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

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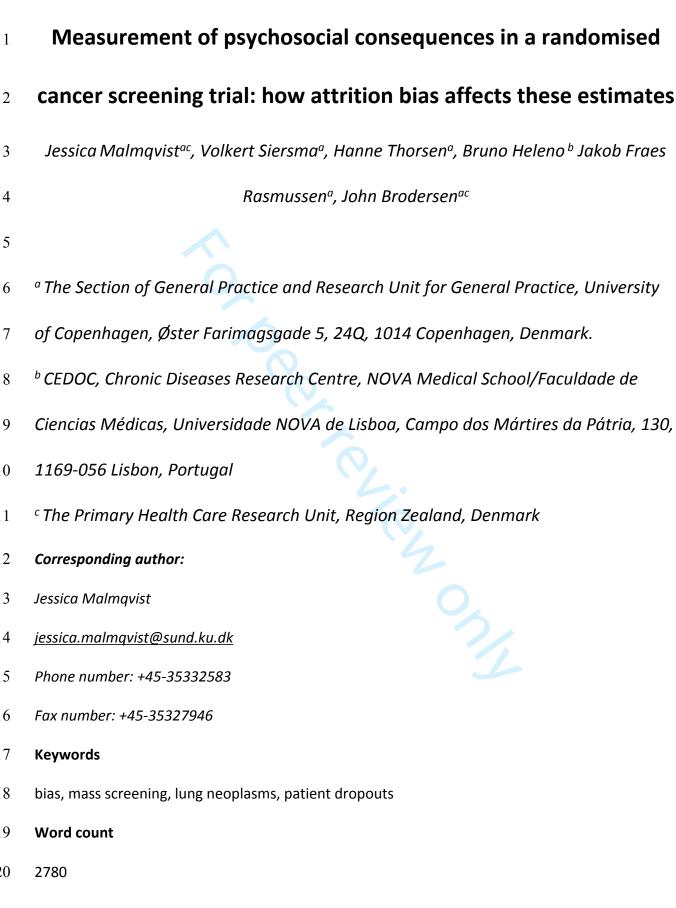
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3 4 5	21	
6 7 8	22	Abstract
9 10 11	23	Objectives: We investigated if psychosocial status, socio-demographics and smoking status
12 13	24	affected non-response in the control group in the randomized Danish Lung Cancer Screening Trial
14 15 16	25	(DLCST).
17 18	26	Design & setting: This study was an observational study nested in the DLCST. Due to a large
19 20 21	27	dropout in the control group in the second screening round we made an additional effort to
22 23	28	collect questionnaire data from dropouts in this group in the third screening round. We used a
24 25 26	29	condition-specific questionnaire to assess psychosocial status. We analysed the differences in
20 27 28	30	psychosocial status in the third and preceding rounds between dropouts and attenders in the
29 30 31	31	control group in multivariable linear regression models adjusted for socio-demographics and
32 33	32	smoking status reported at baseline. Differences in socio-demographics and smoking status were
34 35	33	analysed with chi-squared tests.
36 37 38	34	Primary outcome measure: Primary outcome was psychosocial status.
39 40	35	Participants: All control persons still participating at the third screening round in the DLCST were
41 42 43	36	included.
44 45	37	Results: Dropouts in the third round had significantly worse psychosocial status than attenders in
46 47 48	38	the scales: "Behaviour" 0.77 (99% Cl 0.18;1.36), "Self-blame" 0.59 (99% Cl 0.14;1.04), "Focus on
49 50	39	airway symptoms" 0.22 (99% CI 0.08;0.36), "Stigmatisation" 0.51 (99% CI 0.16;0.86), "Introvert"
51 52 53	40	0.56 (99% CI 0.23;0.89), and "Harms of smoking" 0.35 (99% CI 0.11;0.59). Moreover, Dropouts had
53 54 55	41	worse scores than attenders in the preceding screening rounds. Dropouts also reported worse
56 57 58 59 60	42	socio-demographics at baseline.

2 3								
4 5	43	Conclusions: Dropouts had a significantly worse psychosocial status and worse socio-						
6 7 8	44	demographics compared with attenders. The results of our study contribute with evidence of non-						
9 10	45	response and attrition driven by psychosocial status, which in turn may be influenced by the						
11 12 13	46	screening intervention itself. This can be used to adjust cancer screening trial results for bias due						
14 15	47	to differential dropout.						
16 17 18	48	Trial registration: The trial is registered in <u>Clinicaltrials.gov</u> Protocol Registration System						
19 20	49	(identification no. <u>NCT00496977</u>)						
21 22 23	50							
24 25	51	Article summary						
26 27 28	52	Strengths and limitations						
29 30	53	Use of a condition-specific questionnaire with adequate psychometric properties ensured						
31 32 33	54	valid measures.						
34 35 36	55	• Patient-reported data on dropouts gave valuable empirical insight in drivers for dropout.						
37 38	56	Testing a previously hypothesized model for dropout empirically is another strength of the						
39 40 41	57	study.						
41 42 43	58	 No comparison between dropouts in the intervention and the control group was 						
44 45	59	performed.						
46 47 48	60	No longer-term follow up on dropouts was performed.						
49 50	61							
51 52 53 54	62	Introduction						
55 56	63	Attrition and non-response may affect trial results and introduce bias in randomized controlled						
57 58 59 60	64	trials (RCTs).[1,2] Non-response reduces the power of the trial and, if non-response differs						

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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.

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

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88	compared with annual clinical examinations only in the control group.[8] Furthermore, all the
89	participants were asked to complete a condition-specific questionnaire, measuring psychosocial
90	consequences of lung cancer screening at these annual clinical assessments.[9] The results
91	showed that people experienced negative psychosocial consequences merely by participating in
92	the trial, and that negative consequences were higher for participants allocated to the control
93	group.[7,10] A large number of controls did not attend the second annual examination (n=513,
94	26.1%) while dropout in the intervention group was low (n=71, 3.5%) (<i>Fig. 1</i>). To adjust for this
95	differential dropout, inverse probability weighting was used.[7] In this method the observed
96	outcomes are weighted with the inverse of the probability of being non missing.[3] We
97	hypothesised that these probabilities were adequately estimated from socio-demographic profile
98	including smoking status, randomization group and psychosocial status in previous rounds.[7,11–
99	13]
00	If these hypotheses were confirmed, then these factors would explain the witnessed difference in
01	response between the trial groups and could be used to render them comparable. Analysed
02	without such adjustments the assessment of the trial groups, and thereby the means of the scores
03	from the responses to the questionnaire from the remaining trial participants would no longer be
04	comparable.[14] Hence, the assessment of psychosocial harms of lung cancer screening could be
05	biased.
06	Therefore, the overall aim of this study was to empirically assess whether control participants who
07	dropped out of the study had different psychosocial profiles compared with control participants
	aropped out of the study had unterent psychosocial promes compared with control participants

1 2	
3 4 5 111	Materials and methods
6	
7 112 8	Study design and population
9 10 113 11	The design and study population of DLCST have been described in detail previously.[7,8] Briefly,
12 114 13	the DLCST was an RCT, conducted at the Copenhagen University hospital Gentofte in Denmark
14 15 115 16	from October 2004 to March 2010. Heavy current and former smokers (at least 20 pack-years),
17 116 18	aged 50-70 years old, were randomized to either five rounds of screening with low-dose CT-scans
19 20 117	including clinical examinations (n=2052) or five clinical examinations only (n=2052). In the
21 22 118 23	enrolment visit, participants provided socio-demographic data, lifestyle and health information
24 25 119	(including smoking status), completed a questionnaire on their psychosocial status and underwent
26 27 120 28	spirometry. Participants randomized to screening also had a low-dose chest CT-scan within one
²⁹ 121 30	month of randomisation. In the following screening rounds, participants in the screened and
31 32 122	control groups were invited to a visit in the screening clinic where lung function tests were
33 34 123 35	performed, and questionnaires concerning health, lifestyle, smoking habits and psychosocial
³⁶ 37 124	status were completed and lung function tests were performed. Participants randomized to
38 39 125 40	screening also received a low-dose chest CT-scan.
41 42 126	This study is an observational study nested in the DLCST. During the second screening round, the
43 44 127 45	steering committee noted that a large number of control participants did not attend the screening
46 47 47	clinic visit when compared with the number of screened participants. Thus, the committee
48 49 129	decided to make additional efforts to collect questionnaire data for dropouts in the control group
50 51 130 52	in the third screening round to perform post hoc analyses on whether psychosocial status was an
53 54 131	influencing factor (Fig.2).
55 56 132 57	During the third round, participants in the control group who dropped out were contacted by
58 59 60	phone and part 1 of the questionnaire was sent with a postage paid envelope to those who gave

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3 4 5 134	their oral consent. The data was used to supplement the data collected on site at the screening		
6 7 135 8	clinic.[7] This yielded three groups within the control group, denoting the extent of response to		
9 136 10	the clinical examination and the questionnaire defined as:		
11 12 137 13			
¹⁴ 138 15	1. Attenders: participants who attended the third screening round.		
16 17 139 18	2. Dropouts:		
19 140 20	a) <u><i>Responders</i></u> : participants who dropped out but completed and returned the COS-LC		
²¹ 22 22	after the phone interview.		
23 24 142 25	b) <i>Non-responders</i> : participants who dropped out and did not complete the COS-LC.		
²⁶ 143			
28 29 144 30	Outcomes & Questionnaires		
³¹ 145 32	Primary outcome was psychosocial status measured with the Consequences Of Screening for Lung		
³³ 34 146 35	Cancer (COS-LC) questionnaire.[9] Part 1 of COS-LC comprised nine scales measuring various		
36 147 37	aspects of consequences of screening; a second part of COS-LC addressed the screening outcome		
³⁸ 39 148 40	and was therefore not applicable to the present analysis. Moreover, the primary part of COS-LC		
40 41 149 42	included four core scales: "Anxiety", "Behaviour", "Dejection" and "Sleep" that are not lung cancer		
43 44 150	specific. These scales have originally been developed from a breast cancer screening assessment		
45 46 151 47	instrument.[15] Additionally COS-LC comprised five lung cancer specific scales: "Self-blame",		
48 49 152	"Focus on airway symptoms", "Stigmatisation", "Introvert", and "Harm of smoking", which were		
50 51 153 52	developed from focus groups and other screening assessment instruments during the first DLCST		
53 154 54	screening round.[9,15] Therefore, only the core scales were used in the first round, while in the		
⁵⁵ 56 155	following four screening rounds both the core scales and the lung cancer specific scales were used		
57 58 156 59 60	to assess psychosocial status.[9]		

1 2	
3 4 157 5	
5 6 7 158	Statistics
8 9 159	Covariates
10 ¹⁰ 11 12 160	Socio-demographic characteristics were defined by: social class (I highest social class to V lowest
13 ¹⁴ 161	social class), school and vocational education (from 9 years of elementary school to a university
15 16 17 162	education), employment status, living alone, smoking status (current or former smoker), smoking
18 19 163	history (pack-years), motivation for smoking cessation (from very strong to no wish to quit) and
20 21 22 164	Charlson Comorbidity Index (CCI). Furthermore, we adjusted for region of residence (Denmark is
23 24 165	divided into five health-administrative regions).
25 26 27 166	
28 29 167	Statistical analyses
30 ³¹ 168 32	We performed three different analyses:
33 34 169	1. Analyses of differences in psychosocial status in the third round between Attenders and
35 36 170	Dropout-responders.
37 38 39 171	2. Analyses of differences in psychosocial status in the second round between <i>Attenders,</i>
40 41 172	Dropout-responders and Dropout-non-responders.
42 43 44 173	3. Analyses of differences in psychosocial status in the first round, between Attenders,
45 46 174	Dropout-responders and Dropout-non-responders.
47 48 49 175	Covariates at the first screening round were compared between Attenders and Dropouts by chi-
50 51 176	squared tests (categorical characteristics) and t-tests (continuous characteristics). Analyses of
52 53 177 54	psychosocial status at various points in the follow-up were performed in linear regression models
55 56 178	both unadjusted and in multivariable models adjusted for sex, age, region of residence, social
57 58 179 59	class, living alone, smoking status, pack years, motivation for smoking cessation and CCI. To adjust
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3 4 180 5	for multiple testing a p-value <0.01 was considered statistically significant. All analyses were
6 7 181	performed with SAS 9.4 (SAS Institute, Inc., Cary, NC).
8 9 182	Patient and Public Involvement
10 ¹⁰ 11 12 183	Patients and public were not involved in the design of the study.
13	
¹⁴ 184 15 16	
17 185 18	Results
19 20 186 21	The inclusion process and participation rate of the DLCST are illustrated in Figure 1. The
²² 187 23	participation rate in the control group fell from 73.9% in the second round to 57.5% in the fourth
24 25 188 26	round. The participation rate increased in the fifth, final, round (68.9%).
27 189 28	Figure 2 depicts the inclusion process of the present study and showed a dropout rate of 29.6%
29 30 190	(n=607) in the third screening round with a higher distribution of <i>Dropout-non-responders</i> (16.9%
31 32 191 33	n=347) compared with <i>Dropout-responders</i> (12.7% n=260).
³⁴ 192	In the first screening round we compared differences in socio-demographic characteristics in the
36 37 193 38	two overarching groups (Attenders, Dropouts) (Table 1).
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	Missing observations,	Attenders	Dropouts	p-value
	total	n=1388	n=607	
Covariates	n	n (%)**	n(%)**	
Sex	0			0.0963
Male		773 (55.7)	313 (51.6)	
Female		615 (44.3)	294 (48.4)	
Age, <i>mean (SD)</i>	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			0.776
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		363 (26.2)	153 (25.3)	
school				
Other		7 (0.5)	2 (0.3)	
Vocational education	4			0.126
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, <i>mean (SD)</i>		0.26 (0.73)	0.31 (0.83)	0.0062
Living alone	17			0.005
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)	

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Table 1, Socio-demographics

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Pack-years, <i>mean (SD)</i>	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

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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*.

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

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

	Range	Responding	Attenders	Dropout-	p-value	Difference in	p-value
	of	rate per item	n=1388	responders		scores between	adjusted
	values	n/n	mean (SD)	n=260		the two groups	
			5	mean (SD)		mean (99%Cl) ^a	
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	0-24	1363/239	0.3 (0.8)	0.6 (1.0)	<0.001	0.22 (0.08;0.36)	<0.001
symptoms							
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

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^{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,

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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
COS scales, mean (SD)				11-200	11-047		
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	0-24	1226/118/90	0.4 (0.8)	0.4 (0.8)	0.5 (0.9)	0.408	0.579
symptoms							
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

³⁵ 272

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.

40 276 Dropouts had significantly worse crude scores compared with Attenders in all but one scale

42 277 ("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

47 279 adjusted "Self-blame"-scale score was significantly worse for Dropouts.

The differences in psychosocial status in the first screening round between Attenders, Dropout-

52 281 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

57 283 disappeared in all but one scale, "Anxiety" when adjusting for covariates.

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

286			Range of values	Responding rate per item n/n/n	Attenders n=1388 mean (SD)	Dropout- responders n=260	Dropout-non- responders n=347	p-value	p-value adjusted ^a
287	со	S-scales				mean (SD)	mean (SD)		
288	Bel De	xiety haviour jection	0-18 0-21 0-18	1353/253/334 1365/257/340 1372/257/339	1.46 (2.16) 0.75 (1.89) 1.25 (2.05)	1.75 (2.54) 1.05 (2.44) 1.54 (2.48)	2.11 (2.66) 1.04 (2.43) 1.68 (2.33)	<0.001 0.0134 0.0018	0.0028 0.0976 0.0512
289	Sle	ер	0-12	1368/253/344	0.62 (1.64)	0.86 (1.98)	0.90 (1.86)	0.0072	0.0530
290									
291 292				on of residence, soc and pack years) are					
293		andous values va	nables (age	anu pack years) are	included as a qua		to allow for possible	e nonimear enec	15.
294									
295	Discussio	n							
296	The presen	t study sho	wed con	siderable att	rition in the	e control gr	oup of the D	LCST. Data	in the
297	control gro	up was not	missing	at random. I	ndividuals v	who droppe	d out had le	ss favoural	ble
298	baseline so	cio-demogr	aphic pr	ofile when c	ompared w	ith attende	rs. More imp	oortantly, ii	ndividuals
299	who dropp	ed out from	n their ar	nnual clinical	work-up ha	ad worse ps	ychosocial s	tatus than	the
300	individuals	who attend	led the d	linic in the p	revious rou	nds. This ca	in be used to	adjust for	
301	differential	dropout. F	urtherm	ore, these in	dividuals al	so had wors	se psychosod	cial status o	during
302	their misse	d round (as	sessed i	n the present	t study in th	e third rou	nd). This can	not be use	d to
303	adjust diffe	rential drop	oout bec	ause this info	ormation is	generally n	ot available	but proves	the
304	concept.								
305	The use of	a condition	-specific	questionnai	re is a stren	gth of the s	tudy. Previo	us researcl	n has
306	demonstra	ted that cor	ndition-s	pecific quest	ionnaires a	re superior	to generic q	uestionnai	res when
307	measuring	psychosocia	al conse	quences in ca	ancer scree	ning setting	s.[16] Furthe	ermore, we	e used an
308	appropriate	e longitudin	al desig	n i.e. we colle	ected data a	at the same	timepoints	for both At	tenders

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and Drenaute at various times in the trial, as well as we measured nevelopsed at the in both
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

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332	secretary in the screening clinic received calls from participants randomized to the control group
333	expressing their disappointment of not being screened. Furthermore, the trial put focus on the
334	harms of smoking, which could have increased the anxiety and fear of disease in this subgroup
2 335	even more, which may have been a reason to subsequent dropout.
4 336	Low social status, younger age and current smoking status have previously been seen among
5 7 337	dropouts in lung health studies.[22–25] A systematic review reporting dropout from longitudinal
9338)	studies in elderly concluded that higher age and declining health were high predictors of dropout.
¹ 339	The latter is in agreement with our findings, although higher age is in contrast to our findings.[26]
3 4 340 5	To our knowledge, this is the first cancer screening study testing hypotheses on reasons for
5341	differential dropout empirically. The results of this study confirmed the hypotheses we made in
3 9342	our previous study, using inverse probability weighting to adjust for differential dropout.[3,7,27]
¹ 343	More importantly, the results of the two other lung cancer screening trials investigating dropout
³ 4 344	are consistent with ours. Hence, it is plausible that our results are generalisable to other cancer
5 345 7	screening trials as well.
³ 346	Therefore, future cancer screening trials should concurrently assess psychosocial status during the
) 1 347 2	trial, not only to be able to assess the psychosocial effect of screening, but also to use this
³ 348	information to adjust any effect in the trial for bias due to differential attrition.
5 5349 7	
³ 350	Conclusions
) 351	In conclusion, Dropouts in the control group in the DLCST had a worse psychosocial status and a
³ 4 352	less favourable socio-demographic profile than Attenders.
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3 4 353	
5	The results of our study contribute with evidence of non-response driven by psychosocial status,
6 7 354 8	which in turn may be influenced by the screening intervention itself. This can be used to adjust
9 355 10	cancer screening trial results for bias due to differential dropout.
11 12 356 13	
14 357 15	Abbreviations
16 17 358 18	RCT: Randomized controlled trial; PROM: Patient-reported outcome measure; CT: Computed
19 359 20	tomography; DLCST: Danish Lung Cancer Screening Trial; COS-LC: Consequences of screening in
$\frac{21}{22}$ 360	lung cancer; COS: Consequences of screening; CCI: Charlson comorbidity index
23 24 361 25	
26 27 362	Declarations
28 29 30 363	Ethics approval and consent to participate
30 505 31	
32 364 33	The Ethical Committee of Copenhagen County approved the DLCST on 31 January 2003.
³⁴ 35 36	All participants signed an informed consent form. The trial is registered
37 366 38	in <u>Clinical.Trials.gov</u> Protocol Registration System (identification no. <u>NCT00496977</u>)
³⁹ 367	
41 42 368 43	Availability of data and materials
⁴⁴ 369 45	The corresponding author can provide the questionnaires and datasets generated and analysed
46 47 370 48	during the study on reasonable request.
49 371 50	
⁵¹ 52 372	Competing interests
53 54 373 55	None declared.
56 57 374	
58 59 375	Funding
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1 2	
3 4 5 376	This work was supported by the Danish Ministry of Interior and Health, grant number <u>0900814</u> .
6 7 377 8	The funding source had no role in study design, data collection and analysis, decision to publish, or
9 10 378	preparation of the manuscript.
11 12 379 13	
14 380 15	Author contributions
16 17 381 18	JB and HT developed and designed the study. JB, HT and the DLCST staff collected data. VS
19 382 20	performed the statistical analyses. JM drafted the manuscript. JB, HT, BH, JFR, and VS all
²¹ 383 22 23	contributed to parts of the manuscript as well as revisions of the manuscript. All authors approved
24 384 25 26	the final version of the manuscript, and no editorial assistance was received. All authors had full
²⁶ 385 27 28	access to all data in the study and are responsible of data retention and the accuracy of the data
29 386 30	analysis. JM and JB are guarantors of the study.
31 387 32 33	
34 388 35	Acknowledgement
36 389 37	We wish to thank data manager Willy Karlslund for his contribution to generation of the databases
³⁸ 39 390 40	and we also wish to thank the DLCST steering committee.
41 391 42	Fig 1 Flowchart DI CST
43 44 45392	Fig.1 Flowchart, DLCST
46 47 48 393	Fig.2 Flowchart, present study
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3 4 References 395 5 6 7 396 1. Tierney JF. Investigating patient exclusion bias in meta-analysis. Int J Epidemiol [Internet]. 8 9 10 3 9 7 2004;34:79-87. Available from: https://academic.oup.com/ije/article-11 12 398 lookup/doi/10.1093/ije/dyh300 13 14 15 399 2. Zhang Y, Alyass A, Vanniyasingam T, Sadeghirad B, Flórez ID, Pichika SC, et al. A systematic 16 17 18 400 survey of the methods literature on the reporting quality and optimal methods of handling 19 ²⁰ 401 participants with missing outcome data for continuous outcomes in randomized controlled trials. J 21 22 23 402 Clin Epidemiol [Internet]. 2017;88:67–80. Available from: 24 25 403 http://www.ncbi.nlm.nih.gov/pubmed/28579378 26 27 28 4 0 4 3. Dufouil C, Brayne C, Clayton D. Analysis of longitudinal studies with death and drop-out: a case 29 30 405 study. Stat Med [Internet]. 2004;23:2215–26. Available from: 31 32 http://www.ncbi.nlm.nih.gov/pubmed/15236426 33 406 34 35 36 407 4. Humphrey LL, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP, et al. Screening for lung 37 ³⁸ 408 cancer with low-dose computed tomography: a systematic review to update the US Preventive 39 40 ₄₁ 409 services task force recommendation. Ann Intern Med [Internet]. 2013 [cited 2014 Feb 42 43 410 26];159:411–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23897166 44 45 46 4 1 1 5. Wu GX, Raz DJ, Brown L, Sun V. Psychological Burden Associated With Lung Cancer Screening: A 47 ⁴⁸ 412 Systematic Review. Clin Lung Cancer [Internet]. 2016;17:315–24. Available from: 49 50 http://linkinghub.elsevier.com/retrieve/pii/S1525730416300535 51 413 52 53 ₅₄ 414 6. Brain K, Lifford KJ, Carter B, Burke O, McRonald F, Devaraj A, et al. Long-term psychosocial 55 56 4 1 5 outcomes of low-dose CT screening: results of the UK Lung Cancer Screening randomised 57 58 59 416 controlled trial. Thorax [Internet]. 2016;71:996–1005. Available from:

60

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2	
3 4 5 417 6	http://thorax.bmj.com/lookup/doi/10.1136/thoraxjnl-2016-208283
7 418 8	7. Rasmussen JF, Siersma V, Pedersen JH, Brodersen J. Psychosocial consequences in the Danish
9 10 419	randomised controlled lung cancer screening trial (DLCST). Lung Cancer [Internet]. 2015;87:65–72.
11 12 420 13	Available from: http://www.ncbi.nlm.nih.gov/pubmed/25433982
14 15 421 16	8. Pedersen JH, Ashraf H, Dirksen A, Bach K, Hansen H, Toennesen P, et al. The Danish randomized
17 18 422	lung cancer CT screening trialoverall design and results of the prevalence round. J Thorac Oncol
19 20 423 21	[Internet]. 2009 [cited 2013 Sep 18];4:608–14. Available from:
²² 424 23 24	http://www.ncbi.nlm.nih.gov/pubmed/19357536
²⁵ 425 26	9. Brodersen J, Thorsen H, Kreiner S. Consequences of screening in lung cancer: development and
²⁷ 28 426	dimensionality of a questionnaire. Value Health [Internet]. 2010 [cited 2013 Oct 1];13:601–12.
29 30 427 31 32	Available from: http://www.ncbi.nlm.nih.gov/pubmed/20345552
33 428 34	10. Aggestrup LM, Hestbech MS, Siersma V, Pedersen JH, Brodersen J. Psychosocial consequences
³⁵ 429	of allocation to lung cancer screening: a randomised controlled trial. BMJ Open [Internet]. 2012
37 38 430 39	[cited 2013 Oct 1];2:e000663. Available from:
40 431 41	http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3293139&tool=pmcentrez&renderty
42 43 432 44	pe=abstract
45 46 433	11. Heydarpour B, Saeidi M, Ezzati P, Soroush A, Komasi S. Sociodemographic Predictors in Failure
47 48 434 49	to Complete Outpatient Cardiac Rehabilitation. Ann Rehabil Med [Internet]. 2015;39:863–71.
50 51 52	Available from: http://www.ncbi.nlm.nih.gov/pubmed/26798599
⁵³ 436 54	12. de Graaf R, van Dorsselaer S, Tuithof M, ten Have M. Sociodemographic and psychiatric
55 56 437 57	predictors of attrition in a prospective psychiatric epidemiological study among the general
58 438 59 60	population. Result of the Netherlands Mental Health Survey and Incidence Study-2. Compr

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1 2	
3 4 5 439	Psychiatry [Internet]. 2013;54:1131–9. Available from:
6 7 440 8	http://linkinghub.elsevier.com/retrieve/pii/S0010440X13001284
9 10 441 11	13. Field JK, Duffy SW, Baldwin DR, Whynes DK, Devaraj A, Brain KE, et al. UK Lung Cancer RCT Pilot
12 442 13	Screening Trial: baseline findings from the screening arm provide evidence for the potential
14 15 443 16	implementation of lung cancer screening. Thorax [Internet]. 2015;1–10. Available from:
17 444 18	http://www.ncbi.nlm.nih.gov/pubmed/26645413
19 20 445 21	14. McCaffery KJ. Assessing psychosocial/quality of life outcomes in screening: how do we do it
²² 446 23	better? J Epidemiol Community Heal [Internet]. 2004;58:968–70. Available from:
24 25 447 26	http://jech.bmj.com/cgi/doi/10.1136/jech.2004.025114
27 28 448 29	15. Brodersen J, Thorsen H. Consequences of Screening in Breast Cancer (COS-BC): development of
30 449 31	a questionnaire. Scand J Prim Health Care [Internet]. 2008 [cited 2013 Oct 1];26:251–6. Available
³² 33450	from:
34 35 451 36	http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3406644&tool=pmcentrez&renderty
³⁷ 452 38 39	pe=abstract
40 453 41	16. Brodersen J, Thorsen H, Cockburn J. The adequacy of measurement of short and long-term
42 43 454 44	consequences of false-positive screening mammography. J Med Screen. 2004;11:39–44.
45 46 47	17. DeFrank JT, Barclay C, Sheridan S, Brewer NT, Gilliam M, Moon AM, et al. The psychological
48 456 49	harms of screening: the evidence we have versus the evidence we need. J Gen Intern Med
50 51 52	[Internet]. 2015;30:242–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25150033
⁵³ 458 54	18. van den Bergh KAM, Essink-Bot ML, Borsboom GJJM, Scholten ET, van Klaveren RJ, de Koning
55 56 459 57	HJ. Long-term effects of lung cancer computed tomography screening on health-related quality of
58 460 59 60	life: the NELSON trial. Eur Respir J [Internet]. 2011 [cited 2014 Oct 3];38:154–61. Available from:

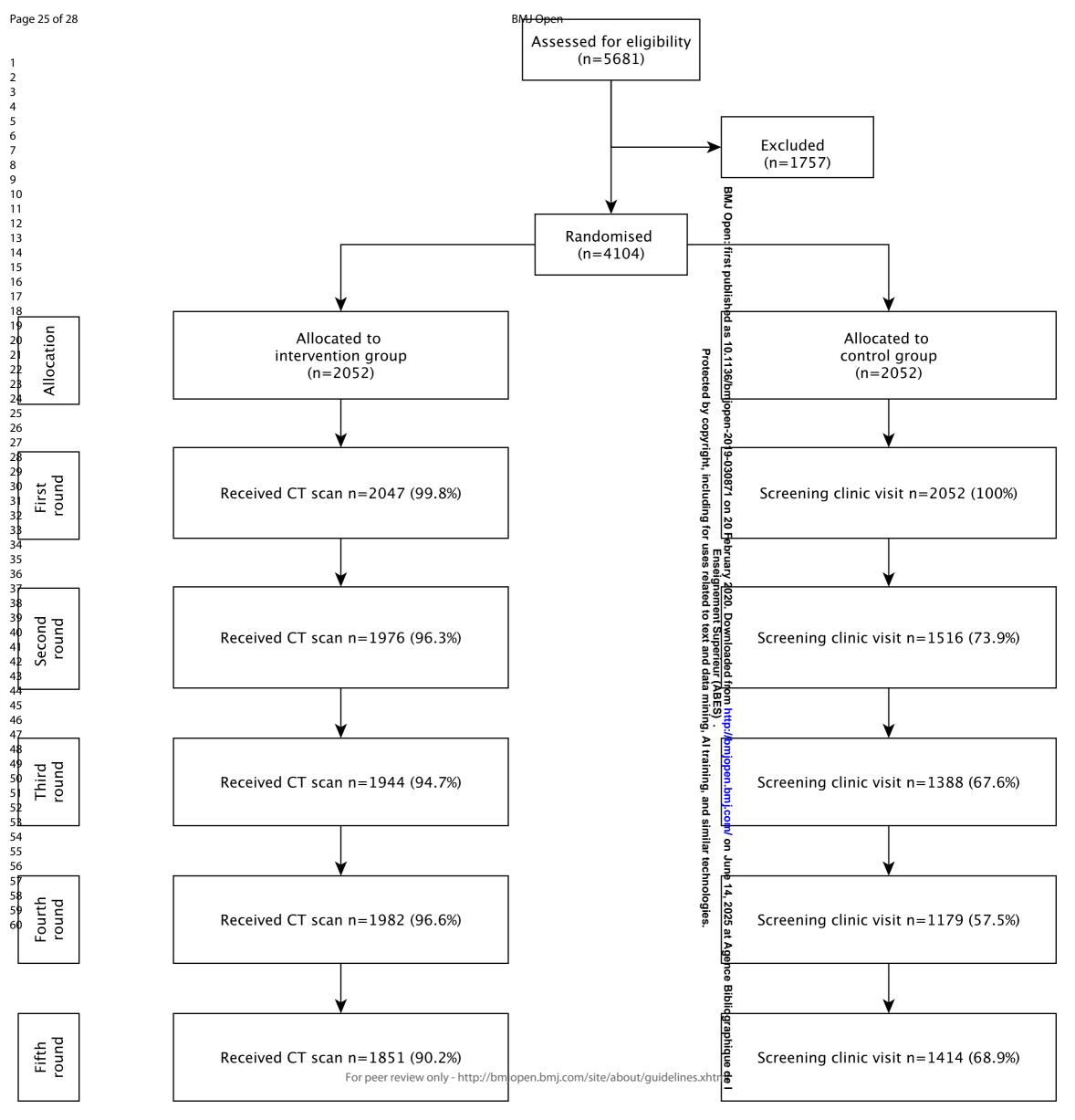
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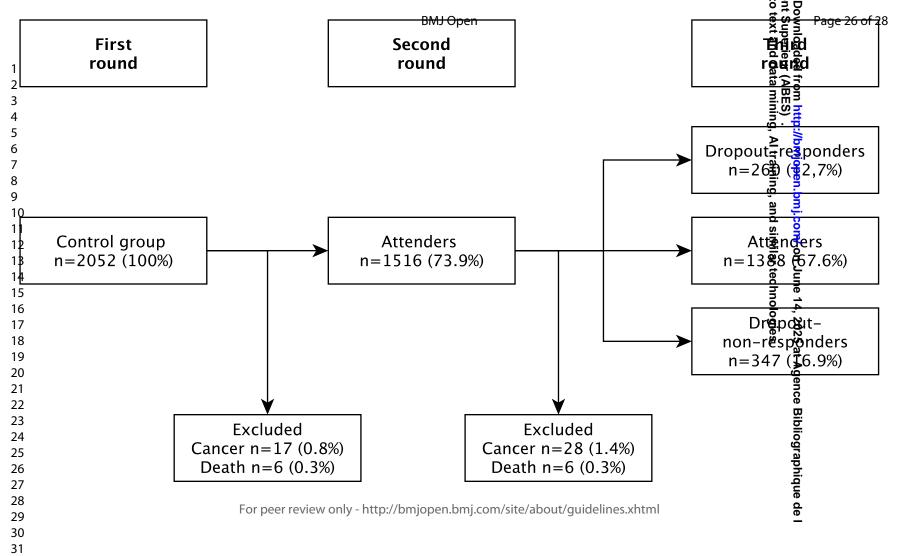
1

BMJ Open

2	
3 4 5 461	http://www.ncbi.nlm.nih.gov/pubmed/21148229
6 7 462 8	19. Mercieca-Bebber RL, Price MA, Bell ML, King MT, Webb PM, Butow PN, et al. Ovarian cancer
9 10 463	study dropouts had worse health-related quality of life and psychosocial symptoms at baseline and
11 12 464 13	over time. Asia Pac J Clin Oncol [Internet]. 2017;13:e381–8. Available from:
$^{14}_{15}465$	http://www.ncbi.nlm.nih.gov/pubmed/27573704
16 ¹⁷ 466 18	20. Østerø J, Siersma V, Brodersen J. Breast cancer screening implementation and reassurance. Eur
19 20 467 21	J Public Health. 2014;24:258–63.
22 23 468	21. Wendler D, Krohmal B, Emanuel EJ, Grady C. Why patients continue to participate in clinical
24 25 469 26	research. Arch Intern Med [Internet]. 2008 [cited 2013 Oct 1];168:1294–9. Available from:
27 28 470	http://www.ncbi.nlm.nih.gov/pubmed/18574086
29 ³⁰ 31 471	22. Snow WM, Connett JE, Sharma S, Murray RP. Predictors of attendance and dropout at the Lung
32 33 472 34	Health Study 11-year follow-up. Contemp Clin Trials [Internet]. 2007;28:25–32. Available from:
³⁵ 473 ₃₆	http://linkinghub.elsevier.com/retrieve/pii/S1551714406001157
37 ³⁸ 474 39	23. Nohlert E, Öhrvik J, Helgason ÁR. Non-responders in a quitline evaluation are more likely to be
40 41 475 42	smokers - a drop-out and long-term follow-up study of the Swedish National Tobacco Quitline. Tob
42 43 476 44	Induc Dis [Internet]. 2016;14:5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26843854
45 46 477 47	24. Abrahamsen R, Svendsen MV, Henneberger PK, Gundersen GF, Torén K, Kongerud J, et al. Non-
48 49478	response in a cross-sectional study of respiratory health in Norway. BMJ Open [Internet].
50 51 479 52	2016;6:e009912. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26739738
53 54 480	25. Oleske DM, Kwasny MM, Lavender SA, Andersson GBJ. Participation in occupational health
55 56 481 57	longitudinal studies: predictors of missed visits and dropouts. Ann Epidemiol [Internet].
58 59 482 60	2007;17:9–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17140810

1 2	
3	
⁴ 483	26. Chatfield MD, Brayne CE, Matthews FE. A systematic literature review of attrition between
6 7 484 8	waves in longitudinal studies in the elderly shows a consistent pattern of dropout between
9 485 10	differing studies. J Clin Epidemiol [Internet]. 2005 [cited 2014 Mar 13];58:13–9. Available from:
11 12 486 13	http://www.ncbi.nlm.nih.gov/pubmed/15649666
14 15 487	27. Rotnitzky A, Robins J. Analysis of semi-parametric regression models with non-ignorable non-
16 17 488 18	response. Stat Med [Internet]. 16:81–102. Available from:
¹⁹ 489	http://www.ncbi.nlm.nih.gov/pubmed/9004385
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STROBE Statement—checklist of items that should be included in reports of observational studies

		Recommendation	Page No
a) Indicat	(/) Indicate the study's design with a commonly used term in the	1
itle or the	ti	e or the abstract	
b) Provid	(Provide in the abstract an informative and balanced summary of	1
<i>,</i>		hat was done and what was found	
-		plain the scientific background and rationale for the investigation ing reported	2-4
		ate specific objectives, including any prespecified hypotheses	4
resent ke	P	esent key elements of study design early in the paper	5
	_	escribe the setting, locations, and relevant dates, including periods	5
		recruitment, exposure, follow-up, and data collection	
		<i>Cohort study</i> —Give the eligibility criteria, and the sources and	6
	`	ethods of selection of participants. Describe methods of follow-up	
		<i>use-control study</i> —Give the eligibility criteria, and the sources	
		d methods of case ascertainment and control selection. Give the	
		ionale for the choice of cases and controls	
		oss-sectional study—Give the eligibility criteria, and the sources	
		d methods of selection of participants	
		<i>Cohort study</i> —For matched studies, give matching criteria and	Not
		mber of exposed and unexposed	applicabl
		use-control study—For matched studies, give matching criteria	
nd the nu	a	d the number of controls per case	
Clearly de	C	early define all outcomes, exposures, predictors, potential	6 and 7
onfounde pplicable		nfounders, and effect modifiers. Give diagnostic criteria, if plicable	
For each	J	or each variable of interest, give sources of data and details of	
nethods o	n	ethods of assessment (measurement). Describe comparability of	
ssessmen	а	sessment methods if there is more than one group	
		escribe any efforts to address potential sources of bias	
Explain ho	F	plain how the study size was arrived at	Not
			applicabl
Explain ho	F	plain how quantitative variables were handled in the analyses. If	6-8
pplicable	a	plicable, describe which groupings were chosen and why	
		Describe all statistical methods, including those used to control	7-8
,		confounding	
		Describe any methods used to examine subgroups and	7
<i>,</i>		eractions	,
		Explain how missing data were addressed	Not applicabl
d) Cohor		<i>Cohort study</i> —If applicable, explain how loss to follow-up was	Not
ddressed	a	dressed	applicabl
		<i>use-control study</i> —If applicable, explain how matching of cases d controls was addressed	

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	<i>Cross-sectional study</i> —If applicable, describe analytical methods
	taking account of sampling strategy (e) Describe any sensitivity analyses
Continued on next page	(<u>e</u>) Describe any sensitivity analyses
Continued on next page	

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially	Fig.1
-		eligible, examined for eligibility, confirmed eligible, included in the study,	
		completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Fig.2
		(c) Consider use of a flow diagram	Fig.2
Descriptive	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and	7
data		information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	Table
		(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	Tabl
			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	Tabl
		their precision (eg, 95% confidence interval). Make clear which confounders were	2-4
		adjusted for and why they were included	
		(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	N/A
		meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and	N/A
		sensitivity analyses	
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	10
		imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	10
		multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-
			12
Other informati	on		
Funding	22	Give the source of funding and the role of the funders for the present study and, if	13
0		applicable, for the original study on which the present article is based	

*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.

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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Secondary Subject Heading:	Research methods, General practice / Family practice
Keywords:	Bias, Mass screening, Lung neoplasms, Patient dropout

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1	Did psychosocial status, sociodemographics and smoking status
2	affect non-attendance in control participants in the Danish Lung
3	Cancer Screening Trial? A nested observational study
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3	Keywords
)	bias, mass screening, lung neoplasms, patient dropouts
)	Word count 2780

2		
4 5 6	21	Abstract
7 8	22	Objectives: We investigated if psychosocial status, socio-demographics and smoking status
9 10 11	23	affected non-attendance in the control group in the randomized Danish Lung Cancer Screening
11 12 13	24	Trial (DLCST).
14 15	25	Design & setting: This study was an observational study nested in the DLCST. Due to large non-
16 17 18	26	attendance in the control group in the second screening round we made an additional effort to
19 20	27	collect questionnaire data from non-attenders in this group in the third screening round. We used
21 22 23	28	a condition-specific questionnaire to assess psychosocial status. We analysed the differences in
23 24 25	29	psychosocial status in the third and preceding rounds between non-attenders and attenders in the
26 27	30	control group in multivariable linear regression models adjusted for socio-demographics and
28 29 30	31	smoking status reported at baseline. Differences in socio-demographics and smoking status were
31 32	32	analysed with chi-squared tests (categorical variables) and t-tests (continuous variables).
33 34 35	33	Primary outcome measure: Primary outcome was psychosocial status.
36 37	34	Participants: All control persons participating in the third screening round in the DLCST were
38 39 40	35	included.
40 41 42	36	Results: Non-attenders in the third round had significantly worse psychosocial status than
43 44	37	attenders in the scales: "Behaviour" 0.77 (99% CI 0.18;1.36), "Self-blame" 0.59 (99% CI 0.14;1.04),
45 46 47	38	"Focus on airway symptoms" 0.22 (99% CI 0.08;0.36), "Stigmatisation" 0.51 (99% CI 0.16;0.86),
48 49	39	"Introvert" 0.56 (99% CI 0.23;0.89), and "Harms of smoking" 0.35 (99% CI 0.11;0.59). Moreover,
50 51 52	40	non-attenders had worse scores than attendees in the preceding screening rounds. Non-attenders
53 54	41	also reported worse socio-demographics at baseline.
55 56	42	Conclusions: Non-attenders had a significantly worse psychosocial status and worse socio-
57 58 59 60	43	demographics compared with attenders. The results of our study contribute with evidence of non-
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2 3									
4 5 6	44	response and attrition driven by psychosocial status, which in turn may be influenced by the							
7 8	45	screening intervention itself. This can be used to adjust cancer screening trial results for bias due							
9 10 11	46	to differential non-attendance.							
12 13	47	Trial registration: The trial is registered in <u>Clinicaltrials.gov</u> Protocol Registration System							
14 15 16	48	(identification no. <u>NCT00496977</u>)							
17 18	49								
19 20 21	50	Article summary							
22 23	51	Strengths and limitations							
24 25 26	52	Use of a condition-specific questionnaire with adequate psychometric properties ensured							
27 28 29	53	valid measures.							
30 31	54	Patient-reported data on non-respondents gave valuable empirical insight in drivers for							
32 33 34	55	non-attendance.							
35 36	56	 Testing a previously hypothesized model for non-attendance empirically is another 							
37 38 39	57	strength of the study.							
40 41 42	58	 No comparison between non-attenders in the intervention and the control group was 							
42 43 44	59	performed.							
45 46	60	 No longer-term follow up on non-attenders was performed. 							
47 48 49	61								
50 51	62	Introduction							
52 53 54	63	Non-attendance may affect trial results and introduce bias in randomized controlled trials							
55 56	64	(RCTs).[1,2] Non-attendance reduces the power of the trial and, if non-attendance differs between							
57 58 59 60	65	the randomized groups, conventional effect estimates can be biased.[2] While we cannot change							

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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

they did not receive. Despite these potential problems, few lung cancer screening RCTs have

return questionnaires enquiring into their experiences with a potentially beneficial intervention

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reported on non-attendance in both study groups let alone adjusted for potential differential non-

0 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

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1

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 sociodemographic 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 withcontrol participants who attended the annual clinical examination.

Materials and methods

Study design and population

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3	
4 112 5	The design and study population of DLCST have been described in detail previously.[7,8] Briefly,
6 7 113 8	the DLCST was an RCT, conducted at the Copenhagen University hospital Gentofte in Denmark
9 114 10	from October 2004 to March 2010. Heavy current and former smokers (at least 20 pack-years),
11 12 115 13	aged 50-70 years old, were randomized to either five rounds of screening with low-dose CT-scans
14 116 15	including clinical examinations (n=2052) or five clinical examinations only (n=2052). In the
16 17 117	enrolment visit, participants provided socio-demographic data, lifestyle and health information
18 19 118 20	(including smoking status), completed a questionnaire on their psychosocial status and underwent
21 22 119	spirometry. Participants randomized to screening also had a low-dose chest CT-scan within one
23 24 120 25	month of randomisation. In the following screening rounds, participants in the screened and
²⁶ 121 27	control groups were invited to a visit in the screening clinic where lung function tests were
28 29 122 30	performed, and questionnaires concerning health, lifestyle, smoking habits and psychosocial
³¹ 123 32	status were completed and lung function tests were performed. Participants randomized to
33 34 124 35	screening also received a low-dose chest CT-scan.
36 125 37	This study is an observational study nested in the DLCST. During the second screening round, the
³⁸ 39 126 40	steering committee noted that a large number of control participants did not attend the screening
40 41 127 42	clinic visit when compared with the number of screened participants. Thus, the committee
43 44 128	decided to make additional efforts to collect questionnaire data for non-attenders in the control
45 46 129 47	group in the third screening round to perform post hoc analyses on whether psychosocial status
48 130 49	was an influencing factor (Fig.2).
50 51 131 52	During the third round, participants in the control group who did not attend the annual
53 132 54	examination were contacted by phone and part 1 of the questionnaire was sent with a postage
55 56 133 57 58 59 60	paid envelope to those who gave their oral consent. The data was used to supplement the data

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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) <u><i>Respondents</i></u> : participants who did not attend the annual examination but
completed and returned the COS-LC after the phone interview.
b) <u>Non-respondents</u> : 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]

1 2		
3 4 5	157	Statistics
	158	Covariates
8 9 10	159	Socio-demographic characteristics were defined by: social class (I highest social class to V lowest
11 12 13	160	social class), school and vocational education (from 9 years of elementary school to a university
14 15	161	education), employment status, living alone, smoking status (current or former smoker), smoking
16 17 18	162	history (pack-years), motivation for smoking cessation (from very strong to no wish to quit) and
19 20	163	Charlson Comorbidity Index (CCI). Furthermore, we adjusted for region of residence (Denmark is
21 22 23	164	divided into five health-administrative regions).
	165	
26 27	166	Statistical analyses
28 29 30	167	We performed three different analyses:
32	168	1. Analyses of differences in psychosocial status in the third round between Attenders and
33 34 35	169	Non-attenders-respondents.
37	170	2. Analyses of differences in psychosocial status in the second round between <i>Attenders</i> ,
38 39 40	171	Non-attenders-respondents and Non-attenders-non-respondents.
42		3. Analyses of differences in psychosocial status in the first round, between <i>Attenders, Non</i> -
43 44 45	173	attenders-respondents and Non-attenders-non-respondents.
46 47	174	Covariates at the first screening round were compared between Attenders and Non-attenders by
48 49 50	175	chi-squared tests (categorical characteristics) and t-tests (continuous characteristics). Analyses of
51 52	176	psychosocial status at various points in the follow-up were performed in linear regression models
54	177	both unadjusted and in multivariable models adjusted for sex, age, region of residence, social
55 56 57	178	class, living alone, smoking status, pack years, motivation for smoking cessation and CCI. To adjust
58 59 60		

1 2	
3 4 5	for multiple testing a p-value <0.01 was considered statistically significant. All analyses were
6 7 180	performed with SAS 9.4 (SAS Institute, Inc., Cary, NC).
8 9 181	
10 11	
12 182 13	Patient and Public Involvement
14 183 15	Patients and public were not involved in the design of the study.
16 17 184	
18 19 20 185	Results
21 22 23 23	The inclusion process and participation rate of the DLCST are illustrated in Figure 1. The
24 25 187 26	participation rate in the control group fell from 73.9% in the second round to 57.5% in the fourth
27 188 28	round. The participation rate increased in the fifth, final, round (68.9%).
29 30 189 31	Figure 2 depicts the inclusion process of the present study and showed a dropout rate of 29.6%
32 190 33	(n=607) in the third screening round with a higher distribution of <i>Non-attenders-non-respondents</i>
³⁴ 35 191	(16.9% n=347) compared with <i>Non-attenders-respondents</i> (12.7% n=260).
36 37 192 38	In the first screening round we compared differences in socio-demographic characteristics in the
³⁹ ₄₀ 193	two overarching groups (Attenders, Non-attenders) (Table 1).
41 42 194	
43 44 195	
45 46 196	
47 48 197	
49 198	
50 51 199	
$\frac{52}{53}200$	
⁵⁴ 201	
55 56 202	
57 58 203	
59	
60	
	9

18 2 1 2

Table	1,	Socio-demographics
-------	----	--------------------

	Missing	Attenders	Non-attenders	p-value
	observations,			
	total	n=1388	n=607	
Covariates	n	n (%)**	n(%)**	
Sex	0			0.0963
Male		773 (55.7)	313 (51.6)	
Female		615 (44.3)	294 (48.4)	
Age, <i>mean (SD)</i>	0	57.4 (4.7)	56.9 (4.9)	0.0538
Social class	12			0.0079
l (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		363 (26.2)	153 (25.3)	
school				
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, <i>mean (SD)</i>		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)	

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Smoking status	0			0.0122
Current smoker	0	1046 (75.4)	489 (80.6)	0.0122
Former smoker		342 (24.6)	118 (19.4)	
Pack-years, <i>mean (SD)</i>	4	35.7 (13.7)	35.8 (12.3)	0.4207
Motivation for smoking cessation	30		0010 (1210)	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 leftmo				

4 246 5								
б	There was a significant difference between the study groups for social class with more Non-							
7 247 8	attenders in the lo	west social c	lass (V) and	a greater n	umber of Att	enders	in the highest	social
9 248 10	classes (I-II).							
11 12 249 13	Moreover, Non-at	tenders had a	a significantl	y higher CC	CI score indica	ating th	at they had m	ore severe
14 250 15	or a greater numb	er of co-occu	rring condit	ions than A	<i>ttenders</i> . The	ey were	also to a grea	iter extent
16 17 251	living alone. Furth	ermore, a no	n-statisticall	y significan	it trend of mo	ore curr	ent smokers v	with a
18 19 252 20	higher wish of smo	oking cessatio	on were see	n among N	on-attenders			
²¹ 22 253	The results of the	third screeni	ng round are	e listed in T	able 2.			
23 ²⁴ 254	Table 2	2. Difference	es in psych	osocial sta	atus in the th	nird scre	eening round	1
25 26 255		_,						
²⁷ 256 28 257 29 258 30		Range of values	Responding rate per item n/n	Attenders n=1388 mean (SD)	Non- attenders- respondents n=260	p-value	Difference in scores between the two groups mean (99%CI)ª	p-value adjusted
31 32				\sim	mean (SD)			
33	COS-scales	0-18	1349/249	1.7 (2.8)	2.1 (3.2)	0.0441	0.28 / 0.12.0.80)	0.0548
34	Anxiety Behaviour	0-18	1343/249	2.1 (3.1)	2.9 (3.8)	0.0441 <0.001	0.38 (-0.13;0.89) 0.77 (0.18;1.36)	<0.0048
35	Dejection	0-18	1354/255	1.9 (3.0)	2.4 (3.5)	0.013	0.49 (-0.06;1.04)	0.0225
86 77	Sleep	0-12	1357/252	1.9 (2.6)	2.3 (3.0)	0.041	0.35 (-0.12;0.82)	0.0599
57 58	COS-LC scale						,	
9	Self-blame	0-15	1356/234	2.2 (2.8)	3.1 (3.8)	<0.001	0.59 (0.14;1.04)	<0.001
0	Focus on airwa		1363/239	0.3 (0.8)	0.6 (1.0)	<0.001	0.22 (0.08;0.36)	<0.001
1	symptoms							
2	Stigmatisation	0-12	1361/241	1.5 (1.9)	2.1 (2.4)	<0.001	0.51 (0.16;0.86)	<0.001
3	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 smol	king 0-6	1356/248	0.9 (1.2)	1.3 (1.6)	<0.001	0.35 (0.11;0.59)	<0.001
5 2 5 9	^{a)} A positive value	of the difference ind	icates that the pers	ons that were inte	erviewed by phone a	and later retu	Irned COS-LC had or	n average higher
6 260	scores, i.e. more r	negative outcomes (e	e.g. higher anxiety)	than the persons	that showed up and	d completed	the COS-LC on site.	The differences
7 261	are adjusted for se	ex, age, region of res	sidence, social grou	up, living alone, si	moking status, pack	years, motiv	ation for smoking ces	sation and CCI.
8 262	The continuous va	lues variables (age	and pack years) ar	e included as a q	uadratic function as	to allow for p	possible nonlinear effe	ects.
⁹ 263								
0								
1 2 264	In the core question	onnaire COS (Consequence	ces of Scree	ening) <i>, Non-a</i>	ttender	s-respondents	s had a
53 54 265 55	statistically signific	cant higher (v	vorse) score	than Atter	nders in the s	cale "Be	ehaviour". Thi	s effect
56 57 266	was still present w	vhen adjustin	g for covaria	ates. Morec	over, there w	as a nor	n-significant tr	end of
58								

of the COS-LC, Non-attenders-respondents had statistically significantly higher scores in all scales

5 6

7

268

p-value

0.018

0.071

<0.001

0.002

0.005

0.579

0.146

0.021

0.422

269 both crude and adjusted. 8 9 270 Table 3 shows differences in psychosocial status between all three subgroups in the second 10 11 12 271 screening round. 13 14 272 15 16 273 17 18 19274 20 21 275 22 23 24 276 Table 3, Differences in psychosocial status in the second screening round 25 26 27 28 Range of values Responding rate Attenders Non-Nonp-value 29 per item n=1388 attendersadjusteda attenders-30 n/n/n respondent non-31 s respondents 32 n=260 n=347 33 COS scales, mean (SD) 34 0-18 1.6 (2.7) 0.003 Anxietv 1201/117/89 2.0 (3.0) 2.6 (3.8) 35 0-21 1.9 (2.9) 0.012 Behaviour 1195/114/88 2.4 (3.3) 2.8 (4.0) 36 Dejection 1.8 (2.8) 0-18 1217/117/87 2.3 (3.3) 3.0 (4.0) < 0.001 37 Sleep 1220/116/88 2.3 (2.9) 2.6 (3.2) <0.001 0-12 1.7 (2.5) 38 COS-LC scales, mean 39 (SD) 40 Self-blame 0-15 1210/118/88 1.7 (2.3) 2.1 (2.4) 2.6(3.0)< 0.001 41 Focus on airway 0-24 1226/118/90 0.4 (0.8) 0.4 (0.8) 0.5 (0.9) 0.408 42 symptoms 43 Stigmatisation 0-12 1225/121/90 1.5 (1.9) 1.8 (2.1) 2.1 (2.4) 0.028 44 Introvert 0-18 1223/116/90 1.3 (1.8) 1.8 (2.0) 1.4 (1.8) 0.012 45 1232/118/89 Harms of smoking 0-6 1.1 (1.3) 1.3 (1.3) 1.2 (1.4) 0.134 46 47 277 48 278 a) A test for differences between the three groups adjusted for sex, age, region of residence, social group, living alone, smoking status, pack years, 49 279 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 ⁵⁰ 280 possible nonlinear effects. 51 281 Non-attenders had significantly worse crude scores compared with Attenders in all but one scale 52 53 54 282 ("Behaviour") in the COS scales. When adjusting for covariates the difference in scores was still 55 56 283 significant in two scales "Dejection" and "Sleep". In the lung cancer specific part, the crude and 57 58 59 284 adjusted "Self-blame"-scale score was significantly worse for Non-attenders. 60

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The differences in psychosocial status in the first screening round between Attenders, Non-5

attenders-respondents and Non-attenders-non-responders showed a statistically significant worse 6

7 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 adjustedª
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.

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Discussion 0

The present study showed considerable non-attendance in the control group of the DLCST. Data in 1 the control group was not missing at random. Non-attenders had less favourable baseline socio-2 3 demographic profile when compared with attenders. More importantly, individuals who did not 4 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-5 5 attendance. Furthermore, these individuals also had worse psychosocial status during their missed 7 round (assessed in the present study in the third round). This cannot be used to adjust differential 8 non-attendance because this information is generally not available but proves the concept. 60

1 2	
3 4 5 309	The use of a condition-specific questionnaire is a strength of the study. Previous research has
6 7 310 8	demonstrated that condition-specific questionnaires are superior to generic questionnaires when
9 311 10	measuring psychosocial consequences in cancer screening settings.[16] Furthermore, we used an
11 12 312 13	appropriate longitudinal design i.e. we collected data at the same timepoints for both Attenders
14 313 15	and Non-attenders at various times in the study, as well as we measured psychosocial status in
16 17 314	both groups at baseline.[17] A limitation of the study is that we did not collect psychosocial
18 19 315 20	outcomes of Non-attenders in the intervention group. This study was designed to gain knowledge
$\frac{21}{22}316$	of factors motivating such a large drop in participation in the control group. In hindsight, data on
23 24 317 25	Non-attenders in the screened group could further help us understand the reasons for differential
26 27 318	non-response.
28 29 319 30	In addition to the DLCST, two other trials assessed psychosocial consequences in lung cancer
³¹ 320 32	screening with low-dose CT.[6,18] Participants in the NELSON trial were invited to complete
33 34 321 35	questionnaires at baseline and at the second round of screening (two years after baseline
36 322 37	screening). Participants in the UKLS completed a questionnaire at baseline, two weeks after
³⁸ 39 323 40	randomisation/CT-scan and 10-29 months after baseline. Unlike the DLCST, in these two trials the
41 324 42	control group were not invited to an annual visit at the screening clinic. Although there were some
⁴³ ₄₄ 325	differences in study design, non-response rates in the control groups in these three trials were
45 46 326 47	similar and in all three trials there was differential non-response between the intervention and
48 49327	control group. Differences between attenders and non-attenders were reported in the UKLS trial.
50 51 328 52	As in the DLCST, non-attenders had worse socio-demographic profile i.e. lower social class, and
53 329 54	they were more likely single, younger and current smokers compared with attenders. However,
55 56 330 57	these were pooled estimates for both the screening group and the control group.
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331	In individuals diagnosed with cancer, anxiety and worse health-related quality of life have been
7 332 3	associated with dropout, which is consistent with our findings.[19] Since Non-attenders in our
333 0	study experienced a higher level of anxiety than Attenders in the first screening round (i.e.
11 12 334 13	baseline), this could have been the motivation for attending the trial; to get reassured of being
14 335 15	healthy.[20] Therefore, randomization to the control group may have caused disappointment, but
16 17 336 18	also attention drawn to not being part of a possibly beneficial intervention.[21] For example, the
19 337 20	secretary in the screening clinic received calls from participants randomized to the control group
²¹ 338 22 338	expressing their disappointment of not being screened. Furthermore, the trial put focus on the
24 339 25	harms of smoking, which could have increased the anxiety and fear of disease in this subgroup
$\frac{26}{27}$ 340	even more, which may have been a reason to subsequent non-attendance. Finally, missing data on
28 29 341 30	psychosocial status in a previous round may also have been a predictor for non-attendance in the
³¹ 342	next screening round, which was not the scope for this study.
33 34 343 35	Low social status, younger age and current smoking status have previously been seen among
36 344 37	dropouts and non-respondents in lung health studies.[22–25] A systematic review reporting
³⁸ 39 345	dropout from longitudinal studies in elderly concluded that higher age and declining health were
41 346 42	high predictors of dropout. The latter is in agreement with our findings, although higher age is in
¹³ 347 14 347 15 16 348 17	contrast to our findings.[26]
¹⁸ 349 19	To our knowledge, this is the first cancer screening study testing hypotheses on reasons for
50 51 350	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

1 2	
3 4 5 353	investigating dropout are consistent with ours. Hence, it is plausible that our results are
6 7 354 8	generalisable to other cancer screening trials as well.
9 10 355	Therefore, future cancer screening trials should concurrently assess psychosocial status during the
11 12 356 13	trial, not only to be able to assess the psychosocial effect of screening, but also to use this
14 357 15	information to adjust any effect in the trial for bias due to differential non-attendance.
16 17 358 18	
19 359 20	Conclusions
21 22 360 23	In conclusion, Non-attenders in the control group in the DLCST had a worse psychosocial status
24 361 25 26	and a less favourable socio-demographic profile than Attenders.
27 362 28	The results of our study contribute with evidence of non-response driven by psychosocial status,
29 363 30 31	which in turn may be influenced by the screening intervention itself. This can be used to adjust
₃₂ 364 33	cancer screening trial results for bias due to differential attendance.
34 365 35 36 2 6 6	Ċ,
37 ³⁶⁶ 38	Abbreviations
39 367 40 41 ₂₆₈	RCT: Randomized controlled trial; PROM: Patient-reported outcome measure; CT: Computed
42 ⁵⁰⁸ 43	tomography; DLCST: Danish Lung Cancer Screening Trial; COS-LC: Consequences of screening in
44 369 45 46 a = 0	lung cancer; COS: Consequences of screening; CCI: Charlson comorbidity index
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49 371 50 51	Declarations
52 372 53	Ethics approval and consent to participate
54 373 55 56	The Ethical Committee of Copenhagen County approved the DLCST including this observational
57 374 58	study nested in the DLCST on 31 January 2003: approval number KA-02045.
59 60	

2 3	
⁴ ₅ 375	All participants signed an informed consent form and received an information letter about the
6 7 376 8	project and information about the ethical approval and data protection agency approval. The trial
9 377 10	is registered in <u>Clinicaltrials.gov</u> Protocol Registration System (identification no. <u>NCT00496977</u>)
11 12 378 13	
14 379 15	Availability of data and materials
16 17 380 18	The corresponding author can provide the questionnaires and datasets generated and analysed
19 381 20	during the study on reasonable request.
²¹ 22 23	
24 383 25	Competing interests
²⁶ 384 27 28	None declared.
29 385 30	
³¹ 386 32 33	Funding
33 34 387 35	This work was supported by the Danish Ministry of Interior and Health, grant number <u>0900814</u> .
36 388 37 28	The funding source had no role in study design, data collection and analysis, decision to publish, or
³⁸ 39 389 40	preparation of the manuscript.
41 390 42	
43 44 45	Author contributions
46 392 47	JB and HT developed and designed the study. JB, HT and the DLCST staff collected data. VS
⁴⁸ 393 49 50	performed the statistical analyses. JM drafted the manuscript. JB, HT, BH, JFR, and VS all
51 394 52	contributed to parts of the manuscript as well as revisions of the manuscript. All authors approved
53 395 54 55 20 (the final version of the manuscript, and no editorial assistance was received. All authors had full
56 ³⁹⁶ 57	access to all data in the study and are responsible of data retention and the accuracy of the data
58 397 59 60	analysis. JM and JB are guarantors of the study.

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6 7 399 8	Acknowledgement
9 400 10	We wish to thank data manager Willy Karlslund for his contribution to generation of the databases
11 12 401 13	and we also wish to thank the DLCST steering committee.
¹⁴ 402 15 16	
17 18 403 19	Fig.1 Flowchart, DLCST
20 21 404 22	Fig.2 Flowchart, present study
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1 2	
3 4 5 406 6	References
8 407	1. Tierney JF. Investigating patient exclusion bias in meta-analysis. Int J Epidemiol [Internet].
9 10 408 11	2004;34:79–87. Available from: https://academic.oup.com/ije/article-
¹² 13 409 14	lookup/doi/10.1093/ije/dyh300
$^{15}_{16}410$	2. Zhang Y, Alyass A, Vanniyasingam T, Sadeghirad B, Flórez ID, Pichika SC, et al. A systematic
17 18 41 1 19	survey of the methods literature on the reporting quality and optimal methods of handling
²⁰ 412 21	participants with missing outcome data for continuous outcomes in randomized controlled trials. J
22 23 413 24	Clin Epidemiol [Internet]. 2017;88:67–80. Available from:
25 414 26	http://www.ncbi.nlm.nih.gov/pubmed/28579378
27 28 415 29	3. Dufouil C, Brayne C, Clayton D. Analysis of longitudinal studies with death and drop-out: a case
³⁰ 31416	study. Stat Med [Internet]. 2004;23:2215–26. Available from:
32 33 417 34	http://www.ncbi.nlm.nih.gov/pubmed/15236426
35 36 418 37	4. Humphrey LL, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP, et al. Screening for lung
³⁸ 419 39	cancer with low-dose computed tomography: a systematic review to update the US Preventive
40 41 42	services task force recommendation. Ann Intern Med [Internet]. 2013 [cited 2014 Feb
43 421 44	26];159:411–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23897166
45 46 422 47	5. Wu GX, Raz DJ, Brown L, Sun V. Psychological Burden Associated With Lung Cancer Screening: A
48 49423	Systematic Review. Clin Lung Cancer [Internet]. 2016;17:315–24. Available from:
50 51 424 52	http://linkinghub.elsevier.com/retrieve/pii/S1525730416300535
53 54 425	6. Brain K, Lifford KJ, Carter B, Burke O, McRonald F, Devaraj A, et al. Long-term psychosocial
55 56 426 57	outcomes of low-dose CT screening: results of the UK Lung Cancer Screening randomised
⁵⁸ 427 60	controlled trial. Thorax [Internet]. 2016;71:996–1005. Available from:

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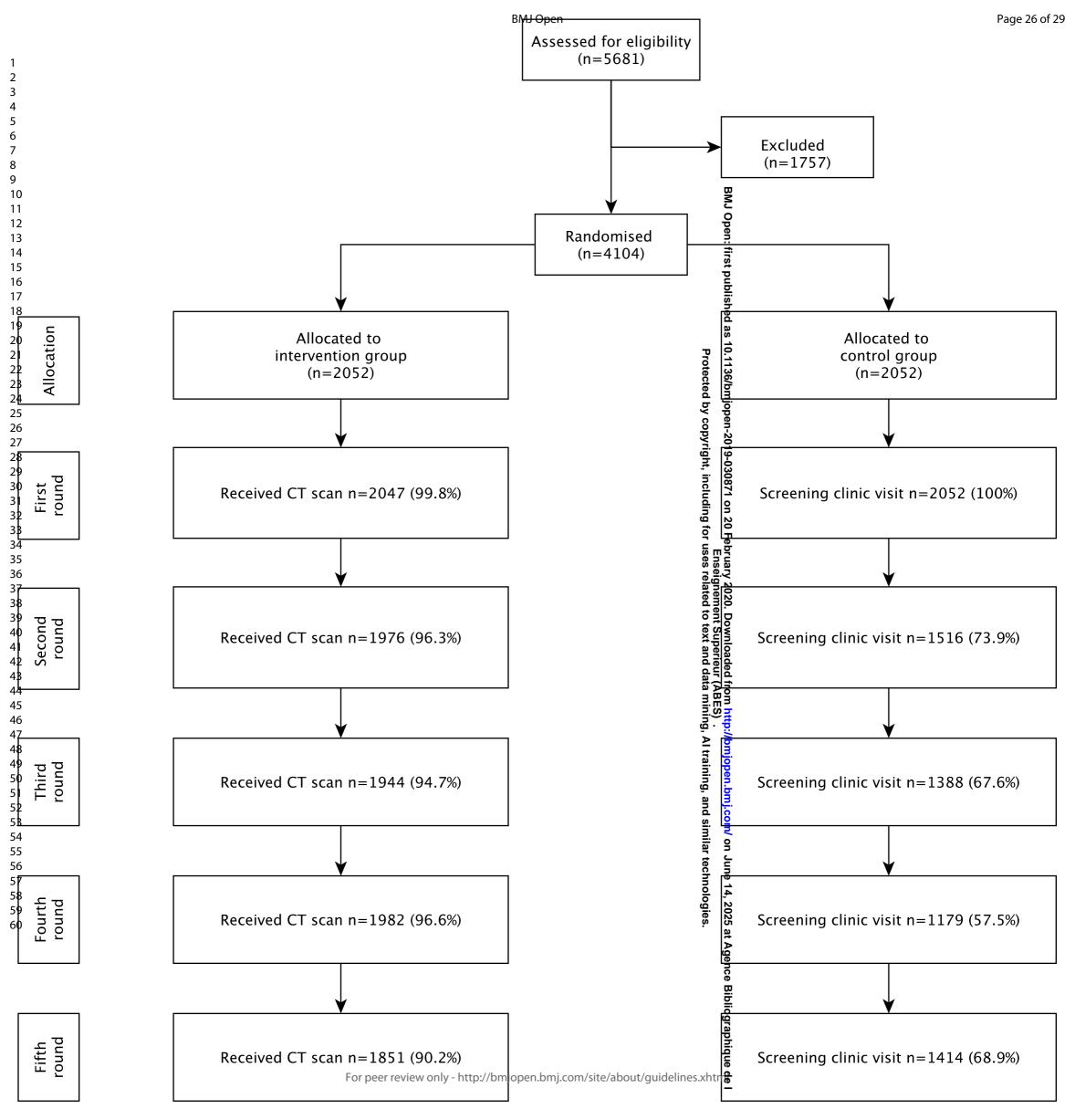
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3 4 ₄₂₈	
⁴ 428 5	http://thorax.bmj.com/lookup/doi/10.1136/thoraxjnl-2016-208283
б	
7 429	7. Rasmussen JF, Siersma V, Pedersen JH, Brodersen J. Psychosocial consequences in the Danish
8	
9 10 430	randomised controlled lung cancer screening trial (DLCST). Lung Cancer [Internet]. 2015;87:65–72.
10	
12 431	Available from: http://www.ncbi.nlm.nih.gov/pubmed/25433982
13	
14	
15 432 16	8. Pedersen JH, Ashraf H, Dirksen A, Bach K, Hansen H, Toennesen P, et al. The Danish randomized
17	
¹⁷ 433	lung cancer CT screening trialoverall design and results of the prevalence round. J Thorac Oncol
19	
20 434	[Internet]. 2009 [cited 2013 Sep 18];4:608–14. Available from:
21	
²² 435 23	http://www.ncbi.nlm.nih.gov/pubmed/19357536
24	
²⁵ 436	9. Brodersen J, Thorsen H, Kreiner S. Consequences of screening in lung cancer: development and
26 27	
27 28 437	dimensionality of a questionnaire. Value Health [Internet]. 2010 [cited 2013 Oct 1];13:601–12.
29	
30 4 38	Available from: http://www.ncbi.nlm.nih.gov/pubmed/20345552
31	
32 33 439	10. Aggestrup LM, Hestbech MS, Siersma V, Pedersen JH, Brodersen J. Psychosocial consequences
33 4 5 7 34	10. Aggestrup Livi, hestbech wis, siersina v, redersen sin, brodersen s. rsychosocial consequences
³⁵ 440	of allocation to lung cancer screening: a randomised controlled trial. BMJ Open [Internet]. 2012
30	of anocation to fung cancer screening, a randomised controlled that, bivis Open [internet], 2012
37 38 441	[cited 2013 Oct 1];2:e000663. Available from:
38 44 I 39	
⁴⁰ 442	http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3293139&tool=pmcentrez&renderty
442	http://www.pubmedcentral.nin.gov/articlerender.rtgi?artid=5295159&t001=pmcentrez&renderty
42	no-abstract
43 443	pe=abstract
44 45 444	
45 444 46	11. Heydarpour B, Saeidi M, Ezzati P, Soroush A, Komasi S. Sociodemographic Predictors in Failure
47	
48 445	to Complete Outpatient Cardiac Rehabilitation. Ann Rehabil Med [Internet]. 2015;39:863–71.
49 50	
⁵⁰ 446 51	Available from: http://www.ncbi.nlm.nih.gov/pubmed/26798599
52	
⁵³ 447	12. de Graaf R, van Dorsselaer S, Tuithof M, ten Have M. Sociodemographic and psychiatric
54	
55 56 448	predictors of attrition in a prospective psychiatric epidemiological study among the general
57	
58 449	population. Result of the Netherlands Mental Health Survey and Incidence Study-2. Compr
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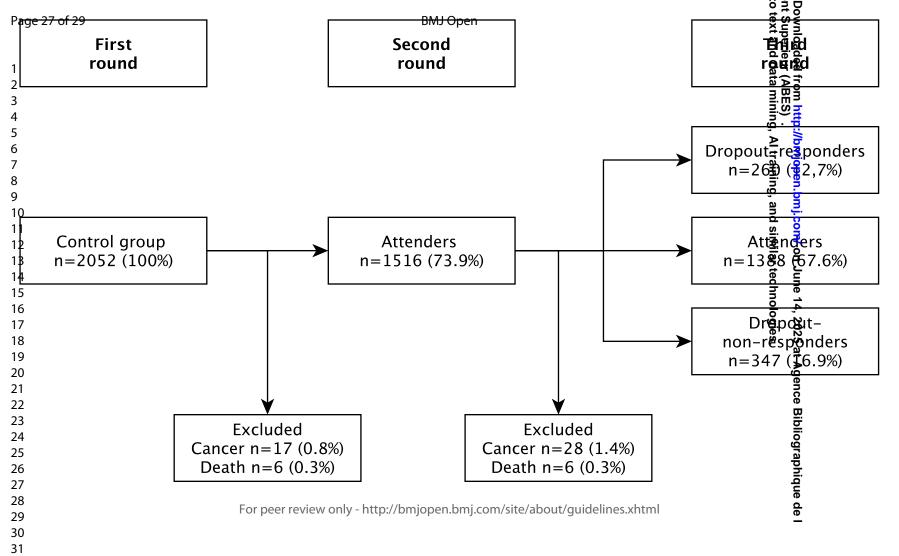
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1 2	
3 4 5 450	Psychiatry [Internet]. 2013;54:1131–9. Available from:
6 7 451 8	http://linkinghub.elsevier.com/retrieve/pii/S0010440X13001284
9 10 452 11	13. Field JK, Duffy SW, Baldwin DR, Whynes DK, Devaraj A, Brain KE, et al. UK Lung Cancer RCT Pilot
12 453 13	Screening Trial: baseline findings from the screening arm provide evidence for the potential
$^{14}_{15}454$	implementation of lung cancer screening. Thorax [Internet]. 2015;1–10. Available from:
16 17 455 18	http://www.ncbi.nlm.nih.gov/pubmed/26645413
19 20 456 21	14. McCaffery KJ. Assessing psychosocial/quality of life outcomes in screening: how do we do it
²² 457 23	better? J Epidemiol Community Heal [Internet]. 2004;58:968–70. Available from:
24 25 458 26	http://jech.bmj.com/cgi/doi/10.1136/jech.2004.025114
27 28 459	15. Brodersen J, Thorsen H. Consequences of Screening in Breast Cancer (COS-BC): development of
29 30 460 31	a questionnaire. Scand J Prim Health Care [Internet]. 2008 [cited 2013 Oct 1];26:251–6. Available
³² 33 461	from:
34 35 462 36	http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3406644&tool=pmcentrez&renderty
³⁷ 463 38 39	pe=abstract
40 464 41	16. Brodersen J, Thorsen H, Cockburn J. The adequacy of measurement of short and long-term
42 43 465 44	consequences of false-positive screening mammography. J Med Screen. 2004;11:39–44.
45 46 46	17. DeFrank JT, Barclay C, Sheridan S, Brewer NT, Gilliam M, Moon AM, et al. The psychological
47 48 467 49	harms of screening: the evidence we have versus the evidence we need. J Gen Intern Med
⁵⁰ 468 51 52	[Internet]. 2015;30:242–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25150033
⁵³ 469 54	18. van den Bergh KAM, Essink-Bot ML, Borsboom GJJM, Scholten ET, van Klaveren RJ, de Koning
55 56 470 57	HJ. Long-term effects of lung cancer computed tomography screening on health-related quality of
57 58 471 59 60	life: the NELSON trial. Eur Respir J [Internet]. 2011 [cited 2014 Oct 3];38:154–61. Available from:

1 2	
3	
4 5 6	http://www.ncbi.nlm.nih.gov/pubmed/21148229
7 473 8	19. Mercieca-Bebber RL, Price MA, Bell ML, King MT, Webb PM, Butow PN, et al. Ovarian cancer
9 10 474 11	study dropouts had worse health-related quality of life and psychosocial symptoms at baseline and
12 475 13	over time. Asia Pac J Clin Oncol [Internet]. 2017;13:e381–8. Available from:
14 15 476 16	http://www.ncbi.nlm.nih.gov/pubmed/27573704
17 18 477	20. Østerø J, Siersma V, Brodersen J. Breast cancer screening implementation and reassurance. Eur
19 20 478 21	J Public Health. 2014;24:258–63.
22 23 479	21. Wendler D, Krohmal B, Emanuel EJ, Grady C. Why patients continue to participate in clinical
24 25 480 26	research. Arch Intern Med [Internet]. 2008 [cited 2013 Oct 1];168:1294–9. Available from:
27 28 481 29	http://www.ncbi.nlm.nih.gov/pubmed/18574086
³⁰ 31482	22. Snow WM, Connett JE, Sharma S, Murray RP. Predictors of attendance and dropout at the Lung
32 33 483 34	Health Study 11-year follow-up. Contemp Clin Trials [Internet]. 2007;28:25–32. Available from:
³⁵ 484 36 37	http://linkinghub.elsevier.com/retrieve/pii/S1551714406001157
³⁸ 485 39	23. Nohlert E, Öhrvik J, Helgason ÁR. Non-responders in a quitline evaluation are more likely to be
40 41 486 42	smokers - a drop-out and long-term follow-up study of the Swedish National Tobacco Quitline. Tob
43 487 44 45	Induc Dis [Internet]. 2016;14:5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26843854
46 488 47	24. Abrahamsen R, Svendsen MV, Henneberger PK, Gundersen GF, Torén K, Kongerud J, et al. Non-
⁴⁸ 489 49 50	response in a cross-sectional study of respiratory health in Norway. BMJ Open [Internet].
51 490 52	2016;6:e009912. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26739738
53 54 491 55	25. Oleske DM, Kwasny MM, Lavender SA, Andersson GBJ. Participation in occupational health
56 492 57	longitudinal studies: predictors of missed visits and dropouts. Ann Epidemiol [Internet].
58 59 493 60	2007;17:9–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17140810

2 3	
4 5 494	26. Chatfield MD, Brayne CE, Matthews FE. A systematic literature review of attrition between
6 7 495 8	waves in longitudinal studies in the elderly shows a consistent pattern of dropout between
9 10 9	differing studies. J Clin Epidemiol [Internet]. 2005 [cited 2014 Mar 13];58:13–9. Available from:
11 12 497 13	http://www.ncbi.nlm.nih.gov/pubmed/15649666
14 15 498	27. Rotnitzky A, Robins J. Analysis of semi-parametric regression models with non-ignorable non-
16 17 499 18	response. Stat Med [Internet]. 16:81–102. Available from:
¹⁹ 500	http://www.ncbi.nlm.nih.gov/pubmed/9004385
21 22 501 23	
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25 26	
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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	(<i>a</i>) 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	1
		what was done and what was found	1
Introduction			1
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	5
C		of recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and	6
1		methods of selection of participants. Describe methods of follow-up	
		<i>Case-control study</i> —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	
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources	
		and methods of selection of participants	
		(b) Cohort study—For matched studies, give matching criteria and	Not
		number of exposed and unexposed	applicable
		Case-control study—For matched studies, give matching criteria	application
		and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential	6 and 7
variables	,	confounders, and effect modifiers. Give diagnostic criteria, if applicable	o and 7
Data sources/	8*	For each variable of interest, give sources of data and details of	
measurement	0	methods of assessment (measurement). Describe comparability of	
medsurement		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
, ,		1 5	applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If	6-8
C		applicable, describe which groupings were chosen and why	
Statistical methods	12	(<i>a</i>) Describe all statistical methods, including those used to control	7-8
Statistical methods	12	for confounding	
		(<i>b</i>) Describe any methods used to examine subgroups and	7
		interactions	/
		(c) Explain how missing data were addressed	Not applicable
		(<i>d</i>) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	Not applicable
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	

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	<i>Cross-sectional study</i> —If applicable, describe analytical methods
	taking account of sampling strategy
	(<u>e</u>) Describe any sensitivity analyses
Continued on next page	
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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially	Fig.1
1		eligible, examined for eligibility, confirmed eligible, included in the study,	
		completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Fig.2
		(c) Consider use of a flow diagram	Fig.2
Descriptive	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and	7
data		information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	Table
		(c) <i>Cohort study</i> —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
		<i>Case-control study</i> —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	Table
		their precision (eg, 95% confidence interval). Make clear which confounders were	2-4
		adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	N/A
		(<i>c</i>) 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		6.	
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	10
		imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	10
		multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-
			12
Other informati	on		
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.

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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Secondary Subject Heading:	Research methods, General practice / Family practice
Keywords:	Bias, Mass screening, Lung neoplasms, Patient dropout

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1	Did psychosocial status, sociodemographics and smoking status
2	affect non-attendance in control participants in the Danish Lung
3	Cancer Screening Trial? A nested observational study
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3	Keywords
)	bias, mass screening, lung neoplasms, patient dropouts
)	Word count 2780

2		
4 5 6	21	Abstract
7 8	22	Objectives: We investigated if psychosocial status, socio-demographics and smoking status
9 10 11	23	affected non-attendance in the control group in the randomized Danish Lung Cancer Screening
12 13	24	Trial (DLCST).
14 15 16	25	Design & setting: This study was an observational study nested in the DLCST. Due to large non-
16 17 18	26	attendance in the control group in the second screening round we made an additional effort to
19 20	27	collect questionnaire data from non-attenders in this group in the third screening round. We used
21 22 23	28	a condition-specific questionnaire to assess psychosocial status. We analysed the differences in
24 25	29	psychosocial status in the third and preceding rounds between non-attenders and attenders in the
26 27 28	30	control group in multivariable linear regression models adjusted for socio-demographics and
20 29 30	31	smoking status reported at baseline. Differences in socio-demographics and smoking status were
31 32 33	32	analysed with chi-squared tests (categorical variables) and t-tests (continuous variables).
33 34 35	33	Primary outcome measure: Primary outcome was psychosocial status.
36 37	34	Participants: All control persons participating in the third screening round in the DLCST were
38 39 40	35	included.
41 42	36	Results: Non-attenders in the third round had significantly worse psychosocial status than
43 44 45	37	attenders in the scales: "Behaviour" 0.77 (99% CI 0.18;1.36), "Self-blame" 0.59 (99% CI 0.14;1.04),
46 47	38	"Focus on airway symptoms" 0.22 (99% CI 0.08;0.36), "Stigmatisation" 0.51 (99% CI 0.16;0.86),
48 49	39	"Introvert" 0.56 (99% CI 0.23;0.89), and "Harms of smoking" 0.35 (99% CI 0.11;0.59). Moreover,
50 51 52	40	non-attenders had worse scores than attendees in the preceding screening rounds. Non-attenders
53 54	41	also reported worse socio-demographics at baseline.
55 56 57	42	Conclusions: Non-attenders had a significantly worse psychosocial status and worse socio-
58 59	43	demographics compared with attenders. The results of our study contribute with evidence of non-
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4 5 6	44	response and attrition driven by psychosocial status, which in turn may be influenced by the
7 8	45	screening intervention itself. This can be used to adjust cancer screening trial results for bias due
9 10 11	46	to differential non-attendance.
12 13	47	Trial registration: The trial is registered in <u>Clinicaltrials.gov</u> Protocol Registration System
14 15 16	48	(identification no. <u>NCT00496977</u>)
17 18	49	
19 20 21	50	Article summary
22 23	51	Strengths and limitations
24 25 26	52	Use of a condition-specific questionnaire with adequate psychometric properties ensured
27 28 29	53	valid measures.
30 31	54	Patient-reported data on non-respondents gave valuable empirical insight in drivers for
32 33 34	55	non-attendance.
35 36	56	Testing a previously hypothesized model for non-attendance empirically is another
37 38 39	57	strength of the study.
40 41 42	58	No comparison between non-attenders in the intervention and the control group was
42 43 44	59	performed.
45 46	60	 No longer-term follow up on non-attenders was performed.
47 48 49	61	
50 51	62	Introduction
52 53 54	63	Non-attendance may affect trial results and introduce bias in randomized controlled trials
55 56 57	64	(RCTs).(1,2) Non-attendance reduces the power of the trial and, if non-attendance differs between
57 58 59 60	65	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

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participants were asked to complete a condition-specific questionnaire, measuring psychosocial

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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 sociodemographic 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

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3	
4 111 5	The design and study population of DLCST have been described in detail previously.(7,8) Briefly,
6 7 112 8	the DLCST was an RCT, conducted at the Copenhagen University hospital Gentofte in Denmark
9 113 10	from October 2004 to March 2010. Heavy current and former smokers (at least 20 pack-years),
11 12 114 13	aged 50-70 years old, were randomized to either five rounds of screening with low-dose CT-scans
14 115 15	including clinical examinations (n=2052) or five clinical examinations only (n=2052). In the
16 17 116	enrolment visit, participants provided socio-demographic data, lifestyle and health information
18 19 117 20	(including smoking status), completed a questionnaire on their psychosocial status and underwent
21 22 118	spirometry. Participants randomized to screening also had a low-dose chest CT-scan within one
23 24 119 25	month of randomisation. In the following screening rounds, participants in the screened and
²⁶ 120 27	control groups were invited to a visit in the screening clinic where lung function tests were
28 29 121 30	performed, and questionnaires concerning health, lifestyle, smoking habits and psychosocial
³¹ 122 32	status were completed and lung function tests were performed. Participants randomized to
33 34 123 35	screening also received a low-dose chest CT-scan.
36 124 37	This study is an observational study nested in the DLCST. During the second screening round, the
³⁸ 39 125 40	steering committee noted that a large number of control participants did not attend the screening
40 41 126 42	clinic visit when compared with the number of screened participants. Thus, the committee
⁴³ 127	decided to make additional efforts to collect questionnaire data for non-attenders in the control
45 46 128 47	group in the third screening round to perform post hoc analyses on whether psychosocial status
⁴⁸ 129 49	was an influencing factor (Fig.2).
50 51 130 52	During the third round, participants in the control group who did not attend the annual
53 131 54	examination were contacted by phone and part 1 of the questionnaire was sent with a postage
55 56 57 58 59 60	paid envelope to those who gave their oral consent. The data was used to supplement the data

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1 2	
3 4 122	collected on site at the coreaning clinic (7) This violded three groups within the control group
4 133 5 6	collected on site at the screening clinic.(7) This yielded three groups within the control group,
7 134 8	denoting the extent of response to the clinical examination and the questionnaire defined as:
9 135 10	
11 12 136 13	1. Attenders: participants who attended the third screening round.
14 137 15	2. Non-attenders:
16 17 138	a) <u><i>Respondents</i></u> : participants who did not attend the annual examination but
18 19 139 20	completed and returned the COS-LC after the phone interview.
²¹ 22 140	b) <i>Non-respondents</i> : participants who did not attend the annual examination and did
23 24 141 25	not complete the COS-LC.
25 26 27 142	
28 29 143	Outcomes & Questionnaires
30 31 144 32	Primary outcome was psychosocial status measured with the Consequences Of Screening for Lung
33 34 145	Cancer (COS-LC) questionnaire.(9) Part 1 of COS-LC comprised nine scales measuring various
35 36 146 37	aspects of consequences of screening; a second part of COS-LC addressed the screening outcome
38 39 147	and was therefore not applicable to the present analysis. Moreover, the primary part of COS-LC
40 41 148	included four core scales: "Anxiety", "Behaviour", "Dejection" and "Sleep" that are not lung cancer
42 43 44 149	specific. These scales have originally been developed from a breast cancer screening assessment
45 46 150	instrument.(15) Additionally COS-LC comprised five lung cancer specific scales: "Self-blame",
47 48 49 151	"Focus on airway symptoms", "Stigmatisation", "Introvert", and "Harm of smoking", which were
50 51 152	developed from focus groups and other screening assessment instruments during the first DLCST
52 53 153 54	screening round.(9,15) Therefore, only the core scales were used in the first round, while in the
55 56 154	following four screening rounds both the core scales and the lung cancer specific scales were used
57 58 155	to assess psychosocial status.(9)
59 60	

1 2		
3 4 5	156	Statistics
6 7	157	Covariates
8 9 10	158	Socio-demographic characteristics were defined by: social class (I highest social class to V lowest
11 12	159	social class), school and vocational education (from 9 years of elementary school to a university
13 14 15	160	education), employment status, living alone, smoking status (current or former smoker), smoking
	161	history (pack-years), motivation for smoking cessation (from very strong to no wish to quit) and
18 19 20	162	Charlson Comorbidity Index (CCI). Furthermore, we adjusted for region of residence (Denmark is
21 22	163	divided into five health-administrative regions).
23 24 25	164	
26 27	165	Statistical analyses
28 29 30	166	We performed three different analyses:
31 32	167	1. Analyses of differences in psychosocial status in the third round between Attenders and
33 34 35	168	Non-attenders-respondents.
36 37	169	2. Analyses of differences in psychosocial status in the second round between Attenders,
38 39 40	170	Non-attenders-respondents and Non-attenders-non-respondents.
41 42		3. Analyses of differences in psychosocial status in the first round, between Attenders, Non-
43 44 45	172	attenders-respondents and Non-attenders-non-respondents.
46 47	173	Covariates at the first screening round were compared between Attenders and Non-attenders by
48 49 50	174	chi-squared tests (categorical characteristics) and t-tests (continuous characteristics). Analyses of
50 51 52	175	psychosocial status at various points in the follow-up were performed in linear regression models
54	176	both unadjusted and in multivariable models adjusted for sex, age, region of residence, social
55 56 57	177	class, living alone, smoking status, pack years, motivation for smoking cessation and CCI. To adjust
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3	1 = 0	
5 6	178	for multiple testing we used the Benjamini-Hochberg procedure and the False Discovery Rate
	179	(FDR) was set to 5% (16). All analyses were performed with SAS 9.4 (SAS Institute, Inc., Cary, NC).
~	180	
	181	Patient and Public Involvement
15	182	Patients and public were not involved in the design of the study.
16 17 18	183	
19 20	184	Results
23	185	The inclusion process and participation rate of the DLCST are illustrated in Figure 1. The
24 25 26	186	participation rate in the control group fell from 73.9% in the second round to 57.5% in the fourth
	187	round. The participation rate increased in the fifth, final, round (68.9%).
29 30 31	188	Figure 2 depicts the inclusion process of the present study and showed a dropout rate of 29.6%
32 33	189	(n=607) in the third screening round with a higher distribution of <i>Non-attenders-non-respondents</i>
34 35 36	190	(16.9% n=347) compared with <i>Non-attenders-respondents</i> (12.7% n=260).
37 38	191	In the first screening round we compared differences in socio-demographic characteristics in the
39 40 41	192	two overarching groups (Attenders, Non-attenders) (Table 1).
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Table 1, Socio-demographics

	Missing	Attenders	Non-attenders	p-value
	observations,			
	total	n=1388	n=607	
Covariates	n	n (%)**	n(%)**	
Sex	0			0.0963
Male		773 (55.7)	313 (51.6)	
Female		615 (44.3)	294 (48.4)	
Age, <i>mean (SD)</i>	0	57.4 (4.7)	56.9 (4.9)	0.0538
Social class	12			0.0079
l (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		363 (26.2)	153 (25.3)	
school				
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, <i>mean (SD)</i>		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)	

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) 0.424 Motivation for smoking cessation 30 0.054 Very strong 141 (10.3) 74 (12.4) 74 (12.4) Strong 324 (23.7) 166 (27.8) 94 Weak 331 (24.2) 144 (24.8) 94 Very weak 116 (8.5) 42 (7.0) 94 No wish to quit 113 (8.3) 54 (9.0) 118 (19.7)	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) 0.42 Motivation for smoking cessation 30 0.05 0.05 Very strong 141 (10.3) 74 (12.4) 0.05 Strong 324 (23.7) 166 (27.8) 0.05 Weak 331 (24.2) 1144 (24.8) 0.05 Very weak 116 (8.5) 42 (7.0) 0.05 No wish to quit 113 (8.3) 54 (9.0) 0.05 Current non-smoker 342 (25.0) 118 (19.7) 0.05	Smoking status	0			0.01
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		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						
	* Benjamini-Hochberg rejects all p-values above 0.0321 to control the FDR at 0.05	* Benjamini-Hochberg rejects all p-value	s above 0.0321	to control the FDR at 0.0	15	

1 2								
3 4 5 247	There was a significant	differen	ice between	the study	groups for sc	ocial clas	s with more <i>I</i>	lon-
6 7 248 8	attenders in the lowest	social c	lass (V) and	a greater n	number of At	tenders	in the highest	social
9 10 249	classes (I-II).							
11 12 250 13	Moreover, Non-attenders had a significantly higher CCI score indicating that they had more severe							
¹⁴ 251 15	or a greater number of co-occurring conditions than Attenders. They were also to a greater extent							
$^{16}_{17}252$	living alone. Furthermo	ore, ther	e were signi	ficantly mo	ore current sr	nokers a	and a non-sigr	nificant
18 19 253 20	trend of a higher wish t	to quit si	moking in th	ne group of	Non-attende	ers comp	oared with Att	enders.
²¹ 22 ²⁵⁴	The results of the third	screenii	ng round are	e listed in T	able 2.			
23 24 255 25	Table 2, Dr	fference	es in psych	osocial sta	atus in the th	nird scre	eening round	I
26 256 27 257				A #	Nee		Difference in	
²⁸ 258 ²⁹ 259 30		Range of values	Responding rate per item n/n	Attenders n=1388 mean (SD)	Non- attenders- respondents n=260	p-value*	Difference in scores between the two groups mean (99%Cl)ª	p-value adjusted*
31 32					mean (SD)			
33	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
34	Behaviour	0-18	1343/246	2.1 (3.1)	2.9 (3.8)	< 0.001	0.77 (0.18;1.36)	<0.001
35 36	Dejection	0-18	1354/255	1.9 (3.0)	2.4 (3.5)	0.013	0.49 (-0.06;1.04)	0.0225
30 37	Sleep	0-12	1357/252	1.9 (2.6)	2.3 (3.0)	0.041	0.35 (-0.12;0.82)	0.0599
38	COS-LC scales			(,			,,	
39	Self-blame	0-15	1356/234	2.2 (2.8)	3.1 (3.8)	<0.001	0.59 (0.14;1.04)	<0.001
40	Focus on airway	0-24	1363/239	0.3 (0.8)	0.6 (1.0)	<0.001	0.22 (0.08;0.36)	<0.001
41	symptoms							
42	Stigmatisation	0-12	1361/241	1.5 (1.9)	2.1 (2.4)	<0.001	0.51 (0.16;0.86)	<0.001
43	Introvert	0-18	1361/243	1.3 (1.8)	1.8 (2.2)	<0.001	0.56 (0.23;0.89)	<0.001
44	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
45 260	^{a)} A positive value of the d	ifference indi	cates that the pers	sons that were int	erviewed by phone	and later retu	Irned COS-LC had or	average higher
46 261	scores, i.e. more negative	outcomes (e	e.g. higher anxiety)) than the persons	s that showed up an	d completed	the COS-LC on site.	The differences
47 262	are adjusted for sex, age,	region of res	idence, social grou	up, living alone, s	moking status, pack	years, motiv	ation for smoking ces	sation and CCI.
48 263	The continuous values va	riables (age a	and pack years) ar	e included as a q	uadratic function as	to allow for p	oossible nonlinear eff	ects.
⁴⁹ 264	* Benjamini-Hochberg rejec	ts all p-values	above 0.0321 to cor	ntrol the FDR at 0.0)5.			
⁵⁰ 265 51 52		·						
53 266 54	In the core questionnai	ire COS (Consequen	ces of Scree	ening), Non-d	attender	s-respondents	had a
⁵⁵ 267 56	statistically significant l	nigher (v	vorse) score	e than Atter	<i>nders</i> in the s	cales "B	ehaviour" and	k
57 58 268 59 60	"Dejection". These effe	ects were	e still preser	nt when adj	justing for co	variates	. Moreover, t	nere was a

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⁴ 269	non-significant trend of worse scores in all COS scales among Non-attenders-respondents. In the
5 209	non-significant trend of worse scores in an COS scales among Non-attenders-respondents. In t

6 270 lung cancer specific part of the COS-LC, Non-attenders-respondents had statistically significantly 7

9 271 higher scores in all scales both crude and adjusted. 10

11 12 272 Table 3 shows differences in psychosocial status between all three subgroups in the second

14 273 screening round. 15

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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- respondent s n=260	Non- attenders- non- respondents n=347	p-value*	p-value adjusted ^{at}
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	0-24	1226/118/90	0.4 (0.8)	0.4 (0.8)	0.5 (0.9)	0.408	0.579
symptoms							
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

50 ₅₁ 280

a) A test for differences between the three groups adjusted for sex, age, region of residence, social group, living alone, smoking status, pack years,

₅₂ 281 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 ₅₃ 282 possible nonlinear effects. 54 283

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

56285 Non-attenders had significantly worse crude scores compared with Attenders in all the COS scales.

58 286 When adjusting for covariates the difference in scores was still significant in the three scales

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$\frac{4}{5}$ 287	"Anxiety	", "Dejection	" and "Sle	eep". In the lu	ung cancer	specific part	t, the crude	and adjust	ed "Self-
6 7 288	blame" a	and "Introver	t"-scale s	cores were si	gnificantly	worse for N	on-attendei	rs. The diffe	erence in
8 9 289 10	"Stigmat	tisation" scale	e score wa	as statistically	/ significan	t in the unac	ljusted anal	yses, but	
11 12 290	disappeared in the adjusted analyses.								
13 14 291 15	The diffe	erences in psy	chosocia	l status in the	e first scree	ening round l	between At	tenders, No	on-
16 17 292	attenders-respondents and Non-attenders-non-responders showed a statistically significant worse								
18 19 293	unadjust	ted score in a	ll COS-sca	ales, for the ty	wo Non-at	tenders subg	roups (Tabl	e 4). That e	effect
20 21 22 294	disappea	ared in all but	one scal	e, "Anxiety" v	vhen adjus	sting for cova	ariates.		
23									
24 295 25 <u>296</u>		Table 4	Differen	ces in psycho	osocial sta	tus in the fir	st screening	round	
26			Range	Responding rate	Attenders	Non-attenders-	Non-	p-value*	p-value
²⁷ 297 28			of values	per item n/n/n	n=1388 mean (SD)	respondents n=260	attenders- non-	produc	adjusted ^{a*}
29 200			Vulues	.,,,,,		mean (SD)	respondents n=347		
30 21							mean (SD)		
³¹ 32 299		COS-scales Anxiety	0-18	1353/253/334	1.46 (2.16)	1.75 (2.54)	2.11 (2.66)	<0.001	0.0028
33 200		Behaviour	0-21	1365/257/340	0.75 (1.89)	1.05 (2.44)	1.04 (2.43)	0.0134	0.0976
³³ ₃₄ 300		Dejection Sleep	0-18 0-12	1372/257/339 1368/253/344	1.25 (2.05) 0.62 (1.64)	1.54 (2.48) 0.86 (1.98)	1.68 (2.33) 0.90 (1.86)	0.0018 0.0072	0.0512 0.0530
$\frac{35}{36}301$									
$\frac{37}{38}$ 302									
20 303	^{a)} The differer	nces are adjusted for	sex, age, regi	on of residence, soci	al group, living a	lone, smoking statu	is, pack years, mo	tivation for smok	ing cessation
40 304	and CCI. The	e continuous values v	ariables (age a	and pack years) are i	included as a qu	adratic function as t	o allow for possibl	e nonlinear effec	ets.
41 305	* Benjamini-Ho	ochberg rejects all p-va	ues above 0.03	21 to control the FDR a	at 0.05.				
42 306									
43 44 307	Discuss	sion							
44 ⁵⁰⁷ 45									
46 308	The pres	ent study sho	owed con	siderable nor	n-attendan	ice in the cor	ntrol group	of the DLC	ST. Data in
47 49									
48 49 309	the cont	rol group was	s not miss	sing at randor	n. Non-att	enders had l	ess favoura	ble baselin	e socio-
50									
51 310	demogra	aphic profile v	when com	npared with a	ttenders.	More import	antly, indiv	iduals who	did not
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⁵³ 311 54	attend t	heir annual cl	inical wo	rk-up had wo	rse psycho	osocial status	than the in	idividuals v	vho
55 56 312 57	attended	d the clinic in	the previ	ous rounds. T	This can be	used to adju	ust for diffe	rential non	-
⁵⁸ 313 59	attendar	nce. Furtherm	ore, thes	e individuals	also had v	vorse psycho	osocial statu	s during th	eir missed
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3 4 5 314	round (assessed in the present study in the third round). This cannot be used to adjust differential
6 7 315 8	non-attendance because this information is generally not available but proves the concept.
9 10 ³¹⁶	The use of a condition-specific questionnaire is a strength of the study. Previous research has
11 12 317 13	demonstrated that condition-specific questionnaires are superior to generic questionnaires when
14 318 15	measuring psychosocial consequences in cancer screening settings.(17) Furthermore, we used an
16 17 319 18	appropriate longitudinal design i.e. we collected data at the same timepoints for both Attenders
19 320 20	and <i>Non-attenders</i> at various times in the study, as well as we measured psychosocial status in
²¹ 22 23	both groups at baseline.(18) A limitation of the study is that we did not collect psychosocial
24 322 25	outcomes of Non-attenders in the intervention group. This study was designed to gain knowledge
²⁶ 323 27 28	of factors motivating such a large drop in participation in the control group. In hindsight, data on
29 324 30	Non-attenders in the screened group could further help us understand the reasons for differential
³¹ 325 32 ³³	non-response.
₃₄ 326 35	In addition to the DLCST, two other trials assessed psychosocial consequences in lung cancer
33	
36 327 37	screening with low-dose CT.(6,19) Participants in the NELSON trial were invited to complete
36 327	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
36 327 37 38 39 328 40 41 329 42	
36 327 37 38 39 328 40 41 329 42 43 330	questionnaires at baseline and at the second round of screening (two years after baseline
36 327 37 38 39 328 40 41 329 42 43 330 45 46 331 47	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
36 327 37 38 39 328 40 41 329 42 43 330 44 330 45 46 331 47 48 332 49	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
36 327 37 38 39 328 40 41 329 42 43 330 45 46 331 47 48 332 49 50 51 333 52	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
36 327 37 38 39 328 40 41 329 42 43 330 44 330 45 46 331 47 48 332 50 51 333 52 53 334 54	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
36 327 37 38 39 328 40 41 329 42 43 330 44 330 45 46 331 47 48 332 49 50 51 333 52 53 334	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

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336	they were more likely single, younger and current smokers compared with attenders. However,
337	these were pooled estimates for both the screening group and the control group.
0 ³³⁸	In individuals diagnosed with cancer, anxiety and worse health-related quality of life have been
1 2 339	associated with dropout, which is consistent with our findings.(20) Since Non-attenders in our
3 4 340 5	study experienced a higher level of anxiety than Attenders in the first screening round (i.e.
6 7 341	baseline), this could have been the motivation for attending the trial; to get reassured of being
8 9 342 0	healthy.(21) Therefore, randomization to the control group may have caused disappointment, but
¹ ₂ 343	also attention drawn to not being part of a possibly beneficial intervention.(22) For example, the
3 4 344 5	secretary in the screening clinic received calls from participants randomized to the control group
6 ₇ 345	expressing their disappointment of not being screened. Furthermore, the trial put focus on the
8 9 346 0	harms of smoking, which could have increased the anxiety and fear of disease in this subgroup
0 ¹ 347 2	even more, which may have been a reason to subsequent non-attendance. Finally, missing data on
3 4 348	psychosocial status in a previous round may also have been a predictor for non-attendance in the
5 6 349 7	next screening round, which was not the scope for this study.
8 9 350	Low social status, younger age and current smoking status have previously been seen among
0 1 351 2	dropouts and non-respondents in lung health studies. (23–26) A systematic review reporting
³ 4 352	dropout from longitudinal studies in elderly concluded that higher age and declining health were
5 6 353 7	high predictors of dropout. The latter is in agreement with our findings, although higher age is in
⁸ 354	contrast to our findings.(27)
0 1 355	
2 3 356 4	To our knowledge, this is the first cancer screening study testing hypotheses on reasons for
5 6 357	differential non-response empirically. The results of this study confirmed the hypotheses we made
7 8 358 9	in our previous study, using inverse probability weighting to adjust for differential non-
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4 359 5 6	response.(3,7,28) More importantly, the results of the two other lung cancer screening trials
7 360 8	investigating dropout are consistent with ours. Hence, it is plausible that our results are
9 361 10	generalisable to other cancer screening trials as well.
11 12 362 13	Therefore, future cancer screening trials should concurrently assess psychosocial status during the
14 363 15	trial, not only to be able to assess the psychosocial effect of screening, but also to use this
16 17 364 18	information to adjust any effect in the trial for bias due to differential non-attendance.
19 365 20	
²¹ 22 366 23	Conclusions
²³ ²⁴ 25	In conclusion, Non-attenders in the control group in the DLCST had a worse psychosocial status
26 27 368	and a less favourable socio-demographic profile than Attenders.
28 29 369 30	The results of our study contribute with evidence of non-response driven by psychosocial status,
$31 \\ 32 370$	which in turn may be influenced by the screening intervention itself. This can be used to adjust
33 34 371 35	cancer screening trial results for bias due to differential attendance.
³⁶ 37372	
38 39 373 40	Abbreviations
41 42 374	RCT: Randomized controlled trial; PROM: Patient-reported outcome measure; CT: Computed
43 44 375 45	tomography; DLCST: Danish Lung Cancer Screening Trial; COS-LC: Consequences of screening in
46 47 376	lung cancer; COS: Consequences of screening; CCI: Charlson comorbidity index
48 49 377 50	
51 52 378	Declarations
53 54	
⁵⁴ 379	Ethics approval and consent to participate
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59 60	

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⁴ ₅ 380	The Ethical Committee of Copenhagen County approved the DLCST including this observational
6 7 381 8	study nested in the DLCST on 31 January 2003: approval number KA-02045.
9 382 10	All participants signed an informed consent form and received an information letter about the
11 12 383 13	project and information about the ethical approval and data protection agency approval. The trial
14 384 15	is registered in <u>Clinicaltrials.gov</u> Protocol Registration System (identification no. <u>NCT00496977</u>)
16 17 385 18	
19 386 20	Availability of data and materials
²¹ 22 387 23	The corresponding author can provide the questionnaires and datasets generated and analysed
24 388 25	during the study on reasonable request.
²⁶ 389 27 28	
29 390 30	Competing interests
³¹ 391 32 ³³ 34 392	None declared.
35 36 393 37	Funding
³⁸ 39394 40	This work was supported by the Danish Ministry of Interior and Health, grant number <u>0900814</u> .
41 395 42	The funding source had no role in study design, data collection and analysis, decision to publish, or
43 44 45	preparation of the manuscript.
46 397 47	
48 49 50	Author contributions
50 51 399 52	JB and HT developed and designed the study. JB, HT and the DLCST staff collected data. VS
53 400 54	performed the statistical analyses. JM drafted the manuscript. JB, HT, BH, JFR, and VS all
55 56 401 57	contributed to parts of the manuscript as well as revisions of the manuscript. All authors approved
58 402 59 60	the final version of the manuscript, and no editorial assistance was received. All authors had full

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4 403	access to all data in the study and are responsible of data retention and the accuracy of the data
6 7 404 8	analysis. JM and JB are guarantors of the study.
9 405 10	
11 12 406 13	Acknowledgement
14 407 15	We wish to thank data manager Willy Karlslund for his contribution to generation of the databases
16 17 408 18	and we also wish to thank the DLCST steering committee.
19 409 20	
21 22 23 410	Fig.1 Flowchart, DLCST
24 25	
26 411 27	Fig.2 Flowchart, present study
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3 4 5 413 6	3 References						
7 8 414 9	1.	Tierney JF. Investigating patient exclusion bias in meta-analysis. Int J Epidemiol [Internet].					
9 10 415 11		2004 Aug 27;34(1):79–87. Available from: https://academic.oup.com/ije/article-					
12 13 416 14		lookup/doi/10.1093/ije/dyh300					
¹⁵ 417 16 17	2.	Zhang Y, Alyass A, Vanniyasingam T, Sadeghirad B, Flórez ID, Pichika SC, et al. A systematic					
18 418 19		survey of the methods literature on the reporting quality and optimal methods of handling					
²⁰ 419 21		participants with missing outcome data for continuous outcomes in randomized controlled					
22 23 420 24		trials. J Clin Epidemiol [Internet]. 2017 Aug;88:67–80. Available from:					
25 421 26		http://www.ncbi.nlm.nih.gov/pubmed/28579378					
27 28 422 29	3.	Dufouil C, Brayne C, Clayton D. Analysis of longitudinal studies with death and drop-out: a					
$\frac{30}{31}423$		case study. Stat Med [Internet]. 2004 Jul 30;23(14):2215–26. Available from:					
32 33 424 34		http://www.ncbi.nlm.nih.gov/pubmed/15236426					
35 36 425 37	4.	Humphrey LL, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP, et al. Screening for					
³⁸ 426 39		lung cancer with low-dose computed tomography: a systematic review to update the US					
40 41 427 42		Preventive services task force recommendation. Ann Intern Med [Internet]. 2013 Sep 17					
43 428 44		[cited 2014 Feb 26];159(6):411–20. Available from:					
45 46 47		http://www.ncbi.nlm.nih.gov/pubmed/23897166					
48 430 49	5.	Wu GX, Raz DJ, Brown L, Sun V. Psychological Burden Associated With Lung Cancer					
50 51 431 52		Screening: A Systematic Review. Clin Lung Cancer [Internet]. 2016 Sep;17(5):315–24.					
⁵³ 432 54		Available from: http://linkinghub.elsevier.com/retrieve/pii/S1525730416300535					
55 56 433 57	6.	Brain K, Lifford KJ, Carter B, Burke O, McRonald F, Devaraj A, et al. Long-term psychosocial					
⁵⁸ 59 434 60		outcomes of low-dose CT screening: results of the UK Lung Cancer Screening randomised					

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1 2 3		
$\frac{4}{5}$ 435		controlled trial. Thorax [Internet]. 2016 Nov;71(11):996–1005. Available from:
6 7 436 8		http://thorax.bmj.com/lookup/doi/10.1136/thoraxjnl-2016-208283
9 10 437	7.	Rasmussen JF, Siersma V, Pedersen JH, Brodersen J. Psychosocial consequences in the
11 12 438 13		Danish randomised controlled lung cancer screening trial (DLCST). Lung Cancer [Internet].
14 15 439		2015;87(1):65–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25433982
16 17 18 440	8.	Pedersen JH, Ashraf H, Dirksen A, Bach K, Hansen H, Toennesen P, et al. The Danish
19 20 441 21		randomized lung cancer CT screening trialoverall design and results of the prevalence
²¹ ²² 23 442		round. J Thorac Oncol [Internet]. 2009 May [cited 2013 Sep 18];4(5):608–14. Available from:
24 25 443 26		http://www.ncbi.nlm.nih.gov/pubmed/19357536
27 28 444	9.	Brodersen J, Thorsen H, Kreiner S. Consequences of screening in lung cancer: development
29 30 445 31		and dimensionality of a questionnaire. Value Health [Internet]. 2010 Aug [cited 2013 Oct
³² 33 446		1];13(5):601–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20345552
34 ³⁵ 447 36	10.	Aggestrup LM, Hestbech MS, Siersma V, Pedersen JH, Brodersen J. Psychosocial
37 38 448		consequences of allocation to lung cancer screening: a randomised controlled trial. BMJ
39 40 449 41		Open [Internet]. 2012 Jan [cited 2013 Oct 1];2(2):e000663. Available from:
42 43 450		http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3293139&tool=pmcentrez&re
44 45 451		ndertype=abstract
46 47 48 452	11.	Heydarpour B, Saeidi M, Ezzati P, Soroush A, Komasi S. Sociodemographic Predictors in
49 50 51 453	11.	
52		Failure to Complete Outpatient Cardiac Rehabilitation. Ann Rehabil Med [Internet]. 2015
53 454 54		Dec;39(6):863–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26798599
55 56 455	12.	de Graaf R, van Dorsselaer S, Tuithof M, ten Have M. Sociodemographic and psychiatric
57 58 456 59		predictors of attrition in a prospective psychiatric epidemiological study among the general
60		

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1 2 3		
$\frac{4}{5}$ 457		population. Result of the Netherlands Mental Health Survey and Incidence Study-2. Compr
6 7 458 8		Psychiatry [Internet]. 2013 Nov;54(8):1131–9. Available from:
9 459 10		http://linkinghub.elsevier.com/retrieve/pii/S0010440X13001284
11 12 460 13	13.	Field JK, Duffy SW, Baldwin DR, Whynes DK, Devaraj A, Brain KE, et al. UK Lung Cancer RCT
$^{14}_{15}461$		Pilot Screening Trial: baseline findings from the screening arm provide evidence for the
16 17 462 18		potential implementation of lung cancer screening. Thorax [Internet]. 2015;1–10. Available
¹⁹ 20 463		from: http://www.ncbi.nlm.nih.gov/pubmed/26645413
²¹ ²² ²³ ⁴⁶⁴	14.	McCaffery KJ. Assessing psychosocial/quality of life outcomes in screening: how do we do it
24 25 465		better? J Epidemiol Community Heal [Internet]. 2004 Dec 1;58(12):968–70. Available from:
26 27 466 28		http://jech.bmj.com/cgi/doi/10.1136/jech.2004.025114
29 30 467 31	15.	Brodersen J, Thorsen H. Consequences of Screening in Breast Cancer (COS-BC):
³² 33468		development of a questionnaire. Scand J Prim Health Care [Internet]. 2008 Jan [cited 2013
34 35 469 36		Oct 1];26(4):251–6. Available from:
$\frac{37}{38}470$		http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3406644&tool=pmcentrez&re
39 40 471 41		ndertype=abstract
42 43 472	16.	Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful
44 45 473 46		Approach to Multiple Testing. J R Stat Soc Ser B [Internet]. 1995;57(1):289–300. Available
47 48 474		from: http://www.jstor.org/stable/2346101
49 ⁵⁰ 475 51	17.	Brodersen J, Thorsen H, Cockburn J. The adequacy of measurement of short and long-term
52 53 476		consequences of false-positive screening mammography. J Med Screen. 2004;11(1):39–44.
54 55 56 477	18.	DeFrank JT, Barclay C, Sheridan S, Brewer NT, Gilliam M, Moon AM, et al. The psychological
57 58 478		harms of screening: the evidence we have versus the evidence we need. J Gen Intern Med
59 60		

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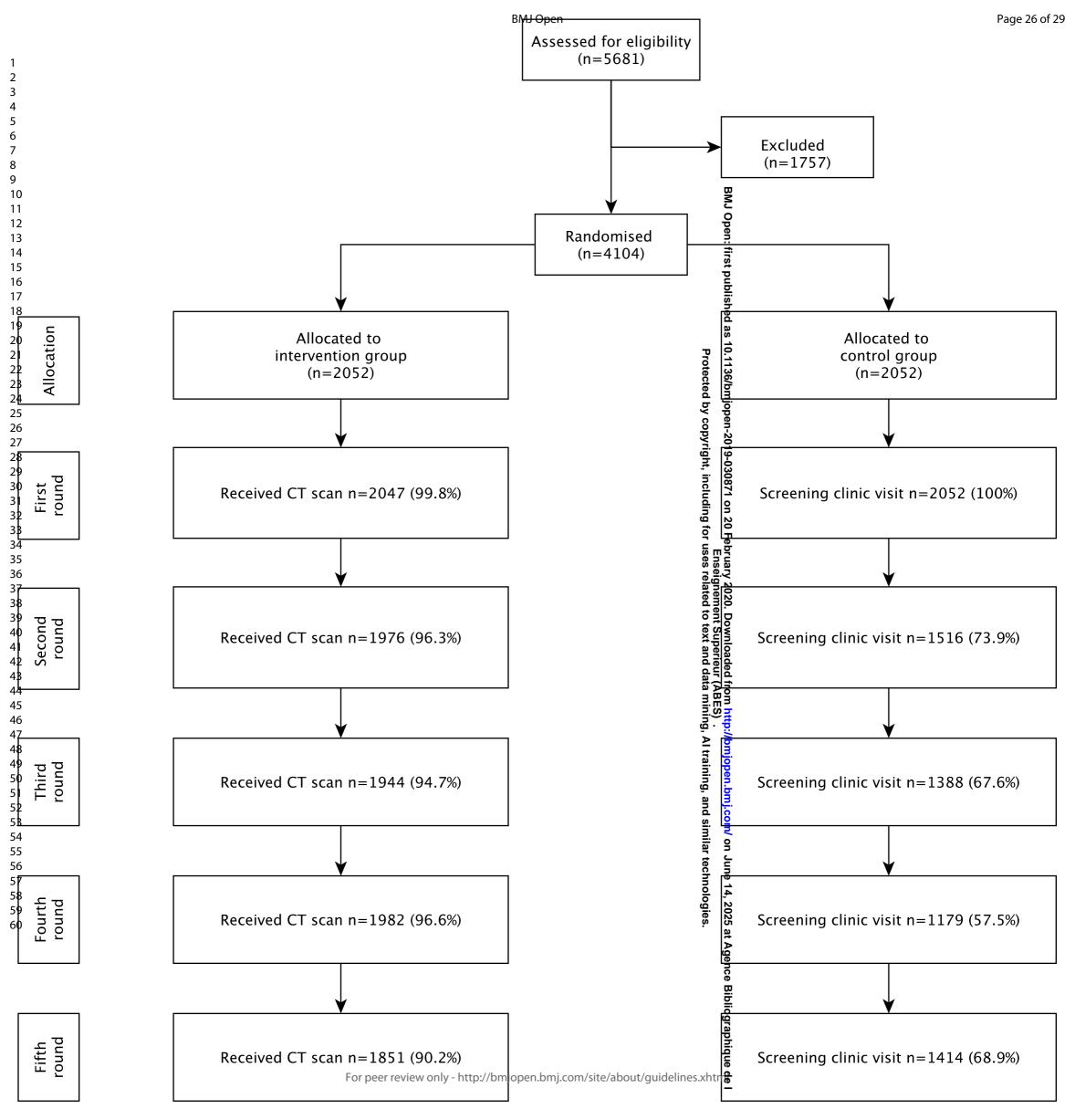
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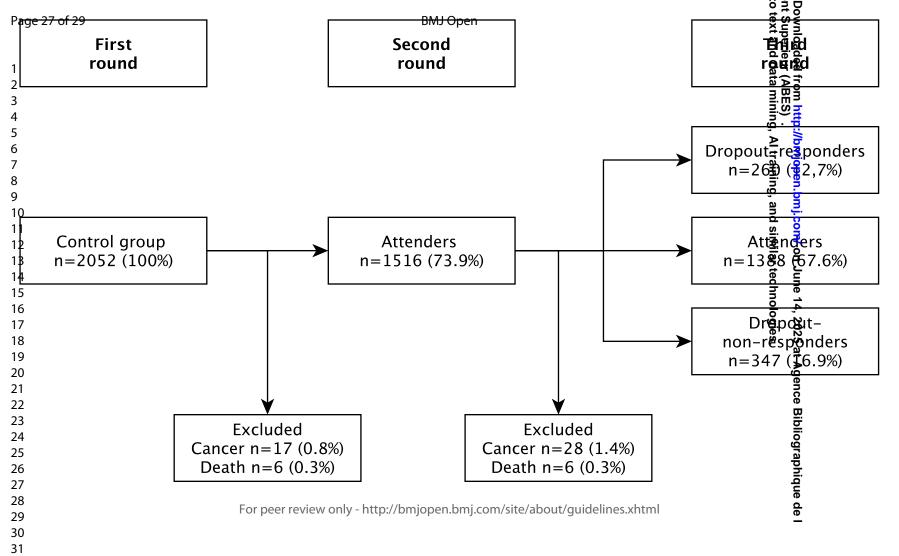
1 2		
3 4 479 5		[Internet]. 2015;30(2):242–8. Available from:
6 7 480		http://www.ncbi.nlm.nih.gov/pubmed/25150033
8 9 10 481	19.	van den Bergh KAM, Essink-Bot ML, Borsboom GJJM, Scholten ET, van Klaveren RJ, de
11 12 482 13		Koning HJ. Long-term effects of lung cancer computed tomography screening on health-
$^{14}_{15}483$		related quality of life: the NELSON trial. Eur Respir J [Internet]. 2011 Jul [cited 2014 Oct
16 17 484 18		3];38(1):154–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21148229
19 20 485	20.	Mercieca-Bebber RL, Price MA, Bell ML, King MT, Webb PM, Butow PN, et al. Ovarian cancer
21 22 486 23		study dropouts had worse health-related quality of life and psychosocial symptoms at
24 25 487		baseline and over time. Asia Pac J Clin Oncol [Internet]. 2017 Oct;13(5):e381–8. Available
26 27 488 28		from: http://www.ncbi.nlm.nih.gov/pubmed/27573704
29 30 489	21.	Østerø J, Siersma V, Brodersen J. Breast cancer screening implementation and reassurance.
31 ³² 33490		Eur J Public Health. 2014;24(2):258–63.
34 ³⁵ 491 36	22.	Wendler D, Krohmal B, Emanuel EJ, Grady C. Why patients continue to participate in clinical
37 38 492		research. Arch Intern Med [Internet]. 2008 Jun 23 [cited 2013 Oct 1];168(12):1294–9.
39 40 493 41		Available from: http://www.ncbi.nlm.nih.gov/pubmed/18574086
41 42 43 494	23.	Snow WM, Connett JE, Sharma S, Murray RP. Predictors of attendance and dropout at the
44 45 46 495		Lung Health Study 11-year follow-up. Contemp Clin Trials [Internet]. 2007 Jan;28(1):25–32.
40 47 48 496		Available from: http://linkinghub.elsevier.com/retrieve/pii/S1551714406001157
49 50 51 497	24.	Nohlert E, Öhrvik J, Helgason ÁR. Non-responders in a quitline evaluation are more likely to
51 497 52 53 498	24.	be smokers - a drop-out and long-term follow-up study of the Swedish National Tobacco
54 55 56 499		Quitline. Tob Induc Dis [Internet]. 2016;14:5. Available from:
57 58 500		http://www.ncbi.nlm.nih.gov/pubmed/26843854
59 60		

Page 25 of 29

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2			
5	01	25.	Abrahamsen R, Svendsen MV, Henneberger PK, Gundersen GF, Torén K, Kongerud J, et al.
6 7 5 8	02		Non-response in a cross-sectional study of respiratory health in Norway. BMJ Open
~	03		[Internet]. 2016;6(1):e009912. Available from:
11 12 5 13	04		http://www.ncbi.nlm.nih.gov/pubmed/26739738
14 15 5	05	26.	Oleske DM, Kwasny MM, Lavender SA, Andersson GBJ. Participation in occupational health
16 17 5 18	06		longitudinal studies: predictors of missed visits and dropouts. Ann Epidemiol [Internet].
19 20 21	07		2007 Jan;17(1):9–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17140810
²¹ 22 23	08	27.	Chatfield MD, Brayne CE, Matthews FE. A systematic literature review of attrition between
24 25 5	09		waves in longitudinal studies in the elderly shows a consistent pattern of dropout between
26 27 5 28	10		differing studies. J Clin Epidemiol [Internet]. 2005 Jan [cited 2014 Mar 13];58(1):13–9.
29 30 5	11		Available from: http://www.ncbi.nlm.nih.gov/pubmed/15649666
31 32 33 5	512	28.	Rotnitzky A, Robins J. Analysis of semi-parametric regression models with non-ignorable
34 35 5 36	13		non-response. Stat Med [Internet]. 16(1–3):81–102. Available from:
³⁷ 385	14		http://www.ncbi.nlm.nih.gov/pubmed/9004385
39 40 5	15		
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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	1
		title or the abstract	
		(b) Provide in the abstract an informative and balanced summary of	1
		what was done and what was found	
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	5
8		of recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and	6
I	-	methods of selection of participants. Describe methods of follow-up	
		<i>Case-control study</i> —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	
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources	
		and methods of selection of participants	
		(b) Cohort study—For matched studies, give matching criteria and	Not
		number of exposed and unexposed	applicable
		<i>Case-control study</i> —For matched studies, give matching criteria	appneasi
		and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential	6 and 7
	,	confounders, and effect modifiers. Give diagnostic criteria, if	o unu ,
		applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of	
measurement	Ũ	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	6-8
C		applicable, describe which groupings were chosen and why	
Statistical methods	12	(<i>a</i>) Describe all statistical methods, including those used to control	7-8
Statistical methods	12	for confounding	
		(b) Describe any methods used to examine subgroups and	7
		interactions	,
		(c) Explain how missing data were addressed	Not applicable
		(d) Cohort study—If applicable, explain how loss to follow-up was	Not
		addressed	applicable
		<i>Case-control study</i> —If applicable, explain how matching of cases	
		and controls was addressed	

	Cross-sectional study—If applicable, describe analytical methods
	taking account of sampling strategy
	(<u>e</u>) Describe any sensitivity analyses
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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially	Fig.1
1		eligible, examined for eligibility, confirmed eligible, included in the study,	
		completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Fig.2
		(c) Consider use of a flow diagram	Fig.2
Descriptive	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and	7
data		information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	Table
		(c) <i>Cohort study</i> —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
		<i>Case-control study</i> —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	Table
		their precision (eg, 95% confidence interval). Make clear which confounders were	2-4
		adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	N/A
		(<i>c</i>) 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		6.	
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	10
		imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	10
		multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-
			12
Other informati	on		
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.

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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Complete List of Authors:	Malmqvist, Jessica; University of Copenhagen, Department of Public Health Siersma, Volkert; University of Copenhagen, Department of Public Health, the Research Unit for General Practice Thorsen, Hanne; University of Copenhagen, Department of Public Health, the Research Unit for General Practice Heleno, B; Universidade Nova de Lisboa, Rasmussen, Jakob; University of Copenhagen, Department of Public Health, the Research Unit for General Practice Brodersen, John; University of Copenhagen, Centre of Research & Education in General Practice Primary Health Care Research Unit, Zealand Region
Primary Subject Heading :	Public health
Secondary Subject Heading:	Research methods, General practice / Family practice
Keywords:	Bias, Mass screening, Lung neoplasms, Patient dropout

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1	Did psychosocial status, sociodemographics and smoking status
2	affect non-attendance in control participants in the Danish Lung
3	Cancer Screening Trial? A nested observational study
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7	Fax number: +45-35327946
3	Keywords
)	bias, mass screening, lung neoplasms, patient dropouts
)	Word count 2780

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4 5 6	21	Abstract
7 8	22	Objectives: We investigated if psychosocial status, socio-demographics and smoking status
9 10 11	23	affected non-attendance in the control group in the randomised Danish Lung Cancer Screening
12 13	24	Trial (DLCST).
14 15 16	25	Design & setting: This study was an observational study nested in the DLCST. Due to large non-
17 18	26	attendance in the control group in the second screening round we made an additional effort to
19 20	27	collect questionnaire data from non-attenders in this group in the third screening round. We used
21 22 23	28	a condition-specific questionnaire to assess psychosocial status. We analysed the differences in
24 25	29	psychosocial status in the third and preceding rounds between non-attenders and attenders in the
26 27 28	30	control group in multivariable linear regression models adjusted for socio-demographics and
29 30	31	smoking status reported at baseline. Differences in socio-demographics and smoking status were
31 32 33	32	analysed with chi-squared tests (categorical variables) and t-tests (continuous variables).
34 35	33	Primary outcome measure: Primary outcome was psychosocial status.
36 37	34	Participants: All control persons participating in the third screening round in the DLCST were
38 39 40	35	included.
41 42	36	Results: Non-attenders in the third round had significantly worse psychosocial status than
43 44 45	37	attenders in the scales: "Behaviour" 0.77 (99% CI 0.18;1.36), "Self-blame" 0.59 (99% CI 0.14;1.04),
46 47	38	"Focus on airway symptoms" 0.22 (99% CI 0.08;0.36), "Stigmatisation" 0.51 (99% CI 0.16;0.86),
48 49 50	39	"Introvert" 0.56 (99% CI 0.23;0.89), and "Harms of smoking" 0.35 (99% CI 0.11;0.59). Moreover,
50 51 52	40	non-attenders had worse scores than attendees in the preceding screening rounds. Non-attenders
53 54	41	also reported worse socio-demographics at baseline.
55 56 57	42	Conclusions: Non-attenders had a significantly worse psychosocial status and worse socio-
58 59	43	demographics compared with attenders. The results of our study contribute with evidence of non-
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4 5 6	44	response and attrition driven by psychosocial status, which in turn may be influenced by the
7 8	45	screening intervention itself. This can be used to adjust cancer screening trial results for bias due
9 10 11	46	to differential non-attendance.
12 13	47	Trial registration: The trial is registered in <u>Clinicaltrials.gov</u> Protocol Registration System
14 15 16	48	(identification no. <u>NCT00496977</u>)
17 18	49	
19 20 21	50	Article summary
22 23	51	Strengths and limitations
24 25 26	52	Use of a condition-specific questionnaire with adequate psychometric properties ensured
27 28 29	53	valid measures.
30 31	54	Patient-reported data on non-respondents gave valuable empirical insight in drivers for
32 33 34	55	non-attendance.
35 36	56	 Testing a previously hypothesized model for non-attendance empirically is another
37 38 39	57	strength of the study.
40 41 42	58	No comparison between non-attenders in the intervention and the control group was
42 43 44	59	performed.
45 46	60	 No longer-term follow up on non-attenders was performed.
47 48 49	61	
50 51	62	Introduction
52 53 54	63	Non-attendance may affect trial results and introduce bias in randomised controlled trials
55 56	64	(RCTs).(1,2) Non-attendance reduces the power of the trial and, if non-attendance differs between
57 58 59 60	65	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

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participants were asked to complete a condition-specific questionnaire, measuring psychosocial

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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 sociodemographic 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

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4 111 5	The design and study population of DLCST have been described in detail previously.(7,8) Briefly,
6 7 112 8	the DLCST was an RCT, conducted at the Copenhagen University hospital Gentofte in Denmark
9 113 10	from October 2004 to March 2010. Heavy current and former smokers (at least 20 pack-years),
11 12 114 13	aged 50-70 years old, were randomised to either five rounds of screening with low-dose CT-scans
14 115 15	including clinical examinations (n=2052) or five clinical examinations only (n=2052). In the
16 17 116	enrolment visit, participants provided socio-demographic data, lifestyle and health information
18 19 117 20	(including smoking status), completed a questionnaire on their psychosocial status and underwent
21 22 118	spirometry. Participants randomised to screening also had a low-dose chest CT-scan within one
23 24 119 25	month of randomisation. In the following screening rounds, participants in the screened and
²⁶ 120 27	control groups were invited to a visit in the screening clinic where lung function tests were
28 29 121 30	performed, and questionnaires concerning health, lifestyle, smoking habits and psychosocial
³¹ 122 32	status were completed and lung function tests were performed. Participants randomised to
33 34 123 35	screening also received a low-dose chest CT-scan.
36 124 37	This study is an observational study nested in the DLCST. During the second screening round, the
³⁸ 39 125 40	steering committee noted that a large number of control participants did not attend the screening
40 41 126 42	clinic visit when compared with the number of screened participants. Thus, the committee
⁴³ 127	decided to make additional efforts to collect questionnaire data for non-attenders in the control
45 46 128 47	group in the third screening round to perform post hoc analyses on whether psychosocial status
⁴⁸ 129 49	was an influencing factor (Fig.2).
50 51 130 52	During the third round, participants in the control group who did not attend the annual
53 131 54	examination were contacted by phone and part 1 of the questionnaire was sent with a postage
55 56 57 58 59 60	paid envelope to those who gave their oral consent. The data was used to supplement the data

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1 2	
3 4 122	collected on site at the coreaning clinic (7) This violded three groups within the control group
4 133 5 6	collected on site at the screening clinic.(7) This yielded three groups within the control group,
7 134 8	denoting the extent of response to the clinical examination and the questionnaire defined as:
9 135 10	
11 12 136 13	1. Attenders: participants who attended the third screening round.
14 137 15	2. Non-attenders:
16 17 138	a) <u><i>Respondents</i></u> : participants who did not attend the annual examination but
18 19 139 20	completed and returned the COS-LC after the phone interview.
²¹ 22 140	b) <i>Non-respondents</i> : participants who did not attend the annual examination and did
23 24 141 25	not complete the COS-LC.
25 26 27 142	
28 29 143	Outcomes & Questionnaires
30 31 144 32	Primary outcome was psychosocial status measured with the Consequences Of Screening for Lung
33 34 145	Cancer (COS-LC) questionnaire.(9) Part 1 of COS-LC comprised nine scales measuring various
35 36 146 37	aspects of consequences of screening; a second part of COS-LC addressed the screening outcome
38 39 147	and was therefore not applicable to the present analysis. Moreover, the primary part of COS-LC
40 41 148	included four core scales: "Anxiety", "Behaviour", "Dejection" and "Sleep" that are not lung cancer
42 43 44 149	specific. These scales have originally been developed from a breast cancer screening assessment
45 46 150	instrument.(15) Additionally COS-LC comprised five lung cancer specific scales: "Self-blame",
47 48 49 151	"Focus on airway symptoms", "Stigmatisation", "Introvert", and "Harm of smoking", which were
50 51 152	developed from focus groups and other screening assessment instruments during the first DLCST
52 53 153 54	screening round.(9,15) Therefore, only the core scales were used in the first round, while in the
55 56 154	following four screening rounds both the core scales and the lung cancer specific scales were used
57 58 155	to assess psychosocial status.(9)
59 60	

1 2		
3 4 5	156	Statistics
6 7	157	Covariates
8 9 10	158	Socio-demographic characteristics were defined by: social class (I highest social class to V lowest
11 12	159	social class), school and vocational education (from 9 years of elementary school to a university
13 14 15	160	education), employment status, living alone, smoking status (current or former smoker), smoking
	161	history (pack-years), motivation for smoking cessation (from very strong to no wish to quit) and
18 19 20	162	Charlson Comorbidity Index (CCI). Furthermore, we adjusted for region of residence (Denmark is
21 22	163	divided into five health-administrative regions).
23 24 25	164	
26 27	165	Statistical analyses
28 29 30	166	We performed three different analyses:
31 32	167	1. Analyses of differences in psychosocial status in the third round between Attenders and
33 34 35	168	Non-attenders-respondents.
36 37	169	2. Analyses of differences in psychosocial status in the second round between Attenders,
38 39 40	170	Non-attenders-respondents and Non-attenders-non-respondents.
41 42		3. Analyses of differences in psychosocial status in the first round, between Attenders, Non-
43 44 45	172	attenders-respondents and Non-attenders-non-respondents.
46 47	173	Covariates at the first screening round were compared between Attenders and Non-attenders by
48 49 50	174	chi-squared tests (categorical characteristics) and t-tests (continuous characteristics). Analyses of
50 51 52	175	psychosocial status at various points in the follow-up were performed in linear regression models
54	176	both unadjusted and in multivariable models adjusted for sex, age, region of residence, social
55 56 57	177	class, living alone, smoking status, pack years, motivation for smoking cessation and CCI. To adjust
58 59 60		

1 2		
3	1 = 0	
5 6	178	for multiple testing we used the Benjamini-Hochberg procedure and the False Discovery Rate
	179	(FDR) was set to 5% (16). All analyses were performed with SAS 9.4 (SAS Institute, Inc., Cary, NC).
~	180	
	181	Patient and Public Involvement
15	182	Patients and public were not involved in the design of the study.
16 17 18	183	
19 20	184	Results
23	185	The inclusion process and participation rate of the DLCST are illustrated in Figure 1. The
24 25 26	186	participation rate in the control group fell from 73.9% in the second round to 57.5% in the fourth
	187	round. The participation rate increased in the fifth, final, round (68.9%).
29 30 31	188	Figure 2 depicts the inclusion process of the present study and showed a dropout rate of 29.6%
32 33	189	(n=607) in the third screening round with a higher distribution of <i>Non-attenders-non-respondents</i>
34 35 36	190	(16.9% n=347) compared with Non-attenders-respondents (12.7% n=260).
37 38	191	In the first screening round we compared differences in socio-demographic characteristics in the
39 40 41	192	two overarching groups (Attenders, Non-attenders) (Table 1).
	193	
44	194	
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47 48	196	
49	197	
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52 53	199	
	200	
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58. 59	202	
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Table 1, Socio-demographics

	Missing	Attenders	Non-attenders	p-value
	observations,			
	total	n=1388	n=607	
Covariates	n	n (%)**	n(%)**	
Sex	0			0.0963
Male		773 (55.7)	313 (51.6)	
Female		615 (44.3)	294 (48.4)	
Age, <i>mean (SD)</i>	0	57.4 (4.7)	56.9 (4.9)	0.0538
Social class	12			0.0079
l (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		363 (26.2)	153 (25.3)	
school				
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, <i>mean (SD)</i>		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)	

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) 0.424 Motivation for smoking cessation 30 0.054 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)	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) 0.42 Mutivation for smoking cessation 30 0.05 0.05 Very strong 141 (10.3) 74 (12.4) 0.05 Strong 324 (23.7) 166 (27.8) 0.42 Weak 331 (24.2) 144 (24.8) 0.05 Very weak 116 (8.5) 42 (7.0) 0.05 No wish to quit 113 (8.3) 54 (9.0) 0.05 Current non-smoker 342 (25.0) 118 (19.7) 0.05	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) 0.422 Motivation for smoking cessation 30 0.054 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)	Smoking status	0			0.01
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Current non-smoker 342 (25.0) 118 (19.7)	242 (25.0) 118 (19.7)		Very weak				
		* Benjamini-Hochberg rejects all p-values above 0.0321 to control the FDR at 0.05	No wish to quit		113 (8.3)	54 (9.0)	
		* Benjamini-Hochberg rejects all p-values above 0.0321 to control the FDR at 0.05	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					
		* 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					
		**Except when indicated in the leftmost column that the mean and standard deviation (SD) are listed					

1 2										
3 4 5 247	There was a significant	differen	ice between	the study	groups for sc	ocial clas	s with more <i>I</i>	lon-		
6 7 248 8	attenders in the lowest	social c	lass (V) and	a greater n	number of At	tenders	in the highest	social		
9 10 249	classes (I-II).									
11 12 250 13	Moreover, Non-attende	ers had a	a significant	ly higher C	CI score indic	ating th	at they had m	ore severe		
¹⁴ 251 15	or a greater number of	co-occu	rring condit	ions than A	A <i>ttenders</i> . Th	ey were	also to a grea	ater extent		
$^{16}_{17}252$	living alone. Furthermo	living alone. Furthermore, there were significantly more current smokers and a non-significant								
18 19 253 20	trend of a higher wish t	to quit si	moking in th	ne group of	Non-attende	ers comp	pared with Att	enders.		
²¹ 22 ²⁵⁴	The results of the third	screenii	ng round are	e listed in T	able 2.					
23 24 255 25	Table 2, Dr	fference	es in psych	osocial sta	atus in the th	hird scr	eening round	1		
26 256 27 257				A #	Nee		Difference in			
²⁸ 258 ²⁹ 259 30		Range of values	Responding rate per item n/n	Attenders n=1388 mean (SD)	Non- attenders- respondents n=260	p-value*	Difference in scores between the two groups mean (99%Cl)ª	p-value adjusted*		
31 32					mean (SD)					
33	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		
34	Behaviour	0-18	1343/246	2.1 (3.1)	2.9 (3.8)	< 0.001	0.77 (0.18;1.36)	<0.001		
35 36	Dejection	0-18	1354/255	1.9 (3.0)	2.4 (3.5)	0.013	0.49 (-0.06;1.04)	0.0225		
30 37	Sleep	0-12	1357/252	1.9 (2.6)	2.3 (3.0)	0.041	0.35 (-0.12;0.82)	0.0599		
38	COS-LC scales			(,			,,			
39	Self-blame	0-15	1356/234	2.2 (2.8)	3.1 (3.8)	<0.001	0.59 (0.14;1.04)	<0.001		
40	Focus on airway	0-24	1363/239	0.3 (0.8)	0.6 (1.0)	<0.001	0.22 (0.08;0.36)	<0.001		
41	symptoms									
42	Stigmatisation	0-12	1361/241	1.5 (1.9)	2.1 (2.4)	<0.001	0.51 (0.16;0.86)	<0.001		
43	Introvert	0-18	1361/243	1.3 (1.8)	1.8 (2.2)	<0.001	0.56 (0.23;0.89)	<0.001		
44	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		
45 260	^{a)} A positive value of the d	ifference indi	cates that the pers	sons that were int	erviewed by phone	and later retu	Irned COS-LC had or	average higher		
46 261	scores, i.e. more negative	outcomes (e	e.g. higher anxiety)) than the persons	s that showed up an	d completed	the COS-LC on site.	The differences		
47 262	are adjusted for sex, age,	region of res	idence, social grou	up, living alone, s	moking status, pack	years, motiv	ation for smoking ces	sation and CCI.		
48 263	The continuous values va	riables (age a	and pack years) ar	e included as a q	uadratic function as	to allow for	oossible nonlinear eff	ects.		
⁴⁹ 264	* Benjamini-Hochberg rejec	ts all p-values	above 0.0321 to cor	ntrol the FDR at 0.0)5.					
⁵⁰ 265 51 52		·								
53 266 54	In the core questionnai	ire COS (Consequen	ces of Scree	ening), Non-d	attender	s-respondents	s had a		
⁵⁵ 267 56	statistically significant l	nigher (v	vorse) score	e than Atter	<i>nders</i> in the s	cales "B	ehaviour" and	b		
57 58 268 59 60	"Dejection". These effe	ects were	e still preser	nt when adj	justing for co	variates	. Moreover, t	here was a		

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⁴ 269	non-significant trend of worse scores in all COS scales among Non-attenders-respondents. In the
5 209	non-significant trend of worse scores in an COS scales among Non-attenders-respondents. In t

6 270 lung cancer specific part of the COS-LC, Non-attenders-respondents had statistically significantly 7

9 271 higher scores in all scales both crude and adjusted. 10

11 12 272 Table 3 shows differences in psychosocial status between all three subgroups in the second

14 273 screening round. 15

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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- respondent s n=260	Non- attenders- non- respondents n=347	p-value*	p-value adjustedª⁺
COS scales, mean (SD)				11-200	11-347		
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)	0.000	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	0-24	1226/118/90	0.4 (0.8)	0.4 (0.8)	0.5 (0.9)	0.408	0.579
symptoms							
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

50 ₅₁ 280

a) A test for differences between the three groups adjusted for sex, age, region of residence, social group, living alone, smoking status, pack years,

₅₂ 281 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 ₅₃ 282 possible nonlinear effects. 54 283

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

56285 Non-attenders had significantly worse crude scores compared with Attenders in all the COS scales.

58 286 When adjusting for covariates the difference in scores was still significant in the three scales

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Stigmatisation" scale score was statistically significant in the unadjusted analyses but disapped 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 we 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 between Attenders of 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 Non-attenders and Non-attenders and Non-attenders are solved as a statistically significant we used to adjust for differential non-attenders are adjusted for sex, age, region of residence. Social status function as b allow for possible nonlinear effects. Provide: 0.11 (0.11									
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$\frac{4}{5}$ 314	round (assessed in the present study in the third round). This cannot be used to adjust differential
6 7 315 8	non-attendance because this information is generally not available but proves the concept.
9 316 10 316	The use of a condition-specific questionnaire is a strength of the study. Previous research has
11 12 317 13	demonstrated that condition-specific questionnaires are superior to generic questionnaires when
14 318 15	measuring psychosocial consequences in cancer screening settings.(17) Furthermore, we used an
16 17 319 18	appropriate longitudinal design i.e. we collected data at the same timepoints for both Attenders
19 320 20	and Non-attenders at various times in the study, as well as we measured psychosocial status in
²¹ 22 23	both groups at baseline.(18)
23 24 322 25	A limitation of the study is that we did not collect psychosocial outcomes of Non-attenders in the
²⁶ 323	intervention group. This study was designed to gain knowledge of factors motivating such a large
28 29 324 30	drop in participation in the control group. In hindsight, data on Non-attenders in the screened
³¹ 325 32	group could further help us understand the reasons for differential non-response.
³³ 34 326 35	The distribution of psychosocial outcomes was left-skewed (Table 2, 3, and 4). To assure that the
36 327 37	conclusions were not affected by this skewness, we repeated the analyses on log-transformed
³⁸ 39 328 40	outcomes. The results of these sensitivity analyses reached conclusions similar to the original
41 329 42	conclusions.
⁴³ 44 45	In addition to the DLCST, two other trials assessed psychosocial consequences in lung cancer
46 331 47	screening with low-dose CT.(6,19) Participants in the NELSON trial were invited to complete
48 332 49 50	questionnaires at baseline and at the second round of screening (two years after baseline
50 51 333 52	screening). Participants in the UKLS completed a questionnaire at baseline, two weeks after
53 334 54	randomisation/CT-scan and 10-29 months after baseline. Unlike the DLCST, in these two trials the
55 56 335 57	control group were not invited to an annual visit at the screening clinic. Although there were some
58 336 59 60	differences in study design, non-response rates in the control groups in these three trials were

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⁴ ₅ 337	similar and in all three trials there was differential non-response between the intervention and
6 7 338 8	control group. Differences between attenders and non-attenders were reported in the UKLS trial.
9 339 10	As in the DLCST, non-attenders had worse socio-demographic profile i.e. lower social class, and
11 12 340 13	they were more likely single, younger and current smokers compared with attenders. However,
14 341 15	these were pooled estimates for both the screening group and the control group.
16 17 342 18	In individuals diagnosed with cancer, anxiety and worse health-related quality of life have been
19 343 20	associated with dropout, which is consistent with our findings.(20) Since <i>Non-attenders</i> in our
²¹ 22 344 23	study experienced a higher level of anxiety than <i>Attenders</i> in the first screening round (i.e.
24 345 25	baseline), this could have been the motivation for attending the trial; to get reassured of being
²⁶ 346 27 28	healthy.(21) Therefore, randomisation to the control group may have caused disappointment, but
29 347 30	also attention drawn to not being part of a possibly beneficial intervention.(22) For example, the
31 348 32	secretary in the screening clinic received calls from participants randomised to the control group
33 34 349 35	expressing their disappointment of not being screened. Furthermore, the trial put focus on the
36 350 37	harms of smoking, which could have increased the anxiety and fear of disease in this subgroup
³⁸ 39351 40	even more, which may have been a reason to subsequent non-attendance. Finally, missing data on
41 352 42	psychosocial status in a previous round may also have been a predictor for non-attendance in the
43 44 45	next screening round, which was not the scope for this study.
46 354 47	Low social status, younger age and current smoking status have previously been seen among
⁴⁸ 355 49	dropouts and non-respondents in lung health studies. (23–26) A systematic review reporting
50 51 356 52	dropout from longitudinal studies in elderly concluded that higher age and declining health were
53 357 54	high predictors of dropout. The latter is in agreement with our findings, although higher age is in
55 56 358 57 58 59 60	contrast to our findings.(27)

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3 4 5 359	To our knowledge, this is the first cancer screening study testing hypotheses on reasons for
6 7 360 8	differential non-response empirically. The results of this study confirmed the hypotheses we made
9 10 ³⁶¹	in our previous study, using inverse probability weighting to adjust for differential non-
11 12 362 13	response.(3,7,28) More importantly, the results of the two other lung cancer screening trials
14 363 15	investigating dropout are consistent with ours. Hence, it is plausible that our results are
16 17 364 18	generalisable to other cancer screening trials as well.
19 365 20	Therefore, future cancer screening trials should concurrently assess psychosocial status during the
²¹ 22 23	trial, not only to be able to assess the psychosocial effect of screening, but also to use this
23 24 367 25	information to adjust any effect in the trial for bias due to differential non-attendance.
²⁶ 368	
28 29 369 30	Conclusions
31 32 370 33	In conclusion, Non-attenders in the control group in the DLCST had a worse psychosocial status
34 371 35	and a less favourable socio-demographic profile than Attenders.
$\frac{36}{37}372$	The results of our study contribute with evidence of non-response driven by psychosocial status,
38 39 373 40	which in turn may be influenced by the screening intervention itself. This can be used to adjust
41 42 374	cancer screening trial results for bias due to differential attendance.
43 44 375 45	
46 376 47	Abbreviations
48 49 377 50	RCT: Randomised controlled trial; PROM: Patient-reported outcome measure; CT: Computed
51 378 52	tomography; DLCST: Danish Lung Cancer Screening Trial; COS-LC: Consequences of screening in
53 54 379 55	lung cancer; COS: Consequences of screening; CCI: Charlson comorbidity index
56 380 57	
58 59 381 60	Declarations

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⁴ 382 6	Ethics approval and consent to participate
7 383 8	The Ethical Committee of Copenhagen County approved the DLCST including this observational
9 10 ³⁸⁴	study nested in the DLCST on 31 January 2003: approval number KA-02045.
11 12 385 13	All participants signed an informed consent form and received an information letter about the
14 386 15	project and information about the ethical approval and data protection agency approval. The trial
16 17 387	is registered in <u>Clinicaltrials.gov</u> Protocol Registration System (identification no. <u>NCT00496977</u>)
18 19 388 20	
21 22 389	Availability of data and materials
23 24 390 25	The corresponding author can provide the questionnaires and datasets generated and analysed
²⁶ 391	during the study on reasonable request.
28 29 392	
30 31 393 32	Competing interests
33 34 394	None declared.
35 36 395	
37 38 39 396	Funding
39 ^{3 9 0} 40	
41 397 42	This work was supported by the Danish Ministry of Interior and Health, grant number <u>0900814</u> .
43 44 398	The funding source had no role in study design, data collection and analysis, decision to publish, or
45 46 399 47	preparation of the manuscript.
48 49400	
50 51 401 52	Author contributions
53 402 54	JB and HT developed and designed the study. JB, HT and the DLCST staff collected data. VS
55 56 403	performed the statistical analyses. JM drafted the manuscript. JB, HT, BH, JFR, and VS all
57 58 404 59	contributed to parts of the manuscript as well as revisions of the manuscript. All authors approved
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${}^{4}_{5}$ 405	the final version of the manuscript, and no editorial assistance was received. All authors had full
6 7 406 8	access to all data in the study and are responsible of data retention and the accuracy of the data
9 407 10	analysis. JM and JB are guarantors of the study.
11 12 408 13	
14 409 15	Acknowledgement
16 17 410 18	We wish to thank data manager Willy Karlslund for his contribution to generation of the databases
19 411 20 21	and statistician Christine Winther Bang for performing the log-transformed analyses. Finally, we
²¹ 22412	wish to thank the DLCST steering committee.
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²⁷ 414 28	Fig.1 Flowchart, DLCST
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30 31 415	Fig.2 Flowchart, present study
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56	
57	
58	
59 60	
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1 2 3		
4 5 417 6	Refe	rences
7 8 418 9	1.	Tierney JF. Investigating patient exclusion bias in meta-analysis. Int J Epidemiol [Internet].
10 419 11		2004 Aug 27;34(1):79–87. Available from: https://academic.oup.com/ije/article-
¹² 13 14		lookup/doi/10.1093/ije/dyh300
¹⁵ 421 16 17	2.	Zhang Y, Alyass A, Vanniyasingam T, Sadeghirad B, Flórez ID, Pichika SC, et al. A systematic
18 422 19		survey of the methods literature on the reporting quality and optimal methods of handling
²⁰ 423 21		participants with missing outcome data for continuous outcomes in randomized controlled
22 23 424 24		trials. J Clin Epidemiol [Internet]. 2017 Aug;88:67–80. Available from:
25 425 26		http://www.ncbi.nlm.nih.gov/pubmed/28579378
27 28 426 29	3.	Dufouil C, Brayne C, Clayton D. Analysis of longitudinal studies with death and drop-out: a
³⁰ 31 32		case study. Stat Med [Internet]. 2004 Jul 30;23(14):2215–26. Available from:
33 428 34		http://www.ncbi.nlm.nih.gov/pubmed/15236426
35 36 429 37	4.	Humphrey LL, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP, et al. Screening for
³⁸ 430 39		lung cancer with low-dose computed tomography: a systematic review to update the US
40 41 431 42		Preventive services task force recommendation. Ann Intern Med [Internet]. 2013 Sep 17
43 432 44		[cited 2014 Feb 26];159(6):411–20. Available from:
45 46 43 47		http://www.ncbi.nlm.nih.gov/pubmed/23897166
48 49 50	5.	Wu GX, Raz DJ, Brown L, Sun V. Psychological Burden Associated With Lung Cancer
50 51 435 52		Screening: A Systematic Review. Clin Lung Cancer [Internet]. 2016 Sep;17(5):315–24.
⁵³ 436 54 55		Available from: http://linkinghub.elsevier.com/retrieve/pii/S1525730416300535
56 437 57	6.	Brain K, Lifford KJ, Carter B, Burke O, McRonald F, Devaraj A, et al. Long-term psychosocial
58 59 438 60		outcomes of low-dose CT screening: results of the UK Lung Cancer Screening randomised

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1 2 3		
$\frac{4}{5}$ 439		controlled trial. Thorax [Internet]. 2016 Nov;71(11):996–1005. Available from:
6 7 440 8		http://thorax.bmj.com/lookup/doi/10.1136/thoraxjnl-2016-208283
9 10 441 11	7.	Rasmussen JF, Siersma V, Pedersen JH, Brodersen J. Psychosocial consequences in the
12 442 13		Danish randomised controlled lung cancer screening trial (DLCST). Lung Cancer [Internet].
14 15 443 16		2015;87(1):65–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25433982
17 18 444	8.	Pedersen JH, Ashraf H, Dirksen A, Bach K, Hansen H, Toennesen P, et al. The Danish
19 20 445 21		randomized lung cancer CT screening trialoverall design and results of the prevalence
²² 446		round. J Thorac Oncol [Internet]. 2009 May [cited 2013 Sep 18];4(5):608–14. Available from:
24 25 447 26		http://www.ncbi.nlm.nih.gov/pubmed/19357536
27 28 448	9.	Brodersen J, Thorsen H, Kreiner S. Consequences of screening in lung cancer: development
29 30 449 31		and dimensionality of a questionnaire. Value Health [Internet]. 2010 Aug [cited 2013 Oct
$32 \\ 33 \\ 34 \\ 34$		1];13(5):601–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20345552
³⁵ 451 36	10.	Aggestrup LM, Hestbech MS, Siersma V, Pedersen JH, Brodersen J. Psychosocial
37 38 452		consequences of allocation to lung cancer screening: a randomised controlled trial. BMJ
39 40 453 41		Open [Internet]. 2012 Jan [cited 2013 Oct 1];2(2):e000663. Available from:
42 43 454		http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3293139&tool=pmcentrez&re
44 45 455 46		ndertype=abstract
47 48 456	11.	Heydarpour B, Saeidi M, Ezzati P, Soroush A, Komasi S. Sociodemographic Predictors in
49 50 51 457		Failure to Complete Outpatient Cardiac Rehabilitation. Ann Rehabil Med [Internet]. 2015
51 ⁻⁵⁷ 52 53 458		Dec;39(6):863–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26798599
54 55		Dec,59(0).805-71. Available from. http://www.htbh.inin.inin.gov/publice/20798599
₅₆ 459 57	12.	de Graaf R, van Dorsselaer S, Tuithof M, ten Have M. Sociodemographic and psychiatric
⁵⁸ 460 59		predictors of attrition in a prospective psychiatric epidemiological study among the general
60		

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1

1 2 3		
$\frac{4}{5}$ 461		population. Result of the Netherlands Mental Health Survey and Incidence Study-2. Compr
6 7 462		Psychiatry [Internet]. 2013 Nov;54(8):1131–9. Available from:
8 9 463 10		http://linkinghub.elsevier.com/retrieve/pii/S0010440X13001284
11 12 464 13	13.	Field JK, Duffy SW, Baldwin DR, Whynes DK, Devaraj A, Brain KE, et al. UK Lung Cancer RCT
14 15 465		Pilot Screening Trial: baseline findings from the screening arm provide evidence for the
16 17 466 18		potential implementation of lung cancer screening. Thorax [Internet]. 2015;1–10. Available
19 20 467		from: http://www.ncbi.nlm.nih.gov/pubmed/26645413
21 22 23 468	14.	McCaffery KJ. Assessing psychosocial/quality of life outcomes in screening: how do we do it
24 25 469		better? J Epidemiol Community Heal [Internet]. 2004 Dec 1;58(12):968–70. Available from:
26 27 470 28		http://jech.bmj.com/cgi/doi/10.1136/jech.2004.025114
29 30 471 31	15.	Brodersen J, Thorsen H. Consequences of Screening in Breast Cancer (COS-BC):
³² 33472		development of a questionnaire. Scand J Prim Health Care [Internet]. 2008 Jan [cited 2013
34 35 473 36		Oct 1];26(4):251–6. Available from:
³⁷ 474		http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3406644&tool=pmcentrez&re
39 40 475 41		ndertype=abstract
42 43 476	16.	Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful
44 45 477 46		Approach to Multiple Testing. J R Stat Soc Ser B [Internet]. 1995;57(1):289–300. Available
47 48478		from: http://www.jstor.org/stable/2346101
49 ⁵⁰ 479 51	17.	Brodersen J, Thorsen H, Cockburn J. The adequacy of measurement of short and long-term
52 53 480 54		consequences of false-positive screening mammography. J Med Screen. 2004;11(1):39–44.
55 56 481	18.	DeFrank JT, Barclay C, Sheridan S, Brewer NT, Gilliam M, Moon AM, et al. The psychological
57 58 482 59		harms of screening: the evidence we have versus the evidence we need. J Gen Intern Med
60		

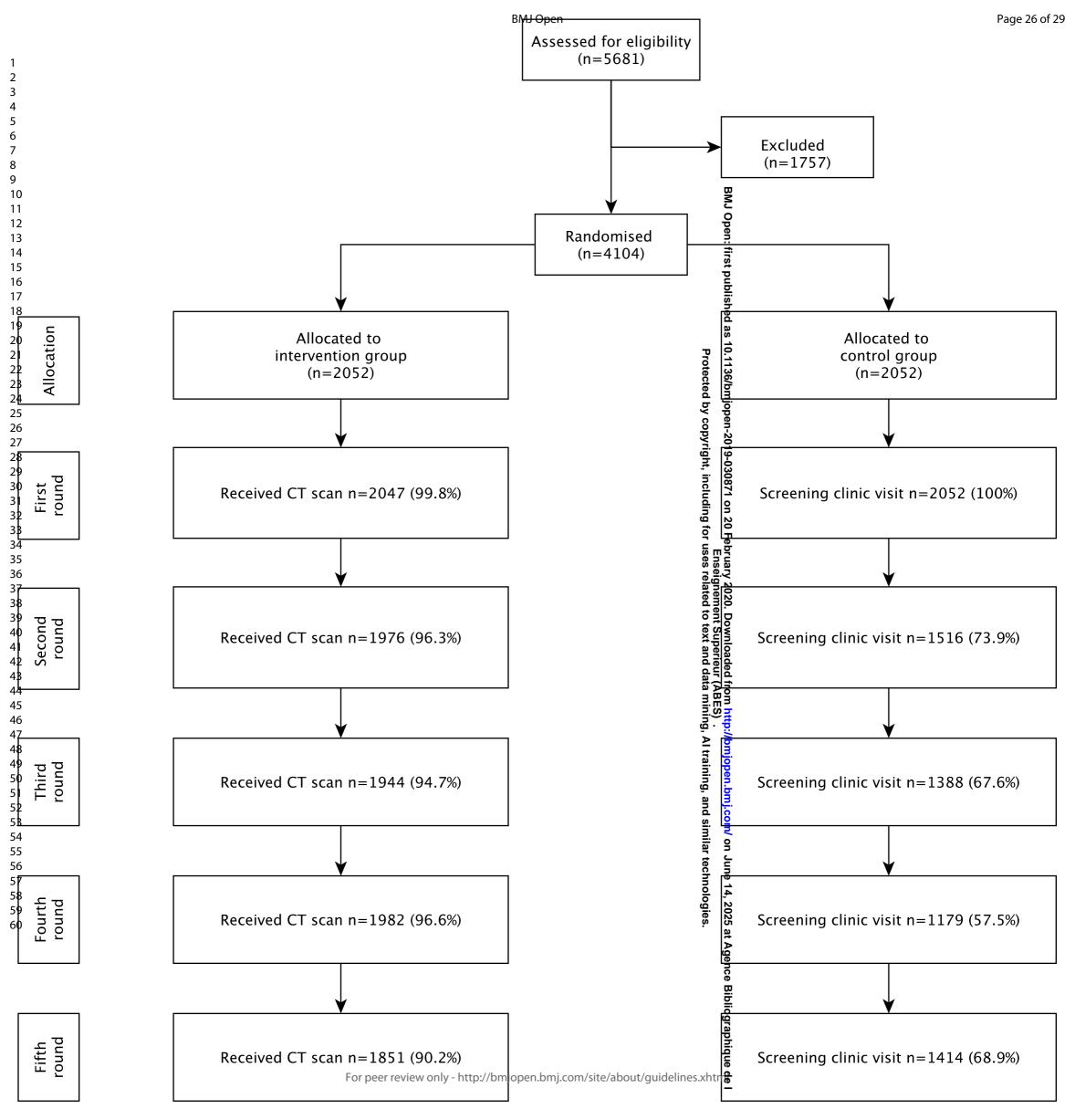
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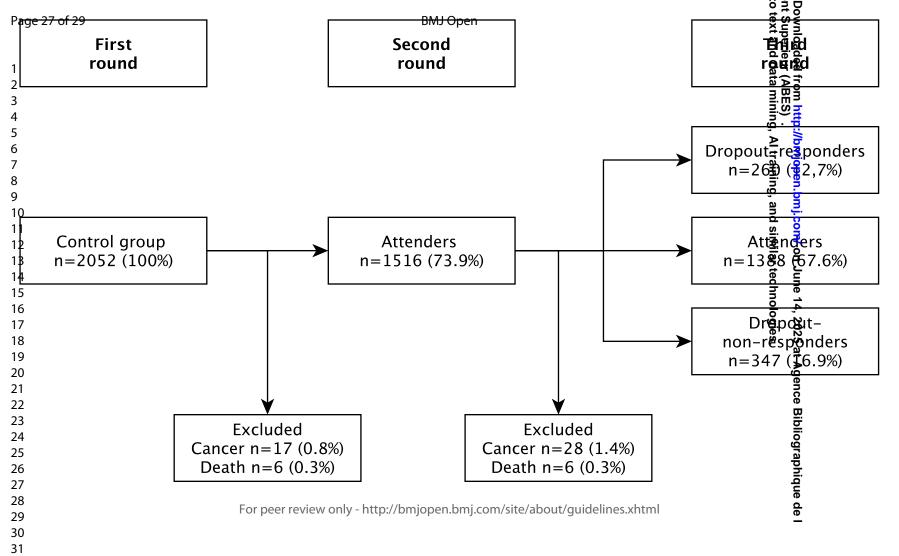
BMJ Open

1 2 3		
$\frac{4}{5}$ 483		[Internet]. 2015;30(2):242–8. Available from:
6 7 484 8		http://www.ncbi.nlm.nih.gov/pubmed/25150033
9 10 485	19.	van den Bergh KAM, Essink-Bot ML, Borsboom GJJM, Scholten ET, van Klaveren RJ, de
11 12 486 13		Koning HJ. Long-term effects of lung cancer computed tomography screening on health-
14 15 487		related quality of life: the NELSON trial. Eur Respir J [Internet]. 2011 Jul [cited 2014 Oct
16 17 488 18		3];38(1):154–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21148229
19 20 489 21	20.	Mercieca-Bebber RL, Price MA, Bell ML, King MT, Webb PM, Butow PN, et al. Ovarian cancer
²² 490 23		study dropouts had worse health-related quality of life and psychosocial symptoms at
24 25 491 26		baseline and over time. Asia Pac J Clin Oncol [Internet]. 2017 Oct;13(5):e381–8. Available
²⁷ 492 28		from: http://www.ncbi.nlm.nih.gov/pubmed/27573704
29 30 493 31	21.	Østerø J, Siersma V, Brodersen J. Breast cancer screening implementation and reassurance.
³² 33494		Eur J Public Health. 2014;24(2):258–63.
34 ³⁵ 495 36	22.	Wendler D, Krohmal B, Emanuel EJ, Grady C. Why patients continue to participate in clinical
37 38 496		research. Arch Intern Med [Internet]. 2008 Jun 23 [cited 2013 Oct 1];168(12):1294–9.
39 ⁴⁰ 497 41		Available from: http://www.ncbi.nlm.nih.gov/pubmed/18574086
42 43 498	23.	Snow WM, Connett JE, Sharma S, Murray RP. Predictors of attendance and dropout at the
44 45 46 499		Lung Health Study 11-year follow-up. Contemp Clin Trials [Internet]. 2007 Jan;28(1):25–32.
47 48 500		Available from: http://linkinghub.elsevier.com/retrieve/pii/S1551714406001157
49 50 51 501	24.	Nohlert E, Öhrvik J, Helgason ÁR. Non-responders in a quitline evaluation are more likely to
52 53 502		be smokers - a drop-out and long-term follow-up study of the Swedish National Tobacco
54 55 56 503		Quitline. Tob Induc Dis [Internet]. 2016;14:5. Available from:
57 58 504		http://www.ncbi.nlm.nih.gov/pubmed/26843854
59 60		
1		

Page 25 of 29

1 2		
3 4 505	25.	Abrahamsen R, Svendsen MV, Henneberger PK, Gundersen GF, Torén K, Kongerud J, et al.
6 7 506 8	i	Non-response in a cross-sectional study of respiratory health in Norway. BMJ Open
9 10 507	,	[Internet]. 2016;6(1):e009912. Available from:
11 12 508 13		http://www.ncbi.nlm.nih.gov/pubmed/26739738
14 15 509	26.	Oleske DM, Kwasny MM, Lavender SA, Andersson GBJ. Participation in occupational health
16 17 510 18)	longitudinal studies: predictors of missed visits and dropouts. Ann Epidemiol [Internet].
19 20 511		2007 Jan;17(1):9–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17140810
21 22 23 512	27.	Chatfield MD, Brayne CE, Matthews FE. A systematic literature review of attrition between
24 25 513		waves in longitudinal studies in the elderly shows a consistent pattern of dropout between
26 27 514 28		differing studies. J Clin Epidemiol [Internet]. 2005 Jan [cited 2014 Mar 13];58(1):13–9.
29 30 515		Available from: http://www.ncbi.nlm.nih.gov/pubmed/15649666
31 32 33 516	28.	Rotnitzky A, Robins J. Analysis of semi-parametric regression models with non-ignorable
34 35 517	,	non-response. Stat Med [Internet]. 16(1–3):81–102. Available from:
36 37 38518		http://www.ncbi.nlm.nih.gov/pubmed/9004385
39 40 519	1	
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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	1
		title or the abstract	
		(b) Provide in the abstract an informative and balanced summary of	1
		what was done and what was found	
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	5
8		of recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and	6
I	-	methods of selection of participants. Describe methods of follow-up	
		<i>Case-control study</i> —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	
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources	
		and methods of selection of participants	
		(b) Cohort study—For matched studies, give matching criteria and	Not
		number of exposed and unexposed	applicable
		<i>Case-control study</i> —For matched studies, give matching criteria	uppneuer
		and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential	6 and 7
	,	confounders, and effect modifiers. Give diagnostic criteria, if	o unu ,
		applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of	
measurement	Ũ	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	6-8
C		applicable, describe which groupings were chosen and why	
Statistical methods	12	(<i>a</i>) Describe all statistical methods, including those used to control	7-8
Statistical methods	12	for confounding	
		(b) Describe any methods used to examine subgroups and	7
		interactions	,
		(c) Explain how missing data were addressed	Not applicable
		(d) Cohort study—If applicable, explain how loss to follow-up was	Not
		addressed	applicable
		<i>Case-control study</i> —If applicable, explain how matching of cases	
		and controls was addressed	

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	<i>Cross-sectional study</i> —If applicable, describe analytical methods	
	taking account of sampling strategy	
	(e) Describe any sensitivity analyses	
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Results Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially	Fig.1
1		eligible, examined for eligibility, confirmed eligible, included in the study,	
		completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Fig.2
		(c) Consider use of a flow diagram	Fig.2
Descriptive	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and	7
data		information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	Table
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A
Outcome data 15*	15*	Cohort study—Report numbers of outcome events or summary measures over time	Table 2-4
		<i>Case-control study</i> —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	Table
		their precision (eg, 95% confidence interval). Make clear which confounders were	2-4
		adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	N/A
		(<i>c</i>) 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		6.	·
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	10
		imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	10
		multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-
			12
Other informati	on		
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.