Increased Coronary Mortality in Relatives of Hypercholesterolemic School Children: The Muscatine Study

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Assisted by Kathleen M. Schreiber and Joy Eyman

SUMMARY From 2,874 school children participating in the 1971 and 1973 Muscatine Coronary Risk Factor Survey, we selected three groups of index cases for detailed family study: the HIGH group (n = 56), with cholesterol levels greater than the 95th percentile twice; the MIDDLE group (n = 46), cholesterol levels between the 5th and 95th percentile; and the LOW group (n = 46), cholesterol levels less than the 5th percentile twice. Coronary mortality determined from death certificates was increased in the young relatives (ages 30–59) of the HIGH group index cases, as follows: twofold excess in HIGH male relatives compared with the MIDDLE or LOW group (p < 0.05); tenfold excess in the HIGH female relatives compared with the MIDDLE and LOW group combined (p < 0.01). After correction for years at risk, there was an approximately twofold significantly-increased coronary mortality. Stroke mortality was higher, although not significantly, in the older relatives (ages ≥ 60) of the HIGH index cases. Cancer mortality was not significantly different among the relatives of the three groups of index cases. This study indicates that school children's cholesterol levels cluster with those of their family members and that persistent hypercholesterolemia in children identifies families at risk for coronary artery disease.

THE INCREASED FREQUENCY of ischemic heart disease in relatives of heart attack victims compared with relatives of control subjects1–3 and a concordance of ischemic heart disease higher among monozygous twins than dizygous twins4 suggest that hereditary factors play a role in the development of occlusive coronary disease. Studies of families reveal a greater frequency of hypercholesterolemia, an established risk factor in coronary artery disease,5–12 among first-degree relatives of heart attack cases under age 60 years.13 Monogenic hyperlipidemia has been identified in approximately 20% of these families.14 Indeed, 16–21% of the progeny of myocardial infarction patients under age 50 have an elevated cholesterol level.15–17 The familial aggregation of ischemic heart disease18 may result in part from the increased familial frequency of hypercholesterolemia.

Recent studies have focused on the repeated measurement of coronary risk factors in childhood populations.19–22 The successive measurement of blood cholesterol levels provides population estimates of cholesterol values by age and sex, the temporal variability of lipid determinations, the consistency of the percentile rank between surveys, and the effect of maturation on cholesterol levels. However, to study the relationship between childhood hypercholesterolemia and the development of coronary artery disease in the same children would require an inordinately long time. We pursued a question of more immediate interest: Are elevated cholesterol levels in children associated with an increase of coronary disease deaths in their families? We made detailed studies of families of children with either elevated, normal, or low cholesterol levels measured in school surveys carried out in 1971 and 1973, and found a significant increase in the frequency of myocardial infarction deaths among the relatives of children with elevated cholesterol levels.

Materials and Methods

School Survey

Details of the school survey have been presented elsewhere.22 Briefly, a cross section of children in Muscatine, Iowa participated in repeated school surveys. The 1971 survey included grades 3–12 in the 1970–71 school year and grades 1–3 in the 1971–72 school year. The 1973 survey included grades 1–12 from January to May, 1973 and grades K and 1 from March to May, 1974. Blood samples were obtained for cholesterol and triglyceride determinations. In 1973, children were asked to fast overnight and a blood sample was obtained in the fasting state the next morning; 3% of the children sampled were non-fasting. In 1971, 4,823 students participated and 4,053 participated in 1973. The number of students in both the 1971 and 1973 studies was 2,874.
Family Selection

We selected three groups of index cases for family studies. Children with cholesterol levels above the 95th percentile for age and sex on both the 1971 and 1973 surveys were designated the HIGH group; children with levels less than the 5th percentile in both surveys made up the LOW group; and children with levels between the 5th and 95th percentile were selected randomly for the MIDDLE group. The 95th percentile ranged from 219 mg/dl at 8 years of age to 237 mg/dl at 16 years. The 5th percentile ranged from 138 mg/dl at 5 years to 132 mg/dl at 16 years.

Family Study

The detailed family study included a standard pedigree with first- and second-degree relatives of each index case and a medical history of each living relative. Height, weight, systolic and diastolic blood pressures, triceps skinfold thickness and fasting plasma lipids were measured on participating local relatives. We contacted relatives living outside the local area and obtained medical histories and blood specimens; we emphasized the importance of fasting. The plasma samples were returned to the Lipid Research Clinic Core Laboratory at ambient temperature, arriving approximately 24–36 hours after mailing. Samples were received from 3.7% of first-degree and 41% of second-degree participating relatives, or 27.4% overall. All participants gave informed consent.

Participation in Family Studies

In the HIGH group there were 67 children coming from 65 families. Two children were adopted, four families had moved away, and three families refused to participate. We obtained pedigrees from 56 families, but three families later refused to participate. Mortality data were available from 56 families. We contacted the families of 80 children in the MIDDLE or control group and explained the nature of the program. A pedigree was taken from 46 families and mortality data were available from this group; two families later refused to participate and lipid data were available on 44 families. In the LOW group there were 60 children. Five families moved away, five families refused to participate, and four families could not be located. Of the 46 families with pedigrees taken, one later refused to participate. Lipid data were available from 45 families and mortality data were available from 46 families.

Persistence of High or Low Cholesterol Levels

In the 1971 survey, 255 children had a cholesterol level above the 95th percentile for age and sex. Of these, 154 were sampled again in 1973, and 67 (44%) were again above the 95th percentile.

There were fewer children in the 1973 sample due to graduation, lower participation of high school students, and students moving away. Of the children whose cholesterol levels were elevated in both 1971 and 1973, 60.4% (29 of 48) had an elevated cholesterol level when sampled a third time in 1975. Thus, the probability that a child with an elevated cholesterol level would have two subsequent elevated levels is 0.26 (SEM = 0.04).

In the 1971 survey, 207 children had a cholesterol level less than the 5th percentile for age and sex. Of these, 140 were sampled again in 1973 and 60 (43%) were found to be low again. Of the children with low cholesterol levels in both 1971 and 1973, (63.2%) (24 of 38) had low values again in 1975. Thus, the probability that a child with a single low cholesterol level will have two subsequent low levels was 0.27 (SEM = 0.04).

Characteristics of Index Cases

Table 1 presents means for selected characteristics of the study group index cases. No one had thyroid disease, diabetes mellitus, or renal disease and no one was receiving medication at the time of resampling.

Participation Rate in Living Relatives

Fasting blood specimens and questionnaires were obtained from 83.8% (571 of 681) of all first-degree relatives and from 72.8% (979 of 1344) of all second-degree relatives.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of Index Cases*</th>
</tr>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Male/female</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Ponderal index</td>
</tr>
<tr>
<td>Relative weight</td>
</tr>
<tr>
<td>Triceps skinfold (mm)</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
</tr>
</tbody>
</table>

*The entries are mean ± sd as observed in the 1971 school survey.
degree relatives. The participation of the living first-degree and second-degree relatives respectively by group was as follows: HIGH group, 82% (210 of 256) and 73% (395 of 541); MIDDLE group, 89.4% (169 of 189) and 74.9% (271 of 362); and LOW group, 81.4% (192 of 236) and 71% (313 of 441). Fewer second-degree relatives participated because many lived far from the study site, requiring a greater proportion of mailed-in samples.

**Documentation of Cause of Death**

The vital status of all first- and second-degree relatives was determined by contact through letter or phone, or by communication with a close relative. A history of medical illnesses and causes of death was obtained for each deceased relative from the closest living relative. Death certificates were obtained on all deceased relatives who were 30 years or older at death. Myocardial infarction at death was recorded when the following conditions were listed: coronary occlusion, coronary thrombosis, myocardial infarction, sudden occlusion, coronary embolism or coronary atherosclerosis. Less specific terms, such as generalized arteriosclerosis, arteriosclerotic cardiovascular disease, arteriosclerosis, myocarditis, atherosclerotic heart disease, and acute myocardial failure, were not considered to specify the presence of myocardial infarction at death.

On death certificates, the “most probable diagnosis” is reliable for cancer (85.5%), stroke (85%), and coronary occlusion (78.6%).24 The diagnostic accuracy for arteriosclerotic heart disease increases as the age at death decreases. The reliability of diagnosis also improves when the more specific disease category of myocardial infarction is considered, compared with the more general category of arteriosclerotic heart disease.25 The reliability of death certificates to determine conditions at death has also been documented by others.26-28 Conditions such as hypertension and diabetes tend to be under-reported.29 We recorded for analysis all conditions reported on the death certificate, thus avoiding problems of judgment and bias when attempting to select a single cause of death.30

Death certificates were obtained on 93.8% (256 of 273) of all deceased first- and second-degree relatives 30 years of age or older, as follows: HIGH group, 93.3% (125 of 134); MIDDLE group, 97% (64 of 66); and LOW group, 91.8% (67 of 73). In nine cases from the HIGH group we could not obtain death certificates. From the nearest relatives we learned that three died of a myocardial infarction, and one each of stroke, diabetes, childbirth, old age, lung problem, and an accident. Among the two dead relatives without available death certificates in the MIDDLE group, the nearest relatives reported one death by suicide and one death from emphysema. Of six persons from the LOW group without death certificates, relatives claimed that two died of a myocardial infarction, three died of cancer, and one of a stroke.

**Biological Measurements**

The analysis for cholesterol and triglyceride content of the plasma samples was performed by the Core Lipid Laboratory,31 which participates in the standardization and surveillance programs of the Center for Disease Control (CDC) in Atlanta, Georgia. The second year of surveillance ended June 1975, and the average coefficients of variation for cholesterol and triglyceride were 1.67% and 2.9% respectively.

**Data Analysis**

While the ages of the living relatives were similar, consideration of both living and dead relatives indicated that those in the HIGH group were born somewhat earlier than those in the other two groups. Thus the HIGH group was at risk longer than either the MIDDLE or LOW groups. In order to correct for these possibly confounding factors, age and time standardizations were performed, using methods reported by Woolson et al.32 Deaths in each of the six study cohorts were compared with the expected mortality for the Iowa population during the same period. Mortality data for the Iowa population were taken from

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### Table 2. Cholesterol Means in Relatives of Index Case Groups*

<table>
<thead>
<tr>
<th>Relationship</th>
<th>High group</th>
<th>Middle group</th>
<th>Low group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siblings</td>
<td>179 ± 36 (120)†</td>
<td>157 ± 31 (84)</td>
<td>138 ± 26 (113)†</td>
</tr>
<tr>
<td>Parents</td>
<td>232 ± 46 (90)†</td>
<td>188 ± 33 (85)</td>
<td>172 ± 35 (79)†</td>
</tr>
<tr>
<td>Aunts and uncles</td>
<td>218 ± 44 (265)†</td>
<td>192 ± 37 (166)</td>
<td>188 ± 37 (189)</td>
</tr>
<tr>
<td>Grandparents</td>
<td>235 ± 49 (95)†</td>
<td>213 ± 48 (98)</td>
<td>210 ± 45 (101)</td>
</tr>
</tbody>
</table>

*The entries are mean ± SD mg/dl with number of relatives in parentheses.
†Mean significantly different from MIDDLE group, p < 0.01.

### Table 3. Triglyceride Means in Relatives of Index Case Groups*

<table>
<thead>
<tr>
<th>Relationship</th>
<th>High group</th>
<th>Middle group</th>
<th>Low group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siblings</td>
<td>82 ± 38†</td>
<td>72 ± 34</td>
<td>66 ± 31</td>
</tr>
<tr>
<td>Parents</td>
<td>135 ± 99†</td>
<td>117 ± 70</td>
<td>116 ± 81</td>
</tr>
<tr>
<td>Aunts and uncles</td>
<td>119 ± 67</td>
<td>120 ± 78</td>
<td>119 ± 80</td>
</tr>
<tr>
<td>Grandparents</td>
<td>146 ± 89</td>
<td>129 ± 72</td>
<td>153 ± 83</td>
</tr>
</tbody>
</table>

*For the numbers in each group see Table 2; entries are mean ± SD mg/dl.
†Mean significantly different from MIDDLE or LOW group, p < 0.05.
‡Mean significantly different from the LOW group, p < 0.01.
National Center for Health Statistics publications\textsuperscript{39-35} and population figures from U.S. Census Summaries.\textsuperscript{36-38} Expected numbers of deaths were calculated for total mortality, stroke, cancer, and myocardial infarction. Only deaths from 1936-1975 were used. While results for all decades were consistent, only mortality comparisons for the decade 1966-1975 are reported. Other data comparisons, when appropriate, were analysis of variance, Tukey's Multiple Comparison Procedure and chi square.

**Results**

**Lipid Values and Coronary Risk Factors in Living Relatives**

Comparison of the mean cholesterol levels (table 2), not adjusted for age, showed a statistically significant, stepwise difference in siblings and parents of the HIGH, MIDDLE and LOW groups. For the grandparents and aunts and uncles, only the difference in mean cholesterol levels between the HIGH and MIDDLE or HIGH and LOW groups was significant. Comparing the mean triglyceride concentrations (table 3), we observed a stepwise difference in the mean triglyceride levels of the siblings and parents in the three groups. There was no significant triglyceride difference between any of the groups of aunts and uncles or of grandparents.

**Table 5. Conditions Reported at Death in Relatives\textsuperscript{*}**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>High group</th>
<th>Middle group</th>
<th>Low group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarctions</td>
<td>38.8 (52/134)\textsuperscript{†}</td>
<td>28.8 (19/66)</td>
<td>32.9 (24/73)</td>
</tr>
<tr>
<td>Stroke</td>
<td>12.7 (17/134)</td>
<td>10.6 (7/66)</td>
<td>8.2 (6/73)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14.9 (20/134)</td>
<td>9.1 (6/66)</td>
<td>8.2 (6/73)</td>
</tr>
<tr>
<td>Cancer</td>
<td>16.4 (22/134)</td>
<td>25.8 (17/66)</td>
<td>24.7 (18/73)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8.2 (11/134)</td>
<td>3.0 (2/66)</td>
<td>5.5 (4/73)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>5.2 (7/134)</td>
<td>3.0 (2/66)</td>
<td>6.8 (5/73)</td>
</tr>
<tr>
<td>Accidents</td>
<td>4.5 (6/134)</td>
<td>10.6 (7/66)</td>
<td>8.2 (6/73)</td>
</tr>
<tr>
<td>Suicide</td>
<td>0</td>
<td>3.0 (2/66)</td>
<td>2.7 (2/73)</td>
</tr>
<tr>
<td>Other</td>
<td>47.8 (64/134)</td>
<td>43.9 (29/66)</td>
<td>38.4 (28/73)</td>
</tr>
</tbody>
</table>

\textsuperscript{*}All conditions listed on the death certificate are counted in this tabulation. For example, in the deceased relative, greater than 30 years of age, of the HIGH index cases, there are 199 different conditions listed on the death certificate among the 134 deceased adults.

\textsuperscript{†}Percent (number with condition/total deceased).

The frequency of diabetes, hypertension and smoking was not significantly different among the participating relatives of the HIGH, MIDDLE, and LOW index children (table 4).

**Conditions Reported on Death Certificates**

The total number of conditions reported on the death certificate (table 5) exceeds 100% because some persons had more than one condition reported. Although the differences were not significant, there were more myocardial infarction and stroke deaths among the HIGH relatives (51.5%) than among the MIDDLE relatives (39.4%) or LOW relatives (42.5%). Hypertension and diabetes were reported more often among the HIGH relatives (23.1%) than among the MIDDLE relatives (12.1%) or LOW relatives (13.7%). In contrast, there were more frequent cancer deaths among the LOW relatives than among the HIGH relatives.

**Rate and Cause of Death**

The death rate of adult relatives (table 6) was greater in the HIGH group than in the MIDDLE or LOW groups. Mortality among relatives of the HIGH group was significantly higher \((p < 0.05)\) than among either the MIDDLE or LOW group relatives. More myocardial infarctions were noted among the deceased relatives 30-59 years old (table 7) of the HIGH group than among their counterparts in the MIDDLE or LOW groups \((p < 0.01)\); among deceased relatives 60 years and older we found a similar trend. The excess of total mortality among the HIGH relatives and the excess of stroke mortality among the relatives of the HIGH group 60 years and older, correlated with the excess of mortality from atherosclerosis. There was no difference in the cancer rate between the three groups in either age group.

The HIGH group had 52 myocardial infarction deaths in 31 families, 55.4\% of all families; the MIDDLE group had 19 in 16 families, 34.8\% of all families; and the LOW group had 24 in 20 families, 43.4\% of all families. These figures suggest that more families in the HIGH group are at risk for coronary artery disease than in the MIDDLE or LOW groups.
Death from myocardial infarction was twice as frequent among HIGH group male relatives 30-50 years old (table 8) as among their counterparts in the MIDDLE and LOW groups (p < 0.05). Among female relatives the frequency of myocardial infarction at death was 10 times greater in the HIGH group than in the MIDDLE and LOW groups (p < 0.01). Women in the HIGH group had the same frequency of myocardial infarction at death as the men in the MIDDLE and LOW groups. Among those 60 years and older, the frequency of myocardial infarction at death in both male and female relatives was slightly greater in the HIGH group than in the MIDDLE and LOW groups.

Age at Death from Coronary Occlusion

The mean age at death of first- and second-degree relatives with myocardial infarctions suggests earlier mortality for relatives of the HIGH group than for relatives of the MIDDLE or LOW groups: for male relatives, the mean age (±SD) was 62 ± 11 (n = 35) in the HIGH group, 65 ± 8 (n = 15) in the MIDDLE group, and 69 ± 15 (n = 17) in the LOW group; for female relatives the mean age was 61 ± 13 (n = 17) in the HIGH group, 68 ± 5 (n = 4) in the MIDDLE group, and 70 ± 9 (n = 7) in the LOW group. Small numbers probably prevented reaching statistical significance. The frequency of coronary occlusions at death under the age of 60 was 42.3% (22 of 52) in the HIGH group, 26.3% (five of 19) in the MIDDLE group and 25% (six of 24) in the LOW group.

Mortality

The results of comparisons between observed and expected mortality of both men and women for the decade 1966-1975 indicate an excess of myocardial infarctions in the HIGH group. While similar trends were observed for the other decades (1936-1945, 1946-1955, and 1956-1965), comparisons were statistically significant only for the decade 1966-1976, and for all decades combined. For all groups the number of years at risk was relatively small in the first two decades. Also, it was necessary to adjust the death rate from coronary artery disease to obtain the death rate from myocardial infarction for the first 3 decades, since more than one kind of condition was included in this classification. Both factors may affect the accuracy of the comparisons so we report the last decade only.

In the decade 1966-1975, total mortality among the male and female relatives of the HIGH group exceeded expectations, but only slightly. Total mortality in the MIDDLE and LOW groups was lower than expected. Myocardial infarction mortality was significantly higher than expected for both males (p < 0.01) and females (p < 0.02) in the HIGH group. In men, the ratios of observed to expected coronary mortality for each age group were as follows: ages 45-59, 1.82 (5/2.74); ages 60-74, 2.13 (11/5.17); and ages 30-74, 1.89 (16/8.478). In women, the ratios were as follows: ages 45-59, 3.67 (3/0.817); ages 60-74, 2.47 (5/2.028); and ages 30-74, 2.72 (8/2.946). There were very few deaths among those 30-44 years old and no myocardial infarction deaths were recorded. Cancer mortality was near the expected level, paralleling the earlier observation (table 7).

Discussion

The risk of developing coronary heart disease is greater for the relatives of children with cholesterol
levels elevated on two occasions. Coronary mortality was significantly increased, while the trend toward increased stroke mortality was noted in the older relatives of the HIGH group as compared with the MIDDLE or LOW group relatives. More families in the HIGH group had at least one deceased relative who had a coronary occlusion than families in the MIDDLE or LOW groups. Cholesterol levels among relatives of the HIGH group were higher than for relatives of the MIDDLE and LOW groups. Neither triglyceride levels nor the frequency of other coronary risks such as hypertension, diabetes, and smoking were statistically different among the three groups of living relatives. Thus, the higher cholesterol levels of the adult relatives of the HIGH group may account, in large part, for the significantly increased coronary mortality.

One might ask whether the selection of children with cholesterol levels above the 95th percentile on two occasions might have identified families with autosomal dominant type IIa hyperlipoproteinemia, thus explaining the excess of coronary mortality. This was not the case. Two of the 56 index cases had cholesterol levels greater than 300 mg/dl and the median cholesterol level of the subjects was at approximately the 98th percentile, with a slight excess toward the higher values. Furthermore, only 13% of the families (seven of 53) had one or more first-degree relatives with an age-adjusted cholesterol level above the 99th percentile. These families contributed approximately 10% (five of 52) of the myocardial infarction deaths. Thus, it appears likely the majority of the index cases had hypercholesterolemia of multifactorial causation.

Our findings are consistent with previously reported observations: coronary artery disease has familial aggregation; adults with elevated cholesterol levels are predisposed to early coronary occlusion; elevated cholesterol levels demonstrate a strong familial component; survivors of myocardial infarction have higher cholesterol levels and more lipid abnormalities among their relatives, and offspring of young myocardial infarction survivors have a fourfold enrichment of elevated cholesterol levels as compared with controls. Studies of the progeny of young myocardial infarction subjects, or families of young survivors of coronary occlusion, or hyperlipidemia patients have, by design, a concentration of subjects with either coronary artery disease or lipid abnormalities or both. Such concentrations are absent in our study where the index cases are drawn from a large, apparently healthy population of children.

Single elevations of serum cholesterol in adult subjects have been documented to be a coronary risk factor by prospective studies. However, no such prospective studies have been carried out beginning with childhood populations. A study of Muscatine school children whose cholesterol levels were monitored over a 6-year period showed a significant degree of percentile tracking \( r = 0.6 \) of cholesterol values, even though half of the children with a cholesterol level above the 95th percentile fell below this level on repeated measurement. Does a single elevated cholesterol level in a child predict coronary disease, as it appears to do in adults? Our data indicate an increased propensity in the families of children with persistently elevated cholesterol levels to develop coronary artery disease. Our observations support the hypothesis that hypercholesterolemia in childhood probably predisposes to coronary disease. This is particularly important when considering the observation that atherosclerotic lesions such as fibrous plaques over lipid depositions are in evidence during early adolescence.

This community-wide screening program related the cholesterol measurements of school children to cholesterol measurements in their relatives, and then related the elevated cholesterol levels in the school children to excess coronary mortality in their families. The significantly increased frequency of cardiovascular disease mortality in the HIGH group relatives compared to the expected frequency in the population, with cancer mortality near the expected frequency, suggests that childhood cholesterol elevation predicts atherosclerotic coronary mortality in families. In addition, since coronary artery disease aggregates in families, it is likely that persistently elevated cholesterol levels also predict coronary disease in the child. The strength of this prediction must be clarified.

Acknowledgments

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