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Clinical research

Smoking decreases the duration of life lived with and without cardiovascular disease: a life course analysis of the Framingham Heart Study

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KEYWORDS
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Aims To compare the burden of cardiovascular disease in terms of lifetime risk and life years lived with disease between smokers and non-smokers.
Methods and results We constructed multi-state life tables describing transitions through various cardiovascular diseases for 4723 smokers and non-smokers observed during 20 biannual observations in the Original Framingham Heart Study. Non-smokers live 8.66 (95% CI 7.61–9.63) (men) and 7.59 (95% CI 6.33–8.92) (women) years longer than smokers and more years free of cardiovascular disease: 6.22 (95% CI 5.09–7.30) years for males and 4.93 (95% CI 3.54–6.29) for females. But non-smokers spend more years with cardiovascular disease over the life course: 2.43 (95% CI 1.72–3.16) years for males and 2.66 (95% CI 1.87–3.38) years for females. The risk of cardiovascular disease before age 70 is higher among smokers, but over the entire lifecourse male non-smokers have higher risks of coronary heart disease, myocardial infarction, stroke and congestive heart failure, and female non-smokers have higher risks of coronary heart disease and congestive heart failure.
Conclusion Smoking, by shortening life, decreases both the probability and duration of cardiovascular disease throughout the life course. Non-smokers live many years longer and longer free of cardiovascular disease than smokers, but at the end of their life non-smokers will have lived longer with cardiovascular disease.
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Introduction

The thesis of compression of morbidity, as put forward by Fries,[1] suggested that lifestyle modification may decrease morbidity. The main propositions of Fries were based on the observations that the length of life is limited and that chronic disease can be postponed. He pointed to the decline of tobacco consumption as an example. If incidence (inflow) decreases, and mortality (outflow) remains constant, the prevalence (stock) will decrease. Following this theory, an eradication of smoking would lead to a decrease in the societal burden of cardiovascular disease, a major smoking-related morbidity. However, while incidence of cardiovascular disease is less in non-smokers than smokers, so is the risk of mortality. As the risk of cardiovascular disease increases sharply with age, non-smokers, who are more likely than smokers to survive to older ages, may actually

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have a higher lifetime risk of experiencing cardiovascular disease, and may on an average live longer with cardiovascular disease.

A previous theoretical analysis did indeed suggest that smokers live longer with coronary heart disease than non-smokers.[2] However, this study, lacking observed transition rates by smoking status, had to make assumptions about both the increased risk of mortality after disease incidence among smokers and the age dependence of the relative risks associated with smoking.

The present study uses observed follow-up data to compare the cardiovascular life histories of smokers and non-smokers in the first 40 years of follow-up from the original Framingham Heart Study cohort. The question addressed is whether a non-smoking population would live less time with cardiovascular disease, given the competing forces of an increased risk of cardiovascular disease at each age and an increased risk of mortality in smokers.

Methods

We constructed multi-state life tables by estimating smoking, gender and age-specific transition rates from the first 20 biannual examinations from the original Framingham Heart Study cohort. This allows comparison of the life years lived with and without cardiovascular disease and lifetime risk of cardiovascular disease in the life table cohorts of smokers and non-smokers.

Data and definitions

The original Framingham Heart Study cohort consisted of 5209 respondents (45% male) from a random sample of adults aged 28–62 years residing in Framingham, MA, between 1948 and 1951. The participants were tracked by standardised biennial cardiovascular examination, daily surveillance of hospital admissions, death information and information from physicians and other sources outside the clinic, ensuring highly accurate follow-up of death and clinically presenting cardiovascular disease. In the Framingham Heart Study current smoking status (yes or no) was potentially recorded at all but 4 of the 20 biennial exams.

For the current study we used the data regarding age at onset of cardiovascular disease or death over forty years of follow-up (exam rounds 1–21) for the 4723 participants without cardiovascular disease at study entry and with smoking status recorded for at least two exams. Those with only one recorded measure of smoking because they died before the second exam were included.

Smoking status for each participant was allocated based on the current smoking status recorded at each available exam between study entry and death or study exit. We classified never-smokers as those with all available smoking records coded as a non-smoker and always-smokers as those with all available smoking records coded as a smoker. Ever-smokers were the rest of the participants, characterised by a mixture of smoking and non-smoking throughout the study. Of the 4723 respondents for whom smoking status was allocated, 13% had missing smoking status information at more than half of the rounds (excluding the four rounds with no information at all).

Hazard ratios

The risk relative to never-smokers for an event throughout the forty years of follow-up was calculated using Cox proportional hazards analysis. The events considered were death and onset of: all cardiovascular diseases (CVD); all coronary heart diseases; acute myocardial infarction; stroke; and congestive heart failure.[3,4] All coronary heart diseases include angina pectoris, coronary insufficiency, myocardial infarction and sudden death. All cardiovascular diseases include all coronary heart diseases, all cerebrovascular diseases (including stroke), intermittent claudication and congestive heart failure. Analyses were performed separately for each sex with adjustment for age at baseline or event, as relevant.

Multi-state life tables

Separate multi-state life tables were created to analyse annual transitions through each of the cardiovascular disease types described above. The basic multi-state life table structure has the state space {Healthy, history of CVD*, dead},[5] where each of the five life table models has CVD* represented by one of the specific CVD states (all cardiovascular diseases, all coronary heart diseases, acute myocardial infarction, stroke, or congestive heart failure). For example, in the life table for all CVDs, the possible transitions are, "no CVD" to "death", "no CVD" to "history of CVD", and "history of CVD" to "death".

For each single year of age, the observed transition rate is calculated by dividing the number of events by the corresponding risk period of exposure in each state. Each set of rates is calculated separately for male never-smokers, male always-smokers, female never-smokers and female always-smokers. For smoothing observed age-specific transition rates, we have applied Gompertz regression models.[6] In this model the transition rate only depends on age. By using observed transition rates, we could avoid making assumptions about the increased risk of mortality after disease incidence among smokers and about the age dependence of the relative risks associated with smoking.

For life table construction, the rates are converted to probabilities by assuming that within each single year age interval the hazard remains constant and taking into account the competition between risks.[7] Since for the CVD sub-types the number of incidence and mortality cases before age 50 was too small to start the life table, all life tables are constructed from age 50 and closed at age 90 using the Massachusetts life expectancy at age 90 for 1989–1991 (males 3.93 years and females 4.76 years).[8] The measures directly available from the multi-state life tables are life expectancy with and without disease and the lifetime risk of an event over a certain period (inclusive lifelong). Confidence intervals are derived using a non-parametric bootstrap procedure, based on 2000 replicates, in S-plus 2000 (MathSoft Inc., Washington, USA). We report the bootstrap bias-correct, adjusted 95% confidence intervals.[9]

Results

Of the 4723 participants included, 381 (18%) men were classified as never-smokers, 674 (33%) as always-smokers. One thousand, three hundred and eighty four1384 (52%) women were considered never-smokers and 448 (17%) as always-smokers. The remaining 1018 (49%) men

and 818 (31%) women were classified in the rest group of ever-smokers.

The risk of death or cardiovascular disease incidence was analysed for ever and always-smokers relative to never-smokers using proportional hazards regression. As expected, always-smokers were found to have increased risk of all cardiovascular disease sub-types examined, ranging from a hazard ratio of 1.29 [95% CI 1.04—1.60] for coronary heart disease (females) to 2.00 [95% CI 1.38—2.91 for stroke (males) (Table 1). Always-smokers also had a significantly higher risk of dying once they had cardiovascular disease compared to never-smokers (Table 2), ranging from 1.28 [95% CI 0.99—1.66] from myocardial infarction (males) to 2.23 [95% CI 1.85—2.68] from cardiovascular disease (females). The risk of death for non-cardiovascular disease was significantly higher compared to never-smokers (Table 2), that was a mixed group, including healthy people and people with cancer, and other diseases.

Except for stroke among male ever-smokers, ever smoking was not significantly associated with an increased risk of any of the cardiovascular disease sub-types examined. The increased risk of stroke, but not of other cardiovascular diseases, among male ever-smokers has to be explained by a low rate of stroke in the reference group, the never-smokers. Male never-smokers are a small group, as few males had never smoked. Ever-smokers, on the other hand, are a heterogeneous population, mixing different intensities of smoking, different durations since quitting and different reasons for quitting. At a certain age, disease and smoking history, surviving ever-smokers are selected by their lethal habit: this is the suggested reason why surviving ex-smokers have a better prognosis after coronary artery bypass than both smokers and never-smokers.[10] A similar explanation may hold for the better prognosis of ever-smokers after disease incidence in the Framingham Heart Study (table 2). However, any interpretation is bound to be speculative. To make comparisons between smokers and non-smokers, we choose the more homogeneous groups of never- and always-smokers for all further analyses.

The dynamics of differential incidence and mortality over increasing age cannot be determined intuitively. Therefore, the age-specific rates for each transition

Table 1 Risk of cardiovascular disease (including sudden death) by smoking status, relative to never-smokers (95% confidence intervals in parentheses)

	CVD	CHD	MI	CHF	Stroke	Total number
Male						
Never-smoker	1.00	1.00	1.00	1.00	1.00	381
Ever-smoker	1.10	0.98	0.98	1.03	1.45	1018
	(0.94—1.28)	(0.82—1.18)	(0.79—1.22)	(0.75—1.4)	(1.02—2.06)	
Always-smoker	1.65	1.41	1.38	1.65	2.00	674
	(1.40—1.94)	(1.17—1.70)	(1.09—1.75)	(1.19—2.29)	(1.38—2.91)	
Female						
Never-smoker	1.00	1.00	1.00	1.00	1.00	1384
Ever-smoker	1.01	0.96	1.17	1.24	1.04	818
	(0.88—1.15)	(0.81—1.15)	(0.91—1.51)	(0.96—1.59)	(0.81—1.33)	
Always-smoker	1.39	1.29	1.98	1.56	1.75	448
	(1.18—1.64)	(1.04—1.60)	(1.48—2.65)	(1.12—2.17)	(1.31—2.35)	

CVD, cardiovascular disease; CHD, coronary heart disease; MI, acute myocardial infarction; CHF, congestive heart failure.

Table 2 Risk of death (from given states) by smoking status, relative to never-smokers (95% confidence intervals in parentheses)

	Non-CVD	CVD	CHD	MI	CHF	Stroke
Male						
Never-smoker	1.00	1.00	1.00	1.00	1.00	1.00
Ever-smoker	0.92	0.81	0.78	0.71	1.14	1.07
	(0.71—1.21)	(0.68—0.98)	(0.63—0.96)	(0.55—0.91)	(0.81—1.60)	(0.72—1.58)
Always-smoker	2.51	1.62	1.55	1.28	1.64	2.00
	(1.93—3.27)	(1.34—1.95)	(1.26—1.91)	(0.99—1.66)	(1.15—2.34)	(1.32—3.02)
Female						
Never-smoker	1.00	1.00	1.00	1.00	1.00	1.00
Ever-smoker	1.05	0.94	1.05	1.20	1.01	0.92
	(0.86—1.29)	(0.79—1.12)	(0.84—1.31)	(0.88—1.65)	(0.76—1.34)	(068—1.25)
Always-smoker	2.31	2.23	2.13	1.96	1.48	2.08
	(1.86—2.87)	(1.85—2.68)	(1.67—2.72)	(1.40—2.75)	(1.05—2.10)	(1.49—2.90)

CVD, cardiovascular disease; CHD, coronary heart disease; MI, acute myocardial infarction; CHF, congestive heart failure.

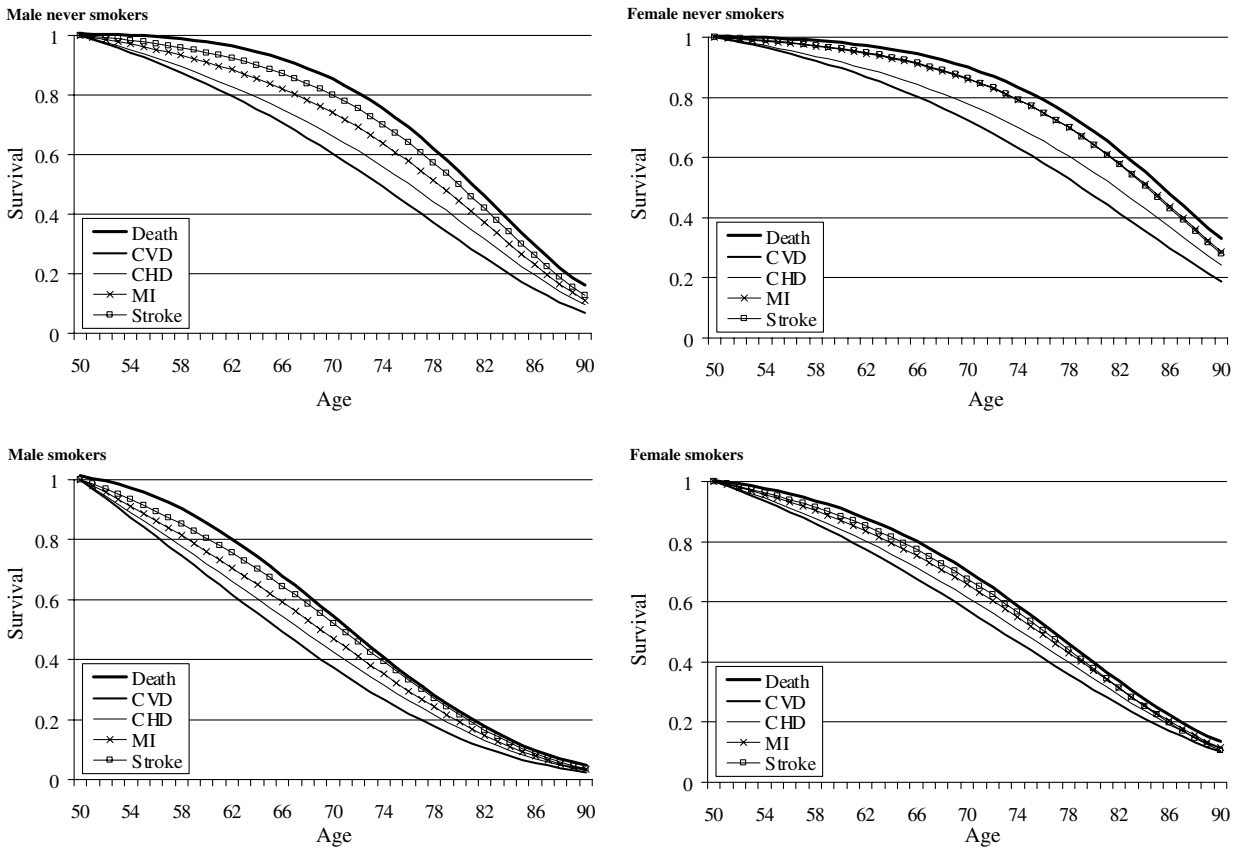

Fig. 1 Survival curves illustrating the probability of surviving and surviving free of cardiovascular disease (CVD), coronary heart disease (CHD), myocardial infarction (MI), or stroke with age.

were combined using multi-state life tables. Fig. 1 shows the survival free of cardiovascular disease, coronary heart disease, acute myocardial infarction, stroke or death of 50-year-old smokers and never-smokers. While never-smokers overall lead a longer life and survive longer free of cardiovascular disease than always smokers, they have a much larger gap between total survival and disease-free survival (i.e., survival with disease). The differences in mortality and incidence of cardiovascular disease between the different smoking groups lead to large differences in early mortality and morbidity. Among males 46% of always-smokers and 15% of never-smokers die before the age of 70. Among females, these figures are 30% of always-smokers but only 10% of never-smokers. While on an average six in 10 male never-smokers free of cardiovascular disease at age 50 will still be alive and free of cardiovascular disease twenty years later, only four in 10 always-smokers will remain in this state (Fig. 1). Of females free of cardiovascular disease at age 50, only 6 in 10 always smokers compared to 7 in 10 never-smokers will be alive and free of cardiovascular disease at age 70. As can be seen in Table 3, always smokers experience a significantly greater risk than never-smokers for developing every cardiovascular subtype examined before the age of 70. However, over a lifetime never-smokers have approximately the same risk of cardiovascular disease as always-smokers, because they live longer (Table 3). For males, while never-smokers tended to have a higher lifetime risk of any coronary heart disease, myocardial infarction, stroke and congestive heart failure than always-smokers, this was only statistically significant for myocardial infarction and coronary heart disease.

Concordant with the often higher lifetime risk of disease and the lower mortality rates post-disease, the duration of disease is generally longer among never-smokers (Table 4). Male never-smokers live 2.43 [95% CI 1.72—3.16] years longer with a history of cardiovascular disease, 2.01 [95% CI 1.43—2.66] years longer with a history of coronary heart disease, 1.13 [95% CI 0.60—1.68] years longer with a history of myocardial infarction, 0.68 [95% CI 0.33—0.96] years longer with a history of stroke and 0.39 [95% CI 0.13—0.65] years longer with heart failure. Female never-smokers live 2.66 [95% CI 1.87—3.38] years longer with a history of cardiovascular disease, 1.82 [95% CI 1.26—2.47] years longer with a history of coronary heart disease and 0.49 [95% CI 0.11—0.83] years longer with a history of stroke, but show no significant difference in time spent with a history of myocardial infarction or heart failure. Importantly, the life years lost to cardiovascular disease for never-smokers fall predominantly late in life, with always-smokers living more years with cardiovascular disease throughout middle age (Fig. 2). Non-smokers live

Table 3 Risk of developing cardiovascular disease before age 70 or death (Ninety five percent confidence intervals are presented in parentheses)

	CVD	CHD	MI	CHF	Stroke
Before age 70					
Males					
Never-smoker	34.12% (31.93–36.67)	26.17% (24.16–28.18)	15.37% (13.77–17.26)	5.78% (4.68–6.86)	5.70% (4.68–6.88)
Always-smoker	46.27% (42.64–49.97)	33.32% (29.72–36.22)	19.83% (16.95–23.00)	9.61% (7.72–11.89)	7.89% (6.15–10.13)
Difference (never – always)	−12.15% (−16.76–7.92)	−7.16% (−10.54–2.90)	−4.46% (−8.04 −0.90)	−3.83% (−6.48–1.63)	−2.19% (−4.67–0.11)
Females					
Never-smoker	21.99% (20.33–23.70)	14.62% (13.23–15.87)	4.76% (3.95–5.59)	3.92% (3.22–4.69)	4.19% (3.51–5.03)
Always-smoker	25.90% (22.52–29.93)	16.81% (13.93–19.88)	8.62% (6.50–11.25)	5.49% (3.79–7.67)	6.06% (4.39–8.44)
Difference (never – always)	−3.91% (−8.15–0.03)	−2.18% (−5.43–1.11)	−3.86% (−6.62–1.59)	−1.57% (−3.89–0.31)	−1.87% (−4.25–0.04)
Before death					
Males					
Never-smoker	67.53% (64.46–70.41)	50.78% (47.56–53.33)	35.27% (32.33–38.26)	20.32% (17.74–23.09)	18.88% (16.33–21.37)
Always-smoker	65.97% (62.04–69.47)	46.48% (42.36–49.54)	28.55% (24.99–32.45)	16.71% (14.05–19.94)	14.90% (12.22–18.28)
Difference (never – always)	1.56% (−2.98–6.58)	4.30% (0.02–9.26)	6.72% (1.83–11.16)	3.62% (−0.30–7.82)	3.98% (−0.59–7.45)
Females					
Never-smoker	56.37% (53.87–58.85)	33.88% (31.5–35.8)	17.06% (15.28–19.16)	17.75% (15.65–19.88)	19.08% (16.98–21.21)
Always-smoker	54.80% (48.42–60.1)	31.04% (25.98–35.55)	19.55% (14.98–24.02)	15.82% (11.71–20.59)	19.03% (14.25–23.87)
Difference (never – always)	1.57% (−4.43–8.27)	2.84% (−2.08–8.49)	−2.49% (−7.37–2.37)	1.93% (−2.98–6.56)	0.01% (−5.27–5.28)

CVD, cardiovascular disease; CHD, coronary heart disease; MI, acute myocardial infarction; CHF, congestive heart failure.

Table 4 The burden of cardiovascular disease in always-smokers versus never-smokers free of any cardiovascular disease at age 50 (Ninety five percent confidence intervals are presented in parentheses)

	CVD	CHD	MI	Stroke	CHF	Total LE
Males						
Never-smokers	7.25 (6.77–7.81)	5.36 (4.92–5.75)	3.20 (2.85–3.58)	1.33 (1.10–1.57)	1.00 (0.82–1.19)	30.42 (29.79–30.92)
Always-smokers	4.81 (4.34–5.35)	3.34 (2.87–3.75)	2.07 (1.73–2.51)	0.64 (0.49–0.90)	0.61 (0.46–0.78)	21.77 (20.96–22.66)
Difference (never – always)	2.43 (1.72–3.16)	2.01 (1.43–2.66)	1.13 (0.60–1.68)	0.68 (0.33–0.96)	0.39 (0.13–0.65)	8.66 (7.61– 9.63)
Females						
Never-smokers	6.23 (5.83–6.68)	4.05 (3.71–4.41)	1.30 (1.12–1.51)	1.36 (1.18–1.60)	1.06 (0.90–1.23)	34.14 (33.68–34.63)
Always-smokers	3.57 (3.04–4.34)	2.23 (1.74–2.76)	1.07 (0.78–1.49)	0.87 (0.59–1.20)	0.71 (0.48–1.27)	26.55 (25.35–27.69)
Difference (never – always)	2.66 (1.87-3.38)	1.82 (1.26–2.47)	0.23 (−0.17–0.61)	0.49 (0.11–0.83)	0.35 (−0.19–0.63)	7.59 (6.33– 8.92)

Life years lived with a history of cardiovascular disease. CVD, cardiovascular disease; CHD, coronary heart disease; MI, acute myocardial infarction; CHF, congestive heart failure; LE, life expectancy.

longer with cardiovascular disease, but predominantly at older ages.

Most impressive is the change in life expectancy free of any cardiovascular disease: 50-year-old always-smokers live 5–6 years less free of cardiovascular disease than never-smokers (men 6.22 [95% CI 5.09–7.30] years and women 4.93 [95% CI 3.54–6.29] years). Both male and female always-smokers live significantly less years free

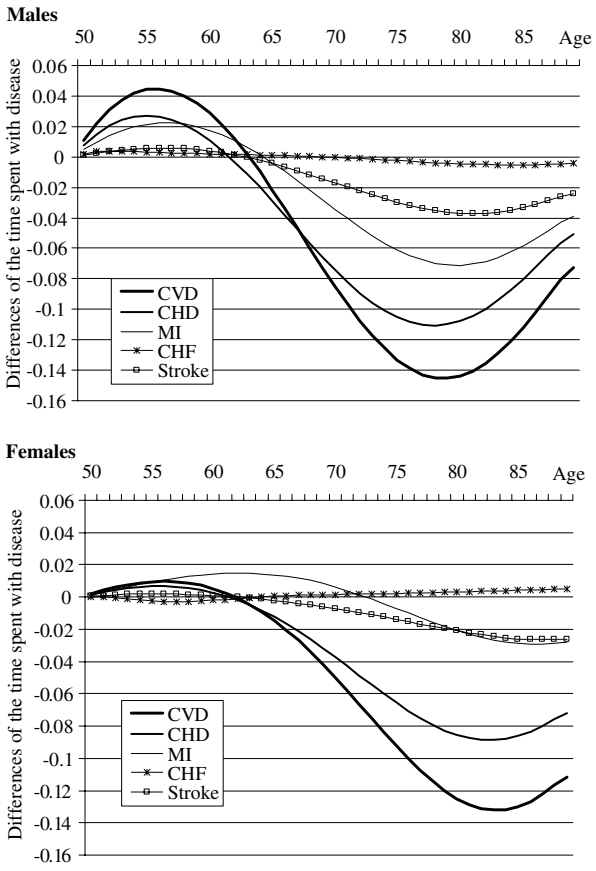

Fig. 2 Difference in life years lived with cardiovascular disease (CVD), coronary heart disease (CHD), myocardial infarction (MI), stroke, or congestive heart failure (CHF), by age (smokers—never-smokers).

of myocardial infarction, stroke and congestive heart failure than never-smokers. The combination of the extra years lived with and without cardiovascular disease leads to a difference in total life expectancy from age 50 between never-smokers and always-smokers of around 8 years (men 8.66 [95% CI 7.61—9.63] and women 7.59 [95% CI 6.32—8.92], Table 4).

Discussion

This paper shows the cardiovascular life course of the Framingham Heart Study cohort by smoking status. Smoking both shortens the duration of life free of cardiovascular disease and the duration of life with cardiovascular disease. Over a life course, never-smokers live longer with cardiovascular disease and its manifestations such as cerebrovascular and coronary disease. We find that male and female never-smokers live 2.43 and 2.66 years, respectively, more with a history of cardiovascular disease than always-smokers. Importantly, never-smokers also live more years free of cardiovascular disease: 6.22 years for males and 4.93 years for females. We demonstrate that this is the result of a combination of (i) the increased rate of cardiovascular disease, (ii) the increased rate of mortality from the cardiovascular disease state and and (iii) the higher rate of mortality from the non-cardiovascular disease state associated with smoking at each age.

While the increased incidence and mortality rates together lead to less years lived with each form of cardiovascular disease for always-smokers throughout the life course, this is a combination of more years lived with disease at younger ages and less at older ages. Similarly, the risk of incident cardiovascular disease before age 70 was consistently greater for always-smokers, in both males and females. Six out of 10 never smoking males and seven out of 10 never-smoking females could expect to reach age 70 alive and free of any cardiovascular disease. This was strikingly less for smokers: four out of 10 males and six out of 10 females. For a cohort followed up from age 40, the main results are comparable to a cohort starting at age 50 (data not shown).

The main power of this study is in the Framingham Heart Study, giving us 40 years of follow-up of a single cohort. All transition rates are estimated from this study and treated with the time-honoured methods of the multi-state life-table.[7,11] Such life-tables are intuitively simple and appealing because they transparently describe the disease epidemiology as a life course. But, as discussed previously,[5] the transition rates at every age are the result of a mixture of both the broad age range at entry and the long follow-up, and they may come from very different periods. However, as long as the dynamics between "always-smokers" and "never-smokers" are not very different in these periods, this should not bias the results presented here.

Correct estimation of the transition rates is crucial. By estimating separate transition rates for never-smokers and always-smokers, we were able to take into account the increased risk of mortality after disease incidence among smokers and the age-dependence of the relative risks associated with smoking. Testing the modifying effect of potential confounders, such as obesity, blood pressure and cholesterol level, increased the numbers of missing values, and selected a healthier sub-group with more complete observations. As this may introduce selection bias, we presented the outcomes without further adjustment.

Here, we have chosen our case definitions to maximise transparency, power and homogeneity. If, instead, one uses smoking as a time varying co-variate, the same individual is able to participate in both cohorts, non-smoking and smoking. However, timing of incidence and mortality after starting and quitting smoking is different, which makes interpretation of the so constructed synthetic cohorts difficult. Smoking status at baseline yields cohorts which are too heterogeneous, including future quitters as smokers and re-starters as non-smokers. We therefore described the life course for "always-smokers" and "never-smokers", defined as smoking or non-smoking for 100% of the recorded exams in the Framingham cohort. This may only underestimate the effect of long-term smoking as smokers who acquire disease may be more likely to quit.

The findings describe cohorts of smokers and non-smokers that may differ in more characteristics than measured and accounted for. In recent periods, more smokers are of lower socio-economic class than non-smokers.[12] However, this socio-economic gradient changed over time. In the first Cancer Prevention Study (ACS-CPSI), recruited in 1959, smokers attained higher levels of education than non-smokers.[12] This holds also for the Original Framingham Heart Cohort (data on file). From a pragmatic viewpoint, it is hard to imagine which determinants, unknown and differentially distributed among smokers and non-smokers, would be sufficiently important to bias the transition rates changing the described findings.

The life course analysis translates transition rates into dwelling times and gives more transparent information about the consequences of risk. The risks of smoking translate into the loss of 8.66 (men) and 7.59 (women) life years. This is in the same order of magnitude as many other studies,[13–15], but this study adds the consequences of smoking for cardiovascular disease in terms of incidence and duration throughout the life course. Male never-smokers have a greater lifetime risk of all forms of cardiovascular disease, including those considered most severe such as congestive heart failure and stroke. However, female never-smokers show no difference in the lifetime risk of myocardial infarction, congestive heart failure or stroke compared to always smokers. The additional cardiovascular disease events occur at the oldest old ages, when most smokers already have died. The risk of incident cardiovascular disease before age 70 was consistently greater for always-smokers than for never-smokers.

It appears that in smokers the higher outflow through mortality more than compensates the higher inflow through cardiovascular disease incidence: smoking leads to a shorter life expectancy with cardiovascular disease by increasing mortality from all causes. Smoking may differ from other common cardiovascular risk factors in this respect. While factors such as hypertension and hypercholesterolaemia increase mortality primarily through their increased risk of cardiovascular disease, smoking also increases the risk of non-cardiovascular death. In contrast to smoking, modification of these risk factors may lead to a compression of cardiovascular disease.

The large gains illustrated here in life expectancy and life expectancy free of cardiovascular disease in a non-smoking population should provide further support for strong anti-smoking measures. But this paper shows that public policy should not conclude simplistically that morbidity will decrease if people stop smoking. Incidence of cardiovascular morbidity will be postponed, years lived free of cardiovascular disease will be gained, but incidence as well as the life years lived with cardiovascular disease will be increased in the older population of never-smokers.

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