OBJECTIVES  The aim of this study was to derive and validate a prediction model for cardiovascular events based on quantification of coronary and aortic calcium volume in lung cancer screening chest computed tomography (CT).

BACKGROUND  CT-based lung cancer screening in heavy smokers is a very timely topic. Given that the heavily smoking screening population is also at risk for cardiovascular disease, CT-based screening may provide the opportunity to additionally identify participants at high cardiovascular risk.

METHODS  Inspiratory screening CT of the chest was obtained in 3,648 screening participants. Next, smoking characteristics, patient demographics, and physician-diagnosed cardiovascular events were collected from 10 years before the screening CT (i.e., cardiovascular history) until 3 years after the screening CT (i.e., follow-up time). Cox proportional hazards analysis was used to derive and validate a prediction model for cardiovascular risk. Age, smoking status, smoking history, and cardiovascular history, together with automatically quantified coronary and aortic calcium volume from the screening CT, were included as independent predictors. The primary outcome measure was the discriminatory value of the model.

RESULTS  Incident cardiovascular events occurred in 145 of 1,834 males (derivation cohort) and 118 of 1,725 males and 2 of 89 females (validation cohort). The model showed good discrimination in the validation cohort with a C-statistic of 0.71 (95% confidence interval: 0.67 to 0.76). When high risk was defined as a 3-year risk of 6% and higher, 589 of 1,725 males were regarded as high risk and 72 of all events were correctly predicted by the model.

CONCLUSIONS  Quantification of coronary and aortic calcium volumes in lung cancer screening CT images—information that is readily available—can be used to predict cardiovascular risk. Such an approach might prove useful in the reduction of cardiovascular morbidity and mortality and may enhance the cost-effectiveness of CT-based screening in heavy smokers. (J Am Coll Cardiol Img 2013;6:899–907) © 2013 by the American College of Cardiology Foundation
Cardiovascular disease is a major cause of mortality in heavy cigarette smokers. In the NLST (National Lung Cancer Screening Trial) trial most participants died from cardiovascular disease (1), which confirms observations in other cohorts (2,3). The NLST achievement is remarkable as this is the first cancer screening trial demonstrating an all-cause mortality reduction. This raises high expectations for chest computed tomography (CT)-based lung cancer screening (1,4). Nevertheless, CT-based screening for lung cancer will be costly and may therefore not be adopted by many countries (5).

It has recently been shown that CT-based screening can aid in the automatic identification of additional subjects with chronic obstructive pulmonary disease (6). Interestingly, the test that is used for lung cancer screening (i.e., CT), is also suitable for quantification of vascular calcifications, which are strong predictors for cardiovascular events in multiple other settings (7–12). Because cardiovascular morbidity and mortality can be reduced through primary and secondary preventive efforts (13,14), inclusion of cardiovascular disease in the screening protocol may enhance the benefits and the cost-effectiveness of chest CT-based screening of heavy smokers. However, it is currently unknown how well lung cancer screening chest CT can predict cardiovascular events.

In this study, we developed and validated a prediction model using the extent of coronary and aortic calcifications quantified in lung cancer screening chest CT scans to predict cardiovascular events and re-events. 

METHODS

Ethics statement. This present study is an ancillary study of the population-based NELSON (NEderlands LeuvenLongkanker Screenings Onderzoek; ISRCTN63545820) trial (15), which was approved by the Ministry of Health of the Netherlands and the institutional ethical boards of the participating centers. Written informed consent was obtained from all participants.

Subjects. The eligibility criteria and recruitment practices of the NELSON trial have been described in detail elsewhere (15). Briefly, participants are all current and former heavy smokers between the ages of 50 and 75 years old with a smoking history of at least 16.5 pack-years. Exclusion criteria for participating in the lung cancer screening trial were self-reported moderate or bad health with inability to climb 2 flights of stairs, a recent chest CT, current or past cancer, and body weight ≥ 140 kg.

We included subjects from 2 centers (N = 3,648). The derivation cohort included 1,834 males from the University Medical Center in Groningen. The validation cohort included 1,725 males and 89 females from the University Medical Center in Utrecht. At baseline, participants in the NELSON trial filled in a questionnaire on their current and former smoking behavior.

CT scanning and calcium analysis. Subjects underwent at baseline a volumetric chest CT in full inspiration between January 2004 and December 2007. CTs were obtained without cardiac or respiratory gating on 16-slice multidetector CT scanners with a collimation of 16 × 0.75 mm. The derivation cohort was scanned on a Sensation-16 CT (Siemens Medical Solutions, Forchheim, Germany), whereas the validation cohort was scanned on either an Mx8000 or Brilliance-16P CT (Philips Medical Systems, Cleveland, Ohio). Exposure settings were adjusted according to body weight: 120 kVp (<80 kg) or 140 kVp (≥80 kg) both at 30 mAs, yielding an effective dose of <0.9 and <1.6 mSv, respectively. Axial images with a slice thickness of 2 mm were reconstructed using a standard kernel.

Abbreviations and Acronyms

CI = confidence interval
CT = computed tomography

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Manuscript received November 7, 2012; revised manuscript received February 8, 2013, accepted February 14, 2013.
1 mm at 0.7-mm increment were reconstructed using a smooth reconstruction filter (Siemens B30f, Philips B-filter).

Reconstruction slice thickness for calcium quantification was 3.1 mm. Four slices were averaged with 1.4 mm increment. Calcium quantification was performed with dedicated, noncommercial, in-house developed software: calcifications in the coronary arteries were automatically quantified based on the algorithm described by Isgum et al. (16), and calcifications in the aorta were quantified as previously described (17). Briefly, a threshold of 130 Hounsfield units in combination with 3-dimensional connected component labeling was used to identify potential calcifications. Subsequently, aortic calcifications were extracted based on multiatlas-based segmentation of the aorta, followed by a supervised pattern recognition system detecting aortic calcifications based on spatial, size, and texture features. Given the excellent agreement between automatic and manual calcium scoring of aortic lesions in low-dose CT (17), only outliers in aortic calcium scores were inspected and manually corrected if needed. Coronary calcifications were extracted based on a probabilistic coronary calcium map providing an a priori probability for appearance of coronary calcifications on a chest CT scan, followed by a supervised pattern recognition system detecting calcifications based on spatial and texture features. All coronary calcifications were inspected and manually corrected if needed. Calcifications were quantified in terms of total calcium volume (mm³). Additionally, Agatston score was calculated for coronary calcifications.

Cardiovascular events. We retrieved physician-diagnosed cause of death and hospital admission diagnosis through linkage with the National Death Registry and the National Registry of Hospital Discharge Diagnoses. This linkage was performed using a validated probabilistic method (18,19). All deaths and hospital diagnosis are coded by medical doctors; we did not adjudicate the hospital diagnosis and causes of death. We included fatal and nonfatal cardiovascular events that occurred between January 1995 and January 2008. All events were classified using the 9th (discharge diagnoses) and 10th (cause of death) revision of the International Classification of Diseases. Hypertensive disease (codes 401–405), ischemic heart disease (codes 410–414), heart failure (code 428), diseases of arteries, arterioles and capillaries (codes 440–448), cerebrovascular disease (codes 430–438), or other heart disease (code 429) were included as cardiovascular events. Revascularization procedures were not considered valid endpoints. Cardiovascular death prevailed over hospital admissions. In case of multiple valid hospital admissions the first hospital discharge diagnosis was used. A positive history for cardiovascular disease was defined as any cardiovascular diagnosis between 1995 and the CT (on average 10 years).

Derivation of the prediction model. Cox proportional hazards analysis was used to predict 3-year cardiovascular events (i.e., the average follow-up time of the cohort). The prediction model was derived from the center with most events (Groningen, 145 events). First, coronary calcium volume and aortic calcium volume were truncated at the 99th percentile because it is undesirable that prognostic accuracy is influenced by biologically implausible outliers. Second, imputation based on regression techniques was performed in case of missing values (20); coronary calcium volume was missing in 1, aortic calcium volume in 2, smoking status in 3, and pack-years in 7 subjects. Subsequently, a preliminary model was fitted using the pre-specified predictors age, smoking status, smoking history, history of cardiovascular disease, coronary calcium volume, and aortic calcium volume. Also, the biologically plausible interaction between age and calcium was added to the model. In order to improve model fit, we determined the functional form to be used for each continuous predictor by examining univariate nonlinear restricted cubic spline transformations (21). It showed that in our dataset a smoking history >50 pack-years, coronary calcium volume >1,500 mm³, and aortic calcium volume >4,000 mm³ had no added predictive value. Consequently, smoking history, coronary calcium volume, and aortic calcium volume were truncated at these cutoff values. Next, the model was specified using backward stepwise selection based on Akaike Information Criterion (22), but no predictors were excluded. To assess the proportional hazards assumption, correlations between scaled Schoenfeld residuals for various predictors and time were tested (23). Bootstrap resampling was used to quantify the degree of over-optimism of the model, which was consequently corrected for by uniformly shrinking the regression coefficients by the same amount (24). Finally, a nomogram was generated to illustrate the model.

The primary analysis was performed in all subjects, because we believe that an absolute risk estimate should also be applicable to subjects who previously experienced a cardiovascular event. Therefore, we included cardiovascular history as a predictor in the model and did not exclude these subjects from our analysis. Secondary analyses were performed in subjects without cardiovascular history (n = 1,620, 106 events), in subjects with ischemic
heart disease and cerebrovascular disease as outcome event \((n = 1,834, 111\) events), and using Agatston score instead of coronary calcium volume \((n = 1,834, 145\) events).

Validation of the prediction model. The prediction model was validated in males from the Utrecht location \((118\) events). The 89 females were not incorporated into the analysis as the variable sex was not included in the prediction model due to the absence of females in the derivation cohort. Imputation based on regression techniques was performed in case of missing values \((20)\); smoking status was missing in 3 subjects and pack-years was missing in 7 subjects. Model discrimination and calibration were evaluated to assess the performance of the model. Discrimination is the ability of the model to separate those with and without a cardiovascular event, and was assessed by using C-indexes \((25)\). Calibration refers to the agreement between the predicted risk and the observed values, and was evaluated with the Grønnesby and Borgan goodness-of-fit test \((26,27)\). Event-free survival was calculated for 1-, 2-, and 3-year follow-up.

To illustrate the model, we evaluated several cutoff values for high-risk by using receiver-operating characteristic and Kaplan-Meier survival analysis, although eventually the cutoff depends on formal cost-effectiveness analysis. Nevertheless, we aimed to illustrate the model at a cutoff value that provided a sufficiently large number of correctly predicted events at a reasonable number of referred cases.

Because we used ungated CT, which overestimated coronary calcium scores compared to gated CT \((28,29)\), we simulated a systematic overestimation of coronary calcium volume of 100\% in the validation cohort by dividing the measured coronary calcium volumes by 2. The number of events incorrectly reclassified to the non–high-risk subgroup was determined.

All analyses were performed with R statistical software, version 2.10.2 \((R\) Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study population. The subjects in both cohorts were about 60 years old and had smoked 38 pack-years. Current and former smokers were about equally present. A cardiovascular history was present in 214 \((11.7\%)\) subjects in the derivation cohort, and in 238 \((13.1\%)\) of the validation cohort. During follow-up 145 \((11\) fatal, 134 nonfatal) and 120 \((7\) fatal, 113 nonfatal) cardiovascular events occurred in the derivation and validation cohort, respectively. The majority of events were from ischemic heart disease or cerebrovascular disease; 109 of 145 \((75\%)\) in the derivation cohort and 74 of 120 \((62\%)\) in the

<table>
<thead>
<tr>
<th>Table 1. Baseline Demographics of the Study Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Derivation Cohort</strong> (n = 1,834)</td>
</tr>
<tr>
<td>Age, yrs</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Current smoker</td>
</tr>
<tr>
<td>Former smoker</td>
</tr>
<tr>
<td>Pack-years, yrs</td>
</tr>
<tr>
<td>Time before CT*, yrs</td>
</tr>
<tr>
<td>Cardiovascular history</td>
</tr>
<tr>
<td>Time to event, yrs</td>
</tr>
<tr>
<td>Cardiovascular event</td>
</tr>
<tr>
<td>Ischemic heart disease or cerebrovascular disease</td>
</tr>
<tr>
<td>Cardiovascular death</td>
</tr>
<tr>
<td>All-cause death</td>
</tr>
<tr>
<td>Coronary calcium volume, mm(^3)</td>
</tr>
<tr>
<td>Aorta calcium volume, mm(^3)</td>
</tr>
</tbody>
</table>

Values are median \((25th to 75th interquartile range)\) or \(n\) \((\%\)\). \(^*\)The period prior to the screening computed tomography (CT) for which data on cardiovascular history was collected.

<table>
<thead>
<tr>
<th>Table 2. The Effect of the Predictors on the 3-Year Risk of Cardiovascular Events in the Derivation Cohort (n = 1,834)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predictor</strong></td>
</tr>
<tr>
<td>Age (per 10 yrs)</td>
</tr>
<tr>
<td>Former smoker</td>
</tr>
<tr>
<td>Smoking history (per 10 pack-yrs)</td>
</tr>
<tr>
<td>Cardiovascular history present</td>
</tr>
<tr>
<td>Coronary calcium volume (per 500 mm(^3))</td>
</tr>
<tr>
<td>Aortic calcium volume (per 500 mm(^3))</td>
</tr>
</tbody>
</table>
validation cohort. Full details on the incident events and mortality are provided in Online Table 1. Overall, baseline survival was 0.976 (1 year), 0.955 (2 year), and 0.940 (3 year). The characteristics of the derivation and validation cohort are summarized in Table 1.

**Derivation of the prediction model.** On testing the proportional hazards assumption, no statistically significant proportionality was found (p = 0.48). The interaction term between age and calcium scores was not included in the final model as it did not improve the model fit. The final model included age, smoking status, pack-years, history of cardiovascular disease, coronary calcium volume, and aortic calcium volume as independent predictors. Table 2 lists the regression coefficients and the hazard ratios of the predictors. The increase in hazard ratios with increasing extent of coronary and aortic calcium is further illustrated in Table 3. Discrimination of the model in the derivation set was good, showing a C-statistic of 0.74 (95% confidence interval [CI]: 0.70 to 0.78). Overoptimism was found to be 3.4%, therefore, the coefficients were shrunk by a factor 0.966. The resulting C-statistic was 0.74 (95% CI: 0.70 to 0.78). Last, when Agatston score was used instead of coronary calcium volume, the model showed a C-statistic of 0.74 (95% CI: 0.70 to 0.78).

**Validation of the prediction model.** In the validation cohort discrimination remained good and yielded a C-statistic of 0.71 (95% CI: 0.67 to 0.76). Calibration of the model was good, without statistically significant differences between predicted and observed values (goodness-of-fit test, p = 0.65). The calibration plot is presented in the supplement (Online Fig. 1). The individual risk can be calculated by using the nomogram presented in Figure 1.

We judged that the proportions of true positive, false negative, and the total amount of referred subjects was reasonable at a risk equal to or greater than 6%, and will use this arbitrary cutoff for further illustration. This cutoff was also the optimum in the receiver-operating characteristic analysis and corresponds favorably to a 10-year risk of 20%, which is commonly used in cardiovascular medicine to define high risk. The performance of the prediction model at this and other cut-off values is presented in Table 4. The characteristics of the resulting high-risk males as identified by the model at the chosen cutoff level at 6% are listed in Table 5. Compared to subjects the model identified as non–high risk, the subjects predicted to have high risk had substantial higher coronary and aortic calcium volumes. The probability for an event in the selected high-risk subgroup was 12.2% (72 of 589), compared with 4.0% (46 of 1,136) in the non–high-risk subgroup. Figure 2 shows the Kaplan-Meier survival curves for both the high-risk and non–high-risk subgroup.

**Simulated overestimation of coronary calcium volume.** In the simulation with coronary calcium volume reduced by 50% the number of correctly detected high-risk subjects dropped only slightly from 72 to 66 whilst the proportion defined as high risk decreased from 34% to 30%, reducing the number of false positives (Online Table 2).

**DISCUSSION**

This study shows that automated quantification of coronary and aortic calcium in lung cancer screening CT scans, combined with few patient demographics and smoking characteristics, can be used to predict cardiovascular events and re-events. This
information, which is readily available in the screening test, may be utilized in the screening of current and former heavy smokers to identify those with highest risk for cardiovascular events. These subjects may benefit most from targeted and intensive primary and secondary preventive strategies.

**Implications for practice.** Practically, when males are identified as high-risk using CT-based screening, initiation, and optimization of preventive measures and intensification of smoking cessation efforts may be the most viable way through which to improve subjects’ outcome. Primary and secondary preventive efforts are

---

### Table 4. Approximation of the Performance of the Prediction Model in the Derivation Cohort at Various Cutoff Values for High Risk

<table>
<thead>
<tr>
<th>3-Year Risk* (%)</th>
<th>True Positive</th>
<th>False Negative</th>
<th>True Negative</th>
<th>False Positive</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>High-Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>118</td>
<td>0</td>
<td>2</td>
<td>1,605</td>
<td>6.9</td>
<td>100.0</td>
<td>99.9</td>
</tr>
<tr>
<td>2.5%</td>
<td>111</td>
<td>7</td>
<td>307</td>
<td>1,300</td>
<td>7.9</td>
<td>97.8</td>
<td>81.8</td>
</tr>
<tr>
<td>6%</td>
<td>72</td>
<td>46</td>
<td>1,100</td>
<td>507</td>
<td>12.4</td>
<td>96.0</td>
<td>33.6</td>
</tr>
<tr>
<td>10%</td>
<td>48</td>
<td>70</td>
<td>1,349</td>
<td>258</td>
<td>15.7</td>
<td>95.1</td>
<td>17.7</td>
</tr>
<tr>
<td>15%</td>
<td>34</td>
<td>84</td>
<td>1,474</td>
<td>133</td>
<td>20.4</td>
<td>94.6</td>
<td>9.7</td>
</tr>
<tr>
<td>20%</td>
<td>23</td>
<td>95</td>
<td>1,540</td>
<td>67</td>
<td>25.6</td>
<td>94.2</td>
<td>5.2</td>
</tr>
<tr>
<td>25%</td>
<td>15</td>
<td>103</td>
<td>1,566</td>
<td>41</td>
<td>26.8</td>
<td>93.8</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Values are n or %. *Three-year risk cutoff value to divide high-risk and non-high-risk subjects. (Percentage of the screening population the model defined as high risk for a cardiovascular event within 3 years using to the corresponding cutoff value. NPV = negative predicted value; PPV = positive predicted value.

---

**Figure 1. Nomogram to Calculate Individual 3-Year Risk for a Cardiovascular Event**

Patient characteristics are filled in and points earned are determined per variable. The sum of all points yields a total score, corresponding to a 3-year event-free survival is read of. A total of 21 points yields a cardiovascular risk over 6% (event-free survival below 0.94), classifying the subject into the high-risk subgroup based on the cutoff value chosen in this study.
risk subject. Also, the weight-adjusted kVp calcium needed for our purpose of identifying high-
excellent for the detection of the high amounts of CT can not exclude coronary heart disease, it is 
that both the lack of electrocardiography gating and 
coronary calcium leads to only modest decrease in 
score. Nevertheless, we showed that even a reduc-
and mortality (13,14). In particular, smoking 
cessation significantly reduces the risk for cardio-
evacular events and death, especially coronary heart 
disease, within a short time period (30). While the 
potential benefits are promising, establishing their 
magnitude and the cost-effectiveness of chest CT-
Based screening for multiple diseases is beyond the 
scope of this study and requires a formal outcome 
study. Nevertheless, multiple disease screening is an interesting concept and may increase the ben-
efits of screening heavy smokers with a chest CT 
2013:899-907 Predicting CV Risk From Lung Screening CT 
AUGUST 2013:899

Study limitations. First, we note that the derivation 
and validation cohort originate from the same lung 
cancer screening trial. Nevertheless, the 2 locations 
are situated in geographically distant parts of the 
Netherlands, with substantial differences in popu-
lation density and migration rate. Furthermore, CT 
scanners from different vendors were used in the 
different locations. Second, calcium volume scores 
may be influenced by the applied scanning protocol. 
Ungated CT may lead to systematic overestimation of 
coronary calcium (but not aortic calcium) due to 
cardiac motion (28,29). However, while ungated 
CT can not exclude coronary heart disease, it is 
reibent to determine if different kVp do not importantly influence the 
model performance in this population. Third, it 
would be advantageous to provide separate risk 
predictions for cerebrovascular disease, coronary 
heart disease, and aorta and peripheral arterial dis-
ease. However, our dataset lacked power for such 
detailed subgroup analyses. Fourth, caution is 
needed regarding the generalizability of our results 
outside a lung cancer screening setting and to fe-
males, given that no females were included in our 
derivation cohort. Last, our study may be limited by 
a nonstandard cardiovascular disease endpoint as we 
relied on the coded medical data from the national 
registry to define patient history and cardiovascular 
events. Furthermore, because we operated within a 
ung cancer screening setting, conventional 
Table 5. Characteristics of the Model-Based High-Risk and Non–High-Risk Males 
in the Validation Cohort

<table>
<thead>
<tr>
<th></th>
<th>Non–High Risk (&lt;6%)</th>
<th>High Risk (≥6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>1,136 (61.9)</td>
<td>589 (34.1)</td>
</tr>
<tr>
<td>3-yr cardiovascular risk, %</td>
<td>3.4 (2.4–4.5)</td>
<td>10.3 (7.7–16.3)</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>58.6 (55.9–62.3)</td>
<td>62.9 (59.3–67.6)</td>
</tr>
<tr>
<td>Pack-yrs</td>
<td>34.2 (28.0–43.7)</td>
<td>43.7 (34.2–55.2)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>544 (47.9)</td>
<td>375 (63.7)</td>
</tr>
<tr>
<td>Cardiovascular history</td>
<td>42 (3.7)</td>
<td>192 (32.6)</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>46 (4.0)</td>
<td>72 (12.2)</td>
</tr>
<tr>
<td>Re-event</td>
<td>4 (8.7)</td>
<td>34 (47.2)</td>
</tr>
<tr>
<td>Coronary calcium volume, mm³</td>
<td>27 (0–161)</td>
<td>863 (313–1834)</td>
</tr>
<tr>
<td>Aortic calcium volume, mm³</td>
<td>212 (33–666)</td>
<td>2,073 (775–4551)</td>
</tr>
</tbody>
</table>

Values are n (%) or median (25th to 75th interquartile range). *Proportion of cardiovascular events occurring in subjects with any cardiovascular history.

Figure 2. Kaplan-Meier Survival Curves of Cardiovascular Event-Free Survival in Non–High-Risk and High-Risk Subgroups

The survival curves show a distinct difference in the event free survival over a 3-year period between computed tomography-based high-risk (≥6%, dotted line) and non–high-risk (<6%, solid line) males.
cardiovascular risk factors are mostly unknown. Evidence is growing that arterial calcifications can predict cardiovascular disease independent from smoking and traditional risk factors (33–35), which is also supported by the good performance of our model that is based on smoking details and calcifications. One has to realize that measuring risk factors such as blood pressure and lipid levels is not part of current lung cancer screening protocols, and will significantly alter the logistics and feasibility of screening practice. Although the coded registry may not be faultless, this national registry has been validated and provides high-quality data. The present study validates the prognostic value of vascular calcifications and clearly demonstrates the ability of cardiovascular risk assessment from screening chest CT.

CONCLUSIONS

We showed that automated quantification of coronary and aortic calcium in a CT-based lung cancer screening setting can be used to predict events and re-events in a population of current and former heavy smokers. This additional information on cardiovascular disease, which is readily available in the screening test, may enhance the cost-effectiveness of CT screening in heavy smokers, although a randomized clinical trial is needed to establish the exact magnitude.

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Key Words: cardiovascular disease ■ computed tomography ■ lung cancer screening ■ tobacco smoking ■ vascular calcification.

For additional tables and figure, please see the online version of this article.