A Novel Approach to Assessing Family History in the Prevention of Coronary Heart Disease

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Family history serves as the most important risk factor in prevention of coronary heart disease from youth. Prevalent methods of assessing family history, however, have serious drawbacks: a sudden rise of risk when a family member develops the disease; insufficient control for age among family members. We propose a simple quantitative method overcoming such drawbacks. Data on family history were obtained by questionnaires sent to 2,393 male high school students and their cholesterol levels were measured. Family risk from each family member was calculated by $(30 / \text{Risk age})^4$, where the risk age was age at onset expressed by decade; if absent, it was replaced by present age or age at death. A mean score in a family served as the family risk. A total of 1,584 students and 17,127 family members were analyzed. The proposed method yielded a statistically significant association (Odds ratio=1.60; 95% confidence interval: 1.15-2.25) between the family risk (above or below the median) and the student's atherogenic index (above or below the 90th percentile) calculated from cholesterol. This association was stronger than those by conventional methods. The proposed method may be useful in prevention activities and its efficiency needs to be confirmed in other studies.

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Prevention of adult cardiovascular diseases from childhood and youth has been attracting more attention recently, and a WHO expert committee recommended action to be taken¹. In parallel with health education identifying high risk children occupies a large part of these activities. Family history, some claimed, is the most important known risk factor at present^{2,3}, and the nationwide strategy in selective screening of children in the U. S. A. employs family history as the risk factor of the first choice⁴. Thus, a proper evaluation of family history seems to be crucial. However, prevalent methods are inadequate, and no standard method for evaluating family history was proposed by the WHO committee.

In the literature there have been two widely used methods⁴⁻⁷ and one complex method⁸. The most frequently used and familiar is a "qualitative" method in which the number of family members who have developed a disease in question is taken as a

risk score⁶. Another is a "semi-quantitative" method in which the number of family members who developed the disease before a certain age, 55, 65 or 50, is taken as a risk score^{4,6,7}. In the other, complex method a family score is calculated based on the difference between the observed number of affected family members and the expected number calculated from age-specific cumulative incidence in the general population⁸. These methods, however, contain several serious drawbacks in the prevention programs in childhood and youth.

The qualitative method has four serious drawbacks. First, no measure is taken to control for age of family members. The risk is assessed as equal when a family member developed the disease at age 40 or at 60. It is also assessed equally as no risk when a family member is 40 years of age or 60 without the disease. This is inappropriate; incidence, prevalence or cumulative incidence of coronary heart disease increases nearly expo-

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nentially with age¹¹; an age increase of 5 years would lead to a 1.37 times increase in the presence of a positive history of coronary heart disease in a family member⁶. In addition, in diseases under multifactorial inheritance a younger age at onset should be heavily weighted, and a reduced risk should be given to the absence of the disease at old age; this notion was confirmed for cardiovascular diseases⁶.

The second drawback is discontinuity of risk. When a family member develops the disease, the risk is increased suddenly at this point. In a method where young age at onset is more heavily weighted, the risk jumps up. This causes serious problems in the prevention program, since a child at low risk becomes a high risk child suddenly.

The third drawback is inequality in the number of family members. This may result from premature deaths by other disease or from unequal numbers of uncles and aunts in families. There is a higher chance of positive history in a family of larger size. Some measures need to be taken to account for this factor.

The fourth drawback is the young age of parents for the diseases in question. Most parents of children and youth at target are in their 40s, too young to assess familial loads sufficiently from the presence or absence of the past history. This drawback provided arguments on the screening strategies based on family history¹⁰ as recommended by the National Cholesterol Education Program in the U. S. A.⁴.

The "semi-quantitative" method compensates for the first drawback to some extent; age at onset is dichotomized at the threshold, but age at onset in the range below the threshold or above the threshold is not controlled at all. Also the method is not free from the third and fourth drawbacks. The second drawback appears at the age of threshold for risk.

The complex method compensates for the first, third and fourth drawbacks well, but it is not free from the second drawback: a sudden rise of risk. It also bears a practical disadvantage: age-specific incidence in the general population is required. Probably because of this requirement and the complexity of the calculations, it has rarely been used.

We propose here a new simple quantitative method which compensates for the four drawbacks.

MATERIALS AND METHODS

Sources of Data

Questionnaires asking for the family history of adult atherosclerotic diseases were distributed to all the 2nd-year high school students, aged 16 or 17, at a male high school in Japan as part of the school health program. The total number of students in three study years was 2,393. The questionnaire, filled in at home by parents, collected data on parents, grandparents and uncles and aunts; the data included: present age or age at death, and age at onset, by decade, of angina pectoris and

myocardial infarction which had been diagnosed or treated by physicians. A recall bias was avoided by collecting the questionnaire before the students' routine health examinations.

In the students' routine health examination at school the total cholesterol was measured by the enzyme method¹², and the high density lipoprotein cholesterol (HDL cholesterol) by the dextran sulfate Mg ion precipitation method¹³. All the measurements were carried out at the Sumitomo Bioscience Laboratories (Sagamihara, Kanagawa-ken). Precision and accuracy of the measurement were checked routinely. The atherogenic index was obtained by $[(\text{Total cholesterol} - \text{HDL cholesterol}) / \text{HDL cholesterol}]$. This index has been most widely used in Japan as a risk indicator for coronary heart disease^{13,14} including among children^{15,16}. The high atherogenic index students were defined here as those above the 90th percentile.

Calculation of Risk Score

The quantitative evaluation of the family history of coronary heart disease was done in the following way. The procedure is summarized in Table 1. For each family member, a term (30 / Risk age)⁴ was calculated. The "Risk age" was age at onset, by decade, of coronary heart disease, that is angina pectoris or myocardial infarction. If the family member had not developed the disease, present age or age at death served as the "Risk age". Age at onset was obtained by decade age for easy acquisition of such data. This also yields an advantage of giving some weight to a family member with an onset of the disease: the created difference between present age and onset age rounded to decade serves as the weight in the formula. When the risk age was below 30, it was replaced by 30. This was to avoid giving a high score to a family where an uncle or an aunt died at a very young age. The figure 30 was employed since we are concerned with the diseases after this age. In the formula the "Risk age" is placed in the denominator and 30 is placed

Table 1. Calculation of the family risk score.

1. Calculate a score for an individual member by $(30/\text{Risk age})^4$.
Risk age is either age at onset by decade, present age, or age at death.
2. Adjust the uncle-aunt score to a 2-uncle-aunt family at a paternal and maternal side.
 - (1) No uncle-aunt family: replace with the twice of a parent's score.
 - (2) One uncle-aunt family: add a parent's score.
 - (3) More than two uncle-aunt family: the sum was divided by the number and multiplied by 2.
3. Calculate a family score.
 - (1) Double the parents' score.
 - (2) Sum up grandparents' scores, 2-uncle-aunt scores and doubled parents' scores.
 - (3) Divide the sum by 12.

in the numerator so that the calculated risk varies from near 0, the lowest risk when the risk age is around 100, to 1, the highest risk when the risk age is 30. In this connection it is noted that the formula gives more weight to younger age. This is appropriate in assessing familial loads under multifactorial inheritance in which a heavily loaded person develops the disease earlier. This is also appropriate for diseases whose age-specific prevalence tapers off at very old age. In addition, it is advantageous to give more weight to younger age in prevention activities from childhood and youth. The 4th power of (30 / Risk age) was employed to make the power closest to that of age-specific proportion of a positive history of coronary heart disease. The power 4 was obtained from the study data in the following way. If a proportion of a positive history of coronary heart disease, p , is expressed as $p = a(\text{Age})^n$, where a is a constant, then $\log(p) = n \log(\text{Age}) + \log(a)$, where $\log(a)$ is a constant. The parameter n was estimated from this formula by giving the age-specific proportion of a positive history by decade age, obtained from the study data, to the left side and mid-years of the decade age, for example 45 for the 40s, to the right side. The estimated $n \pm$ standard error was 4.0 ± 0.4 . The closest integer 4 was taken. This procedure would be justified as the regression line of the $\log(p)$ against the $\log(\text{Age})$ was very straight from age 30s to 60s, followed by a convex curve afterwards. This can be seen from the age-specific proportion of a positive history of coronary heart disease plotted against an age scale⁸. The estimated n was fairly stable when the estimation was done for the separate 3 study years: 4.1 ± 0.5 , 3.5 ± 0.4 , and 3.4 ± 0.7 .

Adjustment by the number of uncles and aunts was made for the paternal and the maternal side separately. When no uncle or aunt existed, twice the parent's calculated risk score was supplied. When the number of uncle or aunt was one, the father's or the mother's calculated risk was supplemented. When the number was more than 2, the sum of the calculated scores was divided by the number and multiplied by 2. In all the cases the resultant risk score became the equivalent of a 2-uncle-aunt family on each side. The number 2 was taken for two reasons. First, 2-uncle-aunt families were the highest in frequency. Second, the number was made equal, on each side, to that of grandparents whose genetic correlation to the student is equal to that of uncles or aunts. This adjustment was done to avoid giving lower scores to a family with less than two uncles/aunts.

A family risk for each student was calculated by incorporating the risk scores of all family members. After doubling the father's and the mother's risk scores, the parents', grandparents', and number-adjusted uncles'-aunts' risk scores were summed up followed by the division by 12. The parental risk scores were doubled to reflect their twofold genetic correlation to the student as compared with that of other members¹². Division by 12—not by 10, the number of family members—was done

to make the family risk between near 0 and 1, responding to the doubling of parental scores. The family risk was calculated for angina pectoris and myocardial infarction separately and their mean served as the family risk score of coronary heart disease.

It is noted here that the adjustment to the equal number of uncles and aunts was done to avoid giving lower scores to families with less than two uncle-aunt families. This is illustrated in the following simple example. Suppose a 2-uncle-aunt family in each parental side with the following risk age: parents: 40, 40; grandparents: 70, 70, 70, 70; uncles or aunts: 40, 50, 40, 50. The family risk score became 0.1910. The family risk score for a similar family with one uncle or aunt with age 50 in each parental side becomes 0.1660, when the sum is divided by 10. The lower score results from a fewer number of young members, that is uncles or aunts, compared to the full 2-uncle-aunt family. Even if a mean is taken for a family score, it becomes lower reflecting a fewer number of young members.

In addition to the proposed method described above, the two alternative methods mentioned in the introduction were employed as comparisons. One was the "qualitative" method where 2 points were given when a parent developed a coronary heart disease and 1 point was given when other members developed the disease. The summed points served as the family risk. Usually no adjustment is made for missing members who died of other causes, and uncles and aunts are not included⁹. The other method is the "semi-quantitative" method^{4,6,7}. One point was given for the onset of angina pectoris or myocardial infarction below age 60 in a family, inclusive of uncles and aunts.

Characteristics of the Method

The basic principle of the proposed method is that the risk score of a family member decreases from unity at age 30 as the family member grows older without developing the diseases, and if the family member develops a disease in question, the risk score for that member is set at a certain level at that age. In this sense, this method should be called a "risk-subtracting" approach, whereas other conventional family risk evaluation methods are of a "risk-adding" approach. In this risk-subtracting approach family members are treated as having 100% potential of developing the disease until age 30, followed by a gradual decrease with aging. In the conventional risk-adding approach family members without the disease are treated as non-burdened members regardless of their age until they develop the disease. The point is how to deal with a family member without the disease in question. In the conventional methods described in "Introduction", such a member is treated as having 0% risk at any age.

Statistical Analysis

The degree of association was measured by the odds ratio,

and the statistical test used was the chi-square test of independence¹⁹. All the calculations were performed by the PC-SAS¹⁹.

RESULTS

The questionnaire was returned by 1,714 students (a return rate of 71.6%). Among these, 39 students missed cholesterol determination, so data for 1,675 students and 18,115 family members were available in the qualitative and semi-quantitative methods. In 91 families an age variable serving as the "Risk age" was missing, so data for 1,584 students with 17,127 family members were available in the proposed method.

Among the 1,675 analyzed family histories 167 (10.0%) were returned after the health examination. A possibility of recall bias was assessed by checking the proportion of students with positive family histories of angina pectoris or myocardial infarction. Among the high (above the 90th percentile) atherogenic index students, the proportion was low in the late returners. Furthermore, the student's atherogenic index was not told, though the total and HDL cholesterol levels were released. Therefore, it is unlikely that a recall bias produced positively distorted results.

The 90th percentile of the high atherogenic index was 2.74. The 90th percentile has been recommended as the dividing point to classify high risk children and youth for adulthood cardiovascular disease^{20,21}.

The atherogenic index has not been widely used outside Japan. Rather, the ratio of low density lipoprotein (LDL) cholesterol to HDL cholesterol has been frequently used. But both are highly correlated as can be easily understood from their definitions. In this study data the Pearson correlation coefficient between the index and the ratio was 0.97 among the students in the latter 2 years in whom triglyceride was measured and where the LDL cholesterol was estimated by [Total cholesterol - HDL cholesterol - 1/5 triglyceride]²⁰.

The distribution of the family risk score by the proposed method is shown in Figure 1. The score ranged from 0.0456 to 0.3439 with a mean of 0.1516. The quartile values were: 25th percentile=0.1199; 50th percentile (median)=0.1469; 75th percentile=0.1785. The distribution is slightly skewed to higher scores. Its normality was not accepted by the significance test using the UNIVARIATE procedure in the SAS software¹⁹. However, the logarithm of the risk score did not depart from the normal distribution ($p>0.05$).

Table 2 shows the results regarding students' atherogenic

Figure 1. The distribution of the family risk score. The scale of the risk score is 0.02 except for both ends. The figures on the scale indicate the left end of the risk score category.

Table 2. Students' atherogenic index and family history risk by the proposed method among 1584 students.

		Family risk score by percentile			
		0-25	25-50	50-75	75-100 Total
Students' atherogenic index	<90 percentile	366	364	350	347
	(%)	(23.6)	(23.5)	(24.5)	(24.3)
	>90 percentile	30	32	46	49
	(%)	(19.1)	(20.4)	(29.3)	(31.2)

Table 3. Students' atherogenic index and family history risk by the qualitative method among 1675 students.

		Family risk by point ^a			
		0	1	2	>=3 Total
Students' atherogenic index	<90 percentile	1004	345	120	40
	(%)	(66.5)	(22.9)	(8.0)	(2.7)
	>90 percentile	103	40	14	9
	(%)	(62.0)	(24.1)	(8.4)	(5.4)

^a Two points for the presence of a disease concerned in the past history of a parent, and 1 point for the presence in the past history of a grandparent.

index and the family risk of coronary heart disease by the study method. Among the 157 "high atherogenic index" students, the proportion in the quartile family risk groups gradually rose, whereas among 1427 "normal" students the proportion was nearly equal: around 25% in the 4 groups. The chi-square test of independence was significant ($p < 0.05$). When the family risk was divided into two, below or above the 50th percentile [easily constructed from Table 1: 730 (51.2%) and 697 (48.8%) for the normal students and 62 (39.5%) and 95 (60.5%) for the high atherogenic students], it showed a significant difference ($p < 0.01$), with an odds ratio of 1.60 (95% confidence interval: 1.15 - 2.25). When the lowest quartile group and the highest quartile group were compared, the odds ratio was 1.72 (95% confidence interval: 1.07-2.78).

Table 3 shows the results of the qualitative method. Wherever the 4 groups were regrouped into two groups by risk point, there was no statistically significant difference ($p > 0.05$). The odds ratio, when the risk groups were divided by point between 0 and 1, was 1.22 (95% confidence interval: 0.87-1.69). Other divisions would be of less meaning in practical application, resulting in identifying a small proportion of high atherogenic students. In the analysis in which uncles and aunts were included, though data are not shown, the difference in the proportions between the high and normal atherogenic index groups was similar to the difference in Table 3.

Table 4 shows the results of the semi-quantitative method. Wherever the 4 groups were regrouped into two, there was no statistically significant difference ($p > 0.05$). Since one point was given when a family member developed a coronary heart disease below age 60, the proportion in the 0 point group was much higher than that in Table 3. The odds ratio, when the risk groups were divided by point between 0 and 1, became a little larger than that of the qualitative method: 1.38 (95% confidence interval: 0.92-2.07). However, the proportion of students

identified as high risk became much smaller. The results when 2 points were given for a parental onset were very close to the results in Table 4.

DISCUSSION

The method we propose here yielded better results than the frequently used conventional methods in selecting high atherogenic index students, thereby in identifying candidates for coronary disease from family history. The semi-quantitative method, which controls for age of family members to some degree, yielded a larger odds ratio than that of the qualitative method without any control for age of family members. The inefficiency, some claimed, in finding high cholesterol children from family history by the semi-quantitative method used in the U. S. A.²⁰ would be improved to some extent by the use of this proposed method. However, sensitivity, specificity, and positive and negative predictive values may not be high enough to use this family risk as a single index for screening. Combination with other risk factors will be necessary if applied to screening. The above indices for screening when applied to ongoing screening programs combined with other risk factors need to be determined together with cut-off points which meet various purposes.

A possible argument against the proposed method exists: there is no assurance that the high atherogenic index students will develop coronary heart disease after age 30. Strictly speaking, full credit to this study will be given after an analysis 40 or 50 years later when the students become old enough to have developed such diseases. As a long term research strategy, we selected the school for that aim. But there exist backup and reinforcement. Tracking of serum cholesterol, a risk factor for adulthood coronary disease, through adolescence and adulthood is not low particularly among those above the 80th²¹ and 90th percentile²². In addition, young men with high serum cholesterol levels were reported to have an increased risk of coronary heart disease in mid-life 27 to 42 years later²³. The relative risk between the below 25th and over 75th percentile of serum cholesterol was 2.01 for coronary heart disease and 1.72 for cardiovascular diseases²⁴—incidentally very close to the results in this study.

Another question is misclassification in the family history. The questionnaire was filled in by parents. Therefore, they filled in the information on themselves and on their brothers, sisters and parents. It is unlikely that people in their 40s and 50s were mistaken in answering present age and age at death of their siblings and parents. The grandparents in the questionnaire were mostly in their 60s and 70s by present age or age at death. Their sons and daughters—parents in the questionnaire—most likely know the past history of such serious diseases like angina pectoris and myocardial infarction among their parents and onset should be fairly reliable if

Table 4. Students' atherogenic index and family history risk by the semi-quantitative method among 1675 students.

	Family risk by point ^a				Total
	0	1	2	≥3	
Students' <90 percentile	1279	179	39	12	1509
athero- (%)	(84.8)	(11.9)	(2.6)	(0.8)	(100)
genic >90 percentile	133	25	6	2	166
index (%)	(80.1)	(15.1)	(3.6)	(1.2)	(100)

^a One point for the presence of angina pectoris or myocardial infarction below age 60 in the past history of a parent, grandparent, uncle and aunt.

expressed by decade age. We examined the precision, or reliability of the family history questionnaire used in this study²⁰. The questionnaire was administered twice with a one-year interval. The proportion of contradicting answers—namely interchange between presence and absence of the past history, and discrepancy in age at onset—between the two surveys was low. In myocardial infarction it was below 1% among parents, uncles and aunts, and around 4% among grandparents. In angina pectoris it was below 2% among parents, uncles and aunts, and around 5% among grandparents. Inaccuracy, namely discrepancy between answers and true evidence, is difficult to confirm. There has been no epidemiological study, to our knowledge, which examined the accuracy of a questionnaire on the family history of coronary heart disease. From these results it can be said that misclassification in the past history would not have distorted the results so greatly as to endanger the conclusion of the present study.

Seemingly inconsistent results were projected in some studies. The inconsistency seems to derive from a different study design and a different study population. In a study in Utah, the U. S. A.²¹, the presence of two or more first-degree relatives with coronary heart disease before age 50 in a family—the semi-quantitative method—showed a good discriminatory ability with high relative risks against families without such members. In the study, however, subsequent incidence among non-affected family members, rather than high school students, was examined. In another report²², the results obtained in adults were extrapolated to a pediatric-age population. In these approaches the relative risk was unstable and small among young families²³. Therefore, these methods seem to be inefficient when applied to a pediatric-age population. The risk-subtracting approach of our method was devised to overcome this type of problem, especially in evaluating young families where most parents are in their 40s and early 50s. There remains a possibility that the inconsistency may be due to differences in the study population: a U. S. population with a much higher mortality of coronary heart disease than a Japanese population²⁰. In this case, this proposed method will yield a higher odds ratio than the odds ratio projected in this study and the method should be quite useful.

The formula for the risk calculation is generalized as $(A / \text{Risk age})^n$. The rationale for this formula is based on observations that age-specific incidence in cardiovascular diseases and the proportion of a positive history in this study are approximated by $a(\text{age})^n$, where a is a constant. To obtain the score which varies from 0 to 1, its inverse was taken. In this study the term A in the formula was 30, which meant the earliest age of onset of the diseases concerned. The power n of 4 was used to make the power in the model closest to the age-specific proportion of a positive history of the disease obtained from the study data. Different powers will be employed responding to different age-specific proportions in different diseases. With

the study data, however, when n was changed from 3 to 7, the results were very similar to those shown in Table 2.

The method can be modified. Some weight may be given to death from the disease. In this risk-subtracting approach a family member who is alive without the disease at age 40 and a member who died of the disease at age 40 give the same risk score. This sounds inappropriate, but when 5 years were subtracted from age at death and age at onset, the results did not depart much from those of Table 2. This seeming disadvantage was not a serious one. Some ways of dealing with young age at death, say by censoring methods, may reduce the proportion of families falsely ranked in high risk groups due to premature deaths. One of the possible methods is a life-table approach, but this also shares some of the drawbacks described in the introduction. Use of age-specific proportion of a positive history by sex instead of the n th power of the risk age may result in more accurate risk assessment. But these measures require a consensus on the weights, more complex calculations or detailed data from outside sources. Simplicity, we think, surpasses a little increase in efficiency by modification, if a method is to be used widely.

The risk-subtracting approach, a new concept in genetic epidemiology, has a practical advantage if used in a prevention program. Since the life-style established during childhood seems to facilitate atherosclerosis through adolescence and adulthood²⁴, the preventive program needs to start at childhood when identifying those at high risk is not an easy task. Therefore, the program, mostly educational, may better be directed to all children and youth rather than to high risk individuals who are not easily identified. As family members grow older and children reach adolescence, those at high risk or low risk become apparent gradually from family history and from other screening methods. Those found to be at high risk can be requested more strongly to adopt a healthy life-style established through health education with necessary medical intervention. Those at low risk may maintain their life-style, and when the decrease of risk slows down because some family members develop such diseases, necessary intervention can be taken. The risk-subtracting nature of the proposed method is most appropriate for this approach. In this sense the method is of a "preventive" nature, whereas the conventional risk-adding methods are of a "curative" nature.

Since the proposed method is fully quantitative ranging from near 0 to 1 following a near-normal distribution—made normal by logarithm transformation—, and no area- or country-specific data, such as age-specific incidence or prevalence, are required, it can be used anywhere as a standard method for various purposes. The calculated score for a family serves as a risk indicator of that family. The mean and the standard deviation of a population serve as population risk indicators. Their comparisons among different ethnic and cultural populations or at different times will be useful in analyzing genetic and environ-

mental interactions affecting various diseases. A cut-off point for high risk groups is set at various levels in the family risk score to meet various purposes.

Obtaining required data including age at onset by decade does not present much difficulty. The validity and usefulness of our method may well be verified in other countries and in other diseases where appropriate data are available.

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