Health consequences of sustained smoking cessation

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ABSTRACT
Objectives: To estimate the risk of dying from all causes and from specified smoking-related diseases in people who were ex-smokers at two consecutive examinations, compared with never smokers and with people who were ex-smokers at the first examination but who had resumed smoking at the following examination.
Design: A prospective cohort study.
Setting: Three counties in Norway.
Participants: A total of 23 560 men and 25 122 women, aged 20–49, screened for cardiovascular disease risk factors in the mid 1970s, rescreened after 3–13 years and followed throughout 2005 participated in this study.
Outcomes: Absolute mortality and relative risks adjusted for confounding variables, of dying from all causes, cardiovascular disease, ischaemic heart disease, stroke, lung cancer and other smoking-related cancer.
Results: With sustained never smokers as reference, the sustained ex-smokers had adjusted relative risk (95% CI), of dying from any cause, for men 0.97 (0.80 to 1.18), for women 0.98 (0.65 to 1.48). Corresponding risk for ex-smokers who resumed smoking was for men 1.59 (1.32 to 1.91), for women 1.40 (1.08 to 1.81). For the specified smoking-related diseases, the risk in sustained ex-smokers was not significantly different from the risk in sustained never-smokers, except for lung cancer in men. For ex-smokers who resumed smoking, the corresponding risk was on the whole significantly higher.
Conclusions: A more valid and favourable picture of ex-smokers' risk will be obtained if exposure is being based upon people with two consecutive examinations, years apart. The study confirms clearly the large health benefit of quitting smoking for good.

Have the health benefits of smoking cessation been underestimated?

In the beginning of the 1960s, the well known reports by the Royal College of Physicians of London and by the Advisory Committee to the US Surgeon General established that cessation of smoking leads to lower mortality of serious smoking related diseases.[1][2] This conclusion was in particular based upon results from 4–5 prospective cohort studies. According to the US report these study populations (only men) had been followed for 22 to 120 months. The British report concluded that "… the risk (of lung cancer) among those who have given up smoking is less than among those who continue to smoke", and "… there is a substantial reduction in mortality from coronary heart disease in those who give up smoking". The US report concluded that "… cigarette smokers who had stopped smoking prior to enrolment in the study had (total) mortality ratios about 1.4 as against 1.7 for current cigarette smokers".

Since then, numerous cohort studies reports have given more optimistic conclusions on the benefits of smoking cessation. The 1990 report from the US Surgeon General concentrated on health benefits of smoking cessation, and concluded that "after 10 to 15 years of abstinence, risk of all-cause mortality (among former smokers) returns nearly to that of persons who never smoked".[3] After 40 years' observation in the British Doctors Study it was found that "…those who stopped smoking before middle age subsequently avoided almost all of the excess risk that they otherwise have suffered".[4] Nevertheless, in a recent report from the Nurses' Health Study in the US, based on 121 519 female participants who were followed for 24 years, past smokers were still found to have a total mortality risk significantly above the risk of never smokers. Adjusted for a series of confounding variables, the risk, relative to never smokers, was 1.39 (95% CI 1.33 to 1.45).[5]

Most of the prospective cohort analyses have been based on one survey only. People's smoking habits, however, change considerably over time, as has been shown from regular surveys of representative samples of the adult population of Norway.[6] It is a general experience that many ex-smokers resume smoking after some time, and thereby may worsen the follow-up results for the total group of ex-smokers registered at baseline. Therefore, if we separate out a group who were ex-smokers at two surveys, years apart, it is more likely that we will have people whose habits are more stable throughout the whole follow-up period. This approach has been used in Danish and Swedish studies.[7][8]

The present study is based upon smoking habits registered at two or three surveys. The aim was to determine the risk in sustained ex-smokers, compared with sustained never smokers and sustained smokers. We also examine the risk in participants who changed their smoking behaviour between two screenings. The report includes a population of 48 682 men and women, aged 20–49 years, living in three Norwegian counties. They were surveyed in the mid-1970s for cardiovascular disease risk factors and were screened again during the next 3–13 years at least once. These people have been followed throughout 2005 for deaths from serious smoking-related diseases and from all causes. The mean observation period is 23 years, maximum 29 years, counting from the time of the last screening. A subgroup attended three screenings. This gave us the opportunity to check further changes of the participants' smoking habits.

METHODS
The study population and data collection have been described previously[9][10] and will be repeated briefly below.

Initial screening
Between 1974 and 1978, screening examinations for cardiovascular disease were undertaken in three

Norwegian counties with a mainly rural settlement (Finnmark, Sogn og Fjordane, Oppland). All male and female residents aged 35–49 years were invited, as well as a 10% random sample of residents aged 20–34. The attendance was 88%.[11]

An identical protocol was applied for the screening program in the three counties concerned. It included a questionnaire related to well known risk factors of cardiovascular disease. Height, weight and blood pressure were measured, and a non-fasting blood sample was drawn and serum analysed at the same laboratory for total cholesterol, triglycerides and glucose. Details on the first screening have been published previously.[12]

Extensive reports on this study population with relevance to smoking and mortality after 13 and 26 years of observation have been published previously.[13] [14] Two other reports compiled after 25 and 27 years of observation have been issued, concentrating on risk in persons smoking 1–4 cigarettes per day and on risk in heavy smokers who reduced their daily consumption by more than 50%.[9] [10]

Second and third screening

In one county, Finnmark, two new screenings were conducted after 3 and 13 years. In the two other counties (75% of the total study population), the rescreenings were carried out 5 and 10 years after the initial screening.[15–17]

At the second screening, all those invited to the initial screening were reinvited, and in addition, a 9% random sample of people aged 20–34 years who were not invited to the first examination. The attendance was 88%.[18]

At the third screening, minor modifications were made in the eligibility to the examinations; the main core of participants in the previous rounds, however, were reinvited. Owing to capacity constraints, only a 10% random sample of the cohort aged 40–49 years at the first screening was invited. The attendance was 84%.[16] [19] [20]

The most important elements of the screening programme were kept unchanged throughout all screenings; in particular that part of the questionnaire covering smoking habits.

The study population

For each individual who underwent two or more examinations, paired results were selected according to the following priority, on the basis of attendance to first and second screening (n = 51 952), second and third screening (n = 7061) and first and third screening (n = 1463).

Consequently, there was a total of 60 476 people (30 318 men and 30 158 women) who had results from two examinations.

The follow-up period started from the last examination.

Exclusions

We excluded the following people: men and women who at the last examination reported a history of myocardial infarction, angina pectoris, stroke, diabetes, atherosclerosis of legs, treatment for hypertension, use of glycerine trinitrate and symptoms indicative of angina pectoris or atherosclerosis obliterans, totalling 7335 people. They were excluded to avoid the problem of reverse causality that might occur if people changed smoking habits owing to illness. Also excluded were pipe/cigar smokers and persons with smoking history that was incomplete or did not fulfil the definitions of the categories applied in the study (altogether 4457 people).

Hence, 48 682 people (23 560 men and 25 122 women) remained as participants for analysis. All of them underwent two examinations, and at the time of the last investigation they reported neither a history related to cardiovascular disease or diabetes or symptoms indicative of angina pectoris or atherosclerosis obliterans. They were present or previous daily cigarette smokers, or had never smoked cigarettes daily. For a negligible number of participants, information was missing on some of the confounding variables.

Questions about smoking behaviour

The attending present and former smokers reported the actual number of cigarettes smoked per day in a special box in the questionnaire. Here, they were allowed to cite a range, such as 10–15 cigarettes.

People who stated that they did not smoke cigarettes at present, were asked if they had smoked cigarettes daily before, and if so, how long time had elapsed since they stopped. Here, four alternatives were given, ranging from less than 3 months to more than 5 years.

At the examination site, the nurses carefully checked through the questionnaire with the participants. Factory made and hand-rolled cigarettes had to be counted together. The nurses were instructed that 1 pack of tobacco for hand rolling (50 g) equalled 50 cigarettes. For those who gave a range of consumption, we used the highest figure. In another box in the questionnaire, those who smoked or had smoked previously reported how many years altogether they had smoked daily.

Categories of participants

In this report we applied the following categories:
▶ Sustained never smokers: people who at both examinations stated that they did not smoke daily, and at the first examination said that they had never smoked previously.
▶ "Starters": people who at the first examination stated that they did not smoke daily and had never done so previously, but at the last examination said that they smoked daily.
▶ Sustained ex-smokers: people who at both examinations stated that they did not smoke daily, but had done so previously, regardless of daily cigarette consumption. At the second examination, the time elapsed since they quit smoking had to be longer than the interval between the two examinations.
▶ "Resumers": people who at the first examination stated that they did not smoke daily, and that they had done so previously, but at the last examination stated that they smoked daily.
▶ Sustained smokers: people who at both examinations stated that they smoked daily, regardless of daily consumption.
▶ "Quitters": people who at the first examination stated that they smoked daily, but at the last examination stated that they did not smoke daily.

Determination of serum thiocyanate

In 1976, determination of serum thiocyanate was introduced at the initial screening in one of the counties.

Methods and quality assurance have been described by Foss and Lund-Larsen, who has also reported the results from the initial survey.[21] Tobacco smoke contains hydrogen cyanide, which is absorbed in the lungs and then metabolised to thiocyanate. Due to its long half-life, serum thiocyanate has the advantage that it better reflects the average exposure to tobacco smoke during the previous couple of weeks, than the exposure on a given day. The authors underline, however, that diet also contributes to the level of thiocyanate in serum and, therefore, that this level is not a specific indicator for tobacco

smoking. A single determination can neither confirm nor weaken a statement on present individual tobacco consumption.

Analyses of serum thiocyanate in large population groups, however, will give valuable information on the group's tobacco consumption. This is demonstrated by results from the initial screening, which show a remarkable dose response relationship between mean serum thiocyanate concentration and mean cigarette consumption of the group, based on questionnaire answers of the individuals.[21]

At the second screening, thiocyanate determinations were carried out only in Finnmark county; therefore we have information on serum thiocyanate for no more than 4787 men and 4654 women (ie, 19% of the total number of the participants).

Endpoints

We carried out a mortality follow-up by linking our records with the National Register of Causes of Death, using the 11 digit personal identification number as record linkage. Each person accrued person years from the day of the last examination until date of death, date of emigration or 31 December 2005.

In addition to deaths from all causes, we studied deaths from the following:

▶ Cardiovascular disease: International Classification of Diseases (ICD), eighth edition: 390–444.1, 444.3–458; ICD-9: 390–459; ICD-10: I00–I99.
▶ Ischaemic heart disease: ICD-8 and ICD-9: 410–414; ICD-10: I20–I25.
▶ Stroke: ICD-8 and ICD-9: 430–438; ICD-10: I60–I69.
▶ Lung cancer: ICD-8 and ICD-9: 161–162; ICD-10: C32–C34.
▶ Other smoking-related cancer: types of cancer that the International Agency for Research on Cancer has classed as liable to be caused by smoking, and later applied by Doll et al.[22 23] Thus, the following types of cancer were included:
  – lip, oral cavity and pharynx: ICD-8 and ICD-9: 140–149; ICD-10: C00–C14
  – nose and nasal sinuses: ICD-8 and ICD-9: 160; ICD-10: C30–C31
  – oesophagus: ICD-8 and ICD-9: 150; ICD-10: C15
  – stomach: ICD-8 and ICD-9: 151; ICD-10: C16
  – pancreas: ICD-8 and ICD-9: 157; ICD-10: C25
  – liver: ICD-8: 155, 197.8; ICD-9: 155; ICD-10: C22
  – kidney and renal pelvis: ICD-8 and ICD-9: 189.0–1; ICD-10: C64–C65
  – bladder and ureter: ICD-8 and ICD-9: 188; ICD-10: C66–C67
  – myeloid leukaemia: ICD-8 and ICD-9: 205; ICD-10: C92.

Statistical methods

Comparisons of baseline factors between sustained ex-smokers and sustained never smokers were made by Student t test or the χ^2 test.

Relative risks (hazard ratios) were estimated by the Cox proportional hazards model with person years as the time variable. We assessed the proportional hazards assumption by the test based on Schoenfeld residuals. This was performed separately for men and women and for all endpoints. The null hypothesis of proportional hazards was not rejected except for women with total death as endpoint. Visual inspection of the hazard curves revealed that the hazard for the sustained ex-smokers was somewhat higher during the first 7 years of follow-up, compared with the hazard for the other smoking groups, which ran in parallel on the log scale. We partitioned the time axis in two: <7 and ≥7 years and estimated the relative risk in each interval.

Two adjustments were made: for age only, and for age, systolic blood pressure, total serum cholesterol, serum triglycerides, physical activity during leisure, height, body mass index, disability pension, sickness leave and family history of coronary heart disease recorded at the last examination. Additionally, we produced Nelson–Aalen plots of the cumulative mortality rate vs person years. Values of p<0.05 were considered significant.

RESULTS

Table 1 shows baseline characteristics of the participants at the start of follow-up.

In men, sustained ex-smokers had significantly higher mean values for age, systolic and diastolic blood pressure, total serum cholesterol, serum triglycerides and body mass index than had the never smokers, while the sustained ex-smokers had significantly lower physical activity during leisure. In women, the sustained ex-smokers had significantly lower mean values for age, systolic and diastolic blood pressure and body mass index than had the never smokers, whereas there were no significant differences in total serum cholesterol, serum triglycerides and physical activity during leisure. For both sexes, frequencies of disability pension were lower in the sustained ex-smokers than in the never smokers, while the opposite was the case for frequencies of sick leave.

Compared with the sustained never smokers, female sustained ex-smokers had a significantly higher frequency of coronary heart disease in their families; while in men, there was no significant difference between these categories.

Comparing the categories, sustained smokers of both sexes have the highest mean values for total serum cholesterol and sick leave; and the lowest mean values for physical activity during leisure and body mass index. Further, they have higher daily cigarette consumption and a longer duration of smoking than have the other categories with present or past cigarette smoking, with the exception of cigarette consumption in male "quitters".

It may be added that 2.1% of the categories with daily smokers at the last examination, smoked a pipe, either exclusively, or in combination with cigarettes. More specifically, this was the case for 0.6% of the "starters", 1.6% of the "resumers" and 2.2% of the sustained smokers.

Table 2 presents mean serum thiocyanate at the last examination in Finnmark County.

For both sexes, all categories with smokers at the last examination (sustained smokers, "starters" and "resumers") had clearly higher mean values of serum thiocyanate than had categories with non-smokers (sustained never smokers, sustained ex-smokers and "quitters"). In men, there was no significant difference between sustained ex-smokers and sustained never smokers, while female sustained ex-smokers had significantly higher mean serum thiocyanate than sustained never smokers.

Table 3 shows deaths from all causes and from selected smoking related causes, by sex and smoking category, number and per 100 000 person years.

For both sexes and for all death causes, a similar pattern is found: sustained smokers have by far the highest mortality, and sustained never smokers the lowest. In women, sustained ex-smokers have an even lower death rate than the sustained never

Table 1 Background characteristics at the last examination of participants*, by category of smoking

	Sustained never smokers	"Starters"	Sustained ex-smokers	"Resumers"	Sustained smokers	"Quitters"	p Value†
Men (n = 23 560):							
Age (years)	43.6 (6.8)	39.5 (9.1)	46.3 (6.0)	43.8 (7.3)	44.1 (7.4)	43.9 (7.5)	<0.001
Cigarette consumption (no. per day)	–	8.1 (4.7)	13.8 (8.1)	11.7 (6.1)	14.1 (6.4)	15.0 (8.0)	–
Duration of smoking (years)	–	9.1 (7.6)	13.8 (6.8)	19.4 (8.8)	24.2 (7.9)	20.3 (8.4)	–
Systolic BP (mmHg)	135.5 (17.9)	133.3 (16.7)	136.9 (16.9)	135.2 (17.0)	135.6 (17.3)	137.2 (17.5)	<0.001
Diastolic BP (mmHg)	85.2 (10.9)	82.6 (10.9)	87.3 (11.0)	84.9 (11.4)	84.6 (11.2)	86.1 (11.8)	<0.001
Total serum cholesterol (mmol/litre)	5.98 (1.17)	5.74 (1.17)	6.16 (1.18)	6.14 (1.26)	6.30 (1.24)	6.22 (1.24)	<0.001
Serum triglycerides (mmol/litre)	1.95 (1.01)	1.80 (1.34)	2.10 (1.25)	2.03 (1.15)	2.06 (1.20)	2.13 (1.25)	<0.001
Physical activity leisure‡	2.32 (0.65)	2.28 (0.70)	2.28 (0.68)	2.18 (0.66)	2.10 (0.65)	2.20 (0.67)	0.005
BMI (kg/m²)	25.3 (3.9)	24.9 (4.0)	25.9 (3.3)	25.2 (3.5)	24.8 (3.6)	26.0 (3.6)	<0.001
Height (cm)	176.3 (9.0)	177.0 (9.7)	176.1 (8.6)	176.3 (9.0)	175.2 (8.9)	175.6 (9.0)	0.142
Disability pension (%)	3.3 (2.1)	3.3 (2.3)	2.4 (1.8)	1.9 (1.7)	4.1 (2.3)	2.6 (2.2)	0.008
Sick leave (%)	2.0 (1.7)	7.0 (2.1)	3.0 (1.9)	4.0 (2.0)	5.0 (2.2)	4.0 (2.2)	<0.001
Family history of CHD (%)§	25.5 (4.6)	23.6 (4.6)	30.3 (4.7)	34.4 (4.7)	28.3 (4.7)	26.7 (4.6)	0.066
Women (n = 25 122):							
Age (years)	45.3 (6.6)	43.1 (8.5)	44.9 (6.4)	42.5 (7.6)	43.5 (7.6)	42.5 (8.0)	0.004
Cigarette consumption (no. per day)	–	5.8 (3.7)	8.6 (5.2)	8.8 (4.8)	10.8 (5.1)	9.9 (5.6)	–
Duration of smoking (years)	–	7.1 (6.8)	10.0 (5.8)	14.4 (7.9)	19.8 (7.3)	15.2 (7.5)	–
Systolic BP (mmHg)	132.2 (18.1)	128.9 (16.3)	129.5 (16.1)	127.1 (17.3)	128.7 (17.2)	128.8 (16.9)	<0.001
Diastolic BP (mmHg)	82.6 (10.3)	80.1 (10.1)	81.8 (10.0)	79.2 (10.7)	80.5 (10.5)	80.4 (10.7)	0.001
Total serum cholesterol (mmol/litre)	6.09 (1.16)	5.97 (1.18)	6.05 (1.23)	5.98 (1.23)	6.25 (1.26)	6.06 (1.27)	0.141
Serum triglycerides (mmol/litre)	1.34 (0.73)	1.55 (1.22)	1.32 (0.81)	1.38 (0.71)	1.52 (0.90)	1.42 (0.80)	0.258
Physical activity leisure‡	2.01 (0.57)	1.92 (0.61)	2.03 (0.56)	1.98 (0.56)	1.93 (0.57)	1.96 (0.55)	0.099
BMI (kg/m²)	25.0 (4.0)	24.9 (4.0)	24.6 (3.6)	23.8 (3.5)	23.7 (3.7)	25.0 (4.1)	<0.001
Height (cm)	162.8 (6.1)	162.5 (6.6)	163.7 (5.9)	163.4 (5.7)	162.9 (6.0)	162.8 (6.2)	<0.001
Disability pension (%)	4.0 (2.0)	5.7 (2.3)	2.3 (1.5)	3.2 (1.8)	4.6 (2.1)	3.7 (1.9)	<0.001
Sick leave (%)	2.8 (1.6)	1.4 (1.2)	3.8 (1.9)	4.3 (2.0)	5.2 (2.2)	3.9 (1.9)	0.003
Family history of CHD (%)§	29.9 (4.6)	31.9 (4.7)	33.2 (4.7)	31.8 (4.7)	32.8 (4.7)	30.9 4.6)	0.014

Values are mean (SD) or % (SD).

*Participants not reporting cardiovascular disease, diabetes or treatment for hypertension, or symptoms of angina pectoris or atherosclerosis obliterans; †p values represent differences between the sustained ex-smokers and the sustained never smokers; ‡physical activity during leisure was graded 1–4, with 4 denoting the heaviest activity; §One or more of parents or siblings reported to have had a heart infarction or angina pectoris.

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease.

smokers from any cause and from specific diseases, with the exception of lung cancer. In men, all mortality figures for sustained ex-smokers are slightly higher than for the never smokers. In general, "resumers" and "quitters" have mortality rates that are higher than in sustained ex-smokers, but lower than in sustained smokers. For both sexes, "starters" have higher total mortality than never smokers. In men, their total mortality is lower than in sustained ex-smokers, while the reverse is the case in women.

A separate analysis has been carried out for people who at both examinations stated that they had been ex-smokers for more than 5 years. Details are not given here, but their total and cause-specific mortality did not differ substantially from people in the total category of sustained ex-smokers.

It is noted that of the ex-smokers at the first examination, 17.0% of the men and 26.7% of the women had resumed smoking at the last examination. Of the never smokers at the first examination, 1.9% of the men and 1.7% of the women had started to smoke at the last examination. In contrast, of the daily smokers at the first examination, 17.4% of the men and 13.4% of the women, had quit smoking at the last examination.

We have traced 30 431 participants at the last examination, who also turned up for a third screening. Their smoking behaviour at that time is shown in table 4, by category at the second examination and sex.

Very few of the sustained never smokers and the sustained ex-smokers had started to smoke at the third examination, while 14% of the male and 10% of the female sustained smokers

Table 2 Determination of serum thiocyanate at the last examination, by category of smoking

	Sustained never smokers	"Starters"	Sustained ex-smokers	"Resumers"	Sustained smokers	"Quitters"	p Value† (two-sided)
Men (n = 4787):*							
Number of participants	814	16	569	163	2688	537	
Mean (SD) serum thiocyanate (μmol/litre)	26.2 (11.5)	41.4 (15.6)	25.4 (13.0)	56.9 (22.0)	65.6 (22.8)	27.0 (14.3)	0.25
Women (n = 4654):*							
Number of participants	1819	34	297	130	2046	328	
Mean (SD) serum thiocyanate (μmol/litre)	26.7 (11.6)	45.0 (19.4)	29.1 (14.2)	61.7 (28.4)	74.5 (25.8)	33.0 (17.9)	0.001

*Participants not reporting cardiovascular disease, diabetes or treatment for hypertension, or symptoms of angina pectoris or atherosclerosis obliterans; †p values represent differences between the sustained ex-smokers and the sustained never smokers.

Table 3 Number of participants and person years; and deaths from all causes, cardiovascular disease, ischaemic heart disease, stroke, lung cancer or other smoking-related cancer, number and per 100 000 person years, by sex and smoking category*

	Sustained never smokers	"Starters"	Sustained ex-smokers	"Resumers"	Sustained smokers	"Quitters"
Men (n = 23 560)						
Participants (n)	6246	123	3838	787	10 380	2186
Number of person years	144 668	2735	88 805	17 662	227 114	50 570
All causes:						
Deaths	725	15	596	139	3133	394
Deaths per 100 000 person years	501	549	671	787	1379	779
Cardiovascular disease:						
Deaths	249	6	198	60	1233	154
Deaths per 100 000 person years	172	219	223	340	543	305
Ischaemic heart disease:						
Deaths	159	6	128	40	855	101
Deaths per 100 000 person years	110	219	144	226	376	200
Stroke:						
Deaths	41	0	43	7	168	29
Deaths per 100 000 person years	28	0	48	40	74	57
Lung cancer:						
Deaths	9	0	21	7	388	18
Deaths per 100 000 person years	6	0	24	40	171	36
Other smoking-related cancer:						
Deaths	71	2	45	9	283	36
Deaths per 100 000 person years	49	73	51	51	125	71
Women (n = 25 122)						
Number of participants	12 076	210	1957	713	8803	1363
Number of person years	287 545	4952	45 961	16 385	203 519	32 238
All causes:						
Deaths	1043	19	158	63	1554	157
Deaths per 100 000 person years	363	384	344	384	764	487
Cardiovascular disease:						
Deaths	211	7	27	18	446	34
Deaths per 100 000 person years	73	141	59	110	219	105
Ischaemic heart disease:						
Deaths	101	2	11	8	232	21
Deaths per 100 000 person years	35	40	24	49	114	65
Stroke:						
Deaths	64	2	8	7	123	8
Deaths per 100 000 person years	22	40	17	43	60	25
Lung cancer:						
Deaths	15	0	3	3	216	6
Deaths per 100 000 person years	5	0	7	18	106	19
Other smoking-related cancer:						
Deaths	107	1	13	6	144	12
Deaths per 100 000 person years	37	20	28	37	71	37

*Participants not reporting cardiovascular disease, diabetes or treatment for hypertension, or symptoms of angina pectoris or atherosclerosis obliterans at the last examination.

Table 4 Participants who attended a third examination, by smoking category at the second examination and sex

Status at the second examination, by smoking category	Percentage smoking at the third examination			
	Men		Women	
	%*	n†	%*	n†
Sustained never smokers	1.2	3966	1.6	7759
"Starters"	58.8	68	71.7	120
Sustained ex-smokers	4.9	2338	6.8	1234
"Resumers"	67.0	442	75.1	405
Sustained smokers	86.1	6210	89.8	5527
"Quitters"	28.2	1474	37.0	888

Percentage smoking at the third examination and number in each category.
*Percentage smoking in the category; †no. of participants in the category.

had quit smoking. A substantial proportion of the "starters", "resumers" and "quitters", however, had changed smoking behaviour from the second to the third examination.

Table 5 displays adjusted relative risks of deaths with sustained never smokers as reference, and with the two sets of adjustments described in Methods. Within the categories, there are only minor differences between the two sets of risk figures.

For both sexes, and for mortality from any cause and from the cause specific diseases, the sustained ex-smokers have adjusted relative risks that do not differ significantly from those of the sustained never smokers. An exception is risk of dying from lung cancer in men.

Table 5 Adjusted relative risk (RR) (95% CIs) of death from all causes, cardiovascular disease, ischaemic heart disease, stroke, lung cancer and other smoking-related cancer, by smoking category and sex, with sustained never smokers as reference. (23 560 male and 25 122 female participants aged 20–49 at initial screening*)

Deaths from	Sustained never smokers	"Starters"	Sustained ex-smokers	"Resumers"	Sustained smokers	"Quitters"
Men (n = 23 560 aged 20–49 years)						
All causes:						
RR†	1.00	1.40 (0.84 to 2.33)	1.11 (1.00 to 1.24)	1.60 (1.34 to 1.92)	2.75 (2.54 to 2.99)	1.51 (1.34 to 1.71)
RR‡	1.00	1.42 (0.85 to 2.37)	1.07 (0.96 to 1.19)	1.59 (1.32 to 1.91)	2.61 (2.40 to 2.83)	1.39 (1.23 to 1.58)
Cardiovascular disease:						
RR†	1.00	1.64 (0.73 to 3.69)	1.06 (0.88 to 1.27)	2.02 (1.52 to 2.67)	3.16 (2.75 to 3.61)	1.72 (1.41 to 2.11)
RR‡	1.00	1.76 (0.79 to 3.97)	0.97 (0.80 to 1.18)	2.01 (1.51 to 2.67)	2.99 (2.60 to 3.43)	1.55 (1.26 to 1.90)
Ischaemic heart disease:						
RR†	1.00	2.55 (1.13 to 5.75)	1.08 (0.85 to 1.36)	2.10 (1.49 to 2.97)	3.43 (2.89 to 4.06)	1.79 (1.39 to 2.29)
RR‡	1.00	2.81 (1.24 to 6.35)	0.99 (0.78 to 1.26)	2.11 (1.49 to 2.99)	3.24 (2.72 to 3.86)	1.58 (1.23 to 2.04)
Stroke:						
RR†	1.00	NA	1.36 (0.88 to 2.08)	1.45 (0.65 to 3.23)	2.63 (1.87 to 3.71)	1.96 (1.22 to 3.15)
RR‡	1.00	NA	1.34 (0.87 to 2.08)	1.45 (0.57 to 3.20)	2.57 (1.82 to 3.66)	1.88 (1.16 to 3.04)
Lung cancer:						
RR†	1.00	NA	3.13 (1.44 to 6.86)	6.49 (2.42 to 17.44)	27.44 (14.17 to 53.15)	5.51 (2.47 to 12.27)
RR‡	1.00	NA	3.17 (1.45 to 6.94)	6.31 (2.35 to 16.97)	25.22 (13.00 to 38.94)	5.19 (2.31 to 11.64)
Other smoking-related cancer:						
RR†	1.00	1.90 (0.47 to 7.75)	0.86 (0.59 to 1.25)	1.06 (0.53 to 2.13)	2.56 (1.97 to 3.32)	1.42 (0.95 to 2.13)
RR‡	1.00	1.93 (0.47 to 7.88)	0.84 (0.57 to 1.22)	1.07 (0.53 to 2.13)	2.41 (1.85 to 3.13)	1.28 (0.85 to 1.94)
Women (n = 25 122 aged 20–49 years)						
All causes:						
RR†	1.00	1.22 (0.77 to 1.92)	1.01 (0.85 to 1.19)	1.37 (1.06 to 1.77)	2.49 (2.30 to 2.70)	1.65 (1.39 to 1.95)
RR‡	1.00	1.22 (0.77 to 1.92)	1.06 (0.90 to 1.26)	1.40 (1.08 to 1.81)	2.49 (2.29 to 2.71)	1.64 (1.38 to 1.95)
Cardiovascular disease:						
RR†	1.00	2.29 (1.08 to 4.86)	0.87 (0.58 to 1.29)	2.09 (1.29 to 3.38)	3.73 (3.16 to 4.40)	1.86 (1.30 to 2.67)
RR‡	1.00	2.28 (1.07 to 4.86)	0.98 (0.65 to 1.48)	2.09 (1.26 to 3.38)	3.99 (3.35 to 4.73)	1.93 (1.34 to 2.78)
Ischaemic heart disease:						
RR†	1.00	1.37 (0.34 to 5.55)	0.73 (0.40 to 1.37)	1.94 (0.95 to 3.99)	4.07 (3.22 to 5.15)	2.42 (1.51 to 3.87)
RR‡	1.00	1.33 (0.33 to 5.41)	0.84 (0.45 to 1.57)	1.82 (0.84 to 3.92)	4.12 (3.23 to 5.26)	2.42 (1.51 to 3.88)
Stroke:						
RR†	1.00	2.15 (0.53 to 8.80)	0.84 (0.40 to 1.76)	2.63 (1.20 to 5.73)	3.36 (2.48 to 4.55)	1.43 (0.69 to 2.98)
RR‡	1.00	2.03 (0.50 to 8.30)	0.86 (0.39 to 1.88)	2.50 (1.08 to 5.79)	3.46 (2.52 to 4.74)	1.46 (0.70 to 3.05)
Lung cancer:						
RR†	1.00	NA	1.32 (0.38 to 4.58)	4.48 (1.30 to 15.50)	23.99 (14.20 to 40.51)	4.34 (1.68 to 11.18)
RR‡	1.00	NA	1.38 (0.40 to 4.82)	4.58 (1.32 to 15.97)	23.47 (13.58 to 40.55)	4.64 (1.78 to 12.07)
Other smoking-related cancer:						
RR†	1.00	0.61 (0.09 to 4.40)	0.80 (0.45 to 1.42)	1.23 (0.54 to 2.79)	2.19 (1.70 to 2.82)	1.19 (0.66 to 2.17)
RR‡	1.00	0.63 (0.09 to 4.49)	0.83 (0.46 to 1.47)	1.26 (0.55 to 2.88)	2.17 (1.67 to 2.83)	1.01 (0.53 to 1.94)

*Participants not reporting cardiovascular disease, diabetes or treatment for hypertension, or symptoms of angina pectoris or atherosclerosis obliterans at the last examination;
†adjusted for age; ‡adjusted for age, systolic blood pressure, total serum cholesterol, serum triglycerides, physical activity during leisure, body mass index (kg/m²), height, disability pension, sickness leave and family history of coronary heart disease recorded at the last examination.
NA, data not applicable.

Men and women who resumed smoking have significantly higher adjusted risks than the sustained never smokers; exceptions are deaths from stroke (men), ischaemic heart disease (women) and other smoking related cancer (both sexes). Nonetheless, their adjusted risks are markedly lower than in sustained smokers for deaths of any cause (p<0.001 for men and women) and for the cause specific diseases.

The sustained smokers have by far the highest adjusted risks for all mortality groups for both sexes. Men and women who stopped smoking after the first examination have lower adjusted risks than those who continued to smoke; their adjusted risks are, however, significantly higher than in the sustained never smokers, with the exception of deaths from stroke in women and from other smoking related cancer for both sexes. Never smokers who took up smoking after the first examination, have significantly higher adjusted risks for dying from ischaemic heart disease (men), and from cardiovascular disease (women); otherwise their risks do not differ significantly from the sustained never smokers.

The data referred to above concern people without a history of cardiovascular disease or diabetes, or without symptoms of angina pectoris or atherosclerosis obliterans. If this group is not excluded, however, we find age-adjusted risks of dying from any cause that are substantially the same as those presented in table 5.

Figure 1 demonstrates the all cause cumulative mortality rate in the various categories. In male sustained smokers, the rate reaches 0.5, which translates into a cumulative survival probability of 61%. The corresponding figure for male sustained never smokers is 85%. In women, the figures are 80% in sustained smokers and 90% in sustained never smokers. The curve for male sustained ex-smokers fits with the curve for

female sustained smokers. In men, the curves for "resumers" and "quitters" are clustered above the curve for sustained ex-smokers, but distinctly beneath the curve for sustained smokers. The curve for male "starters" lies between the curves for sustained ex-smokers and sustained never smokers. In women, there is no difference between the curves for sustained never smokers and sustained ex-smokers, while the curves for "resumers" and "starters" lie somewhat above the curve for sustained never smokers. The curve for female "starters" lies more or less slightly above the curve for sustained never smokers.

Figure 2 A–D concentrates on participants with sustained smoking behaviour, and relates to cumulate mortality rate of ischaemic heart disease, stroke, lung cancer and other smoking related cancer. For ischaemic heart disease (fig 2A), female sustained smokers experienced roughly the same cumulative mortality rate as male sustained never smokers. The curves for female sustained ex-smokers and never smokers are concurrent during the first 20 years of observation. For stroke (fig 2B), there are interesting contrasts between the sexes. In men, the curve for sustained ex-smokers lies between the curves for sustained smokers and never smokers; in women, the curve for sustained ex-smokers lies beneath the curve for sustained never smokers. For lung cancer (fig 2C) in men, the curve for sustained ex-smokers lies slightly above the curve for never smokers, while in women, the curves for female sustained ex-smokers and sustained never smokers can hardly be separated. Female sustained smokers reach a cumulative mortality rate of 0.04 roughly 6 years later than corresponding males. For other smoking related cancer (fig 2D), the curves for sustained ex-smokers and never smokers are concurrent during the first 15 years (both sexes); where after they part: In men, the curve for sustained ex-smokers lies above the curve for sustained never smokers, while in women, the reverse is the case.

DISCUSSION

We have found that there is no significant difference in risks between sustained ex-smokers and never smokers. This observation was made for both sexes, and after adjustment for a series of confounders, and it relates to deaths from any cause and from selected smoking related diseases (cardiovascular disease, ischaemic heart disease, stroke, smoking related cancer). One exception is lung cancer in men, where the risk is slightly higher than in never smokers (table 5).

In particular, the results are striking for women, where the cumulative mortality rates estimates for all causes are identical in sustained ex-smokers and never smokers (fig 1). For stroke, female cumulative mortality rates estimates are even lower in sustained ex-smokers than in sustained never smokers (fig 2C). This may, at least partly, be explained by a lower mean systolic and diastolic blood pressure in sustained ex-smokers than in sustained never smokers. Adjusted relative risk for deaths from stroke, however, is not significantly different between sustained ex-smokers and never smokers.

The favourable mortality pattern in female sustained ex-smokers may be related to socio-economic factors. Among the categories applied in the present study, female sustained ex-smokers have the highest stature; the mean is 0.9 cm higher than in female sustained never smokers. Previously, in a sample of the same study population, it has been found a very strong positive association between income, educational level and body height.[24]

In addition, the results show that people's smoking behaviour is drifting over time (tables 3 and 4):

▶ Among smokers at the first examination, 17% of the men and 13% of the women had quit smoking at the second examination, but of these, 28% men and 37% women had taken up smoking again at the third examination.

▶ Among ex-smokers at the first examination, 17% of the men and 27% of the women had resumed smoking at the second examination. Of those who resumed smoking, 33% men and 25% women had quit smoking again at the third examination,
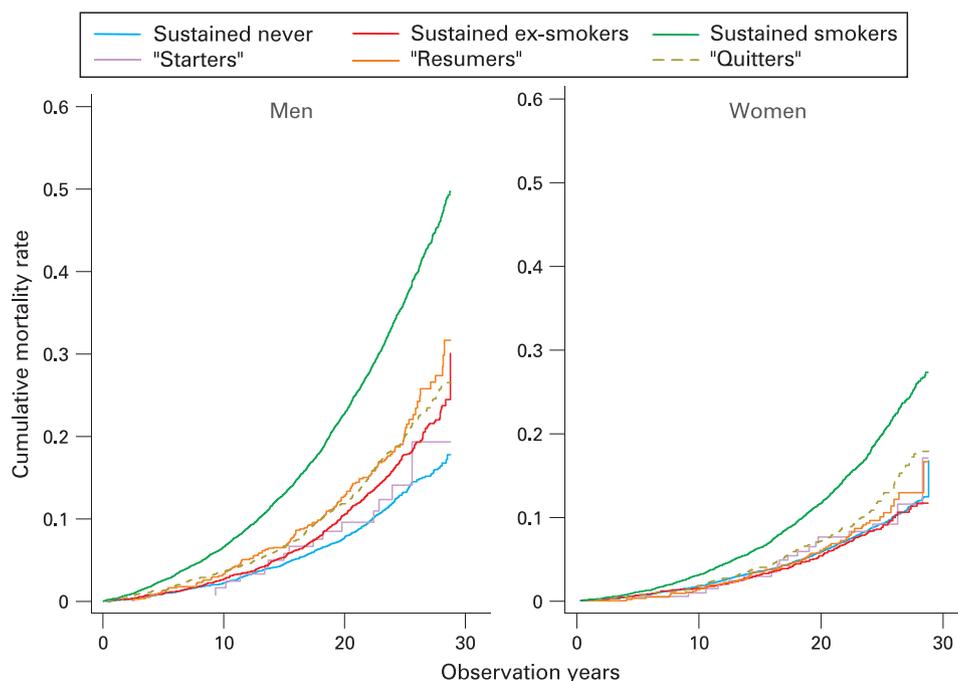

Figure 1 Nelson–Aalen cumulative mortality rates from all causes in each smoking category, by observation years. The x axis shows the observation years and the y axis shows the cumulative mortality rates. Men and women not reporting cardiovascular disease, diabetes or treatment for hypertension, or symptoms of angina pectoris or atherosclerosis obliterans at the last examination.
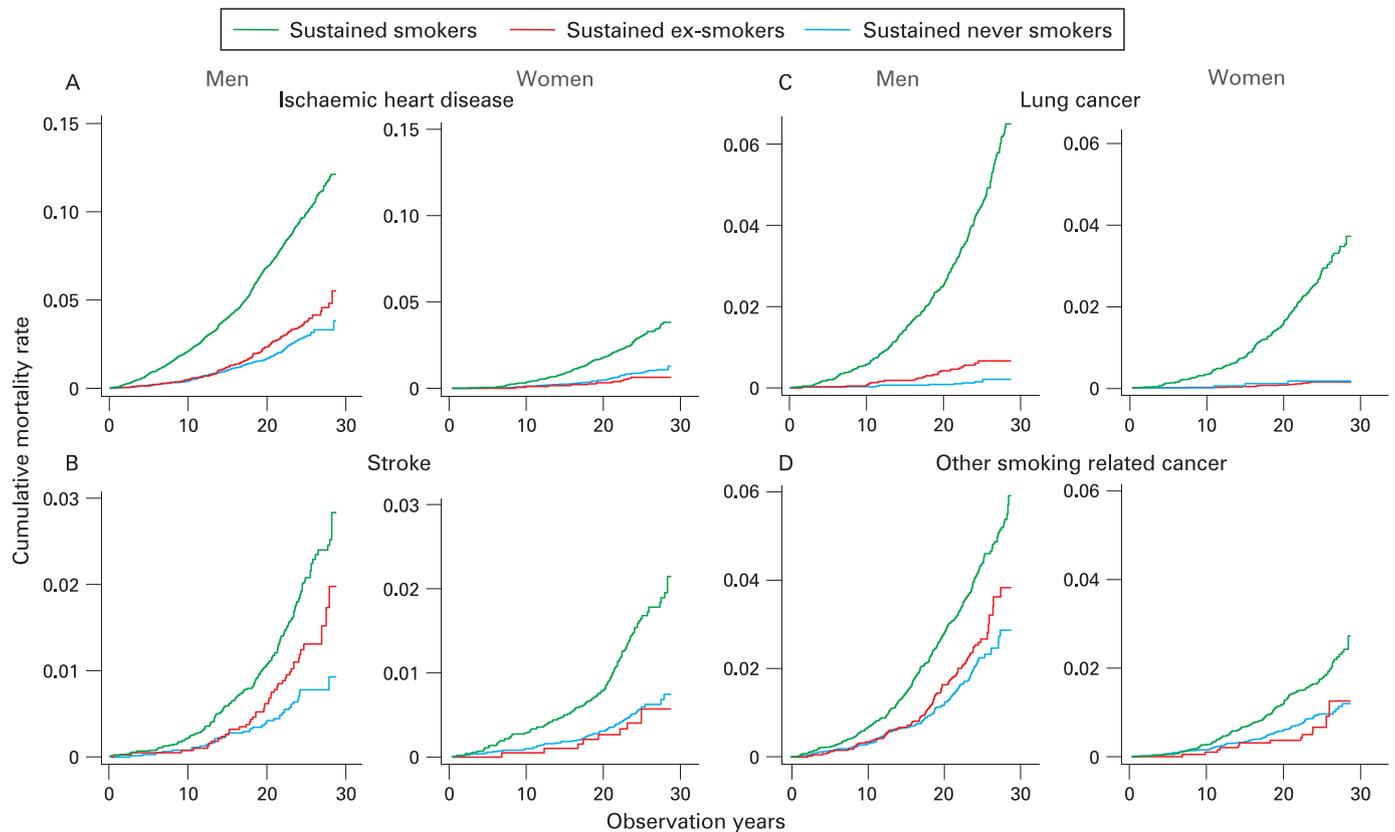
Figure 2 Nelson–Aalen cumulative mortality rates from (A) ischaemic heart disease, (B) stroke, (C) lung cancer and (D) other smoking related cancer in categories with sustained smoking behaviour, by observation years. The x axis shows the observation years and the y axis shows the cumulative mortality. Men and women not reporting cardiovascular disease, diabetes or treatment for hypertension, or symptoms of angina pectoris or atherosclerosis obliterans at the last examination.

▶ Among never smokers at the first examination, only 2% (both sexes) had started to smoke at the second examination, and of these 41% men and 28% women had returned to a non-smoker status at the third examination.

In contrast to these movements, we find only minor changes from the second to the third examination in sustained never smokers and sustained ex-smokers. At the third examination, 1% of the male and 2% of the female sustained never smokers, and 5% of the male and 7% of the female sustained ex-smokers, had taken up smoking.

What this study adds

▶ Numerous studies have revealed that people who have given up smoking, reduces their risk of serious tobacco-related diseases. Only a few large prospective cohort studies have been based upon people who at two examinations, years apart, stated that they were ex-smokers.
▶ This study, which includes a population of nearly 49 000 persons, and observed over a mean of 23 years, found that sustained ex-smokers, confirmed at two examinations 3–13 years apart, had a risk of dying from all causes and from selected cause-specific tobacco-related diseases that did not differ significantly from sustained never smokers.
▶ In contrast, ex-smokers at the first examination who later resumed smoking, had mortality risks that were significantly higher than in sustained never smokers.

Men and women who at the first examination were registered as ex-smokers, but had resumed smoking at the second examination, have a significantly higher adjusted relative risk for deaths from any cause, from cardiovascular disease and from lung cancer, than have sustained never smokers. In men, this applies also for deaths from ischaemic heart disease, and in women, for deaths from stroke. For both sexes, the adjusted relative risk for deaths from other smoking related cancer is not significantly different between "resumers" and sustained never smokers.

The shifting smoking behaviour among the "resumers" may give a clue to why this category still have adjusted risks that are markedly lower than in sustained smokers. After some years of uncertainty, a substantial proportion of them may have settled as permanent ex-smokers and thereby obtained a considerably health benefit. Regrettably, we do not have data on further developments in smoking behaviour throughout the mortality follow-up period, which may have enlightened this assumption.

Based on findings referred to above, however, it is reasonable to assume that the sustained never smokers and the sustained ex-smokers have reached a stable stage with regards to smoking.

Among sustained smokers at the second examination, 14% of the men and 10% of the women had stopped smoking at the third examination. This development may be seen in light of tobacco control activities that started in the 1970s in Norway (ban on tobacco advertising, health warnings on tobacco packages, information campaigns etc.).[6]

One may ask whether or not people's questionnaire answers have been correct at the three screenings. As the main findings

of this paper do not deal with consumption size, the answers are more likely to be truthful. People would know, at the time of examination, whether they smoke daily or not, or have done so previously. Moreover, the thiocyanate analysis in one of the counties, gives mean results that correspond well with a level that could be expected for the various categories (table 2).

The contrast in risk between sustained ex-smokers and "resumers", indicates that a more valid and favourable picture of ex-smokers' risk will be obtained if follow-up is being based upon people with sustained smoking behaviour registered at two surveys with an interval of some years. Our results correspond well with similar observations in prospective cohort studies in Denmark and Sweden. In Copenhagen, information from two consecutive examinations was obtained for 19 714 men and women, who were followed for up to 31 years. All-cause mortality in sustained ex-smokers and sustained never smokers was found to be of the same order of magnitude.[7] In Göteborg, it was found that smoking habits in the total study population were far from stable between the first and second screening, carried out 4 years apart. In 3981 men, aged 47–55, however, smoking habits were identical at both screenings. After 7.1 years of follow-up it was found that all-cause mortality, adjusted for a series of confounding variables, was not significantly different between sustained ex-smokers and sustained never smokers.[8]

Strengths and weaknesses of the study
The strength of the study is that it includes close to 49 000 men and women who were examined according to standardised procedures, and observed for a mean of 23 years. The number of person years is for men 531 553 years; for women 590 599 years. We have also information on a series of relevant confounding variables, which have been adjusted for. Furthermore, the follow-up is complete with respect to death and emigration.

It would have been desirable to have more detailed information on the time period that ex-smokers had refrained from smoking. A separate analysis, however, of people who at both examinations stated that they had been ex-smokers for more than 5 years, gave mortality rates that did not differ essentially from people in the total category of sustained ex-smokers. Although we have results from a third examination for 62% of the sustained ex-smokers, it would have been advantageous to have a new screening of a sample of all participants later in the observation period, in order to follow developments in cigarette consumption within the categories.

Another weakness is that we do not have information on smoking in people who characterise themselves as non-daily smokers. Non-daily smokers may suffer some significant smoking-related harm, and those who smoked daily and switched to non-daily would be characterised as quitters. Both would tend to underestimate the harm of smoking and the benefits of quitting.

Possible implications for policymakers
In health education and patient counselling it is often heard people say that the damage is already done and that they will hardly benefit of quitting since they had smoked so heavily and for such a long time.

This study confirms clearly the enormous benefit of quitting smoking permanently. This message should be steadily repeated by health educators and in patient counselling. Ex-smokers who stay the course will over the years reach the same risk level as those who have never smoked.

Conclusions
Ex-smokers registered at two consecutive screenings, years apart, obtain a risk of dying from all causes and from specified smoking related diseases that are not significantly different from the risk in sustained never smokers. People who were ex-smokers at the first examination, but at the second examination stated that they had resumed smoking, had a risk that was significantly higher than in sustained never smokers.

In prospective cohort studies based on only one examination, the beneficial effects of quitting smoking may be attenuated by an increased risk in ex-smokers who resume smoking during the observation period.

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