

## Comparing coronary artery calcium and thoracic aorta calcium for prediction of all-cause mortality and cardiovascular events on low-dose non-gated computed tomography in a high-risk population of heavy smokers

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### ABSTRACT

**Background:** Coronary artery calcium (CAC) and thoracic aorta calcium (TAC) can be detected simultaneously on low-dose, non-gated computed tomography (CT) scans. CAC has been shown to predict cardiovascular (CVD) and coronary (CHD) events. A comparable association between TAC and CVD events has yet to be established, but TAC could be a more reproducible alternative to CAC in low-dose, non-gated CT. This study compared CAC and TAC as independent predictors of all-cause mortality and cardiovascular events in a population of heavy smokers using low-dose, non-gated CT.

**Methods:** Within the NELSON study, a population-based lung cancer screening trial, the CT screen group consisted of 7557 heavy smokers aged 50–75 years. Using a case-cohort study design, CAC and TAC scores were calculated in a total of 958 asymptomatic subjects who were followed up for all-cause death, and CVD, CHD and non-cardiac events (stroke, aortic aneurysm, peripheral arterial occlusive disease). We used Cox proportional-hazard regression to compute hazard ratios (HRs) with adjustment for traditional cardiovascular risk factors.

**Results:** A close association between the prevalence of TAC and increasing levels of CAC was established ( $p < 0.001$ ). Increasing CAC and TAC risk categories were associated with all-cause mortality ( $p$  for trend = 0.01 and 0.001, respectively) and CVD events ( $p$  for trend < 0.001 and 0.03, respectively). Compared with the lowest quartile (reference category), multivariate-adjusted HRs across categories of CAC were higher (all-cause mortality, HR: 9.13 for highest quartile; CVD events, HR: 4.46 for highest quartile) than of TAC scores (HR: 5.45 and HR: 2.25, respectively). However, TAC is associated with non-coronary events (HR: 4.69 for highest quartile,  $p$  for trend = 0.01) and CAC was not (HR: 3.06 for highest quartile,  $p$  for trend = 0.40).

**Conclusions:** CAC was found to be a stronger predictor than TAC of all-cause mortality and CVD events in a high-risk population of heavy smokers scored on low-dose, non-gated CT. TAC, however, is stronger associated with non-cardiac events than CAC and could prove to be a preferred marker for these events.

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### 1. Introduction

In the past, several studies using both ultrasound and plain radiography have shown an association between calcified plaques in the thoracic aorta (TAC) and cardiovascular and cerebrovascular events [1–4]. CAC, measured by computed tomography (CT), has proven to be a strong and independent predictor of coronary events and all-cause mortality [5,6]. Non-enhanced computed tomography (CT) can simultaneously detect both CAC and TAC. Several

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studies using non-enhanced CT have demonstrated a close association of TAC and CAC [7–11]. Based on these results, TAC has recently been suggested as an independent predictor of cardiovascular disease, but only two follow-up studies have been reported on this topic [12,13]. The intuitive advantage of using TAC instead of CAC lies primarily in the fact that CAC measurement may be hampered by motion artifacts of the beating heart while this will hardly affect TAC measurements. As has recently been suggested [9], TAC could prove to be a substitute of CAC for prediction of cardiovascular events in non-gated CT.

Since the heart and thoracic aorta are both depicted on low-dose CT scans for lung cancer screening, and lung cancer and cardiovascular disease share an increased risk with the prolonged use of tobacco, CAC and TAC measurements could be employed to expand the scope of the screening effort and include estimation of cardiovascular risk of screening subjects as well. Adding these measurements at baseline could lead to improved detection of high-risk individuals and, consequently, improved primary prevention of CVD events through optimized preventive treatment of cardiovascular risk factors. So far, no large follow-up studies have investigated the relationship between TAC and CAC in a cohort of asymptomatic smokers. In this study, we investigated whether TAC, as measured on low-dose, non-gated CT, can be used as an independent predictor of all-cause mortality and cardiovascular events compared with CAC. As a secondary analysis, we compared the role of CAC and TAC for the prediction of coronary and non-cardiac events separately.

## 2. Methods

### 2.1. Study population

The NELSON study is a randomized controlled population-based trial comprising 15,822 men and women aged 50–75 years. Its overall aim is to investigate the beneficial effects of screening for lung cancer with low-dose CT. In 2003–2004, in three regions in the Netherlands and one region in Belgium all men born between 1928 and 1953 living in 101 distinct municipalities, and all women born between 1930 and 1955 living in the remaining 46 municipalities were invited by mail to participate in this study. Every participant had a history of  $\geq 15$  pack years of smoking. From 2004 to 2006, baseline CT scans were performed in 7557 participants randomly allocated to the screen group. The Medical Ethics Committees of all four participating hospitals approved the NELSON study protocol, and written informed consent was obtained from all participants. A more detailed description of patient selection and data collection has been published elsewhere [14].

For the present study we used a case-cohort design [15] in which cases are defined as all participants from the screen group experiencing an outcome of interest (all-cause death or cardiovascular events) during follow-up. A random sample of 925 participants was drawn from the baseline screen group (so-called subcohort). All cases ( $n=226$ ) were obtained through linkage with the national death registry and the national registry of hospital discharge diagnoses (Appendix A). The choice of the sample fraction was calculated to correspond to approximately 4 controls per case detected. Through linkage with the national registry of hospital discharge diagnoses, we first excluded participants with a known history of hospitalization for cardiovascular disease (cases,  $n=72$ ; subcohort,  $n=97$ ). This database linkage was performed for the years 1995–2003. Prior to 1995 this information could not be retrieved, since database linkage is only possible from 1995 onwards. Then, we excluded those participants who had missing baseline CT scans (cases,  $n=4$ ; subcohort,  $n=17$ ), or a baseline CT scan performed after follow-up had ended (cases,  $n=0$ ; subcohort,  $n=3$ ). This results in a final study cohort for this study of 958 sub-

jects (additional cases,  $n=150$ ; subcohort,  $n=808$ ). Baseline CAC and TAC scores were measured in all 958 subjects.

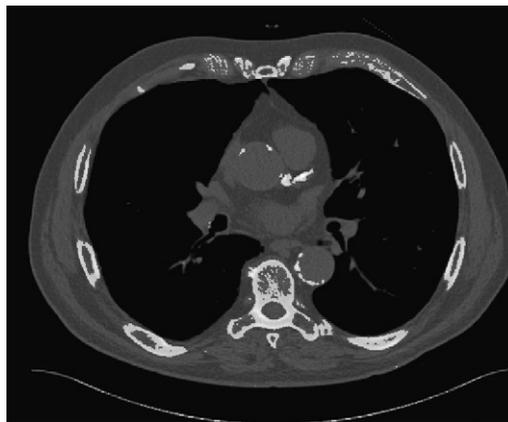
### 2.2. CT scan acquisition and image analysis

Baseline low-dose CT scans were conducted with a 16-slice MDCT scanner (Mx8000 IDT; Philips Medical Systems, Cleveland, Ohio in two participating hospitals; Sensation-16, Siemens AG, Forchheim, Germany in the third hospital). The scanning protocol consists of the following parameters were applied: 16 mm  $\times$  0.75 mm collimation; pitch 1.3–1.5; caudocranial scan direction; smallest field of view to include the outer rib margins. This way, transverse images with 1.0 mm section thickness and 0.7 mm increment were acquired from the level of the lung bases to the lung apices. No electrocardiographic triggering was performed; no contrast agent was administered. Low-dose exposure settings were applied based on body weight: 30 mAs at a tube voltage of 120 kVp for subjects  $\leq 80$  kg and 140 kVp for subjects  $>80$  kg. This corresponds to an effective radiation dose of 0.6–1.1 mSv.

All 958 CT scans were equally divided between two observers with 2 and 3 years of experience in reading cardiac CT who subsequently performed calcium scoring of the coronary arteries and the thoracic aorta. The readers were blinded to other participant data. Prior to the start of the study, inter-observer variability of CAC scoring was measured in a subset of 50 baseline scans not included in this study ( $\kappa=0.72$ ). To reduce image noise and to use data comparable to previously published studies [16] all scans were reconstructed to 3.1 mm thick slices with an increment of 1.4 mm by averaging four neighboring slices. Calcium scoring was performed in these reconstructed images using a technique described in Isgum et al. [17]: all regions of  $\geq 3$  adjoining voxels ( $0.7 \text{ mm}^3$ ) with attenuation above 130 HU [18] were shown with a colored overlay. An investigator identified a point in each calcified lesion. Subsequently, three-dimensional component labeling using 26-connectivity was automatically performed [19] to mark all connected voxels as calcification. Agatston scores were computed as outlined in Ulzheimer [20,21]. TAC was measured in the ascending aorta, aortic arch and descending aorta inferiorly to the upper limit of the eleventh thoracic vertebra (Fig. 1).

### 2.3. Classification of end points

All participants in the screen group of the NELSON study ( $n=7557$ ) were linked with the national death registry and the national registry of hospital discharge diagnoses. This database



**Fig. 1.** Example of low-dose, non-gated CT image showing calcified plaques in the ascending and descending thoracic aorta, and the left main (LM) and left anterior descending (LAD) coronary arteries. In this image an automatic overlay indicates all areas of  $>3$  voxels with an attenuation  $>130$  HU to facilitate calcium scoring.

linkage was performed on the basis of birth date, sex and postal code with a validated probabilistic method [22–25].

Through linkage with the national death registry for the years 2004–2007 a total of 56 all-cause deaths were detected. Other end points were defined as (1) a composite CVD end point consisting of cardiovascular deaths and all nonfatal cardiovascular hospital admissions; that was subdivided in (2) a coronary (CHD) end point consisting of all fatal myocardial infarctions and nonfatal CHD admissions and (3) a composite end point of non-cardiac events consisting of all fatal and nonfatal cases of cerebrovascular disease, peripheral arterial occlusive disease (PAOD), and aortic aneurysms. To retrieve information on cardiovascular hospital admissions, all participants from the screen group were linked with the national registry of hospital discharge diagnoses for the years 2004–2006. In this registry, all diagnoses are coded according to the International Classification of Diseases, 9th revision (ICD-9-CM). One research physician selected all cardiovascular discharge diagnoses and classified them as heart failure (code 428) and coronary heart disease (CHD) (codes 410–414), or other CVD hospitalizations including PAOD (codes 440, 443–444), aortic aneurysm (code 441), cerebrovascular disease (codes 430–438), and non-rheumatic valvular disease (code 424). All other codes included in the ICD-9-CM as diseases of the circulatory system were not included as valid end points. Through this linkage a total of 94 nonfatal cardiovascular events could be identified.

Follow-up started after the baseline CT scan. Follow-up time differed for all-cause mortality and the other two end points, because of the differential availability of the two registries used. For all-cause mortality, follow-up was complete until January 1, 2007 (median: 21.5 months); for both other end points, until January 1, 2006 (median: 9.5 and 10.0 months). For all participants who experienced an event, follow-up ended at the date of diagnosis or death. In participants with multiple cardiovascular hospital admissions during follow-up, the first hospital discharge diagnosis was used as end point.

#### 2.4. Assessment of covariates

At baseline, all participants from the NELSON study were asked to return a questionnaire containing information on prior and current smoking behavior. For subjects in this case-cohort substudy, a research physician collected information from their general practitioners (GPs) using a standardized questionnaire. The obtained information included the current use of drugs, specifically the use of antihypertensive drugs (defined as diuretics, ACE inhibitors, angiotensin II receptor antagonists,  $\beta$ -blockers and/or calcium channel blockers); lipid-lowering drugs; oral hypoglycemic agents; and insulin; systolic and diastolic blood pressure (BP); and non-fasting blood glucose, HbA1c, total cholesterol, LDL cholesterol and HDL cholesterol levels. The overall response rate was 70%. For all covariates obtained through the GP, missing values were imputed using regression methods implemented in SPSS software (SPSS 14.0, Chicago, Illinois) [26]. We defined diabetes mellitus as a nonfasting glucose level  $\geq 11.1$  mmol/L and/or the use of oral hypoglycemic agents or insulin. Hypertension was defined as a diastolic BP  $> 90$  mmHg, systolic BP  $> 140$  mmHg and/or the use antihypertensive drugs. Hypercholesterolaemia was defined as a total cholesterol level  $> 5.0$  mmol/L, an LDL level  $> 3.0$  mmol/L and/or the use of lipid-lowering drugs.

### 3. Statistical methods

Baseline characteristics were summarized for the subcohort and the three different case-groups separately. Categorical variables were compared with a  $\chi^2$  statistic; continuous variables with the Mann–Whitney *U*-test. Unadjusted annualized event rates for all-

cause mortality and CVD events were calculated per CAC and TAC quartile in the subcohort.

In the subcohort, the association between continuous measures of TAC and CAC was investigated with Spearman's rank correlation. Prevalence of CAC and TAC across age groups was compared for men and women separately. Association between the distribution of TAC and CAC risk categories was investigated using a  $\chi^2$  test. Since no accepted thresholds exist on cut-offs for TAC risk categories, we chose to divide both TAC and CAC scores into quartiles to maximize comparability.

The association of TAC and CAC with all-cause mortality and the composite CVD, CHD and non-coronary end point was evaluated with Cox proportional-hazard analyses. To account for the case-cohort design, modification of the standard errors was based on robust variance estimates. We used the method according to Prentice in which all subcohort members are equally weighted. Cases outside the subcohort are not weighted before failure and at failure receive the same weight as members of the subcohort [14]. This method has been shown to resemble most closely estimates from a full-cohort analysis [27].

Cox proportional-hazard analyses for all four end points were performed for increasing TAC and CAC categories and adjusted for cardiovascular risk factors (age, sex, current smoking, hypertension, diabetes and hypercholesterolaemia). The lowest quartiles of TAC and CAC scores were used as reference categories. In the test for trend analysis, quartiles of TAC and CAC were replaced with continuous TAC and CAC scores.

Statistical analyses were performed with SPSS 14.0 software for Windows (SPSS Inc., Chicago, IL) and R 6.2.

### 4. Results

Table 1 shows the baseline characteristics of a representative baseline sample (subcohort) and all four event-groups. The subcohort included 808 subjects (671 men, 137 women; mean age,  $60 \pm 6$ ). Compared with the subcohort, subjects in all four event-groups were more often men ( $p < 0.0001$ ) and more were classified as having diabetes (7% versus 11–18%;  $p = 0.001$ ). In subjects from the composite CVD, CHD and non-cardiac event-groups, hypertension was more frequent compared with the subcohort ( $p < 0.0001$ ). Subjects in all four event-groups had higher CAC and TAC scores ( $p < 0.0001$ ) compared with subjects from the subcohort. Highest median CAC scores were recorded in the CHD event-group, whereas highest median TAC scores were found for the all-cause mortality and non-cardiac event-groups (Table 1).

In the subcohort, cut-offs for quartiles of CAC score were 0–1 (1st quartile), 1–74 (2nd quartile), 75–592 (3rd quartile), and  $> 592$  (4th quartile); cut-offs for TAC score quartiles were 0–99 (1st quartile), 100–536 (2nd quartile), 537–1937 (3rd quartile), and  $> 1937$  (4th quartile). Seventy-four percent ( $n = 599$ ) of subjects had both TAC  $> 0$  and CAC  $> 0$  scores; 23% ( $n = 177$ ) had only TAC; 1% ( $n = 12$ ) had only CAC; and only 2% ( $n = 20$ ) of subjects had no detectable CAC or TAC. The distribution of TAC and CAC scores in risk categories was closely associated ( $p < 0.0001$ ) (Fig. 2). A strong correlation existed between the continuous CAC and TAC scores (Spearman's  $r$ : 0.49,  $p < 0.001$ ).

The prevalence of both CAC and TAC increases by age group in men and women (Fig. 3A and B). A striking difference between sexes is the higher prevalence of CAC compared with TAC in men aged  $< 65$ , whereas in women TAC is consistently more prevalent than CAC in all age categories. Throughout all age categories CAC is more prevalent in men compared with women, but TAC is more prevalent in women than in men.

Unadjusted annualized event rates for all-cause mortality with increasing quartiles of CAC and TAC score were 0, 0.28, 1.17, and 0.88% and 0, 0.57, 0.29, and 1.54%, respectively. For total CVD events

**Table 1**  
Baseline characteristics.

Variables <sup>a</sup>	Subcohort (n = 808)	All-cause mortality (n = 56)	CVD end point (n = 127)	CHD end point (n = 61)	Non-CHD end point (n = 38)
Age, years	59.5 ± 5.6	63.7 ± 5.8	61.0 ± 5.9	60.1 ± 5.6	61.4 ± 5.5
Men, %	83	95	97	93	100
Hypertension, %	64	63	87	93	76
Hypercholesterolaemia, %	75	77	80	85	76
Diabetes, %	7	13	15	18	11
Current smokers, %	56	68	63	62	82
TAC score (AS) <sup>b</sup>	536 (1837)	3411 (6820)	1548 (3358)	1236 (2997)	2604 (5375)
CAC score (AS) <sup>b</sup>	74 (591)	685 (1828)	769 (2063)	1055 (2017)	268 (1716)

AS: Agatston score; CAC: coronary artery calcium; SD: standard deviation; TAC: thoracic aortic calcium.

<sup>a</sup> Expressed as percentage or mean ± SD.

<sup>b</sup> Median (interquartile range).

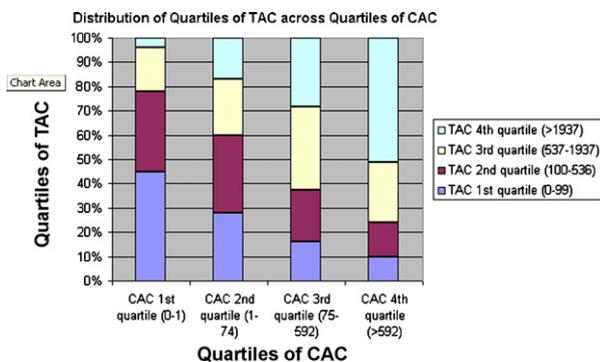
the corresponding event rates with increasing quartiles of CAC and TAC scores were 2.35, 1.87, 2.02, and 4.11% and 2.11, 2.56, 1.99, and 3.79%, respectively.

During a median follow-up 21.5 months (range: 1–1003 days), 56 subjects died. Both CAC and TAC scores were associated with risk of all-cause mortality ( $p$  for trend = 0.01 and 0.001, respectively) (Table 2). Compared with the first quartile of TAC, risk factor-adjusted hazard ratios (HRs) for the second, third, and fourth quartile were 1.22, 2.12, and 5.45, respectively. Only in case of subjects in the highest quartile did this association reach statistical significance. Compared with risk factor-adjusted hazard ratios for quartiles of CAC (HR: 3.70, 5.75, and 9.13 for the second, third and fourth risk category, respectively), hazard ratios for TAC were consistently lower.

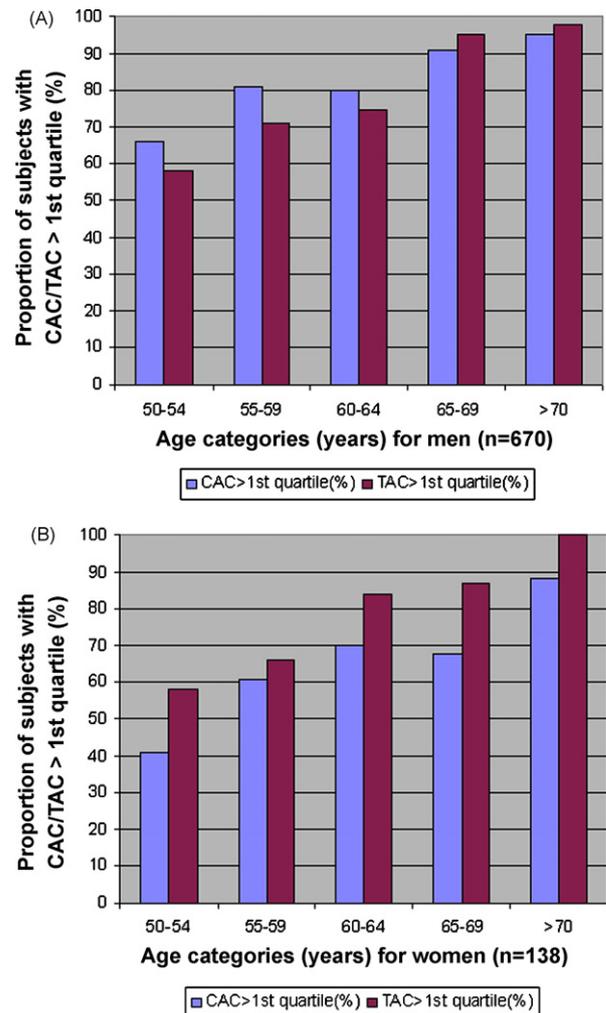
During a median follow-up 9.5 months (range: 1–638 days) and 10.0 months (range: 1–638 days) incident fatal and nonfatal cardiovascular events occurred in 127 subjects. CAC and TAC again showed a graded association with the risk of fatal and nonfatal CVD events ( $p$  for trend < 0.001 and 0.03, respectively). Risk factor-adjusted hazard ratios for the second, third, and fourth quartile compared with the first quartile of TAC were 0.87, 1.51, and 2.25, respectively (Table 2). Only in case of subjects in the highest quartile did this association reach statistical significance. As with all-cause mortality, risk factor-adjusted hazard ratios for CAC risk categories (HR: 1.74, 1.88, and 4.46 for the second, third and fourth category, respectively) were consistently higher compared with the same hazard ratios for TAC.

By breaking down the composite CVD end point into coronary cases (61 events) and non-cardiac cases (including stroke, aortic aneurysm, and PAOD) (38 events), we performed a secondary analysis (Table 3) investigating the specific patterns of association between TAC/CAC and cardiovascular events. Only CAC was found to be associated with coronary events. Compared with the first quartile of CAC, multivariate-adjusted hazard ratios for the second,

third, and fourth quartile were 1.62, 2.12, and 6.86, respectively ( $p$  for trend < 0.001 compared with  $p$  for trend = 0.33 for TAC). Conversely, only TAC was associated with the composite end point of non-cardiac events. After adjustment for cardiovascular risk factors, hazard ratios for the second, third, and fourth quartile were 1.14, 1.39, and 4.69, respectively ( $p$  for trend = 0.02). CAC was not associated with this end point ( $p$  for trend = 0.40) (Table 3).



**Fig. 2.** Distribution of quartiles of thoracic aortic calcium (TAC) score across quartiles of coronary artery calcium (CAC) score. Increasing levels of CAC scores are closely associated with increasing levels of TAC score ( $p < 0.001$ ).



**Fig. 3.** Prevalence of calcifications in the coronary arteries with an Agatston score > 1st quartile (AS > 99), and calcifications in the thoracic aorta with an Agatston score > 1st quartile (AS > 99) by age category. Panel A, for men ( $n = 670$ ). The  $\chi^2$  test indicated a trend across age categories for CAC ( $p < 0.001$ ) and TAC ( $p < 0.001$ ). Panel B, for women ( $n = 138$ ). The  $\chi^2$  test indicated a trend across age categories for CAC ( $p = 0.001$ ) and TAC ( $p = 0.03$ ).

**Table 2**

Multivariate-adjusted hazard ratios (95% CI) for all-cause mortality and cardiovascular (CVD) events according to quartiles of coronary artery calcium (CAC) and thoracic aortic calcium (TAC).

Quartile of CAC (AS)	Quartiles of CAC	Quartile of TAC (AS)	Quartiles of TAC
All-cause mortality (n = 56)			
1 (0–1)	1.00	1 (0–99)	1.00
2 (1–74)	3.70 (0.74–18.39)	2 (100–536)	1.22 (0.33–4.58)
3 (75–592)	5.75 (1.25–26.53)	3 (537–1937)	2.12 (0.64–7.05)
4 (>592)	9.13 (2.01–41.48)	4 (>1937)	5.45 (1.73–17.16)
P for trend	0.01	P for trend	0.001
CVD end point (n = 127)			
1 (0–1)	1.00	1 (0–99)	1.00
2 (1–74)	1.74 (0.77–3.92)	2 (100–536)	0.87 (0.43–1.77)
3 (75–592)	1.88 (0.84–4.18)	3 (537–1937)	1.51 (0.80–2.89)
4 (>592)	4.46 (2.11–9.45)	4 (>1937)	2.25 (1.17–4.34)
P for trend	<0.001	P for trend	0.03

All models adjusted for age, sex, current smoking, hypertension, hypercholesterolaemia, and diabetes. AS: Agatston score. Cut-off values of absolute Agatston scores for quartiles of CAC and TAC in parenthesis.

## 5. Discussion

CAC has previously been found to be independently associated with all-cause mortality and cardiovascular events [5,6]. In the present study, TAC was closely associated with CAC. Although both CAC and TAC were associated with all-cause mortality and CVD events in this population of heavy smokers, risk factor-adjusted hazard ratios were consistently higher for CAC compared with TAC. Furthermore, only CAC was associated with coronary events, whereas TAC – and not CAC – was found to be associated with non-cardiac events (stroke, aortic aneurysm, PAOD).

A number of previous studies reported on the positive association of TAC and CAC [7–10]. In these studies a wide array of different measurement techniques for detecting calcified plaques in the thoracic aorta has generally been used, ranging from plain radiography to ECG-gated multislice CT. Furthermore, these studies were conducted in very different populations, ranging from symptomatic CVD patients to population-based cohorts. Also, the part of the aorta evaluated for plaques ranged from the parts of the descending segment depicted on a cardiac CT scan to the full stretch of the intrathoracic aorta. Therefore, a direct comparison between the results reported by these studies should be undertaken with caution. Our study was performed within the NELSON study, a large randomized controlled population-based trial in subjects aged 50–75 years. We used low-dose, non-gated CT to simultaneously detect plaques in the coronary arteries and all three segments of the thoracic aorta. This technique has shown to be valid for detecting CAC with an accuracy of up to 90% compared with dedicated cardiac CT [28]. Furthermore, since motion artifacts do occasionally cause blurring of calcified plaques and – consequently

– intra-individual variability of CAC scores, we grouped all absolute CAC and TAC scores into quartiles and all analyses for this study were performed on a quartile-by-quartile basis thus reducing the impact of this effect on our results.

These observations all contribute to the overall higher prevalence of TAC in our study compared with two previously published population-based CT cohorts [9,10]. However, in a number of key aspects our results are consistent with earlier results. In all studies TAC was more prevalent than CAC among women of all ages, whereas CAC occurred more than TAC in men under age 65. It has been suggested that this might result from the interplay between osteoporotic and atherosclerotic pathophysiological mechanisms [29,30]. Our study likewise demonstrated a more pronounced increase in TAC with increasing age compared with CAC.

To our knowledge, only two studies have been reported on the association between TAC and all-cause mortality or cardiovascular events. In a study among 361 stable angina pectoris patients (mean age, 62) hazard ratios of 2.84 and 2.70 were demonstrated for the risk of total events (defined as fatal/nonfatal CVD events, non-cardiac fatalities, and peripheral revascularization) and CVD events in patients with TAC > 0 compared with patients with TAC = 0 [12]. However, this is a smaller study in symptomatic angina patients, and since TAC was only visually assessed as present/absent only very crude estimates could be presented. To be useful in clinical practice, screening for TAC should improve existing risk stratification tools, and should consequently be targeted at asymptomatic subjects since symptomatic CVD patients already fall – by the very nature of their condition – in the highest risk category. Furthermore, TAC is shown to be very prevalent and small quantities of TAC are not necessarily associated with an increased risk of adverse

**Table 3**

Multivariate-adjusted hazard ratios (95% CI) for coronary (CHD) and non-cardiac (non-CHD) events according to quartiles of coronary artery calcium (CAC) and thoracic aorta calcium (TAC).

Quartile of CAC (AS)	Quartiles of CAC	Quartile of TAC (AS)	Quartiles of TAC
CHD end point (n = 61)			
1 (0–1)	1.00	1 (0–99)	1.00
2 (1–74)	1.62 (0.45–5.75)	2 (100–536)	0.74 (0.28–1.91)
3 (75–592)	2.12 (0.61–7.35)	3 (537–1937)	1.55 (0.68–3.55)
4 (>592)	6.86 (2.22–9.45)	4 (>1937)	1.48 (0.60–3.62)
P for trend	<0.001	P for trend	0.33
Non-CHD end point (n = 38)			
1 (0–1)	1.00	1 (0–99)	1.00
2 (1–74)	2.56 (0.64–10.28)	2 (100–536)	1.14 (0.29–4.51)
3 (75–592)	2.08 (0.50–8.63)	3 (537–1937)	1.39 (0.37–5.28)
4 (>592)	3.06 (0.76–12.34)	4 (>1937)	4.69 (1.30–16.88)
P for trend	0.40	P for trend	0.01

All models adjusted for age, sex, current smoking, hypertension, hypercholesterolaemia, and diabetes. AS: Agatston score. Cut-off values of absolute Agatston scores for quartiles of CAC and TAC in parenthesis.

events; so the choice of any TAC as a cut-off point is probably not the best. Using quartiles of semi-automatically scored TAC, we have demonstrated a graded association of TAC with all-cause mortality and CVD events, providing a more accurate tool for risk stratification.

In another study, a direct comparison between CAC and TAC showed a strong relation between CAC risk categories and CVD/CHD events in physician-referred or self-referred patients, but no such relation was found for TAC [12]. Although results in our study similarly show that association with CVD and CHD events is stronger for CAC than for TAC, our results do show an association between TAC and CVD events. This may be caused by a higher prevalence of TAC in our study. The higher prevalence of TAC can in part be explained by our population (heavy smokers), but more likely will be caused by differences in the CT protocols used. In our low-dose chest CT protocol, we evaluated the whole intrathoracic aorta for presence of TAC instead of only those parts of the aorta visible on a dedicated cardiac CT protocol. Excluding TAC plaques in the aortic arch is likely to influence the association with incident stroke cases which are an important part of the composite CVD end point. We therefore feel that the distribution of subjects in their study would have been radically different had they included all TAC plaques and, consequently, would have resulted in different associations. Furthermore, the authors have applied the same cut-off values for TAC risk categories as for CAC risk categories since there are no accepted thresholds for TAC score at present. In our opinion, the caliber of the thoracic aorta is incomparable with the combined caliber of the coronary arteries making a one-on-one comparison using the same cut-off values for both scores inappropriate. In the absence of well-established cut-offs we feel that using quartiles of CAC/TAC is the best option when comparing them.

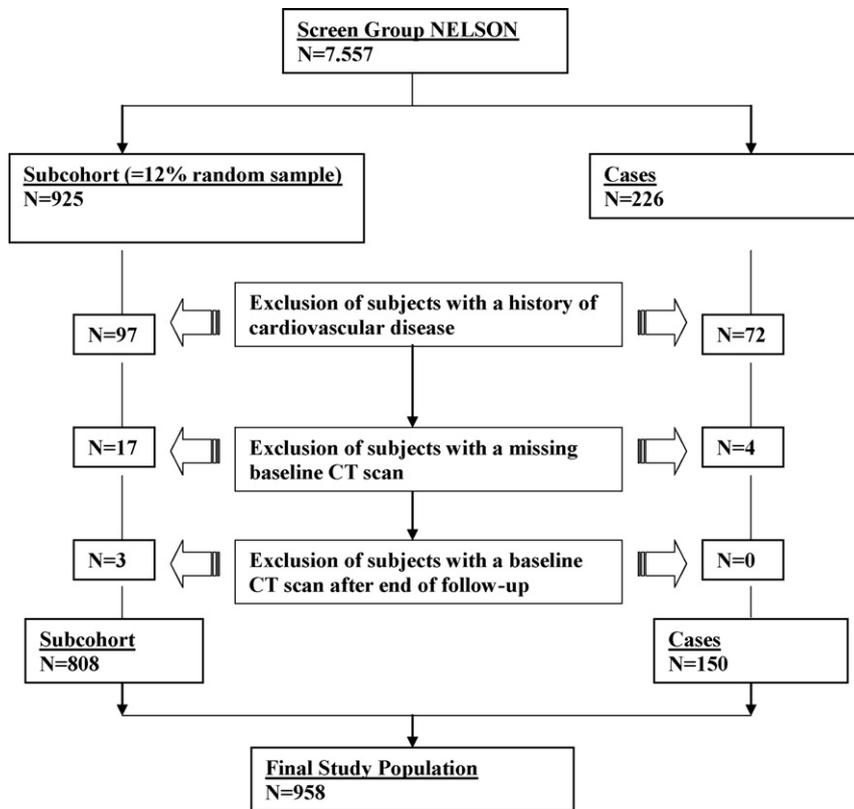
Choosing quartiles as cut-off, is also the reason why event/hazard rates for CAC quartiles from this study should not be compared one-on-one with event/hazard rates from previous studies. Furthermore, the lack of a stepwise increase in event rates for the combined CVD end point can be explained by the fact that event rates – unlike hazard rates – were presented unadjusted for traditional CVD risk factors. Given the high prevalence of these risk factors among our population even participants with low or intermediate CAC/TAC scores had unadjusted event rates of ~2% per year.

Although hampered by a limited number of events, we found in our secondary analysis that TAC was associated with non-cardiac

events, but not with coronary events. This pattern is completely reversed in the case of CAC, being more strongly associated with coronary events and showing no association with non-cardiac events. Based on these observations, we hypothesize that TAC – although at a certain level strongly correlated with the extent of CAC – is perhaps more than CAC a measure of generalized atherosclerosis and therefore possibly better suited as a predictor of non-cardiac CVD events. Longer follow-up with more non-cardiac CVD events are needed to confirm this hypothesis.

From a clinical perspective, imaging of atherosclerotic disease has generally been described as having added value in a population at intermediate risk of future CVD events [31]. Therefore, a possible limitation of this study could be the 'high-risk' profile of this population of heavy smokers. For this reason, we calculated the Framingham Risk Score [32] in this population and found that approximately 50% is at intermediate risk (10-year risk 10–20%) and only 35% at high risk (10-year risk >20%) which emphasize the potential clinical implications of CAC/TAC imaging as part of lung cancer screening. Limited number of events caused some of the associations not to reach statistical significance. Taking into account the consistent and statistically significant trends across quartiles, we believe that with more events these associations would have become statistically significant. Furthermore, baseline covariate information was obtained through the GPs and was not 100% complete. A response rate of 70%, however, should not introduce a large bias and imputation of missing covariate information has been shown superior to a complete case analysis [26,33]. Finally, exclusion of subjects with a history of cardiovascular disease was performed through database linkage. Since this information was unavailable prior to 1995, this could have resulted in false inclusion of a number of subjects with a positive history of CVD. We believe, however, this number to be small – taking into account the mean age of our population prior to 1995 – and think this will not have influenced the results of this study.

In conclusion, our results provide further evidence that TAC and CAC are closely associated markers of cardiovascular disease. This study in a high-risk population of heavy smokers has demonstrated that CAC is a stronger predictor than TAC for all-cause mortality, CVD events, and coronary events. However, TAC appears to be a stronger predictor for non-cardiac CVD events (stroke, aortic aneurysm, PAOD). Future studies with more non-cardiac events are needed to gain a more profound insight into these effects.

**Appendix A. Flowchart case-cohort design****References**

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