
<td>1.34 ± 1.18 (117 ± 102)</td>
<td>≥1.79 (≥155)</td>
<td>0.89 ± 0.82 (77 ± 71)</td>
<td>≥1.19 (≥103)</td>
</tr>
<tr>
<td>Plasma glucose, mmol/L (mg/dL)</td>
<td>5.89 ± 0.94 (106 ± 17)</td>
<td>≥6.82 (≥112)</td>
<td>5.50 ± 0.78 (99 ± 14)</td>
<td>≥5.83 (≥105)</td>
</tr>
</tbody>
</table>

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Among the 1759 men and 1818 women aged 30-74 years who did not have CHD at baseline, there were 229 incident cases of CHD in men and 79 in women during 16 years of follow-up. The association of the risk factor sum with CHD incidence appears in Table 4. Estimates of relative risk, prevalence, number of CHD events, and population attributable risk percent for the risk factor sums are presented. Separate analyses were undertaken for men and women, using a risk factor sum of zero as the referent group. Clustering of 3 or more risk factors was associated with a relative risk for CHD that was 2.39 (95% CI, 1.56-3.66) in men and 5.90 (95% CI, 2.54-13.73) in women. The greatest relative risks were observed for persons with 3 or more risk factors, and 30% of the CHD cases in men and 56% of the CHD cases in women had 3 or more risk factors. The population attributable risk percent associated with 3 or more risk factors was 0.20 in men and 0.48 in women, signifying that clustering of 3 or more risk factors in this study was associated with 20% of the CHD events in men and 48% of the events in women. The age-adjusted risk factor sum was also associated with an increased risk of hard CHD events (myocardial infarction or coronary death) in both sexes, and the trends were similar to what was observed for the overall CHD incidence (Table 5). Although there were fewer cases of coronary death during follow-up, this event was also highly associated with an increasing risk factor sum in men. Coronary deaths were exceedingly uncommon among the women, but some evidence of increased risk of this event was associated with a risk factor sum of 3 or greater.

For many years clinicians and researchers have recognized that risk factors tend to cluster, and the hazard of developing coronary disease in persons with any particular risk factor has been noted to increase in proportion to the degree of associated clustering. In this study the tendency for risk factors to cluster was examined systematically in the Framingham Offspring Study, investigating its impact in 2406 men and 2569 women aged 18 to 74 years. The variables considered were metabolic

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**Table 2. Risk Factor Means at Baseline and Follow-up by Baseline Body Mass Index (BMI) Quintile, Ages 18 to 74 Years, 1971-1974**

<table>
<thead>
<tr>
<th>Risk Factor Score</th>
<th>According to BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;23.7 (n = 449)</td>
</tr>
<tr>
<td><strong>Men</strong> Baseline</td>
<td>0.51 ± 0.79</td>
</tr>
<tr>
<td>Follow-up</td>
<td>0.80 ± 0.93</td>
</tr>
<tr>
<td><strong>Women</strong> Baseline</td>
<td>0.58 ± 0.76</td>
</tr>
<tr>
<td>Follow-up</td>
<td>0.82 ± 1.03</td>
</tr>
</tbody>
</table>

*Risk factor sum range is 0 to 5; entries represent mean ± SD.
†Age-adjusted trend across BMI (P < .001).
factors that have been hypothesized to be atherogenic, including serum total and HDL-C levels, triglyceride levels, systolic blood pressure, BMI, and blood glucose levels. The extreme quintile values of each were defined as risk factors and the prevalence of their occurrence in isolation and in clusters was evaluated.

It was found that these risk factors occurred in isolation only 28% to 30% of the time (Table 3), and clusters of 3 or more risk factors occurred 17% of the time in both sexes. This evidence of clustering in the general population suggests a metabolic connection among the risk factors under consideration.

Obesity and weight gain were important determinants of clustering (Tables 3-5), and in the present report the tendency for risk factors to cluster increased with weight gain and decreased with weight loss. Weight change had a greater impact than initial level of obesity in men, while both initial obesity level and weight change were highly associated with change in the risk factor sum in women (Table 5). Insulin resistance has been postulated as the inciting cause for such clustering, but insulin levels were not available at the baseline or follow-up examinations.

Understanding the basis for risk factor clustering is important, because it provides insight into the pathogenesis of atherosclerosis and it has implications for the prevention of coronary disease. Clustering of 3 or more of the aforementioned risk factors was found to be associated with a high risk of developing coronary disease and coronary disease death (Table 4, Table 5, and Table 6). Because of the large risk ratio and substantial prevalence of 3 or more risk factors in the general population, about 20% of coronary events in men and 48% in women can be attributed to clusters of metabolically related risk factors.

Hypertension, dyslipidemia, and glucose intolerance are well-established atherogenic risk factors. The coronary disease hazard imposed was related to the level of each risk factor, with no discernible critical values. It has been recognized that the risk of atherosclerotic cardiovascular sequelae associated with any particular risk factor varies, depending on the concomitant burden of other risk factors. The major atherogenic risk factors seldom occur in isolation, tending instead to cluster with 3 or more other risk factors well beyond chance expectation. This suggests that many are metabolically linked, reflecting some more fundamental process. Insulin resistance promoted by abdominal obesity, and abnormal sympathoadrenal activity have been postulated according to quintile (Q) at baseline examination. The top panel shows data for men and the bottom panel, for women. Each cluster sums to approximately 20% (rounding errors may exist) and the individual bars represent weight loss of more than 2.25 kg (<–2.25 kg), weight gain of more than 2.25 kg.

<table>
<thead>
<tr>
<th>Risk Factor Sum</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>Prevalence, %</th>
<th>CHD Events, No. (%)</th>
<th>Population Attributable Risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (Referent)</td>
<td>33</td>
<td>41 (18)</td>
<td>Referent</td>
</tr>
<tr>
<td>1</td>
<td>1.54 (1.01-2.35)</td>
<td>29</td>
<td>61 (27)</td>
<td>0.14</td>
</tr>
<tr>
<td>2</td>
<td>2.02 (1.31-3.12)</td>
<td>19</td>
<td>58 (25)</td>
<td>0.16</td>
</tr>
<tr>
<td>≥3</td>
<td>2.39 (1.56-3.66)</td>
<td>18</td>
<td>69 (30)</td>
<td>0.20</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (Referent)</td>
<td>32</td>
<td>7 (9)</td>
<td>Referent</td>
</tr>
<tr>
<td>1</td>
<td>1.21 (0.45-3.23)</td>
<td>30</td>
<td>10 (13)</td>
<td>0.06</td>
</tr>
<tr>
<td>2</td>
<td>2.89 (1.17-7.13)</td>
<td>19</td>
<td>18 (23)</td>
<td>0.26</td>
</tr>
<tr>
<td>≥3</td>
<td>5.90 (2.54-13.73)</td>
<td>19</td>
<td>44 (56)</td>
<td>0.48</td>
</tr>
</tbody>
</table>
Inglis effects, contributing to the pathogenesis of hypertension and its atherogenic consequences. Abdominal obesity promotes insulin resistance, which is accompanied by hyperinsulinemia and a down-regulation of lipoprotein lipase activity, leading to dyslipidemia that is characterized by elevated triglyceride and reduced HDL-C levels. This combination of lipid aberrations is often associated with a change in low-density lipoprotein cholesterol to smaller and denser particles. Hyperinsulinemia, resulting from insulin resistance, has been postulated by Reaven and Chen to stimulate the sympathetic nervous system. The consequences may include cardiac, vascular, and renal effects, contributing to the pathogenesis of hypertension. Insulin resistance can subsequently lead to glucose intolerance and type 2 diabetes mellitus.

Insulin resistance can be assessed in the population setting by using a variety of methods, typically requiring multiple glucose and insulin measurements. Such a requirement puts accurate assessment of insulin resistance beyond the scope of most large population studies, and largely out of consideration for older studies. On the other hand, abdominal obesity, low HDL-C and high triglyceride levels, hyperglycemia, and elevated blood pressure have been proposed as components of the insulin resistance syndrome, and prevalence of the syndrome in the general population may range from 25% to 80%, depending on the age and ethnicity of the study sample. Also important, weight reduction was associated with an improvement in risk factor sums, as shown in Table 3. Earlier research by us and others has reported similar beneficial effects on risk factors in association with a modest degree of weight loss, and favorable changes in levels of triglycerides, HDL-C, and hemostatic factors plasminogen activator inhibitor and factor VII, but little change in fibrinogen levels, have been observed.

The Framingham Heart Study clustering data reported in this study do not constitute the insulin resistance syndrome, but do highlight the importance of obesity and weight gain in middle-aged subjects, as clustering of 3 or more risk factors occurs in about 17% of both sexes and is associated with an increased risk for CHD. Clustering of major atherogenic risk factors was common in the Framingham Heart Study data, and that when confronted with any particular risk factor, screening for the other metabolically linked risk factors would appear mandatory. Obesity, glucose intolerance, dyslipidemia, and hypertension are jointly atherogenic. Weight reduction and other interventions to improve insulin resistance should enhance the correction of other associated risk factors and reduce the atherogenic potential.

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