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CORRESPONDENCE

Research Correspondence

Development and Progression of Coronary Artery Calcification in Long-Term Smokers: Adverse Effects of Continued Smoking

To the Editor: Smoking has a major negative impact on global health. The adverse effects of smoking continuation relative to smoking cessation on coronary atherosclerosis are not well elucidated. The aim of this study was in a cohort of long-term smokers to assess the effects of continued smoking on the development and progression of subclinical coronary artery calcification (CAC) over time.

A total of 1,265 current or previous smokers 50 to 70 years old with at least 20 pack-years and without coronary artery disease

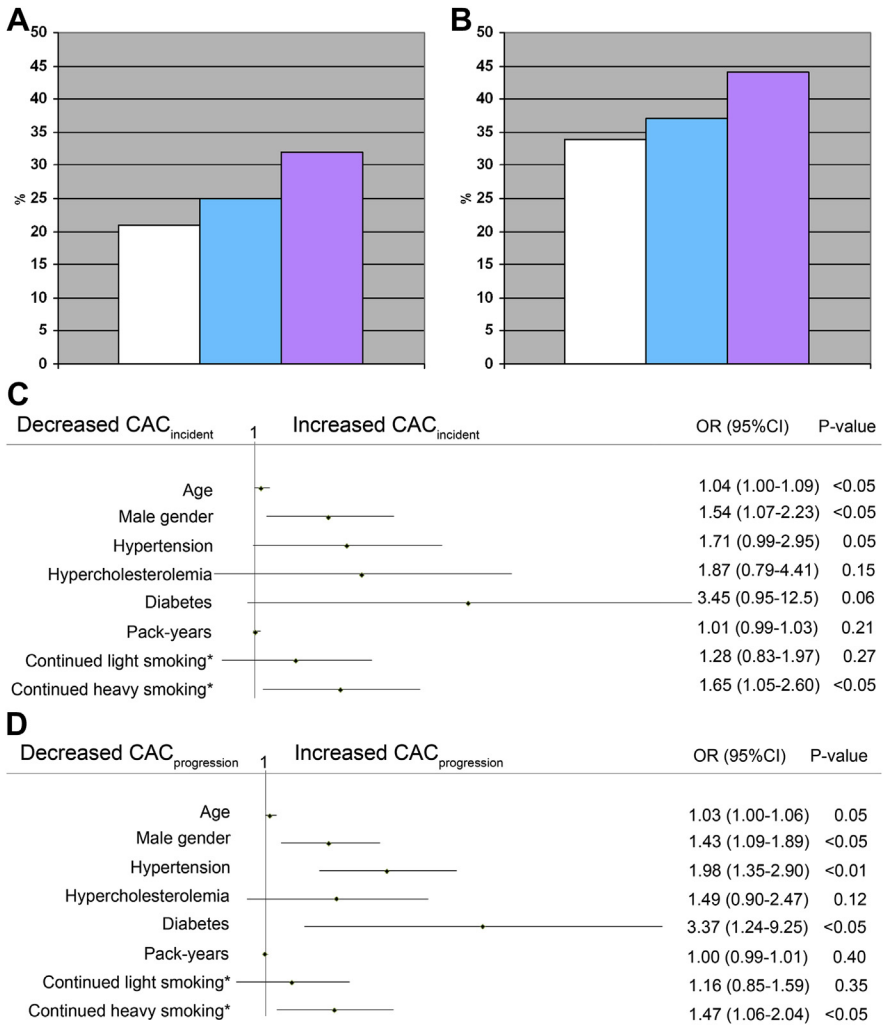

Figure 1 CAC Progression

Frequency of incident coronary artery calcium (CAC) among participants with CAC = 0 at baseline (n = 683) in ex-smokers **(white)**, continued light **(blue)**, and heavy smokers **(purple)** (p for trend < 0.05) **(A)**. Frequency of CAC progression in ex-smokers **(white)**, continued light **(blue)**, and heavy smokers **(purple)** (n = 1,265) (p for trend < 0.01) **(B)**. Forest plots showing odds ratios of incident CAC **(C)** and CAC progression **(D)**. Based on logistic regression models, adjusted for follow-up time (baseline to follow-up period). Furthermore, the model for CAC progression was adjusted for baseline CAC scores in CAC risk groups (0, 1 to 10, 11 to 100, 100 to 400, and >400). *Compared to ex-smoking. OR = odds ratio; CI = confidence interval.

(CAD) were recruited from the Danish Lung Cancer Screening Trial, a randomized controlled trial initiated in 2004. All participants completed questionnaires on smoking annually as well as undergoing multidetector computed tomography (MDCT) for a period of 4 years. Only continuous smokers or ex-smokers without CAD events during the study period were included. Continuous smokers were categorized as light (1 to 17 cigarettes per day) and heavy smokers (>17 cigarettes per day). Volumetric CAC scores were measured at baseline and after 4 years. CAC development, so-called incident CAC (CAC_i) and CAC progression (CAC_p) were analyzed as proposed by McEvoy et al. (1). CAC_p was defined according to Hokanson et al. (2). Multivariable logistic regression was used to determine associations between clinical variables and CAC_i and CAC_p. Interaction analyses between clinical parameters and CAC at baseline were included in the analysis of CAC_p to account for potential change in effect dependent of CAC at baseline. Statistical analyses were performed using SAS for Windows, version 9.1 (SAS Institute, Cary, North Carolina).

Baseline characteristics included 45% women, with a median age of 57 years and 34 pack-years. The frequency of CAC_i was higher in continued smokers compared to ex-smokers and showed a dose-response relationship with respect to extent of smoking (Fig. 1A). Participants in whom CAC_i was observed (n = 173) were older (57 vs. 56 years of age, $p = 0.008$) and were more likely to be male (52% vs. 40%, $p < 0.01$) and to be treated with antihypertensive agents (17% vs. 9%, $p < 0.01$), statins (8% vs. 3%, $p < 0.01$), and/or antidiabetic agents (5% vs. 1%, $p < 0.001$). Similarly, participants with CAC_i had more pack-years at study inclusion (35 vs. 31 years, $p < 0.001$). Age, male gender, and continued heavy smoking compared to ex-smoking were found to be independently associated with an increased risk of CAC_i (Fig. 1C). There was no interaction between pack-years and years of smoking cessation. The frequency of CAC_p (n = 481) was higher in continued smokers compared to ex-smokers and showed a dose-response relationship with respect to extent of smoking (Fig. 1B). Furthermore, participants with CAC_p were more likely to be older (59 vs. 57 years of age, $p < 0.0001$) and male (66% vs. 48%, $p < 0.0001$), and have hypertension (21% vs. 10%, $p < 0.0001$), hypercholesterolemia (12% vs. 4%, $p < 0.0001$), or diabetes (4% vs. 1%, $p < 0.001$) requiring treatment. Participants with CAC_p had higher baseline CAC scores compared to participants without CAC_p (median volumetric CAC 31 vs. 0, $p < 0.0001$). Furthermore, participants with CAC_p had more pack-years (56 vs. 33 years, $p < 0.0001$). Male gender, medical treatment of hypertension, and diabetes in addition to continued heavy smoking when compared to ex-smoking were found to be independently associated to CAC_p (Fig. 1D). There were no interactions between smoking and clinical parameters.

This is the first longitudinal study to report the deleterious effects of smoking continuation in long-term smokers with regard to subclinical CAD.

One previous study found that age >40 years, smoking, and diabetes were predictive of converting from CAC = 0 to CAC >0 during a 5-year period, which is in correlation with our results (3). Earlier studies have sought to evaluate the effect of smoking and smoking cessation on CAC cross-sectionally, although the effect measured was in a population level rather than in an individual level. A substudy of the Heinz Nixdorf Recall Study sought to evaluate the effect of smoking in accumulation of CAC (4). Based on findings they hypothesized that smoking cessation by the age of 45, 55, and 65 years was associated with a CAC score at the age of 75 years that would have been reached 9, 6, and 3 years earlier, respectively, had smoking been continued. Although, these statistically modeled results are not directly comparable to our study, the conclusion was concordant. In the CARDIA study (5), risk factors for the prediction of CAC_i 15 years after baseline were studied in a young cohort. Being a current smoker at baseline was independently associated with CAC_i. However, the study could not document an association between a 15-year change in smoking habit and CAC_i. Our study population was older, smoking habits were recorded in much greater detail and frequencies and quantitative levels of CAC were by far higher than in the CARDIA study, which might explain the discrepant results.

The following limitations should be taken into account. Our study is only representative of current or former long-term smokers. MDCT was performed without electrocardiography gating. However, previous comparisons of CAC obtained by gated versus ungated MDCT have shown a high degree of concordance. According to study design we did not measure cardiovascular outcomes but rather the rate of CAC development and progression. Furthermore, participants who developed manifest CAD during the study period, possibly representing a group with higher rates of CAC_p, were excluded.

In long-term smokers without known CAD continuation of smoking is associated with more frequent development (odds ratio: 1.65; 95% confidence interval: 1.05 to 2.65) and more aggressive progression (odds ratio: 1.47; 95% confidence interval: 1.06 to 2.04) of CAC. These findings support smoking cessation in long-term smokers irrespective of the number of previous pack-years to reduce the extent of CAC accumulation and thus potentially to reduce the subsequent risk of CAD events.

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Letters to the Editor

The Way to Determine Coenzyme Q

Coenzyme Q (CoQ, ubiquinone) is a lipophilic molecule present in all cells, located mainly in the inner mitochondrial membrane. It is composed of a redox active benzoquinone ring conjugated to an isoprenoid chain. The length of the chain differs among species; in humans, it contains predominantly 10 isoprenoid units (CoQ_{10}). The synthesis of this chain shares the mevalonate pathway with cholesterol and dolichol biosynthesis (1), in which 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-Co A) reductase is a key enzyme and target for statins. CoQ shuttles electrons from complex I and complex II, to complex III of the mitochondrial respiratory chain. It also functions as a lipid-soluble antioxidant, and is involved in multiple aspects of cellular metabolism, including pyrimidine nucleotide biosynthesis and beta-oxidation of fatty acids (1).

Recently, Larsen et al. (2) studied the role of simvastatin on skeletal muscle of patients with hypercholesterolemia. This work indicates that simvastatin compromises glucose intolerance and decreases insulin sensitivity, and also indicates a decrease of coenzyme Q_{10} (CoQ_{10}) in human skeletal muscle. However, these results are based on an analytical mistake because the authors have confused the lipid antioxidant CoQ_{10} with the encoded protein by the *COQ10B* gene. *COQ10B* encodes for a mitochondrial protein that does not participate in CoQ_{10} biosynthesis and apparently contributes to CoQ_{10} function in respiration (3).

Their paper claims the changes of CoQ_{10} are caused by simvastatin, but the authors have analyzed the expression of Coq10b peptide using the antibody ab41997 (Abcam, Cambridge, United Kingdom), included in their Figure 6, that should not be confused with the lipid CoQ_{10} content. The analysis of CoQ_{10} is carried out in hexane-ethanol extracts by a high-performance liquid chromatography system with a C18 reversed-phase column and an electrochemical detector (4). This approach has previously demonstrated that statin drug–related myopathy is associated with a mild decrease in muscle CoQ_{10} concentration (5). The overall work of Larsen et al. (2) is not invalidated by this comment, but the results on CoQ_{10} levels should be revised.

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Reply

We appreciate the comment from Dr. Navas regarding our recent report on simvastatin's effect on skeletal muscle (1).

We agree with Dr. Navas that the coenzyme Q–binding protein COQ10 homolog B (COQ10B) was measured. As Dr. Navas writes in his letter, COQ10B is essential to the function of coenzyme Q10 (CoQ10) in regard to mitochondrial respiration (1). In a paper by Barros et al. (2), it is suggested that COQ10B in yeast is binding coenzyme Q6 (CoQ6), which is necessary for CoQ6 to transport electrons in the electron transport chain, which subsequently leads to the transport of electrons and production of ATP (2). CoQ6 is present in yeast and bacteria, and is equivalent to CoQ10 in humans (3). Previously, it has been reported that statin treatment decreases the amount of CoQ10 in skeletal muscle (4), and in combination with the results from our present report observing a reduced content of COQ10B (1), this indicates that statin treatment has a similar effect on CoQ10 and COQ10B.

COQ10B is essential for electron transport in the mitochondrial electron transport chain, and therefore, we believe that our conclusion in the report is valid, as Dr. Navas also writes in his letter.

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