A Quantitative Evaluation of the Effects of Sex and Age on the Positivity of Family History of Hypertension

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The purpose of this study was to call attention to a potential bias or misclassification resulting from disregarding sex and age of family members in assessing family history of hypertension. Family history of hypertension was obtained among 23,803 family members through a questionnaire survey of 2,316 high school students. From the obtained data sex- and age-specific proportion of a positive history of hypertension was calculated. The effects of sex and age on a positive history was assessed by the logistic regression analysis of the family history. Below age 70 the odds ratios for sex difference were at least 1.24 (p<0.05) and odds ratios for age difference were at least 1.05 (p<0.05). This indicated that below age 70 male members had a positive history at least 1.24 times more frequently than females of the same age, and that a positive history increased by at least (1.05)^y, where y was age difference by year. Above age 70 the odds ratios for sex and age differences were small. A potential bias or misclassification resulting from sex and age difference can be substantial below age 70. Some measures to control for sex and age of family members are required in assessing the family history. J Epidemiol, 1998 ; 8 : 99-105.

hypertension, family; risk, age factor, human genetics

Primary hypertension is regarded as a disease under multifactorial inheritance ¹. Therefore, family history is assessed as one of the risk factors. Since prevalence of hypertension increases nearly exponentially with age ², age of family members needs to be controlled in such assessment. Otherwise, such assessment can result in an error: a difference in the family history may reflect only a difference in age of the family member rather than the familial load. However, the control for age of family members is not a common practice in assessing family history of hypertension as a risk factor ³⁻¹⁰.

Age-specific prevalence of hypertension differs between men and women ². Therefore, sex of family members also needs to be controlled in assessing the family history. A familial load of a family in which a member with hypertension is male may be different from a familial load of a family in which a member with hypertension is female, given that those members are of the same age. However, the control for sex of family members is not a common practice, either ³⁻⁶,⁸,¹⁰.

Under these circumstances the objective of this study is fourfold. First, to present sex- and age-specific proportion of a positive history of hypertension. This proportion is different from prevalence of hypertension and has been rarely available. In family history studies not the prevalence nor the incidence but this proportion is pertinent. The latter includes information on deceased family members, whereas the former two indices do not. Sex- and age-specific proportion of a positive history serves best in discussing the effects of sex and age of family members on the family risk assessment. The second objective is to compare this proportion with prevalence. The third objective is to present numerically, for the first time, the effects of sex and age on the positivity of past history which is useful in designing family history studies. The fourth objective is to call attention to potential bias and misclassification resulting from disregarding sex and age of family members.

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METHODS

Family history of hypertension was obtained from a questionnaire survey of family members among high school students. The questionnaire contained information on the parents, grandparents and uncles and aunts; the collected data included the present age or age at death, and age at onset, by decade, of hypertension. Positive history of hypertension was defined and stated in the questionnaire as hypertensive condition which was found by health screening, was told to by a physician, or led to medical treatment or death. The questionnaire noted that absence of such a condition should be clearly stated so and that if the presence or absence could never be determined, a blank should be filled in with a question mark. The questionnaire was handed to 3,145 students as part of school health programs, and filled in at home by parents. The questionnaire was returned by 2,316 students (a return rate of 73.6%). Two uncle-aunt families were most frequent on both paternal and maternal sides. Among the total of 25,139 family members listed in the returned questionnaire, 23,985 family members (95.4%) had full information on the items asked for this study. Among the 1,154 members with missing information, 259 members lacked either present age, age at death or sex (uncle or aunt), 367 members lacked history of hypertension and the remaining 528 members lacked information on the three items. Among the 23,985 members 182 were below 30 years of present age or age at death who were excluded in the following analyses. Thus, the remaining 23,803 family members were used in calculating, as described below, the sex- and age-specific proportion of a positive history of hypertension and in the logistic analysis.

First, the 23,803 members were stratified in both sexes into 10-year age intervals either by present age or age at death. Those whose present age or age at death was 90 or more were grouped together with those in the 80s because of the small numbers after age 90. As the representing age for each group, a mean age that is a mean of either present age or age at death, was taken. Second, in each age group, the number of those with a positive history of hypertension and also the number of those without a past history of hypertension were obtained. Third, the age-specific proportion of a positive history for the age intervals in each sex was calculated by the following: [(the number with a positive history) / (the number with a positive history + the number without a positive history)].

In quantifying the effects of sex and age on a positive history, which lead to potential bias and misclassification when sex and age of family members are disregarded, the following logistic regression model was formulated:

\[
\log\left( \frac{p}{1-p} \right) = \text{intercept} + b \times \text{sex} + c \times \text{age},
\]

where \( p \) was the probability of a positive history and the age was either present age or age at death. From the logistic model, the parameter \( b \) and \( c \) were estimated. Then, the odds ratios were obtained by an exponent of the estimated \( b \) or \( c \) together with its 95 percent confidence interval by an exponent of \[ b \text{ or } c \pm 1.96 \times \text{Standard error of } b \text{ or } c \]. An interaction between sex and age was also examined, followed by further logistic analyses. The goodness of fit of the logistic regression model was assessed by the Hosmer and Lemeshow goodness of fit test \(^{11}\).

In addition, the logistic analyses were carried out excluding dead family members. Inclusion of only live family members in the analyses corresponds to the analysis of prevalence of hypertension rather than family history.

The calculations were performed by the PC-SAS \(^{10}\) and the logistic analysis was carried out by the procedure LOGISTIC.

RESULTS

The study subjects by sex, age and history of hypertension were shown in Table 1. The percentage of “unknown” was the highest at 3.2% in the age interval of 80-89 in male members. In all the other age groups they were below 2.2%. Excluding...
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"unknown" members, 23,803 members were used in the following analyses.

Figure 1 shows the age-specific proportion of a positive history of hypertension in both sexes. The vertical axis is on a log scale. The representing age for each age interval is the mean age of that interval (See legends). Both curves are convex, but from the age 40s to the 60s they are fairly straight. Both curves cross each other in the 60s and the proportion of a positive history in the female members surpasses that in the male members from this age interval onward.

The effects of sex and age on a positive history were the following. The odds ratio for sex difference for all the age intervals was 1.036 with its 95% confidence interval of 0.958-1.121. It was not statistically significant (p>0.05), as can be seen from the 95% confidence interval including unity. The odds ratio for age difference for all the age intervals was 1.059 with its 95% confidence interval of 1.056-1.062. It was statistically significant (p<0.01). From these results it can be said that age of family members affects the proportion of a positive history and the proportion increases on the average 1.059 times with an increase of age by one year. However, it was statistically significant in the Hosmers and Lemeshow goodness-of-fit test (p<0.01) and the interaction between sex and age was also significant (p<0.01). The logistic regression model did not fit well in the whole age range. Therefore, the logistic regression analysis was done separately in each sex and age interval.

The results of the separate analyses are shown in Table 2. The age interval in the table was the interval extending over two adjacent age intervals. In other words the logistic analysis was done separately for the 5 intervals made up of two adjoining points in Figure 1. For each age interval the logistic regression model including only age variable was carried out in the male and female groups and this results are shown in the rows Male and Female in “From age difference”. The logistic regression model including sex and age variables was also carried out. Odds ratios from age difference are shown in the row “From age difference” and those form sex difference are shown in the row “From sex difference”. Interaction between sex and age was evaluated in each age interval and this results are shown in the last row.

In both sexes the odds ratios from age difference decreased with the advancement of age. Except for the age interval of 70-99, the odds ratios were statistically significant (p<0.05).

<table>
<thead>
<tr>
<th>Age interval</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-79</th>
<th>80-89</th>
<th>90-99</th>
<th>Total</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td>313</td>
<td>263</td>
<td>531</td>
<td>217</td>
<td>12</td>
<td>1607</td>
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<tr>
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<td>3735</td>
<td>2401</td>
<td>1023</td>
<td>1577</td>
<td>753</td>
<td>68</td>
<td>10207</td>
</tr>
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<td>10</td>
<td>51</td>
<td>51</td>
<td>26</td>
<td>46</td>
<td>32</td>
<td>0</td>
<td>216</td>
</tr>
<tr>
<td>Female</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>9</td>
<td>1500</td>
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<tr>
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<td>4470</td>
<td>1995</td>
<td>1330</td>
<td>1619</td>
<td>461</td>
<td>17</td>
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<td>5</td>
<td>32</td>
<td>37</td>
<td>21</td>
<td>40</td>
<td>14</td>
<td>0</td>
<td>149</td>
</tr>
</tbody>
</table>

Table 1. Study subjects by sex, age and history of hypertension.

Table 2. The effects of sex and age on a positive history expressed by odds ratio.

<table>
<thead>
<tr>
<th>Age interval</th>
<th>30-49</th>
<th>40-59</th>
<th>50-69</th>
<th>60-79</th>
<th>70-99</th>
</tr>
</thead>
<tbody>
<tr>
<td>From age diff.</td>
<td>1.148</td>
<td>1.096</td>
<td>1.071</td>
<td>1.036</td>
<td>0.996</td>
</tr>
<tr>
<td></td>
<td>(1.110-1.187)</td>
<td>(1.081-1.111)</td>
<td>(1.060-1.082)</td>
<td>(1.026-1.047)</td>
<td>(0.984-1.007)</td>
</tr>
<tr>
<td>Male</td>
<td>1.126</td>
<td>1.070</td>
<td>1.054</td>
<td>1.028</td>
<td>0.987</td>
</tr>
<tr>
<td></td>
<td>(1.084-1.170)</td>
<td>(1.052-1.089)</td>
<td>(1.039-1.069)</td>
<td>(1.013-1.043)</td>
<td>(0.971-1.002)</td>
</tr>
<tr>
<td>Female</td>
<td>1.177</td>
<td>1.141</td>
<td>1.090</td>
<td>1.045</td>
<td>1.006</td>
</tr>
<tr>
<td></td>
<td>(1.106-1.253)</td>
<td>(1.115-1.167)</td>
<td>(1.074-1.106)</td>
<td>(1.029-1.106)</td>
<td>(0.989-1.023)</td>
</tr>
<tr>
<td>From sex diff.</td>
<td>2.517</td>
<td>1.918</td>
<td>1.245</td>
<td>0.887</td>
<td>0.766</td>
</tr>
<tr>
<td></td>
<td>(2.018-3.140)</td>
<td>(1.656-2.222)</td>
<td>(1.091-1.420)</td>
<td>(0.796-0.987)</td>
<td>(0.682-0.859)</td>
</tr>
<tr>
<td>Interaction between sex&amp;age</td>
<td>0.949</td>
<td>0.938</td>
<td>0.967</td>
<td>0.984</td>
<td>0.981</td>
</tr>
<tr>
<td></td>
<td>(0.880-1.023)</td>
<td>(0.912-0.966)</td>
<td>(0.947-0.987)</td>
<td>(0.964-1.005)</td>
<td>(0.959-1.004)</td>
</tr>
</tbody>
</table>
The odds ratios in female members were larger than those in male members. The odds ratio from age difference in the top row can be regarded as an average of both sexes. The Hosmer and Lemeshow goodness-of-fit test became statistically significant (p<0.05) only in the age interval of 70-79 in both sexes and in the age interval of 40-59 in male members. This was ascribed to yearly fluctuations in the proportion of a positive history in these age intervals. From these results the following can be said. The effect of age on a positive history of hypertension is fairly large before age 70, particularly in female members, as the proportion of a positive history increases with (odds ratio), where y is a difference in age expressed by year. Before age 70, a difference of 5 years will yield at least a 1.30 times increase in a positive history in male members and at least a 1.54 times increase in female members.

Odds ratios from sex difference decreased with the advancement of age and became below 1 in the age interval of 60-79 onward. All the odds ratios were statistically significant (p<0.05). Interaction between sex and age was statistically significant (p<0.05) in the age intervals of 40-59 and 50-69. Therefore, odds ratios from sex difference changed statistically significantly with age and the obtained odds ratios should be regarded as rough averages in these age intervals. What can be said from these results are the following. Before age 60, the effect of sex on a positive history is fairly large and male members will have a positive history at least twice as frequently as female members of the same age. After age 60, female members will have a positive history more frequently but the difference from male members will not be large.

A close look at the sex- and age-specific proportion of a positive history and the detailed analyses provided different odds ratios from age difference and from sex difference. The odds ratio of 1.059 from age difference for all the age intervals stood as summary statistics.

Results of the logistic analyses on the "prevalence of hypertension" including 20,338 live members only were the following. The odds ratio for sex difference for all the age intervals was 1.055 with its 95% confidence interval of 0.964-1.156. It was close to the odds ratio for the proportion of positive history data. The odds ratios for the 5 age intervals - shown in Table 2 - were 2.493, 2.003, 1.244, 0.833 and 0.752, and they were all close to those of the proportion of positive history data. The odds ratio for age difference was 1.064 with its 95% confidence interval of 1.060-1.067. It was again close to that of the proportion of positive history data with a slight increase of 0.005. The odds ratios for the 5 age intervals were 1.149, 1.084, 1.077, 1.036 and 1.008, and were close to those of the proportion of positive history data.

**DISCUSSION**

The magnitude of potential bias or misclassification resulting from sex and age difference was shown to be substantial. An age difference of five years would yield a 1.3 times higher chance of having a positive history in an elder family member in comparison. This degree can be paralleled with the relative risks of other risk factors. In a study in which childhood risk factors for adulthood hypertension were sought for, the odds ratio for a positive family history estimated by the logistic regression analysis was in the range of 1.2-1.3. The control for age among families needs to be less than five years under age 70 to evaluate family history as a risk factor singly or together with other risk factors. The control for sex may be more complex, but under age 60 it will be required.

A possible question in this study is whether information on the family history was reliable. The questionnaire was filled in at home by parents. Therefore, present age and age at death of parents, uncles, aunts and grandparents in the questionnaire should be reliable. These members were parents themselves who filled in the questionnaire, and brothers, sisters and parents of the parents. It is unlikely that people in their 40s and 50s were mistaken in answering present age and age at death of their first-degree relatives. The past history of hypertension and its onset by decade age may not be very accurate. Inaccuracies would derive from two sources: unrecognized hypertension and errors in reporting. Regarding unrecognized hypertension, it is noted that the presence of hypertension among living members in the working age should not have been grossly missed. Most employees undergo annual health examination including blood pressure stipulated by the labor law in Japan. The self-employed and the retired are also covered by the health examination schemes provided by local governments. Therefore, unrecognized would occur more likely among elder members and deceased members. Age at onset is also affected by unrecognized towards later years. In this case the curve of the true age-specific proportion of a positive history shifts towards younger age.

Errors in reporting is of two types: under-reporting and over-reporting. Since age at onset was asked in the questionnaire, over-reporting would have occurred less likely than under-reporting. Under-reporting would have occurred more frequently in uncles, aunts and grandparents.

There is also a possibility of recall bias. Parents with hypertension may report a positive history in uncles, aunts and grandparents more frequently than parents without hypertension. Consequently, parents without hypertension would report a negative history in uncles, aunts and grandparents more frequently than parents with hypertension. Parents with uncles, aunts or grandparents with hypertension may report a positive history among themselves more frequently than parents without such relatives, and vice versa.

The problems of inaccurate information mentioned above are not specific to this study but inherent in other family history studies. The important question here is the following: what...
effects would this inaccuracy produce on the estimated odds ratio? If the inaccuracy occurs to the same degree in all the age groups, the odds ratio by the logistic regression model differs little. If the inaccuracy occurs more frequently, that is under-reporting of the presence of the disease, in elder age groups, the odds ratio becomes larger. In this case more strict and urgent control for age is required. The opposite, that is more under-reporting in younger age groups, is probably less likely to happen. In any way, what counts here is the slope of the age-specific proportion of a positive history against the log scale shown in Figure 1. The magnitude of the odds ratio reflects the steepness of the slope.

The effects of unrecognized hypertension and under-reporting on the estimated odds ratio were examined by simulation using the data shown in Figure 1. If the used data had been underestimated ones, the true proportion should be higher than that in Figure 1. A 20% increase in the age-specific proportion of a positive history in the 60s and a 30% increase in the 70s and above yielded a revised odds ratio of 1.063. The difference from the odds ratio presented in the results was very small: less than a 1% increase. Thus, the results in this study are not vulnerable to a foreseen level of misclassification in the past history of hypertension and the age at onset among the family members in the questionnaire. The odds ratio from sex difference is also vulnerable to possible inaccuracies if such inaccuracies differ between sexes. The discrepancy reflects the difference in the distance against the log scale. The effect of inaccuracies on the odds ratio for sex difference is not small and it is of the similar magnitude of the inaccurate proportions. A 20% increase in the proportion of positive history in males resulted in 24% increase in the odds ratio for sex difference, and a 20% increase in females resulted in 17% decrease.

As a comparison with other data in Japan, the similar analysis using the logistic model was carried out. Since sex- and age-specific proportion of a positive history of hypertension is not available in the literature, prevalence data were used. One source was the results of the National Survey of Circulatory Disorders, which presented sex- and age-specific prevalence of hypertension inclusive of those under medication for hypertension. Age used in the logistic analysis was decade age and the numbers of subjects in age intervals were used as weights in the logic analysis. The odds ratio for sex difference for the whole age range was 1.198 with the 95% confidence interval of 1.048-1.052. The odds ratio for the 4 age intervals were 1.134, 1.089, 1.056 and 1.053. These figures were close to those of the prevalence data of this study. This source of prevalence data also provided prevalence excluding those under medication. The odds ratio for sex difference for the whole age range for this data was 1.456 with the 95% confidence interval of 1.330-1.485. The odds ratios for the 4 age intervals were 2.042, 1.702, 1.439 and 1.159 respectively. These figures were larger than those of the prevalence data including subjects under medication, and became closer to the prevalence data of this study. Inclusion of those under medication made the difference in prevalence of hypertension between males and females smaller. The odds ratio for age difference for the whole age range was 1.053 with the 95% confidence interval of 1.049-1.058. The odds ratios for the 4 age intervals were 1.124, 1.067, 1.037 and 1.028 respectively. These figures were smaller than those of the prevalence including subjects under medication, but the difference was not large.

Another source of prevalence data for comparison was the data of the National Nutrition Survey. Presence of hypertension was presented by sex and decade age after the criteria of the WHO, but it was not clearly indicated whether medication for hypertension was taken into account. Five annual data from 1993 to 1997 were combined for this analysis. The logistic analyses were done in the same way described above. The odds ratio for sex difference for the whole age range was 1.405 with the 95% confidence interval of 1.330-1.485. The odds ratios for the 4 age intervals were 2.328, 1.650, 1.350 and 1.066 respectively. The closest figures were those of the prevalence data excluding subjects under medication in the National Survey of Circulatory Disorders. The odds ratio for age difference for the whole age range was 1.050 with the 95% confidence interval of 1.048-1.052. The odds ratios for the 4 age intervals were 1.113, 1.076, 1.030 and 1.020 respectively. These figures were not much different from those of other prevalence data described above. From above comparisons it can be said that the odds ratio for sex difference may differ greatly depending on data used but the odds ratio for age difference would differ little among Japanese data.

Prevalence of hypertension of this study calculated by including only live family members was a little lower than the proportion of positive history, as shown in Figure 1, which included deceased family members. The sex- and age-specific prevalence of hypertension was the following. Male prevalence for the age intervals of 30-39, 40-49, 50-59, 60-69, 70-99 was 1.3%, 6.3%, 10.3%, 18.5% and 23.2% respectively. Female prevalence for the same age intervals was 0.4%, 2.5%, 6.9%, 19.5% and 28.5% respectively. These figures were lower than those of the National Survey of Circulatory Disorders and those of
the National Nutrition Survey. The lower prevalence may partly be ascribed to the different study population. The study subjects came from rather affluent families who send their sons to the prestigious private high school near Tokyo. However, it is more likely ascribed to the difference in the methods of data collection. In a questionnaire survey on the history of hypertension understating would occur. But this discrepancy in prevalence will not discredit the purpose, the conclusion and the message of this study. The effect of age difference expressed by odds ratio on the proportion of positive history or on prevalence differed very little among the four different data from three different sources. The estimate of 1.059 will remain consistent among Japanese data. The effect of sex difference expressed by odds ratio differed much more, but the tendency of the high odds ratios in younger age groups and the low odds ratios, often below 1 in elder age groups, was consistent among the four data. This odds ratio differed much between the two data - one excluding those under medication and the other including those under medication — from the same source of the National Survey of Circulatory Disorders. The message from this study, therefore, is that the magnitude of the effect of sex difference on the proportion of positive history will differ among different studies and that the control of sex of family members is required.

The proportion of a positive history has not been used frequently in epidemiology. Nor is this index widely available. Therefore, the relations of this index with other frequently used epidemiological indices need to be stated. This will help to understand and extrapolate the result of this study in other countries where prevalence or incidence would differ. The concept of proportion of a positive history of a certain disease is close to that of cumulative incidence, the proportion of a fixed population that becomes diseased in a stated period of time. A major difference between them is that the proportion of a positive history includes, in the denominator, persons who died from other diseases whereas in cumulative incidence dead persons is counted in the numerator.

The theoretical relation between cumulative incidence and incidence is not simple. But cumulative incidence approximates $\sum_{i} \Delta t_{i}$ when $\Delta t_{i}$ is small, where $\Delta t_{i}$ denotes age-specific incidence at age $i$ and $\Delta t_{i}$ denotes an age interval. Prevalence of a disease is defined as the proportion of a population that is affected by the disease at a given point in time. This index includes only persons alive at that point in time. The relation between prevalence of a disease and incidence is not simple, but if prevalence is small, it approximates to the product of $[\text{incidence}] \times [\text{the mean duration of the illness}]$.

From the above relations the following can be said. In countries where the incidence or the prevalence of hypertension is high, the proportion of a positive past history among family members should be high. If the incidence or the prevalence in a certain country increases more steeply with age than that of other countries, the proportion of a positive history should also increase more steeply with age. In such countries a more strict control for age in assessing the family history will be required.

This study aimed at quantifying the effects of sex and age difference on the positivity of family history of hypertension. Inquiry into the mode of inheritance or into the degree of genetic component in this condition is beyond the scope of this study. It requires a study of a different design. The datum used in this analysis was sex-and age-specific proportion of a positive history of hypertension, which is not of genetic nature. Therefore, lack of information in this study on the true biological relationship between family members does not pose a threat to the results of this study.

The degree of actual bias or misclassification resulting from disregarding sex and age of family members depends on the study type and the genetic model working in this disorder. The results would be biased in a case-control study, and diluted towards no association due to misclassification in a cohort study. The degree of actual bias or misclassification in a study cannot be accurately assessed because the genetic model, possibly a multifactorial inheritance, is not clearly determined yet. However, in a particular study in which a genetic model is assumed, a possible bias or misclassification will be estimated using the methods or the results of this study. Even under uncertainty in a genetic model, the numerical figures will be helpful and useful in deciding whether or not to control for sex and age of family members, and if to control, in planning how strict the control needs to be.

An age difference larger than five years between parents or grandparents of different families will not be infrequent, as speculated from the distributions of age at marriage of bridegrooms and brides, and age of mothers at delivery. When family history of hypertension is assessed as a risk factor in epidemiologic studies or in clinical practice for a patient, the points raised in this study and the magnitude of possible bias or misclassification need to be considered. In epidemiologic studies some measures to control sex and age of family members should be employed: stratification, matching, multivariate analysis or the use of some family risk indices. With these measures the age of family members needs to be controlled preferably within five years.

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