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PREDICTIVE ACCURACY OF ORIGINAL AND RECALIBRATED FRAMINGHAM RISK SCORE IN THE SWISS POPULATION

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ABSTRACT

Objective: to compare the predictive accuracy of the original and recalibrated Framingham risk function on current morbidity from coronary heart disease (CHD) and mortality data from the Swiss population.

Methods: data from the CoLaus study, a cross-sectional, population-based study conducted between 2003 and 2006 on 5,773 participants aged 35-74 without CHD were used to recalibrate the Framingham risk function. The predicted number of events from each risk function were compared with those issued from local MONICA incidence rates and official mortality data from Switzerland.

Results: with the original risk function, 57.3%, 21.2%, 16.4% and 5.1% of men and 94.9%, 3.8%, 1.2% and 0.1% of women were at very low (<6%), low (6-10%), intermediate (10-20%) and high (>20%) risk, respectively. With the recalibrated risk function, the corresponding values were 84.7%, 10.3%, 4.3% and 0.6% in men and 99.5%, 0.4%, 0.0% and 0.1% in women, respectively. The number of CHD events over 10 years predicted by the original Framingham risk function was 2-3 fold higher than predicted by mortality + case fatality or by MONICA incidence rates (men: 191 vs. 92 and 51 events, respectively). The recalibrated risk function provided more reasonable estimates, albeit slightly overestimated (92 events, 5–95th percentile: 26 – 223 events); sensitivity analyses showed that the magnitude of the overestimation was between 0.4 and 2.2 in men, and 0.7 and 3.3 in women.
Conclusion: the recalibrated Framingham risk function provides a reasonable alternative to assess CHD risk in men, but not in women.

Keywords: epidemiology; primary prevention; mortality; coronary heart disease; Switzerland; Framingham risk function

INTRODUCTION

Cardiovascular disease is the worldwide leading cause of death [1], and its burden is expected to increase by 2030 [2]. Current guidelines indicate that coronary heart disease (CHD) prevention should rely on absolute risk assessment and not on individual risk factors [1,3-9]. To facilitate absolute CHD risk calculation, several risk functions and charts have been developed, based on prospective data collected in different countries and settings [10-13]. To enable adequate and cost-effective treatment, the available risk functions must provide reliable estimates of CHD risk within a given population. Since CHD morbidity and mortality vary considerably by country or ethnicity [14-16], population-specific equations have been proposed [17-19]. Nevertheless, several studies have shown that even risk functions developed in a given country might not be fully usable “as is” in a neighbouring country [20].

Of particular concern is the fact that most risk functions have been developed in countries with high CHD incidence. When applied to populations with a lower CHD risk, those functions might considerably overestimate CHD risk. For instance, the widely used Framingham risk function [7,21] has been shown to adequately predict CHD risk in the United States, Australia, and New Zealand, but to overestimate CHD risk if directly applied to populations with low CHD levels, including many European populations [18-20,22-27]. Overestimation of the risk leads to unnecessary anxiety and prescription of costly medicines to the subject [28,29] with considerable inadequate resource allocation, while risk underestimation leads to undertreatment of subjects who would benefit from risk reduction. Further, the risk functions are not interchangeable as they evaluate different CHD risks (fatal and/or nonfatal cardiovascular events; with or without angina) [10-13].

In order to compute absolute CHD risk for a specific population, recalibration of the risk functions has been suggested [11,18,19]. Recalibration is based on the assumption that the effect of a given cardiovascular risk factor on CHD morbidity and mortality is constant across populations [30,31], and that only the classification of an individual relative to the population average influences individual risk. Thus, recalibration is made by replacing the initial population means by the means of the population to which the equation is recalibrated, using the same coefficients [17-19]. Indeed, recalibration of the original Framingham risk function was shown to correctly predict CHD risk in populations characterized by a low incidence of CHD such as Spain [18] or China [19].

CHD mortality rates are low in Switzerland [14], with a favorable declining trend during the last decade [32]. However, it is currently unknown whether the available risk functions adequately predict ten-year CHD risk in Switzerland. Thus, our aim was to

compare the results of the Framingham CHD risk function in its original form [13] and after recalibration on the Swiss population with the official national CHD mortality rates in Switzerland and the predicted number of events based on incidence rates from the Vaud-Fribourg MONICA study [14].

SUBJECTS AND METHODS

Study population

The CoLaus Study was approved by the Institutional Ethic's Committee of the University of Lausanne and took place in the city of Lausanne in Switzerland, a town of 117,161 inhabitants, of which 79,420 are of a Swiss nationality[1]. The CoLaus Study is a cross-sectional study aimed at assessing the prevalence and deciphering the molecular determinants of cardiovascular risk factors in the Caucasian population of Lausanne, Switzerland.

The sampling procedure of the CoLaus Study has been described previously [33]. Briefly, the complete list of Lausanne inhabitants aged 35-75 years (n=56,694) was provided by the population registry of the city. A simple, non-stratified random sample of 35% of the overall population was drawn. The following inclusion criteria were applied: a) written informed consent; b) aged 35-75 years; c) willingness to take part in the examination and donate blood sample and d) Caucasian origin. The CoLaus study included only Caucasians to reduce heterogeneity for genetic analyses. Caucasian origin was defined as having both Caucasian parents and grandparents.

Assessment process

Recruitment began in June 2003 and ended in May 2006. All participants attended the outpatient clinic of the University Hospital of Lausanne in the morning after an overnight fast. Data were collected by trained field interviewers in an single visit lasting about 60 minutes. The first questionnaire mailed with the appointment's letter and completed by the participant prior to the morning visit was reviewed and a second questionnaire was applied by interview prior to clinical measurements and blood collection.

Clinical data

Blood pressure and heart rate were measured three times on the left arm after at least 10 minutes rest in the seated position using a clinically validated automated oscillometric sphygmomanometer (Omron® HEM-907, Matsusaka, Japan) [34], using an appropriately sized cuff. The average of the last two readings was used for analyses.

Biological data

Venous blood samples (50 ml) were drawn in the fasting state. All measurements were conducted using a Modular P apparatus (Roche Diagnostics, Switzerland) by the Clinical Laboratory of the Centre Hospitalier Universitaire Vaudois (CHUV). Total cholesterol was assessed by enzymatic method (maximum inter-batch CV: 1.6%; maximum intra-batch CV: 1.7%); HDL-cholesterol was also assessed by the same enzymatic method after precipitation of apolipoprotein B carrying lipoproteins by polyethylene-glycol + cyclodextrin (maximum inter-batch CV: 3.6%; maximum intra-batch CV: 0.9%); glucose was assessed by glucose dehydrogenase (maximum inter-batch CV: 2.1% %; maximum intra-batch CV: 1.0%). In order to comply with the original Framingham risk equation [13], diabetes was defined as fasting plasma glucose ≥7.8 mmol/L and/or presence of oral hypoglycaemic or insulin treatment.

Statistical analyses

Statistical analyses were conducted using Stata v9.2 for Windows (Stata Corp, Texas, USA). Ten year CHD risks were computed using the original [13] and recalibrated Framingham risk functions. To ensure comparability with the established Framingham function, hypertension was defined according to the Fifth Joint National Committee on Hypertension [35] and the cut-points for total and HDL cholesterol were from the

[1] http://www.lausanne.ch/view.asp?DomId=63584 data for 2003 ; site assessed February 2007

National Cholesterol Education Program Adult Treatment Panel II (ATP-II) [36]. Similar to the Framingham approach [13], treatments for high blood pressure and high blood cholesterol were not included in the formulations. As relative comparisons of risks have been shown to be valid using recalibration in diverse populations [17-19], we recalibrated the Framingham equations by replacing the mean of each risk factor used in the original equation by the gender-specific mean derived from the CoLaus study, under the assumption that the effects of the risk factors are reasonably universal [30,31]. Subjects were further classified into very low risk (<6%), low risk (6 – 10%), intermediate risk (10 – 20%) and high risk (>20%) according to international recommendations [8,9].

The Framingham risk functions described above (original and recalibrated) were then used to calculate CHD risk in the CoLaus sample. For each gender and age group, the mean risk and the corresponding 5th and 95th percentiles were obtained. The computed 10-year rates were then applied to the CoLaus subjects in order to estimate the mean number and 95% confidence interval of fatal and non-fatal CHD events. Gender- and age group-specific CHD mortality rates (ICD-10 codes I21 to I23, corresponding to "acute myocardial infarction", "subsequent myocardial infarction" and "certain current complications following acute myocardial infarction", respectively) for 2003 were obtained from the Swiss Statistical Bureau (Office Fédéral de la Statistique). In men, fatal and non-fatal CHD events were further assessed using age-specific first event incidence rates from the MONICA study (corresponding to MONICA definition 1 for coronary events) obtained separately for two regions (*cantons* Vaud + Fribourg and *canton* Tessin) [37] and in-hospital MI mortality rates for year 2003 from the Swiss AMIS plus register [38]. MONICA definition 1 for coronary events included non-fatal events satisfying the criteria for definite myocardial infarction, and fatal events classified as definite, possible, and unclassifiable coronary deaths, the latter comprising mainly sudden deaths with no available diagnostic information [14]. Incidence rates were not available for women, as the Swiss MONICA project did not collect outcome data for women [14]. Since about half of CHD deaths occur before reaching hospital [39-41], the actual Swiss case-fatality rate for 2003 (about 6% for all patients) [38] was doubled and a more conservative value of 12% was used to compute the number of fatal and non-fatal CHD events, defined as:

number of CHD events = number of fatal events / MI case-fatality rate.

A sensitivity analysis was also conducted, in which each rate was independently modified; for instance, case-fatality rates were modified while holding mortality rates constant (the 2003 age- and gender-specific mortality rates were used); similarly, mortality rates were modified holding the case-fatality rates constant at 18% [42]. Descriptive results were expressed as number of subjects and (percentage) or as mean ± standard deviation. Statistical analysis was conducted using Chi-square or Student's t-test. Statistical significance was considered for two-tailed $p<0.05$.

RESULTS

Sampling results and sample characteristics

Of the initial 19,830 subjects sampled, 15,109 (76%) responses were obtained. Of the responses, 6,189 (41%) subjects refused, 799 (5%) were considered as non-eligible and 8,121 accepted (57% of the eligible responders, 54% of the responders and 41% of the sampled population). Of the 8,121 subjects who agreed to participate, the first 6,738 were invited to attend the clinic and completed the examination; of them 549 (8.1%) were not of Caucasian ethnicity and were excluded and one withdraw after consent because of personal reasons. It should be noted that since the number of subjects who agreed to participate (8,121) was higher than the number of subjects initially planned for the CoLaus study (6,000), then 1,383 subjects were not assessed although actually they were willing to participate. Thus, the final CoLaus study (n=6,188 participants) represents 43% of the eligible responders, 41% of the responders and 31% of the sampled population. Finally, of the 6,188 subjects, 397 were not included in the present analysis because of previous history of cardiovascular disease at baseline, defined as a

self-reported diagnosis of CHD (angina, prior myocardial infarction, PTCA, or CABG), stroke, or peripheral arterial disease. Another 18 subjects were not considered because of missing data for the calculation of the CHD risks. The characteristics of the remaining 5,773 subjects (3,074 women and 2,699 men) are summarized in **Table 1**. Women were significantly older and presented with higher HDL cholesterol levels than men, while men were more frequently smokers, presented more frequently with diabetes and had higher SBP and DBP levels than women. No differences were found regarding total cholesterol levels.

Results of the Framingham risk function

The mean and 5 – 95th percentiles for CHD risk and the CHD risk categories according to gender are summarized in **Table 1**. Men had significantly higher risk than women, and the recalibrated function gave mean risks that were about half of those estimated by the original equation. Very few women were categorized as presenting with intermediate/high risk using the original equation, and this number further decreased with the recalibrated function; also, 21% of men presented with intermediate/high risk using the original equation, and this percentage decreased to slightly less than 5% using the recalibrated equation (**Table 1**).

The number of predicted events over 10 years as estimated from the original and the recalibrated Framingham risk equations according to gender and age group are presented in **Table 2** and in **Figure 1**. Since no age-specific incidence rates for men were available from MONICA, only the overall estimated events for the 35-64 age group are presented. In both genders, the original Framingham risk function overestimated the number of events by two-fold, with the notable exception of age group 65-74, where the estimated number of events was close to the projected ones. Conversely, the recalibrated Framingham risk function provided somewhat better estimates, but underestimated the number of events in age group 65-74 years (**Figure 1**). In both genders, the recalibrated Framingham risk function provided overall estimates closer to those predicted by mortality and case-fatality rates or by the MONICA incidence rates. The numbers for the original Framingham equation were considerably higher than those obtained for the recalibrated Framingham equation or from data on mortality + case-fatality rates: in women, the number of events was 54.1, 23.8 and 32.2, respectively; the corresponding numbers for men were 190.6, 62.3 and 83.0; using incidence data from the MONICA study led to 51 (for Vaud + Fribourg) to 68 (for canton Tessin) events in men, values within the range of the estimations obtained using the recalibrated Framingham equation.

Since CHD events were estimated using age- and gender-specific mortality + case-fatality rates, a sensitivity analysis was conducted, in which each rate was independently modified. Using the 2003 CHD mortality rates, the recalibrated Framingham risk function overestimated the total number of events for any case-fatality rate over 11% in men and 17% in women. Conversely, for a constant case-fatality rate of 18%, the recalibrated Framingham risk function overestimated the total number of events for mortality rates 10% higher than those reported in 2003 for women and 65% higher in men (**Table 3**). The ratio (number of events by the recalibrated Framingham function)/(number of events issued from mortality + case fatality rates) was between 0.5 and 2.0 (not shown), except for age group 35-44 years for which the ratio were between 0.7 and 6. Finally, increasing case-fatality rates over 44% led to an overestimation of the number of events by the recalibrated risk function (not shown).

DISCUSSION

In agreement with previous studies performed in populations with relatively low CHD risk [18-20,22,24], the original Framingham risk function overestimated by a factor of 2 to 3 the number of events predicted by the MONICA incidence rates or by the joint use of mortality and case-fatality rates. The recalibrated risk function provided estimates that better matched but still slightly overestimated the projected number of events, except for a large overestimation in women aged over 65. A possible explanation is the fact that the Swiss case-fatality rate used to compute the number of cases was only 12%, which is very low compared to the literature [43,44] and might have artificially

inflated the number of events. Indeed, increasing case-fatality rates to 25%, a more reasonable [43] estimate, led to more consistent results (**Table III**), while increasing case-fatality rates to 44% as reported by others [44] led to an overestimation of the number of events. Still, sensitivity analysis showed that this overestimation was relatively small within a reasonable range of mortality and case-fatality rates, as compared to the original Framingham function, which considerably overestimates the number of CHD events in the Swiss population, whereas the recalibrated risk function might provide better, albeit slightly overestimated, risks. The underestimation of the number of events among participants aged over 64 years might be related to the fact that a single case-fatality rate was applied for all age groups, and it is known that case-fatality tends to increase with age [39,42]. Indeed, as indicated in **table III**, applying a 20% case-fatality rate to subjects aged over 64 years as reported in the literature [42] led to a slight overestimation of the number of events by the recalibrated Framingham function.

European guidelines recommend the use of the EU-SCORE, a risk score based on data from European cohort studies which estimates of ten-year risk of fatal cardiovascular disease (stroke + coronary heart disease + sudden death) [11]. Still, the SCORE function has not yet been validated in the Swiss population and it is not possible to compare its predictive accuracy relative to the Framingham risk function as those two risk functions do not estimate the same risk (cardiovascular mortality for SCORE, fatal and nonfatal CHD events for Framingham).

This study has several limitations that must be accounted for. First, no prospective data were available in Switzerland for women. Thus, we used official mortality data and case-fatality rates to compute the number of events for comparison with the results from the risk functions. This type of approach has been used in the past by others [45,46] for recalibration of risk equations. We rely here on the high quality of coding the cause of death in Switzerland, especially for persons aged less than 80 as previously published [32,47], and which have shown a very good agreement between official CHD deaths codes and CHD deaths reported by the MONICA investigators [14]. Although this methodology might lead to less precise results, the sensitivity analyses showed that, for the original Framingham risk function, the predicted risks were too high to be compatible with the current mortality and case-fatality rates. By contrast, the results from the recalibrated Framingham risk function were actually compatible with, or slightly overestimated within a reasonable range, observed mortality and case-fatality rates. The CoLaus study might not be fully representative of the overall Swiss population, as it was drawn from a single Canton (Vaud) and only included Caucasian subjects, i.e. the majority of the population of Switzerland, and questions might arise whether the genetic mix of Caucasians in Lausanne is representative of the whole country. Still, a considerable proportion of the Lausanne population is non-Swiss or comes from other cantons, including Italian and Germanic origin: in 2006, out of the 128,231 Lausanne inhabitants, 49,330 (38%) were non-Swiss, 38,513 (30%) came from other cantons, and only 40,388 subjects (32%) were actually from the Vaud canton [1]. We thus believe that the genetic mix of the CoLaus sample is relatively large and that the results may be extrapolated with reasonable confidence to the Swiss population. A sampling bias might also have occurred, participants presenting with a better health (and thus a lower risk) than non-participants; this could partly explain the underestimation of the number of events by the recalibrated Framingham equation in participants aged over 64 years. Unfortunately, no health data regarding non-participants could be collected. Still, in the absence of a representative sample for the whole Swiss population, these currently represent the best estimates available for the calibration of the Framingham risk function.

The strengths of our study were its population-based design, with limited exclusion criteria and a large range of age, and the availability of all traditional

[1] http://www.lausanne.ch/view.asp?docId=22884&domId=63584&language=F, site assessed November 19, 2007

cardiovascular risk factors. Finally, the CoLaus study will enable better estimates of the incidence of CHD and thus a better recalibration of the risk scores.

In summary, our population-based study indicates that the original Framingham risk function overestimates the risk of CHD events in the Swiss population by a magnitude of 2 to 3. The recalibrated risk function might provide a reasonable alternative for the calculation of 10-year CHD risk in men, while it tends to underestimate risk in women aged over 65. When prospective data will be available in Switzerland, its validity should be further assessed using longitudinal data.

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TABLES

Table I: sample characteristics and ten-year CHD risks according to the risk function used, by gender.

	Women (n=3,074)	Men (n=2,699)	test
Age (years)	53.1 ± 10.6	51.8 ± 10.5	4.70 ***
Diabetes (%)	86 (2.8)	178 (6.6)	47.49 ***
Smokers (%)	776 (25.2)	793 (29.4)	12.48 ***
SBP (mm Hg)	124 ± 18	132 ± 16	15.94 ***
DBP (mm Hg)	78 ± 11	81 ± 11	13.72 ***
Total cholesterol (mg/dL)	217 ± 40	217 ± 40	0.63 NS
HDL cholesterol (mg/dL)	70 ± 16	56 ± 14	34.89 ***
All CHD events			
Framingham, original			
Mean risk	1.8 (0.1 – 6.1)	7.1 (1.1 – 20.2)	2270 ***
Risk categories (%)			
Very low (<6%)	2918 (94.9)	1547 (57.3)	
Low (6 – 10%)	117 (3.8)	572 (21.2)	1177 ***
Intermediate (10 – 20%)	37 (1.2)	442 (16.4)	
High (>20%)	2 (0.1)	138 (5.1)	
Framingham, recalibrated			
Mean risk	0.8 (0.1 – 2.7)	3.4 (0.5 – 9.9)	2415 ***
Risk categories (%)			
Very low (<6%)	3059 (99.5)	2287 (84.7)	
Low (6 – 10%)	13 (0.4)	278 (10.3)	459 ***
Intermediate (10 – 20%)	0 (0.0)	117 (4.3)	
High (>20%)	2 (0.1)	17 (0.6)	

Results are expressed as mean (5 – 95th percentile) for risks and as number of subjects and (percentage) or mean ± standard deviation for the other variables. SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density cholesterol. Statistical analysis by chi-square, Student's t-test or Mann-Whitney test (for risks): NS, not significant; ***, p<0.001.

Table II: predicted number of CHD events after 10 years according to the original and recalibrated Framingham risk function, compared to those estimated using mortality + case-fatality rates or incidence rates (men only), by age group and gender.

	Framingham original	Framingham recalibrated	Mortality + case-fatality	MONICA incidence rates
Women				
35 – 44 (854)	4 (1 – 10)	2 (0 – 4)	1 – 2	
45 – 54 (880)	11 (2 – 34)	5 (1 – 15)	4 – 7	
55 – 34 (887)	22 (5 – 63)	10 (2 – 28)	7 – 12	
65 – 74 (453)	18 (5 – 43)	8 (2 – 19)	20 – 35	
All (3,074)	54 (13 – 151)	24 (5 – 66)	32 – 55	
Men				
35 – 44 (867)	27 (6 – 70)	13 (3 – 33)	5 – 8	4 – 8
45 – 54 (808)	44 (12 – 101)	21 (6 – 49)	15 – 26	13 – 18
55 – 34 (671)	67 (21 – 158)	32 (10 – 79)	29 – 50	19 – 25
65 – 74 (353)	53 (16 – 119)	26 (8 – 62)	34 – 58	14 – 18
All (2,699)	191 (55 – 449)	92 (26 – 223)	83 – 142	51 – 68

Results expressed as mean and (5 – 95th percentile) for the original and recalibrated Framingham risk function and as range for the mortality + case-fatality rates. Incidence rates were available for men only; the first value corresponds to incidence rates from the *cantons* Vaud + Fribourg, the second from the *canton* Tessin.

Table III: sensitivity analysis for the recalibrated Framingham risk function, by gender and age group.

	Mortality					
	2003 rates	2003 + 10%	2003 + 25%	2003 + 50%	2003 + 75%	Recalibrated Framingham
Men						
35-44 years	3.1	3.4	3.9	4.7	5.5	12.7
45-54 years	10.0	11.0	12.5	15.1	17.6	21.1
55-64 years	19.6	21.6	24.5	29.4	34.2	32.3
65-74 years	22.5	24.8	28.1	33.7	39.3	26.2
All	**55.3**	**60.8**	**69.1**	**82.8**	**96.6**	**92.3**
Women						
35-44 years	0.6	0.7	0.8	0.9	1.1	1.5
45-54 years	2.6	2.8	3.2	3.9	4.5	4.7
55-64 years	4.8	5.3	6.0	7.2	8.4	9.7
65-74 years	13.5	14.8	16.8	20.2	23.5	7.9
All	**21.5**	**23.6**	**26.9**	**32.2**	**37.6**	**23.8**
	Case-fatality					
	5%	10%	15%	20%	25%	Recalibrated Framingham
Men						
35-44 years	11.3	5.6	3.8	2.8	2.3	12.7
45-54 years	36.1	18.1	12.0	9.0	7.2	21.1
55-64 years	70.5	35.3	23.5	17.6	14.1	32.3
65-74 years	81.1	40.6	27.0	20.3	16.2	26.2
All	**199.1**	**99.6**	**66.4**	**49.8**	**39.8**	**92.3**
Women						
35-44 years	2.3	1.1	0.8	0.6	0.5	1.5
45-54 years	9.3	4.7	3.1	2.3	1.9	4.7
55-64 years	17.4	8.7	5.8	4.3	3.5	9.7
65-74 years	48.4	24.2	16.1	12.1	9.7	7.9
All	**77.4**	**38.7**	**25.8**	**19.3**	**15.5**	**23.8**

Results are expressed in number of CHD events at 10 years according to mortality and case-fatality rates used. The upper part of the table uses a constant case-fatality rate of 18% with increasing CHD mortality rates starting from the original 2003 gender and age-specific rates. The lower part of the tables uses the original 2003 gender and age-specific CHD mortality rates with varying levels of case-fatality rates. The last column indicates the number of CHD events as predicted by the recalibrated Framingham risk function.

FIGURE LEGENDS

Figure 1: expected number of CHD events after 10 years in the CoLaus study according to the original and recalibrated Framingham risk function, compared with results from mortality + case-fatality or from incidence rates (men only).

Figure 1: Men

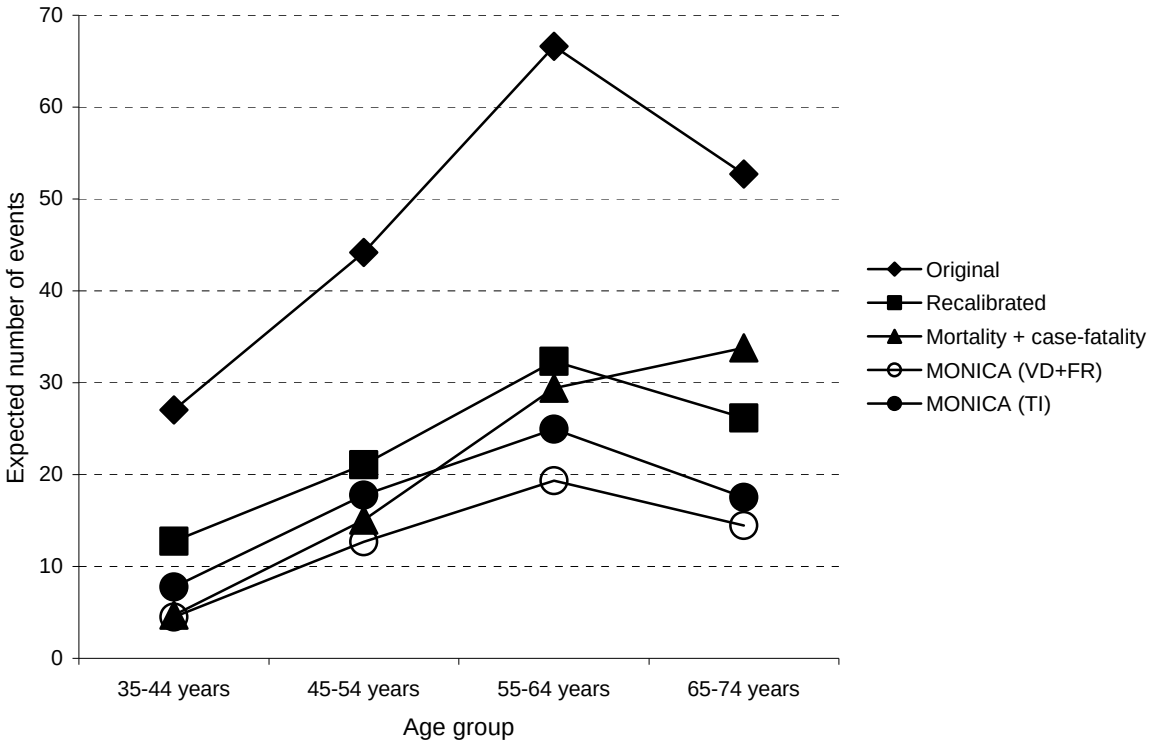

Figure 1: Women