Cardiovascular disease risk factors in relation to smoking behaviour and history: a population-based cohort study

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ABSTRACT
Objective: To investigate how individual risk factors for cardiovascular disease (CVD) (blood pressure, lipid levels, body mass index, waist and hip circumference, use of antihypertensive or hypolipidemic medication, and diagnosed diabetes) differ in people aged 46 years with different smoking behaviour and history.

Methods: This population-based cohort study is based on longitudinal data from the Northern Finland Birth Cohort 1966 project. Data were collected at the 31-year and 46-year follow-ups, when a total of 5038 and 5974 individuals participated in clinical examinations and questionnaires. Data from both follow-ups were available for 3548 participants. In addition to individual CVD risk factors, Framingham and Systematic Coronary Risk Evaluation (SCORE) algorithms were used to assess the absolute risk of a CVD event within the next decade.

Results: The differences in individual risk factors for CVD reached statistical significance for some groups, but the differences were not consistent or clinically significant. There were no clinically significant differences in CVD risk as measured by Framingham or SCORE algorithms between never smokers, recent quitters and former smokers (7.5%, 7.4%, 8.1% for men; 3.3%, 3.0%, 3.2% for women; p<0.001).

Conclusions: The effect of past or present smoking on individual CVD risk parameters such as blood pressure and cholesterol seems to be of clinically minor significance in people aged 46 years. In other words, smoking seems to be above all an independent risk factor for CVD in the working-age population. Quitting smoking in working age may thus reduce calculated CVD risk nearly to the same level with people who have never smoked.

INTRODUCTION
Smoking is the most important preventable cause of death in the Western world, causing some 5 million premature deaths globally each year.1 Cigarette smoke is a major risk factor for cardiovascular disease (CVD) and the second leading cause for CVD mortality after high blood pressure. Other major risk factors for CVD mortality include high blood glucose, physical inactivity, obesity and elevated cholesterol levels, all of which are associated with smoking according to previous research.2-3 CVD accounts for >17 million deaths globally each year, of which more than 10% are estimated to be caused by cigarette smoke.2,3

According to the WHO, more than 1 billion people smoke, and the prevalence is constantly rising.4 Several environmental and genetic factors contribute to the initiation of smoking, and although most smokers want to quit, they commonly continue due to strong...
nicotine addiction. Smoking is more common among men and in lower socioeconomic classes, appearing concomitantly with other harmful health behaviour. Men also have a two to five times higher risk of CVD. These factors contribute to the substantial gender imbalance in life expectancy. In Finland, for example, life expectancy is 77.5 years for men and 83.4 years for women.

In this study, we set out to investigate gender-specific CVD risk factors in relation to smoking status and history in the population aged 46 years. We employed the well-established Framingham risk score as a tool to estimate risk of a CVD event within the next 10 years among current smokers, individuals who had quit smoking recently or in the past and those who had never smoked. Smoking greatly raises CVD risk points in the Framingham equation, but other risk parameters, such as blood pressure, are included as well. We hypothesised that past smoking would be visible as an increase in these risk parameters and thus raise the risk of a CVD event for a former smoker when compared with a never smoker. In other words, we expected to find significant differences in CVD risk factors between recent quitters, former smokers and never smokers. We also hypothesised that current smokers would have significantly higher rates of individual CVD risk factors than non-smokers.

The analyses were based on the unique, prospective, population-based Northern Finland Birth Cohort 1966 study sample, which consists of >5000 well-characterised individuals. As serious cardiovascular events often take place in the population aged 60 and over, it is of key importance to characterise the risk of a CVD event within the next decade for people in their late 40s.

METHODS
Study population
This study is based on the Northern Finland Birth Cohort 1966 study sample, which is a longitudinal research programme in Finland’s two northernmost provinces. The study is based on clinical measurements and questionnaires performed at examinations during a 31-year follow-up in 1997 and during a 46-year follow-up in 2012. All participants provided written informed consent, and the Ethical Committee of the Northern Ostrobothnia Hospital District has approved the Northern Finland Birth Cohort study (§94/2011), which is performed according to the Declaration of Helsinki of 1983.

The Northern Finland Birth Cohort 1966 initially included all of the 12,058 children whose expected time of delivery was in 1966. The entire cohort has been followed up since pregnancy with clinical examinations and questionnaires covering health, lifestyle and socioeconomic indicators at 0, 1, 14, 31 and 46 years of age. The present study is based on the 31-year and 46-year follow-ups, in which 5038 and 5974 individuals participated, respectively. The CVD risk estimation carried out in this study was based on smoking status and other risk parameters mapped at the age of 46. The 31-year smoking status was used to investigate changes in smoking habits and development of CVD risk factors between ages 31 and 46. This analysis could be performed on 3548 participants for whom there were data from both follow-ups. Study sample selection is presented in figure 1. Characteristics of the study sample are presented in table 1.

Clinical examinations
During the 31-year and 46-year follow-up examinations, the participants gave blood samples and underwent physical examination, anthropometry and blood pressure determination performed by a study nurse or physician.

Weight and height, as well as waist and hip circumference, were measured with the participants wearing light underwear. Body height and weight were measured to an accuracy of 0.1 cm and 0.1 kg, respectively. Based on these measurements, body mass index (BMI; kg/m²) was calculated. The waist-to-hip ratio (WHR) was also calculated.

Systolic and diastolic blood pressure was measured on the right arm of the seated participants using an automated oscillometric blood pressure device (Omron...
Digital Automatic Blood Pressure Monitor Model M10-IT) and an appropriately sized cuff. The mean of two lowest values out of three measurements was recorded as blood pressure.

Serum total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglycerides were determined from fasting samples using an enzymatic assay method. All plasma samples were analysed in a University Hospital of Oulu laboratory according to a standardised protocol.

Information on diagnosed type 2 diabetes, in addition to the use of antihypertensive and hypolipidemic medication, was acquired by a questionnaire at the 31-year and 46-year follow-ups.

Smoking status and study groups

Smoking status assessment was based on standards of the Finland Cardiovascular Risk (FINRISK) study and four smoking-related questions (‘Have you ever smoked’, ‘Have you ever smoked regularly, almost daily for at least a year’, ‘Do you smoke now?’ and ‘When was the last time you smoked?’) collected at the 31-year and 46-year follow-ups. Participants were divided into four groups based on their smoking status at age 46: (1) current smokers (n=1408; 665 women, 743 men), (2) recent quitters (n=121; 57 women, 64 men), (3) former smokers (n=1401; 694 women, 707 men) and (4) never smokers (n=3044; 1822 women, 1222 men). Those who answered ‘no’ to a question ‘Have you ever smoked?’ were considered never smokers. Those who had smoked almost daily for at least a year but had quit at least 6 months ago were considered former smokers, whereas those who had quit more recently were considered recent quitters. Those who smoked 2–7 days a week or whose last smoke was today or yesterday were considered current smokers.

CVD risk factor assessment

Framingham risk score
We adopted the gender-specific 2008 Framingham risk score prediction equation by D’Agostino et al.\(^\text{10}\) to estimate the individual’s absolute risk (%) for a first cardiovascular event within 10 years. The events assessed were fatal or non-fatal coronary heart disease, stroke, peripheral artery disease or heart failure. Parameters included in the algorithm are smoking status, age, systolic blood pressure, total cholesterol, HDL cholesterol, type 2 diabetes status and treatment for hypertension. All parameters have varying contribution to the total score, age being the variable with main effect. The method is based on a cohort of inhabitants of Framingham, Massachusetts, with the mean age of 49. The method has since been validated for the white, middle-aged population, and can be thought to estimate cardiovascular risk in our population fairly well without further ethnical calibration.\(^\text{10}\)

Systematic Coronary Risk Evaluation (SCORE)

The Systematic Coronary Risk Evaluation (SCORE) algorithm includes smoking status, age, systolic blood pressure, total cholesterol and HDL cholesterol. It is calculated on the basis of national cardiovascular disease mortality, stroke and myocardial infarction death rates, related to the total population, and hence, can be considered a risk estimate for the same population.

<table>
<thead>
<tr>
<th>Database</th>
<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td>Database</td>
<td>NFBC 1966</td>
<td>NFBC 1966</td>
</tr>
<tr>
<td>n</td>
<td>2 736</td>
<td>3 238</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.6±0.6</td>
<td>46.6±0.6</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>743 (27.5)</td>
<td>665 (20.3)</td>
</tr>
<tr>
<td>Recent quitters, n (%)</td>
<td>64 (2.3)</td>
<td>57 (1.8)</td>
</tr>
<tr>
<td>Former smokers n, (%)</td>
<td>707 (25.8)</td>
<td>694 (21.4)</td>
</tr>
<tr>
<td>Never smokers n, (%)</td>
<td>1 222 (44.7)</td>
<td>1 822 (56)</td>
</tr>
<tr>
<td>Use of antihypertensive medication (%)</td>
<td>18.5</td>
<td>16.6</td>
</tr>
<tr>
<td>Use of hypolipidemic medication (%)</td>
<td>6.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Type 2 diabetes (%)</td>
<td>3.0</td>
<td>2.6</td>
</tr>
<tr>
<td>BMI</td>
<td>27.3±4.3</td>
<td>26.5±5.2</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>97.5±11.8</td>
<td>87.3±13.1</td>
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<tr>
<td>Hip (cm)</td>
<td>99.3±7.8</td>
<td>100.5±10.9</td>
</tr>
<tr>
<td>WHR</td>
<td>0.98±0.06</td>
<td>0.87±0.06</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.54±1.0</td>
<td>5.18±0.85</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.40±0.33</td>
<td>1.67±0.39</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>3.74±0.94</td>
<td>3.24±0.86</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.49±0.96</td>
<td>1.08±0.58</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>128.2±13.9</td>
<td>118.5±15.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>86.5±10.2</td>
<td>82.4±10.7</td>
</tr>
<tr>
<td>SCORE risk score (%)</td>
<td>1.7±0.8</td>
<td>0.3±0.2</td>
</tr>
<tr>
<td>Framingham risk score (%)</td>
<td>9.4±5.1</td>
<td>3.7±2.6</td>
</tr>
</tbody>
</table>

The values are presented as mean±SD unless otherwise indicated. BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NFBC 1966, Northern Finland Birth Cohort 1966; SCORE, Systematic Coronary Risk Evaluation; WHR, waist to hip ratio.
pressure and total cholesterol as risk factors for a fatal cardiovascular event in the next 10 years.\textsuperscript{11} The SCORE risk was calculated for each participant according to a gender-specific algorithm. The high-risk population version of the SCORE algorithm we used is based on Finnish, Danish and Norwegian cohorts, and is thus especially well applicable for our data set. Including the SCORE algorithm in our study was thus also a means to validate the Framingham method for our population, even though the end points are slightly different for these two models.

Other CVD risk factors
In addition to the risk factors included in the Framingham and SCORE equations, we examined weight, BMI, waist and hip circumference, serum triglycerides and LDL cholesterol, which are known risk factors for CVD.

Statistical analysis
Distributions of continuous variables were expressed as means±SD, and categorical variables as numbers and percentage of proportions. Log transformation was used to normalise the skewness of the distributions. The $\chi^2$ test, independent-sample t-test or analysis of variance (ANOVA) were used to study the association between different smoking habits and cardiovascular risk factors. Logistic regression analysis was used to examine the associations between smoking habits and binary cardiovascular risk factors. Moreover, analysis of covariance (ANCOVA) was used to examine the association between smoking habits and known cardiovascular risk factors. Post hoc analyses between the groups were performed using multiple-comparison Dunnett’s test, and current smokers were used as control group. Potential confounding factors, BMI and the use of antihypertensive medication or hypolipidemic medication, as appropriate, were controlled in multivariate analysis. A $p<0.05$ was considered statistically significant. Statistical analyses were conducted using the open-source software package R V.3.1.0.

RESULTS
Of the 12 058 live-born participants, 11 322 participants were alive and their addresses were known at the age of 31 and 10 282 participants at the age of 46. At the 31-year time point, 5038 people answered the questionnaire and participated in clinical examinations. In the 46-year follow-up, the corresponding number was 5974. Data from the 31-year and 46-year follow-ups were available for 3548 participants, who had given written informed consent to use their data in this study (figure 1).

Smoking history and individual cardiovascular risk factors
The mean values of CVD risk factors analysed in the present study are presented in table 2. BMI was adjusted for when testing for differences between groups with different smoking histories.

BMI, waist circumference and WHR
Smokers had a higher BMI and greater waist circumference than individuals who had never smoked ($p<0.001$ for both genders).

Cholesterol, triglycerides and use of hypolipidemic medication
Currently smoking men had higher total cholesterol ($p<0.028$) and triglyceride levels ($p<0.001$) than never smokers. Currently smoking women also had a significantly poorer lipid profile than never smokers: the levels of LDL and triglycerides were higher ($p=0.002$ and $p<0.001$, respectively), whereas HDL was lower ($p<0.001$; use of hypolipidemic medication adjusted).

Among women, currently smoking and recently quit individuals used hypolipidemic medication more often than former and never smokers ($p=0.007$). Such a difference was not observed among men.

Blood pressure
In men, former smokers had the highest mean systolic and diastolic blood pressure ($p<0.001$ and $p<0.011$; use of antihypertensive medication adjusted) and they also used more antihypertensive medication than other groups ($p=0.015$). In women, never smokers had the highest systolic blood pressure ($p=0.016$; use of antihypertensive medication adjusted). No difference was found in diastolic blood pressure between the female groups.

Diabetes
Type 2 diabetes rate was similar among former and current male smokers, whereas never smokers had significantly less type 2 diabetes ($p<0.001$). For women, no statistical difference was found between the groups.

Smoking history and risk of a cardiovascular event
Framingham risk score was calculated to assess the absolute risk of a first CVD event in the next 10 years across study groups. The mean Framingham risk score for currently smoking men was 14.7%, whereas the risk for never smokers was 7.5% ($p<0.001$). For currently smoking women, the mean Framingham risk score was 5.9% and 3.3% for never smokers ($p<0.001$). Current smokers also had a higher CVD risk in comparison with former smokers and recent quitters ($p<0.001$ for both genders). There were no clinically significant differences in the Framingham risk scores among never smokers, recent quitters and former smokers (table 2, figure 2). Smoking was also associated with a higher risk of a fatal cardiovascular event defined by the SCORE equation for both genders ($p<0.001$), validating the Framingham risk score for CVD events (table 2).

Changes in smoking behaviour over time
At age 31, 38% of men and 26% of women smoked. Approximately 40% (41% of men; 39% of women) had quit smoking by age 46 and ~60% (60% of men; 61% of
Table 2  CVD risk factors in the Northern Finland Birth Cohort 1966 study sample, measured at the age of 46

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td></td>
<td>Current smokers</td>
<td>Recent quitters</td>
</tr>
<tr>
<td>n</td>
<td>743</td>
<td>64</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.2±4.5</td>
<td>27.5±4.0</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>98.3±12.3</td>
<td>99.6±10.9</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>98.8±8.2</td>
<td>99.9±8.3</td>
</tr>
<tr>
<td>WHR</td>
<td>1.0±0.1</td>
<td>1.0±0.1</td>
</tr>
<tr>
<td>Total cholesterol†‡ (mmol/L)</td>
<td>5.6±1.0</td>
<td>5.5±1.0</td>
</tr>
<tr>
<td>HDL cholesterol† (mmol/L)</td>
<td>1.35±0.3</td>
<td>1.36±0.3</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.61±1.0</td>
<td>3.69±0.9</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.7±1.0</td>
<td>1.4±0.6</td>
</tr>
<tr>
<td>Systolic BP†‡ (mm Hg)</td>
<td>127.1±13.8</td>
<td>126.4±13.0</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>86.3±10.2</td>
<td>86.1±9.5</td>
</tr>
<tr>
<td>Antihypertensive medication (%)†</td>
<td>17.4</td>
<td>16.9</td>
</tr>
<tr>
<td>Hypolipidemic medication (%)</td>
<td>6.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Type 2 diabetes (%)†</td>
<td>4.0</td>
<td>0</td>
</tr>
<tr>
<td>SCORE risk score (%)</td>
<td>2.6±1.0</td>
<td>1.3±0.4</td>
</tr>
<tr>
<td>Framingham risk score (%)</td>
<td>14.7±6.0</td>
<td>7.4±2.3</td>
</tr>
</tbody>
</table>

The values are presented as mean±SD unless otherwise indicated.

*BMI is adjusted for when testing for differences between groups.
†Included in Framingham risk score.
‡Included in SCORE risk score.
§Use of antihypertensive and lipid profile-lowering medication is adjusted for when testing for differences between groups.

BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SCORE, Systematic Coronary Risk Evaluation; WHR, waist to hip ratio.
women) continued smoking at age 46. Over 80% of those who had quit smoking before age 31 remained non-smokers at age 46 (84% of men; 84% of women; figure 3).

Changes in risk factors over time
All CVD risk factors tracked between ages 31 and 46 (blood pressure, total cholesterol, LDL and HDL values, triglycerides, BMI, hip and waist circumference) increased with age. The greatest numerical difference was observed among current smokers, but there were no statistical differences between the groups.

DISCUSSION
In the present study, we set out to investigate CVD risk factors among men and women aged 46 years based on their smoking history.

Smoking history and cardiovascular risk factors
Smoking, lipid abnormalities and high blood pressure are well-established risk factors for CVD. Apart from being an individual risk factor for CVD, smoking has generally been associated with many of the other risk factors such as a poorer lipid profile and elevated blood pressure. According to previous research, smokers have higher serum cholesterol, triglyceride and LDL levels, and lower levels of HDLs than non-smokers, but the effect of smoking cessation on lipid profile seems to be quite modest. A meta-analysis of 27 prospective studies on the effect of smoking cessation found a small but significant increase in the level of HDL, favouring former smokers over current smokers when the measurement intervals ranged from 30 days to 2 or more years. The same study found no significant changes in the level of total cholesterol, LDL or triglycerides. In the present analysis, we observed statistically significant differences in lipid levels, favouring individuals who had never smoked over current smokers. However, these differences were modest and clinically insignificant at the group level. Interestingly, lipid levels were slightly above recommendations in all groups studied. The use of antihypertensive or hypolipidemic medication was slightly more common among current smokers when compared with the group of never smokers. Also, type 2 diabetes was more common among smokers than never smokers, contributing to the higher Framingham total score in this group.

In the present study, there were no clinically major differences in blood pressure between the groups, and the mean blood pressure was within recommendations in all groups. Smoking causes acute increase in blood pressure, which declines quickly after smoking. However, there is no consensus regarding the role of smoking in long-term blood pressure in generally healthy people. Though lifelong non-smokers seem to have lower blood pressure than current smokers, the effect of smoking cessation on blood pressure remains unclear with contradictory findings. In one study, no significant change in blood pressure was found after two and a half years after smoking cessation in either the group of former smokers or the control group of never smokers. We were not able to find such a long-term effect in our population aged 46 years either.

Obesity and diabetes are also known to contribute to the absolute risk of CVD. In the present study, the group of former smokers had the highest BMI. Indeed, people who stop smoking often gain weight, which is probably due to nicotine acting as an appetite suppressant. While the risk of CVD decreases immediately after smoking cessation, the extent and speed of the risk reduction are not clear. Depending on the study, the CVD risk of former smokers reverts to the level of lifelong non-smokers within 3–15 years. In our study, the total increase in CVD risk among current smokers resulted mainly from the smoking itself, rather than from the aggregation of multiple risk factors in these individuals. Therefore, our results support the assumption that smoking is predominantly a major individual risk factor for CVD, instead of increasing other risk factors or being an indicator for harmful lifestyle habits. Indeed, contrary to our hypothesis, the differences in individual risk factors for CVD were not
clinically significant among smokers, non-smokers, former smokers and recent quitters.

**Mechanisms of smoking-induced cardiovascular events**

The mechanisms underlying cigarette smoke-induced atherosclerosis, arterial thrombosis and their clinical manifestations as CVD are only partially understood and can be divided into several systemic pathways. First, reactive oxygen species induce cardiac remodelling, seen as left ventricular hypertrophy and atrial fibrosis, which increase the risk of stroke. Second, nicotine-stimulated release of adrenal medulla hormones modifies cardiac output by increasing heart rate, ventricular contractility and blood pressure, which might lead to cardiac ischaemia. Third, compounds in cigarette smoke expose smokers to myocardial ischaemia by causing deficient vasomotor functions, which is seen as thickening of the arterial wall and intima media, reduced ability to expand and contract vessels, as well as increased arterial stenosis. There are currently also many other known mechanisms by which smoking contributes to the increased CVD risk.

**Strengths and limitations of the study**

While the rate of cardiovascular mortality is at a steady decline in the Western world, CVD remains the leading cause of death in our Finnish setting. Even though cardiovascular events lead to death all the more seldom, they are extremely costly for the healthcare system. Moreover, especially non-fatal stroke can have devastating consequences for the quality of life of the patient and their family. It is thus of key importance to recognise which measures are impactful in CVD prevention.

Large, prospective, population-based study samples, such as the Northern Finland Birth Cohort used in the present study, are optimal for studying common diseases and their risk factors. In the present sample, the participants’ smoking history and changes to it were thoroughly mapped throughout their lives. Considering the fact that participation in the study takes several days at each point of data collection, the dropout rate has been very small. This may indicate high motivation of the participants, which is likely to increase the reliability of the self-reported data on smoking status and history. On the other hand, it is also possible that individuals with little interest in health issues may be under-represented in the sample. In the present study, we deliberately did not adjust analyses for the participants’ socioeconomic status, which was expected to further highlight the differences in CVD risk factors between the groups. This is
because smoking and other harmful health behaviour, such as an unhealthy diet, high alcohol consumption or lack of physical exercise, typically occur in lower socio-economic classes. However, we did adjust for a common indicator of these harmful habits—BMI—when comparing individual risk factors and absolute risk scores between people with different smoking histories. Adjusting for family history might have further strengthened our results but could not be done with our data.

Clinical conclusions

Our aim was to characterise gender-specific CVD risk factors in relation to smoking behaviour and history in a large population-based Finnish study sample. Many risk factors were elevated among smokers in comparison with never smokers or to the group of participants who had quit smoking. However, these differences were modest and are not likely to have major clinical implications. The difference in these risk factors was so small between those who had smoked in some point in their lives but later quit and those who had never smoked that a statistically significant difference in absolute CVD risk for these groups could not be detected. Many deleterious changes caused by smoking are relatively quickly reversible, and therefore smoking cessation could have a great significance in reducing cardiovascular morbidity and mortality. In the UK, a 35% decline in smoking prevalence over two decades has resulted in nearly 30 000 (24%) fewer coronary heart disease deaths. This effect was much greater than that achieved by lowering cholesterol, which resulted in some 4700 (4%) fewer deaths. Based on the results presented here, only modest aggregation of other CVD risk factors exists in smokers aged 46 years when compared with never smokers or ex-smokers. Therefore, quitting smoking at this age might even decrease CVD risk to approximately the same level with non-smokers.

Acknowledgements

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Contributors

JK, HV, TY, SK-K and MT conceived the original idea for the paper. JJ and JA conducted the data analyses. JK and HV produced the initial draft of the paper. All authors were involved in the interpretation of the analyses and writing of the paper. All authors approved the final version of the paper and take responsibility for its content.

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Competing interests

At the time of the study, JK was an employee of a medical agency that serves several pharmaceutical companies. Please find full list of competing interests of all authors in the manuscript.

Ethics approval

Ethical Committee of the Northern Ostrobothnia Health District.

Provenance and peer review

Not commissioned; externally peer reviewed.

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