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Keywords:	Lung cancer, Health-related quality of life, low-dose chest CT, screening, early detection

Health-Related Quality of Life and Anxiety in the PAN-CAN Lung Cancer Screening Study

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Strengths and Limitation of this Study:

- This study is the first to describe the psychological and quality of life impacts of lung cancer screening on *discrete* individuals undergoing low-dose CT examinations.
- This allows the calculation of number-needed-to-harm estimates based on the minimal clinically significant difference of each instrument rather than mean group changes, important in the informed decision-making process with individuals considering this intervention.
- Our cohort was drawn from a multi-center study with high follow-up rates using a participant's baseline status to detect any changes post-screening.
- Limitations include the lack of an unscreened control group and the relative homogeneity of our participants (Canadian, Caucasian).

Abbreviation list

AFB: Autofluorescence bronchoscopy

GGO: Ground-glass opacity

HRQoL: Health-related quality of life

LDCT: Low-dose computed tomography

MCID: Minimal Clinically Important Difference

NLST: The National Lung Screening Trial

NNH: Number-needed-to-harm

SF-12: Physical and Mental Component Scales

SIFs: Incidental findings

STAI: State Trait Anxiety Inventory

Abstract

Objectives: The impact of lung cancer screening with low-dose chest CT (LDCT) on participants' anxiety levels and health-related quality of life (HRQoL) is an important consideration in the implementation of such programs. We aimed to describe changes in anxiety and HRQoL in a high-risk Canadian cohort undergoing LDCT lung cancer screening.

Methods: 2,537 subjects who had 2% or greater lung cancer risk over 6 years using a risk prediction tool were recruited from 8 centers across Canada in the Pan-Canadian Early Detection of Lung Cancer Study (2008-2010). We compared HRQoL and anxiety levels before and after screening of 1,237 participants with LDCT, (excluding a subset of 1,300 participants who also underwent autofluorescence bronchoscopy screening), as well as after investigations performed because of a positive screening examination. The 12-item short-form Physical and Mental Component Scales (SF-12), EQ-5D-3L scores, and State Trait Anxiety Inventory (STAI) - State anxiety were used at each assessment.

Results: Overall, there were no clinically significant differences in HRQoL outcomes between baseline and each of the survey time points following initial screening. No mean change in anxiety in the overall cohort was noted following baseline LDCT, but more participants had clinically significant increase in anxiety vs. decrease after baseline screening [increase > Minimal Clinically Important Difference (MCID) (n=180) vs. decrease >MCID (n=50), p<0.001]. This finding persisted but to a lesser degree at the 12-month time point [increase >MCID (n=146) vs. decrease >MCID (n=87), p<0.001] and was present in both the cohort with negative and positive examinations.

Conclusions: CT Screening for Lung Cancer has no major overall impact on HRQoL among participants, although a minority of participants (number-needed-to-harm = 7 after baseline screening and 18 at one year) demonstrated clinically significant increased anxiety levels.

Clinical Trial Registration: ClinicalTrials.gov; No.: NCT00751660; URL: www.clinicaltrials.gov.

Keywords: Health-related quality of life, lung cancer, low-dose chest CT, screening, early detection

INTRODUCTION

Lung cancer is the leading cause of cancer death in North America and around the world,[1]. Early detection and treatment of lung cancer through screening is a promising strategy to reduce lung cancer mortality,[2]. The largest trial performed to date, the National Lung Screening Trial (NLST), demonstrated that low-dose computed tomography (LDCT) screening in high risk individuals (i.e., ever smokers aged 55 to 74 years, ≥30 pack-years of smoking and <15 years since quitting) significantly reduced lung cancer mortality,[3]. American and Canadian preventative health care agencies have since published recommendations in favor of LDCT lung cancer screening,[3,4]. However, no screening intervention is without potential harm, including adverse psychological impact of the screening intervention, screening results, or subsequent investigations in most participants who will not be found to have cancer. Potential detriments of lung cancer screening include anxiety, and distress from the evaluation of both CT detected false positive and over-diagnosed cancers. A small proportion of the screen-detected tumors would never lead to clinical symptoms, but these over-diagnosed lung cancers are frequently treated, with associated risks of adverse effects,[5,6]. Moreover, studies have shown that CT lung screening has a high rate of significant lung cancer-unrelated incidental findings (SIFs),[7]. These SIFs may require additional investigations and therefore can be associated with adverse psychological impact on participants in a screening program,[6].

A recent systematic review on the psychological burden of LDCT revealed that LDCT screening may be associated with a short-term psychological burden in participants,[8]. Studies to date have explored mean changes in groups of individuals rather than rates of clinically significant changes in individuals screened. Effective policy decisions regarding the implementation of lung cancer screening and informed decision making by individuals requires reliable evidence on its potential impacts on Health Related Quality of

Life (HRQoL) and psychological wellbeing of individual participants,[9]. Therefore, this study aimed to evaluate the impact of screening modalities on the quality of life and anxiety of participants in the Pan-Canadian Early Detection of Lung Cancer Study.

METHODS

Study design and population

The Pan-Canadian Early Detection of Lung Cancer Study, which has been described in detail previously,[10,11], enrolled current or former smokers aged between 50-75 years and with a 2% or greater lung cancer risk over 6 years using a risk-prediction model developed using Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial data,[12]. Participants were recruited in 8 centers across Canada (Calgary, Halifax, Hamilton, Laval, Ottawa, St-John's, Toronto and Vancouver) from September 2008 to December 2010 with each centers' institutional review board approving the study. Signed informed consent was obtained from each participant.

All participants were offered baseline LDCT with repeat screening at year 1 and 4 in addition to LDCT scans as appropriate for nodule follow-up, with the first half of the recruited subjects to receive autofluorescence bronchoscopy (AFB) as an additional screening modality,[13]. However, since AFB does not appear effective in the screening environment,[13], and to avoid the potential confounding impact of AFB on HRQL, participants in the AFB arm of the study are excluded from the current analysis.

LDCT scan follow-up protocol were determined by the maximum long axis diameter of the largest nodule identified. Participants with any semi-solid or solid nodule 5 to 10 mm, or ground-glass opacity (GGO) 8-10 mm were to receive an additional LDCT at 3 months, with larger lesion being referred for clinical consultation. Any participant requiring repeat LDCT or investigation for a lung lesion other than a planned 12-month follow-up examination were considered to have a positive screening exam for the purpose of this analysis (figure 1). Participants were informed of the various possible findings which may be found on CT examinations and general protocols for investigations at the time of study consent.

Individualized results letters with description of findings appropriate for a non-medical reader were developed by each study site.

Health-Related Quality of life (HRQoL), and anxiety

The 12-item short-form (SF-12) Physical and Mental Component Scales (PCS, and MCS, respectively),[14] and the EuroQoL questionnaire [EQ-5D-3L (Three-level version of EQ-5D)] were used to determine the participants' HRQoL at each assessment. The test–retest reliability coefficient is reported to be 0.89 for the PCS and 0.76 for the MCS. The EQ-5D-3L consists of a preference-based index score and a visual analogue scale (VAS); the index scores were derived from the current Canadian tariff,[15], (a maximum (best) value of 1 (for health state 11111) and a minimum value of -0.34 (for 33333)). The VAS is a likert scale asking participants to draw a line to their current health status on a visual scale ranging between 0 and 100. Scores on the SF-12 are standardized (i.e., mean = 50 and SD = 10), with a higher score indicating better HRQoL.

To evaluate potential anxiety induced by the results of the screening tests, we used the Spielberger State Trait Anxiety Inventory (STAI),[16]. Additional methodology details are provided in the online supplement.

The questionnaires were administered in person at the time of study enrolment (baseline), then by phone within 1 month after the CT results were received by the participants, 1 month after any additional follow-up CT scan or other testing following a positive screen (post investigations) and prior to the 1st annual repeat LDCT (12 months post baseline) (figure 1).

Statistical analyses

Descriptive analyses of the participants' characteristics and screening outcome were performed. We calculated summary scores of outcome measures for participants in each category at each of the study time points (at baseline, 1 month post baseline CT scan, 12 months after baseline, and post investigations). In addition, the above scores were compared separately in the subset of participants with a positive screening intervention.

To compare overall differences in HRQoL and State-anxiety scores between baseline and each of the survey time points, Generalized Linear Mixed Models were used to take into account the clustering of data within the 8 study sites and the repeated measurement of each individuals as well as non-normally distributed/skewed outcomes. The estimated margin of means with adjustment for multiple comparisons (Bonferroni correction) was calculated to contrast baseline versus each of the study time points. In these estimations, margins involving empty cells were treated as not estimable. When significant long-term differences were noted in our mixed model, we further explored the factor association with the observed changes using a multivariate regression model with adjustment for scan results, age, gender, self-reported race, smoking status, pack-years, alcohol consumption, education, family history of any cancer, participants' concern about getting lung cancer at baseline, and for the clustering of data within 8 study sites.

We further calculated the proportion of individuals with improvement vs. deterioration greater than the MCID for each instrument. MCIDs for outcome measures were selected based on previously published results as follows: EQ visual analog scale (VAS)=8,[17], EQ-5D-3L index values=0.05,[18], PCS=8.1,[19], MCS=4.7,[14], STAI-State Anxiety=10,[20]. The comparisons between these two proportions were performed using Z-test and if significant, the excess number of cases with improvement vs. worsening scores were calculated as a percentage of cases with available data. When significant

differences were noted, a number-needed-to-harm (NNH) calculation was applied (total number of case/excess cases with worsened score).

Two-sided p-values < 0.05 were considered as statistically significant. All analyses were performed using SPSS, version 24 (IBM Corp., Armonk, N.Y., USA) or STATA version 14 (StataCorp, College Station, Texas). Sample size was determined by other primary study factors relating to the screening intervention and not the current analysis.

Patient and Public Involvement

Patient and public involvement in the design of the research was included through the main funding agencies collaborating on the project. This includes the Terry Fox Research Institute, the research arm of The Terry Fox Foundation. In addition, public input was obtained through involvement of the Canadian Partnership Against Cancer, an independent organization funded by the federal government to accelerate action on cancer control for all Canadians. Patients were not specifically involved in the recruitment and conduct of the study and no specific plan to disseminate research findings to participants has been made.

RESULTS

Participant characteristics

Two thousand five hundred and thirty-seven participants were enrolled in the Pan-Can study, and 1,237 underwent LDCT alone (without AFB). The mean (SD) age of these participants was 62·9 (6.1) at baseline. Males 558 (45.1 %), Caucasian 1201 (97·1 %), current smokers 768 (62.1 %), and regular alcohol drinkers 961 (77.7 %) comprised the largest groups of participants. The median (IQR) pack-years of smokers was 51.3 (21.6) and mean (SD) duration of smoking was 43.9 (6.1) years. A family history of lung cancer was present in 392 participants (26.6 %), (table 1). Median (IQR) lung cancer risk score was 3.5% (2.9) over 6 years. Positive baseline LDCT examinations were noted in 279 (22.6 %) participants of which 110 (15·1 %) led to a diagnosis of lung cancer.

Table 1-Baseline characteristics of Pan-Canadian Early Detection of Lung Cancer Study participants.

Characteristics	**All Enrolled (n=1237)**
Age, mean (SD)	62.9 (6.1)
Gender (males), n (%)	558 (45.1)
Race *	
Caucasian	1201 (97.1)
Asian	15 (1.2)
Black or African Canadian	7 (0.6)
Aboriginal	4 (0.3)
Pacific Islander	0 (0.0)
Other	10 (0.8)
Education	
8th grade or less	32 (2.3)
9th to 12th grade	153 (12.4)

High school graduate	337 (27.2)
Bachelor's degree	107 (8.7)
Technical/Vocational/School certificate	260 (21.0)
Associate degree/some college	205 (16.6)
Advanced Degree	144 (11.6)
Smoking habits	
Current smokers, n (%)	768 (62.1)
Pack- years, median (IQR, range)	51.3 (21.6, 2.2-230)
Smoking duration, mean (SD)	43.9 (6.1)
Alcohol consumption	
Current regular drinkers**	961 (77.7)
Family history of lung cancer, n (%)	392 (31.7)
Being worried about getting lung cancer	
Rarely or never	267 (21.6)
Sometimes	656 (53.0)
Often	235 (19.0)
All of the time	75 (6.1)
Scan results at baseline	
Positive	279 (22.6)
Negative	958 (77.4)
Lung cancer risk score, median (IQR, range)	3.5 (2.9, 2.0-33.5)

* Missing, n (%)=5 (0·2).

**Regular alcohol consumption: having more than one drink per week for a period of 6 months or more. Missing, n=11.

Health-related quality of life and anxiety measures

Baseline

At baseline, participants reported being concerned about getting lung cancer always (6.1 %), often (19.0%) and sometimes (53.0 %). General health problems were reported by 65·0% of respondents on at least one item on the EQ-5D-3L. Average baseline EQ visual analogue scale (VAS), EQ-5D-3L index values, PCS, MCS, and STAI-State Anxiety scores were 76.3, 0.84, 46.1, 51.1, and 30.9, respectively (Table 2).

Initial screening

No statistically significant mean changes in EQ VAS, EQ-5D-3L index values, PCS, or MCS levels were noted following baseline CT screening. In addition, the proportion of individuals experiencing a deterioration vs. improvement greater than the MCID for EQ VAS(figure 2), EQ-5D-3L(figure 3), PCS(figure 4) and MCS(figure 5) were not significantly different. However, the STAI-State Anxiety levels increased in participants following baseline LDCT [change (95% CI): 2.27 (0.57 to 3.96), p-value <0.001] (Table 2). A greater proportion of individuals experienced a deterioration vs. improvement greater than the MCID of 10 for the STAI - State Anxiety levels was also noted [increase >MCID (n=180) vs. decrease >MCID (n=50), p-value <0·001](figure 6). The excess number of participants with increased vs. decreased anxiety represents 13.8% [(180-50)/937, NNH = 7] of participants with available data. This change remained significant even if only participant with a negative screen were considered [increase >MCID (n=129) vs. decrease >MCID (n=40), p-value < 0.0001]. Multivariate regression analysis demonstrated female gender and increased baseline concern about getting lung cancer to be associated with increased anxiety following screening (Table 3).

Table 2- HRQoL, and anxiety measures at baseline and at different time-points within the study. Generalized linear mixed model.

	Baseline (n=1,237)	1-month post baseline CT scan Mean, change (95% CI) (n=953)	12-months after baseline CT Mean, change (95% CI) (n=1066)
EQ VAS[1]	76.3	76.8, 0.42 (-1.39 to 2.23)	76.8, 0.22 (-0.88 to 1.32)
EQ-5D-3L index values	0.84	0.84, -0.00 (-0.02 to 0.01)	0.84, -0.00 (-0.01 to 0.01)
SF-12: PCS[2]	46.1	46.8, 0.61 (-0.15 to 1.37)	46.4, 0.31 (-0.55 to 1.17)
SF-12: MCS[3]	51.1	50.9, -0.26 (-1.04 to 0.52)	51.2, -0.14 (-1.14 to 0.86)
STAI-State Anxiety [4]	30.9	**33.1, 2.27 (0.57 to 3.96)** [5]	31.7, 1.11 (-1.11 to 3.33)

[1] EQ Visual Analogue Scale "We would like to know how good or bad your health is today" (100 – best imaginable, 0 – worst imaginable).

[2] Physical Health Composite Scores (US population mean = 50 +/- 10), with higher score corresponding to better state.

[3] Mental Health Composite Scores (US population mean = 50 +/- 10), with higher score corresponding to better state.

[4] STAI-State score >39 considered clinically significant symptoms.

[5] P-value < 0.05 compared with baseline. Post-estimated marginal means with adjustment for multiple comparison (Bonferroni).

Table 3-Factor associated with changes in anxiety levels from baseline to 1-month post baseline CT scan.

	Changes in anxiety levels (STAI-S) Beta coefficient (95 % CI)
Positive scan results	-0.70 (-1.91 to 0.51)
Age	-0.09 (-0.18 to 0.01)
Females	**1.01 (0.02 to 2.16)***
Current smokers	0.57 (-0.50 to 1.64)
Pack-years	-0.01 (-0.03 to 0.01)
Current alcohol consumption	-0.63 (-1.86 to 0.60)
Family history of any cancer	-1.14 (-2.28 to 0.01)
Participants' concern about getting lung cancer	
All the time	**3.79 (0.24 to 7.32)***
Often	1.73 (-0.00 to 3.47)
Sometimes	0.99 (-0.12 to 2.10)

Multivariate regression model with adjustment for scan results, age, gender, race, smoking status, pack-years, alcohol consumption, education, family history of any cancer, participants' concern about getting lung cancer at baseline, and for the clustering of data within 8 study sites. *p<0.05

Twelve-month assessment

No statistically significant mean changes in EQ VAS, EQ-5D-3L index values, PCS, or STAI - State Anxiety levels were detected in participants at the 12 month interview. The proportion of individuals with deterioration vs. improvement greater than the MCID for the instrument remained significant for the State anxiety levels [increase >MCID (n=146) vs. decrease >MCID (n=87), p-value <0.0001], representing 5.5% [(146-87)/1066, NNH=18] of participants (figure 6). The proportion of individuals experiencing a deterioration vs. improvement greater than the MCID for EQ VAS(figure 2), EQ-5D-3L(figure 3), PCS(figure 4) and MCS(figure 5) were not significantly different.

Positive screen and investigation

Among participants receiving a positive scan results (n=279), no statistically significant mean changes in EQ VAS, EQ-5D-3L index values, PCS, or MCS were detected following baseline LDCT (online Supplementary Table 1). However, more participants experienced a clinically significant increase vs. decrease in anxiety score [increase >MCID (n= 20) vs. decrease >MCID (n=41), p-value=0.002] representing 8.8% [(41-20)/238, NNH=11] of these participants (figure 7). This increase persisted at the 12 month interview [increase >MCID (n=14) vs. decrease >MCID (n=35), p-value=0.003] representing 8.5% [(35-14)/246, NNH=12] of participants (figure 8).

Following investigation examinations, no statistically significant mean changes in EQ VAS, EQ-5D-3L index values, PCS, MCS, or anxiety were detected. Post-investigation changes revealed no statistically significant changes in the proportion of individuals with deterioration vs. improvement greater than the MCID (figure 7).

The proportion of different levels of each questionnaires' dimensions by study visits, as well as number of missing values, are shown in the online Supplementary Table 2 to 4.

DISCUSSION

This study offers detailed information on HRQoL and anxiety following LDCT for lung cancer screening in a Canadian high-risk selected population using validated assessment tools measuring overall HRQoL as well as specific physical, psychological and anxiety scores. Our study found no clinically significant differences in HRQoL outcomes between baseline and each of the survey time points following initial screening in the cohort as a whole. However, more participants experienced a clinically significant increased anxiety (vs. decreased) following baseline LDCT. This finding was more pronounced among females and participants who were concerned about getting lung cancer at baseline. Higher anxiety was also more frequent in the subgroup with positive baseline scan, although the impact of scan results did not reach statistical significance in the multivariate analysis. Over the long-term, no adverse effects on HRQoL were noted but some of the excess in increased anxiety levels persisted.

In line with our findings, analyses of other screening cohorts including NLST,[21] NELSON,[22] PLCO,[23] and UKLS,[24] as well as two recent meta-analyses have demonstrated that lung cancer screening is associated with little to no adverse physical or psychological long-term impact on participants[8,25]. While analysis of the Danish Lung Cancer Screening Trial did show negative consequences at 1 year,[26] and 2 year,[27] follow-up, the degree of change was actually greater in the control (no screening) arm of the trial.

Our finding of increased anxiety following a positive screen is in line with those reported in the UKLS,[24] and NLST trials,[21] which observed a short-term increase in distress levels two weeks or 2 months respectively after a positive result notification of baseline screening. Results from NELSON,[28] and from the Pittsburgh Lung Screening Study,[29] also reported a short-term lung cancer-specific

distress, a poorer quality of life and a higher level of anxiety among participants with indeterminate scan results compared with those with negative results. However, in both studies these negative impacts disappeared over time.

Similar to our findings, NELSON study reported a worse HRQoL outcomes among females compared to males,[28]. Furthermore, our observation regarding females is also consistent with the results of a study of PLCO participants,[23] that found a poorer MCS outcomes in females compared to males.

In most cases reported to date, statistically significant mean changes in HRQoL-related scores detected in groups of screened individuals have been small and of questionable clinical significance limiting the impact of such findings in clinical decision-making. Conversely, lack of statistically significant changes in population means can mask clinically meaningful changes in individuals. The MCID has been suggested to be a useful benchmark to define the smallest difference in HRQoL that individuals perceive as beneficial or harmful and that mandates a change in management,[30]. Only two previous lung cancer screening trial have reported MCID levels to interpret the changes in HRQoL of participants,[22,24,28]. However, both applied this concept to mean population changes rather than to discrete individual changes. Our study is unique in providing discrete participant data on the proportion of individuals with improvement vs. deterioration greater than the MCID for each assessment tool. This has allowed us to attribute to the intervention excess cases of deterioration vs. improvement given normal expected variations in each individual over time. This is not only helpful in determining if a true clinically significant impact is present, but also in specifying how many individuals are impacted by such a change, in order to calculate a "number-needed-to-harm" value. With this approach, we found that the proportion of individuals with improvement vs. deterioration greater than the MCID for the STAI was significantly different among all participants with a number needed to harm of 7 in the short term following screening,

and 18 at one-year post screening. Our data adds to an evolving body of evidence which suggests that LDCT screening for lung cancer does not have overall significant negative impacts on the HRQoL of the population screened. However, a minority of individuals do experience small but clinically significant increases in anxiety levels following screening.

The major strengths of our study include the use of a large multicenter sample of eligible participants, and reporting of individual participant data using three different and well-established instruments for measuring HRQoL and anxiety as well as the risk prediction model used for the recruitment,[31]. Another strength of our study is the longitudinal design with a high follow-up and response rate, which enabled us to assess short- and long-term outcomes at different time points during screening process with each participant serving as his/her own control. While we enrolled a high risk cohort using a risk prediction model, our participants' baseline HRQoL metrics appeared comparable to those of similarly aged individuals in the general population [Adult aged 55-69; mean EQ VAS: 76,[32] State anxiety: 32.2-34.5,[15]. Adult aged 50-69; PCS: 50.9-51.3, MCS: 50.7-50.9,[13]] suggesting that our findings could be generalizable to a broader population of screen-eligible individuals but with lower risk of lung cancer than in our population.

The current study has potential limitations. Our population was made up almost entirely of Caucasians, so that a differential impact of screening on other ethnic communities cannot be determined. Owing to the study design for HRQoL assessments, we were unable to address the impacts of incidental findings on HRQoL and anxiety of participants. Another potential limitation is that we did not compare our results to an unscreened control group but instead used each participant's baseline scores. As such, other factors unrelated to the screening intervention, such as aging or changes in smoking status, could affect the longitudinal changes (or lack thereof) noted in our study,[34]. However, two previous studies with a

randomized design and a control group reported the HRQoL results that were comparable to our findings,[14,20]. Another potential limitation is that the EQ-5D-3L is usually associated with a ceiling effect (i.e., scores recording perfect health),[35] and has limited ability to determine small changes in health status compared to the five-level EQ-5D-5L, which might offer improved measure of population-weighted health state utility,[36,37]. In our study, 35 % of participants reported perfect scores on EQ-5D-3L at baseline; suggesting a ceiling effect that was adjusted for with a generalized linear mixed modeling approach,[38]. Moreover, HRQoL in our study was also measured by SF-12, which has been known to demonstrate a smaller ceiling/floor effect compared to EQ-5D-3L,[35]. In our study, no ceiling/floor effect was observed for the SF-12 scores. Finally, the statistical power to detect changes in some participant subgroups such as those with positive screens may be limited because of low number of participants with a positive scan results. Therefore, caution should be used in drawing conclusions.

The complexity of longitudinal analysis of HRQoL and the lack of agreed upon standardized approach compromise the comparison of results between studies,[39]. Even the specific MCID level for each instrument can be debated. Ideally such levels are determined in the specific population of interest, but such information is rarely available. Levels chosen for our analysis were determined prior to any data analysis based on best evidence for each instrument. As a confirmatory step, MCIDs selected in this study were found to approximate estimates obtained as half a Standard Deviation (SD) (MID) of HRQol measures in our population (results not shown), an alternative distribution-based approach to MCID determination,[40].

The findings of our study corroborate and expand the current evidence-based information on lung cancer screening decision making by showing that there is a minimal overall psychological impact associated with lung cancer screening. However, certain populations (i.e., females, participants with higher baseline

concern about lung cancer) may be at a higher risk of negative psychological impact. This suggests that an improved communication is needed throughout the entire lung cancer screening process, especially for the potentially vulnerable subgroups. Since most positive screens do not result in a lung cancer diagnosis, approaches to better define screening exam findings and reduce false positive rates could be effective in reducing the anxiety burden in this subgroup. Despite the high rate of false positive CT results in lung cancer screening, there is no clear recommendation yet on psychological interventions to help individuals cope with abnormal CT screening results. However, literature on mammography screening has shown that immediate follow-up and consultation can significantly reduce anxieties after receiving abnormal mammograms,[41].

In conclusion, our study demonstrated that CT Screening for Lung Cancer has no major impact on HRQoL among participants overall, but some individuals experience clinically significant increase in anxiety with a number needed to harm of 18 at one year post initial screen. While these impacts may appear minor in view of the robust mortality reduction associated with LDCT screening, ongoing work to further define and minimize these negative aspects of screening is warranted given recommendations for broad screening of at risk populations in North America.

Author's contributions:

AT, SCL, MCT, NT, SC and SAK had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects as well as the final version of the manuscript. AMC, PM, SP, MJ, JG, GG, GN, SM, FL, RB, GL, HR, MST, contributed substantially to the study design, data interpretation, and review of the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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Data Sharing Statement

No additional unpublished data from the study is made available.

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Figure legends

Figure 1- Assessments of the health-related quality of life (HRQoL) and anxiety in the Pan-Canadian Early Detection of Lung Cancer Study.

Figure 2: Changes in EuroQoL Visual Analog Scale (VAS) from baseline to post baseline CT(A), and 12 months after baseline(B).

Figure 3: Changes in EuroQoL(EQ)-5D-3L from baseline to post baseline CT(A), and 12 months after baseline(B).

Figure 4: Changes in 12-item short-form Physical Component Scale(PCS) from baseline to post baseline CT(A), and 12 months after baseline(B).

Figure 5: Changes in 12-item short-form Mental Component Scale (MCS) from baseline to post baseline CT(A), and 12 months after baseline(B).

Figure 6: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT(A), and 12 months after baseline(B).

Figure 7: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT (A) and post investigation (B) among participants with a positive scan results.

Figure 8: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to 12 months among participants with a positive scan results.

Figure 1- Assessments of the health-related quality of life (HRQoL) and anxiety in the Pan-Canadian Early Detection of Lung Cancer Study.

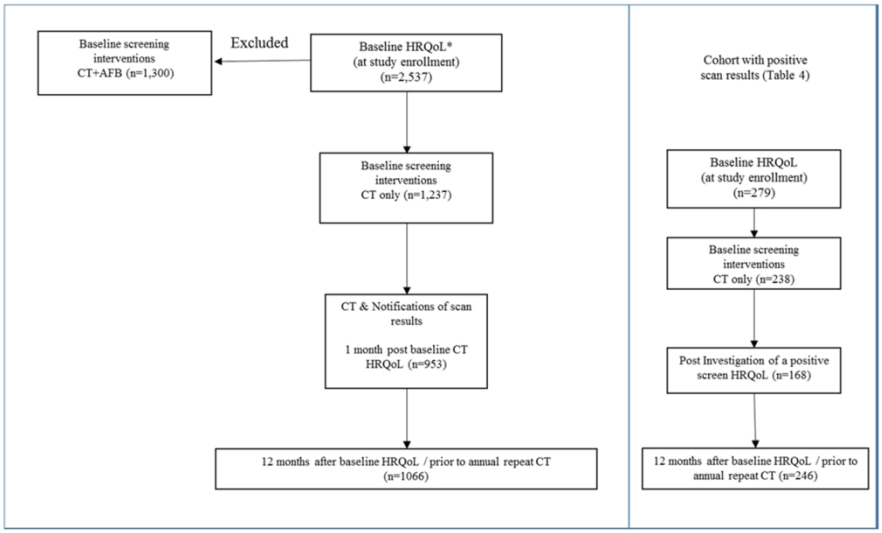

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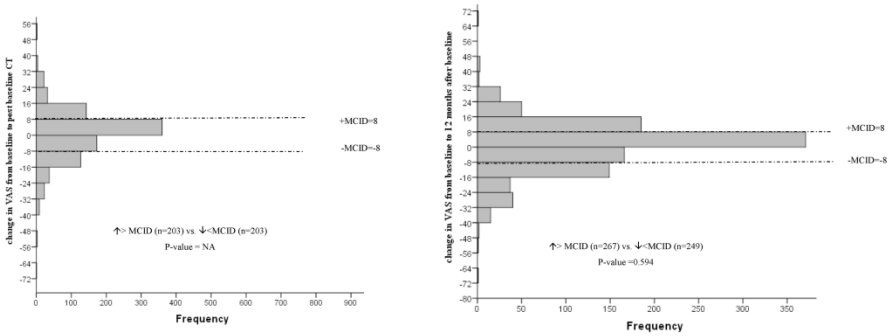
Figure 2: Changes in EuroQoL Visual Analog Scale (VAS) from baseline to post baseline CT(A), and 12 months after baseline(B).



(A) **(B)**

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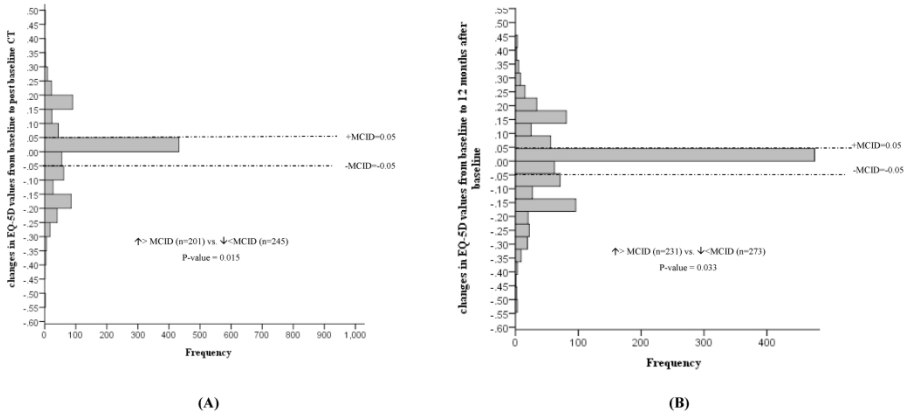
Figure 3: Changes in EuroQoL(EQ)-5D-3L from baseline to post baseline CT(A), and 12 months after baseline(B).



(A) (B)

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Figure 4: Changes in 12-item short-form Physical Component Scale(PCS) from baseline to post baseline CT(A), and 12 months after baseline(B).

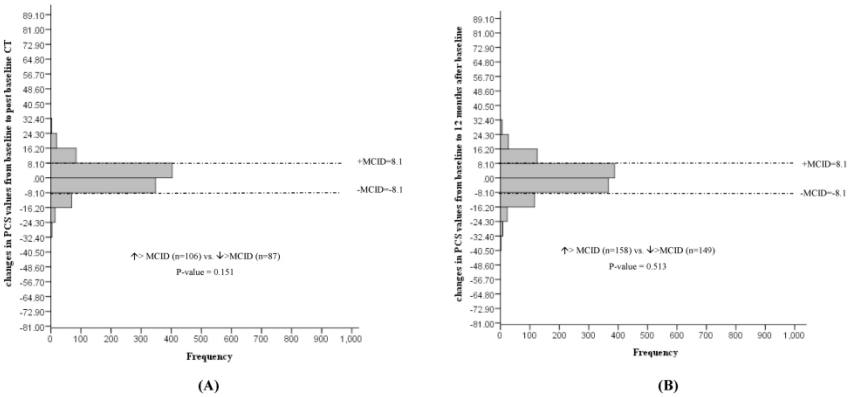

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Figure 5: Changes in 12-item short-form Mental Component Scale (MCS) from baseline to post baseline CT(A), and 12 months after baseline(B).

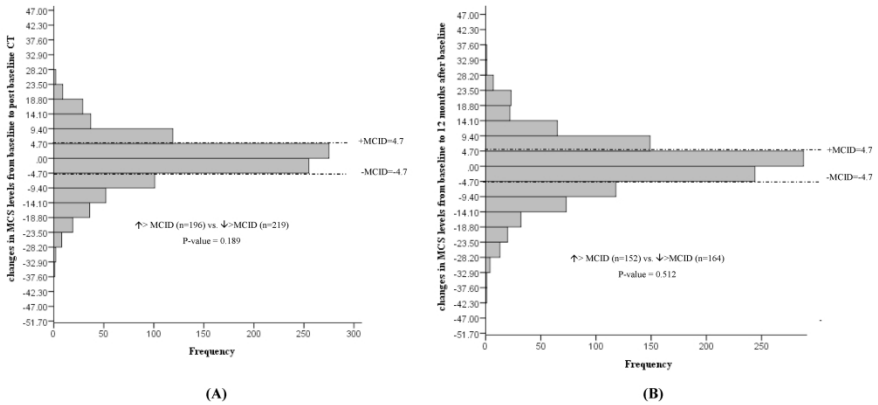

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Figure 6: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT(A), and 12 months after baseline(B).

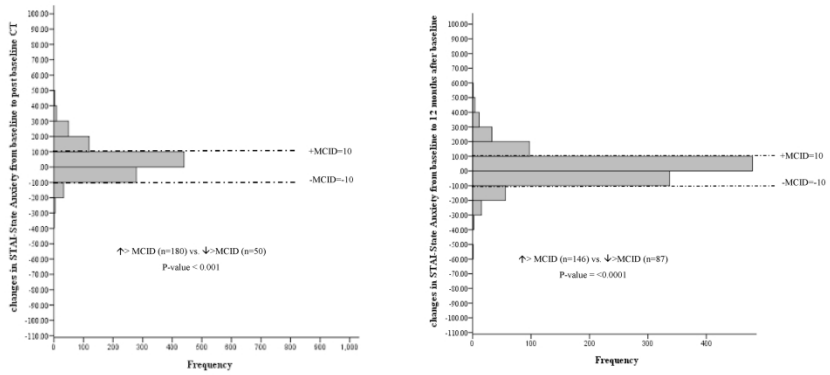

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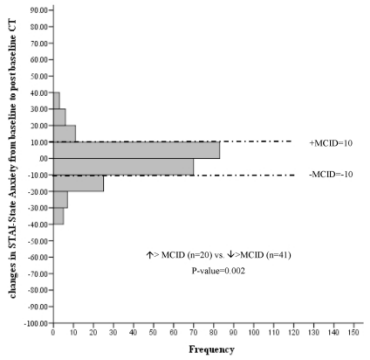
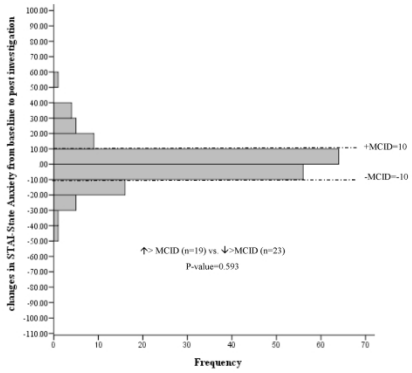
Figure 7: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT (A) and post investigation (B) among participants with a positive scan results.



(A)



(B)

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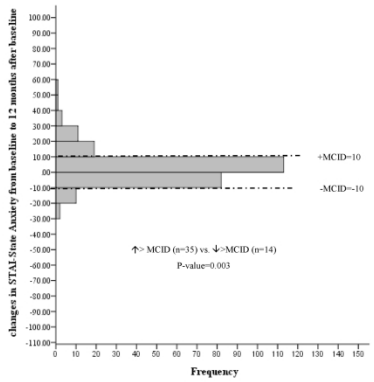
Figure 8: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to 12 months among participants with a positive scan results.



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Health-Related Quality of Life and Anxiety in the PAN-CAN Lung Cancer Screening Study

Niloofar Taghizadeh[1], Alain Tremblay[1], Sonya Cressman[2], Stuart Peacock[2], Annette M. McWilliams[3], Paul MacEachern[1], Michael Johnston[4], John Goffin[5], Glen Goss[6], Garth Nicholas[6], Simon Martel[7], Francis Laberge[7], Rick Bhatia[8], Geoffrey Liu[9], Heidi Roberts[9], Martin C. Tammemagi[10], Sukhinder Atkar-Khattra[2], Ming-Sound Tsao[9], Stephen C. Lam[2], for the Pan-Canadian Early Lung Cancer Study Group.

e-Appendix 1:

Study design and population

Institutional Review Board (IRB) Approvals:

Vancouver: UBC BCCA Research Ethics Board (UBC BCCA REB) H08-01132

Calgary: Conjoint Health Research Ethics Board (CHREB) ethics ID: 21852

Hamilton: McMaster University Research Ethics Board; ID: 08-367

Toronto: University Health Network Research Ethics Board; ID: 08-0576-C

Ottawa: The Ottawa Hospital Research Ethics Board; ID 2008581-01H

Quebec: Institute Universitaire de Cardiologie et de Pneumologie; ID: CER: 20319

Halifax: Capital Health Research Ethics Board; ID: CDHA-RS/2009-097

St.John's: Eastern Health Department of Reseasrch/Knowledge transfer; ID; HIC#10.070

Supplementary Table 1 – HRQoL, and anxiety levels in participants with positive baseline LDCT.

	Baseline (n=279)	1-month post baseline CT scan Mean, change (95% CI) (n=238)	Post investigation Mean, change (95% CI) (n=168)	12-months after baseline Mean, change (95% CI) (n= 246)
EQ VAS[1]	76.2	76.1, -0.21 (-2.54 to 2.13)	76.9, 0.89 (-3.28 to 5.07)	76.4, 0.19 (-1.73 to 2.11)
EQ-5D-3L index values	0.84	0.84, -0.00 (-0.03 to 0.03)	0.85, 0.00 (-0.03 to 0.04)	0.83, -0.01 (-0.05 to 0.02)
SF-12: PCS[2]	46.2	46.5, 0.22 (-0.83 to 1.28)	46.6, 0.45 (-0.93 to 1.83)	45.3, -0.86 (-1.90 to 1.67)
SF-12: MCS[3]	51.3	51.2, 0.01 (-1.66 to 1.67)	51.4, 0.54 (-2.06 to 3.15)	51.3, 0.01 (-2.30 to 2.33)
STAI-State Anxiety [4]	29.9	33.2, 3.28 (-0.42 to 6.97)	32.9, 2.42 (-1.14 to 5.99)	31.7, 1.79 (-0.62 to 4.19)

[1] EQ Visual Analogue Scale "We would like to know how good or bad your health is today" (100 – best imaginable, 0 – worst imaginable).

[2] Physical Health Composite Scores (US population mean = 50 +/- 10), with higher score corresponding to better state.

[3] Mental Health Composite Scores (US population mean = 50 +/- 10), with higher score corresponding to better state.

[4] STAI-State score >39 considered clinically significant symptoms.

Supplementary Table 2 - Proportion of different levels of EQ-5D-3L dimensions by study visits (Total n=1237).

EQ-5D-3L Dimensions	Baseline (n=1237)	1 month post baseline CT scan (n=953)	12 months after baseline (n=1066)
Mobility			
I have no problems in walking about	918 (74.2)	705 (74.0)	782 (73.4)
I have some problems in walking about	311 (25.2)	240 (25.2)	278 (26.1)
I am confined to bed	4 (0.3)	3 (0.3)	0 (0.0)
Missing	4 (0.3)	5 (0.5)	6 (0.6)
Self-care			
I have no problems with self-care	1191 (96.2)	914 (95.9)	1018 (95.5)
I have some problems washing or dressing myself	36 (2.9)	31 (3.3)	39 (3.7)
I am unable to wash or dress myself	7 (0.6)	2 (0.2)	3 (0.3)
Missing	3 (0.3)	6 (0.6)	6 (0.6)
Usual activities			
I have no problems with performing my usual activities	930 (75.1)	710 (74.5)	785 (73.6)
I have some problems with performing my usual activities	284 (22.9)	228 (23.9)	261 (24.5)
I am unable to perform my usual activities	18 (1.5)	8 (0.8)	15 (1.4)
Missing	5 (0.5)	7 (0.7)	5 (0.5)
Pain/discomfort			
I have no pain or discomfort	575 (46.4)	471 (49.4)	498 (46.7)
I have moderate pain or discomfort	622 (50.2)	443 (46.5)	520 (48.8)
I have extreme pain or discomfort	36 (2.9)	33 (3.5)	40 (3.8)
Missing	4 (0.4)	6 (0.6)	8 (0.8)
Anxiety/depression			
I am not anxious or depressed	835 (64.4)	610 (64.0)	708 (66.4)
I am moderately anxious or depressed	375 (30.3)	307 (32.2)	332 (31.1)
I am extremely anxious or depressed	23 (1.9)	28 (2.9)	19 (1.8)
Missing	4 (0.4)	8 (0.8)	7 (0.7)

Supplementary Table 3- Proportion of different levels of SF_12 dimensions by study visits (Total n=2537).

SF_12 Dimensions	Baseline (n=1237)	1 month post baseline CT scan (n=953)	12 months after baseline (n=1066)
General health, n (%)			
Excellent	93 (7.5)	85 (8.9)	89 (8.3)
Very good	453 (36.6)	367 (38.5)	392 (36.8)
Good	532 (43.0)	381 (40.0)	450 (42.2)
Fair	138 (11.1)	105 (11.0)	108 (10.1)
Poor	18 (1.5)	12 (1.3)	20 (1.9)
Missing	3 (0.3)	3 (0.3)	7 (0.7)
Moderate activities			
Yes, limited a lot	97 (7.8)	77 (8.1)	75 (7.0)
Yes, limited a little	310 (25.0)	256 (26.9)	267 (25.0)
No, not limited at all	827 (66.8)	617 (64.7)	714 (67.0)
Missing	3 (0.3)	3 (0.3)	10 (0.9)
Climbing several flights of stairs			
Yes, limited a lot	191 (15.4)	140 (14.7)	161 (15.1)
Yes, limited a little	551 (44.5)	432 (45.3)	462 (43.3)
No, not limited at all	491 (39.7)	376 (39.5)	436 (40.9)
Missing	4 (0.3)	5 (0.5)	7 (0.7)
Accomplished less than you would like (physically)			
Yes	335 (27.1)	221 (23.2)	265 (24.9)
No	899 (72.6)	727 (76.3)	795 (74.6)
Missing	3 (0.3)	5 (0.5)	6 (0.6)
Limited in kind of activities			
Yes	299 (24.2)	221 (23.2)	265 (24.9)
No	934 (75.4)	729 (76.5)	795 (74.6)
Missing	4 (0.4)	3 (0.3)	6 (0.6)
Accomplished less than you would like (emotionally)			
Yes	251 (20.3)	212 (22.2)	222 (20.8)
No	982 (79.3)	735 (77.1)	833 (78.1)
Missing	4 (0.4)	6 (0.6)	11 (1.0)
Did not do activities as carefully as usual			
Yes	215 (17.4)	181 (19.0)	181 (17.0)
No	1018 (82.2)	764 (80.2)	875 (82.1)
Missing	4 (0.4)	8 (0.8)	10 (0.9)
Pain interferes with normal work			
Not at all	596 (48.1)	479 (50.3)	515 (48.3)
A little bit	312 (25.2)	243 (25.5)	288 (27.0)
Moderately	194 (15.7)	138 (14.5)	142 (13.3)
Quite a bit	109 (8.8)	77 (8.1)	98 (9.2)
Extremely	20 (1.6)	13 (1.4)	18 (1.7)
Missing	6 (0.5)	3 (0.3)	5 (0.5)
Felt calm and peaceful			
All of the time	87 (7.0)	73 (7.7)	84 (7.9)
Most of the time	630 (50.9)	460 (48.3)	527 (49.4)
A good bit of the time	184 (14.9)	163 (17.1)	176 (16.5)
Some of the time	214 (17.3)	171 (17.9)	164 (15.4)
A little of the time	96 (7.8)	70 (7.3)	88 (8.3)
None of the time	23 (1.9)	11 (1.2)	18 (1.7)
Missing	3 (0.3)	5 (0.5)	9 (0.8)
Have a lot of energy			
All of the time	36 (2.9)	36 (3.8)	41 (3.8)
Most of the time	416 (33.6)	317 (33.3)	375 (35.2)
A good bit of the time	263 (21.2)	206 (21.6)	213 (20.0)
Some of the time	322 (26.0)	240 (25.2)	249 (23.4)
A little of the time	156 (12.6)	116 (12.2)	145 (13.6)
None of the time	41 (3.3)	34 (3.6)	34 (3.2)
Missing	3 (0.3)	4 (0.4)	9 (0.8)
Felt downhearted and blue			
All of the time	4 (0.3)	5 (0.5)	4 (0.4)
Most of the time	37 (3.0)	37 (3.9)	34 (3.2)
A good bit of the time	79 (6.4)	51 (5.4)	76 (7.1)
Some of the time	273 (22.1)	196 (20.6)	216 (20.3)
A little of the time	480 (38.8)	399 (41.9)	414 (38.8)
None of the time	361 (29.2)	261 (27.4)	312 (29.3)
Missing	3 (0.3)	4 (0.4)	10 (0.9)
Health interferes/social activities			
All of the time	8 (0.6)	10 (1.0)	16 (1.5)
Most of the time	63 (5.1)	42 (4.4)	54 (5.1)
Some of the time	203 (16.4)	150 (15.7)	169 (15.9)
A little of the time	238 (19.2)	182 (19.1)	200 (18.8)
None of the time	722 (58.3)	565 (59.3)	617 (57.9)
Missing	3 (0.3)	4 (0.4)	10 (0.9)

Supplementary Table 4- Proportion of different levels of State anxiety dimensions by study visits (Total n=2537).

State	Baseline (n=1237)					1 month post baseline CT scan (n=953)					12 months after baseline (n=1066)				
Dimensions	**Not at all**	**Somewhat**	**Moderately so**	**Very much so**	**Missing**	**Not at all**	**Somewhat**	**Moderately so**	**Very much so**	**Missing**	**Not at all**	**Somewhat**	**Moderately so**	**Very much so**	**Missing**
I feel calm	17 (1.4)	167 (13.5)	407 (32.9)	643 (51.9)	3 (0.3)	31 (3.3)	136 (14.3)	338 (35.5)	442 (46.4)	6 (0.6)	18 (1.7)	131 (12.3)	393 (36.9)	516 (48.4)	8 (0.8)
I feel secure	16 (1.3)	106 (8.6)	304 (24.6)	808 (65.3)	3 (0.3)	21 (2.2)	115 (12.1)	283 (29.7)	528 (55.4)	6 (0.6)	24 (2.3)	83 (7.8)	330 (31.0)	621 (58.3)	8 (0.8)
I feel tense	685 (55.3)	319 (25.8)	192 (15.5)	36 (2.9)	3 (0.3)	465 (48.8)	300 (31.5)	144 (15.1)	39 (4.1)	5 (0.5)	562 (52.7)	282 (26.5)	177 (16.6)	35 (3.3)	10 (1.0)
I feel strained	834 (67.4)	231 (18.7)	131 (10.6)	38 (3.1)	3 (0.3)	543 (57.0)	261 (27.4)	109 (11.4)	35 (3.7)	5 (0.5)	652 (61.2)	240 (22.5)	134 (12.6)	33 (3.1)	7 (0.7)
I feel at ease	41 (3.3)	154 (12.4)	361 (29.2)	678 (54.8)	3 (0.3)	45 (4.7)	154 (16.2)	289 (30.3)	460 (48.3)	5 (0.5)	27 (2.5)	170 (15.9)	323 (30.3)	538 (50.5)	8 (0.8)
I feel upset	1003 (81.0)	137 (11.1)	75 (6.1)	19 (1.5)	3 (0.3)	660 (69.3)	182 (19.1)	78 (8.2)	28 (2.9)	5 (0.5)	792 (74.3)	175 (16.4)	75 (7.0)	16 (1.5)	8 (0.8)
I am presently worrying over possible misfortunes	694 (56.1)	332 (26.8)	156 (12.6)	52 (4.2)	3 (0.3)	480 (50.4)	295 (31.0)	121 (12.7)	52 (5.5)	5 (0.5)	555 (52.1)	339 (31.8)	115 (10.8)	49 (4.6)	8 (0.8)
I feel satisfied	36 (2.9)	193 (15.6)	469 (37.9)	536 (43.3)	3 (0.3)	47 (4.9)	167 (17.5)	324 (34.0)	410 (43.0)	5 (0.5)	33 (3.1)	192 (18.0)	378 (35.5)	456 (42.8)	7 (0.7)
I feel frightened	1008 (81.4)	149 (12.0)	56 (4.5)	21 (1.7)	3 (0.3)	718 (75.3)	150 (15.7)	59 (6.2)	21 (2.2)	5 (0.5)	846 (79.4)	148 (13.9)	53 (5.0)	11 (1.0)	8 (0.8)
I feel comfortable	30 (2.4)	133 (10.7)	352 (28.4)	719 (58.1)	3 (0.3)	31 (3.3)	135 (14.2)	291 (30.5)	490 (51.4)	6 (0.6)	23 (2.2)	142 (13.3)	333 (31.2)	561 (52.6)	7 (0.7)
I feel self-confident	36 (2.9)	127 (10.3)	439 (35.5)	632 (51.1)	3 (0.3)	38 (4.0)	106 (11.1)	359 (37.7)	445 (46.7)	5 (0.5)	24 (2.3)	127 (11.9)	394 (37.0)	514 (48.2)	7 (0.7)
I feel nervous	780 (63.0)	308 (24.9)	117 (9.5)	29 (2.3)	3 (0.3)	559 (58.7)	255 (26.8)	99 (10.4)	35 (3.7)	5 (0.5)	662 (62.1)	261 (24.5)	114 (10.7)	22 (2.1)22	7 (0.7)
I am jittery	968 (78.2)	174 (14.1)	73 (5.9)	18 (1.5)	4 (0.4)	692 (72.6)	152 (15.9)	77 (8.1)	27 (2.8)	5 (0.5)	811 (76.1)	155 (14.5)	77 (7.2)	15 (1.4)	8 (0.8)
I feel indecisive	846 (68.3)	269 (21.7)	97 (7.8)	22 (1.8)	3 (0.3)	557 (58.4)	246 (25.8)	113 (11.9)	32 (3.4)	5 (0.5)	662 (62.1)	256 (24.0)	100 (9.4)	39 (3.7)	9 (0.9)
I am relaxed	48 (3.9)	181 (14.6)	394 (31.8)	611 (49.4)	3 (0.3)	52 (5.5)	173 (18.2)	313 (32.8)	409 (42.9)	6 (0.6)	30 (2.8)	172 (16.1)	377 (35.4)	480 (45.0)	7 (0.7)
I feel content	48 (3.9)	161 (13.0)	436 (35.2)	589 (47.6)	3 (0.3)	52 (5.5)	147 (15.4)	339 (35.6)	410 (43.0)	5 (0.5)	37 (3.5)	151 (14.2)	408 (38.3)	463 (43.4)	7 (0.7)
I am worried	651 (52.6)	390 (31.5)	146 (11.8)	47 (3.8)	3 (0.3)	423 (44.4)	333 (34.9)	134 (14.1)	58 (6.1)	5 (0.5)	518 (48.6)	361 (33.9)	129 (12.1)	51 (4.8)	7 (0.7)
I feel confused	1075 (86.8)	112 (9.0)	32 (2.6)	12 (1.0)	6 (0.5)	755 (79.2)	135 (14.2)	40 (4.2)	18 (1.9)	5 (0.5)	887 (83.2)	99 (9.3)	50 (4.7)	20 (1.9)	10 (1.0)
I feel steady	43 (3.5)	141 (11.4)	327 (26.4)	720 (58.2)	6 (0.5)	43 (4.5)	126 (13.2)	272 (28.5)	507 (53.2)	5 (0.5)	41 (3.8)	120 (11.3)	316 (29.6)	581 (54.5)	8 (0.8)
I feel pleasant	25 (2.0)	118 (9.5)	416 (33.6)	672 (54.3)	6 (0.5)	30 (3.1)	117 (12.3)	319 (33.5)	482 (50.6)	5 (0.5)	25 (2.3)	115 (10.8)	365 (34.2)	552 (51.8)	9 (0.9)

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

PAGE		Item No	Recommendation
4	**Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
4			(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
	Introduction		
6	Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
7	Objectives	3	State specific objectives, including any prespecified hypotheses
	Methods		
8	Study design	4	Present key elements of study design early in the paper
8	Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
8	Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
n/a			(*b*) For matched studies, give matching criteria and number of exposed and unexposed
8-9	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
9	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
n.a.	Bias	9	Describe any efforts to address potential sources of bias
11	Study size	10	Explain how the study size was arrived at
10	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
10	Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
10			(*b*) Describe any methods used to examine subgroups and interactions
10			(*c*) Explain how missing data were addressed
10			(*d*) If applicable, explain how loss to follow-up was addressed
n/a			(*e*) Describe any sensitivity analyses
	Results		
12	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
n.a.			(b) Give reasons for non-participation at each stage
FIG 1			(c) Consider use of a flow diagram
12	Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
14			(b) Indicate number of participants with missing data for each variable of interest
n.a.			(c) Summarise follow-up time (eg, average and total amount)
14-17	Outcome data	15*	Report numbers of outcome events or summary measures over time
14-17	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
n.a.			(*b*) Report category boundaries when continuous variables were categorized
14, 16			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Suppl	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
	Discussion		
18	Key results	18	Summarise key results with reference to study objectives
20	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
21-22	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
22	Generalisability	21	Discuss the generalisability (external validity) of the study results
	Other information		
23	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

*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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Health-Related Quality of Life and Anxiety in the PAN-CAN Lung Cancer Screening Cohort

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Health-Related Quality of Life and Anxiety in the PAN-CAN Lung Cancer Screening Cohort

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Word Count: 3509

Abbreviation list

AFB: Autofluorescence bronchoscopy

GGO: Ground-glass opacity

HRQoL: Health-related quality of life

LDCT: Low-dose computed tomography

MCID: Minimal Clinically Important Difference

NLST: The National Lung Screening Trial

NNH: Number-needed-to-harm

SF-12: Physical and Mental Component Scales

SIFs: Incidental findings

STAI: State Trait Anxiety Inventory

Abstract

Objectives: The impact of lung cancer screening with low-dose chest CT (LDCT) on participants' anxiety levels and health-related quality of life (HRQoL) is an important consideration in the implementation of such programs. We aimed to describe changes in anxiety and HRQoL in a high-risk Canadian cohort undergoing LDCT lung cancer screening.

Methods: 2,537 subjects who had 2% or greater lung cancer risk over 6 years using a risk prediction tool were recruited from 8 centers across Canada in the Pan-Canadian Early Detection of Lung Cancer Study (2008-2010). We compared HRQoL and anxiety levels before and after screening of 1,237 participants with LDCT, (excluding a subset of 1,300 participants who also underwent autofluorescence bronchoscopy screening), as well as after investigations performed because of a positive screening examination. The 12-item short-form Physical and Mental Component Scales (SF-12), EQ-5D-3L scores, and State Trait Anxiety Inventory (STAI) - State anxiety were used at each assessment.

Results: Overall, there were no clinically significant differences in HRQoL outcomes between baseline and each of the survey time points following initial screening. No mean change in anxiety in the overall cohort was noted following baseline LDCT, but more participants had clinically significant increase in anxiety vs. decrease after baseline screening [Increase > Minimal Clinically Important Difference (MCID) (n=180) vs. decrease >MCID (n=50), p<0.001]. This finding persisted but to a lesser degree at the 12-month time point [increase >MCID (n=146) vs. decrease >MCID (n=87), p<0.001].

Conclusions: CT Screening for Lung Cancer has no major overall impact on HRQoL among participants, although a minority of participants (number-needed-to-harm = 7 after baseline screening and 18 at one year) demonstrated clinically significant increased anxiety levels.

Clinical Trial Registration: ClinicalTrials.gov; No.: NCT00751660; URL: www.clinicaltrials.gov.

Keywords: Health-related quality of life, lung cancer, low-dose chest CT, screening, early detection, cohort study

Strengths and Limitation of this Study:

- This study is the first to describe the psychological and quality of life impacts of lung cancer screening on *discrete* individuals undergoing low-dose CT examinations.
- This allows the calculation of number-needed-to-harm estimates based on the minimal clinically significant difference of each instrument rather than mean group changes, important in the informed decision-making process with individuals considering this intervention.
- Our cohort was drawn from a multi-center study with high follow-up rates using a participant's baseline status to detect any changes post-screening.
- Limitations include the lack of an unscreened control group and the relative homogeneity of our participants (Canadian, Caucasian).

INTRODUCTION

Lung cancer is the leading cause of cancer death in North America and around the world,[1]. Early detection and treatment of lung cancer through screening is a promising strategy to reduce lung cancer mortality,[2]. The largest trial performed to date, the National Lung Screening Trial (NLST), demonstrated that low-dose computed tomography (LDCT) screening in high risk individuals (i.e., ever smokers aged 55 to 74 years, ≥30 pack-years (number of cigarettes per day / 20 x number of years of smoking) and <15 years since quitting) of smoking significantly reduced lung cancer and overall mortality,[3]. American and Canadian preventative health care agencies have since published recommendations in favor of LDCT lung cancer screening,[3,4]. However, no screening intervention is without potential harm, including adverse psychological impact of the screening intervention, screening results, or subsequent investigations in most participants who will not be found to have cancer. Potential detriments of lung cancer screening include anxiety, and distress from the evaluation of both CT detected false positive and over-diagnosed cancers. A small proportion of the screen-detected tumors would never lead to clinical symptoms, but these over-diagnosed lung cancers are frequently treated, with associated risks of adverse effects,[5,6]. Moreover, studies have shown that CT lung screening has a high rate of significant lung cancer-unrelated incidental findings (SIFs),[7]. These SIFs may require additional investigations and therefore can be associated with adverse psychological impact on participants in a screening program,[6].

A recent systematic review on the psychological burden of LDCT revealed that LDCT screening may be associated with a short-term psychological burden in participants,[8]. Studies to date have explored mean changes in groups of individuals rather than rates of clinically significant changes in individuals screened. Effective policy decisions regarding the implementation of lung cancer screening and

informed decision making by individuals requires reliable evidence on its potential impacts on Health Related Quality of Life (HRQoL) and psychological wellbeing of individual participants,[9]. Therefore, this study aimed to evaluate the impact of screening modalities on the quality of life and anxiety of participants in the Pan-Canadian Early Detection of Lung Cancer Study.

METHODS

Study design and population

The Pan-Canadian Early Detection of Lung Cancer Study, which has been described in detail previously,[10,11], enrolled current or former smokers aged between 50-75 years and with a 2% or greater lung cancer risk over 6 years using a risk-prediction model developed using Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial data,[12]. Participants were recruited in 8 centers across Canada (Calgary, Halifax, Hamilton, Laval, Ottawa, St-John's, Toronto and Vancouver) from September 2008 to December 2010 with each centers' institutional review board approving the study (e-Appendix 1). Signed informed consent was obtained from each participant.

All participants were offered baseline LDCT with repeat screening at year 1 and 4 in addition to LDCT scans as appropriate for nodule follow-up, with the first half of the recruited subjects to receive autofluorescence bronchoscopy (AFB) as an additional screening modality,[13]. However, since AFB does not appear effective in the screening environment,[13], and to avoid the potential confounding impact of AFB on HRQL, participants in the AFB arm of the study are excluded from the current analysis.

LDCT scan follow-up protocol were determined by the maximum long axis diameter of the largest nodule identified. Participants with any semi-solid or solid nodule 5 to 10 mm, or ground-glass opacity (GGO) 8-10 mm were to receive an additional LDCT at 3 months, with larger lesion being referred for clinical consultation. Any participant requiring repeat LDCT or investigation for a lung lesion other than a planned 12-month follow-up examination were considered to have a positive screening exam for the purpose of this analysis (figure 1). Participants were informed of the various possible findings which

may be found on CT examinations and general protocols for investigations at the time of study consent. Individualized results letters with description of findings appropriate for a non-medical reader were developed by each study site.

Health-Related Quality of life (HRQoL), and anxiety

The 12-item short-form (SF-12) Physical and Mental Component Scales (PCS, and MCS, respectively),[14] and the EuroQoL questionnaire [EQ-5D-3L (Three-level version of EQ-5D)] were used to determine the participants' HRQoL at each assessment. The test–retest reliability coefficient is reported to be 0.89 for the PCS and 0.76 for the MCS. The EQ-5D-3L consists of a preference-based index score and a visual analogue scale (VAS); the index scores were derived from the current Canadian tariff,[15], (a maximum (best) value of 1 (for health state 11111) and a minimum value of -0.34 (for 33333)). The VAS is a Likert scale asking participants to draw a line to their current health status on a visual scale ranging between 0 and 100. Scores on the SF-12 are standardized (i.e., mean = 50 and SD = 10), with a higher score indicating better HRQoL.

To evaluate potential anxiety induced by the results of the screening tests, we used the Spielberger State Trait Anxiety Inventory Form Y (STAI),[16]. Additional methodology details are provided in the online supplement.

The questionnaires were administered in person at the time of study enrolment (baseline), then by phone within 1 month after the CT results were received by the participants, 1 month after any additional follow-up CT scan or other testing following a positive screen (post investigations) and prior to the 1st annual repeat LDCT (12 months post baseline) (figure 1).

Statistical analyses

Descriptive analyses of the participants' characteristics and screening outcome were performed. We calculated summary scores of outcome measures for participants in each category at each of the study time points (at baseline, 1 month post baseline CT scan, 12 months after baseline, and post investigations). In addition, the above scores were compared separately in the subset of participants with a positive screening intervention.

To compare overall differences in HRQoL and State-anxiety scores between baseline and each of the survey time points, Generalized Linear Mixed Models were used to take into account the clustering of data within the 8 study sites, the repeated measurement of each individual, the non-normally distributed/skewed outcomes, and any missing data. The estimated margin of means with adjustment for multiple comparisons (Bonferroni correction) was calculated to contrast baseline versus each of the study time points. In these estimations, margins involving empty cells were treated as not estimable. When significant long-term differences were noted in our mixed model, we further explored the factor association with the observed changes using a multivariate regression model with adjustment for scan results, age, gender, self-reported race, smoking status, pack-years, alcohol consumption, education, family history of any cancer, participants' concern about getting lung cancer at baseline, and for the clustering of data within 8 study sites.

We further compared the proportion of individuals with improvement vs. deterioration greater than the Minimal Clinically Important Difference (MCID) for each instrument. MCIDs for outcome measures were selected based on previously published results as follows: EQ visual analog scale (VAS)=8,[17], EQ-5D-3L index values=0.05,[18], PCS=8.1,[19], MCS=4.7,[14], STAI-State Anxiety=10,[20]. The

comparisons between these two proportions were performed using Z-test and if significant, the excess number of cases with improvement vs. worsening scores were calculated as a percentage of cases with available data. When significant differences were noted, a number-needed-to-harm (NNH) or number-needed-to-treat (NNT) calculation was applied as appropriate (total number of case/excess cases with worsened or improved score).

Two-sided p-values < 0.05 were considered as statistically significant. All analyses were performed using SPSS, version 24 (IBM Corp., Armonk, N.Y., USA) or STATA version 14 (StataCorp, College Station, Texas). Sample size was determined by other primary study factors relating to the screening intervention and not the current analysis.

Patient and Public Involvement

Patient and public involvement in the design of the research was included through the main funding agencies collaborating on the project. This includes the Terry Fox Research Institute, the research arm of The Terry Fox Foundation. In addition, public input was obtained through involvement of the Canadian Partnership Against Cancer, an independent organization funded by the federal government to accelerate action on cancer control for all Canadians. Patients were not specifically involved in the recruitment and conduct of the study and no specific plan to disseminate research findings to participants has been made.

RESULTS

Participant characteristics

Two thousand five hundred and thirty-seven participants were enrolled in the Pan-Can study, and 1,237 underwent LDCT alone (without AFB). The mean (SD) age of these participants was 62.9 (6.1) at baseline. Males 558 (45.1 %), Caucasian 1201 (97.1 %), current smokers 768 (62.1 %), and regular alcohol drinkers 961 (77.7 %) comprised the largest groups of participants. The median (IQR) pack-years of smokers was 51.3 (21.6) and mean (SD) duration of smoking was 43.9 (6.1) years. A family history of lung cancer was present in 392 participants (31.7%), (table 1). Median (IQR) lung cancer risk score was 3.5% (2.9) over 6 years. Positive baseline LDCT examinations were noted in 279 (22.6%) participants of which 35 (2.8%) led to a diagnosis of lung cancer.

Table 1-Baseline characteristics of Pan-Canadian Early Detection of Lung Cancer Study participants.

Characteristics	**All Enrolled (n=1237)**
Age, mean (SD)	62.9 (6.1)
Gender (males), n (%)	558 (45.1)
Race *, n (%)	
Caucasian	1201 (97.1)
Asian	15 (1.2)
Black or African Canadian	7 (0.6)
Aboriginal	4 (0.3)
Pacific Islander	0 (0.0)
Other	10 (0.8)
Education, n (%)	
8th grade or less	32 (2.3)
9th to 12th grade	153 (12.4)

High school graduate	337 (27.2)
Bachelor's degree	107 (8.7)
Technical/Vocational/School certificate	260 (21.0)
Associate degree/some college	205 (16.6)
Advanced Degree	144 (11.6)
Smoking habits	
Current smokers, n (%)	768 (62.1)
Pack- years, median (IQR, range)	51.3 (21.6, 2.2-230)
Smoking duration (years), mean (SD)	43.9 (6.1)
Alcohol consumption	
Current regular drinkers**, n (%)	961 (77.7)
Family history of lung cancer, n (%)	392 (31.7)
Being worried about getting lung cancer, n (%)	
Rarely or never	267 (21.6)
Sometimes	656 (53.0)
Often	235 (19.0)
All of the time	75 (6.1)
Scan results at baseline, n (%)	
Positive	279 (22.6)
Negative	958 (77.4)
Lung cancer risk score, median (IQR, range)	3.5 (2.9, 2.0-33.5)

* Missing, n (%)=5 (0·2).

**Regular alcohol consumption: having more than one drink per week for a period of 6 months or more. Missing, n=11.

Health-related quality of life and anxiety measures

Baseline

At baseline, participants reported being concerned about getting lung cancer always (6.1 %), often (19.0%) and sometimes (53.0 %). General health problems were reported by 65.0% of respondents on at least one item on the EQ-5D-3L. Average baseline EQ visual analogue scale (VAS), EQ-5D-3L index values, PCS, MCS, and STAI-State Anxiety scores were 76.3, 0.84, 46.1, 51.1, and 30.9, respectively (Table 2).

Baseline screening

No statistically significant mean changes in EQ VAS, EQ-5D-3L index values, PCS, or MCS levels were noted following baseline CT screening. In addition, the proportion of individuals experiencing a deterioration vs. improvement greater than the MCID for EQ VAS(figure 2), EQ-5D-3L(figure 3), PCS(figure 4) and MCS(figure 5) were not significantly different. However, the STAI-State Anxiety levels increased in participants following baseline LDCT [change (95% CI): 2.27 (0.57 to 3.96), p-value <0.001] (Table 2). A greater proportion of individuals experiencing a deterioration vs. improvement greater than the MCID of 10 for the STAI - State Anxiety levels was also noted [increase >MCID (n=180) vs. decrease >MCID (n=50), p-value <0·001](figure 6). The excess number of participants with increased vs. decreased anxiety represents 13.8% [(180-50)/937, NNH = 7] of participants with available data. This change remained significant even if only participant with a negative screen were considered [mean baseline STAI 31.2; increase >MCID (n=129) vs. decrease >MCID (n=40), p-value < 0.0001]. Multivariate regression analysis demonstrated female gender and increased baseline concern about getting lung cancer to be associated with increased anxiety following screening (Table 3).

Table 2- HRQoL, and anxiety measures at baseline and at different time-points within the study. Generalized linear mixed model.

	Baseline (n=1,237)	1-month post baseline CT scan Mean, change (95% CI) (n=953)	12-months after baseline CT Mean, change (95% CI) (n=1066)
EQ VAS[1]	76.3	76.8, 0.42 (-1.39 to 2.23)	76.8, 0.22 (-0.88 to 1.32)
EQ-5D-3L index values	0.84	0.84, -0.00 (-0.02 to 0.01)	0.84, -0.00 (-0.01 to 0.01)
SF-12: PCS[2]	46.1	46.8, 0.61 (-0.15 to 1.37)	46.4, 0.31 (-0.55 to 1.17)
SF-12: MCS[3]	51.1	50.9, -0.26 (-1.04 to 0.52)	51.2, -0.14 (-1.14 to 0.86)
STAI-State Anxiety [4]	30.9	**33.1, 2.27 (0.57 to 3.96) [5]**	31.7, 1.11 (-1.11 to 3.33)

[1] EQ Visual Analogue Scale "We would like to know how good or bad your health is today" (100 – best imaginable, 0 – worst imaginable).

[2] Physical Health Composite Scores (US population mean = 50 +/- 10), with higher score corresponding to better state.

[3] Mental Health Composite Scores (US population mean = 50 +/- 10), with higher score corresponding to better state.

[4] STAI-State score >39 considered clinically significant symptoms.

[5] P-value < 0.05 compared with baseline. Post-estimated marginal means with adjustment for multiple comparison (Bonferroni).

Table 3-Factor associated with changes in anxiety levels from baseline to 1-month post baseline CT scan.

	Changes in anxiety levels (STAI-S) Beta coefficient (95 % CI)
Positive scan results	-0.70 (-1.91 to 0.51)
Age	-0.09 (-0.18 to 0.01)
Females	**1.01 (0.02 to 2.16)***
Current smokers	0.57 (-0.50 to 1.64)
Pack-years	-0.01 (-0.03 to 0.01)
Current alcohol consumption	-0.63 (-1.86 to 0.60)
Family history of any cancer	-1.14 (-2.28 to 0.01)
Participants' concern about getting lung cancer	
All the time	**3.79 (0.24 to 7.32)***
Often	1.73 (-0.00 to 3.47)
Sometimes	0.99 (-0.12 to 2.10)

Multivariate regression model with adjustment for scan results, age, gender, race, smoking status, pack-years, alcohol consumption, education, family history of any cancer, participants' concern about getting lung cancer at baseline, and for the clustering of data within 8 study sites. *p<0.05

Twelve-month assessment

No statistically significant mean changes in EQ VAS, EQ-5D-3L index values, PCS, or STAI - State Anxiety levels were detected in participants at the 12 month interview. The proportion of individuals with deterioration vs. improvement greater than the MCID for the instrument remained significant for the STAI - State anxiety levels [increase >MCID (n=146) vs. decrease >MCID (n=87), p-value <0.0001], representing 5.5% [(146-87)/1066, NNH=18] of participants (figure 6). The proportion of individuals experiencing a deterioration vs. improvement greater than the MCID for EQ VAS(figure 2), EQ-5D-3L(figure 3), PCS(figure 4) and MCS(figure 5) were not significantly different.

Positive screen and investigation

Among participants receiving a positive scan results (n=279), no statistically significant mean changes in EQ VAS, EQ-5D-3L index values, PCS, or MCS were detected following baseline LDCT (Online supplementary Table 1). However, more participants experienced a clinically significant decrease vs. increase in anxiety score [increase >MCID (n= 20) vs. decrease >MCID (n=41), p-value=0.002] representing 8.8% [(41-20)/238, NNT=11] of these participants (figure 7). This decreased anxiety persisted at the 12-month interview [increase >MCID (n=14) vs. decrease >MCID (n=35), p-value=0.003] representing 8.5% [(35-14)/246, NNT=12] of participants (figure 8).

Following investigation examinations, no statistically significant mean changes in EQ VAS, EQ-5D-3L index values, PCS, MCS, or anxiety were detected. Post-investigation changes revealed no statistically significant changes in the proportion of individuals with deterioration vs. improvement greater than the MCID (figure 7).

The proportion of different levels of each questionnaires' dimensions by study visits, as well as number of missing values, are shown in the online supplementary Tables 2 to 4.

DISCUSSION

This study offers detailed information on HRQoL and anxiety following LDCT for lung cancer screening in a Canadian high-risk selected population using validated assessment tools measuring overall HRQoL as well as specific physical, psychological and anxiety scores. Our study found no clinically significant differences in HRQoL outcomes between baseline and each of the survey time points following initial screening in the cohort as a whole. However, more participants experienced a clinically significant increased anxiety (vs. decreased) following baseline LDCT. This finding was more pronounced among females and participants who were concerned about getting lung cancer at baseline. Paradoxically, decreased anxiety was more frequent in the subgroup with positive baseline scan, although the impact of scan results did not reach statistical significance in the multivariate analysis. Over the long-term, no adverse effects on HRQoL were noted but some of the excess in increased anxiety levels persisted.

In line with our findings, analyses of other screening cohorts including NLST,[21] NELSON,[22] PLCO,[23] and UKLS,[24] as well as two recent meta-analyses have demonstrated that lung cancer screening is associated with little to no adverse physical or psychological long-term impact on participants[8,25]. While analysis of the Danish Lung Cancer Screening Trial did show negative consequences at 1 year,[26] and 2 year,[27] follow-up, the degree of change was actually greater in the control (no screening) arm of the trial.

Our finding of decreased anxiety following a positive screen is in contrast with those reported in the UKLS,[24] and NLST trials,[21] which observed a short-term increase in distress levels two weeks or 2 months respectively after a positive result notification of baseline screening. Results from

NELSON,[28] and from the Pittsburgh Lung Screening Study,[29] also reported a short-term lung cancer-specific distress, a poorer quality of life and a higher level of anxiety among participants with indeterminate scan results compared with those with negative results. However, in both studies these negative impacts disappeared over time. The explanation for this finding may relate to the small size of our program and personalized communication process for results in the study. The absolute number of participants with significant changes in this metric was also relatively small, so that this finding should not be over-interpreted.

Similar to our findings, NELSON study reported a worse HRQoL outcomes among females compared to males,[28]. Furthermore, our observation regarding females is also consistent with the results of a study of PLCO participants,[23] that found a poorer MCS outcomes in females compared to males.

In most studies reported to date, statistically significant mean changes in HRQoL-related scores detected in groups of screened individuals have been small and of questionable clinical significance limiting the impact of such findings in clinical decision-making. Conversely, lack of statistically significant changes in population means can mask clinically meaningful changes in individuals. The MCID has been suggested to be a useful benchmark to define the smallest difference in HRQoL that individuals perceive as beneficial or harmful and that mandates a change in management,[30]. Only two previous lung cancer screening trial have reported MCID levels to interpret the changes in HRQoL of participants,[22,24,28]. However, both applied this concept to mean population changes rather than to discrete individual changes. Our study is unique in providing discrete participant data on the proportion of individuals with improvement vs. deterioration greater than the MCID for each assessment tool. This has allowed us to attribute to the intervention excess cases of deterioration vs. improvement given normal expected variations in each individual over time. This can suggest if a true clinically significant impact is present,

and specifying how many individuals are impacted by such a change, in order to calculate a "number-needed-to-harm" value. With this approach, we found that the proportion of individuals with improvement vs. deterioration greater than the MCID for the STAI was significantly different among all participants with a number needed to harm of 7 in the short term following screening, and 18 at one-year post screening. Our data adds to an evolving body of evidence which suggests that LDCT screening for lung cancer does not have overall significant negative impacts on the HRQoL of the population screened. However, a minority of individuals do experience small but clinically significant increases in anxiety levels following screening.

The major strengths of our study include the use of a large multicenter sample of eligible participants, and reporting of individual participant data in relation to their MCID using three different and well-established instruments for measuring HRQoL and anxiety as well as the risk prediction model used for the recruitment,[31]. Another strength of our study is the longitudinal design with a high follow-up and response rate (see online supplementary tables 2-4), which enabled us to assess short- and long-term outcomes at different time points during screening process with each participant serving as his/her own control. While we enrolled a high risk cohort using a risk prediction model, our participants' baseline HRQoL metrics appeared comparable to those of similarly aged individuals in the general population [Adults aged 55-69, mean EQ VAS: 76,[32]; age 50-59, mean STAI: 32.2(female)/34.5(male),[16]; age 50-69, PCS: 50.9-51.3, MCS: 50.7-50.9,[33]] suggesting that our findings could be generalizable to a broader population of screen-eligible individuals but with lower risk of lung cancer than in our population. Our study is also the first to use the full EQ-5D score in this population, which can be used to calculate quality-adjusted-life-years.

The current study has potential limitations. Our population was made up almost entirely of Caucasians, so that a differential impact of screening on other ethnic communities cannot be determined. Owing to the study design for HRQoL assessments, we were unable to address the impacts of incidental findings on HRQoL and anxiety of participants. Another potential limitation is that we did not compare our results to an unscreened control group but instead used each participant's baseline scores. As such, other factors unrelated to the screening intervention, such as aging or changes in smoking status, could affect the longitudinal changes (or lack thereof) noted in our study [34]. However, two previous studies with a randomized design and a control group reported the HRQoL results that were comparable to our findings,[14,20]. Another potential limitation is that the EQ-5D-3L is usually associated with a ceiling effect (i.e., scores recording perfect health),[35] and has limited ability to determine small changes in health status compared to the five-level EQ-5D-5L, which might offer improved measure of population-weighted health state utility,[36,37]. In our study, 35 % of participants reported perfect scores on EQ-5D-3L at baseline; suggesting a ceiling effect that was adjusted for with a generalized linear mixed modeling approach,[38]. Moreover, HRQoL in our study was also measured by SF-12, which has been known to demonstrate a smaller ceiling/floor effect compared to EQ-5D-3L,[35]. In our study, no ceiling/floor effect was observed for the SF-12 scores. Finally, the statistical power to detect changes in some participant subgroups such as those with positive screens may be limited because of low number of participants with a positive scan results. Therefore, caution should be used in drawing conclusions.

The complexity of longitudinal analysis of HRQoL and the lack of agreed upon standardized approach compromise the comparison of results between studies,[39]. Even the specific MCID level for each instrument can be debated. Ideally such levels are determined in the specific population of interest, but such information is rarely available. Levels chosen for our analysis were determined prior to any data

analysis based on best evidence for each instrument. As a confirmatory step, MCIDs selected in this study were found to approximate estimates obtained as half a Standard Deviation (SD) (MID) of HRQol measures in our population (results not shown), an alternative distribution-based approach to MCID determination,[40].

The findings of our study corroborate and expand the current evidence-based information on lung cancer screening decision making by showing that there is a minimal overall psychological impact associated with lung cancer screening. However, certain populations (i.e., females, participants with higher baseline concern about lung cancer) may be at a higher risk of negative psychological impact. This suggests that an improved communication is needed throughout the entire lung cancer screening process, especially for the potentially vulnerable subgroups. Since most positive screens do not result in a lung cancer diagnosis, approaches to better define screening exam findings and reduce false positive rates could be effective in reducing the anxiety burden in this subgroup. Despite the high rate of false positive CT results in lung cancer screening, there is no clear recommendation yet on psychological interventions to help individuals cope with abnormal CT screening results. However, literature on mammography screening has shown that immediate follow-up and consultation can significantly reduce anxieties after receiving abnormal mammograms,[41].

In conclusion, our study demonstrated that CT Screening for Lung Cancer has no major impact on HRQoL among participants overall, but some individuals experience clinically significant increase in anxiety with a number needed to harm of 18 at one year post initial screen. While these impacts may appear minor in view of the robust mortality reduction associated with LDCT screening, ongoing work to further define and minimize these negative aspects of screening is warranted given recommendations for broad screening of at risk populations.

Author's contributions:

NT: led data analysis & data interpretation; prepared the draft manuscript; approved final manuscript; agrees to be accountable for all aspects of the work.

AT: contributed to study conception and design, data acquisition, analysis and interpretation; prepared the draft manuscript; approved final manuscript; agrees to be accountable for all aspects of the work.

SCL: contributed to study conception and design, data acquisition and interpretation; critically reviewed and approved final manuscript; agrees to be accountable for all aspects of the work.

MCT: contributed to study conception and design, data analysis and interpretation; critically reviewed and approved final manuscript; agrees to be accountable for all aspects of the work.

MST: contributed to study conception and design, data analysis and interpretation; critically reviewed and approved final manuscript; agrees to be accountable for all aspects of the work.

SC: contributed to study conception and design, data analysis and interpretation; critically reviewed and approved final manuscript; agrees to be accountable for all aspects of the work.

SAK: contributed to study conception, design and data acquisition; critically reviewed and approved final manuscript; agrees to be accountable for all aspects of the work.

AMC: contributed to study conception and design, data acquisition and interpretation; critically reviewed and approved final manuscript; agrees to be accountable for all aspects of the work.

PM, SP, MJ, JG, GG, GN, SM, FL, RB, GL, HS: contributed to study conception and design, data acquisition and interpretation; critically reviewed and approved final manuscript; agrees to be accountable for all aspects of the work.

Conflict of interest

The authors declare that there is no conflict of interest.

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Data Sharing Statement

No additional unpublished data from the study is made available.

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Figure legends

Figure 1- Assessments of the health-related quality of life (HRQoL) and anxiety in the Pan-Canadian Early Detection of Lung Cancer Study.

Figure 2: Changes in EuroQoL Visual Analog Scale (VAS) from baseline to post baseline CT(A), and 12 months after baseline(B).

Figure 3: Changes in EuroQoL(EQ)-5D-3L from baseline to post baseline CT(A), and 12 months after baseline(B).

Figure 4: Changes in 12-item short-form Physical Component Scale(PCS) from baseline to post baseline CT(A), and 12 months after baseline(B).

Figure 5: Changes in 12-item short-form Mental Component Scale (MCS) from baseline to post baseline CT(A), and 12 months after baseline(B).

Figure 6: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT(A), and 12 months after baseline(B).

Figure 7: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT (A) and post investigation (B) among participants with a positive scan results.

Figure 8: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to 12 months among participants with a positive scan results.

Figure 1- Assessments of the health-related quality of life (HRQoL) and anxiety in the Pan-Canadian Early Detection of Lung Cancer Study.

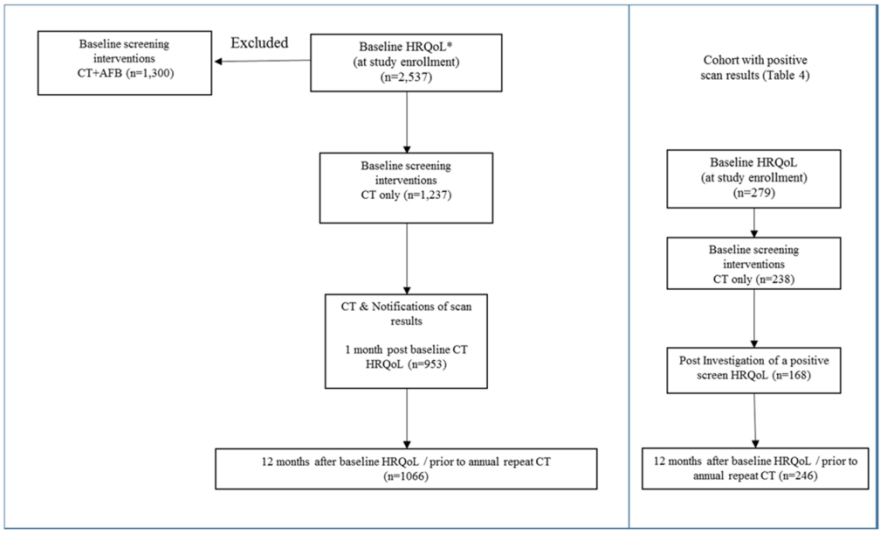

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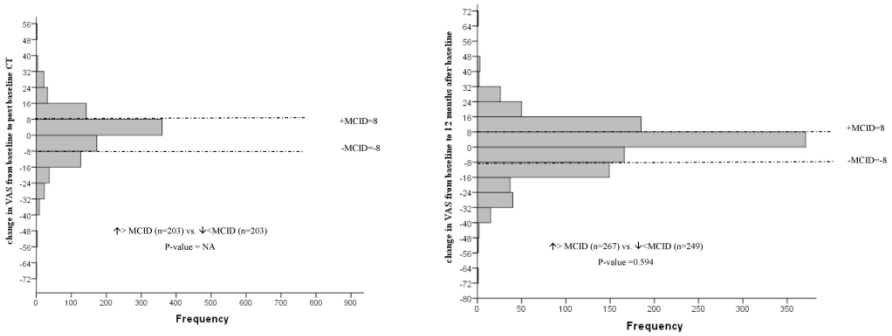
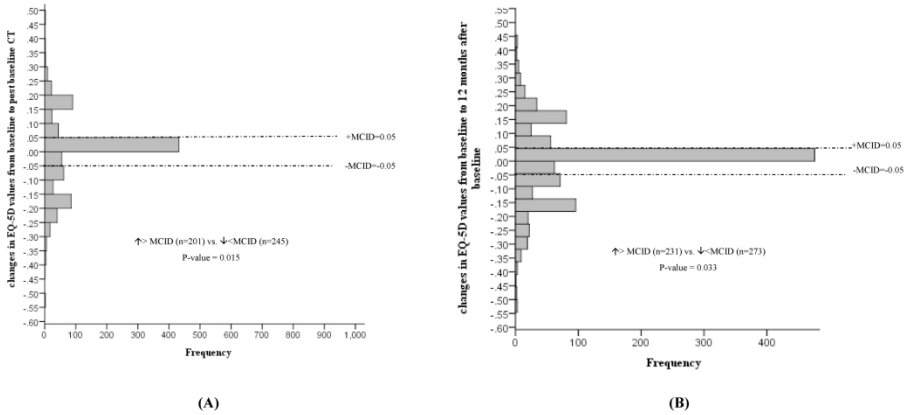
Figure 2: Changes in EuroQoL Visual Analog Scale (VAS) from baseline to post baseline CT(A), and 12 months after baseline(B).



(A) (B)

279x361mm (300 x 300 DPI)

Figure 3: Changes in EuroQoL(EQ)-5D-3L from baseline to post baseline CT(A), and 12 months after baseline(B).



(A) (B)

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Figure 4: Changes in 12-item short-form Physical Component Scale(PCS) from baseline to post baseline CT(A), and 12 months after baseline(B).

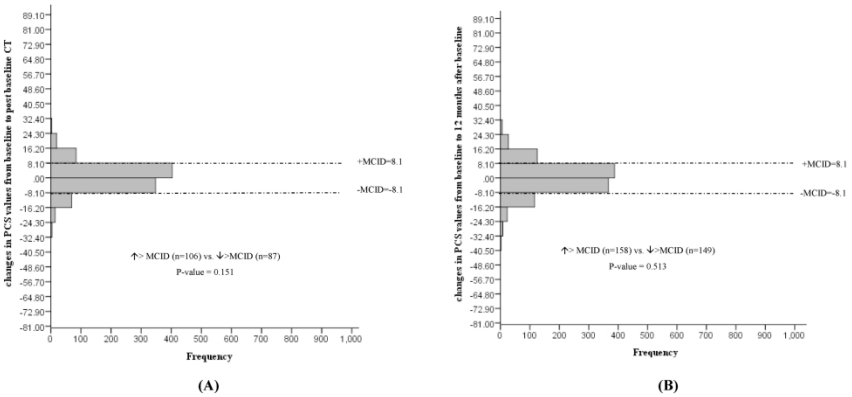

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Figure 5: Changes in 12-item short-form Mental Component Scale (MCS) from baseline to post baseline CT(A), and 12 months after baseline(B).

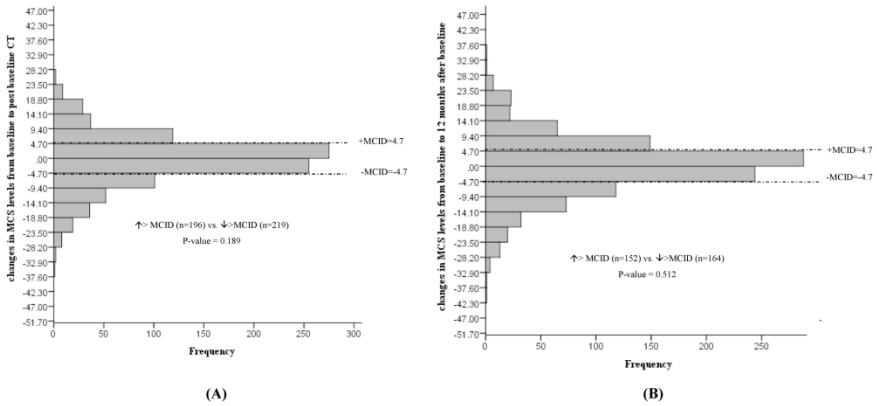

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Figure 6: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT(A), and 12 months after baseline(B).

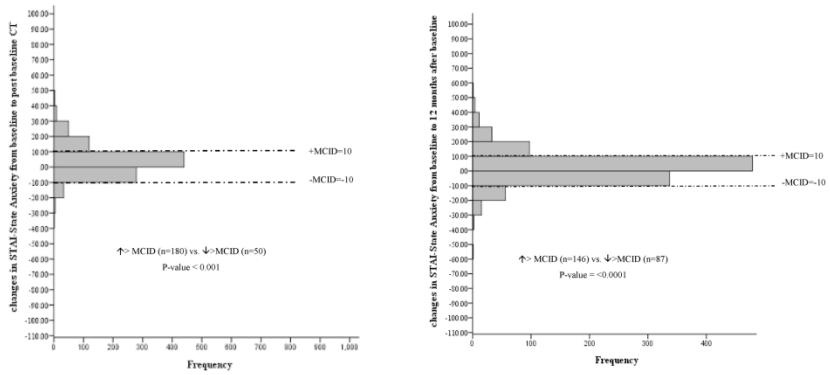

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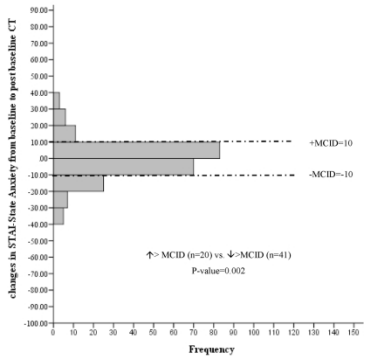
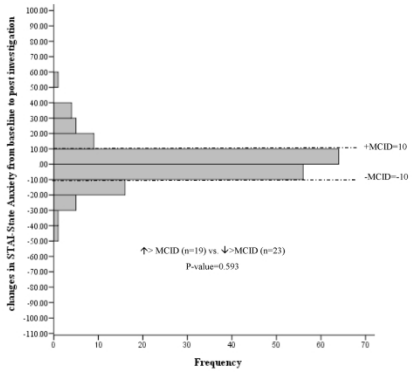
Figure 7: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to post baseline CT (A) and post investigation (B) among participants with a positive scan results.



(A)



(B)

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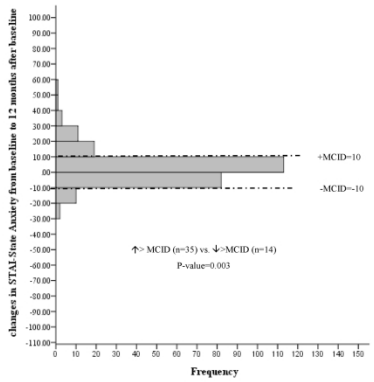
Figure 8: Changes in Spielberger State Trait Anxiety Inventory (STAI) from baseline to 12 months among participants with a positive scan results.



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Health-Related Quality of Life and Anxiety in the PAN-CAN Lung Cancer Screening Study

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e-Appendix 1:

Study design and population

Institutional Review Board (IRB) Approvals:

Vancouver: UBC BCCA Research Ethics Board (UBC BCCA REB) H08-01132

Calgary: Conjoint Health Research Ethics Board (CHREB) ethics ID: 21852

Hamilton: McMaster University Research Ethics Board; ID: 08-367

Toronto: University Health Network Research Ethics Board; ID: 08-0576-C

Ottawa: The Ottawa Hospital Research Ethics Board; ID 2008581-01H

Quebec: Institute Universitaire de Cardiologie et de Pneumologie; ID: CER: 20319

Halifax: Capital Health Research Ethics Board; ID: CDHA-RS/2009-097

St.John's: Eastern Health Department of Reseasrch/Knowledge transfer; ID; HIC#10.070

Supplementary Table 1 – HRQoL, and anxiety levels in participants with positive baseline LDCT.

	Baseline (n=279)	1-month post baseline CT scan Mean, change (95% CI) (n=238)	Post investigation Mean, change (95% CI) (n=168)	12-months after baseline Mean, change (95% CI) (n= 246)
EQ VAS[1]	76.2	76.1, -0.21 (-2.54 to 2.13)	76.9, 0.89 (-3.28 to 5.07)	76.4, 0.19 (-1.73 to 2.11)
EQ-5D-3L index values	0.84	0.84, -0.00 (-0.03 to 0.03)	0.85, 0.00 (-0.03 to 0.04)	0.83, -0.01 (-0.05 to 0.02)
SF-12: PCS[2]	46.2	46.5, 0.22 (-0.83 to 1.28)	46.6, 0.45 (-0.93 to 1.83)	45.3, -0.86 (-1.90 to 1.67)
SF-12: MCS[3]	51.3	51.2, 0.01 (-1.66 to 1.67)	51.4, 0.54 (-2.06 to 3.15)	51.3, 0.01 (-2.30 to 2.33)
STAI-State Anxiety [4]	29.9	33.2, 3.28 (-0.42 to 6.97)	32.9, 2.42 (-1.14 to 5.99)	31.7, 1.79 (-0.62 to 4.19)

[1] EQ Visual Analogue Scale "We would like to know how good or bad your health is today" (100 – best imaginable, 0 – worst imaginable).

[2] Physical Health Composite Scores (US population mean = 50 +/- 10), with higher score corresponding to better state.

[3] Mental Health Composite Scores (US population mean = 50 +/- 10), with higher score corresponding to better state.

[4] STAI-State score >39 considered clinically significant symptoms.

Supplementary Table 2 - Proportion of different levels of EQ-5D-3L dimensions by study visits (Total n=1237).

EQ-5D-3L Dimensions, n (%)	Baseline (n=1237)	1 month post baseline CT scan (n=953)	12 months after baseline (n=1066)
Overall score missing	9 (0.7)	12 (1.3)	16 (1.5)
Mobility			
I have no problems in walking about	918 (74.2)	705 (74.0)	782 (73.4)
I have some problems in walking about	311 (25.2)	240 (25.2)	278 (26.1)
I am confined to bed	4 (0.3)	3 (0.3)	0 (0.0)
Missing	4 (0.3)	5 (0.5)	6 (0.6)
Self-care			
I have no problems with self-care	1191 (96.2)	914 (95.9)	1018 (95.5)
I have some problems washing or dressing myself	36 (2.9)	31 (3.3)	39 (3.7)
I am unable to wash or dress myself	7 (0.6)	2 (0.2)	3 (0.3)
Missing	3 (0.3)	6 (0.6)	6 (0.6)
Usual activities			
I have no problems with performing my usual activities	930 (75.1)	710 (74.5)	785 (73.6)
I have some problems with performing my usual activities	284 (22.9)	228 (23.9)	261 (24.5)
I am unable to perform my usual activities	18 (1.5)	8 (0.8)	15 (1.4)
Missing	5 (0.5)	7 (0.7)	5 (0.5)
Pain/discomfort			
I have no pain or discomfort	575 (46.4)	471 (49.4)	498 (46.7)
I have moderate pain or discomfort	622 (50.2)	443 (46.5)	520 (48.8)
I have extreme pain or discomfort	36 (2.9)	33 (3.5)	40 (3.8)
Missing	4 (0.4)	6 (0.6)	8 (0.8)
Anxiety/depression			
I am not anxious or depressed	835 (64.4)	610 (64.0)	708 (66.4)
I am moderately anxious or depressed	375 (30.3)	307 (32.2)	332 (31.1)
I am extremely anxious or depressed	23 (1.9)	28 (2.9)	19 (1.8)
Missing	4 (0.4)	8 (0.8)	7 (0.7)

Supplementary Table 3- Proportion of different levels of SF_12 dimensions by study visits (Total n=2537).

SF_12 Dimensions	Baseline (n=1237)	1 month post baseline CT scan (n=953)	12 months after baseline (n=1066)
General health, n (%)			
Excellent	93 (7.5)	85 (8.9)	89 (8.3)
Very good	453 (36.6)	367 (38.5)	392 (36.8)
Good	532 (43.0)	381 (40.0)	450 (42.2)
Fair	138 (11.1)	105 (11.0)	108 (10.1)
Poor	18 (1.5)	12 (1.3)	20 (1.9)
Missing	3 (0.3)	3 (0.3)	7 (0.7)
Moderate activities			
Yes, limited a lot	97 (7.8)	77 (8.1)	75 (7.0)
Yes, limited a little	310 (25.0)	256 (26.9)	267 (25.0)
No, not limited at all	827 (66.8)	617 (64.7)	714 (67.0)
Missing	3 (0.3)	3 (0.3)	10 (0.9)
Climbing several flights of stairs			
Yes, limited a lot	191 (15.4)	140 (14.7)	161 (15.1)
Yes, limited a little	551 (44.5)	432 (45.3)	462 (43.3)
No, not limited at all	491 (39.7)	376 (39.5)	436 (40.9)
Missing	4 (0.3)	5 (0.5)	7 (0.7)
Accomplished less than you would like (physically)			
Yes	335 (27.1)	221 (23.2)	265 (24.9)
No	899 (72.6)	727 (76.3)	795 (74.6)
Missing	3 (0.3)	5 (0.5)	6 (0.6)
Limited in kind of activities			
Yes	299 (24.2)	221 (23.2)	265 (24.9)
No	934 (75.4)	729 (76.5)	795 (74.6)
Missing	4 (0.4)	3 (0.3)	6 (0.6)
Accomplished less than you would like (emotionally)			
Yes	251 (20.3)	212 (22.2)	222 (20.8)
No	982 (79.3)	735 (77.1)	833 (78.1)
Missing	4 (0.4)	6 (0.6)	11 (1.0)
Did not do activities as carefully as usual			
Yes	215 (17.4)	181 (19.0)	181 (17.0)
No	1018 (82.2)	764 (80.2)	875 (82.1)
Missing	4 (0.4)	8 (0.8)	10 (0.9)
Pain interferes with normal work			
Not at all	596 (48.1)	479 (50.3)	515 (48.3)
A little bit	312 (25.2)	243 (25.5)	288 (27.0)
Moderately	194 (15.7)	138 (14.5)	142 (13.3)
Quite a bit	109 (8.8)	77 (8.1)	98 (9.2)
Extremely	20 (1.6)	13 (1.4)	18 (1.7)
Missing	6 (0.5)	3 (0.3)	5 (0.5)
Felt calm and peaceful			
All of the time	87 (7.0)	73 (7.7)	84 (7.9)
Most of the time	630 (50.9)	460 (48.3)	527 (49.4)
A good bit of the time	184 (14.9)	163 (17.1)	176 (16.5)
Some of the time	214 (17.3)	171 (17.9)	164 (15.4)
A little of the time	96 (7.8)	70 (7.3)	88 (8.3)
None of the time	23 (1.9)	11 (1.2)	18 (1.7)
Missing	3 (0.3)	5 (0.5)	9 (0.8)
Have a lot of energy			
All of the time	36 (2.9)	36 (3.8)	41 (3.8)
Most of the time	416 (33.6)	317 (33.3)	375 (35.2)
A good bit of the time	263 (21.2)	206 (21.6)	213 (20.0)
Some of the time	322 (26.0)	240 (25.2)	249 (23.4)
A little of the time	156 (12.6)	116 (12.2)	145 (13.6)
None of the time	41 (3.3)	34 (3.6)	34 (3.2)
Missing	3 (0.3)	4 (0.4)	9 (0.8)
Felt downhearted and blue			
All of the time	4 (0.3)	5 (0.5)	4 (0.4)
Most of the time	37 (3.0)	37 (3.9)	34 (3.2)
A good bit of the time	79 (6.4)	51 (5.4)	76 (7.1)
Some of the time	273 (22.1)	196 (20.6)	216 (20.3)
A little of the time	480 (38.8)	399 (41.9)	414 (38.8)
None of the time	361 (29.2)	261 (27.4)	312 (29.3)
Missing	3 (0.3)	4 (0.4)	10 (0.9)
Health interferes/social activities			
All of the time	8 (0.6)	10 (1.0)	16 (1.5)
Most of the time	63 (5.1)	42 (4.4)	54 (5.1)
Some of the time	203 (16.4)	150 (15.7)	169 (15.9)
A little of the time	238 (19.2)	182 (19.1)	200 (18.8)
None of the time	722 (58.3)	565 (59.3)	617 (57.9)
Missing	3 (0.3)	4 (0.4)	10 (0.9)

Supplementary Table 4- Proportion of different levels of State anxiety dimensions by study visits (Total n=2537).

State	Baseline (n=1237)					1 month post baseline CT scan (n=953)					12 months after baseline (n=1066)				
Dimensions	**Not at all**	**Somewhat**	**Moderately so**	**Very much so**	**Missing**	**Not at all**	**Somewhat**	**Moderately so**	**Very much so**	**Missing**	**Not at all**	**Somewhat**	**Moderately so**	**Very much so**	**Missing**
I feel calm	17 (1.4)	167 (13.5)	407 (32.9)	643 (51.9)	3 (0.3)	31 (3.3)	136 (14.3)	338 (35.5)	442 (46.4)	6 (0.6)	18 (1.7)	131 (12.3)	393 (36.9)	516 (48.4)	8 (0.8)
I feel secure	16 (1.3)	106 (8.6)	304 (24.6)	808 (65.3)	3 (0.3)	21 (2.2)	115 (12.1)	283 (29.7)	528 (55.4)	6 (0.6)	24 (2.3)	83 (7.8)	330 (31.0)	621 (58.3)	8 (0.8)
I feel tense	685 (55.3)	319 (25.8)	192 (15.5)	36 (2.9)	3 (0.3)	465 (48.8)	300 (31.5)	144 (15.1)	39 (4.1)	5 (0.5)	562 (52.7)	282 (26.5)	177 (16.6)	35 (3.3)	10 (1.0)
I feel strained	834 (67.4)	231 (18.7)	131 (10.6)	38 (3.1)	3 (0.3)	543 (57.0)	261 (27.4)	109 (11.4)	35 (3.7)	5 (0.5)	652 (61.2)	240 (22.5)	134 (12.6)	33 (3.1)	7 (0.7)
I feel at ease	41 (3.3)	154 (12.4)	361 (29.2)	678 (54.8)	3 (0.3)	45 (4.7)	154 (16.2)	289 (30.3)	460 (48.3)	5 (0.5)	27 (2.5)	170 (15.9)	323 (30.3)	538 (50.5)	8 (0.8)
I feel upset	1003 (81.0)	137 (11.1)	75 (6.1)	19 (1.5)	3 (0.3)	660 (69.3)	182 (19.1)	78 (8.2)	28 (2.9)	5 (0.5)	792 (74.3)	175 (16.4)	75 (7.0)	16 (1.5)	8 (0.8)
I am presently worrying over possible misfortunes	694 (56.1)	332 (26.8)	156 (12.6)	52 (4.2)	3 (0.3)	480 (50.4)	295 (31.0)	121 (12.7)	52 (5.5)	5 (0.5)	555 (52.1)	339 (31.8)	115 (10.8)	49 (4.6)	8 (0.8)
I feel satisfied	36 (2.9)	193 (15.6)	469 (37.9)	536 (43.3)	3 (0.3)	47 (4.9)	167 (17.5)	324 (34.0)	410 (43.0)	5 (0.5)	33 (3.1)	192 (18.0)	378 (35.5)	456 (42.8)	7 (0.7)
I feel frightened	1008 (81.4)	149 (12.0)	56 (4.5)	21 (1.7)	3 (0.3)	718 (75.3)	150 (15.7)	59 (6.2)	21 (2.2)	5 (0.5)	846 (79.4)	148 (13.9)	53 (5.0)	11 (1.0)	8 (0.8)
I feel comfortable	30 (2.4)	133 (10.7)	352 (28.4)	719 (58.1)	3 (0.3)	31 (3.3)	135 (14.2)	291 (30.5)	490 (51.4)	6 (0.6)	23 (2.2)	142 (13.3)	333 (31.2)	561 (52.6)	7 (0.7)
I feel self-confident	36 (2.9)	127 (10.3)	439 (35.5)	632 (51.1)	3 (0.3)	38 (4.0)	106 (11.1)	359 (37.7)	445 (46.7)	5 (0.5)	24 (2.3)	127 (11.9)	394 (37.0)	514 (48.2)	7 (0.7)
I feel nervous	780 (63.0)	308 (24.9)	117 (9.5)	29 (2.3)	3 (0.3)	559 (58.7)	255 (26.8)	99 (10.4)	35 (3.7)	5 (0.5)	662 (62.1)	261 (24.5)	114 (10.7)	22 (2.1)22	7 (0.7)
I am jittery	968 (78.2)	174 (14.1)	73 (5.9)	18 (1.5)	4 (0.4)	692 (72.6)	152 (15.9)	77 (8.1)	27 (2.8)	5 (0.5)	811 (76.1)	155 (14.5)	77 (7.2)	15 (1.4)	8 (0.8)
I feel indecisive	846 (68.3)	269 (21.7)	97 (7.8)	22 (1.8)	3 (0.3)	557 (58.4)	246 (25.8)	113 (11.9)	32 (3.4)	5 (0.5)	662 (62.1)	256 (24.0)	100 (9.4)	39 (3.7)	9 (0.9)
I am relaxed	48 (3.9)	181 (14.6)	394 (31.8)	611 (49.4)	3 (0.3)	52 (5.5)	173 (18.2)	313 (32.8)	409 (42.9)	6 (0.6)	30 (2.8)	172 (16.1)	377 (35.4)	480 (45.0)	7 (0.7)
I feel content	48 (3.9)	161 (13.0)	436 (35.2)	589 (47.6)	3 (0.3)	52 (5.5)	147 (15.4)	339 (35.6)	410 (43.0)	5 (0.5)	37 (3.5)	151 (14.2)	408 (38.3)	463 (43.4)	7 (0.7)
I am worried	651 (52.6)	390 (31.5)	146 (11.8)	47 (3.8)	3 (0.3)	423 (44.4)	333 (34.9)	134 (14.1)	58 (6.1)	5 (0.5)	518 (48.6)	361 (33.9)	129 (12.1)	51 (4.8)	7 (0.7)
I feel confused	1075 (86.8)	112 (9.0)	32 (2.6)	12 (1.0)	6 (0.5)	755 (79.2)	135 (14.2)	40 (4.2)	18 (1.9)	5 (0.5)	887 (83.2)	99 (9.3)	50 (4.7)	20 (1.9)	10 (1.0)
I feel steady	43 (3.5)	141 (11.4)	327 (26.4)	720 (58.2)	6 (0.5)	43 (4.5)	126 (13.2)	272 (28.5)	507 (53.2)	5 (0.5)	41 (3.8)	120 (11.3)	316 (29.6)	581 (54.5)	8 (0.8)
I feel pleasant	25 (2.0)	118 (9.5)	416 (33.6)	672 (54.3)	6 (0.5)	30 (3.1)	117 (12.3)	319 (33.5)	482 (50.6)	5 (0.5)	25 (2.3)	115 (10.8)	365 (34.2)	552 (51.8)	9 (0.9)

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

PAGE		Item No	Recommendation
4	**Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
4			(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
	Introduction		
6	Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
7	Objectives	3	State specific objectives, including any prespecified hypotheses
	Methods		
8	Study design	4	Present key elements of study design early in the paper
8	Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
8	Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
n/a			(*b*) For matched studies, give matching criteria and number of exposed and unexposed
8-9	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
9	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
n.a.	Bias	9	Describe any efforts to address potential sources of bias
11	Study size	10	Explain how the study size was arrived at
10	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
10	Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
10			(*b*) Describe any methods used to examine subgroups and interactions
10			(*c*) Explain how missing data were addressed
10			(*d*) If applicable, explain how loss to follow-up was addressed
n/a			(*e*) Describe any sensitivity analyses
	Results		
12	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
n.a.			(b) Give reasons for non-participation at each stage
FIG 1			(c) Consider use of a flow diagram
12	Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
14			(b) Indicate number of participants with missing data for each variable of interest
n.a.			(c) Summarise follow-up time (eg, average and total amount)
14-17	Outcome data	15*	Report numbers of outcome events or summary measures over time
14-17	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
n.a.			(*b*) Report category boundaries when continuous variables were categorized
14, 16			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Suppl	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
	Discussion		
18	Key results	18	Summarise key results with reference to study objectives
20	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
21-22	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
22	Generalisability	21	Discuss the generalisability (external validity) of the study results
	Other information		
23	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

*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.