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Measurement of psychosocial consequences in a randomised cancer screening trial: how attrition bias affects these estimates

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Abstract

Objectives: We investigated if psychosocial status, socio-demographics and smoking status affected non-response in the control group in the randomized Danish Lung Cancer Screening Trial (DLCST).

Design & setting: This study was an observational study nested in the DLCST. Due to a large dropout in the control group in the second screening round we made an additional effort to collect questionnaire data from dropouts in this group in the third screening round. We used a condition-specific questionnaire to assess psychosocial status. We analysed the differences in psychosocial status in the third and preceding rounds between dropouts and attenders in the control group in multivariable linear regression models adjusted for socio-demographics and smoking status reported at baseline. Differences in socio-demographics and smoking status were analysed with chi-squared tests.

Primary outcome measure: Primary outcome was psychosocial status.

Participants: All control persons still participating at the third screening round in the DLCST were included.

Results: Dropouts in the third round had significantly worse psychosocial status than attenders in the scales: “Behaviour” 0.77 (99% CI 0.18;1.36), “Self-blame” 0.59 (99% CI 0.14;1.04), “Focus on airway symptoms” 0.22 (99% CI 0.08;0.36), “Stigmatisation” 0.51 (99% CI 0.16;0.86), “Introvert” 0.56 (99% CI 0.23;0.89), and “Harms of smoking” 0.35 (99% CI 0.11;0.59). Moreover, Dropouts had worse scores than attenders in the preceding screening rounds. Dropouts also reported worse socio-demographics at baseline.

Conclusions: Dropouts had a significantly worse psychosocial status and worse socio-demographics compared with attenders. The results of our study contribute with evidence of non-response and attrition driven by psychosocial status, which in turn may be influenced by the screening intervention itself. This can be used to adjust cancer screening trial results for bias due to differential dropout.

Trial registration: The trial is registered in Clinicaltrials.gov Protocol Registration System (identification no. NCT00496977)

Article summary

Strengths and limitations

- Use of a condition-specific questionnaire with adequate psychometric properties ensured valid measures.
- Patient-reported data on dropouts gave valuable empirical insight in drivers for dropout.
- Testing a previously hypothesized model for dropout empirically is another strength of the study.
- No comparison between dropouts in the intervention and the control group was performed.
- No longer-term follow up on dropouts was performed.

Introduction

Attrition and non-response may affect trial results and introduce bias in randomized controlled trials (RCTs).[1,2] Non-response reduces the power of the trial and, if non-response differs

between the randomized groups, conventional effect estimates can be biased.[2] While we cannot change the loss of power, we may remove bias due to differential non-response if we know and have measured the factors that cause this non-response.[3] For some outcome measures, such as disease incidence or mortality, attrition can be partially addressed if data can be obtained from national electronic registers. Non-response will be larger for outcome measures that depend on direct data collection such as clinical measurements and patient reported outcome measures (PROMs). Moreover, the factors driving non-response for these measures may be very heterogeneous and may also be driven by the experiences of the trial participants in the trial process.

The problems with differential attrition may be aggravated in trials assessing psychosocial consequences of cancer screening as well as other interventions where it is impossible to blind participants to allocation. Notably, a control group not offered screening may be less inclined to return questionnaires enquiring into their experiences with a potentially beneficial intervention they did not receive. Despite these potential problems, few cancer screening RCTs have reported on non-response let alone adjusted for potential differential attrition.[4–7] The trials that do, seldom report on the factors involved in non-response. Since cancer screening trials are investigating potentially life-threatening diseases there may be emotional drivers of non-response, not typical for trials in general. Hence, it is of interest to know which factors drive non-response in PROMs in cancer screening trials as this data is to be collected in these trials and then used in adjusting for differential non-response.

The Danish Lung Cancer Screening Trial (DLCST) was an RCT including five annual screening rounds of low-dose chest computed tomography (CT) plus clinical examinations in the intervention group

compared with annual clinical examinations only in the control group.[8] Furthermore, all the participants were asked to complete a condition-specific questionnaire, measuring psychosocial consequences of lung cancer screening at these annual clinical assessments.[9] The results showed that people experienced negative psychosocial consequences merely by participating in the trial, and that negative consequences were higher for participants allocated to the control group.[7,10] A large number of controls did not attend the second annual examination (n=513, 26.1%) while dropout in the intervention group was low (n=71, 3.5%) (*Fig. 1*). To adjust for this differential dropout, inverse probability weighting was used.[7] In this method the observed outcomes are weighted with the inverse of the probability of being non missing.[3] We hypothesised that these probabilities were adequately estimated from socio-demographic profile including smoking status, randomization group and psychosocial status in previous rounds.[7,11–13]

If these hypotheses were confirmed, then these factors would explain the witnessed difference in response between the trial groups and could be used to render them comparable. Analysed without such adjustments the assessment of the trial groups, and thereby the means of the scores from the responses to the questionnaire from the remaining trial participants would no longer be comparable.[14] Hence, the assessment of psychosocial harms of lung cancer screening could be biased.

Therefore, the overall aim of this study was to empirically assess whether control participants who dropped out of the study had different psychosocial profiles compared with control participants who attended the study.

Materials and methods

Study design and population

The design and study population of DLCST have been described in detail previously.[7,8] Briefly, the DLCST was an RCT, conducted at the Copenhagen University hospital Gentofte in Denmark from October 2004 to March 2010. Heavy current and former smokers (at least 20 pack-years), aged 50-70 years old, were randomized to either five rounds of screening with low-dose CT-scans including clinical examinations (n=2052) or five clinical examinations only (n=2052). In the enrolment visit, participants provided socio-demographic data, lifestyle and health information (including smoking status), completed a questionnaire on their psychosocial status and underwent spirometry. Participants randomized to screening also had a low-dose chest CT-scan within one month of randomisation. In the following screening rounds, participants in the screened and control groups were invited to a visit in the screening clinic where lung function tests were performed, and questionnaires concerning health, lifestyle, smoking habits and psychosocial status were completed and lung function tests were performed. Participants randomized to screening also received a low-dose chest CT-scan.

This study is an observational study nested in the DLCST. During the second screening round, the steering committee noted that a large number of control participants did not attend the screening clinic visit when compared with the number of screened participants. Thus, the committee decided to make additional efforts to collect questionnaire data for dropouts in the control group in the third screening round to perform post hoc analyses on whether psychosocial status was an influencing factor *(Fig.2)*.

During the third round, participants in the control group who dropped out were contacted by phone and part 1 of the questionnaire was sent with a postage paid envelope to those who gave

their oral consent. The data was used to supplement the data collected on site at the screening clinic.[7] This yielded three groups within the control group, denoting the extent of response to the clinical examination and the questionnaire defined as:

1. *Attenders*: participants who attended the third screening round.
2. *Dropouts:*
    a) *Responders*: participants who dropped out but completed and returned the COS-LC after the phone interview.
    b) *Non-responders*: participants who dropped out and did not complete the COS-LC.

Outcomes & Questionnaires

Primary outcome was psychosocial status measured with the Consequences Of Screening for Lung Cancer (COS-LC) questionnaire.[9] Part 1 of COS-LC comprised nine scales measuring various aspects of consequences of screening; a second part of COS-LC addressed the screening outcome and was therefore not applicable to the present analysis. Moreover, the primary part of COS-LC included four core scales: “Anxiety”, “Behaviour”, “Dejection” and “Sleep” that are not lung cancer specific. These scales have originally been developed from a breast cancer screening assessment instrument.[15] Additionally COS-LC comprised five lung cancer specific scales: “Self-blame”, “Focus on airway symptoms”, “Stigmatisation”, “Introvert”, and “Harm of smoking”, which were developed from focus groups and other screening assessment instruments during the first DLCST screening round.[9,15] Therefore, only the core scales were used in the first round, while in the following four screening rounds both the core scales and the lung cancer specific scales were used to assess psychosocial status.[9]

Statistics

Covariates

Socio-demographic characteristics were defined by: social class (I highest social class to V lowest social class), school and vocational education (from 9 years of elementary school to a university education), employment status, living alone, smoking status (current or former smoker), smoking history (pack-years), motivation for smoking cessation (from very strong to no wish to quit) and Charlson Comorbidity Index (CCI). Furthermore, we adjusted for region of residence (Denmark is divided into five health-administrative regions).

Statistical analyses

We performed three different analyses:

1. Analyses of differences in psychosocial status in the **third** round between *Attenders* and *Dropout-responders*.
2. Analyses of differences in psychosocial status in the **second** round between *Attenders, Dropout-responders* and *Dropout-non-responders*.
3. Analyses of differences in psychosocial status in the **first** round, between *Attenders*, *Dropout-responders* and *Dropout-non-responders*.

Covariates at the first screening round were compared between *Attenders* and *Dropouts* by chi-squared tests (categorical characteristics) and t-tests (continuous characteristics). Analyses of psychosocial status at various points in the follow-up were performed in linear regression models both unadjusted and in multivariable models adjusted for sex, age, region of residence, social class, living alone, smoking status, pack years, motivation for smoking cessation and CCI. To adjust

for multiple testing a p-value <0.01 was considered statistically significant. All analyses were performed with SAS 9.4 (SAS Institute, Inc., Cary, NC).

Patient and Public Involvement

Patients and public were not involved in the design of the study.

Results

The inclusion process and participation rate of the DLCST are illustrated in Figure 1. The participation rate in the control group fell from 73.9% in the second round to 57.5% in the fourth round. The participation rate increased in the fifth, final, round (68.9%).

Figure 2 depicts the inclusion process of the present study and showed a dropout rate of 29.6% (n=607) in the third screening round with a higher distribution of *Dropout-non-responders* (16.9% n=347) compared with *Dropout-responders* (12.7% n=260).

In the first screening round we compared differences in socio-demographic characteristics in the two overarching groups (*Attenders, Dropouts*) (Table 1).

Table 1, Socio-demographics

	Missing observations, total	Attenders n=1388	Dropouts n=607	p-value
Covariates	n	n (%)**	n(%)**	
Sex	0			0.0963
Male		773 (55.7)	313 (51.6)	
Female		615 (44.3)	294 (48.4)	
Age, *mean (SD)*	0	57.4 (4.7)	56.9 (4.9)	0.0538
Social class	12			0.0079
I (highest social status)		103 (7.5)	35 (5.8)	
II		296 (21.4)	100 (16.6)	
III		256 (18.5)	114 (18.9)	
IV		375 (27.2)	161 (26.7)	
V (lowest social status)		168 (12.2)	107 (17.7)	
Employed, social class uncertain		112 (8.1)	49 (8.1)	
Outside the labour market		70 (5.1)	37 (6.1)	
School education	5			0.7765
9 years of elementary school		473 (34.2)	220 (36.3)	
10 years of elementary school		541 (39.1)	231 (38.1)	
3 years of upper secondary school		363 (26.2)	153 (25.3)	
Other		7 (0.5)	2 (0.3)	
Vocational education	4			0.1267
None		124 (9.0)	72 (11.9)	
Semi-skilled worker		17 (1.2)	10 (1.7)	
Vocational training		491 (35.4)	212 (35.0)	
Short further education		142 (10.2)	48 (7.9)	
Middle range training		357 (25.8)	167 (27.6)	
Long further education		153 (11.0)	64 (10.6)	
Other		102 (7.4)	32 (5.3)	
Employment status	6			0.8394
Employed		901 (65.2)	387 (63.9)	
Studying		8 (0.6)	4 (0.7)	
Job seeking		67 (4.8)	35 (5.8)	
Retired		407 (29.4)	180 (29.7)	
CCI, *mean (SD)*		0.26 (0.73)	0.31 (0.83)	0.0062
Living alone	17			0.0057
No		1011 (73.5)	405 (67.3)	
Yes		365 (26.5)	197 (32.7)	
Smoking status	0			0.0122
Current smoker		1046 (75.4)	489 (80.6)	
Former smoker		342 (24.6)	118 (19.4)	

Pack-years, *mean (SD)*	4	35.7 (13.7)	35.8 (12.3)	0.4207
Motivation for smoking cessation	30			0.0540
Very strong		141 (10.3)	74 (12.4)	
Strong		324 (23.7)	166 (27.8)	
Weak		331 (24.2)	144 (24.8)	
Very weak		116 (8.5)	42 (7.0)	
No wish to quit		113 (8.3)	54 (9.0)	
Current non-smoker		342 (25.0)	118 (19.7)	

**Except when indicated in the leftmost column that the mean and standard deviation (SD) are listed

There was a significant difference between the study groups for social class with more *Dropouts* in the lowest social class (V) and a greater number of *Attenders* in the highest social classes (I-II). Moreover, *Dropouts* had a significantly higher CCI score indicating that they had more severe or a greater number of co-occurring conditions than *Attenders*. They were also to a greater extent living alone. Furthermore, a non-statistically significant trend of more current smokers with a higher wish of smoking cessation were seen among *Dropouts*.

The results of the third screening round are listed in Table 2.

Table 2, Differences in psychosocial status in the third screening round

	Range of values	Responding rate per item n/n	Attenders n=1388 mean (SD)	Dropout-responders n=260 mean (SD)	p-value	Difference in scores between the two groups mean (99%CI)[a]	p-value adjusted
COS-scales							
Anxiety	0-18	1349/249	1.7 (2.8)	2.1 (3.2)	0.0441	0.38 (-0.13;0.89)	0.0548
Behaviour	0-21	1343/246	2.1 (3.1)	2.9 (3.8)	<0.001	0.77 (0.18;1.36)	<0.001
Dejection	0-18	1354/255	1.9 (3.0)	2.4 (3.5)	0.013	0.49 (-0.06;1.04)	0.0225
Sleep	0-12	1357/252	1.9 (2.6)	2.3 (3.0)	0.041	0.35 (-0.12;0.82)	0.0599
COS-LC scales							
Self-blame	0-15	1356/234	2.2 (2.8)	3.1 (3.8)	<0.001	0.59 (0.14;1.04)	<0.001
Focus on airway symptoms	0-24	1363/239	0.3 (0.8)	0.6 (1.0)	<0.001	0.22 (0.08;0.36)	<0.001
Stigmatisation	0-12	1361/241	1.5 (1.9)	2.1 (2.4)	<0.001	0.51 (0.16;0.86)	<0.001
Introvert	0-18	1361/243	1.3 (1.8)	1.8 (2.2)	<0.001	0.56 (0.23;0.89)	<0.001
Harms of smoking	0-6	1356/248	0.9 (1.2)	1.3 (1.6)	<0.001	0.35 (0.11;0.59)	<0.001

[a)] A positive value of the difference indicates that the persons that were interviewed by phone and later returned COS-LC had on average higher scores, i.e. more negative outcomes (e.g. higher anxiety) than the persons that showed up and completed the COS-LC on site. The differences are adjusted for sex, age, region of residence, social group, living alone, smoking status, pack years, motivation for smoking cessation and CCI. The continuous values variables (age and pack years) are included as a quadratic function as to allow for possible nonlinear effects.

In the core questionnaire COS (Consequences of Screening), *Dropout-responders* had a statistically significant higher (worse) score than *Attenders* in the scale "Behaviour". This effect was still present when adjusting for covariates. Moreover, there was a non-significant trend of worse scores in all COS scales among *Dropout-responders*. In the lung cancer specific part of the COS-LC,

Dropout-responders had statistically significantly higher scores in all scales both crude and adjusted.

Table 3 shows differences in psychosocial status between all three subgroups in the second screening round.

Table 3, Differences in psychosocial status in the second screening round

	Range of values	Responding rate per item n/n/n	Attenders n=1388	Dropout-responders n=260	Dropout-non-responders n=347	p-value	p-value adjusted[a]
COS scales, mean (SD)							
Anxiety	0-18	1201/117/89	1.6 (2.7)	2.0 (3.0)	2.6 (3.8)	0.003	0.018
Behaviour	0-21	1195/114/88	1.9 (2.9)	2.4 (3.3)	2.8 (4.0)	0.012	0.071
Dejection	0-18	1217/117/87	1.8 (2.8)	2.3 (3.3)	3.0 (4.0)	<0.001	<0.001
Sleep	0-12	1220/116/88	1.7 (2.5)	2.3 (2.9)	2.6 (3.2)	<0.001	0.002
COS-LC scales, mean (SD)							
Self-blame	0-15	1210/118/88	1.7 (2.3)	2.1 (2.4)	2.6 (3.0)	<0.001	0.005
Focus on airway symptoms	0-24	1226/118/90	0.4 (0.8)	0.4 (0.8)	0.5 (0.9)	0.408	0.579
Stigmatisation	0-12	1225/121/90	1.5 (1.9)	1.8 (2.1)	2.1 (2.4)	0.028	0.146
Introvert	0-18	1223/116/90	1.3 (1.8)	1.8 (2.0)	1.4 (1.8)	0.012	0.021
Harms of smoking	0-6	1232/118/89	1.1 (1.3)	1.3 (1.3)	1.2 (1.4)	0.134	0.422

[a)] A test for differences between the three groups adjusted for sex, age, region of residence, social group, living alone, smoking status, pack years, motivation for smoking cessation and the CCI. The continuous values variables (age and pack years) are included as a quadratic function as to allow for possible nonlinear effects.

Dropouts had significantly worse crude scores compared with *Attenders* in all but one scale ("Behaviour") in the COS scales. When adjusting for covariates the difference in scores was still significant in two scales "Dejection" and "Sleep". In the lung cancer specific part, the crude and adjusted "Self-blame"-scale score was significantly worse for *Dropouts*.

The differences in psychosocial status in the first screening round between *Attenders*, *Dropout-responders* and *Dropout-non-responders* showed a statistically significant worse unadjusted score in all but one COS-scale ("Behaviour"), for the two *Dropout* subgroups (Table 4). That effect disappeared in all but one scale, "Anxiety" when adjusting for covariates.

Table 4, Differences in psychosocial status in the first screening round

	Range of values	Responding rate per item n/n/n	Attenders n=1388 mean (SD)	Dropout-responders n=260 mean (SD)	Dropout-non-responders n=347 mean (SD)	p-value	p-value adjusted[a]
COS-scales							
Anxiety	0-18	1353/253/334	1.46 (2.16)	1.75 (2.54)	2.11 (2.66)	<0.001	0.0028
Behaviour	0-21	1365/257/340	0.75 (1.89)	1.05 (2.44)	1.04 (2.43)	0.0134	0.0976
Dejection	0-18	1372/257/339	1.25 (2.05)	1.54 (2.48)	1.68 (2.33)	0.0018	0.0512
Sleep	0-12	1368/253/344	0.62 (1.64)	0.86 (1.98)	0.90 (1.86)	0.0072	0.0530

[a] The differences are adjusted for sex, age, region of residence, social group, living alone, smoking status, pack years, motivation for smoking cessation and CCI. The continuous values variables (age and pack years) are included as a quadratic function as to allow for possible nonlinear effects.

Discussion

The present study showed considerable attrition in the control group of the DLCST. Data in the control group was not missing at random. Individuals who dropped out had less favourable baseline socio-demographic profile when compared with attenders. More importantly, individuals who dropped out from their annual clinical work-up had worse psychosocial status than the individuals who attended the clinic in the previous rounds. This can be used to adjust for differential dropout. Furthermore, these individuals also had worse psychosocial status during their missed round (assessed in the present study in the third round). This cannot be used to adjust differential dropout because this information is generally not available but proves the concept.

The use of a condition-specific questionnaire is a strength of the study. Previous research has demonstrated that condition-specific questionnaires are superior to generic questionnaires when measuring psychosocial consequences in cancer screening settings.[16] Furthermore, we used an appropriate longitudinal design i.e. we collected data at the same timepoints for both *Attenders*

and *Dropouts* at various times in the trial, as well as we measured psychosocial status in both groups at baseline.[17] A limitation of the study is that we did not collect psychosocial outcomes of dropouts in the intervention group. This study was designed to gain knowledge of factors motivating such a large drop in participation in the control group. In hindsight, data on dropouts in the screened group could further help us understand the reasons for differential dropout.

In addition to the DLCST, two other trials assessed psychosocial consequences in lung cancer screening with low-dose CT.[6,18] Participants in the NELSON trial were invited to complete questionnaires at baseline and at the second round of screening (two years after baseline screening). Participants in the UKLS completed a questionnaire at baseline, two weeks after randomisation/CT-scan and 10-29 months after baseline. Unlike the DLCST, in these two trials the control group were not invited to an annual visit at the screening clinic. Although there were some differences in study design, dropout rates in the control groups in these three trials were similar and in all three trials there was a differential dropout rate between the intervention and control group. Differences between attenders and participants who dropped out were reported in the UKLS trial. As in the DLCST, dropouts had worse socio-demographic profile i.e. lower social class, and they were more likely single, younger and current smokers compared with attenders. However, these were pooled estimates for both the screening group and the control group.

In individuals diagnosed with cancer, anxiety and worse health-related quality of life have been associated with dropout, which is consistent with our findings.[19] Since *Dropouts* in our study experienced a higher level of anxiety than *Attenders* in the first screening round (i.e. baseline), this could have been the motivation for attending the trial; to get reassured of being healthy.[20] Therefore, randomization to the control group may have caused disappointment, but also attention drawn to not being part of a possibly beneficial intervention.[21] For example, the

secretary in the screening clinic received calls from participants randomized to the control group expressing their disappointment of not being screened. Furthermore, the trial put focus on the harms of smoking, which could have increased the anxiety and fear of disease in this subgroup even more, which may have been a reason to subsequent dropout.

Low social status, younger age and current smoking status have previously been seen among dropouts in lung health studies.[22–25] A systematic review reporting dropout from longitudinal studies in elderly concluded that higher age and declining health were high predictors of dropout. The latter is in agreement with our findings, although higher age is in contrast to our findings.[26] To our knowledge, this is the first cancer screening study testing hypotheses on reasons for differential dropout empirically. The results of this study confirmed the hypotheses we made in our previous study, using inverse probability weighting to adjust for differential dropout.[3,7,27] More importantly, the results of the two other lung cancer screening trials investigating dropout are consistent with ours. Hence, it is plausible that our results are generalisable to other cancer screening trials as well.

Therefore, future cancer screening trials should concurrently assess psychosocial status during the trial, not only to be able to assess the psychosocial effect of screening, but also to use this information to adjust any effect in the trial for bias due to differential attrition.

Conclusions

In conclusion, *Dropouts* in the control group in the DLCST had a worse psychosocial status and a less favourable socio-demographic profile than *Attenders*.

The results of our study contribute with evidence of non-response driven by psychosocial status, which in turn may be influenced by the screening intervention itself. This can be used to adjust cancer screening trial results for bias due to differential dropout.

Abbreviations

RCT: Randomized controlled trial; PROM: Patient-reported outcome measure; CT: Computed tomography; DLCST: Danish Lung Cancer Screening Trial; COS-LC: Consequences of screening in lung cancer; COS: Consequences of screening; CCI: Charlson comorbidity index

Declarations

Ethics approval and consent to participate

The Ethical Committee of Copenhagen County approved the DLCST on 31 January 2003. All participants signed an informed consent form. The trial is registered in Clinical.Trials.gov Protocol Registration System (identification no. NCT00496977)

Availability of data and materials

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

Competing interests

None declared.

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Author contributions

JB and HT developed and designed the study. JB, HT and the DLCST staff collected data. VS performed the statistical analyses. JM drafted the manuscript. JB, HT, BH, JFR, and VS all contributed to parts of the manuscript as well as revisions of the manuscript. All authors approved the final version of the manuscript, and no editorial assistance was received. All authors had full access to all data in the study and are responsible of data retention and the accuracy of the data analysis. JM and JB are guarantors of the study.

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Fig.1 Flowchart, DLCST

Fig.2 Flowchart, present study

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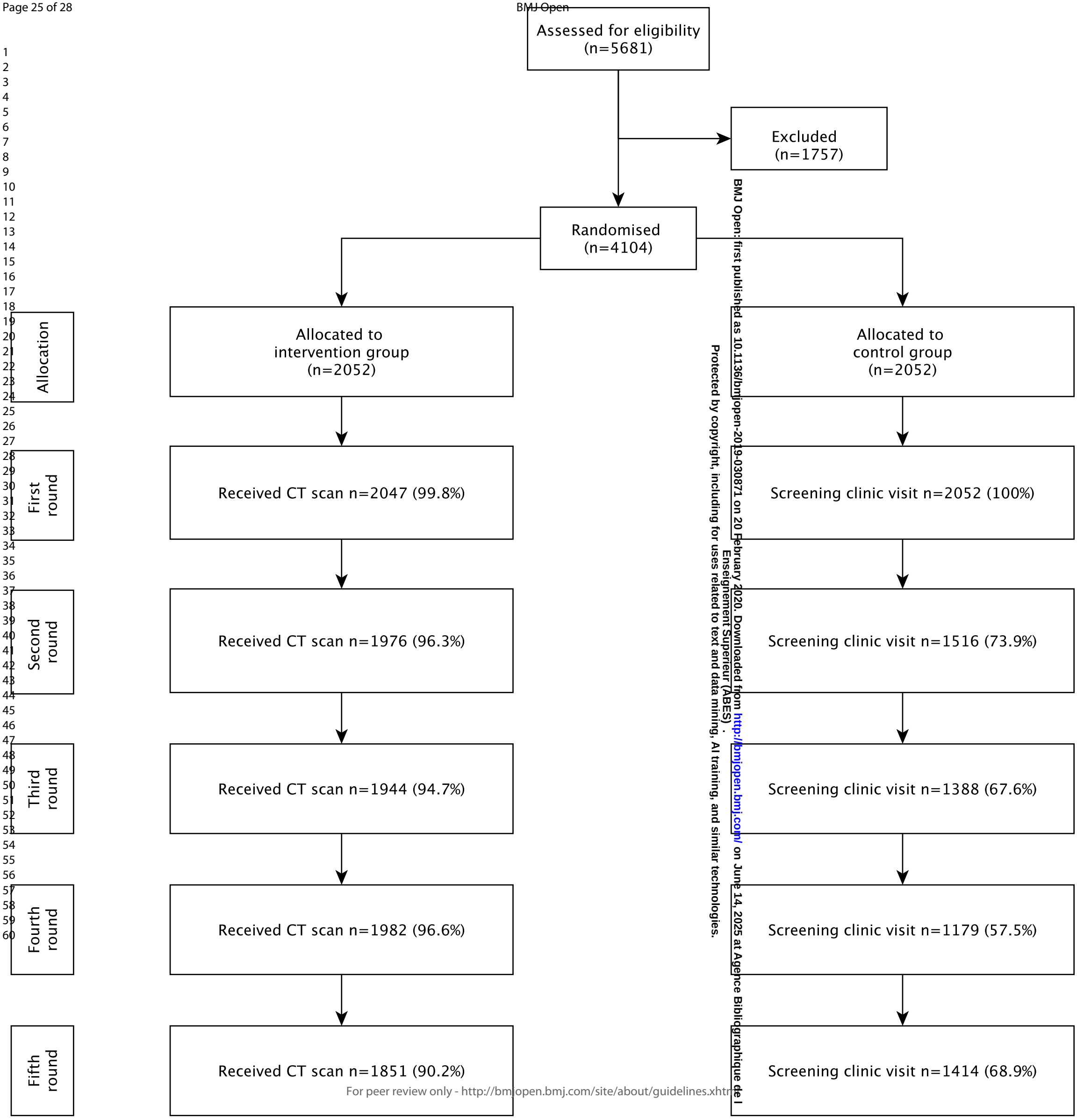

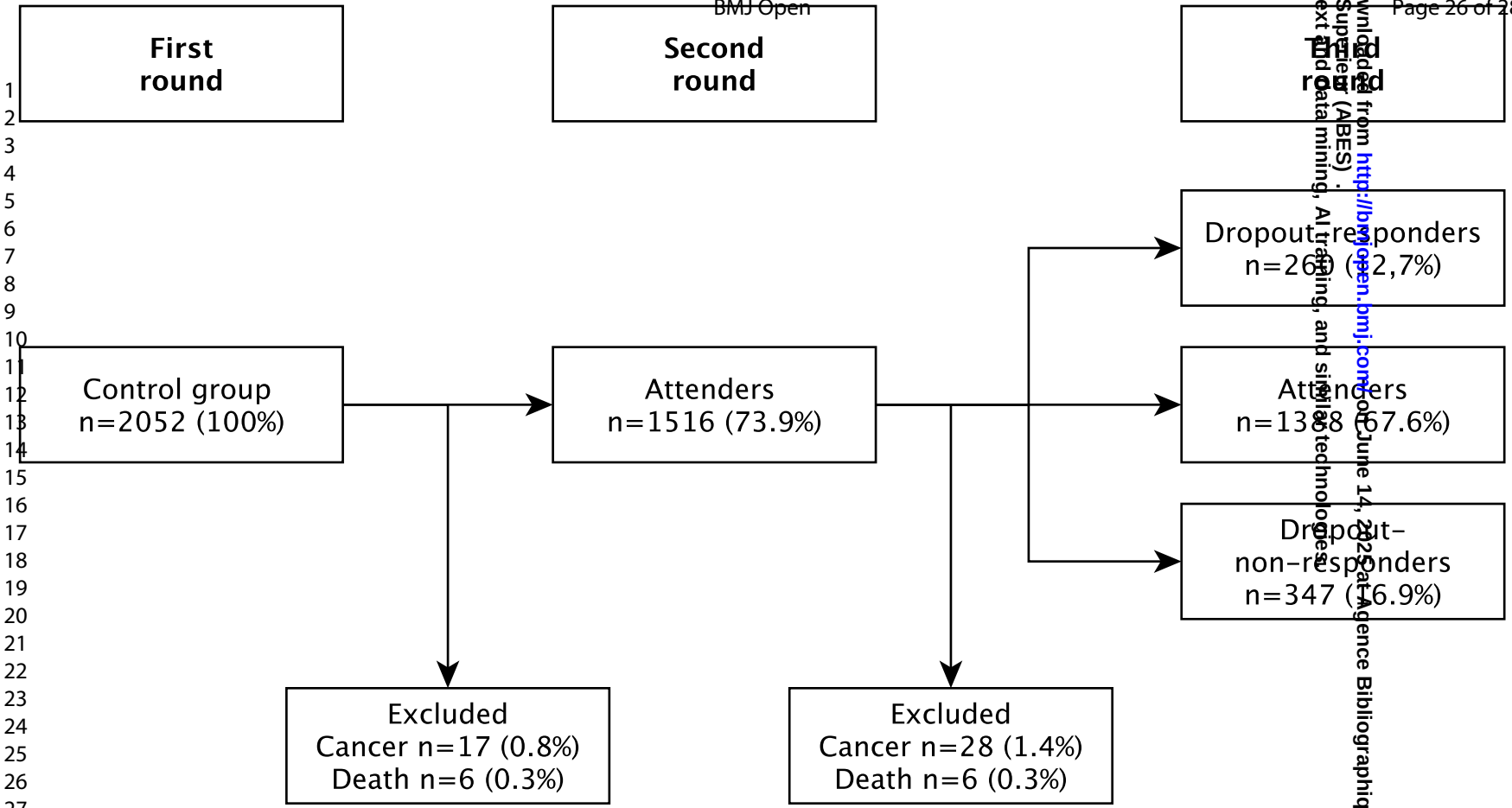

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6 and 7
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	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Not applicable

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig.1
		(b) Give reasons for non-participation at each stage	Fig.2
		(c) Consider use of a flow diagram	Fig.2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*Table 2-4*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	Table 2-4
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
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	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

BMJ Open

Did psychosocial status, sociodemographics and smoking status affect non-attendance in control participants in the Danish Lung Cancer Screening Trial? A nested observational study

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Did psychosocial status, sociodemographics and smoking status affect non-attendance in control participants in the Danish Lung Cancer Screening Trial? A nested observational study

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Abstract

Objectives: We investigated if psychosocial status, socio-demographics and smoking status affected non-attendance in the control group in the randomized Danish Lung Cancer Screening Trial (DLCST).

Design & setting: This study was an observational study nested in the DLCST. Due to large non-attendance in the control group in the second screening round we made an additional effort to collect questionnaire data from non-attenders in this group in the third screening round. We used a condition-specific questionnaire to assess psychosocial status. We analysed the differences in psychosocial status in the third and preceding rounds between non-attenders and attenders in the control group in multivariable linear regression models adjusted for socio-demographics and smoking status reported at baseline. Differences in socio-demographics and smoking status were analysed with chi-squared tests (categorical variables) and t-tests (continuous variables).

Primary outcome measure: Primary outcome was psychosocial status.

Participants: All control persons participating in the third screening round in the DLCST were included.

Results: Non-attenders in the third round had significantly worse psychosocial status than attenders in the scales: “Behaviour” 0.77 (99% CI 0.18;1.36), “Self-blame” 0.59 (99% CI 0.14;1.04), “Focus on airway symptoms” 0.22 (99% CI 0.08;0.36), “Stigmatisation” 0.51 (99% CI 0.16;0.86), “Introvert” 0.56 (99% CI 0.23;0.89), and “Harms of smoking” 0.35 (99% CI 0.11;0.59). Moreover, non-attenders had worse scores than attendees in the preceding screening rounds. Non-attenders also reported worse socio-demographics at baseline.

Conclusions: Non-attenders had a significantly worse psychosocial status and worse socio-demographics compared with attenders. The results of our study contribute with evidence of non-

response and attrition driven by psychosocial status, which in turn may be influenced by the screening intervention itself. This can be used to adjust cancer screening trial results for bias due to differential non-attendance.

Trial registration: The trial is registered in Clinicaltrials.gov Protocol Registration System (identification no. NCT00496977)

Article summary

Strengths and limitations

- Use of a condition-specific questionnaire with adequate psychometric properties ensured valid measures.
- Patient-reported data on non-respondents gave valuable empirical insight in drivers for non-attendance.
- Testing a previously hypothesized model for non-attendance empirically is another strength of the study.
- No comparison between non-attenders in the intervention and the control group was performed.
- No longer-term follow up on non-attenders was performed.

Introduction

Non-attendance may affect trial results and introduce bias in randomized controlled trials (RCTs).[1,2] Non-attendance reduces the power of the trial and, if non-attendance differs between the randomized groups, conventional effect estimates can be biased.[2] While we cannot change

the loss of power, we may remove bias due to differential non-attendance if we know and have measured the factors that cause this non-attendance.[3] For some outcome measures, such as disease incidence or mortality, non-attendance can be partially addressed if data can be obtained from national electronic registers. However, non-attendance will be larger for outcome measures that depend on direct data collection such as clinical measurements and patient reported outcome measures (PROMs). Moreover, the factors driving non-attendance for these measures may be very heterogeneous and may also be driven by the experiences of the trial participants in the trial process.

The problems with differential non-attendance may be aggravated in trials assessing psychosocial consequences of cancer screening as well as other interventions where it is impossible to blind participants to allocation. Notably, a control group not offered screening may be less inclined to return questionnaires enquiring into their experiences with a potentially beneficial intervention they did not receive. Despite these potential problems, few lung cancer screening RCTs have reported on non-attendance in both study groups let alone adjusted for potential differential non-attendance.[4–7] The trials that do, seldom report on the factors involved in non-attendance. Since cancer screening trials are investigating potentially life-threatening diseases there may be emotional drivers of non-attendance, not typical for trials in general. Hence, it is of interest to know which factors drive non-attendance in PROMs in cancer screening trials as this data is to be collected in these trials and then used in adjusting for differential non-attendance.

The Danish Lung Cancer Screening Trial (DLCST) was an RCT including five annual screening rounds of low-dose chest computed tomography (CT) plus clinical examinations in the intervention group compared with annual clinical examinations only in the control group.[8] Furthermore, all the

participants were asked to complete a condition-specific questionnaire, measuring psychosocial consequences of lung cancer screening at these annual clinical assessments.[9] The results showed that people experienced negative psychosocial consequences merely by participating in the trial, and that negative consequences were higher for participants allocated to the control group.[7,10] A large number of control persons did not attend the second annual examination (n=513, 26.1%) while the non-attendance rate in the intervention group was low (n=71, 3.5%) (*Fig. 1*). To adjust for this differential non-attendance, inverse probability weighting was used.[7] In this method the observed outcomes are weighted with the inverse of the probability of being non missing.[3] We hypothesised that these probabilities were adequately estimated from socio-demographic profile including smoking status, randomization group and psychosocial status in previous rounds.[7,11–13]

If these hypotheses were confirmed, then these factors would explain the witnessed difference in attendance between the trial groups and could be used to render them comparable. Analysed without such adjustments the assessment of the trial groups, and thereby the means of the scores from the responses to the questionnaire from the remaining trial participants would no longer be comparable.[14] Hence, the assessment of psychosocial harms of lung cancer screening could be biased.

Therefore, the overall aim of this study was to empirically assess whether control participants who did not attend the annual clinical examination had different psychosocial profiles compared with control participants who attended the annual clinical examination.

Materials and methods

Study design and population

The design and study population of DLCST have been described in detail previously.[7,8] Briefly, the DLCST was an RCT, conducted at the Copenhagen University hospital Gentofte in Denmark from October 2004 to March 2010. Heavy current and former smokers (at least 20 pack-years), aged 50-70 years old, were randomized to either five rounds of screening with low-dose CT-scans including clinical examinations (n=2052) or five clinical examinations only (n=2052). In the enrolment visit, participants provided socio-demographic data, lifestyle and health information (including smoking status), completed a questionnaire on their psychosocial status and underwent spirometry. Participants randomized to screening also had a low-dose chest CT-scan within one month of randomisation. In the following screening rounds, participants in the screened and control groups were invited to a visit in the screening clinic where lung function tests were performed, and questionnaires concerning health, lifestyle, smoking habits and psychosocial status were completed and lung function tests were performed. Participants randomized to screening also received a low-dose chest CT-scan.

This study is an observational study nested in the DLCST. During the second screening round, the steering committee noted that a large number of control participants did not attend the screening clinic visit when compared with the number of screened participants. Thus, the committee decided to make additional efforts to collect questionnaire data for non-attenders in the control group in the third screening round to perform post hoc analyses on whether psychosocial status was an influencing factor *(Fig.2)*.

During the third round, participants in the control group who did not attend the annual examination were contacted by phone and part 1 of the questionnaire was sent with a postage paid envelope to those who gave their oral consent. The data was used to supplement the data

collected on site at the screening clinic.[7] This yielded three groups within the control group, denoting the extent of response to the clinical examination and the questionnaire defined as:

1. *Attenders*: participants who attended the third screening round.
2. *Non-attenders:*
   a) *Respondents*: participants who did not attend the annual examination but completed and returned the COS-LC after the phone interview.
   b) *Non-respondents*: participants who did not attend the annual examination and did not complete the COS-LC.

Outcomes & Questionnaires

Primary outcome was psychosocial status measured with the Consequences Of Screening for Lung Cancer (COS-LC) questionnaire.[9] Part 1 of COS-LC comprised nine scales measuring various aspects of consequences of screening; a second part of COS-LC addressed the screening outcome and was therefore not applicable to the present analysis. Moreover, the primary part of COS-LC included four core scales: “Anxiety”, “Behaviour”, “Dejection” and “Sleep” that are not lung cancer specific. These scales have originally been developed from a breast cancer screening assessment instrument.[15] Additionally COS-LC comprised five lung cancer specific scales: “Self-blame”, “Focus on airway symptoms”, “Stigmatisation”, “Introvert”, and “Harm of smoking”, which were developed from focus groups and other screening assessment instruments during the first DLCST screening round.[9,15] Therefore, only the core scales were used in the first round, while in the following four screening rounds both the core scales and the lung cancer specific scales were used to assess psychosocial status.[9]

Statistics

Covariates

Socio-demographic characteristics were defined by: social class (I highest social class to V lowest social class), school and vocational education (from 9 years of elementary school to a university education), employment status, living alone, smoking status (current or former smoker), smoking history (pack-years), motivation for smoking cessation (from very strong to no wish to quit) and Charlson Comorbidity Index (CCI). Furthermore, we adjusted for region of residence (Denmark is divided into five health-administrative regions).

Statistical analyses

We performed three different analyses:

1. Analyses of differences in psychosocial status in the **third** round between *Attenders* and *Non-attenders-respondents*.
2. Analyses of differences in psychosocial status in the **second** round between *Attenders, Non-attenders-respondents* and *Non-attenders-non-respondents*.
3. Analyses of differences in psychosocial status in the **first** round, between *Attenders*, *Non-attenders-respondents* and *Non-attenders-non-respondents*.

Covariates at the first screening round were compared between *Attenders* and *Non-attenders* by chi-squared tests (categorical characteristics) and t-tests (continuous characteristics). Analyses of psychosocial status at various points in the follow-up were performed in linear regression models both unadjusted and in multivariable models adjusted for sex, age, region of residence, social class, living alone, smoking status, pack years, motivation for smoking cessation and CCI. To adjust

for multiple testing a p-value <0.01 was considered statistically significant. All analyses were performed with SAS 9.4 (SAS Institute, Inc., Cary, NC).

Patient and Public Involvement

Patients and public were not involved in the design of the study.

Results

The inclusion process and participation rate of the DLCST are illustrated in Figure 1. The participation rate in the control group fell from 73.9% in the second round to 57.5% in the fourth round. The participation rate increased in the fifth, final, round (68.9%).

Figure 2 depicts the inclusion process of the present study and showed a dropout rate of 29.6% (n=607) in the third screening round with a higher distribution of *Non-attenders-non-respondents* (16.9% n=347) compared with *Non-attenders-respondents* (12.7% n=260).

In the first screening round we compared differences in socio-demographic characteristics in the two overarching groups (*Attenders, Non-attenders*) (Table 1).

Table 1, Socio-demographics

	Missing observations, total	Attenders n=1388	Non-attenders n=607	p-value
Covariates	n	n (%)**	n(%)**	
Sex	0			0.0963
Male		773 (55.7)	313 (51.6)	
Female		615 (44.3)	294 (48.4)	
Age, *mean (SD)*	0	57.4 (4.7)	56.9 (4.9)	0.0538
Social class	12			0.0079
I (highest social status)		103 (7.5)	35 (5.8)	
II		296 (21.4)	100 (16.6)	
III		256 (18.5)	114 (18.9)	
IV		375 (27.2)	161 (26.7)	
V (lowest social status)		168 (12.2)	107 (17.7)	
Employed, social class uncertain		112 (8.1)	49 (8.1)	
Outside the labour market		70 (5.1)	37 (6.1)	
School education	5			0.7765
9 years of elementary school		473 (34.2)	220 (36.3)	
10 years of elementary school		541 (39.1)	231 (38.1)	
3 years of upper secondary school		363 (26.2)	153 (25.3)	
Other		7 (0.5)	2 (0.3)	
Vocational education	4			0.1267
None		124 (9.0)	72 (11.9)	
Semi-skilled worker		17 (1.2)	10 (1.7)	
Vocational training		491 (35.4)	212 (35.0)	
Short further education		142 (10.2)	48 (7.9)	
Middle range training		357 (25.8)	167 (27.6)	
Long further education		153 (11.0)	64 (10.6)	
Other		102 (7.4)	32 (5.3)	
Employment status	6			0.8394
Employed		901 (65.2)	387 (63.9)	
Studying		8 (0.6)	4 (0.7)	
Job seeking		67 (4.8)	35 (5.8)	
Retired		407 (29.4)	180 (29.7)	
CCI, *mean (SD)*		0.26 (0.73)	0.31 (0.83)	0.0062
Living alone	17			0.0057
No		1011 (73.5)	405 (67.3)	
Yes		365 (26.5)	197 (32.7)	

Smoking status	0			0.0122
Current smoker		1046 (75.4)	489 (80.6)	
Former smoker		342 (24.6)	118 (19.4)	
Pack-years, *mean (SD)*	4	35.7 (13.7)	35.8 (12.3)	0.4207
Motivation for smoking cessation	30			0.0540
Very strong		141 (10.3)	74 (12.4)	
Strong		324 (23.7)	166 (27.8)	
Weak		331 (24.2)	144 (24.8)	
Very weak		116 (8.5)	42 (7.0)	
No wish to quit		113 (8.3)	54 (9.0)	
Current non-smoker		342 (25.0)	118 (19.7)	

**Except when indicated in the leftmost column that the mean and standard deviation (SD) are listed

There was a significant difference between the study groups for social class with more *Non-attenders* in the lowest social class (V) and a greater number of *Attenders* in the highest social classes (I-II).

Moreover, *Non-attenders* had a significantly higher CCI score indicating that they had more severe or a greater number of co-occurring conditions than *Attenders*. They were also to a greater extent living alone. Furthermore, a non-statistically significant trend of more current smokers with a higher wish of smoking cessation were seen among *Non-attenders*.

The results of the third screening round are listed in Table 2.

Table 2, Differences in psychosocial status in the third screening round

	Range of values	Responding rate per item n/n	Attenders n=1388 mean (SD)	Non-attenders-respondents n=260 mean (SD)	p-value	Difference in scores between the two groups mean (99%CI)[a]	p-value adjusted
COS-scales							
Anxiety	0-18	1349/249	1.7 (2.8)	2.1 (3.2)	0.0441	0.38 (-0.13;0.89)	0.0548
Behaviour	0-21	1343/246	2.1 (3.1)	2.9 (3.8)	<0.001	0.77 (0.18;1.36)	<0.001
Dejection	0-18	1354/255	1.9 (3.0)	2.4 (3.5)	0.013	0.49 (-0.06;1.04)	0.0225
Sleep	0-12	1357/252	1.9 (2.6)	2.3 (3.0)	0.041	0.35 (-0.12;0.82)	0.0599
COS-LC scales							
Self-blame	0-15	1356/234	2.2 (2.8)	3.1 (3.8)	<0.001	0.59 (0.14;1.04)	<0.001
Focus on airway symptoms	0-24	1363/239	0.3 (0.8)	0.6 (1.0)	<0.001	0.22 (0.08;0.36)	<0.001
Stigmatisation	0-12	1361/241	1.5 (1.9)	2.1 (2.4)	<0.001	0.51 (0.16;0.86)	<0.001
Introvert	0-18	1361/243	1.3 (1.8)	1.8 (2.2)	<0.001	0.56 (0.23;0.89)	<0.001
Harms of smoking	0-6	1356/248	0.9 (1.2)	1.3 (1.6)	<0.001	0.35 (0.11;0.59)	<0.001

[a)] A positive value of the difference indicates that the persons that were interviewed by phone and later returned COS-LC had on average higher scores, i.e. more negative outcomes (e.g. higher anxiety) than the persons that showed up and completed the COS-LC on site. The differences are adjusted for sex, age, region of residence, social group, living alone, smoking status, pack years, motivation for smoking cessation and CCI. The continuous values variables (age and pack years) are included as a quadratic function as to allow for possible nonlinear effects.

In the core questionnaire COS (Consequences of Screening), *Non-attenders-respondents* had a statistically significant higher (worse) score than *Attenders* in the scale "Behaviour". This effect was still present when adjusting for covariates. Moreover, there was a non-significant trend of worse scores in all COS scales among *Non-attenders-respondents*. In the lung cancer specific part

of the COS-LC, *Non-attenders-respondents* had statistically significantly higher scores in all scales both crude and adjusted.

Table 3 shows differences in psychosocial status between all three subgroups in the second screening round.

Table 3, Differences in psychosocial status in the second screening round

	Range of values	Responding rate per item n/n/n	Attenders n=1388	Non-attenders-respondents n=260	Non-attenders-non-respondents n=347	p-value	p-value adjusted[a]
COS scales, mean (SD)							
Anxiety	0-18	1201/117/89	1.6 (2.7)	2.0 (3.0)	2.6 (3.8)	0.003	0.018
Behaviour	0-21	1195/114/88	1.9 (2.9)	2.4 (3.3)	2.8 (4.0)	0.012	0.071
Dejection	0-18	1217/117/87	1.8 (2.8)	2.3 (3.3)	3.0 (4.0)	<0.001	<0.001
Sleep	0-12	1220/116/88	1.7 (2.5)	2.3 (2.9)	2.6 (3.2)	<0.001	0.002
COS-LC scales, mean (SD)							
Self-blame	0-15	1210/118/88	1.7 (2.3)	2.1 (2.4)	2.6 (3.0)	<0.001	0.005
Focus on airway symptoms	0-24	1226/118/90	0.4 (0.8)	0.4 (0.8)	0.5 (0.9)	0.408	0.579
Stigmatisation	0-12	1225/121/90	1.5 (1.9)	1.8 (2.1)	2.1 (2.4)	0.028	0.146
Introvert	0-18	1223/116/90	1.3 (1.8)	1.8 (2.0)	1.4 (1.8)	0.012	0.021
Harms of smoking	0-6	1232/118/89	1.1 (1.3)	1.3 (1.3)	1.2 (1.4)	0.134	0.422

[a] A test for differences between the three groups adjusted for sex, age, region of residence, social group, living alone, smoking status, pack years, motivation for smoking cessation and the CCI. The continuous values variables (age and pack years) are included as a quadratic function as to allow for possible nonlinear effects.

Non-attenders had significantly worse crude scores compared with *Attenders* in all but one scale ("Behaviour") in the COS scales. When adjusting for covariates the difference in scores was still significant in two scales "Dejection" and "Sleep". In the lung cancer specific part, the crude and adjusted "Self-blame"-scale score was significantly worse for *Non-attenders*.

The differences in psychosocial status in the first screening round between *Attenders*, *Non-attenders-respondents* and *Non-attenders-non-responders* showed a statistically significant worse unadjusted score in all but one COS-scale ("Behaviour"), for the two *Non-attenders* subgroups (Table 4). That effect disappeared in all but one scale, "Anxiety" when adjusting for covariates.

Table 4, Differences in psychosocial status in the first screening round

	Range of values	Responding rate per item n/n/n	Attenders n=1388 mean (SD)	Non-attenders-respondents n=260 mean (SD)	Non-attenders-non-respondents n=347 mean (SD)	p-value	p-value adjusted[a]
COS-scales							
Anxiety	0-18	1353/253/334	1.46 (2.16)	1.75 (2.54)	2.11 (2.66)	<0.001	0.0028
Behaviour	0-21	1365/257/340	0.75 (1.89)	1.05 (2.44)	1.04 (2.43)	0.0134	0.0976
Dejection	0-18	1372/257/339	1.25 (2.05)	1.54 (2.48)	1.68 (2.33)	0.0018	0.0512
Sleep	0-12	1368/253/344	0.62 (1.64)	0.86 (1.98)	0.90 (1.86)	0.0072	0.0530

[a)] The differences are adjusted for sex, age, region of residence, social group, living alone, smoking status, pack years, motivation for smoking cessation and CCI. The continuous values variables (age and pack years) are included as a quadratic function as to allow for possible nonlinear effects.

Discussion

The present study showed considerable non-attendance in the control group of the DLCST. Data in the control group was not missing at random. Non-attenders had less favourable baseline socio-demographic profile when compared with attenders. More importantly, individuals who did not attend their annual clinical work-up had worse psychosocial status than the individuals who attended the clinic in the previous rounds. This can be used to adjust for differential non-attendance. Furthermore, these individuals also had worse psychosocial status during their missed round (assessed in the present study in the third round). This cannot be used to adjust differential non-attendance because this information is generally not available but proves the concept.

The use of a condition-specific questionnaire is a strength of the study. Previous research has demonstrated that condition-specific questionnaires are superior to generic questionnaires when measuring psychosocial consequences in cancer screening settings.[16] Furthermore, we used an appropriate longitudinal design i.e. we collected data at the same timepoints for both *Attenders* and *Non-attenders* at various times in the study, as well as we measured psychosocial status in both groups at baseline.[17] A limitation of the study is that we did not collect psychosocial outcomes of Non-attenders in the intervention group. This study was designed to gain knowledge of factors motivating such a large drop in participation in the control group. In hindsight, data on Non-attenders in the screened group could further help us understand the reasons for differential non-response.

In addition to the DLCST, two other trials assessed psychosocial consequences in lung cancer screening with low-dose CT.[6,18] Participants in the NELSON trial were invited to complete questionnaires at baseline and at the second round of screening (two years after baseline screening). Participants in the UKLS completed a questionnaire at baseline, two weeks after randomisation/CT-scan and 10-29 months after baseline. Unlike the DLCST, in these two trials the control group were not invited to an annual visit at the screening clinic. Although there were some differences in study design, non-response rates in the control groups in these three trials were similar and in all three trials there was differential non-response between the intervention and control group. Differences between attenders and non-attenders were reported in the UKLS trial. As in the DLCST, non-attenders had worse socio-demographic profile i.e. lower social class, and they were more likely single, younger and current smokers compared with attenders. However, these were pooled estimates for both the screening group and the control group.

In individuals diagnosed with cancer, anxiety and worse health-related quality of life have been associated with dropout, which is consistent with our findings.[19] Since *Non-attenders* in our study experienced a higher level of anxiety than *Attenders* in the first screening round (i.e. baseline), this could have been the motivation for attending the trial; to get reassured of being healthy.[20] Therefore, randomization to the control group may have caused disappointment, but also attention drawn to not being part of a possibly beneficial intervention.[21] For example, the secretary in the screening clinic received calls from participants randomized to the control group expressing their disappointment of not being screened. Furthermore, the trial put focus on the harms of smoking, which could have increased the anxiety and fear of disease in this subgroup even more, which may have been a reason to subsequent non-attendance. Finally, missing data on psychosocial status in a previous round may also have been a predictor for non-attendance in the next screening round, which was not the scope for this study.

Low social status, younger age and current smoking status have previously been seen among dropouts and non-respondents in lung health studies.[22–25] A systematic review reporting dropout from longitudinal studies in elderly concluded that higher age and declining health were high predictors of dropout. The latter is in agreement with our findings, although higher age is in contrast to our findings.[26]

To our knowledge, this is the first cancer screening study testing hypotheses on reasons for differential non-response empirically. The results of this study confirmed the hypotheses we made in our previous study, using inverse probability weighting to adjust for differential non-response.[3,7,27] More importantly, the results of the two other lung cancer screening trials

investigating dropout are consistent with ours. Hence, it is plausible that our results are generalisable to other cancer screening trials as well.

Therefore, future cancer screening trials should concurrently assess psychosocial status during the trial, not only to be able to assess the psychosocial effect of screening, but also to use this information to adjust any effect in the trial for bias due to differential non-attendance.

Conclusions

In conclusion, *Non-attenders* in the control group in the DLCST had a worse psychosocial status and a less favourable socio-demographic profile than *Attenders*.

The results of our study contribute with evidence of non-response driven by psychosocial status, which in turn may be influenced by the screening intervention itself. This can be used to adjust cancer screening trial results for bias due to differential attendance.

Abbreviations

RCT: Randomized controlled trial; PROM: Patient-reported outcome measure; CT: Computed tomography; DLCST: Danish Lung Cancer Screening Trial; COS-LC: Consequences of screening in lung cancer; COS: Consequences of screening; CCI: Charlson comorbidity index

Declarations

Ethics approval and consent to participate

The Ethical Committee of Copenhagen County approved the DLCST including this observational study nested in the DLCST on 31 January 2003: approval number KA-02045.

All participants signed an informed consent form and received an information letter about the project and information about the ethical approval and data protection agency approval. The trial is registered in Clinicaltrials.gov Protocol Registration System (identification no. NCT00496977)

Availability of data and materials

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

Competing interests

None declared.

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Author contributions

JB and HT developed and designed the study. JB, HT and the DLCST staff collected data. VS performed the statistical analyses. JM drafted the manuscript. JB, HT, BH, JFR, and VS all contributed to parts of the manuscript as well as revisions of the manuscript. All authors approved the final version of the manuscript, and no editorial assistance was received. All authors had full access to all data in the study and are responsible of data retention and the accuracy of the data analysis. JM and JB are guarantors of the study.

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Fig.1 Flowchart, DLCST

Fig.2 Flowchart, present study

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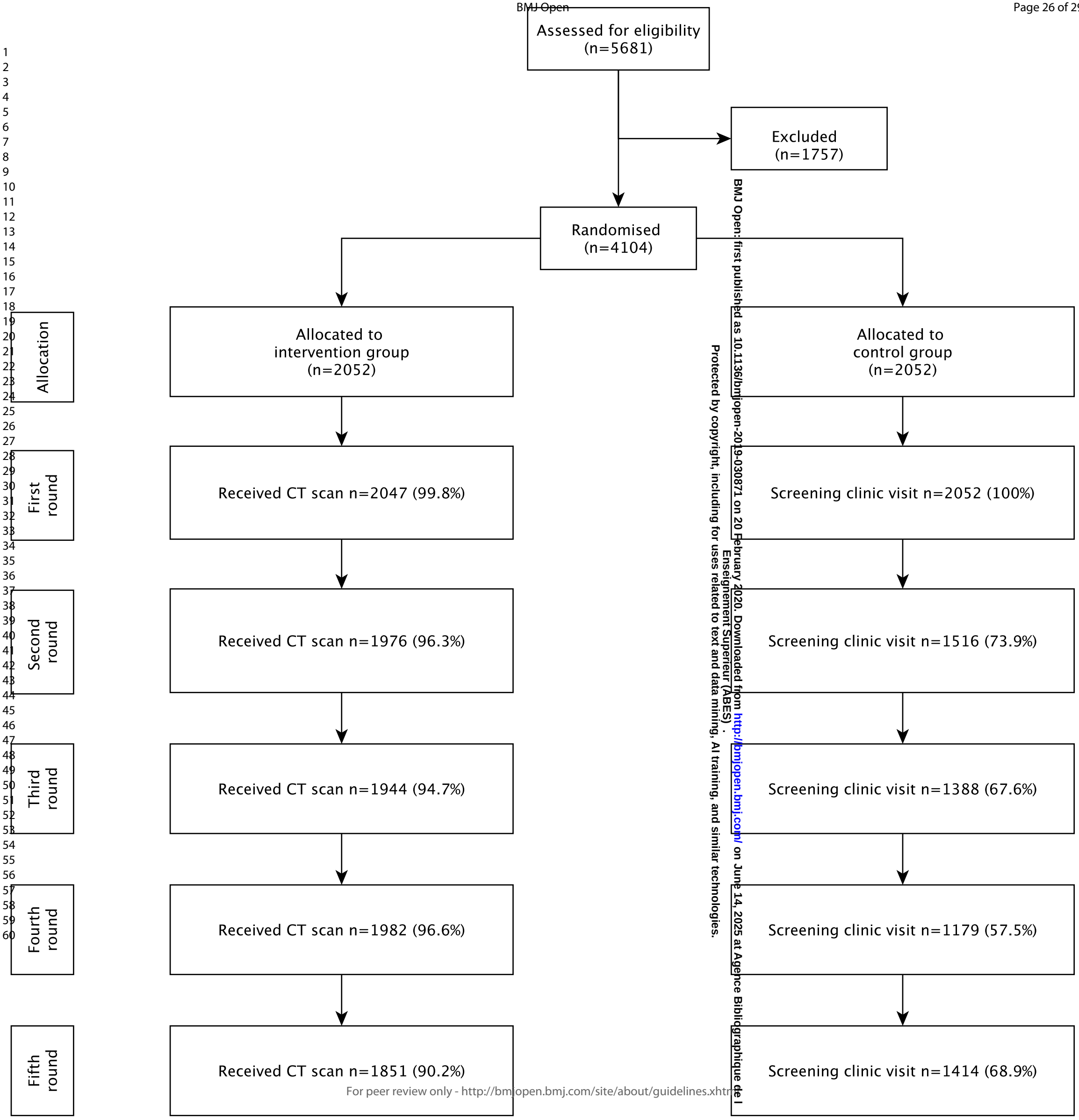

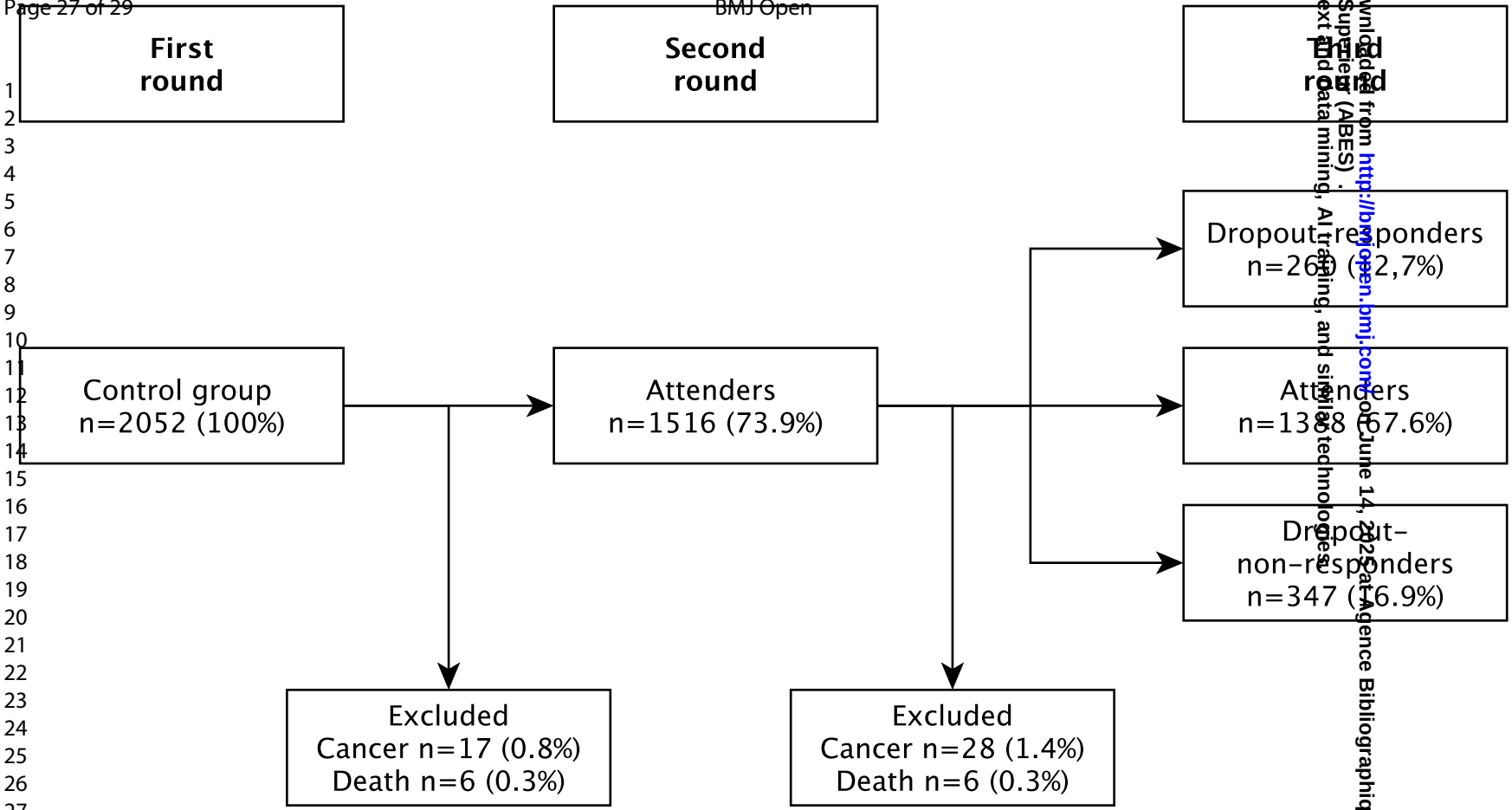

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6 and 7
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	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Not applicable

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig.1
		(b) Give reasons for non-participation at each stage	Fig.2
		(c) Consider use of a flow diagram	Fig.2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*Table 2-4*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	Table 2-4
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
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	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

BMJ Open

Did psychosocial status, sociodemographics and smoking status affect non-attendance in control participants in the Danish Lung Cancer Screening Trial? A nested observational study

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Did psychosocial status, sociodemographics and smoking status affect non-attendance in control participants in the Danish Lung Cancer Screening Trial? A nested observational study

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Abstract

Objectives: We investigated if psychosocial status, socio-demographics and smoking status affected non-attendance in the control group in the randomized Danish Lung Cancer Screening Trial (DLCST).

Design & setting: This study was an observational study nested in the DLCST. Due to large non-attendance in the control group in the second screening round we made an additional effort to collect questionnaire data from non-attenders in this group in the third screening round. We used a condition-specific questionnaire to assess psychosocial status. We analysed the differences in psychosocial status in the third and preceding rounds between non-attenders and attenders in the control group in multivariable linear regression models adjusted for socio-demographics and smoking status reported at baseline. Differences in socio-demographics and smoking status were analysed with chi-squared tests (categorical variables) and t-tests (continuous variables).

Primary outcome measure: Primary outcome was psychosocial status.

Participants: All control persons participating in the third screening round in the DLCST were included.

Results: Non-attenders in the third round had significantly worse psychosocial status than attenders in the scales: “Behaviour” 0.77 (99% CI 0.18;1.36), “Self-blame” 0.59 (99% CI 0.14;1.04), “Focus on airway symptoms” 0.22 (99% CI 0.08;0.36), “Stigmatisation” 0.51 (99% CI 0.16;0.86), “Introvert” 0.56 (99% CI 0.23;0.89), and “Harms of smoking” 0.35 (99% CI 0.11;0.59). Moreover, non-attenders had worse scores than attendees in the preceding screening rounds. Non-attenders also reported worse socio-demographics at baseline.

Conclusions: Non-attenders had a significantly worse psychosocial status and worse socio-demographics compared with attenders. The results of our study contribute with evidence of non-

response and attrition driven by psychosocial status, which in turn may be influenced by the screening intervention itself. This can be used to adjust cancer screening trial results for bias due to differential non-attendance.

Trial registration: The trial is registered in Clinicaltrials.gov Protocol Registration System (identification no. NCT00496977)

Article summary

Strengths and limitations

- Use of a condition-specific questionnaire with adequate psychometric properties ensured valid measures.
- Patient-reported data on non-respondents gave valuable empirical insight in drivers for non-attendance.
- Testing a previously hypothesized model for non-attendance empirically is another strength of the study.
- No comparison between non-attenders in the intervention and the control group was performed.
- No longer-term follow up on non-attenders was performed.

Introduction

Non-attendance may affect trial results and introduce bias in randomized controlled trials (RCTs).(1,2) Non-attendance reduces the power of the trial and, if non-attendance differs between the randomized groups, conventional effect estimates can be biased.(2) While we cannot change

the loss of power, we may remove bias due to differential non-attendance if we know and have measured the factors that cause this non-attendance.(3) For some outcome measures, such as disease incidence or mortality, non-attendance can be partially addressed if data can be obtained from national electronic registers. However, non-attendance will be larger for outcome measures that depend on direct data collection such as clinical measurements and patient reported outcome measures (PROMs). Moreover, the factors driving non-attendance for these measures may be very heterogeneous and may also be driven by the experiences of the trial participants in the trial process.

The problems with differential non-attendance may be aggravated in trials assessing psychosocial consequences of cancer screening as well as other interventions where it is impossible to blind participants to allocation. Notably, a control group not offered screening may be less inclined to return questionnaires enquiring into their experiences with a potentially beneficial intervention they did not receive. However, the psychosocial dimensions of non-attendance and potential consequences of these in lung cancer screening trials are only partially researched.(4–7) Since cancer screening trials are investigating potentially life-threatening diseases there may be emotional drivers of non-attendance, not typical for trials in general. Hence, it is of interest to know which factors drive non-attendance in PROMs in cancer screening trials as this data is to be collected in these trials and then used in adjusting for differential non-attendance.

The Danish Lung Cancer Screening Trial (DLCST) was an RCT including five annual screening rounds of low-dose chest computed tomography (CT) plus clinical examinations in the intervention group compared with annual clinical examinations only in the control group.(8) Furthermore, all the participants were asked to complete a condition-specific questionnaire, measuring psychosocial

consequences of lung cancer screening at these annual clinical assessments.(9) The results showed that people experienced negative psychosocial consequences merely by participating in the trial, and that negative consequences were higher for participants allocated to the control group.(7,10) A large number of control persons did not attend the second annual examination (n=513, 26.1%) while the non-attendance rate in the intervention group was low (n=71, 3.5%) (*Fig. 1*). To adjust for this differential non-attendance, inverse probability weighting was used.(7) In this method the observed outcomes are weighted with the inverse of the probability of being non missing.(3) We hypothesised that these probabilities were adequately estimated from socio-demographic profile including smoking status, randomization group and psychosocial status in previous rounds.(7,11–13)

If these hypotheses were confirmed, then these factors would explain the witnessed difference in attendance between the trial groups and could be used to render them comparable. Analysed without such adjustments the assessment of the trial groups, and thereby the means of the scores from the responses to the questionnaire from the remaining trial participants would no longer be comparable.(14) Hence, the assessment of psychosocial harms of lung cancer screening could be biased.

Therefore, the overall aim of this study was to empirically assess whether control participants who did not attend the annual clinical examination had different psychosocial profiles compared with control participants who attended the annual clinical examination.

Materials and methods

Study design and population

The design and study population of DLCST have been described in detail previously.(7,8) Briefly, the DLCST was an RCT, conducted at the Copenhagen University hospital Gentofte in Denmark from October 2004 to March 2010. Heavy current and former smokers (at least 20 pack-years), aged 50-70 years old, were randomized to either five rounds of screening with low-dose CT-scans including clinical examinations (n=2052) or five clinical examinations only (n=2052). In the enrolment visit, participants provided socio-demographic data, lifestyle and health information (including smoking status), completed a questionnaire on their psychosocial status and underwent spirometry. Participants randomized to screening also had a low-dose chest CT-scan within one month of randomisation. In the following screening rounds, participants in the screened and control groups were invited to a visit in the screening clinic where lung function tests were performed, and questionnaires concerning health, lifestyle, smoking habits and psychosocial status were completed and lung function tests were performed. Participants randomized to screening also received a low-dose chest CT-scan.

This study is an observational study nested in the DLCST. During the second screening round, the steering committee noted that a large number of control participants did not attend the screening clinic visit when compared with the number of screened participants. Thus, the committee decided to make additional efforts to collect questionnaire data for non-attenders in the control group in the third screening round to perform post hoc analyses on whether psychosocial status was an influencing factor *(Fig.2)*.

During the third round, participants in the control group who did not attend the annual examination were contacted by phone and part 1 of the questionnaire was sent with a postage paid envelope to those who gave their oral consent. The data was used to supplement the data

collected on site at the screening clinic.(7) This yielded three groups within the control group, denoting the extent of response to the clinical examination and the questionnaire defined as:

1. *Attenders*: participants who attended the third screening round.
2. *Non-attenders:*
   a) *Respondents*: participants who did not attend the annual examination but completed and returned the COS-LC after the phone interview.
   b) *Non-respondents*: participants who did not attend the annual examination and did not complete the COS-LC.

Outcomes & Questionnaires

Primary outcome was psychosocial status measured with the Consequences Of Screening for Lung Cancer (COS-LC) questionnaire.(9) Part 1 of COS-LC comprised nine scales measuring various aspects of consequences of screening; a second part of COS-LC addressed the screening outcome and was therefore not applicable to the present analysis. Moreover, the primary part of COS-LC included four core scales: “Anxiety”, “Behaviour”, “Dejection” and “Sleep” that are not lung cancer specific. These scales have originally been developed from a breast cancer screening assessment instrument.(15) Additionally COS-LC comprised five lung cancer specific scales: “Self-blame”, “Focus on airway symptoms”, “Stigmatisation”, “Introvert”, and “Harm of smoking”, which were developed from focus groups and other screening assessment instruments during the first DLCST screening round.(9,15) Therefore, only the core scales were used in the first round, while in the following four screening rounds both the core scales and the lung cancer specific scales were used to assess psychosocial status.(9)

Statistics

Covariates

Socio-demographic characteristics were defined by: social class (I highest social class to V lowest social class), school and vocational education (from 9 years of elementary school to a university education), employment status, living alone, smoking status (current or former smoker), smoking history (pack-years), motivation for smoking cessation (from very strong to no wish to quit) and Charlson Comorbidity Index (CCI). Furthermore, we adjusted for region of residence (Denmark is divided into five health-administrative regions).

Statistical analyses

We performed three different analyses:

1. Analyses of differences in psychosocial status in the **third** round between *Attenders* and *Non-attenders-respondents*.
2. Analyses of differences in psychosocial status in the **second** round between *Attenders, Non-attenders-respondents* and *Non-attenders-non-respondents*.
3. Analyses of differences in psychosocial status in the **first** round, between *Attenders*, *Non-attenders-respondents* and *Non-attenders-non-respondents*.

Covariates at the first screening round were compared between *Attenders* and *Non-attenders* by chi-squared tests (categorical characteristics) and t-tests (continuous characteristics). Analyses of psychosocial status at various points in the follow-up were performed in linear regression models both unadjusted and in multivariable models adjusted for sex, age, region of residence, social class, living alone, smoking status, pack years, motivation for smoking cessation and CCI. To adjust

for multiple testing we used the Benjamini-Hochberg procedure and the False Discovery Rate (FDR) was set to 5% (16). All analyses were performed with SAS 9.4 (SAS Institute, Inc., Cary, NC).

Patient and Public Involvement

Patients and public were not involved in the design of the study.

Results

The inclusion process and participation rate of the DLCST are illustrated in Figure 1. The participation rate in the control group fell from 73.9% in the second round to 57.5% in the fourth round. The participation rate increased in the fifth, final, round (68.9%).

Figure 2 depicts the inclusion process of the present study and showed a dropout rate of 29.6% (n=607) in the third screening round with a higher distribution of *Non-attenders-non-respondents* (16.9% n=347) compared with *Non-attenders-respondents* (12.7% n=260).

In the first screening round we compared differences in socio-demographic characteristics in the two overarching groups (*Attenders, Non-attenders*) (Table 1).

Table 1, Socio-demographics

	Missing observations, total	Attenders n=1388	Non-attenders n=607	p-value*
Covariates	n	n (%)**	n(%)**	
Sex	0			0.0963
Male		773 (55.7)	313 (51.6)	
Female		615 (44.3)	294 (48.4)	
Age, *mean (SD)*	0	57.4 (4.7)	56.9 (4.9)	0.0538
Social class	12			0.0079
I (highest social status)		103 (7.5)	35 (5.8)	
II		296 (21.4)	100 (16.6)	
III		256 (18.5)	114 (18.9)	
IV		375 (27.2)	161 (26.7)	
V (lowest social status)		168 (12.2)	107 (17.7)	
Employed, social class uncertain		112 (8.1)	49 (8.1)	
Outside the labour market		70 (5.1)	37 (6.1)	
School education	5			0.7765
9 years of elementary school		473 (34.2)	220 (36.3)	
10 years of elementary school		541 (39.1)	231 (38.1)	
3 years of upper secondary school		363 (26.2)	153 (25.3)	
Other		7 (0.5)	2 (0.3)	
Vocational education	4			0.1267
None		124 (9.0)	72 (11.9)	
Semi-skilled worker		17 (1.2)	10 (1.7)	
Vocational training		491 (35.4)	212 (35.0)	
Short further education		142 (10.2)	48 (7.9)	
Middle range training		357 (25.8)	167 (27.6)	
Long further education		153 (11.0)	64 (10.6)	
Other		102 (7.4)	32 (5.3)	
Employment status	6			0.8394
Employed		901 (65.2)	387 (63.9)	
Studying		8 (0.6)	4 (0.7)	
Job seeking		67 (4.8)	35 (5.8)	
Retired		407 (29.4)	180 (29.7)	
CCI, *mean (SD)*		0.26 (0.73)	0.31 (0.83)	0.0062
Living alone	17			0.0057
No		1011 (73.5)	405 (67.3)	
Yes		365 (26.5)	197 (32.7)	

Smoking status	0			0.0122
Current smoker		1046 (75.4)	489 (80.6)	
Former smoker		342 (24.6)	118 (19.4)	
Pack-years, *mean (SD)*	4	35.7 (13.7)	35.8 (12.3)	0.4207
Motivation for smoking cessation	30			0.0540
Very strong		141 (10.3)	74 (12.4)	
Strong		324 (23.7)	166 (27.8)	
Weak		331 (24.2)	144 (24.8)	
Very weak		116 (8.5)	42 (7.0)	
No wish to quit		113 (8.3)	54 (9.0)	
Current non-smoker		342 (25.0)	118 (19.7)	

* Benjamini-Hochberg rejects all p-values above 0.0321 to control the FDR at 0.05

**Except when indicated in the leftmost column that the mean and standard deviation (SD) are listed

There was a significant difference between the study groups for social class with more *Non-attenders* in the lowest social class (V) and a greater number of *Attenders* in the highest social classes (I-II).

Moreover, *Non-attenders* had a significantly higher CCI score indicating that they had more severe or a greater number of co-occurring conditions than *Attenders*. They were also to a greater extent living alone. Furthermore, there were significantly more current smokers and a non-significant trend of a higher wish to quit smoking in the group of *Non-attenders* compared with Attenders.

The results of the third screening round are listed in Table 2.

Table 2, Differences in psychosocial status in the third screening round

	Range of values	Responding rate per item n/n	Attenders n=1388 mean (SD)	Non-attenders-respondents n=260 mean (SD)	p-value*	Difference in scores between the two groups mean (99%CI)[a]	p-value adjusted*
COS-scales							
Anxiety	0-18	1349/249	1.7 (2.8)	2.1 (3.2)	0.0441	0.38 (-0.13;0.89)	0.0548
Behaviour	0-21	1343/246	2.1 (3.1)	2.9 (3.8)	<0.001	0.77 (0.18;1.36)	<0.001
Dejection	0-18	1354/255	1.9 (3.0)	2.4 (3.5)	0.013	0.49 (-0.06;1.04)	0.0225
Sleep	0-12	1357/252	1.9 (2.6)	2.3 (3.0)	0.041	0.35 (-0.12;0.82)	0.0599
COS-LC scales							
Self-blame	0-15	1356/234	2.2 (2.8)	3.1 (3.8)	<0.001	0.59 (0.14;1.04)	<0.001
Focus on airway symptoms	0-24	1363/239	0.3 (0.8)	0.6 (1.0)	<0.001	0.22 (0.08;0.36)	<0.001
Stigmatisation	0-12	1361/241	1.5 (1.9)	2.1 (2.4)	<0.001	0.51 (0.16;0.86)	<0.001
Introvert	0-18	1361/243	1.3 (1.8)	1.8 (2.2)	<0.001	0.56 (0.23;0.89)	<0.001
Harms of smoking	0-6	1356/248	0.9 (1.2)	1.3 (1.6)	<0.001	0.35 (0.11;0.59)	<0.001

[a)] A positive value of the difference indicates that the persons that were interviewed by phone and later returned COS-LC had on average higher scores, i.e. more negative outcomes (e.g. higher anxiety) than the persons that showed up and completed the COS-LC on site. The differences are adjusted for sex, age, region of residence, social group, living alone, smoking status, pack years, motivation for smoking cessation and CCI. The continuous values variables (age and pack years) are included as a quadratic function as to allow for possible nonlinear effects.

* Benjamini-Hochberg rejects all p-values above 0.0321 to control the FDR at 0.05.

In the core questionnaire COS (Consequences of Screening), *Non-attenders-respondents* had a statistically significant higher (worse) score than *Attenders* in the scales “Behaviour” and “Dejection”. These effects were still present when adjusting for covariates. Moreover, there was a

non-significant trend of worse scores in all COS scales among *Non-attenders-respondents*. In the lung cancer specific part of the COS-LC, *Non-attenders-respondents* had statistically significantly higher scores in all scales both crude and adjusted.

Table 3 shows differences in psychosocial status between all three subgroups in the second screening round.

Table 3, Differences in psychosocial status in the second screening round

	Range of values	Responding rate per item n/n/n	Attenders n=1388	Non-attenders-respondents n=260	Non-attenders-non-respondents n=347	p-value*	p-value adjusted[a]*
COS scales, mean (SD)							
Anxiety	0-18	1201/117/89	1.6 (2.7)	2.0 (3.0)	2.6 (3.8)	0.003	0.018
Behaviour	0-21	1195/114/88	1.9 (2.9)	2.4 (3.3)	2.8 (4.0)	0.012	0.071
Dejection	0-18	1217/117/87	1.8 (2.8)	2.3 (3.3)	3.0 (4.0)	<0.001	<0.001
Sleep	0-12	1220/116/88	1.7 (2.5)	2.3 (2.9)	2.6 (3.2)	<0.001	0.002
COS-LC scales, mean (SD)							
Self-blame	0-15	1210/118/88	1.7 (2.3)	2.1 (2.4)	2.6 (3.0)	<0.001	0.005
Focus on airway symptoms	0-24	1226/118/90	0.4 (0.8)	0.4 (0.8)	0.5 (0.9)	0.408	0.579
Stigmatisation	0-12	1225/121/90	1.5 (1.9)	1.8 (2.1)	2.1 (2.4)	0.028	0.146
Introvert	0-18	1223/116/90	1.3 (1.8)	1.8 (2.0)	1.4 (1.8)	0.012	0.021
Harms of smoking	0-6	1232/118/89	1.1 (1.3)	1.3 (1.3)	1.2 (1.4)	0.134	0.422

[a] A test for differences between the three groups adjusted for sex, age, region of residence, social group, living alone, smoking status, pack years, motivation for smoking cessation and the CCI. The continuous values variables (age and pack years) are included as a quadratic function as to allow for possible nonlinear effects.

* Benjamini-Hochberg rejects all p-values above 0.0321 to control the FDR at 0.05.

Non-attenders had significantly worse crude scores compared with *Attenders* in all the COS scales. When adjusting for covariates the difference in scores was still significant in the three scales

"Anxiety", "Dejection" and "Sleep". In the lung cancer specific part, the crude and adjusted "Self-blame" and "Introvert"-scale scores were significantly worse for *Non-attenders*. The difference in "Stigmatisation" scale score was statistically significant in the unadjusted analyses, but disappeared in the adjusted analyses.

The differences in psychosocial status in the first screening round between *Attenders*, *Non-attenders-respondents* and *Non-attenders-non-responders* showed a statistically significant worse unadjusted score in all COS-scales, for the two *Non-attenders* subgroups (Table 4). That effect disappeared in all but one scale, "Anxiety" when adjusting for covariates.

Table 4, Differences in psychosocial status in the first screening round

	Range of values	Responding rate per item n/n/n	Attenders n=1388 mean (SD)	Non-attenders-respondents n=260 mean (SD)	Non-attenders-non-respondents n=347 mean (SD)	p-value*	p-value adjusted[a*]
COS-scales							
Anxiety	0-18	1353/253/334	1.46 (2.16)	1.75 (2.54)	2.11 (2.66)	<0.001	0.0028
Behaviour	0-21	1365/257/340	0.75 (1.89)	1.05 (2.44)	1.04 (2.43)	0.0134	0.0976
Dejection	0-18	1372/257/339	1.25 (2.05)	1.54 (2.48)	1.68 (2.33)	0.0018	0.0512
Sleep	0-12	1368/253/344	0.62 (1.64)	0.86 (1.98)	0.90 (1.86)	0.0072	0.0530

[a)] The differences are adjusted for sex, age, region of residence, social group, living alone, smoking status, pack years, motivation for smoking cessation and CCI. The continuous values variables (age and pack years) are included as a quadratic function as to allow for possible nonlinear effects.

[*] Benjamini-Hochberg rejects all p-values above 0.0321 to control the FDR at 0.05.

Discussion

The present study showed considerable non-attendance in the control group of the DLCST. Data in the control group was not missing at random. Non-attenders had less favourable baseline socio-demographic profile when compared with attenders. More importantly, individuals who did not attend their annual clinical work-up had worse psychosocial status than the individuals who attended the clinic in the previous rounds. This can be used to adjust for differential non-attendance. Furthermore, these individuals also had worse psychosocial status during their missed

round (assessed in the present study in the third round). This cannot be used to adjust differential non-attendance because this information is generally not available but proves the concept.

The use of a condition-specific questionnaire is a strength of the study. Previous research has demonstrated that condition-specific questionnaires are superior to generic questionnaires when measuring psychosocial consequences in cancer screening settings.(17) Furthermore, we used an appropriate longitudinal design i.e. we collected data at the same timepoints for both *Attenders* and *Non-attenders* at various times in the study, as well as we measured psychosocial status in both groups at baseline.(18) A limitation of the study is that we did not collect psychosocial outcomes of Non-attenders in the intervention group. This study was designed to gain knowledge of factors motivating such a large drop in participation in the control group. In hindsight, data on Non-attenders in the screened group could further help us understand the reasons for differential non-response.

In addition to the DLCST, two other trials assessed psychosocial consequences in lung cancer screening with low-dose CT.(6,19) Participants in the NELSON trial were invited to complete questionnaires at baseline and at the second round of screening (two years after baseline screening). Participants in the UKLS completed a questionnaire at baseline, two weeks after randomisation/CT-scan and 10-29 months after baseline. Unlike the DLCST, in these two trials the control group were not invited to an annual visit at the screening clinic. Although there were some differences in study design, non-response rates in the control groups in these three trials were similar and in all three trials there was differential non-response between the intervention and control group. Differences between attenders and non-attenders were reported in the UKLS trial. As in the DLCST, non-attenders had worse socio-demographic profile i.e. lower social class, and

they were more likely single, younger and current smokers compared with attenders. However, these were pooled estimates for both the screening group and the control group.

In individuals diagnosed with cancer, anxiety and worse health-related quality of life have been associated with dropout, which is consistent with our findings.(20) Since *Non-attenders* in our study experienced a higher level of anxiety than *Attenders* in the first screening round (i.e. baseline), this could have been the motivation for attending the trial; to get reassured of being healthy.(21) Therefore, randomization to the control group may have caused disappointment, but also attention drawn to not being part of a possibly beneficial intervention.(22) For example, the secretary in the screening clinic received calls from participants randomized to the control group expressing their disappointment of not being screened. Furthermore, the trial put focus on the harms of smoking, which could have increased the anxiety and fear of disease in this subgroup even more, which may have been a reason to subsequent non-attendance. Finally, missing data on psychosocial status in a previous round may also have been a predictor for non-attendance in the next screening round, which was not the scope for this study.

Low social status, younger age and current smoking status have previously been seen among dropouts and non-respondents in lung health studies.(23–26) A systematic review reporting dropout from longitudinal studies in elderly concluded that higher age and declining health were high predictors of dropout. The latter is in agreement with our findings, although higher age is in contrast to our findings.(27)

To our knowledge, this is the first cancer screening study testing hypotheses on reasons for differential non-response empirically. The results of this study confirmed the hypotheses we made in our previous study, using inverse probability weighting to adjust for differential non-

response.(3,7,28) More importantly, the results of the two other lung cancer screening trials investigating dropout are consistent with ours. Hence, it is plausible that our results are generalisable to other cancer screening trials as well.

Therefore, future cancer screening trials should concurrently assess psychosocial status during the trial, not only to be able to assess the psychosocial effect of screening, but also to use this information to adjust any effect in the trial for bias due to differential non-attendance.

Conclusions

In conclusion, *Non-attenders* in the control group in the DLCST had a worse psychosocial status and a less favourable socio-demographic profile than *Attenders*.

The results of our study contribute with evidence of non-response driven by psychosocial status, which in turn may be influenced by the screening intervention itself. This can be used to adjust cancer screening trial results for bias due to differential attendance.

Abbreviations

RCT: Randomized controlled trial; PROM: Patient-reported outcome measure; CT: Computed tomography; DLCST: Danish Lung Cancer Screening Trial; COS-LC: Consequences of screening in lung cancer; COS: Consequences of screening; CCI: Charlson comorbidity index

Declarations

Ethics approval and consent to participate

The Ethical Committee of Copenhagen County approved the DLCST including this observational study nested in the DLCST on 31 January 2003: approval number KA-02045.

All participants signed an informed consent form and received an information letter about the project and information about the ethical approval and data protection agency approval. The trial is registered in Clinicaltrials.gov Protocol Registration System (identification no. NCT00496977)

Availability of data and materials

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

Competing interests

None declared.

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Author contributions

JB and HT developed and designed the study. JB, HT and the DLCST staff collected data. VS performed the statistical analyses. JM drafted the manuscript. JB, HT, BH, JFR, and VS all contributed to parts of the manuscript as well as revisions of the manuscript. All authors approved the final version of the manuscript, and no editorial assistance was received. All authors had full

access to all data in the study and are responsible of data retention and the accuracy of the data analysis. JM and JB are guarantors of the study.

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Fig.1 Flowchart, DLCST

Fig.2 Flowchart, present study

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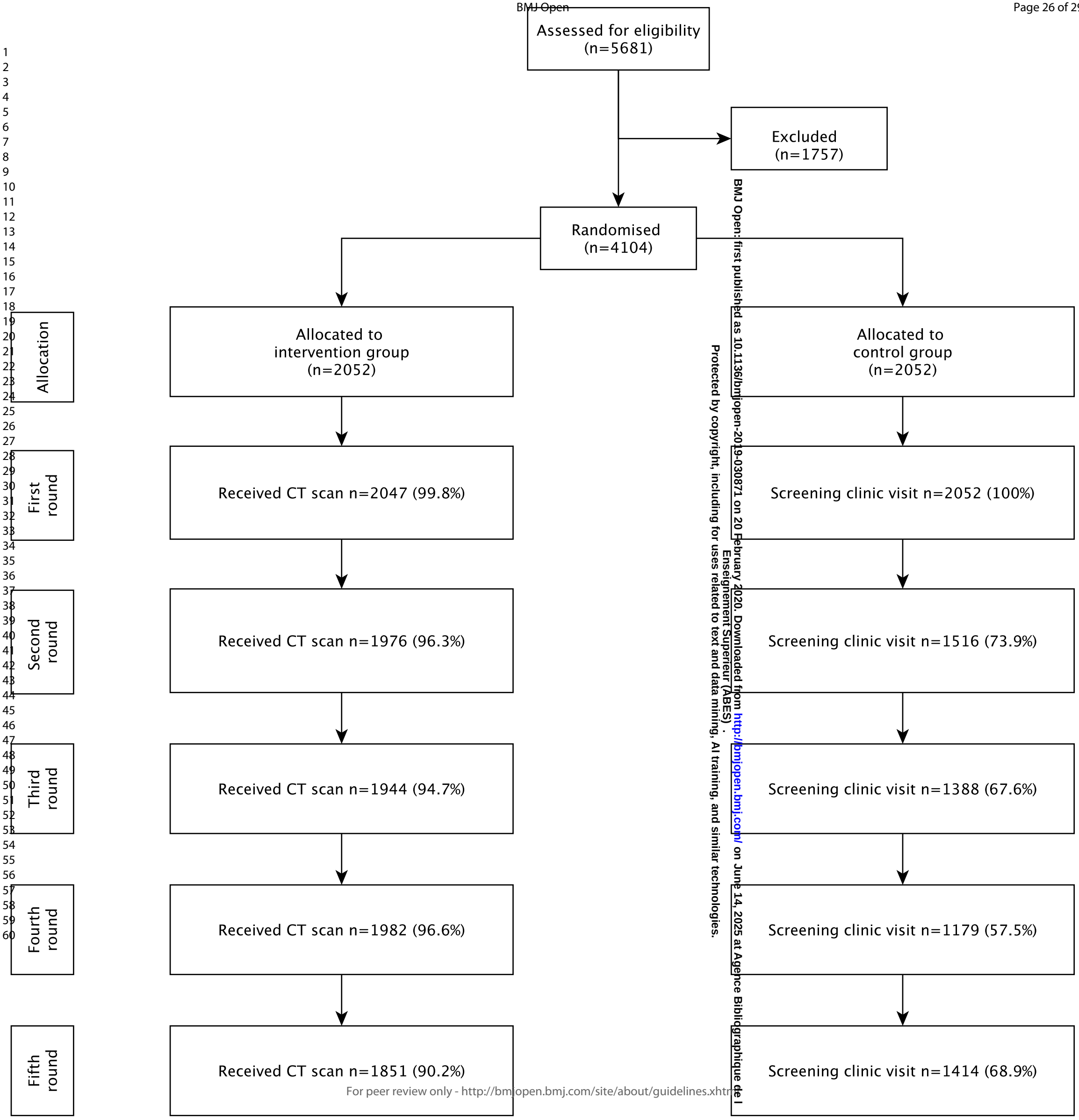

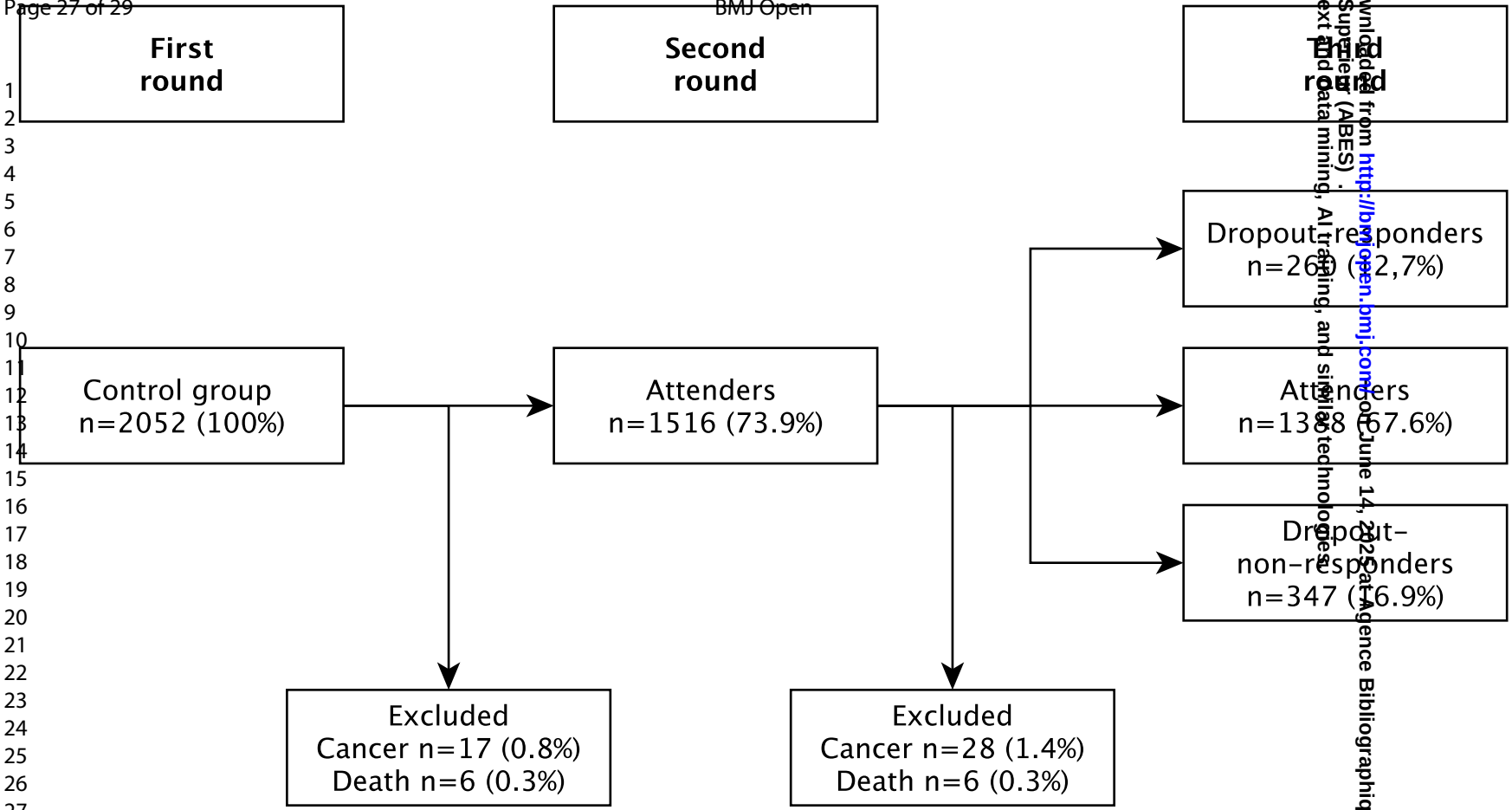

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6 and 7
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	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Not applicable

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig.1
		(b) Give reasons for non-participation at each stage	Fig.2
		(c) Consider use of a flow diagram	Fig.2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*Table 2-4*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	Table 2-4
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
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	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

BMJ Open

Did psychosocial status, sociodemographics and smoking status affect non-attendance in control participants in the Danish Lung Cancer Screening Trial? A nested observational study

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Did psychosocial status, sociodemographics and smoking status affect non-attendance in control participants in the Danish Lung Cancer Screening Trial? A nested observational study

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Abstract

Objectives: We investigated if psychosocial status, socio-demographics and smoking status affected non-attendance in the control group in the randomised Danish Lung Cancer Screening Trial (DLCST).

Design & setting: This study was an observational study nested in the DLCST. Due to large non-attendance in the control group in the second screening round we made an additional effort to collect questionnaire data from non-attenders in this group in the third screening round. We used a condition-specific questionnaire to assess psychosocial status. We analysed the differences in psychosocial status in the third and preceding rounds between non-attenders and attenders in the control group in multivariable linear regression models adjusted for socio-demographics and smoking status reported at baseline. Differences in socio-demographics and smoking status were analysed with chi-squared tests (categorical variables) and t-tests (continuous variables).

Primary outcome measure: Primary outcome was psychosocial status.

Participants: All control persons participating in the third screening round in the DLCST were included.

Results: Non-attenders in the third round had significantly worse psychosocial status than attenders in the scales: “Behaviour” 0.77 (99% CI 0.18;1.36), “Self-blame” 0.59 (99% CI 0.14;1.04), “Focus on airway symptoms” 0.22 (99% CI 0.08;0.36), “Stigmatisation” 0.51 (99% CI 0.16;0.86), “Introvert” 0.56 (99% CI 0.23;0.89), and “Harms of smoking” 0.35 (99% CI 0.11;0.59). Moreover, non-attenders had worse scores than attendees in the preceding screening rounds. Non-attenders also reported worse socio-demographics at baseline.

Conclusions: Non-attenders had a significantly worse psychosocial status and worse socio-demographics compared with attenders. The results of our study contribute with evidence of non-

response and attrition driven by psychosocial status, which in turn may be influenced by the screening intervention itself. This can be used to adjust cancer screening trial results for bias due to differential non-attendance.

Trial registration: The trial is registered in Clinicaltrials.gov Protocol Registration System (identification no. NCT00496977)

Article summary

Strengths and limitations

- Use of a condition-specific questionnaire with adequate psychometric properties ensured valid measures.
- Patient-reported data on non-respondents gave valuable empirical insight in drivers for non-attendance.
- Testing a previously hypothesized model for non-attendance empirically is another strength of the study.
- No comparison between non-attenders in the intervention and the control group was performed.
- No longer-term follow up on non-attenders was performed.

Introduction

Non-attendance may affect trial results and introduce bias in randomised controlled trials (RCTs).(1,2) Non-attendance reduces the power of the trial and, if non-attendance differs between the randomised groups, conventional effect estimates can be biased.(2) While we cannot change

the loss of power, we may remove bias due to differential non-attendance if we know and have measured the factors that cause this non-attendance.(3) For some outcome measures, such as disease incidence or mortality, non-attendance can be partially addressed if data can be obtained from national electronic registers. However, non-attendance will be larger for outcome measures that depend on direct data collection such as clinical measurements and patient reported outcome measures (PROMs). Moreover, the factors driving non-attendance for these measures may be very heterogeneous and may also be driven by the experiences of the trial participants in the trial process.

The problems with differential non-attendance may be aggravated in trials assessing psychosocial consequences of cancer screening as well as other interventions where it is impossible to blind participants to allocation. Notably, a control group not offered screening may be less inclined to return questionnaires enquiring into their experiences with a potentially beneficial intervention they did not receive. However, the psychosocial dimensions of non-attendance and potential consequences of these in lung cancer screening trials are only partially researched.(4–7) Since cancer screening trials are investigating potentially life-threatening diseases there may be emotional drivers of non-attendance, not typical for trials in general. Hence, it is of interest to know which factors drive non-attendance in PROMs in cancer screening trials as this data is to be collected in these trials and then used in adjusting for differential non-attendance.

The Danish Lung Cancer Screening Trial (DLCST) was an RCT including five annual screening rounds of low-dose chest computed tomography (CT) plus clinical examinations in the intervention group compared with annual clinical examinations only in the control group.(8) Furthermore, all the participants were asked to complete a condition-specific questionnaire, measuring psychosocial

consequences of lung cancer screening at these annual clinical assessments.(9) The results showed that people experienced negative psychosocial consequences merely by participating in the trial, and that negative consequences were higher for participants allocated to the control group.(7,10) A large number of control persons did not attend the second annual examination (n=513, 26.1%) while the non-attendance rate in the intervention group was low (n=71, 3.5%) (*Fig. 1*). To adjust for this differential non-attendance, inverse probability weighting was used.(7) In this method the observed outcomes are weighted with the inverse of the probability of being non missing.(3) We hypothesised that these probabilities were adequately estimated from socio-demographic profile including smoking status, randomisation group and psychosocial status in previous rounds.(7,11–13)

If these hypotheses were confirmed, then these factors would explain the witnessed difference in attendance between the trial groups and could be used to render them comparable. Analysed without such adjustments the assessment of the trial groups, and thereby the means of the scores from the responses to the questionnaire from the remaining trial participants would no longer be comparable.(14) Hence, the assessment of psychosocial harms of lung cancer screening could be biased.

Therefore, the overall aim of this study was to empirically assess whether control participants who did not attend the annual clinical examination had different psychosocial profiles compared with control participants who attended the annual clinical examination.

Materials and methods

Study design and population

The design and study population of DLCST have been described in detail previously.(7,8) Briefly, the DLCST was an RCT, conducted at the Copenhagen University hospital Gentofte in Denmark from October 2004 to March 2010. Heavy current and former smokers (at least 20 pack-years), aged 50-70 years old, were randomised to either five rounds of screening with low-dose CT-scans including clinical examinations (n=2052) or five clinical examinations only (n=2052). In the enrolment visit, participants provided socio-demographic data, lifestyle and health information (including smoking status), completed a questionnaire on their psychosocial status and underwent spirometry. Participants randomised to screening also had a low-dose chest CT-scan within one month of randomisation. In the following screening rounds, participants in the screened and control groups were invited to a visit in the screening clinic where lung function tests were performed, and questionnaires concerning health, lifestyle, smoking habits and psychosocial status were completed and lung function tests were performed. Participants randomised to screening also received a low-dose chest CT-scan.

This study is an observational study nested in the DLCST. During the second screening round, the steering committee noted that a large number of control participants did not attend the screening clinic visit when compared with the number of screened participants. Thus, the committee decided to make additional efforts to collect questionnaire data for non-attenders in the control group in the third screening round to perform post hoc analyses on whether psychosocial status was an influencing factor *(Fig.2)*.

During the third round, participants in the control group who did not attend the annual examination were contacted by phone and part 1 of the questionnaire was sent with a postage paid envelope to those who gave their oral consent. The data was used to supplement the data

collected on site at the screening clinic.(7) This yielded three groups within the control group, denoting the extent of response to the clinical examination and the questionnaire defined as:

1. *Attenders*: participants who attended the third screening round.
2. *Non-attenders:*
   a) *Respondents*: participants who did not attend the annual examination but completed and returned the COS-LC after the phone interview.
   b) *Non-respondents*: participants who did not attend the annual examination and did not complete the COS-LC.

Outcomes & Questionnaires

Primary outcome was psychosocial status measured with the Consequences Of Screening for Lung Cancer (COS-LC) questionnaire.(9) Part 1 of COS-LC comprised nine scales measuring various aspects of consequences of screening; a second part of COS-LC addressed the screening outcome and was therefore not applicable to the present analysis. Moreover, the primary part of COS-LC included four core scales: “Anxiety”, “Behaviour”, “Dejection” and “Sleep” that are not lung cancer specific. These scales have originally been developed from a breast cancer screening assessment instrument.(15) Additionally COS-LC comprised five lung cancer specific scales: “Self-blame”, “Focus on airway symptoms”, “Stigmatisation”, “Introvert”, and “Harm of smoking”, which were developed from focus groups and other screening assessment instruments during the first DLCST screening round.(9,15) Therefore, only the core scales were used in the first round, while in the following four screening rounds both the core scales and the lung cancer specific scales were used to assess psychosocial status.(9)

Statistics

Covariates

Socio-demographic characteristics were defined by: social class (I highest social class to V lowest social class), school and vocational education (from 9 years of elementary school to a university education), employment status, living alone, smoking status (current or former smoker), smoking history (pack-years), motivation for smoking cessation (from very strong to no wish to quit) and Charlson Comorbidity Index (CCI). Furthermore, we adjusted for region of residence (Denmark is divided into five health-administrative regions).

Statistical analyses

We performed three different analyses:

1. Analyses of differences in psychosocial status in the **third** round between *Attenders* and *Non-attenders-respondents*.
2. Analyses of differences in psychosocial status in the **second** round between *Attenders, Non-attenders-respondents* and *Non-attenders-non-respondents*.
3. Analyses of differences in psychosocial status in the **first** round, between *Attenders*, *Non-attenders-respondents* and *Non-attenders-non-respondents*.

Covariates at the first screening round were compared between *Attenders* and *Non-attenders* by chi-squared tests (categorical characteristics) and t-tests (continuous characteristics). Analyses of psychosocial status at various points in the follow-up were performed in linear regression models both unadjusted and in multivariable models adjusted for sex, age, region of residence, social class, living alone, smoking status, pack years, motivation for smoking cessation and CCI. To adjust

for multiple testing we used the Benjamini-Hochberg procedure and the False Discovery Rate (FDR) was set to 5% (16). All analyses were performed with SAS 9.4 (SAS Institute, Inc., Cary, NC).

Patient and Public Involvement

Patients and public were not involved in the design of the study.

Results

The inclusion process and participation rate of the DLCST are illustrated in Figure 1. The participation rate in the control group fell from 73.9% in the second round to 57.5% in the fourth round. The participation rate increased in the fifth, final, round (68.9%).

Figure 2 depicts the inclusion process of the present study and showed a dropout rate of 29.6% (n=607) in the third screening round with a higher distribution of *Non-attenders-non-respondents* (16.9% n=347) compared with *Non-attenders-respondents* (12.7% n=260).

In the first screening round we compared differences in socio-demographic characteristics in the two overarching groups (*Attenders, Non-attenders*) (Table 1).

Table 1, Socio-demographics

	Missing observations, total	Attenders n=1388	Non-attenders n=607	p-value*
Covariates	n	n (%)**	n(%)**	
Sex	0			0.0963
Male		773 (55.7)	313 (51.6)	
Female		615 (44.3)	294 (48.4)	
Age, *mean (SD)*	0	57.4 (4.7)	56.9 (4.9)	0.0538
Social class	12			0.0079
I (highest social status)		103 (7.5)	35 (5.8)	
II		296 (21.4)	100 (16.6)	
III		256 (18.5)	114 (18.9)	
IV		375 (27.2)	161 (26.7)	
V (lowest social status)		168 (12.2)	107 (17.7)	
Employed, social class uncertain		112 (8.1)	49 (8.1)	
Outside the labour market		70 (5.1)	37 (6.1)	
School education	5			0.7765
9 years of elementary school		473 (34.2)	220 (36.3)	
10 years of elementary school		541 (39.1)	231 (38.1)	
3 years of upper secondary school		363 (26.2)	153 (25.3)	
Other		7 (0.5)	2 (0.3)	
Vocational education	4			0.1267
None		124 (9.0)	72 (11.9)	
Semi-skilled worker		17 (1.2)	10 (1.7)	
Vocational training		491 (35.4)	212 (35.0)	
Short further education		142 (10.2)	48 (7.9)	
Middle range training		357 (25.8)	167 (27.6)	
Long further education		153 (11.0)	64 (10.6)	
Other		102 (7.4)	32 (5.3)	
Employment status	6			0.8394
Employed		901 (65.2)	387 (63.9)	
Studying		8 (0.6)	4 (0.7)	
Job seeking		67 (4.8)	35 (5.8)	
Retired		407 (29.4)	180 (29.7)	
CCI, *mean (SD)*		0.26 (0.73)	0.31 (0.83)	0.0062
Living alone	17			0.0057
No		1011 (73.5)	405 (67.3)	
Yes		365 (26.5)	197 (32.7)	

Smoking status	0			0.0122
Current smoker		1046 (75.4)	489 (80.6)	
Former smoker		342 (24.6)	118 (19.4)	
Pack-years, *mean (SD)*	4	35.7 (13.7)	35.8 (12.3)	0.4207
Motivation for smoking cessation	30			0.0540
Very strong		141 (10.3)	74 (12.4)	
Strong		324 (23.7)	166 (27.8)	
Weak		331 (24.2)	144 (24.8)	
Very weak		116 (8.5)	42 (7.0)	
No wish to quit		113 (8.3)	54 (9.0)	
Current non-smoker		342 (25.0)	118 (19.7)	

* Benjamini-Hochberg rejects all p-values above 0.0321 to control the FDR at 0.05

**Except when indicated in the leftmost column that the mean and standard deviation (SD) are listed

There was a significant difference between the study groups for social class with more *Non-attenders* in the lowest social class (V) and a greater number of *Attenders* in the highest social classes (I-II).

Moreover, *Non-attenders* had a significantly higher CCI score indicating that they had more severe or a greater number of co-occurring conditions than *Attenders*. They were also to a greater extent living alone. Furthermore, there were significantly more current smokers and a non-significant trend of a higher wish to quit smoking in the group of *Non-attenders* compared with Attenders.

The results of the third screening round are listed in Table 2.

Table 2, Differences in psychosocial status in the third screening round

	Range of values	Responding rate per item n/n	Attenders n=1388 mean (SD)	Non-attenders-respondents n=260 mean (SD)	p-value*	Difference in scores between the two groups mean (99%CI)[a]	p-value adjusted*
COS-scales							
Anxiety	0-18	1349/249	1.7 (2.8)	2.1 (3.2)	0.0441	0.38 (-0.13;0.89)	0.0548
Behaviour	0-21	1343/246	2.1 (3.1)	2.9 (3.8)	<0.001	0.77 (0.18;1.36)	<0.001
Dejection	0-18	1354/255	1.9 (3.0)	2.4 (3.5)	0.013	0.49 (-0.06;1.04)	0.0225
Sleep	0-12	1357/252	1.9 (2.6)	2.3 (3.0)	0.041	0.35 (-0.12;0.82)	0.0599
COS-LC scales							
Self-blame	0-15	1356/234	2.2 (2.8)	3.1 (3.8)	<0.001	0.59 (0.14;1.04)	<0.001
Focus on airway symptoms	0-24	1363/239	0.3 (0.8)	0.6 (1.0)	<0.001	0.22 (0.08;0.36)	<0.001
Stigmatisation	0-12	1361/241	1.5 (1.9)	2.1 (2.4)	<0.001	0.51 (0.16;0.86)	<0.001
Introvert	0-18	1361/243	1.3 (1.8)	1.8 (2.2)	<0.001	0.56 (0.23;0.89)	<0.001
Harms of smoking	0-6	1356/248	0.9 (1.2)	1.3 (1.6)	<0.001	0.35 (0.11;0.59)	<0.001

[a)] A positive value of the difference indicates that the persons that were interviewed by phone and later returned COS-LC had on average higher scores, i.e. more negative outcomes (e.g. higher anxiety) than the persons that showed up and completed the COS-LC on site. The differences are adjusted for sex, age, region of residence, social group, living alone, smoking status, pack years, motivation for smoking cessation and CCI. The continuous values variables (age and pack years) are included as a quadratic function as to allow for possible nonlinear effects.

* Benjamini-Hochberg rejects all p-values above 0.0321 to control the FDR at 0.05.

In the core questionnaire COS (Consequences of Screening), *Non-attenders-respondents* had a statistically significant higher (worse) score than *Attenders* in the scales “Behaviour” and “Dejection”. These effects were still present when adjusting for covariates. Moreover, there was a

non-significant trend of worse scores in all COS scales among *Non-attenders-respondents*. In the lung cancer specific part of the COS-LC, *Non-attenders-respondents* had statistically significantly higher scores in all scales both crude and adjusted.

Table 3 shows differences in psychosocial status between all three subgroups in the second screening round.

Table 3, Differences in psychosocial status in the second screening round

	Range of values	Responding rate per item n/n/n	Attenders n=1388	Non-attenders-respondents n=260	Non-attenders-non-respondents n=347	p-value*	p-value adjusted[a]*
COS scales, mean (SD)							
Anxiety	0-18	1201/117/89	1.6 (2.7)	2.0 (3.0)	2.6 (3.8)	0.003	0.018
Behaviour	0-21	1195/114/88	1.9 (2.9)	2.4 (3.3)	2.8 (4.0)	0.012	0.071
Dejection	0-18	1217/117/87	1.8 (2.8)	2.3 (3.3)	3.0 (4.0)	<0.001	<0.001
Sleep	0-12	1220/116/88	1.7 (2.5)	2.3 (2.9)	2.6 (3.2)	<0.001	0.002
COS-LC scales, mean (SD)							
Self-blame	0-15	1210/118/88	1.7 (2.3)	2.1 (2.4)	2.6 (3.0)	<0.001	0.005
Focus on airway symptoms	0-24	1226/118/90	0.4 (0.8)	0.4 (0.8)	0.5 (0.9)	0.408	0.579
Stigmatisation	0-12	1225/121/90	1.5 (1.9)	1.8 (2.1)	2.1 (2.4)	0.028	0.146
Introvert	0-18	1223/116/90	1.3 (1.8)	1.8 (2.0)	1.4 (1.8)	0.012	0.021
Harms of smoking	0-6	1232/118/89	1.1 (1.3)	1.3 (1.3)	1.2 (1.4)	0.134	0.422

[a] A test for differences between the three groups adjusted for sex, age, region of residence, social group, living alone, smoking status, pack years, motivation for smoking cessation and the CCI. The continuous values variables (age and pack years) are included as a quadratic function as to allow for possible nonlinear effects.

* Benjamini-Hochberg rejects all p-values above 0.0321 to control the FDR at 0.05.

Non-attenders had significantly worse crude scores compared with *Attenders* in all the COS scales. When adjusting for covariates the difference in scores was still significant in the three scales

"Anxiety", "Dejection" and "Sleep". In the lung cancer specific part, the crude and adjusted "Self-blame" and "Introvert"-scale scores were significantly worse for *Non-attenders*. The difference in "Stigmatisation" scale score was statistically significant in the unadjusted analyses but disappeared in the adjusted analyses.

The differences in psychosocial status in the first screening round between *Attenders*, *Non-attenders-respondents* and *Non-attenders-non-responders* showed a statistically significant worse unadjusted score in all COS-scales, for the two *Non-attenders* subgroups (Table 4). That effect disappeared in all but one scale, "Anxiety" when adjusting for covariates.

Table 4, Differences in psychosocial status in the first screening round

	Range of values	Responding rate per item n/n/n	Attenders n=1388 mean (SD)	Non-attenders-respondents n=260 mean (SD)	Non-attenders-non-respondents n=347 mean (SD)	p-value*	p-value adjusted[a*]
COS-scales							
Anxiety	0-18	1353/253/334	1.46 (2.16)	1.75 (2.54)	2.11 (2.66)	<0.001	0.0028
Behaviour	0-21	1365/257/340	0.75 (1.89)	1.05 (2.44)	1.04 (2.43)	0.0134	0.0976
Dejection	0-18	1372/257/339	1.25 (2.05)	1.54 (2.48)	1.68 (2.33)	0.0018	0.0512
Sleep	0-12	1368/253/344	0.62 (1.64)	0.86 (1.98)	0.90 (1.86)	0.0072	0.0530

[a)] The differences are adjusted for sex, age, region of residence, social group, living alone, smoking status, pack years, motivation for smoking cessation and CCI. The continuous values variables (age and pack years) are included as a quadratic function as to allow for possible nonlinear effects.

[*] Benjamini-Hochberg rejects all p-values above 0.0321 to control the FDR at 0.05.

Discussion

The present study showed considerable non-attendance in the control group of the DLCST. Data in the control group was not missing at random. Non-attenders had less favourable baseline socio-demographic profile when compared with attenders. More importantly, individuals who did not attend their annual clinical work-up had worse psychosocial status than the individuals who attended the clinic in the previous rounds. This can be used to adjust for differential non-attendance. Furthermore, these individuals also had worse psychosocial status during their missed

round (assessed in the present study in the third round). This cannot be used to adjust differential non-attendance because this information is generally not available but proves the concept.

The use of a condition-specific questionnaire is a strength of the study. Previous research has demonstrated that condition-specific questionnaires are superior to generic questionnaires when measuring psychosocial consequences in cancer screening settings.(17) Furthermore, we used an appropriate longitudinal design i.e. we collected data at the same timepoints for both *Attenders* and *Non-attenders* at various times in the study, as well as we measured psychosocial status in both groups at baseline.(18)

A limitation of the study is that we did not collect psychosocial outcomes of Non-attenders in the intervention group. This study was designed to gain knowledge of factors motivating such a large drop in participation in the control group. In hindsight, data on Non-attenders in the screened group could further help us understand the reasons for differential non-response.

The distribution of psychosocial outcomes was left-skewed (Table 2, 3, and 4). To assure that the conclusions were not affected by this skewness, we repeated the analyses on log-transformed outcomes. The results of these sensitivity analyses reached conclusions similar to the original conclusions.

In addition to the DLCST, two other trials assessed psychosocial consequences in lung cancer screening with low-dose CT.(6,19) Participants in the NELSON trial were invited to complete questionnaires at baseline and at the second round of screening (two years after baseline screening). Participants in the UKLS completed a questionnaire at baseline, two weeks after randomisation/CT-scan and 10-29 months after baseline. Unlike the DLCST, in these two trials the control group were not invited to an annual visit at the screening clinic. Although there were some differences in study design, non-response rates in the control groups in these three trials were

similar and in all three trials there was differential non-response between the intervention and control group. Differences between attenders and non-attenders were reported in the UKLS trial. As in the DLCST, non-attenders had worse socio-demographic profile i.e. lower social class, and they were more likely single, younger and current smokers compared with attenders. However, these were pooled estimates for both the screening group and the control group.

In individuals diagnosed with cancer, anxiety and worse health-related quality of life have been associated with dropout, which is consistent with our findings.(20) Since *Non-attenders* in our study experienced a higher level of anxiety than *Attenders* in the first screening round (i.e. baseline), this could have been the motivation for attending the trial; to get reassured of being healthy.(21) Therefore, randomisation to the control group may have caused disappointment, but also attention drawn to not being part of a possibly beneficial intervention.(22) For example, the secretary in the screening clinic received calls from participants randomised to the control group expressing their disappointment of not being screened. Furthermore, the trial put focus on the harms of smoking, which could have increased the anxiety and fear of disease in this subgroup even more, which may have been a reason to subsequent non-attendance. Finally, missing data on psychosocial status in a previous round may also have been a predictor for non-attendance in the next screening round, which was not the scope for this study.

Low social status, younger age and current smoking status have previously been seen among dropouts and non-respondents in lung health studies.(23–26) A systematic review reporting dropout from longitudinal studies in elderly concluded that higher age and declining health were high predictors of dropout. The latter is in agreement with our findings, although higher age is in contrast to our findings.(27)

To our knowledge, this is the first cancer screening study testing hypotheses on reasons for differential non-response empirically. The results of this study confirmed the hypotheses we made in our previous study, using inverse probability weighting to adjust for differential non-response.(3,7,28) More importantly, the results of the two other lung cancer screening trials investigating dropout are consistent with ours. Hence, it is plausible that our results are generalisable to other cancer screening trials as well.

Therefore, future cancer screening trials should concurrently assess psychosocial status during the trial, not only to be able to assess the psychosocial effect of screening, but also to use this information to adjust any effect in the trial for bias due to differential non-attendance.

Conclusions

In conclusion, *Non-attenders* in the control group in the DLCST had a worse psychosocial status and a less favourable socio-demographic profile than *Attenders*.

The results of our study contribute with evidence of non-response driven by psychosocial status, which in turn may be influenced by the screening intervention itself. This can be used to adjust cancer screening trial results for bias due to differential attendance.

Abbreviations

RCT: Randomised controlled trial; PROM: Patient-reported outcome measure; CT: Computed tomography; DLCST: Danish Lung Cancer Screening Trial; COS-LC: Consequences of screening in lung cancer; COS: Consequences of screening; CCI: Charlson comorbidity index

Declarations

Ethics approval and consent to participate

The Ethical Committee of Copenhagen County approved the DLCST including this observational study nested in the DLCST on 31 January 2003: approval number KA-02045.

All participants signed an informed consent form and received an information letter about the project and information about the ethical approval and data protection agency approval. The trial is registered in Clinicaltrials.gov Protocol Registration System (identification no. NCT00496977)

Availability of data and materials

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

Competing interests

None declared.

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The funding source had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author contributions

JB and HT developed and designed the study. JB, HT and the DLCST staff collected data. VS performed the statistical analyses. JM drafted the manuscript. JB, HT, BH, JFR, and VS all contributed to parts of the manuscript as well as revisions of the manuscript. All authors approved

the final version of the manuscript, and no editorial assistance was received. All authors had full access to all data in the study and are responsible of data retention and the accuracy of the data analysis. JM and JB are guarantors of the study.

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Fig.1 Flowchart, DLCST

Fig.2 Flowchart, present study

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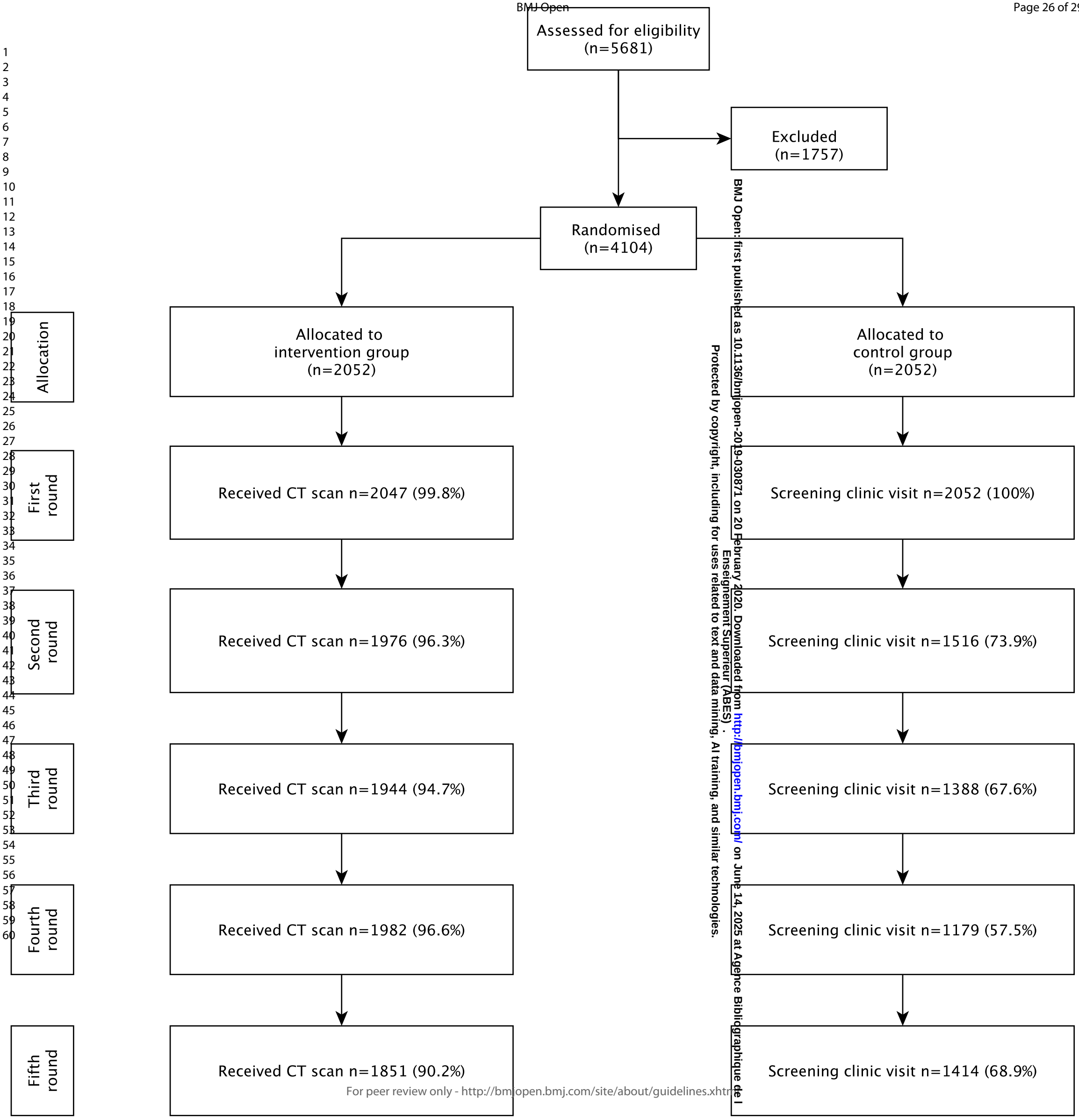

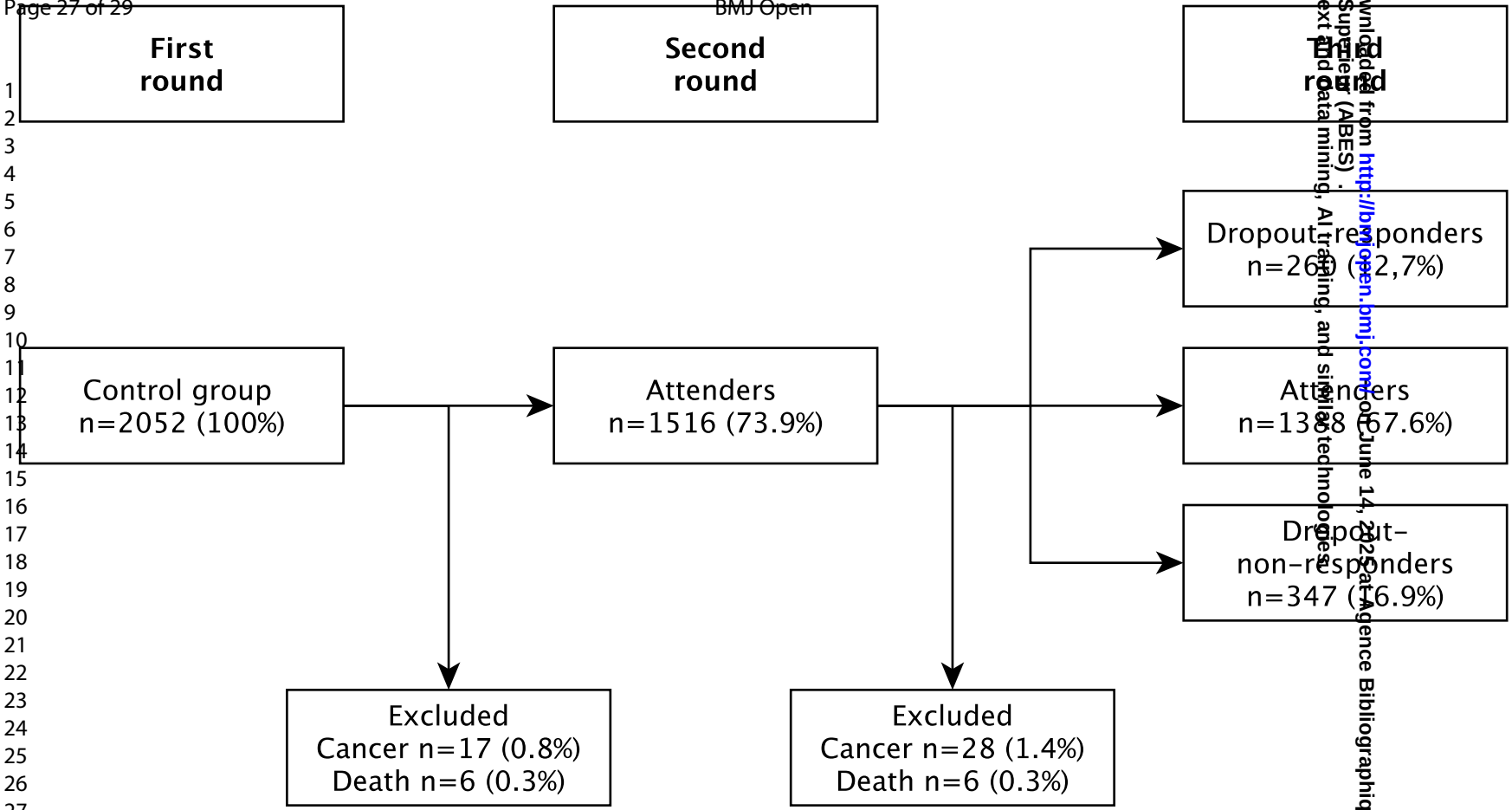

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6 and 7
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	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Not applicable

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig.1
		(b) Give reasons for non-participation at each stage	Fig.2
		(c) Consider use of a flow diagram	Fig.2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*Table 2-4*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	Table 2-4
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
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	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.