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.
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. 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. 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 quintiles 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:

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

Extreme quintile levels were given a weight of 1 and all other quintiles were weighted as 0. Overall risk factor sums were represented as integers and ranged from 0 to 6. Risk factor sums ranged from 0 to 5 for analyses within the BMI quintiles. The relative odds for a risk factor sum of 3 or greater was calculated using the \( \chi^2 \) test, comparing observed frequencies with those expected from the binomial equation.

Morbidity and mortality were monitored with routine clinic examinations and hospital surveillance. New cardiovascular events were adjudicated by a panel of experienced investigators, using previously established criteria for angina pectoris, myocardial infarction, and CHD death. Detailed descriptions of the sampling methods, examination procedures, and criteria for various cardiovascular end points have been reported elsewhere.

General linear regression models were used to test for associations between BMI, weight change, and the risk factor sum over time. The association of BMI quintiles with the sum of the other factors was tested at baseline and at the follow-up examination using a linear regression model that incorporated age and BMI categories. The BMI quintiles were represented as a single categorical variable that ranged from 0 to 4, and the test for trend represented the statistical significance of this variable in the analysis of variance.

Data for 1759 men and 1818 women free of CHD and aged 30 to 74 years at the baseline examination were available for analyses of coronary disease incidence. The end point total CHD included first occurrence of angina pectoris, unstable angina, myocardial infarction, or coronary death. The end point “hard CHD” was restricted to include first myocardial infarction and coronary death. Cox proportional hazards statistical methods were used to examine the association of the baseline risk factor sum after adjusting for age. Analyses included testing for proportionality, and multivariate adjusted odds ratios and their 95% confidence intervals (CIs) were estimated from the \( \beta \) coefficients and the SE of the \( \beta \) coefficients according to specified number of units for the variables. Subjects remained at risk as long as they were free of coronary disease during follow-up. Attributable risk was estimated from multivariate proportional hazards analysis that included age, using relative risk estimates that were derived from exponentiating the \( \beta \) coefficients in these analyses, according to the formula \[ \text{prevalence} \times (\text{relative risk} - 1) / (1 + \text{prevalence} \times (\text{relative risk} - 1)) \].

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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>Men (n = 2406)</th>
<th>Cutoff</th>
<th>Women (n = 2569)</th>
<th>Cutoff</th>
</tr>
</thead>
<tbody>
<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>≥6.22 (≥112)</td>
<td>5.50 ± 0.78 (99 ± 14)</td>
<td>≥5.83 (≥105)</td>
</tr>
</tbody>
</table>

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).
In analyses restricted to persons who attended the baseline and follow-up examinations, the mean risk factor sum was positively associated with the quintile of baseline BMI in both sexes at each point in time (tests for trend across BMI quintile after age adjustment, \( P < .001 \)) (Table 2). Change in weight during follow-up was related to the BMI at the baseline examination, and leaner persons at baseline tended to gain 2.25 kg or more during follow-up (Figure 2). The data in this table are presented according to quintile of BMI at baseline. Participants who were more obese at the outset typically gained weight, but weight loss of 2.25 kg or more also occurred more commonly in these individuals.

Results for the impact of baseline age, initial quintile of BMI, weight loss and weight gain of 2.25 kg or more on change in risk factor sum appear in Table 3. After adjusting for age and baseline level of obesity, weight loss of 2.25 kg or more was highly associated with a favorable change in risk factor sum (\( P < .001 \) for both men and women). Compared with baseline risk factor sums, taken from Table 3, the risk factor sums increased 20% in men and 37% in women. Correspondingly, weight gain of 2.25 kg or more was significantly associated with the opposite effect (\( P < .001 \) for both men and women), representing risk factor sums that declined 48% in men and 40% in women.

![Figure 1. Distribution of risk factor sums in Framingham Offspring Study participants aged 18 to 74 years. Bars represent observed frequencies for men and women and the line plots represent the expected frequencies (from the binomial equation).](image)

For many years clinicians and researchers have recognized that risk factors tend to cluster, and the hazard of developing coronary disease is 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

### 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* According to BMI</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline examination</td>
<td>Follow-up examination</td>
</tr>
<tr>
<td></td>
<td>( n = 449 )</td>
<td>( n = 454 )</td>
</tr>
<tr>
<td>(&lt; 23.7 )</td>
<td>0.51 ± 0.79</td>
<td>0.80 ± 0.93</td>
</tr>
<tr>
<td>( 23.7-25.5 )</td>
<td>0.71 ± 0.95</td>
<td>0.96 ± 1.50</td>
</tr>
<tr>
<td>( 25.6-27.3 )</td>
<td>0.92 ± 1.02</td>
<td>1.27 ± 1.18</td>
</tr>
<tr>
<td>( 27.4-29.5 )</td>
<td>1.15 ± 1.19</td>
<td>1.33 ± 1.16</td>
</tr>
<tr>
<td>( \geq 29.5 )</td>
<td>1.46 ± 1.23</td>
<td>1.63 ± 1.22</td>
</tr>
<tr>
<td>Overall</td>
<td>0.96 ± 1.10</td>
<td>1.21 ± 1.15</td>
</tr>
</tbody>
</table>

* Risk factor sum range is 0 to 5; entries represent mean ± SD.
† Age-adjusted trend across BMI (\( P < .001 \)).

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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.23,24

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.23,24 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.22 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.23,24 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 as the inciting cause for such clustering, but insulin resistance has also been postulated as the inciting cause for such clustering.
Insulin resistance can subsequently lead to glucose effects, contributing to the pathogenesis of hypertension, which 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.

As responsible underlying mechanisms for risk factor clustering 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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REFERENCES


