Age at quitting smoking as a predictor of risk of cardiovascular disease incidence independent of smoking status, time since quitting and pack-years

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Abstract

Background: Risk prediction for CVD events has been shown to vary according to current smoking status, pack-years smoked over a lifetime, time since quitting and age at quitting. The latter two are closely and inversely related. It is not known whether the age at which one quits smoking is an additional important predictor of CVD events. The aim of this study was to determine whether the risk of CVD events varied according to age at quitting after taking into account current smoking status, lifetime pack-years smoked and time since quitting.

Findings: We used the Cox proportional hazards model to evaluate the risk of developing a first CVD event for a cohort of participants in the Framingham Offspring Heart Study who attended the fourth examination between ages 30 and 74 years and were free of CVD. Those who quit before the median age of 37 years had a risk of CVD incidence similar to those who were never smokers. The incorporation of age at quitting in the smoking variable resulted in better prediction than the model which had a simple current smoker/non-smoker measure and the one that incorporated both time since quitting and pack-years. These models demonstrated good discrimination, calibration and global fit. The risk among those quitting more than 5 years prior to the baseline exam and those whose age at quitting was prior to 44 years was similar to the risk among never smokers. However, the risk among those quitting less than 5 years prior to the baseline exam and those who continued to smoke until 44 years of age (or beyond) was two and a half times higher than that of never smokers.

Conclusions: Age at quitting improves the prediction of risk of CVD incidence even after other smoking measures are taken into account. The clinical benefit of adding age at quitting to the model with other smoking measures may be greater than the associated costs. Thus, age at quitting should be considered in addition to smoking status, time since quitting and pack-years when counselling individuals about their cardiovascular risk.

Introduction

CVD risk associated with smoking varies not only with smoking status but also with intensity and duration of smoking or smoking pack-years, time since quitting and age at quitting. Many studies have examined the lag in health benefit of smoking cessation measured by time since quitting and occurrence of a CVD event [1-8]. However age at quitting also affects the health benefits of smoking cessation [9,10]. The risks of mortality and smoking-related disease increase with age at quitting. However, the role of age at quitting as a predictor of CVD risk in the presence of time since quitting and pack-years is unclear. As CVD is more common among elderly people it is likely that age at quitting and time since quitting, inversely correlated, influence CVD risk in opposite directions.

This study explores whether and how age at quitting influences risk of CVD incidence, using data from the Framingham Offspring Heart Study. It uses a smoking status variable with and without incorporating other smoking variables such as time since quitting among...
past smokers and pack-years among current smokers, while controlling for common risk factors.

Methods & Results
Study Design and Sample
The Framingham Offspring Heart Study details for design, selection criteria, examination procedures and criteria for CVD events have been described elsewhere [11-15]. Participants were eligible for the present study if at examination 4 (1988 to 1992) they were CVD-free and aged 30-74 with nonmissing data on covariates. The final study sample consisted of 3751 participants (mean age 51.61; 1937 women).

Measurement of CVD Risk Factors
The risk factors included were smoking status with various definitions (expanded below), systolic and diastolic blood pressure (SBP & DBP), total cholesterol/high-density-lipoprotein (HDL) ratio or both (depending on which provided a better prediction of outcome), age, sex, diabetes status and body-mass index (BMI). Smoking status was initially defined as a dichotomous current smoker/non-smoker variable. The other definitions of smoking status included four, six and eight categories. The four category smoking status variable was defined as: never smokers, former smokers with age at quitting below 37 years, former smokers with age at quitting of 37 years or older, and current smokers. The six category smoking status variable was defined as: never smokers, former smokers with time since quitting 5 years or less and over 5 years and current smokers with under 20, 20-39, and 40 or more pack-years. The eight category smoking status variable was defined as: never smokers, past smokers quitting ≤44, >44 years) at each of two levels of time since quitting (≤5, and >5 years) and current smokers with under 20, 20-39, and 40 or more pack-years.

Blood pressure was the average of two physician-obtained measures. Cholesterol and various smoking measures were based on standardized enzymatic methods and self-report, respectively. Diabetes was defined as a fasting glucose ≥126 mg/dL. Age at quitting and time since quitting were calculated at examination 4 by combining smoking status information at each examination with history of smoking status from examination 1 [8].

Development & assessment of predictive models
The Cox proportional-hazards model [16] was used to relate risk factors to the risk of CVD incidence during follow-up from examinations 4 to 7. The assumption of proportionality of hazards was satisfied; tested by taking interaction between a covariate and log (survival time) [17] and plotting Schoenfeld residuals against survival time.

To improve the interpretability of the predictive models we categorized time since quitting, age at quitting and pack-years. It was observed that the lag time for a beneficial effect of smoking cessation on risk of CVD incidence was five years after which the risk stabilized [8]. In the literature there is no maximum age for quitting without increasing the risk of a CVD event compared to a never smoker and there was no apparent cutpoint to dichotomise this variable as the predicted time to the onset of a CVD event declined almost linearly with age at quitting (results not shown). Thus the median, shown by simulation to result in minimum loss in efficiency [18], was used to dichotomise age at quitting.

Four models were fitted for the outcome. Each included a composite measure of smoking status and all other risk factors found to be significantly related to the outcome. Model 1 included smoking status as a simple current smoker/non-smoker variable with current non-smoker as the reference category. To incorporate the effect of age at quitting into smoking status, quitters were separated from current non-smokers and categorized by age at quitting in Model 2, which incorporated smoking status with categories <37 and ≥37 years for age at quitting, never smokers and current smokers. To examine whether incorporating age at quitting to smoking status improved risk prediction, Model 2 was compared to Model 1. To examine whether incorporating age at quitting improves risk prediction to a model which already includes time since quitting and pack-years in smoking status, Models 3 and 4 were fitted and compared. Model 3 incorporated smoking status that included categories for never smokers, ≤5 and >5 years for time since quitting, and <20, 20-39 and 40+ for pack-years. Other categorizations for pack-years and time since quitting were found to be less effective in terms of predictive ability. Model 4 added age at quitting to Model 3 with smoking status having six categories - never smoker, current smoker, and past smokers quitting ≤5 years and whose age at quitting was ≤44 or >44 years, and those quitting >5 years and whose age at quitting was ≤44 or >44 years. Compared with Model 2 age at quitting was categorized differently because for the initial categorization of age at quitting at <37 and ≥37 years there were inadequate numbers of cases in one of the joint categories of this variable with time since quitting resulting in inefficient estimation of its regression coefficient. The other cutpoints prior to reaching age 44 produced the same result until the cutpoint reached age 44 which did not yield inadequate number of cases in any of the joint categories. In Models 2 through 4 the reference category for smoking status was never smoker.
For assessing the discriminative ability of a model and improvement between two nested models we used Harrell’s c statistic [19,20] and a test for difference in two correlated c statistics [21]. Large ‘independent’ association of the new covariate with the outcome is required to result in a meaningfully larger c statistic [22-24] for models possessing reasonably good discrimination, and the c statistic does not assist a physician in treatment decisions about an individual [25,26] while reclassification statistics NRI [27] and IDI [27] do [25,26]. Thus, we used the latter to supplement c-statistic analyses [27,28]. For calculating NRI we assessed risk reclassification [27] by sorting the predicted risk for each model into four clinically meaningful categories (<6%, 6% to < 10%, 10% to < 20%, and ≥ 20%). The benefit and cost of using a new model compared to a baseline model can be measured by the proportions of subjects with and without subsequent events, respectively, who are classified as high risk (eg. ≥ 20%) according to the new model [26]. There was negligible overoptimism in c and NRI estimates obtained by bootstrapping as these were less than 0.007 and 0.005 respectively.

For assessing calibration of the fitted models and improvement in global fit between two nested models we computed the Hosmer-Lemeshow statistic and its improvement between two nested models we used Harrell’s c statistic [19,20] and a test for difference in two correlated c statistics [21]. Large ‘independent’ association of the new covariate with the outcome is required to result in a meaningfully larger c statistic [22-24] for models possessing reasonably good discrimination, and the c statistic does not assist a physician in treatment decisions about an individual [25,26] while reclassification statistics NRI [27] and IDI [27] do [25,26]. Thus, we used the latter to supplement c-statistic analyses [27,28]. For calculating NRI we assessed risk reclassification [27] by sorting the predicted risk for each model into four clinically meaningful categories (<6%, 6% to < 10%, 10% to < 20%, and ≥ 20%). The benefit and cost of using a new model compared to a baseline model can be measured by the proportions of subjects with and without subsequent events, respectively, who are classified as high risk (eg. ≥ 20%) according to the new model [26]. There was negligible overoptimism in c and NRI estimates obtained by bootstrapping as these were less than 0.007 and 0.005 respectively.

For assessing calibration of the fitted models and improvement in global fit between two nested models we computed the Hosmer-Lemeshow statistic and its modification [27] by sorting the predicted risk for each model into four clinically meaningful categories (<6%, 6% to < 10%, 10% to < 20%, and ≥ 20%). The benefit and cost of using a new model compared to a baseline model can be measured by the proportions of subjects with and without subsequent events, respectively, who are classified as high risk (eg. ≥ 20%) according to the new model [26]. There was negligible overoptimism in c and NRI estimates obtained by bootstrapping as these were less than 0.007 and 0.005 respectively.

Results

Sample characteristics

The sample risk factor characteristics at baseline examination 4 are shown in Table 1. The sample consists of 26.7% never smokers, 48.4% quitters (15.1% of whom quit within 5 years of the baseline measurement and 33.1% of whom quit before age 37 years), and 14.5% current smokers (of whom 16.6% have exposure ≥ 40 pack-years).

Model comparisons

Table 2 shows that Model 2 improved predictive ability significantly compared to Model 1. Model 3 performed well in terms of model discrimination and overall fit but less well in terms of calibration. Model 4 performed well on all model performance indicators; significantly improving predictive ability compared to Model 3 (Table 3). Thus, age at quitting was an independent predictor of risk of CVD incidence regardless of including time since quitting and pack-years in the model.

Compared to never smokers, the risk of CVD incidence based on Model 2 was 7.3% higher (RR = 1.073, 95% CI 0.804 – 1.433) for those who quit before age 37 years and 58.1% higher (RR = 1.581, 95% CI 1.193 – 2.094) for those who quit at least at age 37 years (Table 4). For the former category the relative risk was not significantly different from the never smokers while for the latter category it was. Based on the final model (Model 4), the risk among those quitting more than 5 years prior to the baseline exam and whose age at quitting was 44 years or less was close to never smokers. Risk among those quitting within 5 years prior to the baseline exam and whose age at quitting was over 44 years was about three times higher than that of never smokers (Table 5).

Reclassification of subjects

This section describes how many subjects were reclassified overall and with respect to ‘high risk’ category of ≥ 20% when we compared the preferred full model against the reference model. Comparing Model 2 against Model 1, for participants who experienced a CVD event, the net gain in reclassification proportion was significantly different from zero (p = 0.0113) (Table 6) and significant for participants who did not experience an event (p = 0.0025) and for all participants (p = 0.0112). For those who experienced a CVD event, using Model 4 rather than Model 3 did not improve net gain in reclassification proportion significantly (p = 0.2935) (Table 7). The result was similar for
Table 2 Improvement in CVD risk prediction due to including age at quitting among past smokers in Model 1

| Likelihood ratio | Value     | Degrees of freedom | p-value  |
|------------------|-----------|---------------------|----------|
| Vs model 1       | 11.4732   | 2                   | 0.0032   |

Difference between two correlated C

| Estimate (SE)    | 95% CI     | Chi-square | p-value |
|------------------|------------|------------|---------|
| Vs model 1       | 0.0047(0.0022) | 0.0004, 0.0090 | 4.5340 | 0.0332 |

NRI

| Vs model 1       | 0.0512     | 0.0117, 0.0906 | 2.5343 | 0.0113 |

IDI

| Vs model 1       | 0.0014     | -0.0010, 0.0037 | 1.1012 | 0.2707 |

Note: Model 1 included current smoking status, systolic and diastolic blood pressure, total cholesterol/HDL ratio, triglycerides, age, sex and diabetes status.

Table 3 Improvement in CVD risk prediction due to including age at quitting among past smokers in Model 3

| Likelihood ratio | Value     | Degrees of freedom | p-value  |
|------------------|-----------|---------------------|----------|
| Vs model 3       | 25.8845   | 2                   | <0.0001  |

Difference between two correlated C

| Estimate (SE)    | 95% CI     | Chi-square | p-value |
|------------------|------------|------------|---------|
| Vs model 3       | 0.0079(0.0036) | 0.0088, 0.0150 | 4.7266 | 0.0297 |

NRI

| Vs model 3       | 0.0294     | -0.0111, 0.0701 | 1.4192 | 0.1558 |

IDI

| Vs model 3       | 0.0029     | 0.0010, 0.0057 | 2.0362 | 0.0417 |

Note: Model 3 incorporated smoking status that included categories for never smokers (reference group), ≤5 and >5 years for time since quitting, and <20, 20-39 and 40+ for pack-years, systolic and diastolic blood pressure, total cholesterol/HDL ratio, triglycerides, age, sex and diabetes status.

Table 4 Risk equation with a simple current/non-smoker smoking status variable (Model 1)

| Variable               | Parameter Estimate | Standard Error | Chi-Square | P value | Hazard Ratio | 95% CI |
|------------------------|--------------------|----------------|------------|---------|--------------|--------|
| Sex                    | 0.6391             | 0.1119         | 32.6222    | <.0001  | 1.895        | 1.522  | 2.360 |
| Age                    | 0.0768             | 0.0069         | 123.1031   | <.0001  | 1.080        | 1.065  | 1.095 |
| Sbp                    | 0.0142             | 0.0036         | 14.9743    | 0.0001  | 1.014        | 1.007  | 1.022 |
| Dbp                    | -0.0176            | 0.0069         | 6.3866     | 0.0115  | 0.983        | 0.969  | 0.996 |
| Total/HDL ratio        | 0.2127             | 0.0347         | 37.4452    | <.0001  | 1.237        | 1.156  | 1.324 |
| Diabetes               | 0.8101             | 0.1518         | 28.4764    | <.0001  | 2.248        | 1.670  | 3.028 |
| Triglycerides          | -0.0015            | 0.0005         | 7.9721     | 0.0069  | 0.998        | 0.997  | 1.000 |
| Current smoker         | 0.5594             | 0.1251         | 19.9779    | <.0001  | 1.750        | 1.369  | 2.236 |

Test

| Total | Event | Censored | % Censored |
|-------|-------|----------|------------|
| 3751  | 383   | 3368     | 89.79      |

Chi-Square: 437.1565, DF: 8, P value: <.0001
Hosmer Lemeshow: 18.6207, DF: 9, P value: 0.0286
Modified HL: 17.4569, DF: 9, P value: 0.0420

Note: The reference categories for sex, diabetes and the smoking variable are female, no diabetes and non-current smoker respectively.
### Table 5 Risk equation with age at quitting incorporated into smoking status variable (Model 2)

| Variable          | Parameter Estimate | Standard Error | Chi-Square | P value | Hazard Ratio | 95% CI     |
|-------------------|--------------------|----------------|------------|---------|--------------|------------|
| Sex               | 0.5967             | 0.1133         | 27.7286    | <.0001  | 1.816        | 1.454      | 2.268      |
| Age               | 0.0730             | 0.0070         | 107.9667   | <.0001  | 1.076        | 1.061      | 1.091      |
| Sbp               | 0.0140             | 0.0036         | 14.7801    | 0.0001  | 1.014        | 1.007      | 1.021      |
| Dbp               | -0.00172           | 0.0069         | 61574      | 0.0131  | 0.983        | 0.970      | 0.996      |
| Total/HDL ratio   | 0.2148             | 0.0354         | 36.7663    | <.0001  | 1.240        | 1.157      | 1.329      |
| Diabetes          | 0.7941             | 0.1520         | 27.2897    | <.0001  | 2.213        | 1.642      | 2.981      |
| Triglycerides     | -0.00162           | 0.0005         | 8.2076     | 0.0042  | 0.998        | 0.997      | 0.999      |
| Current smoker    | 0.7248             | 0.1505         | 23.1684    | <.0001  | 2.064        | 1.537      | 2.773      |
| Age at quitting   |                    |                |            |         |              |            |            |
| <37               | 0.0708             | 0.1474         | 0.2307     | 0.6310  | 1.073        | 0.804      | 1.433      |
| ≥37               | 0.4578             | 0.1435         | 10.1778    | 0.0014  | 1.581        | 1.193      | 2.094      |

#### Test

| Total | Event | Censored | % Censored |
|-------|-------|----------|------------|
| 3751  | 383   | 3368     | 89.79      |

#### Chi-Square

- Likelihood Ratio: 448.6297, 10, <0.0001
- Hosmer Lemeshow: 11.3628, 9, 0.2516
- Modified HL: 10.5026, 9, 0.3113

#### C statistic

- Estimate: 0.8085, SE: 0.0108, 95% CI: 0.7873, 0.8296

Note: The reference categories for sex, diabetes and the smoking variable are female, no diabetes and never smoker respectively.

### Table 6 Risk equation incorporating time since quitting and pack-years into smoking status (Model 3)

| Variable          | Parameter Estimate | Standard Error | Chi-Square | P value | Hazard Ratio | 95% CI     |
|-------------------|--------------------|----------------|------------|---------|--------------|------------|
| Sex               | 0.66172            | 0.11252        | 34.5854    | <.0001  | 1.938        | 1.555      | 2.416      |
| Sbp               | 0.03508            | 0.00306        | 131.2240   | <.0001  | 1.036        | 1.030      | 1.042      |
| Dbp               | -0.04076           | 0.00621        | 43.1167    | <.0001  | 0.960        | 0.948      | 0.972      |
| Total/HDL ratio   | 0.22727            | 0.03592        | 40.0381    | <.0001  | 1.255        | 1.170      | 1.347      |
| Diabetes          | 0.88176            | 0.15423        | 32.6873    | <.0001  | 2.415        | 1.785      | 3.268      |
| Triglycerides     | -0.00170           | 0.00059        | 8.2356     | 0.0041  | 0.998        | 0.997      | 0.999      |
| Time since quitting |                |                |            |         |              |            |            |
| < = 5 years       | 0.75854            | 0.18123        | 15.1899    | <.0001  | 2.135        | 1.497      | 3.046      |
| >5 years          | 0.13762            | 0.13059        | 1.1106     | 0.2920  | 1.148        | 0.888      | 1.482      |
| Pack years        |                    |                |            |         |              |            |            |
| <20               | 0.15632            | 0.34319        | 0.2075     | 0.6487  | 1.169        | 0.597      | 2.291      |
| 20-39             | 0.50078            | 0.21593        | 5.3785     | 0.0204  | 1.650        | 1.081      | 2.519      |
| 40+               | 0.81008            | 0.16219        | 24.9470    | <.0001  | 2.248        | 1.636      | 3.089      |

#### Test

| Total | Event | Censored | % Censored |
|-------|-------|----------|------------|
| 3751  | 383   | 3368     | 89.79      |

#### Chi-Square

- Likelihood Ratio: 324.1494, 11, <0.0001
- Hosmer Lemeshow: 11.4700, 9, 0.2448
- Modified HL: 11.0293, 9, 0.3113

#### C statistic

- Estimate: 0.7601, SE: 0.0130, 95% CI: 0.7346, 0.7856

Note: The reference categories for sex, diabetes and the smoking variable are female, no diabetes and never smoker respectively.
participants who did not experience an event \( (p = 0.1545) \) and for all participants \( (p = 0.1558) \).

Table 8 shows that based on Model 2 instead of Model 1, 16.5% of those developing a CVD event would have moved up to the ‘high risk’ category of ≥20% while of those not having a CVD event 9.4% would have moved to this risk category, the difference of which is highly significant \( (p < 0.0001) \). Similarly, Table 9 shows that if we had used Model 4 rather than Model 3, 14.6% of those who develop CVD would be appropriately assessed for their cardiovascular risk while only 7.6% of those who do not develop CVD would be falsely assessed for their cardiovascular risk, the difference of which is highly significant \( (p < 0.0001) \).

### Sensitivity of the results

We have adjusted for all major confounders of smoking to address confounding bias in the risk models. To address the possibility of distortion due to medical treatments affecting the risk of a CVD event we found that the regression coefficients of the models were fairly insensitive to the inclusion of cardioactive medications. To address the possibility of reverse causation, we excluded from the baseline cohort those with a cancer history and other non-CVD conditions. This did not substantially influence the results. Sub-analyses conducted by excluding from baseline cohort those smokers who quit after examination 4 and those quitters who took up smoking after examination 4, and later those current smokers from baseline cohort whose pack-years changed substantially in subsequent examinations did not influence our results.

### Table 7 Risk equation for CVD incidence incorporating age at quitting, time since quitting & pack-years into smoking status (Model 4)

| Variable       | Parameter Estimate | Standard Error | Chi-Square | P value | Hazard Ratio | 95% CI |
|----------------|--------------------|----------------|------------|---------|--------------|-------|
| Sex            | 0.66579            | 0.11303        | 34.6954    | <.0001  | 1.946        | 1.559 | 2.429 |
| Sbp            | 0.03269            | 0.00315        | 107.7472   | <.0001  | 1.033        | 1.027 | 1.040 |
| Dbp            | -0.03884           | 0.00632        | 37.8124    | <.0001  | 0.962        | 0.950 | 0.974 |
| Total/HDL ratio| 0.22400            | 0.03635        | 37.9841    | <.0001  | 1.251        | 1.165 | 1.343 |
| Diabetes       | 0.85100            | 0.15482        | 30.2145    | <.0001  | 2.342        | 1.729 | 3.172 |
| Triglycerides  | -0.00185           | 0.00061        | 9.1876     | 0.0024  | 0.998        | 0.997 | 0.999 |

| Pack-years     |                   |                |            |         |             |       |
|----------------|--------------------|----------------|------------|---------|--------------|-------|
| < = 19         | 0.15082            | 0.34314        | 0.1932     | 0.6603  | 1.163        | 0.593 | 2.278 |
| 20-39          | 0.48640            | 0.21593        | 5.0743     | 0.0243  | 1.626        | 1.065 | 2.483 |
| 40+            | 0.81617            | 0.16208        | 25.3579    | <.0001  | 2.262        | 1.646 | 3.108 |

| Time since quitting |                   |                |            |         |             |       |
|---------------------|--------------------|----------------|------------|---------|--------------|-------|
| < = 5 years & Age at quitting |       |                |            |         |             |       |
| ≤ 44                | -0.9483            | 0.71256        | 1.7711     | 0.1832  | 0.387        | 0.096 | 1.566 |
| >44                 | 1.0505             | 0.18672        | 31.6533    | <.0001  | 2.859        | 1.983 | 4.123 |

| Age at quitting    |                   |                |            |         |             |       |
|---------------------|--------------------|----------------|------------|---------|--------------|-------|
| ≤ 44                | -0.1047            | 0.1595         | 0.4315     | 0.5113  | 0.901        | 0.659 | 1.231 |
| >44                 | 0.5923             | 0.1789         | 10.9580    | 0.0009  | 1.808        | 1.273 | 2.568 |

| Test                | Total | Event | Censored | % Censored |       |     |
|---------------------|-------|-------|----------|------------|------|-----|
|                     | 3751  | 383   | 3368     | 89.79      |      |     |

| Estimate SE 95% CI | Chi-Square | DF | P value |
|--------------------|------------|----|---------|
| Likelihood Ratio   | 347.7915   | 13 | <.0001  |
| Hosmer Lemeshow    | 6.5337     | 9  | 0.6855  |
| Modified HL        | 6.1388     | 9  | 0.7259  |

| C statistic | SE     | 95% CI   |
|-------------|--------|----------|
| 0.7680      | 0.0130 | 0.7426, 0.7934 |

Note: The reference categories for sex, diabetes and the smoking variable are female, no diabetes and never smoker respectively.

### Merits and demerits of this study

The study’s key strength is that it not only evaluates improvement in predicting CVD risk when models incorporate age at quitting but also quantifies the proportions of people receiving clinical benefits and costs.
Table 8 Reclassification table for risk of CVD incidence between the model with age at quitting incorporated into smoking status (Model 2) and the model with a current/non-smoker smoking measure (Model 1) as the reference model

| Model 1 | Model 2 |
|---------|---------|
| Frequency (Row per cent) | <6% | 6-<10% | 10-<20% | >= 20% | Total |
| Participants who experience a CVD Event | | | | | |
| <6% | 158 | 16 | 0 | 0 | 174 |
| 6-<10% | 8 | 53 | 12 | 0 | 73 |
| 10-<20% | 0 | 5 | 60 | 6 | 71 |
| >= 20% | 0 | 0 | 8 | 57 | 65 |
| Total | 166 | 74 | 80 | 63 | 383 |
| Net gain in reclassification proportion (p-value) | 0.0339 (0.0796) | |
| Participants who do not experience a CVD Event | | | | | |
| <6% | 1750 | 53 | 0 | 0 | 1803 |
| 6-<10% | 75 | 469 | 67 | 0 | 611 |
| 10-<20% | 0 | 79 | 499 | 36 | 614 |
| >= 20% | 0 | 0 | 60 | 280 | 340 |
| Total | 1825 | 601 | 626 | 316 | 3368 |
| Net gain in reclassification proportion (p-value) | 0.0172 (0.0025) | |
| NRI (p-value) | 0.0511 (0.0112) | |
| Overall net gain in reclassification proportion with respect to risk category >= 20% (p-value) | 0.0019 (0.8518) | |
| Overall gross gain in reclassification proportion with respect to risk category >= 20% (p-value) | 0.0263 (<0.0001) | |

Table 9 Reclassification table for risk of CVD incidence between the model with age at quitting, time since quitting and pack-years incorporated into smoking status (Model 4) and a reduced model without age at quitting (Model 3) as the reference model

| Model 3 | Model 4 |
|---------|---------|
| Frequency (Row per cent) | <6% | 6-<10% | 10-<20% | >= 20% | Total |
| Participants who experience a CVD Event | | | | | |
| <6% | 164 | 13 | 0 | 0 | 177 |
| 6-<10% | 10 | 56 | 12 | 0 | 78 |
| 10-<20% | 1 | 5 | 57 | 8 | 71 |
| >= 20% | 1 | 0 | 8 | 48 | 57 |
| Total | 176 | 74 | 77 | 56 | 383 |
| Net gain in reclassification proportion (p-value) | 0.0208 (0.2935) | |
| Participants who do not experience a CVD Event | | | | | |
| <6% | 1402 | 85 | 0 | 0 | 1487 |
| 6-<10% | 83 | 742 | 64 | 0 | 889 |
| 10-<20% | 25 | 84 | 596 | 44 | 749 |
| >= 20% | 10 | 2 | 18 | 213 | 243 |
| Total | 1520 | 913 | 678 | 257 | 3368 |
| Net gain in reclassification proportion (p-value) | 0.0086 (0.1545) | |
| NRI (p-value) | 0.0294 (0.1558) | |
| Overall net gain in reclassification proportion with respect to risk category >= 20% (p-value) | 0.0015 (0.8888) | |
| Overall gross gain in reclassification proportion with respect to risk category >= 20% (p-value) | 0.0339 (<0.0001) | |
However, a cost-benefit analysis of including this variable was not possible as the same number of CVD events was prevented by the full and reduced models. Also, as the Framingham cohort has an ethnically white predominance the generalizability of our models to other ethnic groups is unknown.

Conclusion
The incorporation of age at quitting in smoking status resulted in better prediction compared to the model which had a current smoker/non-smoker measure and to the model which incorporated both time since quitting and pack-years in smoking status. Thus, age at quitting was an independent predictor of CVD incidence even after accounting for time since quitting and pack-years.

We also showed that if we had incorporated age at quitting in smoking status instead of a current/non-smoker measure, a significantly higher proportion of those developing a CVD event would have moved up to the ‘high risk’ category compared to those not having a CVD event who moved up to this category. The result was similar if the model added age at quitting in smoking status which already incorporated time since quitting and pack-years. The former would be appropriately treated while the latter would be falsely treated if we included age at quitting in smoking status. Those appropriately treated can benefit from additional screening for CVD risk and would require more aggressive intervention for smoking cessation [29] and would thus aid in preventing more deaths. However, this benefit would be at the cost of falsely identifying people who do not develop CVD as high risk who may unnecessarily receive additional screening and may cause undue stress and burden to the smoking cessation programs. From a CVD prevention perspective the benefits associated with smoking cessation clearly outweigh the costs for CVD screening and smoking cessation programs. Age at quitting should be taken into account, as well as other smoking measures, when counselling individuals about their cardiovascular risk.

Acknowledgements
The Framingham Heart Study - Offspring (FHS-O) is conducted and supported by the NHLBI in collaboration with the FHS-O Study Investigators. This Manuscript was prepared using a limited access dataset obtained from the NHLBI and does not necessarily reflect the opinions or views of the NHLBI or the NHLB. This research was supported by an NHMRC health services research grant (no. 465130), an NHMRC/NHF PhD scholarship and a Vichealth Fellowship.

Authors’ contributions
HRM was involved in all stages of this research as the principal author. CES, AP and HLW read the draft of the paper and provided useful suggestions. JIM is the Principal Investigator of the grant which enabled this research to be carried out. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

References
1. Lightwood JM, Glantz SA: Short-term economic and health benefits of smoking cessation: myocardial infarction and stroke. Circulation 1997, 96(8):1089-96.
2. Ockene JK, Kuller LH, Svendsen K, Meilahn M: The Relationship of Smoking Cessation to Coronary Heart Disease and Lung Cancer in the Multiple Risk Factor Intervention Trial (MRFIT), AJPH 1990, 90(8).
3. Ockene IS, Miller NH: Cigarette Smoking, Cardiovascular Disease, and Stroke: A Statement for Healthcare Professionals From the American Heart Association. Circulation 1997, 96:3243-3247.
4. Wannamethee SG, Shaper AG, Whincup PH, Walker M: Smoking cessation and the risk of stroke in middle-aged men. JAMA 1995, 274:155-160.
5. Tamura U, Tanaka T, Okamura T, Kadowaki T, Yamato H, Tanaka H, Nakamura M, Okayama A, Ueshima H, Yamagata Z: Changes in weight, cardiovascular risk factors and estimated risk of coronary heart disease following smoking cessation in Japanese male workers: HIPPO-OHP study. Journal of Atherosclerosis & Thrombosis 2010, 17(1):12-20.
6. Teo KK, Durrupu S, Hawien S, Pandey MR, Valentin V, Hunt D, Diaz R, Rashed W, Freeman R, Jiang L, Zhang X, Yuusuf S, INTERHEART Study Investigators: Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. Lancet 2006, 368(9536):647-58.
7. Honjo K, Isu H, Tsugane S, Tanakasii A, Sato H, Tajima K, Suzuki T, Sobue T: The effects of smoking and smoking cessation on mortality from cardiovascular disease among Japanese: pooled analysis of three large-scale cohorts. Tobacco Control 2010, 19:505-57.
8. Mannan H, Stevenson C, Peeters A, Walls H, McNiel J: Framingham risk prediction equations for CVD incidence using detailed measures for smoking. Heart International 2010, 5:2149-57.
9. Doll R, Peto R, Boreham J, Sutherland I: Mortality in relation to smoking: 50 years’ observations on male British doctors. BMJ 2004, 328:1519, (D6) June AE (published 22 June 2004).
10. Ostbye T, Taylor DH Jr: The Effect of Smoking on Years of Healthy Life (YHL) Lost among Middle-Aged and Older Americans. Health Services Research 2004, 39:531-551.
11. Wood D, Wray R, Poutier N, et al.: JBS 2: Joint British Societies’ guidelines on prevention of cardiovascular disease in clinical practice. Heart 2005, 91(Suppl 5):v1-v52.
12. D’Agostino S, Grundy S, Sullivan JM, Wilson P, for the CHD Risk Prediction Group: Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001, 286:180-187.
13. Beswick A, Brindle P: Risk scoring in the assessment of cardiovascular risk. Curr Opin Lipidol 2006, 17:375-386, 1999, 159: 1197-1204.
14. Liu J, Hong Y, D’Agostino RB Sr, Wu Z, Wang W, Sun J, Wilson PW, Kannel WB, Zhao D: Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA 2004, 291:2591-2599.
15. D’Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JA, Kannel WB: General Cardiovascular Risk Profile for Use in Primary Care. Circulation 2008, 117:743-753.
16. Cox DR: Regression models and life tables. J Royal Stat Soc 1972, 34(series B):187-220.
17. Hosmer DW Jr, Lemeshow S: Applied Survival Analysis: Regression Modeling of Time to Event Data.
18. Taylor JMG, Yu M: Bias and Efficiency Loss Due to Categorizing an Explanatory Variable, Journal of Multivariate Analysis. 2002, 83:248-263.
19. Hamell FE Jr, Lee KL, Mark DB: Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996, 15:361-387.
20. D’Agostino R, Nam BH: Evaluation of the performance of survival analysis models: discrimination and calibration measures. In: Handbook of Statistics. Amsterdam, The Netherlands: Elsevier, 2004, 1-25.
21. Antolins L, Nam BH, D’Agostino RB: Inference on correlated discrimination measures in survival analysis: a nonparametric approach. Commun Stat Theory Methods 2004, 33:2117-2139.
22. Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P: Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. American Journal of Epidemiology 2004, 159:882-890.
23. Greenland P, O'Malley PG. When is a new prediction marker useful? A consideration of lipoprotein-associated phospholipase A2 and C-reactive protein for stroke risk. Archives of Internal Medicine 2005, 165(21):2454-2456.
24. Ware JH. The limitations of risk factors as prognostic tools. New England Journal of Medicine 2006, 355:2615-2617.
25. Janes H, Pepe MS, Gu W. Assessing the value of risk predictions by using risk stratification tables. Annals of Internal Medicine 2008, 149(10):751-760.
26. Vickers AJ, Cronin AM. Traditional statistical methods for evaluating prediction models are uninformative as to clinical value: Towards a decision analytic framework. Seminars in Oncology 2010, 37(1):31-38.
27. Pencina MJ, D’Agostino RB Sr, D’Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008, 27:157-172.
28. Pencina MJ, D’Agostino RB Jr. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. Stat Med 2004, 23:2109-2123.
29. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001, 285:2486-2497.

doi:10.1186/1756-0500-4-39
Cite this article as: Mannan et al: Age at quitting smoking as a predictor of risk of cardiovascular disease incidence independent of smoking status, time since quitting and pack-years. BMC Research Notes 2011 4:39.