Journal of the American Heart Association

ORIGINAL RESEARCH

Tobacco Consumption and High-Sensitivity Cardiac Troponin I in the General Population: The HUNT Study

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BACKGROUND: Cardiac troponins represent a sensitive index of subclinical myocardial injury and are associated with increased risk of cardiovascular events in the general population. Despite positive associations with cardiovascular risk of both cardiac troponins and cigarette smoking, concentrations of cardiac troponin I measured by high-sensitivity assays (hs-cTnI) are paradoxically lower in current smokers than in never-smokers. The impact of smoking intensity and time from smoking cessation on hs-cTnI remains unknown.

METHODS AND RESULTS: hs-cTnI concentrations were measured in 32028 subjects free from cardiovascular disease enrolled in the prospective, population-based HUNT (Trøndelag Health Study). Tobacco habits were self-reported and classified as never (n=14 559), former (n=14 248), and current (n=3221) smokers. Current smokers exhibited significantly lower concentrations of hs-cTnI than never-smokers (P<0.001). In adjusted models, both current smoking (–17.3%; 95% CI, –20.6 to –13.9%) and former smoking (–6.6%; 95% CI, –8.7 to –4.5%) were associated with significantly lower hs-cTnI concentrations. Among former smokers, higher smoking burden (>10 pack-years) were associated with lower concentrations of hs-cTnI. Time since smoking cessation was associated with increasing concentrations of hs-cTnI in a dose-dependent manner (P for trend<0.001), and subjects who quit smoking >30 years ago had concentrations of hs-cTnI comparable with those of never-smokers.

CONCLUSIONS: In the general population, both current and former cigarette smoking is associated with lower concentrations of hs-cTnI. In former smokers, there was a dose-response relationship between pack-years of smoking, and hs-cTnI. Time since smoking cessation was associated with increasing concentrations of hs-cTnI, indicating a continuum of hs-cTnI from current smoker to never-smokers.

Key Words: cardiac troponins ■ cardiovascular disease ■ tobacco

Concentrations of cardiac troponins (cTn) measured with high-sensitivity (hs) assays are strongly associated with the risk of heart failure and cardiovascular death both in the general population and in patients with stable ischemic heart disease.[1–5] A number of cardiac risk factors are associated with increasing concentrations of hs-cTn. Still, for cigarette smoking an inverse association with concentrations of hs-cTn has been demonstrated both in the general population and in patients with stable coronary artery disease.[6–8] Given the established and strong relationship between smoking and cardiovascular risk, lower concentrations of hs-cTn in current smokers remains an unexpected and so far, elusive observation.

Cigarette smoking has detrimental effects on the cardiovascular system.[9] Smoking promotes both atherogenesis and thrombosis,[10] and cigarette smoking is an especially strong risk factor for coronary artery disease.[11] In contrast to the strong association between tobacco smoking and atherothrombotic events, the relationship

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Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.021776

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In this large population-based cohort, we demonstrate a dose-response relationship between pack-years of smoking and circulating concentrations of cardiac troponin I in former smokers.
- In former smokers, increasing time since smoking cessation was associated with higher cardiac troponin I. After >30 years of cessation, concentrations of cardiac troponin I did not differ between former smokers and never-smokers.

What Are the Clinical Implications?

- The results demonstrate that both current and former smoking exposure may impact the cardiac troponin complex.
- Cigarette smoking should therefore be considered when interpreting cardiac troponin concentrations in the general population.
- The focus of future studies should be to identify mechanistic explanations for this observation.

Nonstandard Abbreviations and Acronyms

cTn	cardiac troponin
cTnI	cardiac troponin I
hs	high sensitivity
HUNT	Trøndelag Health Study

between cigarette smoking and the risk of heart failure has not been fully elucidated. Some studies have demonstrated associations between smoking and heart failure independently of coronary artery disease,[12,13] but the direct effect of tobacco smoking on cardiomyocyte health is incompletely understood. Structural myocardial alterations preceding overt heart failure, such as left ventricular hypertrophy and fibrosis, are more strongly associated with elevations in hs-cTn than the extent and severity of atherosclerosis[5,14,15] The inverse association between smoking and hs-cTn is controversial, the evidence is limited and there is a need for additional investigations. Smoking status alone may be insufficient to adjust for the detrimental effects of smoking, and results from the Multi-Ethnic Study of Atherosclerosis study indicates that the harmful effects of smoking may be more related to intensity of smoking than the duration.[16] Increasing time since smoking cessation is associated with a reduction in cardiovascular risk, but whether time from cessation impacts concentrations of cardiac troponin I (cTnI) has not been explored.

Accordingly, using data from one of the largest population cohorts with measurements of hs-cTnI and a comprehensive characterization of tobacco habits currently available, we hypothesized that increasing consumption and duration of cigarette smoking would be associated with lower concentrations of hs-cTnI in a dose-dependent fashion. Further, as current smokers have lower concentrations of hs-cTnI than never-smokers, we hypothesized that concentrations of hs-cTnI would increase with time from smoking cessation in former smokers.

METHODS

The data from HUNT (Trøndelag Health Study) used in the current study are available on application to the HUNT Data Access Committee in accordance with the policy on data availability (further information and contact information: https://www.ntnu.edu/hunt/data).

Study Overview and Participants

HUNT is a population-based, cross-sectional, and prospective observational study conducted in the county of Nord-Trøndelag in Norway. Between 1984 and 2019, all residents in the county from aged ≥20 years were invited to participate in both HUNT 1 (1984–86), HUNT 2 (1995–1997), HUNT 3 (2006–2008), and HUNT 4 (2017–2019). Details of the study design and participants have been described previously.[17] The present study represents a cross-sectional analysis of a subsample of 37 840 individuals participating in the fourth wave of the HUNT Study (HUNT 4) with measurement of cTnI. Participants with a history of cardiovascular disease (CVD, n=3428), or missing data on CVD (n=2258) and smoking exposure (n=126) were excluded, leaving 32 028 individuals available for the main analysis. The Regional Committee for Medical Research Ethics approved the main study and this substudy (REC 2012/859), and all participants provided informed written consent.

Baseline Data

Clinical examinations were performed in a standardized manner and included height, weight, waist and hip circumference, and blood pressure. Systolic and diastolic blood pressure were measured in a sitting position by the use of an automated device (Dinamap CARESCAPE V100, GE Healthcare), and the average of the second and third measurement was used. Information on health and lifestyle related items were gathered from self-reported written questionnaires. A full description of the examinations and the questionnaire is available from http://www.ntnu.edu/hunt.

Measurements of Smoking

Data on past and current cigarette smoke exposure were collected via the HUNT 4 questionnaire. Smoking

status was classified into 3 different groups based on self-reported tobacco consumption; never, former, and current smoking. Of the total population of 32 028, a subgroup of 82% of the current smokers and 59% of the former smokers had available data on smoking duration and intensity. Information on intensity of smoking was assessed as current or former daily cigarette consumption. Duration of current or former smoking was calculated by age (age at cessation in former smokers) minus age first started smoking. Pack-years were calculated as packs of cigarettes smoked daily multiplied by duration of smoking in years. Years since cessation in former smokers were calculated as age minus age at time of cessation.

Blood Sampling Procedures and Biochemical Assays

Samples of non-fasting venous blood samples were collected by trained nurses, centrifuged at room temperature and serum aspirated. Samples were kept at +4 °C until final analysis. The serum samples were shipped to Levanger Hospital, Norway for analysis of hs-cTnI within 24 hours. cTnI concentrations were measured with the Abbott Diagnostics Architect STAT High Sensitive Troponin assay, with a lower detection limit of 1.2 ng/L.[18] cTnI concentrations below lower detection limit were assigned a value of 0.6 ng/L. The manufacturer reports sex-specific 99th percentiles: 15.6 ng/L in women and 34.2 ng/L in men. The assay has a analytical coefficient of variation of 20% at 1.3 ng/L, 10% at 4.7 ng/L, and 4% at 26.2 ng/L. During the period of the HUNT samples analysis, coefficient of variation in our laboratory were 5.7%, 6.8%, and 7.7% in the low range (20, 15, and 11 ng/L, respectively) and 4.9%, 6.9%, and 6.4% in the high range (2150, 2790, and 3100 ng/L, respectively).

Estimated glomerular filtration rate was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.[19] CRP (C-reactive protein) concentrations were determined using an hs assay with latex immunoassay methodology from Abbott. The limit of detection for CRP was 0.1 mg/L with a analytical coefficient of variation of 2.4% in the low range and 1.1% in the high range. Measurement of triglycerides was performed by enzymatic colorimetric methodology. Total cholesterol and high-density lipoprotein cholesterol were analyzed by the enzymatic colorimetric cholesterol esterase method.

Statistical Analysis

Categorical variables are reported as absolute numbers (proportions) and continuous variables as median with interquartile range. Baseline participant characteristics were compared with the Mann-Whitney *U*-test (continuous variables) and the Fisher Exact test (categorical variables). Pack-years, smoking intensity, and time since smoking cessation were each modeled as a categorical variable. Based on the distribution of median values in former and current smokers, pack-years were categorized as ≤10 and >10 and intensity of smoking (cigarettes/day) was categorized as ≤10 and >10. Categorization of time since cessation was based on quintile values. Linear regression analyses were performed to investigate the association between cigarette smoking, pack-years, smoking intensity, and time since cessation and log-transformed hs-cTnI concentrations. The regression models were adjusted for a priori selected variables influencing concentrations of hs-cTnI, and include sex, age, current usage of moist powder smokeless tobacco (snus), total and high-density lipoprotein cholesterol, systolic blood pressure, body mass index, diabetes, estimated glomerular filtration rate, CRP, alcohol consumption (frequency of intake last 12 months), and socioeconomic status (quantified by family income and education level). Because of possible different impact of smoking status on hs-cTnI concentrations according to age, we also performed linear regression analyses in which participants were categorized in 4 groups on the basis of age (≤40, >40–53, >53–65.2, and >65.2 years). Possible modification of the effect of age on the association between cigarette smoking and log-transformed hs-cTnI concentrations was examined generating an interaction term. Finally, we performed 2 separate sensitivity analyses. First, we performed a sensitivity analysis that included all participants (and not only participants without CVD). Second, we performed a sensitivity analysis excluding outliers from the data set, ie, participants with the 1% highest hs-cTn concentrations were excluded. Statistical analyses were performed by using IBM SPSS Statistics 26 (IBM Corp) and STATA 16 (StataCorp).

RESULTS

Baseline Characteristics

A total of 5840 (40.5%) never-smokers, 5031 (35.3%) former smokers, and 1439 (44.7%) current smokers had cTnI concentrations below the lower detection limit. Clinical characteristics of the participants according to tobacco habits are summarized in Table 1. Current smokers were older and more likely to be women than never-smokers. Compared with never-smokers, current and former smokers had higher concentrations of CRP, triglycerides, and total cholesterol. Furthermore, current and former smokers were less likely to be in a high-income or high-education group compared with never-smokers.

Table 1. Baseline Characteristics According to Smoking Status

Variable	Never-smoker		Former smoker		Current smoker	
	n	Value	n	Value	n	Value
Female sex, n (%)	14 559	8149 (56.0)	14 248	7865 (55.2)	3221	1966 (61.0)*§
Age, y	14 559	49.2 (35.6–62.0)	14 248	56.7 (42.6–67.7)*	3221	53.8 (41.7–63.8)*§
Weight, kg	14 411	77.9 (67.4–89.4)	14 075	79.9 (69.5–91.2)*	3199	76.2 (66.2–88.7)*§
BMI, kg/m^2	14 491	26.3 (23.6–29.5)	14 169	27.1 (24.4–30.3)*	3207	26.5 (23.5–29.6)§
Waist-hip ratio	14 088	0.94 (0.88–1.0)	13 814	0.96 (0.91–1.02)*	3145	0.96 (0.9–1.02)*
Systolic blood pressure, mm Hg	14 524	124 (113–136)	14 213	126 (116–139)*	3212	124 (114–137)§
Diastolic blood pressure, mm Hg	14 524	72 (65–79)	14 213	73 (66–80)*	3212	71 (64–79)†§
Alcohol consumption	14 442		14 067		3183	
Nondrinker		1978 (13.7)		1069 (7.6)		323 (10.1)
1 or less a month		4405 (30.5)		3430 (24.4)		969 (30.4)
2–4 times a month		6029 (41.7)		6336 (45.0)		1336 (42.0)
2–3 times a week		1821 (12.6)		2758 (19.6)		455 (14.3)
More than 4 times a week		209 (1.4)		474 (3.4)		100 (3.1)
Cardiac troponin I, ng/L	14 559	1.54 (0.6–3.02)	14 248	1.67 (0.6–3.19)*	3221	1.33 (0.6–2.32)*§
HbA1c mmol/mol	14 520	33 (31–35)	14 204	33 (31–36)*	3209	33 (31–36)*
Triglycerides non-fasting, mmol/L	14 559	1.30 (0.92–1.88)	14 248	1.42 (1.0–2.05)*	3221	1.58 (1.12–2.27)*§
Total cholesterol, mmol/L	14 559	5.17 (4.47–5.94)	14 248	5.34 (4.60–6.10)*	3221	5.41 (4.66–6.23)*§
HDL cholesterol, mmol/L	14 559	1.36 (1.15–1.61)	14 248	1.37 (1.15–1.63)†	3221	1.3 (1.09–1.54)*§
Total HDL cholesterol	14 559	3.72 (3.07–4.58)	14 248	3.80 (3.14–4.68)*	3221	4.11 (3.31–5.09)*
eGFR, mL/min/1.73m^2	14 559	96 (84–109)	14 248	92 (80–104)*	3221	97 (87–108)‡§
CRP, mg/L	14 559	1.12 (0.55–2.45)	14 248	1.29 (0.64–2.76)*	3221	1.50 (0.73–3.14)*§
Diabetes, n (%)	14 542	572 (3.9)	14 232	806 (5.7)*	3216	153 (4.8)‡¶
Snus habits	14 410		14 058		3142	
Former		1113 (7.6)		2177 (15.3)		324 (10.1)
Current		1460 (10.0)		3093 (21.7)		482 (15.0)
Smoking habits, pack-years			8338	10 (4.5–18.0)	2629	18.5 (11.4–25.9)§
Higher education, n (%)	14 492	6755 (46.4)	14 189	5068 (35.6)*	3202	722 (22.4)*§
Income	14 183		13 919		3120	
Low		3752 (25.8)		4039 (28.3)		1323 (41.1)
Middle		7206 (49.5)		7546 (53.0)		1498 (46.5)
High		3225 (22.2)		2334 (16.4)		299 (9.3)

BMI indicates body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; *HbA1c*, glycated hemoglobin A1c; and HDL, high-density lipoprotein cholesterol.

*P<0.001, †P<0.01; ‡P<0.05 compared with never-smokers.

§P<0.001, ‖P<0.01, ¶P<0.05 compared with former smokers.

Associations Between Smoking Status and hs-cTnI

After adjustment for age and sex, a gradient in hs-cTnI concentrations was apparent with current smokers having −22.2% (95% CI, −25.5 to −19.0) lower concentrations and former smokers −8.5% (95% CI, −10.5 to −6.5) lower concentrations compared with never-smokers (P for trend<0.001). This gradient remained in the fully adjusted models (P for trend <0.001, Table 2). The sensitivity analysis also including participants with CVD and the sensitivity analysis excluding outliers also showed similar results (Table S1 and S2). We found no evidence of an interaction with age on the association between smoking status and concentrations of hs-cTnI (Table S3).

Table 2. Association Between Smoking Status and hs-cTnI

	Model 1	Model 2
	Change in cTnI	Change in cTnI
Never	Reference	Reference
Former smoker	−8.5% (−10.5 to −6.5)	−6.6 % (−8.7 to −4.5)
Current smoker	−22.2% (−25.5 to −19.0)	−17.3% (−20.6 to −13.9)

A positive percentage indicates a relative increase in continuous concentrations of troponin compared with never smokers, whereas a negative percentage indicates an inverse association. Model 1 adjusted for sex, age, Model 2 adjusted for sex, age, current snus, total and high-density lipoprotein cholesterol, systolic blood pressure, body mass index, diabetes mellitus, estimated glomerular filtration rate, C-reactive protein, alcohol consumption, educational level, and family income.

Associations of hs-cTnI With Burden, Intensity, and Time Since Smoking Cessation

Pack-Years

In fully adjusted models, increasing numbers of pack-years of smoking were associated with lower concentrations of hs-cTnI in the total population (−3.0%; 95% CI, −4.3% to −1.7% per 10 pack-years). Using never-smokers as the reference (0%), ever smokers with a history of >10 pack-years had significantly lower concentrations of hs-cTnI than those with a history of ≤10 pack-years (−13.9%; 95% CI, −16.5% to −11.3% versus −7.8%; 95% CI, −10.6 to −5.1, *P* for comparison=0.001). In former smokers, a history of >10 pack-years was associated with significantly lower concentrations of hs-cTnI than a history of ≤10 pack-years (−11.7%; 95% CI, −15.0 to −8.5 versus −7.2%; 95% CI, −10.2 to −4.1, *P* for comparison=0.02) in fully adjusted models (Table 3). In current smokers, concentrations of hs-cTnI did, however, not differ according to number of pack-years consumed (*P*=0.70, Table 3).

Intensity

Concentrations of hs-cTnI did not differ according to smoking intensity in current (*P* for comparison=0.81, Table 3) or former smokers (*P* for comparison=0.56).

Years Since Smoking Cessation and Concentrations of hs-cTnI

Time since smoking cessation was positively associated with concentrations of hs-cTnI in fully adjusted models. Overall, there was a significant trend (*P*<0.001) of increasing concentrations of hs-cTnI from current smokers, to increasing time since cessation in former smokers, to never-smoker with the highest concentrations of cTnI (Figure).

DISCUSSION

The main findings in this cohort of 32 028 subjects free from established CVD, are that not only smoking status,

Table 3. Association Between Smoking Variables: Pack-Years, Intensity of Smoking, and hs-cTnI

	Model 1	Model 2
	Change in cTnI	Change in cTnI
Pack, y		
Never	Reference	Reference
Former smokers≤10 pack, y n=4239	−10.2% (−13.1 to −7.3)	−7.2% (−10.2 to −4.1)
Former smokers>10 pack, y n=4099	−14.5% (−17.6 to −11.5)	−11.7% (−15.0 to −8.5)
Current smokers≤10 pack, y n=543	−20.7% (−28.1 to −13.4)	−16.7% (−24.2 to −9.2)
Current smokers>10 pack, y n=2086	−25.0% (−29.0 to −21.0)	−18.3% (−22.5 to −14.0)
Intensity, number of cigarettes/day		
Never smokers	Reference	Reference
Former smokers, ≤ 10 cigarettes/day n=5358	−12.0% (−14.8 to −9.3)	−8.9% (−11.8 to −6.0)
Former smokers, >10 cigarettes/day n=3123	−12.6% (−15.9 to −9.3)	−10.1% (−13.6 to −6.5)
Current smokers, ≤ 10 cigarettes/day n=1705	−23.9% (−28.2 to −19.6)	−18.3% (−22.8 to−13.7)
Current smokers, >10 cigarettes/day n=936	−24.4% (−30.1 to −18.8)	−17.4% (−23.3 to −11.5)

A positive percentage indicates a relative increase in continuous concentrations of troponin compared with never smokers, whereas a negative percentage indicates an inverse association. Model 1 adjusted for sex, age, Model 2 adjusted for sex, age, current snus, total and high-density lipoprotein cholesterol, systolic blood pressure, body mass index, diabetes mellitus, estimated glomerular filtration rate, C-reactive protein, alcohol consumption, educational level, and family income.

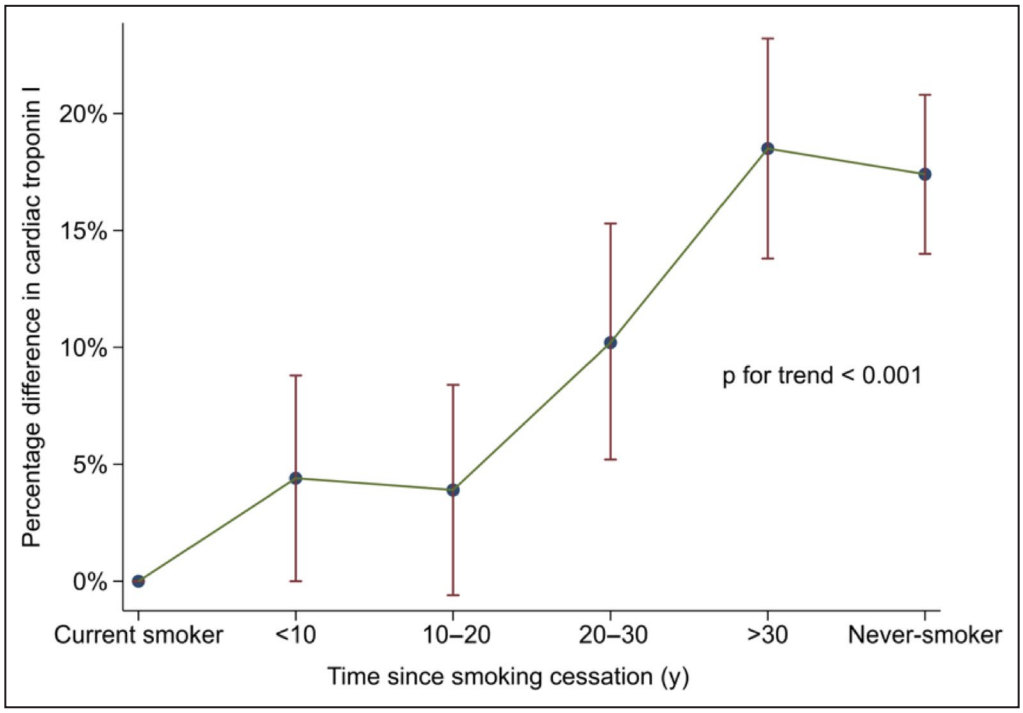

Figure. Association between time since smoking cessation and cardiac troponin I.

but also measures of smoking intensity and duration are associated with concentrations of hs-cTnI. Authors of the current report and other groups have previously demonstrated lower cardiac troponin concentrations in current smokers compared with never-smokers in the general population.[6,8] We now add to this knowledge by demonstrating lower hs-cTnI concentrations also in former smokers. Intriguingly, increasing time since smoking cessation was associated with higher concentrations of hs-cTnI in a dose-response fashion, with subjects who stopped smoking >30 years ago exhibiting concentrations comparable with those of never-smokers.

There are several different ways to quantify smoking exposure, and smoking status alone insufficiently adjusts for the effects of smoking on the cardiovascular system.[16] In the current investigation, we found that in addition to smoking status, intensity and pack-years of smoking were associated with lower concentrations of hs-cTnI. In the ARIC (The Atherosclerosis Risk in Communities Study), a positive association with number of pack-years and elevated hs-cTnT was found among ever smokers.[20] This discrepancy may be attributed to a less sensitive hs-cTn assay and dichotomization of hs-cTnT concentrations in ARIC. Although the increased risk of CVD persist for multiple years after smoking cessation, the difference in risk between former and never-smokers ceases with time.[11] In this study, time since smoking cessation was associated with increasing concentrations of hs-cTnI and concentrations of hs-cTnI did not differ between former smokers with >30 years since cessation and never-smokers.

Further, we found inverse associations between smoking measures investigated and hs-cTnI. The consistency of the present analysis supports the validity of our results and highlights that smoking exposure may impact the cardiac troponin complex. The mechanisms behind these observations are unknown. Atherosclerotic disease is a major contributor to the detrimental cardiovascular effects of cigarette smoking[21] and current and former smoking status is associated with subclinical atherosclerotic disease in subjects free from CVD.[22] Low-level concentrations of circulating hs-cTn are, however, more strongly associated with remodeling of the myocardium and direct myocyte injury[5,14] than atherosclerosis, and are strongly predictive of heart failure. Whether subclinical atherosclerotic disease could attenuate the association between fibrosis and hs-cTnI is unclear but is a plausible mechanism of lower hs-cTnI in current and former smokers.

Cigarette smoking induces systemic inflammation, and smoking is associated with an increased inflammatory biomarker response.[23] Although the net effect of cigarette smoke exposure is proinflammatory, nicotine could have anti-inflammatory effects. Specifically, nicotine binds to the α7 subunit of the nicotinic acetylcholine receptor resulting in activation of the cholinergic anti-inflammatory pathway, which in turn

inhibits macrophage tumor necrosis factor release.[24,25] Accordingly, smoking exposure could potentially inhibit immune-mediated myocardial remodeling, and the inverse association between smoking measures and hs-cTnI in our study could possibly be explained by cigarette-induced attenuation of cardiomyocyte turnover.

The smoker's paradox refers to improved survival and more favorable outcomes in cigarette smokers after acute myocardial infarction.[26–28] A proposed mechanism for this association has been that constituents of tobacco induce ischemic preconditioning and thereby confers cardioprotection.[27] If cigarette smoking renders the myocardium more resistant to ischemic damage, the inverse association between smoking measures and hs-cTnI could reflect reduced myocardial damage attributable to cigarette smoke exposure. However, the smoker's paradox could also be explained by younger age and better cardiac risk profile in smokers compared with non-smokers.[29] In the present study however, the models were adjusted for age and cardiac risk factors, thereby making this possible confounding factor unlikely to explain our findings. Furthermore, the inverse association between hs-cTnI and smoking remained similar in the sensitivity analysis including participants with CVD. Importantly, our study and results do not question the harmful effects of smoking and we support all efforts of reducing tobacco consumption.

Numerous studies have demonstrated the prognostic merits of hs-cTn in populations that included both smokers and non-smokers, suggesting that measurement of hs-cTn could help the clinician to identify individuals with increased risk for CVD.[3–5] Moreover, hs-cTnI measurements may identify those who benefit more from statin therapy.[30,31] The potential interaction by smoking on the association between hs-cTn and outcomes is, however, less studied. In the HUNT 2 study, smoking status was found to modify the association between hs-cTnI and cardiovascular death, admission for MI, and heart failure.[6] However, no significant interaction by smoking status was found on the association between hs-cTnT and hs-cTnI and cardiovascular events in the prevention of events with angiotensin converting enzyme inhibition cohort.[7] Moreover, in the Generation Scotland population-based study, no interaction by smoking on the prognostic value of hs-cTnI was observed.[32] Because of the cross-sectional design of the current analysis, we could not evaluate if smoking affects the prognostic value of hs-cTnI.

Demographic characteristics, ie, sex and gender, impact on hs-cTn concentrations, and in the context of acute myocardial injury, it is debated if these characteristics should be considered when evaluating hs-cTn concentrations. Whether the inverse association between hs-cTnI concentrations and cigarette smoking also holds true in the setting of acute myocardial injury has yet to be determined, but smoking status could represent another relevant covariate for individualized hs-cTn cut-offs in the future.

Strengths and Limitations

This study has several strengths, most importantly the large study sample consisting of both men and women in a wide age range and quantification of hs-cTnI with one of the most sensitive assays available. Moreover, data on income and education are included in the multivariable models to adjust for socioeconomical factors. Several limitations of this study should also be acknowledged. First, all data on tobacco habits are self-reported and not confirmed by biochemical tests. However, the correlation between self-reported tobacco/non-tobacco use and nicotine exposure, assessed by blood cotinine and nicotine, has been shown to be high. Secondly, information on second-hand cigarette smoke exposure was not available, and whether this affects hs-cTnI concentrations is unknown. However, data on snus tobacco, an oral tobacco product commonly used in Scandinavia, was available and adjusted for in the multivariable models. Thirdly, missing data on smoking duration and intensity (18% in current smokers, and 41% in former smokers) could have resulted in under- or over- estimation of the association between these parameters and hs-cTnI. Fourthly, since smoking both affects left ventricular mass and coronary artery disease, the addition of cardiac imaging to the study could have provided better understanding of the mechanisms underlying the difference in hs-cTnI. Lastly, regardless of the adjustment for education level and family income, residual confounding could theoretically explain our findings.

CONCLUSIONS

In this general population cohort free of CVD, both current and former smoking status and pack-years were associated with lower concentrations of hs-cTnI compared with never-smokers. Increasing time from smoking cessation was associated with elevation of hs-cTnI, and after >30 years of cessation, hs-cTnI concentrations did not differ significantly in former and never-smokers. This observation suggests that tobacco smoking affects the cardiac troponin complex even after smoking cessation. Future research should further investigate the mechanisms of these associations, and whether smoking directly affects the release or degradation of cardiac troponins.

ARTICLE INFORMATION

Received April 7, 2021; accepted November 11, 2021.

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Acknowledgments

The HUNT study is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. We thank Elin Øien, Department of Medical Biochemistry, Levanger Hospital, for skillfully performing the hs-cTnI analyses.

Sources of Funding

Dr Skranes was supported by a PhD fellowship from South-Eastern Norway Regional Health Authority. The cTnI measurements were sponsored by a grant from Abbott Diagnostics.

Disclosures

Dr. Røsjø has received honoraria from SpinChip Diagnostics and CardiNor AS. Dr. Omland reports consulting fees and research grant support via Akershus University Hospital from Abbott Laboratories, CardiNor, Novartis, Roche Diagnostics, Singulex, and SomaLogic. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Association between smoking status and hs-cTnI.

	Model 1		Model 2	
		P value		P value
Never	Reference		Reference	
Former smoker	-8.6% (-10.5 to -6.7)	< 0.001	-6.7 % (-8.7 to -4.7)	< 0.001
Current smoker	-22.3% (-25.3 to – 19.2)	< 0.001	-17.0% (-20.2 to -13.7)	< 0.001

* The analysis includes all participants (and not only participants without cardiovascular disease). N=35417 (16281 never smokers, 16988 former smokers and 3791 current smokers)

** A positive percentage indicates a relative increase in cardiac troponin I compared to never users, whereas a negative percentage indicates an inverse association

Model 1 adjusted for sex, age, Model 2 adjusted for sex, age, current snus, total and high-density lipoprotein cholesterol, systolic blood pressure, body mass index, diabetes mellitus, eGFR, CRP, alcohol consumption, educational level and family income.

Table S2. Association between smoking status and hs-cTnI.

	Model 1		Model 2	
		P value		P value
Never	Reference		Reference	
Former smoker	-7.6% (-9.4 to -5.8)	< 0.001	-5.9 % (-7.9 to -4.0)	< 0.001
Current smoker	-20.0% (-23.0 to – 17.0)	< 0.001	-15.1% (-18.2 to -12.0)	< 0.001

*The analysis includes participants without cardiovascular disease, participants with the one percent highest hs-cTn concentrations are excluded. N=31723 (14399 never smokers, 14103 former smokers and 3206 current smokers)

* A positive percentage indicates a relative increase in cardiac troponin I compared to never users, whereas a negative percentage indicates an inverse association

Model 1 adjusted for sex, age, Model 2 adjusted for sex, age, current snus, total and high-density lipoprotein cholesterol, systolic blood pressure, body mass index, diabetes mellitus, eGFR, CRP, alcohol consumption, educational level and family income.

Table S3. Association between smoking status and hs-cTnI according to age.

	Model 1		Model 2	
		P value		P value
Never	Reference		Reference	
Former smoker				
Age ≤ 40	-7.6% (-11.2 to -4.0)	<0.001	-5.8% (-9.8 to -1.9)	0.004
Age > 40-53	-7.1 % (-11.1 to -3.0)	0.001	-4.5% (-8.8 to 0.2)	0.041
Age > 53-65.2	-3.5% (-7.6 to 0.7)	0.099	-3.4 % (-7.7 to 0.8)	0.113
Age > 65.2	-10.1% (-14.4 to -5.8)	<0.001	-5.1% (-9.6 to -0.7)	0.023
Current smoker				
Age ≤ 40	-20.8% (-26.9 to -14.7)	<0.001	-16.1% (-22.6 to -9.7)	<0.001
Age > 40-53	-19.6% (-26.0 to -13.1)	<0.001	-10.4% (-17.2 to -3.6)	0.003
Age > 53-65.2	-18.3% (-24.5 to -12.0)	<0.001	- 11.6% (-18.1 to -5.1)	<0.001
Age > 65.2	-24.4 (-32.0 to -16.8)	<0.001	-11.7% (-19.4 to -3.9)	0.003

* A positive percentage indicates a relative increase in cardiac troponin I compared to never users, whereas a negative percentage indicates an inverse association.

Model 1 adjusted for sex, Model 2 adjusted for sex, current snus, total and high-density lipoprotein cholesterol, systolic blood pressure, body mass index, diabetes mellitus, eGFR, CRP, alcohol consumption, educational level and family income and model 1.

p for interaction between age and smoking status > 0.05 for all regressions models.