

Self-Reported Cardiovascular Disease and the Risk of Lung Cancer, the HUNT Study

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Introduction: Inflammation is involved in development of lung cancer and cardiovascular disease (CVD), and we hypothesize that self-reported CVD is an independent risk factor for lung cancer.

Methods: Data from the Nord-Trøndelag Health Study (1984–2008) linked to the Norwegian Cancer and Death Cause Registry were analyzed stratified by smoking status. In total, 97,087 persons (1,634,967 person years) were included (never smokers 567,575 person years, former smokers 295,685 person years, current smokers 444,922 person years, and unknown 326,785 person years) and followed for an average of 15 years. The proportional hazard model was applied to estimate the hazard ratio (HR) with a 95% confidence interval (CI) for self-reported CVD on lung cancer incidence rate adjusted for age, sex, body mass index, burden of tobacco smoking and chronic cough with phlegm.

Results: 1080 cases of lung cancer (1.1%) occurred. A total of 5981 (6.9%) participants had at baseline or developed during follow-up self-reported CVD. After adjusting for confounders, self-reported CVD was an independent risk factor for the development of lung cancer in former (HR [95% CI] 1.74 [1.11–2.73]) and current smokers (HR [95% CI] 1.38 [1.04–1.83]), but not in never smokers (HR [95% CI] 0.87 [0.34–2.23]).

Conclusions: Self-reported CVD was independently associated with increased occurrence of lung cancer in former and current smokers. CVD may be a novel risk factor for lung cancer screening.

Key Words: Lung cancer, Inflammation, Cardiovascular disease, Risk, Epidemiology

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Lung cancer has the second highest incidence of all cancers, is the leading cause of cancer mortality,¹ and there has been only minor improvement in overall five years survival

during the last decades. In Norway, the overall 5-year survival increased from 7.7% to 11.0% and from 11.5% to 14.3% in men and women, respectively, from 1969 to 2008. This is primarily related to improved curative treatment of limited disease.¹ Accordingly, early detection of lung cancer and identification of new indicators of risk or disease development are warranted. Tobacco smoking is the major cause of lung cancer, but also other factors like sex, age, body mass index (BMI), asbestos, and radon are related to the risk of lung cancer.^{2,3}

Inflammation plays a central role in the development of both lung cancer^{4,5} and cardiovascular disease (CVD)⁶ and CVD is frequently seen in patients with lung cancer.⁷ The high prevalence of CVD in lung cancer patients could be because of common risk factors for both diseases (age, smoking), but beyond these and genetic/epigenetic factors, specific traits associated with CVD could be independent risk factors for lung cancer. Chronic inflammation is associated with an increased cell turnover with the potential of generating genetic errors, stimulate angio-neogenesis, and apoptosis⁸ and plays a role in the pathogenesis of CVD with an influence on all stages of the disease.⁶

Airway inflammation might also influence lung cancer development, for example, chronic obstructive pulmonary disease (COPD) has been found to be an independent risk factor for lung cancer.⁹ Both COPD and CVD are associated with chronic inflammation^{10,11} and represent the most prevalent comorbidities in lung cancer patients. Still, the specific inflammatory processes involved in development of the two comorbidities may have independent influence on the occurrence of lung cancer. We hypothesized that self-reported CVD is an independent risk factor for lung cancer. Our hypothesis was studied in a large Norwegian cohort study, the Nord-Trøndelag Health Study (HUNT study).

MATERIALS AND METHODS

Study Subjects

The HUNT study is a large population-based prospective cohort study in Norway.¹² So far, three surveys have been performed, the HUNT1 (1984–1986), the HUNT2 (1995–1997), and the HUNT3 (2006–2008). All residents of the Nord-Trøndelag County, 20 years or older, have been invited to each survey. In total, 74,599 (88%), 65,333 (70%), and 50,839 (54%) persons attended HUNT1, HUNT2, and HUNT3, respectively. In total, 106,456 persons have participated at least once. In all three surveys, data on demographics,

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personal and family medical history, and clinical examinations were collected. In January 2009, the total population in Nord-Trøndelag counted approximately 130,000 inhabitants.

The present study includes participants from all three surveys. Self-reported CVD status at time of participation for the persons attending just one survey defined the study groups for comparison. Participants, who attended more than one survey and had altered self-reported CVD status from “no” to “yes” between the surveys, changed group allocation for the rest of the follow up, Figure 1.

The observation period was from the day of inclusion in the HUNT study (HUNT1, HUNT2, or HUNT3) until the event of lung cancer, death, at the time the answer regarding self-reported CVD changed from “self-reported CVD no” to “self-reported CVD yes” in HUNT2 or HUNT3 or at the end of the study at December 31, 2008, which ever occurred first. Persons with an observation period less than 1 year were excluded from the study. Data from HUNT were merged with data from the Cancer Registry of Norway (CRN) and the Norwegian Cause of Death Registry at Statistics Norway (SSB)¹³ that are mandatory registries in Norway (Fig. 1).

Outcome Variable

Lung Cancer

Lung cancer diagnosis was based on the classification system established by the World Health Organization, Histological Typing of Lung Tumours, second edition.¹⁴ Both patients with non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) were included in this study.

Norwegian law dictates that all cases of cancer must be registered in the Cancer Registry of Norway.

Exposure Variable

Self-reported CVD

The definition of self-reported CVD was based on baseline questionnaires in all three surveys. Self-reported CVD was defined by the answer “yes” to one or more of the following questions: “Do you have or have you had myocardial infarction?,” “Do you have or have you had angina pectoris?,” or “Do you have or have you had stroke?”.

Confounders

BMI (four categories according to the World Health Organization criteria; underweight = <18.5 kg/m², normal weight = ≥18.5 to <25 kg/m², overweight = ≥25 to <30 kg/m², obesity ≥ 30 kg/m²) and sex were included in the proportional hazard regression model. Age was included as a time variable in the model. In addition, we included chronic cough and phlegm, as a proxy variable for chronic inflammation in the airways into the model. Chronic cough and phlegm was based on the questions “Do you normally cough in the morning?” and “Do you normally expectorate phlegm from your chest in the morning?” in HUNT1, whereas in HUNT2 and HUNT3 it was based on the questions “Do you cough daily during periods of the year?” and “Do you usually bring up phlegm when coughing?”. In the analyses of former and current smokers, the burden of smoking was included and dichotomized into light smokers (1–20 pack years) and heavy smokers (>20 pack years).

Flowchart of inclusion over the period from HUNT 1 to 2008. Participants that changed the CVD status under observation (in HUNT 2 or HUNT3) marked with a circle, were included as a new observation from the time they answered yes to the question regarding CVD status. Sum person years: 1634967.

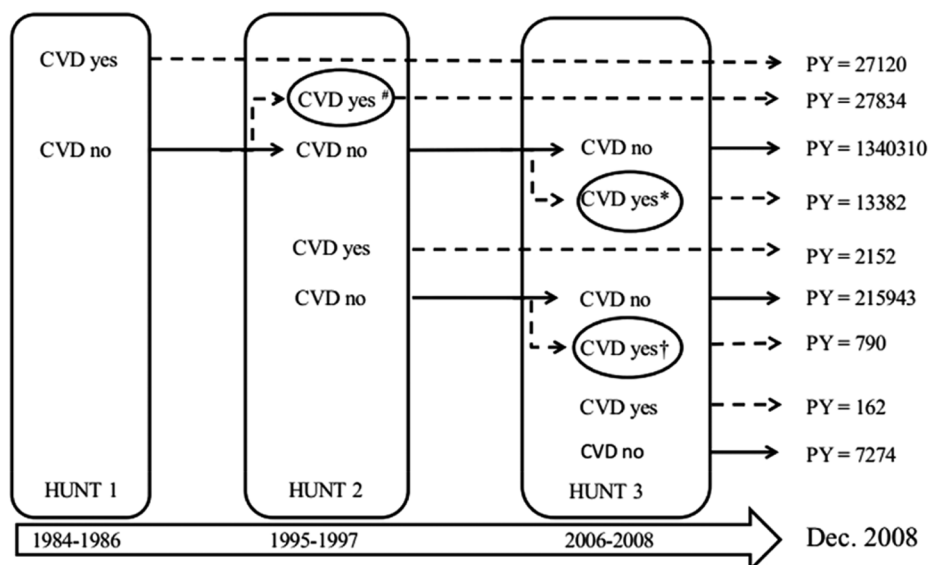


FIGURE 1. Flowchart of the inclusion over the period from HUNT1 to 2008. Numbers of participants that changed the cardiovascular disease (CVD) status during observation (in HUNT2 or HUNT3) are marked with a circle and were included as persons being exposed from the time they answered yes to the question defining CVD status.

[#], those who had “CVD no” in HUNT1 and changed to “CVD yes” in HUNT 2; ^{*} those who had “CVD no” in HUNT 1 and 2 and changed to “CVD yes” in HUNT 3; [†], those who had “CVD no” in HUNT 2 and changed to “CVD yes” in HUNT 3; PY, person years

Questions on tobacco smoking were included in a follow-up questionnaire in HUNT1, whereas in HUNT2 and HUNT3 these were included in the main baseline questionnaire. This influenced the response rate on these questions; 78%, 98%, and 97% in HUNT1, HUNT2, and HUNT3, respectively. In the whole HUNT population, smoking status was known in $n = 86,674$ (81%) persons. Missing data on pack years (burden of smoking) $n = 10,432$ (22%) and chronic cough with phlegm $n = 23,013$ (22%) reduced the number of persons eligible for complete cases analyses.

Statistical Methods

All analyses were performed separately for never, former and current smokers. The characteristics according to smoking status and self-reported CVD status were compared by χ^2 test for categorical variables and t test for continuous variables.

The effect of self-reported CVD on lung cancer incidence rates was estimated by proportional hazard regression models controlling for confounders and including age as a time variable in all analyses and therefore not as an own covariate in the model. Because of a high number of cases having missing values on chronic cough with phlegm or burden of tobacco smoking, maximum likelihood estimation was performed on 3 groups: (1) complete cases and (2) cases with a missing value on either chronic cough with phlegm or (3) cases with a missing value on burden of tobacco smoking. For cases with missing values on chronic cough with phlegm, a logistic regression model with self-reported CVD, sex, BMI, burden of tobacco smoking, and age at the time of inclusion as covariates was used. For cases with missing values on burden of tobacco smoking, a logistic regression model with self-reported CVD, sex, BMI, chronic cough with phlegm, and age at time of inclusion as covariates was used. A Wald test was used to compare the effect of self-reported CVD for complete cases and cases with the 1 or the other missing values mentioned above.

Potential interactions and proportional hazard assumption between the exposure variable and confounders were tested. The hazard ratio (HR) is reported with 95% confidence interval (CI). Because we did not adjust for multiple testing a P value less than 0.01 was defined as statistically significant.

Except for survival analysis, which was performed with the statistical program R version 2.13.1 (October 26, 2012) for Windows, all statistical analyses were performed with the statistical program PASW version 19 (Predictive Analytics Software IBM Corporation, NY).

Ethical Considerations

The Regional Committee for Medical and Health Research Ethics approved the current study (REK# 2010/1081). All participants in HUNT have signed informed consent for use of their data in research.

RESULTS

Study Participants

A total of 97,087 persons (52% females and 48% males) were included in the study. A complete dataset was available in 65,828 persons, in never smokers $n = 33,121$ (86% of all

never smokers), former smokers $n = 11,776$ (56% of all former smokers), and current smokers $n = 20,931$ (78% of all current smokers). The participants were followed for an average of 15 years at risk, for a total of 1,634,967 person years. The mean age at inclusion was 46 ± 18 years.

During follow up, 1080 cases (1.1%) of lung cancer occurred (20% SCLC, 80% NSCLC, 721 cases (1.5%) in men, and 359 cases (0.7%) in women. The mean age at diagnosis of lung cancer was 70.2 ± 10 years for both sexes. The cumulative incidence of lung cancer among never smokers, former smokers, current smokers, and unclassified was 72 (0.2%), 182 (0.9%), 698 (2.6%), and 128 (1.2%), respectively. Baseline characteristics of the study population are shown in Table 1.

Self-Reported CVD and Lung Cancer

In never smokers, 37 cases of lung cancer/100,000 person years were seen in those with self-reported CVD versus 12 cases/100,000 person years in those without self-reported CVD. In former and current smokers, 280 cases of lung cancer/100,000 person years were seen in those with self-reported CVD versus 64 cases of lung cancer/100,000 person years in those without self-reported CVD. Persons with self-reported CVD were older than those without self-reported CVD, 70.4 ± 11.2 versus 43.7 ± 17.3 years. There were more former and current smokers among persons with self-reported CVD. Men had more often self-reported CVD. There was no difference in the stage (metastatic versus non metastatic disease and the histology (NSCLC versus SCLC in lung cancer patients with self-reported CVD compared with those patients without self-reported CVD (data not shown).

Results from the Regression Models

In univariate regression model, former (HR: 2.47, 95% CI: 1.77–3.45) and current smokers (HR: 1.59, 95% CI: 1.26–2.01) with self-reported CVD were at higher risk for lung cancer but not never smokers with self-reported CVD (HR: 1.04, 95% CI: 0.41–2.67), compared with those without self-reported CVD (Fig. 2).

After adjustment for sex, BMI, burden of tobacco smoking, and chronic cough with phlegm, former and current smokers with self-reported CVD were still at higher risk (1.4–1.7) getting lung cancer (Tables 2–4). The Wald test did not show any significant change of the estimate of the HR for self-reported CVD, in never, former, and current smokers, comparing results from cases with missing data with results from analyses including missing cases and complete cases. In a separate analysis of cases with unknown smoking status ($n = 17,433$) and after adjustment for BMI and sex, the HR for self-reported CVD was (HR [95% CI] 1.80 [1.12–2.90]).

Among never and current smokers, no interactions were found between self-reported CVD and confounders. In former smokers, however, the impact of self-reported CVD on the risk of lung cancer was four times higher in light smokers compared with heavy smokers ($P = 0.001$). No major deviation from the proportional hazard function was found. All analyses were recalculated with three and five categories for pack years. The results remained unchanged in the three groups (never, former, and current smokers) (results not shown).

TABLE 1. Baseline Characteristics (BMI, Sex, Chronic Cough With Phlegm, Person Years, and Age at Inclusion), for the Study Population with Available Smoking Status

		Never Smokers (n = 38,656)		Former Smokers (n = 20,914)		Current Smokers (n = 26,894)	
		CVD		CVD		CVD	
		Yes n = 2205	No n = 36,451	Yes n = 2304	No n = 18,610	Yes n = 1472	No n = 25,422
BMI*	<18.5	1	1	1	1	2	2
	≥18.5 to <25.0	30	51	29	47	45	58
	≥25.0 to <30.0	45	36	50	40	42	31
	≥30.0	23	13	20	12	12	9
Sex	Female	69	59	18	43	25	51
	Male	31	41	82	57	75	49
Chronic cough with phlegm	Yes	5	3	8	4	18	10
Smoking	Light smoker	—	—	60	89	53	84
	Heavy smoker	—	—	40	11	47	16
Person years†		14.6 ± 8.3		14.1 ± 9.0		16.5 ± 7.8	
Age at inclusion†		44.2 ± 19.1		46.9 ± 17.2		42.4 ± 15.6	

Figures are percentage of participants in each group, The HUNT study.

*Kg/m².

†Mean and standard deviation.

CVD, cardiovascular disease; BMI, body mass index; n, numbers.

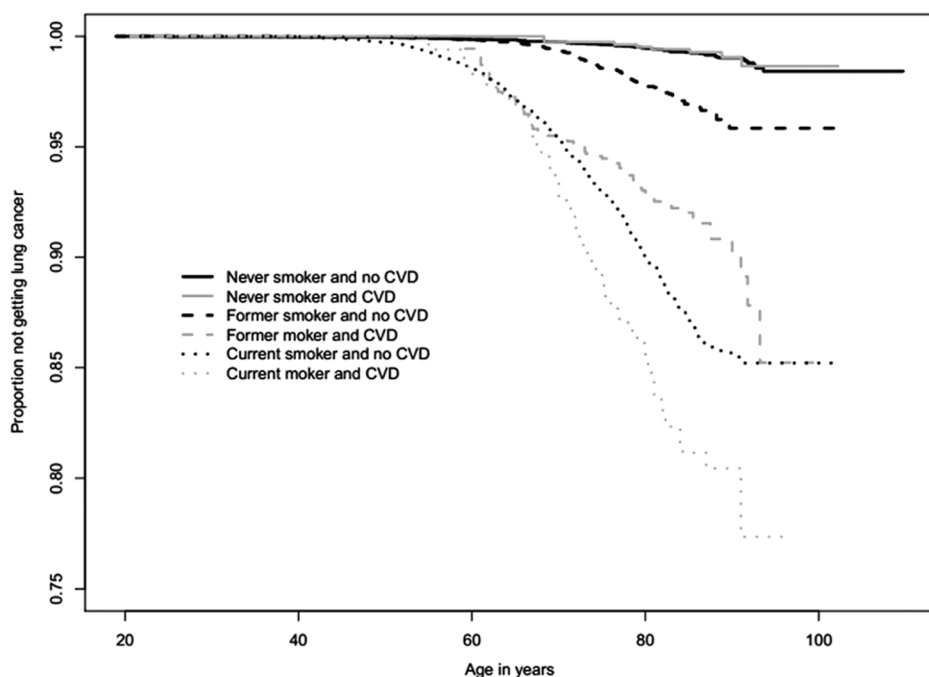


FIGURE 2. Plot of proportion “not getting lung cancer” by age for never smokers (n = 38,656), former smokers (n = 20,914), and current smokers (n=26,894), separately presented for persons with (n = 5981) and without cardiovascular disease (n = 80,483). The HUNT study.

DISCUSSION

The present study indicates that self-reported CVD is an independent risk factor for lung cancer in former and current smokers. Adjusting for other risk factors like BMI, sex, chronic cough, or phlegm, as a proxy variable for chronic inflammation in the airways, and the burden of smoking,

weakened the associations, but CVD was still an independent risk factor for lung cancer. To our knowledge, this is the first study investigating the association between self-reported CVD and the incidence of lung cancer.

CVD is prevalent among patients with lung cancer, approximately 20%^{7,15} and chronic inflammation seems to be a

TABLE 2. Cox Regression Model to Analyze the Association Between CVD and Lung Cancer in Never Smokers, Adjusted for BMI, Sex, and Chronic Cough with Phlegm, With Age Used as the Time Variable

	HR	95% CI
CVD	0.87	0.34–2.23
BMI*		
<18.5	4.57	0.60–34.76
≥18.5 to <25.0	1	
≥25.0 to <30.0	2.13	1.16–3.92
≥30.0	1.03	0.39–2.69
Sex		
Male vs. female	2.34	1.37–3.96
Chronic cough with phlegm		
Yes vs. no	2.51	0.78–8.09

n = 33,121, 58 cases of lung cancer.
*Kg/m²
CVD, cardiovascular disease; BMI, body mass index; *n*, numbers; HR, hazard ratio; CI, confidence interval

TABLE 3. Cox Regression Model to Analyze the Association Between CVD and Lung Cancer in Former Smokers, Adjusted for BMI, Sex, Burden of Smoking and Chronic Cough with Phlegm, with Age Used as the Time Variable

	HR	95% CI
CVD	1.74	1.11–2.73
BMI*		
<18.5	2.60	0.36–19.01
≥18.5 to <25.0	1	
≥25.0 to <30.0	0.81	0.53–1.25
≥30.0	0.80	0.43–1.48
Sex		
Male vs. female	1.43	0.82–2.49
Chronic cough with phlegm		
Yes vs. no	0.88	0.32–2.42
Heavy vs. light smoker	3.56	2.33–5.45

n = 11,776, 102 cases of lung cancer.
*Kg/m²
CVD, cardiovascular disease; BMI, body mass index; *n*, numbers; HR, hazard ratio; CI, confidence interval.

major pathophysiologic factor in the development of CVD.^{16,17} We found a positive association between self-reported CVD and lung cancer in both former and current smokers, but not in never smokers in our study population. This might be indicate that smoking and CVD could have an additive or synergistic effect in the development lung cancer. However, because the analyses with increasing numbers of categories for pack years did not changes the results, we think residual confounding by smoking is a minor problem in this study. The number of lung cancer cases in former smokers was small. Accordingly, the results in this group may be biased by a low power. This inconsistency may also be explained by competing risk, that is, heavy former smokers may die of other diseases before they get lung cancer.

TABLE 4. Cox Regression Model to Analyze the Association Between CVD and Lung Cancer in Current Smokers, Adjusted for BMI, Sex, Burden of Smoking and Chronic Cough with Phlegm, with Age Used as the Time Variable

	HR	95% CI
CVD	1.38	1.04–1.83
BMI*		
<18.5	1.36	0.67–2.75
≥18.5 to <25.0	1	
≥25.0 to <30.0	0.98	0.81–1.17
≥30.0	0.89	0.65–1.23
Sex		
Male vs. female	1.09	0.90–1.31
Chronic cough with phlegm		
Yes vs. no	1.55	1.22–1.97
Heavy vs. light smoker	2.11	1.75–2.54

n = 20,931, 521 cases of lung cancer.
*Kg/m²
CVD, cardiovascular disease; BMI, body mass index; *n*, numbers; HR, hazard ratio; CI, confidence interval.

Because smoking causes both lung cancer and CVD, our results could be confounded by the effect of smoking. Stratification by smoking status and adjustment for smoking burden (light and heavy smokers) did, however, not change the estimates. Concerning the interaction between the burden of tobacco smoking and self-reported CVD in former smokers, this may depend on bias related to self-reported smoking. Those with less education and/or heavy smokers are likely to report inaccurate number of cigarettes per day¹⁸ and this is especially seen in former smokers.¹⁹

Chronic inflammation plays a key role in the underlying pathophysiology of both CVD and lung cancer and could theoretically explain our findings, at least to some extent. Chronic inflammation is associated with an increased cell turnover with the potential of generating genetic errors, and stimulating angio-neogenesis and apoptosis.⁸ Different types of chronic inflammatory diseases are positively associated with cancers, for example, ankylosing spondylitis and kidney cancer,²⁰ inflammatory bowel disease and colon cancer,²¹ and COPD and lung cancer.^{9,22} Genetic factors responsible for our immune response may have impact on who will develop specific inflammations leading to COPD and/or CVD. Our genetic constitution may be crucial for the susceptibility of a distinct inflammation and in the next step for the development of lung cancer and may explain why only a minor percentage of tobacco smokers develop COPD and lung cancer. A certain exposure may be necessary, but not sufficient to develop a specific disease, and may illustrate the importance of the interplay between both exposure and genetic constitution or susceptibility to cancer. Other factors such as nutrition, vitamins, physical activity, and indoor air pollution may also contribute to the development of lung cancer^{23–25} and are not tested in our study.

However, our observation in the current study showing that self-reported CVD in former and current smokers may represent an additional risk factor for lung cancer is noteworthy

but not surprising given the high prevalence of CVD in patients with lung cancer.⁷ Smokers with self-reported CVD seem to be at higher risk of developing lung cancer compared with smokers without self-reported CVD. Thus, it may have a significant influence on the detection and definition of the population that would benefit from screening for lung cancer. To date, screening for lung cancer is not recommended in Europe. The National Lung Screening Trial, the largest and most reliable screening study for lung cancer to date, included people 55–74 years of age having smoked 30 pack years or more (7% of all smokers in United States).²⁶ A worldwide debate discussing future widespread screening is running, and the hottest question is how to define the risk group for screening. CVD are highly prevalent in smokers, and this subgroup may be a new and important risk group for lung cancer screening, making the results of the present study highly relevant.

Strengths and Limitations

This study has several strengths. First, the present study is a cohort study from a well-defined geographic area, with a stable and large number of inhabitants and a high participant rate, especially in the first two surveys, 88% and 70%, respectively. Second, the HUNT study includes comprehensive data on known risk factors and confounders for CVD and lung cancer which were included in the analyses in the present study. Third, our study has a long observation period with a median at 15.3 years. Fourth, the use of our national cancer registry, with obligatory registration of all new cases of cancer, ensures a high validity of the cancer diagnosis and cause of death. Fifth, representativity, where the prevalence of lung cancer, distribution of SCLC and NSCLC, and median age of the lung cancer patients of 71 years is in line with other studies and indicates high external validity of the present study.

One limitation is the relatively high number of missing data regarding smoking status, pack years and data about chronic cough with phlegm. However, including cases with missing data did not change the results. Self-reported CVD diagnosis in our study is based on questionnaire and we cannot rule out that we have missed patients with CVD among nonresponders a fact that may bias our results. Further, we have adjusted for confounders at baseline but not included changes during observation, which might bias the results.

Most patients with lung cancer have attended the HUNT1 study (69%). In HUNT1, no blood samples were taken so we have not the opportunity to analyze inflammation markers like IL-6, neither Vitamin D nor calcium.

CONCLUSION

Self-reported CVD is associated with a higher risk of lung cancer in former smokers and current smokers independent of the burden of tobacco smoking, whereas no association was found in never smokers. CVD may be a novel risk factor for lung cancer screening, a task for future studies.

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