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Psychosocial consequences of false positives in the Danish lung cancer CT-screening trial: a nested matched cohort study

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Objectives

Lung cancer is the most lethal cancer worldwide. Lung cancer CT-screening can reduce lung-cancer mortality, but high false-positive rates might cause adverse psychosocial consequences. The aim was to analyse the psychosocial consequences of false-positive lung-cancer computed tomography screening (CT) using the lung-cancer-screening-specific questionnaire Consequences of Screening-Lung Cancer (COS-LC).

Design and setting

This study was a matched cohort study, nested in the randomised Danish Lung Cancer Screening Trial (DLCST).

Participants

All participants in the DLCST with positive CT-screening results in round 2-5, who completed COS-LC were included in the study. These 130 participants were split into a true- and a false-positive group and were matched on sex, age (+/- three years) and the time (within seven days) of screening (CT group) or clinic visit (control group) 1:2 with participants in the control group (n=248) and 1:2 with participants with (true-)negative CT-screening results (n=252).

Primary outcomes

Primary outcomes were psychosocial consequences measured with COS-LC at five time points.

Results

The false-positive group experienced significantly more negative psychosocial consequences at 1 week in seven outcomes and at 1 month in three outcomes compared with the control group and the

true-negative group (mean Δ score > 0 and $p<0.001$). The true-positive group experienced significantly more negative psychosocial consequences in one outcome at 1 week (mean Δ score 2.86 (95% CI 1.01 to 4.70) $p=0.0024$) and in five outcomes (mean Δ score > 0 and $p<0.004$) at 1 month compared with the true-negative group and the control group. No long-term psychosocial consequences were identified.

Conclusions

False-positive results were associated with negative short-term psychosocial consequences.

Trial registration

The DLCST has been approved by the Danish Scientific Ethical Committee: number of approval KA-02045. The DLCST has been approved by the Danish Data Protection Agency (approval number 2005-53-1083). All participants signed an informed consent form. ClinicalTrials.gov: NCT00496977

Strengths and limitations

- This study used a lung-cancer-screening-specific questionnaire with high content validity and adequate psychometric properties in a randomised design to measure the psychosocial consequences of the screening results
- Besides the false-positive group, both the true-positive group and the true-negative group were assessed, serving as benchmarks: those with respectively most- and least psychosocial consequences, for comparison with the consequences of the false positives.

- A limitation is that the control group, not invited to screening, reported more negative psychosocial consequences than the screening group.
- Another limitation is that the study participants had a more robust psychosocial profile compared with a matched background population.

Introduction

Lung cancer is the most lethal cancer worldwide.[1] Several randomised controlled screening trials using low dose computed tomography (CT) scans have investigated the effect of CT screening on lung-cancer-specific mortality.[2] The largest trial, the National Lung Screening Trial (NLST), found a relative lung-cancer-specific mortality reduction of 16% after five years follow-up, and lung cancer CT screening is now recommended in the United States.[3-5] However, according to a Cochrane review more data are needed on false-positive results and overdiagnosis before recommendations can be made for large-scale CT-screening programmes.[6] The Danish Lung Cancer Screening Trial (DLCST) could not show a reduction in lung-cancer-specific- or total mortality after five years follow-up.[7] The European trials are expected to publish the pooled follow-up analyses of both the mortality data and the consequences of overdiagnosis and false positives.[8] This will provide the additional evidence of benefits and harms of lung cancer CT screening requested in the Cochrane review.[6]

In cancer screening programmes, positive screening results lead to either false-positive results or true-positive results after further diagnostic workup.[9] A false-positive screening result can cause both physical and psychosocial harms [10-13] as well as being costly for the healthcare system.[14 15] The average false-positive rate per screening round varies substantially in lung cancer screening trials, e.g. 23% in the NLST and 3% in the DLCST (appendix table 1).[3 16] Qualitative and quantitative studies have shown that false-positive lung-cancer-screening results can cause negative psychosocial consequences both during workup and after the final diagnosis.[13 17 18] By nature qualitative studies cannot measure the degree or the extent of psychosocial consequences.[17] All the quantitative studies used generic questionnaires with lack of content validity and unknown psychometric properties.[13 18-20] Measurement of psychosocial consequences of screening using

questionnaires with high content validity and adequate psychometric properties is therefore of importance.[21]

Therefore, the aim of this study was to measure the short- and long-term psychosocial consequences of false-positive lung cancer CT-screening results using the questionnaire Consequences of Screening - Lung Cancer (COS-LC) and compare these COS-LC scores with the COS-LC scores from 3 other groups of participants in the DLCST: 1) the true-negative group, 2) the true-positive group and 3) a control group that was not screened.

Methods

Study design and participants

The overall design of the DLCST has been reported in detail elsewhere.[16 22] In summary, the DLCST was a single-centre, randomised, controlled trial and participants were randomly allocated to a CT group and a control group (figure 1). Eligible participants were current and former smokers with a smoking history of minimum 20 cigarettes/day for 20 years aged 50–70 years.[16 22] In five rounds during 2004–2010 both groups were offered annual spirometry and smoking counselling and were asked to complete the questionnaire COS-LC. Participants in the CT group were also offered annual lung CT scans.

This study was a matched cohort study nested in the DLCST. Participants from the CT group with positive CT-screening results during round 2–5 were matched 1:2 with participants with negative CT-screening results and 1:2 with participants from the control group. Participants were matched on sex, age (+/- three years) and the time (within seven days) of screening (CT group) or clinic visit (control group). The group with positive CT-screening results was divided into a true-positive group

and a false-positive group after receiving the final diagnosis. Participants completed the COS-LC at five time points (figure 1):

- Baseline: COS-LC was completed shortly before the annual CT screening (CT group) or clinic visit (control group)
- 1 week after receiving the CT-screening result (CT group) and 1 week after the annual clinic visit (control group)
- 1, 6 and 18 months after receiving the final diagnosis of the screening result (CT group) or after the annual clinic visit (control group)

At the latter four time points, participants were sent the COS-LC and asked to return it in an enclosed stamped addressed envelope. A reminder was sent to those who did not return it within two weeks.

Information about region of residence, smoking status, smoking history, social group, employment status, school education and whether participants lived alone was obtained from baseline and annual questionnaires. Charlson's comorbidity index was calculated from hospital admissions three years before randomisation.

Questionnaire

The COS-LC is a condition-specific questionnaire with high content validity and adequate psychometric properties and was developed and validated to measure the psychosocial consequences of participants in lung cancer CT screening.[17] To ensure high content validity, 20 participants from the first screening round in the DLCST were interviewed in five group

interviews.[17] Subsequently, during the screening rounds 2–4 in the years 2006–2007, questionnaire data from participants were used to validate the COS-LC using Item Response Theory Rasch models.[17] Because these data were only a part of the present data, the psychometric properties of the 15 COS-LC scales were re-tested for homogeneity and differential item functioning (DIF) relative to participant group, sex, age, social status and smoking status by using likelihood ratio tests on appropriately conditioned Rasch models at the 1 month follow-up time point.[23] Reliability of the scales was examined using Cronbach's alpha.

The COS-LC consists of two parts where Part-I encompasses 24 COS items (four COS-scales) and 25 lung-cancer-screening-specific items (five lung-cancer-screening-specific scales) (appendix table 2). Part-I can be used before, during and after screening and the DLCST participants in both the CT group and the control group have completed Part-I.[17] The higher the scale-score, the more negative the psychosocial consequences.[17]

Part-II measures the long-term psychosocial consequences after lung-cancer CT screening and can therefore only be completed by the screening participants after they have received their final diagnosis.[17]

Part-II encompasses 24 items (six scales) and was designed and validated to measure changes, both positive and negative, and high scores denote more change (appendix table 2).

Statistical analysis

The differences in characteristics of the four groups of participants (true-negative, true-positive, false-positive and control) were tested with Pearson χ^2 tests for categorical variables and Kruskal-Wallis non-parametric tests for continuous variables.

For each of the 15 COS-LC scales, the mean score for each of the four participant groups at the five

time points was analysed with linear regression models, both unadjusted and adjusted for the participant characteristics: round, sex, (a quadratic function of) age, region, (a quadratic function of) pack years, smoking status, social group, living alone, employment status, school education and Charlson's comorbidity index. Generalised estimating equations were used to account for repeated measurement. To adjust for differential dropout, the non-missing scales at each time point were weighted by the inverse of the probability of this scale being observed at that time.[24] These probabilities were estimated from the data in logistic regression models for the scale being missing, which included the participant characteristics, the participant groups, and the corresponding scale outcomes from previous time points.

The statistical level of significance was set using the method of Benjamini-Hochberg to adjust for multiple testing.[25] Statistical Analysis Software (SAS) 9.3 was used to analyse the data.

Participant and public involvement

DLCST-participants were involved in the development of the questionnaire COS-LC. Neither participants nor public were involved in the design and recruitment of the study.

Results

Participation

Distribution of final diagnostic results and participation rates are presented in figure 1. In round 2–5, 193 participants received a positive screening result; of those, 130 (67%) completed the COS-LC and were included in this study. The reasons for non-response were 1) never receiving the COS-LC due to administrative reasons (n=39, 20%), refusing to complete the COS-LC (n=6, 3%) and 3) other reasons (n=18, 9%).

Of the 130 respondents, 24 (19%) had received one false-positive result in the previous rounds and one (0.8%) participant had previously received two false-positive results. The COS-LC was sent to 252 participants with true-negative results and 248 control participants. Response rates for the four groups during the five time points were 64–97% (figure 1).

There was a significant difference between the four groups regarding age and smoking history: the participants in the true-positive group were older and had a longer smoking history (Table 1). A significant difference was observed in the region of residence where false positives to a larger extent lived outside the capital region compared with the other groups. No significant difference was found in the remaining participant characteristics.

Table 1

Characteristics of Screening Participants

		CT group n = 382			Control group n = 248		
	Total *n = 630*	True-negative *n = 252*	False-positive *n = 91*	True-positive *n = 39*	*n = 248*	p-value*	missing
Round, *n (%)*						0.543	0
2	158 (25.1)	68 (27.0)	26 (28.6)	9 (23.1)	55 (22.2)		
3	196 (31.1)	76 (30.2)	24 (26.4)	14 (35.9)	82 (33.1)		
4	76 (12.1)	31 (12.3)	10 (11.0)	8 (20.5)	27 (10.9)		
5	200 (31.8)	77 (30.6)	31 (34.1)	8 (20.5)	84 (33.9)		
Sex, *n (%)*						0.174	0
Men	298 (47.3)	118 (46.8)	37 (40.7)	24 (61.5)	119 (48.0)		
Women	332 (52.7)	134 (53.2)	54 (59.3)	15 (38.5)	129 (52.0)		
Age (years), *median (IQR)*	58 (55-62)	58 (55-62)	58 (54-61)	60 (58-65)	59 (55-62)	0.017	0
Social Group, *n (%)*						0.334	1
I	42 (6.7)	23 (9.2)	3 (3.3)	1 (2.6)	15 (6.1)		
II	132 (21.0)	51 (20.3)	13 (14.3)	9 (23.1)	59 (23.8)		
III	126 (30.0)	53 (21.1)	15 (16.5)	6 (15.4)	52 (21.0)		
IV	158 (25.1)	57 (22.7)	28 (30.8)	13 (33.3)	60 (24.2)		
V	81 (12.9)	29 (11.6)	13 (14.3)	6 (15.4)	33 (13.3)		
Employed, social group uncertain	54 (8.6)	21 (8.4)	12 (13.2)	1 (2.6)	20 (8.1)		
Outside the labour market	36 (5.7)	17 (6.8)	7 (7.7)	3 (7.7)	9 (3.6)		
School education, *n (%)*						0.321	0
7-9 years in school	242 (38.4)	88 (34.9)	45 (49.5)	16 (41.0)	93 (37.5)		
10 years in school	229 (36.4)	99 (39.3)	27 (29.7)	15 (38.5)	88 (35.5)		
11-13 years in school	159 (25.2)	65 (25.8)	19 (20.9)	8 (20.5)	67 (27.0)		
Employment status, *n (%)*						0.219	1
Employed	374 (59.5)	158 (62.7)	48 (52.8)	18 (47.4)	150 (60.5)		

Studying	2 (0.3)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.4)		
Job seeking	35 (5.6)	17 (6.8)	7 (7.7)	3 (7.9)	8 (3.2)		
Retired	218 (34.7)	77 (30.6)	35 (38.5)	17 (44.7)	89 (35.9)		
Region of residence, *n (%)*						0.043	1
Capital Region	522 (83.0)	310 (83.3)	70 (76.9)	32 (82.1)	210 (85.0)		
Region Zealand	98 (15.6)	34 (13.5)	20 (22.0)	7 (18.0)	37 (15.0)		
Region of Southern Denmark	9 (1.4)	8 (3.2)	1 (1.1)	0 (0.0)	0 (0.0)		
Living alone, *n (%)*						0.147	4
No	430 (68.7)	175 (69.7)	54 (59.3)	25 (64.1)	176 (71.8)		
Yes	196 (31.3)	76 (30.3)	37 (40.7)	14 (35.9)	69 (28.2)		
Smoking status, *n (%)*						0.195	0
Current smoker	473 (75.1)	183 (72.6)	72 (79.1)	34 (87.2)	184 (74.2)		
Former smoker	157 (24.9)	69 (27.4)	19 (20.9)	5 (12.8)	64 (25.8)		
Smoking history (pack years), *median (IQR)*	34 (27-43)	34 (27-43)	34 (27-43)	43 (34-49)	33 (26-42)	0.001	1
Charlson comorbidity index, *n (%)*						0.913	0
0	590 (93.7)	235 (93.3)	83 (91.2)	36 (92.3)	236 (95.2)		
1	25 (4.0)	10 (4.0)	5 (5.5)	2 (5.1)	8 (3.2)		
≥2	15 (2.4)	7 (2.8)	3 (3.3)	1 (2.6)	4 (1.6)		

*p-value of a Pearson chi-squared test (categorical variables) or a Kruskal-Wallis test (continuous variables); p-values are estimates of the exact p-values based on 10,000 Monte Carlo simulations under the null-hypothesis; CT=computed tomography; IQR=interquartile range.

The 15 COS-LC scales exhibited overall adequate fit to the partial credit Rasch model for polytomous items. No DIF was revealed and Cronbach's Alpha was 0.693–0.962 (Table 2).

Table 2

Conditional likelihood ratio (CLR) fit statistics and Cronbach's alpha for the 15 domains of the Consequences of Screening for Lung Cancer (COS-LC) questionnaire

Scales (no. of items)	CLR	Degrees of freedom	p*	Cronbach's Alpha

Anxiety (7)	23.0	20	0.286	0.903
Behaviour (7)	19.0	20	0.520	0.893
Dejection (6)	14.9	17	0.603	0.916
Negative impact on sleep (4)	22.3	11	0.022	0.874
Selfblame (5)	20.2	14	0.124	0.962
Focus on airway symptoms (2)	1.0	5	0.966	0.802
Stigmatisation (4)	24.6	11	0.010	0.916
Introvert (4)	11.2	11	0.425	0.851
Harm of smoking (2)	9.8	5	0.082	0.857
Existential values (6)	9.3	11	0.591	0.851
Calm/relaxed (2)	0.6	3	0.887	0.693
Social network (3)	5.5	5	0.362	0.754
Impulsivity (6)	4.5	11	0.954	0.854
Empathy (3)	5.9	5	0.314	0.699
Regretful of still smoking (4)	1.0	7	0.795	0.863

*After adjustment for multiple testing by using the methods of Benjamini-Hochberg the level of statistical significance was assessed at a level of 0.0033.

COS-LC Part-I

Figure 2a presents the mean score of the nine outcomes for COS-LC Part-I for the four groups at the five time points. For Part-I in general, participants with a positive CT-screening result reported more negative psychosocial consequences in the short-term follow-up points of 1 week and 1 month (figure 2a). The false-positive group experienced significantly more negative psychosocial consequences at 1 week in seven outcomes (Anxiety, Behaviour, Dejection, Selfblame, Focus on airway symptoms, Introvert, and Harm of smoking) and at 1 month in three outcomes (Selfblame, Focus on airway symptoms, and Harm of smoking) (mean Δ score > 0 and p<.001) compared with either the control group or the true-negative group (figure 2a, appendix table 3). At 6 and 18

months, there was a trend towards more negative psychosocial consequences in three outcomes, but no statistically significant differences were found. The true-positive group showed the same general pattern and experienced significantly more negative psychosocial consequences only in the outcome Dejection at 1 week (mean Δ score 2.86 (95% CI 1.01 to 4.70) p=0.0024) and in the three outcomes Behaviour, Dejection, and Focus on airway symptoms at 1 month (mean Δ score > 0 and p<.004) compared with the true-negative group and the control group (figure 2a, appendix table 3). At baseline, the true-positive group showed a significantly more positive psychosocial profile in the outcomes Anxiety and Self-blame.

COS-LC Part-II

Figure 2b presents the mean scores of the six outcomes for COS-LC Part-II for the three groups at the three follow-up points after receiving the final screening result. The false-positive group showed a trend towards more negative psychosocial consequences in two outcomes at 1 month compared with the true-negative group, but no significant differences were seen. The true-positive group showed significant differences in the outcome Social network at 1 month and 6 months and in the outcome Empathy at 1 month (figure 2b, appendix table 3). Trends towards more negative psychosocial consequences were seen in five outcomes at 1 month compared with the true-negative group. This difference diminished at 6 and 18 months. The true-negative group showed no variation in psychosocial consequences through the three follow-up points.

Discussion

False-positive lung-cancer CT-screening results were associated with negative short-term psychosocial consequences compared with the control group and the true-negative group. There

were not identified any long-term consequences of false-positive results. Contrary to expectation, neither were there any long-term consequences experienced by the true-positive group.

The tendency of more negative long-term psychosocial consequences in the false-positive group, was limited to three lung-cancer-specific scales in Part-I. The same pattern was seen for the true-positive group. Additionally, this group reported more negative psychosocial consequences in the scales Social Network and Empathy in Part-II of COS-LC (figure 2b). Smoking causes approximately 90% of all lung cancers and on a societal level smokers are often blamed for their lung cancer, which can lead to feelings of self-blame and guilt.[26] This could explain the tendency of long-term negative psychosocial consequences in the lung-cancer-specific scales: Self-blame, Focus on Airway Symptoms and Harm of Smoking in Part-I. In contrast, no negative long-term consequences were seen in the remaining six scales in Part-I. There might be several explanations to our findings: 1) The true-positive group had a more positive psychosocial profile at baseline than the other groups. Hence, no long-term differences compared with the control group were seen, when the short-term negative psychosocial consequences diminished with time towards the more positive set point. 2) Selection bias was identified among DLCST participants being better educated and having a more positive psychosocial profile compared with a matched background population.[27] Thus, DLCST participants were probably more psychosocially robust than average and therefore false-positive or true-positive findings might have had less negative consequences than expected for the general population.

3) Those diagnosed with lung cancer via screening and who remained alive and asymptomatic after 18 months were convinced, they were cured of a lethal disease. This reassurance is likely since lung cancer symptom lead time is longer than 18 months and a minimum of 20% of the screening detected lung cancers are overdiagnosed.[28] If those diagnosed with lung cancer via screening do not

suffer any substantial long-term negative psychosocial consequences, it is not expected that other screening groups suffer. 4) Another study showed that the control group experienced more negative psychosocial consequences than the CT group through screening rounds 2-5 in DLCST[29]—thus, the reference level of psychosocial consequences in the control group is more negative, which decreases the difference between the control group and the positive CT-screening groups. 5) During the development of the COS-LC, the qualitative interviews were conducted 0–5 months after screening; therefore, Part-II of the COS-LC might not capture all relevant long-term psychosocial consequences for those with false-positive findings. 6) Approximately 20% of the participants receiving a positive screening result had previously received a false-positive result. Therefore, the participants might get accustomed to receiving a positive screening result and this could decrease the level of negative psychosocial consequences. In contrast, the COS-LC was developed in the first round and a first-round effect, which most likely would have had a more negative psychosocial impact on the participants, was not seen. 7) Contamination of the control group could have biased our results; nevertheless, contamination of the DLCST was found to be minor[30] Finally, participants with false-positive results could have received a negative screening result between the 6- and 18-month assessments, which could be perceived as reassurance, consequently lowering the negative psychosocial consequences.

This is the first study to present both short- and long-term psychosocial consequences of false-positive results using a lung-cancer-specific questionnaire with high content validity and adequate psychometric properties developed in a randomised, controlled lung cancer CT screening trial. Therefore, the COS-LC most likely presents stronger results compared with generic questionnaires. Secondly, the true-positive group was included in this study. When both the true-positive- and the true-negative groups are included, the extent of the psychosocial harm in the false-positive group

can be compared with that of those who should be worst off (true positives) and those who are reassured (true negatives). However, no significant differences in the long-term psychosocial consequences in either the false-positive group or the true-positive group compared with the control group were shown.

Other quantitative studies have investigated the health-related quality of life (HRQoL) in CT screening using generic questionnaires not validated for lung cancer.[13 18-20] Although one lung-cancer-specific questionnaire was used, no information about validation was reported.[18] These studies found that CT screening had only short-term and no long-term negative effects on HRQoL for participants with false-positive results. Our study, using a more accurate and validated survey instrument, has confirmed this. However, the absence of long-term psychosocial consequences also for the true-positive group suggests that certain long-term consequences may have been overlooked or that the development of a certain resilience or relief (of feeling cured) may play a long-term role.[31] A meta-analysis of the psychosocial consequences of false-positive mammograms including both generic and condition-specific outcome measures showed both short-term and long-term (up to three years) negative psychosocial consequences compared with true-negative mammograms.[12 32] This study recommends the use and further development of condition-specific measures instead of generic measures in mammography screening. Therefore, condition-specific measures should also be improved and used in lung cancer CT-screening to obtain the most valid results of psychosocial outcomes.

Interpreting the effect size of the results, the mean increase of 2.16 in Selfblame in the false-positive group at the 1 month time point compared with the control group is used (appendix table 3). This increase corresponds to two shifts in the response category of one item, e.g. from “not at all” to

"quite a bit", for all participants with false-positive results, while all the participants in the control group had no shift in response category. As the false-positive rates differ substantially in the NLST (23%) and the DLCST (3%), which has been discussed in detail previously[15], the negative psychosocial consequences on a population level would probably be higher in countries with higher false-positive rates. The knowledge of psychosocial consequences of false-positive results contributes to the evidence of benefits and harms of lung-cancer CT screening and should be included in the overall assessment of the European trials.

Conclusion: In the Danish Lung Cancer Screening Trial, false-positive results were associated with more negative short-term psychosocial consequences compared with the control group and the true-negative group.

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Contribution

The study was devised and designed by JB. Data collection was conducted by JB. Statistical analysis was done by JFR and VS. JFR drafted the manuscript and JB, VS and JM contributed to parts of the manuscript and to revisions of the manuscript. All three authors have approved the final version of the manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. The authors received no writing assistance.

Conflict of interest statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Availability of data and materials

The corresponding author can provide the questionnaires and datasets generated and analysed during the study on reasonable request.

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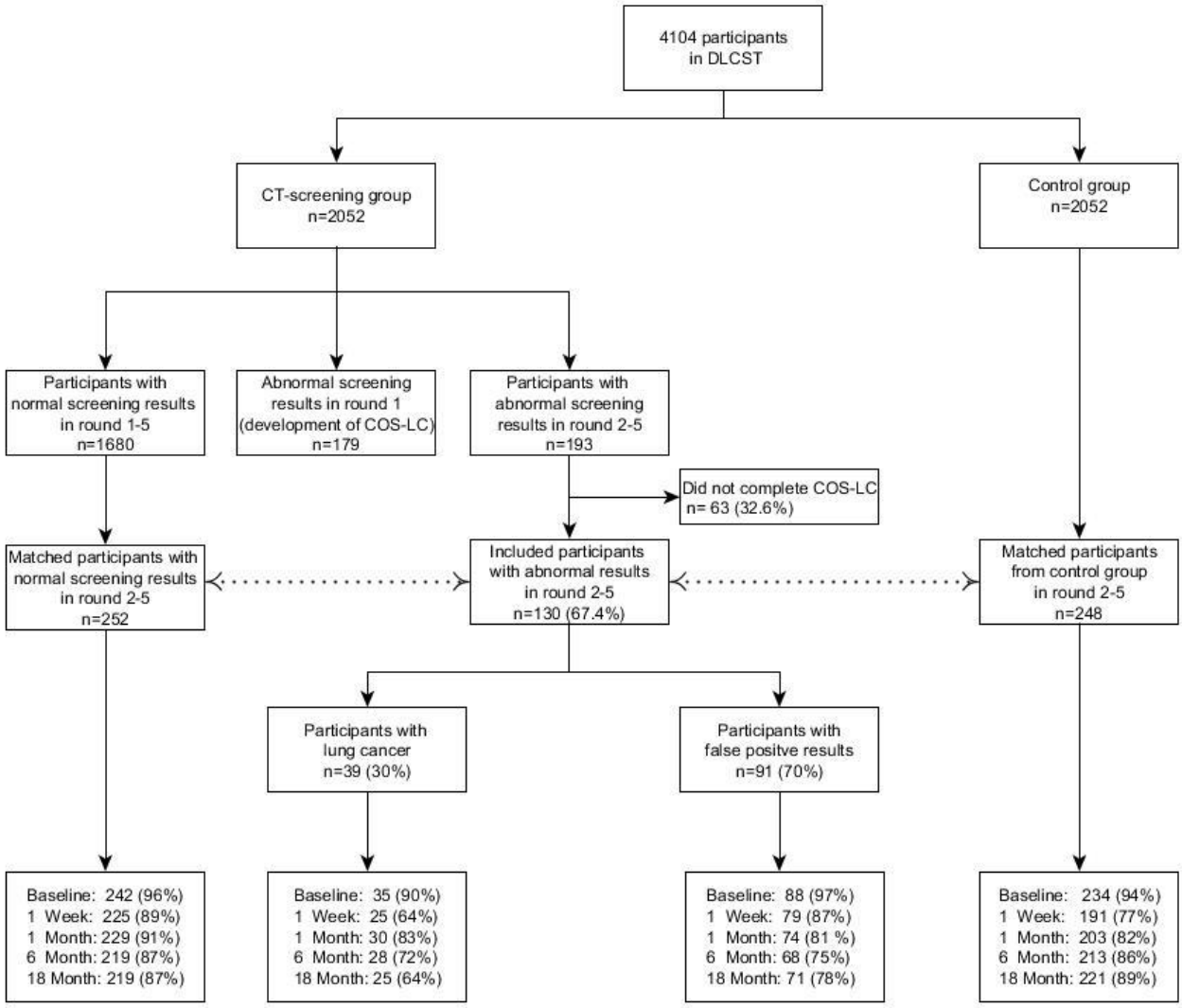
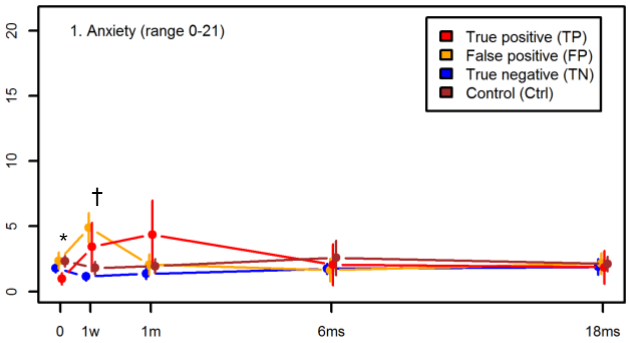
Figure 1:

Distribution of screening results and final diagnoses in the DLCST, and response rates of the matched groups at five time points: baseline, 1 week, 1,6 and 18 months



DLCST=Danish lung cancer screening trial; CT=Computed Tomography; COS-LC=Consequences of screening-lung cancer.

Table 2a. The mean score of the 9 psychosocial outcomes of COS-LC Part-I for the diagnostic groups and the control group in the DLCST at five time points: Baseline, 1 week, 1, 6 and 18 months



*= Significant difference between: Ctrl - TP, TN - TP, FP - TP
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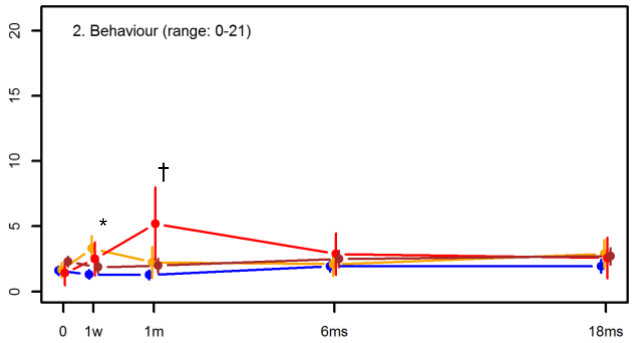

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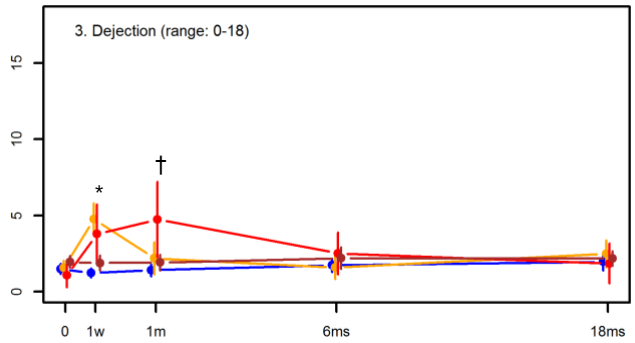

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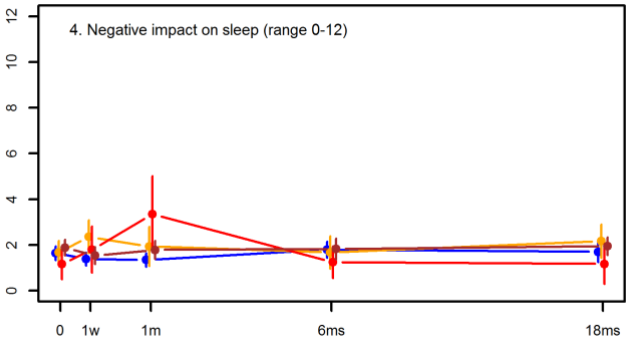
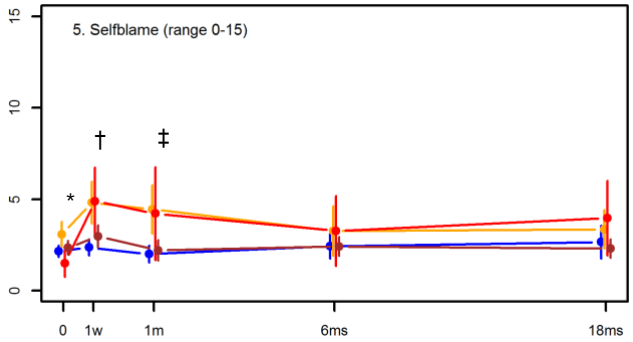
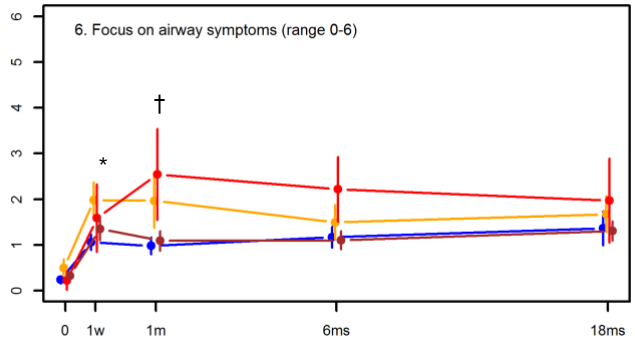
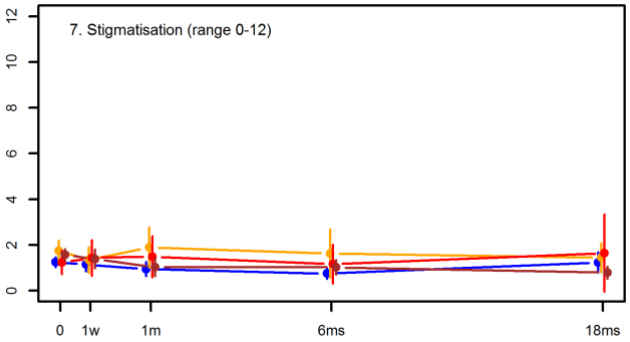


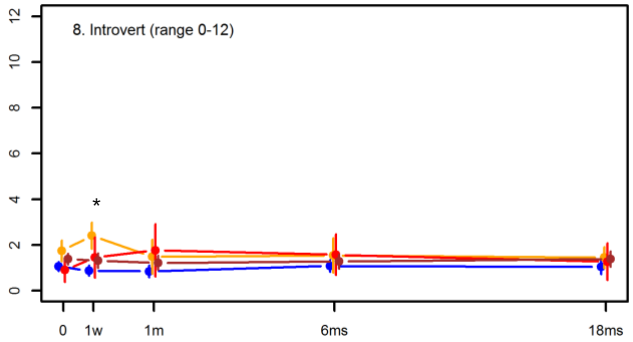


*= Significant difference between: Ctrl - TP, FP - TP
†= Significant difference between: TN - FP
‡= Significant difference between: Ctrl – FP, TN - FP



*= Significant difference between: TN - FP
†= Significant difference between: Ctrl - TP, TN - FP, TN - TP





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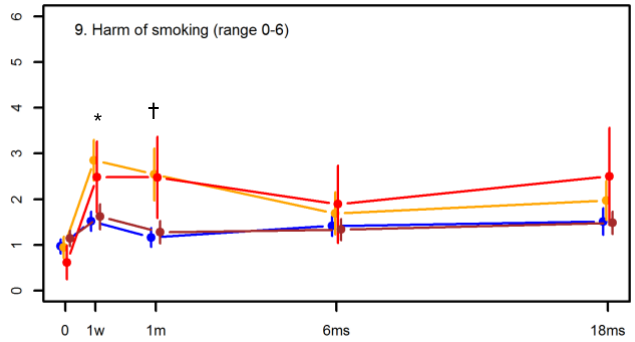

*= Significant difference between: Ctrl – FP, TN - FP
†= Significant difference between: Ctrl – FP, TN - FP

Table 2b. The mean score of the 6 psychosocial outcomes of COS-LC Part-II for the diagnostic groups in the DLCST at three time points: 1, 6 and 18 months

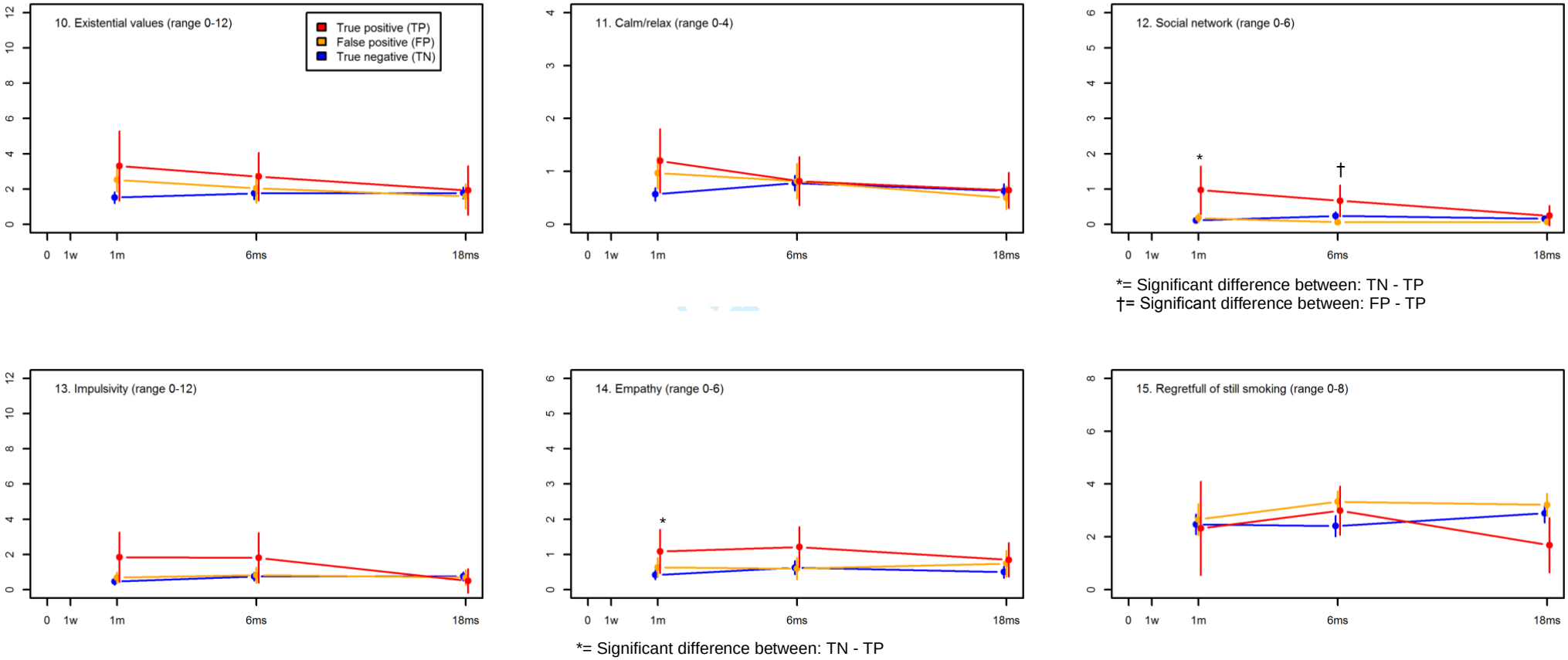

Table 2a and 2b: The mean estimates are compared between all groups at each time point and significant differences between the groups are described below each scale (see appendix table 1 for details of the adjusted analyses). After adjustment for multiple testing by using the methods of Benjamini-Hochberg the level of statistical significance was assessed at a level of 0.0043; 0=baseline; 1W=1 week after screening; 1m, 6ms and 18 ms=1,6 and 18 months after final diagnostic result; TP=true-positive group; FP=false-positive group; TN=true-negative group; Ctrl=control group; COS-LC=Consequences of screening–lung cancer; The higher the score the more negative psychosocial reaction.

Appendix Table 1

False-positive rates in the National Lung Screening Trial (NLST) and the Danish Lung Cancer Screening Trial (DLCST)

Trial	Study threshold of an abnormal non-calcified lung nodule (screening test positive)*	Round of screening	Number screened	Abnormal lung nodules over study threshold (screening test positive)	Lung cancer nodules (true positives)	Nodules not lung cancer (false positives)	False-positive rate (nodules not lung cancer / no. screened)	Average false-positive rate
NLST	≥4 mm	Baseline	26 309	7191	270	6921	0.2631	
		Year 1	24 715	6901	168	6733	0.2724	
		Year 2	24 102	4054	211	3843	0.1594	
Total			*75 126*			*17 497*		*0.2329*
DLCST	≥5 mm	Baseline	2047	179	17	162	0.0791	
		Year 1	1976	45	11	34	0.0172	
		Year 2	1944	52	13	39	0.0201	
		Year 3	1982	44	12	32	0.0161	
		Year 4	1851	51	16	35	0.0189	
Total			*9800*			*302*		*0.0308*

*In the DLCST, a CT-screening test result was categorised as abnormal (screening test positive) if a non-calcified lung nodule was ≥5 mm which lead to diagnostic evaluation. The test result was categorised as normal (screening test negative) if the nodule was < 5 mm. In the DLCST non-benign nodules between 5-15 mm found on a CT-screening scan lead to a three months follow-up scan. Nodules > 15 mm were referred to diagnostic work-up. In the NLST non-calcified lung nodules of at least 4 mm found on a CT-screening scan were classified as abnormal screening results (screening test positive) and nodules < 4 mm were classified as normal screening results (screening test negative).

Appendix Table 2.

List of items included in the 15 scales of the questionnaire Consequences of Screening – Lung Cancer (COS-LC)

	Scales	Items
Part I	**1. Anxiety**	Worried about my future
		Nervous
		Scared
		Restless
		Shocked
		Upset
		Terrified
	2. Behaviour	Difficulty doing things around the house
		Difficulty dealing with work or other commitments
		Quieter than normal
		Hard to concentrate
		Withdrawn into myself
		Change in appetite
		Irritable
	3. Dejection	Worried
		Uneasy
		Sad
		Depressed
		Time passed slowly
		Unable to cope
	4. Negative impact on sleep	Woken up far too early in the morning
		Slept badly
		Taken long time to fall a sleep
		Been awake most of the night
	5. Selfblame	Felt guilty
		Blamed oneself
		Been annoyed with oneself
		Disappointed in oneself
		Angry with oneself
	6. Focus on airways symptoms	Aware of being short of breath
		Been aware of one's coughing
	7. Stigmatisation	Felt stigmatised

		Being told off by other people
		A finger wagging from others
		Blamed by other people
	8. Introvert	Insecure
		Mood Swings
		Thought one´s situation hopeless
		Sorry for oneself
	9. Harm of smoking	Thought of smoking as harmful
		Sorry for having smoked for many years
Part II	**10. Existential Values**	Broader aspects of life
		Value of life
		Enjoyment of life
		Awareness of life
		Thought about future
		Well-being
	11. Calm/Relax	Relaxed
		Calm
	12. Social Network	Family
		Friends
		Other people
	13. Impulsivity	Energy
		Lived life to the full
		Being impulsive
		Desire to venture into something risky
		Desire to venture into something new
		Done some things that overstepped one´s bounds
	14. Empathy	Understands other people´s problems
		Responsibility for one's family
		Ability to listen to other people's problems
	15. Regretful of still smoking	Thought about quitting smoking
		Disappointed in oneself for smoking
		Annoyed with oneself for smoking
		Having second thoughts about one´s smoking

Appendix Table 3.

Adjusted analyses of the 15 scales in the questionnaire Consequences of Screening – Lung Cancer (COS-LC): Mean differences between each pair of the diagnostic groups and the control group during five time points

		Follow up time									
		Baseline		1 week		1 Month		6 Month		18 Month	
Scale (Range)	Comparison	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value
1. Anxiety	Con-Neg	-0.46 (-0.99 to 0.07)	0.0864	-0.63 (-1.20 to -0.06)	0.0317	-0.66 (-1.40 to 0.07)	0.0768	-0.58 (-1.35 to 0.19)	0.1375	-0.36 (-1.13 to 0.40)	0.3519
(0-21)	Con-FP	-0.02 (-0.78 to 0.74)	0.9582	2.77 (1.63 to 3.92)	<.0001	-0.25 (-1.25 to 0.75)	0.6249	-1.20 (-2.43 to 0.04)	0.0578	-0.26 (-1.16 to 0.65)	0.5821
	Con-TP	-1.52 (-2.18 to -0.86)	<.0001	1.89 (0.01 to 3.78)	0.0487	2.72 (0.08 to 5.37)	0.0438	-0.54 (-2.30 to 1.21)	0.5426	-0.69 (-2.41 to 1.04)	0.4360
	Neg-FP	0.44 (-0.27 to 1.16)	0.2257	3.40 (2.33 to 4.48)	<.0001	0.41 (-0.48 to 1.31)	0.3649	-0.62 (-1.64 to 0.41)	0.2390	0.11 (-0.75 to 0.97)	0.8047
	Neg-TP	-1.06 (-1.68 to -0.43)	0.0010	2.52 (0.71 to 4.33)	0.0063	3.38 (0.77 to 6.00)	0.0112	0.04 (-1.66 to 1.74)	0.9666	-0.32 (-1.98 to 1.34)	0.7036
	FP-TP	-1.50 (-2.29 to -0.71)	0.0002	-0.88 (-2.95 to 1.19)	0.4043	2.97 (0.14 to 5.81)	0.0400	0.65 (-1.25 to 2.55)	0.5012	-0.43 (-2.20 to 1.34)	0.6342
No. Respondents		607		514		444		509		518	
2. Behaviour	Con-Neg	-0.74 (-1.26 to -0.23)	0.0046	-0.58 (-1.15 to -0.01)	0.0469	-0.74 (-1.41 to -0.08)	0.0284	-0.51 (-1.27 to 0.24)	0.1838	-1.00 (-1.80 to -0.20)	0.0144
(0-21)	Con-FP	-0.75 (-1.50 to 0.01)	0.0520	1.21 (0.19 to 2.23)	0.0198	-0.09 (-1.34 to 1.16)	0.8843	-0.60 (-1.72 to 0.51)	0.2873	-0.07 (-1.30 to 1.17)	0.9143
	Con-TP	-1.05 (-2.16 to 0.06)	0.0632	0.65 (-0.65 to 1.94)	0.3260	3.31 (0.50 to 6.11)	0.0209	0.03 (-1.66 to 1.73)	0.9698	-0.81 (-2.66 to 1.05)	0.3948
	Neg-FP	0.00 (-0.70 to 0.70)	0.9953	1.79 (0.84 to 2.74)	0.0002	0.65 (-0.46 to 1.76)	0.2522	-0.09 (-1.09 to 0.90)	0.8551	0.93 (-0.21 to 2.07)	0.1106
	Neg-TP	-0.31 (-1.39 to 0.78)	0.5793	1.23 (-0.02 to 2.47)	0.0544	4.05 (1.27 to 6.83)	0.0043	0.54 (-1.13 to 2.22)	0.5236	0.19 (-1.61 to 2.00)	0.8340
	FP-TP	-0.30 (-1.48 to 0.87)	0.6117	-0.56 (-2.06 to 0.94)	0.4636	3.40 (0.38 to 6.42)	0.0275	0.64 (-1.22 to 2.49)	0.5005	-0.74 (-2.80 to 1.32)	0.4834
No. Respondents		611		518		438		507		517	
3. Dejection	Con-Neg	-0.41 (-0.92 to 0.10)	0.1142	-0.66 (-1.25 to -0.07)	0.0291	-0.55 (-1.24 to 0.13)	0.1113	-0.36 (-1.07 to 0.35)	0.3231	-0.35 (-1.04 to 0.34)	0.3216
(0-18)	Con-FP	-0.41 (-1.04 to 0.22)	0.2017	2.63 (1.53 to 3.74)	<.0001	-0.09 (-1.21 to 1.04)	0.8815	-1.04 (-2.07 to 0.00)	0.0492	-0.01 (-1.04 to 1.03)	0.9903
	Con-TP	-0.89 (-1.81 to 0.02)	0.0562	2.20 (0.28 to 4.12)	0.0245	2.92 (0.57 to 5.27)	0.0147	0.16 (-1.32 to 1.64)	0.8308	-0.74 (-2.37 to 0.89)	0.3726
	Neg-FP	0.00 (-0.62 to 0.62)	0.9981	3.29 (2.27 to 4.31)	<.0001	0.47 (-0.55 to 1.49)	0.3695	-0.68 (-1.59 to 0.23)	0.1438	0.34 (-0.64 to 1.32)	0.4928
	Neg-TP	-0.48 (-1.39 to 0.43)	0.2974	2.86 (1.01 to 4.70)	0.0024	3.48 (1.15 to 5.80)	0.0034	0.52 (-0.94 to 1.98)	0.4857	-0.39 (-2.04 to 1.25)	0.6397
	FP-TP	-0.48 (-1.44 to 0.47)	0.3217	-0.43 (-2.49 to 1.63)	0.6812	3.01 (0.44 to 5.58)	0.0219	1.20 (-0.38 to 2.77)	0.1365	-0.74 (-2.55 to 1.08)	0.4270
No. Respondents		606		521		449		518		526	
4. Negative impact on sleep	Con-Neg	-0.16 (-0.62 to 0.31)	0.5047	-0.16 (-0.65 to 0.33)	0.5191	-0.38 (-0.90 to 0.14)	0.1549	-0.06 (-0.60 to 0.48)	0.8321	-0.29 (-0.82 to 0.24)	0.2786
(0-12)	Con-FP	-0.26 (-0.89 to 0.37)	0.4235	0.65 (-0.14 to 1.44)	0.1056	-0.10 (-1.01 to 0.81)	0.8308	-0.32 (-1.20 to 0.56)	0.4770	0.11 (-0.68 to 0.90)	0.7909
	Con-TP	-0.71 (-1.50 to 0.08)	0.0770	0.47 (-0.61 to 1.54)	0.3928	1.94 (0.33 to 3.55)	0.0182	-0.53 (-1.36 to 0.30)	0.2116	-0.90 (-1.96 to 0.15)	0.0938
	Neg-FP	-0.10 (-0.71 to 0.51)	0.7458	0.81 (0.07 to 1.55)	0.0314	0.28 (-0.56 to 1.12)	0.5130	-0.26 (-1.07 to 0.54)	0.5242	0.40 (-0.37 to 1.17)	0.3127
	Neg-TP	-0.55 (-1.32 to 0.21)	0.1572	0.63 (-0.40 to 1.66)	0.2303	2.32 (0.71 to 3.93)	0.0047	-0.47 (-1.24 to 0.31)	0.2356	-0.61 (-1.65 to 0.42)	0.2452
	FP-TP	-0.45 (-1.32 to 0.42)	0.3057	-0.18 (-1.38 to 1.02)	0.7662	2.04 (0.24 to 3.83)	0.0260	-0.21 (-1.25 to 0.84)	0.6968	-1.01 (-2.19 to 0.17)	0.0938
No. Respondents		612		515		444		515		524	

		Follow up time									
		Baseline		1 week		1 Month		6 Month		18 Month	
Scale (Range)	Comparison	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value
5. Selfblame	Con-Neg	-0.14 (-0.61 to 0.32)	0.5511	-0.52 (-1.25 to 0.20)	0.1589	-0.21 (-0.94 to 0.51)	0.5644	-0.13 (-0.90 to 0.64)	0.7424	0.26 (-0.63 to 1.16)	0.5642
(0-15)	Con-FP	0.54 (-0.19 to 1.27)	0.1461	1.58 (0.32 to 2.83)	0.0136	2.16 (0.84 to 3.48)	0.0013	0.23 (-0.98 to 1.43)	0.7132	0.74 (-0.34 to 1.83)	0.1787
	Con-TP	-1.15 (-1.91 to -0.39)	0.0030	1.89 (0.09 to 3.70)	0.0401	1.51 (-0.23 to 3.25)	0.0895	0.31 (-1.56 to 2.18)	0.7476	1.45 (-0.74 to 3.64)	0.1930
	Neg-FP	0.68 (-0.02 to 1.38)	0.0557	2.10 (0.91 to 3.29)	0.0005	2.38 (1.05 to 3.70)	0.0004	0.36 (-0.92 to 1.63)	0.5844	0.48 (-0.67 to 1.64)	0.4145
	Neg-TP	-1.01 (-1.74 to -0.28)	0.0069	2.41 (0.67 to 4.16)	0.0067	1.72 (0.00 to 3.45)	0.0501	0.44 (-1.47 to 2.34)	0.6534	1.19 (-1.04 to 3.42)	0.2957
	FP-TP	-1.69 (-2.59 to -0.80)	0.0002	0.32 (-1.70 to 2.34)	0.7590	-0.65 (-2.66 to 1.36)	0.5249	0.08 (-2.07 to 2.23)	0.9411	0.71 (-1.65 to 3.07)	0.5559
No. Respondents		606		507		445		517		525	
6. Focus on airway symptoms	Con-Neg	-0.07 (-0.19 to 0.05)	0.2702	-0.23 (-0.51 to 0.04)	0.0948	-0.16 (-0.45 to 0.13)	0.2807	0.00 (-0.30 to 0.30)	0.9937	-0.09 (-0.39 to 0.22)	0.5773
(0-6)	Con-FP	0.19 (-0.02 to 0.39)	0.0819	0.57 (0.13 to 1.02)	0.0112	0.68 (0.13 to 1.24)	0.0160	0.23 (-0.16 to 0.63)	0.2443	0.28 (-0.15 to 0.71)	0.1951
	Con-TP	-0.19 (-0.43 to 0.04)	0.1103	0.21 (-0.51 to 0.93)	0.5650	1.60 (0.64 to 2.55)	0.0011	0.90 (0.21 to 1.58)	0.0100	0.54 (-0.45 to 1.53)	0.2861
	Neg-FP	0.25 (0.05 to 0.46)	0.0149	0.81 (0.39 to 1.22)	<.0001	0.84 (0.29 to 1.39)	0.0026	0.23 (-0.18 to 0.65)	0.2666	0.37 (-0.06 to 0.80)	0.0912
	Neg-TP	-0.12 (-0.36 to 0.11)	0.2992	0.44 (-0.26 to 1.15)	0.2139	1.76 (0.81 to 2.71)	0.0003	0.90 (0.22 to 1.58)	0.0098	0.62 (-0.38 to 1.63)	0.2213
	FP-TP	-0.38 (-0.66 to -0.09)	0.0094	-0.36 (-1.14 to 0.42)	0.3639	0.91 (-0.16 to 1.98)	0.0950	0.66 (-0.06 to 1.39)	0.0733	0.25 (-0.79 to 1.30)	0.6340
No. Respondents		613		516		447		517		527	
7. Stigmatization	Con-Neg	-0.25 (-0.58 to 0.07)	0.1281	-0.22 (-0.71 to 0.28)	0.3872	-0.14 (-0.64 to 0.35)	0.5693	-0.30 (-0.71 to 0.10)	0.1395	0.45 (-0.05 to 0.95)	0.0753
(0-12)	Con-FP	0.12 (-0.39 to 0.63)	0.6387	-0.01 (-0.69 to 0.67)	0.9761	0.82 (-0.10 to 1.73)	0.0803	0.46 (-0.49 to 1.41)	0.3393	0.64 (0.00 to 1.28)	0.0492
	Con-TP	-0.40 (-0.98 to 0.18)	0.1715	-0.37 (-1.25 to 0.51)	0.4066	0.01 (-0.83 to 0.85)	0.9841	-0.35 (-1.30 to 0.60)	0.4697	0.63 (-1.06 to 2.31)	0.4664
	Neg-FP	0.38 (-0.13 to 0.88)	0.1444	0.21 (-0.44 to 0.85)	0.5311	0.96 (0.07 to 1.85)	0.0340	0.76 (-0.17 to 1.70)	0.1082	0.19 (-0.52 to 0.90)	0.5981
	Neg-TP	-0.15 (-0.73 to 0.43)	0.6107	-0.15 (-0.95 to 0.64)	0.7021	0.15 (-0.65 to 0.95)	0.7098	-0.05 (-0.97 to 0.88)	0.9216	0.17 (-1.52 to 1.87)	0.8401
	FP-TP	-0.53 (-1.21 to 0.16)	0.1302	-0.36 (-1.32 to 0.60)	0.4614	-0.81 (-1.93 to 0.31)	0.1576	-0.81 (-2.15 to 0.53)	0.2345	-0.02 (-1.79 to 1.76)	0.9857
No. Respondents		609		505		440		511		522	
8. Introvert	Con-Neg	-0.37 (-0.68 to -0.06)	0.0191	-0.50 (-0.89 to -0.11)	0.0117	-0.42 (-0.85 to 0.01)	0.0527	-0.22 (-0.61 to 0.18)	0.2888	-0.38 (-0.84 to 0.09)	0.1130
(0-12)	Con-FP	0.22 (-0.29 to 0.73)	0.3948	0.84 (0.20 to 1.48)	0.0102	0.02 (-0.72 to 0.76)	0.9601	-0.14 (-0.71 to 0.42)	0.6160	-0.10 (-0.69 to 0.49)	0.7378
	Con-TP	-0.78 (-1.39 to -0.17)	0.0120	0.08 (-0.79 to 0.96)	0.8527	0.63 (-0.5 to 1.77)	0.2754	0.11 (-0.81 to 1.02)	0.8172	-0.31 (-1.35 to 0.72)	0.5535
	Neg-FP	0.59 (0.09 to 1.09)	0.0199	1.34 (0.74 to 1.94)	<.0001	0.44 (-0.31 to 1.20)	0.2496	0.07 (-0.49 to 0.63)	0.8031	0.28 (-0.28 to 0.83)	0.3327
	Neg-TP	-0.41 (-1.01 to 0.19)	0.1834	0.59 (-0.28 to 1.45)	0.1834	1.06 (-0.06 to 2.17)	0.0634	0.32 (-0.60 to 1.24)	0.4922	0.06 (-0.97 to 1.10)	0.9059
	FP-TP	-1.00 (-1.71 to -0.29)	0.0058	-0.76 (-1.75 to 0.23)	0.1335	0.61 (-0.74 to 1.96)	0.3741	0.25 (-0.74 to 1.25)	0.6192	-0.21 (-1.32 to 0.89)	0.7052
No. Respondents		609		508		444		513		524	

		Follow up time									
		Baseline		1 week		1 Month		6 Month		18 Month	
Scale (Range)	Comparison	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value
9. Harm of smoking	Con-Neg	-0.11 (-0.35 to 0.12)	0.3319	-0.07 (-0.39 to 0.26)	0.6823	-0.10 (-0.41 to 0.22)	0.5513	0.03 (-0.29 to 0.35)	0.8669	0.00 (-0.35 to 0.36)	0.9888
(0-6)	Con-FP	-0.25 (-0.55 to 0.05)	0.1057	1.08 (0.61 to 1.56)	<.0001	1.12 (0.56 to 1.67)	<.0001	0.22 (-0.25 to 0.68)	0.3560	0.32 (-0.15 to 0.79)	0.1796
	Con-TP	-0.50 (-0.92 to -0.09)	0.0179	0.75 (-0.05 to 1.55)	0.0651	0.99 (0.14 to 1.84)	0.0225	0.32 (-0.51 to 1.14)	0.4546	0.80 (-0.26 to 1.85)	0.1376
	Neg-FP	-0.13 (-0.43 to 0.16)	0.3730	1.15 (0.70 to 1.60)	<.0001	1.21 (0.66 to 1.76)	<.0001	0.19 (-0.27 to 0.65)	0.4209	0.32 (-0.18 to 0.82)	0.2096
	Neg-TP	-0.39 (-0.81 to 0.03)	0.0665	0.82 (0.04 to 1.59)	0.0382	1.08 (0.25 to 1.92)	0.0106	0.29 (-0.53 to 1.10)	0.4892	0.79 (-0.27 to 1.86)	0.1445
	FP-TP	-0.26 (-0.70 to 0.19)	0.2612	-0.33 (-1.18 to 0.52)	0.4424	-0.13 (-1.07 to 0.82)	0.7922	0.10 (-0.80 to 0.99)	0.8317	0.47 (-0.65 to 1.60)	0.4071
No. Respondents		615		517		450		519		529	
10. Existential values	Neg-FP	NA		NA		0.92 (0.23 to 1.61)	0.0090	0.40 (-0.54 to 1.35)	0.4043	0.11 (-0.48 to 0.70)	0.7075
(0-12)	Neg-TP	NA		NA		2.10 (0.45 to 3.75)	0.0125	1.57 (0.31 to 2.83)	0.0149	0.24 (-1.01 to 1.50)	0.7031
	FP-TP	NA		NA		1.18 (-0.55 to 2.92)	0.1805	1.16 (-0.30 to 2.63)	0.1193	0.13 (-1.14 to 1.40)	0.8385
No. Respondents						262		306		307	
11. Calm/relax	Neg-FP	NA		NA		0.46 (0.13 to 0.78)	0.0054	0.05 (-0.33 to 0.44)	0.7852	-0.03 (-0.26 to 0.21)	0.8222
(0-4)	Neg-TP	NA		NA		0.82 (0.19 to 1.44)	0.0101	0.17 (-0.29 to 0.64)	0.4722	-0.01 (-0.42 to 0.40)	0.9611
	FP-TP	NA		NA		0.36 (-0.30 to 1.03)	0.2882	0.12 (-0.45 to 0.68)	0.6866	0.02 (-0.44 to 0.47)	0.9427
No. Respondents						265		310		308	
12. Social network	Neg-FP	NA		NA		0.05 (-0.09 to 0.19)	0.4732	-0.21 (-0.36 to -0.06)	0.0075	-0.11 (-0.26 to 0.03)	0.1248
(0-6)	Neg-TP	NA		NA		0.92 (0.31 to 1.54)	0.0032	0.45 (0.03 to 0.86)	0.0360	0.08 (-0.23 to 0.39)	0.6139
	FP-TP	NA		NA		0.87 (0.25 to 1.50)	0.0061	0.66 (0.24 to 1.07)	0.0022	0.19 (-0.12 to 0.51)	0.2230
No. Respondents						269		312		309	
13. Impulsivity	Neg-FP	NA		NA		0.15 (-0.20 to 0.51)	0.3963	0.19 (-0.24 to 0.62)	0.3857	-0.06 (-0.54 to 0.41)	0.7908
(0-12)	Neg-TP	NA		NA		1.76 (0.35 to 3.17)	0.0146	1.27 (-0.04 to 2.58)	0.0572	0.10 (-0.71 to 0.90)	0.8172
	FP-TP	NA		NA		1.61 (0.20 to 3.02)	0.0257	1.08 (-0.23 to 2.39)	0.1072	0.16 (-0.75 to 1.07)	0.7311
No. Respondents						265		304		307	
14. Empathy	Neg-FP	NA		NA		0.12 (-0.19 to 0.43)	0.4394	0.02 (-0.32 to 0.35)	0.9219	0.21 (-0.17 to 0.59)	0.2719
(0-6)	Neg-TP	NA		NA		0.79 (0.27 to 1.30)	0.0027	0.71 (0.17 to 1.25)	0.0094	0.29 (-0.36 to 0.94)	0.3819
	FP-TP	NA		NA		0.66 (0.11 to 1.22)	0.0191	0.69 (0.12 to 1.27)	0.0182	0.08 (-0.63 to 0.78)	0.8313
No. Respondents						266		306		308	

15. Regretful of still smoking	Neg-FP	NA	NA	0.28 (-0.48 to 1.04)	0.4676	0.59 (0.00 to 1.18)	0.0500	0.06 (-0.54 to 0.65)	0.8475
(0-8)	Neg-TP	NA	NA	0.12 (-1.17 to 1.40)	0.8575	0.74 (-0.12 to 1.59)	0.0903	-0.83 (-1.75 to 0.08)	0.0742
	FP-TP	NA	NA	-0.16 (-1.66 to 1.33)	0.8301	0.15 (-0.82 to 1.12)	0.7673	-0.89 (-1.85 to 0.07)	0.0681
No. Respondents				137		148		150	

Mean Δ = The mean difference of the outcome between the compared groups adjusted for possible confounders; The mean differences of the scales listed in the table are the differences beyond the differences that may be present at baseline (scale 1-9) or at 1 Month (scale 10-15); CI = confidence interval; p value = the statistical significant level was assessed to 0.0043 after adjusting for multiple testing with the method of Benjamini-Hochberg and significant differences between the groups are marked with yellow(1); Con = Control group; Neg = True-negative group; FP = false-positive group; TP = true-positive group; NA = Not applicable.

Protocol

Screening for lung cancer

A randomised controlled screening trial of low-dose CT-scanning

The Danish Lung Cancer Group

September 1, 2004

Contents

1. Introduction

1.1 Background and rationale of the study

Lung cancer is the most common malignant disease among men in the Western hemisphere, and is becoming the most common malignant disease among women as well because of increasing tobacco consumption. In Denmark 3.500 new cases are reported yearly. The majority of these patients succumb to lung cancer, because only few are cured, and the 5 year survival rate is only 5% (1). The prognosis for lung cancer is considerably better, if the disease is diagnosed at an early stage the survival rate is above 50% (2). Thus, much may be gained by screening for lung cancer (3-5).

It has been reported that the common chest X-ray is not sufficiently sensitive, because the tumor cannot be seen before it measures at least around 2 cm. (6, 7). However recent technological advances in CT-scanning has made it possible to diagnose tumors as small as 3-5 mm. Thus, tumors may be detected around 1 year earlier than when employing common chest X-ray (8). The technological advances have also substantially reduced the costs and the radiation dose previously associated with CT-scans. Radiation dose has been reduced to less than 1 mSv, which is comparable to mammography, and the duration of the CT-scan has been reduced from minutes to seconds. Hence, it is feasible to repeat scans and thus determine with great accuracy whether a tumour is malignant or benign before scheduling biopsy or surgery (9-11).

On account of these promising results (12-15) low-dose CT scanning is already being offered by private clinics in several countries, even though a proper randomized trial has yet to determine whether low – dose CT scans truly are beneficiary (17). Thus, the National Cancer Institute (NCI) in the USA has decided to initiate a large randomized trial to assess low-dose CT screening for lung cancer. The trial is scheduled to enroll 50,000 participants and has a budget of over 200 million US $. The most important aspect of the study will be to determine whether low-dose CT screening can save lives. Furthermore, a number of European countries within the EU have established collaboration to assess CT screening for lung cancer (16). In the European collaboration a common protocol has been agreed upon to assess low dose CT as a mode of screening for lung cancer in a randomized fashion. Results will be collected in a common database in London. The Danish Lung Cancer Group has from an early stage been very active in this collaboration. The European protocol has to a large extent been based upon a Danish draft from as early as May 2000 (16).

Since then the Danish protocol has been adjusted to focus on prerequisites that could lead to a decision on whether to offer screening for lung cancer in Denmark, as well as on other conditions which we feel we have an optimum possibility to address in a Danish study. Such as psychosocial consequences of undergoing screening for lung cancer, consequences of receiving a false positive diagnosis of lung cancer, and whether participation in a screening protocol for lung cancer has any effect on smoking habits. Cessation of smoking is still the only documented preventive measure to avoid lung cancer. Thus, enrolled participants in a screening investigation for lung cancer will be questioned about smoking habits and recommended to quit smoking.

2. Aims of the study

A. In a European collaboration to contribute to the clarification of whether screening with low-dose CT can reduce mortality of lung cancer.
B. To assess psychosocial consequences of undergoing screening for lung cancer, and in particular the consequences of receiving a false positive diagnosis of lung cancer.
C. To establish whether smoking habits and cessation of smoking are influenced by participation in a protocol concerning CT screening for lung cancer.

D. To gain practical experiences with the new method and to assess socioeconomic consequences of screening for lung cancer with low-dose CT.

3. Overall protocol

- **Aim A:** Parallel randomized controlled trial comparing *either* a yearly low dose CT scan *or* no screening. It is scheduled to enroll 4000 smokers and former smokers, and the study is scheduled to last 5 years, i.e. an initial (prevalence) screening is followed by 4 annual (incidence) screenings (for further details, see Appendix A).
- **Aim B:** A prospective, longitudinal questionnaire assessment of enrolled participants who have received a false positive diagnosis. The questionnaire will focus on the consequences of receiving a false positive diagnosis. Answers from enrolled subjects who have received a false positive diagnosis will be compared to their own "baseline" responses, and responses from subjects who have received a negative result of their own low-dose CT scans (for further details, see Appendix B)
- **Aim C:** All participants will annually be questioned regarding smoking habits, their motivation for cessation of smoking and will be advised to refrain from smoking to assess the effect of participation in a screening protocol for lung cancer on cessation of smoking (for further details, see Appendix C).
- **Aim D:** Socioeconomic consequences of screening for lung cancer will be assessed by longitudinal registration of costs and benefits (e.g. morbidity, hospitalization, GP consultations etc. (A detailed plan is pending)
- **Aim E:** Assess the value of PET scanning when screening for lung cancer (See Appendix D).
- **Organization:** The practical part of the study will take place in 2 units at Gentofte University Hospital: A *screening unit* and a *scanning unit*. Formally the screening unit will be a section under the Department of Respiratory Disease Y and the scanning unit will be part of the Department of Radiology. An appropriate multi-slice spiral CT-scanner has been installed at the Department of Radiology. The database will be placed in care of the screening unit, and skilled personnel from this unit will undertake recruitment, inclusion procedures, information about cessation of smoking and the follow up on abnormal scans. Formal collaboration has been established with the Institute of General Medicine, the Danish Cancer Society, the University of Copenhagen, the EU Early Lung Cancer Detection Group (EU ELCDG) and the NELSON group in the Netherlands.
- **Ethics:** All participants will be informed both orally and in writing (Appendix G) and informed consent will be signed before entry into the trial (Appendix G). Further ethical considerations regarding screening for lung cancer has been described in Appendix F.
- **Approvements:** The trial is approved by the local Ethical Committee in Copenhagen (Københavns Amt) (reg.Nr. KA 02045) and will submitted to the Danish Data Protection Agency .
- **Registration of data:** The study will be conducted in accordance with the Danish Data Protection Agency. Raw data (i.e. scanning profiles) and picture data from the CT scans will be stored electronically (MOD) at Gentofte University Hospital. Data transfer to a common database in Rotterdam will be without information on the identity of the partcipants. Data will conform to the agreement concerning the European collaboration (EU ELCDG), i.e. "minimal data set".
- **Budget / costs:** Acquisition of a new multi-slice spiral CT-scanner (including a diagnostic work station and a service contract for maintenance) costs DKK 8 million. To reduce costs the CT scans will be performed on overtime using an already installed CT scanner. Running the CT scanner including personnel for 5 years amounts to DKK 11.698.000 (1.56 mio Euro). Running the screening unit including the cessation of smoking study amounts to DKK 4.750.000 (0,63 mio Euro), and PET scanning costs amount to DKK 565.000 (75.000 Euro). The total cost of the study amounts to DKK 17.363.000 (2,3 mio Euro) in the period from 2004-2009, and has been granted by the Ministry of Health on June 28, 2004. PhD.-studies will be financed separately by applications to foundations and the Danish Cancer Society.
- **Advisory Board:** An advisory board consisting of experts in screening, lung cancer and thoracic radiology will be founded in order to ensure state of the art expertise.

- **Publications:** Results will be published in Danish and international scientific journals. Drafts must be approved by the Steering Committee prior to submission.

4. Steering committee

Jesper Holst Pedersen, Chairman, Department of Cardiothoracic Surgery, Gentofte University Hospital
John Brodersen, Dep of General Medicine, The Panum Instituttet
Hanne Thorsen, Institut for Population health Science, The Panum Institute
Mark Krasnik, Department of Cardiothoracic Surgery, Gentofte University Hospital
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Jann Mortensen, Dep of Nuclear Medicine , Rigshospitalet, University of Copenhagen
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Niels Seersholm, Dep of Respiratory Disease Y, Gentofte University Hospital
Martin Døssing, Dep. of Medicine, Frederikssund Hospital

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APPENDIX A

This part of the study is a part of a common European project, which is described in detail in Appendix I. Furthermore this part of the study includes an evaluation of PET as described in Appendix D.

The effect of screening using low-dose CT on survival of lung cancer

1. Study population

1.1 Participants

Smokers and former smokers from 50 – 65 years of age, who are deemed to be able to tolerate lung resection, will be included. Participants must have smoked at least 20 cigarettes per day for 20 years (20 packs/years), and former smokers must have stopped smoking within the last ten years. The lung function (FEV1) must be better than 30% of an expected value. A participant must be able to climb 2 flights of stairs (around 36 steps) without pausing, and must be able to understand and sign a written consent. Furthermore he or she must be able to lie still and to hold his or her breath for more than 20 seconds.

Exclusion criteria:

Body weight above 130 kg.
Previous treatment for lung cancer, breast cancer, malignant melanoma or hypernephroma
Serious concomitant diseases with a life expectancy of less than 10 years
Treatment for other malignant disease within the last 5 years
Treatment for pulmonary tuberculosis within the last 2 years
Is being controlled radio graphically because of pulmonary opacity.
Under current investigation for disease
Cannot participate in a yearly check up scheduled for a total of 5 years.

1.2 Recruitment and scheduled examinations

Participants will be recruited by means of ads in newspapers and weeklies, and also by contact to larger work sites. The aim is to enroll 4.000 subjects in 1 year. People who appear to be interested in enrollment will receive additional information and be asked to answer a questionnaire regarding motivation for cessation of smoking and quality of life. FEV1 will be measured, and if the person currently smokes, he or she will receive written information regarding cessation of smoking. Individuals who still wish to participate in the trial will be randomized to either annual screening by low-dose CT scanning (the screening group) or the control group, which will not be offered CT scans. Like the screening group they will, however have yearly FEV1 measurements performed as well as continued monitoring of their motivation for cessation of smoking and quality of life.

The study is scheduled to last 5 years, i.e. an initial (prevalence) screening followed by 4 annual (incidence) screenings. The first screening may be expected to be associated with several false positive results. Thus, follow up procedures are expected to be numerous in the initial stage of the study, i.e. it is expected to include around 1000 subjects.

2. Screening modalities and diagnostic strategy

2.1 Multi-slice low-dose spiral CT scanning.

The scans will be performed using a multi-slice spiral CT equipment of the following parameters: 16×1.25 mm collimation, 140 kV, 40 mA, 3 cm "table feed per rotation" (pitch = 1.5*M). The scanning direction will be caudal cranial to minimize the number of breathing related artifacts. The field of vision

will be the smallest possible that includes the entire ribcage. The scan will be performed in the supine position with the subject holding his or her breath following 3 hyper ventilations. The picture will be reconstructed in 2 fashions: Using a soft algorithm and a section width of 5 mm and 50% overlapping (increment 2,5 mm), and using a soft algorithm with a section width of 1,25 mm (HRCT) without overlapping in order to achieve superior spatial dissolution. Raw data and reconstructed pictures will be stored on electronic media (e.g. MOD) in a standard format (DICOM), and data will be preserved for at least 10 years.

Evaluation of the CT scans will be performed independently by 2 radiologists using digital working stations that allow "cine mode viewing". Lung tissue will be evaluated using standard "window/center" settings of: W= 1500 HU, C = -600 HU. However, settings may be changed during radiological evaluation to ensure a more certain diagnosis. Evaluations will primarily be performed using section widths of 5 mm. Hence, they may be supplemented by additional evaluations of the 1 mm sections if needed. The radiologists will focus on opacities in the lung tissue, the mediastinum and the bronchiae. Other abnormalities than lung tissue disease, e.g. aneurysms, kidney tumors etc will if found be disclosed to the patient and his/her general practitioner.

2.2 Diagnostic strategy

The further diagnostic evaluation of an opacity shown by a CT scan will depend upon the morphology and size of the opacity as described in the European joint protocol (Appendix I). Opacities are classified as benign in case they are less than 20 mm with “smooth borders” and calcifications in a benign pattern. Evaluation of other opacities depend upon their size (mean value of their length and width), the character of the opacity (solid, partly solid, not solid) and whether the opacity was found during the first (prevalence) screening procedure or following one of the following (incidence) screening procedures.

Opacities found during the prevalence screening are followed up as follows.

< 5 mm: The localization and size of the opacity is recorded. No further evaluation is done. The subject follows the remaining screening protocol, i.e. a yearly low-dose CT scan.

5-15 mm: Individual assessment. Usually an additional CT scan is performed 3 months later. In case the opacity has expanded, a biopsy is performed (surgically or CT guided). If the opacity has remained stationary in size the next CT scan is scheduled 9 months later. If a biopsy or a resection is deemed necessary, the subject is remitted to a pulmonary clinic, either at Gentofte University Hospital or at Bispebjerg Hospital. In this group FDG-PET scanning will be employed to determine whether the opacity is metabolically active (see Appendix D).

> 15 mm: Will be scheduled for biopsy, perhaps a clinical PET scan or bronchoscopy, a CT scan with an additional use of contrast or possibly resection. Other diagnostic procedures are pending on the morphology of the opacity. Opacities with speculae will be biopsied, while benign looking opacities will be followed as described under opacities of between 5 – 15 mm.

Opacities found during subsequent incidence screenings will be followed up using HRCT 1 month later, following two weeks of antibiotic treatment. In case the opacity:

- Is disappeared: low-dose CT scan a year later according to schedule
- Unchanged, and < 5 mm: a low dose CT scan is performed after 3 and 6 months.
- Unchanged and > 5 mm: a low-dose CT scan is performed after 3 months, and a PET scan. If the PET scan is positive, it will be followed by a biopsy. A negative PET scan will be followed by an additional low dose CT scan 3 months later.
- Has shown growth: a biopsy is performed

2.3 Staff requirements

The screening unit will employ:

- 1 research nurse, who in general will be in charge of the screening unit
- 1 secretary

It is planned to employ physicians to conduct PhD studies in accordance with the proposed studies on psychological effects of screening and effects on smoking behaviour.

The scanning unit will employ

- 2 radiologists, each on half time, amounting to the cost of 1 full time radiologist
- 2 technicians (overtime)
- 1 secretary (full time)

3. Follow up.

The study will be registered with the Danish Institute of Data Security and annual follow of participants will be made in danish national central registries. It will be possible to monitor address, vital status , admittance to hospital, lung cancer cases and other malignant diagnoses based on the enrolled participants unique national identification number (Central Personal Registration number).

APPENDIX B

Psychosocial consequences of a false positive CT scan when screening for lung cancer

A questionnaire assessment of enrolled subjects who have received a false positive diagnosis. Editing of a questionnaire

Introduction

It seems appropriate to introduce screening for lung cancer, because this malignancy causes as many deaths as the combined death toll of breast cancer, prostate cancer and colonic cancer[1]. The value of screening for lung cancer has been assessed in a number of randomized studies using common chest X-rays and cytological evaluations. Such screening protocols have not been associated with reduced mortality[2]. More novel techniques, i.e. low-dose CT scans appear to be more promising as a modality for screening, because it is feasible to diagnose small lung tumours[3].

However, a drawback by using this technique is that 25-60% of the enrolled subjects may be given a false positive diagnosis[4]. This will lead to the endurance of invasive procedures, such as a percutaneous biopsy, or repeated CT scans and long term uncertainty about having lung cancer or not[4-5].

I Holland and the United States randomized trials of screening for lung cancer with low-dose CT scans are currently being carried out[4;6.] Similarly a trial under the auspices of the Danish Lung Caner group is going to be initiated October 1, 2004 at the University Hospital of Gentofte. The project has been financed by the Danish Ministry of the Interior.

Before another screening protocol is initiated in Denmark, this renders a unique opportunity to more closely determine advantages and drawbacks of screening, such as e.g. psychosocial consequences of a false positive diagnosis. Thus, unanimous recommendations as rendered by the WHO and the Ethical Committee in Denmark have been met [7-8].

International evaluations of the psychosocial consequences of a false positive diagnosis of cancer in relation to screening have previously been carried out. The focus of these studies has been the assessment of general health, fear, depression and psychiatric morbidity[9]. In some cases, such as the assessment of mammography screening, questionnaires have been employed that were specifically drawn up for the purpose in question[10-20].

Thus, the use of questionnaires that were drawn up to assess general well being as well as other non related or specific questions have proven to be insufficient to monitor the psychosocial consequences of screening for breast cancer[21].

It is generally regarded as a prerequisite to use questionnaires that were specifically drawn up to monitor the response in question [22.] Hence, the international group EORTC that specializes in development of questionnaires to assess the quality of life in cancer patients does not use the same questionnaire to monitor patients with breast cancer as the one they use to monitor patients of both genders with colonic cancer [23].

A questionnaire in Danish entitled KAS-BK[a] has been developed to assess psychosocial consequences of a false positive mammography. It is currently being employed by H:S Fyen´s County and monitors both short (KAS-BK/1) and long term (KAS-BK/2) psychosocial consequences.

Many questions asked in the KAS-BK are probably of relevance for participants in a screening protocol for lung cancer. However, it is equally probable that KAS-BK cannot sufficiently cover all psychosocial consequences of a false positive CT scan for lung cancer. Thus, a qualitative study of patients with lung cancer has reported that such patients feel stigmatized, not least because smokers felt that they themselves were to blame for their condition[24]. Items covering e.g. remorse are not included in KAS-BK.

The aim of the study is to asses the psychosocial consequences of a false positive CT scan when screening for lung cancer. The questionnaire KAS-BL will be employed after editing to ensure that the questions asked monitor conditions of great importance for patients with lung cancer.

Editing of the questionnaire

Methods and materials

Some questions in the KAS-BK/1 are so specific for participants in mammography screening that they do not belong in a questionnaire for monitoring subjects who have been enrolled in a screening study of lung cancer. Such questions are left out.

It is not likely that remaining items in the KAS-BK/1 cover all psychosocial consequences of a false positive CT scan for lung cancer (see above). When the KAS-BK was drawn up only women were interviewed. In assessing patients with lung cancer it is necessary to include both men and women. Thus, new items will be included in the KAS-BK/1, and some of the existing questions will need editing.

Assessment of relevance and understandability of such new items included in the KAS-BK/1will take place during focused group interviews[25] and individual interviews of enrolled subjects immediately following an abnormal CT scan. Over a period of 2 years some of the same subjects will be interviewed again, so long as lung cancer is suspected. This is to ensure that the new questionnaire is of relevance for the entire screening

period. Interviews are first repeated 3 months following the primary interviews, and depending on the results of the subsequent following interviews, one or more interviews will take place later on.
The KAS-BK/2 covers general existential aspects. Thus, it may be deemed that KAS-BK/2 also is of relevance for individuals who get a false positive diagnosis of lung cancer. Nevertheless in headings and in question 3, breast cancer needs to be changed to lung cancer.
Also the KAS-BK/2 will be tested for relevance and coverage of during the prevalence period of the screening project. Participants who later on learn that their diagnosis of lung cancer was false positive will be interviewed. In case none of the enrolled subjects during the prevalence period of the screening project can be informed that the diagnosis of lung cancer was false positive, the KAS-BK/2 will be employed edited with only the modifications already described above.

As a result of screening for lung cancer with low-dose CT scans other pathological conditions than lung cancer will be diagnosed such as extra pulmonary tumors, aortic aneurysms etc [26]. If this occurs in the prevalence period of the screening project, the edited KAS-BK/2 will be assessed as for relevance to these observed abnormalities as well.

[a] **KAS-BK**: A Danish acronym for consequences of screening mammography. The questionnaire has been developed by PhD-student John Brodersen with Hanne Thorsen as supervisor
The aim of the PhD project is to measures false screening mammography. This project is financially supported by PSU. The measure is developed and validated following the international gold standard. It has been found highly reliable and valid. Publications are in progress.

Validation of the edited questionnaire:

The non breast related topics in the KAS-BK will be preserved, and putative new topics can be expected to cover new subjects that are not currently included in the KAS-BK. A validation of the questionnaire prior to commencement of the screening protocol will therefore not take place. This short cut may be deemed acceptable, because the KAS-BK has been found to be of high accuracy and precision (see foot note page 2) Accuracy and precision of the questionnaire KAS-LK[1] will in stead be analyzed at a later stage of the screening study based on incoming data[c].

[1] **KAS-LK**: Danish acronym for consequences of screening for lung cancer
[c] Reliability will be assessed by *test/retest*[27], *internal consistency*[28] and *item response theory*[28-30]. *Construct validity*[28-30] will be assessed by *floor and ceiling effect*[28-29], *content validity* covering *content relevance* and *content coverage*[28], *convergent validity*[29] by comparison with the Nottingham Health Profile[31-32] and *know group validity*[28].

Enrollment of subjects for questionnaire editing purposes

Recruitment will take place among individuals who in the prevalence phase of the randomized screening study were diagnosed with an opacity that however, was not clearly malignant.

The questionnaire assessment

Methods and materials

When the subjects were enrolled in the screening study, they also accepted to answer questionnaires. Socio demographic data are collected from basic information in the edited questionnaire (KAS-LK) and will therefore only be supplemented with questions regarding self assessment of health.

Purpose

To assess psychosocial consequences of a false positive CT scan in a randomized screening study of lung cancer, and to determine whether such psychosocial consequences are linked to

- Age and gender
- Subsequent follow up
- Time passed before a definite diagnosis can be rendered.

Hypotheses:

- False positive CT scans are associated with negative consequences as compared to normal scans
- A false positive CT scan is worse for women than for men
- A false positive CT scan is worse for younger than for older individuals
- Follow up intensity of a false positive CT scan is linked to negative consequences
- Time passed from a CT scan to the rendering of a false positive diagnosis is linked to negative consequences
- Self assessment of health will be lower among subjects who are suspected of having lung cancer for 2 years than among subjects who have been rendered normal CT scans, or among subjects from the control group.

The design is prospective and longitudinal. The same questionnaire must and will be answered several times.

Inclusion criteria

Subjects with an abnormal CT scan in the incidence phase of the study (i.e. the 2nd year of the screening study) are enrolled consecutively, and are followed for a maximum of 2.5 years.

Subjects with a normal CT scan, and subjects from the control group will be chosen so that they match the subjects who have been rendered an abnormal CT scan with regard to time of CT scan (former group only),

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Analyses by *Traditional Test Theory* and *Latent Test Theory*[28-30] will be used and it will be possible to assess

- how single items function together with the rest of the items,
- if the questionnaire measures one or more dimensions;
- if it is necessary to exclude or reformulate certain items.

age and gender. Subjects with a normal CT scan will additionally be chosen to this procedure will be test trialed during the prevalence phase of the study in close collaboration with the screening unit.

Exclusion criteria
Subjects randomized to undergo CT scans who are rendered a false negative diagnosis are excluded, as well as individuals from the control group who are diagnosed with lung cancer.

Answering the questionnaire
A subject who is rendered an abnormal CT scan from the screening unit will also be advised to answer the KAS-LK/1 within 1 week. If the subject in question needs a follow up, the questionnaire must be answered before additional testes are run.
Subjects, who only need a control CT scan 3 months later, will be asked to answer the KAS-BK/1 again immediately prior to the control CT scan. The same goes for subjects who need a control scan after 6, 12 or 24 months.
On corresponding dates matched subjects as described above will be asked to answer the KAS-LK/1.

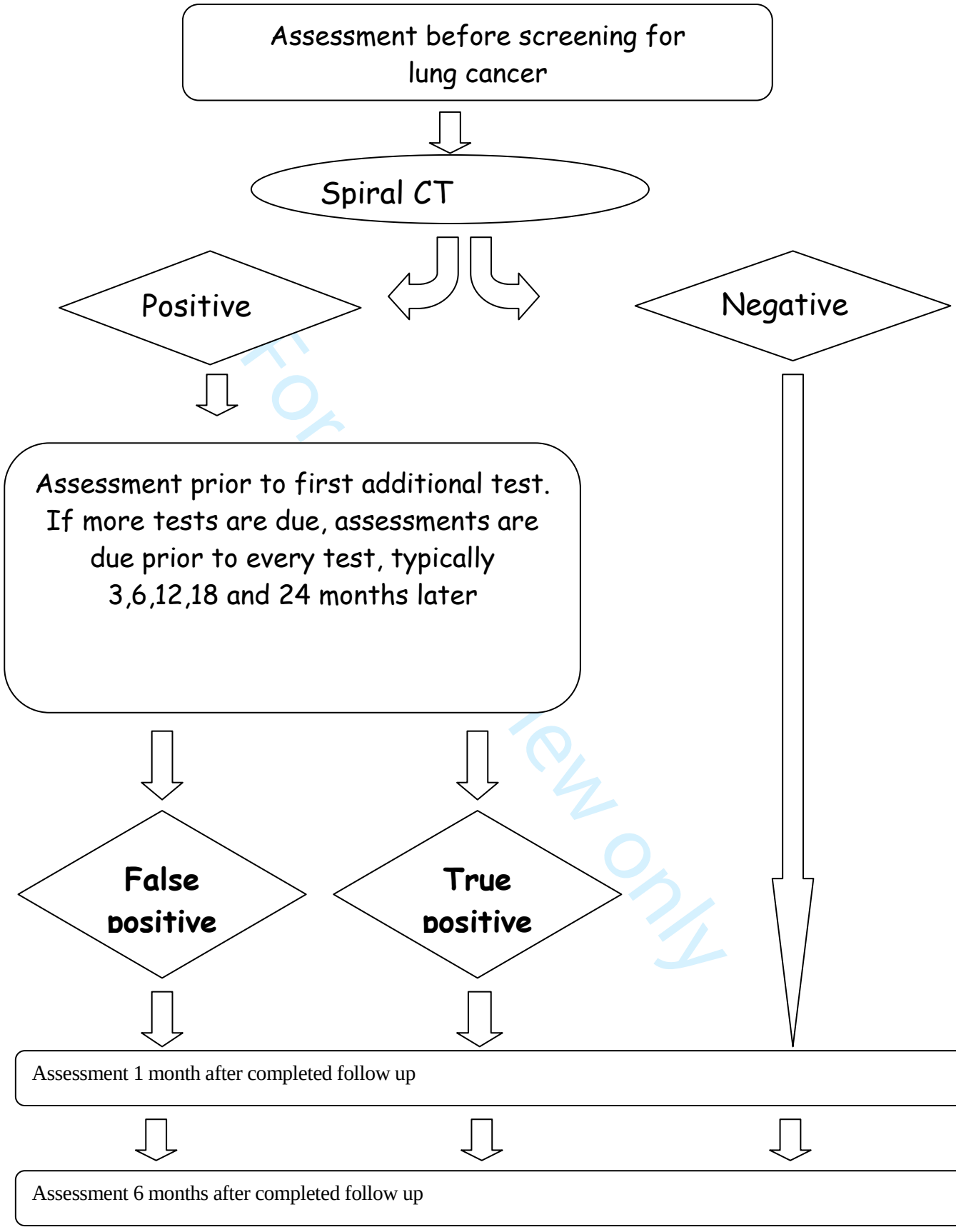
Subjects with a false positive diagnosis of lung cancer will be required to answer the KAS-LK/1+2 one and 6 months after it was determined that the diagnosis rendered was false positive. On corresponding dates subjects with a normal CT scan, and subjects from the control group as described above will also be asked to answer the KAS-LK/1+2.

Number of subjects and statistical power
Depending on the number of abnormal CT scans observed in the prevalence phase is expected that around 150 – 300 individuals (15%) will be rendered an abnormal CT scan in the first incidence phase. This may be deemed a sufficient amount of observations to ensure proper statistical power.

Statistics
Data obtained from assessing questionnaires are not expected to show a Gaussian distribution. Thus non parametric statistics will be employed to locate possible differences over time (Wilcoxon matched-pair signed test) and between groups (Mann-Whitney U test).

Ethical considerations
The study has been approved by the local Ethical Committee. (Reg.nr KA 02045) and approvement from the Data Inspection Counsel is pending.

Time schedule
2005 - 2006 Editing and test trial of the questionnaire
Ultimo 2005 - 2009: Questionnaire assessment and evaluation of data



APPENDIX C

Effect of cessation of smoking and questionnaire concerning smoking habits

Introduction:

As for smokers not much is known about the effect of participating in a screening trial for lung cancer on the enrolled subjects´smoking habits - in spite of a number of large trials of screening for lung cancer with ordinary chest X-rays, sputum analysis and CT scans. Out of 1520 enrolled subjects in a US screening trial at the Mayo Clinic, 901 of them were smokers. Out of these 14% had stopped smoking at the 1 year follow up, while 10% of the 574 former smokers again had started smoking. The only predictors for cessation of smoking were advanced age and poor lung function (1). It would appear to be important to gain more knowledge about a possible effect of screening with CT scans on the enrolled subjects´smoking habits. First, cessation of smoking is still the only documented way of preventing lung cancer, because the risk of lung cancer is halved after 5 – 10 years of not smoking (2). Second, it could be important for the evaluation of survival data from screening trials to determine whether or not participation in screening trials per se has an effect on smoking habits. In theory there are 3 possibilities – screening could give a false sense of security – ”now I am going to be screened, so I might as well continue smoking” – and thus, secure a continuation of the habit. Screening could have no impact on smoking habits, and finally it is feasible that participation in a screening trial for lung cancer would actualize the risk of lung cancer and thus promote enrolled subjects to think twice about smoking. This then might increase the subjects' motivation to stop smoking, and hence lead to cessation of smoking. We feel that the latter possibility is most probable, and have thus chosen it to be the hypothesis of our study. Every year the Department of Prevention at the Danish National Board of Health runs a questionnaire based spot test that includes questions regarding motivation for cessation of smoking and plans to stop smoking. Such questions are based on two US psychologists Prochaska and DiClementes mode of enquiring about changes in habits (3, 4). We have chosen to combine the results of these validated questions with a simple VAS (visual analogue scale) method. This method has been used in a number of studies ranging from assessment of quality of life to severity of pain. It is our intention to evaluate whether this simple method may be used to assess the motivation to stop smoking. Additionally we plan to combine data regarding smoking habits with biochemical parameters of smoking, such as determining cotinine concentrations in blood, sputum and exhaled air. From the Lung Health Study we know that such a link is unchanged over a 5 year period in US subjects, meaning that bias with regard to smoking information is constant throughout a trial and more or less associated to the same individuals (5).

Aims:

To test the hypothesis that participation in a screening protocol for lung cancer increases the enrolled subjects´ motivation to stop smoking and results in more cessation of smoking than will be observed in a control group.

To evaluate whether there are differences between the group being screened and the control group with regard to cessation of smoking / taking up smoking again related to demographic smoking and social related variables such as age, level of nicotine addiction , motivation to stop smoking, education, etc.

To evaluate whether the VAS method may be used to assess the level of motivation to stop smoking.

Methods:

The subjects in the screening study fill out a modified edition of the Danish National Board of Health´s "Questionnaire for monitoring the populations smoking habbits". The modified edition of the questionnaire contains a number of demographi questions and questions regarding current and previous smoking habbits (at which age smoking was started, previous attempts to stop smoking and nicotine addiction as evaluated by the scale of Fagerströms), use of nicotine substitution and motivation to stop smoking. We have included a question regarding the motivation to stop smoking base on the VAS method as described above. A drawback of this method is that some individuals tend to seek out a mid value, while others tend to seek out more peripheral values Thus, their marks do not necessarily correlate with a more objective use of a VAS scale.

Additionally a sputum test is sampled to measure cotinine and CO is measured in exhaled air. Filling out of questionnaires, collection of sputum samples and exhaled air are carried out during the yearly controls that are scheduled for a total of 5 years.

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QUESTIONNAIRE:

1. How old are you? _____

2. Gender

(1) ❒ Male
(2) ❒ Female

3. Do you smoke?

(1) ❒ Yes, daily ➔ Proceed to question no 4
(2) ❒ Yes, at least once a week ➔ proceed to question no 8
(3) ❒ Yes, but less than weekly ➔ Proceed to question no 8
(4) ❒ No, I do not smoke ➔ Proceed to question no 8

4. Mark appropriately

	Mark
4.1. After waking up when so you smoke your first cigarette?	No more than 5 min later. ❒ 6 to 30 min later ❒
4.2. Do you have a hard time abiding by a prohibition of smoking	Yes ❒ No ❒
4.3. Which cigarette could you most likely be without	The first cigarette of the day ❒ All the other cigarettes ❒
4.4. How many cigarettes do you smoke a day?	< 10 ❒ 11-20 ❒ 21-30 ❒ > 31 ❒
4.5. Do you smoke more during day time than in the evening?	Yes ❒ No ❒
4.6. Do you smoke even when you are in bed feeling bad (e.g. with a cold)?	Yes ❒ No ❒

5. Do you smoke anything else than cigarettes?

(1) ❒ Yes Specify_____

(2) ❒ No

6. Have you stated smoking regularly *within the last year* – or have you *within the last year* begun to smoke again?

(1) ❒ Yes, I have started smoking within the last year

(2) ❒ Yes, I have begun smoking again within the last year

(3) ❒ No

7. Do you use nicotine products – e.g. chewing gum

(1) ❒ Yes, daily

(2) ❒ Yes, but not daily

(3) ❒ No

Note Question no 8 should only be answered by non smokers (you have marked 4 i question no 3)

8. Have you ever smoked? (If yes, mark when you stopped smoking)

(1) ❒ No, I have never smoked

(2) ❒ Yes, less than 3 months ago

(3) ❒ Yes, less than 6 months ago

(4) ❒ Yes, 6-12 months ago

(5) ❒ Yes, 1-5 years ago

(6) ❒ Yes, more than 5 years ago

(7) ❒ Do not know

9. How old were you when you started smoking regularly?

(1) ❒ Under 10 years of age

(2) ❒ 10 years old

(3) ❒ 11 years old

(4) ❒ 12 years old

(5) ❒ 13 years old

(6) ❒ 14 years old

(7) ❒ 15 years old

(8) ❒ 16 years old

(9) ❒ 17 years old

(10) ❒ 18 years old

(11) ❒ Over 18 years old

Note! Question no. 10 must be answered by all smokers – having marked 1,2 or 3 i question no 3.

10. Have you ever tried to stop smoking?

(1) ❒ Yes ➔ Proceed to question no 11
(2) ❒ No ➔ Proceed to question no 13

11. How long did you refrain from smoking last time you quit?

(1) ❒ Less than a day
(2) ❒ 1 - 2 days
(3) ❒ Around 1 week
(4) ❒ A couple of weeks
(5) ❒ Around 1 month
(6) ❒ A couple of months
(7) ❒ Around half a year
(8) ❒ About 1 year
(9) ❒ More than a year
(10) ❒ Do not remember

12. Have you tried to stop smoking within the last year?

(1) ❒ Yes
(2) ❒ No

13. Would you like to stop smokng?

(1) ❒ Yes
(2) ❒ No ➔ Proceed to question no 15
(3) ❒ Do not know ➔ Proceed to question no 15

14. Why would you like to quit

(1) ❒ To improve my health / feel better
(1) ❒ Because of health problems / disease or symptoms of disease
(1) ❒ Because your spouse is pregnant
(1) ❒ It is too difficult to be a smoker
1) ❒ Out of consideration for others
(1) ❒ Because it is too expensive
(1) ❒ For my children
(1) ❒ For my pet

(1) ❒ Other, please specify: _____

15. Do you plan to stop smoking?

(1) ❒ Within the nearest future
(2) ❒ In 1-6 months
(3) ❒ Some time in the future
(4) ❒ Do not plan to stop smoking ➔ Proceed to question no 17
(5) ❒ Do not know ➔ Proceed to question no 17

16. Give (mark) an indication of how great your motivation is to stop smoking

No motivation |—|—|—|—|—| Very motivated

17. Education?

❒ Seven years of school or less ❒ Eight - 9 years of school
❒ Ten years of school
❒ Business school
❒ High school
❒ Other, please specify _____
❒ Have not finished basic schooling yet ➔ Proceed to question no 19
❒ Do not wish to answer

18. Do you have more than basic schooling ?

❒ Under education
❒ No
❒ Craftsman
❒ Higher education (less than 3 years)
❒ Higher education (3 - 4 years)
❒ Higher education (more than 4 år)
❒ Do not wish to answer

19. What is your profession?

(1) ❒ Worker, unskilled
(2) ❒ Worker, skilled
(3) ❒ Sallaried employee, lower (i.e. paid for overtime)
(4) ❒ Sallaried employee, higher (i.e. not paid for overtime, part of management)
(5) ❒ Self employed farmer/gardner/fisherman
(6) ❒ Self employed shopowner
(7) ❒ Self employed, other
(8) ❒ Apprentice
(9) ❒ Pupil / student
(10) ❒ Not emplyed (retired)
(11) ❒ Married / housewife
(12) ❒ Helping spouse
(13) ❒ Do not wish to answer

Thank you

APPENDIX D

The value of PET scanning when screening for lung cancer

The purpose of the PET study:

To evaluate FDG-PET scanning as a modality to differentiate malignant from non malignant non calcified 7 – 15 mm opacities observed by high resolution CT scans. The level of accumulation (i.e. the metabolism) in the opacity will be assessed both visually, i.e. in comparison to surrounding tissue and semi quantitatively by calculating a standard uptake value (SUV). Whatever the result of the PET scan is the information rendered is likely to be of value in further follow ups:

1 In case there is a pronounced focal FDG accumulation in the opacity there would appear to be a high probability of malignant disease – and a histological diagnosis should be obtained quickly.
2 In case there is no FDG accumulation the opacity is probably not caused by malignant disease (1-3) – and tests may either be terminated or first run after a suitable longer period of time.
3 Because there appears to be a link between SUV and tumor growth (4), in case there is a moderate accumulation of FDG it should be feasible based on SUVs to individualize and thus, determine a suitable time span between control CT scans of putative tumor growth,.

Design

110 individuals with non calcified opacities in the range of 6-15 mm will be evaluated with FDG-PET no more than 1 month following the CT scan. The level of accumulation (i.e. the metabolism) in the opacity will be assessed both visually, i.e. in comparison to surrounding tissue and semi quantitatively by calculating a standard uptake value (SUV). In the prevalence phase of the study the results (around 50 evaluations) will be filed and not used for further assessment, whereas during the incidence phase of the study PET scans will be used for further assessment.

Execution of the FDG PET study

Where: The FDG-PET scans will be performed at the Department of Clinical Physiology at Rigshospitalet.
How: Following a 6 h fast 400 MBq F-18 FDG will be administered intravenously. Around 1 h later a PET scan will be performed of the thorax (including the adrenal glands and the neck) either as (a) successive transmission and emission scans in a GE Advance PET-scanner; or (b) as a combined PET/CT scan in a GE Discovery PET/CT scanner (2).
In about 1/3 of the cases scans are supplemented by a respiration gated evaluation (4-D PET), in which the respiratory pattern of the patient is registered simultaneously with the emission scan. It is not feasible to do this in every case, because a 4-D PET is very time consuming.

The effective dose equivalent amounts to 5-10 mSv which is comparable to a conventional thoracic CT scan.
Evaluations: The PET scans are analyzed visually and by calculation of the SUV. Evaluations are performed by a lung cancer PET expert.
The results are filed, as is the actual PET scan in order to allow evaluation by another expert if necessary. Results are classified as:

1. probably benign (low accumulation and SUV <<2,5),
2. borderline (moderate accumulation and or SUV around 2,5),
3. Probably malignant (pronounced accumulation and SUV >> 2.5).

Background

More than 90% of the opacities that are detected by low dose spiral CT scans turn out to be benign. Thus, another radiographic modality is needed to further asses whether opacities are benign or malignant. Malignant cells have a higher growth rate and a higher metabolism than benign cells. Tumor growth may be determined by

repeating HR-CT every 3 – 12 months. The increased glucose metabolism which is characteristic of most types of lung cancer can be demonstrated by PET scanning using the radioactive glucose analogue F-18 marked fluorodeoxyglucose (FDG-PET).

In the USA FDG-PET is recognized as a routine evaluation for distinguishing between benign and malignant solitary lung opacities. This is due to the pronounced diagnostic value of FDG-PET as established in over 800 clinical evaluations (1-2, 4): The sensitivity of FDG-PET is 96%, the specificity is around 78%, and the negative and positive predictive values are 91% and 90% respectively for showing malignant solitary lung opacities (4). Nevertheless in these studies most lung opacities were relatively large, i.e. 2 – 4 cm.

There are only very limited studies of the value of PET scans for evaluating smaller lung opacities. In a prospective multi center study using PET on 34 patients with solitary opacities ranging from 1 and 2 cm 16 opacities were shown to be malignant, The negative predictive value was 100% (13/13), the positive predictive value was 76% (16/21) – when evaluations were performed visually – but 85% and 93% when evaluations were based on semi quantitative analysis (SUV) (5).

In our own limited prospective study of 300 patients with COLD 10 subjects were found to have a small opacity (7 of them were <15 mm) which were shown by HR-CT, but they were not visible on ordinary chest X-ray: Five of the opacities were malignant and all 5 FDG-PET positive, while the remaining were 5 FDG-PET negative and non malignant (3). Precise detection of opacities less than 7 mm cannot be expected due to limited dissolution of PET scanners and the patients' respiratory movements. Accordingly there are no published data regarding FDG-PET applied on opacities < 7 mm.

It has now become feasible to correct for the effects of respiratory movements using a so called respiration gated PET technique (4-D PET, the 4th dimension is time) (6). The respiratory pattern is identified using video and a marker attached to the thorax concomitantly with the FDG-PET scanning. The subsequent data assessment is rather demanding. However when the artifact of respiratory movement is corrected for, FDG metabolism in opacities of less than 1 cm may be evaluated both visually and semi quantitatively (6).

A US cost effectiveness study showed that FDG PET (sensitivity/specificity of 0.92/0.83) as the next test following CT was more cost efficient than a "wait and see" strategy based on repeated CT controls to asses tumor growth. It was a prerequisite that the pre test probability of malignancy was between 10-70%. If the pretest probability of malignancy is less than 10% CT controls are to be preferred (7). In Henschke et al´s study of low-dose CT screening 233 out of 1000 patients had between 1-6 solitary opacities. In 22 (9%) cases the largest opacity was between 11-20 mm, and 8 of them were malignant (8 out of 22 = 36%). In 70 cases the largest opacity was between 6-10 mm, and 14 out of these were malignant (14 out of 70 = 20%). If these results can be transferred to Danish conditions it seems that FDG PET would appear to be an important subsequent test to follow up on opacities detected by CT scans.

The value of gamma camera PET is not as well established as dedicated PET (1, 2, 8). Gamma camera PET has a lower sensitivity when evaluating small opacities (<2 cm) than when evaluating large opacities (9) and a somewhat lesser sensitivity than dedicated PET. The aim of the current study is to evaluate the value of dedicated PET to assess small opacities.

It is feasible to perform gamma camera PET subsequent to dedicated PET using the already administrated FDG dose. Thus, we have an opportunity to also evaluate the value of gamma camera PET on small opacities as a sort of secondary aim. This could be carried out on a sub group of the patients (around 50). This could be done by sending the patients by cab to a department in the vicinity with a gamma camera PET scanner. e.g. the University Hospital of Gentofte. We have previously used such a model to assess the diagnostic value of FDG-PET in 86 patients with a larger tumor suspicious lesion viewed on ordinary chest X-ray. Dedicated PET was in these cases performed at Rigshospitalet and subsequently gamma camera PET was performed at Bispebjerg Hospital. It was shown that gamma camera PET was of almost equal sensitivity as dedicated PET to assess larger lesions (>1.5 cm). However, none of the lesions were less than 1 cm, so it is as yet not known whether gamma camera PET is of any value to assess lesions of less than 1 cm (8). The aim of the proposed sub study would thus, be to evaluate the value of gamma PET in assessing small lesions.

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APPENDIX E

Layman's resume

Every year 3500 people die of lung cancer in Denmark. This amounts to 6% of all deaths. The survival rate may perhaps be improved, if a new method to detect lung cancer were to be introduced in Denmark.

Results from the US and Japan indicate that by scanning heavy smokers using a so called low dose CT scan it is feasible to diagnose lung cancer in its early stages. This would improve survival because survival is good following an operation for lung cancer in its initial stage, i.e. around 70%. However, in Denmark today lung cancer in its initial stage is only diagnosed in around 10% of the patients. In the later stages of lung cancer it is not feasible to operate and cure the patient, because the tumor already has metastasized. Thus, the average survival rate for lung cancer in Denmark is only around 5%.

It is feasible by way of CT-scanning to determine the exact size of the tumor. If the tumor is small, it is possible 2 to 3 months later to determine whether the size of the tumor is unchanged (benign) following a renewed scan, or whether the tumor has increased in size (perhaps malignant) and therefore should be removed. Thus biopsy and operation can be limited to a smaller group of individuals, who in most cases will be in need of such procedures.

Nevertheless we do not yet know whether CT scans to detect lung cancer are of true value. In the promising US and Japanese studies described above the results were not the outcome of determining mortality in a group of patients that were screened for lung cancer and comparing them to another group who were not. The current study which has been proposed by the Danish Lung Cancer Group intends to do so which will be an important contribution.

The study will include 4000 smokers or former smokers from the Copenhagen are in the age group ranging from 50 – 65 years of age. The enrolled subjects will be randomized to a yearly screening using low-dose CT scans for 5 years or a control group that will not be screened. Both groups will be offered a program to promote cessation of smoking. The project will run over 6 years, and apart from assessing mortality it will assess mental and social consequences of participating in a screening study for lung cancer.

The study will cost DKK 17.3 million and has been financed by the Danish Ministry of Health. The study is expected to determine which groups in the future should be offered screening for lung cancer.

APPENDIX F Ethical considerations

The results of the current study will contribute significantly to our knowledge regarding screening for lung cancer. Combined with the results of the European collaboration it will form the basis for a more qualified decision on whether or not to promote a general screening program for lung cancer.

Putative beneficiary effects of project participation:

- Early detection of lung cancer, and hence a greater possibility for cure and increased survival*.
- Greater motivation for cessation of smoking.

Putative negative effects of project participation:

- Time necessarily spent on tests, increased focus on disease and subsequent fear of disease.
- In cases lesions are detected, the following assessment and treatment (e.g. operation, chemo therapy etc) will be associated with a risk of complications and / or death. This risk will of course be discussed with the patient in every case before commencement of treatment.
- CT-screening is associate with radiation (1 mSv), amounting to the background radiation dose one on average is exposed to in Denmark over 3 to 4 months.

In our opinion it seems probable that the benefits of study participation counterbalance the drawbacks, but this not least must be assessed individually by each subject.

*Foot note: Calculation of putative spared lives associated with the screening study.
In the study it is scheduled to screen 2000 individual and to compare them with a control group of an additional 2000 people.
As a result of the first – prevalence – screening – it may be expected to find lung cancer of all stages (I-IV), while as a result of the following – incidence – screening it may be expected that 70-85 % of the patients are in stadium I with a good prognosis. The number of interval malignant tumors is expected to be 1 – 2 per 1000 scanned subjects, and here the disease is often of a higher stage with a poorer prognosis.
The frequency of lung cancer at the first screening (prevalence) is estimated to be 2-3%, but only ½ - 1% at the subsequent incidence screenings.
If we assume that lung cancer amounts to ½% yearly in the screened group it would amount to 10 cases of lung cancer yearly during 5 years, i.e. 50 cases of lung cancer during incidence screenings for the duration of the protocol.

1) In the control group it may be assumed that the number of lung cancers will be the same as in the screening group, but, the quota of stage I tumors will only be around 10%, which means that there are (50 x 0.1 = 5) 5 cases of stage I lung cancer. This means that 5 x 0.75 = 3.75, i.e. around 4 patients with lung cancer will be cured in this group.

2) I the screening group the quota of lung cancers in stage I is expected to be between 70-85 %.
If the quota is 80% it means that 40 cases of stage I lung cancer will be diagnosed, in which the odds for survival is 75%, i.e. 30 cases will be cured.
If the quota is 70% it means that 35 cases of stage I lung cancer will be diagnosed, in which the odds for survival is 75%, i.e. 26 cases will be cured.

For the duration of the study between (30 – 40 =) 26 and (26 - 4 =) 22 patients with lung cancer may be expected to be cured, i.e. be alive after 5 years as a result of enrollment in the study. This difference reaches the level of statistical significance ($p<0,001$) in favor of screening.

APPENDIX G

Information and agreement of informed consent for the study:

"Trial of screening for lung cancer"

General information:

We kindly ask you to participate in a scientific study. On the following page we shall describe what the study is about and what it would have in store for you to participate.
It is our hope that you agree to be enrolled in the study. However, we wish to point out that it is completely up to you to participate in the study or not. In case you agree to participate, you are furthermore completely at liberty to refuse further participation at any time without having to state why you wish to stop. This is also true notwithstanding that you have signed informed consent to participate.

Please sign below if you wish to enroll in the study. We request that you return the current page after signing it. You will be given an appropriate copy.

With kind regards

Jesper Holst Pedersen, Chief physician, MD, DSc Asger Dirksen, Professor, MD, DSc
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– at your service.

"I confirm that I have been given the information above both orally and in writing, and I agree to enroll in the study in question.

I have been informed that enrollment is voluntary, and that I have the right to withdraw my undertaking enrollment at any time without any mal effects on current or future treatment

Date: Signature:

Participant

I confirm that I have given the information as stated above both orally and in writing to the patient in question, and that he / she has agreed to enroll in the current study.

Date: Signature:

Physician / nurse

Information concerning"Trial of screening for lung cancer"

Only smokers and former smokers from 50 to 65 years of age may participate in the study

We are asking you to participate in a scientific study that hopefully may help people who smoke or have smoked.

Before you decide to participate, we kindly ask you to read the information about the study, and what it would have in store for you to participate.

This document is the information in writing. The nurse of physician who is part of the study will give additionally inform you orally.

Take your time reading, and feel free to consult family of friends before deciding. Take as much time as you wish to decide whether you want to enroll in the study or not. Please also feel free to bring an accompanying person for your first appointment at the clinic.

You are welcome to call the Screening Clinic if you should have any questions regarding the trial.

We also recommend that you read the pamphlet *'Before you make up your mind'.*

Background and aim
Currently in Denmark more people die of lung cancer than any other malignant disease. Most people who get lung cancer are smokers or former smokers.
Usually it is too late to administer a treatment that will cure the disease, when a patient consults his or her physician with symptoms of lung cancer.

Trials carried out abroad seem to indicate that it is feasible to diagnose lung cancer at an early stage by means of CT scans, which is a special type of X ray. Thus, it is possible to detect the tumor while it still is small.

As yet it has not been proved that *screening* (i.e. testing people with no symptoms) with CT-scans of the thorax leads to early treatment of lung cancer and reduces the risk of dying of the disease. The aim of the current study is to evaluate whether it does.

CT-scans cannot prevent you from getting lung cancer in the future, but perhaps they may detect the disease in an early stage improving your odds of a cure.

Trial enrollment
If you are between 50 and 65 years of age and smoke, or if you have stopped smoking after 50, you are eligible for enrollment in the study. It is also required that you if necessary would be able to tolerate an operation for lung cancer, i.e. you need to be in rather good shape, and must be able to clime two flights of stairs without pausing.

What happens if you agree to participate?
You will be invited to an interview with a nurse at the Screening Clinic at the University Hospital at Gentofte. You will be asked about your current or former smoking habits. The interview takes about 1 h.
You will be asked to perform a forced expiration to evaluate how well your respiratory status is. If your respiratory status is sufficiently good, you will be asked to sign informed consent and thus you have been enrolled in the study
Today we do not know whether screening for lung cancer with CT scans is beneficiary. Therefore it is paramount to randomize enrolled subjects into two groups: One group will be CT scanned and the other group will not. You will not be able to choose which group you want to participate in.

Subjects in the CT scan group will be scanned after agreeing to participate in the study and henceforth once a year for 5 years. When the study is over results obtained from the two groups will be compared. Thus, it is feasible to determine whether CT scans for lung cancer are beneficiary.

In case we during trial establish that an enrolled person is in need of treatment for another pulmonary disease than lung cancer (e.g. bronchitis, pneumonia etc), he or she will be treated by his or her doctor, but study participation will not change. In case we diagnose other than pulmonary disease as a result of the CT scans, you will be so informed and referred for treatment.

CT-scans of the thorax.
CT scans involve X rays and data computerization. This procedure gives high resolution images of the lung tissue. The scan takes about 2 min, and is performed with you holding your breath a few seconds in the supine position. The images are later reviewed by a radiologist. The test in total takes around half an hour. Within 2 weeks you will be informed or the results. In case a lesion is found you will be summoned to speak to a physician. The physician will advise you about further tests in case lung cancer is suspected.

A CT scan is a sensitive modality. Therefore a number of participants will be informed that we have seen a so called opacity. In most cases opacity is of no importance, and only a few will turn out to be cancer. Thus, it is often sufficient with a follow up scan after around 3 months.

If opacity is found, it may in some cases be necessary to perform a biopsy, bronchoscopy or an operation. Such evaluations are associated with minor risks of which you will be informed if pending.
Please observe that you yourself decide whether you want to go ahead with further tests, if the need should arrive.

Very seldom lung cancer cannot be diagnosed by way of CT scans. Thus, if a tumor is located centrally in the chest, it may be difficult to see on a CT scan. Even though the radiologist is skilled and diligent, in particular very small tumors may be difficult to diagnose.

Rarely lung cancer may develop so rapidly that it may appear and metastasize in between two scheduled scans.

Side effects of CT scanning.
CT scans are performed using radiation. Therefore a CT scan is associated with radiation that you would not be exposed to otherwise. However the amount of radiation you are exposed to is only equivalent to the dose you get from your ordinary surroundings in 4 months. The risk that such a small amount of radiation would harm you is therefore rather small.

Benefits of participation.
When lung cancer is diagnosed early the odds for becoming cure and for survival are therefore better than if lung cancer is diagnosed at a later stage. But as yet it has not been proved that screening with CT scans leads to lower mortality and better survival. It is the aims of the current study to assess these questions. Even though no advantage is gained in case you have normal lung tissue, it is our hope that others may benefit from our investigation also in the future.

Effects on your well being as a result of screening.
From other screening evaluations **(e.g. for breast cancer)** it is known that some participants become nervous and afraid. We do not know if this also is the case for screening for lung cancer, but we would like to find out. This means that some participants, before and after the trial will be asked to answer a questionnaire concerning how it affects them to be involved in the study.

Help to stop smoking
All participants will regardless of whether they are offered CT scans or not be questioned about their smoking habits, including how addicted they are to nicotine, and whether or not they would like to stop smoking. This part of the study also includes answering a questionnaire. Smokers and former smokers will receive information in writing about cessation of smoking. If you cannot or do not wish to stop smoking, it does not in the least affect our participation in the study.

If new test modalities are introduced during the trial period.
During a trial it is feasible that something new will appear of importance for the study. In this case however, it does not appear likely, because the employed scanner is modern and of a high quality. Should something new nevertheless occur the trial nurse will inform you about it.

Data storage
All personal information and test results will be stored at the Screening Center at the University Hospital of Gentofte. Information is only accessible to authorized personnel and supervising authorities. Such people must observe professional secrecy.
If you want your own physician to be informed of CT scan results, you will need to let us know. Results not including names and addresses will be submitted to a database in Holland. Other European centers that also work on similar projects will do the same. It will not be feasible to track individual subjects in any way.

All participants who so wish will be informed of the results of the trial. However final results of the trial may take 3 to 5 years to finalize after the end of the trial. Results will be published in scientific medical journals and in the news media.

Economy
The trial has been organized by a group of various specialists in the Copenhagen area. The specialists belong to The Danish Lung Cancer Group. The trial is financially supported by the Danish Ministry of the Interior

Trial approval

The trial has been assessed and approved by the Copenhagen County Ethical Committee (Reg.Nr. KA 02045) and has been reported to the Danish Data Protection Agency.

APPENDIX H

EU-US Collaborative Spiral CT Core Protocol

Authors: "EU – US Spiral CT Collaborative Group"

Introduction and background

It has long been established that the best way to control lung cancer is to reduce cigarette smoking in the population, foremost through prevention, and secondarily through smoking cessation. However, even after stopping smoking long-term smokers remain at high risk for lung cancer. Although prevention and cessation strategies are obvious investments for intervention, presently there is no agreed upon control policy for subjects already at high risk due either to prolonged exposure to tobacco smoke or occupational exposures. Lung cancer when clinically diagnosed has a poor outcome with 10-16% survival at 5 years. If the tumour is small enough to be removed surgically, the outcome is much better, more than 70% for stage 1 tumours. This led to speculation in the past as to whether long-term smokers or others at high risk might benefit from earlier detection.

In the 1970's the screening modality of interest was chest X-ray, and several trials were conducted. These trials had discouraging results, suggesting that screening by chest X-ray did not lead to a significant reduction in lung cancer mortality. Increased numbers of tumours in the screened arms of the Czech Trial and Mayo Lung Project, both of which compared chest X-ray to usual care, suggested a degree of overdiagnosis of histologically confirmed lung cancers due to the screening [1,2]. The Mayo project in particular had an excess of early stage tumours in the screened arm, but no deficit of late stage[2]. Although no clear evidence of benefit from early detection emerged from these studies, they had a number of methodological shortcomings, so significant that a recent international lung cancer screening conference in Varese, Italy in December 1998 concluded that they were an "imperfect basis for public policy.[1]" The studies suggested shortcomings in chest X-ray as a screening tool, including doubts about sensitivity. This and other aspects of chest X-ray screening should be clarified when the lung cancer results of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) are published[1].

With the development of low-dose spiral computerised tomography (CT) scanning, there is new hope for a sensitive screening tool for lung cancer [3-5]. In a Japanese study, five-year survival of lung cancer cases diagnosed by CT screening was around 85%[5]. In the Early Lung Cancer Action Project (ELCAP), the stage of the non-small cell cancers diagnosed suggest that a similar outcome will be observed in these cases after five-year follow-up [3,4]. Due to potentially manageable costs, acceptable levels of radiation exposure and improved detection sensitivity, there are grounds for hope that this new technology might allow for detection at a sufficiently early stage to allow successful treatment of lung malignancies that would be certainly fatal otherwise.

Since the Varese Conference, much of the discussion of early detection of lung cancer has been dominated by lively debate on aspects of study design, including whether randomised trials were necessary or whether observational studies were sufficient. To resolve these issues, the National Cancer Institute and the American Cancer Society jointly sponsored the Early Lung Cancer Screening Workshop, with the aim of bringing together experts to address issues of study design. The workshop concluded that both randomised trials and observational studies were necessary to answer key questions about early lung cancer detection. Since then, there has evolved a general consensus that both randomised comparative trials and single arm studies are desirable. In addition it is generally appreciated that establishment in advance of minimum core features of the both randomised and non-randomised studies will be a worthwhile investment for the future, as it will allow clearer interpretation of the body of evidence from all studies.

Also, since the Varese Conference, the European Union Early Lung Cancer Detection Group (EUELCDG), and within this, the EU Spiral CT Sub-group, were set up. Recognizing the potential benefits of collaborative efforts in terms of evaluation in the short to medium term, the EU group and interested investigators and organisations in the US have come together to work on the potential for harmonisation of certain key features of studies to evaluate spiral CT screening for lung cancer. Four joint EU/US meetings, under the auspices of the American Cancer Society, the National Cancer Institute, and the EU Early Lung Cancer Detection Group, have been held so far (July, August and November, 2001; January 2002). The focus of the meetings has been on three areas in particular: core data elements, radiology protocols and pathology protocols (including biomarker studies).

In addition, considerable progress has been made on the setting up of a large collaborative trial of spiral CT screening for lung cancer in the USA. This is the National Lung Screening Trial, a collaboration between the American College of Radiology Imaging Network (ACRIN) and the Lung Screening Study, which has evolved from the PLCO. Recruitment is scheduled to begin by June 2002 and it is aimed to achieve a total accrual of 50,000 subjects.

It is clearly desirable that there should be more than one study evaluating this technology. Interest has been expressed in such a study in various countries worldwide. The feasibility of carrying out a randomised study will vary across populations, in particular the willingness, with informed consent, of subjects at high risk to be randomised with the possibility of not receiving the intervention. This has led some researchers to consider a non-randomised study and others to include some active intervention in the control arm. Further, the likelihood of control group contamination and experimental group non-compliance also will vary across populations.

Because of the expense of the technology and the logistic problems in obtaining a suitable high-risk population, it is possible that some single centres or even single countries will find it difficult to perform a sufficiently large study in isolation. Indeed, historically there have been very few large screening trials, and the daunting resource requirements of single studies have meant that some have been initiated years after the first indication that a new intervention was promising, and with hindsight have been seen to have no sample size safety net for an effect of screening somewhat smaller than initially anticipated. Thus, the idea of an international collaborative study or group of studies is therefore indicated and gaining greater interest.
In addition, since the primary lung cancers detected by spiral CT, especially in the incidence screens, are so much smaller than the clinical community is accustomed to, the best management for these very small primary cancers is not evident. This challenge also applies to the diagnostic work-up of these small lesions. Prospective collection of data on the diagnosis and management of such lesions is crucial to the development and cost-evaluation of population screening strategies, including the diagnostic and therapeutic implications.

A promising strategy at this stage is to seek international consensus on essential elements of evaluation of the intervention between interested centres. The aim is not to achieve a standard protocol that is followed identically in all centres and countries, since numerous and disparate factors influence study design elements, but to develop a collaborative programme of parallel studies which have sufficient common core elements to allow a reliable pooled estimate of the benefit, or at the very least, fewer limitations on comparisons of end results across studies. This approach should in no way compromise the independence of the individual trials, but agreement on common features and core data would permit an overview which could provided a clearer consensus answer in a shorter period and allow exploration of subgroup effects that could not be reliably addressed in the individual trials. As stated above, a series of meetings has been under way for the last few months to develop such a programme. This core protocol is one of the products of the meetings and aims to summarise the basis for the collaborative programme.

As previously stated, prior preferences for study design vary from centre to centre, but certain basic principles are generally agreed.

(1) The appropriate study population is that of persons at high risk of lung cancer, notably long-term smokers or recent ex-smokers.

(2) The experimental intervention of most interest is annual low-dose spiral CT scanning, although there is a possibility that some studies may investigate two-yearly scanning.
(3) The ELCAP protocol provides a reasonable basis for diagnostic workup of features suspicious on spiral CT[3].
(4) The appropriate primary endpoint is mortality from lung cancer.

In addition to the primary target for evaluation, there are issues of screening process and disease natural history to be addressed by both randomised and non-randomised studies. The former include estimation of screening sensitivity and specificity, extent of length bias or overdiagnosis (if any), and incidence of clinical tumours in the interval between screens. The latter include estimation of the impact of spiral CT screening on stage of disease, the extent to which histological and cytological markers of prognosis relate to screen detectability, and downstream research on biomarkers for risk of disease, prognosis or response to treatment.

We therefore propose the following international collaborative effort based on the above.

Design

We propose a programme of parallel randomised controlled trials, with sufficient compatibility that a pooled estimate of the effect on lung cancer mortality is meaningful. The study groups will be offered annual spiral CT screening. It is anticipated that the control groups will for the most part be offered usual care or advice on smoking cessation. There are three minority exceptions to this, however.

(1) Some studies will have regular chest X-ray offered to controls. This may have some early detection benefit and may therefore attenuate the observed effect on mortality. If this were the case it would also reduce statistical power. On the basis of the results of the Mayo Lung Project and the Czech Republic Trial, however, the direct benefit of chest X-ray is unlikely to be large. However, it is likely to improve outcomes to a limited extent in the control group, as would partial contamination by spiral CT screening, and hence reduce power.
(2) Some studies are considering giving the entire study population a baseline spiral CT screen, and exclude those with suspicious abnormalities prior to randomisation to annual CT or usual care. Others may offer an exit screen to the control group contemporaneously with the final screen of the study group. The former strategy leads to a substantial loss of statistical power and will mean that any benefit of the intervention will take significantly longer to appear, since initial incidence of disease will be very low due to the removal of prevalent subclinical cases by the universal screen. As such it is a trial of the benefit of repeat screening at specified intervals and does not incorporate the value of the prevalence screen. This strategy is acceptable, although an exit CT scan of the control group would be preferable to one at baseline.
(3) Some countries and centres propose single arm demonstration projects, in which there will be no control group. While these cannot contribute to the primary comparison of lung cancer mortality in the intervention arms with that in the control arms, they can contribute information on side effects, screening sensitivity and natural history studies. Thus, the single arm studies will be useful for determining optimal screening parameters without contributing directly to the mortality evaluation. Finally, demonstration projects with operational protocols similar to the randomised trials offer the opportunity to observe the extent of biases that randomisation is intended to overcome.
(4) As mentioned above, some studies may wish to investigate two-yearly spiral CT scanning. Such studies are acceptable within the collaboration.

The individual trials will have their own ethics and data monitoring committees. The collaborative project will also have an independent data monitoring and ethics committee to oversee progress of the study and its endpoints. There will also be a central data management facility which individual trials will be free to use if they wish. This will be particularly useful for smaller centres, which may not have the infrastructure for full project and data management.

We propose a minimum screening period of four years, and an analysis of the effect on mortality at three, four, five and six years after beginning recruitment (thus the average follow-up at each analysis will depend on the recruitment period). There will also be an analysis of the effect on the incidence of advanced disease at three, four, five and six years. These analyses may be curtailed if the individual trials' or collaborative project data monitoring committees decide to stop the study. We also propose a further analysis of mortality and incidence of advanced disease after all subjects have been followed up for at least six years. A minimum ten-year follow-up is desirable but not essential for inclusion in the collaboration. These later analyses do not exclude the possibility of earlier publication of results.

Role of single-arm studies

The impetus for this collaboration stems from the demonstration of this screening technology in cohort studies in which all subjects were offered CT scanning [3-5]. Both the ELCAP and the Japanese studies have demonstrated the detection of disease at an early stage without excessive diagnostic activity in lesions which subsequently transpire to be benign. The ELCAP has pioneered a diagnostic work-up scheme and data system which are both practical and effective [3,4]. These cohort studies have shown superior sensitivity of spiral CT to chest X-ray and small numbers of clinical cases after negative CT screens.

The single arm studies in this collaboration will prove very valuable in several areas. These include significant contributions to the data for further quantification of sensitivity, specificity and lead-time. In particular they will provide a substantial enhancement of the tumour data, enabling more precise estimation of detection rates, interval cancer rates, sensitivity, lead time and other parameters in subgroups delineated by histological type, anatomical subsite and age or risk group of subjects. They will also add precision to stage-specific analyses of detection rates. They will therefore be of considerable value in developing models to predict the effects of refining the screening regime, and in delineating which tumours benefit from early detection in terms of curability. In addition, they will add to the case base for biomarker and natural history studies.

Study aims- primary

- To estimate the reduction in lung cancer mortality, if any, associated with annual spiral CT screening in groups at high risk of lung cancer.

Thus the primary endpoint is death from lung cancer.

Study aims- secondary

- To estimate the reduction, if any, in cumulative incidence of advanced stage lung cancer associated with annual spiral CT screening.
- To estimate the effect of annual spiral CT on rates of diagnosis of lung cancer by size, shape, histology and location.
- To estimate the consequent demands on further diagnostic and treatment facilities.
- To estimate other side effects of annual spiral CT.
- To estimate disease progression parameters, other aspects of natural history, lead time and screening sensitivity.
- To obtain country-specific cost-effectiveness estimates.
- To estimate all-cause mortality in the intervention and control arms.
- To further define best practices in lung imaging and quality assurance.
- To define the molecular dynamics of very early lung cancer.
- To further define best practice and quality assurance in nodule evaluation and early stage lung cancer management.

Incidence of advanced disease is probably the most important secondary endpoint. It should be noted that this is absolute incidence of advanced disease and not proportion of cases, to avoid problems of length bias or overdiagnosis of early stage disease. Other secondary endpoints include lung cancer incidence rates by histological type and anatomic subsite, detection rates, interval cancer incidence rates and estimates of disease progression, lead-time and sensitivity from these. Other secondary endpoints include deaths from all causes, untoward effects of the intervention, all procedures related to lung cancer screening, and diagnosis and treatment costs. Ancillary studies of natural history, the molecular biology of early lesions, psychosocial effects of the intervention, and details of the economic analysis will the subject of separate protocols. Also the subject of separate protocols will be inter-centre radiology, diagnostic work-up, surgery and pathology quality reviews, and procedures for sampling and storage of biological material for future biomarker studies.

Inclusion- centres

Included centres will be those which can provide the screening, low-dose spiral CT scanning, and which provide or have a direct referral line to facilities for diagnostic workup, including radiologically guided percutaneous fine needle aspiration (FNA), and specialist treatment, including thoracoscopic surgery for resection of nodules. Ideally, all spiral CT examination would be conducted using new multi-channel CT technology.

Inclusion- subjects

Exact inclusion criteria may vary from country to country, but a criterion common to all will be that subjects must be judged to be at elevated risk, usually based on smoking history although some studies may recruit on the basis of high occupational risk, in order to be considered eligible. Clearly, prime candidates for inclusion would be current long-term smokers and ex-smokers who have given up within the last five years.

As a guideline we will attempt to focus recruitment on subjects whose risk of lung cancer exceeds 3 per thousand per year. To assist in pooled analysis and interpretation all subjects will have smoking history recorded, including current smoking status and total pack-years exposure. In the main, subjects will be aged 50-74 at recruitment, although the age range may be narrower in some countries, and some studies may recruit purely on the basis of risk, without age limits.

Exclusion- subjects

Subjects will be excluded if they:

- refuse to take part or are unable to give fully informed consent;
- have a history of cancer of the lung or breast, or cutaneous malignant melanoma;
- have a recurrence of any tumour within the last five years;
- have current persistent respiratory symptoms;
- are too ill or infirm to attend for screening;
- have any condition that would preclude screening, diagnosis or surgical treatment.

Study size

Power and sample size must be calculated on the basis of anticipated mortality from lung cancer in the intervention and control groups. We anticipate a relatively high-risk group, with an incidence rate in the absence of screening of around 3.6 per thousand per year, and mortality rates of 3 per thousand per year. This corresponds roughly to former long-term smokers who have recently stopped, in the UK male population aged 50-69. To incorporate a 'healthy volunteer' effect, we assume that in the first year after recruitment, these rates are attenuated by a third, with an incidence rate of 2.4 and mortality of 2 per thousand per year.

For simplicity, we assume that for those trials with a prior prevalence screen to exclude pre-existing occult tumours, this would essentially remove the first year's clinical incidence. It was assumed that non-compliance in the study group would not be a major problem (although clearly there will be a degree of non-compliance) but that contamination by screening in the control group would be. For purposes of sample size calculations, we considered the situation where no trials had such a prior prevalence screen, and that where 20% of the trial populations were covered by such a prevalence screen. The sample sizes required for 90% power (5% significance, two–sided testing) were calculated for mortality analyses at 3, 4, 5 and 6 years, assuming 10%, 20% and 30% control group contamination rates, and underlying mortality reductions (for 100% coverage with CT screening against 0%) of 30% 40%, 50% and 60%. Active control regimes (for example, regular chest X-ray) in some of the trials are not considered separately but assumed to contribute to the dilution of effect in a similar way to control group contamination.

Required sample sizes are shown for combinations of these features in Appendix 1. The follow-up times pertain to time since starting recruitment rather than to average follow-up time for all subjects recruited. Also shown is the time at which the same power would be obtained for a comparison of incidence rates of advanced tumours, assuming 80% of tumours in the control group would be advanced, and a reduction in advanced tumours in the study group 10% larger than the mortality reduction.

A wide variety of required study sizes results from the possible combinations of design, contamination, and mortality reduction. If we were to recruit our study population in 1 year, that 20% of the population will be covered by a prior prevalence screen and exclusion of prevalent occult cases, and that there will be 20% contamination of the control groups by CT or other early detection measures. With this background, between 10000 and 11000 subjects per arm will yield 90% power for an underlying mortality reduction of 60% (observed 55%) at 3 years, 50% (observed 44%) at four years and 40% (observed 35%) at six years. A sample size of 18,000 per arm would give 90% power for a 30% mortality reduction (observed 24%) at six years, and additionally would confer adequate power on subgroup analyses at six years. We therefore aim to recruit at least 36000 subjects in the trials as a whole (at least 18000 per arm). In addition to having sufficient power for mortality comparisons, this study size is likely to yield in excess of 700 cancers, which will be an invaluable resource for the necessary accompanying natural history studies. If, on the other hand, recruitment takes two years, this study size will give in excess of 90% power for a 40% (observed 35%) mortality reduction at 5 years, and between 80% and 90% power for a true 30% reduction (observed 24%) at 6 years.

Varying sample size/study period requirements are calculated depending on the assumptions used regarding screening sensitivity, disease natural history, and curability of screen-detected lesions [6,7]. Using simulation of longitudinal models, Flehinger et al[6] showed that assuming sensitivity consistent with the Mayo Lung Project results of chest X-ray screening, a study size of 18000 would require a study period of 18 years to achieve 80% power. They also found that improved sensitivity would lead to greater benefits, with a consequently smaller study size/period evidence base. Similar modelling exercises, but using estimates more consistent with ELCAP results on spiral CT screening [3,4], have yielded sample sizes and study periods similar to those reported here (details available from SWD).

The likely control group mortality from lung cancer which is a basic ingredient of the power calculations is not predictable with certainty. Individual studies have used various prior estimates. For example, the UK proposal [8] postulated a mortality rate of 2.5 per thousand throughout. This yields similar sample sizes required for the early (3-4 years) analysis, but slightly larger sizes for the later analyses. For example, for a 40% reduction at six years, instead of the 11000 per arm calculated above, we would require 12000 per arm.

Use of a prevalence screen with exclusion of pre-existing occult disease in 100% of the study population would require an increase in study size of 25-30%. This is so even with the rather optimistic assumption that the only effect of this is to eliminate the first year's incidence in which we have postulated a lower mortality rate.

Conduct of study

Recruitment and randomisation practice will vary from country to country, but the majority of subjects will be recruited from primary care and will be randomised at individual level. A centralised registration and randomisation service will be available but individual studies may choose to register or randomise in-house.

Those randomised to the intervention group will be invited to annual low-dose spiral CT scanning. There are slight variations in clinical practice from centre to centre, but diagnostic workup is typically based on the accompanying EU-US protocol (see in particular the section ***Regimen of Early Diagnosis***), with minor local variations.

Full evaluation of subjects diagnosed to have lung cancer will be carried out. These will typically include patient evaluation by lung and myocardial function to determine suitability for surgery, and further diagnostic and staging workup, including other investigations such as bronchoscopy. Full details are given in the accompanying radiology protocol. Subsequent to treatment, lung cancer cases will be subject to standard clinical follow-up.

Treatment and diagnostic centres will be regularly checked for presentation of members of either the control or the intervention group for screening outwith the study or for diagnosis following respiratory symptoms.

Ethical approval will be obtained before the study commences within each country separately. See below for further details on ethical issues. There will be a small collaborative study management group, responsible for day-to-day decisions. The overview will be conducted under the auspices of a larger steering group, which will meet twice yearly, and will include representatives from the contributing groups and other relevant individuals. There will be ongoing inter-centre radiology and pathology quality reviews.

Following a common measurement protocol, the following minimum data will be collected from each study (this does not exclude individual studies collecting other information as part of their individual protocol).

Data collection- baseline

For each subject, the following data will be collected:

- Age
- Sex
- Date of randomisation/recruitment
- Smoking status (current or former)
    - If a former smoker, years since quitting
    - Lifetime pack-years exposure
    - Duration of smoking
    - Usual number of cigarettes smoked per day, while a smoker
    - Age at starting smoking
- Brief health history (see also inclusion/exclusion criteria)
- Occupational exposure to asbestos or ionising radiation

For some countries this will be obtained at interview, for others by postal questionnaire. Baseline spirometry is encouraged but is not a condition for participation in the collaboration. COPD status will be included in the health history. Both study and control group members will have their smoking status ascertained by follow-up at least once in the course of the study.

Data collection- screening

For each screening episode in the intervention group, we will record:

- Date of invitation
- Attendance (Yes or No)
- Date of screen (if attended)
- Finding of screen
  - Type of abnormality (if applicable)
  - Size of abnormality (if applicable)
  - Shape of abnormality (if applicable)
  - Location of abnormality (if applicable)
  - Other investigations
  - Results of these
  - Side effects of screening and further investigations
  - If referred for 3-monthly follow-up, results of this follow-up

Diagnostic facilities will be requested to check against control lists for elective screening and diagnostic activity among controls and for such activity outwith scheduled screens in the study group. Details of such will be recorded as above. It is recommended but optional that a blood sample be taken at least once from all participants, and that sputum samples be taken for those subject to further workup. Costs of procedures will be calculated for purposes of economic analysis.

Data collection- lung cancers

Information on the tumours diagnosed provides the basis for many of the secondary endpoints. We will record:

- All available pathology data on all lung cancers diagnosed in the study. Lung cancers in the study include screen-detected cancers, interval cancers, and clinically diagnosed cancers in non-attenders in the intervention arm, and all cancers diagnosed in the control arm. Pathology data will include TNM staging, histological type, and location of tumours.
- Mode of detection (screen, interval non-attender, control) and round of screening (if screen-detected or interval cancer).
- Initial treatment details.
- Concomitant information from radiological and other investigations. This will be of crucial importance for those tumours that are not operable.
- Dates of diagnosis and (if applicable) surgery.

There is a separate pathology protocol. It is encouraged for purposes of future studies that as a basic minimum tissue arrays from all tumours are stored.

Case notifications and detailed information on each case will be sought locally from treatment centres, backed up by regular searches of local and national cancer registries. Costs of treatment will also be estimated.

Data collection- primary endpoints

All subjects will be flagged nationally for death and cause of death. The unbiased classification of cause of death is an essential element of this study, and the endpoint committee will have a key role. The endpoint committee will determine the cause of death blind to study arm. The committee will include a thoracic surgeon, a chest physician, an epidemiologist and a radiation oncologist. Cause of death will be based on review of

- death in subjects with lung cancer specified on a death certificate;

- death from any cause but with a previous diagnosis of lung cancer;
- death from unknown cause;
- death from other malignancies which might suggest misdiagnosed or comorbid lung cancer;
- death contributed to by investigative procedures initiated for suspicion of lung cancer.
- Death from any cause that could be due to treatment of a suspected lung cancer.

Death will be classified as due to, probably due to, probably not due to or not due to lung cancer. We propose to analyse two measures of death from lung cancer.
(1) Only those deaths classified as due to lung cancer.
(2) Deaths classified as due to or probably due to lung cancer (or treatment or diagnosis thereof).

Further details of the endpoint review process are given on a separate endpoint review protocol.

Numbers of tumours by stage will be obtained from treatment centres, backed up with cancer registry searches.

Data collection- secondary endpoints

Screening results, further investigations and results of these, treatment details and costs of these will be obtained from the screening, diagnostic and treatment centres. Cancer data will also be obtained from these centres, augmented by cancer registry information. All-cause deaths will be obtained from national death registers.

Ethical and safety issues

There will be individual trial and overall collaborative study data monitoring and ethics committees (DMEC), which will have access to the ongoing results and will regularly check whether there is already a clear result or if the intervention is thought to be causing serious harm to the subjects. In addition to monitoring incidence and mortality from lung cancer, the outcomes for which data monitoring and ethics committees will be vigilant include:

- excessive numbers of subjects recalled for further investigation
- excessive numbers of invasive investigations, such as fine-needle aspirations and bronchoscopies
- excessive numbers of biopsies resulting in a benign diagnosis
- complications resulting from investigations
- morbidity associated with treatment of early stage lesions
- compliance with referral for further workup
- attendance at repeat screens

Only DMEC's for individual studies will have authority to stop those studies. The overall committee will have an advisory role in the decision of when to stop studies. Informed consent with explicit permission for retention of follow-up details and information on subsequent examinations and their results including pathology reports will be sought. Studies are encouraged to seek permission from all subjects from whom biological material is provided to use biopsy and other biological material for further natural history and molecular level studies.

Statistical analysis

In addition to a simple comparison of the proportion dying from lung cancer or metastatic disease therefrom in the intervention arm with that in the control arm, random effects models will also be fitted which take account of variation in design features and allow consequent variation in the benefit from country to country [9,10]. Sources of heterogeneity, both spatial and temporal, will be investigated. Estimation of disease

progression parameters and screening sensitivity will use both microsimulation[11] and analytic[12] techniques. Individual studies may wish to make additional analyses of their own data.

Secondary studies, notably biomarker studies

The many tumours and diagnostic specimens likely to arise from this study will constitute an invaluable source of material for the study and quantification of the detectability, progression, and behaviour post-treatment of early stage lung cancer. Tissue arrays and if possible more extensive biological material, should be stored for biomarker studies. As noted above, there is particular interest in estimation of screening sensitivity, detection rates, disease progression rates, recurrence and new primary risks, and survival specific to histological type and to other microscopic, clinical and biological attributes of the tumours detected. In addition, the data will give opportunities to study markers for risk of future development of disease in biopsied nodules which prove benign. Finally, protocols are in development at the moment for studies of natural history of early lung cancer at the molecular level.

Dissemination and implications of results

Results will be published in peer-reviewed scientific journals. The publication schedule will be arranged so that each collaborative unit can publish its own results prior to or simultaneously with the publication of the overall result. The results will have considerable implications for policy. Whether positive or negative results are observed, there will still be a strong priority for tobacco control. However, if there is a substantial mortality benefit associated with the intervention, this at last gives a potential for saving lives from a disease for which the survival rates have changed little in several decades. If not, it will indicate the need to find other management strategies for long-term smokers and ex-smokers.

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Core Protocol Workgroup Participants

Note that the participants below are those who contributed to the discussions which resulted in this protocol. Their own individual studies do not necessarily conform to this protocol in every detail, for reasons described in the protocol.

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Appendix 1. Required sample sizes for various design features, effect sizes and contamination rates

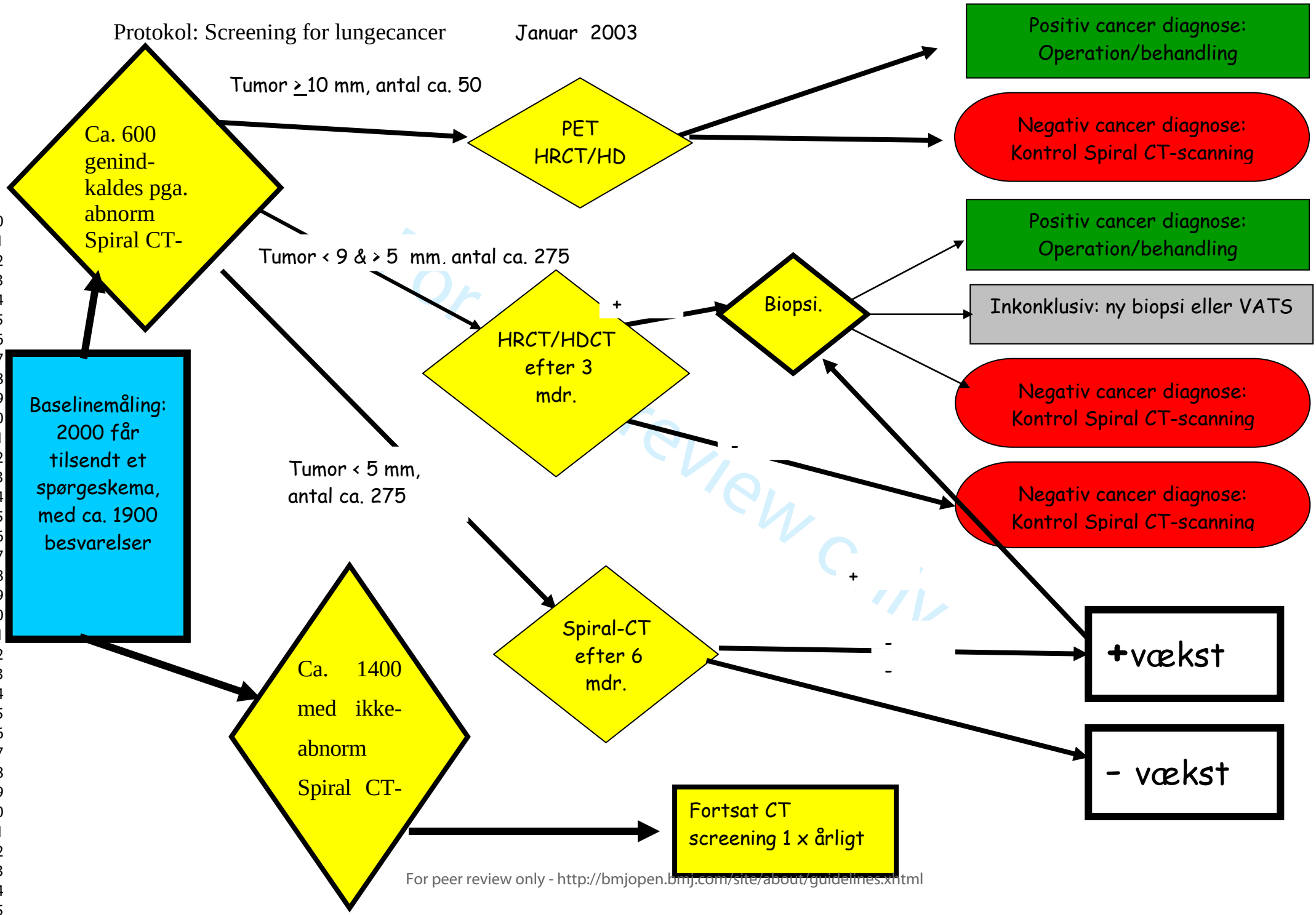
The tables on the following pages give required sample sizes for 90% power at 5% significance level (two-sided testing), for comparison of lung cancer mortality. The sample sizes are calculated dependent on the size of the anticipated reduction in mortality (30%, 40%, 50%, and 60%), contamination of the control group (10%, 20%, 30%), the recruitment period (1 year, 2 years) and the percentage of the study populations given a prior prevalence screen to exclude pre-existing subclinical tumours (0%, 20%). We have assumed an underlying incidence of lung cancer in an unscreened group to be 2.4 per thousand in the first year and 3.6 per thousand thereafter, with corresponding mortality rates of 2 and 3 per thousand respectively.

Sample sizes for 90% power for a mortality comparison at 3 years from starting recruitment						
Recruitment period (years)	Percent of study population with prior prevalence screen	Percentage mortality reduction (100% CT vs no CT)	Contamination of control group (%)	Observed cumulative mortality Reduction (%)	Number of subjects required per arm	Time (years) at which a comparison of advanced tumours has 90% power
1	0	30	10	27	26228	2.5
1	0	30	20	24	33698	2.6
1	0	30	30	21	44682	2.6
1	0	40	10	37	19710	2.3
1	0	40	20	35	24231	2.3
1	0	40	30	32	30726	2.3
1	0	50	10	47	11919	2.6
1	0	50	20	44	14486	2.5
1	0	50	30	41	18149	2.5
1	0	60	10	57	7857	2.7
1	0	60	20	55	9415	2.7
1	0	60	30	51	11619	2.7
1	20	30	10	27	27931	2.5
1	20	30	20	24	33191	2.6
1	20	30	30	21	46663	2.6
1	20	40	10	37	21009	2.3
1	20	40	20	35	25827	2.3
1	20	40	30	32	32750	2.3
1	20	50	10	47	12703	2.6
1	20	50	20	44	15439	2.5
1	20	50	30	41	19344	2.5
1	20	60	10	57	8374	2.7
1	20	60	20	55	10034	2.7
1	20	60	30	51	12384	2.7
2	0	30	10	27	31186	2.5
2	0	30	20	24	40069	2.6
2	0	30	30	21	53131	2.6
2	0	40	10	37	25651	2.3
2	0	40	20	35	31534	2.3
2	0	40	30	32	39987	2.3
2	0	50	10	47	15509	2.6
2	0	50	20	44	18849	2.5
2	0	50	30	41	23616	2.5
2	0	60	10	57	10223	2.7
2	0	60	20	55	12249	2.7
2	0	60	30	51	15118	2.7
2	20	30	10	27	32838	2.5
2	20	30	20	24	42192	2.6
2	20	30	30	21	55947	2.6
2	20	40	10	37	27890	2.3
2	20	40	20	35	34287	2.3
2	20	40	30	32	43476	2.3
2	20	50	10	47	16863	2.6
2	20	50	20	44	20494	2.5
2	20	50	30	41	25677	2.5
2	20	60	10	57	11114	2.7
2	20	60	20	55	13318	2.7
2	20	60	30	51	16436	2.7

Sample sizes for 90% power for a mortality comparison at 4 years from starting recruitment						
Recruitment period (years)	Percent of study population with prior prevalence screen	Percentage mortality reduction (100% CT vs no CT)	Contamination of control group (%)	Observed cumulative mortality Reduction (%)	Number of subjects required per arm	Time (years) at which a comparison of advanced tumours has 90% power
1	0	30	10	27	19883	3.4
1	0	30	20	24	25543	3.4
1	0	30	30	21	33867	3.4
1	0	40	10	37	13456	3.1
1	0	40	20	35	16543	3.1
1	0	40	30	32	20978	3.1
1	0	50	10	47	8139	3.4
1	0	50	20	44	9892	3.4
1	0	50	30	41	12394	3.4
1	0	60	10	57	5367	3.6
1	0	60	20	55	6431	3.6
1	0	60	30	51	7937	3.6
1	20	30	10	27	20547	3.4
1	20	30	20	24	26397	3.4
1	20	30	30	21	35000	3.4
1	20	40	10	37	14051	3.1
1	20	40	20	35	17275	3.1
1	20	40	30	32	21906	3.1
1	20	50	10	47	8499	3.4
1	20	50	20	44	10329	3.4
1	20	50	30	41	12942	3.4
1	20	60	10	57	5604	3.6
1	20	60	20	55	6716	3.6
1	20	60	30	51	8288	3.6
2	0	30	10	27	22623	3.4
2	0	30	20	24	29065	3.4
2	0	30	30	21	38538	3.4
2	0	40	10	37	15997	3.1
2	0	40	20	35	19666	3.1
2	0	40	30	32	24938	3.1
2	0	50	10	47	9674	3.4
2	0	50	20	44	11758	3.4
2	0	50	30	41	14732	3.4
2	0	60	10	57	6379	3.6
2	0	60	20	55	7644	3.6
2	0	60	30	51	9433	3.6
2	20	30	10	27	23485	3.4
2	20	30	20	24	30172	3.4
2	20	30	30	21	40006	3.4
2	20	40	10	37	16843	3.1
2	20	40	20	35	20707	3.1
2	20	40	30	32	26258	3.1
2	20	50	10	47	10186	3.4
2	20	50	20	44	12380	3.4
2	20	50	30	41	15512	3.4
2	20	60	10	57	6716	3.6
2	20	60	20	55	8048	3.6
2	20	60	30	51	9932	3.6

Sample sizes for 90% power for a mortality comparison at 5 years from starting recruitment						
Recruitment period (years)	Percent of study population with prior prevalence screen	Percentage mortality reduction (100% CT vs no CT)	Contamination of control group (%)	Observed cumulative mortality Reduction (%)	Number of subjects required per arm	Time (years) at which a comparison of advanced tumours has 90% power
1	0	30	10	27	15993	4.2
1	0	30	20	24	20546	4.3
1	0	30	30	21	27240	4.3
1	0	40	10	37	10203	3.9
1	0	40	20	35	12545	3.8
1	0	40	30	32	15909	3.8
1	0	50	10	47	6173	4.2
1	0	50	20	44	7503	4.2
1	0	50	30	41	9402	4.2
1	0	60	10	57	4072	4.5
1	0	60	20	55	4880	4.5
1	0	60	30	51	6023	4.5
1	20	30	10	27	16423	4.2
1	20	30	20	24	21097	4.3
1	20	30	30	21	27971	4.3
1	20	40	10	37	10544	3.9
1	20	40	20	35	12963	3.8
1	20	40	30	32	16439	3.8
1	20	50	10	47	6379	4.2
1	20	50	20	44	7753	4.2
1	20	50	30	41	9715	4.2
1	20	60	10	57	4207	4.5
1	20	60	20	55	5042	4.5
1	20	60	30	51	6223	4.5
2	0	30	10	27	17730	4.2
2	0	30	20	24	22777	4.3
2	0	30	30	21	30199	4.3
2	0	40	10	37	11608	3.9
2	0	40	20	35	14271	3.8
2	0	40	30	32	18098	3.8
2	0	50	10	47	7022	4.2
2	0	50	20	44	8535	4.2
2	0	50	30	41	10694	4.2
2	0	60	10	57	4631	4.5
2	0	60	20	55	5550	4.5
2	0	60	30	51	6849	4.5
2	20	30	10	27	18257	4.2
2	20	30	20	24	23455	4.3
2	20	30	30	21	31098	4.3
2	20	40	10	37	12050	3.9
2	20	40	20	35	14814	3.8
2	20	40	30	32	18786	3.8
2	20	50	10	47	7289	4.2
2	20	50	20	44	8859	4.2
2	20	50	30	41	11100	4.2
2	20	60	10	57	4807	4.5
2	20	60	20	55	5760	4.5
2	20	60	30	51	7109	4.5

Sample sizes for 90% power for a mortality comparison at 6 years from starting recruitment						
Recruitment period (years)	Percent of study population with prior prevalence screen	Percentage mortality reduction (100% CT vs no CT)	Contamination of control group (%)	Observed cumulative mortality Reduction (%)	Number of subjects required per arm	Time (years) at which a comparison of advanced tumours has 90% power
1	0	30	10	27	13365	5.1
1	0	30	20	24	17169	5.1
1	0	30	30	21	22761	5.1
1	0	40	10	37	8210	4.6
1	0	40	20	35	10095	4.6
1	0	40	30	32	12802	4.6
1	0	50	10	47	4969	5.1
1	0	50	20	44	6039	5.0
1	0	50	30	41	7568	5.0
1	0	60	10	57	3278	5.4
1	0	60	20	55	3929	5.4
1	0	60	30	51	4849	5.4
1	20	30	10	27	13666	5.1
1	20	30	20	24	17554	5.1
1	20	30	30	21	23272	5.1
1	20	40	10	37	8430	4.6
1	20	40	20	35	10365	4.6
1	20	40	30	32	13145	4.6
1	20	50	10	47	5101	5.1
1	20	50	20	44	6201	5.0
1	20	50	30	41	7770	5.0
1	20	60	10	57	3366	5.4
1	20	60	20	55	4034	5.4
1	20	60	30	51	4979	5.4
2	0	30	10	27	14563	5.1
2	0	30	20	24	18708	5.1
2	0	30	30	21	24803	5.1
2	0	40	10	37	9100	4.6
2	0	40	20	35	11188	4.6
2	0	40	30	32	14189	4.6
2	0	50	10	47	5506	5.1
2	0	50	20	44	6693	5.0
2	0	50	30	41	8386	5.0
2	0	60	10	57	3633	5.4
2	0	60	20	55	4353	5.4
2	0	60	30	51	5373	5.4
2	20	30	10	27	14920	5.1
2	20	30	20	24	19166	5.1
2	20	30	30	21	25409	5.1
2	20	40	10	37	9371	4.6
2	20	40	20	35	11521	4.6
2	20	40	30	32	14610	4.6
2	20	50	10	47	5670	5.1
2	20	50	20	44	6891	5.0
2	20	50	30	41	8635	5.0
2	20	60	10	57	3740	5.4
2	20	60	20	55	4482	5.4
2	20	60	30	51	5532	5.4



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4 and 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4 and 5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	4 and 5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5 and 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 and 6
Bias	9	Describe any efforts to address potential sources of bias	5 and 8
Study size	10	Explain how the study size was arrived at	4, 5 and Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-10
		(*b*) Describe any methods used to examine subgroups and interactions	6 and 7
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-6
		(b) Give reasons for non-participation at each stage	5

		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Appendix Table 1
		(c) Summarise follow-up time (eg, average and total amount)	Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Figure 2a, 2b and Appendix Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figure 2a, 2b and Appendix Table 1 5-6
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6 and 7
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Psychosocial consequences of false positives in the Danish lung cancer CT-screening trial: a nested matched cohort study

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Objectives

Lung cancer computed tomography (CT) screening can reduce lung-cancer mortality, but high false-positive rates may cause adverse psychosocial consequences. The aim was to analyse the psychosocial consequences of false-positive lung-cancer CT screening using the lung cancer screening-specific questionnaire, Consequences of Screening in Lung Cancer (COS-LC).

Design and setting

This study was a matched cohort study, nested in the randomised Danish Lung Cancer Screening Trial (DLCST).

Participants

Our study included all 130 participants in the DLCST with positive CT results in screening rounds 2-5, who had completed the COS-LC questionnaire. Participants were split into a true-positive and a false-positive group and were then matched 1:2 with a control group (n=248) on sex, age (+/- three years), and the time of screening for the positive CT groups or clinic visit for the control group. The true-positives and false-positives were also matched 1:2 with participants with negative CT screening results (n=252).

Primary outcomes

Primary outcomes were psychosocial consequences measured at five time points.

Results

False positives experienced significantly more negative psychosocial consequences in seven outcomes at one week and in three outcomes at one month compared with the control group and the true-negative group (mean Δ score > 0 and $p<0.001$). True positives experienced significantly more negative psychosocial consequences in one outcome at one week (mean Δ score 2.86 (95% CI 1.01 to 4.70) $p=0.0024$) and in five outcomes at one month (mean Δ score > 0 and $p<0.004$) compared

with the true-negative group and the control group. No long-term psychosocial consequences were identified either in false positives or true positives.

Conclusions

Receiving a false-positive result in lung cancer screening was associated with negative short-term psychosocial consequences. These findings contribute to the evidence on harms of screening and should be taken into account when considering implementation of lung cancer screening programmes.

Trial registration

The DLCST was approved by the Danish Scientific Ethical Committee (approval number KA-02045). The DLCST was approved by the Danish Data Protection Agency (approval number 2005-53-1083). All participants signed an informed consent form. ClinicalTrials.gov: NCT00496977

Strengths and limitations

- This study used a lung-cancer-screening-specific questionnaire with high content validity and adequate psychometric properties to measure the psychosocial consequences of the screening results
- As well as the false-positive group, the true-positive group and the true-negative group were assessed, serving as benchmarks against which to compare the psychosocial consequences in the false positives.
- A limitation is that the control group, who were not invited to screening, reported more negative psychosocial consequences than the screening group.

- Another limitation is that the study participants had a more robust psychosocial profile compared with a matched background population.

Introduction

Lung cancer has the highest mortality worldwide.[1] Several randomised controlled screening trials using low dose computed tomography (CT) scans have investigated the effect of CT screening on lung cancer-specific mortality.[2] The largest trial, the National Lung Screening Trial (NLST), found a relative lung cancer-specific mortality reduction of 16% after five-year follow-up, and lung cancer CT screening is now recommended in the United States.[3-5] However, according to a Cochrane systematic review, more data are needed on false-positive results and overdiagnosis before recommendations can be made for large-scale CT-screening programmes.[6] The Danish Lung Cancer Screening Trial (DLCST) could not show a reduction in lung-cancer-specific or total mortality after a five-year follow-up.[7] The European trials are expected to publish the pooled follow-up analyses of both the mortality data and the consequences of overdiagnosis and false-positive results.[8] This will provide the additional evidence of benefits and harms of lung cancer CT screening requested in the Cochrane systematic review.[6]

In cancer screening programmes, positive screening results lead to either false-positive results or true-positive results after further diagnostic workup.[9] A false-positive screening result can cause both physical and psychosocial harms [10-13] as well as being costly for the healthcare system.[14 15] The average false-positive rate per screening round varies substantially in lung cancer screening trials, e.g. 23% in the NLST and 3% in the DLCST (appendix 1).[3 16] Qualitative and quantitative studies have shown that false-positive lung-cancer-screening results can be associated with negative psychosocial consequences both during workup and after the final diagnosis.[13 17 18] By their nature, qualitative studies cannot measure the degree or the extent of psychosocial consequences[17], and all the published quantitative studies used generic questionnaires which lack content validity and have unknown psychometric properties.[13 18-20] Measurement of the psychosocial consequences of

screening using questionnaires with high content validity and adequate psychometric properties is important.[21]

The aim of this study, therefore, was to measure the short and long-term psychosocial consequences of false-positive lung cancer CT screening results using the questionnaire Consequences of Screening in Lung Cancer (COS-LC) and to compare these scores with the COS-LC scores from 3 other groups of participants in the DLCST: 1) the true-negative group, 2) the true-positive group, and 3) a control group that did not participate in screening.

Methods

Study design and participants

The overall design of the DLCST has been reported in detail elsewhere.[16 22] In summary, the DLCST was a single-centre, randomised, controlled trial and participants were randomly allocated to a CT group and a control group (figure 1). Eligible participants were current and former smokers with a smoking history of minimum 20 cigarettes/day for 20 years, and were aged 50–70 years.[16 22] In five rounds between 2004–2010, both groups were offered annual spirometry and smoking counselling and were asked to complete the COS-LC questionnaire. Participants in the CT group were also offered annual lung CT scans.

This study was a matched cohort study nested in the DLCST. Participants from the CT group with positive CT screening results during rounds 2–5 were matched 1:2 with participants with negative CT screening results, and 1:2 with participants from the control group. Participants were matched on sex, age (+/- three years), and the time of screening, within seven days for the CT group, or clinic visit for the control group. The group with positive CT screening results was further divided

into a true-positive group and a false-positive group after receiving the final diagnosis. Participants completed the COS-LC at five time points (figure 1):

- Baseline: COS-LC was completed shortly before the annual CT screening (CT group) or clinic visit (control group)
- One week after receiving the CT-screening result (CT group) and one week after the annual clinic visit (control group)
- 1, 6 and 18 months after receiving the final diagnosis of the screening result (CT group) and at these time points after the annual clinic visit (control group)

At the latter four time points, participants were sent the COS-LC by post and asked to return it in an enclosed stamped addressed envelope. A reminder was sent to participants who did not return the COS-LC within two weeks.

Information about region of residence, smoking status, smoking history, social group, employment status, school education, and whether participants lived alone was obtained from baseline and annual questionnaires. The Charlson comorbidity index was calculated from hospital admissions three years before randomisation.

Questionnaire

The COS-LC is a condition-specific questionnaire with high content validity and adequate psychometric properties and it was developed and validated to measure the psychosocial consequences of participation in lung cancer CT screening.[17] To ensure high content validity, 20 participants from the first screening round in the DLCST were interviewed in five group interviews.[17] Subsequently, during screening rounds 2–4 in the years 2006–2007, questionnaire data

from participants were used to validate the COS-LC using Item Response Theory Rasch models.[17] As these data were only a part of the present data, the psychometric properties of the 15 COS-LC scales were re-tested for homogeneity and differential item functioning (DIF) relative to participant group, sex, age, social status, and smoking status by using likelihood ratio tests on appropriately conditioned Rasch models at the one month follow-up time point.[23] Reliability of the scales was examined using Cronbach's alpha.

The COS-LC has two parts where Part-I encompasses 24 COS items (four COS-scales) and 25 lung cancer screening-specific items (five lung cancer screening-specific scales) (appendix 2). Part-I can be used before, during and after screening and the DLCST participants in both the CT group and the control group completed Part-I.[17] The higher the scale score, the more negative the psychosocial consequences.[17]

Part-II measures the long-term psychosocial consequences after lung-cancer CT screening and can therefore only be completed by the screening participants (CT group) after they have received their final diagnosis.[17]

Part-II encompasses 24 items (six scales) and was designed and validated to measure changes, both positive and negative; high scores denote more change (appendix 2).

Statistical analysis

The differences in the characteristics of the four groups of participants (true-negative, true-positive, false-positive and control) were tested with Pearson χ^2 tests for categorical variables and Kruskal-Wallis non-parametric tests for continuous variables.

For each of the 15 COS-LC scales, the mean score for each of the four participant groups at the five time points was analysed with linear regression models, both unadjusted and adjusted for the

participant characteristics: round, sex, (a quadratic function of) age, region, (a quadratic function of) pack years, smoking status, social group, living alone, employment status, school education and Charlson's comorbidity index. Generalised estimating equations were used to account for repeated measurement. To adjust for differential dropout, the non-missing scales at each time point were weighted by the inverse of the probability of this scale being observed at that time.[24] These probabilities were estimated from the data in logistic regression models for the scale being missing, which included the participant characteristics, the participant groups, and the corresponding scale outcomes from previous time points.

The statistical level of significance was set using the method of Benjamini-Hochberg to adjust for multiple testing.[25] Statistical Analysis Software (SAS) 9.3 was used to analyse the data.

Participant and public involvement

DLCST participants were involved in the development of the questionnaire COS-LC. Neither participants nor the Danish general public were involved in the design and recruitment of the study.

Results

Participation

Distribution of final diagnostic results and participation rates are presented in figure 1. In rounds 2–5, 193 participants received a positive screening result; of those, 130 (67%) completed the COS-LC and were included in this study. The reasons for non-response were: 1) never receiving the COS-LC because the participant contact details were not available to the researchers (n=39, 20%), 2) declining to complete the COS-LC (n=6, 3%); and 3) other reasons (n=18, 9%).

Of the 130 respondents included in the study, 24 (19%) had received one false-positive result in the previous rounds and one (0.8%) had previously received two false-positive results. The COS-LC

was sent to 252 participants with true-negative results and 248 control participants. Response rates for the four groups during the five time points were 64–97% (figure 1).

There was a significant difference between the four groups regarding age and smoking history: the participants in the true-positive group were older and had a longer smoking history (table 1). A significant difference was also observed in the region of residence, where false positives, to a greater extent, lived outside the capital region compared with the other groups. No significant differences were found in the remaining participant characteristics.

Table 1

Characteristics of Participants

		CT group n = 382			Control group n = 248		
	Total *n = 630*	True-negative *n = 252*	False-positive *n = 91*	True-positive *n = 39*	*n = 248*	p-value*	missing
Round, *n (%)*						0.543	0
2	158 (25.1)	68 (27.0)	26 (28.6)	9 (23.1)	55 (22.2)		
3	196 (31.1)	76 (30.2)	24 (26.4)	14 (35.9)	82 (33.1)		
4	76 (12.1)	31 (12.3)	10 (11.0)	8 (20.5)	27 (10.9)		
5	200 (31.8)	77 (30.6)	31 (34.1)	8 (20.5)	84 (33.9)		
Sex, *n (%)*						0.174	0
Men	298 (47.3)	118 (46.8)	37 (40.7)	24 (61.5)	119 (48.0)		
Women	332 (52.7)	134 (53.2)	54 (59.3)	15 (38.5)	129 (52.0)		
Age (years), *median (IQR)*	58 (55-62)	58 (55-62)	58 (54-61)	60 (58-65)	59 (55-62)	0.017	0
Social Group, *n (%)*						0.334	1
I	42 (6.7)	23 (9.2)	3 (3.3)	1 (2.6)	15 (6.1)		
II	132 (21.0)	51 (20.3)	13 (14.3)	9 (23.1)	59 (23.8)		
III	126 (30.0)	53 (21.1)	15 (16.5)	6 (15.4)	52 (21.0)		
IV	158 (25.1)	57 (22.7)	28 (30.8)	13 (33.3)	60 (24.2)		
V	81 (12.9)	29 (11.6)	13 (14.3)	6 (15.4)	33 (13.3)		
Employed, social group uncertain	54 (8.6)	21 (8.4)	12 (13.2)	1 (2.6)	20 (8.1)		
Outside the labour market	36 (5.7)	17 (6.8)	7 (7.7)	3 (7.7)	9 (3.6)		
School education, *n (%)*						0.321	0
7-9 years in school	242 (38.4)	88 (34.9)	45 (49.5)	16 (41.0)	93 (37.5)		
10 years in school	229 (36.4)	99 (39.3)	27 (29.7)	15 (38.5)	88 (35.5)		
11-13 years in school	159 (25.2)	65 (25.8)	19 (20.9)	8 (20.5)	67 (27.0)		
Employment status, *n (%)*						0.219	1
Employed	374 (59.5)	158 (62.7)	48 (52.8)	18 (47.4)	150 (60.5)		

Studying	2 (0.3)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.4)		
Job seeking	35 (5.6)	17 (6.8)	7 (7.7)	3 (7.9)	8 (3.2)		
Retired	218 (34.7)	77 (30.6)	35 (38.5)	17 (44.7)	89 (35.9)		
Region of residence, *n (%)*						0.043	1
Capital Region	522 (83.0)	310 (83.3)	70 (76.9)	32 (82.1)	210 (85.0)		
Region Zealand	98 (15.6)	34 (13.5)	20 (22.0)	7 (18.0)	37 (15.0)		
Region of Southern Denmark	9 (1.4)	8 (3.2)	1 (1.1)	0 (0.0)	0 (0.0)		
Living alone, *n (%)*						0.147	4
No	430 (68.7)	175 (69.7)	54 (59.3)	25 (64.1)	176 (71.8)		
Yes	196 (31.3)	76 (30.3)	37 (40.7)	14 (35.9)	69 (28.2)		
Smoking status, *n (%)*						0.195	0
Current smoker	473 (75.1)	183 (72.6)	72 (79.1)	34 (87.2)	184 (74.2)		
Former smoker	157 (24.9)	69 (27.4)	19 (20.9)	5 (12.8)	64 (25.8)		
Smoking history (pack years), *median (IQR)*	34 (27-43)	34 (27-43)	34 (27-43)	43 (34-49)	33 (26-42)	0.001	1
Charlson comorbidity index, *n (%)*						0.913	0
0	590 (93.7)	235 (93.3)	83 (91.2)	36 (92.3)	236 (95.2)		
1	25 (4.0)	10 (4.0)	5 (5.5)	2 (5.1)	8 (3.2)		
≥2	15 (2.4)	7 (2.8)	3 (3.3)	1 (2.6)	4 (1.6)		

*p-value of a Pearson chi-squared test (categorical variables) or a Kruskal-Wallis test (continuous variables); p-values are estimates of the exact p-values based on 10,000 Monte Carlo simulations under the null-hypothesis; CT=computed tomography; IQR=interquartile range.

The 15 COS-LC scales exhibited overall adequate fit to the partial credit Rasch model for polytomous items. No DIF was revealed and Cronbach's Alpha was 0.693–0.962 (table 2).

Table 2

Conditional likelihood ratio (CLR) fit statistics and Cronbach's alpha for the 15 domains of the Consequences of Screening in Lung Cancer (COS-LC) questionnaire

Scales (no. of items)	CLR	Degrees of freedom	p*	Cronbach's Alpha
Anxiety (7)	23.0	20	0.286	0.903
Behaviour (7)	19.0	20	0.520	0.893
Dejection (6)	14.9	17	0.603	0.916
Negative impact on sleep (4)	22.3	11	0.022	0.874
Selfblame (5)	20.2	14	0.124	0.962
Focus on airway symptoms (2)	1.0	5	0.966	0.802
Stigmatisation (4)	24.6	11	0.010	0.916
Introvert (4)	11.2	11	0.425	0.851
Harm of smoking (2)	9.8	5	0.082	0.857
Existential values (6)	9.3	11	0.591	0.851
Calm/relaxed (2)	0.6	3	0.887	0.693
Social network (3)	5.5	5	0.362	0.754
Impulsivity (6)	4.5	11	0.954	0.854
Empathy (3)	5.9	5	0.314	0.699
Regretful about still smoking (4)	1.0	7	0.795	0.863

*After adjustment for multiple testing by using the methods of Benjamini-Hochberg the level of statistical significance was assessed at 0.0033.

COS-LC Part-I

Figure 2 presents the mean score of the nine outcomes for COS-LC Part-I for the four groups at the five time points. For Part-I in general, participants with a positive CT screening result reported more negative psychosocial consequences at the short-term follow-up points of one week and one

month (figure 2). The false-positive group experienced significantly more negative psychosocial consequences at one week in seven outcomes (Anxiety, Behaviour, Dejection, Self-blame, Focus on airway symptoms, Introvert, and Harm of smoking) and at one month in three outcomes (Self-blame, Focus on airway symptoms, and Harm of smoking) (mean Δ score > 0 and $p<.001$) compared with both the control group and the true-negative group (figure 2, appendix 3). At six and 18 months, there was a trend towards more negative psychosocial consequences in three outcomes, but no statistically significant differences were found. The true-positive group showed the same general pattern and experienced significantly more negative psychosocial consequences only in the outcome Dejection at one week (mean Δ score 2.86 (95% CI 1.01 to 4.70) $p=0.0024$) and in the three outcomes Behaviour, Dejection, and Focus on airway symptoms at one month (mean Δ score > 0 and $p<.004$) compared with the true-negative group and the control group (figure 2, appendix 3). At baseline, the true-positive group showed a significantly more positive psychosocial profile in the outcomes Anxiety and Self-blame.

COS-LC Part-II

Figure 3 presents the mean scores of the six outcomes for COS-LC Part-II for the three groups at the three follow-up points after receiving the final screening result. The false-positive group showed a trend towards more negative psychosocial consequences in two outcomes at one month compared with the true-negative group, but no significant differences were seen. The true-positive group showed significant differences in the outcome Social network at one month and six months and in the outcome Empathy at one month (figure 3, appendix 3). Trends towards more negative psychosocial consequences were seen in five outcomes at one month compared with the true-negative group. This difference diminished at six and 18 months. The true-negative group showed no variation in psychosocial consequences through the three longer-term follow-up points.

Discussion

False-positive lung-cancer CT screening results were associated with negative short-term psychosocial consequences compared with the control group and the true-negative group. There were no identified long-term consequences of false-positive results. Contrary to expectation, neither were there any long-term consequences experienced by the true-positive group.

The tendency towards more negative long-term psychosocial consequences in the false-positive group, was limited to three lung-cancer-specific scales in Part-I of COS-LC. The same pattern was seen for the true-positive group. Additionally, this group reported more negative psychosocial consequences in the scales Social Network and Empathy in Part-II of COS-LC (figure 3). Smoking causes approximately 90% of all lung cancers and on a societal level smokers are often blamed for their lung cancer, which can lead to feelings of self-blame and guilt.[26] This could explain the tendency towards long-term negative psychosocial consequences in the lung-cancer-specific scales: Self-blame, Focus on Airway Symptoms, and Harm of Smoking in Part-I. In contrast, no negative long-term consequences were seen in the remaining six scales in Part-I. There might be several explanations for our findings: 1) the true-positive group had a more positive psychosocial profile at baseline than the other groups. Hence, no long-term differences compared with the control group were seen, when the short-term negative psychosocial consequences diminished with time towards the more positive set point. 2) Selection bias was identified among DLCST participants, who were better educated and with a more positive psychosocial profile compared with a matched background population.[27] Thus, DLCST participants were probably more psychosocially robust than average

and therefore false-positive or true-positive findings might have had fewer negative consequences than could be expected for the general population.

3) Those diagnosed with lung cancer via screening and who remained alive and asymptomatic after 18 months were convinced, they had been cured of a lethal disease. This reassurance is likely since lung cancer symptom lead time is longer than 18 months and a minimum of 20% of screening detected lung cancers are overdiagnosed.[28] If those diagnosed with lung cancer via screening do not experience any substantial long-term negative psychosocial consequences, it is not expected that the experiences of other screening groups will differ. 4) Another explanation for the long-term results could be the fact that the control group experienced more negative psychosocial consequences than the CT group through screening rounds 2-5 in DLCST.[29] The level of psychosocial consequences in the control group was therefore more negative (higher COS-LC scores) which decreases the difference between the control group and the positive CT screening groups. 5) During the development of the COS-LC, the qualitative interviews were conducted 0–5 months after screening; therefore, Part-II of the COS-LC might not capture all relevant long-term psychosocial consequences for those with false-positive findings. 6) Approximately 20% of the participants who received a positive screening result had previously received a false-positive result. Participants might therefore become accustomed to receiving a (false-) positive screening result, which could decrease the level of negative psychosocial consequences. In contrast, the COS-LC was developed in the first round and a first-round effect, which most likely would have had a more negative psychosocial impact on the participants, was not seen. 7) Contamination of the control group could have biased our results; nevertheless, contamination of the DLCST was found to be minor.[30] Finally, 8) participants with false-positive results could have received a negative screening result between the six and the 18-month assessments, which could be perceived as reassurance, consequently lowering the negative psychosocial consequences.

This is the first study to present both short and long-term psychosocial consequences of false-positive results using a lung-cancer-specific questionnaire with high content validity and adequate psychometric properties developed in a randomised, controlled lung cancer CT screening trial. Therefore, the COS-LC most likely presents stronger results compared with generic questionnaires. The true-positive group was included in this study and when both the true-positive- and the true-negative groups are included, the extent of the psychosocial harm in the false-positive group can be compared with the extent of harm in those who should be worst off (true positives) and those who are reassured (true negatives). No significant differences were shown, however, in the long-term psychosocial consequences for either the false-positive group or the true-positive group compared with the control group.

Other quantitative studies have investigated the health-related quality of life (HRQoL) in CT screening using generic questionnaires that have not been validated for lung cancer.[13 18-20] Although one lung cancer-specific questionnaire was used, no information about validation was reported.[18] These studies found that CT screening had only short-term and no long-term negative effects on HRQoL for participants with false-positive results. Our study, using a more accurate and validated survey instrument, has confirmed this. However, the absence of long-term psychosocial consequences in the true-positive group as well suggests that certain long-term consequences may have been overlooked or that the development of a certain resilience or relief (at feeling cured) may play a long-term role.[31]

A study investigating the risk of receiving a prescription on antidepressants or anxiolytics in the CT group (mixed negative and positive results) compared with the control group in DLCST found no differences between these groups.[32] These outcomes measure extremes of psychosocial

consequences, which is a plausible explanation for the negative results. However, another study, that investigated healthcare use and costs in DLCST participants showed higher use of the healthcare system among false positives and true positives compared with the control group in the time period between two screening rounds.[15] This may be associated with an increased attention drawn to the risk of not being healthy subsequent to receiving a false-positive result. A meta-analysis of the psychosocial consequences of false-positive mammograms including both generic and condition-specific outcome measures showed both short-term and long-term (up to three years) negative psychosocial consequences compared with true-negative mammograms.[12 33] This study recommends the use and further development of condition-specific measures instead of generic measures in mammography screening. Condition-specific measures should also be improved and used in lung cancer CT-screening to obtain the most valid results for psychosocial outcomes.

In interpreting the effect size of the results, we used the mean increase of 2.16 in Selfblame in the false-positive group at the one-month time point compared with the control group (appendix 3). This increase corresponds to two shifts in the response category of one item for all participants with false-positive results, e.g. from “not at all” to “quite a bit”, while all the participants in the control group had no shift in response category. The false-positive rates differ substantially in the NLST (23%) and the DLCST (3%), which has been discussed in detail previously[15]. The negative consequences may seem small or transient but in a mass screening programme targeting a large population, a small change in the frequency with which they appear, may be a large increase in the number of presumably healthy people affected by these consequences. The knowledge of psychosocial consequences from false-positive results contributes to the evidence for the benefits and harms of lung-cancer CT screening and should be included in the overall assessment of the European trials.

Conclusion: In the Danish Lung Cancer Screening Trial, false-positive results were associated with more negative short-term psychosocial consequences compared with the control group and the true-negative group.

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Contribution

The study was devised and designed by JB. Data collection was conducted by JB. Statistical analyses were done by JFR and VS. JFR drafted the manuscript and JB, VS and JM contributed to parts of the manuscript and to revisions of the manuscript. All four authors have approved the final version of the manuscript. All authors had full access to all of the data in the study (including statistical reports and tables) and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Availability of data and materials

The corresponding author can provide the questionnaires and datasets generated and analysed during the study on reasonable request.

Figure 1 Distribution of screening results and final diagnoses in the DLCST, and response rates of the matched groups at five time points: baseline, one week, one, six, and 18 months

Figure 2 The mean score of the nine psychosocial outcomes of COS-LC Part-I for the diagnostic groups and the control group in the DLCST at five time points: Baseline, one week, one, six, and 18 months

Figure 3 The mean score of the six psychosocial outcomes of COS-LC Part-II for the diagnostic groups in the DLCST at three time points: one, six and 18 months

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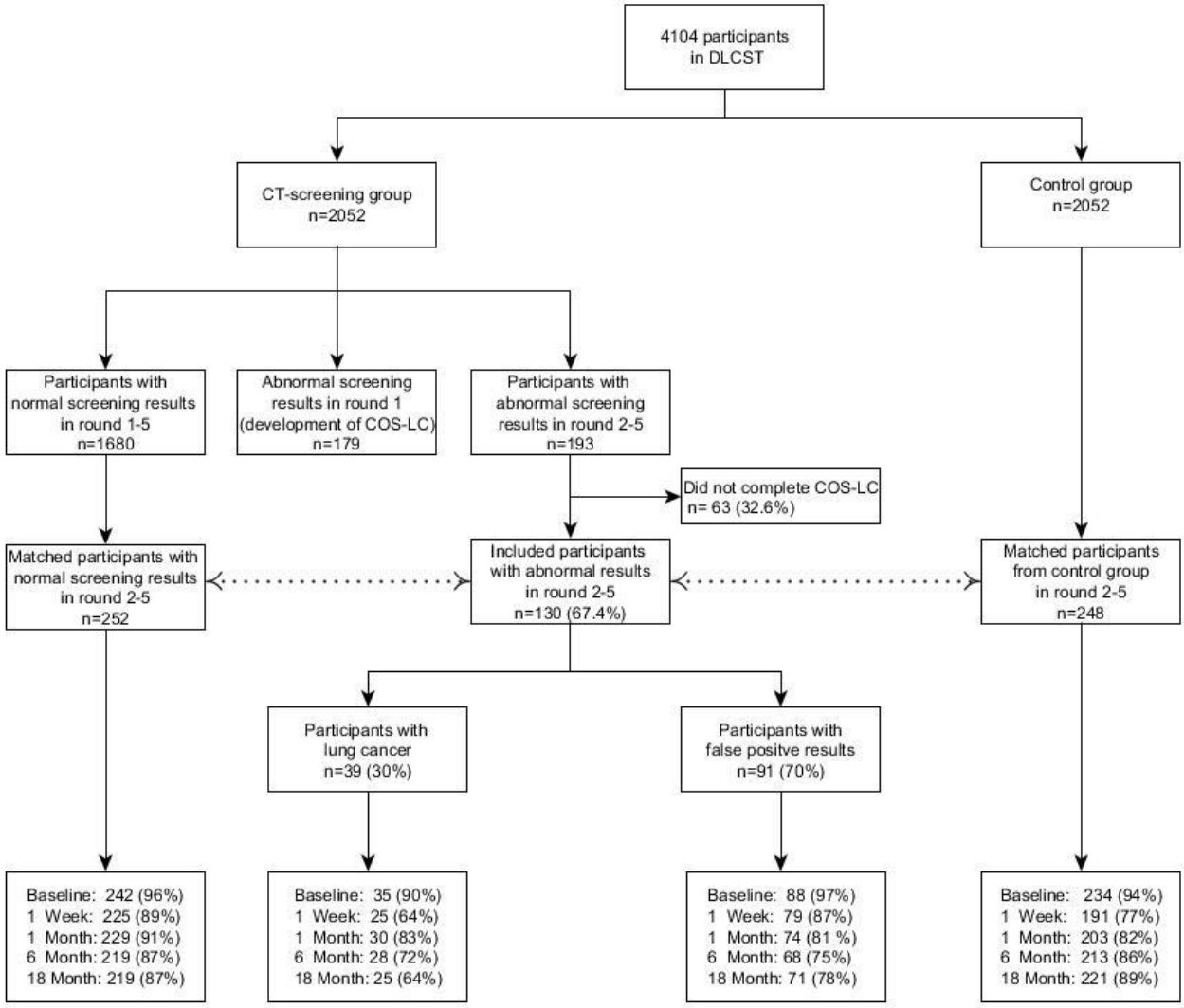
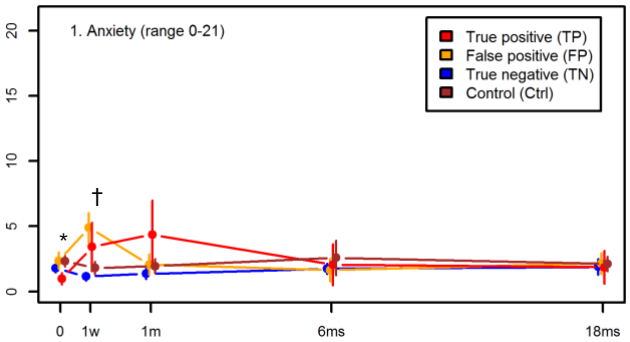
Figure 1, Distribution of screening results and final diagnoses in the DLCST, and response rates of the matched groups at five time points: baseline, 1 week, 1,6 and 18 months



DLCST=Danish lung cancer screening trial; CT=Computed Tomography; COS-LC=Consequences of screening-lung cancer.

Figure 2



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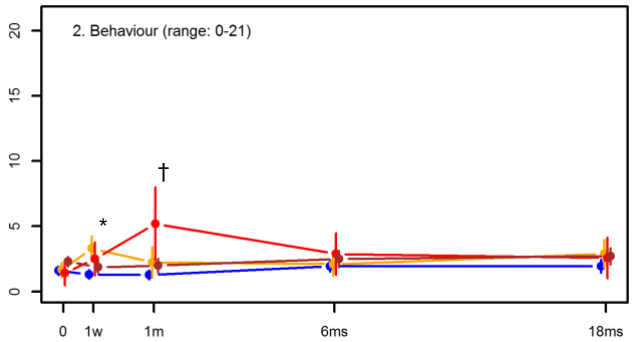

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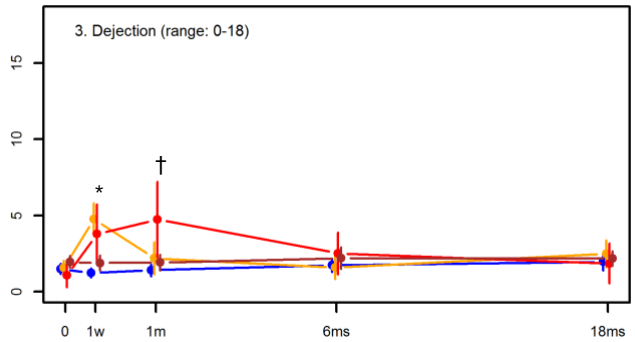

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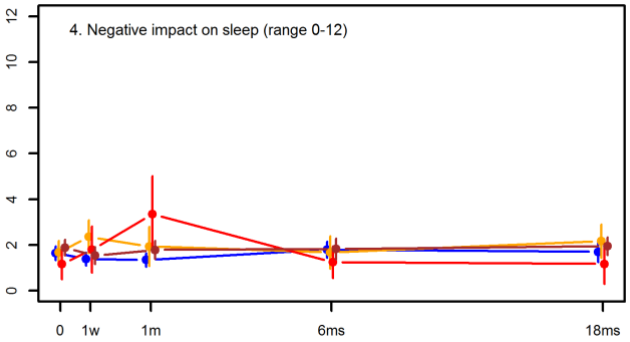

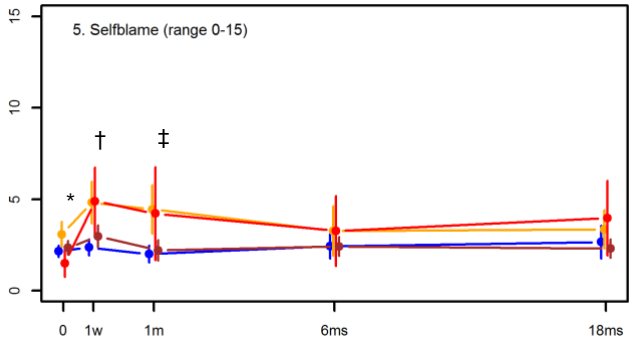

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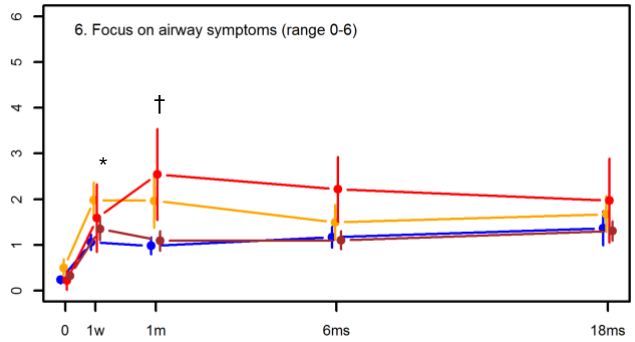

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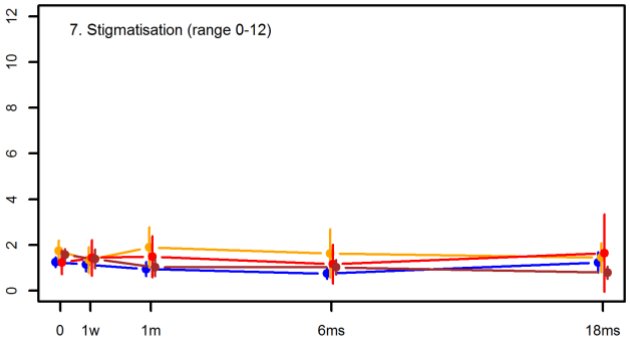

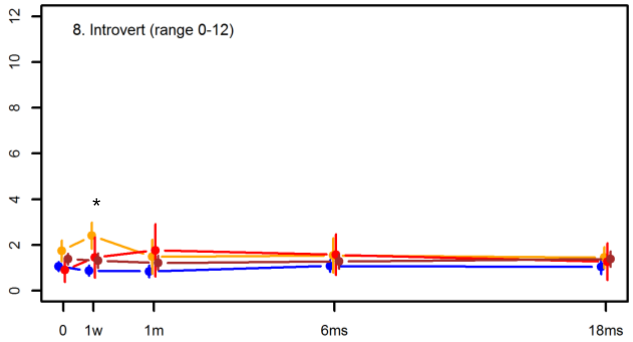

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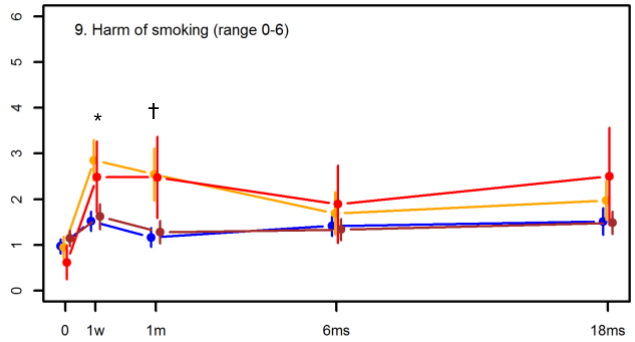

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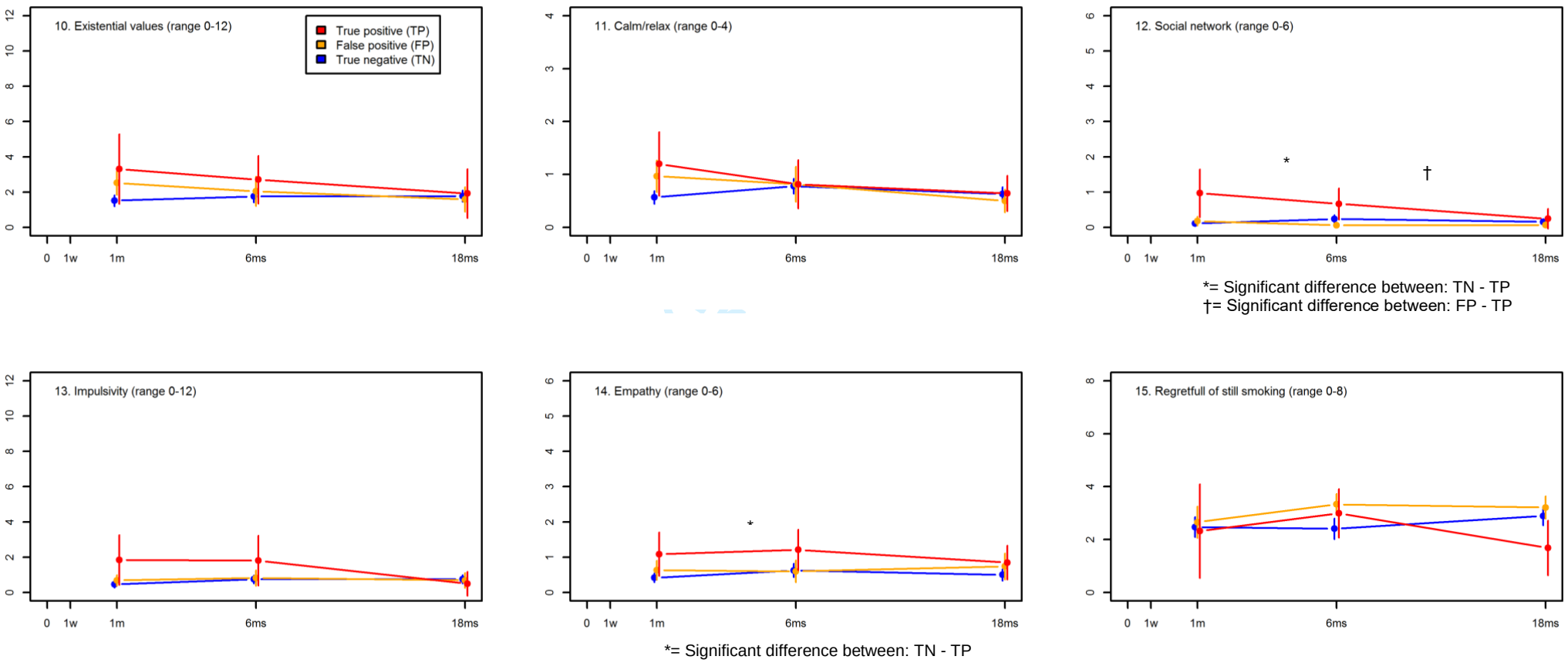
Figure 2: The mean estimates are compared between all groups at each time point and significant differences between the groups are described below each scale (see appendix 1 for details of the adjusted analyses). After adjustment for multiple testing by using the methods of Benjamini-Hochberg the level of statistical significance was assessed at 0.0043; 0=baseline; 1W=1 week after screening; 1m, 6ms and 18 ms=1,6 and 18 months after final diagnostic result; TP=true-positive group; FP=false-positive group; TN=true-negative group; Ctrl=control group; COS-LC=Consequences of screening–lung cancer; The higher the score the more negative psychosocial reaction.

Figure 3



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Appendix 1

False-positive rates in the National Lung Screening Trial (NLST) and the Danish Lung Cancer Screening Trial (DLCST)

Trial	Study threshold of an abnormal non-calcified lung nodule (screening test positive)*	Round of screening	Number screened	Abnormal lung nodules over study threshold (screening test positive)	Lung cancer nodules (true positives)	Nodules not lung cancer (false positives)	False-positive rate (nodules not lung cancer / no. screened)	Average false-positive rate
NLST	≥4 mm	Baseline	26 309	7191	270	6921	0.2631	
		Year 1	24 715	6901	168	6733	0.2724	
		Year 2	24 102	4054	211	3843	0.1594	
Total			*75 126*			*17 497*		*0.2329*
DLCST	≥5 mm	Baseline	2047	179	17	162	0.0791	
		Year 1	1976	45	11	34	0.0172	
		Year 2	1944	52	13	39	0.0201	
		Year 3	1982	44	12	32	0.0161	
		Year 4	1851	51	16	35	0.0189	
Total			*9800*			*302*		*0.0308*

*In the DLCST, a CT-screening test result was categorised as abnormal (screening test positive) if a non-calcified lung nodule was ≥5 mm which lead to diagnostic evaluation. The test result was categorised as normal (screening test negative) if the nodule was < 5 mm. In the DLCST non-benign nodules between 5-15 mm found on a CT-screening scan lead to a three months follow-up scan. Nodules > 15 mm were referred to diagnostic work-up. In the NLST non-calcified lung nodules of at least 4 mm found on a CT-screening scan were classified as abnormal screening results (screening test positive) and nodules < 4 mm were classified as normal screening results (screening test negative).

Appendix 2

List of items included in the 15 scales of the questionnaire Consequences of Screening – Lung Cancer (COS-LC)

	Scales	Items
Part I	**1. Anxiety**	Worried about my future
		Nervous
		Scared
		Restless
		Shocked
		Upset
		Terrified
	2. Behaviour	Difficulty doing things around the house
		Difficulty dealing with work or other commitments
		Quieter than normal
		Hard to concentrate
		Withdrawn into myself
		Change in appetite
		Irritable
	3. Dejection	Worried
		Uneasy
		Sad
		Depressed
		Time passed slowly
		Unable to cope
	4. Negative impact on sleep	Woken up far too early in the morning
		Slept badly
		Taken long time to fall a sleep
		Been awake most of the night
	5. Selfblame	Felt guilty
		Blamed oneself
		Been annoyed with oneself
		Disappointed in oneself
		Angry with oneself
	6. Focus on airways symptoms	Aware of being short of breath
		Been aware of one's coughing
	7. Stigmatisation	Felt stigmatised

		Being told off by other people
		A finger wagging from others
		Blamed by other people
	8. Introvert	Insecure
		Mood Swings
		Thought one´s situation hopeless
		Sorry for oneself
	9. Harm of smoking	Thought of smoking as harmful
		Sorry for having smoked for many years
Part II	**10. Existential Values**	Broader aspects of life
		Value of life
		Enjoyment of life
		Awareness of life
		Thought about future
		Well-being
	11. Calm/Relax	Relaxed
		Calm
	12. Social Network	Family
		Friends
		Other people
	13. Impulsivity	Energy
		Lived life to the full
		Being impulsive
		Desire to venture into something risky
		Desire to venture into something new
		Done some things that overstepped one´s bounds
	14. Empathy	Understands other people´s problems
		Responsibility for one's family
		Ability to listen to other people's problems
	15. Regretful of still smoking	Thought about quitting smoking
		Disappointed in oneself for smoking
		Annoyed with oneself for smoking
		Having second thoughts about one´s smoking

Appendix 3

Adjusted analyses of the 15 scales in the questionnaire Consequences of Screening – Lung Cancer (COS-LC):

Mean differences between each pair of the diagnostic groups and the control group during five time points

		Follow up time									
		Baseline		1 week		1 Month		6 Month		18 Month	
Scale (Range)	Comparison	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value
1. Anxiety	Con-Neg	-0.46 (-0.99 to 0.07)	0.0864	-0.63 (-1.20 to -0.06)	0.0317	-0.66 (-1.40 to 0.07)	0.0768	-0.58 (-1.35 to 0.19)	0.1375	-0.36 (-1.13 to 0.40)	0.3519
(0-21)	Con-FP	-0.02 (-0.78 to 0.74)	0.9582	2.77 (1.63 to 3.92)	<.0001	-0.25 (-1.25 to 0.75)	0.6249	-1.20 (-2.43 to 0.04)	0.0578	-0.26 (-1.16 to 0.65)	0.5821
	Con-TP	-1.52 (-2.18 to -0.86)	<.0001	1.89 (0.01 to 3.78)	0.0487	2.72 (0.08 to 5.37)	0.0438	-0.54 (-2.30 to 1.21)	0.5426	-0.69 (-2.41 to 1.04)	0.4360
	Neg-FP	0.44 (-0.27 to 1.16)	0.2257	3.40 (2.33 to 4.48)	<.0001	0.41 (-0.48 to 1.31)	0.3649	-0.62 (-1.64 to 0.41)	0.2390	0.11 (-0.75 to 0.97)	0.8047
	Neg-TP	-1.06 (-1.68 to -0.43)	0.0010	2.52 (0.71 to 4.33)	0.0063	3.38 (0.77 to 6.00)	0.0112	0.04 (-1.66 to 1.74)	0.9666	-0.32 (-1.98 to 1.34)	0.7036
	FP-TP	-1.50 (-2.29 to -0.71)	0.0002	-0.88 (-2.95 to 1.19)	0.4043	2.97 (0.14 to 5.81)	0.0400	0.65 (-1.25 to 2.55)	0.5012	-0.43 (-2.20 to 1.34)	0.6342
No. Respondents		607		514		444		509		518	
2. Behaviour	Con-Neg	-0.74 (-1.26 to -0.23)	0.0046	-0.58 (-1.15 to -0.01)	0.0469	-0.74 (-1.41 to -0.08)	0.0284	-0.51 (-1.27 to 0.24)	0.1838	-1.00 (-1.80 to -0.20)	0.0144
(0-21)	Con-FP	-0.75 (-1.50 to 0.01)	0.0520	1.21 (0.19 to 2.23)	0.0198	-0.09 (-1.34 to 1.16)	0.8843	-0.60 (-1.72 to 0.51)	0.2873	-0.07 (-1.30 to 1.17)	0.9143
	Con-TP	-1.05 (-2.16 to 0.06)	0.0632	0.65 (-0.65 to 1.94)	0.3260	3.31 (0.50 to 6.11)	0.0209	0.03 (-1.66 to 1.73)	0.9698	-0.81 (-2.66 to 1.05)	0.3948
	Neg-FP	0.00 (-0.70 to 0.70)	0.9953	1.79 (0.84 to 2.74)	0.0002	0.65 (-0.46 to 1.76)	0.2522	-0.09 (-1.09 to 0.90)	0.8551	0.93 (-0.21 to 2.07)	0.1106
	Neg-TP	-0.31 (-1.39 to 0.78)	0.5793	1.23 (-0.02 to 2.47)	0.0544	4.05 (1.27 to 6.83)	0.0043	0.54 (-1.13 to 2.22)	0.5236	0.19 (-1.61 to 2.00)	0.8340
	FP-TP	-0.30 (-1.48 to 0.87)	0.6117	-0.56 (-2.06 to 0.94)	0.4636	3.40 (0.38 to 6.42)	0.0275	0.64 (-1.22 to 2.49)	0.5005	-0.74 (-2.80 to 1.32)	0.4834
No. Respondents		611		518		438		507		517	
3. Dejection	Con-Neg	-0.41 (-0.92 to 0.10)	0.1142	-0.66 (-1.25 to -0.07)	0.0291	-0.55 (-1.24 to 0.13)	0.1113	-0.36 (-1.07 to 0.35)	0.3231	-0.35 (-1.04 to 0.34)	0.3216
(0-18)	Con-FP	-0.41 (-1.04 to 0.22)	0.2017	2.63 (1.53 to 3.74)	<.0001	-0.09 (-1.21 to 1.04)	0.8815	-1.04 (-2.07 to 0.00)	0.0492	-0.01 (-1.04 to 1.03)	0.9903
	Con-TP	-0.89 (-1.81 to 0.02)	0.0562	2.20 (0.28 to 4.12)	0.0245	2.92 (0.57 to 5.27)	0.0147	0.16 (-1.32 to 1.64)	0.8308	-0.74 (-2.37 to 0.89)	0.3726
	Neg-FP	0.00 (-0.62 to 0.62)	0.9981	3.29 (2.27 to 4.31)	<.0001	0.47 (-0.55 to 1.49)	0.3695	-0.68 (-1.59 to 0.23)	0.1438	0.34 (-0.64 to 1.32)	0.4928
	Neg-TP	-0.48 (-1.39 to 0.43)	0.2974	2.86 (1.01 to 4.70)	0.0024	3.48 (1.15 to 5.80)	0.0034	0.52 (-0.94 to 1.98)	0.4857	-0.39 (-2.04 to 1.25)	0.6397
	FP-TP	-0.48 (-1.44 to 0.47)	0.3217	-0.43 (-2.49 to 1.63)	0.6812	3.01 (0.44 to 5.58)	0.0219	1.20 (-0.38 to 2.77)	0.1365	-0.74 (-2.55 to 1.08)	0.4270
No. Respondents		606		521		449		518		526	
4. Negative impact on sleep	Con-Neg	-0.16 (-0.62 to 0.31)	0.5047	-0.16 (-0.65 to 0.33)	0.5191	-0.38 (-0.90 to 0.14)	0.1549	-0.06 (-0.60 to 0.48)	0.8321	-0.29 (-0.82 to 0.24)	0.2786
(0-12)	Con-FP	-0.26 (-0.89 to 0.37)	0.4235	0.65 (-0.14 to 1.44)	0.1056	-0.10 (-1.01 to 0.81)	0.8308	-0.32 (-1.20 to 0.56)	0.4770	0.11 (-0.68 to 0.90)	0.7909
	Con-TP	-0.71 (-1.50 to 0.08)	0.0770	0.47 (-0.61 to 1.54)	0.3928	1.94 (0.33 to 3.55)	0.0182	-0.53 (-1.36 to 0.30)	0.2116	-0.90 (-1.96 to 0.15)	0.0938
	Neg-FP	-0.10 (-0.71 to 0.51)	0.7458	0.81 (0.07 to 1.55)	0.0314	0.28 (-0.56 to 1.12)	0.5130	-0.26 (-1.07 to 0.54)	0.5242	0.40 (-0.37 to 1.17)	0.3127
	Neg-TP	-0.55 (-1.32 to 0.21)	0.1572	0.63 (-0.40 to 1.66)	0.2303	2.32 (0.71 to 3.93)	0.0047	-0.47 (-1.24 to 0.31)	0.2356	-0.61 (-1.65 to 0.42)	0.2452
	FP-TP	-0.45 (-1.32 to 0.42)	0.3057	-0.18 (-1.38 to 1.02)	0.7662	2.04 (0.24 to 3.83)	0.0260	-0.21 (-1.25 to 0.84)	0.6968	-1.01 (-2.19 to 0.17)	0.0938
No. Respondents		612		515		444		515		524	

		Follow up time									
		Baseline		1 week		1 Month		6 Month		18 Month	
Scale (Range)	Comparison	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value
5. Selfblame	Con-Neg	-0.14 (-0.61 to 0.32)	0.5511	-0.52 (-1.25 to 0.20)	0.1589	-0.21 (-0.94 to 0.51)	0.5644	-0.13 (-0.90 to 0.64)	0.7424	0.26 (-0.63 to 1.16)	0.5642
(0-15)	Con-FP	0.54 (-0.19 to 1.27)	0.1461	1.58 (0.32 to 2.83)	0.0136	2.16 (0.84 to 3.48)	0.0013	0.23 (-0.98 to 1.43)	0.7132	0.74 (-0.34 to 1.83)	0.1787
	Con-TP	-1.15 (-1.91 to -0.39)	0.0030	1.89 (0.09 to 3.70)	0.0401	1.51 (-0.23 to 3.25)	0.0895	0.31 (-1.56 to 2.18)	0.7476	1.45 (-0.74 to 3.64)	0.1930
	Neg-FP	0.68 (-0.02 to 1.38)	0.0557	2.10 (0.91 to 3.29)	0.0005	2.38 (1.05 to 3.70)	0.0004	0.36 (-0.92 to 1.63)	0.5844	0.48 (-0.67 to 1.64)	0.4145
	Neg-TP	-1.01 (-1.74 to -0.28)	0.0069	2.41 (0.67 to 4.16)	0.0067	1.72 (0.00 to 3.45)	0.0501	0.44 (-1.47 to 2.34)	0.6534	1.19 (-1.04 to 3.42)	0.2957
	FP-TP	-1.69 (-2.59 to -0.80)	0.0002	0.32 (-1.70 to 2.34)	0.7590	-0.65 (-2.66 to 1.36)	0.5249	0.08 (-2.07 to 2.23)	0.9411	0.71 (-1.65 to 3.07)	0.5559
No. Respondents		606		507		445		517		525	
6. Focus on airway symptoms	Con-Neg	-0.07 (-0.19 to 0.05)	0.2702	-0.23 (-0.51 to 0.04)	0.0948	-0.16 (-0.45 to 0.13)	0.2807	0.00 (-0.30 to 0.30)	0.9937	-0.09 (-0.39 to 0.22)	0.5773
(0-6)	Con-FP	0.19 (-0.02 to 0.39)	0.0819	0.57 (0.13 to 1.02)	0.0112	0.68 (0.13 to 1.24)	0.0160	0.23 (-0.16 to 0.63)	0.2443	0.28 (-0.15 to 0.71)	0.1951
	Con-TP	-0.19 (-0.43 to 0.04)	0.1103	0.21 (-0.51 to 0.93)	0.5650	1.60 (0.64 to 2.55)	0.0011	0.90 (0.21 to 1.58)	0.0100	0.54 (-0.45 to 1.53)	0.2861
	Neg-FP	0.25 (0.05 to 0.46)	0.0149	0.81 (0.39 to 1.22)	<.0001	0.84 (0.29 to 1.39)	0.0026	0.23 (-0.18 to 0.65)	0.2666	0.37 (-0.06 to 0.80)	0.0912
	Neg-TP	-0.12 (-0.36 to 0.11)	0.2992	0.44 (-0.26 to 1.15)	0.2139	1.76 (0.81 to 2.71)	0.0003	0.90 (0.22 to 1.58)	0.0098	0.62 (-0.38 to 1.63)	0.2213
	FP-TP	-0.38 (-0.66 to -0.09)	0.0094	-0.36 (-1.14 to 0.42)	0.3639	0.91 (-0.16 to 1.98)	0.0950	0.66 (-0.06 to 1.39)	0.0733	0.25 (-0.79 to 1.30)	0.6340
No. Respondents		613		516		447		517		527	
7. Stigmatization	Con-Neg	-0.25 (-0.58 to 0.07)	0.1281	-0.22 (-0.71 to 0.28)	0.3872	-0.14 (-0.64 to 0.35)	0.5693	-0.30 (-0.71 to 0.10)	0.1395	0.45 (-0.05 to 0.95)	0.0753
(0-12)	Con-FP	0.12 (-0.39 to 0.63)	0.6387	-0.01 (-0.69 to 0.67)	0.9761	0.82 (-0.10 to 1.73)	0.0803	0.46 (-0.49 to 1.41)	0.3393	0.64 (0.00 to 1.28)	0.0492
	Con-TP	-0.40 (-0.98 to 0.18)	0.1715	-0.37 (-1.25 to 0.51)	0.4066	0.01 (-0.83 to 0.85)	0.9841	-0.35 (-1.30 to 0.60)	0.4697	0.63 (-1.06 to 2.31)	0.4664
	Neg-FP	0.38 (-0.13 to 0.88)	0.1444	0.21 (-0.44 to 0.85)	0.5311	0.96 (0.07 to 1.85)	0.0340	0.76 (-0.17 to 1.70)	0.1082	0.19 (-0.52 to 0.90)	0.5981
	Neg-TP	-0.15 (-0.73 to 0.43)	0.6107	-0.15 (-0.95 to 0.64)	0.7021	0.15 (-0.65 to 0.95)	0.7098	-0.05 (-0.97 to 0.88)	0.9216	0.17 (-1.52 to 1.87)	0.8401
	FP-TP	-0.53 (-1.21 to 0.16)	0.1302	-0.36 (-1.32 to 0.60)	0.4614	-0.81 (-1.93 to 0.31)	0.1576	-0.81 (-2.15 to 0.53)	0.2345	-0.02 (-1.79 to 1.76)	0.9857
No. Respondents		609		505		440		511		522	
8. Introvert	Con-Neg	-0.37 (-0.68 to -0.06)	0.0191	-0.50 (-0.89 to -0.11)	0.0117	-0.42 (-0.85 to 0.01)	0.0527	-0.22 (-0.61 to 0.18)	0.2888	-0.38 (-0.84 to 0.09)	0.1130
(0-12)	Con-FP	0.22 (-0.29 to 0.73)	0.3948	0.84 (0.20 to 1.48)	0.0102	0.02 (-0.72 to 0.76)	0.9601	-0.14 (-0.71 to 0.42)	0.6160	-0.10 (-0.69 to 0.49)	0.7378
	Con-TP	-0.78 (-1.39 to -0.17)	0.0120	0.08 (-0.79 to 0.96)	0.8527	0.63 (-0.5 to 1.77)	0.2754	0.11 (-0.81 to 1.02)	0.8172	-0.31 (-1.35 to 0.72)	0.5535
	Neg-FP	0.59 (0.09 to 1.09)	0.0199	1.34 (0.74 to 1.94)	<.0001	0.44 (-0.31 to 1.20)	0.2496	0.07 (-0.49 to 0.63)	0.8031	0.28 (-0.28 to 0.83)	0.3327
	Neg-TP	-0.41 (-1.01 to 0.19)	0.1834	0.59 (-0.28 to 1.45)	0.1834	1.06 (-0.06 to 2.17)	0.0634	0.32 (-0.60 to 1.24)	0.4922	0.06 (-0.97 to 1.10)	0.9059
	FP-TP	-1.00 (-1.71 to -0.29)	0.0058	-0.76 (-1.75 to 0.23)	0.1335	0.61 (-0.74 to 1.96)	0.3741	0.25 (-0.74 to 1.25)	0.6192	-0.21 (-1.32 to 0.89)	0.7052
No. Respondents		609		508		444		513		524	

		Follow up time									
		Baseline		1 week		1 Month		6 Month		18 Month	
Scale (Range)	Comparison	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value
9. Harm of smoking	Con-Neg	-0.11 (-0.35 to 0.12)	0.3319	-0.07 (-0.39 to 0.26)	0.6823	-0.10 (-0.41 to 0.22)	0.5513	0.03 (-0.29 to 0.35)	0.8669	0.00 (-0.35 to 0.36)	0.9888
(0-6)	Con-FP	-0.25 (-0.55 to 0.05)	0.1057	1.08 (0.61 to 1.56)	<.0001	1.12 (0.56 to 1.67)	<.0001	0.22 (-0.25 to 0.68)	0.3560	0.32 (-0.15 to 0.79)	0.1796
	Con-TP	-0.50 (-0.92 to -0.09)	0.0179	0.75 (-0.05 to 1.55)	0.0651	0.99 (0.14 to 1.84)	0.0225	0.32 (-0.51 to 1.14)	0.4546	0.80 (-0.26 to 1.85)	0.1376
	Neg-FP	-0.13 (-0.43 to 0.16)	0.3730	1.15 (0.70 to 1.60)	<.0001	1.21 (0.66 to 1.76)	<.0001	0.19 (-0.27 to 0.65)	0.4209	0.32 (-0.18 to 0.82)	0.2096
	Neg-TP	-0.39 (-0.81 to 0.03)	0.0665	0.82 (0.04 to 1.59)	0.0382	1.08 (0.25 to 1.92)	0.0106	0.29 (-0.53 to 1.10)	0.4892	0.79 (-0.27 to 1.86)	0.1445
	FP-TP	-0.26 (-0.70 to 0.19)	0.2612	-0.33 (-1.18 to 0.52)	0.4424	-0.13 (-1.07 to 0.82)	0.7922	0.10 (-0.80 to 0.99)	0.8317	0.47 (-0.65 to 1.60)	0.4071
No. Respondents		615		517		450		519		529	
10. Existential values	Neg-FP	NA		NA		0.92 (0.23 to 1.61)	0.0090	0.40 (-0.54 to 1.35)	0.4043	0.11 (-0.48 to 0.70)	0.7075
(0-12)	Neg-TP	NA		NA		2.10 (0.45 to 3.75)	0.0125	1.57 (0.31 to 2.83)	0.0149	0.24 (-1.01 to 1.50)	0.7031
	FP-TP	NA		NA		1.18 (-0.55 to 2.92)	0.1805	1.16 (-0.30 to 2.63)	0.1193	0.13 (-1.14 to 1.40)	0.8385
No. Respondents						262		306		307	
11. Calm/relax	Neg-FP	NA		NA		0.46 (0.13 to 0.78)	0.0054	0.05 (-0.33 to 0.44)	0.7852	-0.03 (-0.26 to 0.21)	0.8222
(0-4)	Neg-TP	NA		NA		0.82 (0.19 to 1.44)	0.0101	0.17 (-0.29 to 0.64)	0.4722	-0.01 (-0.42 to 0.40)	0.9611
	FP-TP	NA		NA		0.36 (-0.30 to 1.03)	0.2882	0.12 (-0.45 to 0.68)	0.6866	0.02 (-0.44 to 0.47)	0.9427
No. Respondents						265		310		308	
12. Social network	Neg-FP	NA		NA		0.05 (-0.09 to 0.19)	0.4732	-0.21 (-0.36 to -0.06)	0.0075	-0.11 (-0.26 to 0.03)	0.1248
(0-6)	Neg-TP	NA		NA		0.92 (0.31 to 1.54)	0.0032	0.45 (0.03 to 0.86)	0.0360	0.08 (-0.23 to 0.39)	0.6139
	FP-TP	NA		NA		0.87 (0.25 to 1.50)	0.0061	0.66 (0.24 to 1.07)	0.0022	0.19 (-0.12 to 0.51)	0.2230
No. Respondents						269		312		309	
13. Impulsivity	Neg-FP	NA		NA		0.15 (-0.20 to 0.51)	0.3963	0.19 (-0.24 to 0.62)	0.3857	-0.06 (-0.54 to 0.41)	0.7908
(0-12)	Neg-TP	NA		NA		1.76 (0.35 to 3.17)	0.0146	1.27 (-0.04 to 2.58)	0.0572	0.10 (-0.71 to 0.90)	0.8172
	FP-TP	NA		NA		1.61 (0.20 to 3.02)	0.0257	1.08 (-0.23 to 2.39)	0.1072	0.16 (-0.75 to 1.07)	0.7311
No. Respondents						265		304		307	
14. Empathy	Neg-FP	NA		NA		0.12 (-0.19 to 0.43)	0.4394	0.02 (-0.32 to 0.35)	0.9219	0.21 (-0.17 to 0.59)	0.2719
(0-6)	Neg-TP	NA		NA		0.79 (0.27 to 1.30)	0.0027	0.71 (0.17 to 1.25)	0.0094	0.29 (-0.36 to 0.94)	0.3819
	FP-TP	NA		NA		0.66 (0.11 to 1.22)	0.0191	0.69 (0.12 to 1.27)	0.0182	0.08 (-0.63 to 0.78)	0.8313
No. Respondents						266		306		308	

15. Regretful of still smoking	Neg-FP	NA	NA	0.28 (-0.48 to 1.04)	0.4676	0.59 (0.00 to 1.18)	0.0500	0.06 (-0.54 to 0.65)	0.8475
(0-8)	Neg-TP	NA	NA	0.12 (-1.17 to 1.40)	0.8575	0.74 (-0.12 to 1.59)	0.0903	-0.83 (-1.75 to 0.08)	0.0742
	FP-TP	NA	NA	-0.16 (-1.66 to 1.33)	0.8301	0.15 (-0.82 to 1.12)	0.7673	-0.89 (-1.85 to 0.07)	0.0681
No. Respondents				137		148		150	

Mean Δ = The mean difference of the outcome between the compared groups adjusted for possible confounders; The mean differences of the scales listed in the table are the differences beyond the differences that may be present at baseline (scale 1-9) or at 1 Month (scale 10-15); CI = confidence interval; p value = the statistical significant level was assessed to 0.0043 after adjusting for multiple testing with the method of Benjamini-Hochberg and significant differences between the groups are marked with yellow(1); Con = Control group; Neg = True-negative group; FP = false-positive group; TP = true-positive group; NA = Not applicable.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4 and 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4 and 5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	4 and 5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5 and 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 and 6
Bias	9	Describe any efforts to address potential sources of bias	5 and 8
Study size	10	Explain how the study size was arrived at	4, 5 and Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-10
		(*b*) Describe any methods used to examine subgroups and interactions	6 and 7
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-6
		(b) Give reasons for non-participation at each stage	5

		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Appendix Table 1
		(c) Summarise follow-up time (eg, average and total amount)	Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Figure 2a, 2b and Appendix Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figure 2a, 2b and Appendix Table 1 5-6
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6 and 7
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Psychosocial consequences of false positives in the Danish lung cancer CT-screening trial: a nested matched cohort study

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Objectives

Lung cancer computed tomography (CT) screening can reduce lung-cancer mortality, but high false-positive rates may cause adverse psychosocial consequences. The aim was to analyse the psychosocial consequences of false-positive lung-cancer CT screening using the lung cancer screening-specific questionnaire, Consequences of Screening in Lung Cancer (COS-LC).

Design and setting

This study was a matched cohort study, nested in the randomised Danish Lung Cancer Screening Trial (DLCST).

Participants

Our study included all 130 participants in the DLCST with positive CT results in screening rounds 2-5, who had completed the COS-LC questionnaire. Participants were split into a true-positive and a false-positive group and were then matched 1:2 with a control group (n=248) on sex, age (+/- three years), and the time of screening for the positive CT groups or clinic visit for the control group. The true-positives and false-positives were also matched 1:2 with participants with negative CT screening results (n=252).

Primary outcomes

Primary outcomes were psychosocial consequences measured at five time points.

Results

False positives experienced significantly more negative psychosocial consequences in seven outcomes at one week and in three outcomes at one month compared with the control group and the true-negative group (mean Δ score > 0 and $p<0.001$). True positives experienced significantly more negative psychosocial consequences in one outcome at one week (mean Δ score 2.86 (95% CI 1.01 to 4.70) $p=0.0024$) and in five outcomes at one month (mean Δ score > 0 and $p<0.004$) compared

with the true-negative group and the control group. No long-term psychosocial consequences were identified either in false positives or true positives.

Conclusions

Receiving a false-positive result in lung cancer screening was associated with negative short-term psychosocial consequences. These findings contribute to the evidence on harms of screening and should be taken into account when considering implementation of lung cancer screening programmes.

Trial registration

The DLCST was approved by the Danish Scientific Ethical Committee (approval number KA-02045). The DLCST was approved by the Danish Data Protection Agency (approval number 2005-53-1083). All participants signed an informed consent form. ClinicalTrials.gov: NCT00496977

Strengths and limitations

- This study used a lung-cancer-screening-specific questionnaire with high content validity and adequate psychometric properties to measure the psychosocial consequences of the screening results
- As well as the false-positive group, the true-positive group and the true-negative group were assessed, serving as benchmarks against which to compare the psychosocial consequences in the false positives.
- A limitation is that the control group, who were not invited to screening, reported more negative psychosocial consequences than the screening group.

- Another limitation is that the study participants had a more robust psychosocial profile compared with a matched background population.

Introduction

Lung cancer has the highest mortality worldwide.[1] Several randomised controlled screening trials using low dose computed tomography (CT) scans have investigated the effect of CT screening on lung cancer-specific mortality.[2] The largest trial, the National Lung Screening Trial (NLST), found a relative lung cancer-specific mortality reduction of 16% after five-year follow-up, and lung cancer CT screening is now recommended in the United States.[3-5] However, according to a Cochrane systematic review, more data are needed on false-positive results and overdiagnosis before recommendations can be made for large-scale CT-screening programmes.[6] The Danish Lung Cancer Screening Trial (DLCST) could not show a reduction in lung-cancer-specific or total mortality after a five-year follow-up.[7] The European trials are expected to publish the pooled follow-up analyses of both the mortality data and the consequences of overdiagnosis and false-positive results.[8] This will provide the additional evidence of benefits and harms of lung cancer CT screening requested in the Cochrane systematic review.[6]

In cancer screening programmes, positive screening results lead to either false-positive results or true-positive results after further diagnostic workup.[9] A false-positive screening result can cause both physical and psychosocial harms [10-13] as well as being costly for the healthcare system.[14 1516] The average false-positive rate per screening round varies substantially in lung cancer screening trials, e.g. 23% in the NLST and 3% in the DLCST (appendix 1).[3 17] Qualitative and quantitative studies have shown that false-positive lung-cancer-screening results can be associated with negative psychosocial consequences both during workup and after the final diagnosis.[13 18 19] By their nature, qualitative studies cannot measure the degree or the extent of psychosocial consequences[18], and all the published quantitative studies used generic questionnaires which lack content validity and have unknown psychometric properties.[13 19-21] Measurement of the psychosocial consequences of

screening using questionnaires with high content validity and adequate psychometric properties is important.[22]

The aim of this study, therefore, was to measure the short and long-term psychosocial consequences of false-positive lung cancer CT screening results using the questionnaire Consequences of Screening in Lung Cancer (COS-LC) and to compare these scores with the COS-LC scores from 3 other groups of participants in the DLCST: 1) the true-negative group, 2) the true-positive group, and 3) a control group that did not participate in screening.

Methods

Study design and participants

The overall design of the DLCST has been reported in detail elsewhere.[17 23] In summary, the DLCST was a single-centre, randomised, controlled trial and participants were randomly allocated to a CT group and a control group (figure 1). Eligible participants were current and former smokers with a smoking history of minimum 20 cigarettes/day for 20 years, and were aged 50–70 years.[17 23] In five rounds between 2004–2010, both groups were offered annual spirometry and smoking counselling and were asked to complete the COS-LC questionnaire. Participants in the CT group were also offered annual lung CT scans.

This study was a matched cohort study nested in the DLCST. Participants from the CT group with positive CT screening results during rounds 2–5 were matched 1:2 with participants with negative CT screening results, and 1:2 with participants from the control group. Participants were matched on sex, age (+/- three years), and the time of screening, within seven days for the CT group, or clinic visit for the control group. The group with positive CT screening results was further divided

into a true-positive group and a false-positive group after receiving the final diagnosis. Participants completed the COS-LC at five time points (figure 1):

- Baseline: COS-LC was completed shortly before the annual CT screening (CT group) or clinic visit (control group)
- One week after receiving the CT-screening result (CT group) and one week after the annual clinic visit (control group)
- 1, 6 and 18 months after receiving the final diagnosis of the screening result (CT group) and at these time points after the annual clinic visit (control group)

At the latter four time points, participants were sent the COS-LC by post and asked to return it in an enclosed stamped addressed envelope. A reminder was sent to participants who did not return the COS-LC within two weeks.

Information about region of residence, smoking status, smoking history, social group, employment status, school education, and whether participants lived alone was obtained from baseline and annual questionnaires. The Charlson comorbidity index was calculated from hospital admissions three years before randomisation.

Questionnaire

The COS-LC is a condition-specific questionnaire with high content validity and adequate psychometric properties and it was developed and validated to measure the psychosocial consequences of participation in lung cancer CT screening.[18] To ensure high content validity, 20 participants from the first screening round in the DLCST were interviewed in five group interviews.[18] Subsequently, during screening rounds 2–4 in the years 2006–2007, questionnaire data

from participants were used to validate the COS-LC using Item Response Theory Rasch models.[18] As these data were only a part of the present data, the psychometric properties of the 15 COS-LC scales were re-tested for homogeneity and differential item functioning (DIF) relative to participant group, sex, age, social status, and smoking status by using likelihood ratio tests on appropriately conditioned Rasch models at the one month follow-up time point.[24] Reliability of the scales was examined using Cronbach's alpha.

The COS-LC has two parts where Part-I encompasses 24 COS items (four COS-scales) and 25 lung cancer screening-specific items (five lung cancer screening-specific scales) (appendix 2). Part-I can be used before, during and after screening and the DLCST participants in both the CT group and the control group completed Part-I.[18] The higher the scale score, the more negative the psychosocial consequences.[18]

Part-II measures the long-term psychosocial consequences after lung-cancer CT screening and can therefore only be completed by the screening participants (CT group) after they have received their final diagnosis.[18]

Part-II encompasses 24 items (six scales) and was designed and validated to measure changes, both positive and negative; high scores denote more change (appendix 2).

Statistical analysis

The differences in the characteristics of the four groups of participants (true-negative, true-positive, false-positive and control) were tested with Pearson χ^2 tests for categorical variables and Kruskal-Wallis non-parametric tests for continuous variables.

For each of the 15 COS-LC scales, the mean score for each of the four participant groups at the five time points was analysed with linear regression models, both unadjusted and adjusted for the

participant characteristics: round, sex, (a quadratic function of) age, region, (a quadratic function of) pack years, smoking status, social group, living alone, employment status, school education and Charlson's comorbidity index. Generalised estimating equations were used to account for repeated measurement. To adjust for differential dropout, the non-missing scales at each time point were weighted by the inverse of the probability of this scale being observed at that time.[25] These probabilities were estimated from the data in logistic regression models for the scale being missing, which included the participant characteristics, the participant groups, and the corresponding scale outcomes from previous time points.

The statistical level of significance was set using the method of Benjamini-Hochberg to adjust for multiple testing.[26] Statistical Analysis Software (SAS) 9.3 was used to analyse the data.

Participant and public involvement

DLCST participants were involved in the development of the questionnaire COS-LC. Neither participants nor the Danish general public were involved in the design and recruitment of the study.

Results

Participation

Distribution of final diagnostic results and participation rates are presented in figure 1. In rounds 2–5, 193 participants received a positive screening result; of those, 130 (67%) completed the COS-LC and were included in this study. The reasons for non-response were: 1) never receiving the COS-LC because the participant contact details were not available to the researchers (n=39, 20%), 2) declining to complete the COS-LC (n=6, 3%); and 3) other reasons (n=18, 9%).

Of the 130 respondents included in the study, 24 (19%) had received one false-positive result in the previous rounds and one (0.8%) had previously received two false-positive results. The COS-LC

was sent to 252 participants with true-negative results and 248 control participants. Response rates for the four groups during the five time points were 64–97% (figure 1).

There was a significant difference between the four groups regarding age and smoking history: the participants in the true-positive group were older and had a longer smoking history (table 1). A significant difference was also observed in the region of residence, where false positives, to a greater extent, lived outside the capital region compared with the other groups. No significant differences were found in the remaining participant characteristics.

Table 1

Characteristics of Participants

		CT group n = 382			Control group n = 248		
	Total *n = 630*	True-negative *n = 252*	False-positive *n = 91*	True-positive *n = 39*	*n = 248*	p-value*	missing
Round, *n (%)*						0.543	0
2	158 (25.1)	68 (27.0)	26 (28.6)	9 (23.1)	55 (22.2)		
3	196 (31.1)	76 (30.2)	24 (26.4)	14 (35.9)	82 (33.1)		
4	76 (12.1)	31 (12.3)	10 (11.0)	8 (20.5)	27 (10.9)		
5	200 (31.8)	77 (30.6)	31 (34.1)	8 (20.5)	84 (33.9)		
Sex, *n (%)*						0.174	0
Men	298 (47.3)	118 (46.8)	37 (40.7)	24 (61.5)	119 (48.0)		
Women	332 (52.7)	134 (53.2)	54 (59.3)	15 (38.5)	129 (52.0)		
Age (years), *median (IQR)*	58 (55-62)	58 (55-62)	58 (54-61)	60 (58-65)	59 (55-62)	0.017	0
Social Group, *n (%)*						0.334	1
I	42 (6.7)	23 (9.2)	3 (3.3)	1 (2.6)	15 (6.1)		
II	132 (21.0)	51 (20.3)	13 (14.3)	9 (23.1)	59 (23.8)		
III	126 (30.0)	53 (21.1)	15 (16.5)	6 (15.4)	52 (21.0)		
IV	158 (25.1)	57 (22.7)	28 (30.8)	13 (33.3)	60 (24.2)		
V	81 (12.9)	29 (11.6)	13 (14.3)	6 (15.4)	33 (13.3)		
Employed, social group uncertain	54 (8.6)	21 (8.4)	12 (13.2)	1 (2.6)	20 (8.1)		
Outside the labour market	36 (5.7)	17 (6.8)	7 (7.7)	3 (7.7)	9 (3.6)		
School education, *n (%)*						0.321	0
7-9 years in school	242 (38.4)	88 (34.9)	45 (49.5)	16 (41.0)	93 (37.5)		
10 years in school	229 (36.4)	99 (39.3)	27 (29.7)	15 (38.5)	88 (35.5)		
11-13 years in school	159 (25.2)	65 (25.8)	19 (20.9)	8 (20.5)	67 (27.0)		
Employment status, *n (%)*						0.219	1
Employed	374 (59.5)	158 (62.7)	48 (52.8)	18 (47.4)	150 (60.5)		

Studying	2 (0.3)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.4)		
Job seeking	35 (5.6)	17 (6.8)	7 (7.7)	3 (7.9)	8 (3.2)		
Retired	218 (34.7)	77 (30.6)	35 (38.5)	17 (44.7)	89 (35.9)		
Region of residence, *n (%)*						0.043	1
Capital Region	522 (83.0)	310 (83.3)	70 (76.9)	32 (82.1)	210 (85.0)		
Region Zealand	98 (15.6)	34 (13.5)	20 (22.0)	7 (18.0)	37 (15.0)		
Region of Southern Denmark	9 (1.4)	8 (3.2)	1 (1.1)	0 (0.0)	0 (0.0)		
Living alone, *n (%)*						0.147	4
No	430 (68.7)	175 (69.7)	54 (59.3)	25 (64.1)	176 (71.8)		
Yes	196 (31.3)	76 (30.3)	37 (40.7)	14 (35.9)	69 (28.2)		
Smoking status, *n (%)*						0.195	0
Current smoker	473 (75.1)	183 (72.6)	72 (79.1)	34 (87.2)	184 (74.2)		
Former smoker	157 (24.9)	69 (27.4)	19 (20.9)	5 (12.8)	64 (25.8)		
Smoking history (pack years), *median (IQR)*	34 (27-43)	34 (27-43)	34 (27-43)	43 (34-49)	33 (26-42)	0.001	1
Charlson comorbidity index, *n (%)*						0.913	0
0	590 (93.7)	235 (93.3)	83 (91.2)	36 (92.3)	236 (95.2)		
1	25 (4.0)	10 (4.0)	5 (5.5)	2 (5.1)	8 (3.2)		
≥2	15 (2.4)	7 (2.8)	3 (3.3)	1 (2.6)	4 (1.6)		

*p-value of a Pearson chi-squared test (categorical variables) or a Kruskal-Wallis test (continuous variables); p-values are estimates of the exact p-values based on 10,000 Monte Carlo simulations under the null-hypothesis; CT=computed tomography; IQR=interquartile range.

The 15 COS-LC scales exhibited overall adequate fit to the partial credit Rasch model for polytomous items. No DIF was revealed and Cronbach's Alpha was 0.693–0.962 (table 2).

Table 2

Conditional likelihood ratio (CLR) fit statistics and Cronbach's alpha for the 15 domains of the Consequences of Screening in Lung Cancer (COS-LC) questionnaire

Scales (no. of items)	CLR	Degrees of freedom	p*	Cronbach's Alpha
Anxiety (7)	23.0	20	0.286	0.903
Behaviour (7)	19.0	20	0.520	0.893
Dejection (6)	14.9	17	0.603	0.916
Negative impact on sleep (4)	22.3	11	0.022	0.874
Selfblame (5)	20.2	14	0.124	0.962
Focus on airway symptoms (2)	1.0	5	0.966	0.802
Stigmatisation (4)	24.6	11	0.010	0.916
Introvert (4)	11.2	11	0.425	0.851
Harm of smoking (2)	9.8	5	0.082	0.857
Existential values (6)	9.3	11	0.591	0.851
Calm/relaxed (2)	0.6	3	0.887	0.693
Social network (3)	5.5	5	0.362	0.754
Impulsivity (6)	4.5	11	0.954	0.854
Empathy (3)	5.9	5	0.314	0.699
Regretful about still smoking (4)	1.0	7	0.795	0.863

*After adjustment for multiple testing by using the methods of Benjamini-Hochberg the level of statistical significance was assessed at 0.0033.

COS-LC Part-I

Figure 2 presents the mean score of the nine outcomes for COS-LC Part-I for the four groups at the five time points. For Part-I in general, participants with a positive CT screening result reported more negative psychosocial consequences at the short-term follow-up points of one week and one

month (figure 2). The false-positive group experienced significantly more negative psychosocial consequences at one week in seven outcomes (Anxiety, Behaviour, Dejection, Self-blame, Focus on airway symptoms, Introvert, and Harm of smoking) and at one month in three outcomes (Self-blame, Focus on airway symptoms, and Harm of smoking) (mean Δ score > 0 and $p<.001$) compared with both the control group and the true-negative group (figure 2, appendix 3). At six and 18 months, there was a trend towards more negative psychosocial consequences in three outcomes, but no statistically significant differences were found. The true-positive group showed the same general pattern and experienced significantly more negative psychosocial consequences only in the outcome Dejection at one week (mean Δ score 2.86 (95% CI 1.01 to 4.70) $p=0.0024$) and in the three outcomes Behaviour, Dejection, and Focus on airway symptoms at one month (mean Δ score > 0 and $p<.004$) compared with the true-negative group and the control group (figure 2, appendix 3). At baseline, the true-positive group showed a significantly more positive psychosocial profile in the outcomes Anxiety and Self-blame.

COS-LC Part-II

Figure 3 presents the mean scores of the six outcomes for COS-LC Part-II for the three groups at the three follow-up points after receiving the final screening result. The false-positive group showed a trend towards more negative psychosocial consequences in two outcomes at one month compared with the true-negative group, but no significant differences were seen. The true-positive group showed significant differences in the outcome Social network at one month and six months and in the outcome Empathy at one month (figure 3, appendix 3). Trends towards more negative psychosocial consequences were seen in five outcomes at one month compared with the true-negative group. This difference diminished at six and 18 months. The true-negative group showed no variation in psychosocial consequences through the three longer-term follow-up points.

Discussion

False-positive lung-cancer CT screening results were associated with negative short-term psychosocial consequences compared with the control group and the true-negative group. There were no identified long-term consequences of false-positive results. Contrary to expectation, neither were there any long-term consequences experienced by the true-positive group.

The tendency towards more negative long-term psychosocial consequences in the false-positive group, was limited to three lung-cancer-specific scales in Part-I of COS-LC. The same pattern was seen for the true-positive group. Additionally, this group reported more negative psychosocial consequences in the scales Social Network and Empathy in Part-II of COS-LC (figure 3). Smoking causes approximately 90% of all lung cancers and on a societal level smokers are often blamed for their lung cancer, which can lead to feelings of self-blame and guilt.[27] This could explain the tendency towards long-term negative psychosocial consequences in the lung-cancer-specific scales: Self-blame, Focus on Airway Symptoms, and Harm of Smoking in Part-I. In contrast, no negative long-term consequences were seen in the remaining six scales in Part-I. There might be several explanations for our findings: 1) the true-positive group had a more positive psychosocial profile at baseline than the other groups. Hence, no long-term differences compared with the control group were seen, when the short-term negative psychosocial consequences diminished with time towards the more positive set point. 2) Selection bias was identified among DLCST participants, who were better educated and with a more positive psychosocial profile compared with a matched background population.[28] Thus, DLCST participants were probably more psychosocially robust than average

and therefore false-positive or true-positive findings might have had fewer negative consequences than could be expected for the general population.

3) Those diagnosed with lung cancer via screening and who remained alive and asymptomatic after 18 months were convinced, they had been cured of a lethal disease. This reassurance is likely since lung cancer symptom lead time is longer than 18 months and a minimum of 20% of screening detected lung cancers are overdiagnosed.[29] If those diagnosed with lung cancer via screening do not experience any substantial long-term negative psychosocial consequences, it is not expected that the experiences of other screening groups will differ. 4) Another explanation for the long-term results could be the fact that the control group experienced more negative psychosocial consequences than the CT group through screening rounds 2-5 in DLCST.[30] The level of psychosocial consequences in the control group was therefore more negative (higher COS-LC scores) which decreases the difference between the control group and the positive CT screening groups. 5) During the development of the COS-LC, the qualitative interviews were conducted 0–5 months after screening; therefore, Part-II of the COS-LC might not capture all relevant long-term psychosocial consequences for those with false-positive findings. 6) Approximately 20% of the participants who received a positive screening result had previously received a false-positive result. Participants might therefore become accustomed to receiving a (false-) positive screening result, which could decrease the level of negative psychosocial consequences. In contrast, the COS-LC was developed in the first round and a first-round effect, which most likely would have had a more negative psychosocial impact on the participants, was not seen. 7) Contamination of the control group could have biased our results; nevertheless, contamination of the DLCST was found to be minor.[31] Finally, 8) participants with false-positive results could have received a negative screening result between the six and the 18-month assessments, which could be perceived as reassurance, consequently lowering the negative psychosocial consequences.

This is the first study to present both short and long-term psychosocial consequences of false-positive results using a lung-cancer-specific questionnaire with high content validity and adequate psychometric properties developed in a randomised, controlled lung cancer CT screening trial. Therefore, the COS-LC most likely presents stronger results compared with generic questionnaires. The true-positive group was included in this study and when both the true-positive- and the true-negative groups are included, the extent of the psychosocial harm in the false-positive group can be compared with the extent of harm in those who should be worst off (true positives) and those who are reassured (true negatives). No significant differences were shown, however, in the long-term psychosocial consequences for either the false-positive group or the true-positive group compared with the control group.

Other quantitative studies have investigated the health-related quality of life (HRQoL) in CT screening using generic questionnaires that have not been validated for lung cancer.[13 19-21] Although one lung cancer-specific questionnaire was used, no information about validation was reported.[19] These studies found that CT screening had only short-term and no long-term negative effects on HRQoL for participants with false-positive results. Our study, using a more accurate and validated survey instrument, has confirmed this. However, the absence of long-term psychosocial consequences in the true-positive group as well suggests that certain long-term consequences may have been overlooked or that the development of a certain resilience or relief (at feeling cured) may play a long-term role.[32]

A study investigating the risk of receiving a prescription on antidepressants or anxiolytics in the CT group (mixed negative and positive results) compared with the control group in DLCST found no differences between these groups.[33] These outcomes measure extremes of psychosocial

consequences, which is a plausible explanation for the negative results. However, another study, that investigated healthcare use and costs in DLCST participants showed higher use of the healthcare system among false positives and true positives compared with the control group in the time period between two screening rounds.[15] This may be associated with an increased attention drawn to the risk of not being healthy subsequent to receiving a false-positive result. A meta-analysis of the psychosocial consequences of false-positive mammograms including both generic and condition-specific outcome measures showed both short-term and long-term (up to three years) negative psychosocial consequences compared with true-negative mammograms.[12 34] This study recommends the use and further development of condition-specific measures instead of generic measures in mammography screening. Condition-specific measures should also be improved and used in lung cancer CT-screening to obtain the most valid results for psychosocial outcomes.

In interpreting the effect size of the results, we used the mean increase of 2.16 in Selfblame in the false-positive group at the one-month time point compared with the control group (appendix 3). This increase corresponds to two shifts in the response category of one item for all participants with false-positive results, e.g. from “not at all” to “quite a bit”, while all the participants in the control group had no shift in response category. The false-positive rates differ substantially in the NLST (23%) and the DLCST (3%), which has been discussed in detail previously[15]. The negative consequences may seem small or transient in relative terms; however, in absolute terms they might be large. There are two reasons for this: firstly, a mass screening programme targeting a large population, a small change in the frequency with which they appear, may be a large increase in the absolute number of presumably healthy people affected by these consequences; secondly, the positive predictive value (PPV) of an abnormal low dose CT screening result might be much lower in an on-going screening programme compared with the PPV obtained in a research setting, e.g. in

the Veterans Health Administration in U.S. there was nearly a false-positive rate of 60% in their first screening round[35].This will also increase the costs even more. We have in previous research shown that low dose CT screening for lung cancer will in a Danish context with a public funded healthcare system increase total health costs by 60%[16] and specifically for those with false-positive results the cost will increase by 66%[15]. The knowledge of psychosocial consequences from false-positive results contributes to the evidence for the benefits and harms of lung-cancer CT screening and should be included in the overall assessment of the European trials.

Conclusion: In the Danish Lung Cancer Screening Trial, false-positive results were associated with more negative short-term psychosocial consequences compared with the control group and the true-negative group.

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Contribution

The study was devised and designed by JB. Data collection was conducted by JB. Statistical analyses were done by JFR and VS. JFR drafted the manuscript and JB, VS and JM contributed to parts of the manuscript and to revisions of the manuscript. All four authors have approved the final version of the manuscript. All authors had full access to all of the data in the study (including statistical reports and tables) and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Availability of data and materials

The corresponding author can provide the questionnaires and datasets generated and analysed during the study on reasonable request.

Figure 1 Distribution of screening results and final diagnoses in the DLCST, and response rates of the matched groups at five time points: baseline, one week, one, six, and 18 months

Figure 2 The mean score of the nine psychosocial outcomes of COS-LC Part-I for the diagnostic groups and the control group in the DLCST at five time points: Baseline, one week, one, six, and 18 months

Figure 3 The mean score of the six psychosocial outcomes of COS-LC Part-II for the diagnostic groups in the DLCST at three time points: one, six and 18 months

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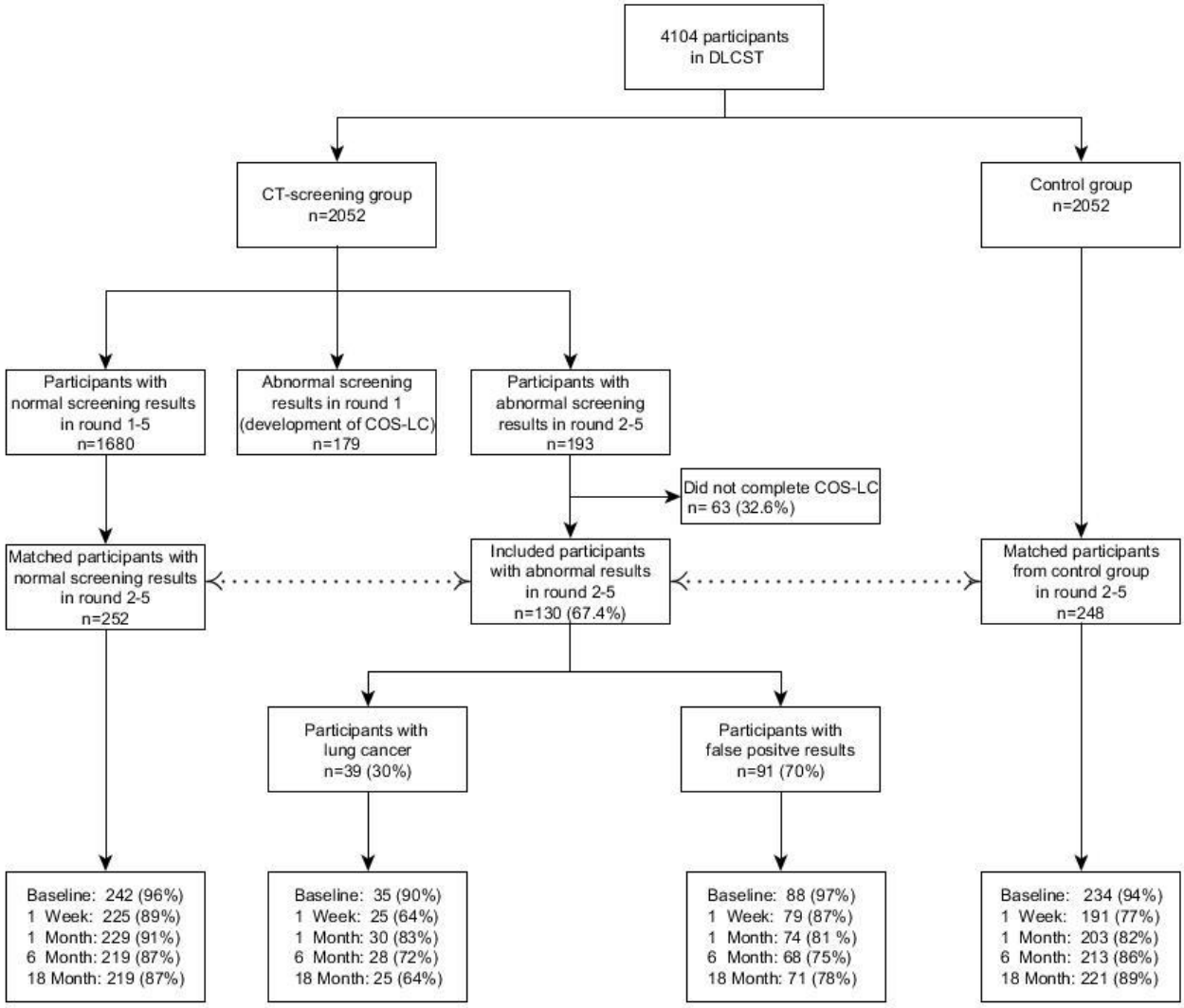
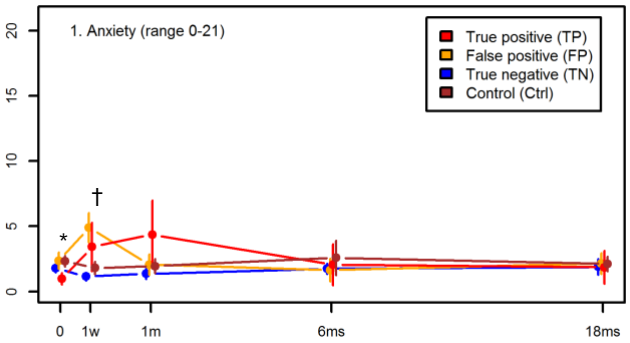
Figure 1, Distribution of screening results and final diagnoses in the DLCST, and response rates of the matched groups at five time points: baseline, 1 week, 1,6 and 18 months



DLCST=Danish lung cancer screening trial; CT=Computed Tomography; COS-LC=Consequences of screening-lung cancer.

Figure 2: The COS-LC Part I scales' means are compared between all groups at each time point and significant differences between the groups are described below each scale (see appendix 1 for details of the adjusted analyses). After adjustment for multiple testing by the method of Benjamini-Hochberg, the level of statistical significance was assessed at 0.0043; 0=baseline; 1w=1 week after screening; 1m, 6ms and 18ms=1,6 and 18 months after final diagnostic result; the higher the score the more negative psychosocial reaction.



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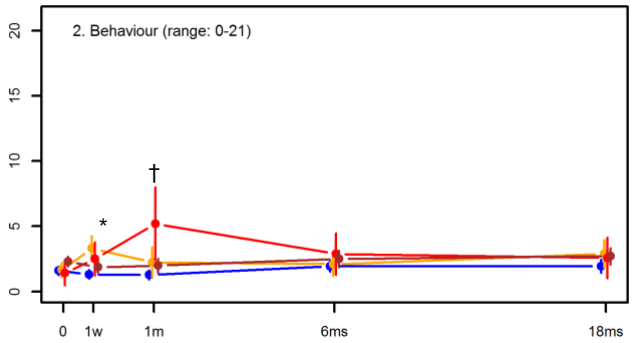

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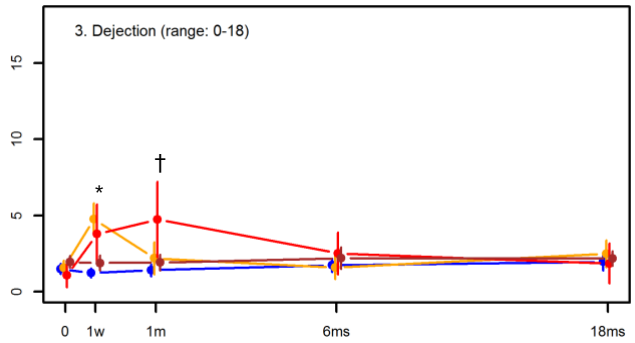

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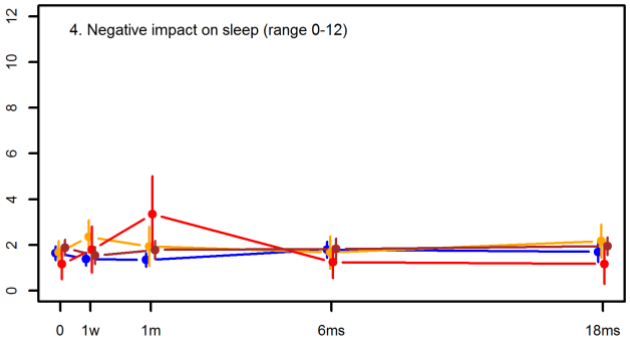

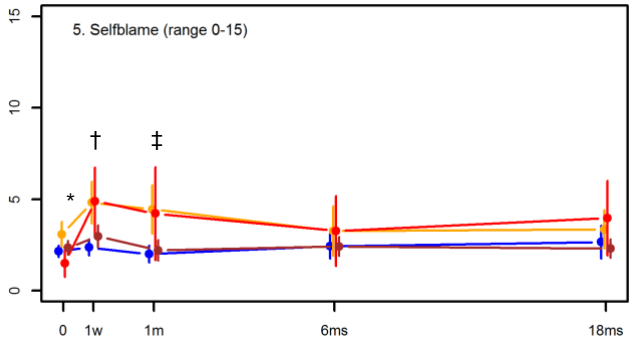

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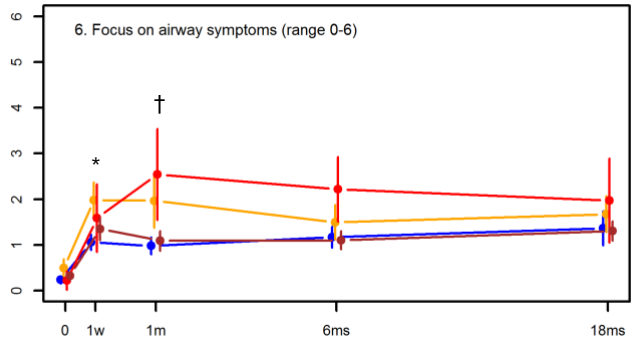

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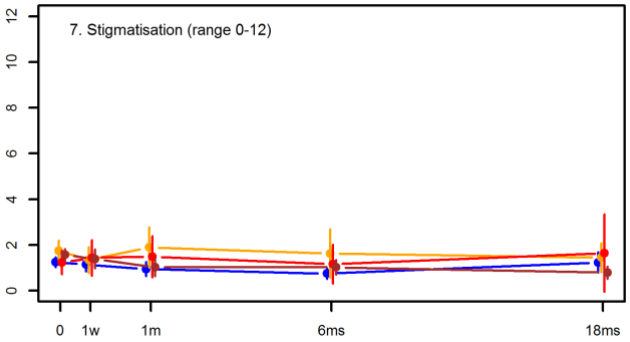

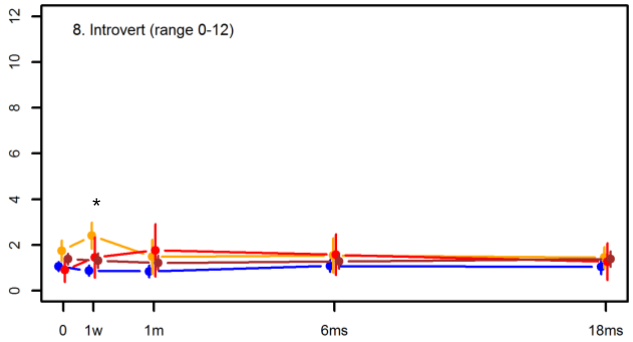

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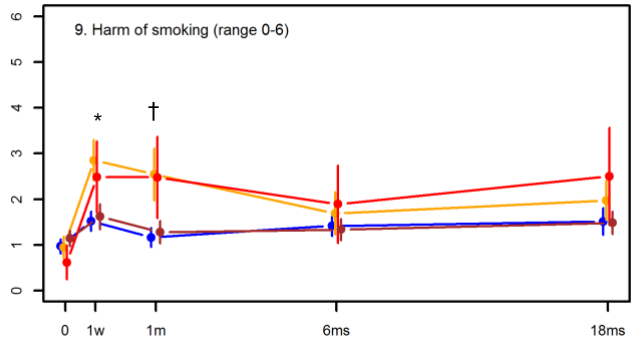

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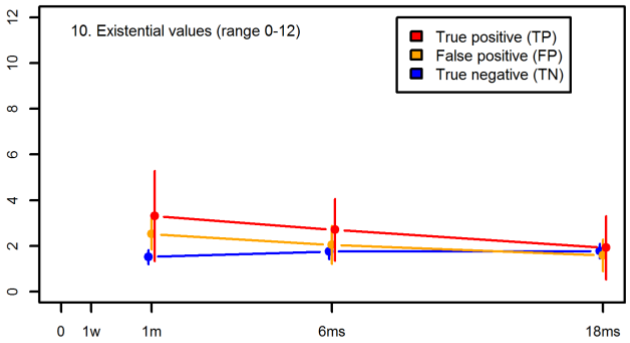
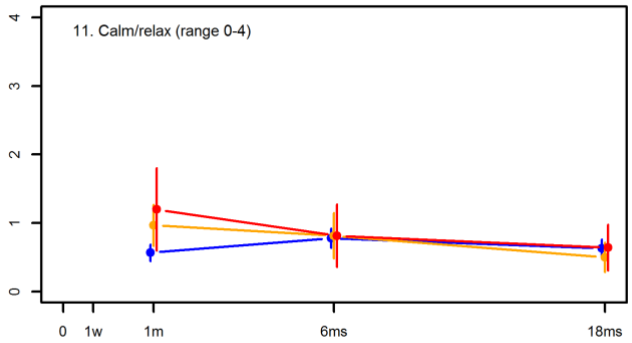
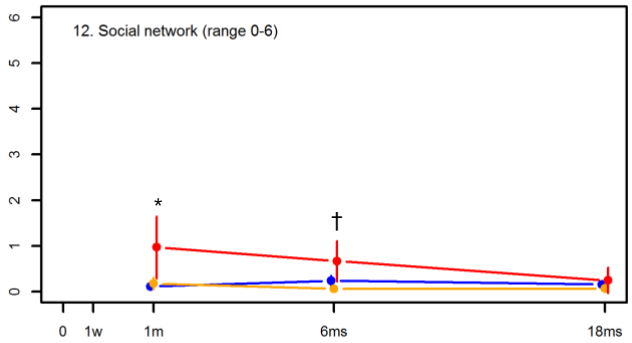
Figure 3: The COS-LS Part II scales' means are compared between the three screened groups at each time point after the final diagnostic result and significant differences between the groups are described below each scale (see appendix 1 for details of the adjusted analyses). After adjustment for multiple testing by the method of Benjamini-Hochberg, the level of statistical significance was assessed at 0.0043; 0=baseline; 1w=1 week after screening; 1m, 6ms and 18ms=1,6 and 18 months after final diagnostic result; the higher the score the more psychosocial reaction.







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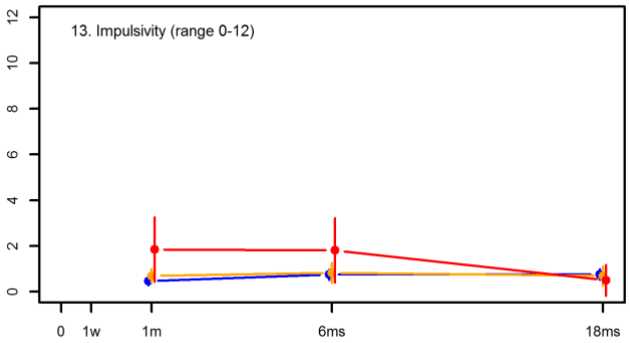

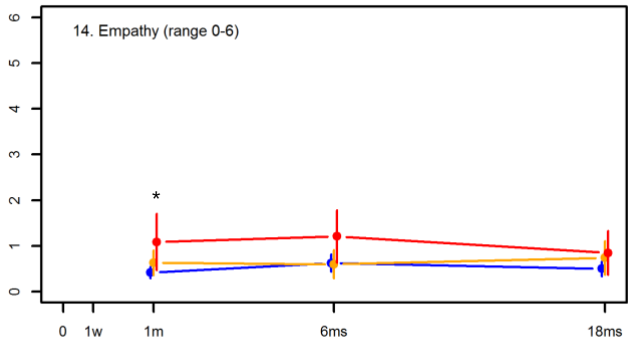

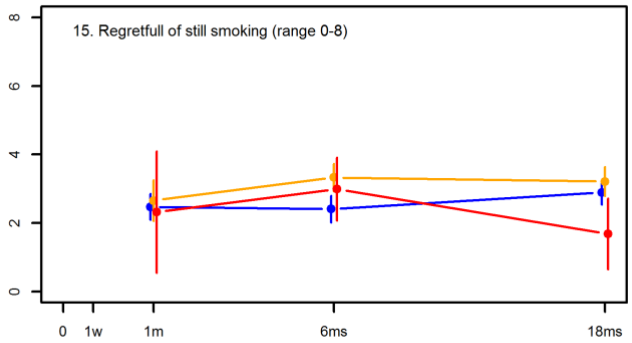

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Appendix 1

False-positive rates in the National Lung Screening Trial (NLST) and the Danish Lung Cancer Screening Trial (DLCST)

Trial	Study threshold of an abnormal non-calcified lung nodule (screening test positive)*	Round of screening	Number screened	Abnormal lung nodules over study threshold (screening test positive)	Lung cancer nodules (true positives)	Nodules not lung cancer (false positives)	False-positive rate (nodules not lung cancer / no. screened)	Average false-positive rate
NLST	≥4 mm	Baseline	26 309	7191	270	6921	0.2631	
		Year 1	24 715	6901	168	6733	0.2724	
		Year 2	24 102	4054	211	3843	0.1594	
Total			*75 126*			*17 497*		*0.2329*
DLCST	≥5 mm	Baseline	2047	179	17	162	0.0791	
		Year 1	1976	45	11	34	0.0172	
		Year 2	1944	52	13	39	0.0201	
		Year 3	1982	44	12	32	0.0161	
		Year 4	1851	51	16	35	0.0189	
Total			*9800*			*302*		*0.0308*

*In the DLCST, a CT-screening test result was categorised as abnormal (screening test positive) if a non-calcified lung nodule was ≥5 mm which lead to diagnostic evaluation. The test result was categorised as normal (screening test negative) if the nodule was < 5 mm. In the DLCST non-benign nodules between 5-15 mm found on a CT-screening scan lead to a three months follow-up scan. Nodules > 15 mm were referred to diagnostic work-up. In the NLST non-calcified lung nodules of at least 4 mm found on a CT-screening scan were classified as abnormal screening results (screening test positive) and nodules < 4 mm were classified as normal screening results (screening test negative).

Appendix 2

List of items included in the 15 scales of the questionnaire Consequences of Screening – Lung Cancer (COS-LC)

	Scales	Items
Part I	**1. Anxiety**	Worried about my future
		Nervous
		Scared
		Restless
		Shocked
		Upset
		Terrified
	2. Behaviour	Difficulty doing things around the house
		Difficulty dealing with work or other commitments
		Quieter than normal
		Hard to concentrate
		Withdrawn into myself
		Change in appetite
		Irritable
	3. Dejection	Worried
		Uneasy
		Sad
		Depressed
		Time passed slowly
		Unable to cope
	4. Negative impact on sleep	Woken up far too early in the morning
		Slept badly
		Taken long time to fall a sleep
		Been awake most of the night
	5. Selfblame	Felt guilty
		Blamed oneself
		Been annoyed with oneself
		Disappointed in oneself
		Angry with oneself
	6. Focus on airways symptoms	Aware of being short of breath
		Been aware of one's coughing
	7. Stigmatisation	Felt stigmatised

		Being told off by other people
		A finger wagging from others
		Blamed by other people
	8. Introvert	Insecure
		Mood Swings
		Thought one´s situation hopeless
		Sorry for oneself
	9. Harm of smoking	Thought of smoking as harmful
		Sorry for having smoked for many years
Part II	**10. Existential Values**	Broader aspects of life
		Value of life
		Enjoyment of life
		Awareness of life
		Thought about future
		Well-being
	11. Calm/Relax	Relaxed
		Calm
	12. Social Network	Family
		Friends
		Other people
	13. Impulsivity	Energy
		Lived life to the full
		Being impulsive
		Desire to venture into something risky
		Desire to venture into something new
		Done some things that overstepped one´s bounds
	14. Empathy	Understands other people´s problems
		Responsibility for one's family
		Ability to listen to other people's problems
	15. Regretful of still smoking	Thought about quitting smoking
		Disappointed in oneself for smoking
		Annoyed with oneself for smoking
		Having second thoughts about one´s smoking

Appendix 3

Adjusted analyses of the 15 scales in the questionnaire Consequences of Screening – Lung Cancer (COS-LC):

Mean differences between each pair of the diagnostic groups and the control group during five time points

		Follow up time									
		Baseline		1 week		1 Month		6 Month		18 Month	
Scale (Range)	Comparison	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value
1. Anxiety	Con-Neg	-0.46 (-0.99 to 0.07)	0.0864	-0.63 (-1.20 to -0.06)	0.0317	-0.66 (-1.40 to 0.07)	0.0768	-0.58 (-1.35 to 0.19)	0.1375	-0.36 (-1.13 to 0.40)	0.3519
(0-21)	Con-FP	-0.02 (-0.78 to 0.74)	0.9582	2.77 (1.63 to 3.92)	<.0001	-0.25 (-1.25 to 0.75)	0.6249	-1.20 (-2.43 to 0.04)	0.0578	-0.26 (-1.16 to 0.65)	0.5821
	Con-TP	-1.52 (-2.18 to -0.86)	<.0001	1.89 (0.01 to 3.78)	0.0487	2.72 (0.08 to 5.37)	0.0438	-0.54 (-2.30 to 1.21)	0.5426	-0.69 (-2.41 to 1.04)	0.4360
	Neg-FP	0.44 (-0.27 to 1.16)	0.2257	3.40 (2.33 to 4.48)	<.0001	0.41 (-0.48 to 1.31)	0.3649	-0.62 (-1.64 to 0.41)	0.2390	0.11 (-0.75 to 0.97)	0.8047
	Neg-TP	-1.06 (-1.68 to -0.43)	0.0010	2.52 (0.71 to 4.33)	0.0063	3.38 (0.77 to 6.00)	0.0112	0.04 (-1.66 to 1.74)	0.9666	-0.32 (-1.98 to 1.34)	0.7036
	FP-TP	-1.50 (-2.29 to -0.71)	0.0002	-0.88 (-2.95 to 1.19)	0.4043	2.97 (0.14 to 5.81)	0.0400	0.65 (-1.25 to 2.55)	0.5012	-0.43 (-2.20 to 1.34)	0.6342
No. Respondents		607		514		444		509		518	
2. Behaviour	Con-Neg	-0.74 (-1.26 to -0.23)	0.0046	-0.58 (-1.15 to -0.01)	0.0469	-0.74 (-1.41 to -0.08)	0.0284	-0.51 (-1.27 to 0.24)	0.1838	-1.00 (-1.80 to -0.20)	0.0144
(0-21)	Con-FP	-0.75 (-1.50 to 0.01)	0.0520	1.21 (0.19 to 2.23)	0.0198	-0.09 (-1.34 to 1.16)	0.8843	-0.60 (-1.72 to 0.51)	0.2873	-0.07 (-1.30 to 1.17)	0.9143
	Con-TP	-1.05 (-2.16 to 0.06)	0.0632	0.65 (-0.65 to 1.94)	0.3260	3.31 (0.50 to 6.11)	0.0209	0.03 (-1.66 to 1.73)	0.9698	-0.81 (-2.66 to 1.05)	0.3948
	Neg-FP	0.00 (-0.70 to 0.70)	0.9953	1.79 (0.84 to 2.74)	0.0002	0.65 (-0.46 to 1.76)	0.2522	-0.09 (-1.09 to 0.90)	0.8551	0.93 (-0.21 to 2.07)	0.1106
	Neg-TP	-0.31 (-1.39 to 0.78)	0.5793	1.23 (-0.02 to 2.47)	0.0544	4.05 (1.27 to 6.83)	0.0043	0.54 (-1.13 to 2.22)	0.5236	0.19 (-1.61 to 2.00)	0.8340
	FP-TP	-0.30 (-1.48 to 0.87)	0.6117	-0.56 (-2.06 to 0.94)	0.4636	3.40 (0.38 to 6.42)	0.0275	0.64 (-1.22 to 2.49)	0.5005	-0.74 (-2.80 to 1.32)	0.4834
No. Respondents		611		518		438		507		517	
3. Dejection	Con-Neg	-0.41 (-0.92 to 0.10)	0.1142	-0.66 (-1.25 to -0.07)	0.0291	-0.55 (-1.24 to 0.13)	0.1113	-0.36 (-1.07 to 0.35)	0.3231	-0.35 (-1.04 to 0.34)	0.3216
(0-18)	Con-FP	-0.41 (-1.04 to 0.22)	0.2017	2.63 (1.53 to 3.74)	<.0001	-0.09 (-1.21 to 1.04)	0.8815	-1.04 (-2.07 to 0.00)	0.0492	-0.01 (-1.04 to 1.03)	0.9903
	Con-TP	-0.89 (-1.81 to 0.02)	0.0562	2.20 (0.28 to 4.12)	0.0245	2.92 (0.57 to 5.27)	0.0147	0.16 (-1.32 to 1.64)	0.8308	-0.74 (-2.37 to 0.89)	0.3726
	Neg-FP	0.00 (-0.62 to 0.62)	0.9981	3.29 (2.27 to 4.31)	<.0001	0.47 (-0.55 to 1.49)	0.3695	-0.68 (-1.59 to 0.23)	0.1438	0.34 (-0.64 to 1.32)	0.4928
	Neg-TP	-0.48 (-1.39 to 0.43)	0.2974	2.86 (1.01 to 4.70)	0.0024	3.48 (1.15 to 5.80)	0.0034	0.52 (-0.94 to 1.98)	0.4857	-0.39 (-2.04 to 1.25)	0.6397
	FP-TP	-0.48 (-1.44 to 0.47)	0.3217	-0.43 (-2.49 to 1.63)	0.6812	3.01 (0.44 to 5.58)	0.0219	1.20 (-0.38 to 2.77)	0.1365	-0.74 (-2.55 to 1.08)	0.4270
No. Respondents		606		521		449		518		526	
4. Negative impact on sleep	Con-Neg	-0.16 (-0.62 to 0.31)	0.5047	-0.16 (-0.65 to 0.33)	0.5191	-0.38 (-0.90 to 0.14)	0.1549	-0.06 (-0.60 to 0.48)	0.8321	-0.29 (-0.82 to 0.24)	0.2786
(0-12)	Con-FP	-0.26 (-0.89 to 0.37)	0.4235	0.65 (-0.14 to 1.44)	0.1056	-0.10 (-1.01 to 0.81)	0.8308	-0.32 (-1.20 to 0.56)	0.4770	0.11 (-0.68 to 0.90)	0.7909
	Con-TP	-0.71 (-1.50 to 0.08)	0.0770	0.47 (-0.61 to 1.54)	0.3928	1.94 (0.33 to 3.55)	0.0182	-0.53 (-1.36 to 0.30)	0.2116	-0.90 (-1.96 to 0.15)	0.0938
	Neg-FP	-0.10 (-0.71 to 0.51)	0.7458	0.81 (0.07 to 1.55)	0.0314	0.28 (-0.56 to 1.12)	0.5130	-0.26 (-1.07 to 0.54)	0.5242	0.40 (-0.37 to 1.17)	0.3127
	Neg-TP	-0.55 (-1.32 to 0.21)	0.1572	0.63 (-0.40 to 1.66)	0.2303	2.32 (0.71 to 3.93)	0.0047	-0.47 (-1.24 to 0.31)	0.2356	-0.61 (-1.65 to 0.42)	0.2452
	FP-TP	-0.45 (-1.32 to 0.42)	0.3057	-0.18 (-1.38 to 1.02)	0.7662	2.04 (0.24 to 3.83)	0.0260	-0.21 (-1.25 to 0.84)	0.6968	-1.01 (-2.19 to 0.17)	0.0938
No. Respondents		612		515		444		515		524	

		Follow up time									
		Baseline		1 week		1 Month		6 Month		18 Month	
Scale (Range)	Comparison	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value
5. Selfblame	Con-Neg	-0.14 (-0.61 to 0.32)	0.5511	-0.52 (-1.25 to 0.20)	0.1589	-0.21 (-0.94 to 0.51)	0.5644	-0.13 (-0.90 to 0.64)	0.7424	0.26 (-0.63 to 1.16)	0.5642
(0-15)	Con-FP	0.54 (-0.19 to 1.27)	0.1461	1.58 (0.32 to 2.83)	0.0136	2.16 (0.84 to 3.48)	0.0013	0.23 (-0.98 to 1.43)	0.7132	0.74 (-0.34 to 1.83)	0.1787
	Con-TP	-1.15 (-1.91 to -0.39)	0.0030	1.89 (0.09 to 3.70)	0.0401	1.51 (-0.23 to 3.25)	0.0895	0.31 (-1.56 to 2.18)	0.7476	1.45 (-0.74 to 3.64)	0.1930
	Neg-FP	0.68 (-0.02 to 1.38)	0.0557	2.10 (0.91 to 3.29)	0.0005	2.38 (1.05 to 3.70)	0.0004	0.36 (-0.92 to 1.63)	0.5844	0.48 (-0.67 to 1.64)	0.4145
	Neg-TP	-1.01 (-1.74 to -0.28)	0.0069	2.41 (0.67 to 4.16)	0.0067	1.72 (0.00 to 3.45)	0.0501	0.44 (-1.47 to 2.34)	0.6534	1.19 (-1.04 to 3.42)	0.2957
	FP-TP	-1.69 (-2.59 to -0.80)	0.0002	0.32 (-1.70 to 2.34)	0.7590	-0.65 (-2.66 to 1.36)	0.5249	0.08 (-2.07 to 2.23)	0.9411	0.71 (-1.65 to 3.07)	0.5559
No. Respondents		606		507		445		517		525	
6. Focus on airway symptoms	Con-Neg	-0.07 (-0.19 to 0.05)	0.2702	-0.23 (-0.51 to 0.04)	0.0948	-0.16 (-0.45 to 0.13)	0.2807	0.00 (-0.30 to 0.30)	0.9937	-0.09 (-0.39 to 0.22)	0.5773
(0-6)	Con-FP	0.19 (-0.02 to 0.39)	0.0819	0.57 (0.13 to 1.02)	0.0112	0.68 (0.13 to 1.24)	0.0160	0.23 (-0.16 to 0.63)	0.2443	0.28 (-0.15 to 0.71)	0.1951
	Con-TP	-0.19 (-0.43 to 0.04)	0.1103	0.21 (-0.51 to 0.93)	0.5650	1.60 (0.64 to 2.55)	0.0011	0.90 (0.21 to 1.58)	0.0100	0.54 (-0.45 to 1.53)	0.2861
	Neg-FP	0.25 (0.05 to 0.46)	0.0149	0.81 (0.39 to 1.22)	<.0001	0.84 (0.29 to 1.39)	0.0026	0.23 (-0.18 to 0.65)	0.2666	0.37 (-0.06 to 0.80)	0.0912
	Neg-TP	-0.12 (-0.36 to 0.11)	0.2992	0.44 (-0.26 to 1.15)	0.2139	1.76 (0.81 to 2.71)	0.0003	0.90 (0.22 to 1.58)	0.0098	0.62 (-0.38 to 1.63)	0.2213
	FP-TP	-0.38 (-0.66 to -0.09)	0.0094	-0.36 (-1.14 to 0.42)	0.3639	0.91 (-0.16 to 1.98)	0.0950	0.66 (-0.06 to 1.39)	0.0733	0.25 (-0.79 to 1.30)	0.6340
No. Respondents		613		516		447		517		527	
7. Stigmatization	Con-Neg	-0.25 (-0.58 to 0.07)	0.1281	-0.22 (-0.71 to 0.28)	0.3872	-0.14 (-0.64 to 0.35)	0.5693	-0.30 (-0.71 to 0.10)	0.1395	0.45 (-0.05 to 0.95)	0.0753
(0-12)	Con-FP	0.12 (-0.39 to 0.63)	0.6387	-0.01 (-0.69 to 0.67)	0.9761	0.82 (-0.10 to 1.73)	0.0803	0.46 (-0.49 to 1.41)	0.3393	0.64 (0.00 to 1.28)	0.0492
	Con-TP	-0.40 (-0.98 to 0.18)	0.1715	-0.37 (-1.25 to 0.51)	0.4066	0.01 (-0.83 to 0.85)	0.9841	-0.35 (-1.30 to 0.60)	0.4697	0.63 (-1.06 to 2.31)	0.4664
	Neg-FP	0.38 (-0.13 to 0.88)	0.1444	0.21 (-0.44 to 0.85)	0.5311	0.96 (0.07 to 1.85)	0.0340	0.76 (-0.17 to 1.70)	0.1082	0.19 (-0.52 to 0.90)	0.5981
	Neg-TP	-0.15 (-0.73 to 0.43)	0.6107	-0.15 (-0.95 to 0.64)	0.7021	0.15 (-0.65 to 0.95)	0.7098	-0.05 (-0.97 to 0.88)	0.9216	0.17 (-1.52 to 1.87)	0.8401
	FP-TP	-0.53 (-1.21 to 0.16)	0.1302	-0.36 (-1.32 to 0.60)	0.4614	-0.81 (-1.93 to 0.31)	0.1576	-0.81 (-2.15 to 0.53)	0.2345	-0.02 (-1.79 to 1.76)	0.9857
No. Respondents		609		505		440		511		522	
8. Introvert	Con-Neg	-0.37 (-0.68 to -0.06)	0.0191	-0.50 (-0.89 to -0.11)	0.0117	-0.42 (-0.85 to 0.01)	0.0527	-0.22 (-0.61 to 0.18)	0.2888	-0.38 (-0.84 to 0.09)	0.1130
(0-12)	Con-FP	0.22 (-0.29 to 0.73)	0.3948	0.84 (0.20 to 1.48)	0.0102	0.02 (-0.72 to 0.76)	0.9601	-0.14 (-0.71 to 0.42)	0.6160	-0.10 (-0.69 to 0.49)	0.7378
	Con-TP	-0.78 (-1.39 to -0.17)	0.0120	0.08 (-0.79 to 0.96)	0.8527	0.63 (-0.5 to 1.77)	0.2754	0.11 (-0.81 to 1.02)	0.8172	-0.31 (-1.35 to 0.72)	0.5535
	Neg-FP	0.59 (0.09 to 1.09)	0.0199	1.34 (0.74 to 1.94)	<.0001	0.44 (-0.31 to 1.20)	0.2496	0.07 (-0.49 to 0.63)	0.8031	0.28 (-0.28 to 0.83)	0.3327
	Neg-TP	-0.41 (-1.01 to 0.19)	0.1834	0.59 (-0.28 to 1.45)	0.1834	1.06 (-0.06 to 2.17)	0.0634	0.32 (-0.60 to 1.24)	0.4922	0.06 (-0.97 to 1.10)	0.9059
	FP-TP	-1.00 (-1.71 to -0.29)	0.0058	-0.76 (-1.75 to 0.23)	0.1335	0.61 (-0.74 to 1.96)	0.3741	0.25 (-0.74 to 1.25)	0.6192	-0.21 (-1.32 to 0.89)	0.7052
No. Respondents		609		508		444		513		524	

		Follow up time									
		Baseline		1 week		1 Month		6 Month		18 Month	
Scale (Range)	Comparison	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value	Mean Δ (95% CI)	p value
9. Harm of smoking	Con-Neg	-0.11 (-0.35 to 0.12)	0.3319	-0.07 (-0.39 to 0.26)	0.6823	-0.10 (-0.41 to 0.22)	0.5513	0.03 (-0.29 to 0.35)	0.8669	0.00 (-0.35 to 0.36)	0.9888
(0-6)	Con-FP	-0.25 (-0.55 to 0.05)	0.1057	1.08 (0.61 to 1.56)	<.0001	1.12 (0.56 to 1.67)	<.0001	0.22 (-0.25 to 0.68)	0.3560	0.32 (-0.15 to 0.79)	0.1796
	Con-TP	-0.50 (-0.92 to -0.09)	0.0179	0.75 (-0.05 to 1.55)	0.0651	0.99 (0.14 to 1.84)	0.0225	0.32 (-0.51 to 1.14)	0.4546	0.80 (-0.26 to 1.85)	0.1376
	Neg-FP	-0.13 (-0.43 to 0.16)	0.3730	1.15 (0.70 to 1.60)	<.0001	1.21 (0.66 to 1.76)	<.0001	0.19 (-0.27 to 0.65)	0.4209	0.32 (-0.18 to 0.82)	0.2096
	Neg-TP	-0.39 (-0.81 to 0.03)	0.0665	0.82 (0.04 to 1.59)	0.0382	1.08 (0.25 to 1.92)	0.0106	0.29 (-0.53 to 1.10)	0.4892	0.79 (-0.27 to 1.86)	0.1445
	FP-TP	-0.26 (-0.70 to 0.19)	0.2612	-0.33 (-1.18 to 0.52)	0.4424	-0.13 (-1.07 to 0.82)	0.7922	0.10 (-0.80 to 0.99)	0.8317	0.47 (-0.65 to 1.60)	0.4071
No. Respondents		615		517		450		519		529	
10. Existential values	Neg-FP	NA		NA		0.92 (0.23 to 1.61)	0.0090	0.40 (-0.54 to 1.35)	0.4043	0.11 (-0.48 to 0.70)	0.7075
(0-12)	Neg-TP	NA		NA		2.10 (0.45 to 3.75)	0.0125	1.57 (0.31 to 2.83)	0.0149	0.24 (-1.01 to 1.50)	0.7031
	FP-TP	NA		NA		1.18 (-0.55 to 2.92)	0.1805	1.16 (-0.30 to 2.63)	0.1193	0.13 (-1.14 to 1.40)	0.8385
No. Respondents						262		306		307	
11. Calm/relax	Neg-FP	NA		NA		0.46 (0.13 to 0.78)	0.0054	0.05 (-0.33 to 0.44)	0.7852	-0.03 (-0.26 to 0.21)	0.8222
(0-4)	Neg-TP	NA		NA		0.82 (0.19 to 1.44)	0.0101	0.17 (-0.29 to 0.64)	0.4722	-0.01 (-0.42 to 0.40)	0.9611
	FP-TP	NA		NA		0.36 (-0.30 to 1.03)	0.2882	0.12 (-0.45 to 0.68)	0.6866	0.02 (-0.44 to 0.47)	0.9427
No. Respondents						265		310		308	
12. Social network	Neg-FP	NA		NA		0.05 (-0.09 to 0.19)	0.4732	-0.21 (-0.36 to -0.06)	0.0075	-0.11 (-0.26 to 0.03)	0.1248
(0-6)	Neg-TP	NA		NA		0.92 (0.31 to 1.54)	0.0032	0.45 (0.03 to 0.86)	0.0360	0.08 (-0.23 to 0.39)	0.6139
	FP-TP	NA		NA		0.87 (0.25 to 1.50)	0.0061	0.66 (0.24 to 1.07)	0.0022	0.19 (-0.12 to 0.51)	0.2230
No. Respondents						269		312		309	
13. Impulsivity	Neg-FP	NA		NA		0.15 (-0.20 to 0.51)	0.3963	0.19 (-0.24 to 0.62)	0.3857	-0.06 (-0.54 to 0.41)	0.7908
(0-12)	Neg-TP	NA		NA		1.76 (0.35 to 3.17)	0.0146	1.27 (-0.04 to 2.58)	0.0572	0.10 (-0.71 to 0.90)	0.8172
	FP-TP	NA		NA		1.61 (0.20 to 3.02)	0.0257	1.08 (-0.23 to 2.39)	0.1072	0.16 (-0.75 to 1.07)	0.7311
No. Respondents						265		304		307	
14. Empathy	Neg-FP	NA		NA		0.12 (-0.19 to 0.43)	0.4394	0.02 (-0.32 to 0.35)	0.9219	0.21 (-0.17 to 0.59)	0.2719
(0-6)	Neg-TP	NA		NA		0.79 (0.27 to 1.30)	0.0027	0.71 (0.17 to 1.25)	0.0094	0.29 (-0.36 to 0.94)	0.3819
	FP-TP	NA		NA		0.66 (0.11 to 1.22)	0.0191	0.69 (0.12 to 1.27)	0.0182	0.08 (-0.63 to 0.78)	0.8313
No. Respondents						266		306		308	

15. Regretful of still smoking	Neg-FP	NA	NA	0.28 (-0.48 to 1.04)	0.4676	0.59 (0.00 to 1.18)	0.0500	0.06 (-0.54 to 0.65)	0.8475
(0-8)	Neg-TP	NA	NA	0.12 (-1.17 to 1.40)	0.8575	0.74 (-0.12 to 1.59)	0.0903	-0.83 (-1.75 to 0.08)	0.0742
	FP-TP	NA	NA	-0.16 (-1.66 to 1.33)	0.8301	0.15 (-0.82 to 1.12)	0.7673	-0.89 (-1.85 to 0.07)	0.0681
No. Respondents				137		148		150	

Mean Δ = The mean difference of the outcome between the compared groups adjusted for possible confounders; The mean differences of the scales listed in the table are the differences beyond the differences that may be present at baseline (scale 1-9) or at 1 Month (scale 10-15); CI = confidence interval; p value = the statistical significant level was assessed to 0.0043 after adjusting for multiple testing with the method of Benjamini-Hochberg and significant differences between the groups are marked with yellow(1); Con = Control group; Neg = True-negative group; FP = false-positive group; TP = true-positive group; NA = Not applicable.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4 and 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4 and 5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	4 and 5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5 and 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 and 6
Bias	9	Describe any efforts to address potential sources of bias	5 and 8
Study size	10	Explain how the study size was arrived at	4, 5 and Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-10
		(*b*) Describe any methods used to examine subgroups and interactions	6 and 7
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-6
		(b) Give reasons for non-participation at each stage	5

		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Appendix Table 1
		(c) Summarise follow-up time (eg, average and total amount)	Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Figure 2a, 2b and Appendix Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figure 2a, 2b and Appendix Table 1 5-6
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6 and 7
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.