The emotional impact of screening for lung cancer

Laura Elizabeth Bedford, BSc (hons), MSc

Thesis submitted to the University of Nottingham
for the degree of Doctor of Philosophy

Abstract

Lung cancer is the most commonly diagnosed cancer and the most common cause of cancer-related death worldwide. Population-based lung cancer screening programmes have been initiated in the USA and could soon be implemented in other countries. The overarching purpose of this thesis was to explore the emotional impact of lung cancer screening. The research was conducted as part of a clinical trial that was investigating the effectiveness of a blood autoantibody test, EarlyCDT®-Lung, in identifying individuals at the risk of lung cancer.

A systematic review was conducted that aimed to identify factors associated with the emotional impact of screening for lung cancer. Participants with indeterminate test results, current smokers and females were more likely to experience negative non-specific and specific emotional outcomes. In addition to highlighting several key factors associated with higher levels of emotional distress following screening, factors that warranted further research were also identified. Such factors included age, education level, marital status, ethnic origin, and perceived risk of developing lung cancer. Finally, important methodological and theoretical limitations in the literature were identified. One key methodological limitation was that no studies measured positive emotional outcomes.

A longitudinal study was conducted exploring the impact of lung cancer screening on positive affect, negative affect, lung cancer worry and distress specific to screening for lung cancer. Participants from each of the EarlyCDT®-positive, EarlyCDT®-negative, and control groups completed questionnaires containing emotional outcome measures at pre-randomisation and then at one, three, six and 12 months post randomisation. Scores for each outcome measure were described by groups over time and multilevel regression modelling was used to compare

scores over time within and between groups. Results were reassuring as screening was found to have no clinically important impact on positive affect, negative affect, frequency of lung cancer worry or impact of lung cancer worry on mood and ability to perform daily activities. Although screening specific distress in the EarlyCDT®-positive group was significantly higher than that of the EarlyCDT®-negative group, it did reduce over time. Statistically significant and clinically important increases in the proportion of participants reporting anxiety about the results of future tests/treatments were identified. As a result of this finding, a further study was carried out to identify factors that could influence an individual's level of anxiety about the results of future tests/treatment. Participants more at risk of reporting anxiety about the results of future tests/treatment were younger participants, non-white participants, current smokers and participants who did not own or have a mortgage on their home. Psychological variables associated with increased anxiety were: higher general anxiety scores, higher depression scores, higher negative affect scores, participants who reported that they were upset when they thought about their risk of lung cancer, participants who were worried about getting lung cancer, and those who reported the highest impact of lung cancer worry on mood and ability to perform daily activities.

The final chapter of this thesis presents the results of a randomised controlled trial embedded within the emotional outcomes study (described above), which evaluated the effect of timing of monetary incentives (£5 voucher sent with questionnaire *vs*. £5 voucher sent on receipt of questionnaire) on the following outcomes: study participation rates, questionnaire response rates over time, the number of reminders sent and the completeness of returned questionnaires over time. Previous research had found that monetary incentives were useful in increasing response rates in clinical trials. Results from this trial extended the evidence base by showing that the timing of monetary incentives makes no difference to the above outcomes.

In each chapter the findings of this thesis are discussed in terms of their contribution to knowledge. Recommendations for future research and clinical practice are also made within each chapter.

Acknowledgements

First, thank you to my four supervisors: Professor Denise Kendrick, Professor Kavita Vedhara, Professor Roshan das Nair and Professor John Robertson. Thank you to Ben Young and Marcia Clarke and also to Kay Arnold for the excellent administration assistance.

Thank you to the ECLS Trial Management Group, the Tayside Clinical Trials Unit, the Glasgow Clinical Research Facility, and the Health Informatics Centre for the support with this research.

Very importantly, I wish to thank all the ECLS study participants who gave up their time to take part in the studies encompassed in this PhD.

I would like to thank Dr Victoria Sedman for always being available for a PhD-related chat. Your guidance throughout has been so helpful.

Thank you to my thesis writing buddies, Gareth and Céline. Special thanks to Dr Heather Peto for your friendship and support, particularly when I was writing up.

A big thank you to my family and friends for supporting me during this PhD and throughout all of my studies. To my parents, Steven and Susan. Thank you for everything. You gave me the best start and have always been so supportive. It is because of you that I have been able to complete this thesis.

Table of contents

Chapter 1. Lung cancer screening 20

1.1. Epidemiology of lung cancer 20

1.2. Prevention of lung cancer 37

1.3. Screening 39

1.4. Lung cancer screening 43

1.5. EarlyCDT®-lung 59

1.6. Early Cancer Detection Test – Lung Cancer Scotland Study 60

Chapter 2. The emotional impact of lung cancer screening 65

2.1. The importance of understanding the emotional impact of lung cancer screening 65

2.2. The current evidence on the emotional impact of lung cancer screening 69

2.2.1. Pre-screening emotional impact 94

2.2.2. Short-term emotional impact 95

2.2.3. Long-term emotional impact 99

2.3. Discussion 105

2.3.1. Summary of results 105

2.3.2. Methodological issues 107

2.3.3. Theoretical issues 114

2.3.4. Clinical implications 121

2.3.5. Implications for further research 123

Chapter 3. A systematic review of factors associated with the emotional impact of lung cancer screening 124

3.1. Introduction 124
3.2. Methods 127
3.3. Results 131
3.3.1. Selection of studies 131
3.3.2. Study characteristics 133
3.3.3. Quality assessment 160
3.3.4. Features of the screening process 160
3.3.5. Behavioural predictors 162
3.3.6. Psychosocial predictors 163
3.3.7. Sociodemographic predictors 163
3.3.8. Other predictors 165
3.4. Discussion 165
3.4.1. Summary of the main findings 165
3.4.2. Discussion of findings 166
3.4.3. Strengths and limitations 170
3.4.4. Comparison with existing reviews 175
3.4.5. Implications for future research 175
3.4.6. Clinical implications 176
3.4.7. Conclusion 176
Chapter 4. A longitudinal study exploring the emotional impact of screening for lung cancer 178
4.1. Introduction 178
4.2. Aims and hypotheses 180
4.3. Method 182

4.3.1. Study design 182
4.3.2. Participants 182
4.3.3. Procedure 183
4.3.4. Outcome measures 185
4.3.5. Potential confounding factors 188
4.3.6. Sample size 192
4.3.7. Missing data 193
4.3.8. Data checking prior to analysis 194
4.3.9. Statistical methods 196
4.4. Results 200
4.4.1. Participant flow 200
4.4.2. Participation in the emotional outcomes sub-study 207
4.4.3. Pre-randomisation data 216
4.4.4. Outcome one: Positive affect 224
4.4.5. Outcome two: Negative affect 241
4.4.6. Outcome three: Frequency of worries about getting lung cancer 267
4.4.7. Outcome four: Anxiety about the results of future tests/treatment 282
4.4.8. Outcome five: The extent to which lung cancer worry impacts mood and ability to perform daily activities 297
4.4.9. Outcome six. Screening specific distress 321
4.5. Discussion 338
4.5.1. Summary of the main findings 338
4.5.2. Discussion of findings 344
4.5.3. Strengths and limitations 353
4.5.4. Generalisability 357

4.5.5. Implications for future research 358
4.5.6. Clinical implications 360
4.5.7. Conclusion 362
4.6. Additional information 363
Chapter 5. A longitudinal study exploring predictors of the emotional impact of screening for lung cancer 364
5.1. Introduction 364
5.2. Aims and hypotheses 367
5.3. Method 368
5.3.1. Study design 368
5.3.2. Participants 368
5.3.3. Procedure 369
5.3.4. Outcome measure 369
5.3.5. Potential predictor factors 370
4.3.6. Missing data 372
4.3.7. Data checking prior to analysis 373
4.3.8. Statistical methods 373
5.4. Results 374
5.4.1. Participant flow 374
5.4.2. Pre-randomisation data 374
5.4.3. Univariate analyses 377
5.4.4. Multivariable analyses 383
5.5. Discussion 389
5.5.1. Summary of the main findings 389

5.5.2. Discussion of findings 389
5.5.3. Strengths and limitations 393
5.5.4. Generalisability 395
5.5.5. Implications for future research 396
5.5.6. Clinical implications 397

Chapter 6: A randomised controlled trial to explore the effect of the timing of monetary incentives on participation rates and questionnaire response rates in the ECLS study 399

6.1. Introduction 399
6.2. Aims and hypotheses 415
6.3. Method 417
6.3.1. Trial design 417
6.3.2. Participants 417
6.3.3. Interventions 418
6.3.4. Outcomes 419
6.3.5. Sample size 420
6.3.6. Randomisation 420
6.3.7. Statistical methods 421
6.4. Results 422
6.4.1. Participant flow 422
6.4.2. Recruitment 424
6.4.3. Pre-randomisation data 427
6.4.4. Outcomes and estimation 431
6.5. Discussion 443

6.5.1. Summary of the main findings 443
6.5.2. Discussion of findings 444
6.5.3. A theoretical framework to explain these findings 447
6.5.4. Strengths and limitations 448
6.5.5. Generalisability 450
6.5.6. Implications for future research 450
6.5.7. Clinical implications 451
6.5.8. Conclusion 452

References 456

Appendices 479

Appendix 1. Permission to republish figures depicting the Stress and Coping Model 479
Appendix 2. Permission to republish a figure illustrating the Self-Regulation Model of illness beliefs 480
Appendix 3. Systematic review data extraction form 481
Appendix 4. Systematic review quality assessment results 484
Appendix 5. Ethical approval documents 494
Appendix 6. Sample questionnaire cover letter 499
Appendix 7. Sample study questionnaire 500
Appendix 8. Chapter four model checking results 515
Appendix 9. Power calculation output for chapter 6 548

List of tables

Table 1. Lung Cancer (C33-C34), Number of New Cases, Crude and European Age-Standardised Incidence Rates per 100,000 Population, United Kingdom, 2013, published by Cancer Research UK [14] 26

Table 2. Lung Cancer (C33-C34), Number of Deaths, Crude and European Age-Standardised Mortality Rates per 100,000 Population, UK, 2012, published by Cancer Research UK [19]..... 28

Table 3. Wilson and Jungner's screening criteria 40

Table 4. A two by two table illustrating the potential outcomes of screening and how the sensitivity, specificity, PPV and NPV are calculated 42

Table 5. A summary of randomised controlled trials of lung cancer screening using LDCT ... 49

Table 6. Inclusion and exclusion criteria for the ECLS study (taken from the Sullivan et al. 2017) [100] 61

Table 7. Characteristics of publications that have reported on the emotional impact of screening for lung cancer. 71

Table 8. Characteristics of included studies and associations between predictor factors and emotional outcomes..... 135

Table 9. Pre-randomisation sociodemographic and emotional characteristics amongst participants and non-participants in the emotional outcomes sub-study..... 210

Table 10. Pre-randomisation sociodemographic and emotional characteristics amongst participants in each test result group (EarlyCDT®-positive, EarlyCDT®-negative, control).... 218

Table 11. Positive affect scores amongst participants in each screening group (EarlyCDT®-positive, EarlyCDT®-negative, control) at each study time-point..... 225

Table 12. Unadjusted analyses comparing positive affect scores within groups (EarlyCDT®-positive, EarlyCDT®-negative, control) over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation scores 229
Table 13. Adjusted analyses comparing positive affect scores within groups (EarlyCDT®-positive, EarlyCDT®-negative, control) over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation scores 232
Table 14. Unadjusted analyses comparing positive affect scores between groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point 235
Table 15. Adjusted analyses comparing positive affect scores between groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point 238
Table 16. Negative affect scores amongst participants in each screening group at each study time-point 242
Table 17. Unadjusted analyses comparing negative affect scores, logarithmic transformed scores, and anti-logged scores within groups (EarlyCDT®-positive, EarlyCDT®-negative, control) over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation scores 246
Table 18. Adjusted analyses comparing negative affect scores, logarithmic transformed scores and anti-logged scores within groups (EarlyCDT®-positive, EarlyCDT®-negative, control) over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation scores 250
Table 19. Unadjusted analyses comparing negative affect scores, logarithmic transformed scores and anti-logged scores between groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point 255

Table 20. Adjusted analyses comparing negative affect scores, logarithmic transformed scores, and anti-logged scores between groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point..... 261

Table 21. Frequency of worries about getting lung cancer amongst participants in each screening group at each study time point 268

Table 22. Unadjusted analyses comparing frequency of worries about getting lung cancer within groups (EarlyCDT®-positive, EarlyCDT®-negative, control) over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation..... 272

Table 23. Adjusted analyses comparing frequency of worries about getting lung cancer within groups (EarlyCDT®-positive, EarlyCDT®-negative, control) over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation..... 273

Table 24. Unadjusted analyses comparing frequency of worries about getting lung cancer between screening groups across all study time-points and at each study time-point..... 277

Table 25. Adjusted analyses comparing frequency of worries about getting lung cancer between screening groups across all study time-points and at each study time-point 279

Table 26. Current level of anxiety about the results of future tests/treatment amongst participants in each screening group at each study time point 283

Table 27. Unadjusted analyses comparing current level of anxiety about the results of future tests/treatment within screening groups over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation 287

Table 28. Adjusted analyses comparing current level of anxiety about the results of future tests/treatment within groups (EarlyCDT®-positive, EarlyCDT®-negative, control) over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation 288

Table 29. Unadjusted analyses comparing current level of anxiety about the results of future tests/treatment between screening groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point..... 292
Table 30. Adjusted analyses comparing current level of anxiety about the results of future tests/treatment between groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point..... 294
Table 31. Impact of lung cancer worry on mood and ability to perform daily activities amongst participants in each screening group 298
Table 32. Unadjusted analyses comparing impact of lung cancer worry scores, logarithmic transformed scores, and anti-logged scores within screening groups over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation..... 303
Table 33. Adjusted analyses comparing impact of lung cancer worry scores, logarithmic transformed scores and anti-logged scores within screening groups over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation..... 306
Table 34. Unadjusted analyses comparing impact of lung cancer worry scores, logarithmic transformed scores and anti-logged scores between test result groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point..... 312
Table 35. Adjusted analyses comparing impact of lung cancer worry scores, logarithmic transformed scores, and anti-logged negative scores between groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point..... 316
Table 36. Unadjusted analyses comparing total IES scores amongst participants in the EarlyCDT®-positive group and the EarlyCDT®-negative group..... 322
Table 37. Unadjusted analyses comparing IES total scores, logarithmic transformed scores, and anti-logged scores within groups (EarlyCDT®-positive, EarlyCDT®-negative) over time (three, six and 12 months post-randomisation)..... 327

Table 38. Adjusted analyses comparing IES total scores, logarithmic transformed scores and anti-logged scores within groups (EarlyCDT®-positive, EarlyCDT®-negative) over time (one, three, six and 12 months post-randomisation) 329
Table 39. Unadjusted analyses comparing IES total scores, logarithmic transformed scores and anti-logged scores between groups (EarlyCDT®-positive, EarlyCDT®-negative) across all study time-points and at each study time-point 333
Table 40. Adjusted analyses comparing IES total scores, logarithmic transformed scores, and anti-logged scores between groups (EarlyCDT®-positive, EarlyCDT®-negative) across all study time-points and at each study time-point 335
Table 41. Illness Perception Questionnaire-Revised scores amongst participants in each screening group (EarlyCDT®-positive, EarlyCDT®-negative, control) 375
Table 42. Univariate analyses for sociodemographic, clinical, behavioural and psychological predictors of current level of anxiety about the results of future tests/treatment 378
Table 43. Multivariable analysis of factors associated with current level of worry about the results of future tests/treatments 385
Table 44. Results of the significant interaction identified in the analyses for both multivariate models 388
Table 45. Characteristics and results of publications that have reported on monetary incentives to increase participant rates and questionnaire response rates in randomised controlled trials 406
Table 46. Pre-randomisation sociodemographic characteristics for each group of study participants 428
Table 47. Analyses comparing questionnaire response rates by voucher condition at each study time-point 432

Table 48. Multivariate analyses comparing questionnaire response rates between voucher condition groups across all study time-points and at each study time-point 434
Table 49. Analyses comparing reminders sent by voucher condition at each study time-point 437
Table 50. Multivariate analyses comparing reminders sent between voucher condition groups across all study time-points and at each study time-point..... 438
Table 51. Analyses comparing questionnaires with incomplete data by voucher condition at each study time-point..... 441
Table 52. Multivariate analyses comparing questionnaires with incomplete data between voucher condition groups across all study time-points and at each study time-point..... 442

List of figures

Figure 1. Lung Cancer (C33-C34) European Age-Standardised Incidence Rates and Smoking Prevalence, Great Britain, 1948-2012, published by Cancer Research UK [6] 22

Figure 2. Lung Cancer Age-Adjusted Incidence Rates per 100,000 Population, By Sex and By Country, 2003 - 2012, published by Cancer Research UK [7] 23

Figure 3. Lung Cancer (C33-C34), European Age-Standardised Mortality Rates, UK, 1971 - 2012, published by Cancer Research UK [9] 24

Figure 4. ECLS study flow chart (adapted from flow chart in ECLS study protocol) 64

Figure 5. The original stress and coping model developed by Lazarus & Folkman in 1984[122] and published in Folkman 2008[123] 115

Figure 6. The revised stress and coping model introduced by Folkman in 1997 [123] and published in Folkman 2008[123] 116

Figure 7. Schematic representation of Leventhal et al's (1980) Self-Regulation Model (SRM) of illness beliefs, published by Hagger and Orbell [132] 120

Figure 8. Search strategy for MEDLINE 129

Figure 9. PRISMA flowchart detailing the selection of studies for the review..... 132

Figure 10. Flow chart illustrating the number of participants from each screening group (control, EarlyCDT®-negative, EarlyCDT®-positive) who were selected to take part in the emotional outcomes sub-study, the number sent study questionnaires at each time-point (one, three, six and 12 month), the number who returned each questionnaire and details of those sent no further questionnaires. 204

Figure 11. Positive affect scores amongst participants in each group (EarlyCDT®-positive, EarlyCDT®-negative, control) at each study time-point (pre-randomisation, one month, three month, six month and 12 month) 227
Figure 12. Negative affect scores amongst participants in each group (EarlyCDT®-positive, EarlyCDT®-negative, control) at each study time-point (pre-randomisation, one month, three month, six month and 12 month) 244
Figure 13. Frequency of worries about getting lung cancer amongst participants in each screening group (EarlyCDT®-positive, EarlyCDT®-negative, control) at each study time-point 270
Figure 14. Current level of anxiety about the results of future tests/treatment amongst participants in each screening group (EarlyCDT®-positive, EarlyCDT®-negative, control) at each study time-point 285
Figure 15. Impact of lung cancer worry scores amongst participants in each screening group at each study time-point..... 300
Figure 16. IES total scores amongst participants in each test result group (EarlyCDT®-positive, EarlyCDT®-negative) at each study time-point (pre-randomisation, one month, three month, six month and 12 month)..... 324
Figure 17. Strategies found to have no significant impact on postal questionnaire responses in the review and meta-analysis published by Brueton et al. in 2014 [192] and the RCT published subsequent to the review [193]..... 405
Figure 18. CONSORT 2010 Flow Diagram illustrating the number of participants randomly assigned in each group, the number who received the intervention and the number who were analysed for the primary and secondary outcomes. 426

Chapter 1. Lung cancer screening

This chapter outlines the epidemiology, causes and approaches to prevention of lung cancer. A brief history of screening for disease is provided, which includes Wilson and Jungner's Screening Criteria. This is followed by a definition of screening and clarification of key terms associated with screening (sensitivity, specificity, negative predictive value and positive predictive value). Screening for lung cancer is discussed, including potential benefits and harms. Finally, a new autoantibody test for the early detection of lung cancer (EarlyCDT®-Lung), and the randomised controlled trial (RCT) currently determining its clinical effectiveness, are described.

1.1. Epidemiology of lung cancer

1.1.1. Lung cancer incidence and mortality trends over time

Lung cancer incidence trends

Lung cancer was an extremely rare disease at the start of the 20th century. However, since 1985, it has been the most commonly diagnosed cancer worldwide [1]. It is estimated that 85 – 90% of lung cancers are caused by cigarette smoking [1]. As there is a latency period between when an individual starts smoking and when they are diagnosed with lung cancer, trends in lung cancer incidence reflect the patterns in smoking prevalence from 20 to 30 years earlier [2]. Smoking rates in developed countries were highest in the middle of the 20th century and have since declined[3]. Lung cancer rates, therefore, increased and then peaked among males in

developed countries in the 1980s and have subsequently declined [2]. As females started smoking several decades later than males, lung cancer rates among females are still rising in a number of countries [4]. Of concern is that, compared with more developed countries, lung cancer rates in less developed countries are increasing. Worldwide estimates for 1980 showed that 31% of lung cancers were diagnosed in less developed countries and 69% in more developed countries. In 2002, 50% of lung cancers were diagnosed in less developed countries, and in 2012, this figure had increased to 58% (1,066,000 in less developed countries *vs.* 758,000 in more developed countries) [5].

Figure one, published by Cancer Research UK, depicts trends in smoking prevalence and lung cancer incidence rates in the United Kingdom (UK) [6]. Lung cancer rates were at their highest among males in the UK in the 1980s and have since decreased. Lung cancer incidence rates among females are still increasing in the UK.

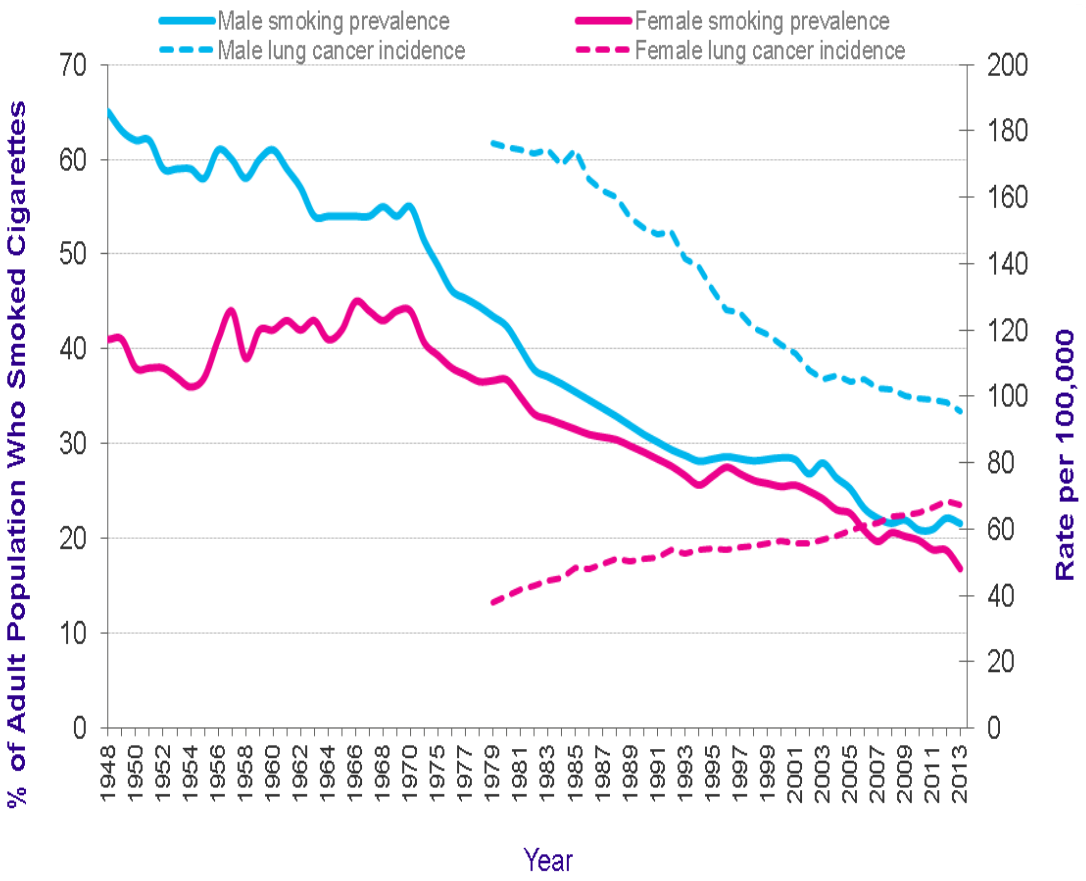


Figure 1. Lung Cancer (C33-C34) European Age-Standardised Incidence Rates and Smoking Prevalence, Great Britain, 1948-2012, published by Cancer Research UK [6]

Incidence rates per 100,000 population for England, Northern Ireland, Scotland and Wales from 2003 to 2012 are presented in figure two[7]. Lung cancer rates have decreased in males but increased in females across all four countries [7]. In 2011, UK cancer incidence projections to 2030 were published [8]. Lung cancer incidence rates are expected to decrease for males and plateau in females. However, the authors emphasise that due to a growing and aging population, the number of cases will actually increase for all cancers, including those with decreasing rates. It is predicted that between 2007 and 2030, the number of cancers in males will increase by 55% and the number of cases in females will increase by 35%.

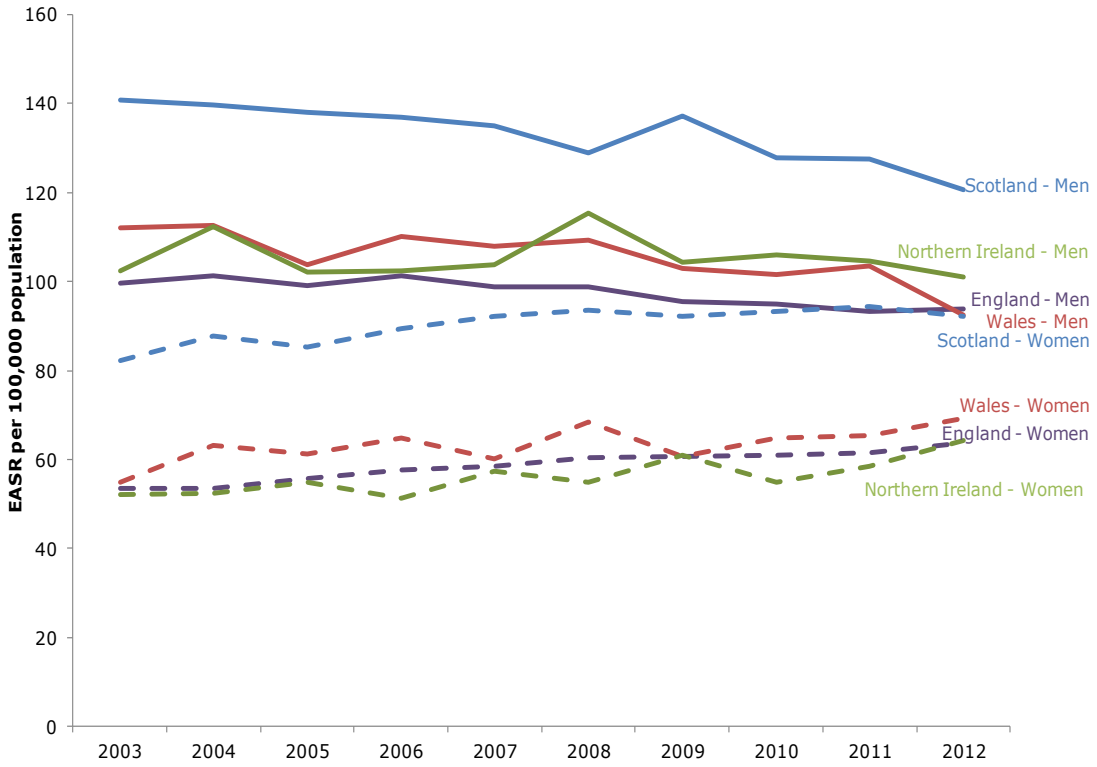


Figure 2. Lung Cancer Age-Adjusted Incidence Rates per 100,000 Population, By Sex and By Country, 2003 - 2012, published by Cancer Research UK [7]

Original data sources: 1. Welsh Cancer Intelligence and Surveillance Unit's National Cancer Registry, 2. Office for National Statistics, 3. Scottish Cancer Registry and 4. Northern Ireland Cancer Registry

Lung cancer mortality trends

Lung cancer mortality trends closely reflect incidence trends in a particular country [2]. A paper that explored the international epidemiology of lung cancer reported trends in lung cancer mortality between 1980 and 2005 for 24 countries that could provide adequate mortality data [2]. Lung cancer mortality rates for males and females were found to be declining over time in five developed countries. Mortality rates for both sexes have remained stable in Bulgaria. However, in four countries, mortality rates have continued to increase for both sexes. These countries included China, Israel, Romania and South Korea. In 11 European countries, mortality rates

have declined in males but increased in females. In Canada, Denmark and the United States, mortality rates have declined in males and have increased and then plateaued in females [2].

Lung cancer mortality trends for the UK are displayed in figure three, which was published by Cancer Research UK [9]. Between 1971 and 2012, lung cancer mortality has decreased in males and increased in females, which reflects incidence trends. The same patterns have been observed across England [10], Northern Ireland [11], Scotland [12] and Wales [13].

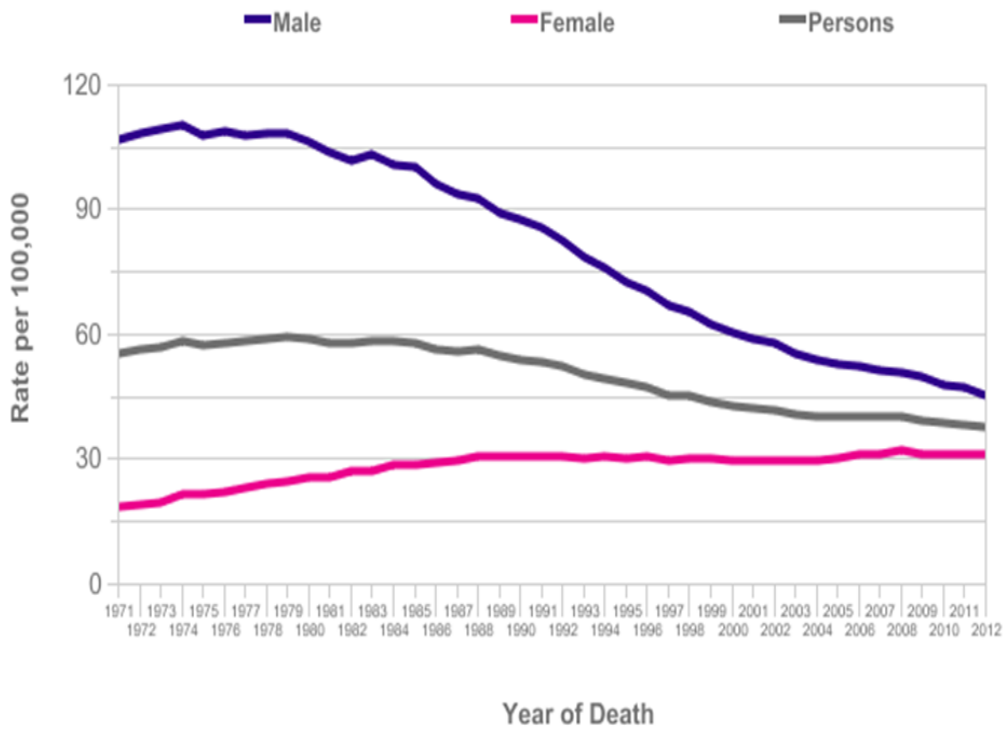


Figure 3. Lung Cancer (C33-C34), European Age-Standardised Mortality Rates, UK, 1971 - 2012, published by Cancer Research UK [9]

Original data sources: 1. Office for National Statistics, 2. General Register Office for Scotland and, 3. Northern Ireland Statistics and Research Agency

1.1.2. Current incidence, mortality and survival rates

Incidence rates

It is estimated that in 2012, 1.82 million people were diagnosed with lung cancer worldwide [5]. Lung cancer is the most common cancer in males and the third most common cancer in females. In 2012, 1.2 million males (16.7% of all male cases) and 583,000 females (8.7% of all female cases) were diagnosed [5].

In the UK, lung cancer is the third most common cancer. The most recent lung cancer incidence rates for the UK are displayed in table one, which was published by Cancer Research UK [14]. In 2013, 45,525 lung cancers were diagnosed, which accounted for 13% of all cases of cancer [14]. Overall, Lung cancer is the second most common cancer in both males and females in the UK[14]. Sub nationally, lung cancer is the second most common cancer for both males and females in England and Scotland [15,16]. Scotland has one of the highest rates of lung cancer in the world [17]. As can be seen in table one, the European age-standardised incidence rates are significantly higher in Scotland compared with England, Northern Ireland and Wales [14]. In Northern Ireland, lung cancer is the third most common cancer for both males and females [18]. In Wales, Lung cancer is the third most common cancer in males and the second most common cancer in females [7].

Table 1. Lung Cancer (C33-C34), Number of New Cases, Crude and European Age-Standardised Incidence Rates per 100,000 Population, United Kingdom, 2013, published by Cancer Research UK [14]

		England	Wales	Scotland	Northern Ireland	UK
Male	Cases	19,830	1,326	2,652	673	24,481
	Crude Rate	74.7	87.5	102.5	75.0	77.6
	AS[1] Rate	92.5	97.1	123.2	102.8	95.6
	AS Rate - 95% LCL	91.2	91.9	118.5	95.0	94.4
	AS Rate - 95% UCL	93.8	102.3	127.9	110.6	96.8
Female	Cases	16,823	1,057	2625	539	21,044
	Crude Rate	61.6	67.4	95.8	57.8	64.6
	AS Rate	64.4	64.0	96.1	66.8	67.2
	AS Rate - 95% LCL	63.4	60.2	92.4	61.1	66.3
	AS Rate - 95% UCL	65.4	67.9	99.7	72.4	68.2
Persons	Cases	36,653	2,383	5,277	1,212	45,525
	Crude Rate	68.0	77.3	99.0	66.2	71.0
	AS Rate	76.5	78.2	107.0	82.3	79.4
	AS Rate - 95% LCL	75.7	75.1	104.1	77.6	78.7
	AS Rate - 95% UCL	77.3	81.4	109.9	86.9	80.1

[1] Cancer Research UK have defined age-standardised rates as rates that have been adjusted to allow for the number of older or younger individuals in the population studied. CITE: http://www.cancerresearchuk.org/cancer-info/utilities/Glossary/news-agestandardised-rate

Mortality rates

Lung cancer is currently the most common cause of cancer-related death worldwide [5]. There were 1.6 million deaths from lung cancer in 2012, which accounts for 19.4% of the total number of cancer deaths [5]. Lung cancer is the leading cause of cancer-related death in both males and females in the UK. Mortality rates for the UK in 2012 are presented in table two[19]. There were 35,371 deaths from lung cancer in 2012 (6% of all deaths and 22% of all deaths from cancer) [19]. Lung cancer accounts for 23% of all male deaths from cancer and 21% of all female deaths from cancer. Sub nationally, lung cancer is the leading cause of cancer-related death in England [20], Northern Ireland [18], Scotland [16] and Wales [13]. As with current incidence rates, the European age-standardised mortality rates are significantly higher in Scotland compared with England, Northern Ireland and Wales [19].

Table 2. Lung Cancer (C33-C34), Number of Deaths, Crude and European Age-Standardised Mortality Rates per 100,000 Population, UK, 2012, published by Cancer Research UK [19]

		England	Wales	Scotland	Northern Ireland	UK
Male	Deaths	15,625	1,044	2,094	541	19,304
	Crude Rate	59.3	69.1	81.3	60.5	61.6
	AS Rate	43.9	46.2	58.9	51.3	45.5
	AS Rate - 95% LCL	43.3	43.4	56.4	47.0	44.9
	AS Rate - 95% UCL	44.6	49	61.4	55.6	46.2
Female	Deaths	12,706	850	2,095	416	16,067
	Crude Rate	46.8	54.3	76.6	44.8	49.6
	AS Rate	29.7	31.7	46.7	32.7	31.4
	AS Rate - 95% LCL	29.1	29.6	44.7	29.6	30.9
	AS Rate - 95% UCL	30.2	33.9	48.7	35.9	31.9
Persons	Deaths	28,331	1,894	4,189	957	35,371
	Crude Rate	53	61.6	78.8	52.5	55.5
	AS Rate	36	38.2	51.8	40.7	37.6
	AS Rate - 95% LCL	35.5	36.5	50.3	38.1	37.2
	AS Rate - 95% UCL	36.4	39.9	53.4	43.2	38

Survival rates

Population data collected from 67 countries from 1995 to 2009 showed that five-year survival rates for lung cancer are very low, generally between 10 and 20% in both developed and non-developed regions [21]. Statistics reported by Cancer Research UK show that the lung cancer survival rates for patients aged 15 to 99 in England and Wales from 2010 to 2011 are: 32.1% (one-year), 9.5% (five-year) and 4.9% (ten-year) [22]. The Information Services Division Scotland reported the one and five-year survival rates for patients diagnosed between 2007 and 2011 as 31.5% and 9.8%, respectively [23]. The Northern Ireland Cancer Registry reported a one-year survival rate of 31.5% and a five-year survival rate of 10.5% for patients diagnosed with lung cancer between 2005 and 2009 [11].

International, population-based studies on several cancers have found that the stage at diagnosis can determine the survival rate [24]. However, at present, only a very limited number of such studies have explored survival rates for the different stages of lung cancer [24]. The first and, to the author's knowledge, only international population-based study to explore lung cancer survival and stage at diagnosis was published in 2013. Six countries were included: Australia, Canada, Denmark, Norway, Sweden and the UK. Analyses included 232,278 patients and were conducted between the years 2004 and 2007. Results showed that lung cancer is generally diagnosed at an advanced stage. As lung cancer is not symptomatic early in the disease process it tends to be diagnosed when patients present with symptoms that can include a persistent cough, haemoptysis, weight loss and chest pain [25]. Once missing data for the UK had been imputed, it was found that 13.5% of patients were diagnosed at stage I, 6.8% at stage II, 28.6% at stage III and 51% at stage IV. One-year age-standardised survival rates for patients diagnosed with stage I lung cancer were 72.5%. For patients diagnosed with stage II, III and IV, the survival rates were 59.8%, 35.3% and 15.9%, respectively [24].

1.1.3. Risk factors for lung cancer

The concept of 'risk' can be defined as the likelihood that a healthy individual will develop a particular condition or disease within a specific period of time [26]. Various factors can affect an individual's risk. According to Dahlgren and Whitehead's (1991) model of the determinants of health, these factors can include: 1) demographic variables (e.g., age, sex, genetic characteristics), 2) individual lifestyle factors, 3) social and community networks, 4) living and working conditions, and 5) socioeconomic, cultural and environmental factors [27]. Risk prediction models incorporate relevant risk factors for a particular condition or disease [28]. Since 2012, there has been a considerable increase in the number of risk prediction models developed to assess the probability that an individual will develop lung cancer [28]. A recently published systematic review of lung cancer risk prediction models identified eight epidemiological models[28]. Since the review searches were conducted, two more epidemiological models have been published: the Prostate, Lung, Colorectal, and Ovarian (PLCO)$_{ALL2014}$ [29] and the Pittsburgh model [30]. Although further validation studies are required to test existing epidemiological risk prediction models, the authors of the systematic review conclude that they do show promise in identifying individuals at high risk of lung cancer [28]. The predictors of lung cancer risk that are included in the epidemiological risk prediction models, in addition to other known predictors not included in the models, are discussed below and are structured according to Dahlgren and Whitehead's (1991) model of the determinants of health [27].

Demographic risk factors

Age

The SEER Cancer Statistics Review reported that the median age of diagnosis in lung cancer patients between 2008 and 2012 was 70 years [31]. In terms of age distribution of incidence cases, 9.9% of patients diagnosed with lung cancer were aged 54 or less, 21.4% were aged between 55 and 64 years, 31.9% were aged between 65 and 74 years, 27.6% were aged between 75 and 84 years and 9.1% were aged 85 years or older [31]. Five risk prediction models for lung cancer have reported that lung cancer risk increases with age [29,30,32-34].

Ethnicity

Ethnicity is a complex factor, which has been found to be associated with socioeconomic status [1]. Ethnic differences in lung cancer risk have been identified. For example, the PLCO risk prediction models incorporated ethnicity and found that when compared with individuals of a white ethnic group, individuals of a black ethnic group had an increased six year ($PLCO_{M2012}$ [34] and $PLCO_{ALL2014}$ [29]) and nine year (PLCO [33]) risk of developing lung cancer. Research has investigated the role of cigarette smoking as a potential cause of this disparity [35]. However, smoking alone has not been found to account for observed differences in lung cancer incidence between African Americans and European Americans [35]. It is therefore important that other potential causes of ethnic differences in lung cancer risk are considered, such as level of occupational exposures (e.g., asbestos) and degree of exposure to urban air pollution [35].

Gender

Global cancer statistics for 2008 revealed that males have a higher risk of developing lung cancer compared with females [4]. The cumulative risk for males was 5.7% in developed areas and 3.3% in less developed areas. The cumulative risk for females was 2.3% in developed areas and 1.3% in less developed areas.

Family history of cancer

A systematic review and meta-analysis were conducted to explore the relationship between family history of lung cancer and risk of lung cancer [36]. Pooled data from cohort and case-control studies revealed that individuals with a family history of lung cancer had an almost two-fold increase in risk of developing the disease (Relative Risk (RR): 1.84, 95% CI 1.64 to 2.05) [36]. This finding is supported by four risk prediction models[29,33,34,37]. Results from the systematic review also showed that risk was further increased with a higher number of relatives diagnosed with lung cancer and relatives who were diagnosed at an earlier age [36].

Furthermore, three risk prediction models have reported that risk of lung cancer is significantly higher in individuals with a personal history of cancer compared with those with no history of cancer [29,34,37]. Cases of smoking related cancer in the family has also been associated with a significantly higher risk of lung cancer [38] as well as having first degree relatives with a diagnosis of any type of cancer [37].

Additional medical conditions

Six risk prediction models incorporated additional medical conditions as risk factors for lung cancer [29,33,34,37-39]. Individuals with a prior diagnosis of pneumonia have been found to be at significantly higher risk of lung cancer compared with individuals with no prior diagnosis of pneumonia [37]. Furthermore, a prior diagnosis of chronic obstructive pulmonary disease (COPD) [29,33,34,39], history of emphysema [38] and a diagnosis of hayfever [38,39] have all been associated with a significantly greater risk of developing lung cancer.

Genetic characteristics

Recent research has considered the role of genetic factors, some of which have been added to existing epidemiological risk prediction models [28]. However, at present, it is unclear as to which genetic predictors have a significant impact on lung cancer risk and further research is required in this area [28].

Individual lifestyle risk factors

Cigarette smoking

The association between smoking and lung cancer was first identified in a pioneering report published by the Surgeon General in 1964 [40]. This report stated that compared with other factors, smoking was the most important predictor of cases of lung cancer in men. Although data for women was limited, the association appeared to be the same [40]. All epidemiological risk prediction models for lung cancer have included cigarette smoking as a key risk factor

[29,30,32-34,37-39,41,42], and, at present, there is strong evidence that 85 – 90% of lung cancers are caused by cigarette smoking [1].

Current smokers are at greater risk of developing lung cancer than former and never smokers [33]. The PLCO model reported that current smokers had a significantly greater nine-year risk of lung cancer compared with former and never smokers (OR 1.72, 95% CI 1.43 to 2.01, $p < 0.001$) [33]. The $PLCO_{M2012}$ model found that current smokers had a significantly higher six-year risk than former smokers (OR 1.3, 95% CI 1.05 to 1.61, $p = 0.02$) [34].

For former smokers, risk prediction models have found that risk of lung cancer significantly decreases as quit time increases [29,32-34,39,41]. However, former smokers are still at significantly higher risk of developing lung cancer when compared with individuals who have never smoked. For example, the $PLCO_{ALL2014}$ model reported that former smokers had a significantly higher six-year risk of lung cancer than never smokers (OR 12.71, 95% CI 5.11 to 31.63, $p < 0.01$) [29].

As well as considering the presence or absence of cigarette smoking as a risk factor for lung cancer, research has explored the impact of smoking duration, smoking pack years, number of cigarettes smoked per day and inhalation depth of cigarette smoke on lung cancer risk. Seven risk prediction models have identified positive associations between smoking duration and lung cancer risk [29,30,33,34,37,41,42]. A greater number of pack years have also been associated with an increased risk of developing lung cancer (four risk prediction models [32,33,38,39]). The same trend has been found for the average number of cigarettes smoked per day (five risk prediction models [29,30,34,41,42]). Age that smoking commenced also predicts risk. For example, individuals who started smoking earlier have been found to have a higher risk of developing lung cancer [42]

Diet

Although not incorporated in any risk prediction models, case-control and prospective cohort studies have found that individuals who consume high quantities of fruit or vegetables have a lower risk of developing lung cancer when compared with individuals who consume low quantities of fruit or vegetables [43]. However, results of studies exploring diet as a risk factor must be interpreted with caution as cigarette smoking is associated with other negative health behaviours, such as a poor diet. Therefore, it is difficult to identify the exact role of dietary behaviours as risk factors for lung cancer [43].

Living and working conditions as risk factors

Exposure to secondhand smoke

Exposure to secondhand smoke (also referred to as 'passive smoking' or 'Environmental Tobacco Smoke') has been investigated as a potential risk factor and incorporated in two risk prediction models. One model, the Spitz model, reported that never smokers exposed to second hand smoke had a significantly higher one-year risk of lung cancer than never smokers not exposed to second hand smoke (OR 1.80, 95% CI 1.20 to 2.69, p = 0.0042) [38]. In addition, although not statistically significant, the Environment and Genetics in Lung cancer Etiology (EAGLE) model found that individuals exposed to secondhand smoke in the workplace had a higher risk of lung cancer than those not exposed to smoke in the workplace (Residual OR 1.54, 95% CI 0.72 to 1.41)[32].

Asbestos exposure

Asbestos exposure is commonly regarded as a key occupational risk factor for lung cancer [1]. Four risk prediction models have reported that individuals exposed to asbestos are at higher risk of developing lung cancer than individuals not exposed to asbestos (table four) [37-39,41].

Dust and wood dust exposure

Both current and former smokers who had been exposed to dust or wood dust have been found to be at higher risk of lung cancer than those not exposed to dust or wood dust [38,39]. The data from the two models that included these risk factors is reported in table four.

Socioeconomic, cultural and environmental risk factors

Socioeconomic status

Individuals of lower socioeconomic status (SES) are at higher risk of developing lung cancer than individuals of higher SES [43]. For example, men and women in the lowest SES groups in England are more likely to be diagnosed with lung cancer than men and women in the highest SES groups (men: RR 2.53, 95% CI 2.48 to 2.58; women: RR 2.73, 95% CI 2.66 to 2.80) [44]. The three PLCO risk prediction models estimated SES using education level and reported that lower SES was associated with a significantly higher six-year [29,34] and nine-year [33] risk of lung cancer. Socioeconomic disparities in lung cancer risk have been observed worldwide and could result from the interaction of a number of different determinants [43]. These include lifestyle factors, such as smoking [43]. For example, smoking rates in England have been found to be four

times higher among the lowest SES groups (60.7% (95% CI 58.2 to 63.3)) compared with the highest SES groups (15.3% (95% CI 14.8 to 15.8)) [45]. Individuals of a lower SES are also more likely to have been exposed to secondhand smoke as well as other environmental and occupational risk factors for lung cancer, such as asbestos [35].

Air pollution

It has been estimated that between 1 – 2% of lung cancers could be caused by exposure to air pollution [43]. However, at present, it is difficult to identify the exact role that different components of air pollution play in the development of cancer and further research is investigating this [1].

1.2. Prevention of lung cancer

There are three different levels of disease prevention: primary, secondary and tertiary [46]. Primary prevention involves inhibiting the development of a disease by reducing exposure to key risk factors [46]. There have been a number of primary prevention interventions to reduce exposure to risk factors for lung cancer. For example, the World Health Organisation (WHO), has worked with the International Labour Organisation and other relevant organisations to eradicate asbestos-related diseases, including lung cancer [47]. Efforts have been made to stop the use of all types of asbestos through information provision on safer alternatives and development of replacements [47]. The World Health Assembly also implemented the "WHO Global Strategy on Diet, Physical Activity and Health" in 2004 [48]. This strategy urged organisations, such as governments, to increase public awareness of healthy food choices and to provide education on the relationship between diet and health [48]. Since the publication of the Surgeon General's report, ongoing effort has been made to reduce the prevalence of smoking

by preventing uptake (e.g., through mass media campaigns, education in schools) and developing and improving smoking cessation services. Of note is the World Health Organisation Framework Convention on Tobacco Control (WHO FCTC) treaty, which was adopted by the 2003 World Health Assembly to address the global tobacco problem [49]. The WHO FCTC has been in place since 2005 and covers around 90% of the world's population [49]. In 2008, the MPOWER package was introduced, which contains six evidence-based tobacco control demand reduction measures that can help countries to meet their WHO FCTC commitments [49]. The six measures are as follows - M: Monitoring tobacco use and prevention policies; P: Protecting people from tobacco smoke; O: Offering help to quit tobacco use; W: Warning about the dangers of tobacco; E: Enforcing bans on tobacco advertising, promotion and sponsorship, and R: Raising taxes on tobacco [49]. Although there is still much to be done, considerable progress has been made since the 1960s and particularly in the ten years since the WHO FCTC was adopted. For example, in 2013, it was estimated that 2.3 billion people worldwide were covered by at least one of the six MPOWER measures [50]. In addition, to protect people from smoke, 32 countries have passed smoking bans that cover work places, public places and public transport. A further achievement is that 24 countries have now banned tobacco advertising, promotion and sponsorship [50].

Secondary prevention involves identifying and diagnosing a condition early in order to improve treatment outcomes [46]. An example of secondary prevention is the well-established mammogram screening programmes for the early detection of breast cancer. Lung cancer is a disease that could be considered for a screening programme as it meets the criteria set out by Wilson and Jungner. The next section moves on to provide a brief history of screening for disease, which includes Wilson and Jungner's screening criteria. This is followed by a definition of screening and clarification of key terms associated with screening.

1.3. Screening

1.3.1 Screening for disease: past and present

In London in 1861, Dr Horace Dobell first introduced the concept of conducting regular health checks on everyone, including those who appeared to be healthy, as a way to protect and promote health [51]. However, during the first half of the 20th century, regular health checks of this sort were unheard of in the UK. Aside from mass screening for tuberculous during the 1940s and 1950s, the only health checks conducted were medical and dental checks for children. In contrast, Dobell's idea was further developed in the United States where, in 1922, the American Medical Association authorized routine health checks with the aim of reducing the risk of future ill health. These checks had become part of normal medical practice in the United States by the 1950s and included a variety of tests [51]. The health checks were positively perceived by the public and enthusiasm for screening grew even though there was no strong evidence for its effectiveness. However, in the 1960s, the belief that screening was a procedure that could only be beneficial was contested. In 1968, two reports were published, one from the Nuffield Provincial Hospitals Trust and the other from the WHO, which was written by Drs Wilson and Jungner [51]. These reports were fundamental in raising important questions concerning the lack of evidence for a positive impact of screening and the possibility of harms that could result from screening. Moreover, Wilson and Jungner's report for the WHO contained the first set of criteria that should be met when considering the implementation of a screening programme, which are still used today. The criteria are listed in table three [52]. In addition to the publication of these two reports, two randomised controlled trials were set up in the 1960s to explore whether regular health checks had an effect on mortality, general health and healthcare utilisation [51]. Results from both trials showed that checks of this nature had no positive impact on either mortality or general health.

Table 3. Wilson and Jungner's screening criteria

Wilson and Jungner's Screening Criteria (1968) [52]
1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Since the positive assumptions concerning screening were first questioned in the 1960s, significant improvements have been made to how screening programmes are developed, delivered and evaluated. In 1996, the UK National Screening Committee (NSC) was formed to ensure that the benefits of screening are balanced against the harms and that high quality screening programmes are conducted. As outlined in their first annual report, the objectives of the UK NSC are to advise on all aspects of screening, including the continuation, modification

or retraction of existing population screening programmes, the implementation of new population screening programmes, and the application of new screening technologies [53].

1.3.2. Defining screening

The UK NSC have defined screening as, "*a process of identifying apparently healthy people who may be at increased risk of a disease or condition. They can then be offered information, further tests and appropriate treatment to reduce their risk and/or any complications arising from the disease or condition"* [54]. This definition of screening will be employed throughout this thesis.

Key terms associated with screening: sensitivity, specificity, positive predictive value and negative predictive value

Screening tests should yield two types of test results: positive and negative. Therefore, the test must be able to:

- Identify individuals who *have* the condition screened for (true positive). The extent to which a test can do this is referred to as its *sensitivity*. And,
- Identify individuals who *do not* have the condition screened for (true negative). The extent to which a test can do this is referred to as its *specificity* [55].

A screening test is never completely accurate, so healthy individuals can receive a positive result (false positive) and individuals who have the condition screened for can receive a negative result (false negative). Therefore, the sensitivity and specificity will never be 100% [55].

In addition to calculating the sensitivity and specificity of a screening test, predictive values (positive predictive value [PPV] and negative predictive value [NPV]) must also be calculated in order to fully evaluate the tests performance. Whereas the sensitivity and specificity of a test determine how effective a test is at detecting/not detecting a condition, predictive values take into account the prevalence of the condition in the population screened for by determining the probability that an individual with a positive test result has the condition (PPV) and the probability that an individual with a negative test result does not have the condition (NPV) [55]. Therefore, the PPV will be higher in a population of individuals who have a greater risk of developing the condition screened for and the NPV will be higher in a population of individuals who have a lower risk of developing the condition screened for. Information used to evaluate the performance of a screening test is included in a 'two by two table' [55]. For an example of a two by two table, please see table four.

Table 4. A two by two table illustrating the potential outcomes of screening and how the sensitivity, specificity, PPV and NPV are calculated

	Individual health status		
Screening test result	*Individual has the condition*	*Individual does not have the condition*	
Positive test result	True positive (A)	False positive (B)	A +B
Negative test result	False negative (C)	True negative (D)	C + D
	A + C	B + D	A + B + C + D

Sensitivity = A/A + C

Specificity = D/B + D

Positive predictive value = A/A + B

Negative predictive value = D/C + D

1.4. Lung cancer screening

1.4.1. Screening for lung cancer using chest x-rays

A number of trials have explored the use of chest x-rays, sometimes combined with sputum cytology, as a screening tool for the early detection of lung cancer. A Cochrane review and meta-analysis first conducted by Manser et al in 1999 [56] and updated in 2004 [57], 2010 [57] and 2012 [58] identified eight such trials (seven randomised controlled trials and one non-randomised controlled trial). Five trials compared more frequent chest x-ray screening with less frequent chest x-ray screening. Two trials reported on annual chest x-ray and four-month sputum cytology compared with annual chest x-ray only. In one trial, participants were randomised to receive either four annual chest x-ray screenings or usual care. The authors concluded that the evidence from the eight trials did not support screening for lung cancer using chest x-rays or sputum cytology as lung cancer mortality and all-cause mortality were not reduced [58]. Although other harms of screening were not systematically reported in the trials, the review identified several harms, one of which was overdiagnosis. Overdiagnosis is where a lung cancer is detected that would not have caused morbidity and/or the patient would have died from other causes. If it were not for screening, the cancer would not have been diagnosed in the patient's lifetime [59]. In the trials that explored the impact of different frequencies of chest x-rays, the incidence of lung cancer was higher in participants in the intervention group who received more frequent chest x-rays compared with the control group who received less frequent x-rays [58]. Although lung cancer incidence was higher in the intervention groups, lung cancer mortality and all-cause mortality did not improve.

1.4.2. Screening for lung cancer using computed tomography

Attention has since turned to the use of computed tomography (CT) as a potential screening tool due to its ability to detect smaller nodules than chest x-rays [60]. Results from observational studies investigating the use of low-dose computed tomography (LDCT) show that it can detect lung cancer at an early stage [58]. For example, the Early Lung Cancer Action Project (ELCAP) screened 31,567 asymptomatic participants using LDCT from 1993 to 2005. A baseline screening took place first, followed by repeated screenings performed seven to 18 months apart. Of the initial group, 27,456 participants had repeated screenings. The study was conducted in China, Europe, Israel, Japan and the United States. Participants were eligible if they were 40 years of age or older and were a current or former cigarette smoker. Never smokers could take part if they had experienced occupational exposure to asbestos, beryllium, uranium or radon, or if they had been exposed to secondhand smoke [61]. All participants diagnosed with lung cancer were followed up annually until death from lung cancer or until May 2006. The duration of follow-up for each participant ranged from one to 123 months (median follow-up = 40 months). Lung cancer was diagnosed in 484 (1.53%) of the participants. Of the participants who were diagnosed with lung cancer, 412 (85%) were diagnosed with stage I cancer. Kaplan–Meier curves were calculated for lung cancer survival and 10-year survival rates were estimated based on the curves. For the participants diagnosed with stage I lung cancer, the estimated ten-year survival rate was 88% (95% CI 84 to 91) [61]. Furthermore, the estimated 10-year survival rate for the 302 (62.40%) participants with stage I cancer who had surgical resection was 92% (95% CI 88 to 95). Based on these results, it was concluded that annual CT screening can detect lung cancer at an early, and curable, stage [61].

Although results from the ELCAP seemed promising, a further observational study conducted at the Mayo clinic included lung cancer specific mortality as the primary outcome rather than survival [62]. In this study, 1,520 participants at high risk of lung cancer received five annual CT scans. Participants were eligible if they were 50 years of age or older and had a cigarette smoking history of 20 pack years or higher. Former smokers were eligible if they had stopped smoking less than ten years ago. The Mayo Lung Project (described in table seven) was used as a historical control group so that results from this study could be compared with what was observed previously. Results suggest that screening for lung cancer using CT scans does not reduce lung cancer-specific mortality as no difference was found when lung cancer mortality rates were compared with those of the Mayo Lung Project (2.8 *vs* 2.0 per 1000 person-years, Poisson regression, p = 0.43). In total, 17 (61%) of the 28 lung cancers diagnosed were at stage I. Compared with the Mayo Lung Project, there was no difference in the proportion of participants diagnosed with stage I lung cancer (47% *vs* 41%, Fisher exact test, p = 0.78). A significantly larger proportion of participants with stage Ia lung cancers were diagnosed (47% vs 21%; Fisher exact test, p = 0.05). This suggests that CT screening could be more effective than chest x-ray and sputum cytology at detecting lung cancer at an early stage. However, the authors of the study emphasised that the higher rate of lung cancers detected at an earlier stage could be the result of overdiagnosis but further research was required to confirm this. Of further concern is that the study also demonstrated a high rate of false-positive findings. For example, of the 805 nodules identified, 32 were cancerous, which gives a false-positive rate of 96% [62].

In another multicentre study, 3,246 asymptomatic participants received annual CT scans [63]. The study was conducted in two medical centres in the USA and at one centre in Italy. Participants were eligible if they were between 50 and 80 years old, had smoked cigarettes for 25 to 60 years and had smoked an average of 10 to 60 cigarettes each day. Former smokers were

eligible provided they had quit within the past 20 years. Participants were followed up for a median period of 3.9 years. Outcomes were compared with benchmarks derived from two risk prediction models used to predict lung cancer incidence and mortality without screening. In total, 144 participants were diagnosed with lung cancer compared with 44.5 predicted cases (RR: 3.2, 95% CI 2.7 to 3.8, P < 0.001). Compared with 10.9 predicted cases, 109 participants had a lung resection (RR 10.0, 95% CI 8.2 to 11.9, p < 0.001). There was no significant reduction in the number of lung cancers diagnosed at an advanced stage as 42 participants were diagnosed with advanced stage lung cancer compared with 33.4 estimated cases (RR and CI's not reported, p = 0.14). In addition, there was no significant reduction in lung cancer mortality as 38 deaths due to lung cancer were observed compared with 38.8 estimated deaths (RR 1.0, 95% CI 0.7 to 1.3, p = 0.90). Based on these results, the authors concluded that CT screening can detect lung cancer early and increase the rate of treatment but not reduce the risk of advanced stage lung cancer or lung cancer mortality. It was therefore recommended that asymptomatic individuals should not be screened for lung cancer using CT until data is available from ongoing randomised controlled trials (RCT) [63]. An RCT is considered to be the most scientifically thorough method to test hypotheses and the 'gold standard' approach for determining whether an intervention, such as screening, is effective [64]. A key advantage of an RCT, compared with an observational design, is that participants are randomised to intervention and comparator arms. Random allocation ensures that characteristics that could potentially influence an outcome (e.g., sex, age) are evenly distributed between arms. Therefore, any differences in outcome between groups should be able to be attributed to the intervention. In other words, selection bias is minimised. It has been stated that an RCT is the only method that can be used to determine whether the benefits of screening compensate for the harms [65].

Eight RCTs have since been conducted investigating the effectiveness of screening for lung cancer using LDCT. The trials are described in table five. In the National Lung Screening Trial (NLST), 53,454 participants at high risk of lung cancer were randomised to receive three annual screenings with either LDCT or a chest x-ray [66]. Participants were eligible if they were between 55 and 74 years old and had a cigarette smoking history of ≥ 30 pack years. Former smokers were also eligible provided they had stopped smoking within the past 15 years [66]. Compared with participants in the chest x-ray group, a 20% (95% CI 6.8 to 26.7, P = 0.004) reduction in lung cancer mortality and a 6.7% (95% CI 1.2 to 13.6, P = 0.02) reduction in all-cause mortality was observed in participants in the LDCT group at a 6.5 year follow-up [66]. Following publication of these results, the US Preventive Services Task Force, endorsed screening programmes for lung cancer using LDCT for adults aged 55 to 80 years who have a 30 pack-year smoking history [67].

However, the results of the Danish Lung Cancer Screening Trial (DLCST), published in 2016, contradict the positive results of the NLST [68]. Compared with participants in the control group, significantly more lung cancers were diagnosed (100 *vs.* 53, hazard ratio (HR) 1.8, 95% CI 1.3 to 2.6, p < 0.001) and a significantly higher number of these cancers were diagnosed at stages one and two (54 *vs.* 10, p < 0.001) in the intervention group. A higher number of stage four cancers were diagnosed in the control group but this finding was not significant (23 *vs.* 32, p = 0.278). No significant differences in lung cancer mortality were found between groups (39 in the intervention group *vs.* 38 in the control group, HR 1.03, 95% CI 0.66 to 1.6, p = 0.888). The same finding was reported for all-cause mortality (165 in the intervention group *vs.* 163 in the control group, HR 1.02, 95% CI 0.82 to 1.27, p = 0.867) [68].

The final results from the Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays (DANTE) trial, published in 2015, and the 5-year results from the Multicentre Italian Lung Detection (MILD) trial, published in 2012, reflect the findings of the DLCST[69,70]. In the DANTE trial, there were significantly more participants in the intervention group diagnosed with stage 1 lung cancer than in the control group (47 (3.71%) *vs.* 16 (1.35%), p = 0.0002). However, lung cancer mortality rates were very similar. In the intervention group, the mortality rate was 543 per 100,000 person-years (95% CI 413 to 700) and 544 per 100,000 person-years (95% CI, 410 to 709) in the control group (HR 0.99, 95% CI, 0.69 to 1.43). Furthermore, no differences in all-cause mortality rates were found between the intervention (1,655 per 100,000 person-years, 95% CI 1,422 to 1,916) and control (1,742 per 100,000 person-years, 95% CI, 1,494 to 2,019) groups (HR 0.95, 95% CI 0.77 to 1.17) [69]. The MILD trial reported a significant difference in five-year lung cancer incidence rates between the control group (311 per 100, 000 person-years) and LDCT groups (biennial LDCT: 457 per 100,000 person-years, annual LDCT: 620 per 100,000 person-years), p = 0.025[70]. However, no significant difference in lung cancer mortality was found when the two LDCT groups were compared with the control group (HR 1.52, 95% CI 0.63 to 3.65, p = 0.21). A similar finding was reported for overall mortality (HR 1.39, 95% CI 0.83 to 2.34, p = 0.13).

Although results from the European trials do not support screening for lung cancer using CT, it is important to note that these trials were statistically underpowered. Data will be pooled to provide important information on mortality and cost-effectiveness of screening for lung cancer using LDCT [71].

Table 5. A summary of randomised controlled trials of lung cancer screening using LDCT

Trial (Acronym)	**Country(s) and year trial commenced**	**Participants** (number, age group, gender, smoking status)	**Intervention group(s) and control**	**Follow-up period**	**Primary and secondary outcome(s)**
Detection and screening of early lung cancer by novel imaging technology and molecular essays (DANTE) [69,72]	Italy 2001	N: 2,450 Age: 60 - 74 Male: 100% Current smokers: 56.5%	CT vs. no screening	Four years	**Primary outcome:** Lung cancer mortality **Secondary outcomes:** - Lung cancer incidence - Lung cancer stage - Resectability rates
National Lung Screening Trial (NLST) [66]	United States 2002	N: 53,454 Age: 55 - 74 Male: 59%	CT vs. chest x-ray	Median duration of follow-up: 6.5 years	**Primary outcome:** Lung cancer mortality **Secondary outcomes:**

Trial (Acronym)	**Country(s) and year trial commenced**	**Participants** (number, age group, gender, smoking status)	**Intervention group(s) and control**	**Follow-up period**	**Primary and secondary outcome(s)**
		Current smokers: 48.2%			- All-cause mortality - Lung cancer incidence - Lung cancer case survival (measured from date of diagnosis) - Lung cancer stage distribution - Screening and treatment related morbidity - Smoking behaviour and beliefs - Healthcare utilization - Health-related quality-of-life - Cost-effectiveness - Diagnostic performance of the two screening tests (CT and chest x-ray) [73].
Italian lung cancer computer tomography screening trial (ITALUNG)	Italy 2003	N: 3,206 Age: 55 - 69 Male: 65%	CT vs. no screening	Seven years	**Primary outcomes:** - Lung cancer incidence - Lung cancer mortality

Trial (Acronym)	**Country(s) and year trial commenced**	**Participants** (number, age group, gender, smoking status)	**Intervention group(s) and control**	**Follow-up period**	**Primary and secondary outcome(s)**
[74,75]		Current smokers: 64.8%			
Danish Lung Cancer Screening Trial (DLCST) [76]	Denmark 2004	N: 4,104 Age: 50 - 70 Male: 55% Current smokers: 76.1%	CT vs. no screening	Ten years	**Primary outcome:** - Lung cancer mortality **Secondary outcomes:** - All-cause mortality - Lung cancer incidence - 5-year survival following lung cancer diagnosis - Stage of lung cancer at diagnosis - Surgical resection rate - Frequency of false-positive diagnoses - Smoking behaviour - Psychosocial consequences of false-positive diagnoses - Cost of CT screening in Denmark

Trial (Acronym)	**Country(s) and year trial commenced**	**Participants** (number, age group, gender, smoking status)	**Intervention group(s) and control**	**Follow-up period**	**Primary and secondary outcome(s)**
Nederlands Leuvens Longkanker Screenings Onderzoek (NELSON) [77]	The Netherlands and Belgium 2004	N: 15,822 Age: 50 - 75 Male: 84% Current smokers: 55%	CT vs. no screening	Two year follow-up after three rounds of screening	**Primary outcome:** - Lung cancer mortality **Secondary outcomes:** - Type and stage of screen-detected and interval lung cancer - Causes of interval cancers by radiological assessment
Multicentre Italian Lung Detection (MILD) [70]	Italy 2005	N: 4,099 Age: 49 and above Male: 66.3% Current smokers: 77.5%	Biennial LDCT screening vs. annual LDCT screening vs. no screening	Six years	**Primary outcomes:** - Lung cancer mortality - Total mortality **Secondary outcomes:** - Lung cancer incidence

Trial (Acronym)	Country(s) and year trial commenced	Participants (number, age group, gender, smoking status)	Intervention group(s) and control	Follow-up period	Primary and secondary outcome(s)
					- Number of procedures for benign lung diseases
Lung cancer screening intervention (LUSI) [78,79]	Germany 2007	N: 4,052 Age: 50 - 69 Male: 66% Current smokers: 61.9%	CT vs. no screening	Three years for participants randomised in April 2011 and up to 6.5 years for participants randomised in October 2007	**Outcomes:** - Early recall rate (Please note: early recall was defined as a participant was recalled due to a suspicious CT result (e.g., a newly observed nodule) - Lung cancer incidence - Interval cancers (Please note: invasive cancers were defined as cancers diagnosed after a negative screen and before the next invitation to screening was due)

Trial (Acronym)	**Country(s) and year trial commenced**	**Participants** (number, age group, gender, smoking status)	**Intervention group(s) and control**	**Follow-up period**	**Primary and secondary outcome(s)**
					- Proportion of advanced cancers (Please note: advanced cancer was defined as stage two or higher) - Overall mortality
UK Lung Cancer Screening (UKLS) [80,81]	United Kingdom 2011	N: 4,000 (pilot), 28,000 (full study) Age: 50 - 75 Gender statistics not yet reported Smoking statistics not yet reported	CT vs. no screening	Ten years	**Primary outcome(s):** - Lung cancer mortality - Total mortality - Cost effectiveness of a national lung cancer screening programme **Secondary outcomes:** - Lung cancer morbidity - Resource implications of screening and the resulting intervention - Feasibility of population screening for lung cancer

1.4.3. The potential benefits and harms of screening for lung cancer

As lung cancer screening programmes could become more widely implemented, and will be targeted at asymptomatic individuals, the benefits must compensate for the harms. The main perceived benefit of lung cancer screening is mortality reduction as screening can detect cancer early when the prognosis is better [82]. In addition, lung cancer screening could potentially have emotional benefits, for example, reassurance following the receipt of a negative test result [83]. However, lung cancer screening can, and will, cause harm. As stated by Raffle and Gray (2007, p. xi), *"all screening programmes do harm. Some do good as well and, of these, some do more good than harm at a reasonable cost"* [51]. In 2014, a taxonomy was developed to classify harms that patients may experience from screening and applied to screening for lung cancer with LDCT [84]. The potential harms of lung cancer screening are discussed below and are structured according to the four domains encompassed in the taxonomy: physical harm, psychological harm, financial harm, opportunity costs [84].

1. Physical harm

Exposure to radiation

Radiation exposure was discussed in the results of a systematic review on the benefits and harms of CT screening for lung cancer [60]. The authors state that it has been estimated that participants in the National Lung Screening Trial (NLST) were exposed to 8 mSv of radiation over three years [60]. This estimate was averaged over the entirety of the screened group and took into account LDCT scans as well as diagnostic imaging examinations. Based on this data, it was estimated that for every 2500 individuals screened using LDCT, around one cancer death

may result from radiation exposure [60]. Results from the NLST show that the numbers of lung cancer deaths that are prevented by LDCT (20% reduction in mortality) outweigh the harms of radiation risk. However, younger participants, or those who are at lower risk, are less likely to be diagnosed with lung cancer following screening. Therefore, the potential harm generated by radiation exposure may not outweigh the benefit of screening in their case [60].

Further investigations following a positive screening test result

Following a positive LDCT test result, participants will undergo further investigations, such as follow-up scans and biopsies. Further investigations can cause physical discomfort, and in some rare cases, medical complications [84]. As previously stated, no screening test is entirely accurate and the specificity will never be 100%, so some patients will receive a false positive test result (see Table 2). The NLST reported that 96.4% of positive LDCT results were found to be false positive [66]. The NELSON trial reported a false positive rate of 59.6% at a two-year follow-up following two rounds of screening [77]. Therefore, over half of the patients who received a positive test result in both of these trials will have been exposed to potential, and unnecessary, harms of further investigations.

Overdiagnosis and overtreatment

As previously stated, overdiagnosis is where a lung cancer is detected that would not have caused morbidity (e.g., a slow-growing cancer) and/or the patient would have died from other causes. If it were not for screening, the cancer would not have been diagnosed in the patient's lifetime [59]. As a result of overdiagnosis, the patient will be harmed by unnecessary treatment (overtreatment) [85]. As the majority of participants taking part in lung cancer screening will be

older, and either a current or former smoker, they will have a higher risk of mortality from other causes, so there could be a greater incidence of overdiagnosis [59,86]. The extent of overdiagnosis following LDCT screening is currently unknown. Data obtained from the NLST estimated that LDCT could result in an overdiagnosis rate of 18.5% (95% CI 5.4% to 30.6%) [87]. Furthermore, a study that used comparative modelling to explore the benefits and harms of CT screening estimated that overdiagnosis could range from 8.7% to 13.5% for lung cancers detected through screening [82]. As the European trials compare LDCT with no screening, once results are pooled, they will be able to provide a more accurate estimate of the overdiagnosis rates following LDCT [59].

2. Psychological harm

The psychological harms of lung cancer screening will be discussed in detail in chapter two of this thesis. In brief, psychological harm can occur during any part of a screening programme but is particularly prominent following receipt of test results or during further investigations following a positive screening test result [84]. For example, studies have reported that indeterminate test results following LDCT screening are associated with negative emotional outcomes [88-91]. These outcomes include those specific to lung cancer (e.g., lung cancer specific distress [89,90] and concern about lung cancer [91]) and those not specific to lung cancer (e.g., state anxiety [88,90]). The effects persisted for varying time periods, taking between 6 months [91] and 1.5 years [89] after screening to return to pre-screening levels. In addition, psychological harm has been found to occur during overtreatment (e.g., surgery, chemotherapy) in patients who have been overdiagnosed [84].

3. Financial harm

The third domain of the taxonomy [84] concerns financial implications of screening. Financial pressures could result from having to miss work to attend screening, to attend further investigations following a positive result, or to receive treatment after a diagnosis of lung cancer [84]. In some countries, where there is no national health service, there could also be a cost to the individual to receive the screening test, for further investigations, and for any treatment [84]. Also, where there is a national health service, there could be additional cost to the taxpayer. As of yet, there is no research evidence on the financial harm of lung cancer screening [84].

4. Opportunity costs

The final domain is opportunity costs. This is where patients could be harmed by opportunities they missed by taking part in the screening programme. Harris et al. [84] provide a number of examples of missed opportunities, which include: health activities, visits to clinicians for other important health problems, spending time with significant others, employment and working on personal projects. The authors found no published evidence relating to this type of harm [84].

1.5. EarlyCDT®-lung

As previously stated, screening for lung cancer using LDCT is now recommended in the USA [67]. Pooled results from the European trials have the potential to strengthen the evidence-base for the effectiveness of LDCT and lead to the wider implementation of population-based lung cancer screening programmes [67,71,92]. If LDCT is to be a tool for population-based screening, efforts must be made to ensure that it is cost-effective. Data from the NLST has estimated that, when compared with no screening, LDCT costs an additional $1,631(£1,256)[2] per person (95% CI 1557 to 1709), provides an additional 0.0316 life-years per person (95% CI 0.0154 to 0.0478) and 0.0201 quality adjusted life-years[3] per person (95% CI 0.0088 to 0.0314) [93]. Incremental cost-effectiveness ratios (ICERs) were $52,000 (£40,044.51) per life-year gained (95% CI 34,000 to 106,000) and $81,000 (£62,377.03) per QALY gained (95% CI 52,000 to 186,000) [93]. A model for a CT screening programme in the UK has estimated that the ICER of one screen for a high-risk male population could be £14,000 per quality adjusted life-year [94]. In order to increase the cost-effectiveness of a CT screening programme, as well as ensure that the benefits outweigh the harms, screening must be implemented in a population at high risk of developing lung cancer. The use of rigorous risk prediction criteria to select a high-risk population will enable the identification of a higher number of cancers and ultimately a reduced ICER [95]. Risk prediction models can be used to facilitate the identification of at-risk populations [26]. In addition to risk prediction models, a biological test could also be administered to identify individuals at the highest risk of lung cancer [96]. These individuals could subsequently be offered LDCT. EarlyCDT®-Lung is one such test that can identify high-risk individuals. EarlyCDT®-Lung is a blood autoantibody (AAb) test developed at the University of Nottingham. It can identify

[2] Please note: The following website was used to convert dollars to pounds http://www.exchangerates.org.uk/Dollars-to-Pounds-currency-conversion-page.html. Date accessed: 16.08.2016.
[3] Please note: a quality adjusted life-year is defined as the quantity and quality of life that could result from a healthcare intervention

individuals at high risk of lung cancer by measuring the level of AAbs produced by the immune system in response to antigens produced by lung cancer cells [97]. EarlyCDT®-Lung measures seven AAbs (p53, NY-ESO-1, CAGE, GBU4-5, HuD, MAGE A4 and SOX2) that have been identified in patients with lung cancer [98]. As well as being identified when lung cancer is first diagnosed, these AAbs have also been found up to five years prior to a diagnosis [98]. Therefore, EarlyCDT®-Lung can detect lung cancer at all stages [97]. The test has been found to have a sensitivity of 41% and a specificity of 90% [98]. It has been tested and validated in case-control studies and results from a clinical audit of 1613 US patients have shown that it has the same sensitivity and specificity in routine clinical practice [97]. As it involves a blood test, EarlyCDT®-Lung is simple to administer. Due to its high specificity, EarlyCDT®-Lung could potentially be combined with LDCT to assess an individual at high risk of lung cancer [97].

Although results from case-control studies and the clinical audit are encouraging, there is not enough evidence to support the application of EarlyCDT®-Lung to a lung cancer screening programme [99]. Therefore, the EarlyCDT®-Lung test is currently the subject of a randomised controlled trial, the *Early Lung Cancer Detection (ECLS) Study*. This trial is taking place in Scotland and started recruiting participants in August 2013. The ECLS study is described in the following section.

1.6. Early Cancer Detection Test – Lung Cancer Scotland Study

The primary aim of the ECLS study is to examine the effectiveness of EarlyCDT®-Lung in detecting early stage lung cancer, thus reducing the incidence of advanced stage lung cancer at diagnosis compared with standard care[100]. Twelve thousand adults who had at least a 2% risk of developing lung cancer over the following two years were recruited from approximately 170 general practices within the lowest quintile of deprivation (as measured by the Scottish

Index of Multiple Deprivation (SIMD)[4]) in NHS Tayside, NHS Greater Glasgow & Clyde and NHS Lanarkshire[100]. Inclusion and exclusion criteria for the ECLS study are listed in table six.

Table 6. Inclusion and exclusion criteria for the ECLS study (taken from the Sullivan et al. 2017) [100]

Inclusion criteria	**Exclusion criteria**
1. Participant is willing and able to give informed consent for participation in the study	1. History of any cancer other than non-melanomatous skin cancer and/or cervical cancer in situ.
2. Male or female aged 50 years to 75 years	2. Complaining of symptoms suggestive of lung cancer within past 6 months e.g. haemoptysis, weight loss
3. Current or ex-smoker with at least 20 year pack history	3. Patients for whom the GP considers invitation to the study would cause undue distress
4. Less than 20 years pack history but with family history of lung cancer in a first degree relative (mother, father, sister, brother, child)	4. Patients with terminal disease
5. Eastern Co-operative Oncology Group (ECOG) Status: 0, 1 and 2 [5] [101]	5. Patients on prolonged /continuous use (> 3 months) of Cyclophosphamide

[4] The SIMD is the Scottish Government's official tool for identifying the deprivation level of an area. The SIMD 2012 combines 38 indicators of deprivation across seven domains: income, employment, health, education, skills and training, housing, geographic access and crime. http://www.scotland.gov.uk/Topics/Statistics/SIMD

[5] The ECOG status score ranges from zero (perfect health) to five (death). A score of one indicates that a participant experiences symptoms but can conduct light work activities. A participant would receive a score of two if they experienced symptoms, were bedridden for more than half of the day but could still complete self-care activities.

A flow chart of the ECLS study is displayed in figure four. Recruitment strategies for the study were identified through four pre-trial focus groups [102]. Eligible participants were invited via an invitation letter sent by their GP, which included the Participant Information Leaflet (PIL). Other recruitment strategies included inviting eligible participants who were registered on research volunteer databases, posters in GP waiting rooms, a media campaign and distribution of posters and leaflets in community venues (e.g., shopping centres, post offices, pubs). Eligible participants had the option to take part in the study at their local clinical research facility, their GP practice or another suitable clinical location [99]. At their recruitment visit, participants gave informed consent, inclusion and exclusion criteria were checked and they completed a study questionnaire (a sample questionnaire is included in appendix seven, page 500). They then provided a blood sample. Once the participant had given their blood sample, a web-based randomisation system (TRuST), was used to allocate them to the intervention or control group. Randomisation was stratified by site (general practice) and minimised by age, gender and smoking history (current or former smoker). The intervention group had their blood sample screened using EarlyCDT®-Lung whereas the control group did not. Participants in the intervention group received either an EarlyCDT®-positive or an EarlyCDT®-negative test result. Participants were informed of their EarlyCDT®-negative test result through a letter, which offered a follow-up visit or phone call to discuss results as well as advice on the most effective method to reduce risk of lung cancer and a list of lung cancer symptoms to be aware of (persistent cough, coughing up blood, shortness of breath, weight loss or loss of appetite). The control group also received a letter to thank them for their contribution to the study. As with the letter sent to participants with a negative test result, this letter also contained advice on symptoms and how to reduce lung cancer risk.

As stated in section 1.5 (page 60) EarlyCDT®-Lung has been found to have a sensitivity of 41% and a specificity of 90%. Therefore, 520 – 550 ECLS study participants were expected to receive an EarlyCDT®-positive test result[100]. Participants were referred for a chest x-ray followed by a non-contrast thoracic CT scan. However, if a suspicious opacity was identified on the chest x-ray, they received a contrast enhanced staging CT instead[100]. If the CT scan does not show signs of lung cancer or suspected lung cancer, then the participant is invited for a repeat CT scan every six months for 24 months. Participants diagnosed with lung cancer receive treatment from their relevant NHS multidisciplinary team. Mortality, morbidity and hospitalisation data for this group of participants are collected.

In addition to the primary aim of the ELCS study, there are a number of secondary aims, one of which is to assess the impact of screening on emotional outcomes. Alongside clinical evidence, an evaluation of emotional harms and benefits is imperative when considering the implementation of a screening programme. The purpose of this PhD is to explore the emotional impact of lung cancer screening using EarlyCDT®-Lung. The next chapter of this thesis highlights the importance of understanding the emotional impact of screening and reviews the literature in this field.

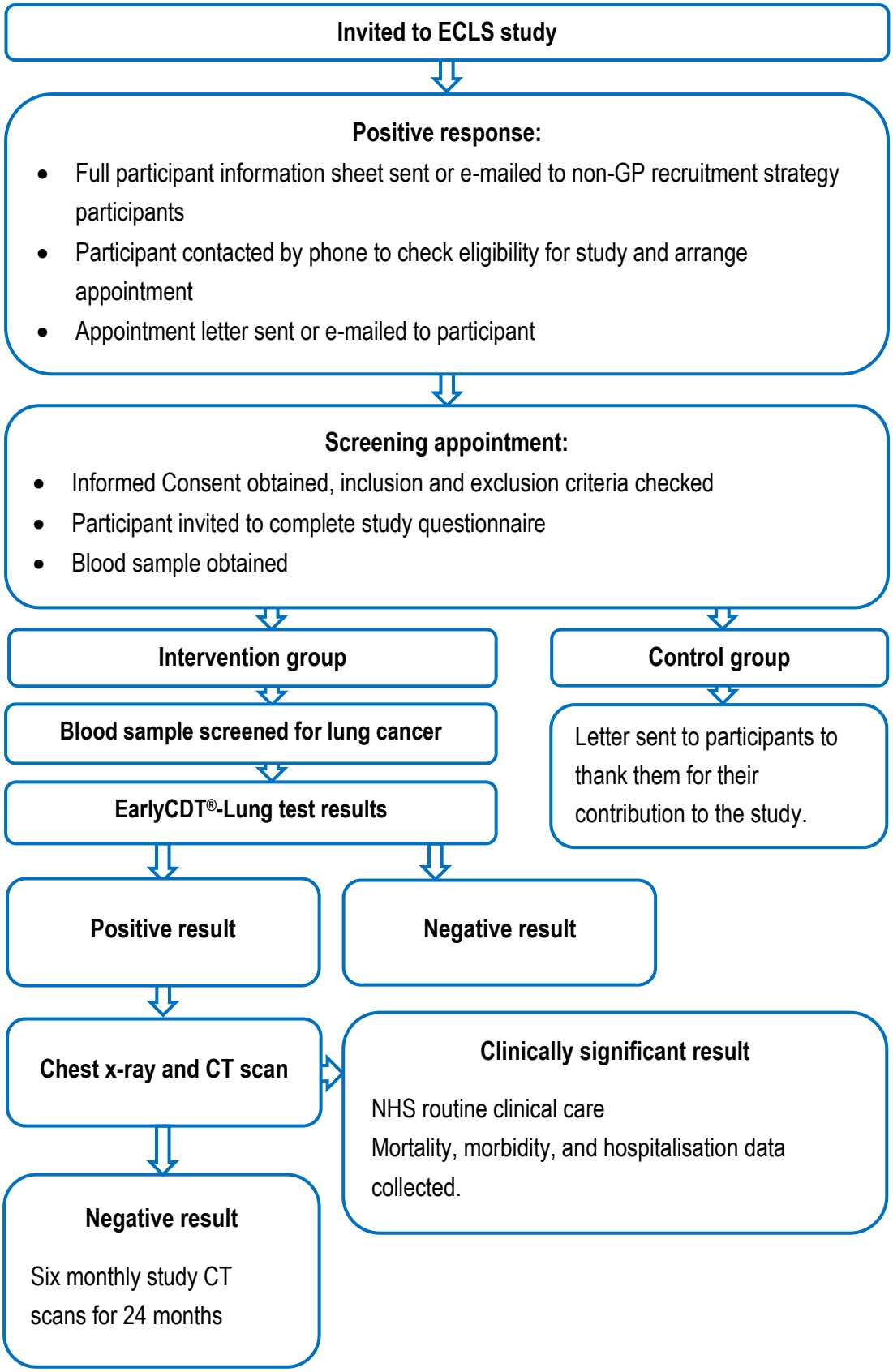


Figure 4. ECLS study flow chart (adapted from flow chart in ECLS study protocol)

Chapter 2. The emotional impact of lung cancer screening

The purpose of chapter two is to review the literature on the emotional impact of lung cancer screening. The chapter is divided into three sections. The first section emphasises the potential for emotional harms and benefits to occur at multiple stages in the screening process and the importance of evaluating emotional outcomes when establishing the harms and benefits of a screening programme. The section that follows describes the current evidence on the emotional impact of lung cancer screening. The final section draws together the key findings and includes a critical discussion of the evidence where methodological, theoretical and clinical issues are considered.

2.1. The importance of understanding the emotional impact of lung cancer screening

The intended benefits of lung cancer screening are mortality reduction and life-years gained [82]. However, in order to benefit, an individual must have a cancer that they would certainly die from if they did not receive screening [103].Therefore, this cancer must be:

1. Destined to be fatal, and
2. Treatable if identified through screening but not treatable if identified at a later date [103].

As lung cancer screening will be targeted at asymptomatic individuals, the majority will not have such a cancer [104]. For example, it has been estimated that 575 computed tomography (CT)

screening examinations would be required to prevent one lung cancer death in a high risk population[6] [82]. As a result, in order to identify the relatively small number who could benefit from early detection, a large number of healthy individuals will have to be screened and will also be exposed to the harms of CT screening [104]. In chapter one of this thesis, a taxonomy to classify the harms that patients may experience from screening was described (pages 55 to 58) [84]. To reiterate, the taxonomy included four domains of harm:

1. Physical harm (e.g., further investigations following a positive screening test result, overdiagnosis),
2. Psychological harm (e.g., increased levels of anxiety, raised distress),
3. Financial harm (e.g., having to miss work to attend screening), and
4. Opportunities missed by taking part in screening (e.g., health activities, visits to clinicians for other important health problems, spending time with significant others).

At present, there is no published evidence for financial harms or opportunity costs of lung cancer screening (domains three and four). Research on physical harms, however, has shown that such harms can potentially impact a large number of patients taking part in screening. A comparative modelling study, published in 2014, included a cohort of 100,000 people born in the United States in 1950 who were followed from ages 45 to 90 years old [82]. Results estimated that of 19,300 high-risk individuals eligible for CT screening, a total of 67,550 false-positive test results would be expected (based on an average of 3.5 false-positive results per individual) and

[6] Please note: a high-risk population was defined as individuals aged between 55 and 80 years old who were current smokers with a cigarette smoking history of at least 30 pack years or former smokers who had stopped smoking within the past 15 years. Of the 100,000-member cohort of adults born in the United States in 1950 that were included in the study, 19,300 individuals were eligible for CT screening.

910 biopsies or surgeries could be performed for non-cancerous lesions. Furthermore, it was estimated that there would be 190 cases of overdiagnosed[7] lung cancer [82].

The second domain of the taxonomy includes emotional harms (e.g., raised anxiety and distress). Like physical harms, emotional harms also have the potential to affect large numbers of healthy screening participants [105]. Such harms can result from the limitations of lung cancer screening described above (e.g., overdiagnosis). Furthermore, there are a number of points in the screening process itself that have the potential to have a negative emotional impact [84], for example, the anticipation of having a screening test, waiting for test results. It has been stated that if screening is found to have a negative emotional impact in the large number of healthy individuals taking part, then this could potentially act as a barrier towards the implementation of a screening programme [106]. It is therefore imperative that the emotional impact of lung cancer screening is studied in order to identify the point in the screening programme at which any negative emotional impact occurs, and whether it is short term or persists in the longer term. In addition, there is an ethical imperative for investigating emotional harms associated with lung cancer screening, as an informed decision process relies on individuals being advised of all potential harms that can result from medical procedures [107].

To ensure that the benefits of lung cancer screening compensate for the harms, positive emotional outcomes must also be investigated. It is very important to explore emotional benefits of lung cancer screening, as demonstrating positive emotional responses in screening participants, in particular those who do not benefit from screening, could provide a rationale for introducing or continuing a screening programme. Results from the Danish Lung Cancer

[7] As stated in chapter one, overdiagnosis is where a lung cancer is detected that would not have resulted in ill health and/or the patient would have died from other causes. If it were not for screening, the patient would not have been diagnosed with, and treated for, lung cancer in their lifetime

Screening Trial (DLCST) suggest that taking part in screening could have a positive emotional impact in itself [108]. DLCST participants completed an emotional outcome measure specific to lung cancer screening prior to randomisation. The same measure was also administered to a comparable sample of participants from the Danish population. Trial participants were found to have significantly lower scores than the comparable sample, indicating better emotional wellbeing. The authors of the study propose that one explanation for this finding is that taking part in a health promoting activity, such as screening, could give participants a sense that they are doing something beneficial for their health, which improves emotional wellbeing [108]. Another potential benefit of lung cancer screening is reassurance following the receipt of a negative test result [90]. Reassurance could be particularly prominent in current and former smokers attending screening who have been found to overestimate their risk of developing lung cancer [88]. For example, participants in the Nederlands Leuvens Longkanker Screening Onderzoek (NELSON) trial who received a negative test result had significantly lower levels of lung cancer-specific distress at two months [89,90] and at 1.5 years [89] post-screening when compared with baseline levels of distress.

To summarise, there are a number of compelling reasons as to why it is important to understand the emotional impact of lung cancer screening. However, despite this, the emotional impact of screening has not been extensively studied [105]. A systematic review that explored the extent of the evidence on emotional harms for five types of screening, including lung cancer, reported that, of the 169 citations identified, 88% focused on physical harms and only 12% on emotional harms [105]. The section that follows moves on to describe the available evidence on the emotional impact of screening for lung cancer.

2.2. The current evidence on the emotional impact of lung cancer screening

In order to fully understand the emotional impact of lung cancer screening, evidence is required on the nature of any such impact. It is also important to identify the point in the screening programme at which the impact occurs and whether it is short term or persists in the longer term. In this section, the evidence on the emotional impact of lung cancer screening is discussed by drawing on the results of publications included in two systematic reviews [109,110] and the empirical evidence published subsequent to the reviews [111].

Two published systematic reviews have explored the emotional impact of lung cancer screening [109,110]. The first review, published by Slatore et al. in 2014, aimed to compare patient-centred outcomes for individuals who were screened for lung cancer and those who were not [110]. Included studies were randomised controlled trials (RCTs) where participants were asymptomatic adults at high risk of lung cancer due to smoking behaviours. Included RCTs had to compare screening with no screening [110]. Five publications from two European RCTs met inclusion criteria. Two publications reported results from the DLCST [112,113] and three reported on the NELSON trial [89,90,114]. As the second aim of the review was to explore the association between type of test result and patient-centred outcomes, cohort studies were also included. One cohort study was identified, which reported results from the Pittsburg Lung Screening Study (PLuSS) [88].

The second review, published by Wu et al. in 2016, aimed to investigate the emotional impact of lung cancer screening and to describe the outcome measures administered to assess such impact. Both RCTs and cohort studies that explored the impact of lung cancer screening on emotional outcomes and health-related quality of life were included. In addition to the

publications identified by Slatore et al [110], a further seven met inclusion criteria. Five of the seven publications reported results from three trials: the NELSON trial ([106,107]), the DLCST ([108,115]) and the National Lung Screening Trial (NLST [116]). Two prospective cohort studies were also identified. One study included Finnish participants who had been exposed to asbestos through work [117]. The other study was conducted in the United States and included participants with a family history of lung cancer [91]. The characteristics of the publications identified by both reviews are listed in table seven.

Following publication of the two systematic reviews, the UK National Lung Screening (UKLS) trial recently published results, which included an analysis of the psychosocial outcomes of lung cancer screening [111,118]. The characteristics and results of this study are also listed in table seven.

Of the 14 publications that have reported on the emotional impact of lung cancer screening, seven used a prospective cohort design, five were RCT's and one was cross-sectional. Sample sizes ranged from 60 to 4,104. One publication from the DLCST measured participant's use of anti-depressive or anti-anxiety medication [113]. The other thirteen publications administered questionnaires containing a range of emotional outcome measures. Generic emotional outcome measures included anxiety [88-90,107,111,114,116], depression [111], health anxiety [117], and emotional quality of life [89,90,106,107,114,116]. Emotional outcome measures specific to lung cancer or lung cancer screening were also administered. Specific outcome measures included fear of lung cancer [88], lung cancer-specific distress [89,90,106,107,114], lung cancer worry [91,111,117], and the psychosocial impact of lung cancer screening [107,108,112,115]. The findings from the publications included in the reviews, and the recently published empirical study, are described in the following three subsections.

Table 7. Characteristics of publications that have reported on the emotional impact of screening for lung cancer.
[Please note: no data is reported in this table as the purpose is to provide a brief overview of the results from each publication].

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
Byrne et al. 2008 [88] United States	N: 400 Source: Individuals taking part in the PLuSS study (50 – 79 year olds with no personal history of lung cancer and a smoking history of at least 25 years) Mean age: 60.2	Prospective cohort 1. Pre-screening 2. One to two weeks after test results 3. Six months post-screening 4. 12 months post-screening	<u>1. State and trait anxiety (STAI)</u> 20 items measuring state anxiety (STAI-S) and 20 measuring trait anxiety (STAI-T). Responses recorded on a 4-point Likert scale, 1 (not at all) to 4 (very much). Score ranges for each scale: 20– 80. Higher scores indicate higher levels of anxiety. <u>2. Fear of lung cancer (three items adapted from the PCQ)</u> Three items rated on a 5-point Likert scale, 1 (never) to 5 (most of the time). Higher scores indicate greater fear of lung cancer.	<u>1. State and trait anxiety</u> At pre-screening, there were no differences in STAI scores between test result groups. There were no significant interactions between STAI-T scores and type of test result or measurement time-point. The change in STAI-S scores over time was significant for the indeterminate group only ($p < 0.001$). Scores increased from baseline to one to two weeks after the test results were received. Scores had declined at 12 months post-

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
	Male: 50.7% Ethnicity: 95% Caucasian Current smokers: 59% Test results: Test-negative (n = 228) Benign (n = 4) Indeterminate (n = 141) Suspicious (n = 27)			screening but were still higher than at pre-screening. <u>2. Fear of lung cancer</u> The change in mean PCQ scores over time was significant for the suspicious group only ($p < 0.001$). Scores increased from baseline to one to two weeks after test results were received. Scores declined at six and 12 months but were still higher than at pre-screening.
Sinicrope et al. 2010 [91]	N: 60 Source: Individuals over	Prospective cohort	<u>Lung cancer worry (CWS adapted to refer to lung cancer)</u>	<u>1. Frequency of thoughts about getting lung cancer</u>

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
United States	30 years old with no personal lung cancer history and a first-degree relative and at least three other blood relatives with lung cancer. Participants were recruited (via letter) through the Mayo Clinic Lung Cancer Genetic Epidemiology Registry. Mean age: 52.5 Male: 50.7%	1. Pre-screening 2. One month after receipt of test result 3. Six months post-screening	The first of four items measures frequency of thoughts about getting lung cancer. The second and third items measure the extent to which lung cancer worry affects mood and ability to perform daily activities. The first three items are rated on a 4-point Likert scale, 1 (not at all or rarely) to 4 (a lot). The fourth item measures level of concern of getting lung cancer. Responses are rated on a 4-point Likert scale, 1 (extremely concerned) to 4 (not at all concerned). For all items, participants grouped into two categories: “not at all” (response one) and “some” (combination of responses options 2, 3 and 4). Please note: no univariate or multivariate analyses were conducted for the data reported in this paper due to the small sample size. No significance tests were undertaken.	At pre-screening, 65% of participants reported having some thoughts about developing lung cancer. At both follow-up time-points, the proportion of the negative group who reported some lung cancer related thoughts was lower than pre-screening. In contrast, the proportion of participants with a non-negative result who reported some LC-related thoughts increased at one month after receipt of test results and then decreased at six months post screening. <u>2. Level of concern about getting lung cancer</u> At pre-screening, 94% of participants reported that they were concerned about developing lung cancer. At both follow-up time-points, the proportion of the negative group who reported concern about lung cancer was lower than at pre-screening. In contrast, the proportion of participants with a non-negative result who reported some LC concern increased at one

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
	Ethnicity: 97% Caucasian Current smokers: 43% Test results: Test negative (n = 40) Indeterminate (n = 19) LC diagnosis (n = 1)			month and then decreased at six months post-screening. <u>3. The impact of lung cancer worry on mood and daily activities</u> At pre-screening, 66% reported that lung cancer worry did not affect their mood and 92% reported that it did not affect their ability to perform daily activities. At both follow-up time-points, the proportion who reported some impact of lung cancer worry on mood was lower than at pre-screening for both groups of participants. The same trends were observed for impact on daily activities.
Vierikko et al. 2009 [117] Finland	N: 633 Source: Three groups	Prospective cohort 1. Pre-screening	<u>1. Lung cancer worry</u> Single item. Response rated on a scale of 0 - 8. Higher scores indicated greater worry.	<u>1. Lung cancer worry</u> No significant difference in lung cancer worry between pre-screening and 12 months post-

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
	of Finnish Asbestos exposed workers Mean age: 64.6 Male: 100% Current smokers: 18.5% Test results: Test-negative (n = 530) False positive (n = 97) Lung cancer (n = 6)	2. 12 months post-screening	2. Health anxiety Single item. Response rated on a scale of 0 – 24. Higher scores indicated greater health anxiety	screening was found between the negative and false positive groups. 2. Health anxiety Compared with pre-screening, health anxiety was significantly lower across all participants at 12 months post-screening.

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
Publications reporting results from the Danish Lung Cancer Screening Trial (DLCST)				
Hestbech et al. 2011 [108] Denmark	N: 4,101 (DLCST participants) 673 (sample population comparable to DLCST participants) Source: Individuals taking part in the DLCST and Danish nationals who met DLCST inclusion criteria	Cross-sectional Pre-screening	<u>Psychosocial impact of lung cancer screening (COS-LC).</u> The COS-LC was adapted from the COS and includes two parts. Part one was used in this study. It consists of nine scales with 41 items. Four scales measure anxiety (seven items), behaviour (seven items), dejection (six items), and sleep (four items). The other five scales are specific to lung cancer screening and measure self-blame (five items), focus on airway symptoms (two items), stigmatisation (four items), introvert (four items), and harm of smoking (two items). Responses to each of the items are recorded on a 4-point Likert scale, 0 (not at	<u>Psychosocial impact of lung cancer screening (COS-LC)</u> Prior to screening, the DLCST participants had significantly lower (better) scores for all COS-LC scales and single items than participants in the comparable sample.

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
	Mean age: 57.3 (DLCST participants) and 60.3 (comparable participants) Male: 55.3% (DLCST participants) and 61.6% (comparable participants) Current smoker: 76.2% (DLCST participants) and 50.8% (comparable participants)		all) to 3 (a lot). Higher scores indicate more negative psychosocial consequences.	

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
Aggestrup et al. 2012 [112] Denmark	N: 1,873 (participants in the screen group with negative test results) and 2052 (control group) Mean age: 57.2 (test-negative) and 57.3 (control group) Male: 57.3 (test-negative) and 54.6 (control group) Current smoker: 75.3 (test-negative) and 77(control group)	RCT 1. Pre-randomisation 2. Twelve months post-screening	<u>1. Psychosocial impact of screening (COS)</u> The COS measures psychosocial aspects of screening and consists of two parts. Part one was used in this study. It includes four scales with 23 items: anxiety (six items), behaviour (seven items), sense of dejection (six items) and sleep (four items). Two single items measure whether participants have kept busy to take their mind off things and if they have less interest in sex. Responses are recorded on a 4-point Likert scale, 0 (not at all) to 3 (a lot). Higher scores indicate more negative psychosocial consequences. Administered at pre-randomisation. <u>2. Psychosocial impact of lung cancer screening (COS-LC)</u>	<u>1. Psychosocial impact of screening (COS)</u> At pre-randomisation, no significant differences in COS scores were found between the negative and control groups. <u>2. Psychosocial impact of lung cancer screening (COS-LC)</u> When compared with the participants in the negative group, the control group had significantly higher (worse) scores on the 'anxiety', 'behaviour', 'dejection', 'self-blame', 'focus on airway symptoms' and 'introvert' scales post-screening. Also, when compared with pre-randomisation scores, both groups had significantly higher (worse) scores on the 'behaviour,' 'dejection,' and 'sleep' scales and the 'busy to take mind off things' and 'less interest in sex' items.

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
			See Hestbech et al. 2011 [108] for a description of this measure. Part one administered at post-screening only.	
Kaerlev et al. 2012 [113] Denmark	N: 2,052 (screen group) and 2,052 (control group) Mean age: 57.4 (screen group) and 57.3 (control group) Male: 55.9 (screen group) and 54.6 (control group) Smoking status not reported	RCT 1. Randomisation 2. Three years post-screening	<u>Use of anti-depressive or anti-anxiety medication</u> Information about redeemed prescriptions was obtained through the Danish National Prescription Registry.	<u>Use of anti-depressive or anti-anxiety medication</u> No difference in prescriptions for anti-depressive or anti-anxiety medication was found between the screen and control groups at randomisation and at three years post-screening.

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
Rasmussen et al. 2015 [115] Denmark	N: 2,052 (screen group) and 2,052 (control group) Mean age: 57 (screen group) and 54 (control group) Male: 55.9 (screen group) and 54.6 (control group) Current smoker: 75.3 (screen group) and 77 (control group)	RCT 1. Pre-randomisation 2. One year post-randomisation (CT screening round 2) 3. Two years post-randomisation (CT round 3) 4. Three years post-randomisation (CT round 4)	<u>Psychosocial impact of lung cancer screening (COS-LC)</u> See Hestbech et al. 2011 [108] for a description of this measure. Four core scales administered at each time-point. Five scales specific to lung cancer screening administered at time-points two, three, four and five.	<u>Psychosocial impact of lung cancer screening (COS-LC)</u> For both the screen and control groups, there was a statistically significant increase in scores on three of the four core scales (behaviour, dejection and sleep) from pre-randomisation to one year post-randomisation. This significant increase continued for the following three time-points. However, it is noted that, for the screen group, 'behaviour' and 'dejection' scale scores were starting to decrease towards pre-randomisation scores at three and four years post-randomisation. Groups were compared at each time-point. The control group had significantly higher (worse) scores on the 'dejection' scale at pre-randomisation and on all four of the core scales at one, two, three and four years post-

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
		5. Four years post-randomisation (CT round 5)		randomisation. The control group also had significantly higher (worse) scores on 'self-blame,' 'focus on airway symptoms,' 'stigmatisation,' and 'harm of smoking' at one year post-randomisation. At two years and four years post-randomisation, the control group had significantly higher (worse) scores on the 'self-blame,' 'stigmatisation,' 'introvert' and 'harm of smoking' scales.
Publications reporting on the Nederlands Leuvens Longkanker Screening Onderzoek (NELSON) trial				
Bunge et al. 2008 [106] The Netherlands and Belgium	N: 351 Age (mean): 60.3 Male: 50.9%	Prospective cohort 1. One day before screening	<u>1. Lung cancer specific distress (IES)</u> The IES contains 15 items, seven of which make up an intrusion subscale and eight of which make up an avoidance subscale. Responses recorded on a 4-point Likert scale, scored 0 (Not at all), 1 (Rarely), 3	<u>1. Lung cancer specific distress</u> At pre-screening, participants with a high risk of lung cancer had significantly higher median IES total scores and IES subscale scores compared with participants with low perceived risk.

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
	Current smoker: 74.7% Test results: Test-negative (n = 239) Indeterminate (all of which were test-negative following a repeat scan (n = 49)	(pre-screening) 2. Six months post-screening	(Sometimes) and 5 (Often). Score ranges: 0 – 35 (intrusion subscale), 0 – 40 (avoidance subscale) and 0 – 75 (total score). Higher scores indicate higher levels of distress. <u>2. Emotional quality of life (MCS-12)</u> The SF-12 is a shortened version of the SF-36. MCS-12 scores range from zero to 100 with higher scores indicating better emotional quality of life.	At six months post-screening, median IES scores were significantly lower than at one day before screening. However, participants with high perceived risk still had significantly higher median scores than participants with low perceived risk. <u>2. Emotional quality of life</u> At pre-screening, participants with high risk perception had significantly lower (worse) MCS-12 scores than participants with low risk perception. At six months post-screening, no significant differences were found between groups.
Van den Berg et al. 2008 [114]	N: 351 Age (mean): 60.3 Male: 50.9%	Prospective cohort	<u>1. Lung cancer specific distress (IES)</u> See Bunge et al [106] for a description of this measure.	<u>Lung cancer specific distress, emotional quality of life and state anxiety</u>

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
The Netherlands and Belgium	Current smoker: 74.7% Test results: Test negative (n = 239) Indeterminate (all of which were negative following a repeat scan) (n = 49)	1. One week before screening 3. One week after screening (before test results received) 3. Six months post-screening	2. Emotional quality of life (MCS of the SF-12) See Bunge et al 2008 [106] for a description of this measure. Administered at pre-screening and six months post-screening. 3. State anxiety (6-item version of the STAI, STAI-6) Each of the six items is rated on a 4-point Likert scale, 1 (not at all) to 4 (very much). Scores are prorated for a scale range of 20 to 80. Higher scores indicate greater state anxiety.	One day before screening, MCS-12 and STAI-6 scores were in the same range as age-adjusted and sex-adjusted Dutch reference scores. Median IES, MCS-12 and STAI-6 scores significantly decreased over time. No significant differences in outcome measure scores were found at six months post-screening between participants in the negative group and participants in the indeterminate group who received a negative result following a repeat CT scan. Participants who reported discomfort while waiting for the CT scan result and dreading the results had statistically higher STAI-6 and IES scores at all three time-points.

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
Van den Berg et al. 2010 [107] The Netherlands and Belgium	N: 155 (made an informed decision to take part in screening) and 133 (did not make an informed decision about screening) Age (mean): 57.3 Male: 49% Current smoker: 49%	Prospective cohort 1. When participants made the decision to participate in the trail 2. Pre-randomisation 3. After receipt of test results	<u>1. Lung cancer specific distress (IES)</u> See Bunge et al [106] for a description of this measure. Administered at pre-randomisation and after receipt of test results. <u>2. Emotional quality of life (MCS-12)</u> See Bunge et al 2008 [106] for a description of this measure. Administered at pre-randomisation and after receipt of test results. <u>3. State anxiety (STAI-6)</u> See van den Berg et al 2008 [114] for a description of this measure. <u>4. Psychosocial impact of lung cancer screening (COS-LC)</u>	<u>Lung cancer specific distress, emotional quality of life, state anxiety and psychosocial impact of lung cancer screening</u> Prior to randomisation, participants who made an informed decision to take part had significantly higher (better) mean MCS-12 scores than participants who did not make an informed decision. Following receipt of test results, no differences were found for outcome measure scores between participants with and without an informed decision. For the indeterminate group, no differences were found at each time-point for any of the outcome measures scores between those who did and did not make an informed decision.

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
			See Hestbech et al. 2011 [108] for a description of this measure. Administered after receipt of test results.	
Van den Berg et al. 2010 [90] The Netherlands and Belgium	N: 630 Age (mean): 57.8 52.9% female Test results: Test-negative (n = 489) Indeterminate (n = 141)	Prospective cohort 1. After eligibility check for trial (pre-randomisation) 2. One week before screening 3. One week after screening (before test	<u>1. Lung cancer specific distress (IES)</u> See Bunge et al [106] for a description of this measure. Administered at all four time-points. <u>2. Emotional quality of life (MCS-12)</u> See Bunge et al [106] for a description of this measure. Administered at pre-randomisation and two months post-screening. <u>3. State anxiety (STAI-6)</u> See van den Berg et al 2008 [114] for a description of this measure. Administered at all four time-points.	<u>1. Lung cancer specific distress (IES)</u> IES scores were significantly higher (worse) one week before screening compared with pre-randomisation scores. Mean scores were significantly lower (better) one day after screening when compared with scores at one week before screening but still significantly higher (worse) than pre-randomisation. The negative group had significantly lower (better) IES scores at two months post-screening screening than at pre-randomisation and one week before screening. The indeterminate group had significantly higher IES scores at two months post-screening than at pre-randomisation and one week before

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
		results received) 4. Two months post-screening		screening. Compared with the negative group, the indeterminate group had significantly higher IES total scores at two months post-screening. <u>2. Emotional quality of life (MCS-12)</u> No significant differences in MCS-12 scores were found between the negative and indeterminate group at pre-randomisation and two months post-screening. <u>3. State anxiety (STAI-6)</u> STAI-6 scores were significantly higher (worse) one week before screening compared with pre-randomisation scores. Mean scores were significantly lower (better) one day after screening when compared with scores at one week before screening but still significantly higher (worse) than pre-randomisation scores.

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
				For the negative group, STAI-6 scores did not change significantly over time. The indeterminate group had significantly higher STAI-6 scores at two months post-screening compared with pre-randomisation scores. No statistically significant differences in scores on the STAI-6 were found between groups at the first three time-points. However, at two months post-screening, the indeterminate group had significantly higher mean scores than participants in the negative group.
Van den Berg et al. 2011 [89] The Netherlands and Belgium	N: 1,466 Age (mean): 57.8 46.2% male (screen group) and 50% male (control group)	Prospective cohort 1. Pre-randomisation 2. Two	<u>1. Lung cancer specific distress (IES)</u> See Bunge et al [106] for a description of this measure. <u>2. Emotional quality of life (MCS-12)</u>	<u>1. Lung cancer specific distress (IES)</u> No significant differences were found in IES scores over time between the screen and control groups. However, scores over time differed significantly between the negative and indeterminate group.

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
	Test results: Test-negative (n = 541) Indeterminate (n = 143) Control group (n = 498)	months post-screening to participants with a test-negative or indeterminate result 3. 1.5 years after baseline screening (to screen participants and a random sample of control participants)	See Bunge et al 2008 [106] for a description of this measure. <u>3. State anxiety (STAI-6)</u> See van den Berg et al 2008 [114] for a description of this measure.	Scores at two months post-screening were higher (worse) for participants in the indeterminate group and lower (better) for participants in the negative group. <u>2. Emotional quality of life (MCS-12)</u> MCS-12 scores over time did not differ significantly between the screen and control groups or between the negative and indeterminate groups. <u>3. State anxiety (STAI-6)</u> STAI-6 scores over time did not differ significantly between the screen and control groups or between the negative and indeterminate groups.

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
Publications reporting on the National Lung Screening Trial (NLST)				
Gareen et al. 2014 [116] United States	N: 1,947 (LDCT group) and 865 (chest x-ray group) Age: 55-59 (41.3%), 60-64 (31.9%), 65-69 (18%), 70-74 (8.9%) Male: 56.9% Ethnicity: 94.2% Caucasian	RCT 1. Pre-screening 2. One month post-screening 3. Six months post-screening	<u>1. State anxiety (STAI-S)</u> The state component of the STAI. This includes 20 items measuring state anxiety. Responses recorded on a 4-point Likert scale, 1 (not at all) to 4 (very much). Score ranges: 20– 80. Higher scores indicate higher levels of state anxiety. <u>2. Emotional quality of life (MCS-36)</u> The MCS-36 includes scales on vitality, social functioning, role-emotional and mental health. Scores range from zero to 100 with higher scores indicating better emotional quality of life.	<u>State anxiety (STAI-S) and emotional quality of life (MCS-36)</u> Changes in STAI-S and MCS-36 scores from pre-screening to one month post-screening did not differ across participants with a negative test result, false positive test result or a significant incidental finding. However, when compared with participants with other test results, change in STAI-S and MCS-36 scores was significantly worse for participants who received a positive test result. The same results were found when six month STAI-S and MCS-36 scores were compared with pre-screening scores. No differences in STAI-S and MCS-36 scores were found between screening groups (LDCT

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
	Current smoker: 47.4% Test results: Test-negative (n = 1381) Significant incidental findings (n = 344) False positive (n = 1024) Test-positive (n = 63)			and chest x-ray) at one and six months post-screening.

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
Publications reporting on the United Kingdom Lung Cancer Screening Trial (UKLS)				
Field et al. 2016 [111] United Kingdom	N: 2,018 (screen group) and 2,019 (control group) Age (mean): 67.7 (screen group) and 67.6 (control group) Male: 75% (screen group) and 74% (control group) Ethnicity: 99% Caucasian in both screen and control groups	RCT 1. At recruitment centre before randomisation result was known 2. Two weeks after receiving either the CT scan result (screen group) or letter detailing that	<u>1. Lung cancer worry (CWS-R)</u> The six-item CWS-R was adapted to measure worry specific to lung cancer. Responses recorded on a four-point Likert scale, scored 1 – 4. Score range: 6 – 24. Higher scores indicate higher lung cancer worry. A score of 12.5 or higher was defined as clinically significant. <u>2. General anxiety and depression (HADS)</u> The HADS contains 14 items, seven of which measure depression (HADS-D) and seven that measure anxiety (HADS-A). For each item, participants are asked to indicate the	<u>1. Lung cancer worry (CWS-R)</u> CWS-R scores were within the normal range for both the screen and control groups at each time-point. However, at two weeks following receipt of test results, CWS-R scores were significantly higher in the screen group but did not reach clinical significance. At two weeks following receipt of test results, participants referred with a major lung abnormality had significantly higher CWS-R scores than the other three result groups. CWS-R scores for this group also approached clinical significance (score of 12.5 or higher). Participants who received a positive result and

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
	Current smoker: 38% (screen group) and 39% (control group) CT scan result: Test-negative (n = 763) Test-negative with incidental finding (n = 41) Test-positive for repeat CT scan in three or 12 months (n = 788) Test-positive for referral with major lung abnormality (n = 48)	participant had been assigned to control group 3. Ten to 27 months after attending recruitment centre	extent to which they have felt each emotion over the past week. Responses recorded on a four-point Likert scale, scored 0 - 3. Score ranges: 0 - 21 for each of the anxiety and depression subscales. Scores of 0 -7 were classed as 'normal,' 8 – 10 as 'mild anxiety or depression,' 11 – 14 as 'moderate' and 15 – 21 as 'severe.'	were referred for a repeat CT scan in three or 12 months had significantly higher CWS-R scores compared with participants in the test-negative group. No significant differences in CWS-R scores were found between groups at ten to 27 months post-screening. Raw scores in all groups were not clinically significant. <u>2. General anxiety and depression (HADS)</u> HADS-A and HADS-D scores were within the normal range for both the screen and control groups at each time-point. At two weeks following receipt of test results, participants referred with a major lung abnormality had significantly higher HADS-A scores than the other three result groups. However, their scores were still within the 'normal' range (0 – 7). No significant differences were found between groups for HADS-D scores.

Author and location	Participants	Study design & measurement time points	Emotional outcome(s) reported	Main results
	Test results at long-term follow-up: Test-negative (n = 763) Incidental finding (n = 78) False positive (n = 445) Test-positive (n = 23)			No significant differences in HADS-A and HADS-D scores were found between groups at ten to 27 months post-screening. Raw scores in all groups were not clinically significant.

Key. COS = Consequences of Screening; COS-LC = Consequences of Screening - Lung Cancer; CWS = Cancer Worry Scale; IES = Impact of Events Scale; MCS-12 of the SF-12 = The Mental Component Summary of the 12-item Short Form Questionnaire; MCS-36 of the SF-36 = The Mental Component Summary of the 36-item Short Form Questionnaire; PCQ = Psychological Consequences Questionnaire; STAI = State and trait anxiety inventory.

2.2.1. Pre-screening emotional impact

Two publications from the NELSON trial [90,114] and one publication from the DLCST [108] reported on pre-screening emotional impact. One publication from the NELSON trial and the DLCST administered emotional outcome measures post-randomisation but prior to screening [108,114]. The NELSON trial found no significant differences in the scores of trial participants on measures of emotional quality of life and state anxiety when compared to age-adjusted and sex-adjusted reference scores [114]. The DLCST compared scores on measures specific to lung cancer screening between trial participants and a comparable sample of participants from the general population who would be invited to lung cancer screening [108]. In contrast to the results from the NELSON trial, it was found that trial participants had significantly better scores than the comparable sample. The authors also identified important sociodemographic disparities between groups. For example, trial participants were more likely to be female and had significantly higher socioeconomic status, education, and employment rates than the comparable sample [108].

The other publication, which reported on the NELSON trial, compared lung cancer specific distress and state anxiety scores at pre-randomisation and then at one week before screening [90]. Scores on both measures were significantly higher at one week prior to screening when compared with pre-randomisation scores [90]. This result suggests that the anticipation of having a screening test could be associated with negative emotional outcomes.

2.2.2. Short-term emotional impact

Wu et al. defined the short-term emotional impact of screening as the period between receiving the screening test and less than six months post-screening [109]. The long-term emotional impact of screening was defined as more than six months post-screening [109]. The same definitions are employed in this chapter.

The short-term emotional impact of clinical trial randomisation (screen vs. control)

Only the UKLS trial reported on the short-term emotional impact of clinical trial randomisation by comparing screen and control groups [111]. Measures of lung cancer worry, anxiety and depression were administered at two weeks following receipt of test results [111]. At this time-point, participants in the screen group had significantly higher levels of lung cancer worry compared with the control group. However, the authors state that once effect modifiers (gender, age group, smoking, socioeconomic deprivation, education, ethnicity, marital group, lung cancer experience, trial site and time since attended recruitment centre) were controlled for, there was insufficient evidence to suggest a meaningful difference between groups. The authors reported that lung cancer worry, anxiety and depression scores were all within the normal range for both groups [111].

The short-term emotional impact of type of screening test (LDCT vs. chest x-ray)

Participants in the NLST were randomised to receive three annual screenings with either LDCT or a chest x-ray [116]. No differences were found between groups in scores on measures of state anxiety and emotional quality of life at one month post-screening [116].

The emotional impact of waiting for screening test results

Two publications from the NELSON trial reported on the emotional impact of waiting for test results [90,114]. Measures of anxiety and distress specific to lung cancer were administered one day after screening. Participants were asked to complete the measures within a week to ensure they would be completed before test results were received. Both publications reported a significant improvement in scores between one week before screening and one week after screening [90,114]. However, the publication that administered measures prior to randomisation reported that scores after screening were still significantly worse than pre-randomisation scores [90]. The authors of both publications defined the minimal important difference (MID) as half of a standard deviation of the mean. Based on this definition, they reported that changes in scores were not clinically meaningful.

Furthermore, one publication from the NELSON trial reported that 46.4% of participants experienced discomfort while they waited for the results of the CT scan and 51.3% had dreaded receiving their results [114]. These participants had significantly higher anxiety and distress scores post-screening compared with the participants who reported no discomfort or dread while waiting for test results [114]. Based on their definition of the MID, the authors state that the difference between groups was clinically meaningful.

The emotional impact of receipt of screening test results

Five publications reported on the emotional impact of receipt of test results [88-91,116]. Emotional outcome measures were administered at one to two weeks after receipt of test results [88], at one month after receipt of test results [91], and at one month [116] and two months post-screening [89,90].

Receipt of an indeterminate test result

An indeterminate result is where small nodules are identified and the participant is advised to attend a follow-up CT scan in several months [88,114]. Four publications reported on receipt of an indeterminate test result; two were from the NELSON trial [89,90] one was from the PLuSS study [88] and the other reported on a population at high risk of lung cancer due to family history [91]. The PLuSS study found significantly higher levels of state anxiety at one to two weeks following receipt of an indeterminate test result [88]. The NELSON trial also reported significantly higher (worse) levels of lung cancer specific distress at two months after screening compared with pre-randomisation [89,90]. Differences in distress scores between participants with an indeterminate and participants with a negative result at two months post screening were statistically and clinically significant according to the author's definition of the MID [89,90]. One publication from the NELSON trial reported that participants who received an indeterminate result had significantly higher levels of state anxiety when compared with pre-randomisation scores and scores amongst those with a negative test result at two months post-screening [90]. Participants with a family history of lung cancer who received indeterminate test results reported increased lung cancer worry at one month after results were received compared with baseline, however it is unclear as to whether this result was statistically significant as no statistical tests were conducted [91].

Receipt of a suspicious or true positive test result

A suspicious test result is where a participant is referred for further investigations for suspected lung cancer [88]. The PLuSS study found that participants who received suspicious results had an increased fear of cancer two weeks after receipt of test results when compared with pre-screening [88,109,110]. The NLST also found that participants with a true positive result had

significantly worse state anxiety and emotional quality of life at one month post-screening when compared with participants with a negative result, false positive result or a significant incidental finding [109,116]. In the UKLS trial, participants with a positive result who were referred with a major lung abnormality had significantly higher levels of lung cancer worry when scores were compared with the other three result groups (please see table one for a description of each group) [111]. The authors state that scores for this group approached clinical significance. Participants referred for a repeat CT scan in three or 12 months had significantly higher lung cancer worry scores when compared with participants who received a negative result. No differences were found between groups for scores on a measure of depression. However, participants referred with a major lung abnormality had significantly higher anxiety scores than the other three result groups [111].

Receipt of a negative test result

Four publications explored the short-term emotional impact of a negative test result; two reported on the NELSON trial [89,90], one on the PLuSS study [88], and the other included participants at high risk of lung cancer due to family history [91]. The publications from the NELSON trial reported no impact of receipt of a negative test result on emotional quality of life and state anxiety at two months post-screening. However, scores on a measure of lung cancer specific distress had significantly decreased when compared with baseline scores [89,90]. The PLuSS study reported no significant change in anxiety and fear of lung cancer at one to two weeks following receipt of test results [88]. The other publication found that lung cancer worry scores for participants with a negative test result were lower at one month post-screening when compared with pre-screening scores, but statistical significance was not reported [91].

A brief summary of the results of publications that have reported on the short-term emotional impact of lung cancer screening

Results from the UKLS trial indicate that there are no important differences in emotional outcome measure scores between participants in the screen and control groups at two weeks following receipt of test results [111]. The NLST also found no differences in emotional outcome measure scores between screen groups (LDCT vs. chest x-ray) at one month post-screening [116]. Receipt of an indeterminate, suspicious or positive test result has the potential to have a short-term negative emotional impact [88-91]. Overall, receipt of a negative test result appears to have no significant impact on non-specific emotional outcomes but is associated with a reduction in some emotional outcomes specific to lung cancer [88-91].

2.2.3. Long-term emotional impact

The long-term emotional impact of clinical trial randomisation (screen vs. control)

The DLCST [112,113,115], the NELSON trial [89], and the UKLS trial [111] reported on the long-term emotional impact of lung cancer screening by comparing the screen and control groups. One publication from the DLCST measured participants' use of anti-depressive and anti-anxiety medication at three years post-screening [113]. The other two publications from the DLCST administered questionnaires containing measures of screening-specific distress at one [112,115], two, three and four years post-screening [115]. The NELSON trial administered measures at 1.5 years post-screening [89]. The UKLS trial administered questionnaires containing emotional outcome measures to all participants in January 2014, which was between 10 and 27 months post-screening, depending on when participants had attended the recruitment centre [111].

No differences were found between the DLCST screen and control groups in terms of prescriptions for anti-depressive and anti-anxiety medications at three years post-screening [113]. The other two publications from the DLCST reported that, when compared with pre-screening scores, participants in both the screen and control groups had significantly higher (worse) scores on measures of screening-specific distress at one [112,115], two, three and four years post-screening [115]. Furthermore, when compared with participants in the screen groups at each time-point, both publications found that the control groups had significantly higher (worse) scores on a number of the scales, which are listed in table seven [112,115].

The results from the NELSON trial and the UKLS trial contradict those of the DLCST. The NELSON trial reported no significant differences in scores on measures of lung cancer specific distress, state anxiety and emotional quality of life between screen and control groups over time (baseline to 1.5 years post-screening) [89]. The UKLS trial also found no significant differences in lung cancer worry scores between participants in the screen and control groups. Raw scores in both groups were not clinically relevant. Although the control group participants had significantly higher anxiety and depression scores than participants in the screen group, the authors emphasise that these differences were minimal and not clinically significant. Furthermore, raw scores for anxiety and depression were within the normal range for participants in both groups.

The long-term emotional impact of type of screening test (LDCT vs. chest x-ray)

The NLST found no statistically significant differences between screen groups in scores on measures of state anxiety and emotional quality of life at six month post-screening [21].

The long-term emotional impact of type of test result received

The NELSON trial [89,114], the PLuSS study [88], and the UKLS trial [111] reported on the long term emotional impact of lung cancer screening test results. Two publications that reported on screening for those with a family history of lung cancer [91] and individuals exposed to asbestos [117] also explored the long-term impact of type of test result received. Emotional outcomes were measured using questionnaires administered at six months [88,91,114], 12 months [88,117], 1.5 years post-screening [89] and between 10 and 27 months post-screening [111].

The UKLS trial reported no significant differences for lung cancer worry, depression and anxiety scores between participants with different types of test result (negative, incidental finding, false positive and true positive). Furthermore, the raw scores of all outcome variables in all groups were within the normal range and therefore not clinically relevant [111].

Receipt of an indeterminate test result

The PLuSS study [88], the NELSON trial [89,114] and a publication that included participants with a strong family history of lung cancer [91] reported on the long-term emotional impact of an indeterminate result. The PLuSS study found a significant change in state anxiety scores over time. Scores at six and twelve months were lower than at one to two weeks post-test results but were still higher than at baseline [88]. At six months post-screening, the proportion of participants with a strong family history of lung cancer who reported some frequency of thoughts about getting lung cancer was lower than at one month but still higher than at pre-screening [91]. The proportion who reported some concern about getting lung cancer had returned to pre-screening levels, whereas the proportion who reported some impact of lung cancer worry on mood and

daily activities was lower at six months than at pre-screening [91]. The statistical significance of the findings from this study was not reported.

One publication from the NELSON trial reported no differences in scores on emotional outcome measures between participants with an indeterminate result and participants with a negative result at six months post-screening [114]. The other publication from the NELSON trial found that lung cancer specific distress had returned to almost baseline levels at 1.5 years post-screening. No impact on emotional quality of life or state anxiety was found at 1.5 years post-screening [89].

Receipt of a false positive test result

The publication that included asbestos exposed workers found significantly lower levels of health anxiety but no difference in lung cancer worry scores at 12 months post-screening when compared with pre-screening scores [117].

Receipt of a suspicious or true positive test result

The PLuSS study reported that change in fear of lung cancer scores over time was significant for participants with a suspicious result. Scores had declined at six months and 12 months post-screening but were still higher than at baseline [88]. The NLST found that participants with a true positive result had significantly worse state anxiety and emotional quality of life from baseline to six months post-screening when compared with participants with a negative result, false positive result or a significant incidental finding [116].

Receipt of a negative test result

The PLuSS study found no significant change over time in anxiety and fear of cancer in participants who received a negative test result [88]. Participants with a family history of lung cancer had lower levels of cancer worry at six months post-screening compared with pre-screening, but statistical significance was not reported [91]. The asbestos exposed participants who underwent screening had significantly lower levels of health anxiety at 12 months when compared with pre-screening scores. No differences in lung cancer worry scores were found over time [117].

The NELSON trial reported no impact on emotional quality of life and state anxiety at 1.5 years post-screening but significantly lower levels of lung cancer specific distress compared with pre-screening [89]. The other publication reported no significant change from pre-screening for measures administered at six months post-screening [114].

A brief summary of the results of publications that have reported on the long-term emotional impact of lung cancer screening

Three publications from the DLCST [112,113,115], and one publication from each of the NELSON [89] and UKLS [111] trials explored the long-term emotional impact of clinical trial randomisation to a screen or control group. The results of two publications from the DLCST [112,115] are of particular concern as, when compared with baseline scores, both the screen and control groups experienced significantly worse emotional outcomes in the longer-term (up to four years post-randomisation [115]). This finding, however, contradicts those of the NELSON trial [89], which reported no emotional impact at 1.5 years post-screening. The inconsistencies in the results

between the DLCST and the NELSON trial could be due to the types of measures administered to assess the emotional impact of screening, which is discussed in section 2.3.

An additional observation from the DLCST is that cross-sectional analyses showed that the screen group experienced fewer negative psychosocial consequences when compared with the control group [112,115]. The UKLS trial also reported that the control group had significantly worse scores on measures of anxiety and depression compared with the screen group, although the authors emphasise that such differences were minimal and not clinically relevant [111]. The same trial found no significant differences between the screen and control groups on lung cancer worry scale scores.

Receipt of an indeterminate, false positive or negative test result was not found to have a negative emotional impact in the longer term [88,89,91,111,114,116,117]. Therefore, the negative emotional impact following receipt of an indeterminate result that was found at the short-term follow-ups appears to be transient.

2.3. Discussion

2.3.1. Summary of results

The purpose of this chapter was to review the literature on the emotional impact of lung cancer screening. As stated in section 2.2 (page 69), in order to understand fully the emotional impact, we need to know the point in the screening programme at which it occurs, the nature of such impact, and whether it is transient or if it persists in the longer term. The evidence suggests that receipt of an indeterminate test result has the potential to have a negative emotional impact. The four publications that reported on the short-term impact of type of test result found that indeterminate results were associated with negative non-specific [88,90] and specific [89-91] emotional outcomes at one to two weeks following receipt of results [88] and at one month [91] and two months [89,90] post-screening. This negative impact appears to be transient as receipt of an indeterminate result was not found to significantly impact non-specific and specific outcomes at six months [91,114], 12 months [88] and 1.5 years post-screening [89]. The systematic reviews conducted by Slatore et al [110] and Wu et al [109] also concluded that participants who received an indeterminate result experienced negative emotional outcomes in the short term.

Furthermore, three publications reported that receipt of a suspicious result [88], true positive result [116], or a positive result with referral for a major lung abnormality [111] were all associated with negative specific [88,111] and non-specific [116] emotional outcomes at one to two weeks following test results [88,111] and at one month post-screening [116]. Evidence for the long-term emotional impact of these types of test results, however, was inconsistent. One publication found no generic and specific negative emotional impact for participants who received a positive result with referral for a major lung abnormality at 10 to 27 months post-screening [111]. Participants

who received suspicious test results had lower scores on a measure of fear of lung cancer at six and 12 months post-screening but scores were still higher than at baseline [88]. Another publication reported that participants with a true positive result still had significantly worse scores on generic emotional outcome measures at six months post-screening [116]. These results suggest that a suspicious, true positive or positive result with referral for a major lung abnormality is associated with a short-term negative emotional impact. Further research is required before conclusions can be drawn regarding the long-term impact of these types of test results as the evidence is inconclusive.

The evidence indicates that receipt of a negative test result has no negative impact on generic emotional outcomes. One publication found that participants with a negative test result had lower levels of health anxiety at 12 months post-screening [117]. Three other publications reported no association between a negative test result and negative generic emotional outcomes at one to two weeks following test results [88], and at two months [89,90], six months [88,114], twelve months [88] and 1.5 years post-screening [89]. Furthermore, there appears to be no negative impact on specific emotional outcomes. Two studies, and one publication from the NELSON trial, found no significant change in specific emotional outcomes at six [114] and 12 months post-screening [88,117]. Two publications from the NELSON trial reported significantly lower levels of lung cancer specific distress at two months [89,90] and at 1.5 years post-screening [89] when compared with baseline scores. This finding is supported by another study where it was found that participants with a negative test result had lower lung cancer worry scores at one-month post-screening when compared with baseline scores, but statistical significance was not reported [91].

At present, it is difficult to draw further conclusions concerning the emotional impact of lung cancer screening. This is due to several reasons. First, it must be emphasised that there is a

paucity of research in this area. Whilst 14 publications have reported on the emotional impact of lung cancer screening, nine of these were from two European RCTs. Furthermore, there is substantial heterogeneity among studies in terms of the time points at which emotional outcome measures have been administered as well as the use of different measurement tools or comparison groups. In the following three subsections, methodological issues, theoretical issues and clinical implications are discussed.

2.3.2. Methodological issues

1. Paucity of research on the emotional impact of lung cancer screening

As stated above, very few studies have investigated the emotional impact of lung cancer screening. According to Wu et al, there are two explanations for this lack of research [109]. The first is that lung cancer screening studies have focused more on the physical impact of screening due to the emotional impact of screening being perceived as trivial. The second that, until recently, there has been no framework available to guide high quality research on the potential harms of screening [109]. The first, and only, framework was published by Harris et al in 2014 and described in chapter one of this thesis (pages 55 – 58) [84]. The framework consists of four domains of harm that can result from screening: physical harm, psychological harm, financial strain and opportunity cost. It is important that this framework is used to inform the design of future studies to ensure that different types of harm are thoroughly investigated and quantified.

2. Evidence from randomised controlled trials

What we know about the emotional impact of lung cancer screening is largely derived from studies conducted within the context of RCTs. For example, 11 of the 14 publications (78%) report results from four RCTs. As stated in chapter one, page 46, a key advantage of a RCT is that participants are randomised to either a screen or control group, which ensures that any characteristics (e.g., age, gender) that have the potential to affect the outcomes measured are evenly distributed between groups, so any differences observed between groups should therefore be attributable to screening [64]. The results of these trials are therefore valuable and do provide important insights into the emotional impact of lung cancer screening. However, it has been shown that results from RCTs have the potential to be biased due to a particular group taking part in the trial. For example, a publication from the UKLS trial found that female gender, older age, lower socioeconomic status, and higher perceived risk of developing lung cancer were all significantly associated with non-participation in the trial [119]. Current smokers were also significantly less likely to take part compared with former smokers [119]. In addition, a publication from the DLCST, described in table seven and section 2.2.1, identified important sociodemographic disparities between trial participants and a comparable sample of participants from the general population who were not taking part in the DLCST [108]. For example, trial participants were more likely to be female and had significantly higher socioeconomic status, education and employment rates than the comparable sample. It was also found that trial participants had significantly better scores on a measure of emotional outcomes specific to lung cancer screening. As stated in section 2.1, this difference could be due to screening participation having a positive emotional impact in itself. However, in the introduction of the publication, the authors cite four studies, which found that volunteers in medical trials were more outgoing, more socially confident, more content, optimistic and self-confident than the general

population. Volunteers were also found to be less neurotic and less anxious. It is therefore possible that the volunteers in the DLCST were more emotionally healthy than the comparable sample. These results raise important questions concerning the external validity of the results of the studies conducted as part of clinical trials. It is possible that trial participants could be more resistant to some of the harmful effects of lung cancer screening than the general population and therefore the extent of any negative emotional outcomes reported following screening for lung cancer could be underestimated. It is very important that efforts are made to investigate the emotional impact of lung cancer screening in nonclinical trial settings, which should soon be possible to do as routine lung cancer screening programmes are implemented.

Furthermore, two observations from the DLCST raise additional concerns regarding the generalisability of results from the studies that were conducted within the context of clinical trials. First, when compared with baseline scores, both the screen and control groups experienced significantly worse emotional outcomes in the longer-term (up to four years post-randomisation)[112,115]. The authors suggest that taking part in a lung cancer screening trial increased participants awareness of their risk of lung cancer, which had a long term negative emotional impact for both groups [115]. The second observation is that the screen group experienced fewer negative psychosocial consequences at each time-point when compared with the control group [112,115]. The authors propose that this difference could be due to reassurance amongst the screen group as 96% received a negative result at each screening round [115]. The UKLS trial also reported that the control group had significantly worse scores on measures of anxiety and depression compared with the screen group at the longer term follow-up, although the authors emphasise that such differences were minimal and not clinically relevant [111,118]. The authors of the UKLS trial argue that the observed differences in scores reflect the control groups' disappointment and frustration at being identified as high risk for

developing lung cancer but then prevented from taking part in screening. Their finding that a significantly greater proportion of participants in the control group were less satisfied with their decision to take part in the trial compared with participants in the screen group supports this argument [111]. The important point to take from these observations is that the results of the studies conducted as part of clinical trials are potentially further biased due to an increase in negative emotional outcomes in the control group. The authors of the DLCST advise that future studies exploring the emotional impact of cancer screening should compare three groups: a screen group, an unblinded control group and a blinded control group who are unaware of the intervention and that they have been randomised to the control group [115]. The unblinded control group would act as a true comparison as they would not experience an increased awareness of their risk of developing lung cancer or disappointment at being randomised to the control group.

3. Measurement of emotional outcomes specific to lung cancer screening

As was pointed out in section 2.2.3, important inconsistencies exist between the results of the two RCTs that reported on the long-term emotional impact of trial randomisation to a screen or control group. The DLCST found that when compared with baseline scores, both the screen and control groups reported significantly worse emotional outcomes in the longer-term (up to four years post-randomisation) [112,115]. In contrast, the NELSON trial reported that allocation to the screen or control group was not associated with negative non-specific and specific emotional outcomes at 1.5 years post-screening. It is possible that these differences in results are due to the measures used to assess the emotional impact of screening. The NELSON trial administered both generic and specific emotional measures. The specific measure administered was the IES, a validated measure that assesses distress caused by a traumatic event [120]. In the NELSON trial, the IES was adapted to refer to lung cancer [89]. The content validity was not

reported [89]. The DLCST only administered a measure specific to lung cancer screening, the COS-LC. This measure was developed from interviews with the target population and validated during the first screening round of the DLCST [112,115]. As the COS-LC is directly relevant to lung cancer screening and reported to have high content validity, it is possible that it may be more effective at detecting changes in specific emotional outcomes than other measures. This could account for why the DLCST found that negative emotional outcomes for both the screen and control group persisted in the longer term and the NELSON trial did not [89,112,115]. This finding raises intriguing questions regarding the results of the other studies that used specific measures to capture negative emotional outcomes [88,90,91,106,111,114,117]. The measures administered by four of these studies were adapted from validated measures [88,90,91,106,111,114], however, the content validity was not reported in any of the publications. It is therefore unclear if the measures were able to capture the full nature or extent of any specific negative emotional outcomes of lung cancer screening. In 2004, an editorial was published that provided guidance on how to improve the assessment of psychosocial and quality of life outcomes in screening [121]. One of the key points emphasised in this publication was the importance of administering measures with high content validity that can adequately capture specific outcomes. Future studies exploring specific emotional outcomes of lung cancer screening should therefore seek to administer a measure with high content validity, such as the COS-LC when it is available for wider use.

4. Measurement of positive emotional outcomes

Despite the importance of exploring the positive emotional impact of lung cancer screening, no studies to date have administered positive emotional outcome measures. As stated in section 2.1, to ensure that the benefits of lung cancer screening outweigh the harms, emotional benefits must be investigated. Furthermore, being able to demonstrate positive emotional responses in

screening participants, particularly those who do not benefit from screening, could provide a rationale for introducing or continuing a screening programme. A theoretical framework that emphasises the importance of measuring positive emotional outcomes is described in section 2.3.3.

5. Emotional outcome measurement time-points

As stated in section 2.1, in order to adequately understand the emotional impact of lung cancer screening, we must be able to identify the point(s) in the screening programme at which any impact occurs and whether it is short term or persists in the longer term. The DLCST [112,115], NELSON trial [89], and the UKLS trial [111] reported on the emotional impact of lung cancer screening by comparing outcomes between the screen and control groups. The DLCST administered their first follow-up measure at one year post-screening and the NELSON trial administered their first, and final, measure at 1.5 years post-screening. The UKLS trial measured emotional outcomes within four weeks of receipt of test results and then between 10 and 27 months post-screening depending on when participants had attended the recruitment centre. There are several issues with the measurement time-points of these three studies, which makes it difficult to understand fully the emotional impact of screening. First, the short-term emotional impact is unclear as only one study, the UKLS trial, investigated this. It is also unclear as to whether outcomes fluctuated in the short-term, as measures were not administered again until at least ten months post-screening. In addition, it is important to note that the NELSON trial measured emotional outcomes only once post-screening. As stated in section 2.1, there are a number of points in the screening programme that have the potential to cause emotional harm. Therefore, emotional outcome measures should be administered at multiple time points. Administering outcome measures once only enables us to identify one point in the screening

programme where emotional harm may occur; it does not enable us to identify any other points in the screening programme where emotional harm may occur or to examine how any emotional effects change over time. It is important that future studies comparing screen and control groups seek to administer multiple emotional outcome measures in both the short and longer term.

Summary of methodological issues

To summarise, there are five key methodological issues that make it difficult to draw conclusions concerning the emotional impact of lung cancer screening. First, there is very little published research in this field. Second, the generalisability of much of the published research is problematic due to heterogeneity in the type of emotional outcomes measured and methods of outcome measurement. Also, a selected group of participants have taken part in the RCTs, which further limits the generalisability. However, it is important to note that not everyone will take part in a national screening programme. It is possible that some of those who declined to participate in a RCT would also not participate in a lung cancer screening programme. Third, there are issues concerning the content validity of some of the specific emotional outcome measures that were administered. It is possible that such measures will not have been able to capture the full extent of specific emotional outcomes following screening for lung cancer. It is also important to note that no studies administered positive emotional outcome measures. Finally, the time-points of administration of emotional outcome measures in the studies that compared screen and control groups make it difficult to determine the short-term emotional impact of clinical trial randomisation as well as explore how emotional outcomes may have changed over time.

2.3.3. Theoretical issues

A striking observation from the literature is that no studies appear to have drawn upon relevant theoretical models to inform objectives and research design. One such model that can be applied to aid understanding of the emotional impact of screening for lung cancer is the stress and coping model, which is described in the following section.

The stress and coping model

The stress and coping model, illustrated in figure five, was developed by Lazarus and Folkman in 1984 [122] (please see Appendix 1, page 479, for documentation of permission to republish figure five). It is an appraisal-based model, which proposes that the emotional impact of a stressor, such as lung cancer screening, is determined by how an individual appraises the stressor. The appraisal process consists of two components: primary appraisal and secondary appraisal. Primary appraisal involves an assessment of the personal significance of the stressor in terms of an individual's dispositions, beliefs and goals. Secondary appraisal is where the individual evaluates the demands of the stressor and whether the coping resources available to them are sufficient to manage it. The two appraisals are then combined to determine whether the stressor is appraised as harmful, threatening or challenging [123]. Following appraisal of the stressor, an appropriate coping strategy is selected. According to the model, two such strategies can be utilised: problem-focused coping or emotion-focused coping. Problem-focused coping involves identifying and using suitable problem-solving strategies, such as obtaining information and decision making [124]. It has been stated that problem-focused coping is used in response to stressors that have the potential to be alleviated [123]. Emotion-focused coping, on the other hand, is applied where stressors cannot be alleviated but have to be accepted and managed.

Emotion-focused coping can help to control negative emotions concerning the stressor, for example, distancing oneself from the stressor, wishful thinking, obtaining appropriate emotional support[124,125]. According to the model, if a stressor is resolved or managed successfully, then this will result in positive emotions. If the stressor is not resolved, then this will result in negative emotions, which leads back to a re-appraisal of the stressor and selection of appropriate coping strategies.

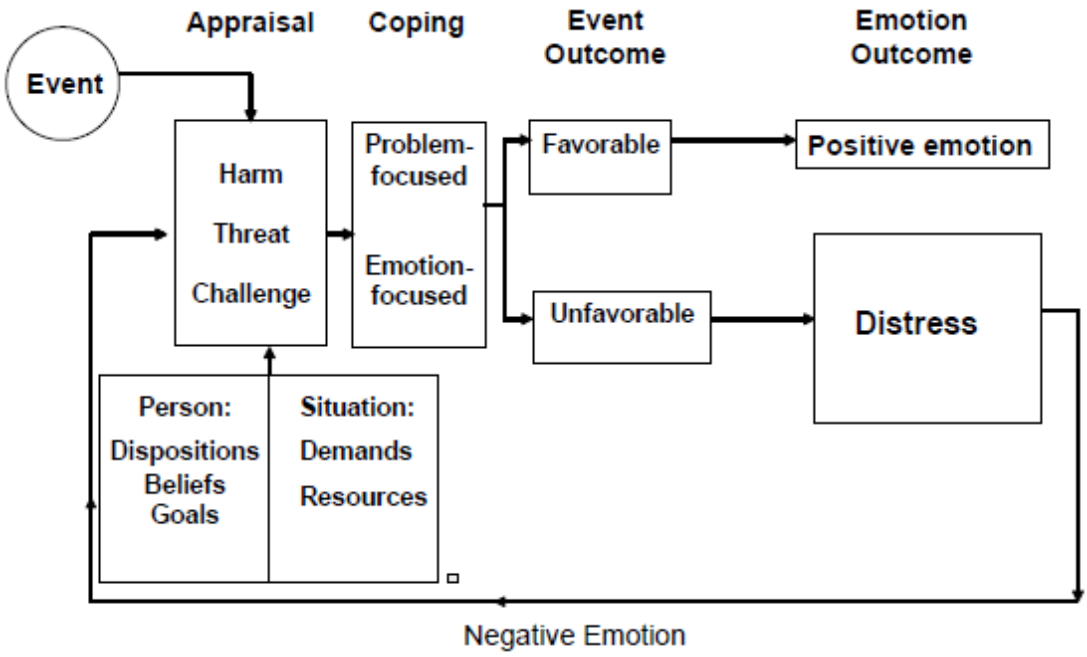


Figure 5. The original stress and coping model developed by Lazarus & Folkman in 1984[122] and published in Folkman 2008[123]

In 1997, the stress and coping model was revised to include meaning-focused coping and positive emotions [126] (figure six, permission to republish figure six is included in appendix one). According to the revised model, if a stressful situation is not resolved, then meaning-focused coping can be instigated. Meaning-focused coping has been defined as a type of coping where the individual utilises their beliefs, principles and goals to stimulate positive emotions. Positive

emotions can impact the stress process by replenishing coping resources and increasing the motivation required to maintain problem or emotion-focused coping in response to the stressor. As well as having an effect on coping, it has been stated that positive emotions can also help to reduce negative emotional outcomes [123].

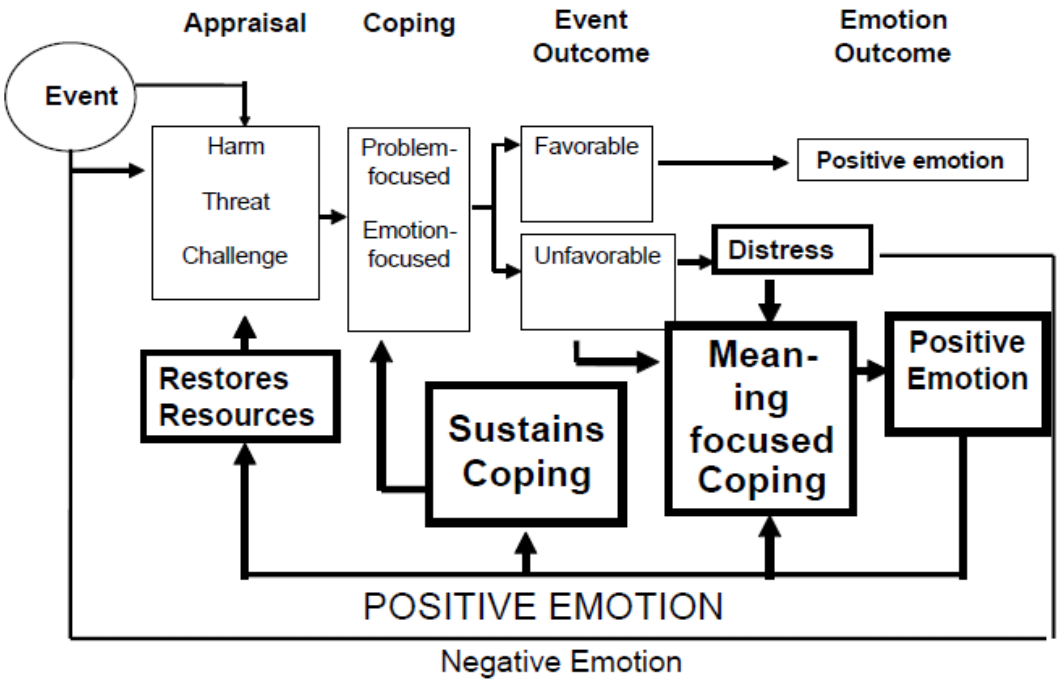


Figure 6. The revised stress and coping model introduced by Folkman in 1997 [123] and published in Folkman 2008[123]

The stress and coping model could be valuable in helping to inform future research on the emotional impact of lung cancer screening. As described above, the model proposes that emotional responses to a stressor can be both positive and negative [123]. Surprisingly, the studies that have explored the emotional impact of lung cancer screening have focused exclusively on negative emotions. To ensure that the benefits of lung cancer screening outweigh

the harms, it is essential that future research explores whether screening enhances positive emotional outcomes (e.g., happiness, enthusiasm).

In addition, by suggesting that emotional outcomes are influenced by an individual's appraisal of screening and their coping behaviours, the stress and coping model has introduced the concept of individual differences in response to stressors. In 2008, the model was used to inform a study that explored breast cancer-related distress following mammography screening for younger women on a family history breast screening programme[127]. Appraising screening as highly relevant and threatening was associated with higher levels of breast cancer worry at one and six months post-screening. In terms of coping strategies, perceived inability to cope emotionally was associated with higher levels of breast cancer worry post-screening. These results provide an important insight as to how psychosocial factors can influence responses to screening as well as demonstrate how theory can effectively inform understanding of the emotional impact of cancer screening. However, in addition to appraisals and coping, it is possible that there are a range of different psychosocial factors that can mediate responses to cancer screening. Another psychological model that incorporates additional factors is the Self-Regulation Model (SRM) of Illness Beliefs. This model is described in the following section

The Self-Regulation Model (SRM) of illness beliefs

The Self-Regulation Model (SRM) of illness beliefs, presented in figure seven, is a health psychology model that was developed in the 1980s [128]. Please see Appendix two, page 480, for documentation of permission to republish figure seven as part of this thesis. The model has mainly been used to aid understanding of emotional and behavioural responses to an illness. However, it can also be used to predict responses to a range of health threats, including

screening for cancer [129]. According to the model, when an individual is confronted with a potential health threat, they simultaneously form cognitive and emotional representations of the threat [130]. Emotional representations consist of the feelings evoked from the threat (e.g., upset, anger, worry) and cognitive representations contain five components [131]:

1. Identity: the label the individual assigns to the condition based on the symptoms they associate with it
2. Cause: an individual's ideas about the causes of the condition
3. Time-line: an individual's perception of the duration of the condition
4. Consequences: an individual's beliefs about the severity of the condition and its potential impact on their physical, social and emotional functioning
5. Curability/controllability: beliefs concerning the availability and effectiveness of treatments that can cure the condition and whether the individual can access them.

Based on their cognitive and emotional representations, the individual selects appropriate coping strategies (e.g., avoidance, problem-focused coping) to manage the threat. Such strategies directly influence illness outcomes (e.g., physical functioning, vitality) and emotional outcomes (e.g., distress). The coping strategies are then appraised and fed back into the cognitive and emotional representations, as illustrated in figure seven. If not effective, the strategies may be modified. It is important to note that as well as informing coping strategies, both cognitive and emotional representations can directly impact both illness and emotional outcomes.

The SRM of illness beliefs was used to inform a study exploring emotional outcomes in individuals with abnormal cervical and colorectal cancer screening test results [131]. After

controlling for demographic variables, it was found that the following representations explained significant variance in emotions: perceived serious consequences of the cancer screened for, identify, the perception of the cancer screened for as being caused by psychological stress (e.g., stress or worry, family problems) and emotional representations [131]. These results highlight the important role of cognition in explaining variations in emotional responses to abnormal screening test results and suggest that the SRM could be a helpful framework for exploring the emotional impact of screening.

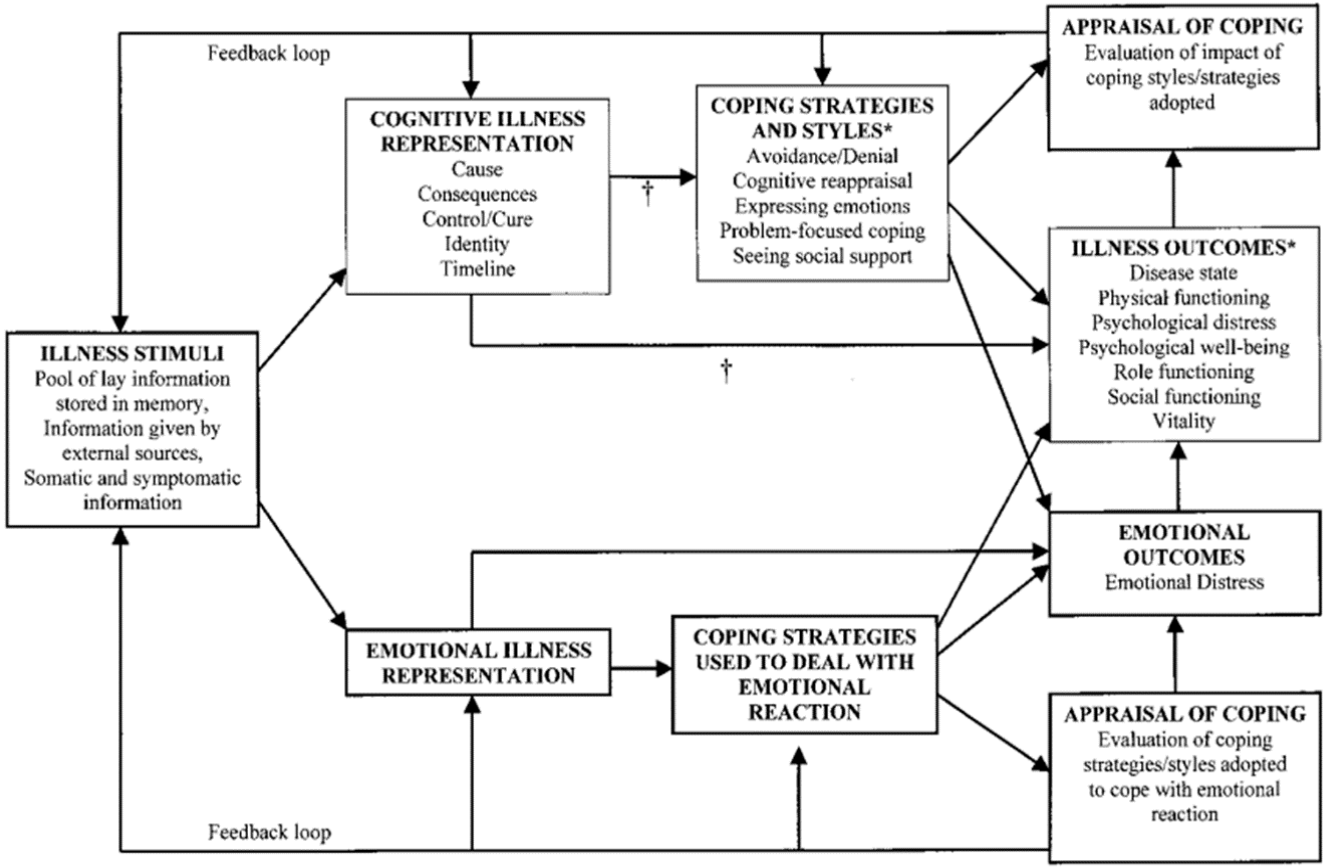


Figure 7. Schematic representation of Leventhal et al's (1980) Self-Regulation Model (SRM) of illness beliefs, published by Hagger and Orbell [132]

A summary of theoretical issues

To summarise, the models described above could be very useful in guiding future research on the emotional impact of lung cancer screening. The models have raised two key questions in need of further investigation in the context of lung cancer screening:

1. Does lung cancer screening result in positive emotional outcomes?, and
2. What factors influence the emotional impact of lung cancer screening?

The first question, derived from the stress and coping model, is very important to answer. There is increasing recognition that a stressor, such as screening for cancer, can have a positive, as well as a negative, emotional impact [133]. As stated in sections 2.1 and 2.3.2, to ensure that the benefits of lung cancer screening outweigh the harms, emotional benefits must be investigated. In terms of the second question, factors that can determine the emotional impact of lung cancer screening must be investigated so that individuals who may be vulnerable to negative emotional impacts can be identified and appropriate interventions developed to support them. Such interventions could be implemented as part of a routine lung cancer screening programme, which would help to improve the standard of care and minimise potentially harmful emotional effects of screening among potentially vulnerable groups.

2.3.4. Clinical implications

As discussed in section 2.2.2, page 97, receipt of an indeterminate test result has the potential to have a short-term negative emotional impact. This finding has important implications for clinical practice. If required, participants who receive an indeterminate result should be offered

additional support following receipt of their results with the aim of improving their emotional wellbeing and experience of taking part in screening. Furthermore, in one of the publications from the NELSON trial, the authors advise that the results letter sent to participants with indeterminate results explicitly states that their risk of lung cancer is small (< 2.5%) [90]. As current and former smokers attending screening have been found to overestimate their risk of developing lung cancer [88], this letter could provide reassurance and decrease levels of negative emotional outcomes. Moreover, as stated in section 2.1, an informed decision process relies on individuals being advised of all potential harms that can result from medical procedures. Individuals making the decision as to whether they take part in lung cancer screening should therefore be informed of the potential for emotional harm to occur following the receipt of an indeterminate test result. In order to reduce the number of indeterminate results, lung cancer screening programmes should be implemented in high risk populations. Such populations can be identified by using risk prediction models, which were described in chapter one.

Finally, as described in section 2.2.2 and 2.2.3, the evidence suggests that receipt of a negative test result has no negative emotional impact in the short or longer-term. This is very reassuring as the majority of participants in a lung cancer screening programme will receive a negative result, so it is good to know that they will not experience emotional harm post-test results. It is important that this information is communicated to individuals when they are invited to take part in lung cancer screening. Also, this evidence should be taken into account by those who are weighing up the benefits and harms of implementing a routine lung cancer screening programme.

2.3.5. Implications for further research

When we consider the evidence that we need to understand the emotional impact of lung cancer screening, it is clear that there is a paucity of evidence in this area. Throughout the discussion, a number of implications for future research have been proposed. First, in addition to clinical trial evidence, evidence from studies conducted out with clinical trials is required. As lung cancer screening programmes are implemented, it is very important that emotional outcomes are evaluated. In addition, future research should be theoretically informed. As described above, the stress and coping model and the SRM of illness beliefs can be applied to aid understanding of the emotional impact of lung cancer screening. From the perspective of the stress and coping model, future research should consider positive as well as negative emotional outcomes. Both models also emphasise that individual responses to a stressor, such as lung cancer screening, will vary. As previously stated, it is important to identify the different factors that influence emotional responses to screening so that interventions can be developed to support the individuals who may be vulnerable to negative emotional outcomes. The systematic reviews conducted by Slatore et al [110] and Wu et al [109] only synthesised the evidence in relation to type of test result and did not focus exclusively on the factors that predict the emotional impact of screening. The next chapter of this thesis presents the results of a systematic review that aimed to identify components of the screening process as well as behavioural, psychosocial, sociodemographic or other measured factors that have been found to predict the emotional impact of screening for lung cancer.

Chapter 3. A systematic review of factors associated with the emotional impact of lung cancer screening

The third chapter of this thesis presents the results of a systematic review that aimed to identify factors associated with the emotional impact of screening for lung cancer. This review has built on the findings of two previous systematic reviews by identifying components of the screening process as well as behavioural, psychological, sociodemographic or other measured factors that could be associated with the emotional impact of lung cancer screening. The findings contribute to existing knowledge and understanding by highlighting several key factors that are associated with higher levels of emotional distress following screening as well as factors that warrant further research. In addition, important methodological and theoretical limitations in the literature are identified.

3.1. Introduction

Chapter two of this thesis introduced two theoretical frameworks, which emphasised that individuals will differ in how they respond to a stressor (section 2.3.3, pages 114 - 121). For example, the stress and coping model stipulates that an individual's dispositions, beliefs and goals influence whether they appraise a stressor as harmful, threatening or challenging. Their appraisal of the stressor then determines the coping strategies that they employ to manage the stressor. If the stressor is managed successfully or resolved, then this will result in positive emotions. However, if the stressor is not resolved, then there will be an increase in negative

emotions. The SRM introduces various illness and emotional representations that can help us to understand and predict emotional outcomes. In addition to the psychological factors included in the two models, there are a wide range of different factors that have the potential to influence an individual's emotional response to a stressor, such as screening for cancer. Examples of such factors are discussed below.

A systematic review of mammogram screening for breast cancer identified a number of sociodemographic factors that were associated with negative emotional outcomes [134]. These risk factors were younger age, lower education level, residing in an urban environment and manual occupation [134]. A study exploring the emotional impact of anal cancer screening in HIV-infected men also found that younger age predicted higher levels of emotional distress post-screening but before test results were received [135]. Other studies on breast, cervical, colorectal and ovarian cancer screening have identified additional psychological risk factors that were associated with negative emotional outcomes, such as high perceived vulnerability to developing the cancer screened for [127,134,136], pre-existing cancer worry [127,134], pre-existing general anxiety [137] and high levels of health anxiety [138]. Features of the screening process itself have also been found to be important. For example, dissatisfaction with the information provided during screening was found to be associated with negative emotional outcomes following screening for breast and cervical cancer [134,139,140].

As discussed in chapter two, 14 publications have reported on the emotional impact of lung cancer screening, 13 of which were included in the systematic reviews conducted by Slatore et al [110] and Wu et al [109] (described in section 2.2). Neither review focused exclusively on factors associated with the emotional impact of screening, however, both reviews did synthesise the evidence in relation to type of test result. It was found that participants who received an indeterminate result experienced negative emotional outcomes in the short term [109,110]. Wu et

al also reported the results of a publication from the NELSON trial that measured perceived risk of lung cancer as a predictor of emotional outcomes [106,109]. Compared with participants who reported low affective risk, participants with high affective risk had significantly worse scores on measures of lung cancer specific distress and emotional quality of life at one day before screening. At six months post-screening, those with high affective risk perception still had significantly higher levels of distress than those with low risk perception. No significant differences in emotional quality of life were found between groups at six months post-screening [106]. In line with the stress and coping model, it is possible that the participants who felt their risk of developing lung cancer was high appraised lung cancer screening as harmful and threatening. This could explain why negative emotions, which have been associated with such appraisals, were elevated.

As previously stated, identifying factors associated with the emotional impact of lung cancer screening can aid the development of interventions to support those individuals who may be susceptible to negative emotional outcomes. However, despite the clinical importance of identifying and understanding the associations between such factors and emotional outcomes, no systematic review has yet synthesised all of the available evidence. The present systematic review builds on the findings of Wu et al [109] and Slatore et al [110] by aiming to identify components of the screening process (e.g., information provision during screening, waiting time for test results) as well as behavioural (e.g., smoking), psychosocial (e.g., appraisals, coping, personality, social support), sociodemographic (e.g., age, gender) or other measured factors that are associated with the emotional impact of screening for lung cancer.

3.2. Methods

Criteria for selecting studies

The inclusion criteria for this systematic review were developed using the PICOS approach [141]. The population was adults (age > 18 years) eligible to take part in screening who did not have a diagnosis of lung cancer. Interventions included all screening programmes that aimed to identify the presence or absence of lung cancer. Studies had to measure at least one emotional outcome following screening and potential predictors of such outcomes. Study designs included RCTs, non-RCTs, cohort studies and case-control studies.

Excluded studies were those on lung cancer screening uptake, or the emotional impact of receiving a lung cancer diagnosis. Qualitative studies and cross-sectional studies were excluded, as were non-peer reviewed articles, unpublished studies (e.g. dissertations), and studies published only in books and conference abstracts. Studies not published in English were also excluded.

Search strategy

The following three electronic databases were searched via OvidSP: MEDLINE, EMBASE and PsycINFO. Two databases were searched via EBSCO: Psychology and Behavioural Sciences Collection and CINAHL. Other electronic databases searched were ASSIA and Web of Science. All databases were searched from January 1980 to April 2014. A forward citation search of included studies was conducted until April 2014 to identify further studies. Reference lists of all included papers were also searched.

A search strategy was developed for MEDLINE and adapted for each database. Five sets of search terms and subject headings were used (figure eight): disease specific terms (e.g., neoplasm*), screening terms (e.g., screen*), emotional terms (e.g., anxi*), measures of emotional outcomes and potential predictors (e.g., Psychological Consequences Questionnaire) and study design (e.g., cohort). The search terms within each set were combined using OR and the five sets of search terms were combined using AND. Limits were set for English language, years 1980 – 2014 and human studies only.

1. Disease specific terms: neoplasms/, cancer*, neoplasm*, tumo?r*, malignan*

2. Screening terms: Mass Screening/, Early Detection of Cancer/, Tumor Markers, Biological/, "mass screen*", screen*, 'cancer screen*', 'population screen*', 'early detection of cancer'

3. Emotional terms: psychology/, anxiety/, depression/, stress, psychological/, emotions/, affect/, fear/, quality of life/, psycholog*, anxi*, depress*, stress*, emotion*, 'emotion* response*', "negative affect", affect, fear*, distress*, mood, worr*, "psycholog* distress", "adverse effect", "risk perception", "cancer specific worr*", reassur*, (wellbeing or well-being), "positive affect", benefi*, optimis*, positiv*, "quality of life"

4. Measures of emotional outcomes and predictors: ('Hospital anxiety and depression scale' or HADS or 'HAD Scale'), ('Positive and Negative Affect Schedule' or PANAS), ('Cancer Worry Scale' or CWS), ("Impact of Events Scale" or IES), ("Psychological Consequences Questionnaire" or PCQ), ("Consequences of Screening" OR COS), ('Consequences of Screening in Breast Cancer' or COS-BC), ('Consequences of Screening in Lung Cancer' or COS-LC), "Psychological Consequences", ('State-Trait Anxiety Inventory' or STAI or STAI-S or STAI-T), ("Illness Attitude Scale" or IAS), SF-36, ('Center for Epidemiologic Studies Depression Scale' or CES-D or CESD), ("Profile of Mood States" or POMS), "cancer risk" , "risk perception", "perceived risk", ("General Health Questionnaire" or GHQ), ("Beck Depression Inventory" or BDI), ('Illness Perceptions Questionnaire' or 'Illness Perception Questionnaire' or IPQ), ("Illness Perceptions Questionnaire-Revised" or "Illness Perception Questionnaire-Revised" or IPQ-R), ("Mental Health Inventory" or MHI), ("Life Orientation Test-Revised" or LOT-R), COPE, "Brief COPE"

5. Study design: Randomized Controlled Trial/, Random Allocation/, Follow-Up Studies/, prospective studies/, case-control studies/, longitudinal studies/, cohort studies/, "Randomi?ed controlled trial", RCT*, 'non-randomi?ed controlled trial', "clinical trial", follow-up, prospective, case-control, longitudinal, observ*, cohort, Survey, questionnaire, evaluation

Figure 8. Search strategy for MEDLINE

Study selection

Records were exported into a reference manager (ENDNOTE version X6) and duplicates removed. Titles and abstracts were screened independently by two reviewers using the inclusion and exclusion criteria. Disagreements were discussed until a consensus was reached, with referral to a third reviewer if necessary. Full-text articles were obtained where they met inclusion criteria at the screening stage or where there was disagreement between reviewers.

Data extraction

Data were extracted by one reviewer (LB) and checked by a second reviewer (BY). The data extraction form was developed specifically for this review and piloted with one of the papers included for full-text review. The following information was extracted: country, aim, screening details (e.g., type of screening test), participants (e.g., age, gender), study design details, randomisation details (if applicable), emotional outcomes (e.g., type of outcomes reported, how and when they were measured), predictors of emotional outcomes (e.g., type of predictor, how measured), description of the analyses employed, results, conclusions, clinical significance (if discussed in paper), and clinical implications (if discussed in paper). If necessary, study authors were contacted to request missing information. The data extraction form template is included in appendix three, page 481.

Quality assessment

Two reviewers independently conducted quality assessment using the Downs and Black checklist [142]. This includes 27 items with five subscales: reporting (n = 10), external validity (n =

3), internal validity bias (n = 7), internal validity confounding (n = 6) and power (n = 1). The total score ranges from 0 to 32, where higher scores indicate higher quality [142]. As cohort and case-control studies were included, not all items on the checklist were relevant. Therefore, two items were excluded from each of the internal validity bias (items 14 and 15) and internal validity confounding subscales (items 23 and 24) when assessing cohort and case-control studies. The total score for the modified checklist ranged from 0 – 28. Discrepancies in item scores were discussed until a consensus was reached and referred to a third reviewer if necessary.

Data synthesis

Due to heterogeneity in the outcomes measured and methods of outcome measurement, data were synthesised using a narrative review.

3.3. Results

3.3.1. Selection of studies

Figure nine shows the process of study selection. In total, 5531 titles and abstracts were reviewed, and of these, 9 publications were selected for full-text review. Six met inclusion criteria and three were excluded as they did not report on predictors of emotional outcomes following lung cancer screening. A forward citation search and reference list search identified one additional publication. In total, seven publications were included in the review [88-91,106,114,117]. It is important to note that four publications reported on the same trial: the Dutch-Belgian Randomised Lung Cancer Screening (NELSON) Trial. These publications are therefore treated as one study rather than four independent studies in order to avoid inclusion of duplicate data and duplicate publication bias.

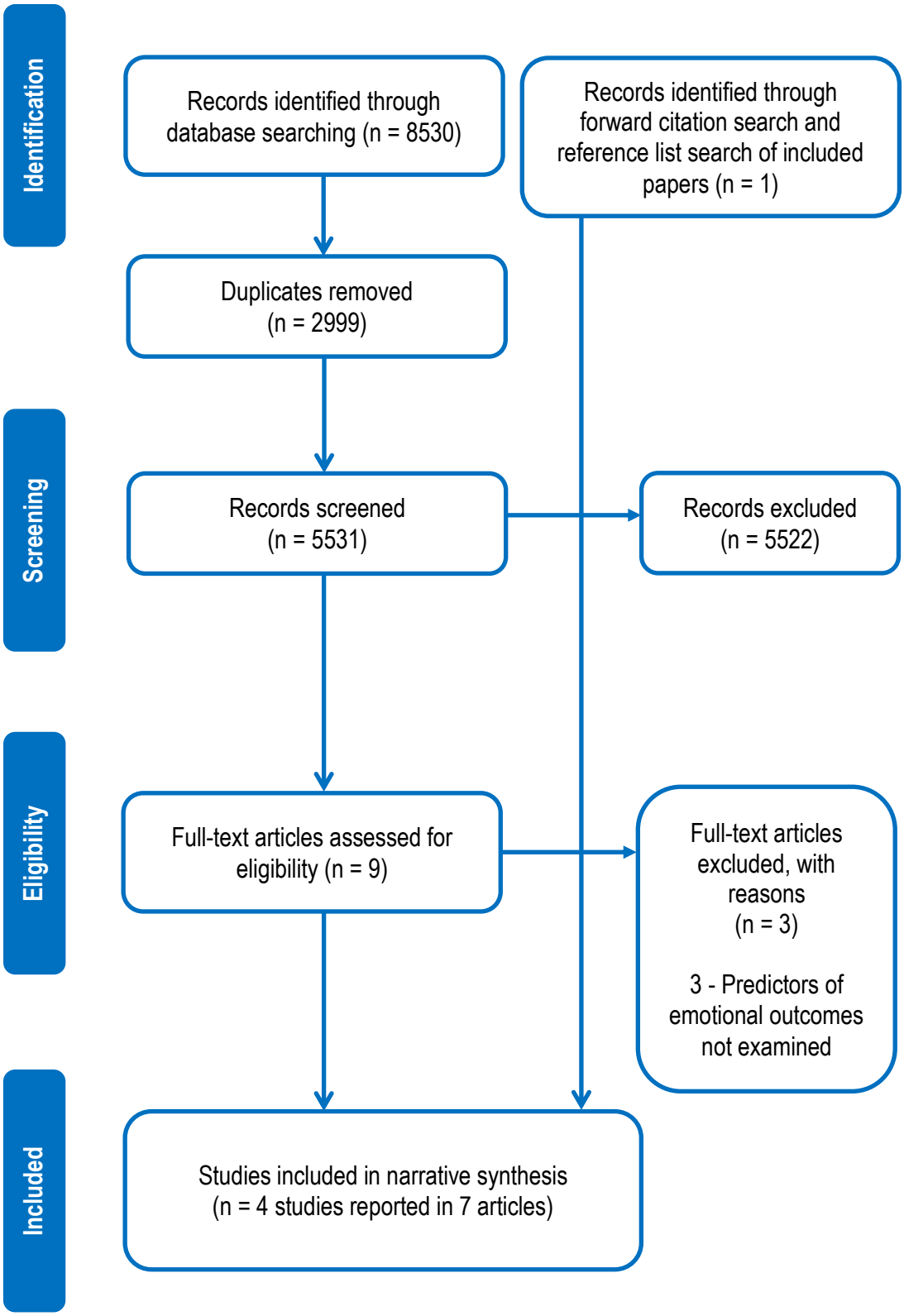


Figure 9. PRISMA flowchart detailing the selection of studies for the review

3.3.2. Study characteristics

Characteristics of included studies are shown in table eight. The four studies were published between 2008 and 2011. Six publications reported studies that used a prospective cohort design [88,90,91,106,114,117] and one publication reported a RCT [89]. As previously stated, four publications reported results from the NELSON trial, which was conducted in the Netherlands and Belgium. Of the other three studies, one reported results from the Pittsburg Lung Screening Study (PLuSS), one was conducted in Finland and included participants who had been exposed to asbestos through work and the other was conducted in the United States and included participants with a family history of lung cancer. Sample sizes ranged from 60 to 1466 and mean ages from 52.5 to 64.6. Three of the four studies included both sexes. Only males took part in the study that included asbestos exposed participants.

Predictor factors reported

All four studies [88-91,114,117] examined associations between type of test result and emotional outcomes. The NELSON trial also reported on type of follow-up scan results [89]. Behavioural predictors were reported, including smoking status (three studies [88-90,114,117]) and smoking pack years (three studies [89,90,117]). One study reported presence of symptoms associated with lung cancer and asbestos exposure [117]. The NELSON trial reported a psychosocial factor, perceived lung cancer risk [106]. Sociodemographic factors were reported, including age (three studies [88-90,114,117]), gender (two studies [88-90,114]), education level (three studies[88,90,117]), ethnicity (one study [88]) and marital status (two studies [88,117]).

Emotional outcomes reported

Non-specific emotional outcomes included emotional quality of life (NELSON trial [89,90,106,114]), health anxiety [117], state anxiety (two studies [88-90,114]), and trait anxiety [88]. Specific emotional outcomes included lung cancer specific distress (NELSON trial [89,90,106,114]), fear of lung cancer [88] and lung cancer worry (two studies [91,117]).

Table 8. Characteristics of included studies and associations between predictor factors and emotional outcomes

Author & location	Participants	Study design & measurement time points	Predictor factor(s) reported	Emotional outcome(s) reported	Associations between predictor factors and emotional outcome(s)
Byrne et al. 2008 [88] USA	N = 400 *Source* 50 -79 year olds with no personal history of lung cancer (LC) and a smoking history of at least 25 years recruited (through mass mailing and physician referral) to the Pittsburgh	Prospective cohort 1. Postal questionnaire prior to screening (pre-screening) 2. Postal questionnaire one to two weeks after test results 3. Postal questionnaire	<u>Predictors related to the screening process</u> Type of test result (test-negative, indeterminate, suspicious) <u>Sociodemographics</u> 1. Age 2. Gender 3. Ethnicity (white non-Hispanic, Hispanic, African American)	State and trait anxiety (STAI). Higher scores indicate higher levels of anxiety. Fear of LC (three items adapted from the PCQ). Higher scores indicate greater fear of LC.	<u>Predictors related to the screening process</u> *STAI-S* Mean (SD) STAI-S scores at each time-point were: Negative / Indeterminate / Suspicious Pre-screening: 35.9 (12.4) / 34.4 (12.3) / 32.6 (12.3) One to two weeks post-test results: 35.9 (12.3) / 37.7 (13.8) / 38.3 (14.4) Six months: 34.4 (12.0) / 37.3 (12.6) / 32.6 (12.1)

Lung Screening Study (PLuSS) *Demographics* Age (mean) = 60.2 49.3% female 95% Caucasian *Test results* Test-negative (n = 228) Benign (n = 4) Indeterminate (n = 141)	six months post-screening 4. Postal questionnaire 12 months post-screening	4. Marital status (married/not married) 5. Education level (high school or less, some post–high school education, university graduate or more) <u>Behavioural</u> Smoking status (current /former smoker)

12 months:	35.1 (12.9)	35.3 (13.5)	35.1 (17.5)

Mixed-model hierarchical regressions showed that the change in scores over time was significant for the indeterminate group only ($p < 0.001$).

STAI-T

Mean (SD) STAI-T scores at each time-point were:

	Negative	Indeterminate	Suspicious
Pre-screening:	37.0 (11.3)	36.7 (11.7)	33.9 (9.8)
One to two weeks post-test results:	36.6 (11.3)	37.5 (12.2)	36.6 (11.2)
Six months:	35.7 (12.0)	36.7 (11.9)	35.4 (11.7)
12 months:	35.8 (11.8)	36.3 (12.4)	35.0 (16.3)

Suspicious (n = 27)

There were no significant interactions between STAI-T scores and type of test result or time-point (*p values not reported in paper)*.

Fear of LC

Mean (SD) PCQ scores at each time-point were:

	Negative	Indeterminate	Suspicious
Pre-screening:	7.0 (2.5)	7.2 (2.8)	6.4 (2.3)
One to two weeks post-test results:	7.0 (2.4)	7.5 (2.7)	8.5 (2.6)
Six months:	6.5 (2.4)	7.1 (2.6)	7.4 (3.0)
12 months:	6.7 (2.3)	7.1 (2.7)	7.1 (2.5)

The change in mean scores over time was significant for the suspicious group only ($p < 0.001$).

Sociodemographic predictors

1. Age

Compared with younger participants, older participants had significantly lower STAI-S scores ($p < 0.03$) across all time-points. No significant differences were found between groups for the other emotional outcomes (*p values not reported in paper*).

2. Gender

Compared with males, females had significantly higher PCQ scores ($p < 0.03$) across all time-points. No significant differences were found between genders for other outcomes (*p values not reported in paper*).

3. Ethnicity

No significant differences were found in outcome measure scores between African-American participants and Caucasian participants (*p values not reported in paper*).

4. Marital status

Compared with non-married participants, participants who were married had significantly lower STAI-T scores ($p < 0.03$) across all time-points. No significant differences were found between groups for STAI-S or PCQ scores (*p values not reported in paper*).

5. Education level

Participants with post-high school or university-level education had significantly lower STAI-T scores ($p < 0.03$), STAI-S scores ($p < 0.03$) and PCQ scores ($p < 0.03$) than participants with less education across all time-points.

Behavioural predictors

Compared with former smokers, current smokers had significantly higher PCQ scores ($p < 0.001$) and higher STAI-S scores ($p < 0.03$) across all time-points. No significant differences were found between current and former smokers for STAI-T scores (*p values not reported in paper*).

Sinicrope et al. 2010 [91] USA	N = 60 *Source* Individuals over 30 years old with no personal LC history and a first-degree relative with LC in a family containing at least three blood relatives with LC recruited (via letter) through the Mayo Clinic Lung Cancer Genetic Epidemiology Registry.	Prospective cohort 1. Postal questionnaire prior to screening (pre-screening) 2. Postal questionnaire one month after receipt of test result 3. Postal questionnaire six months post-screening	<u>Predictors related to the screening process</u> Type of test result (negative, non-negative)	LC worry (CWS adapted to refer to LC) (described in table seven, pages 72 - 73)	<u>Predictors related to the screening process</u> [<u>Please note</u>: no univariate or multivariate analyses were conducted for the data reported in this paper due to the small sample size] *Frequency of thoughts about getting LC* Pre-screening, the proportion of participants who reported some LC-related thoughts was 65%. Percentages of participants in each group who reported some LC thoughts at one month following receipt of test results and six months post-screening were: Negative: One month: 54%; Six months: 59% Indeterminate: One month: 87%; Six months: 69% At both follow-up time-points, the proportion of the test negative group who reported some LC-related thoughts was lower than pre-screening. In contrast, the proportion of participants with a non-negative result who reported some LC-related thoughts

Participants had to have health insurance.

Demographics

Age (mean) = 52.5

49.3% female

97% Caucasian

Test results

Test negative (n = 40)

Indeterminate (n = 19)

LC diagnosis (n = 1)

increased at one month after receipt of test results and then decreased at six months post-screening. No significance tests were undertaken.

Level of concern about getting LC

At baseline, the proportion of participants who reported some concern about LC was 94%. Percentages of participants in each group who reported some concern about LC at one month after receipt of test results and six months post-screening were:

	Negative	Indeterminate
One month:	89%	100%
Six months:	91%	94%

At both follow-up time-points, the proportion of the test negative group who reported some concern about was lower than at pre-screening. In contrast, the proportion of participants with a non-negative result who reported some LC concern increased at one month and then decreased at six months post-screening. No significance tests were undertaken.

The impact of LC worry on mood and daily activities

At pre-screening, the proportion of participants who reported some impact of LC worry on mood and daily activities was 34% and 8%, respectively. Percentages of participants in each group who reported some impact of LC worry on mood and daily activities at one month after receipt of test results and six months post-screening were:

		Negative	Indeterminate
Some mood affected	One month:	29%	27%
	Six months:	21%	31%
Some daily activity affected	One month:	3%	0%
	Six months:	6%	6%

At both follow-up time-points, the proportion who reported some impact of LC worry on mood was lower than at pre-screening for both groups of participants. The same trends were observed for

					impact of LC worry on daily activities. No significance tests were undertaken.
Vierikko et al. 2009 [117] Finland	N = 633 *Source* Three groups of Finnish asbestos-exposed workers. The first group were workers who took part in an asbestos screening program in 1990-1992. Groups two and three consisted of workers with asbestosis or asbestos-	Prospective cohort 1. Postal questionnaire before screening (pre-screening) 2. Postal questionnaire 12 months post-screening	<u>Predictors related to the screening process</u> Type of test result (test-negative, false positive) <u>Sociodemographic</u> 1. Age 2. Education (at least vocational training/lower education) 3. Marital status (unmarried, widowed, divorced/ married, cohabiting) <u>Behavioural</u>	LC worry. Response rated on a scale of 0-8. Higher scores indicated greater worry. Health anxiety. Response rated on a scale of 0 – 24. Higher scores indicated greater health anxiety.	<u>Predictors related to the screening process</u> *LC worry* No significant difference in LC worry between pre-screening and 12 months post-screening was found for the test negative or false positive groups (*p values and data not reported in paper*). *Health anxiety* Mean health anxiety scores for both groups of participants at pre-screening and 12 months post-screening are: Pre-screening: 6.64 (4.63) 7.63 (5.09) 12 months: 5.73 (4.61) 6.42 (4.53) Compared with pre-screening, health anxiety was significantly lower across all participants at 12 months

related plural findings who were recruited from the wards of occupational medicine where they were attending a clinical follow-up.

Demographics

Age (mean) = 64.6

100% male

Ethnic origin not reported

Test results

1. Smoking status (current smoker/former smoker/non-smoker)

2. Smoking pack years

<u>Other</u>

1. Symptoms (cough, phlegm secretion, wheezing, dyspnea)

2. Years of asbestos exposure

3. Year of first asbestos exposure

post-screening ($p < 0.001$). Health anxiety was significantly lower at 12 months post-screening than pre-screening for both the test negative and false positive groups ($p < 0.001$ and $p = 0.027$).

<u>Behavioural and sociodemographic predictors</u>

P values and data were not reported in the paper

<u>Other predictors</u>

1. Symptoms (cough, phlegm secretion, wheezing, dyspnoea)

P values and data not reported in paper.

2. Years of asbestos exposure

High asbestos exposure was associated with lower health anxiety at 12 months post-screening compared with pre-screening ($p = 0.003$).

3. Year of first asbestos exposure

P values and data not reported in paper.

Test-negative
(n = 530)

False positive
(n = 97)

LC (n = 6)

Publications reporting results from the NELSON trial

Bunge et al. 2008 106 The Netherlands and Belgium	N = 351 *Source* 50-75 years old *Demographics* Age (mean) = 60.3 49.1% female	Prospective cohort 1. Postal Q one day before screening (pre-screening) 2. Postal Q six months post-screening	Psychosocial Affective risk perception. Single item. Five response options, very low to very high. Participants grouped into two categories: low affective risk (reported the risk they feel of developing LC as very low, low, or not low/not high) and	LC-specific distress (IES) (table seven, pages 81 - 82) Emotional quality of life (SF-12) (table seven, page 82)	<u>Psychosocial predictor</u> *IES* Median IES scores (IQR not reported) at each time-point were: Low affective risk perception High affective risk perception

Test results	high affective risk (reported the risk they feel as high or very high).		
Test-negative (n = 239)			
Indeterminate (all of which were test-negative following a repeat scan. Repeat scan results were received before completion of the QQ at six months post-screening) (n = 49)			

IES total score	One day before screening:	2.0	11.5
	Six months post-screening:	1.0	6.5
IES-Avoidance	One day before screening:	1.0	5.0
	Six months post-screening:	0.5	3.0
IES-Intrusion	One day before screening:	1.0	5.0
	Six months post-screening:	0.0	3.5

At one day before screening, participants with a high affective risk perception had significantly higher median IES total scores and IES subscale scores compared with participants with a low affective risk perception (all $p < 0.01$). The authors defined the

minimal important difference (MID) as half of a standard deviation of the mean and state that differences in median IES and MCS-12 scores between groups were larger than half a standard deviation so were therefore clinically meaningful.

At six months post-screening, median IES total and subscale scores for both groups of participants were significantly lower than at one day before screening. However, as at one day before screening, participants with a high affective risk perception had significantly higher median IES total and subscale scores than participants with a low affective risk perception (all $p < 0.01$).

MCS-12

Median MCS-12 scores at each time-point were:

	Low affective risk perception	High affective risk perception
One day before screening:	54.5	50.4

					Six months post-screening: 55.5 52.2 At one day before screening, participants with a high affective risk perception had significantly lower (worse) MCS-12 scores than participants with low affective risk perception ($p < 0.01$). At six months post-screening, no significant differences were found between groups for MCS-12 scores (p values not reported in paper).
van den Bergh et al. 2008 [114] The Netherlands and Belgium	N = 351 *Source* 50-75 years old *Demographics* Age (mean) = 60.3 49.1% female	Prospective cohort 1. Postal Q one week before screening 2. Postal Q administered one day after screening, before test results were	<u>Predictors related to the screening process</u> Type of test result (negative, indeterminate) <u>Sociodemographic</u> 1. Age (participants divided into two age categories: aged < 60 years and ≥ 60 years)	Generic health-related quality of life (SF-12). Included at pre-screening and six months post-screening. State anxiety (6-item version of the state scale of the	<u>Predictors related to the screening process</u> *MCS-12, STAI-6, and IES* At one week before screening, the mean MCS-12 score for the whole group was 51.3 (SD = 10.5) and the mean STAI-6 score was 34.1 (SD = 7.7). These scores were in the same range as age-adjusted and gender-adjusted Dutch reference scores (data not reported in paper). At baseline, the mean IES total score was 6.9 (SD = 9.6). No significant differences were found at six months post-screening between participants with a negative result and participants with an indeterminate result who received a negative

	received.	2. Gender	STAI, STAI-6).	result following a repeat CT scan (*p values and data not reported in paper*).
Ethnic origin not reported	Participants asked to complete it	<u>Behavioural</u>	Included at pre-screening, one week	<u>Sociodemographic predictors</u>
Test results	within a week.	Smoking status (current smoker/former smoker)	post-screening and six months post-	1. Age
Test negative (n = 239)	3. Postal Q 6 months post-screening		screening.	No statistically significant differences in scores for outcome measures were found between participants in the two age categories (*p values and data not reported in paper*).
Indeterminate (all of which were negative following a repeat scan) (n = 49)			LC-specific distress (IES). Included at pre-screening, one week post-screening and six months post-screening.	2. Gender Compared with males, females had poorer mean total scores for all emotional outcome measures at each of the three time-points. However, the only differences that were statistically significant were median MCS-12 scores at baseline (male: 55.9, female: 52.2, $p < .01$) and median IES total scores within one week post-screening (male: 1, female: 2, $p < .05$). The authors defined the MID as half of a standard deviation of the mean and state that no differences were clinically meaningful.

					<u>Behavioural predictors</u> No statistically significant differences in scores for outcome measures were found between current and former smokers (*p values and data not reported in paper*).
van den Bergh et al. 2010 [90] The Netherlands and Belgium	N = 630 *Source* 50-75 years olds *Demographics* Age (mean) = 57.8 52.9% female Ethnic origin not reported *Test results*	Prospective cohort 1. Postal Q after eligibility check for trial but before randomisation (pre-randomisation) 2. Postal Q one week before screening (post-randomisation)	Predictors related to the screening process Type of test result (test-negative, indeterminate) Sociodemographics 1. Age 2. Gender 3. Education level (primary education/lower vocational or lower secondary general education/intermediate	Generic health-related quality of life (SF-12). Included at pre-randomisation and two months post-screening. State anxiety (STAI-6). Included at pre-randomisation, post-randomisation,	<u>Predictors related to the screening process</u> *MCS-12* Mean (SD) MCS-12 scores at each time-point were: Negative: Pre-randomisation 51.9 (10.2); Two months post-screening: 51.6 (11.1) Indeterminate: Pre-randomisation 51.8 (10.6); Two months post-screening: 51.9 (11.0) No statistically significant differences in scores on the MCS-12 were found between participants with an indeterminate result and participants with a negative

Test-negative (n = 489) Indeterminate (n = 141)	3. Postal Q administered one day after screening before test results received. Participants asked to complete it within a week. 4. Postal Q two months post-screening	vocational or higher secondary general education/high vocational education or university) Behavioural 1. Smoking status (current smoker/former smoker) 2. Smoking pack years	one day after screening and two months post-screening. LC-specific distress (IES). Included at pre-randomisation, post-randomisation, one day after screening and two months post-screening.	result at pre-randomisation and two months post-screening (p values not reported in paper). *STAI-6* Mean (SD) STAI-6 scores at each time-point were: Negative / Indeterminate Pre-randomisation: 33.1 (8.4) / 33.6 (9.3) Post-randomisation: 34.4 (8.5) / 35.2 (8.9) Within one week post-screening: 32.5 (8.8) / 33.5 (8.9) Two months post-screening: 32.6 (9.2) / 34.8 (9.2) STAI-6 scores did not differ between one week post-screening and two months post-screening and pre-randomisation and two months post-screening for the test-negative group. However, for the indeterminate group, STAI-6 scores were significantly higher at two months post-screening in comparison with pre-randomisation, $p < 0.05$. The authors defined the MID as half of a standard deviation of the mean and state

that differences in STAI-6 scores for the indeterminate group between pre-randomisation and two months post-screening were clinically meaningful.

No statistically significant differences in scores on the STAI-6 were found between groups at pre-randomisation, post-randomisation, and within one week post-screening (p values and results of statistical tests not reported in paper). However, at two months post-screening, participants with an indeterminate result had significantly higher mean scores on the STAI-6 compared with participants with a negative result ($p < 0.01$). Using their definition of the MID, the authors state that differences in STAI-6 scores between groups at two months post-screening were not clinically meaningful.

IES

Mean (SD) IES total scores at each time-point were:

	Negative	Indeterminate
Pre-randomisation:	4.1 (7.4)	4.5 (6.5)
	5.8 (9.1)	6.3 (9.1)

Post-randomisation:		
Within one week post-screening:	4.5 (7.7)	4.9 (7.7)
Two months post-screening:	2.4 (5.5)	8.3 (5.5)

Participants with a negative result had significantly lower IES scores at two months post-screening than at one week and pre-randomisation ($p < 0.01$). In contrast, participants with an indeterminate result had significantly higher IES scores at two months post-screening than one week and pre-randomisation ($p < 0.01$). The authors state that this difference was clinically meaningful as it was larger than half a standard deviation.

No statistically significant differences in IES total scores were found between groups at pre-randomisation, post-randomisation and within one week post-screening (p values and results of statistical tests not reported in paper). At two months post-screening, participants with an indeterminate

result had significantly higher IES total scores compared with participants with a negative result ($p < 0.01$). Using their definition of the MID, the authors state that this difference was clinically meaningful.

Sociodemographic predictors

1. Age

Results and data not reported in the paper.

2. Gender

Compared with males, females had higher scores on the STAI-6 and IES and lower (poorer) MCS-12 scores. These differences were statistically significant ($p < 0.05$) across all study time-points. Using their definition of the MID, the authors state that these differences were not clinically meaningful.

3. Education level

Results and data not reported in paper.

Behavioural predictors

					1. Smoking status Compared with former smokers, current smokers had higher STAI-6 and IES scores. These differences were statistically significant ($p < 0.05$) across all time-points. Using their definition of the MID, the authors state that these differences were not clinically meaningful. 2. Smoking pack years No significant differences were found between participants with more or less pack years on any of the included emotional outcome measures (p values not reported in paper).
van den Bergh et al. 2011 [89] The Netherlands and Belgium	N = 1466 *Source* 50-75 years old *Demographics*	Randomised controlled trial 1. Postal Q before randomisation (pre-randomisation)	<u>Predictors related to the screening process</u> 1. Type of test result (negative/indeterminate) 2. Follow-up scan results for participants	Generic health-related quality of life (SF-12). State anxiety (STAI-6).	<u>Predictors related to the screening process</u> 1. Type of test result (negative/indeterminate) *MCS-12* MCS-12 scores over time did not differ between groups *(p values and data not reported in paper)*.

Age (mean) = 57.8 53.8% female Ethnic origin not reported *Test results* Test-negative (n = 541) Indeterminate (n = 143)	2. Postal Q two months after baseline screening to participants with a test-negative or indeterminate result 3. Postal Q at two-year assessment (1.5 years after baseline screening and six months after the second-round screening) to screened participants	who received an indeterminate result at baseline screening (participants who received at least one indeterminate or positive result at follow-up/participants with only negative results at follow-up) <u>Sociodemographics</u> 1. Age 2. Gender <u>Behavioural</u> 1. Smoking status (current smoker/former smoker) 2. Smoking pack years	LC-specific distress (IES)	*STAI-6* STAI-6 scores over time did not differ between groups (*p values and data not reported in paper)*. *IES* Mean (95%CI) IES total scores at each time-point were: Negative: Pre-randomisation: 4.1 (3.4 – 4.8); Two months post-screening: 2.6 (2.0 – 3.3); 1.5 years post-screening: 3.5 (2.9 - 4.2) Indeterminate: Pre-randomisation: 4.0 (2.8 - 5.3); Two months post-screening: 7.8 (6.5 – 9.0); 1.5 years post-screening: 4.5 (3.3 – 5.8) IES total, intrusion and avoidance scores over time differed between participants with a negative result and an indeterminate result ($p < 0.01$). Differences between groups at pre-randomisation and 1.5 years post-screening were not statistically significant (p

values and data not reported in paper). The authors defined the MID as half of a standard deviation of the mean and state that differences in IES scores between groups at two months post-screening were clinically meaningful.

2. Follow-up scan results for participants who received an indeterminate result at baseline

No statistically significant differences were found in emotional outcome measure scores from pre-randomisation to 1.5 years post-screening between participants who received an indeterminate result and those who received a negative second-round CT scan result (*p values and data not reported in paper)*.

A further subgroup analysis of participants who received an indeterminate result at baseline compared participants who received at least one indeterminate/positive result at follow-up (n = 35) and participants who received only negative results at follow-up scans (n = 100). No significant differences were found on emotional outcome measures between groups (*p values and data not reported in paper)*.

Sociodemographic predictors

1. Age

Age was not associated with scores on emotional outcome measures (*p values and data not reported in paper)*.

2. Gender

Compared with males, females had significantly higher STAI-6 and IES scores and significant lower MCS-12 scores across all time-points ($p < 0.05$). Using their definition of the MID, the authors state that these differences were not clinically meaningful.

Behavioural

1. Smoking status

Current smokers had significantly higher IES total, intrusion and avoidance scores (all $p < 0.01$) than former smokers across all time-points. Using their definition of the MID, the authors state that these differences were not clinically meaningful. There was

		no difference in scores for STAI-6 and MCS-12 between current and former smokers (*p values and data not reported in paper).* 2. Smoking pack years There was no difference in scores for IES, STAI-6 and MCS-12 between smokers with higher and lower numbers of pack years (*p values and data not reported in paper*).

Key. CWS = Cancer Worry Scale; IES = Impact of Events Scale; MCS-12 of the SF-12 = The Mental Component Summary of the 12-item Short Form Questionnaire; MCS-36 of the SF-36 = The Mental Component Summary of the 36-item Short Form Questionnaire; PCQ = Psychological Consequences Questionnaire; STAI = State and trait anxiety inventory.

3.3.3. Quality assessment

Scores ranged from 11 to 20 out of 28 for studies that used a prospective cohort design [88,90,91,106,114,117]. The publication that reported results of an RCT was scored 19 out of 32 [89]. All disagreements were resolved through discussion between reviewers (LB and BY). The results from the quality assessment are reported in appendix four, page 484.

3.3.4. Features of the screening process

Negative test result

Four studies [88-91,114,117] explored the impact of a negative test result. One study reported no significant change from baseline for specific and non-specific emotional outcome measures administered at two weeks, six months and 12 months post-screening [88]. One study found lung cancer worry scale scores were lower at one and six months post-screening than at baseline, but statistical significance was not reported [91]. One study reported significantly lower levels of health anxiety but no significant change in lung cancer worry scale scores 12 months after screening than compared to baseline [117].

Two publications from the NELSON trial reported no impact on emotional well-being and state anxiety but significantly lower levels of lung cancer specific distress at two months [89,90] and 1.5 years post-screening [89] than at baseline. Another publication reported no significant change from baseline for emotional outcome measures administered six months post-screening [114].

Indeterminate test result

Four studies [88-91,114,117] explored the impact of an indeterminate result. One study found significantly higher levels of state anxiety at two months, six months and 12 months post-screening than at baseline [88]. Another study found an increased frequency of thoughts about getting lung cancer at one and six months post-screening than at baseline. An increase in concern about lung cancer was also found at one month but not at six months. The statistical significance of these findings was not reported [91].

The NELSON trial reported significantly higher levels of lung cancer specific distress two months post-screening than at baseline [89,90]. However, scores only increased to within low concern range (i.e. < 8.5 [143]) and had returned almost to baseline levels at 1.5 years post-screening [89]. No impact on emotional well-being was found at two months [89,90] and 1.5 years post-screening [89]. Contrasting results were reported for state anxiety. The publication that reported the long-term outcomes from the trial found no impact on state anxiety over time [89]. However, the publication that reported the short-term outcomes found that state anxiety scores were significantly higher two months after screening when compared with both baseline scores and scores amongst those with a negative test result at the same time-point [90]. Another publication from the NELSON trial reported no significant differences in scores on emotional outcome measures between participants with an indeterminate result and a negative result at six months post-screening [114].

Suspicious test result

One study explored the impact of a suspicious result [88], finding a significantly increased fear of cancer two weeks after receipt of test results compared with baseline. Scores decreased over time but had not returned to baseline at 12 months after screening [88].

False positive test result

One study found significantly lower levels of health anxiety but no significant difference in lung cancer worry scores at 12 months than at baseline [117].

Follow-up scan result

In the NELSON trial, participants who received an indeterminate result underwent follow-up scans. Participants who received one or more positive or indeterminate scan results did not have significantly worse scores on emotional outcome measures than participants who received only negative scan results [89].

3.3.5. Behavioural predictors

Behavioural predictors were reported, including smoking status (three studies [88-90,114,117]) and smoking pack years (two studies [89,90,117]). One study found that current smokers had significantly higher levels of cancer fear and state anxiety across all time-points than former smokers [88]. The NELSON trial reported that current smokers had significantly higher levels of lung cancer specific distress across all time-points than former smokers [89,90]. The publication that reported results for short term outcomes found that current smokers had significantly higher levels of state anxiety across all time points (up to two months post-screening) than former

smokers [90]. The publication that reported results for long term outcomes found no significant differences in state anxiety between current and former smokers across all time-points (up to 1.5 years post-screening) [89]. Another publication from the NELSON trial reported no associations between smoking status and scores on emotional outcome measures [114]. The other study did not report results [117].

The NELSON trial found no associations between pack years and scores on emotional outcome measures across time-points [89,90]. The other study did not report results [117].

3.3.6. Psychosocial predictors

One publication from the NELSON trial reported on affective risk perception [106]. Participants with a high baseline affective risk perception had significantly poorer emotional well-being and significantly higher levels of lung cancer-specific distress than those with low affective risk perception one day before screening. At six months post-screening, those with high affective risk perception still had significantly higher levels of distress than those with low risk perception [106]. No significant differences were found between groups for emotional well-being at six months post-screening [106].

3.3.7. Sociodemographic predictors

Age

Three studies [88-90,114,117] examined associations between age and emotional outcomes. Two publications from the NELSON trial found no significant association between age and non-

specific and specific emotional outcomes [89,114]. However, another study found older participants had lower state anxiety levels than younger participants across all time-points [88]. The same study found no associations between age and trait anxiety or fear of lung cancer [88]. Two publications, including one from the NELSON trial, did not report results [90,117].

Gender

Two studies [88-90,114] included gender. One found that females had significantly higher fear of cancer across all time-points than males [88]. The NELSON trial reported that females had significantly higher levels of state anxiety than males across all time-points [89,90]. Another publication from the same trial found no difference in state anxiety scores by gender at all study time-points [114]. This finding is supported by Byrne et al. who also found no difference in anxiety scores by gender across all study time-points [88]. Two publications from the NELSON trial reported that females had significantly worse scores on measures of emotional well-being and lung cancer-specific distress than males across all study time-points [89,90]. Another publication reported significant differences in lung cancer specific distress between males and females within one week after screening [114].

Education

Three studies [88,90,117] included education. One found that participants with post-high school or university-level education had significantly lower scores on emotional outcome measures than participants with lower levels of education across all time-points [88]. The other two studies did not report results.

Ethnicity

One study found that ethnicity was not associated with scores on emotional outcome measures across time-points [88].

Marital status

Two studies [88,117] explored marital status as a predictor. One study found that married participants had significantly lower trait anxiety scores across all time-points than those who were not married, however, no differences were found between groups for state anxiety and fear of cancer [88]. The other study did not report results [117].

3.3.8. Other predictors

One study measured symptoms associated with lung cancer and asbestos exposure [117]. Results for symptoms were not reported. However, high asbestos exposure was associated with significantly lower levels of health anxiety 12 months after screening than at baseline [117].

3.4. Discussion

3.4.1. Summary of the main findings

This systematic review collated and synthesised the results of all studies that have reported on associations between predictor factors and emotional outcomes in lung cancer screening participants. Seven publications from four studies of variable quality were included. The findings were most consistent for three factors: receipt of an indeterminate test result, smoking status,

and gender. These factors can be considered as risk factors as they were all associated with higher levels of emotional distress. At present, we are unable to draw conclusions about the other predictors assessed due to the very small numbers of studies assessing predictors, measurement at different time points or the use of different measurement tools or comparison groups.

3.4.2. Discussion of findings

Indeterminate test result

Four of six publications reported that indeterminate test results were associated with negative non-specific (two studies [88,90]) and specific (two studies [89-91]) emotional outcomes at one to two weeks following receipt of results [88] and at one month [91] and two months [89,90] post-screening. This negative impact appeared to be temporary as distress diminished over six months, 12 months and 1.5 years post-screening [88,89,91,114]. Therefore, this finding suggests that participants who receive an indeterminate result experience emotional distress during a period of high ambiguity while they wait for further confirmatory testing or the results of confirmatory testing. However, distress appears to reduce once results of further testing confirm that the participant does not show signs of lung cancer or suspected lung cancer at this point.

Smoking status

Three of four publications reported negative specific (two studies [88-90]) and non-specific [90] emotional outcomes in current smokers when compared with former smokers. Two studies found that the effects for specific outcomes persisted at one [88] and 1.5 years [89] post-screening.

What is curious about this result is that, compared with former smokers, current smokers do not appear to be reassured by taking part in lung cancer screening. It is possible that differences in perceived risk could account for this finding. The PLuSS study[88] and the NLST[144] reported that current smokers perceived their risk of developing lung cancer as significantly higher than former smokers. In addition, a qualitative study conducted as part of the NLST reported that current smokers conveyed higher perceived personal risk of lung cancer than former smokers and that 50% of the current smokers who took part believed it was "highly likely" that they would develop lung cancer [145]. Due to a higher perceived risk of developing lung cancer, it is possible that current smokers were not reassured by their test results, which in turn resulted in the observed difference in fear of lung cancer and lung cancer specific distress when compared with former smokers.

An additional, but noteworthy, observation concerns screening uptake among current smokers. Studies exploring lung cancer screening trial uptake have reported lower uptake among current smokers[119,146,147]. One such study, nested within the UKLS trial, used a mixed methods approach to explore barriers to trial participation [119]. Compared with former smokers, current smokers were 30% less likely to take part in the UKLS (OR 0.70, 95% CI 0.63 to 0.78, $p < 0.001$). When asked to identify reasons for not participating, current smokers were twice as likely to report emotional barriers to screening participation (e.g., avoidance of information associated with lung cancer, anxiety, fear) than former smokers (OR 2.02, *CI not reported*, $p = 0.013$) [119]. This finding, and the results of this systematic review, suggest that current smokers are more vulnerable to high levels of emotional distress before, during and after lung cancer screening. It is very important that future research explores in more depth the underlying reasons for this difference in emotional outcomes so that interventions can be developed to

increase screening uptake among current smokers as well as mitigate against emotional harm during screening.

Gender

Four publications reported that, when compared with males, females experienced significantly more negative specific (two studies [88-90]) and non-specific (one study [89,90,114]) emotional outcomes, with effects persisting for between 6 months [114] and 1.5 years [89] post-screening. This finding supports that of survey research where females have been found to have significantly higher levels of cancer fear and worry than males [148-150]. For example, one study administered a survey to a sample of older adults (aged 55 to 64 years) in the UK (n = 7,971) [148]. Compared with males, significantly more females reported that cancer was their greatest fear, that they felt uncomfortable when thinking about cancer and that they worried a lot about cancer (ORs ranged from 1.15 to 1.48). The results of the systematic review suggest that these worries are not alleviated by taking part in cancer screening. Furthermore, when compared with males, females were 36% less likely to take part in the UKLS (OR 0.64, 95% CI 0.58 to 0.71, $p < 0.001$)[119]. A qualitative study identified four attitudinal or behavioural typologies of participants who did not participate in a lung cancer screening programme. One of the four typologies was 'worriers,' which consisted of only female participants who felt that taking part in screening would only raise their anxieties [147]. As with current smokers, it would be beneficial to investigate potential reasons why females report higher levels of adverse emotional outcomes following screening for lung cancer.

Additional considerations

A further finding of the systematic review is that there is limited evidence concerning the following factors: education level, marital status, ethnic origin and perceived risk of lung cancer. All four factors merit further research in order to determine the strength of their association with emotional outcomes as well as whether any association persists over time. First, only the PLuSS study reported results for education, marital status and ethnic origin [88]. Participants with higher levels of education had significantly lower scores on all emotional outcome measures than participants with lower levels of education across all time-points. Participants with lower education levels could therefore be more at risk of experiencing adverse emotional outcomes following screening and this should be explored. In addition, it was found that married participants had significantly lower trait anxiety scores across all time-points than those who were not married [88]. This finding implies that the support obtained through a marriage could function as a protective factor against adverse emotional outcomes following screening. Although the PluSS study found no association between ethnicity and scores on emotional outcome measures, there is evidence that ethnic minorities are less likely to take part in cancer screening [151]. A number of potential reasons have been identified for this, such as higher levels of cancer fear and fatalism[152,153]. Finally, only one publication from the NELSON trial explored the impact of affective risk perception on emotional outcomes [106]. Results suggest that participants with high affective risk perception could be vulnerable to experiencing adverse emotional outcomes and the authors of the study recommend attention for this group.

3.4.3. Strengths and limitations

Systematic review methodology

This review furthers current knowledge by highlighting several key factors that are associated with higher levels of emotional distress following screening as well as factors that warrant further research. In addition, a number of important methodological and theoretical limitations in the literature have been identified (discussed below). There are also a number of key strengths of the review methodology. First, robust systematic review methods were applied that reduced the risk of bias. A wide range of databases were searched, using a comprehensive list of search terms combined with subject headings. When conducting the review, efforts were made to identify all relevant studies by searching several electronic databases and conducting a citation search. The reference lists of all included studies were also searched. During study selection, all identified citations were independently assessed for inclusion by two reviewers. In addition, two reviewers independently conducted quality assessment for each included study. Also, in terms of quality assessment, the Downs and Black checklist was used, which has been identified as one of the most useful checklists for assessing the quality of nonrandomised studies [154].

This systematic review was also subject to several methodological weaknesses. Although, to the author's knowledge, no studies were missed, for an even more comprehensive search of the literature, particular journals could have been handsearched, as well as trial registers. Second, the decision to limit the review to include only English language, peer-reviewed, published studies, could have introduced both language and publication bias and it is possible that some relevant studies may not have been included. A final limitation is that, due to time

constraints, data from included publications was extracted by only one reviewer. Although this approach increased the potential for errors, efforts were made to alleviate this by having a second reviewer independently check all data extraction forms for accuracy and completeness. However, it is acknowledged that there is still the potential for inaccuracies in the data extracted.

Empirical research methodology

There are a number of strengths and limitations concerning the methodology of the studies included in the systematic review. These will be discussed in relation to the predictors measured, outcome measures included, measurement time-points, clinical importance and external validity.

1. Predictors measured

As stated in section 2.3.2 (page 107), very few studies have investigated the emotional impact of lung cancer screening. At the time this systematic review was conducted, 13 publications from six studies had reported on the emotional impact of screening for lung cancer. Of these 13 publications, only seven publications from four studies explored predictors of emotional outcomes following screening. Not only have very few studies reported on predictors but those that have included predictors have been restrictive in the predictors included, particularly in terms of psychosocial predictors. The only psychosocial predictor that has been explored in the context of lung cancer screening is affective risk perception. If we refer back to the two psychological models introduced in chapter 2 (pages 114 to 120), there are a range of predictors that could influence the emotional impact of lung cancer screening, such as appraisals, coping strategies, and illness representations. Psychosocial factors have yet to be properly explored in the context of lung cancer screening. In addition to psychosocial factors, there are a number of components of the screening process that have yet to be investigated. As stated in the introduction, a systematic review of

mammogram screening and two studies exploring the emotional impact of cervical cancer screening have reported that dissatisfaction with the information provided during screening was found to be associated with negative emotional outcomes [134,139,140].

It is also interesting to note that level of socioeconomic deprivation has not been investigated as a potential predictor of emotional outcomes. As stated in chapter one of this thesis (page 36), men and women in the lowest SES groups in England are significantly more likely to be diagnosed with lung cancer than men and women in the highest SES groups (men: RR 2.53, 95% CI 2.48 to 2.58; women: RR 2.73, 95% CI 2.66 to 2.80)[44]. As lung cancer screening programmes will be offered to individuals at greatest risk of developing lung cancer, a high number of those invited to take part will be from the lowest SES groups. A study conducted as part of the UKLS trial found that groups with lower SES were significantly more likely to decline participation in the trial (OR 0.56, $p < 0.001$) [119]. The authors state that a potential explanation for this finding is more fearful and fatalistic beliefs about lung cancer among groups with lower SES, which could be attributed to, or strengthened by, an increased exposure to lung cancer in more deprived communities [119]. An additional study that explored attitudes towards lung cancer screening in socioeconomically deprived and heavy smoking communities in the UK reported that participants had fatalistic beliefs about lung cancer, negative views of treatment and undermined the potential benefits of screening [155]. In view of these findings, there is the potential for participants with lower SES to be more at risk of experiencing negative emotional outcomes during screening. It is important that future research exploring the emotional impact of lung cancer screening investigates this.

2. Outcome measures

In order to fully understand the emotional impact of lung cancer screening, and develop interventions to support those who may be vulnerable to emotional harm, evidence is required on the nature (type) of any such impact. An important strength of the included studies is that both specific and non-specific emotional outcome measures were included so the impact of predictors on both types of outcome could be explored. As stated in section 3.4.2 (page 166), receipt of an indeterminate test result, female gender and being a smoker were all associated with both specific and non-specific negative emotional outcomes.

However, a key limitation, which was also discussed in chapter two (page 111), is that none of the included studies administered positive emotional outcome measures. It is unclear at present as to whether there are factors associated with positive emotional outcomes following screening. In line with an asset based approach to health improvement, it is important to identify, and nurture, the factors (e.g., meaning-focused coping, social support) that enhance emotional wellbeing [156].

3. Measurement time-points

In order to adequately understand the impact of predictors on emotional outcomes, we must be able to identify the point(s) in the screening programme at which impact occurs and whether it is short term or persists in the longer term. It is important to note that three publications reported on emotional outcome measures administered only once post-screening [106,114,117]. This does not enable us to explore trends in emotional outcomes over time or whether different factors predicted emotional outcomes at different time-points.

4. Clinical importance

It is difficult to assess the clinical importance of the changes in emotional outcomes seen in our included studies. The NELSON trial defined the minimal important difference (MID) as half of a standard deviation of the mean, as previously defined by studies reporting health related quality of life measures [157]. Three publications from the trial reported that several of their findings were clinically meaningful based on this MID [89,90,106]. However, in my view, these conclusions should be interpreted with caution as a statistical definition does not take account of patients' views on the importance of such a difference in scores.

5. External validity

In terms of the quality of included studies, it is important to note that external validity subscale scores were low for most studies. It was often not possible to determine how representative participants were of the populations from which they were recruited, or the representativeness of the clinical settings in which the studies were conducted. Two studies recruited predominantly Caucasian participants [88,91], with the other two studies not reporting ethnic group [89,90,106,114,117]. One study required participants to have medical insurance [91]. One study recruited only participants from a previous asbestos screening programme and occupational medicine wards where they were attending a clinical follow-up for asbestosis or asbestos-related plural findings [117]. The extent to which the findings can be generalised to those screened in population lung cancer screening programmes is therefore unclear.

3.4.4. Comparison with existing reviews

This finding supports that of the systematic reviews conducted by Slatore et al [110] and Wu et al [109]. Both reviews concluded that participants who received an indeterminate result following screening for lung cancer experienced negative emotional outcomes that did not persist in the longer term. Reviews of breast [134,158] and ovarian cancer screening [159] also found that false positive results were associated with negative emotional outcomes following screening and our findings support this. The lack of measurement of positive emotional outcomes from screening and variable measurement time points were also identified as limitations in two reviews of breast cancer screening [134,160].

3.4.5. Implications for future research

As discussed in section 3.4.2 (pages 166 to 168), current smokers and females have higher levels of emotional distress when compared with former smokers and males. This is an important issue for future research as there are unanswered questions concerning why these two groups do not appear to be reassured by screening. Further research could utilise qualitative methodology (e.g., semi-structured interviews, focus group discussions) in order to shed light on the reasons why negative emotional outcomes remained elevated in the longer term as well as explore ways to reduce distress for these two groups.

There is very limited research on the impact of marital status, education level and ethnic origin, with only one study reporting results for associations between these factors and emotional outcomes[88]. Future studies exploring the emotional impact of lung cancer screening need to take these variables into account in order to extend and strengthen the evidence base. Finally, results for age were

inconsistent, so more studies need to include age as a predictor before the association between age and emotional outcomes can be more clearly understood.

3.4.6. Clinical implications

Results of this systematic review show that receipt of an indeterminate test result has the potential to have a short-term negative emotional impact. This finding has important implications for clinical practice. As already discussed in section 2.3.4 (page 121), if required, participants who receive an indeterminate result should be offered additional support following receipt of their results with the aim of improving their emotional wellbeing. Furthermore, in one of the publications from the NELSON trial, the authors recommend that the results letter sent to participants with indeterminate results explicitly states that their risk of lung cancer is small (< 2.5%) [90]. This could provide reassurance and reduce levels of negative emotional outcomes. When making the decision as to whether they take part in lung cancer screening, individuals should be informed of the potential for short term emotional harm to occur following the receipt of an indeterminate test result.

3.4.7. Conclusion

Despite the accumulating evidence on the emotional impact of screening for lung cancer, this review provides evidence that little research has been carried out on predictors of emotional well-being post-screening. Receipt of an indeterminate test result, being a smoker and female gender were all associated with higher levels of distress following screening. There are a number of factors that warrant further investigation: age, ethnic origin, marital status and affective risk perception. Future research exploring predictors of the emotional impact of lung

cancer screening should continue to include measures of both non-specific and specific emotional outcomes, and interpret their findings in terms of clinical as well as statistical significance. Future studies should also seek to measure outcomes at similar time-points to enable comparisons. In order to extend and strengthen the evidence base, additional predictors should be explored. The stress and coping model and the SRM of illness beliefs are two theoretical models that can be used to inform future research exploring predictors of the emotional impact of lung cancer screening. Finally, an essential avenue for future research is to explore predictors of the positive emotional impact of lung screening as there is currently no evidence in this area.

Chapter 4. A longitudinal study exploring the emotional impact of screening for lung cancer

Chapter four of this thesis presents the results of the emotional outcomes sub-study that was conducted as part of the ECLS study. This sub-study explored the impact of lung cancer screening on positive affect, negative affect, lung cancer worry and distress specific to screening for lung cancer. Participants from each of the EarlyCDT®-positive, EarlyCDT®-negative, and control groups completed questionnaires containing emotional outcome measures at pre-randomisation and then at one, three, six and 12 months post randomisation. Scores for each outcome measure are described by groups over time and multilevel regression modelling was used to compare scores over time within and between groups. The findings from this study make several important contributions to our understanding of the emotional impact of lung cancer screening and provide a basis for further research.

4.1. Introduction

Chapter two of this thesis reviewed the literature on the emotional impact of lung cancer screening. As stated in chapter two, emotional harms (e.g., raised anxiety, increased worry about lung cancer) have the potential to affect large numbers of individuals taking part in a screening programme [105]. Such harms can result from the limitations of lung cancer screening, which were described in chapter one, section 1.4.3., pages 55 to 58 (e.g., overdiagnosis and

overtreatment). Furthermore, there are a number of points in the screening process itself that have the potential to have a negative emotional impact [84], for example, the anticipation of having a screening test, receipt of a positive result and the further investigations required. If screening is found to have a negative emotional impact in the large number of healthy individuals taking part, then this could act as a barrier towards the implementation of a screening programme [106]. It is therefore imperative that any potential emotional harms are studied and, if appropriate, interventions developed to reduce or mitigate against emotional harm.

In addition, in order to ensure that the benefits of lung cancer screening compensate for the harms, potential positive emotional outcomes of screening must also be investigated. As described in chapter two (section 2.1, page 65), a possible emotional benefit of lung cancer screening is reassurance following the receipt of a negative screening test result [90]. Positive emotional responses in screening participants, particularly in those who do not benefit from screening, could provide a rationale for introducing or continuing a screening programme.

The current sub-study was conducted as part of the ECLS study and was undertaken to establish the emotional harms and benefits of screening for lung cancer using EarlyCDT®-Lung. The following section lists the aims and hypotheses of this study.

4.2. Aims and hypotheses

The two primary aims of this study were as follows:

1. To investigate, within groups (EarlyCDT®-positive, EarlyCDT®-negative, control) how scores on the Positive and Negative Affect Schedule (PANAS), Lung Cancer Worry Scale (LCWS) and Impact of Events Scale (IES; for the (EarlyCDT®-positive and EarlyCDT®-negative groups only) change over time (one, three, six and 12 months post-randomisation).

In line with previous research exploring the emotional impact of lung cancer screening (described in chapter 2), it was hypothesised that the EarlyCDT®-positive group would have significantly higher negative affect, LCWS and IES scores at one month post-screening but that scores would decrease over time (three, six and 12 months post-randomisation). It was expected that positive affect scores would be significantly lower at one month post-screening but would increase over time and return to pre-randomisation levels.

For the EarlyCDT®-negative group, it was hypothesised that there would be no significant change in negative affect, LCWS or IES scores at one, three six or 12 months post-randomisation. In line with the results of a study exploring positive affect following receipt of a normal ovarian cancer screening test[161], it was predicted that positive affect scores would significantly increase over the one and three month time-points but return to pre-randomisation levels over six and 12 months.

For the control group, it was hypothesised that negative affect, LCWS and IES scores would all be significantly higher at one month post-screening but would return to pre-randomisation levels

over three, six and 12 months. It was expected that positive affect scores would be significantly lower at one month post-screening but would increase over time and return to pre-randomisation levels.

2. To explore how scores on the PANAS, LCWS and IES differ between the three groups across all time points and at each questionnaire time-point (one, three, six and 12 months post-randomisation).

Consistent with the results of previous research in this area, it was hypothesised that participants in the EarlyCDT®-positive group would have significantly higher negative affect, LCWS and IES scores, and significantly lower positive affect scores, when compared with the EarlyCDT®-negative group across time and at the one and there month time-points. It was expected that there would be no statistically significant differences in scores between groups at the six and 12 month time-points.

It was expected that the EarlyCDT®-negative group would have significantly lower negative affect, LCWS and IES scores, and significantly higher positive affect scores, when compared with the control group across time and at the one and there month time-points. It was expected that there would be no statistically significant differences in scores between groups at the six and 12 month time-points.

Finally, it was hypothesised that there would be no statistically significant differences in PANAS, LCWS or IES scores between the EarlyCDT®-positive and control groups across time and at each study time-point.

4.3. Method

4.3.1. Study design

This emotional outcomes sub-study is a longitudinal cohort study nested within the ECLS study, which is described in chapter one of this thesis (section 1.6, pages 60 to 63). Recruitment for this study began in January 2014 and data collection for PhD analyses was completed in May 2016. Ethical approval was obtained from the East of Scotland Research Ethics Service. A copy of documentation concerning ethical approval is included in Appendix five (page 494).

4.3.2. Participants

Eligibility criteria

Participants were eligible if they were taking part in the ECLS study. Please see table 6 (chapter one, section 1.6, page 61) for a list of inclusion and exclusion criteria for ECLS study participants. Participants were not eligible if:

- They were diagnosed with lung cancer before the one month questionnaire was due to be sent,
- The pre-randomisation questionnaire had not been completed,
- There were no contact details available in order to send questionnaires, and
- The one and there month questionnaires were not returned.

Settings and locations of data collection

The ECLS study participants who took part in this study were recruited from 159 general practices within the lowest quintile of deprivation (as measured by the Scottish Index of Multiple Deprivation (SIMD)) in NHS Tayside and NHS Greater Glasgow & Clyde.

4.3.3. Procedure

The ECLS study recruitment visit is described in chapter one (section 1.6, page 62). In brief, participants provided informed consent, inclusion and exclusion criteria were checked and they then completed the pre-randomisation questionnaire, which contained emotional and behavioural outcome measures. Once the pre-randomisation questionnaire was completed, participants gave a blood sample. A web-based randomisation system (TRuST) was used to allocate them to the intervention or control group. Randomisation was stratified by site (general practice) and minimised by age, gender and smoking history (current or former smoker). The intervention group had their blood sample screened using EarlyCDT®-Lung whereas the control group did not. Participants in the intervention group received either an EarlyCDT®-positive or an EarlyCDT®-negative test result.

For the emotional outcomes sub-study, all individuals with an EarlyCDT®-positive test result were approached with the aim of recruiting 300 participants [100]. An electronic randomisation tool was used to randomly sample 300 participants from each of the EarlyCDT®-negative and control groups, stratified by two study centres (NHS Tayside and NHS Greater Glasgow & Clyde). A Senior Software Programmer at the Health Informatics Centre, University of Dundee, conducted randomisation. Twenty-one individuals were sampled from each of the EarlyCDT®-negative and

control groups each week for 19 weeks (17 from NHS Greater Glasgow & Clyde and four from NHS Tayside).

As part of the emotional outcomes sub-study, participants were sent four follow-up questionnaires at one, three, six and 12 months post-randomisation. A copy of the one-month follow-up questionnaire administered to participants in the intervention group is provided as an example in appendix seven, page 500 (Please note, subsequent questionnaires were identical to the one month questionnaire). Each questionnaire was sent in a white envelope with an ECLS study logo on the front and included a cover letter (appendix six, page 499) and a 2nd class freepost envelope to return it. If a returned questionnaire was incomplete then the research team called the participant to complete the missing items by phone. A questionnaire was classed as incomplete if an emotional outcome measure had not been completed at all or if less than 50% of a measure had been completed.

A number of strategies were employed to increase participation rates (response to one-month questionnaire) and response rates (completion of questionnaires administered at three, six and 12 months). First, participants received a £5 gift voucher for each questionnaire completed. A response deadline for return of questionnaires was also listed on the cover letter of each questionnaire and a phone number provided for participants to call the research team if they required assistance to complete questionnaires. The research team called participants one week after the one month follow-up questionnaire was sent to check on delivery, offer assistance with completing the questionnaire and provide an opportunity for participants to ask any questions. A reminder letter was sent with a duplicate questionnaire if no response was received within two weeks. Participants who were sent reminder letters at the three, six and 12

month follow-ups were contacted by phone one week after the reminder letter was sent to check on postal delivery.

Participants who wished to be withdrawn from the study (e.g., by contacting the research team directly to inform them of this) were sent no further questionnaires, or reminders, and were recorded as excluded. If participants returned a blank questionnaire then it was assumed that they did not wish to receive further questionnaires and they were also recorded as excluded from the study and sent no further questionnaires or reminders. If no response was received, then at the next follow-up point, the participant was sent a questionnaire (and reminder if necessary), but if unresponsive again, then no further questionnaires were sent. Participants who received a diagnosis of lung cancer were withdrawn from the study subsequent to receiving the diagnosis. Furthermore, participants who had not completed the pre-randomisation questionnaire, and were sampled for the study by mistake, were withdrawn.

4.3.4. Outcome measures

Positive and Negative Affect

The first two outcomes, positive affect and negative affect, were measured by the Positive and Negative Affect Schedule (PANAS).[162] Positive affect denotes the degree to which an individual experiences positive emotions whereas negative affect represents the extent to which an individual experiences distress and unsatisfactory engagement with their environment [163]. The PANAS was included in the pre-randomisation questionnaire and in all follow-up questionnaires. The PANAS consists of 20 items, 10 of which make up a positive affect subscale (e.g., excited, enthusiastic, inspired) and 10 that make up a negative affect subscale (e.g., distressed, upset,

jittery). Participants were asked to indicate the extent to which they had felt each emotion listed over the past week. Responses were recorded on a 5-point Likert scale, ranging from one (very slightly or not at all) to five (extremely). Separate subscale scores for positive affect and negative affect are summed across the 20 items to give a score for positive affect and a score for negative affect. Positive affect scores range from 10 – 50 and higher scores indicate high levels of positive affect. Likewise, negative affect scores range from 10 – 50 and higher scores indicate high levels of negative affect. The PANAS has been found to have adequate reliability (Cronbach's α = 0.89 for positive affect and 0.85 for negative affect) [163].

Lung cancer worry

Lung cancer worry was assessed by the Lung Cancer Worry Scale (LCWS)[164]. The LCWS was included in the pre-randomisation questionnaire and in all follow-up questionnaires in order to identify emotional distress specific to lung cancer risk. This four-item scale was adapted from the Cancer Worry Scale, which was originally developed to assess worry about breast and ovarian cancer risk. The first LCWS item measures the frequency of worries about getting lung cancer. The second and third items assess the extent to which these worries affect mood and ability to perform daily activities. The fourth item measures current level of anxiety about the results of future tests/treatment. Responses for each item were recorded on a 5-point Likert scale, ranging from one (not at all) to five (almost all the time). In line with previous research, the first item was analysed as a separate variable as it measures the frequency of worry rather than the impact of worry[164]. Higher scores for this variable indicate a higher frequency of worry. Frequency of worry was dichotomised into not worried (not at all worried or rarely worried) vs. worried (sometimes worried or often worried or worried almost all of the time). Scores from the second and third items were summed to create a variable that assesses impact of worry; higher

scores show greater impact of worry (score range: one to ten)[164]. As with the first item, the fourth item was analysed as a separate variable where higher scores indicate higher levels of anxiety about the results of future tests/treatment. This variable was dichotomised into not anxious (not at all anxious or a little anxious) *vs*. anxious (somewhat anxious or anxious a lot or anxious almost all of the time).

Distress specific to screening for lung cancer

Distress specific to screening for lung cancer was assessed by the Impact of Events Scale (IES)[120]. The IES was included in questionnaires for participants in the EarlyCDT®-positive and EarlyCDT®-negative groups and at follow-up only as screening had not taken place at the time of the pre-randomisation assessment. The IES includes 15 items, seven of which make up an intrusion subscale and eight of which make up an avoidance subscale. Items on this measure were adapted to assess intrusive thoughts and avoidance of issues associated with being tested for lung cancer. For example, "I thought about being tested for lung cancer when I did not mean to" and "I tried to remove being test for lung cancer from memory." Participants were asked to place a tick next to each item to show how often they have experienced each feeling during the past week, including the present day. Responses were recorded on a 4-point Likert scale, scored 0 (Not at all), 1 (Rarely), 3 (Sometimes) and 5 (Often). Responses can be summed for a subscale score (Intrusion subscale score: range = 0 – 35, Avoidance subscale score: range = 0 – 40). In the current study, a total score was calculated, ranging from 0 to 75, which has clear cut-off points for clinical levels of concern (low < 8.5, moderate 8.6–19 and high >19).[143] Previous studies that have used the IES in a cancer screening context have found scores to have a non-normal distribution and a highly positive skew.[165] [89,90] The IES has been found to have adequate internal reliability (Cronbach's α = 0.86 for the total IES score)[143].

4.3.5. Potential confounding factors

The variables listed below were adjusted for as potential confounding factors for the adjusted analyses of the emotional outcomes measured in this study (PANAS, LCWS, and IES).

ECLS study minimisation variables

1. ECLS study centre (NHS Greater Glasgow & Clyde/NHS Tayside)
2. Age group (50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74, 75 – 79)
3. Gender (female/male)
4. Smoking status (current/former smoker).

Additional variables measured pre-randomisation that have the potential to affect emotional outcomes

Sociodemographic variables

1. Education

One study included in the systematic review conducted as part of this PhD (reported in chapter 3, pages 124 to 177) found that participants with post-high school or university-level education had significantly lower scores on emotional outcome measures than participants with lower levels of education across all time-points [88]. Furthermore, a systematic review of breast cancer screening reported that adverse emotional impact of screening was associated with a lower education level [134]. Therefore, the age at which the participant left full time education, which was recorded pre-randomisation, was adjusted for in analyses.

2. Marital status

Marital status was recorded pre-randomisation (response options: single, in a relationship, married/in a civil partnership, widowed, separated, divorced). Due to small numbers for several of these categories (in a relationship (8.16%), widowed (8.46%), separated (4.82%)), responses to this item were recoded into two categories: 'married, civil partnership, in a relationship' and 'divorced, separated, single, widowed.' Although not extensively studied in the context of lung cancer screening, one study included in the systematic review (chapter 3) found that married participants had significantly lower trait anxiety scores across all time-points than those who were not married [88]. Furthermore, the recently published results of the UK Lung Cancer Screening (UKLS) trial[8] reported that, compared with married participants, those who were single or divorced had significantly higher levels of cancer worry [118]. The decision was therefore made to adjust for marital status in analyses.

3. Level of socioeconomic deprivation

As stated in chapter one, page 60, the ECLS study assessed socioeconomic deprivation using the Scottish Index of Multiple Deprivation (SIMD) score. The SIMD is the Scottish Government's official tool for identifying the deprivation level of an area. The SIMD 2012 combines 38 indicators of deprivation across seven domains: income, employment, health, education, skills and training, housing, geographic access and crime. The SIMD score used in the current study represents quintiles of the SIMD, with quintile 1 representing the least derived areas and quintile

[8] Please note. The results from the UKLS are not included in the systematic review conducted as part of this PhD (chapter 3) as it was published subsequent to completion of the review, and due to time constraints, the review searches could not be re-run.

5 representing the most deprived areas. One of the findings from the systematic review (chapter 3) is that no studies have explored the impact of socioeconomic deprivation on emotional outcomes following screening. Since the review was conducted, the UKLS trial published results, which showed that participants from more socioeconomically deprived areas had significantly higher levels of cancer worry during the trial than participants from less deprived areas [118]. In view of this finding, the decision was made to adjust for SIMD score in analyses.

Clinical variables

1. Family history of lung cancer

The number of first degree relatives (parents, siblings or children) who have had lung cancer was recorded at pre-randomisation. In the UKLS trial, participants who had a friend or close family member diagnosed with lung cancer had significantly higher levels of cancer worry compared with participants who had no experience of lung cancer [118]. Family history of lung cancer was therefore adjusted for in the analyses.

2. Level of worry concerning additional investigations

At pre-randomisation, participants were asked if they were having investigations for any other conditions (response options: yes/no). Worry about such investigations was also measured and responses recorded on a 5-point Likert scale, ranging from one (not at all worried) to four (very worried). The number of participants who reported that they were having further investigations was 138 (14.10%). However, 506 (49.05%) of participants then responded to the following item on the level of worry concerning further investigations. Originally, the number of participants having additional investigations and their level of worry about these investigations were both

going to be described and the level of worry about any investigations then adjusted for in analyses. However, the decision was made to exclude the item concerning level of worry as it appeared that a large number of participants had mistakenly responded to it and the data was therefore not reliable.

3. Pulmonary nodule diagnosis

As described in chapter one, page 63, participants with an EarlyCDT®-positive result received a chest x-ray followed by a CT scan and then a CT scan every six months for two years. Following their CT scan, 102 participants were found to have pulmonary nodules. Such nodules have been defined as round masses of tissue within the lung, which are less than 3 cm in diameter, and surrounded by lung parenchyma [166]. A number of studies have found that patients diagnosed with pulmonary nodules experienced emotional distress as a result (e.g., fear about cancer, anxiety) [167-169]. In view of these findings, the decision was made to adjust for a diagnosis of pulmonary nodules (≤ 8mm in diameter) following a CT scan in the analyses. However, when pulmonary nodule diagnosis (yes/no) was added to the models as a confounding factor, the models would not converge. It is likely that this was due to the small numbers of participants diagnosed with nodules (n = 102, 9.88%). Therefore, pulmonary diagnosis was not included as a potential confounding factor.

<u>Psychological variables</u>

1. Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS)[170] was completed at pre-randomisation only. The HADS consists of 14 items. Seven items measure anxiety (e.g., "I get a sort of

frightened feeling like “butterflies” in the stomach”) and form the HADS-Anxiety subscale (HADS-A). The other seven items measure depression (e.g., “I feel as if I am slowed down“) and form the HADS-Depression subscale (HADS-D). For each item, participants were asked to indicate the extent to which they had felt each emotion over the past week. Each item is scored from 0-3 and there is a total score of 21 for each of the anxiety and depression subscales. Scores can be categorised into ‘normal’ (0-7), ‘borderline’ (8-10) and ‘significant (> 10)[170].

According to the stress and coping model (described in chapter 2), the emotional impact of a stressor, such as lung cancer screening, is determined by how an individual appraises the stressor. A stressor can be appraised as harmful, threatening or challenging. A study that explored how participants appraised and coped with stressors found that participants who had high scores on a measure of depressive symptomatology were more likely to appraisal a stressor as threatening and respond with high levels of worry and fear when compared with participants who had low scores[171]. In view of this finding, the decision was made to adjust for total HADS-D scores in analyses. Furthermore, a study that explored predictors of emotional outcomes following colposcopy in participants who received an abnormal cervical screening test reported that participants who scored in the range for possible or probably caseness on the HADS-A at recruitment had significantly higher levels of cancer worry[137]. HADS-A scores were therefore adjusted for in analyses too.

4.3.6. Sample size

For the emotional outcomes sub-study, 200 participants in each group (EarlyCDT®-positive, EarlyCDT®-negative and the control arm) allowed detection of a mean difference of 3.00 (SD 15.04 in the IES between pre-randomisation and follow up measurements within each group

and a mean difference of 4.2 (SD 15.04), between each of the test groups (EarlyCDT®-positive and EarlyCDT®-negative) and the control arm with 80% power and 2-sided 5% significance level [100]. This estimate is taken from unpublished data comparing pre and post prostate biopsy scores from the ProtecT prostate cancer study. Therefore, to allow for attrition, 300 participants were recruited from each group (EarlyCDT®-positive, EarlyCDT®-negative and control).

4.3.7. Missing data

The procedures for handling missing data for individual items in each measure were as follows:

Hospital Anxiety and Depression Scale (HADS), Positive and Negative Affect Schedule (PANAS) and the Impact of Events Scale (IES)

Although the HADS is a widely used measure, at present, there are no established guidelines for how to handle missing items[172]. Following a review of the literature, there also appeared to be no standard approach to handling missing data for the PANAS and IES. Researchers administering the three measures were found to be employing a broad range of strategies to handle any missing data. For the current study, the decision was made to replace single missing values with the participant's mean response to items within the rest of that subscale. If there was more than one missing value in a subscale, then the subscale was judged as invalid and a subscale score was not calculated. Since the analysis plan was developed, the results of a simulation study that explored how to handle missing items in the HADS was published[172]. Based on the findings, the authors of the study strongly advised that subscale means are imputed for missing items in order to reduce bias and imprecision, which supports the approach chosen for this study [172].

Lung Cancer Worry Scale (LCWS)

If there is no response, or multiple responses, to an item in this measure, then the item was judged as invalid.

4.3.8. Data checking prior to analysis

Data included in the analyses presented in this chapter were verified at two time points:

1. September 2015 (all one to 12 month follow-up questionnaires entered before the 19th of August 2015 were eligible for verification)
2. May 2016 (all questionnaires entered between the 20th of August 2015 and the 3rd of May 2016 were eligible for verification)

The data verification process for this study was as follows:

- Study questionnaires were entered into an online database, OpenClinica. A list of questionnaires that had been entered into OpenClinica was extracted by the Tayside Clinical Trials Unit (TCTU).
- Eligible questionnaires were numbered sequentially and a random number generator was used to select 10% of the numbered questionnaires.
- Within the questionnaires sampled for verification, 100% of the items were checked for accuracy against the paper questionnaire. It was ensured that no researcher checked a questionnaire that they had entered themselves.

- Errors identified were amended in OpenClinica and also recorded on a Microsoft Excel spreadsheet in order to identify any recurring errors and prevent repeating such errors in future data entry. Data were not amended on the paper questionnaires.
- The number of inaccurate items in each questionnaire was recorded in the spreadsheet (numerator), alongside with the number of items in the whole questionnaire (denominator). This enabled an error rate for each questionnaire to be calculated as well as an overall error rate. An error rate of greater than 0.5% at any time point would have resulted in corrective action.

The data checking results for September 2015 and May 2016 were as follows:

1. September 2015: 3702 questionnaires were eligible and 370 were sampled for data verification. In total, 68 errors were found in the 28,193 items that were checked, which gave an error rate of 0.24%.

2. May 2016: 429 questionnaires were eligible and 43 were sampled. In total, three errors were found in the 3,514 items checked, which gave an error rate of 0.09%.

4.3.9. Statistical methods

Data analysis for this study was undertaken using Stata Statistical Software version 14 [173].

Comparison of pre-randomisation data between participants who declined participation in the sub-study and those who agreed to participate

Comparisons between the two groups were made as follows:

- Pearson's chi-squared test for categorical data (screening group, region, age group, gender, ethnic origin, SIMD score, marital status, work status, living situation, smoking status, family history of lung cancer, prescribed medication for low mood, frequency of worries about getting lung cancer (LCWS), level of anxiety about the results of future tests/treatment (LCWS)).

- Mann Whitney U test for continuous data (age, age on leaving full-time education, pack year history, HADS-Anxiety, HADS-Depression, positive affect, negative affect, impact of worry on mood and ability to perform daily activities (LCWS)).

Comparison of pre-randomisation data between screening groups

Although participants in this study had been randomised to the intervention and control group, they had to choose to take part in the questionnaire study, so it is possible that there were differences between groups. Therefore, comparisons between groups (EarlyCDT®-positive, EarlyCDT®-

negative and control) were made using Pearson's chi-squared test for categorical data and Kruskal–Wallis test for continuous data.

Analysis of outcome measures

Scores for all outcome measures were calculated for participants in each of the screening groups at each of the five questionnaire time points (pre-randomisation (excluding the IES as this measure is not administered pre-randomisation), one, three, six and 12 months). Total scores were compared descriptively and graphically (box plots and bar charts) for the three groups at the different time points.

Multi-level linear regression (PANAS subscale scores, IES total scores, LCWS (impact of lung cancer worry on mood and daily activities)) or logistic regression (LCWS: frequency of lung cancer worry and worry about investigations/treatment; dichotomised as described above) was used to take account of repeated measures. The data had a two-level hierarchical structure with observations (data collected at each questionnaire time-point – level 1) being clustered within participants (level 2). Comparisons were made between:

1. Pre-randomisation score and each time-point (one, three, six and 12 months) for each of the three screening groups
2. EarlyCDT®-positive and control groups
3. EarlyCDT®-negative and control groups
4. EarlyCDT®-positive and EarlyCDT®-negative groups

As described in section 4.3.5, page 188, both adjusted models were adjusted for the following variables:

Model one:

- ECLS minimisation variables (study centre[9] (NHS Greater Glasgow & Clyde/NHS Tayside), age group (50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74, 75 – 79), gender and smoking status (current/ex-smoker)
- Time
- Baseline measure of the outcome variable (where measured)
- Group*time interaction (to assess difference in outcomes between groups over time)

Model two:

- ECLS minimisation variables (study centre (NHS Greater Glasgow & Clyde/NHS Tayside), age group (50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74, 75 – 79), gender and smoking status (current/ex-smoker)
- Additional variables measured pre-randomisation that could potentially affect the outcome of interest (age at which participant left full time education, SIMD score, marital status, family history of lung cancer, HADS-A, HADS-D)
- Time
- Baseline measure of the outcome variable (where measured)
- Group*time interaction.

[9] Please note: Although randomisation was stratified by GP practice, analyses of behavioural outcomes for the ECLS study found that models would not converge when GP practice was included as a random or fixed effect. Therefore, the models in this study were adjusted for study centre (Glasgow/Dundee) instead of GP practice (GP practice is contained within study centre).

Significance was assessed using likelihood ratio tests with a p-value of <0.05 taken as significant, except for interaction analyses where a p-value of <0.01 was taken as significant.

Model checking

The multi-level multivariable linear regression models were checked by plotting histograms, P-P plots and Q-Q plots to determine whether level 1 and level 2 residuals were normally distributed and by plotting residual values against fitted values to check for constant variance and to identify observations with large residual values (outliers). For continuous outcomes where the residuals did not appear to be normally distributed or the variance was not constant, the data were logarithmically transformed and model checking repeated to assess whether the logarithmic transformed data resulted in the model assumptions being better met. Examples of model checking plots are presented in appendix eight for an outcome where transforming the data resulted in model assumptions being better met. They are not shown for all models due to word count restrictions, but are available from the candidate on request. Where data was transformed, results are presented on the original scale, on the logarithmic scale (geometric means) and after anti-logging. The difference between the log of two numbers is the log of their ratio[174]; so the antilog of the difference between two geometric means is the ratio of the geometric means[175]. The ratio can be interpreted as the percentage difference between the geometric means, similar to the interpretation of any ratio, such as a relative risk. If the 95% confidence interval (CI) around this ratio includes the value of 1, then there is no significant difference between the means. A sensitivity analysis was undertaken excluding observations with large residual values (large values are defined for each analysis in the results section) to assess the impact on the findings. Logistic regression models used the xtlogit command in STATA as using the xtmelogit command (which does allow more options for model checking)

resulted in models taking an extremely long time to run. Unfortunately, the xtlogit command does not allow estimation of level 1 and level 2 residuals so model checking could not be conducted for logistic regression models.

4.4. Results

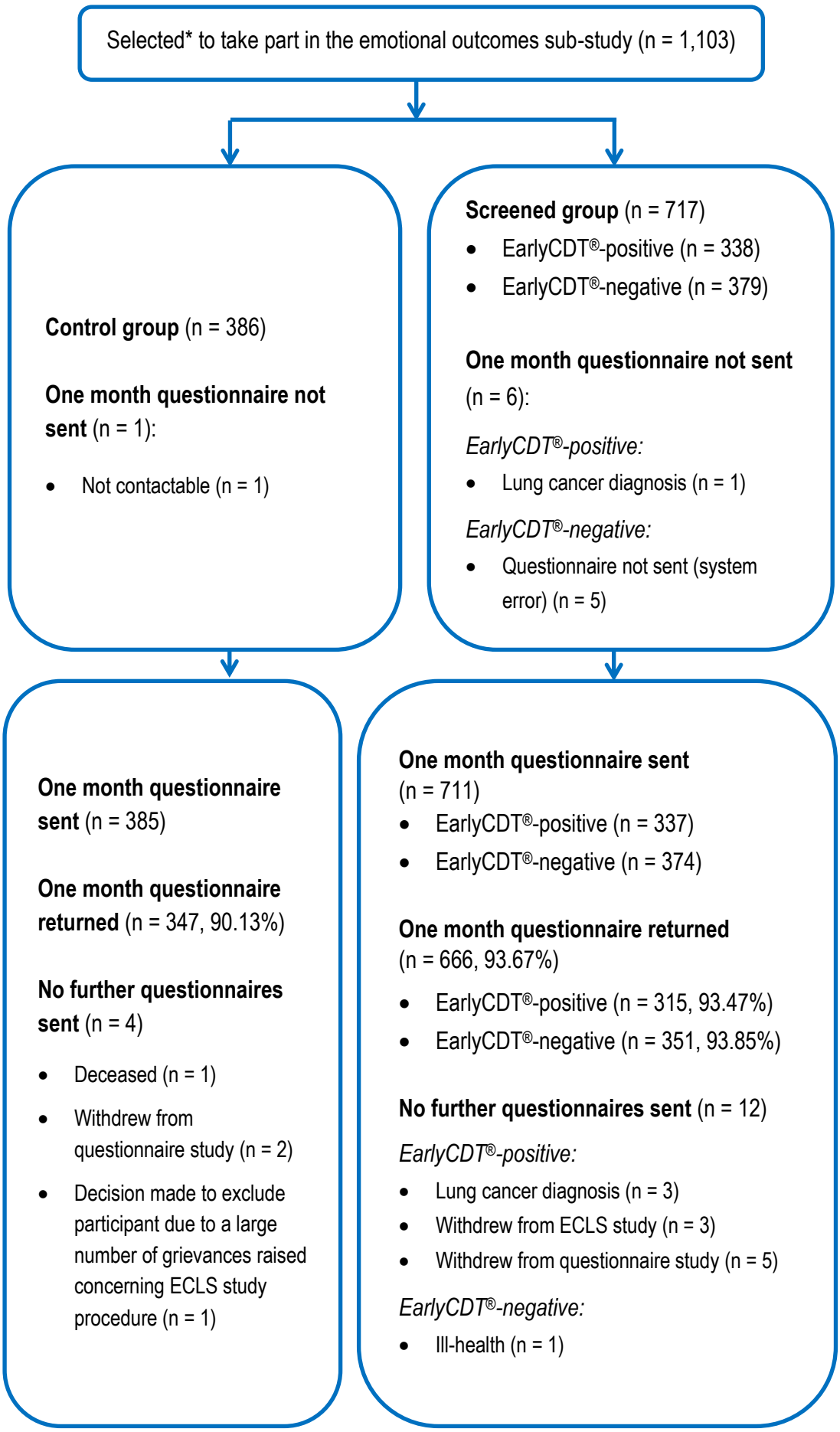
4.4.1. Participant flow

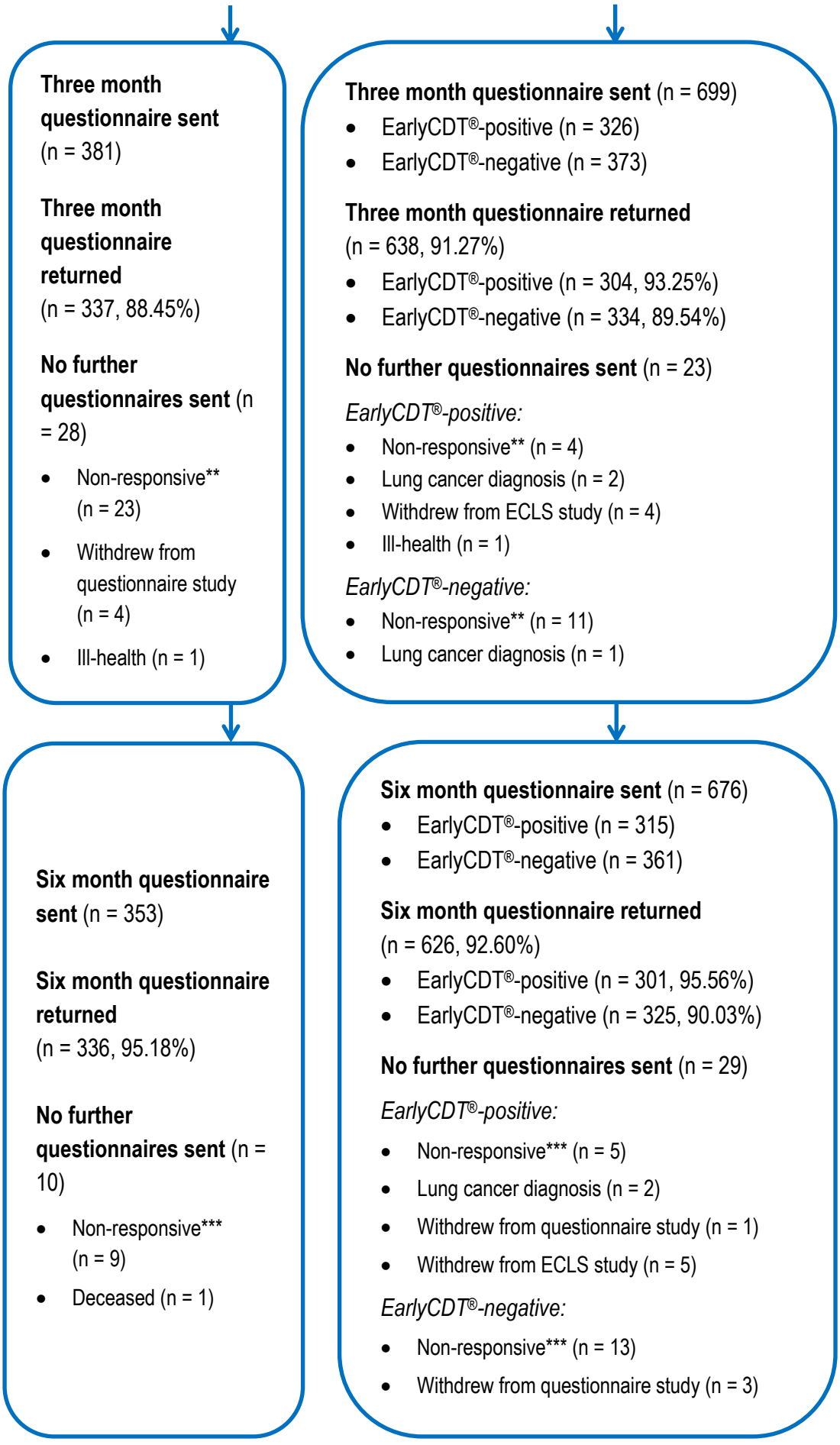
Recruitment to the emotional outcomes sub-study began in January 2014. Recruitment of participants from the control group and from the EarlyCDT®-negative group was completed in June 2014. Recruitment of the EarlyCDT®-positive participants finished in May 2015.

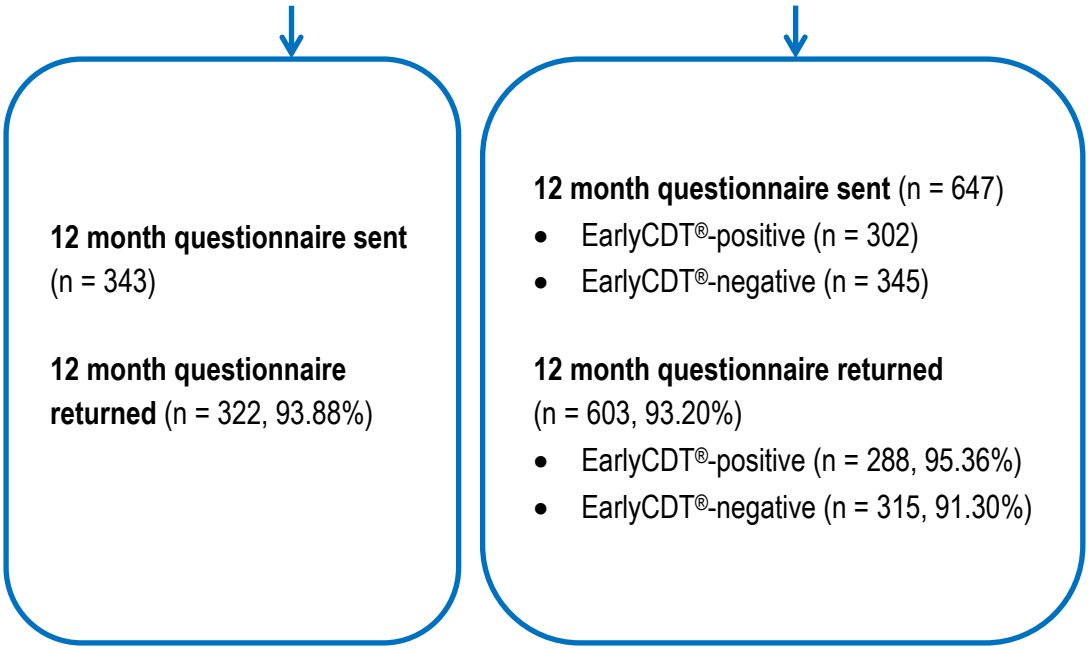
Participant progress through the different phases of the study is illustrated in a flow diagram, figure ten. In total, 1,103 participants were selected to take part in the emotional outcomes sub-study: 386 had been randomised to the control (unscreened) group and 717 to the screened group. Seven participants who were selected to take part were not sent any study questionnaires for the following reasons:

- Contact details (address, phone number) were not provided for one participant in the control group, so the research team were unable to send them a questionnaire.
- One participant, who received an EarlyCDT®-positive test result, was diagnosed with lung cancer before the one month questionnaire was due to be sent.
- Five participants in the EarlyCDT®-negative group were not sent questionnaires due to a system error.

Of the 1,096 participants sent a one month follow-up questionnaire, 1,013 (92.42%) participants returned it (EarlyCDT®-positive (n = 315, 93.47%), EarlyCDT®-negative (n = 351, 93.85%), control (n = 347, 90.13%)). At the three month follow-up, 975 (90.28%) of the 1,080 participants sent a three month questionnaire returned it (EarlyCDT®-positive (n = 304, 93.25%), EarlyCDT®-negative (n = 334, 89.54%), control (n = 337, 88.45%)). At the six month follow-up, 962 (93.49%) of the 1,029 participants sent a questionnaire returned it (EarlyCDT®-positive (n = 301, 95.56%), EarlyCDT®-negative (n = 325, 90.03%), control (n = 336, 95.81%)). Finally, of the 990 participants sent a 12 month follow-up questionnaire, 925 (93.43%), returned it (EarlyCDT®-positive (n = 288, 95.36%), EarlyCDT®-negative (n = 315, 91.30%), control (n = 322, 93.88%)).


Selected* to take part in the emotional outcomes sub-study (n = 1,103)
Control group (n = 386)
One month questionnaire not sent (n = 1):
Not contactable (n = 1)
Screened group (n = 717)
EarlyCDT®-positive (n = 338)
EarlyCDT®-negative (n = 379)
One month questionnaire not sent (n = 6):
EarlyCDT®-positive:
Lung cancer diagnosis (n = 1)
EarlyCDT®-negative:
Questionnaire not sent (system error) (n = 5)
One month questionnaire sent (n = 385)
One month questionnaire returned (n = 347, 90.13%)
No further questionnaires sent (n = 4)
Deceased (n = 1)
Withdrew from questionnaire study (n = 2)
Decision made to exclude participant due to a large number of grievances raised concerning ECLS study procedure (n = 1)
One month questionnaire sent (n = 711)
EarlyCDT®-positive (n = 337)
EarlyCDT®-negative (n = 374)
One month questionnaire returned (n = 666, 93.67%)
EarlyCDT®-positive (n = 315, 93.47%)
EarlyCDT®-negative (n = 351, 93.85%)
No further questionnaires sent (n = 12)
EarlyCDT®-positive:
Lung cancer diagnosis (n = 3)
Withdrew from ECLS study (n = 3)
Withdrew from questionnaire study (n = 5)
EarlyCDT®-negative:
Ill-health (n = 1)


Three month questionnaire sent (n = 381)
Three month questionnaire returned (n = 337, 88.45%)
No further questionnaires sent (n = 28)
• Non-responsive** (n = 23)
• Withdrew from questionnaire study (n = 4)
• Ill-health (n = 1)
Three month questionnaire sent (n = 699)
• EarlyCDT®-positive (n = 326)
• EarlyCDT®-negative (n = 373)
Three month questionnaire returned (n = 638, 91.27%)
• EarlyCDT®-positive (n = 304, 93.25%)
• EarlyCDT®-negative (n = 334, 89.54%)
No further questionnaires sent (n = 23)
EarlyCDT®-positive:
• Non-responsive** (n = 4)
• Lung cancer diagnosis (n = 2)
• Withdrew from ECLS study (n = 4)
• Ill-health (n = 1)
EarlyCDT®-negative:
• Non-responsive** (n = 11)
• Lung cancer diagnosis (n = 1)
Six month questionnaire sent (n = 353)
Six month questionnaire returned (n = 336, 95.18%)
No further questionnaires sent (n = 10)
• Non-responsive*** (n = 9)
• Deceased (n = 1)
Six month questionnaire sent (n = 676)
• EarlyCDT®-positive (n = 315)
• EarlyCDT®-negative (n = 361)
Six month questionnaire returned (n = 626, 92.60%)
• EarlyCDT®-positive (n = 301, 95.56%)
• EarlyCDT®-negative (n = 325, 90.03%)
No further questionnaires sent (n = 29)
EarlyCDT®-positive:
• Non-responsive*** (n = 5)
• Lung cancer diagnosis (n = 2)
• Withdrew from questionnaire study (n = 1)
• Withdrew from ECLS study (n = 5)
EarlyCDT®-negative:
• Non-responsive*** (n = 13)
• Withdrew from questionnaire study (n = 3)



* EarlyCDT®-negative and control participants were randomly allocated to the emotional outcomes sub-study (please see section 4.3.3., page 183, for a description of the randomisation procedure) whereas all participants with an EarlyCDT®-positive test result who consented to further research, were selected.

** One and three month questionnaires not returned

*** Three and six month questionnaires not returned

Figure 10. Flow chart illustrating the number of participants from each screening group (control, EarlyCDT®-negative, EarlyCDT®-positive) who were selected to take part in the emotional outcomes sub-study, the number sent study questionnaires at each time-point (one, three, six and 12 month), the number who returned each questionnaire and details of those sent no further questionnaires.

Participants included and excluded from the analysis

A total of 1,032 (93.6%) of participants from the 1,103 selected to take part in the emotional outcomes sub-study were included in the analysis. The numbers included in the analysis for each screening group are listed below and reasons for exclusion from the study analysis are provided.

1. Control group

In total, 350 participants from the control group were included in the analysis for this study and 36 participants were excluded. The reasons for exclusion from the study analysis are as follows:

- No contact details available, so no questionnaires were sent (n = 1)
- Deceased, no questionnaires returned (n = 1)
- Excluded due to large number of grievances concerning ECLS study procedure, no questionnaires returned (n = 1)
- One, three, six and 12 month questionnaires were returned but it was later found that the participant had not completed a pre-randomisation questionnaire and was therefore not eligible for this study (n = 1)
- Six participants withdrew from the questionnaire study, of which four did not return any questionnaires (n = 4)
- Did not return both the one and three month questionnaires, so were not recruited to this study (n = 23)
- Returned questionnaires but were later found to have potentially been affected by an ECLS study protocol deviation, where a number of participants completed pre-randomisation

questionnaires *after* they were randomised to a trial group (screen or control). Data from these participants was not included in the analysis (n = 5)

2. EarlyCDT®-positive

Data from 321 participants in the EarlyCDT®-positive group was included in the analysis. In total, 17 participants were excluded:

- Two of the participants diagnosed with lung cancer did not return study questionnaires (n = 2)
- Did not return both the one and three month questionnaires, so were not recruited to this study (n = 4)
- Six participants withdrew from the questionnaire study, of which five did not return any questionnaires (n = 5)
- 12 participants withdrew from the ECLS study, of which two did not return any questionnaires. One participant who withdrew did return a one month questionnaire, however, it was later found that no baseline questionnaire was completed, so they were also excluded from the analysis (n = 3)
- Returned questionnaires but were later found to have potentially been affected by the same ECLS study protocol deviation described above. Data from these participants could not be included in the analysis (n = 2)
- One participant withdrew from the ECLS study at the six month time-point. Although they had returned previous questionnaires, they were later found to have potentially been affected by the ECLS study protocol deviation (n = 1)

3. EarlyCDT®-negative

In total, 361 participants from the EarlyCDT®-negative group were included in the analysis for this study and 18 were excluded:

- Not sent the first questionnaire due a system error (n = 5)
- Withdrew from the study due to ill-health, no questionnaires were returned (n = 1)
- Did not return both the one and three month questionnaires, so were not recruited to this study (n = 11)
- Returned all questionnaires but was later found to have potentially been affected by the ECLS study protocol deviation (n = 1).

4.4.2. Participation in the emotional outcomes sub-study

Table nine presents the pre-randomisation sociodemographic and emotional characteristics for participants who agreed to participate in the emotional outcomes sub-study and those who declined participation in the study. Of the 1,103 ECLS study participants who were selected to take part in the emotional outcome sub-study, 1,096 were sent a one month questionnaire. As illustrated in figure 10, page 202, seven participants were not sent questionnaires. Also, just after the one month questionnaire was sent out, the research team were informed that two participants had withdrawn from the ECLS study, one had been diagnosed with lung cancer, one was suffering from ill-health and one participant had passed away. These five participants were therefore excluded from the analyses presented in table nine. Furthermore, the decision was made to exclude one participant due to a number of grievances raised concerning the ECLS study procedure. This participant was also excluded from the analyses presented in table nine.

In total, 1,047 (96.06%) ECLS study participants agreed to take part in the emotional outcomes sub-study and 43 declined participation. Of the 43 who did not participate, five participants directly informed the research team of their decision not to take part (negative responders) and 38 did not return the one or three month questionnaire (non-responders).

As stated in section 4.3.9, Pearson's chi-squared test was applied to the 15 categorical variables to determine whether there were significant differences between those who participated in the emotional outcomes sub-study and those who declined participation. The distribution of the eight sociodemographic and emotional continuous variables were checked to establish whether they were normally distributed. All eight variables were non-normally distributed and so the Mann–Whitney U test was used to determine whether there were significant differences between participants and those who declined participation. The chi squared (χ^2) value, degrees of freedom and p value for each Pearson's chi-squared test and the *z* value for each Mann–Whitney U test are reported in table nine.

Results showed that there were significant differences between the proportion of EarlyCDT®-positive, EarlyCDT®-negative and control group participants who accepted or declined participation in the emotional outcomes sub-study (p = 0.036). Compared with the EarlyCDT®-positive (20.93%) and the EarlyCDT®-negative group (25.58%), a greater proportion of the non-participants were from the control group (34.38%). Region was significantly different between the two groups, with a greater proportion of non-participants being from NHS Greater Glasgow & Clyde (p = 0.002). In addition, age (years) was significantly different between the groups (median age: 60 (participant) *vs*. 55 (non-participant), p = 0.002). HADS-Anxiety scores were significantly different between participants and non-participants (median score: 7 (participant)

vs. 8 (non-participant), p = 0.0186). No other significant differences were found between participants and non-participants for the sociodemographic and emotional characteristics listed in table nine.

Table 9. Pre-randomisation sociodemographic and emotional characteristics amongst participants and non-participants in the emotional outcomes sub-study

Characteristic	**Total** N = 1,090	**Participant** N = 1,047 (96.06%)	**Non-participant** N = 43 (3.94%)	**Statistical test***
Screening group				
EarlyCDT®-positive	334 (30.64%)	325 (31.04%)	9 (20.93%)	$\chi^2(2) = 6.64$
EarlyCDT®-negative	373 (34.22%)	362 (34.57%)	11 (25.58%)	P = 0.036
Control	383 (35.14%)	360 (34.38%)	23 (53.49%)	
Region – N (%)				
NHS Greater Glasgow & Clyde	819 (75.14%)	778 (74.31%)	41 (95.35%)	$\chi^2(1) = 9.79$
NHS Tayside	271 (24.86%)	269 (25.69%)	2 (4.65%)	P = 0.002
Age, years – median (IQR)**	60 (55–66)	60 (55-66)	55 (53-63)	$z = -3.07$ P = 0.002
50 – 54 years **– N (%)**	249 (22.84%)	229 (21.87%)	20 (46.51%)	
55 – 59 years	279 (25.60%)	271 (25.88%)	8 (18.60%)	
60 – 64 years	227 (20.83%)	218 (20.82%)	9 (20.93%)	
65 – 69 years	222 (20.37%)	218 (20.82%)	4 (9.30%)	
70 – 74 years	106 (9.72%)	104 (9.93%)	2 (4.65%)	
75 – 79 years	7 (0.64%)	7 (0.67%)	0 (0.00%)	

Characteristic	Total N = 1,090	Participant N = 1,047 (96.06%)	Non-participant N = 43 (3.94%)	Statistical test*
Gender - N (%)				
Male	541(49.63%)	516 (49.28%)	25 (58.14%)	$\chi^2(1) = 1.30$
Female	549 (50.37%)	531 (50.72%)	18 (41.86%)	P = 0.255
Ethnic origin - N (%)	[18]	[12]	[6]	$\chi^2(1) = 0.5438$
White	1,057 (98.60%)	1,020 (98.55%)	37 (100.00%)	P = 0.461
Other (African, dual heritage, undisclosed)	15 (1.40%)	15 (1.45%)	0 (0.00%)	
Age on leaving full-time education, years - Median (IQR)	[42] 16 (15-16)	[37] 16 (15-16)	[5] 16 (15-16)	$z = 0.47$ p = 0.640
Quintiles of Scottish Index of Multiple Deprivation score – N (%)	[7]	[7]	[0]	
1 (most deprived)	458 (42.29%)	441 (42.40%)	17 (39.53%)	$\chi^2(4) = 1.91$
2	216 (19.94%)	207 (19.90%)	9 (20.93%)	P = 0.752
3	163 (15.05%)	155 (14.90%)	8 (18.60%)	
4	143 (13.20%)	136 (13.08%)	7 (16.28%)	

Characteristic	Total N = 1,090	Participant N = 1,047 (96.06%)	Non-participant N = 43 (3.94%)	Statistical test*
5 (least deprived)	103 (9.51%)	101 (9.71%)	2 (4.65%)	
Marital status - N (%)	[31]	[25]	[6]	
Married, civil partnership, in a relationship	642 (60.62%)	617 (60.37%)	25 (67.57%)	$\chi^2(1) = 0.77$
Divorced, separated, single, widowed	417 (39.38%)	405 (39.63%)	12 (32.43%)	P = 0.379
Work status - N (%)	[30]	[24]	[6]	
Employed or self-employed	420 (39.62%)	402 (39.30%)	18 (48.65%)	$\chi^2(2) = 4.29$
Retired or unemployed but not looking for work or other	430 (40.57%)	421 (41.15%)	9 (24.32%)	P = 0.117
Unable to work due to illness or disability, unemployed but looking for work	210 (19.81%)	200 (19.55%)	10 (27.03%)	
Living situation – N (%)	[30]	[25]	[5]	
Rented or other	422 (39.81%)	408 (39.92%)	14 (36.84%)	$\chi^2(2) = 0.15$
Owned or mortgaged	638 (60.19%)	614 (60.08%)	24 (63.16%)	P = 0.703

Characteristic	Total N = 1,090	Participant N = 1,047 (96.06%)	Non-participant N = 43 (3.94%)	Statistical test*
Smoking status - N (%)				
Current smoker	604 (55.41%)	579 (55.30%)	25 (58.14%)	$\chi^2(1) = 0.13$
Former smoker	486 (44.59%)	468 (44.70%)	18 (41.86%)	P = 0.714
Smoking pack years - Median (IQR)	35 (26-49)	35 (25-50)	35 (25-49)	$z = 0.95$ P = 0.341
First degree relative with lung cancer – N (%)				
Yes	289 (26.51%)	277 (26.46%)	12 (27.91%)	$\chi^2(1) = 0.04$
No	801 (73.49%)	770 (73.54%)	31 (72.09%)	P = 0.833
Prescribed medication for low mood – N (%)	[25]	[19]	[6]	
Yes	191 (17.93%)	181 (17.61%)	10 (27.03%)	$\chi^2(1) = 2.15$
No	874 (82.07%)	847 (82.39%)	27 (72.97%)	P = 0.142
Additional investigations – N (%)	[71]	[64]	[7]	
Yes	144 (13.94%)	139 (14.14%)	3 (8.33%)	$\chi^2(1) = 0.98$
No	877 (86.06%)	844 (85.86%)	33 (91.67%)	P = 0.323

Characteristic	Total N = 1,090	Participant N = 1,047 (96.06%)	Non-participant N = 43 (3.94%)	Statistical test*
Hospital Anxiety and Depression Scale				
HADS-Anxiety*** - Median (IQR)	[16]	[11]	[5]	$z = 2.35$
	7 (5-9)	7 (4-9)	8 (6-11)	P = 0.019
HADS-Depression*** - Median (IQR)	[16]	[11]	[5]	$z = 0.77$
	8 (7-10)	8 (7-10)	8 (7-10)	P = 0.440
Positive and Negative Affect Schedule				
Positive affect score – Median (IQR)	[54]	[48]	[6]	$z = -1.19$
	34 (27-39)	34 (27-39)	32 (25-38)	P = 0.233
Negative affect score – Median (IQR)	[37]	[31]	[6]	$z = 0.41$
	14 (11-18)	14 (11-18)	14 (11-21)	P = 0.679
Lung Cancer Worry Scale				
Frequency of worries about getting lung cancer *(How worried are you about getting lung cancer someday?)* – **N (%)**	[22]	[16]	[6]	
Not worried	437 (40.92%)	424 (41.13%)	13 (35.14%)	$\chi^2(1) = 0.53$
Worried	631 (59.08%)	607 (58.87%)	24 (64.86%)	P = 0.467

Characteristic	Total N = 1,090	Participant N = 1,047 (96.06%)	Non-participant N = 43 (3.94%)	Statistical test*
Current level of anxiety about the results of future tests/treatment (*What is your current level of anxiety about the results of future tests/treatments?)* – **N (%)**	[23]	[17]	[6]	
Not anxious	961 (90.07%)	930 (90.29%)	31 (83.78%)	$\chi^2(1) = 1.69$
Anxious	106 (9.93%)	100 (9.71%)	6 (16.22%)	P = 0.194
Impact of worry on mood and ability to perform daily activities (median, IQR)	[27] 3 (2-3)	[21] 3 (2-3)	[6] 3 (2-5)	$z = 1.38$ P = 0.168

* Please note: The statistical tests used were Pearson's chi-squared test for the categorical variables and Mann–Whitney U test for continuous variables.

4.4.3. Pre-randomisation data

The sociodemographic and emotional characteristics amongst the participants included in the analysis are described in table ten. The majority of the 1,032 participants were from NHS Greater Glasgow & Clyde (74.13%). The median age of participants was 60 years old, 50.97% were female and 98.55% were white. The median age on leaving full-time education was 16 years old (interquartile range: 15-16) and 41.95% of participants were from the most deprived areas. The majority of participants, 60.28%, were in a civil partnership, married or in a relationship and 60.18% either owned or had a mortgage on their home. In terms of employment, 39.39% were employed or self-employed and 40.96% were retired or unemployed but not looking for work. In total, 55.23% of participants were current smokers and the median number of smoking pack years was 35 (interquartile range: 25 - 48). Data on family history showed that 26.55% of participants had a first degree relative (parent, sibling, or child) who had been diagnosed with lung cancer. It was found that 14.10% of participants were currently being investigated for other conditions and 17.60% had been prescribed medication for low mood. The median scores (and interquartile ranges) on the HADS-Anxiety and HADS-Depression measures were 7 (interquartile range: 5 – 9) and 8 (interquartile range: 7 – 10). It is important to note that the median HADS-Depression score was on the cut-off for borderline depression (range for borderline depression 8 - 10).

In terms of pre-randomisation scores for the emotional outcome measures, the median positive affect score (and interquartile range) was 34 (27-39) and the median negative affect score was 14 (11-18). The first item of the LCWS measured frequency of worries about getting lung cancer someday. At pre-randomisation, 607 (59.16%) of participants were worried about getting lung cancer someday and 419 (40.84%) of participants were not worried about getting lung cancer.

The LCWS also measured current level of anxiety about the results of future tests/treatment where it was found that 100 (9.76%) participants were anxious and 925 (90.24%) were not anxious. Finally, the median score (and interquartile range) for impact of lung cancer worry on mood and ability to perform daily activates was 3 (2-3).

Sociodemographic and emotional characteristics for participants in each screening group (EarlyCDT®-positive, EarlyCDT®-negative, control)

Table ten also presents the pre-randomisation sociodemographic and emotional characteristics for participants in each screening group (EarlyCDT®-positive, EarlyCDT®-negative, control). The chi squared value, degrees of freedom and p value for each Pearson's chi-squared test (for categorical data) and Kruskal–Wallis test (for continuous data) are also reported in table ten.

Overall, sociodemographic characteristics and baseline psychosocial scores were similar across the three groups. However, there were significantly more females in the EarlyCDT®-positive group and significantly more males in the EarlyCDT®-negative group. Smoking status was also significantly different between the three groups. There were significantly more current smokers in the EarlyCDT®-negative group and significantly more former smokers in the EarlyCDT®-positive group. Both gender and smoking status were adjusted for in analyses. No other statistically significant differences were found between the screening groups for the above sociodemographic and psychosocial characteristics.

Table 10. Pre-randomisation sociodemographic and emotional characteristics amongst participants in each test result group (EarlyCDT®-positive, EarlyCDT®-negative, control)

Characteristic	**Total** N = 1,032	**EarlyCDT®-positive** N = 321 (31.10%)	**EarlyCDT®-negative** N = 361 (34.98%)	**Control** N = 350 (33.91%)	**Statistical test***
Region – N (%)				255 (72.86%)	
NHS Greater Glasgow & Clyde	765 (74.13%)	235 (73.21%)	275 (76.18%)		$\chi^2(2) = 1.23$
NHS Tayside	267 (25.87%)	86 (26.79%)	86 (23.82%)	95 (27.14%)	P = 0.542
Age, years – median (IQR)**	60 (55–66)	60 (56-66)	59 (55-65)	60 (55-66)	$\chi^2(2) = 3.58$ P = 0.167
50 – 54 years **– N (%)**	225 (21.80%)	62 (19.31%)	88 (24.38%)	75 (21.43%)	
55 – 59 years	268 (25.97%)	83 (25.86%)	97 (26.87%)	88 (25.14%)	
60 – 64 years	215 (20.83%)	62 (19.31%)	73 (20.22%)	80 (22.86%)	
65 – 69 years	217 (21.03%)	77 (23.99%)	69 (19.11%)	71 (20.29%)	
70 – 74 years	101 (9.79%)	34 (10.59%)	32 (8.86%)	35 (10.00%)	
75 – 79 years	6 (0.58%)	3 (0.93%)	2 (0.55%)	1 (0.29%)	

Characteristic	Total N = 1,032	EarlyCDT®-positive N = 321 (31.10%)	EarlyCDT®-negative N = 361 (34.98%)	Control N = 350 (33.91%)	Statistical test*
Gender - N (%)					
Male	506 (49.03%)	139 (43.30%)	198 (54.85%)	169 (48.29%)	$\chi^2(2) = 9.18$
Female	526 (50.97%)	182 (56.70%)	163 (45.15%)	181 (51.71%)	P = 0.010
Ethnic origin - N (%)	[1]	[1]	[0]	[0]	
White	1,016 (98.55%)	314 (98.13%)	355 (98.34%)	347 (99.14%)	$\chi^2(2) = 1.37$
Other	15 (1.45%)	6 (1.88%)	6 (1.66%)	3 (0.86%)	P = 0.503
Age on leaving full-time education, years - Median (IQR)	[27] 16 (15-16)	[10] 16 (15-16)	[9] 16 (15-16)	[8] 16 (15-16)	$\chi^2(2) = 0.44$ P = 0.803
Quintiles of Scottish Index of Multiple Deprivation score – N (%)	[7]	[2]	[1]	[4]	
1 (most deprived)	430 (41.95%)	124 (38.87%)	155 (43.06%)	151 (43.64%)	$\chi^2(8) = 7.55$
2	206 (20.10%)	80 (25.08%)	63 (17.50%)	63 (18.21%)	P = 0.478
3	153 (14.93%)	46 (14.42%)	57 (15.83%)	50 (14.45%)	
4	135 (13.17%)	40 (12.54%)	48 (13.33%)	47 (13.58%)	
5 (least deprived)	101 (9.85%)	29 (9.09%)	37 (10.28%)	35 (10.12%)	

Characteristic	Total N = 1,032	EarlyCDT®-positive N = 321 (31.10%)	EarlyCDT®-negative N = 361 (34.98%)	Control N = 350 (33.91%)	Statistical test*
Marital status - N (%)	[15]	[4]	[6]	[5]	
Married, civil partnership, in a relationship	613 (60.28%)	200 (63.09%)	215 (60.56%)	198 (57.39%)	$\chi^2(2) = 2.26$
Divorced, separated, single, widowed	404 (39.72%)	117 (36.91%)	140 (39.44%)	147 (42.61%)	P = 0.323
Work status - N (%)	[14]	[4]	[5]	[5]	
Employed or self-employed	401 (39.39%)	129 (40.69%)	150 (42.13%)	122 (35.36%)	$\chi^2(4) = 4.68$
Retired or unemployed but not looking for work or other	417 (40.96%)	131 (41.32%)	134 (37.64%)	152 (44.06%)	P = 0.322
Unable to work due to illness or disability, unemployed but looking for work	200 (19.65%)	57 (17.98%)	72 (20.22%)	71 (20.58%)	
Living situation – N (%)	[15]	[6]	[4]	[5]	
Rented or other	405 (39.82%)	119 (37.78%)	145 (40.62%)	141 (40.87%)	$\chi^2(2) = 0.80$
Owned or mortgaged	612 (60.18%)	196 (62.22%)	212 (59.38%)	204 (59.13%)	P = 0.670
Smoking status - N (%)					
Current smoker	570 (55.23%)	165 (51.40%)	218 (60.39%)	187 (53.43%)	$\chi^2(2) = 6.25$
Former smoker	462 (44.77%)	156 (48.60%)	143 (39.61%)	163 (46.57%)	P = 0.044

Characteristic	Total N = 1,032	EarlyCDT®-positive N = 321 (31.10%)	EarlyCDT®-negative N = 361 (34.98%)	Control N = 350 (33.91%)	Statistical test*
Smoking pack years - Median (IQR)	35 (25-48)	33 (25-48)	35 (26-48)	35 (26-48)	$\chi^2(2) = 1.36$ P = 0.506
First degree relative with lung cancer – N (%)					
Yes	274 (26.55%)	95 (29.60%)	92 (25.48%)	87 (24.86%)	$\chi^2(2) = 2.25$
No	758 (73.45%)	226 (70.40%)	269 (74.52%)	263 (75.14%)	P = 0.325
Prescribed medication for low mood – N (%)	[9]	[4]	[1]	[4]	
Yes	180 (17.60%)	54 (17.03%)	62 (17.22%)	64 (18.50%)	$\chi^2(2) = 0.30$
No	843 (82.40%)	263 (82.97%)	298 (82.78%)	282 (81.50%)	P = 0.862
Additional investigations – N (%)	[53]	[19]	[16]	[18]	
Yes	138 (14.10%)	48 (15.89%)	46 (13.33%)	44 (13.25%)	$\chi^2(2) = 1.17$
No	841 (85.90%)	254 (84.11%)	299 (86.67%)	288 (86.75%)	P = 0.558
HADS-Anxiety* - Median (IQR)**	[1] 7 (5-9)	[0] 6 (4-8)	[1] 7 (5-9)	[0] 7 (4-9)	$\chi^2(2) = 1.47$ P = 0.480

Characteristic	Total N = 1,032	EarlyCDT®-positive N = 321 (31.10%)	EarlyCDT®-negative N = 361 (34.98%)	Control N = 350 (33.91%)	Statistical test*
HADS-Depression* - Median (IQR)**	[1] 8 (7-10)	[0] 8 (7-10)	[1] 8 (7-9)	[0] 8 (7-10)	$\chi^2(2) = 0.48$ P = 0.788
Positive and Negative Affect Schedule					
Positive affect score – Median (IQR)	[38] 34 (27-39)	[10] 34.44 (27-40)	[18] 34 (27-39)	[10] 33 (27-39)	$\chi^2(2) = 2.74$ P = 0.254
Negative affect score – Median (IQR)	[21] 14 (11-18)	[8] 13 (11-18)	[6] 14 (11-18)	[7] 13 (11-19)	$\chi^2(2) = 0.35$ P = 0.840
Lung Cancer Worry Scale					
Frequency of worries about getting lung cancer – **N (%)**	[6]	[4]	[1]	[1]	
Not worried	419 (40.84%)	138 (43.53%)	150 (41.67%)	131 (37.54%)	$\chi^2(2) = 2.63$
Worried	607 (59.16%)	179 (56.47%)	210 (58.33%)	218 (62.46%)	P = 0.268

Characteristic	Total N = 1,032	EarlyCDT®-positive N = 321 (31.10%)	EarlyCDT®-negative N = 361 (34.98%)	Control N = 350 (33.91%)	Statistical test*
Level of anxiety about the results of future tests/treatment – **N (%)**	[7]	[4]	[0]	[3]	
Not anxious	925 (90.24%)	291 (91.80%)	320 (88.64%)	314 (90.49%)	$\chi^2(2) = 1.94$
Anxious	100 (9.76%)	26 (8.20%)	41 (11.36%)	33 (9.51%)	P = 0.378
Impact of worry on mood and ability to perform daily activities (median, IQR)	[11] 3 (2-3)	[4] 2 (2-3)	[3] 3 (2-4)	[4] 2 (2-3)	$\chi^2(2) = 2.76$ P = 0.252

[missing values]

* Pearson's chi-squared test (categorical data) and Kruskal–Wallis test (continuous data)

** IQR = Interquartile range

*** In 2002, a systematic review was published that aimed to review the literature of the validity of the HADS [176]. The authors reported that the optimum balance between sensitivity and specificity was reached when clinical cut-off points were 8/21 for both the HADS-A and HADS-D.

4.4.4. Outcome one: Positive affect

Please note: For each emotional outcome, results of analyses exploring changes in outcome scores within groups over time are presented (first aim) followed by results of the analyses exploring changes in outcome scores between groups over time (second aim)

Aim: To investigate, within groups (EarlyCDT®-positive, EarlyCDT®-negative, control), how positive affect scores changed over time (one, three, six and 12 months post-randomisation)

Descriptive statistics for each screening group at each study time-point are displayed in figure 11 and table 11. As can be seen from figure 11 and table 11, the median and mean positive affect scores for all three screening groups were highest at pre-randomisation. The median score for the EarlyCDT®-positive and EarlyCDT®-negative groups declined across the one, three and six month time-points. Scores for both groups increased slightly at 12 months but were still lower than at pre-randomisation. Median and mean scores for the control group declined at one month and remained very similar at the three, six and 12 month time-points. There were statistically significant differences in positive affect scores between study time-points for all three screening groups.

Table 11. Positive affect scores amongst participants in each screening group (EarlyCDT®-positive, EarlyCDT®-negative, control) at each study time-point

Study time-point	Total	EarlyCDT®-positive	EarlyCDT®-negative	Control	Results of statistical analyses comparing scores between groups at each time-point***
Pre-randomisation	N = 994 [38]	N = 311 [10]	N = 343 [18]	N = 340 [10]	$\chi^2(2) = 2.74$
(median, IQR*)	34 (27-39)	34.44 (27-40)	34 (27-39)	33 (27-39)	P = 0.2536
(mean, sd**)	32.70 (8.84)	33.26 (9.19)	32.48 (8.70)	32.41 (8.66)	
One month	N = 984 [19] 32 (26-37.39) 31.29 (8.53)	N = 304 [7] 32 (26-39) 31.76 (8.64)	N = 343 [7] 33 (26-38) 31.77 (8.32)	N = 337 [5] 31 (25-37) 30.38 (8.59)	$\chi^2(2) = 5.28$ P = 0.07
Three months	N = 946 [20] 31 (25-36.70) 30.38 (8.57)	N = 297 [4] 31 (24-36) 30.36 (9.05)	N = 323 [10] 32 (26-37) 30.94 (8.21)	N = 326 [6] 31 (24-36) 29.85 (8.46)	$\chi^2(2) = 2.37$ P = 0.31
Six months	N = 935 [17] 31 (24-37) 30.60 (9.17)	N = 294 [4] 31 (24-38) 30.87 (9.68)	N = 316 [8] 31 (25-37) 30.97 (8.50)	N = 325 [5] 31 (23-37) 29.99 (9.32)	$\chi^2(2) = 1.60$ P = 0.45
12 months	N = 870 [6] 32 (24-38)	N = 243 [0] 32 (23-39)	N = 313 [1] 32 (25-37)	N = 314 [5] 31 (23-37)	$\chi^2(2) = 1.65$ P = 0.44

	30.68 (9.18)	30.99 (9.86)	30.98 (8.18)	30.13 (9.58)
Results of statistical analyses comparing scores within groups over time**		P < 0.001	P < 0.001	P < 0.001

[missing values]

* IQR = Interquartile range

**sd = standard deviation

*** Kruskal-Wallis test

****Unadjusted linear regression analysis

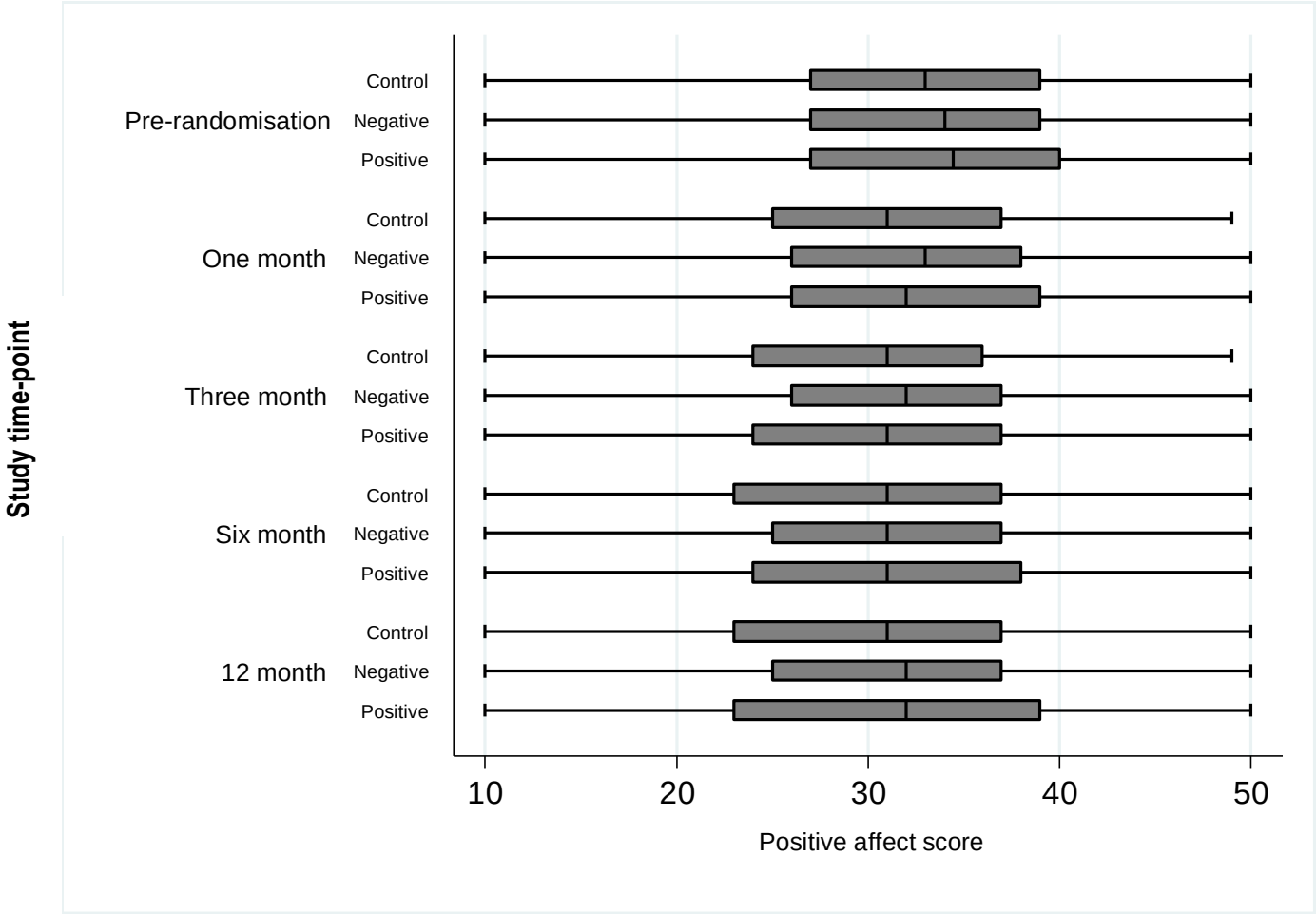


Figure 11. Positive affect scores amongst participants in each group (EarlyCDT®-positive, EarlyCDT®-negative, control) at each study time-point (pre-randomisation, one month, three month, six month and 12 month)

Unadjusted regression analysis

The results of the unadjusted linear regression analysis (difference between the means, 95% CI's and p values for each group at each study time-point) are presented in table 12. No statistically significant differences were found between screening groups for changes in mean scores from pre-randomisation ($p = 0.276$). For the EarlyCDT®-positive and the control groups, mean scores at one, three, six and 12 months were all significantly lower when compared with pre-randomisation scores ($p < 0.001$). For the EarlyCDT®-negative group, the difference in scores between one month and pre-randomisation approached statistical significance ($p = 0.055$). The differences in mean scores between pre-randomisation and the other three time points were all statistically significant ($p < 0.001$). Although these differences were statistically significant, the absolute differences were small in magnitude.

Table 12. Unadjusted analyses comparing positive affect scores within groups (EarlyCDT®-positive, EarlyCDT®-negative, control) over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation scores

		Difference between the means (95% CI)	**P value**
Screening group	**Study time-point**		
EarlyCDT®-positive	One month	-1.55 (-2.31 to -0.78)	P < 0.001
	Three month	-2.86 (-3.63 to -2.09)	P < 0.001
	Six month	-2.40 (-3.18 to -1.63)	P < 0.001
	12 month	-2.30 (-3.12 to -1.48)	P < 0.001
EarlyCDT®-negative	One month	-0.71 (-1.43 to 0.02)	P = 0.055
	Three month	-1.84 (-2.58 to -1.10)	P < 0.001
	Six month	-1.49 (-2.24 to -0.75)	P < 0.001
	12 month	-1.60 (-2.34 to -0.85)	P < 0.001

Control	One month	-2.16 (-2.89 to -1.44)	P < 0.001
	Three month	-2.91 (-3.64 to -2.17)	P < 0.001
	Six month	-2.53 (-3.27 to -1.80)	P < 0.001
	12 month	-2.56 (-3.30 to -1.82)	P < 0.001
P value for whether changes from baseline differ between screening groups			P = 0.276

Adjusted regression analysis

Results of adjusted linear regression analyses are presented in table 13. Adjusting for ECLS minimisation variables (source region, age, gender, and smoking status) showed mean scores at all follow-up time points were significantly lower than pre-randomisation scores ($p < 0.001$) in the EarlyCDT®-positive and the control groups, and significantly lower scores at three, six and 12 months in the EarlyCDT®-negative group ($p < 0.001$). No significant difference was found between screening groups for changes in mean positive affect scores from pre-randomisation ($p = 0.272$). Adjusting for ECLS minimisation variables, age at leaving full time education, SIMD score, marital status, family history of lung cancer, HADS-A, and HADS-D showed mean scores at all follow-up time points were significantly lower when compared with pre-randomisation scores in each screening group. No statistically significant differences were found between screening groups for changes in mean scores from pre-randomisation ($p = 0.453$). Again, although statistically significant differences in scores were found, the absolute differences were small in magnitude.

Model checking found several very large level one residuals (values > 20 and < -20) for each model. Models were robust to excluding these observations. Histograms, P-P plots, Q-Q plots and scatterplots for the two adjusted models are available from the candidate on request.

Table 13. Adjusted analyses comparing positive affect scores within groups (EarlyCDT®-positive, EarlyCDT®-negative, control) over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation scores

		Difference between the means* (95% CI)	P value	Difference between the means ** (95% CI)	P value
Screening group	**Study time-point**				
EarlyCDT®-positive	One month	-1.55 (-2.31 to -0.78)	P < 0.001	-1.37 (-2.14 to -0.60)	P < 0.001
	Three month	-2.86 (-3.63 to -2.09)	P < 0.001	-2.78 (-3.56 to -2.01)	P < 0.001
	Six month	-2.40 (-3.18 to -1.63)	P < 0.001	-2.23 (-3.00 to -1.46)	P < 0.001
	12 month	-2.31 (-3.13 to -1.48)	P < 0.001	-2.04 (-2.87 to -1.22)	P < 0.001
EarlyCDT®-negative	One month	-0.71 (-1.43 to 0.17)	P = 0.056	-0.90 (-1.63 to -0.17)	P = 0.015
	Three month	-1.84 (-2.58 to -1.10)	P < 0.001	-1.97 (-2.71 to -1.23)	P < 0.001
	Six month	-1.49 (-2.24 to -0.75)	P < 0.001	-1.70 (-2.45 to -0.95)	P < 0.001
	12 month	-1.60 (-2.34 to -0.85)	P < 0.001	-1.58 (-2.33 to -0.83)	P < 0.001
Control	One month	-2.16 (-2.89 to -1.44)	P < 0.001	-2.16 (-2.89 to -1.43)	P < 0.001
	Three month	-2.91 (-3.64 to -2.17)	P < 0.001	-2.89 (-3.62 to -2.15)	P < 0.001
	Six month	-2.53 (-3.27 to -1.80)	P < 0.001	-2.52 (-3.26 to -1.79)	P < 0.001
	12 month	-2.56 (-3.30 to -1.82)	P < 0.001	-2.58 (-3.33 to -1.84)	P < 0.001

P value for whether changes from baseline differ between screening groups	P = 0.272	P = 0.453

* Adjusted for ECLS minimisation variables (study centre (GCC/Tayside), age, gender (female/male), and smoking status (current/former)

** Adjusted for ECLS minimisation variables and additional variables (age at which participant left full time education, SIMD score, marital status, family history of lung cancer, HADS-A, HADS-D

<u>Aim</u>: To explore how positive affect scores differ between the three groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all time points and at each questionnaire time-point (one, three, six and 12 months post-randomisation)

As can be seen from table 11, pre-randomisation positive affect scores were very similar for all three groups. At the one, three, six and 12 month time-points, the control group had slightly lower scores than the EarlyCDT®-positive group and the EarlyCDT®-negative group. There were no statistically significant differences in positive affect scores between the groups at each study time-point.

<u>Unadjusted regression analyses</u>

The results of the unadjusted analyses are presented in table 14. The mean positive affect score was higher in the EarlyCDT®-negative group than the control group across all time-points (difference between the means 1.22, 95% CI 0.05 to 2.40, p = 0.041), reflecting the significantly higher score at one month (difference between the means 1.58, 95% CI 0.26 to 2.89, p = 0.019), but not at other time points. There was no significant difference between mean scores for the EarlyCDT®-positive group and the control group across all time points, but the EarlyCDT®-positive group had a significantly higher mean score at one month than the control group (difference between the means 1.45, 95% CI 0.01 to 2.80, p = 0.035). Finally, no statistically significant differences in mean positive affect scores were found between the EarlyCDT®-positive group and the EarlyCDT®-negative group across all time-points or at each study time-point. Where differences were statistically significant, the absolute differences were small in magnitude.

Table 14. Unadjusted analyses comparing positive affect scores between groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point

		Difference between the means (95% CI)	P value
Screening group	**Study time-point**		
EarlyCDT®-negative *vs*. control	Across all time-points	1.22 (0.05 to 2.40)	P = 0.041
	One month	1.58 (0.26 to 2.89)	P = 0.019
	Three month	1.15 (-0.18 to 2.48)	P = 0.089
	Six month	1.07 (-0.26 to 2.40)	P = 0.116
	12 month	1.05 (-0.28 to 2.39)	P = 0.123
EarlyCDT®-positive *vs*. control	Across all time-points	1.08 (-0.10 to 2.32)	P = 0.073
	One month	1.45 (0.10 to 2.80)	P = 0.035
	Three month	0.88 (-0.48 to 2.25)	P = 0.203
	Six month	0.98 (-0.39 to 2.34)	P = 0.161
	12 month	1.10 (-0.30 to 2.49)	P = 0.124

	Across all time-points	-0.12 (-1.32 to 1.09)	P = 0.849
	One month	-0.13 (-1.47 to 1.22)	P = 0.854
EarlyCDT®-positive *vs*. EarlyCDT®-negative	Three month	-0.27 (-1.62 to 1.09)	P = 0.701
	Six month	-0.91 (-1.45 to 1.27)	P = 0.896
	12 month	0.04 (-1.35 to 1.43)	P = 0.951
P value for whether differences in screening groups vary over time			P = 0.908

Adjusted regression analyses

Results of the adjusted regression analyses are presented in table 15. Adjusting for ECLS minimisation variables showed mean positive affect scores were significantly higher in the EarlyCDT®-negative group than the control group across all time points (p = 0.001) and at each study time-point. No statistically significant differences were found in mean positive affect scores between the EarlyCDT®-positive and control groups across all time points or at each study time-point. The mean positive affect score was significantly lower in the EarlyCDT®-positive group than the EarlyCDT®-negative group at three months (difference between the means 1.12, 95% CI -2.20 to -0.05, p = 0.041). No other statistically significant differences were found. Where statistically significant differences were found, the absolute differences were small in magnitude

Adjusting for ELCS minimisation variables and additional variables, resulted in fewer significant differences, with only significantly higher scores across all time points (p = 0.015) and at one month (difference between the means 1.28, 95% CI 0.29 to 2.26, p = 0.011) in the EarlyCDT®-negative group compared to the control group. Again, the absolute differences were small in magnitude.

Model checking found some very large level one (values > 12 and < -12) and level 2 (values > 15 and < -15) residuals for each model. Models were robust to excluding these observations. Histograms, P-P plots, Q-Q plots and scatterplots for the two adjusted models are available from the candidate on request.

Table 15. Adjusted analyses comparing positive affect scores between groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point

		Difference between the means* (95% CI)	P value	Difference between the means ** (95% CI)	P value
Screening group	**Study time-point**				
EarlyCDT®-negative *vs*. Control	Across all time-points	1.41 (0.57 to 2.25)	P = 0.001	0.97 (0.19 to 1.74)	P = 0.015
	One month	1.78 (0.75 to 2.81)	P = 0.001	1.28 (0.29 to 2.26)	P = 0.011
	Three month	1.36 (0.31 to 2.41)	P = 0.011	0.88 (-0.12 to 1.87)	P = 0.084
	Six month	1.27 (0.22 to 2.32)	P = 0.018	0.78 (-0.22 to 1.77)	P = 0.128
	12 month	1.17 (0.11 to 2.23)	P = 0.030	0.91 (-0.10 to 1.91)	P = 0.078
EarlyCDT®-positive *vs*. Control	Across all time-points	0.56 (-0.30 to 1.43)	P = 0.202	0.50 (-0.30 to 1.29)	P = 0.220
	One month	0.92 (-0.13 to 1.98)	P = 0.087	0.85 (-0.16 to 1.86)	P = 0.097
	Three month	0.24 (-0.83 to 1.31)	P = 0.661	0.08 (-0.93 to 1.10)	P = 0.870
	Six month	0.50 (-0.57 to 1.57)	P = 0.359	0.42 (-0.60 to 1.44)	P = 0.422
	12 month	0.58 (-0.53 to 1.69)	P = 0.305	0.65 (-0.40 to 1.70)	P = 0.227

EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	-0.85 (-1.72 to 0.03)	P = 0.057	-0.47 (-1.27 to 0.34)	P = 0.255
	One month	-0.86 (-1.92 to 0.20)	P = 0.113	-0.42 (-1.44 to 0.59)	P = 0.415
	Three month	-1.12 (-2.20 to -0.05)	P = 0.041	-0.79 (-1.82 to 0.23)	P = 0.130
	Six month	-0.77 (-1.86 to 0.31)	P = 0.161	-0.36 (-1.39 to 0.67)	P = 0.497
	12 month	-0.59 (-1.71 to 0.53)	P = 0.301	-0.25 (-1.32 to 0.81)	P = 0.640
P value for whether differences in screening groups vary over time			P = 0.813		P = 0.806

***** Adjusted for ECLS minimisation variables and baseline value of outcome variable.

****** Adjusted for ECLS minimisation variables, baseline value of outcome variable and additional variables

A brief summary of the main findings for the impact of screening on positive affect

Changes in positive affect scores within screening groups over time

- Positive affect scores at one, three, six and 12 months were significantly lower than at pre-randomisation for all three screening groups. However, although statistically significant, the absolute differences were small and cannot be considered clinically important.

Changes in positive affect scores between screening groups over time

- In contrast to what was hypothesised, no statistically significant differences were found between the EarlyCDT®-positive group and the EarlyCDT®-negative group across time or at each study time-point.
- Again, hypotheses were not supported as it was found that the EarlyCDT®-negative group had significantly higher mean positive affect scores compared with the control group across all time-points and at each time-point when ECLS minimisation variables were adjusted for. However, when the additional variables were adjusted for, the differences at three, six and 12 months were no longer statistically significant. Again, it must be emphasised that the absolute differences between the two groups were very small at each time point.
- Finally, as hypothesised, there were no statistically significant differences in positive affect scores between the EarlyCDT®-positive and control groups across time and at each study time-point.

4.4.5. Outcome two: Negative affect

Aim: To investigate, within screening groups, how negative affect scores changed over time

Descriptive statistics for negative affect scores for each screening group at each study time-point are displayed in figure 12 and table 16. As can be seen from figure 12 and table 16, the negative affect scores for all three screening groups were lowest at pre-randomisation. For the EarlyCDT®-positive group, negative affect scores increased at one month, decreased slightly at three months and appear to plateau over six and 12 months. For the EarlyCDT®-negative group, scores increased slightly at one month, decreased a little at three months, increased slightly at six months and then decreased slightly at 12 months. The control group's scores increased at one month, increased a little at three months, and then decreased slightly over six and 12 months. There were statistically significant differences in negative affect scores between study time-points for all three groups.

Table 16. Negative affect scores amongst participants in each screening group at each study time-point

Study time-point	Total	EarlyCDT®-positive	EarlyCDT®-negative	Control	Results of statistical analyses comparing scores between groups at each time-point***
Pre-randomisation (median, IQR*) (mean, sd**)	N = 1,011 [21] 14 (11-18) 15.78 (6.53)	N = 313 [8] 13 (11-18) 15.55 (6.29)	N = 355 [6] 14 (11-18) 15.75 (6.33)	N = 343 [7] 13 (11-19) 16.04 (6.96)	$\chi^2(2) = 0.35$ P = 0.840
One months	N = 988 [15] 14 (11–20) 16.70 (7.49)	N = 305 [6] 14 (11-20) 16.70 (7.55)	N = 345 [5] 14 (11-19) 16.29 (7.33)	N = 338 [4] 14 (11-21) 17.10 (7.58)	$\chi^2(2) = 2.13$ P = 0.345
Three months	N = 951 [15] 14 (11-20) 16.61 (7.44)	N = 297 [4] 13 (11-20) 16.34 (7.45)	N = 326 [7] 13 (11-19) 16.06 (6.90)	N = 328 [4] 15 (11-22) 17.41 (7.90)	$\chi^2(2) = 5.66$ P = 0.060
Six months	N = 933 [19] 14 (11-20) 16.65 (7.59)	N = 294 [4] 14 (11-21) 16.17 (7.15)	N = 313 [11] 14 (11-20) 16.67 (7.45)	N = 326 [4] 14 (11-21) 17.06 (8.08)	$\chi^2(2) = 1.37$ P = 0.504

12 months	N = 861 [15] 14 (11-20) 16.63 (7.66)	N = 241 [2] 13 (11-20) 16.20 (7.66)	N = 306 [8] 14 (11-20) 16.54 (7.01)	N = 314 [5] 14 (11-20) 17.04 (8.25)	$\chi^2(2) = 1.65$ P = 0.438
Results of statistical analyses comparing scores within each group across time**		P = 0.004	P = 0.046	P < 0.001	

[missing values]

* IQR = Interquartile range

** sd = standard deviation

*** Kruskal–Wallis test

**** Unadjusted linear regression analysis

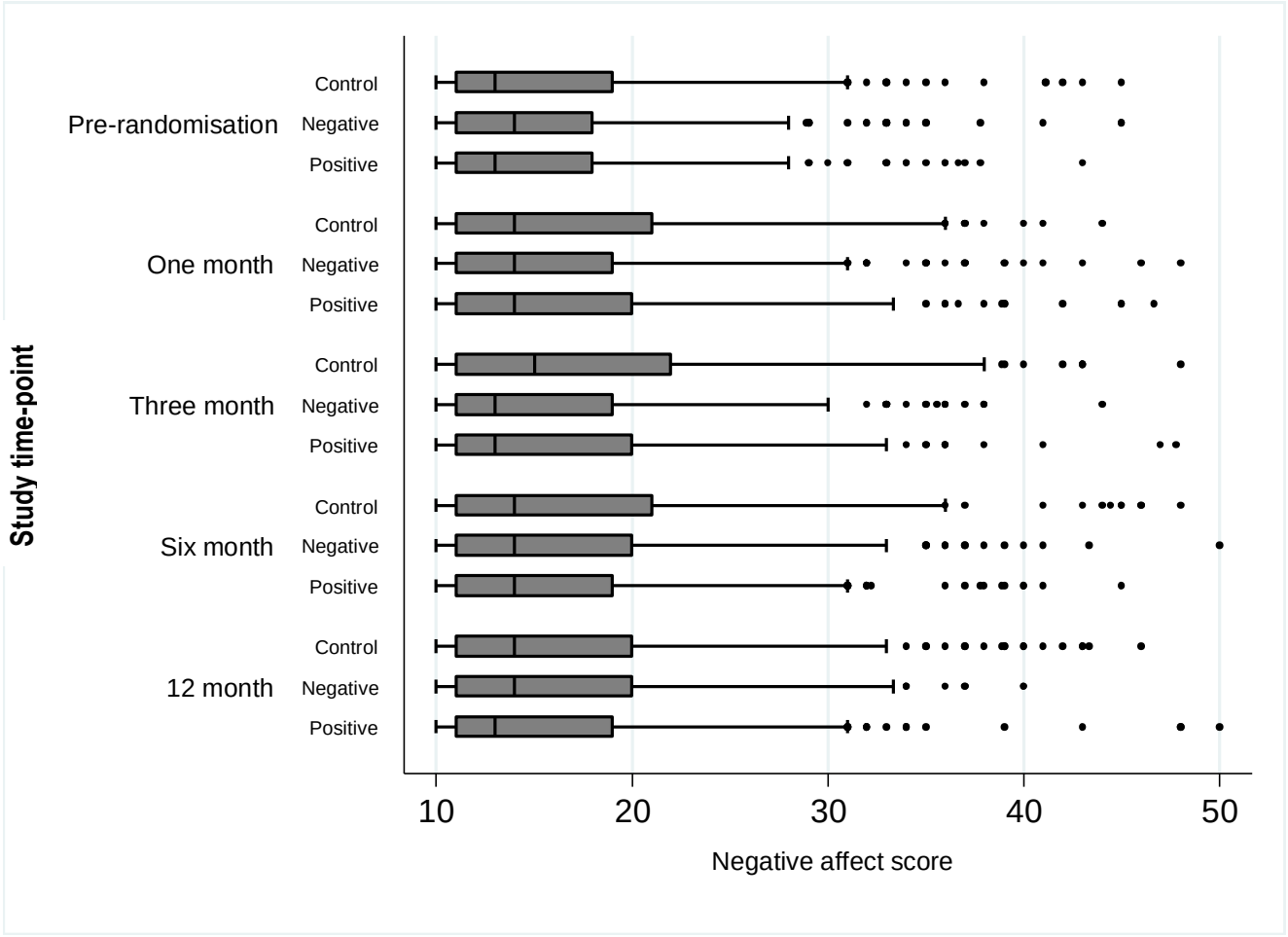


Figure 12. Negative affect scores amongst participants in each group (EarlyCDT®-positive, EarlyCDT®-negative, control) at each study time-point (pre-randomisation, one month, three month, six month and 12 month)

Unadjusted regression analyses

The results of unadjusted linear regression analyses are presented in table 17. No statistically significant differences were found between screening groups for changes in mean scores from pre-randomisation ($p = 0.142$). For the EarlyCDT®-positive and the control groups, mean scores at one, three, and six months were all significantly higher when compared with pre-randomisation scores. The control groups mean scores at 12 months were also significantly higher compared with pre-randomisation scores ($p = 0.001$). For the EarlyCDT®-negative group, mean scores at six and 12 months were significantly higher than at pre-randomisation. Model checking (see adjusted regression analysis section below) indicated residuals were not normally distributed and there was no constant variance hence the negative affect scale was transformed onto a logarithmic scale. Differences between means are therefore presented on the original scale, the logarithmic transformed scale and after anti-logging. Where there were significant differences, the absolute differences were small in magnitude.

Table 17. Unadjusted analyses comparing negative affect scores, logarithmic transformed scores, and anti-logged scores within groups (EarlyCDT®-positive, EarlyCDT®-negative, control) over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation scores

Screening group	Study time-point	Difference between the means (95% CI)	P value
Negative affect scores			
EarlyCDT®-positive	One month	1.14 (0.50 to 1.78)	P < 0.001
	Three month	0.89 (0.25 to 1.54)	P = 0.007
	Six month	0.66 (0.00 to 1.30)	P = 0.047
	12 month	0.68 (-0.00 to 1.37)	P = 0.052
EarlyCDT®-negative	One month	0.44 (-0.16 to 1.04)	P = 0.151
	Three month	0.50 (-0.11 to 1.11)	P = 0.107
	Six month	0.93 (0.31 to 1.55)	P = 0.003
	12 month	0.81 (0.19 to 1.44)	P = 0.011
Control	One month	1.04 (0.43 to 1.65)	P = 0.001
	Three month	1.60 (0.99 to 2.22)	P < 0.001
	Six month	1.00 (0.38 to 1.61)	P = 0.002
	12 month	1.08 (0.46 to 1.70)	P = 0.001

P value for whether changes from baseline differ between screening groups			P = 0.142
Logarithmic transformed negative affect scores			
EarlyCDT®-positive	One month	0.05 (0.02 to 0.09)	P = 0.001
	Three month	0.04 (0.00 to 0.07)	P = 0.027
	Six month	0.03 (-0.00 to 0.06)	P = 0.109
	12 month	0.03 (-0.01 to 0.06)	P = 0.165
EarlyCDT®-negative	One month	0.01 (-0.02 to 0.05)	P = 0.370
	Three month	0.02 (-0.01 to 0.05)	P = 0.225
	Six month	0.04 (0.00 to 0.07)	P = 0.014
	12 month	0.04 (0.00 to 0.07)	P = 0.018
Control	One month	0.06 (0.02 to 0.09)	P < 0.001
	Three month	0.08 (0.05 to 0.11)	P < 0.001
	Six month	0.05 (0.02 to 0.08)	P = 0.004
	12 month	0.05 (0.01 to 0.08)	P = 0.005
P value for whether changes from baseline differ between screening groups			P = 0.048

Anti-logged negative affect scores		
EarlyCDT®-positive	One month	1.05 (1.02 to 1.09)
	Three month	1.04 (1.00 to 1.07)
	Six month	1.03 (1.00 to 1.06)
	12 month	1.03 (0.99 to 1.06)
EarlyCDT®-negative	One month	0.01 (0.98 to 1.05)
	Three month	1.02 (0.99 to 1.05)
	Six month	1.04 (1.00 to 1.07)
	12 month	1.04 (1.00 to 1.07)
Control	One month	1.06 (1.02 to 1.09)
	Three month	1.08 (1.05 to 1.11)
	Six month	1.05 (1.02 to 1.08)
	12 month	1.05 (1.01 to 1.08)

Adjusted regression analyses

Results of the adjusted regression analyses for negative affect are presented in table 18. The first model was adjusted for ECLS minimisation variables. The statistically significant differences found between time points for each screening group mirror those of the unadjusted analyses (described above). The second model was adjusted for ECLS minimisation variables as well as additional variables. Again, the results for the second model reflect those of the unadjusted analyses, except the difference in mean scores between pre-randomisation and six months for the EarlyCDT®-positive group was no longer statistically significant (difference between the means 0.62, 95% CI -0.03 to 1.27, p = 0.062). Differences between the means are presented on the original scale, the logarithmic transformed scale and after anti-logging. As with the unadjusted analyses, where there were significant differences, the absolute differences were small in magnitude.

Model checking suggested residuals for the original negative affect score were not normally distributed and did not have constant variance. Models were rechecked after transforming the negative affect scale (see figures one to 16 (model 1) and 17 to 32 (model 2) in appendix 8), which indicated the transformation resulted in assumptions for undertaking linear regression being better met. Findings using the log transformed data were very similar to those using data on the original scale, except the change in mean scores between pre-randomisation and six months for the EarlyCDT®-positive group in the first model was no longer statistically significant.

Table 18. Adjusted analyses comparing negative affect scores, logarithmic transformed scores and anti-logged scores within groups (EarlyCDT®-positive, EarlyCDT®-negative, control) over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation scores

Screening group	Study time-point	Difference between the means* (95% CI)	P value	Difference between the means ** (95% CI)	P value
Negative affect scores					
EarlyCDT®-positive	One month	1.14 (0.50 to 1.78)	P < 0.001	1.11 (0.47 to 1.76)	P = 0.001
	Three month	0.89 (0.25 to 1.54)	P = 0.007	0.92 (0.27 to 1.57)	P = 0.005
	Six month	0.66 (0.00 to 1.30)	P = 0.047	0.62 (-0.03 to 1.27)	P = 0.062
	12 month	0.69 (-0.00 to 1.38)	P = 0.050	0.69 (-0.00 to 1.38)	P = 0.052
EarlyCDT®-negative	One month	0.44 (-0.16 to 1.04)	P = 0.152	0.33 (-0.27 to 0.94)	P = 0.283
	Three month	0.50 (-0.11 to 1.11)	P = 0.110	0.35 (-0.27 to 0.96)	P = 0.270
	Six month	0.93 (0.31 to 1.55)	P = 0.003	0.74 (0.11 to 1.36)	P = 0.021
	12 month	0.81 (0.19 to 1.44)	P = 0.011	0.79 (0.16 to 1.42)	P = 0.014
Control	One month	1.04 (0.43 to 1.65)	P = 0.001	1.11 (0.50 to 1.72)	P < 0.001
	Three month	1.60 (0.99 to 2.22)	P < 0.001	1.63 (1.02 to 2.25)	P < 0.001
	Six month	0.99 (0.38 to 1.61)	P = 0.001	1.03 (0.41 to 1.64)	P = 0.001
	12 month	1.08 (0.46 to 1.70)	P = 0.001	1.05 (0.43 to 1.68)	P = 0.001

P value for whether changes from baseline differ between screening groups			P = 0.141		P = 0.089
Logarithmic transformed negative affect scores					
EarlyCDT®-positive	One month	0.05 (0.02 to 0.09)	P = 0.001	0.05 (0.02 to 0.09)	P = 0.001
	Three month	0.04 (0.00 to 0.07)	P = 0.027	0.04 (0.00 to 0.07)	P = 0.005
	Six month	0.03 (-0.00 to 0.06)	P = 0.110	0.03 (-0.00 to 0.06)	P = 0.062
	12 month	0.03 (-0.01 to 0.06)	P = 0.161	0.03 (-0.01 to 0.06)	P = 0.052
EarlyCDT®-negative	One month	0.01 (-0.02 to 0.05)	P = 0.371	0.01 (-0.02 to 0.04)	P = 0.561
	Three month	0.02 (-0.01 to 0.05)	P = 0.230	0.01 (-0.02 to 0.04)	P = 0.488
	Six month	0.04 (0.00 to 0.07)	P = 0.014	0.03 (0.00 to 0.07)	P = 0.046
	12 month	0.04 (0.00 to 0.07)	P = 0.018	0.04 (0.00 to 0.07)	P = 0.027
Control	One month	0.06 (0.02 to 0.09)	P < 0.001	0.06 (0.03 to 0.09)	P < 0.001
	Three month	0.08 (0.05 to 0.11)	P < 0.001	0.08 (0.05 to 0.12)	P < 0.001
	Six month	0.05 (0.02 to 0.08)	P = 0.004	0.05 (0.02 to 0.08)	P = 0.003
	12 month	0.05 (0.01 to 0.08)	P = 0.005	0.04 (0.01 to 0.08)	P = 0.009

P value for whether changes from baseline differ between screening groups		P = 0.047	P = 0.026
Anti-logged negative affect scores			
EarlyCDT®-positive	One month	1.05 (1.02 to 1.09)	1.05 (1.02 to 1.09)
	Three month	1.04 (1.00 to 1.07)	1.04 (1.00 to 1.07)
	Six month	1.03 (1.00 to 1.06)	1.03 (1.00 to 1.06)
	12 month	1.03 (0.99 to 1.06)	1.03 (0.99 to 1.06)
EarlyCDT®-negative	One month	1.01 (0.98 to 1.05)	1.01 (0.98 to 1.04)
	Three month	1.02 (0.99 to 1.05)	1.01 (0.98 to 1.04)
	Six month	1.04 (1.00 to 1.07)	1.03 (1.00 to 1.07)
	12 month	1.04 (1.00 to 1.07)	1.04 (1.00 to 1.07)
Control	One month	1.06 (1.02 to 1.09)	1.06 (1.03 to 1.09)
	Three month	1.08 (1.05 to 0.11)	1.08 (1.05 to 0.12)
	Six month	1.05 (1.02 to 1.08)	1.05 (1.02 to 1.08)
	12 month	1.05 (1.01 to 1.08)	1.04 (1.01 to 1.08)

* Adjusted for ECLS minimisation variables and baseline value of outcome variable.

** Adjusted for ECLS minimisation variables, baseline value of outcome variable and additional variables

<u>Aim</u>: To explore how negative affect scores differ between the three screening groups across all time points and at each questionnaire time-point

As can be seen from table 16, pre-randomisation negative affect scores were very similar for all three groups. At the one, three, six and 12 month time-points, the control group had slightly higher (worse) negative affect scores than the EarlyCDT®-positive group and the EarlyCDT®-negative group. There were no statistically significant differences in negative affect scores between the groups at each study time-point.

<u>Unadjusted regression analyses</u>

The results of unadjusted linear regression analyses are presented in table 19. At the three month time-point, the mean negative affect scores were significantly lower in the EarlyCDT®-negative group compared with the control group (difference between the means 1.35, 95% CI -2.48 to -0.22, p = 0.019). No other statistically significant differences were found between the two groups across all time points or at the one, six and 12 month time-points. No statistically significant differences were found for mean negative affect scores between the EarlyCDT®-positive group and the control group, and between the EarlyCDT®-positive and the EarlyCDT®-negative group, at one, three, six and 12 months or across all time-points. Differences between means are presented on the original scale, the logarithmic transformed scale and after anti-logging (table 19). Where there were significant differences between scores, absolute differences were of a small magnitude.

In contrast to the original scale scores, logarithmic transformed negative affect scores varied significantly between screening groups over time (p = 0.028). As with the original scores, the

mean logarithmic transformed negative affect scores and the anti-logged negative affect scores were significantly lower in the EarlyCDT®-negative group compared with the control group at the three month time-point (logarithmic transformed score: -0.06 (95% CI -0.12 to -0.00), anti-logged score: 0.93 (95% CI 0.88 to 0.99)). Unlike the original score, the mean logarithmic transformed negative affect scores were significantly lower in the EarlyCDT®-positive group compared with the control group at the three month time-point (95% CI -0.12 to -0.00, p = 0.041).

Table 19. Unadjusted analyses comparing negative affect scores, logarithmic transformed scores and anti-logged scores between groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point

Screening group	Study time-point	Difference between the means (95% CI)	P value
Negative affect scores			
EarlyCDT®-negative *vs*. control	Across all time-points	-0.76 (-1.77 to 0.25)	P = 0.139
	One month	-0.83 (-1.95 to 0.29)	P = 0.147
	Three month	-1.35 (-2.48 to -0.22)	P = 0.019
	Six month	-0.24 (-1.38 to 0.89)	P = 0.673
	12 month	-0.55 (-1.69 to 0.59)	P = 0.343
EarlyCDT®-positive *vs*. control	Across all time-points	-0.76 (-1.79 to 0.28)	P = 0.153
	One month	-0.33 (-1.48 to 0.83)	P = 0.579
	Three month	-1.14 (-2.30 to 0.02)	P = 0.055
	Six month	-0.79 (-1.95 to 0.37)	P = 0.182
	12 month	-0.84 (-2.03 to 0.35)	P = 0.169

EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	0.00 (-1.03 to 1.03)	P = 0.994
	One month	0.50 (-0.64 to 1.65)	P = 0.391
	Three month	0.21 (-0.95 to 1.37)	P = 0.722
	Six month	-0.55 (-1.70 to 0.61)	P = 0.356
	12 month	-0.28 (-1.47 to 0.90)	P = 0.639
P value for whether differences in screening groups vary over time			P = 0.070
Logarithmic transformed negative affect scores			
EarlyCDT®-negative *vs*. control	Across all time-points	-0.04 (-0.09 to 0.02)	P = 0.187
	One month	-0.05 (-0.10 to 0.01)	P = 0.124
	Three month	-0.07 (-0.13 to -0.01)	P = 0.022
	Six month	-0.01 (-0.07 to 0.05)	P = 0.784
	12 month	-0.01 (-0.07 to 0.05)	P = 0.652
EarlyCDT®-positive *vs*. control	Across all time-points	-0.04 (-0.09 to 0.01)	P = 0.155
	One month	-0.02 (-0.08 to 0.04)	P = 0.522
	Three month	-0.06 (-0.12 to -0.00)	P = 0.041
	Six month	-0.04 (-0.10 to 0.02)	P = 0.211
	12 month	-0.04 (-0.10 to 0.02)	P = 0.223

EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	-0.00 (-0.06 to 0.05)	P = 0.889
	One month	0.03 (-0.03 to 0.09)	P = 0.390
	Three month	0.00 (-0.05 to 0.07)	P = 0.852
	Six month	-0.03 (-0.09 to 0.03)	P = 0.325
	12 month	-0.02 (-0.09 to 0.04)	P = 0.430
P value for whether differences in screening groups vary over time			P = 0.028
Anti-logged negative affect scores			
EarlyCDT®-negative *vs*. control	Across all time-points	0.96 (0.91 to 1.02)	
	One month	0.95 (0.90 to 1.01)	
	Three month	0.93 (0.88 to 0.99)	
	Six month	0.99 (0.93 to 1.05)	
	12 month	0.99 (0.93 to 1.05)	
EarlyCDT®-positive *vs*. control	Across all time-points	0.96 (0.91 to 1.01)	
	One month	0.98 (0.92 to 1.04)	
	Three month	0.94 (0.89 to 1.00)	
	Six month	0.96 (0.90 to 1.02)	
	12 month	0.96 (0.90 to 1.02)	

	Across all time-points	1.00 (0.94 to 1.05)
	One month	1.03 (0.97 to 1.09)
EarlyCDT®-positive *vs*. EarlyCDT®-negative	Three month	1.00 (0.95 to 1.07)
	Six month	0.97 (0.91 to 1.03)
	12 month	0.98 (0.91 to 1.04)

Adjusted regression analyses

Results of the adjusted regression analyses are presented in table 20. For the first model (adjusted for ECLS minimisation variables), differences in mean negative affect scores between screening groups did not vary over time (p = 0.120). Mean negative affect scores were significantly lower for the EarlyCDT®-negative group when compared with the control group across time (p = 0.023) and at the one (p = 0.032) and three (p = 0.003) month time-points. No statistically significant differences were found between the two groups at the six and 12 month time-points. The EarlyCDT®-positive group had significantly lower mean negative affect scores when compared with the control group at the three month time-point only (p = 0.037). No statistically significant differences were found for mean negative affect scores between the EarlyCDT®-positive and the EarlyCDT®-negative groups across time (p = 0.554) or at any of the four time-points. Results for the logarithmic transformed and anti-logged data reflect those for the original negative affect score. However, unlike the original score and anti-logged score, the mean logarithmic transformed negative affect scores were significantly higher in the EarlyCDT®-positive group compared with the EarlyCDT®-negative at the one month time-point.

For the second adjusted model (adjusted for ECLS minimisation variables and additional variables), differences in mean negative affect scores between screening groups did not vary over time (p = 0.085). Mean negative affect scores were significantly lower for the EarlyCDT®-negative group when compared with the control group across time (p = 0.043) and at the three (p = 0.003) month time-point. No statistically significant differences were found between the two groups at the one, six and 12 month time-points. No statistically significant differences were found in mean negative affect scores between the EarlyCDT®-positive group and control group across time (p = 0.490) or at any of the four time points. The EarlyCDT®-positive group had

significantly higher mean negative affect scores when compared with the EarlyCDT®-negative group at the one month time-point only (p = 0.037). No statistically significant differences were found between the two groups across time or at the three, six or 12 month time-points. Logarithmic transformed scores varied significantly between screening groups across time (p = 0.025). For the logarithmic transformed and anti-logged mean scores, the EarlyCDT®-negative group had significantly lower mean scores than the control group at the one and three month time-points. No statistically significant differences were found when the EarlyCDT®-positive group was compared with the control group across time and at each study time-point. The EarlyCDT®-positive group had significantly higher mean scores compared with the EarlyCDT®-negative group at the one month time-point only. Where there were significant differences between scores in either adjusted model, absolute differences were of a small magnitude.

- Model checking

The histograms, P-P plots, Q-Q plots and scatterplots for level one and level two residuals are shown for the original scale negative affect score and in the log transformed score in figures 33 to 48 (model one) and figures 49 to 64 (model 2) in appendix eight. These show that log transforming the data resulted in the assumptions for linear regression being better met. There were no large residual values for the log transformed scores.

Table 20. Adjusted analyses comparing negative affect scores, logarithmic transformed scores, and anti-logged scores between groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point

Screening group	Study time-point	Difference between the means* (95% CI)	P value	Difference between the means ** (95% CI)	P value
Negative affect scores					
EarlyCDT®-negative *vs.* Control	Across all time-points	-0.92 (-1.71 to -0.13)	P = 0.023	-0.72 (-1.42 to -0.02)	P = 0.043
	One month	-1.02 (-1.96 to -0.09)	P = 0.032	-0.84 (-1.69 to 0.02)	P = 0.056
	Three month	-1.44 (-2.38 to -0.50)	P = 0.003	-1.33 (-2.20 to -0.47)	P = 0.003
	Six month	-0.41 (-1.37 to 0.54)	P = 0.393	-0.28 (-1.15 to 0.60)	P = 0.533
	12 month	0.73 (-1.69 to 0.22)	P = 0.133	-0.37 (-1.25 to 0.51)	P = 0.413
EarlyCDT®-positive *vs.* Control	Across all time-points	-0.67 (-1.49 to 0.14)	P = 0.105	-0.25 (-0.97 to 0.47)	P = 0.490
	One month	-0.28 (-1.24 to 0.68)	P = 0.566	0.11 (-0.78 to 0.99)	P = 0.811
	Three month	-1.03 (-2.00 to -0.06)	P = 0.037	-0.61 (-1.51 to 0.28)	P = 0.179
	Six month	-0.70 (-1.67 to 0.27)	P = 0.160	-0.30 (-1.20 to 0.60)	P = 0.514
	12 month	-0.74 (-1.74 to 0.27)	P = 0.151	-0.26 (-1.19 to 0.67)	P = 0.581

EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	0.25 (-0.57 to 1.06)	P = 0.554	0.47 (-0.26 to 1.19)	P = 0.205
	One month	0.74 (-0.22 to 1.70)	P = 0.130	0.94 (0.06 to 1.83)	P = 0.037
	Three month	0.41 (-0.57 to 1.38)	P = 0.412	0.72 (-0.18 to 1.62)	P = 0.115
	Six month	-0.28 (-1.26 to 0.70)	P = 0.570	-0.02 (-0.93 to 0.89)	P = 0.965
	12 month	-0.00 (-1.01 to 1.00)	P = 0.999	0.11 (-0.83 to 1.04)	P = 0.822
P value for differences in means between time points			P = 0.120		P = 0.085
Logarithmic transformed negative affect scores					
EarlyCDT®-negative *vs*. Control	Across all time-points	-0.04 (-0.08 to -0.00)	P = 0.027	-0.03 (-0.07 to -0.00)	P = 0.056
	One month	-0.05 (-0.01 to -0.00)	P = 0.017	-0.05 (-0.09 to -0.00)	P = 0.033
	Three month	-0.07 (-0.12 to -0.03)	P = 0.002	-0.07 (-0.11 to -0.02)	P = 0.002
	Six month	-0.01 (-0.06 to 0.03)	P = 0.530	-0.01 (-0.05 to 0.04)	P = 0.718
	12 month	-0.02 (-0.06 to 0.03)	P = 0.417	-0.00 (-0.05 to 0.04)	P = 0.842
EarlyCDT®-positive *vs*. Control	Across all time-points	-0.02 (-0.60 to 0.01)	P = 0.211	-0.01 (-0.05 to 0.02)	P = 0.407
	One month	-0.00 (-0.05 to 0.04)	P = 0.817	-0.00 (-0.04 to 0.04)	P = 0.991
	Three month	-0.05 (-0.09 to -0.00)	P = 0.041	-0.04 (-0.08 to 0.00)	P = 0.098
	Six month	-0.02 (-0.07 to 0.03)	P = 0.374	-0.01 (-0.06 to 0.03)	P = 0.548
	12 month	-0.02 (-0.07 to 0.03)	P = 0.363	-0.01 (-0.06 to 0.04)	P = 0.667

EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	0.02 (-0.02 to 0.05)	P = 0.353	0.02 (-0.02 to 0.05)	P = 0.310
	One month	0.05 (0.00 to 0.09)	P = 0.036	0.05 (0.00 to 0.09)	P = 0.038
	Three month	0.02 (-0.02 to 0.07)	P = 0.316	0.03 (-0.01 to 0.08)	P = 0.180
	Six month	-0.00 (-0.05 to 0.04)	P = 0.789	-0.00 (-0.05 to 0.04)	P = 0.807
	12 month	-0.00 (-0.05 to 0.04)	P = 0.896	-0.00 (-0.05 to 0.04)	P = 0.812
P value for differences in means between time points			P = 0.04		P = 0.025
Anti-logged negative affect scores					
EarlyCDT®-negative *vs*. Control	Across all time-points	0.96 (0.92 to 1.00)		0.97 (0.93 to 1.00)	
	One month	0.95 (0.99 to 1.00)		0.95 (0.91 to 1.00)	
	Three month	0.93 (0.89 to 0.97)		0.93 (0.90 to 0.98)	
	Six month	0.99 (0.94 to 1.03)		0.99 (0.95 to 1.04)	
	12 month	0.98 (0.94 to 1.03)		1.00 (0.93 to 1.04)	
EarlyCDT®-positive *vs*. Control	Across all time-points	0.98 (0.55 to 1.01)		0.99 (0.95 to 1.02)	
	One month	1.00 (0.95 to 1.04)		1.00 (0.96 to 1.04)	
	Three month	0.95 (0.91 to 1.00)		0.96 (0.92 to 1.00)	
	Six month	0.98 (0.93 to 1.03)		0.99 (0.94 to 1.03)	
	12 month	0.98 (0.93 to 1.03)		0.99 (0.94 to 1.04)	

EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	1.02 (0.98 to 1.05)	1.02 (0.98 to 1.05)
	One month	1.05 (1.00 to 1.09)	1.05 (1.00 to 1.09)
	Three month	1.02 (0.98 to 1.07)	1.03 (0.99 to 1.08)
	Six month	1.00 (0.95 to 1.04)	1.00 (0.95 to 1.04)
	12 month	1.00 (0.95 to 1.04)	1.00 (0.95 to 1.04)

* Adjusted for ECLS minimisation variables and baseline value of outcome variable.

** Adjusted for ECLS minimisation variables, baseline value of outcome variable and additional variables

A brief summary of the main findings for the impact of screening on negative affect

Changes in negative affect scores within screening groups over time

- As hypothesised, statistically significant differences were found between time-points for both the EarlyCDT®-positive and control groups. However, it is very important to note that the absolute differences were small and could not be considered clinically important.
- For the EarlyCDT®-negative group, it was expected that there would be no significant change in negative affect scores over time. However, negative affect scores were significantly higher at six and 12 months when compared with pre-randomisation scores. It must be emphasised though that the increases in scores were very small.

Changes in negative affect scores between screening groups over time

- Results do not support what was hypothesised as no statistically significant differences were found between the EarlyCDT®-positive group and the EarlyCDT®-negative group across time and at each study time-point.
- As expected, when ECLS minimisation variables were adjusted for, the EarlyCDT®-negative group had significantly lower negative affect scores, when compared with the control group across time and at the one and three month time-points. However, when additional variables were adjusted for, it was found that scores between groups varied across all time-points and at the three month time-point only.
- Finally, it was hypothesised that there would be no statistically significant differences in negative affect scores between the EarlyCDT®-positive and control groups across time and at each study time-point. On the whole, results support this hypothesis. However, when

ECLS minimisation variables were adjusted for, the EarlyCDT®-positive group were found to have significantly lower sores at three months post-screening.

4.4.6. Outcome three: Frequency of worries about getting lung cancer

Aim: To investigate, within screening groups, how frequency of worries about getting lung cancer changed over time

Descriptive statistics for each screening group at each time-point are displayed in figure 13 and table 21. As can be seen in table 21, the proportion of participants in the EarlyCDT®-negative and control groups who reported that they were worried about getting lung cancer did not change substantially over time. A greater proportion of participants who received an EarlyCDT®-positive test result reported worry about lung cancer at one month post-screening (62.52%) compared with pre-randomisation (56.47%). The proportion reporting worry decreased slightly at three months (61.79%), increased again at six months (64.09%) and then decreased at 12 months (56.87%) post-screening. There were statistically significant differences in the proportion of participants who reported worry about getting lung cancer between study time-points for the EarlyCDT®-positive group only.

Table 21. Frequency of worries about getting lung cancer amongst participants in each screening group at each study time point

Study time-point	Total	EarlyCDT®-positive	EarlyCDT®-negative	Control	Results of statistical analyses comparing scores between groups at each time-point*
Pre-randomisation – N (%)					
Total	N = 1,026 [6]	N = 317 [4]	N = 360 [1]	N = 349 [1]	
Not worried	419 (40.84%)	138 (43.53%)	150 (41.67%)	131 (37.54%)	$\chi^2(2) = 2.63$
Worried	607 (59.16%)	179 (56.47%)	210 (58.33%)	218 (62.46%)	P = 0.268
One month					
Total	N = 1,000 [3]	N = 310 [1]	N = 341 [1]	N = 341 [1]	
Not worried	385 (38.50%)	110 (35.48%)	148 (42.41%)	127 (37.24%)	$\chi^2(2) = 3.67$
Worried	615 (61.50%)	200 (62.52%)	201 (57.59%)	214 (62.76%)	P = 0.16
Three month					
Total	N = 965 [1]	N = 301 [0]	N = 332 [1]	N = 332 [0]	
Not worried	387 (40.10%)	115 (38.21%)	147 (44.28%)	125 (37.65%)	$\chi^2(2) = 3.69$
Worried	578 (59.90%)	186 (61.79%)	185 (55.72%)	207 (62.35%)	P = 0.16
Six month					
Total	N = 948 [4]	N = 298 [0]	N = 321 [3]	N = 329 [1]	
Not worried	372 (39.24%)	107 (35.91%)	140 (43.61%)	125 (37.99%)	$\chi2(2) = 4.18$

Worried	576 (60.76%)	191 (64.09%)	181 (56.39%)	204 (62.01%)	P = 0.12
12 month					
Total	N = 873 [3]	N = 242 [1]	N = 313 [1]	N = 318 [1]	
Not worried	359 (41.12%)	102 (42.15%)	135 (43.13%)	122 (38.36%)	$\chi2(2) = 1.63$
Worried	514 (58.88%)	140 (57.85%)	178 (56.87%)	196 (61.64%)	P = 0.44
Results of statistical analyses comparing scores within each group across time**		P = 0.008	P = 0.739	P = 0.999	

[missing values]

* Pearson's chi-squared test

** Unadjusted logistic regression analysis

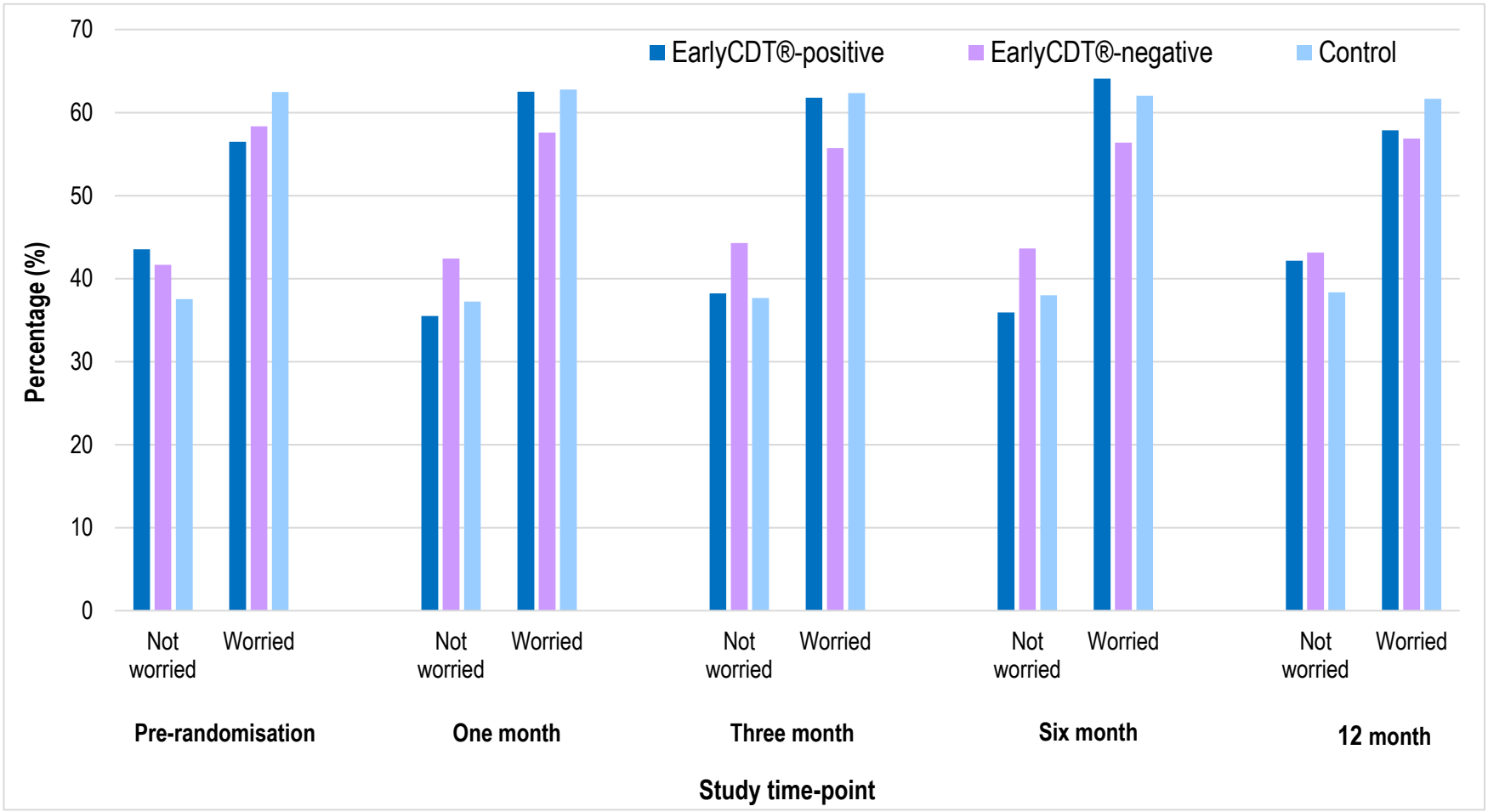


Figure 13. Frequency of worries about getting lung cancer amongst participants in each screening group (EarlyCDT®-positive, EarlyCDT®-negative, control) at each study time-point

Unadjusted and adjusted regression analyses

The results of unadjusted logistic regression analyses are presented in table 22. No statistically significant differences were found between screening groups from pre-randomisation ($p = 0.132$). No statistically significant differences in reported lung cancer worry over time were found for the EarlyCDT®-negative group or the control group. For the EarlyCDT®-positive group, the odds of reporting worry about getting lung cancer were significantly higher at one, three and six months post-screening than at pre-randomisation. No statistically significant difference was found in the odds of reporting worry between 12 months post-screening and pre-randomisation.

The results of the adjusted logistic regression analyses are presented in table 23. The first model was adjusted for ECLS minimisation variables. As with the unadjusted model, no statistically significant differences in reported lung cancer worry over time were found for the EarlyCDT®-negative group or the control group. For the EarlyCDT®-positive group, the odds of reporting worry about getting lung cancer were significantly higher at one, three and six months post-screening than at pre-randomisation. The second adjusted model was adjusted for ECLS minimisation variables as well as additional variables. Results mirror those of the first model. Again, no statistically significant differences in reported lung cancer worry over time were found for the EarlyCDT®-negative group or the control group. For the EarlyCDT®-positive group, the odds of reporting worry about getting lung cancer were significantly higher at one, three and six months post-screening than at pre-randomisation.

Table 22. Unadjusted analyses comparing frequency of worries about getting lung cancer within groups (EarlyCDT®-positive, EarlyCDT®-negative, control) over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation

Screening group	Study time-point	Odds ratio (95% CI)	P value
EarlyCDT®-positive	One month	2.17 (1.34 to 3.51)	P = 0.002
	Three month	1.71 (1.06 to 2.76)	P = 0.028
	Six month	2.15 (1.32 to 3.50)	P = 0.002
	12 month	1.32 (0.79 to 2.20)	P = 0.282
EarlyCDT®-negative	One month	0.94 (0.60 to 1.48)	P = 0.804
	Three month	0.75 (0.47 to 1.18)	P = 0.209
	Six month	0.82 (0.52 to 1.30)	P = 0.399
	12 month	0.83 (0.52 to 1.33)	P = 0.447
Control	One month	1.04 (0.65 to 1.66)	P = 0.877
	Three month	1.06 (0.66 to 1.69)	P = 0.818
	Six month	1.03 (0.64 to 1.66)	P = 0.891
	12 month	0.99 (0.61 to 1.59)	P = 0.959
P value for whether changes from baseline differ between screening groups			P = 0.132

Table 23. Adjusted analyses comparing frequency of worries about getting lung cancer within groups (EarlyCDT®-positive, EarlyCDT®-negative, control) over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation

		Odds ratio* (95% CI)	P value	Odds ratio ** (95% CI)	P value
Screening group	**Study time-point**				
EarlyCDT®-positive	One month	2.18 (1.35 to 3.53)	P = 0.001	2.25 (1.37 to 3.69)	P = 0.001
	Three month	1.73 (1.07 to 2.79)	P = 0.025	1.64 (1.00 to 2.67)	P = 0.049
	Six month	2.17 (1.33 to 3.54)	P = 0.002	2.20 (1.33 to 3.63)	P = 0.002
	12 month	1.33 (0.80 to 2.22)	P = 0.269	1.24 (0.74 to 2.09)	P = 0.417
EarlyCDT®-negative	One month	0.95 (0.60 to 1.48)	P = 0.808	0.97 (0.61 to 1.53)	P = 0.892
	Three month	0.75 (0.47 to 1.18)	P = 0.209	0.70 (0.44 to 1.12)	P = 0.141
	Six month	0.83 (0.52 to 1.31)	P = 0.418	0.75 (0.47 to 1.20)	P = 0.235
	12 month	0.84 (0.53 to 1.33)	P = 0.459	0.77 (0.48 to 1.23)	P = 0.272

Control	One month	1.04 (0.65 to 1.66)	P = 0.873	1.11 (0.68 to 1.79)	P = 0.680
	Three month	1.06 (0.66 to 1.70)	P = 0.799	1.09 (0.67 to 1.76)	P = 0.733
	Six month	1.04 (0.65 to 1.67)	P = 0.871	1.09 (0.67 to 1.77)	P = 0.718
	12 month	0.10 (0.62 to 1.61)	P = 0.986	1.05 (0.65 to 1.71)	P = 0.840
P value for whether changes from baseline differ between screening groups			P = 0.128		P = 0.098

* Adjusted for ECLS minimisation variables and baseline value of outcome variable

** Adjusted for ECLS minimisation variables, baseline value of outcome variable and additional variables

<u>Aim</u>: To explore how frequency of worries about getting lung cancer differ between the three screening groups across all time points and at each questionnaire time-point

As shown in table 21, no statistically significant differences were found between the proportion of participants in each screening group who reported worry about getting lung cancer at each study time-point.

The results of unadjusted regression analyses are presented in table 24. Differences between screening groups did not vary significantly over time (p = 0.672). No statistically significant differences in the odds of reporting worry about getting lung cancer were found between the EarlyCDT®-positive group and the control group across all time-points (p = 0.996) and at each study time-point. The odds of reporting worry about getting lung cancer were 46% lower in the EarlyCDT®-negative group compared to the control group across all time-points (95% CI 0.30 to 1.00, p = 0.048). At three months post-screening, the odds of reporting worry about getting lung cancer were 54% lower in the EarlyCDT®-negative group compared to the control group (95% CI 0.22 to 0.97, p = 0.042). No statistically significant differences in the odds of reporting worry were found between the EarlyCDT®-negative group and the control group at the one, six or 12 month time-points. At three months post-screening, the odds of reporting lung cancer worry were 2.23 times higher in the EarlyCDT®-positive group compared with the EarlyCDT®-negative group (95% CI 1.04 to 4.79, p = 0.041). No other statistically significant differences were found between the EarlyCDT®-positive group and the EarlyCDT®-negative group across all study time-points and at the one, three and 12 month time-points.

The results of the adjusted logistic regression analyses are presented in table 25. When ECLS minimisation variables were adjusted for (model one), differences between screening groups

still did not vary significantly over time (p = 0.757). As with the unadjusted model, no statistically significant differences in the odds of reporting worry about getting lung cancer were found between the EarlyCDT®-positive group and the control group across all time-points (p = 0.263) and at each study time-point. The odds of reporting worry about getting lung cancer were still 46% lower in the EarlyCDT®-negative group compared to the control group across all time-points (95% CI 0.34 to 0.88, p = 0.013). At three months post-screening, the odds of reporting worry about getting lung cancer were 54% lower for the EarlyCDT®-negative group compared to the control group (95% CI 0.24 to 0.88, p = 0.019). In contrast with the unadjusted model, when ECLS minimisation variables were adjusted for, the odds of reporting lung cancer worry were significantly higher for the EarlyCDT®-positive group compared with the EarlyCDT®-negative group across time (p < 0.001) and at the one, three and six month time-points. No statistically significant differences in the odds of reporting worry were found between the two groups at 12 months post-screening.

Results for model two (where ECLS minimisation variables and additional variables were adjusted for), reflect model one. The only difference between the two models was where the odds of reporting lung cancer worry were found to be 49% lower for the EarlyCDT®-negative group compared to the control group at three months post-screening (95% CI 0.27 to 0.97, p = 0.040).

Table 24. Unadjusted analyses comparing frequency of worries about getting lung cancer between screening groups across all study time-points and at each study time-point

Screening group	Study time-point	Odds ratio (95% CI)	P value
EarlyCDT®-negative *vs*. Control	Across all time-points	0.54 (0.30 to 1.00)	P = 0.048
	One month	0.60 (0.29 to 1.26)	P = 0.180
	Three month	0.46 (0.22 to 0.97)	P = 0.042
	Six month	0.53 (0.25 to 1.13)	P = 0.099
	12 month	0.58 (0.27 to 1.23)	P = 0.153
EarlyCDT®-positive *vs*. Control	Across all time-points	1.00 (0.54 to 1.86)	P = 0.996
	One month	1.21 (0.57 to 2.59)	P = 0.618
	Three month	0.91 (0.42 to 1.94)	P = 0.804
	Six month	1.19 (0.55 to 2.56)	P = 0.659
	12 month	0.71 (0.32 to 1.56)	P = 0.391
EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	1.84 (0.99 to 3.42)	P = 0.055
	One month	2.00 (0.94 to 4.26)	P = 0.070
	Three month	1.96 (0.92 to 4.19)	P = 0.081
	Six month	2.23 (1.04 to 4.79)	P = 0.041
	12 month	1.22 (0.56 to 2.69)	P = 0.614

P value for whether differences in screening groups vary over time	P = 0.672

Table 25. Adjusted analyses comparing frequency of worries about getting lung cancer between screening groups across all study time-points and at each study time-point

		Odds ratio* (95% CI)	P value	Odds ratio ** (95% CI)	P value
Screening group	**Study time-point**				
EarlyCDT®-negative *vs*. Control	Across all time-points	0.54 (0.34 to 0.88)	P = 0.013	0.54 (0.34 to 0.87)	P = 0.011
	One month	0.62 (0.33 to 1.18)	P = 0.144	0.67 (0.35 to 1.26)	P = 0.211
	Three month	0.46 (0.24 to 0.88)	P = 0.019	0.47 (0.25 to 0.90)	P = 0.022
	Six month	0.53 (0.22 to 2.32)	P = 0.057	0.51 (0.27 to 0.97)	P = 0.040
	12 month	0.57 (0.29 to 1.09)	P = 0.090	0.54 (0.28 to 1.04)	P = 0.066
EarlyCDT®-positive *vs*. Control	Across all time-points	1.32 (0.81 to 2.18)	P = 0.263	1.35 (0.83 to 2.21)	P = 0.224
	One month	1.61 (0.83 to 3.12)	P = 0.157	1.69 (0.87 to 3.28)	P = 0.123
	Three month	1.16 (0.60 to 2.25)	P = 0.656	1.21 (0.62 to 2.34)	P = 0.576
	Six month	1.59 (0.81 to 3.10)	P = 0.177	1.65 (0.85 to 3.23)	P = 0.142
	12 month	0.99 (0.50 to 1.99)	P = 0.987	0.95 (0.47 to 1.90)	P = 0.886

EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	2.44 (1.49 to 4.00)	P < 0.001	2.49 (1.53 to 4.06)	P < 0.001
	One month	2.59 (1.35 to 4.97)	P = 0.004	2.53 (1.31 to 4.87)	P = 0.005
	Three month	2.52 (1.31 to 4.86)	P = 0.006	2.56 (1.33 to 4.94)	P = 0.005
	Six month	2.97 (1.53 to 5.80)	P = 0.001	3.26 (1.67 to 6.35)	P = 0.001
	12 month	1.75 (0.88 to 3.48)	P = 0.111	1.76 (0.88 to 3.50)	P = 0.109
P value for whether differences in screening groups vary over time			P = 0.757		P = 0.638

* Adjusted for ECLS minimisation variables and baseline value of outcome variable.

** Adjusted for ECLS minimisation variables, baseline value of outcome variable and additional variables

A brief summary of the main findings for the impact of screening on frequency of worries about getting lung cancer

Changes within screening groups over time

- As hypothesised, when compared with pre-randomisation, the proportion of participants in the EarlyCDT®-positive group who reported worry about getting lung cancer was significantly higher at the one, three and six month time-points. At 12 months post-screening, the proportion reporting worry was almost the same as at pre-randomisation.
- No statistically significant differences were found in scores over time for the EarlyCDT®-negative group, which was expected. However, for the control group, scores over time did not change significantly either, which does not support the hypothesis.

Changes between screening groups over time

- As hypothesised, no statistically significant differences were found between the EarlyCDT®-positive and control groups across time or at each study time-point.
- Compared with the EarlyCDT®-negative group, a significantly higher proportion of the EarlyCDT®-positive group reported worry about lung cancer across all time-points and at one, three, and six months post-screening. There were no statistically significant differences between the two groups at 12 months.
- When the EarlyCDT®-negative group and the control group were compared, the odds of reporting lung cancer worry were significantly lower in the EarlyCDT®-negative group across all time-points and at three months post-screening only.

4.4.7. Outcome four: Anxiety about the results of future tests/treatment

Aim: To investigate, within groups, how level of anxiety about the results of future tests/treatment changed over time

Descriptive statistics for each screening group at each time-point are displayed in figure 14 and table 26. As can be seen in table 26, the proportion of participants in the EarlyCDT®-positive group who reported anxiety about the results of future tests/treatment was lowest at pre-randomisation (8.20%) and increased substantially at one month (23.55%). Reported anxiety decreased at three months (18.33%) and plateaued over the six (18.24%) and 12 month (18.18%) time-points. For the EarlyCDT®-negative and control groups, the proportion reporting anxiety about future tests/treatment was lowest at pre-randomisation and then increased steadily over the one, three, six and 12 month time-points. The changes in scores over time for each screening group were statistically significant.

Table 26. Current level of anxiety about the results of future tests/treatment amongst participants in each screening group at each study time point

Study time-point	Total	EarlyCDT®-positive	EarlyCDT®-negative	Control	Results of statistical analyses comparing scores between groups at each time-point*
Pre-randomisation – N (%)	N = 1, 025 [7]	N = 317 [4]	N = 361 [0]	N = 347 [3]	
Not anxious	925 (90.24%)	291 (91.80%)	320 (88.64%)	314 (90.49%)	$\chi^2(2) = 1.94$
Anxious	100 (9.76%)	26 (8.20%)	41 (11.36%)	33 (9.51%)	P = 0.378
One month					
Total	N = 999 [4]	N = 310 [1]	N = 348 [2]	N = 341 [1]	
Not anxious	827 (82.78%)	237 (76.45%)	301 (86.49%)	289 (84.75%)	$\chi^2(2) = 13.00$
Anxious	172 (17.22%)	73 (23.55%)	47 (13.51%)	52 (15.25%)	P = 0.001
Three month					
Total	N = 962 [4]	N = 300 [1]	N = 331 [2]	N = 331 [1]	
Not anxious	798 (82.95%)	245 (81.67%)	278 (83.99%)	275 (83.08%)	$\chi^2(2) = 0.61$
Anxious	164 (17.05%)	55 (18.33%)	53 (16.01%)	56 (16.92%)	P = 0.74
Six month					
Total	N = 943 [9]	N = 296 [2]	N = 321 [3]	N = 326 [4]	

Not anxious	772 (81.87%)	242 (81.76%)	261 (81.31%)	269 (82.52%)	$\chi^2(2) = 0.16$
Anxious	171 (18.13%)	54 (18.24%)	60 (18.69%)	57 (17.48%)	P = 0.92
12 month					
Total	N = 868 [8]	N = 242 [1]	N = 310 [4]	N = 316 [3]	
Not anxious	693 (79.84%)	198 (81.82%)	247 (79.68%)	248 (78.48%)	$\chi^2(2) = 0.96$
Anxious	175 (20.16%)	44 (18.18%)	63 (20.32%)	68 (21.52%)	P = 0.62
Results of statistical analyses comparing scores within each group over time*		P < 0.001	P < 0.001	P < 0.001	

[missing values]

* Pearson's chi-squared test

** Unadjusted regression analysis

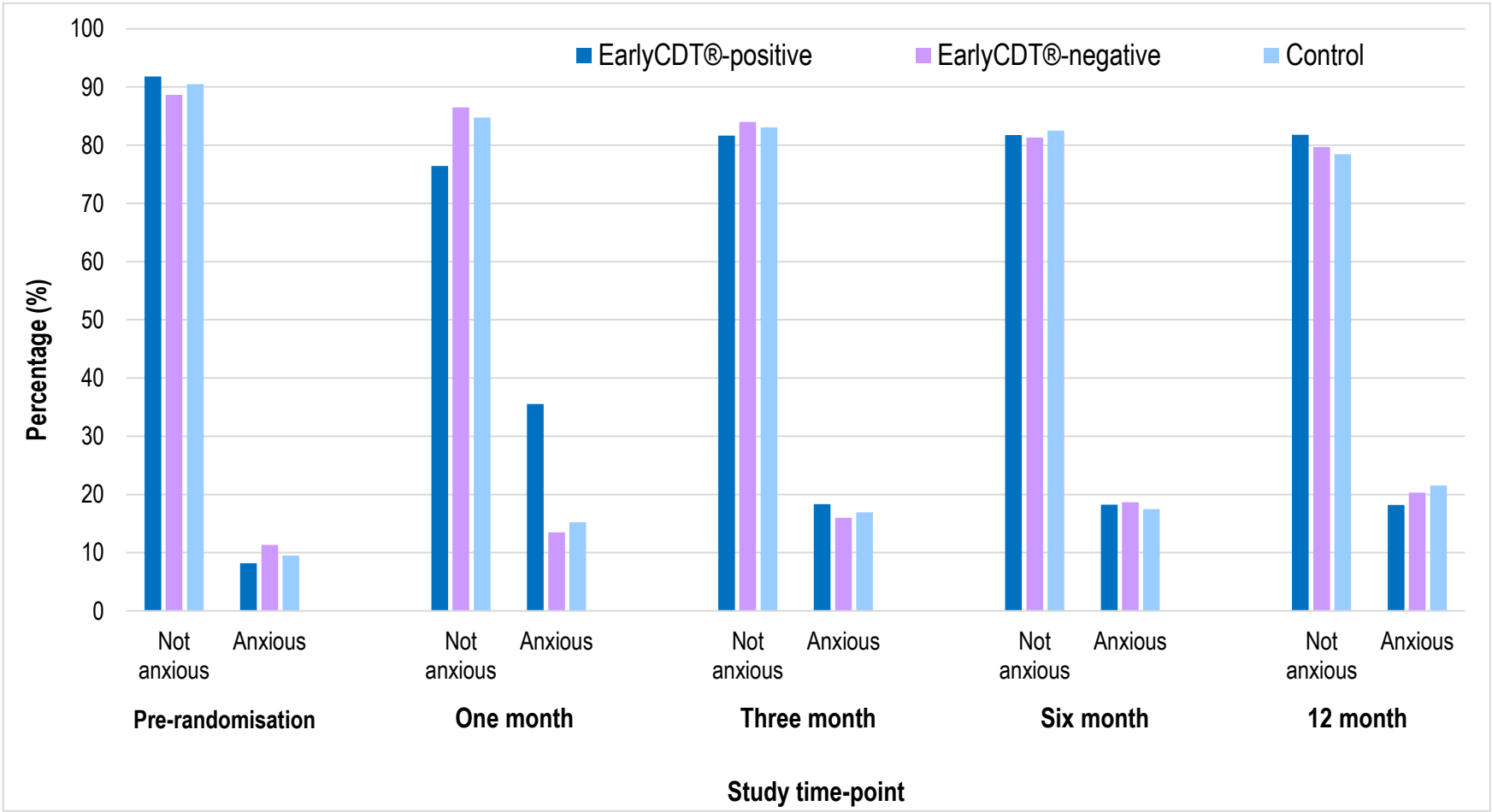


Figure 14. Current level of anxiety about the results of future tests/treatment amongst participants in each screening group (EarlyCDT®-positive, EarlyCDT®-negative, control) at each study time-point

Unadjusted and adjusted regression analyses

The results of unadjusted logistic regression analyses are presented in table 27. Statistically significant differences were found between screening groups from pre-randomisation ($p = 0.001$). For the EarlyCDT®-positive group and control group, the odds of reporting anxiety about the results of future tests/treatment were significantly higher at the one, three, six and 12 month time-points compared with levels at pre-randomisation. For the EarlyCDT®-negative group, no significant difference in the odds of reporting anxiety was found between one month post-screening and pre-randomisation ($p = 0.225$). However, the odds of reporting anxiety were significantly higher at the three, six and 12 month time-points (table 27). The results of the adjusted logistic regression analyses are presented in table 28. Results for both models mirror those of the unadjusted model.

Table 27. Unadjusted analyses comparing current level of anxiety about the results of future tests/treatment within screening groups over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation

Screening group	Study time-point	Odds ratio (95% CI)	P value
EarlyCDT®-positive	One month	9.50 (4.87 to 18.52)	P < 0.001
	Three month	5.21 (2.65 to 10.28)	P < 0.001
	Six month	5.27 (2.66 to 10.41)	P < 0.001
	12 month	5.39 (2.62 to 11.08)	P < 0.001
EarlyCDT®-negative	One month	1.45 (0.79 to 2.66)	P = 0.225
	Three month	2.10 (1.15 to 3.83)	P = 0.016
	Six month	2.93 (1.61 to 5.31)	P < 0.001
	12 month	3.40 (1.88 to 6.17)	P < 0.001
Control	One month	2.76 (1.46 to 5.20)	P = 0.002
	Three month	3.54 (1.87 to 6.69)	P < 0.001
	Six month	3.86 (2.05 to 7.30)	P < 0.001
	12 month	6.12 (3.25 to 11.52)	P < 0.001
P value for whether changes from baseline differ between screening groups			P = 0.001

Table 28. Adjusted analyses comparing current level of anxiety about the results of future tests/treatment within groups (EarlyCDT®-positive, EarlyCDT®-negative, control) over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation

		Odds ratio* (95% CI)	P value	Odds ratio ** (95% CI)	P value
Screening group	**Study time-point**				
EarlyCDT®-positive	One month	9.36 (4.82 to 18.18)	P < 0.001	9.28 (4.73 to 18.20)	P < 0.001
	Three month	5.18 (2.64 to 10.18)	P < 0.001	5.13 (2.59 to 10.16)	P < 0.001
	Six month	5.21 (2.64 to 10.27)	P < 0.001	4.92 (2.47 to 9.79)	P < 0.001
	12 month	5.36 (2.61 to 10.98)	P < 0.001	5.57 (2.69 to 11.52)	P < 0.001
EarlyCDT®-negative	One month	1.45 (0.79 to 2.66)	P = 0.225	1.62 (0.87 to 2.99)	P = 0.126
	Three month	2.09 (1.15 to 3.81)	P = 0.016	2.15 (1.17 to 3.97)	P = 0.014
	Six month	2.93 (1.62 to 5.32)	P < 0.001	3.02 (1.64 to 5.54)	P < 0.001
	12 month	3.40 (1.88 to 6.17)	P < 0.001	3.38 (1.84 to 6.22)	P < 0.001

Control	One month	2.76 (1.46 to 5.22)	P = 0.002	2.80 (1.45 to 5.38)	P = 0.002
	Three month	3.57 (1.89 to 6.74)	P < 0.001	3.42 (1.77 to 6.59)	P < 0.001
	Six month	3.91 (2.07 to 7.38)	P < 0.001	4.09 (2.13 to 7.88)	P < 0.001
	12 month	6.22 (3.30 to 11.72)	P < 0.001	6.15 (3.21 to 11.80)	P < 0.001
P value for whether changes from baseline differ between screening groups			P = 0.002		P = 0.006

* Adjusted for ECLS minimisation variables and baseline value of outcome variable.

** Adjusted for ECLS minimisation variables, baseline value of outcome variable and additional variables

<u>Aim</u>: To explore how anxiety about the results of future tests/treatment differ between the three screening groups across all time points and at each questionnaire time-point

As shown in table 26, at one month post-randomisation, the proportion of participants in the EarlyCDT®-positive group who reported anxiety about the results of future tests/treatment (23.55%) was significantly higher than that of participants in the EarlyCDT®-negative group (13.51%) and the control group (15.25%), p = 0.001. The proportion of participants in each of the three groups who reported anxiety was similar at the three, six and 12 month time-points and therefore not statistically significant.

The results of unadjusted regression analyses are presented in table 29. Differences between screening groups varied significantly over time (p = 0.006). No statistically significant differences in the odds of reporting anxiety about the results of future tests/treatment were found between the EarlyCDT®-negative group and the control group across all time-points (p = 0.545) and at each study time-point. At one month post-screening, the odds of reporting anxiety were 3.08 times higher in the EarlyCDT®-positive group compared with the control group (95% CI 1.43 to 6.66, p = 0.004). No statistically significant differences in the odds of reporting anxiety about the results of future tests/treatment were found between the EarlyCDT®-positive group and the control group across all time-points (p = 0.247) and at the three, six and 12 month time-points. At one month post-screening, the odds of reporting anxiety were 4.21 times higher in the EarlyCDT®-positive group compared with the EarlyCDT®-negative group (95% CI 1.92 to 9.27, p < 0.001). No other statistically significant differences were found between the EarlyCDT®-positive group and the EarlyCDT®-negative group across all study time-points and at the three, six and 12 month time-points.

The results of the adjusted logistic regression analyses are presented in table 30. When ECLS minimisation variables were adjusted for (model one), differences between screening groups varied significantly over time (p = 0.004). As with the unadjusted model, no statistically significant differences in the odds of reporting anxiety about the results of future tests/treatment were found between the EarlyCDT®-negative group and the control group across all time-points (p = 0.211) and at each study time-point. At one month post-screening, the odds of reporting anxiety were 3.54 times higher in the EarlyCDT®-positive group compared with the control group (95% CI 1.70 to 7.39, p = 0.001). No statistically significant differences in the odds of reporting anxiety about the results of future tests/treatment were found between the EarlyCDT®-positive group and the control group across all time-points (p = 0.091) and at the three, six and 12 month time-points. In contrast with the unadjusted model, the odds of reporting anxiety were 2.25 times higher for the EarlyCDT®-positive group compared with the EarlyCDT®-negative group across all time-points (95% CI 1.30 to 3.91, p = 0.004). At one month post-screening, the odds of reporting anxiety were 5.75 times higher in the EarlyCDT®-positive group compared with the EarlyCDT®-negative group (95% CI 2.70 to 12.26, p < 0.001). No statistically significant differences in anxiety were found between the EarlyCDT®-positive group and the EarlyCDT®-negative group at the three, six and 12 month time-points. The results for model two (where ECLS minimisation variables and additional variables were adjusted for), mirror those of model one (table 30).

Table 29. Unadjusted analyses comparing current level of anxiety about the results of future tests/treatment between screening groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point

Screening group	Study time-point	Odds ratio (95% CI)	P value
EarlyCDT®-negative *vs*. Control	Across all time-points	0.84 (0.47 to 1.50)	P = 0.545
	One month	0.73 (0.33 to 1.64)	P = 0.448
	Three month	0.82 (0.37 to 1.80)	P = 0.616
	Six month	1.06 (0.49 to 2.29)	P = 0.890
	12 month	0.77 (0.36 to 1.63)	P = 0.489
EarlyCDT®-positive *vs*. Control	Across all time-points	1.42 (0.79 to 2.55)	P = 0.247
	One month	3.08 (1.43 to 6.66)	P = 0.004
	Three month	1.26 (0.58 to 2.77)	P = 0.558
	Six month	1.19 (0.54 to 2.61)	P = 0.664
	12 month	0.75 (0.34 to 1.67)	P = 0.482
EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	1.70 (0.94 to 3.07)	P = 0.081
	One month	4.21 (1.92 to 9.27)	P < 0.001
	Three month	1.55 (0.70 to 3.44)	P = 0.283
	Six month	1.13 (0.51 to 2.48)	P = 0.766
	12 month	0.98 (0.43 to 2.21)	P = 0.960

P value for whether differences in screening groups vary over time	P = 0.006

Table 30. Adjusted analyses comparing current level of anxiety about the results of future tests/treatment between groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point

		Odds ratio* (95% CI)	P value	Odds ratio ** (95% CI)	P value
Screening group	**Study time-point**				
EarlyCDT®-negative *vs*. Control	Across all time-points	0.71 (0.41 to 1.22)	P = 0.211	0.83 (0.49 to 1.41)	P = 0.496
	One month	0.62 (0.28 to 1.34)	P = 0.221	0.77 (0.36 to 1.66)	P = 0.512
	Three month	0.69 (0.32 to 1.47)	P = 0.334	0.84 (0.40 to 1.79)	P = 0.658
	Six month	0.90 (0.43 to 1.90)	P = 0.788	1.00 (0.48 to 2.09)	P = 0.991
	12 month	0.64 (0.31 to 1.33)	P = 0.235	0.73 (0.36 to 1.51)	P = 0.402
EarlyCDT®-positive *vs*. Control	Across all time-points	1.60 (0.93 to 2.74)	P = 0.091	1.85 (1.09 to 3.13)	P = 0.023
	One month	3.54 (1.70 to 7.39)	P = 0.001	4.06 (1.95 to 8.46)	P < 0.001
	Three month	1.45 (0.68 to 3.06)	P = 0.337	1.76 (0.83 to 3.73)	P = 0.141
	Six month	1.33 (0.63 to 2.81)	P = 0.461	1.40 (0.66 to 2.96)	P = 0.378
	12 month	0.82 (0.38 to 1.78)	P = 0.619	1.03 (0.48 to 2.21)	P = 0.948

EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	2.25 (1.30 to 3.91)	P = 0.004	2.21 (1.30 to 3.78)	P = 0.004
	One month	5.75 (2.70 to 12.26)	P < 0.001	5.25 (2.49 to 11.05)	P < 0.001
	Three month	2.10 (0.98 to 4.52)	P = 0.057	2.08 (0.98 to 4.43)	P = 0.056
	Six month	1.47 (0.69 to 3.12)	P = 0.317	1.39 (0.66 to 2.94)	P = 0.383
	12 month	1.28 (0.58 to 2.80)	P = 0.543	1.40 (0.64 to 3.05)	P = 0.401
P value for whether differences in screening groups vary over time			P = 0.004		P = 0.012

* Adjusted for ECLS minimisation variables and baseline value of outcome variable.

** Adjusted for ECLS minimisation variables, baseline value of outcome variable and additional variables

A brief summary of the main findings for the impact of screening on current level of anxiety about the results of future tests/treatment

Changes within screening groups over time

- The proportion of participants in each of the three screening groups who reported anxiety was significantly higher at one, three, six and 12 months post-screening when compared with pre-randomisation.
- As well as being statistically significant, this finding is clinically important, particularly for the EarlyCDT®-positive group, where the proportion of participants who reported anxiety increased by 27.35% between pre-randomisation and one month post-screening.

Changes between screening groups over time

- In contrast to what was expected, no statistically significant differences in reported anxiety were found between the EarlyCDT®-negative group and the control group across all time-points or at each time-point.
- Analyses identified significant increases in the odds of reporting anxiety for the EarlyCDT®-positive group when compared with the EarlyCDT®-negative group across time and at one month post-screening only.
- The EarlyCDT®-positive group had a significantly higher odds of reporting anxiety compared with the control group across time and at one month post-screening when ECLS minimisation variables and additional variables were adjusted for.

4.4.8. Outcome five: The extent to which lung cancer worry impacts mood and ability to perform daily activities

Aim: To investigate, within screening groups, how impact of lung cancer worry on mood and ability to perform daily activities scores changed over time

Descriptive statistics for impact of lung cancer worry scales for each screening group at each study time-point are displayed in figure 15 and table 31. As can be seen from figure 15 and table 31, scores were for all three screening groups were lowest at pre-randomisation. For the EarlyCDT®-positive group, scores increased a little at one month and decreased slightly over three, six and 12 month time-points. For the EarlyCDT®-negative group, scores increased slightly at one month, decreased a little at three months and then increased slightly over the six and 12 month time-points. The control group's scores increased over all time-points. Changes in scores over time were statistically significant for all three groups.

Table 31. Impact of lung cancer worry on mood and ability to perform daily activities amongst participants in each screening group

Study time-point	Total	EarlyCDT®-positive	EarlyCDT®-negative	Control	Results of statistical analyses comparing scores between groups at each time-point***
Pre-randomisation	N = 1, 021 [11]	N = 317 [4]	N = 358 [3]	N = 346 [4]	$\chi^2(2) = 2.76$
(median, IQR*)	3 (2-3)	2 (2-3)	3 (2-4)	2 (2-3)	P = 0.252
(mean, sd**)	3.03 (1.45)	2.97 (1.37)	3.11 (1.49)	3.01 (1.48)	
	N = 999 [4]	N = 309 [2]	N = 349 [1]	N = 341 [1]	$\chi^2(2) = 2.42$
One month	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	P = 0.300
	3.31 (1.62)	3.39 (1.62)	3.27 (1.62)	3.28 (1.63)	
	N = 963 [3]	N = 299 [2]	N = 332 [1]	N = 332 [0]	$\chi^2(2) = 3.07$
Three month	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	P = 0.216
	3.27 (1.62)	3.34 (1.63)	3.17 (1.62)	3.31 (1.60)	
	N = 942 [10]	N = 295 [3]	N = 322 [2]	N = 325 [5]	$\chi^2(2) = 0.24$
Six month	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	P = 0.889
	3.30 (1.65)	3.29 (1.60)	3.30 (1.69)	3.30 (1.64)	

12 month	N = 868 [8] 3 (2-4) 3.30 (1.68)	N = 243 [0] 3 (2-4) 3.20 (1.68)	N = 310 [4] 3 (2-4) 3.32 (1.77)	N = 315 [4] 3 (2-4) 3.35 (1.60)	$\chi^2(2) = 3.88$ P = 0.144
Results of statistical analyses comparing scores within each group over time****		P < 0.001	P = 0.032	P < 0.001	

[missing values]

* IQR = Interquartile range

**sd = standard deviation

*** Kruskal–Wallis test

**** Unadjusted regression analysis

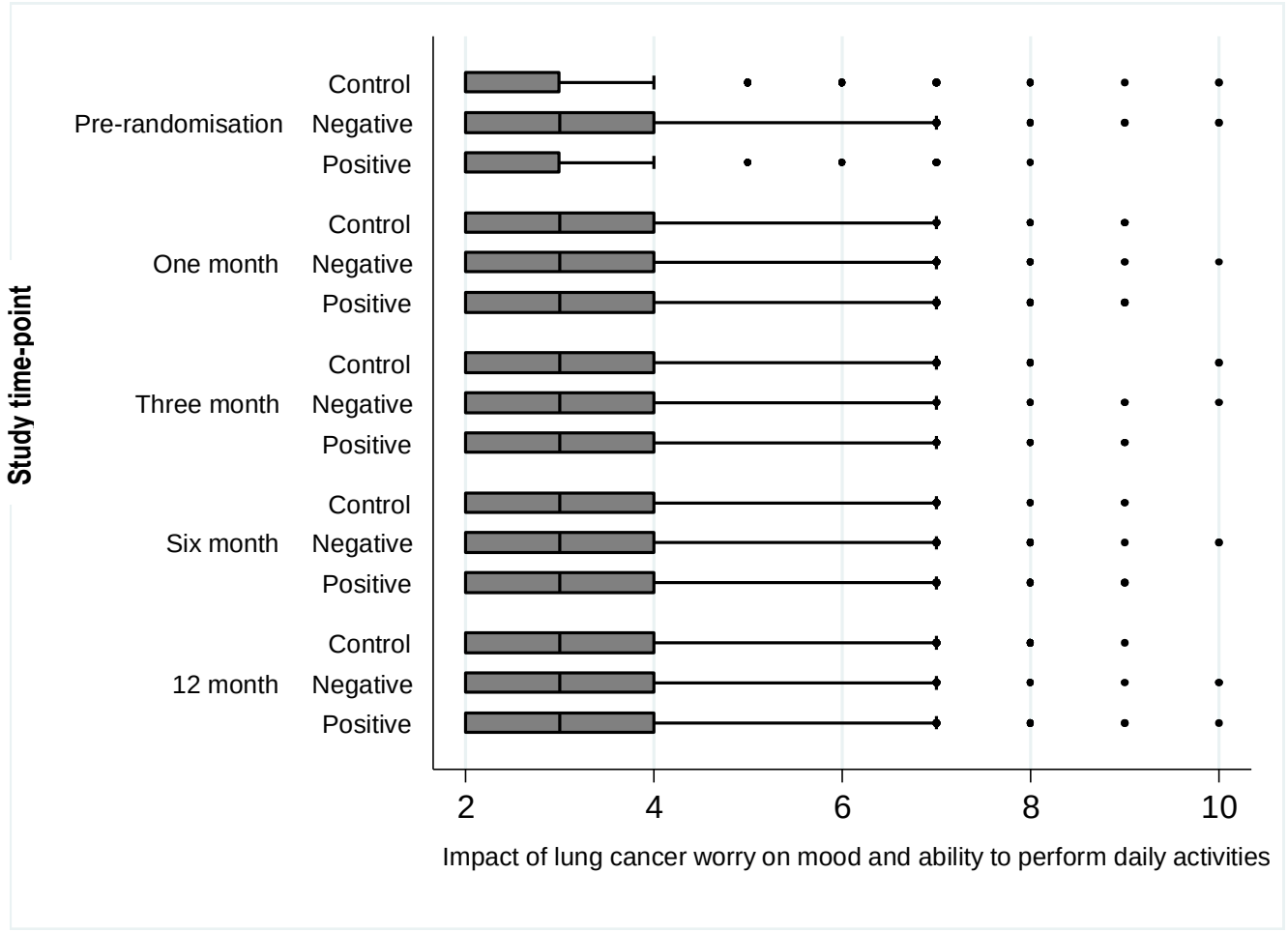


Figure 15. Impact of lung cancer worry scores amongst participants in each screening group at each study time-point

Unadjusted regression analyses

The results of unadjusted regression analyses are presented in table 32. No statistically significant differences were found between screening groups for changes in mean scores from pre-randomisation ($p = 0.048$). For the EarlyCDT®-positive and the control groups, mean scores at one, three, six and 12 months were all significantly higher when compared with pre-randomisation scores. For the EarlyCDT®-negative group, mean scores at one, six and 12 months were significantly higher than at pre-randomisation. It is important to note that where there were significant differences, the absolute differences were small in magnitude. Model checking (see below) indicated model assumptions were better met using logarithmic transformed data, hence findings are presented for data on the original scale, the log transformed scale and for anti-logged data. Findings were similar for original scale data, log transformed data and anti-logged data.

Adjusted regression analyses

Results of adjusted regression analyses are presented in table 33. When ECLS minimisation variables (model one) were adjusted for, the statistically significant differences found between time points for each screening group were the same as those of the unadjusted analyses (described above). When additional variables were also adjusted for (model two), the results still reflected those of the unadjusted analyses. Again, where there were significant differences, the absolute differences were small in magnitude. The results of adjusted analyses for the logarithmic transformed negative affect scores and the anti-logged negative affect scores are presented in table 33. Findings were similar for original scale data, log transformed data and anti-logged data.

- Model checking

Model checking for the log transformed data models showed assumptions for linear regression were met. There were no large value level one or level two residuals for either model using the log transformed data (residuals were < 1.5 and < -1.5).

Table 32. Unadjusted analyses comparing impact of lung cancer worry scores, logarithmic transformed scores, and anti-logged scores within screening groups over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation

Screening group	Study time-point	Difference between the means (95% CI)	P value
Impact of lung cancer worry scores			
EarlyCDT®-positive	One month	0.42 (0.27 to 0.56)	P < 0.001
	Three month	0.38 (0.23 to 0.53)	P < 0.001
	Six month	0.34 (0.20 to 0.49)	P < 0.001
	12 month	0.27 (0.11 to 0.43)	P = 0.001
EarlyCDT®-negative	One month	0.16 (0.02 to 0.30)	P = 0.021
	Three month	0.08 (-0.06 to 0.22)	P = 0.241
	Six month	0.19 (0.05 to 0.33)	P = 0.009
	12 month	0.19 (0.05 to 0.34)	P = 0.008
Control	One month	0.28 (0.14 to 0.41)	P < 0.001
	Three month	0.34 (0.20 to 0.48)	P < 0.001
	Six month	0.33 (0.19 to 0.47)	P < 0.001
	12 month	0.38 (0.23 to 0.52)	P < 0.001

P value for whether changes from baseline differ between screening groups			P = 0.048
Logarithmic transformed impact of lung cancer worry scores			
EarlyCDT®-positive	One month	0.12 (0.08 to 0.16)	P < 0.001
	Three month	0.10 (0.06 to 0.14)	P < 0.001
	Six month	0.10 (0.06 to 0.14)	P < 0.001
	12 month	0.06 (0.02 to 0.11)	P = 0.003
EarlyCDT®-negative	One month	0.04 (0.00 to 0.07)	P = 0.045
	Three month	0.01 (-0.02 to 0.05)	P = 0.448
	Six month	0.04 (0.00 to 0.08)	P = 0.036
	12 month	0.04 (0.00 to 0.08)	P = 0.048
Control	One month	0.08 (0.04 to 0.11)	P < 0.001
	Three month	0.10 (0.06 to 0.13)	P < 0.001
	Six month	0.09 (0.06 to 0.13)	P < 0.001
	12 month	0.11 (0.07 to 0.15)	P < 0.001
P value for whether changes from baseline differ between screening groups			P = 0.003

Anti-logged impact of lung cancer worry scores		
EarlyCDT®-positive	One month	1.13 (1.08 to 1.17)
	Three month	1.11 (1.06 to 1.15)
	Six month	1.13 (1.06 to 1.15)
	12 month	1.06 (1.02 to 1.12)
EarlyCDT®-negative	One month	1.04 (1.00 to 1.07)
	Three month	1.01 (0.98 to 1.05)
	Six month	1.04 (1.00 to 1.08)
	12 month	1.04 (1.00 to 1.08)
Control	One month	1.08 (1.04 to 1.12)
	Three month	1.11 (1.06 to 1.14)
	Six month	1.09 (1.06 to 1.14)
	12 month	1.12 (1.07 to 1.16)

Table 33. Adjusted analyses comparing impact of lung cancer worry scores, logarithmic transformed scores and anti-logged scores within screening groups over time (one, three, six and 12 months post-randomisation) compared to pre-randomisation

Screening group	Study time-point	Difference between the means* (95% CI)	P value	Difference between the means ** (95% CI)	P value
Impact of lung cancer worry scores					
EarlyCDT®-positive	One month	0.42 (0.27 to 0.56)	P < 0.001	0.41 (0.27 to 0.56)	P < 0.001
	Three month	0.38 (0.24 to 0.53)	P < 0.001	0.36 (0.22 to 0.51)	P < 0.001
	Six month	0.35 (0.20 to 0.49)	P < 0.001	0.34 (0.19 to 0.49)	P < 0.001
	12 month	0.27 (0.11 to 0.43)	P = 0.001	0.26 (0.10 to 0.42)	P = 0.002
EarlyCDT®-negative	One month	0.16 (0.03 to 0.30)	P = 0.020	0.17 (0.03 to 0.31)	P = 0.017
	Three month	0.08 (-0.06 to 0.22)	P = 0.240	0.06 (-0.08 to 0.20)	P = 0.392
	Six month	0.19 (0.05 to 0.33)	P = 0.008	0.18 (0.03 to 0.32)	P = 0.016
	12 month	0.19 (0.05 to 0.34)	P = 0.008	0.17 (0.03 to 031)	P = 0.021
Control	One month	0.28 (0.13 to 0.42)	P < 0.001	0.30 (0.16 to 0.44)	P < 0.001
	Three month	0.34 (0.20 to 0.48)	P < 0.001	0.38 (0.24 to 0.52)	P < 0.001
	Six month	0.33 (0.19 to 0.48)	P < 0.001	0.36 (0.22 to 0.50)	P < 0.001
	12 month	0.38 (0.23 to 0.52)	P < 0.001	0.42 (0.27 to 0.56)	P < 0.001
			P = 0.047		P = 0.017

P value for whether changes from baseline differ between screening groups					
Logarithmic transformed impact of lung cancer worry scores					
EarlyCDT®-positive	One month	0.12 (0.08 to 0.16)	P < 0.001	0.12 (0.08 to 0.16)	P < 0.001
	Three month	0.10 (0.07 to 0.14)	P < 0.001	0.10 (0.06 to 0.14)	P < 0.001
	Six month	0.10 (0.06 to 0.14)	P < 0.001	0.09 (0.05 to 0.13)	P < 0.001
	12 month	0.06 (0.02 to 0.11)	P = 0.003	0.06 (0.02 to 0.10)	P = 0.006
EarlyCDT®-negative	One month	0.04 (0.00 to 0.07)	P = 0.044	0.04 (0.00 to 0.08)	P = 0.040
	Three month	0.01 (-0.02 to 0.05)	P = 0.446	0.00 (-0.03 to 0.05)	P = 0.680
	Six month	0.04 (0.00 to 0.08)	P = 0.034	0.03 (-0.00 to 0.07)	P = 0.072
	12 month	0.04 (0.00 to 0.08)	P = 0.047	0.03 (-0.00 to 0.07)	P = 0.089
Control	One month	0.08 (0.04 to 0.11)	P < 0.001	0.08 (0.04 to 0.12)	P < 0.001
	Three month	0.10 (0.06 to 0.13)	P < 0.001	0.11 (0.07 to 0.14)	P < 0.001
	Six month	0.09 (0.06 to 0.13)	P < 0.001	0.10 (0.06 to 0.14)	P < 0.001
	12 month	0.11 (0.07 to 0.15)	P < 0.001	0.12 (0.08 to 0.16)	P < 0.001
P value for whether changes from baseline differ between screening groups			P = 0.047		P = 0.001

Anti-logged impact of lung cancer worry scores			
EarlyCDT®-positive	One month	1.13 (1.08 to 1.17)	1.13 (1.08 to 1.17)
	Three month	1.11 (1.07 to 1.15)	1.11 (1.06 to 1.15)
	Six month	1.11 (1.06 to 1.15)	1.09 (1.05 to 1.14)
	12 month	1.06 (1.02 to 1.12)	1.06 (1.02 to 1.11)
EarlyCDT®-negative	One month	1.04 (1.00 to 1.07)	1.04 (1.00 to 1.08)
	Three month	1.01 (0.98 to 1.05)	1.00 (0.97 to 1.05)
	Six month	1.04 (1.00 to 1.08)	1.03 (1.00 to 1.07)
	12 month	1.04 (1.00 to 1.08)	1.03 (1.00 to 1.07)
Control	One month	1.08 (1.04 to 1.12)	1.08 (1.04 to 1.13)
	Three month	1.11 (1.06 to 1.14)	1.12 (1.07 to 1.15)
	Six month	1.09 (1.06 to 1.14)	1.11 (1.06 to 1.15)
	12 month	1.12 (1.07 to 1.16)	1.13 (1.08 to 1.17)

* Adjusted for ECLS minimisation variables and baseline value of outcome variable.

** Adjusted for ECLS minimisation variables, baseline value of outcome variable and additional variables

Aim: To explore how impact of lung cancer worry on mood and daily activities scores differ between the three screening groups across all time points and at each questionnaire time-point

As can be seen from table 31, at the one and three month time-points, the EarlyCDT®-positive group had slightly higher scores than the EarlyCDT®-negative group and the control group. At six months post-screening, scores were very similar between the three groups. At 12 months post-screening, the EarlyCDT®-positive group had lower scores than the EarlyCDT®-negative group and the control group. No statistically significant differences were found in scores between the groups at each study time-point.

Unadjusted regression analyses

The results of unadjusted regression analyses are presented in table 34. No statistically significant differences were found between groups across time-points or at any of the four time-points. The results of the unadjusted analyses for the logarithmic transformed scores, and the anti-logged negative scores, are presented in table 34. Results reflect those of the original score in that no significant differences were found between groups across all time-points or at each time-point.

Adjusted regression analyses

Results of the adjusted regression analyses are presented in table 35. When ECLS minimisation variables were adjusted for (model one), mean scores were significantly lower for the EarlyCDT®-negative group when compared with the control group across all time points (p =

0.027) and at the three month time-point (p = 0.009). No statistically significant differences were found between the two groups at the one, six and 12 month time-points. No statistically significant differences were found for mean scores between the EarlyCDT®-positive and the control group across all time points (p = 0.821) or at any of the four time-points. The EarlyCDT®-positive group had significantly higher mean scores when compared with the EarlyCDT®-negative group across all time points (p = 0.018) and at the one (p = 0.013) and three month (p = 0.007) time-points only. Results for the logarithmic transformed and anti-logged data for model one are presented in table 35. Unlike the original score, the mean logarithmic transformed scores were also significantly different between the EarlyCDT®-negative and control group at the six and 12 month time-points as well as at one month time point and across all time-points. A statistically significant difference was also found between EarlyCDT®-positive and the EarlyCDT®-negative at six month post-screening. For anti-logged data, significant differences between the means were found between the EarlyCDT®-negative and the control group across all time-points and at the three and 12 month time-points. Statistically significant differences between the means were found across all time-points and at one and three months post-screening when the EarlyCDT®-positive group was compared with the EarlyCDT®-negative group.

For the second adjusted model, differences in mean scores between screening groups did not vary over time (p = 0.138). Mean scores were significantly lower for the EarlyCDT®-negative group when compared with the control group at the three month time-point only (p = 0.010). No statistically significant differences were found between the two groups across all time points, and at the one, six and 12 month time-points. No statistically significant differences were found in mean negative affect scores between the EarlyCDT®-positive group and control group across all time points (p = 0.506) or at any of the four time points. The EarlyCDT®-positive group had

significantly higher mean scores when compared with the EarlyCDT®-negative group across all time points (p = 0.011) and at the one and three month time-points..

Logarithmic transformed scores varied significantly between screening groups across all time points (p = 0.023). In contrast to the original score, the EarlyCDT®-negative group had significantly lower logarithmically transformed and anti-logged mean scores than the control group across all time points and at three and 12 months. Furthermore, the EarlyCDT®-positive had significantly higher logarithmic transformed mean scores compared with the control group at one month. The EarlyCDT®-positive group had significantly higher logarithmic transformed mean scores when compared with the EarlyCDT®-negative group across all time points and at the one, three and six month time-points only. For the anti-logged scores, the EarlyCDT®-positive group had significantly higher mean scores when compared with the EarlyCDT®-negative group across at the one and three month time-points only

- Model checking

Model checking for the log transformed data models showed assumptions for linear regression were met. There were no large value level one or level two residuals for either model using the log transformed data (all residual values were >-1 and <1.5).

Table 34. Unadjusted analyses comparing impact of lung cancer worry scores, logarithmic transformed scores and anti-logged scores between test result groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point

Screening group	Study time-point	Difference between the means* (95% CI)	P value
Impact of lung cancer worry scores			
EarlyCDT®-negative *vs*. control	Across all time-points	-0.08 (-0.30 to 0.13)	P = 0.444
	One month	-0.02 (-0.26 to 0.23)	P = 0.898
	Three month	-0.17 (-0.41 to 0.08)	P = 0.179
	Six month	-0.06 (-0.31 to 0.19)	P = 0.633
	12 month	-0.10 (-0.35 to 0.15)	P = 0.436
EarlyCDT®-positive *vs*. control	Across all time-points	-0.01 (-0.23 to 0.21)	P = 0.920
	One month	0.11 (-0.14 to 0.36)	P = 0.397
	Three month	-0.12 (-0.27 to 0.24)	P = 0.924
	Six month	-0.03 (-0.29 to 0.22)	P = 0.792
	12 month	-0.14 (-0.40 to 0.11)	P = 0.275

	Across all time-points	0.07 (-0.15 to 0.30)	P = 0.518
	One month	0.12 (-0.12 to 0.37)	P = 0.328
EarlyCDT®-positive *vs*. EarlyCDT®-negative	Three month	0.16 (-0.10 to 0.41)	P = 0.224
	Six month	0.03 (-0.23 to 0.28)	P = 0.841
	12 month	-0.05 (-0.31 to 0.21)	P = 0.728
P value for whether differences in screening groups vary over time			P = 0.179
Logarithmic transformed impact of lung cancer worry scores			
	Across all time-points	-0.03 (-0.08 to 0.03)	P = 0.305
	One month	-0.00 (-0.07 to 0.06)	P = 0.874
EarlyCDT®-negative *vs*. control	Three month	-0.05 (-0.11 to 0.01)	P = 0.123
	Six month	-0.02 (-0.09 to 0.04)	P = 0.498
	12 month	-0.04 (-0.11 to 0.02)	P = 0.206
	Across all time-points	-0.00 (-0.06 to 0.05)	P = 0.917
	One month	0.04 (-0.03 to 0.10)	P = 0.263
EarlyCDT®-positive *vs*. control	Three month	-0.00 (-0.07 to 0.06)	P = 0.941
	Six month	-0.00 (-0.07 to 0.06)	P = 0.854
	12 month	-0.05 (-0.12 to 0.01)	P = 0.120

	Across all time-points	0.03 (-0.03 to 0.08)	P = 0.370
	One month	0.04 (-0.02 to 0.11)	P = 0.201
EarlyCDT®-positive *vs*. EarlyCDT®-negative	Three month	0.05 (-0.02 to 0.11)	P = 0.152
	Six month	0.02 (-0.05 to 0.08)	P = 0.634
	12 month	-0.01 (-0.08 to 0.06)	P = 0.730
P value for whether differences in screening groups vary over time			P = 0.041
Anti-logged impact of lung cancer worry scores			
	Across all time-points	0.97 (0.92 to 1.03)	
	One month	1.00 (0.93 to 1.06)	
EarlyCDT®-negative *vs*. control	Three month	0.95 (0.89 to 1.01)	
	Six month	0.98 (0.91 to 1.04)	
	12 month	0.96 (0.90 to 1.02)	
	Across all time-points	1.00 (0.94 to 1.05)	
	One month	1.04 (0.97 to 1.11)	
EarlyCDT®-positive *vs*. control	Three month	1.00 (0.93 to 1.06)	
	Six month	1.00 (0.93 to 1.06)	
	12 month	0.95 (0.89 to 1.01)	

	Across all time-points	1.03 (0.97 to 1.08)
	One month	1.04 (0.98 to 1.11)
EarlyCDT®-positive *vs*. EarlyCDT®-negative	Three month	1.05 (0.98 to 1.11)
	Six month	1.02 (0.95 to 1.08)
	12 month	0.99 (0.92 to 1.06)

Table 35. Adjusted analyses comparing impact of lung cancer worry scores, logarithmic transformed scores, and anti-logged negative scores between groups (EarlyCDT®-positive, EarlyCDT®-negative, control) across all study time-points and at each study time-point

Screening group	Study time-point	Difference between the means* (95% CI)	P value	Difference between the means ** (95% CI)	P value
Impact of lung cancer worry scores					
EarlyCDT®-negative *vs*. Control	Across all time-points	-0.19 (-0.36 to -0.02)	P = 0.027	-0.16 (-0.32 to 0.00)	P = 0.052
	One month	-0.13 (-0.33 to 0.07)	P = 0.209	-0.07 (-0.27 to 0.12)	P = 0.479
	Three month	-0.27 (-0.48 to -0.07)	P = 0.009	-0.26 (-0.46 to -0.06)	P = 0.010
	Six month	-0.17 (-0.38 to 0.04)	P = 0.111	-0.13 (-0.33 to 0.07)	P = 0.191
	12 month	-0.20 (-0.41 to 0.01)	P = 0.067	-0.18 (-0.38 to 0.03)	P = 0.087
EarlyCDT®-positive *vs*. Control	Across all time-points	0.02 (-0.16 to 0.20)	P = 0.821	0.06 (-0.11 to 0.22)	P = 0.506
	One month	0.13 (-0.08 to 0.34)	P = 0.211	0.18 (-0.02 to 0.39)	P = 0.073
	Three month	0.02 (-0.19 to 0.23)	P = 0.874	0.04 (-0.16 to 0.24)	P = 0.696
	Six month	-0.00 (-0.22 to 0.21)	P = 0.966	0.04 (-0.16 to 0.25)	P = 0.691
	12 month	-0.10 (-0.32 to 0.12)	P = 0.378	-0.08 (-0.29 to 0.14)	P = 0.480

EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	0.21 (0.04 to 0.39)	P = 0.018	0.21 (0.05 to 0.38)	P = 0.011
	One month	0.26 (0.05 to 0.47)	P = 0.013	0.26 (0.05 to 0.46)	P = 0.013
	Three month	0.29 (0.08 to 0.50)	P = 0.007	0.30 (0.10 to 0.50)	P = 0.004
	Six month	0.16 (-0.05 to 0.38)	P = 0.132	0.17 (-0.03 to 0.38)	P = 0.096
	12 month	0.10 (-0.12 to 0.32)	P = 0.391	0.10 (-0.11 to 0.31)	P = 0.359
P value for differences in means between time points			P = 0.241		P = 0.138
Logarithmic transformed impact of lung cancer worry scores					
EarlyCDT®-negative *vs*. Control	Across all time-points	-0.06 (-0.10 to -0.02)	P = 0.003	-0.06 (-0.10 to -0.02)	P = 0.005
	One month	-0.04 (-0.09 to 0.01)	P = 0.133	-0.03 (-0.08 to 0.02)	P = 0.294
	Three month	-0.08 (-0.13 to -0.03)	P = 0.002	-0.08 (-0.13 to -0.03)	P = 0.002
	Six month	-0.05 (-0.11 to -0.00)	P = 0.039	-0.05 (-0.10 to 0.00)	P = 0.056
	12 month	-0.07 (-0.12 to -0.02)	P = 0.007	-0.07 (-0.12 to -0.02)	P = 0.008
EarlyCDT®-positive *vs*. Control	Across all time-points	0.00 (-0.04 to 0.05)	P = 0.851	0.01 (-0.03 to 0.05)	P = 0.625
	One month	0.04 (-0.00 to 0.10)	P = 0.103	0.05 (0.00 to 0.11)	P = 0.041
	Three month	0.00 (-0.05 to 0.06)	P = 0.896	0.00 (-0.04 to 0.06)	P = 0.766
	Six month	0.00 (-0.05 to 0.05)	P = 0.990	0.01 (-0.04 to 0.06)	P = 0.724
	12 month	-0.04 (-0.10 to 0.01)	P = 0.130	-0.04 (-0.10 to 0.01)	P = 0.131

EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	0.07 (0.02 to 0.11)	P = 0.003	0.07 (0.03 to 0.11)	P = 0.001
	One month	0.08 (0.03 to 0.14)	P = 0.002	0.08 (0.03 to 0.13)	P = 0.002
	Three month	0.09 (0.03 to 0.14)	P = 0.002	0.09 (0.04 to 0.14)	P = 0.001
	Six month	0.06 (0.00 to 0.11)	P = 0.044	0.06 (0.00 to 0.11)	P = 0.027
	12 month	0.03 (-0.03 to 0.09)	P = 0.303	0.03 (-0.03 to 0.08)	P = 0.318
P value for differences in means between time points			P = 0.062		P = 0.023
Anti-logged impact of lung cancer worry scores					
EarlyCDT®-negative *vs*. Control	Across all time-points	0.94 (0.90 to 0.98)		0.94 (0.90 to 0.98)	
	One month	0.96 (0.91 to 1.01)		0.97 (0.92 to 1.02)	
	Three month	0.92 (0.88 to 0.97)		0.92 (0.88 to 0.97)	
	Six month	0.95 (0.90 to 1.00)		0.95 (0.90 to 1.00)	
	12 month	0.93 (0.89 to 0.98)		0.93 (0.89 to 0.98)	
EarlyCDT®-positive *vs*. Control	Across all time-points	1.00 (0.96 to 1.05)		1.01 (0.97 to 1.05)	
	One month	1.04 (1.00 to 1.11)		1.05 (1.00 to 1.12)	
	Three month	1.00 (0.95 to 1.06)		1.00 (0.96 to 1.06)	
	Six month	1.00 (0.95 to 1.05)		1.01 (0.96 to 1.06)	
	12 month	0.96 (0.90 to 1.01)		0.96 (0.90 to 1.01)	

EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	1.07 (1.02 to 1.12)	1.07 (1.03 to 1.12)
	One month	1.08 (1.03 to 1.15)	1.08 (1.03 to 1.14)
	Three month	1.09 (1.03 to 1.15)	1.09 (1.04 to 1.15)
	Six month	1.06 (0.00 to 1.12)	1.06 (1.00 to 1.12)
	12 month	1.03 (0.97 to 1.09)	1.03 (0.97 to 1.08)

* Adjusted for ECLS minimisation variables and baseline value of outcome variable.

** Adjusted for ECLS minimisation variables, baseline value of outcome variable and additional variables

A brief summary of the main findings for the extent to which lung cancer worry impacts mood and ability to perform daily activities

Changes within screening groups over time

- In contrast to what was hypothesised, mean scores for participants in the EarlyCDT®-positive and the control groups were significantly higher at one, three, six and 12 months post-screening when compared with pre-randomisation.
- Mean scores for the EarlyCDT®-negative group were significantly higher at one, six and 12 months post-screening when compared with pre-randomisation, which was not expected. Again, it must be emphasised that the changes in scores for all three groups were very small and cannot be considered clinically important.

Changes between groups over time

- As predicted, in the adjusted analyses, the EarlyCDT®-negative group were found to have significantly lower impact of lung cancer worry scores across all time-points and at three months post-screening when compared with the control group.
- The EarlyCDT®-positive group had significantly higher impact of lung cancer worry scores across all time-points and at three months post-screening when compared with the EarlyCDT®-negative group.
- No statistically significant differences were found between the EarlyCDT®-positive group and the control group across time or at each study time-point.
- Differences in scores between all groups were very small at each time-point.

4.4.9. Outcome six. Screening specific distress

Aim: To investigate, within groups, how IES total scores changed over time

Descriptive statistics for both screening groups at each study time-point are displayed in figure 16 and table 36. Median and mean total scores were highest for both groups at one month post-screening. For both groups, scores decreased over the three, six and 12 month time-points. There were statistically significant differences in total IES scores between study time-points for the EarlyCDT®-positive group only ($\chi^2(3) = 34.24$, $p < 0.001$).

Table 36. Unadjusted analyses comparing total IES scores amongst participants in the EarlyCDT®-positive group and the EarlyCDT®-negative group

Study time-point	Total	EarlyCDT®-positive	EarlyCDT®-negative	Results of statistical analyses comparing scores between groups at each time-point***
One month (median, IQR*) (mean, sd**)	N = 641 [20] 3 (0–14) 9.45 (13.73)	N = 303 [8] 6 (1 - 18) 11.99 (14.66)	N = 338 [12] 1 (0-9) 7.17 (12.42)	z = -5.97 P < 0.001
Three month	N = 626 [8] 1 (0-11) 7.76 (12.72)	N = 299 [2] 3 (0-13) 9.36 (13.77)	N = 327 [6] 0.14 (0-7) 6.30 (11.52)	z = -3.87 P < 0.001
Six month	N = 613 [9] 1 (0-8) 7.55 (12.69)	N = 294 [4] 1 (0-12) 8.80 (14.00)	N = 319 [5] 0.14 (0-9) 6.39 (11.24)	z = -1.71 P = 0.087
12 month	N = 549 [8] 0 (0-3) 6.86 (12.19)	N = 237 [6] 1 (0-9) 7.40 (12.47)	N = 312 [2] 0 (0-7) 6.45 (11.97)	z = -1.41 P = 0.160

Results of statistical analyses comparing scores within each group over time**	P < 0.001	P = 0.294

[missing values]

*IQR = Interquartile range

** sd = standard deviation

*** Mann–Whitney U test

**** Unadjusted regression analysis

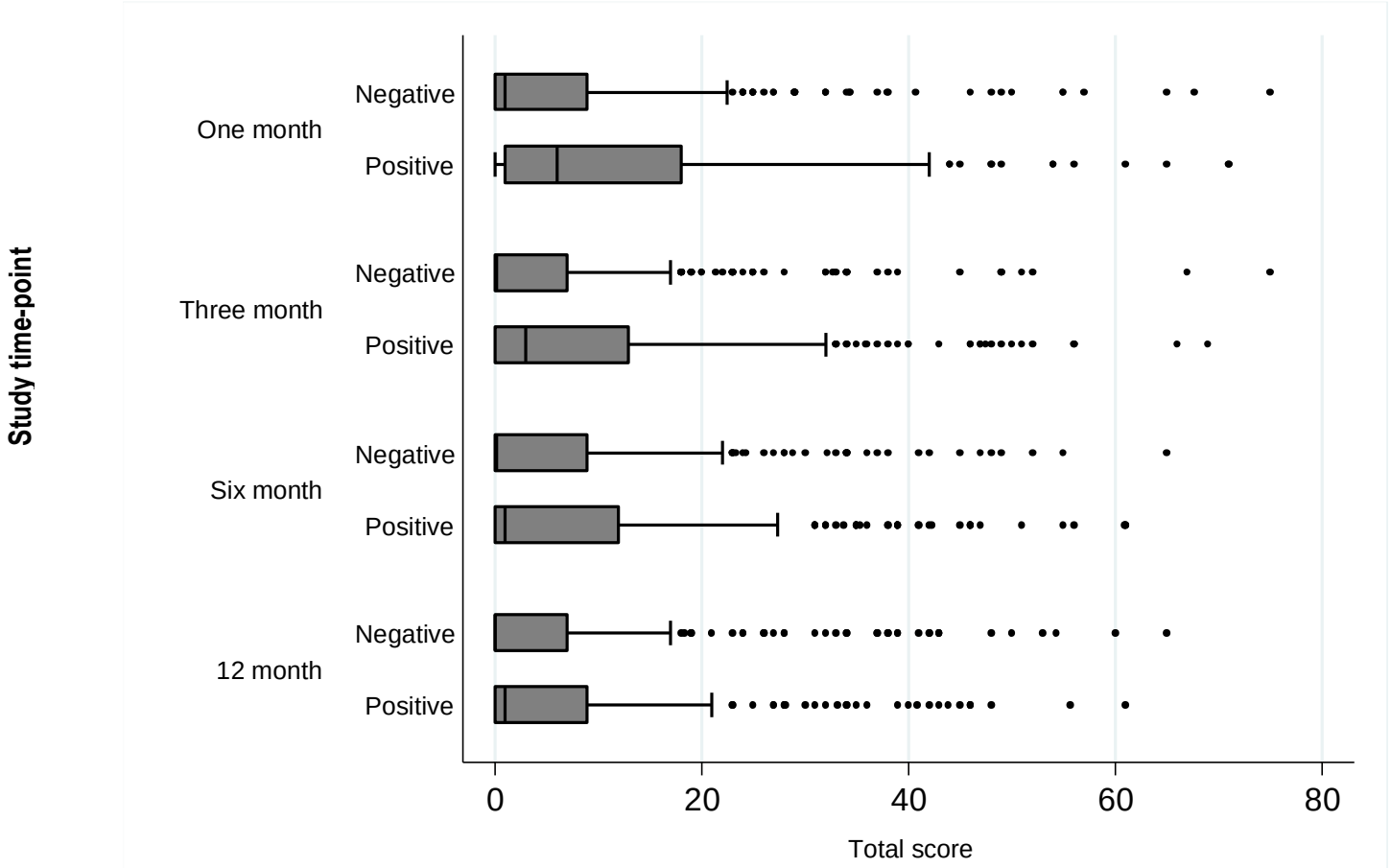


Figure 16. IES total scores amongst participants in each test result group (EarlyCDT®-positive, EarlyCDT®-negative) at each study time-point (pre-randomisation, one month, three month, six month and 12 month)

Unadjusted regression analyses

The results of unadjusted regression analyses are presented in table 37. Statistically significant differences were found between groups for changes in mean scores from one month ($p = 0.001$). For the EarlyCDT®-positive group, mean IES total scores at three, six and 12 months were all significantly lower than one month scores (table 37). For the EarlyCDT®-negative group, no statistically significant differences were found between mean scores at three, six and 12 months when compared with one month scores. Following model checking (see below), scores were logarithmically transformed. The results of unadjusted analyses are presented as original scores, logarithmic transformed scores and anti-logged scores in table 37. Findings were similar regardless of the scale used for the score. It is important to note that although statistically significant differences were found, the absolute differences were small in magnitude.

Adjusted regression analyses

Results of adjusted regression analyses are presented in table 38. When ECLS minimisation variables (model one) were adjusted for, the statistically significant differences found between time points for each screening group were similar to those of the unadjusted analyses (described above). Again, when ECLS minimisation variables and additional variables were adjusted for (model two), the results reflected those of the unadjusted analyses. Results of the analyses for the logarithmic transformed scores and the anti-logged scores for the EarlyCDT®-positive group reflected those of the original score. However, for the EarlyCDT®-negative group, mean IES total scores at three, six and 12 months were all found to be significantly lower than the one month scores.

- Model checking

Model checking for the log transformed data models showed assumptions for linear regression were met. There were no large level one or level two residuals for either model using the log transformed data (all residual values were < 2.5 and > -2.5).

Table 37. Unadjusted analyses comparing IES total scores, logarithmic transformed scores, and anti-logged scores within groups (EarlyCDT®-positive, EarlyCDT®-negative) over time (three, six and 12 months post-randomisation)

Screening group	Study time-point	Difference between the means (95% CI)	P value
IES total scores			
EarlyCDT®-positive	Three month	-2.69 (-3.91 to -1.47)	P < 0.001
	Six month	-2.93 (-4.16 to -1.71)	P < 0.001
	12 month	-4.34 (-5.66 to -3.03)	P < 0.001
EarlyCDT®-negative	Three month	-0.95 (-2.11 to 0.21)	P = 0.110
	Six month	-0.92 (-2.09 to 0.25)	P = 0.123
	12 month	-0.72 (-1.90 to 0.45)	P = 0.229
P value for whether changes from one month differ between screening groups			P = 0.001
Logarithmic transformed IES total scores			
EarlyCDT®-positive	Three month	-0.34 (-0.47 to -0.20)	P < 0.001
	Six month	-0.50 (-0.64 to -0.37)	P < 0.001
	12 month	-0.58 (-0.72 to -0.43)	P < 0.001

EarlyCDT®-negative	Three month	-0.12 (-0.25 to 0.00)	P = 0.063
	Six month	-0.12 (-0.24 to 0.01)	P = 0.076
	12 month	-0.13 (-0.26 to 0.00)	P = 0.053
P value for whether changes from baseline differ between screening groups			P < 0.001
Anti-logged IES total scores			
EarlyCDT®-positive	Three month	0.71 (0.63 to 0.82)	
	Six month	0.61 (0.53 to 0.69)	
	12 month	0.56 (0.49 to 0.65)	
EarlyCDT®-negative	Three month	0.89 (0.78 to 1.00)	
	Six month	0.89 (0.79 to 1.01)	
	12 month	0.88 (0.77 to 1.00)	

Table 38. Adjusted analyses comparing IES total scores, logarithmic transformed scores and anti-logged scores within groups (EarlyCDT®-positive, EarlyCDT®-negative) over time (one, three, six and 12 months post-randomisation)

Screening group	Study time-point	Difference between the means* (95% CI)	P value	Difference between the means ** (95% CI)	P value
IES total scores					
EarlyCDT®-positive	Three month	-2.69 (-3.91 to -1.47)	P < 0.001	-2.57 (-3.81 to -1.34)	P < 0.001
	Six month	-2.93 (-4.16 to -1.71)	P < 0.001	-2.96 (-4.20 to -1.72)	P < 0.001
	12 month	-4.32 (-5.64 to -3.00)	P < 0.001	-4.06 (-5.40 to -2.73)	P < 0.001
EarlyCDT®-negative	Three month	-0.97 (-2.13 to 0.19)	P = 0.102	-1.10 (-2.28 to 0.07)	P = 0.066
	Six month	-0.93 (-2.10 to 0.24)	P = 0.120	-1.13 (-2.32 to 0.05)	P = 0.061
	12 month	-0.72 (-1.90 to 0.46)	P = 0.230	-1.03 (-2.22 to 0.17)	P = 0.093
P value for whether changes from baseline differ between screening groups			P = 0.001		P = 0.010
Logarithmic transformed IES total scores					
EarlyCDT®-positive	Three month	-0.34 (-0.47 to -0.20)	P < 0.001	-0.04 (-0.47 to -0.20)	P < 0.001
	Six month	-0.50 (-0.64 to -0.37)	P < 0.001	-0.52 (-0.65 to -0.38)	P < 0.001
	12 month	-0.57 (-0.72 to -0.43)	P < 0.001	-0.55 (-0.70 to -0.41)	P < 0.001

EarlyCDT®-negative	Three month	-0.12 (-0.25 to 0.00)	P = 0.059	-0.14 (-0.27 to -0.01)	P = 0.036
	Six month	-0.12 (-0.24 to 0.01)	P = 0.075	-0.14 (-0.27 to -0.01)	P = 0.034
	12 month	-0.13 (-0.26 to 0.00)	P = 0.054	-0.15 (-0.28 to -0.02)	P = 0.024
P value for whether changes from baseline differ between screening groups			P < 0.001		P < 0.001
Anti-logged IES total scores					
EarlyCDT®-positive	Three month	0.71 (0.63 to 0.82)		0.96 (0.63 to 0.82)	
	Six month	0.61 (0.53 to 0.69)		0.59 (0.52 to 0.68)	
	12 month	0.57 (0.49 to 0.65)		0.58 (0.50 to 0.66)	
EarlyCDT®-negative	Three month	0.89 (0.78 to 1.00)		0.87 (0.76 to 0.99)	
	Six month	0.89 (0.79 to 1.01)		0.87 (0.76 to 0.99)	
	12 month	0.88 (0.77 to 1.00)		0.86 (0.76 to 0.98)	

* Adjusted for ECLS minimisation variables

** Adjusted for ECLS minimisation variables and additional variables

<u>Aim</u>: To explore how IES scores differ between the three screening groups across all time points and at each questionnaire time-point

As can be seen from table 36, at one month post-screening, mean and median scores were significantly higher in the EarlyCDT®-positive group compared with the EarlyCDT®-negative group (z = - 5.97, $p < 0.001$). The same trend was observed at three months post-screening (z = - 3.87, $p < 0.001$). There were no statistically significant differences between groups at the six and 12 month time-points.

<u>Unadjusted regression analyses</u>

The results of unadjusted linear regression analyses are presented in table 39. Differences in mean scores between the two groups were found to vary significantly over time ($p = 0.001$). Mean IES total scores were 3.08 times higher in the EarlyCDT®-positive group compared with the EarlyCDT®-negative group across all time-points ($p < 0.001$). Mean scores were also significantly higher in the EarlyCDT®-positive group compared with the EarlyCDT®-negative group at one, three and six months post-screening. It is important to note that although these differences were statistically significant, the absolute differences were small in magnitude. No statistically significant differences were found between groups at 12 months post-screening. The results of the unadjusted analyses for the logarithmic transformed scores, and the anti-logged negative scores, are presented in table 39. Results mirror those of the original IES total score.

Adjusted regression analyses

Results of the adjusted multilevel linear regression analyses are presented in table 40. When ECLS minimisation variables were adjusted for (model one), results mirrored those of the unadjusted analyses. For the second adjusted model (adjusted for ECLS minimisation variables and additional variables), when compared with the EarlyCDT®-negative group, mean scores were higher in the EarlyCDT®-positive group at the one, three, six and 12 month time-points. Results for the logarithmic transformed and anti-logged scores mirrored those of the original score for the second model.

- Model checking

Model checking for the log transformed data models showed assumptions for linear regression were met. There were no large value level one or level two residuals for either model using the log transformed data (all residual values were < 2.5 and > -2.5).

Table 39. Unadjusted analyses comparing IES total scores, logarithmic transformed scores and anti-logged scores between groups (EarlyCDT®-positive, EarlyCDT®-negative) across all study time-points and at each study time-point

Screening group	Study time-point	Difference between the means* (95% CI)	P value
IES total scores			
EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	3.08 (1.37 to 4.79)	P < 0.001
	One month	4.80 (2.82 to 6.78)	P < 0.001
	Three month	3.05 (1.06 to 5.05)	P = 0.003
	Six month	2.78 (0.78 to 4.79)	P = 0.007
	12 month	1.18 (-0.89 to 3.25)	P = 0.264
P value for whether differences in screening groups vary over time			P = 0.001
Logarithmic transformed IES total scores			
EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	0.36 (0.19 to 0.53)	P < 0.001
	One month	0.61 (0.41 to 0.81)	P < 0.001
	Three month	0.39 (0.19 to 0.60)	P < 0.001

	Six month	0.22 (0.02 to 0.43)	P = 0.035
	12 month	0.16 (-0.05 to 0.38)	P = 0.134
P value for whether differences in screening groups vary over time			P < 0.001
Anti-logged IES total scores			
EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	1.43 (1.21 to 1.70)	
	One month	1.84 (1.51 to 2.25)	
	Three month	1.48 (1.21 to 1.82)	
	Six month	1.25 (1.02 to 1.54)	
	12 month	1.17 (0.95 to 1.46)	

Table 40. Adjusted analyses comparing IES total scores, logarithmic transformed scores, and anti-logged scores between groups (EarlyCDT®-positive, EarlyCDT®-negative) across all study time-points and at each study time-point

Test result group	Study time-point	Difference between the means* (95% CI)	P value	Difference between the means ** (95% CI)	P value
IES total scores					
EarlyCDT®-positive *vs.* EarlyCDT®-negative	Across all time-points	3.48 (1.79 to 5.18)	P < 0.001	3.60 (1.99 to 5.21)	P < 0.001
	One month	5.19 (3.23 to 7.16)	P < 0.001	5.08 (3.18 to 6.99)	P < 0.001
	Three month	3.47 (1.50 to 5.45)	P = 0.001	3.61 (1.70 to 5.53)	P < 0.001
	Six month	3.19 (1.20 to 5.18)	P = 0.002	3.26 (1.33 to 5.18)	P = 0.001
	12 month	1.59 (-0.46 to 3.64)	P = 0.129	2.05 (0.05 to 4.04)	P = 0.044
P value for differences in means between time points			P = 0.001		P = 0.010
Logarithmic transformed IES total scores					
	Across all time-points	0.41 (0.24 to 0.58)	P < 0.001	0.42 (0.26 to 0.57)	P < 0.001
	One month	0.66 (0.45 to 0.86)	P < 0.001	0.65 (0.45 to 0.84)	P < 0.001
	Three month	0.44 (0.24 to 0.65)	P < 0.001	0.45 (0.25 to 0.64)	P < 0.001

EarlyCDT®-positive *vs*. EarlyCDT®-negative	Six month	0.27 (0.06 to 0.47)	P = 0.010	0.27 (0.08 to 0.47)	P = 0.007
	12 month	0.21 (-0.00 to 0.42)	P = 0.052	0.25 (0.04 to 0.45)	P = 0.018
P value for differences in means between time points			P < 0.001		P < 0.001
Anti-logged IES total scores					
EarlyCDT®-positive *vs*. EarlyCDT®-negative	Across all time-points	1.51 (1.27 to 1.79)		1.52 (1.30 to 1.77)	
	One month	1.93 (1.57 to 2.36)		1.92 (1.57 to 2.32)	
	Three month	1.55 (1.27 to 1.92)		1.57 (1.28 to 1.90)	
	Six month	1.31 (1.06 to 1.60)		1.31 (1.08 to 1.60)	
	12 month	1.23 (1.00 to 1.52)		1.28 (1.04 to 1.57)	

* Adjusted for ECLS minimisation variables

** Adjusted for ECLS minimisation variables and additional variables

A brief summary of the main findings for the IES

Changes within screening groups over time

- Mean scores for participants in the EarlyCDT®-positive group were significantly lower at three, six and 12 months post-screening when compared with one month post-screening.
- No statistically significant differences for original mean scores for participants in the EarlyCDT®-negative group were found between time-points. However, logarithmic transformed scores were found to be significantly lower at three months post-screening when ECLS minimisation variables and additional variables were adjusted for.

Changes between screening groups over time

- The EarlyCDT®-positive group had significantly higher scores across time and at one, three and six months post-screening when compared with the EarlyCDT®-negative group.

4.5. Discussion

4.5.1. Summary of the main findings

The overarching purpose of this study was to investigate the impact of lung cancer screening on a broad spectrum of negative emotional outcomes and a previously unstudied positive emotional outcome. The main findings for each of the three screening groups are summarised below.

EarlyCDT®-positive group

PANAS

The EarlyCDT®-positive group had significantly lower positive affect scores at one, three, six and 12 months than at pre-randomisation. Negative affect scores were highest at one month but did decline over the three, six and 12 month time-points. It is very important to note that, although statistically significant differences were found, the absolute differences between time-points for both outcomes were very small. For negative affect, the largest difference in mean scores was between pre-randomisation (15.55) and one month (16.70) and the largest difference in mean positive affect scores was between pre-randomisation (33.26) and three months post-screening (30.36). These differences are very small when we consider that positive and negative affect scores can range from 10 to 50. To the author's knowledge, there are no established norms for the PANAS. In the paper that reported on the development of the PANAS, the mean positive affect score was found to be 35.0 and the mean negative affect score was 18.1 [162]. Furthermore, another study that included a general adult population (mean age: 42.9 years) reported mean positive and negative affect scores as 31.3 and 16.0, respectively [163].

When we consider these mean scores, we can see that the scores in the current study do not differ substantially and therefore any changes cannot be considered clinically important. Finally, no statistically significant differences were found for both outcomes when the EarlyCDT®-positive group were compared to the EarlyCDT®-negative group and to the control group across time or at each study time-point.

LCWS

The proportion of participants who reported worry about getting lung cancer was significantly higher at the one, three, and six month time-points when compared with pre-randomisation. However, it must be noted that absolute differences between time-points were small and cannot be considered clinically important. Compared with the EarlyCDT®-negative group, the proportion of participants in the EarlyCDT®-positive group who reported worry was significantly higher across time and at one, three and six months post-screening. However, again, it is important to note that the absolute differences between groups at each time-point were small. For example, the largest difference between the groups was at three months (6.07%) and at 12 months, the difference was only 0.98%. Therefore, differences between groups cannot be considered clinically important.

Mean scores for impact of lung cancer worry on mood and ability to perform daily activities were all significantly higher at one, three, six and 12 months post-screening when compared with pre-randomisation. Again, absolute differences between time points for were very small and cannot be considered clinically important. Compared with the EarlyCDT®-negative group, scores were significantly higher across time and at three months post-screening. However, again, it is important to note that the absolute differences between groups at each time-point were small.

It was found that the proportion of participants who reported anxiety about the results of future tests/treatment was lowest at pre-randomisation (8.20%) but increased substantially at one month (23.55%). Reported anxiety decreased at three months (18.33%) and plateaued over the six (18.24%) and 12 month (18.18%) time-points. As well as statistically significant, this finding is clinically important, particularly at one month post-screening. Compared with the EarlyCDT®-negative group, the EarlyCDT®-positive group had significantly higher odds of reporting anxiety across time and at one month post-screening. The same was found when compared with the control group, although only when ECLS minimisation variables and additional variables were controlled for.

IES

IES scores were significantly lower at three, six and 12 months post-screening when compared with one month scores. As stated in section 4.3.4, the IES has cut-off points for clinical levels of concern (low < 8.5, moderate 8.6–19 and high >19).[143] Mean scores were in the 'moderate' range at one, three and six months but then moved to the 'low' range at 12 months post-screening. The EarlyCDT®-positive group had significantly higher scores at one, three and six months when compared with the EarlyCDT®-negative group. Although scores were in the moderate range at three time-points and were significantly higher than scores for the EarlyCDT®-negative group, overall, findings for IES scores are reassuring as screening specific distress reduced over time.

EarlyCDT®-negative group

PANAS

The EarlyCDT®-negative group had significantly lower (worse) positive affect scores at one, three, six and 12 months than at pre-randomisation. For negative affect scores, it was expected that there would be no significant change over time. However, negative affect scores increased from pre-randomisation and were significantly higher at six and 12 months when compared with pre-randomisation scores. However, although statistically significant, the absolute differences in positive and negatives scores over time were very small and cannot be considered clinically important. In contrast to what was hypothesised, no statistically significant differences were found between the EarlyCDT®-positive group and the EarlyCDT®-negative group for positive affect and negative affect scores across time or at any study time-points.

LCWS

For frequency of lung cancer worry, there were no statistically significant differences in the proportion of participants reporting worry over time, which was expected. For impact of lung cancer worry on mood and ability to perform daily activities, mean scores for the EarlyCDT®-negative group were significantly higher at one, six and 12 months post-screening when compared with pre-randomisation, which was not hypothesised. However, it must be emphasised that the changes in scores were very small and cannot be considered clinically important. The proportion of participants who reported anxiety about the results of future tests/treatment was significantly higher at one, three, six and 12 months post-screening when compared with pre-randomisation. This increase could be considered clinically important,

particularly as the proportion reporting anxiety was 8.95% higher at 12 months compared with pre-randomisation. In contrast to what was expected, no statistically significant differences in reported anxiety were found between the EarlyCDT®-negative and control group across all time-points and at each time-point.

IES

Finally, no statistically significant differences for original mean IES scores were found between time-points. However, logarithmic transformed scores were significantly lower at three months post-screening when ECLS minimisation and additional variables were adjusted for. This could have been the result of a type one error (discussed below). Mean IES scores were in the 'low' range (< 8.5) for clinical levels of concern at each study time-point.

Control group

PANAS

The control group had significantly lower (worse) positive affect scores at one, three, six and 12 months than at pre-randomisation. Negative affect scores were significantly higher (worse) at one, three, six and 12 months than at pre-randomisation. It is very important to note that, although statistically significant differences were found, the absolute differences between time-points for both outcomes were very small and cannot be considered clinically important.

As hypothesised, there were no statistically significant differences in positive affect scores between the EarlyCDT®-positive group and the control group across time and at each study

time-point. The EarlyCDT®-negative group had significantly higher (better) positive affect scores when compared with the control group across all time-points and each time-point when ECLS minimisation variables were adjusted for. However, when the additional variables were adjusted for, the differences at three, six and 12 months were no longer statistically significant. Again, it must be emphasised that the absolute differences between the EarlyCDT®-negative and control groups were very small at each time-point and cannot be considered clinically important.

For negative affect scores, no statistically significant differences were found between the EarlyCDT®-positive and control groups across time and at each study time-point. However, when ECLS minimisation variables were adjusted for, the EarlyCDT®-positive group had significantly lower (better) negative affect scores than the control group at three months post-screening. The EarlyCDT®-negative group had significantly lower (better) negative affect scores when compared with the control group across time and at the one and three month time-points. However, absolute differences in scores were small.

LCWS

For frequency of lung cancer worry, there were no statistically significant differences in the proportion of control participants reporting worry over time. When compared with the EarlyCDT®-positive group, no statistically significant differences were found in the odds of reporting worry across time or at each study time-point. However, the odds of reporting worry were significantly lower in the EarlyCDT®-negative group compared with the control group across all time-points and at three months post-screening.

For impact of worry on mood and daily activities, mean scores were significantly higher at one, three, six and 12 months post-screening when compared with pre-randomisation. However, it is important to note that absolute differences were small and cannot be considered clinically important. When the control group were compared with the EarlyCDT®-positive group, no statistically significant differences were found in scores across time or at each study time-point. The EarlyCDT®-negative group had significantly lower impact of lung cancer worry scores across all time-points and at three months post-screening when compared with the control group. Again, differences in scores were small.

The proportion of participants in the control group who reported anxiety about the results of future tests/treatment was significantly higher at one, three, six and 12 months post-screening when compared with pre-randomisation. This finding could be considered clinically relevant, particularly as the proportion reporting anxiety at 12 months was 12.01% higher than at pre-randomisation.

4.5.2. Discussion of findings

In this section, the findings listed above are discussed in relation to screening group. However, first, the possible explanations for a finding must be described: true finding, chance, bias, and confounding.

- **True finding**

The probability that a finding is true is dependent on the power of the study to detect statistical significance and the level of statistical significance [177]. As stated in section 4.3.6, 200

participants from each screening group allowed detection of a mean difference of 3.00 (SD 15.04 in the IES between pre-randomisation and follow up measurements within each group and a mean difference of 4.2 (SD 15.04), between each of the test groups (EarlyCDT®-positive and EarlyCDT®-negative) and the control arm with 80% power and a 2-sided 5% significance level [100]. The study recruitment and high follow-up rates led to exceeding the sample size requirement and the study therefore had adequate power to detect the differences descried above. It is therefore unlikely that the study failed to find a significant, and clinically important, difference in IES where one existed. The sample size was calculated based on the IES as data were available for this from a recent prostate cancer screening trial. It is possible that the study was underpowered to detect clinically important differences in some of the other measures used.

- **Chance**

The analysis used multilevel regression models to take account of multiple observations per person so that multiple comparisons at different time points were not undertaken as this would increase the chance of a type one error (e.g., a spuriously positive finding). The analyses also used a lower p-value for likelihood ratio tests for interactions ($p < 0.01$) to reduce the chance of a type one error. However, due to the fact that six outcomes were studied, multiple significance tests were conducted so it is possible that some statistically significant findings arose by chance.

- **Bias**

Bias is defined as the deficiency of internal validity of a study [178]. Although this study was nested within a RCT where participants were randomly allocated to the screen or control group,

participants chose to take part in the emotional outcomes sub study. It is therefore possible that those choosing to participate differed from those choosing not to participate. As the participation rate was very high (92.42%) and similar across screening groups (EarlyCDT®-positive (93.47%), EarlyCDT®-negative (93.85%), control (90.13%)), any selection bias that occurred is likely to have only a minimal impact on the results. However, the ECLS study was unblinded and assessment of emotional outcomes could potentially be biased due to the control group procedure. For example, results of the current study showed an increase in negative emotional outcomes in the control group, which could be due to an increase in their awareness of their risk of lung cancer as a result of taking part in the ECLS study as well as their disappointment and frustration at being identified as high risk but then prevented from being screened [118]. Unfortunately it is not possible to recruit participants to a lung cancer screening trial without raising their awareness of their risk of lung cancer; so this was unavoidable. Consequently, differences in negative emotional outcomes between each of the screened groups and the control group may potentially underestimate, or overestimate, the emotional impact of lung cancer screening.

Finally, in the current study, participants were asked to report on their beliefs about lung cancer (IPQ-R), their perceived risk of developing lung cancer, their level of worry about getting lung cancer (LCWS), distress specific to lung cancer screening (IES), their use of healthcare services, their attitudes towards smoking and their smoking behaviour. Such topics could have been emotionally distressing and therefore altered participant's mood states by inducing fear and anxiety and therefore enhancing negative emotional outcomes. However, it is important to note that research on potentially emotionally distressing events has also reported that taking part was an emotionally positive experience for participants as they felt good about the possibility of helping other people, were able to discuss their experiences and gained new

insights [179]. Although no data was collected on the occurrence or impact of any negative emotional responses to the questionnaires themselves, it is important to note that participation rates and response rates over time were high in the current study. This would suggest that any emotional distress caused by completing the measures included in the questionnaires was minimal and therefore unlikely to have a considerable impact on results.

- **Confounding**

A confounding factor is associated with the intervention and has the potential to affect the outcome being measured [180]. There were only two differences in pre-randomisation characteristics between screening groups, suggesting they were well balanced. There were significantly more females in the EarlyCDT®-positive group and significantly more males in the EarlyCDT®-negative group. Smoking status was also significantly different between the three groups in that there were significantly more current smokers in the EarlyCDT®-negative group and significantly more former smokers in the EarlyCDT®-positive group. Both gender and smoking status were adjusted for in analyses. Confounding was further minimised in this study by undertaking adjusted analyses that controlled for ECLS minimisation variables as well as a range of additional variables that had the potential to impact on emotional outcomes. It is possible that some residual confounding remains if there were other important factors we did not measure in the study and if their prevalence varied between screening groups.

EarlyCDT®-positive

In terms of non-specific outcomes, results of this study suggest that receipt of an EarlyCDT®-positive test result does not have a clinically important impact on positive or negative mood,

which is reassuring. Although no studies exploring the emotional impact of lung cancer screening have included the PANAS, four studies administered other non-specific emotional outcome measures. The results of this study support those of the PLuSS study, where, although increases in state anxiety scores for the indeterminate group over time were significant, the differences between time points were small (table eight, page 135) and could not be considered clinically important[88]. One publication from the NELSON trial found that state anxiety scores were significantly higher at two months post-screening compared with pre-randomisation. The authors also claimed that this difference was clinically relevant based on their interpretation of the MID (half of a standard deviation of the mean)[90]. However, if we refer back to table eight (page 151), we can see that the mean score at pre-randomisation was 33.6 and had increased to 34.8 at two months post-screening (score range: 20 – 80). The absolute difference appears small and, as stated in chapter three, this MID should be interpreted with caution as a statistical definition does not take account of patients' views on the importance of such a difference in scores.

For lung cancer worry, no clinically important impact was found for frequency of worry or impact of lung cancer worry on mood or ability to perform daily activities. These findings are reassuring, particularly as worry about lung cancer did not impact daily life. However, results suggested that receipt of an EarlyCDT®-positive test result has the potential to have a clinically important impact on level of worry about the results of future tests and treatment, particularly at one month post-screening. This finding makes sense as the period between receipt of the EarlyCDT®-positive test result and the chest x-ray and CT scan will be characterised by high uncertainty: the EarlyCDT®-positive result confirms that there is a possibility that the participant has lung cancer but a diagnosis cannot be confirmed until the first chest x-ray and CT scan has taken place. If we refer back to section 2.1 (page 68), current and former smokers attending screening who

have been found to overestimate their risk of developing lung cancer [88], so it is possible that a number of participants take the view that a EarlyCDT®-positive result means they will receive a diagnosis of lung cancer, which raises their level of anxiety about the results of the chest x-ray and CT scan. As shown in table 26, the proportion of participants reporting anxiety does decrease over the three, six and 12 month time-points but is still higher than at pre-randomisation, which likely reflects on-going anxiety about the results of the six-monthly CT scans administered over the two-year period.

Impact of events scale scores were significantly lower at three, six and 12 months compared with one month post-screening. In terms of clinical significance, mean scores were in the moderate range at one, three and six months and then moved to the low range at 12 months post-screening. This finding shows that screening-specific distress reduces over time and did not move beyond the moderate concern range. This result is consistent with that of the NELSON trial, where it was found that IES scores were significantly higher at two months post-screening but had almost returned to pre-randomisation when the next measure was administered at 1.5 years post-screening[89,90].

EarlyCDT®-negative

In terms of non-specific outcomes, results of this study suggest that receipt of an EarlyCDT®-negative test result does not have a clinically important impact on positive or negative mood. In terms of positive affect, results are surprising. If we refer back to section 2.1 (page 68), current and former smokers attending screening have been found to overestimate their risk of developing lung cancer[88]. Furthermore, a study that examined attitudes towards lung cancer screening in socioeconomically deprived and heavy smoking communities in the UK found that

participants had high levels of fear and fatalistic beliefs about lung cancer[155]. In view of these findings, it was hypothesised that positive affect scores would significantly increase following screening as a result of reassurance. Furthermore, no statistically significant differences were found between the EarlyCDT®-positive group and the EarlyCDT®-negative group for positive affect scores across time or at each study time-point. As previously stated, to the author's knowledge, this study is the first that has explored the impact of the screening for lung cancer on positive emotional outcomes. Therefore, at present, there are no results from lung cancer screening studies to compare our findings with. However, one publication from the UK flexible sigmoidoscopy (FS) screening trial compared specific positive emotional outcomes at three to six months post-screening between participants with three different types of test result: test negative (no polyps detected), lower-risk polyps detected (removed during FS) and higher-risk polyps detected (participant referred for colonoscopy) [138]. Positive emotional outcomes were measured using three items from the positive emotional subscale of the Psychological Consequences Questionnaire (PCQ) of screening (e.g., *'do you think that your experience of having the Flexi-Scope test has given you a greater sense of well-being?'*). A single item, also taken from the PCQ, assessed reassurance *('do you think that your experience of having the Flexi-Scope test has given you a sense of reassurance that you do not have bowel cancer?'*). When groups were compared, no statistically significant differences were found in reported positive emotional consequences of screening or reassurance. This finding supports our result that there were no statistically significant differences in positive affect scores when the EarlyCDT®-positive and the EarlyCDT®-negative were compared at each study time-point. Taken together, results from both the UK FS Trial and our study are interesting because they found that a negative test result did not impact specific and generic positive emotional outcomes. However, it is important to note that the UK FS Trial measured emotional outcomes between three and six months post-screening, so it is possible that any increases in positive

mood had subsided. An interesting, and important, avenue for future research would be to investigate the impact of lung cancer screening on specific positive emotional outcomes in order to see if there is an increase in positive mood in participants with a negative test result or if results support those of the UK FS Trial.

For lung cancer worry, no clinically important impact was found for frequency of worry or impact of lung cancer worry on mood or ability to perform daily activities. However, the proportion of participants who reported anxiety about the results of future tests/treatment gradually increased over time, from 11.36% at pre-randomisation to 20.42% at 12 months post-randomisation. This finding could be considered clinically relevant and further research is required to identify potential reasons for this.

Finally, no statistically significant differences for IES scores were found between time-points. However, logarithmic transformed scores were found to be significantly lower at three, six and 12 months post-screening compared with one month post-screening. It is possible that this finding may have been the result of type one errors (discussed above, page 343) as the absolute differences were small in magnitude. Our results that receipt of an EarlyCDT®-negative had no negative impact on distress specific to lung cancer screening is consistent with two publications from the NELSON trial, which reported significantly lower levels of lung cancer specific distress at two months [89,90] and at 1.5 years post-screening [89] when compared with pre-randomisation scores.

Control

Results of this study suggest that being randomised to the control group does not have a clinically important impact on positive or negative mood, which is reassuring. Furthermore, no clinically relevant impact was found for frequency of worry or impact of lung cancer worry on mood or ability to perform daily activities. However, it is important to note that there were no statistically significant difference for the above four outcome measures between the control and EarlyCDT®-positive groups across time or at each study time-point. This finding suggests that taking part in the ECLS study enhanced the control groups awareness of their risk of lung cancer as well as induce disappointment and frustration at being identified as high risk but then prevented from being screened, which reflects the finding of the UKLS trial [118] and the DLCST [115]. Finally, as with the EarlyCDT®-positive and the EarlyCDT®-negative groups, anxiety about the results of future tests/treatment was significantly higher at one, three, six and 12 months post-screening when compared with pre-randomisation. This finding could be considered clinically important, particularly as the proportion of control participants reporting anxiety at 12 months was 12.01% higher than at pre-randomisation.

4.5.3. Strengths and limitations

There are a number of strengths and limitations concerning this study, which will be discussed in relation to the types of outcomes administered, measurement time-points, and control group procedure.

1. Outcome measures

First, a broad spectrum of both specific and non-specific negative emotional outcomes were administered. This enabled us to assess whether screening had a more general emotional impact or only impacted emotions specific to lung cancer or lung cancer screening. It is important to note though that there was no defined minimal clinically important difference for the PANAS or the LCWS. This study was also the first to examine the potential positive emotional impact of lung cancer screening. However, only one non-specific measure of positive emotional outcomes was administered. In addition to continuing to explore the impact of lung cancer screening on non-specific positive emotions, future research should seek to administer a specific measure with high content validity, such as the COS-LC when it is available for wider use.

In terms of the use of the PANAS, it must be noted that the PANAS can be administered to measure both state (situational) and trait (dispositional) affect[181]. As previously stated, in the current study, there were statistically significant differences in scores for all three groups post-screening. However, the differences in scores between time-points were very small and could not be considered clinically important. In terms of this finding, it could be argued that the PANAS functioned more as a measure of trait affect rather than state affect. However, in the current

study, both negative and positive affectivity would in fact be expected to be reactive as a mood state due to the use of short-term instructions written in the questionnaire (Appendix seven, page 500):

> "This questionnaire lists a number of words that people often use to describe different feelings and emotions. Read each item and then tick the appropriate answer in the space next to the word. **Indicate the extent you have felt this way over the past week**."

According to the researchers who developed the PANAS, when used with short-term instructions, both scales will be sensitive to changes in mood [162]. When longer-term instructions are provided (e.g., "Indicate the extent you have felt this way over the past year" or "indicate the extent you feel this way in general"), then PANAS scores should remain relatively stable over time as they reflect trait affect. Due to the use of short-term instructions, it is highly possible that screening for lung cancer has no clinically important impact on positive or negative mood in both the short and longer term, which is reassuring. However, on reflection, the short form of the PANAS should have been administered in this study[182]. The short form includes 10 items, five of which make up the positive affect subscale (inspired, alert, excited, enthusiastic, determined) and five that make up the negative affect subscale (afraid, upset, nervous, scared, distressed)[183]. The short form of the PANAS has been found to have good reliability (Cronbach's $\alpha = 0.78$ for positive affect and 0.87 for negative affect)[183]. As multiple study questionnaires were administered, which were between 12 and 16 pages long, response fatigue had the potential to occur. Response fatigue has been found to be a particular concern for specific groups, which include older people [184]. Although response rates for the current study were high, data quality could have been reduced due to the length of the questionnaires [184]. Therefore,

future research administering the PANAS as one of a number of emotional outcome measures should consider using the short form.

2. Measurement time-points

Emotional outcome measures were administered up to 12 months post-screening so the long-term emotional impact of lung cancer screening could be explored. Outcome measures were also administered at four follow-up time points (one, three, six and 12 months), which enabled short term emotional outcomes to be investigated as well as trends in outcomes by screening group over time. However, it is important to note that the pre-randomisation questionnaire was administered on the day that participants attended the clinic to provide a blood sample. This cannot be considered a true measure of baseline mood as it was potentially contaminated by the knowledge of possibly being screened for lung cancer.

A further limitation concerning measurement time-points is that emotional outcomes were not measured between screening and receipt of test results. The stress and coping model (described in section 2.3.3) stipulates that an individual's appraisal of a stressful situation can change depending on the *stage* of the stressor [125]. Lung cancer screening consists of an anticipatory stage (pre-screening), a waiting stage (post-screening but before receipt of test results) and an outcome stage (post-test results). According to the stress and coping model, each stage would impact emotions and emotions would be expected to change across these different stages[125]. It is important to note that only three publications from two European trials, the DLCST [108] and the NELSON trial [90,114], have reported on emotional outcomes prior to screening. The results are described in section 2.2.1 (page 94). Due to the limited evidence, and heterogeneity in the methodology employed to assess emotional outcomes, the nature and

extent of any anticipatory emotions in lung cancer screening is unclear. Furthermore, there has been no detailed investigation of the emotional impact of waiting for test results. The NELSON trial was the only study to report on the emotional impact of waiting for test results. However, the findings do offer some important insights that must be investigated further [90,114]. For example, although a significant improvement in scores post-screening was found when compared with pre-screening scores [90,114], the publication that administered measures prior to randomisation reported that scores after screening were still significantly worse than pre-randomisation scores [114]. Furthermore, approximately half the participants reported that they experienced discomfort while they waited for the results of the CT scan or had dreaded receiving their results [114]. These participants had significantly higher anxiety and distress scores while waiting for results. In view of this finding, the authors recommend minimising the waiting time for test results[114]. However, it is important to note that this could incur a greater cost financially and there are also procedures to determine the reliability of test results that would need to be considered. Therefore, before this recommendation can be implemented, or interventions developed to support participants during this stage in screening, additional research must be conducted so that the emotional impact of waiting for test results can be more clearly understood. For example, we need to know the nature and extent of such emotional impact. It would also be helpful to know what factors mediate such emotional responses.

3. Control group procedure

The control group cannot be considered a true control group as taking part in the ECLS study had the potential to enhance their awareness of their risk of lung cancer as well as induce disappointment and frustration at being identified as high risk, having blood taken, but then prevented from being screened [118]. Therefore, the lack of differences in negative emotional

outcomes between the control group and the EarlyCDT®-positive group could be biased and underestimate the emotional impact of receiving an EarlyCDT®-positive result. However, as previously stated, it is not possible to recruit participants to a lung cancer screening trial without raising their awareness of their risk of lung cancer. As discussed in section 2.3.2, the authors of the DLCST suggested that future studies exploring the emotional impact of cancer screening should compare three groups: a screen group, an unblinded control group and a blinded control group who are unaware of the intervention and that they have been randomised to the control group [115]. Future clinical trials could look to implement this method. However, it is important to note that administering questionnaires containing measures of lung cancer and screening-specific distress could possibly increase lung cancer worry in the blinded control group. A potential way to overcome the issue of raised emotional distress in the control group could be to conduct qualitative interviews with participants to explore in more depth their emotional reactions of being randomised to the control group and obtain any suggestions for how the experience of being in the control group could be improved. The results from this study could inform future cancer screening trials as well as other unblinded trials.

4.5.4. Generalisability

Overall, our study population is likely to be similar to those expected to be offered lung cancer screening in the UK. However, there are several aspects that do limit the generalisability of results. First, this study was only conducted within the context of one clinical trial, so findings may not be generalisable to other clinical trials or patient populations. Also, if we were refer back to the ECLS study inclusion criteria (table 6, page 61), eligible participants were:

- Male or female aged 50 years to 75 years

- Current or ex-smokers with at least 20 year pack history, or
- Those with less than 20 years pack history but with family history of lung cancer in a first degree relative (mother, father, sister, brother, child).

It is therefore questionable as to what extent the results of the current study are generalisable to low risk individuals or to other high risk individuals who could potentially be eligible for lung cancer screening, for example, individuals exposed to asbestos, those with a prior diagnosis of chronic obstructive pulmonary disease, or people exposed to high levels of air pollution. Please see chapter one, pages 30 to 37, for a list, and discussion of, the different risk factors for lung cancer. Finally, it is important to note that study participants were predominantly Caucasian (98.55%). As stated in section 3.4.2, there is evidence that ethnic minorities are less likely to take part in cancer screening [151]. Several potential reasons have been identified for this, which include higher levels of cancer fear and fatalism[152,153]. In view of this finding, it is unclear as to what extent the findings from this study may be generalisable to individuals from other ethnic groups.

4.5.5. Implications for future research

The findings from this study strengthen the evidence base on the emotional impact of screening for lung cancer. However, there are still unanswered questions that future research in this area should address. First, it is important that further research continues to administer positive emotional outcome measures. To reiterate section 2.1, in order to ensure that the benefits of lung cancer screening outweigh the harms, emotional benefits must be explored. In addition, if positive emotional responses are demonstrated in screening participants, especially those who do not benefit from screening, then this could provide a rationale for introducing or continuing a

screening programme. A theoretical framework, introduced in section 2.3.3 (page 114), has also emphasised the importance of measuring positive emotional outcomes alongside negative emotional outcomes. Although the current study found no clinically important impact of screening on positive affect, non-specific outcome measures should still be administered in order to confirm or contest this finding and add to the evidence base. In addition, the potential impact of lung cancer screening on specific positive emotional outcomes has not yet been explored. In order to investigate this, the positive emotional subscale of the Psychological Consequences Questionnaire (PCQ) of screening could be administered, or the Consequences of Screening-Lung Cancer (COS-LC) when it is available for wider use.

As discussed in section 4.5.4, little is known about pre-screening emotional impact as well as the potential emotional impact of waiting for test results following screening. It is important that efforts are made to administer emotional outcome measures at these time points. Research should also look to administer the first emotional outcome measure before participants are invited to take part in lung cancer screening in order to obtain a more accurate measure of baseline mood.

To date, research has measured the emotional impact of lung cancer screening by administering questionnaires containing emotional outcome measures. Only the DLCST used an alternative method of data collection, which involved measuring participant's use of anti-depressive or anti-anxiety medication. An interesting avenue for future research could be to explore the role of biomarkers (e.g., cortisol levels) as an indicator of emotional distress.

Finally, to the author's knowledge, no qualitative studies have explored the positive and negative emotional impact of lung cancer screening. On reflection, this should have been done as part

of the current study in order to explore in more depth some of the findings, particularly the control group's emotional reactions to not being screened. As screening specific distress in the EarlyCDT®-positive group was significantly higher than in the EarlyCDT®-negative group at one, three and six months post-screening, and in the 'moderate concern' range, it would be useful to investigate the EarlyCDT®-positive groups thoughts on their result as well as establish whether any additional support could be provided to reduce levels of distress in the short-term. It is important that qualitative studies are undertaken as part of future lung cancer screening trials to explore these findings.

It is important to note that changes in anxiety about future tests/treatment was clinically relevant for all three screening groups. The two models introduced in chapter 2 (stress and coping model and the SRM of illness beliefs) emphasise that individual responses to a stressor, such as lung cancer screening, will vary. It is important to identify the different factors that could potentially influence anxiety about future tests/treatment so that the individuals who may be vulnerable to such anxiety can receive appropriate support, if required. The next chapter of this thesis, chapter five, explores potential predictors of anxiety.

4.5.6. Clinical implications

The evidence suggests that receipt of an EarlyCDT®-positive or an EarlyCDT®-negative test result has no clinically important emotional impact on positive or negative mood in the short or longer-term. Furthermore, there was no clinically important impact for frequency of lung cancer worry post-screening or impact of lung cancer worry on mood and ability to perform daily activities for either test result group. The EarlyCDT®-negative group did not experience screening-specific distress post-screening. Although screening specific distress in the

EarlyCDT®-positive group was significantly higher than in the EarlyCDT®-negative group at one, three and six months post-screening, it is important to note that the higher levels of distress were transient and did not move beyond the moderate concern range. Overall, the results for the above five outcomes are reassuring, particularly as the majority of participants in a lung cancer screening programme that administers EarlyCDT®-Lung will receive an EarlyCDT®-negative result, so it is good to know that they will not experience emotional harm post-test results. It is important that this information is communicated to individuals when they are invited to take part in lung cancer screening. Also, this evidence should be taken into account by those who are considering the benefits and harms of implementing a routine lung cancer screening programme. The findings for level of anxiety about future tests/treatment could be considered clinically important and warrants further research (as stated above).

Furthermore, as already stated in section 2.3.4, in one of the publications from the NELSON trial, the authors advise that the results letter sent to participants with indeterminate results explicitly states that their risk of lung cancer is small (< 2.5%) [90]. As current and former smokers attending screening have been found to overestimate their risk of developing lung cancer [88], such a letter could provide reassurance and decrease levels of distress specific to lung cancer screening as well as anxiety about the results of the first CT scan. In the ECLS study, the following information was provided in the Participant Information Leaflet (PIL) for the two different types of test result:

- **EarlyCDT®-negative group:** "This means it is very unlikely you have lung cancer at the moment. Between 98 and 99 out of every 100 people with a negative test do not have lung cancer at that time"

- **EarlyCDT®-positive group:** "This does not mean you definitely have lung cancer. Only 1 in 9 people with a positive test is likely to develop lung cancer within the next 2 years."

It is possible that this information reassured participants that their risk of being diagnosed with lung cancer was low, which could potentially explain why there was no clinically important change for five of the outcomes. Future screening programmes administering EarlyCDT®-Lung should consider keeping this information in the PIL as well as obtain participants views on the information and identify whether this had an influence on emotional outcomes.

4.5.7. Conclusion

The results of this study are reassuring as they indicate no clinically important changes for four specific and non-specific emotional outcomes following lung cancer screening. Although screening specific distress in the EarlyCDT®-positive group was significantly higher than that of the EarlyCDT®-negative group, it did reduce over time. The result that was more concerning was anxiety about future tests/treatment. The next chapter presents the results of a study that explored predictors of this outcome.

4.6. Additional information

Registration

Trial registration number: NCT01925625 (August 19, 2013)

Funding

Funding for the ECLS study, which included the RCT described in this chapter, was provided by the Chief Scientist Office, Scottish Government and Oncimmune Ltd.

Chapter 5. A longitudinal study exploring predictors of the emotional impact of screening for lung cancer

Chapter five of this thesis presents the results of a study that explored predictors of anxiety about the results of future tests/treatment following screening for lung cancer. A number of potentially important predictors were identified that were associated with higher levels of anxiety.

5.1. Introduction

In the emotional outcomes sub-study, reported in chapter four, the proportion of participants who reported anxiety about the results of future tests/treatment was significantly higher following screening than at pre-randomisation (pages 282 to 296) and this statistical difference was also considered clinically important. As anxiety increased across all three screening groups (EarlyCDT®-positive, EarlyCDT®-negative, control), it was important to identify factors that could influence an individual's level of anxiety about the results of future tests/treatment.

The current study aimed to explore a range of potential sociodemographic, behavioural, clinical and psychological predictors of anxiety about the results of future tests/treatment. A number of these predictors have already been investigated in the context of lung cancer screening: age, gender, ethnic origin, education level, socioeconomic deprivation, marital status, smoking status, smoking pack years, type of test result, and family history of lung cancer. The systematic review conducted as part of this PhD identified smoking status, female gender and receipt of an

indeterminate test result as well established predictors of negative emotional outcomes following screening. Although four lung cancer screening studies have explored age as a potential predictor of emotional outcomes, results have been inconsistent[88-90,114,117,118]. At present, there is very little published research on education (one study[88]), ethnic origin (two studies[88,118]), socioeconomic deprivation (one study[118]), marital status (one study[88]), smoking pack years (one study[89,90]), and family history of lung cancer (one study[118]). This study therefore aimed to provide additional evidence and advance our understanding of the association between the above six factors and emotional outcomes following lung cancer screening.

The present study is, to the author's knowledge, the first to investigate work status as a potential predictor of emotional outcomes following cancer screening. It is possible that work status could predict anxiety about the results of future tests/treatment. For example, participants may be concerned about being given a diagnosis of lung cancer and the financial consequences of missing work to receive treatment as well as the impact that lack of income may have for their family.

Finally, the present research also explores, for the first time, the effect of seven psychological factors on anxiety about the results of future tests/treatment. In chapter two (pages 114 to 120), two psychological frameworks were introduced that could guide future research on the emotional impact of lung cancer screening. One such framework was the Self-Regulation Model (SRM) of illness beliefs (described in pages 117 to 120). According to the SRM, when an individual is confronted with a potential health threat, they simultaneously form cognitive and emotional representations of the threat, which can directly impact on emotional outcomes[130]. Such representations have been found to influence emotional responses to cervical[131], colorectal[131,185], and ovarian[129] cancer screening. The SRM of illness beliefs was used to guide this study and a measure of illness representations (the Illness Perception Questionnaire-

Revised) was assessed as a potential predictor. Another model introduced in chapter two was the stress and coping model (pages 114 to 117), which specifies that the emotional impact of a stressor is determined by how an individual appraises the stressor. A study that explored how participants appraised and coped with stressors found that participants who had high scores on a measure of depressive symptomatology were more likely to appraisal a stressor as threatening and respond with high levels of worry and fear when compared with participants who had low scores[171]. With regard to this finding, it is possible that the participants who score higher on the measures of anxiety, depression and negative affect administered in this study may appraise future tests/treatments as more threatening and harmful and therefore respond with higher levels of anxiety than participants with lower scores. Furthermore, it is also possible that participants who report worry about lung cancer and higher impact of worry on mood and ability to perform daily activities may also appraise future tests/treatment as more threatening.

Chapter two also introduced the revised stress and coping model [126] (pages 115 to 116). According to the revised model, positive emotions can impact the stress process by replenishing coping resources and increasing the motivation required to maintain problem or emotion-focused coping in response to the stressor. As well as having an effect on coping, it has been stated that positive emotions can also help to reduce negative emotional outcomes[123]. Therefore, the current study also looked at the impact of positive affect on reported anxiety about the results of future tests/treatment. The following section lists the aims and hypotheses of this study.

5.2. Aims and hypotheses

The aim of this study was to identify the sociodemographic (e.g., age, gender), clinical (e.g., family history of lung cancer), behavioural (e.g., smoking status) and psychological (e.g., illness representations) factors measured pre-randomisation that predict whether participants reported anxiety about the results of future tests/treatment.

In line with the results of the systematic review (chapter 3) and the UK Lung Screening (UKLS) trial, it was hypothesised that current smokers, females and participants with a positive EarlyCDT®-lung test result would be significantly more likely to report anxiety about the results of future tests/treatment.

Although research exploring the impact of age is inconsistent, in line with the results of the UKLS Trial, it was hypothesised that older age would be associated with lower odds of reporting anxiety.

As previously stated, there is very little evidence for the impact of ethnic origin, education, socioeconomic deprivation, marital status, living situation, smoking pack years and family history of lung cancer on emotional outcomes. However, consistent with the limited evidence available, it was hypothesised that lower education level, higher level of socioeconomic deprivation, not owning or having a mortgage on a home (an indicator of deprivation), not being married or in a relationship, and having a family history of lung cancer would all be associated with higher odds of reporting anxiety. It was hypothesised that neither ethnic origin nor pack years would be associated with the odds of reporting anxiety.

In line with the stress and coping model, it was hypothesised that higher levels of anxiety, depression, negative affect and lung cancer worry would be associated with higher odds of reporting anxiety and that higher positive affect would be associated with lower odds of reporting anxiety.

5.3. Method

5.3.1. Study design

This study is nested within the ECLS study, which is described in chapter one of this thesis (section 1.6, pages 60 to 64). Recruitment began in January 2014 and data collection for PhD analyses was completed in May 2016. A copy of all documentation concerning ethical approval is included in appendix five (page 494 - 498).

5.3.2. Participants

Eligibility criteria

The eligibility criteria for this study was the same as that for the emotional outcomes sub-study reported in chapter four and are described in page 182.

Settings and locations of data collection

The ECLS study participants who took part in this study were recruited from 159 general practices in NHS Tayside and NHS Greater Glasgow & Clyde.

5.3.3. Procedure

The procedure for this study was the same as that for the emotional outcomes sub-study reported in chapter four (pages 183 to 185).

5.3.4. Outcome measure

Analyses exploring predictors of emotional outcomes following screening for lung cancer were only conducted for outcomes where scores differed significantly at one time point from the pre-randomisation score and could be considered clinically important. If we refer back to the results of the within groups analyses conducted as part of chapter four, changes in scores for anxiety about future tests/treatment (lung cancer worry scale) were statistically significant as well as clinically important. The item, which measured current level of anxiety about the results of future tests/treatment, used a 5-point Likert scale for responses, ranging from one (not at all) to five (almost all the time). Higher scores indicate a higher level of anxiety. Item scores were dichotomised into not anxious (not at all anxious or a little anxious) *vs*. anxious (somewhat anxious or anxious a lot or anxious almost all of the time).

5.3.5. Potential predictor factors

The variables listed below were included as potential predictors of reported anxiety about the results of future tests/treatment.

Sociodemographic variables

4. Age (years)

5. Gender (female *vs*. male)

6. Ethnic origin (White *vs*. other (African, dual heritage, undisclosed)).

7. Education (age at which participant left full-time education)

8. Socioeconomic deprivation (SIMD score and living situation (owned home, mortgaged) *vs*. (rented home, other))

9. Marital status ((civil partnership, married, in a relationship) *vs*. (divorced, separated, single, widowed))

10. Work status ((employed, self-employed) *vs*. (retired, unemployed but not looking for work, other) vs. (unable to work due to illness or disability, unemployed but looking for work))

Behavioural variables

1. Smoking status (former smoker *vs*. current smoker)

2. Smoking pack years (continuous variable)

Clinical variables

1. Type of test result (EarlyCDT®-positive, EarlyCDT®-negative, control)

2. First degree relative with lung cancer (yes *vs*. no)

Psychological variables

1. Anxiety and depression (HADS-A and HADS-D, described in chapter 4, pages 191 to 192)

2. Illness beliefs (IPQ-R)

Illness representations were measured by the Illness Perception Questionnaire-Revised (IPQ-R). In order to develop this measure, items with the highest factor loadings were selected from the IPQ-R used by Lancastle et al[129] to measure beliefs about ovarian cancer risk and were adapted to refer to lung cancer or lung cancer risk. Seven items were included in this measure. Each item assessed various aspects of an individual's perception of lung cancer and their lung cancer risk:

- Personal control ("What I do can affect my risk of getting lung cancer"),
- Emotional representations ("When I think about my risk of getting lung cancer, I get upset"),
- Illness coherence ("I do not know how likely it is that I might get lung cancer"),
- Prevention/control of lung cancer ("Finding lung cancer early can improve my chances of survival"),
- Nonspecific consequences ("Lung cancer would have a big impact on my life"),
- Timeline ("Lung cancer lasts for a long time"), and
- Detection/control ("A blood screening test can accurately detect lung cancer").

Reponses for each item were recorded on a five-point Likert scale ranging from one (strongly disagree) to five (strongly agree). Item scores were dichotomised into agree (strongly agree or agree) *vs.* disagree/neutral (strongly disagree or disagree or neutral). Scores on each of the seven IPQ-R items were assessed separately as predictors of current level of anxiety about the results of future tests/treatment.

3. Frequency of worries about getting lung cancer and impact of lung cancer worry on mood and daily activities (LCWS, described in chapter 4, page 186)

4. Positive and negative affect schedule (described in chapter 4, page 185 - 186)

4.3.6. Missing data

Handling of missing data has been described in chapter four, page 193.

4.3.7. Data checking prior to analysis

Data checking has been described in chapter four, page 194.

4.3.8. Statistical methods

Data analysis for this study was undertaken using Stata Statistical Software version 14 [173]. Linearity was assessed for all continuous variables. If variables were non-linear, then they were categorised based on their distribution.

First, univariate analyses for each predictor factor (listed above) for the outcome were undertaken using random effects logistic regression models with observation at level 1 and participant at level 2, with each predictor factor included as a covariate. Significance was assessed using likelihood ratio tests. Linearity of the relationship between covariates and outcome variables was checked by adding higher order term to models, and assessed using likelihood ratio tests (LRTs). All predictors with a p value of <0.2 on univariate analysis were assessed for inclusion in the multivariable model. These were all added to the model and removed one by one in order of decreasing p value and testing the significance of their exclusion using LRTs with a p value of <0.05 taken as significant. Those that had a LRT p value ≥0.05 were left out of the model. Once all predictors that could be removed had been removed, those that had been removed were reassessed for inclusion using LRTs as above. Collinearity was assessed using the covariate correlation matrix and variance inflation factors.

5.4. Results

5.4.1. Participant flow

This has been reported in chapter four, pages 200 to 204.

5.4.2. Pre-randomisation data

Pre-randomisation data for the all of the above predictors are reported in table 10 (page 216) in chapter four. As illness representations were not included in chapter four, pre-randomisation data for the IPQ-R amongst the participants included in this analysis is described and compared by screening group in table 41. The majority of participants (90.71%) reported that what they did could affect their risk of getting lung cancer and 64.86% did not know how likely it was that they might get lung cancer. In terms of emotional representations, 45.26% of participants reported that they got upset when they thought about their risk of getting lung cancer. It was found that 97.27% of participants thought that detecting lung cancer early could improve their chances of survival and 64.49% believed that a blood screening test could accurately detect lung cancer. In total, 96.48% reported that lung cancer would have a big impact on their life and 63.46% thought that lung cancer lasted for a long time. There were no statistically significant differences in illness representations between the three screening groups.

Table 41. Illness Perception Questionnaire-Revised scores amongst participants in each screening group (EarlyCDT®-positive, EarlyCDT®-negative, control)

	Total N = 1,032	**EarlyCDT®-positive** N = 321 (31.10%)	**EarlyCDT®-negative** N = 361 (34.98%)	**Control** N = 350 (33.91%)	**Results of statistical analyses***
Personal control (What I do can affect my risk of getting lung cancer)					
Agree	928 (90.71%)	289 (91.17%)	315 (88.48%)	324 (92.57%)	$\chi^2(2) = 3.61$
Disagree	95 (9.29%)	28 (8.83%)	41 (11.52%)	26 (7.43%)	P = 0.164
Emotional representations (When I think about my risk of getting lung cancer, I get upset)					
Agree	463 (45.26%)	140 (44.16%)	173 (48.32%)	150 (43.10%)	$\chi^2(2) = 2.16$
Disagree	560 (54.74%)	177 (55.84%)	185 (51.68%)	198 (56.90%)	P = 0.339
Illness coherence (I do not know how likely it is that I might get lung cancer)					
Agree	657 (64.86%)	204 (65.18%)	238 (67.61%)	215 (61.78%)	$\chi^2(2) = 2.63$
Disagree	356 (35.14%)	109 (34.82%)	114 (32.39%)	133 (38.22%)	P = 0.268

Prevention/control of lung cancer (Finding lung cancer early can improve my chances of survival)					
Agree	997 (97.27%)	306 (96.23%)	351 (97.77%)	340 (97.70%)	$\chi^2(2) = 1.89$
Disagree	28 (2.73%)	12 (3.77%)	8 (2.23%)	8 (2.30%)	P = 0.389
Nonspecific consequences (Lung cancer would have a big impact on my life)					
Agree	987 (96.48%)	307 (96.85%)	339 (94.96%)	341 (97.71%)	$\chi^2(2) = 4.11$
Disagree	36 (3.52%)	10 (3.15%)	18 (5.04%)	8 (2.29%)	P = 0.128
Timeline (Lung cancer lasts for a long time)					
Agree	646 (63.46%)	200 (62.89%)	219 (61.52%)	227 (65.99%)	$\chi^2(2) = 1.57$
Disagree	372 (36.54%)	118 (37.11%)	137 (38.48%)	117 (34.01%)	P = 0.456
Detection/control (A blood screening test can accurately detect lung cancer)					
Agree	661 (64.49%)	199 (62.58%)	243 (67.88%)	219 (62.75%)	$\chi^2(2) = 2.76$
Disagree	364 (35.51%)	119 (37.42%)	115 (32.12%)	130 (37.25%)	P = 0.251

* Pearson's chi-squared test

5.4.3. Univariate analyses

Table 42 presents the results of the univariate analyses for each predictor factor. The following variables (with p values < 0.2) were assessed for inclusion in the final model:

1. Sociodemographic: age, gender, ethnic origin, age on leaving full-time education, SIMD score, marital status, living situation

2. Behavioural: smoking status, smoking pack years

3. Clinical: first degree relative with lung cancer

4. Psychological: HADS-A, HADS-D, personal control (IPQ-R), emotional representations (IPQ-R), illness coherence (IPQ-R), prevention/control of lung cancer (IPQ-R), timeline (IPQ-R), detection/control (IPQ-R), frequency of worry about getting lung cancer someday (LCWS), impact of lung cancer worry on mood and ability to perform daily activities (LCWS), positive affect and negative affect.

Table 42. Univariate analyses for sociodemographic, clinical, behavioural and psychological predictors of current level of anxiety about the results of future tests/treatment

Variable	OR (95% CI)	P value
Time		
Three month vs. one month	0.99 (0.71 to 1.40)	P = 0.051
Six month vs. one month	1.16 (0.83 to 1.62)	
12 month vs. one month	1.52 (1.08 to 2.14)	
Type of test result		
EarlyCDT®-positive *vs*. control	1.39 (0.77 to 2.50)	P = 0.251
EarlyCDT®-negative vs. control	0.83 (0.47 to 1.49)	
1. Sociodemographic variables		
Age, years	0.92 (0.89 to 0.96)	P < 0.001
Gender		
Female *vs*. male	1.60 (0.99 to 2.58)	P = 0.063
Ethnic origin		

White vs. other (African, dual heritage, undisclosed)	0.16 (0.02 to 1.12)	P = 0.072
Age on leaving full-time education, years	1.00 (0.95 to 1.06)	P = 0.904
Quintiles of the Scottish Index of Multiple Deprivation score		
2 *vs*. 1 (most deprived)	0.68 (0.36 to 1.26)	P < 0.001
3 *vs*. 1	0.36 (0.17 to 0.74)	
4 *vs*. 1	0.23 (0.10 to 0.51)	
5 (least deprived) *vs*. 1	0.13 (0.05 to 0.34)	
Marital status		
(civil partnership, married, in a relationship) *vs*. (divorced, separated, single, widowed)	0.24 (0.15 to 0.39)	P < 0.001
Work status		
(employed, self-employed) *vs*. (retired, unemployed but not looking for work, other)	0.88 (0.52 to 1.50)	P < 0.001
(unable to work due to illness or disability, unemployed but looking for work) *vs*. (retired, unemployed but not looking for work, other)	10.09 (5.42 to 18.80)	
Living situation		
(owned, mortgaged) vs. (rented, other)	0.17 (0.11 to 0.28)	P < 0.001
Smoking status		
Former smoker *vs*. current smoker	0.26 (0.16 to 0.43)	P < 0.001

Smoking pack years	1.01 (1.00 to 1.02)	P = 0.045
2. Clinical variables		
First degree relative with lung cancer Yes *vs*. no	1.54 (0.91 to 2.63)	P = 0.126
3. Psychological variables		
• **Hospital Anxiety and Depression Scale**		
HADS-Anxiety score	1.59 (1.47 to 1.71)	P < 0.001
HADS-Depression score	1.67 (1.50 to 1.86)	P < 0.001
• **Illness Perception Questionnaire Revised**		
Personal control (what I do can affect my risk of getting lung cancer) Agree *vs*. disagree/neutral	2.17 (0.90 to 5.21)	P = 0.090
Emotional representations (when I think about my risk of getting lung cancer, I get upset) Agree *vs*. disagree/neutral	10.18 (6.19 to 16.75)	P < 0.001
Illness coherence (I do not know how likely it is that I might get lung cancer)	2.02 (1.20 to 3.38)	P = 0.009

Agree *vs*. disagree/neutral		
Prevention/control of lung cancer (finding lung cancer early can improve my chances of survival) Agree *vs*. disagree/neutral	0.32 (0.08 to 1.29)	P = 0.126
Nonspecific consequences (lung cancer would have a big impact on my life) Agree *vs*. disagree/neutral	1.89 (0.47 to 7.65)	P = 0.378
Timeline (lung cancer lasts for a long time) Agree *vs*. disagree/neutral	2.59 (1.56 to 4.30)	P < 0.001
Detection/control (a blood screening test can accurately detect lung cancer) Agree *vs*. disagree/neutral	1.94 (1.17 to 3.21)	P = 0.013
• **Lung Cancer Worry Scale**		
How worried are you about getting lung cancer someday? Not worried *vs*. worried	13.31 (7.61 to 23.27)	P < 0.001
Impact of worry on mood and ability to perform daily activities (categorised into tertiles*)		
2 vs. 1	5.86 (3.31 to 10.38)	P < 0.001
3 vs. 1	55.14 (29.64 to 102.57)	

- **Positive and Negative Affect Schedule**

Positive Affect score	0.88 (0.86 to 0.91)	P < 0.001
Negative Affect score (categorised into quartiles**)		
2 vs. 1	2.60 (1.20 to 5.65)	P < 0.001
3 vs. 1	9.71 (4.77 to 19.78)	
4 vs. 1	43.56 (20.77 to 91.37)	

* Tertiles of impact of worry on mood and ability to perform daily activities (score range = one to ten): 1 (score: 2), 2 (score: 3), 3 (scores 4 – 10)

** Quartiles of negative affect (score range = 10 to 50): 1 (scores 10 – 11), 2 (scores 11.11 to 13), 3 (scores 14 to 18), 4 (scores 18.89 to 45)

5.4.4. Multivariable analyses

The results of the first multivariable model are presented in table 43. At 12 months post-screening, the odds of reporting anxiety about the results of current tests/treatment were 1.53 times higher than at one month post-screening (OR 1.53 95% CI 1.07 to 2.18, p = 0.018). One year of increase in age was found to reduce the odds of anxiety by 4% (OR 0.96, 95% CI 0.92 to 0.99, p = 0.008). White participants had 87% lower odds of being anxious than non-white participants and those who did not disclose their ethnic origin (OR 0.13, 95% CI 0.03 to 0.69, p = 0.016). Participants who owned or had a mortgage on their home had 44% lower odds of reporting anxiety than participants who did not own or had a mortgage on their home (OR 0.56, 95% CI 0.35 to 0.88, p = 0.011). Former smokers had 39% lower odds of anxiety than current smokers (OR 0.61, 95% CI 0.39 to 0.95, p = 0.031).

In terms of psychological variables, it was found that a one unit increase in HADS-A scores increased the odds of anxiety by 21% (OR 1.21, 95% CI 1.11 to 1.32, p < 0.001). Participants who reported that they got upset when they thought about their risk of lung cancer had 2.89 times higher odds of anxiety about the results of future tests/treatment when compared with participants who did not get upset about their risk of lung cancer (OR 2.89, 95% 1.80 to 4.65, p < 0.001). Participants who were worried about getting lung cancer had a 3.06-fold increase in odds of reporting anxiety when compared with participants who were not worried about getting lung cancer (OR 3.06, 95% CI 1.78 to 5.28, p < 0.001). Participants who reported the highest impact of lung cancer worry on mood and ability to perform daily activities had a 5.34 fold increase in odds of reporting anxiety about the results of future tests/treatments compared with participants who reported the lowest impact of lung cancer worry (OR 5.34, 95% CI 2.88 to 9.93, p <0.001). Finally, participants with higher negative affect scores had higher odds of reporting

anxiety than participants with lower negative affect scores (ORs, 95% CI's and p values for each quartile are reported in table 43).

The only significant interaction was found between living situation and impact of lung cancer worry on mood and ability to perform daily activities (table 44). High levels of lung cancer worry had a greater impact on anxiety about future tests in those who did not own/have a mortgage on their home (tertile 3 vs. tertile 1: OR 13.24, 95% CI 5.57 to 31.47, $p < 0.001$) than those who owned/had a mortgage on their home (tertile 3 vs. tertile 1: OR 2.81, 95% CI 1.33 to 4.29, $p < 0.001$).

Collinearity was assessed using the covariate correlation matrix and variance inflation factors (VIF). The mean VIF was 1.47 (range: 1.01 to 2.42). All *r*-values were < 0.5 with the exception of HADS-A and negative affect ($r = 0.577$). As the HADS-A is a commonly used standardised tool for measuring clinical anxiety, the decision was made to undertake a sensitivity analysis excluding negative affect. The second multivariable model is presented in table 43. Findings from the two models were broadly similar, with the exception of ethnic origin, which was no longer found to be significantly associated with anxiety, and HADS-D, which became statistically significant (one unit increase in HADS-D scores increased the odds of reporting anxiety by 12% (OR 1.12, 95% CI 1.01 to 1.25, $p = 0.033$)). The only variable where there was a greater than 10% change in the odds ratios between the two models was the impact of worry on mood and ability to perform daily activities, when the highest tertile (3) was compared with the lowest tertile (1). The mean VIF for the second model was 1.35 (range: 1.07 to 1.71). All *r*-values were < 0.5, therefore none of the covariates were highly correlated with each other.

Table 43. Multivariable analysis of factors associated with current level of worry about the results of future tests/treatments

Variable	Odds ratio* (95% CI)	P value	Odds ratio** (95% CI)	P value
Time				
Three month vs. one month	1.00 (0.71 to 1.43)	P = 0.970	0.96 (0.68 to 1.36)	P = 0.839
Six month vs. one month	1.14 (0.80 to 1.62)	P = 0.459	1.15 (0.81 to 1.61)	P = 0.434
12 month vs. one month	1.53 (1.07 to 2.18)	P = 0.018	1.51 (1.06 to 2.14)	P = 0.021
1. Sociodemographic variables				
Age, years	0.96 (0.92 to 0.99)	P = 0.008	0.96 (0.93 to 0.99)	P = 0.013
Ethnic origin				
White vs. other (African, dual heritage, undisclosed)	0.13 (0.03 to 0.69)	P = 0.016	-	-
Living situation* **				
(owned, mortgaged) vs. (rented, other)	0.56 (0.35 to 0.88)	P = 0.011	0.55 (0.35 to 0.86)	P = 0.009
2. Behavioural variables				

Smoking status				
Former smoker *vs*. current smoker	0.61 (0.39 to 0.95)	P = 0.031	0.61 (0.39 to 0.96)	P = 0.032
3. Psychological variables				
• **Hospital Anxiety and Depression Scale**				
HADS-Anxiety score	1.21 (1.11 to 1.32)	P < 0.001	1.22 (1.13 to 1.32)	P < 0.001
HADS-Depression score	-	-	1.12 (1.01 to 1.25)	P = 0.033
• **Illness Perception Questionnaire Revised**				
Emotional representations (when I think about my risk of getting lung cancer, I get upset)				
Agree *vs*. disagree/neutral	2.89 (1.80 to 4.65)	P < 0.001	2.94 (1.85 to 4.68)	P < 0.001
• **Lung Cancer Worry Scale**				
How worried are you about getting lung cancer someday?				
Not worried *vs*. worried	3.06 (1.78 to 5.28)	P < 0.001	2.76 (1.63 to 4.68)	P < 0.001
Impact of worry on mood and ability to perform daily activities (categorised into tertiles)***				P = 0.052
2 vs. 1	1.65 (0.93 to 2.91)	P = 0.086	1.75 (1.00 to 3.08)	P < 0.001

3 vs. 1	5.34 (2.88 to 9.93)	P < 0.001	6.42 (3.48 to 11.82)	

- **Positive and Negative Affect Schedule**

Negative Affect score (categorised into quartiles)				
2 vs. 1	1.51 (0.75 to 3.06)	P = 0.251	-	-
3 vs. 1	2.57 (1.33 to 4.97)	P = 0.005	-	-
4 vs. 1	2.82 (1.33 to 5.99)	P = 0.007	-	-

*Model one: time, age, ethnic origin, living situation, smoking status, HADS-A, emotional representations (IPQ-R), frequency of worry about getting lung cancer (LCWS), impact of lung cancer worry on mood and ability to perform daily activities (LCWS), negative affect

**Model two: time, age, living situation, smoking status, HADS-A, HADS-D, emotional representations (IPQ-R), frequency of worry about getting lung cancer (LCWS), impact of lung cancer worry on mood and ability to perform daily activities (LCWS)

*** Please note. When interaction analyses were conducted, a significant interaction was found between living situation and impact of lung cancer worry on mood and ability to perform daily activities for both models (model one: p = 0.003, model two: p = 0.006).

Table 44. Results of the significant interaction identified in the analyses for both multivariate models

	Odds ratio* (95% CI)	p value	Odds ratio** (95% CI)	p value
Rented or other				
Impact of lung cancer worry				
2 vs. 1	2.39 (0.98 to 5.83)	P = 0.055	2.38 (0.99 to 5.70)	P = 0.052
3 vs. 1	13.24 (5.57 to 31.47)	P < 0.001	14.61 (6.27 to 34.07)	P < 0.001
Owned or mortgaged				
Impact of lung cancer worry				
2 vs. 1	1.10 (-0.39 to 2.60)	P = 0.148	0.98 (-0.47 to 2.44)	P = 0.184
3 vs. 1	2.81 (1.33 to 4.29)	P < 0.001	2.80 (1.37 to 4.23)	P < 0.001

*Results are from the first multivariate model

**Results are from the second multivariate model

5.5. Discussion

5.5.1. Summary of the main findings

The aim of this study was to identify the sociodemographic, clinical, behavioural and psychological factors measured pre-randomisation that predicted whether participants reported anxiety about the results of future tests/treatment. Results of the first multivariable model found that the odds of reporting anxiety about the results of current tests/treatment were significantly higher at 12 months post-screening compared with one month post-screening. Older participants, white participants, former smokers and participants who owned or had a mortgage on their home had significantly lower odds of reporting anxiety than younger participants, non-white participants, current smokers and participants who did not own or have a mortgage on their home. Psychological variables associated with increased anxiety were: higher anxiety scores, higher negative affect scores, participants who reported that they were upset when they thought about their risk of lung cancer, participants who were worried about getting lung cancer, and those who reported the highest impact of lung cancer worry on mood and ability to perform daily activities. Results of the second multivariable model, excluding the negative affect scale, showed that ethnic origin was no longer associated with anxiety. However, it was found that a one unit increase in HADS-D scores increased the odds of reporting anxiety by 12%.

5.5.2. Discussion of findings

Sociodemographic factors

First, a one year of increase in age was found to reduce the odds of anxiety by 4%. This result supports those of the UKLS [118] and the PLuSS trial [88] but contradicts the results of two

publications from the NELSON trial, where no significant association between age and emotional outcomes was found [89,114]. Further quantitative research on emotional outcomes following lung cancer screening should continue to explore the impact of age by including it as a predictor variable. Qualitative research may also be helpful in order to identify any specific age-related concerns that may explain differences in anxiety about future tests/treatment.

White participants had 87% lower odds of being anxious about future tests/treatment than non-white participants and those who did not disclose their ethnic origin. Due to the small number of non-white participants, anxiety could be not assessed in specific non-white groups. As discussed in chapter three (page 169), there is evidence that ethnic minorities are less likely to take part in cancer screening [151]. A number of potential reasons have been identified that could account for reduced cancer screening uptake, such as low health literacy around cancer, fear and stigma about cancer, pessimistic attitudes about a cancer diagnosis and fatalism[152,153]. It is possible that such factors could explain why non-white participants had significantly higher levels of anxiety than white participants in this study. It is important to note, however, that this finding is contrary to that of two previous studies that explored the impact of ethnic origin on emotional outcomes following lung cancer screening. The PLuSS study found that ethnicity was not associated with scores on non-specific and specific emotional outcome measures across time-points[88] (see chapter 3, page 165) and the UKLS found that ethnicity was not associated with higher levels of lung cancer worry [118]. It must also be stated that the finding of this study could be the result of a type one error (false positive result), which is possible as multiple significance tests were conducted so there is the potential for a statistically significant finding to have arisen by chance, and also, the number of non-white participants was very small (n = 15, 1.45% of the sample). Also, ethnic origin was not included in the second model, which does raise questions concerning the strength and significance of its association with anxiety. It is

important that further research is undertaken to establish the association between ethnic origin and emotional outcomes following cancer screening.

Participants who owned or had a mortgage on their home had 44% lower odds of reporting anxiety than participants who did not own or had a mortgage on their home. In the current study, home ownership was included as an indicator of socioeconomic deprivation. To the authors knowledge, the UKLS trial is the only study to have included socioeconomic deprivation as a predictor of emotional outcomes following lung cancer screening[118]. Results showed that participants from more socioeconomically deprived areas had significantly higher levels of cancer worry than participants from less deprived areas [118]. This study supports the evidence from the UKLS. Furthermore, as discussed in chapter three, another study conducted as part of the UKLS trial found that groups with lower socioeconomic status were significantly more likely to decline participation in the trial (OR 0.56, $p < 0.001$) [119]. The authors state that a potential explanation for this finding is more fearful and fatalistic beliefs about lung cancer among groups with lower socioeconomic status, which could be attributed to, or strengthened by, an increased exposure to lung cancer in more deprived communities [119]. This could account for why groups with lower socioeconomic status in this study reported higher levels of anxiety about the results of future tests/treatment.

Behavioural factors

Former smokers had 39% lower odds of reporting anxiety about the results of future tests/treatment than current smokers. It is possible that differences in perceived risk could account for this finding, as former smokers have been found to have lower perceived risk of developing lung cancer compared with current smokers [88,118,145]. This finding supports the

results of the systematic review (chapter three), where three of four publications reported negative emotional outcomes in current smokers when compared with former smokers [88-90].

Psychological factors

Psychological variables associated with increased anxiety about future tests/treatment were: higher HADS-A scores, higher HADS-D scores (model two), higher negative affect scores (model one), participants who reported that they were upset when they thought about their risk of lung cancer (emotional representations), participants who were worried about getting lung cancer (LCWS), and those who reported the highest impact of lung cancer worry on mood and ability to perform daily activities (LCWS). As stated in in section 5.1, the SRM of illness beliefs and the stress and coping model informed the factors assessed as predictors in the current study. In line with the stress and coping model, it is possible that participants with poorer emotional wellbeing in general and those who worried more about their risk of lung cancer appraised lung cancer screening as more threatening and responded with high levels of anxiety about the results of future tests/treatment. In terms of illness representations, participants who reported that they got upset when they thought about their risk of lung cancer had 2.89 times higher odds of anxiety about the results of future tests/treatment when compared with participants who did not get upset about their risk of lung cancer ($p < 0.001$). This was the only representation found to be associated with reported anxiety. This result reflects those of Lancastle et al. who explored illness representations and cancer specific distress in women before they took part in screening for familial ovarian cancer [129]. Negative emotional representations of ovarian cancer risk were moderately associated with higher levels of ovarian cancer distress whereas cognitive illness representations were only weakly associated with

distress. It is possible that emotional representations have a unique impact on emotional outcomes following screening and this should be investigated further.

5.5.3. Strengths and limitations

1. Strengths

One of the key findings from the systematic review (chapter three) was that very little research has been carried out on predictors of emotional well-being post-screening. Furthermore, the studies that explored predictors were restrictive in the predictors measured. The main strength of this study is the inclusion of a wide range of potential predictors of anxiety about the results of future tests/treatment. This study was also theoretically informed. A striking observation from the literature on the emotional impact of lung cancer screening is that no studies appeared to have drawn upon relevant theoretical models to inform objectives and research design. The results of this study highlight the importance of using theory as the decision to include certain factors was done so based on theory (stress and coping model, SRM of illness beliefs). A number of these factors (anxiety, depression, negative affect, emotional representations) were found to be significantly associated with level of anxiety post-screening and could be the focus of interventions to reduce level of anxiety about the results of future tests/treatment. Finally, questionnaire response rates in the current study were excellent, which increased the statistical power of the study. Of the 1,096 participants sent a one month questionnaire, 1,013 (92.42%) returned it, thereby demonstrating high participation rates for the study. Questionnaire response rates also remained high over the three (90.28%), six (93.49%) and 12 month (93.43%) time-points.

2. Limitations

Several limitations to this study need to be acknowledged. First, although a strength of this study was the measurement of a wide range of predictors, it is important to note that the multiple hypothesis testing associated with measuring a greater number of predictors would have increased the potential of a type one error (false positive result) occurring. Second, although the stress and coping model informed the predictors assessed in the current study and the interpretation of the results, it is important to note that as a result of PhD projects being conducted almost concurrently, the study questionnaires were being developed as the systematic review was being conducted and a measure of coping strategies was not incorporated. Future research investigating the emotional impact of lung cancer screening should seek to include a measure of cognitive appraisal and a measure of coping strategies, such as the COPE [186].

Although time was included as a factor in the multivariable model, the impact of predictors at each study time-point was not explored. Therefore, it is unclear as to whether different factors predicted anxiety at different time-points and trends in anxiety by predictor could not be explored. However, it is important to note that investigating predictors at each time-point would have resulted in more hypothesis testing, which would have further increased the potential for type one errors. Finally, although questionnaire response rates in the current study were high, three participation biases identified in chapter four (pages 208 to 209) could have impacted the analyses presented in this chapter. First, a significantly greater proportion of non-participants were from the control group (34.37%) when compared with the EarlyCDT®-positive (20.93%) and EarlyCDT®-negative (25.58%) groups. As discussed in chapter four, the control group experienced an increase in negative emotional outcomes as a result of taking part in the ECLS

study. It is therefore possible that this was why no effect of screening group was found on level of anxiety about future tests/treatment. Furthermore, age (years) was significantly different between participants and non-participants (median age: 60 (participant) *vs*. 55 (non-participant), p = 0.002). The current study found that a one year of increase in age reduced the odds of anxiety by 4%, thereby, younger participants were more at risk of experiencing anxiety about the results of future tests/treatment. As younger participants were less likely to take part in the emotional outcomes sub-study, it is possible that the effect of age on current level of anxiety is underestimated. Finally, non-participants had significantly higher HADS-Anxiety scores than participants (median score: 7 (participant) vs. 8 (non-participant), p = 0.0186). The current study's finding that a one unit increase in HADS-A scores increased the odds of anxiety about future tests/treatment by 21% could again be underestimated as participants with higher HADS-A scores were less likely to take part.

5.5.4. Generalisability

This study was only conducted within a population with high levels of socioeconomic deprivation in two cities in Scotland. The study population was chosen to represent those at higher risk of lung cancer, but in view of the geographical location of the study, the study population was predominantly white, so our findings may not be generalisable to other ethnic groups. Other than ethnicity, our study population is likely to be similar to those expected to be offered lung cancer screening in the UK. The findings may also not be generalisable to populations at lower risk of lung cancer.

5.5.5. Implications for future research

It is important that the factors identified as predictors in this study are explored in more depth using qualitative methodology. First, age-related concerns could be investigated as well as potential ethnic differences that may result in increased levels of anxiety. As discussed previously, it has been suggested that a potential reason for reduced screening attendance among groups with lower SES is fearful and fatalistic beliefs about lung cancer, which could be attributed to, or strengthened by, an increased exposure to lung cancer in more deprived communities [119]. It would be useful to investigate beliefs about lung cancer amongst groups with lower SES and explore how such beliefs may be associated with higher levels of anxiety about results of future tests/treatment. The finding of this study, and the results of the systematic review, suggest that current smokers are more vulnerable to high levels of emotional distress during lung cancer screening compared with former smokers. Although no further research is required to verify this association, it is very important that future research does explore the underlying reasons for this difference in emotional outcomes so that interventions can be developed to mitigate against emotional harm during screening. Finally, it would be interesting to further examine the unique impact of emotional representations about lung cancer on emotional outcomes during screening. Future research should seek to administer the full Illness Perception Questionnaire, which contains additional items measuring emotional representations. In addition, qualitative research could look to examine the role of emotional representations in more depth.

5.5.6. Clinical implications

This study has identified a number of factors that are associated with higher levels of anxiety about the results of future test/treatment, which shows that there are subgroups who are vulnerable to experiencing higher levels of emotional distress. As stated in section 2.3.4, page 121, in one of the publications from the NELSON trial, the authors recommended that the results letter sent to participants with indeterminate results explicitly stated that their risk of lung cancer is small (< 2.5%) [90]. To reiterate section 4.5.6, pages 361 to 362, in the ECLS study, the following information was provided in the Participant Information Leaflet (PIL):

- **EarlyCDT®-negative group:** "This means it is very unlikely you have lung cancer at the moment. Between 98 and 99 out of every 100 people with a negative test do not have lung cancer at that time"
- **EarlyCDT®-positive group:** "This does not mean you definitely have lung cancer. Only 1 in 9 people with a positive test is likely to develop lung cancer within the next 2 years."

As well as conveying this information in the PIL, it could also be ensured that such information is communicated verbally to everyone taking part in a lung cancer screening programme when they first attend the clinic, particularly the vulnerable subgroups identified in this study (e.g., younger participants, non-white participants, current smokers and participants from areas with higher levels of socioeconomic deprivation). If participants are informed that their risk of lung cancer is small then this could help to reduce anxiety about the results of future tests/treatment.

To the author's knowledge, there is no published literature detailing any interventions that have been implemented to improve emotional outcomes in the context of lung cancer screening.

However, in terms of breast cancer screening, an RCT was recently conducted in Spain that explored whether a brief nursing intervention could reduce women's levels of anxiety prior to taking part in a population breast cancer screening programme [187]. In brief, the intervention consisted of the provision of verbal information about the screening programme (e.g., objectives of the programme, benefits of early detection, procedure) followed by the opportunity for women to discuss topics related to mammography and breast cancer. Women were then able to communicate any feelings of anxiety or fear that they had and were able to ask questions. The intervention lasted ten minutes (five minutes for information provision and five minutes for the emotional support). Anxiety was assessed before the mammogram using the State-Trait Anxiety Inventory (STAI). Compared with the control group, who did not receive the intervention, the intervention group were 60% less likely to report high state anxiety (OR 0.40, 95% CI 0.25 to 0.65, $p < 0.001$). No differences were found between groups for trait anxiety scores. The research team did not measure anxiety after screening, so it is unclear as to whether the effect of the intervention changed over time [187]. It is important to note that the intervention only took ten minutes to administer, which means that it has the potential to easily be incorporated as part of a screening programme. Although the intervention was conducted in the context of mammography screening, the concept, and its potential to be adapted for use in lung cancer screening for the high risk groups identified in the current study is worth exploring further, particularly with anxiety about the results of future tests/treatment as the outcome measure. However, before any communication strategies or interventions are developed, it is imperative that the identified risk factors are explored in more depth. As stated in section 5.5.5, future research must be conducted that explores the attitudes and perceptions towards lung cancer and lung cancer screening of these groups as well as seek to identify what support could be offered.

Chapter 6: A randomised controlled trial to explore the effect of the timing of monetary incentives on participation rates and questionnaire response rates in the ECLS study

Chapter six of this thesis presents the results of a randomised controlled trial (RCT) embedded within the emotional outcomes sub study (the results of which are presented in chapters four and five). At present, there is very little published research specifically regarding how to effectively use monetary incentives to enhance questionnaire response rates and maximise participant retention in clinical trials. This RCT evaluates the effect of timing of monetary incentives on study participation rates, questionnaire response rates over time, the number of reminders sent and the completeness of returned questionnaires over time. The results of this RCT add significantly to the body of evidence in this area and will be useful to clinical trialists.

6.1. Introduction

In the ECLS study, postal questionnaires were deemed a practical and cost-effective method to collect longitudinal data on emotional and behavioural outcomes from a sample of participants [188]. However, there were two main issues concerning the use of questionnaires in the ECLS study: non-participation and loss to follow-up. Both issues could result in non-responder bias as well as jeopardise the validity and generalisability of results and reduce the statistical power of

the sub-study [189,190]. In view of the potential for non-participation and loss to follow-up, it was important to identify approaches that increased participant recruitment to the study as well as maximise participant retention over time. In the following section, the evidence on strategies to enhance response rates to postal questionnaires in RCTs is discussed by drawing on the results of the publications included in a systematic review and the most recent empirical evidence published subsequent to the review.

Strategies to enhance response rates to postal questionnaires administered as part of RCTs

One Cochrane systematic review and meta-analysis, published by Brueton et al. in 2014, aimed to quantify the effect of strategies that can potentially increase participant retention in RCTs [191,192]. Included studies were RCTs that evaluated strategies to improve participant retention and were embedded within a host RCT. Thirty-eight studies met inclusion criteria: 28 were published, two were in the grey literature and eight were unpublished. The authors identified six types of strategy:

1. Incentive strategies (e.g., vouchers), 14 trials;
2. Communication strategies (e.g., telephone reminders), 14 trials;
3. Change in questionnaire formats (e.g., changing the order of questionnaire items), eight trials;
4. Behavioural strategies (e.g., goal setting and time management to enable completion of the trial), two trials;
5. Case management strategies (e.g., trial assistants managing participant follow-up by organising services to facilitate participants adherence to any follow-up appointments), one trial; and

6. Methodology strategies (e.g., an unblinded versus blind trial design), one trial.

To the authors knowledge, since Brueton et al's review [192], only one RCT has been published that has explored strategies for increasing follow-up questionnaire response rates. This RCT was published in 2016 and investigated three different strategies for enhancing response rates in an RCT of telehealth for depression [193]. These three strategies were: 1. A pre-call before the 8-month follow-up questionnaire was administered; 2. A research team photograph included with the 12-month questionnaire; and 3. An action-oriented ('ACTION REQUIRED') or standard ('Questionnaire reminder') 12-month email reminder. The results of the publications included in the review, and the recent empirical study, are described below.

Brueton et al [192] identified two strategies that had the clearest impact on postal questionnaire response rates in clinical trials:

1. Adding a monetary incentive

Compared with no monetary incentive, participants who received a monetary incentive were significantly more likely to return postal questionnaires (three trials with 3,166 participants, Risk Ratio (RR) 1.18, 95% CI 1.09 to 1.28, p<0.0001) [192].

2. Higher valued monetary incentives

Compared with lower valued monetary incentives (range: £5 to £10), higher valued incentives (range: £10 to £20) were significantly more effective at increasing postal questionnaire response rates (two trials with 902 participants, RR 1.12, 95% CI 1.04 to 1.22, p = 0.005) [192].

Three other strategies were found to increase questionnaire response. First, compared with a telephone reminder, recorded delivery was found to be more effective at increasing

questionnaires response rates (one trial with 192 participants, RR 2.08, 95% CI 1.11 to 3.87, p = 0.02). Second, an unblinded trial design, where participants knew their treatment allocation, was found to increase postal questionnaire responses compared with a blind trial design (one trial with 538 participants, RR 1.37, 95% CI 1.16 to 1.63, p = 0.0003). In one trial, a standard questionnaire mailing was compared with a total design method (TDM) package. The standard questionnaire mailing included a brown envelope with a return address stamped on, a computer-printed participant address label, and a self-addressed envelope folded and placed behind the forms [194]. The TDM package included a white envelope with the hospital logo and commemorative stamp, the participants address was hand-written, cover letters were hand-signed by the researchers and the self-addressed envelope was folded around the enclosed documents. Participants received a postcard one week after the questionnaire was sent. The postcard either thanked participants for their response or served as a reminder for non-responders. Two reminders were sent if no response was received [194]. The review reported that compared with a standard mailing the TDM package significantly increased postal questionnaire response (226 participants, RR 1.43, 95% CI 1.22 to 1.67, p < 0.0001). Although these three strategies appear promising, the authors of the review emphasise that only single trials have investigated the use of these strategies and therefore further evaluation is required [195].

Results of Brueton et al's review also indicate that, at present, it is unclear as to whether shorter questionnaires increase response rates when compared with longer questionnaires (five trials with 7,277 participants, RR 1.04, 95% CI 1.00 to 1.08, p = 0.07). It is also unclear if questionnaires that are directly relevant to the focus of the trial are more likely to increase questionnaire response compared with unrelated questionnaires (two trials with 3,893 participants, RR 1.07, 95% CI 1.01 to 1.14, p = 0.03).

Finally, 14 strategies have been found to have no significant impact on postal questionnaire response [192,193]. These strategies are listed in Figure 17. Although the results of Brueton et al's [192] review are very useful for trialists, there are a number of retention strategies that require further evaluation. For example, eleven strategies were only evaluated by single trials. The authors also stress that future RCTs should include evaluations of retention strategies at the design stage of a trial in order to ensure that statistical power and sample size are considered [192]. As stated above, Brueton et al [192] found that providing a monetary incentive, and higher valued monetary incentives, had the clearest impact on postal questionnaire response. In the section that follows, the impact of monetary incentives on postal questionnaire response in RCTs is further discussed.

1. Incentive strategies

- Addition of a non-monetary incentive (e.g., certificate, pen) compared to no addition of a non-monetary incentive (three trials with 6,322 participants, RR 1.00, 95% CI 0.98 to 1.02, p = 0.91) [192]
- Offer of a non-monetary incentive compared to no offer of a non-monetary incentive (two trials with 1,138 participants, RR 0.99, 95% CI 0.95 to 1.03, p = 0.52) [192]
- A monetary incentive compared with offering a prize draw (two trials with 297 participants, RR 1.04, 95% CI 0.91 to 1.19, p = 0.56) [192]

2. Communication strategies

- Sending a reminder to participants compared with no reminder (six trials with 3,401 participants, RR 1.03, 95% CI 0.99 to 1.06, p = 0.13) [192]
- Sending a monthly reminder compared with no extra reminder (one trial with 272 participants, RR 0.96, 95% CI 0.83 to 1.11, p = 0.57) [192]
- An action-oriented compared with a standard email reminder (one trial with 231 participants, OR 0.53 95% CI 0.19 to 1.49, p = 0.23) [193]
- Calling participants before a follow-up was questionnaire was administered compared with not calling participants (one trial with 188 participants, OR 0.38, 95 % CI 0.07 to 2.10, p = 0.27) [193]
- Priority postal delivery compared with regular postal delivery (three trials with 1,888 participants, RR 1.02, 95% CI 0.95 to 1.09, p = 0.53) [192]
- Sending questionnaires early (two to three weeks after trial follow-up visit) compared with not sending questionnaires early (one to four months after trial follow-up visit) (one trial with 664 participants, RR 1.10, 95% CI 0.96 to 1.26, p = 0.19) [192]
- Enhanced letters compared to a standard letter (two trials with 2,479 participants, RR 1.01, 95% CI 0.97 to 1.05, p = 0.70) [192]
- A research team photograph included with a questionnaire compared with no photograph (one trial with 251 participants, OR 0.84, 95 % CI 0.26 to 2.66, P = 0.76) [193]

3. Change in questionnaire formats

- Placing disease/condition specific questionnaire items before generic questions compared with vice versa (two trials with 9,435 participants, RR 1.00, 0.97 to 1.02, p = 0.75) [192]
- Long and clear questionnaires compared with shorter condensed questionnaires (one trial with 900 participants, RR 1.01, 95% CI 0.95 to 1.07, p = 0.86) [192]

4. Additional strategies

- Telephone survey compared with a monetary incentive and a questionnaire (one trial with 700 participants, RR 1.08, 95% CI 0.94 to 1.24, p = 0.27) [192]

Figure 17. Strategies found to have no significant impact on postal questionnaire responses in the review and meta-analysis published by Brueton et al. in 2014 [192] and the RCT published subsequent to the review [193]

The role of monetary incentives on postal questionnaire response rates in RCTs

Seven trials, embedded within five host RCTs, have examined the impact of monetary incentives on postal questionnaire response rates in RCT's. The results of two of the seven trials have not been published [192]. The characteristics and results of the publications that have reported on the use of monetary incentives in RCTs are presented in table 45.

Table 45. Characteristics and results of publications that have reported on monetary incentives to increase participant rates and questionnaire response rates in randomised controlled trials

Trial and country	Participants	Intervention group(s) and control	Outcomes reported	Main results
Addition of monetary incentive *vs.* no monetary incentive (two trials)				
Gates et al. 2009 [196] - Managing Injuries of the Neck Trial (MINT) - United Kingdom (UK)	Patients with whiplash injury taking part in the MINT trial (n = 2,144)	£5 voucher *vs.* No voucher	The number of postal questionnaires returned at the four and eight month follow-ups The overall number returned without chasing The overall number of non-responders	Across both time-points, compared with sending no voucher, sending a £5 voucher increased the number of questionnaires returned (RR 1.10, 95% CI, 1.05 to 1.16), the number returned without chasing (RR 1.14, 95% CI 1.05 to 1.24) and decreased the number of non-responders (RR 0.68, 95% CI 0.53 to 0.87). The effect of sending a voucher did not vary between time-points.

			The costs of following up each group	Costs per questionnaire returned were £12.35 for participants sent a voucher and £6.76 for participants not sent a voucher. The cost per additional questionnaire returned for participants who received a £5 voucher was £67.29. *No p values were reported in paper*.
Kenyon et al. 2005 [197] - Overview of the Role of Antibiotics in Curtailing Labour and Early delivery (ORACLE) - UK	Women who experienced preterm labour, or preterm rupture of membranes, taking part in the ORACLE trial who were sent a reminder questionnaire six weeks after being sent the initial study questionnaire (n = 722)	£5 voucher *vs*. no voucher	The number of postal questionnaires returned at the seven-year follow-up	When compared with sending no voucher, sending a £5 voucher resulted in an 11.7% (95% CI 4.7% to 18.6%) increase in the number of postal questionnaires returned ($\chi 2 = 10.6$, P = 0.001).

Addition of monetary incentive *vs* offer of prize draw entry (two trials)				
Kenton et al. 2007 [192,198], conference abstract* - Prevention of postnatal depression - Canada	Women at high risk of postnatal depression (n = 147)	$2 coin *vs*. entry in a prize draw for $50	The overall number of questionnaires returned [Please note. It is unclear as to when questionnaires were administered]	Compared with prize draw entry, participants who received a $2 coin were 1.14 (95% CI 0.95 to 1.37, *p value not reported*) times more likely to return questionnaires.
Kenton et al. 2007 [192,198], conference abstract* - Prevention of postnatal depression - Canada	Women at high risk of postnatal depression (n = 150)	$2 coin *vs*. entry in a prize draw for $50	The overall number of questionnaires returned	Compared with prize draw entry, participants who received a $2 coin were less likely to return questionnaires (RR 0.95, 95% CI 0.78 to 1.15, *p value not reported*).

Addition of a higher monetary incentive *vs*. a lower monetary incentive *vs*. no incentive (one trial)				
Bauer et al. 2004 [199] - Community Intervention Trial for Smoking Cessation (COMMIT) - United States	Current smokers taking part in the COMMIT trial (n = 300)	$10 cheque vs. $2 cheque vs. no cheque	Return of DNA specimen kit and postal questionnaire	Although there was no statistically significant effect of incentive size, it was found that 43% of the participants who received a $10 incentive returned their questionnaire compared with 34% of the participants who received a $2 incentive and 33% of the participants who received no incentive. *No results of significance tests or p values were reported in the paper*.
Offer of £20 shopping voucher *vs*. offer of £10 shopping voucher				
Bailey et al. (1), unpublished [192**] - Sexual health promotion trial	Young people taking part in the trial (n = 417)	Offer of £20 shopping voucher *vs.* offer of £10 shopping voucher	The number of three month follow-up questionnaires returned	Compared with the £10 shopping voucher, the offer of a £20 shopping voucher increased responses rates (RR 1.08, 95% CI 0.97 to 1.21, *p value not reported*).

- UK				
Addition of £10 shopping voucher and offer of £10 shopping voucher *vs.* addition of £5 shopping voucher and offer of £5 shopping voucher				
Bailey et al. (2), unpublished [192]** - Sexual health promotion trial - United Kingdom	Young people taking part in the trial (n = 485)	£10 shopping voucher (added to questionnaire or offered) *vs*. £5 shopping voucher (added to questionnaire or offered)	The number of three month follow-up questionnaires returned and chlamydia kit return	Compared to the £5 shopping voucher, the £10 shopping voucher increased response rates (RR 1.16, 95% CI 1.04 to 1.30 *p value not reported*).

*Please note: As this publication was a conference abstract, it was not possible to obtain data, so characteristics and results were extracted from Brueton et al's review [192]

** Please note: As data for this trial was not published, characteristics and results were extracted from Brueton et al.'s review [192]

Two trials explored the addition of a £5 voucher on questionnaire response rates when compared with no voucher [196,197]. The Overview of the Role of Antibiotics in Curtailing Labour and Early delivery (ORACLE) trial included participants who had already been sent a seven year follow-up questionnaire but had not yet returned it [197]. This group of participants were randomised to either receive a £5 voucher with their reminder questionnaire or not to receive a £5 voucher. It was found that addition of the monetary incentive significantly increased reminder questionnaire response rates. The Managing Injuries of the Neck Trial (MINT) also found that addition of a £5 voucher increased questionnaire response rates at a four month and eight month follow-up [196]. The MINT study also reported on the overall number of questionnaires returned without 'chasing.' 'Chasing' involved a second copy of the questionnaire being sent after two weeks. If no response was received, up to three attempts were made to contact the participant by phone. Participants who received a £5 voucher were more likely to return their questionnaire without any 'chasing' when compared with participants who did not receive a £5 voucher. The third outcome explored was the overall number of non-responders. It was found that participants who received a voucher were less likely to be non-responders than participants who did not receive a voucher. The final outcome was the cost of following up each group. The cost per additional questionnaire returned was reported to be £67.29 for participants who received a £5 voucher. In their discussion, the authors state that in a trial of 1,000 participants, it would cost less than £5,000 to increase the proportion of questionnaires returned by 7%, which is a small amount when compared with the total clinical trial budget. The authors conclude that providing an unconditional monetary incentive is therefore a cost-effective strategy [196].

Three RCTs investigated whether higher valued monetary incentives increased questionnaire responses when compared with lower valued monetary incentives[192,199]. Two of the RCTs were embedded within the same clinical trial, which focused on sexual health promotion in young

people. Both RCTs found that higher valued monetary incentives (range: £10 to £20) increased the proportion of three month follow-up questionnaires returned when compared with lower valued monetary incentives (range: £5 to £10) [192]. The other RCT, embedded within the Community Intervention Trial for Smoking Cessation (COMMIT) trial had three conditions: a $10 cheque (n = 100), $2 cheque (n = 100) and no cheque (n = 100) [199]. Although there was no statistically significant effect of incentive size, it was found that 43% of the participants who received a $10 incentive returned their questionnaire compared with 34% of the participants who received a $2 incentive and 33% of the participants who received no incentive.

Finally, two RCTs embedded within the same trial on prevention of postnatal depression evaluated the addition of a $2 coin compared with entry in a prize draw [192,198]. Contrasting results were found, with one trial reporting that participants who received the $2 coin were more likely to return study questionnaires compared with participants who were offered entry to a $50 prize draw, and the other reporting that participants who received the $2 coin were less likely to respond than those offered entry to the prize draw.

Based on the studies described above, several observations of the literature can be made. At present, the available evidence suggests that unconditional monetary incentives, and higher valued monetary incentives, appear to increase questionnaire response rates in RCTs. However, it must be emphasised that there is a paucity of evidence in this area as only seven RCTs, embedded within five host RCTs, have reported on the impact of monetary incentives on postal questionnaire response rates in RCTs [192]. Furthermore, there is substantial heterogeneity among trials in terms of the type of trial, population, and time points at which the outcomes were measured. It is therefore difficult to determine the extent to which results from these trials can be generalised to other RCTs. It is also important to note that clinical trials may administer postal

questionnaires at multiple time-points over a period of time. The MINT study is the only trial to have measured the impact of monetary incentives at multiple follow-up points, so at present it is unclear as to whether any effects of monetary incentives change with time so it cannot be determined if effects are transient or persistent. Finally, all studies administered unconditional monetary incentives (incentives sent with the questionnaire) as opposed to conditional incentives, where a participant is promised an incentive when they return the questionnaire. The potential role of conditional incentives has yet to be explored in the context of clinical trials. The next section describes the results of a Cochrane systematic review that reported on the impact of unconditional and conditional monetary incentives on postal questionnaire response rates.

The impact of timing of monetary incentives on postal questionnaire response rates

In 2009, an updated Cochrane systematic review was published that aimed to identify methods that enhanced response to both postal and electronic questionnaires [200]. The authors searched 14 electronic databases between 2003 and 2008 for RCTs that evaluated methods of increasing questionnaire response. Searches yielded 481 eligible trials that evaluated 110 distinct methods to enhance response rates to postal questionnaires. In line with Brueton et al's review, the most effective method was monetary incentives, which increased response rates two-fold (94 trials with 160,004 participants, OR 1.87, 95% CI 1.73 to 2.04) [200]. In terms of the timing of monetary incentives, it was found that participants who were sent a voucher with their questionnaire (unconditional monetary incentive) were more likely to respond than participants who were promised a voucher on receipt of their questionnaire (conditional incentive) (24 trials with 27,569 participants, OR 1.61, 95% CI 1.36 to 1.89). It is important to note, however, that there was significant heterogeneity amongst the results of the trials ($P < 0.00001$) [201]. Furthermore, it has been stated that the majority of studies included in the review were not conducted in healthcare

settings and did not include clinical trial participants [196]. It is possible that participants in a clinical trial may have different reasons for responding or not responding to a questionnaire administered as part of a trial that they have taken part in. For example, participants could be more likely to respond as they have committed to take part in the trial or they could be disappointed at the trial arm that they have been randomised to and therefore less likely to respond. The generalisability of the results from Edward et al's review to clinical trials may be limited and further research exploring the effect of the timing of monetary incentives in clinical trials is needed. Furthermore, unconditional monetary incentives could be more expensive, particularly in trials that administer multiple follow-up questionnaires if the effect on response rates is found to decrease with repetition. It would therefore be beneficial for trialists to know which is more effective: a monetary incentive sent with a questionnaire or a monetary incentive sent on receipt of a trial questionnaire. The current study was undertaken to explore the impact of the timing of monetary incentives on study participation rates and questionnaire response rates within the context of clinical trials.

In addition to exploring the effects of the timing of monetary incentives on participation and retention rates, we also explored the potential impact on the number of reminders sent across time and at each study time-point. This is an important outcome in the context of clinical trials as administering reminders increases administrative burden as well as cost. Furthermore, the number of reminders sent provides an indication of how quickly a questionnaire is returned. The timing of the return of outcome measures is particularly important in a number of clinical trials. For example, an aim of the ECLS sub-study was to explore the impact of type of test result on emotional outcomes. It was therefore important for us to capture emotional outcomes as soon as possible following receipt of test result. If there is no difference between unconditional and conditional monetary incentives in terms of study participation or response rates, but the speed

of response is enhanced by using unconditional incentives, then trialists may decide to administer unconditional monetary incentives as opposed to conditional monetary incentives.

The final outcome explored was the potential impact of the timing of monetary incentives on the completeness of returned questionnaires. The available evidence suggests that adding monetary incentives does not have a negative impact on the quality[10] of returned questionnaires [202]. However, this outcome has not yet been explored in the context of clinical trials so it is unclear as to whether the timing of monetary incentives will impact the quality of response. It is important that this is investigated as incomplete data can decrease the power of the study and increase administrative burden (e.g., potentially through telephone calls to collect missing data) as well as cost. The next section lists the aims and hypotheses of this RCT.

6.2. Aims and hypotheses

The primary aim of this RCT was to assess whether a £5 gift voucher sent with the one, three, six, and 12 month follow-up questionnaires increased the total proportion of ECLS study questionnaires returned across all study time-points, and at each study time-point, when compared with a £5 gift voucher sent on receipt of each questionnaire. It is important to note that this aim assesses whether timing of monetary incentive increases questionnaire study participation rates (response to the one month questionnaire) and questionnaire response rates at three, six and 12 months.

[10] Please note: the quality of responses has been measured by nonresponse to questionnaire items as well as length of answers to any open-ended questions.

In line with Edward et al's finding that participants who were sent a voucher with their questionnaire were more likely to respond than participants promised a voucher on receipt of their questionnaire (OR 1.61, 95% CI 1.36 to 1.89), it was hypothesised that sending a £5 gift voucher with each study questionnaire would increase questionnaire response rates across study time-points, and at each study time-point, when compared with promising a £5 gift voucher on receipt of each study questionnaire.

The two secondary aims and hypotheses of this study were as follows:

1. To identify whether the timing of monetary incentive has an effect on the number of reminder questionnaires sent across study time-points and at each study time point.

In line with the MINT study finding that participants who were sent a £5 gift voucher with their questionnaire were more likely to return their questionnaire without any 'chasing' (RR 1.14, 95% CI 1.05 to 1.24), it was hypothesised that that sending a £5 gift voucher with each study questionnaire would reduce the number of reminders sent across time, and at each study time-point, when compared with promising a £5 gift voucher on receipt of each study questionnaire.

2. To identify whether the timing of monetary incentive has an effect on the completeness of returned questionnaires across study time-points and at each study time point.

Consistent with results of studies that have explored the impact of monetary incentives on data quality [202], it was hypothesised that that sending a £5 gift voucher with each study questionnaire would have no effect on the completeness of returned questionnaires when compared with promising a £5 gift voucher on receipt of each study questionnaire.

6.3. Method

6.3.1. Trial design

This RCT was nested within the longitudinal follow-up analysis of behavioural and emotional outcomes in the ECLS study. A copy of all documentation concerning ethical approval is included in Appendix five, page 494 to 498.

6.3.2. Participants

Eligibility criteria

Participants were eligible if they were taking part in the ECLS study and had been selected to take part in the behavioural and emotional outcomes sub-study (please note: the analysis for psychological outcomes is presented in chapter 4 and chapter 5. Participants from all ECLS study groups (control, EarlyCDT®-positive and EarlyCDT®-negative) were eligible for this trial.

Settings and locations of data collection

ECLS study participants who took part in this trial were recruited from 159 general practices within the lowest quintile of deprivation (as measured by the Scottish Index of Multiple Deprivation (SIMD)) in NHS Tayside and NHS Greater Glasgow & Clyde.

6.3.3. Interventions

All participants were randomly allocated, in a 1:1 ratio within each screening group, to one of two trial arms:

1. Unconditional incentive group: the £5 gift voucher was sent *with* the study questionnaire.

2. Conditional incentive group: the £5 gift voucher was sent *on receipt* of the study questionnaire.

The cover letter included with each questionnaire stated that the voucher was to thank the participant their time and the places where the voucher could be spent were listed on the reverse of the letter. For the conditional incentive group, the questionnaire cover letter stated that the participant would be sent a voucher once they had completed and returned the questionnaire. The research team (LB and BY) sent participants the voucher on the same day that their questionnaire was received.

Questionnaire administration was identical for both groups. Study questionnaires were sent by the research team at one, three, six and 12 months post-randomisation. Each questionnaire was sent in a white envelope with an ECLS study logo on the front and included a cover letter and a 2nd class freepost envelope to return it. If a returned questionnaire was incomplete then the research team called the participant to complete the missing items by phone. A questionnaire was classed as incomplete if a measure had not been completed at all or if less than 50% of a measure had been completed.

Aside from the monetary incentive, a number of different strategies were employed to increase participation rates (response to one-month questionnaire) and response rates (completion of questionnaires administered at three, six and 12 months). First, a response deadline for return of questionnaires was listed on the cover letter of each questionnaire. A phone number was provided for participants to call the research team if they required assistance to complete questionnaires. The research team also called participants one week after the first follow-up questionnaire had been sent to check on postal delivery, offer assistance with questionnaire completion and provide an opportunity for participants to ask any questions. A reminder letter was sent with a duplicate questionnaire if no response was received within two weeks. Participants who were sent reminder letters at the three, six and 12 month follow-ups were contacted by phone one week after the reminder letter was sent to check on postal delivery.

Participants who indicated that they wished to be withdrawn from the study were sent no further questionnaires, or reminders, and were recorded as excluded at their request. If no response was received, then for the purposes of this RCT, participants were excluded after the point at which they did not return the questionnaire and recorded as non-responsive. Participants who received a diagnosis of lung cancer were withdrawn from the study subsequent to receiving the diagnosis.

6.3.4. Outcomes

The primary outcome of this RCT was the difference in the total proportion of questionnaires returned between the unconditional and conditional incentive groups across study time-points, and at all study time-points (one month, three month, six month and 12 month).

Secondary outcomes were as follows:

1. The difference in the proportion of reminders sent out between groups across study time-points and at each study time-point

2. The difference in the proportion of questionnaires with incomplete data between groups across study time-points and at each study time-point.

6.3.5. Sample size

It was estimated that a sample size of 279 participants in each group (conditional incentive group and unconditional incentive group) would have 80% power to detect an absolute difference of 10% assuming one month questionnaire response rates of 65% (conditional incentive group) and 75% (unconditional incentive group) with a 0.05 significance level. Output for the power calculation is included in Appendix nine, page 548.

6.3.6. Randomisation

Participants were stratified by study group (control, EarlyCDT®-positive and EarlyCDT®-negative) and randomly ordered on computer generated lists. The first 50% of each list were allocated to one of the two incentive groups (conditional or unconditional). This process ensured that equal numbers of participants from each of the three screening groups would be allocated to each incentive group. A Senior Software Programmer at the Health Informatics Centre, University of Dundee, conducted randomisation.

6.3.7. Statistical methods

Data was analysed using Stata 14 (Stata Corporation, College Station, TX, USA) under the supervision of DK. First, analyses were conducted to assess whether voucher condition had an effect on questionnaire response rates, reminders sent and incomplete data at each study time-point. Pearson's chi-squared test was used to test for statistical significance. Second, multivariate analyses were conducted. Random effects logistic regression was used to take account of repeated measures. The data had a two-level hierarchical structure with observations (data collected at each questionnaire time-point – level one) being clustered within participants (level two). All analyses were adjusted for ECLS minimisation variables: source region (NHS GCC/NHS Tayside), age, gender (female/male), and smoking status (current smoker/former smoker) as well as study group (control, EarlyCDT®-positive and EarlyCDT®-negative). Additional analyses were also conducted for each outcome, which were adjusted for the ECLS minimisation variables as well as screening group (EarlyCDT®-positive, EarlyCDT®-negative, control), socioeconomic deprivation (SIMD score) and whether the participant was invited to, and took part in, an interview for a qualitative study conducted as part of the ECLS study. For each objective, a model was estimated for each outcome (questionnaire response, reminders sent, and questionnaires with incomplete data) and included voucher condition (unconditional monetary incentive *vs*. conditional monetary incentive) and voucher condition interacted with study time-point.

6.4. Results

6.4.1. Participant flow

In accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines [203], participant progress through the different phases of the trial is illustrated in a flow diagram, Figure 6.2.

The total number of participants randomised to take part in the trial was 1,103: 551 were allocated to the unconditional incentive group and 552 to the conditional incentive group. Five participants in the unconditional incentive group and two participants in the conditional incentive group did not receive the allocated intervention.

A total of 1,081 (98.00%) of participants from the 1,103 selected to take part in the emotional outcomes sub-study were included in the analysis. The numbers included in the analysis for each voucher condition group are listed below and reasons for exclusion from the study analysis are provided.

4. Unconditional incentive group

In total, 539 participants were included in the analysis and 12 participants were excluded. The reasons for exclusion from the study analysis are as follows:

- No contact details available, so no questionnaires were sent (n = 1)
- Diagnosed with lung cancer before the one month questionnaire was sent (n = 1)
- Not sent the first questionnaire due a system error (n = 3)

- Returned questionnaires but were later found to have potentially been affected by the ECLS study protocol deviation (n = 4)
- Did not return any questionnaires but was found to have potentially been affected by the protocol deviation (n = 1)
- Excluded due to large number of grievances concerning ECLS study procedure, no questionnaires returned (n = 1)
- Had to withdraw from the study due to ill-health, no questionnaires were returned (n = 1)

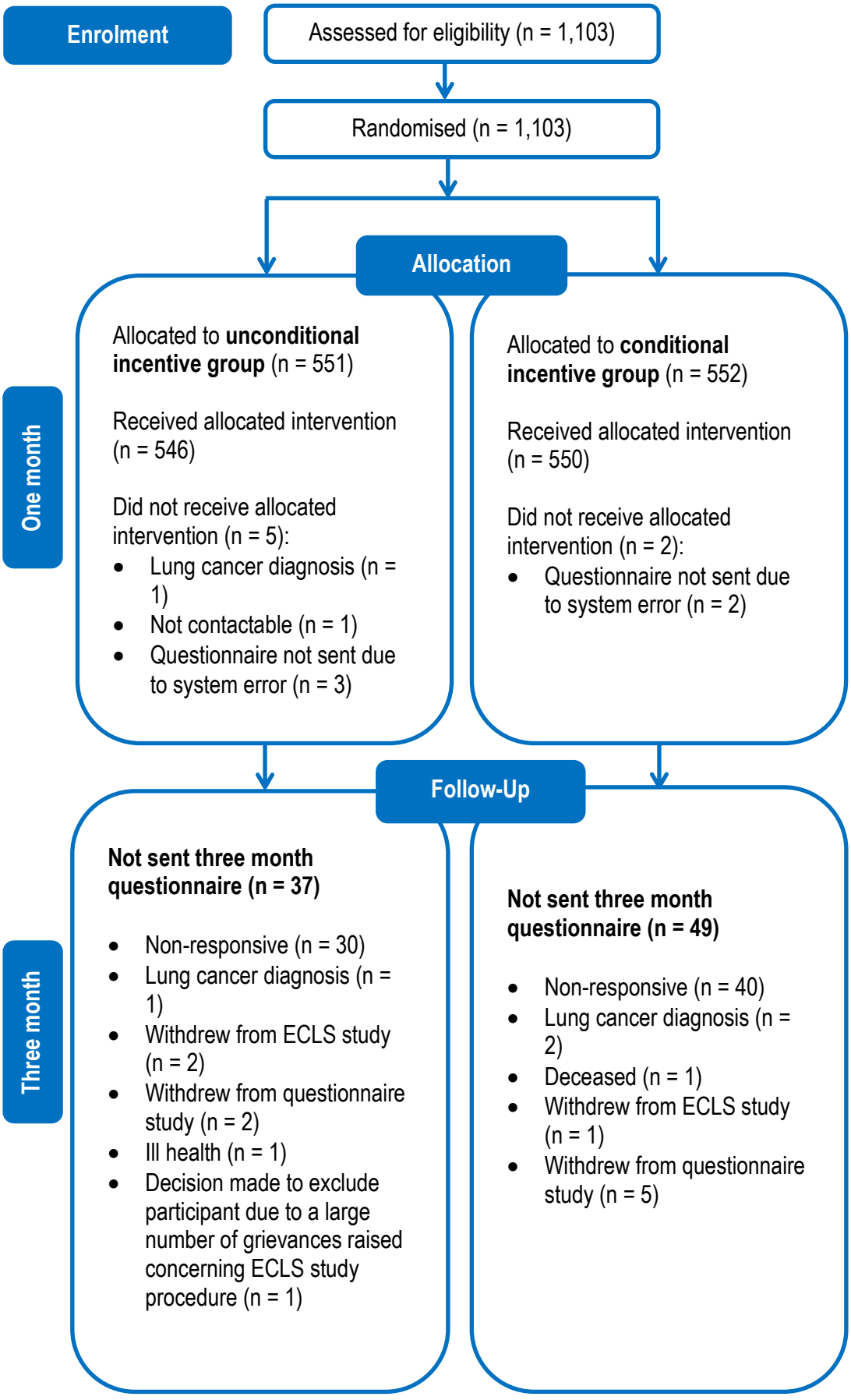
5. Conditional incentive group

In total, 542 participants were included in the analysis for this study and 10 participants were excluded. The reasons for exclusion from the study analysis are as follows:

- Not sent the first questionnaire due a system error (n = 2)
- Deceased, no questionnaires returned (n = 1)
- Diagnosed with lung cancer after the one month study questionnaire was sent. Questionnaire was not returned (n = 1)
- Returned questionnaires but were later found to have potentially been affected by the ECLS study protocol deviation (n = 5)
- One, three, six and 12 month questionnaires were returned but it was later found that the participant had not completed a pre-randomisation questionnaire or given consent and was therefore not eligible for this study (n = 1)

6.4.2. Recruitment

Recruitment to the behavioural and emotional outcomes sub-study began in January 2014 and ended in May 2015.


Enrolment
Assessed for eligibility (n = 1,103)
Randomised (n = 1,103)
Allocation
One month
Allocated to **unconditional incentive group** (n = 551)
Received allocated intervention (n = 546)
Did not receive allocated intervention (n = 5):
• Lung cancer diagnosis (n = 1)
• Not contactable (n = 1)
• Questionnaire not sent due to system error (n = 3)
Allocated to **conditional incentive group** (n = 552)
Received allocated intervention (n = 550)
Did not receive allocated intervention (n = 2):
• Questionnaire not sent due to system error (n = 2)
Follow-Up
Three month
Not sent three month questionnaire (n = 37)
• Non-responsive (n = 30)
• Lung cancer diagnosis (n = 1)
• Withdrew from ECLS study (n = 2)
• Withdrew from questionnaire study (n = 2)
• Ill health (n = 1)
• Decision made to exclude participant due to a large number of grievances raised concerning ECLS study procedure (n = 1)
Not sent three month questionnaire (n = 49)
• Non-responsive (n = 40)
• Lung cancer diagnosis (n = 2)
• Deceased (n = 1)
• Withdrew from ECLS study (n = 1)
• Withdrew from questionnaire study (n = 5)

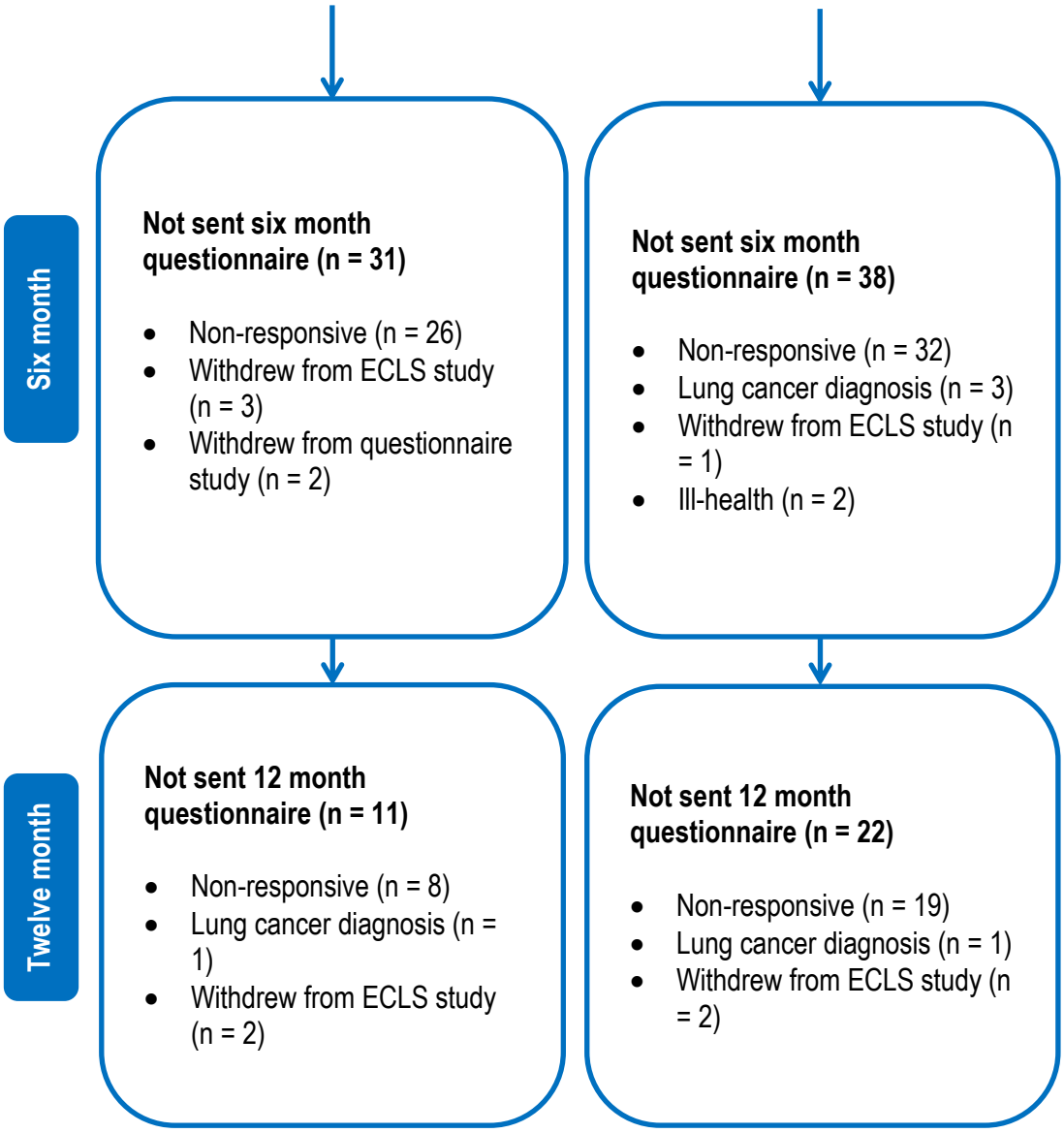


Figure 18. CONSORT 2010 Flow Diagram illustrating the number of participants randomly assigned in each group, the number who received the intervention and the number who were analysed for the primary and secondary outcomes.

6.4.3. Pre-randomisation data

The pre-randomisation sociodemographic characteristics and screening group for the study population are described in table 46. The majority of participants were from NHS Greater Glasgow & Clyde (74.93%). In terms of screening group, 30.80% had a positive test result, 34.32% had a negative test result and 34.88% were in the control group. The median age of participants was 62 years old, 50.51% were female and 41.79% were from the most deprived areas. In terms of smoking status, 55.23% of participants were current smokers. Two qualitative sub-studies were conducted as part of the ELCS study. As shown in table 46, 12.59% of participants who took part in the questionnaire study were also invited to take part in one of the two qualitative studies. In total, 4.91% of the participants took part in a qualitative study.

Table 46 also presents the pre-randomisation sociodemographic characteristics for each group of participants (unconditional incentive *vs*. conditional incentive). Significant differences were found between the proportion of females and males in each voucher condition group ($p = 0.026$). No other significant differences were found between pre-randomisation demographic characteristics and screening group for each group of study participants.

Table 46. Pre-randomisation sociodemographic characteristics for each group of study participants

	Total	**Unconditional incentive** (voucher sent with questionnaire)	**Conditional incentive** (voucher sent on receipt of questionnaire)	**Statistical test***
Participants	1,081	539 (49.86%)	542 (50.14%)	
Region – N (%)				
NHS Greater Glasgow & Clyde	810 (74.93%)	412 (76.44%)	398 (73.43%)	$\chi^2(1) = 1.30$
NHS Tayside	271 (25.07%)	127 (23.56%)	144 (26.57%)	P = 0.254
Screening group – N (%)				
EarlyCDT®-positive	333 (30.80%)	167 (30.98%)	166 (30.63%)	$\chi^2(2) = 0.06$
EarlyCDT®-negative	371 (34.32%)	183 (33.95%)	188 (34.69%)	P = 0.968
Control	377 (34.88%)	189 (35.06%)	188 (34.69%)	
Age (years – median (IQR)**	[6] 62 (57 – 68)	[2] 62 (57 – 68)	[4] 62 (58 – 68)	*Z* = 0.68 P = 0.494

	[6]	[2]	[4]	
50 – 54 years – **N (%)**	126 (11.72%)	65 (12.10%)	61 (11.34%)	$\chi^2(5) = 5.90$
55 – 59 years	270 (25.12%)	143 (26.63%)	127 (23.61%)	P = 0.316
60 – 64 years	252 (23.44%)	125 (23.28%)	127 (23.61%)	
65 – 69 years	241 (22.42%)	105 (19.55%)	136 (25.28%)	
70 – 74 years	144 (13.40%)	76 (14.15%)	68 (12.64%)	
75 – 79 years	42 (3.91%)	23 (4.28%)	19 (3.53%)	
Gender - N (%)				
Female	546 (50.51%)	254 (47.12%)	292 (53.27%)	$\chi^2(1) = 4.93$
Male	535 (49.49%)	285 (52.88%)	250 (46.13%)	P = 0.026
SIMD score – N (%)	[9]	[6]	[3]	
1 (most deprived)	448 (41.79%)	235 (44.09%)	213 (39.52%)	$\chi^2(4) = 3.27$
2	217 (20.24%)	104 (19.51%)	113 (20.96%)	P = 0.514
3	163 (15.21%)	73 (13.70%)	90 (16.70%)	
4	141 (13.15%)	69 (12.95%)	72 (13.36%)	
5 (least deprived)	103 (9.61%)	52 (9.76%)	51 (9.46%)	
Smoking status - N (%)				
Current smoker	597 (55.23%)	286 (53.06%)	311 (57.38%)	$\chi^2(1) = 2.04$
Former smoker	484 (44.77%)	253 (46.947%)	231 (42.62%)	P = 0.153
Pack year history				
Median (IQR)	49 (38 – 63)	49 (39 – 61)	49 (38 – 64)	$Z = -0.01$

				P = 0.999
Invited to qualitative sub-study – N (%)	[1]	[0]	[1]	
Yes	136 (12.59%)	68 (12.62%)	68 (12.57%)	$\chi^2(1) = 0.00$
No	944 (87.41%)	471 (87.38%)	473 (87.43%)	P = 0.982
Recruited to qualitative sub-study – N (%)	[1]	[0]	[1]	
Yes	53 (4.91%)	27 (5.01%)	26 (4.81%)	$\chi^2(2) = 0.03$
No	83 (7.69%)	41 (7.61%)	42 (7.76%)	P = 0.984
N/A	944 (87.41%)	471 (87.38%)	473 (87.43%)	

[missing]

*Pearson's chi-squared test (categorical data) and Mann–Whitney *U* test (continuous data)

** IQR = Interquartile range

6.4.4. Outcomes and estimation

6.4.4.1. Primary outcome

As stated in section 6.3.4, the primary outcome of this trial was the difference in the proportion of questionnaires returned between the unconditional and conditional incentive groups across all study time-points, and at each study time-point (one, three, six and 12 months). Table 47 reports frequencies and percentages for questionnaire response at each study time-point for both voucher conditions. As can be seen from table 47, 94.06% of participants in the unconditional incentive group, and 91.70% of participants in the conditional incentive group, returned the first questionnaire. Participation rates for the questionnaire study were therefore high across both groups. Questionnaire response rates for both groups continued to be high at the three, six and twelve month time-points (range: 91.70% to 98.11%). The unconditional incentive group had higher response rates than the conditional incentive group at the one, three and six month time-points. Voucher condition was found to have a significant effect on questionnaire response rate at the six-month time-point only ($\chi^2(1) = 4.07$, $p = 0.044$).

Table 47. Analyses comparing questionnaire response rates by voucher condition at each study time-point

Study time point	**Unconditional incentive** (voucher sent with questionnaire) **N (%)**	**Conditional incentive** (voucher sent on receipt of questionnaire) **N (%)**	**Results of chi-squared test**
One month			
Questionnaires sent (n = 1,081)	539	542	
Questionnaire returned	507 (94.06%)	497 (91.70%)	$\chi^2(1) = 2.29$, $p = 0.131$
Questionnaire not returned	32 (5.94%)	45 (8.30%)	
Three month			
Questionnaires sent (n = 1,001)	505	496	
Questionnaire returned	477 (94.46%)	460 (92.74%)	$\chi^2(1) = 1.23$, $p = 0.268$
Questionnaire not returned	28 (5.54%)	36 (7.26%)	
Six month			
Questionnaires sent (n = 933)	475	458	
Questionnaire returned	466 (98.11%)	439 (95.85%)	$\chi^2(1) = 4.07$, $p = 0.044$
Questionnaire not returned	9 (1.89%)	19 (4.15%)	
12 month			
Questionnaires sent (n = 901)	464	436	
Questionnaire returned	444 (95.69%)	422 (96.57%)	$\chi^2(1) = 0.46$, $p = 0.496$
Questionnaire not returned	20 (4.31%)	15 (3.43%)	

Results of multilevel logistic regression analyses for the primary outcome are presented in table 48. The first model was adjusted for ECLS minimisation variables (source region, age, gender, and smoking status) and screening group (EarlyCDT®-positive, EarlyCDT®-negative, control). No statistically significant differences were found between groups across all study time-points (OR 1.62, 95% CI 0.97 to 2.71, p = 0.29) and the OR did not vary significantly between time-points (p = 0.320). However, at the six month follow-up, the odds of returning the questionnaire were 2.92 times higher in the unconditional incentive group when compared with the conditional incentive group (95% CI 1.16 to 7.40, p = 0.023). No statistically significant differences were found between groups for the one, three and twelve month time-points. Odds ratios (OR) and 95% CI's are presented for each study time-point in table 48.

The second model was adjusted for ECLS minimisation variables and screening group as well as additional variables that potentially influence questionnaire response rates (socioeconomic deprivation, recruited to qualitative sub-study). When invited to qualitative study was adjusted for, analyses would not work. This variable was removed from the final model. Again, no statistically significant differences were found between groups across all study time-points (p = 0.187). No statistically significant differences were found between groups at each study time-point.

Table 48. Multivariate analyses comparing questionnaire response rates between voucher condition groups across all study time-points and at each study time-point

		Odds ratio* (95% CI)	P value	Odds ratio** (95% CI)	P value
Voucher condition	**Study time-point**				
Voucher with questionnaire *vs.* on receipt of questionnaire	Across all study time-points	1.62 (0.97 to 2.71)	P = 0.064	1.68 (0.78 to 3.61)	P = 0.187
	One month	1.62 (0.87 to 3.05)	P = 0.131	1.60 (0.64 to 3.98)	P = 0.310
	Three month	1.69 (0.87 to 3.26)	P = 0.119	1.76 (0.58 to 5.34)	P = 0.321
	Six month	2.92 (1.16 to 7.40)	P = 0.023	2.87 (0.64 to 12.94)	P = 0.169
	Twelve month	1.05 (0.47 to 2.35)	P = 0.908	1.09 (0.31 to 3.90)	P = 0.892
P value for differences in odds ratios between time points			P = 0.320		P = 0.393

* Adjusted for ECLS minimisation variables and screening group

** Adjusted for ECLS minimisation variables, screening group and additional variables (socioeconomic deprivation, recruited to qualitative sub-study)

6.4.4.2. Secondary outcomes

1. The difference in the proportion of reminders sent out between groups across time and at each study time-point

Table 49 includes frequencies and percentages for the reminders sent out at each study time-point for both voucher conditions. The percentage of reminders sent ranged from 25.05% to 29.11% for the unconditional incentive group and from 24.54% to 30.85% for the conditional incentive group. For the unconditional incentive group, the percentage of reminders sent increased at the three-month time-point and then decreased over the six month and twelve month time-points but was still higher than at one month. For the conditional incentive group, the number of reminders sent increased at three months, decreased at six months and increased again at twelve months. The percentage of reminders sent were highest for both groups at the three-month time point (unconditional incentive (29.11%), conditional incentive group (30.85%). Voucher condition had no statistically significant effect on the number of reminders sent out at any of the study time-points.

Results of multilevel logistic regression analyses are presented in table 50. The first model was adjusted for ECLS minimisation variables and screening group. No statistically significant differences were found between groups across all study time-points (OR 0.96, 95% CI 0.75 to 1.23, p = 0.739) and the OR did not vary significantly between time-points (p = 0.642). The second model was adjusted for ECLS minimisation variables and screening group as well as additional variables that could potentially influence questionnaire response rates. Again, no statistically significant differences were found between groups across all study time-points (OR

0.94, 95% CI 0.74 to 1.21, p = 0.648) and the OR did not vary significantly between time-points (p = 0.626).

.

Table 49. Analyses comparing reminders sent by voucher condition at each study time-point

Study time point	Unconditional incentive (voucher sent with questionnaire) N (%)	Conditional incentive (voucher sent on receipt of questionnaire) N (%)	Results of chi-squared test
One month			
Questionnaires sent	539	542	
Reminder sent	135 (25.05%)	133 (24.54%)	$\chi^2(1) = 0.04$, $p = 0.847$
Reminder not sent	404 (74.95%)	409 (75.46%)	
Three month			
Questionnaires sent	505	496	
Reminder sent	147 (29.11%)	153 (30.85%)	$\chi^2(1) = 0.36$, $p = 0.548$
Reminder not sent	358 (70.89%)	343 (69.15%)	
Six month			
Questionnaires sent	475	458	
Reminder sent	138 (29.05%)	124 (27.07%)	$\chi^2(1) = 0.45$, $p = 0.501$
Reminder not sent	337 (70.95%)	334 (72.93%)	
12 month			
Questionnaires sent	464	437	
Reminder sent	134 (28.88%)	131 (29.98%)	$\chi^2(1) = 0.13$, $p = 0.718$
Reminder not sent	330 (71.12%)	306 (70.02%)	

Table 50. Multivariate analyses comparing reminders sent between voucher condition groups across all study time-points and at each study time-point

		Odds ratio* (95% CI)	**P value**	**Odds ratio**** (95% CI)	**P value**
Voucher condition	**Study time-point**				
Voucher with questionnaire *vs*. on receipt of questionnaire	Across all study time-points	0.96 (0.75 to 1.23)	P = 0.739	0.94 (0.74 to 1.21)	P = 0.648
	One month	1.02 (0.70 to 1.48)	P = 0.907	1.03 (0.71 to 1.49)	P = 0.890
	Three month	0.86 (0.60 to 1.25)	P = 0.427	0.84 (0.58 to 1.22)	P = 0.369
	Six month	1.11 (0.76 to 1.63)	P = 0.591	1.08 (0.74 to 1.59)	P = 0.687
	12 month	0.87 (0.59 to 1.28)	P = 0.472	0.85 (0.58 to 1.25)	P = 0.406
P value for differences in odds ratios between time points			P = 0.642		P = 0.626

* Adjusted for ECLS minimisation variables and screening group

** Adjusted for ECLS minimisation variables, screening group and additional variables

2. The difference in the proportion of questionnaires with incomplete data across time and at each study time-point

Table 51 includes the frequencies and percentages for questionnaires with incomplete data at each study time-point for both voucher conditions. The percentage of questionnaires with incomplete data was relatively low across all time-points (range: 3.91% to 8.39%). The greatest difference between groups was at the three-month time-point (unconditional incentive (8.39%), conditional incentive (3.91%). Voucher condition had a significant effect on the number of questionnaires with incomplete data at the three month time-point only ($\chi^2(1) = 8.07$, $p = 0.005$). There were no statistically significant differences between the groups at the one, six and 12 month time-points.

Results of multilevel logistic regression analyses are presented in table 52. The first model was adjusted for ECLS minimisation variables and screening group. No statistically significant differences were found between groups across all study time-points (OR 1.19, 95% CI 0.87 to 1.64, $p = 0.281$). At the three month time-point, the odds of the questionnaire having incomplete data were 2.39 times higher in the unconditional incentive group when compared with the conditional incentive group (95% CI 1.28 to 4.45, $p = 0.006$). No statistically significant differences were found between groups for the one, six and 12 month time-points.

The second model was adjusted for ECLS minimisation variables and screening group as well as additional variables. Again, no statistically significant differences were found between groups across all study time-points (OR 1.22, 95% CI 0.89 to 1.69, $p = 0.215$). As with the first model, at the three month time-point, the odds of the questionnaire having incomplete data were 2.71 times higher in the unconditional incentive group when compared with the conditional incentive

group (95% CI 1.42 to 5.16, p = 0.002). No statistically significant differences were found between groups for the one, six and 12 month time-points.

Table 51. Analyses comparing questionnaires with incomplete data by voucher condition at each study time-point

Study time point	Unconditional incentive (voucher sent with questionnaire) N (%)	Conditional incentive (voucher sent on receipt of questionnaire) N (%)	Results of chi-squared test
One month			
Questionnaires returned	507	497	
Incomplete data	42 (8.28%)	38 (7.65%)	$\chi^2(1) = 0.14$, $p = 0.709$
No incomplete data	465 (91.70%)	459 (92.35%)	
Three month			
Questionnaires returned	477	460	
Incomplete data	40 (8.39%)	18 (3.91%)	$\chi^2(1) = 8.07$, $p = 0.005$
No incomplete data	437 (91.61%)	442 (96.09%)	
Six month			
Questionnaires returned	466	439	
Incomplete data	26 (5.58%)	31 (7.06%)	$\chi^2(1) = 0.84$, $p = 0.359$
No incomplete data	440 (94.42%)	408 (92.94%)	
12 month			
Questionnaires returned	444	422	
Incomplete data	30 (6.76%)	26 (6.16%)	$\chi^2(1) = 0.13$, $p = 0.722$
No incomplete data	414 (93.24%)	396 (93.84%)	

Table 52. Multivariate analyses comparing questionnaires with incomplete data between voucher condition groups across all study time-points and at each study time-point

		Odds ratio* (95% CI)	**P value**	**Odds ratio**** (95% CI)	**P value**
Voucher condition	**Study time-point**				
	Across all study time-points	1.19 (0.87 to 1.64)	P = 0.281	1.22 (0.89 to 1.69)	P = 0.215
With questionnaire *vs.* on receipt of questionnaire	One month	1.09 (0.66 to 1.82)	P = 0.735	1.06 (0.63 to 1.77)	P = 0.830
	Three month	2.39 (1.28 to 4.45)	P = 0.006	2.71 (1.42 to 5.16)	P = 0.002
	Six month	0.75 (0.41 to 1.35)	P = 0.336	0.80 (0.44 to 1.46)	P = 0.471
	12 month	1.09 (0.60 to 1.98)	P = 0.780	1.08 (0.60 to 1.97)	P = 0.795
P value for differences in odds ratios between time points			P = 0.040		P = 0.025

* Adjusted for ECLS minimisation variables and screening group

** Adjusted for ECLS minimisation variables, screening group and additional variables

6.5. Discussion

6.5.1. Summary of the main findings

Primary aim

The primary aim was to assess whether a £5 gift voucher sent with each questionnaire increased the total proportion of questionnaires returned across all study time-points, and at each study time-point, when compared with a £5 gift voucher sent on receipt of each questionnaire. This aim thereby demonstrates participation rates for the questionnaire study at one month and questionnaire response rates at the three, six and 12 month time-points. It was hypothesised that sending a £5 gift voucher with each study questionnaire would increase questionnaire response rates across study time-points, and at each study time-point, when compared with promising a £5 gift voucher on receipt of each study questionnaire. However, no statistically significant difference was found in questionnaire response rates between groups across all study time-points. The only statistically significant difference between groups was at the six-month time-point, where the unconditional incentive group were found to have higher response rates than the conditional incentive group (unconditional incentive group (98.09%), conditional incentive group (95.84%)). No differences were found between groups at the one, three and 12 month time-points.

Secondary aims

The first of the two secondary aims was to identify whether the timing of monetary incentive has an effect on the number of reminder questionnaires sent across study time-points and at each study time point. It was hypothesised that sending a £5 gift voucher with each study questionnaire would reduce the number of reminders sent across time, and at each study time-point, when compared with promising a £5 gift voucher on receipt of each study questionnaire. Again, results of analyses did not support this hypothesis as voucher condition was found to have no statistically significant effect on the number of reminders sent.

The second aim was to identify whether the timing of monetary incentive had an effect on the completeness of returned questionnaires across study time-points at each study time-point. It was hypothesised that sending a £5 gift voucher with each questionnaire would have no effect on the completeness of returned questionnaires when compared with promising a £5 gift voucher on receipt of each study questionnaire. No statistically significant difference was found in the completeness of returned questionnaires between groups across all study time-points. The only statistically significant difference between groups was at the three-month time-point, where the unconditional incentive group were found to have a higher proportion of questionnaires with incomplete data when compared with the conditional incentive group (unconditional incentive group (8.47%), conditional incentive group (3.92%)). No statistically significant differences were found between groups at the one, six and 12 month time-points.

6.5.2. Discussion of findings

As previously stated, to the authors knowledge, this RCT is the first that has explored the impact of the timing of monetary incentives on postal questionnaire data collection in a clinical trial.

Therefore, at present, there are no results from clinical trials to compare our findings with. However, our findings contradict the existing evidence outwith clinical trials. For example, the Cochrane review that aimed to identify methods that enhanced response to questionnaires found that unconditional monetary incentives significantly increased response rates when compared with conditional monetary incentives (24 trials with 27,569 participants, OR 1.61, 95% CI 1.36 to 1.89) [201]. A potential explanation for this discrepancy is that the Cochrane review included a very large sample size, which had the power to detect a smaller difference in response rates between groups. As stated in section 6.3.5, our RCT was only powered to detect an absolute difference of 10%. Furthermore, it is important to note that differences in response rates between the two incentive groups were always less than 5%, so it is possible that our study was underpowered.

There are a number of potential explanations for our results. First, as detailed in section 6.3.3., other strategies were employed that had the potential to increase participation and questionnaire response rates in the ECLS study. For example, questionnaires were sent in white envelopes with the ECLS study logo printed on the front, questionnaire cover letters were hand-signed by the research team, and a response deadline for the return of questionnaires was listed on the cover letter. Furthermore, all participants received a phone call one week after the first questionnaire was sent to check on postal delivery, offer assistance with questionnaire completion and to provide an opportunity for participants to ask any questions about the longitudinal study. It is important to note that a white envelope with the study logo printed on and hand-written signature on cover letters were two of several strategies found to increase postal questionnaire response in a clinical trial previously described in section 6.1 [194]. Furthermore, in Edward et al's systematic review (described in section 6.1), it was also found that cover letters containing a hand-written signature increased odds of response by a quarter

compared with cover letters containing typed, scanned or printed signatures (OR 1.24, 95% CI 1.08 to 1.41) [200]. A systematic review, published in 2007, aimed to identify strategies employed to retain participants in healthcare research [190]. The key finding of the review was that the use of several different types of retention strategy (e.g., financial incentives, reminders) were most effective in increasing participant retention. It is therefore possible that, in the current RCT, it was also the use of multiple different types of strategy that enhanced participation and response rates for both groups, rather than the monetary incentive alone.

In 2008, Nakash et al [188] published a qualitative study that aimed to explore factors affecting response and non-response to postal questionnaires administered as part of a clinical trial. The study included 22 participants who were currently taking in an acute injury RCT. A number of factors were identified in this study that could potentially be relevant to ECLS study participants and account for why unconditional monetary incentives were not found to be any more effective than conditional monetary incentives. One such factor was the participants' view that they had agreed to take part in the trial and should therefore see it through. It is possible that participants in the ECLS study perceived the questionnaires to be part of the trial that they had consented to take part in, which increased their motivation to take part in the sub-study as well as complete all the included questionnaire measures and return the questionnaires at each time-point. Additional factors identified in the qualitative study were feeling obliged to respond to follow-up questionnaires as the trial team had requested it, altruism, and the perception of the trial as being an important and worthwhile project [188]. All three factors could have potentially been important motivators for ECLS study participants.

Finally, the ECLS study questionnaires contained measures that were very relevant to the focus of the trial. For example, lung cancer worry, distress specific to screening for lung cancer and

questions concerning smoking prevalence, cessation attempts and attitudes and intentions towards smoking cessation. Edward et al's review found that the odds of response were doubled when questionnaires were relevant to study participants (three trials with 2,711 participants, OR 2.00, 95% CI 1.32 to 3.04). The results of the qualitative study described above support this finding. For example, as the trial questionnaires were so relevant, participants felt that they would benefit from completing them, which enhanced their motivation to respond [188]. In Brueton et al's review on clinical trials, it was unclear as to whether questionnaires directly relevant to the trial were more likely to increase questionnaire response compared with unrelated questionnaires (two trials with 3,893 participants, RR 1.07, 95% CI 1.01 to 1.14, p = 0.03). However, it is important to note that only two RCTs have explored the impact of the saliency of questionnaires on response rates, so further research is required. It is possible though that the relevance of the ECLS study questionnaires further enhanced response rates.

6.5.3. A theoretical framework to explain these findings

The Leverage-Saliency theory provides the most relevant theoretical explanation for the results of the current study. This theory is the only theory that has been developed specifically to explain why people respond to questionnaires [204,205]. It is important to note that the request to complete a questionnaire consists of a number of components, such as the topic, the research team administering the questionnaire, and an incentive for completing it. This theory proposes that people differ in the importance that they assign to these different components and whether they perceive them positively or negatively [204]. For example, for some people, the questionnaire topic is very important, whereas for others, the provision of an incentive is most important. The decision to return a questionnaire will depend on the weight given to the component by the person (*leverage*), whether it is perceived in a positive or negative way, and the emphasis of the component (e.g., monetary incentive, topic) within the request to complete the questionnaire

(*salience*). For example, if a monetary incentive is given high positive leverage by a person and it is heavily emphasised on a questionnaire cover letter, then it could have a positive influence on whether the person completes the questionnaire. In a clinical trial, such as the ECLS study, it could be argued that participants are motivated to respond to questionnaires due to some of the reasons identified in Nakash et al's qualitative study[188], for example, obligation to continue with the trial, personal relevance of the questionnaire, altruism and the perceived importance of the trial. It is therefore possible that higher positive leverage was assigned to these components rather than to monetary incentives, rendering them less effective in this context. Although both unconditional and conditional monetary incentives were given high salience in the ECLS longitudinal study cover letter, so too were other components. For example, in terms of obligation to the trial and altruism, the cover letter stated, *"when you gave your blood sample the nurse said we might send you some more surveys to fill in"* and *"completing the surveys is very important as we need to find out about the full impact of the new screening test"* (Appendix six, page 499).

6.5.4. Strengths and limitations

The main strength of the present study is that it is the first to examine the effects of the timing of monetary incentives on longitudinal postal questionnaire data collection in a clinical trial. A further strength is the design of the study as it was a RCT embedded within a clinical trial. A key advantage of a RCT is that participants are randomised to groups, which ensures that any characteristics that could influence the outcome (e.g., age, gender) are evenly distributed between groups, so any differences observed between groups should be attributable to the intervention [64]. Therefore, selection bias was minimised in our study. In addition, this RCT was carefully planned and designed and power calculations conducted. Furthermore, as the sample

size of the current study was larger than expected, our study was powered to detect a difference smaller than the 10% originally powered for. A limitation of previous RCTs conducted within clinical trials is that a number were underpowered [192]. In addition to exploring the effects of the timing of monetary incentives on participation and retention rates, we also explored the potential impact on the number of reminders sent and the completeness of returned questionnaires across time and at each study time-point. As stated in section 6.1, both outcomes are very important in the context of clinical trials. If incentives are to be administered with the aim of enhancing participation and response rates, then trialists must be aware of any additional benefits, such as a reduction in the number of reminders sent, in order to further justify the cost of the incentives. However, trialists must also be aware of any potential compromises of monetary incentives, such as a potential reduction in the quality of data.

Some potential limitations of this study also warrant attention. First, it is important to note that there were very high response rates in our study, which had the potential to create ceiling effects [Please note. A ceiling effect is where an independent variable no longer has an effect on a dependent variable]. Therefore, there was not much scope to extend the response rate further. Second, no cost-effective analysis was undertaken so it is unclear as to whether conditional monetary incentives were more cost-effective than unconditional monetary incentives. Finally, as stated in section 6.5.2, a number of strategies were employed in this study that had the potential to increase response rates. Therefore, it is difficult to determine the full impact of timing of monetary incentive on the outcomes investigated in this trial.

6.5.5. Generalisability

As this RCT was only conducted within one trial, the findings may not be generalisable to other types of clinical trial or participant populations. Furthermore, this study used postal questionnaires, so findings may also not be applicable to other methods of data collection employed in clinical trials, such as electronic questionnaires or questionnaires administered by telephone. Finally, the ECLS study was an unblinded trial design, where participants knew the group they were allocated to (screen or control). As stated in section 6.1, differences in postal questionnaire response rates have been found between unblinded and blinded trials. It is therefore unclear as to what extent our findings are generalisable to blinded trials.

6.5.6. Implications for future research

As stated in section 6.5.4, a key limitation of this study was the failure to conduct a cost-effectiveness analysis. When making decisions concerning the use of monetary incentives, it would be very helpful for trialists to have information on potential costs. Future studies exploring the impact of the timing of monetary incentives in the context of clinical trials should aim to calculate the total costs for each group, which should include the cost of the incentives, of printing questionnaires, envelopes, postage, and any follow-up phone calls. The cost of staff time should also be calculated.

Previous publications exploring the impact of monetary incentives have not reported a theory on which their intervention was based, so it is unclear if such trials were theoretically informed. The Leverage-Saliency theory, described in section 6.5.3, has the potential to be applied to the clinical trial setting. For example, qualitative research could be conducted with participants who

meet inclusion criteria for the trial and identify components of the request to complete a questionnaire that participants perceive positively and would give high leverage to. These components could then be made more salient when recruiting participants to a questionnaire study embedded within a clinical trial.

Finally, future studies exploring methods to increase study participation and questionnaire response rates within the context of clinical trials should endeavour to conduct an RCT embedded within a clinical trial. As stated in section 6.5.4, participants are randomised to groups, which ensures that any characteristics that could influence the outcome are evenly distributed, so any differences observed can be attributed to the intervention [64]. However, in a publication that reported on interventions to improve participant recruitment and retention in clinical trials, it is stated that despite the clear advantages of an RCT (e.g., minimised selection bias), such studies are very rare [206]. It is imperative going forward that, where possible, nested RCTs are conducted. Furthermore, such trials should be planned at the design stage of the trial and power calculations conducted to ensure that sample sizes are sufficient [192].

6.5.7. Clinical implications

Previous research exploring the use of monetary incentives in clinical trials has found that when compared with no monetary incentive, participants who receive an unconditional monetary incentive are more likely to return postal questionnaires [192]. The results of the current RCT found no difference between unconditional and conditional monetary incentives on study participation rates or questionnaire response rates over time. Therefore, based on previous results and results of the current RCT, monetary incentives can be useful but the timing appears to makes no difference. However, as discussed in section 6.5.5, it is important to note that our results

may not be generalisable to other types of trials or population. Therefore, when making decisions regarding whether to administer monetary incentives, and how to effectively administer them, trialists should consider their target population and identify the incentive strategies that may be most applicable to them. Cost and administrative burden should also be considered. For example, conditional monetary incentives have the potential to cost less than unconditional monetary incentives but the administrative burden will be greater. One suggestion for future trials collecting longitudinal postal questionnaire data is to test unconditional and conditional monetary incentives when administering the first questionnaire to see which method is more effective at increasing response rates. If no difference is found, then the most cost-effective option could be implemented for the duration of data collection.

6.5.8. Conclusion

Prior to this RCT, it was not clear how monetary incentives could be used in clinical trials. The present study was designed to determine the effect of the impact of the timing of monetary incentive on study participation rates, questionnaire response rates over time, reminders sent and the completeness of returned questionnaires. Our results suggest that timing of monetary incentives has no impact on any of these four outcomes. However, these results may not be applicable to other clinical trials. It is therefore important that future trials investigate the timing of monetary incentives to see if results are consistent with ours.

Final note. The nature of different individual/team contributions for the projects encompassed in this PhD

As this PhD was conducted within the context of a wider clinical trial, the nature of the different individual/team contributions for each thesis chapter will be briefly described.

- **Chapter 3**

The thesis researcher (LB) conceived of the systematic review topic, developed the protocol (with input from the supervisory team (DK, KV, RdN and JR) and conducted searches, assessed studies for eligibility, extracted data and conducted quality assessment. A second reviewer (BY) assessed studies for eligibility, conducted quality assessment and checked data extraction forms. The chapter was written by LB with feedback from the supervisory team.

- **Chapters 4 and 5**

  - The protocol for the emotional and behavioural outcomes study nested within the ECLS study was developed by LB and BY (researcher of the behavioural outcomes study), with feedback from the supervisory team (DK, KV, RdN and JR), the ECLS trial manager and the Tayside Clinical Trials Unit (TCTU) senior clinical trial manager. The ECLS trial manager and the senior clinical trial manager than merged the protocol for the emotional and behavioural outcomes study into the main ECLS study protocol.

  - KV selected the following emotional outcome measures to include in the pre-randomisation questionnaire: HADS, PANAS, and the LCWS. LB selected an additional measure to

include in the pre-randomisation questionnaire, the IPQ-R, as well as the IES to include in follow-up questionnaires.

- LB and BY set up the sub-study, organised the administration and ordered materials (e.g., questionnaires, envelopes)

- LB and BY carried out follow-up data collection for the study with the assistance of an administrator (KA). Pre-randomisation data was collected by the nurses at the clinic visit.

- Data entered by LB, BY and KA on an online database (developed by the TCTU) using OpenClinica

- An online recruitment tracker database was used for questionnaire administration (developed by the Health Informatics Centre at the University of Dundee)

- An analysis plan was developed by the thesis researcher and feedback received from DK as well as the ECLS trial statistician.

- A data verification plan was developed by LB and BY with feedback from the supervisory team. Data verification was then conducted by LB and BY.

- Data entered into OpenClinica were extracted and sent to LB by the ECLS trial statistician

- Analysis and interpretation of the data was conducted by LB under the supervision of DK

- Chapters 4 and 5 were written by the LB with feedback from the supervisory team

- **Chapter 6**

- This RCT was conceived by the ECLS clinical trial manager, LB, BY and the supervisory team. The protocol was developed by LB with feedback from the supervisory team.

- Data were extracted from the recruitment tracker by LB. Analysis and interpretation of the data was conducted by LB under the supervision of DK.

- Chapter 6 was written by LB with feedback from the supervisory team.

References

1. Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. *Clinics in chest medicine* 2011; **32**(4): 605-44.

2. Youlden DR, Cramb SM, Baade PD. The International Epidemiology of Lung Cancer: Geographical Distribution and Secular Trends. *Journal of Thoracic Oncology* 2008; **3**(8): 819-31.

3. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2010; **19**(8): 1893-907.

4. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA: a cancer journal for clinicians* 2011; **61**(2): 69-90.

5. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer* 2015; **136**(5): 359-86.

6. Cancer Research UK. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#heading-Two. Last accessed: 12.05.2016.

7. Welsh Cancer Intelligence and Surveillance Unit. Lung Cancer in Wales, A detailed analysis of population trends of incidence and stage of diagnosis up to and including 2012. Available at: http://www.wcisu.wales.nhs.uk/sitesplus/documents/1111/141214%20LUNG%20CANCER%20IN%20WALES%20FINAL.pdf. Last accessed: 12.05.2016.

8. Mistry M, Parkin DM, Ahmad AS, Sasieni P. Cancer incidence in the United Kingdom: projections to the year 2030. *Br J Cancer* 2011; **105**(11): 1795-803.

9. Cancer Research UK. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/mortality#heading-Two. Last accessed: 12.05.2016.

10. Office for National Statistics. Available at: http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/no--42--2011/sty-lung-cancer.html. Last accessed: 12.05.2016.

11. Northern Ireland Cancer Registry. Available at: http://www.qub.ac.uk/research-centres/nicr/FileStore/PDF/FactSheets/Filetoupload,631609,en.pdf. Last accessed: 12.05.2016.

12. Information Services Division Scotland. Available at: http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Lung-Cancer-and-Mesothelioma/#summary. Last accessed: 12.05.2016.

13. Welsh Cancer Intelligence and Surveillance Unit. Lung Cancer Mortality. Available at: http://www.wcisu.wales.nhs.uk/mortality. Last accessed: 12.05.2016.

14. Cancer Research UK. Available at:http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#heading-Zero. Last accessed: 12.05.2016.

15. Office for National Statistics. Cancer Registration Statistics, England: 2013. Available at: http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2015-07-10. Last accessed: 12.05.2016.

16. Information Services Division and NHS National Services Scotland. Cancer in Scotland. Available at: http://www.isdscotland.org/Health-Topics/Cancer/Publications/2015-11-17/Cancer_in_Scotland_summary_m.pdf. Last accessed: 12.05.2016.

17. Scottish Public Health Observatory. Lung cancer: key points. Available at: http://www.scotpho.org.uk/health-wellbeing-and-disease/cancer-lung/key-points. Last accessed: 26.06.15.

18. Northern Ireland Cancer Registry. All Cancer Factsheet. Available at: http://www.qub.ac.uk/research-centres/nicr/FileStore/PDF/FactSheets/Filetoupload,631631,en.pdf. Last accessed: 12.05.2016.

19. Cancer Research UK. Lung cancer mortality by sex and UK region. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/mortality#heading-Zero. Last accessed: 12.05.2016.

20. Office for National Statistics. Lung cancer incidence, mortality and survival, England, 1971–2011. Available at: http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/no--42--2011/sty-lung-cancer.html. Last accessed: 12.05.2016.

21. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). *The Lancet*; **385**(9972): 977-1010.

22. Cancer Research UK. One-, five- and ten-year survival for lung cancer. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/survival#heading-Zero. Last accsesed: 12.05.2016.

23. Information Services Division Scotland. Cancer Statistics: Lung Cancer and Mesothelioma. Available at: http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Lung-Cancer-and-Mesothelioma/. Last accessed: 12.05.2016.

24. Walters S, Maringe C, Coleman MP, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. *Thorax* 2013; **68**(6): 551-64.

25. Wood DE, Kazerooni E, Baum SL, et al. Lung cancer screening, version 1.2015: featured updates to the NCCN guidelines. *Journal of the National Comprehensive Cancer Network : JNCCN* 2015; **13**(1): 23-34.

26. Field JK, Chen Y, Marcus MW, McRonald FE, Raji OY, Duffy SW. The contribution of risk prediction models to early detection of lung cancer. *J Surg Oncol* 2013; **108**(5): 304-11.

27. Dahlgren, G., and Whitehead, M. Policies and Strategies to Promote Equity in Health. World Health Organization, Regional Office for Europe, Copenhagen, 1992.

28. Gray EP, Teare MD, Stevens J, Archer R. Risk Prediction Models for Lung Cancer: A Systematic Review. *Clinical Lung Cancer*.

29. Tammemagi MC, Church TR, Hocking WG, et al. Evaluation of the lung cancer risks at which to screen ever- and never-smokers: screening rules applied to the PLCO and NLST cohorts. *PLoS medicine* 2014; **11**(12): e1001764.

30. Wilson DO, Weissfeld J. A simple model for predicting lung cancer occurrence in a lung cancer screening program: The Pittsburgh Predictor. *Lung cancer (Amsterdam, Netherlands)* 2015; **89**(1): 31-7.

31. Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD,

http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015.

32. Kovalchik SA, De Matteis S, Landi MT, et al. A regression model for risk difference estimation in population-based case–control studies clarifies gender differences in lung cancer risk of smokers and never smokers. *BMC Medical Research Methodology* 2013; **13**(1): 1-8.

33. Tammemagi CM, Pinsky PF, Caporaso NE, et al. Lung cancer risk prediction: Prostate, Lung, Colorectal And Ovarian Cancer Screening Trial models and validation. *J Natl Cancer Inst* 2011; **103**(13): 1058-68.

34. Tammemägi MC, Katki HA, Hocking WG, et al. Selection Criteria for Lung-Cancer Screening. *New England Journal of Medicine* 2013; **368**(8): 728-36.

35. Alberg AJ, Nonemaker J. Who is at high risk for lung cancer? Population-level and individual-level perspectives. *Semin Respir Crit Care Med* 2008; **29**(3): 223-32.

36. Matakidou A, Eisen T, Houlston RS. Systematic review of the relationship between family history and lung cancer risk. *Br J Cancer* 2005; **93**(7): 825-33.

37. Cassidy A, Myles JP, van Tongeren M, et al. The LLP risk model: an individual risk prediction model for lung cancer. *Br J Cancer* 2008; **98**(2): 270-6.

38. Spitz MR, Hong WK, Amos CI, et al. A Risk Model for Prediction of Lung Cancer. *Journal of the National Cancer Institute* 2007; **99**(9): 715-26.

39. Etzel CJ, Kachroo S, Liu M, et al. Development and validation of a lung cancer risk prediction model for African-Americans. *Cancer Prev Res* 2008; **1**(4): 255-65.

40. Smoking and health: report of the Advisory Committee to the Surgeon General of the Public Health Service. 1964. http://profiles.nlm.nih.gov/NN/B/B/M/Q/. Last accessed: 26.06.15.

41. Bach PB, Kattan MW, Thornquist MD, et al. Variations in Lung Cancer Risk Among Smokers. *Journal of the National Cancer Institute* 2003; **95**(6): 470-8.

42. Hoggart C, Brennan P, Tjonneland A, et al. A Risk Model for Lung Cancer Incidence. *Cancer Prevention Research* 2012; **5**(6): 834-46.

43. Alberg AJ, Ford JG, Samet JM. Epidemiology of lung cancer*: Accp evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; **132**(3_suppl): 29S-55S.

44. Shack L, Jordan C, Thomson CS, Mak V, Moller H. Variation in incidence of breast, lung and cervical cancer and malignant melanoma of skin by socioeconomic group in England. *BMC Cancer* 2008; **8**: 271.

45. Hiscock R, Bauld L, Amos A, Platt S. Smoking and socioeconomic status in England: the rise of the never smoker and the disadvantaged smoker. *Journal of public health (Oxford, England)* 2012; **34**(3): 390-6.

46. Green J, Tones K, Cross R, Woodall J. Health Promotion: Planning and Strategies. Third Edition. *London, UK: SAGE Publications Ltd* 2015.

47. World Health Organisation (2014). Asbestos: elimination of asbestos-related diseases. Available at: http://www.who.int/mediacentre/factsheets/fs343/en/. Last accessed: 04.03.2016.

48. Global strategy on diet, physical activity and health. Geneva: World Health Organization; 2004. Available from: http://www.who.int/dietphysicalactivity/strategy/eb11344/strategy_english_web.pdf. Last accessed: 28.03.2016.

49. World Health Organisation. Global report on trends in tobacco smoking 2000-2025. Available from: http://www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/. Last accessed: 26.06.2015. 2015.

50. World Health Organisation. WHO report on the global tobacco epidemic 2013. Available at: http://www.who.int/tobacco/global_report/2013/en/. Last accessed: 26.06.2015.

51. Raffle A, Gray M. Screening: Evidence and practice. *New York, NY: Oxford University Press* 2007.

52. Wilson JMG, Jungner G. Principles and practice of screening for disease. 1968. Public health papers no. 34. *Geneva : World Health Organization Available at: http://appswhoint/iris/handle/10665/37650 Last accessed: 26062015*

53. National Screening Committee. First report of the national screening committee. *London: Department of Health* 2000.

54. UK National Screening Committee. Definition of screening. Available at: http://www.screening.nhs.uk/screening. Last accessed: 26.06.2015.

55. Greenhalgh T. How to read a paper. Papers that report diagnostic or screening tests. *BMJ* 1997; **315**(7107): 540-3.

56. Manser RL, Irving LB, Stone C, Byrnes G, Abramson M, Campbell D. Screening for lung cancer. *The Cochrane database of systematic reviews* 2001; (3): CD001991.

57. Manser RL, Irving LB, Stone C, Byrnes G, Abramson M, Campbell D. Screening for lung cancer. *The Cochrane database of systematic reviews* 2004; (1): CD001991.

58. Manser R, Lethaby A, Irving LB, et al. Screening for lung cancer. *The Cochrane database of systematic reviews* 2013; **6**: CD001991.

59. Marshall HM, Bowman RV, Yang IA, Fong KM, Berg CD. Screening for lung cancer with low-dose computed tomography: a review of current status. *J Thorac Dis* 2013; **5 Suppl 5**: S524-39.

60. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of ct screening for lung cancer: A systematic review. *Jama* 2012; **307**(22): 2418-29.

61. The International Early Lung Cancer Action Program Investigators. Survival of Patients with Stage I Lung Cancer Detected on CT Screening. *New England Journal of Medicine* 2006; **355**(17): 1763-71.

62. Swensen SJ, Jett JR, Hartman TE, et al. CT Screening for Lung Cancer: Five-year Prospective Experience. *Radiology* 2005; **235**(1): 259-65.

63. Bach PB, Jett JR, Pastorino U, Tockman MS, Swensen SJ, Begg CB. Computed tomography screening and lung cancer outcomes. *Jama* 2007; **297**(9): 953-61.

64. Akobeng AK. Understanding randomised controlled trials. *Archives of Disease in Childhood* 2005; **90**(8): 840-4.

65. Welch H, Woloshin S, Schwartz LM, et al. Overstating the evidence for lung cancer screening: The international early lung cancer action program (i-elcap) study. *Archives of Internal Medicine* 2007; **167**(21): 2289-95.

66. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *The New England journal of medicine* 2011; **365**(5): 395-409.

67. Field JK, Hansell DM, Duffy SW, Baldwin DR. CT screening for lung cancer: Countdown to implementation. *The Lancet Oncology* 2013; **14**(13): 591-600.

68. Wille MM, Dirksen A, Ashraf H, et al. Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-Risk Profiling. *Am J Respir Crit Care Med* 2016; **193**(5): 542-51.

69. Infante M, Cavuto S, Lutman FR, et al. Long-Term Follow-up Results of the DANTE Trial, a Randomized Study of Lung Cancer Screening with Spiral Computed Tomography. *American Journal of Respiratory and Critical Care Medicine* 2015; **191**(10): 1166-75.

70. Pastorino U, Rossi M, Rosato V, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur J Cancer Prev* 2012; **21**(3): 308-15.

71. Field JK, van Klaveren R, Pedersen JH, et al. European randomized lung cancer screening trials: Post NLST. *Journal of Surgical Oncology* 2013; **108**(5): 280-6.

72. Infante M, Lutman FR, Cavuto S, et al. Lung cancer screening with spiral CT: Baseline results of the randomized DANTE trial. *Lung cancer (Amsterdam, Netherlands)* 2008; **59**(3): 355-63.

73. Aberle DR, Berg CD, Black WC, et al. The National Lung Screening Trial: overview and study design. *Radiology* 2011; **258**(1): 243-53.

74. Lopes Pegna A, Picozzi G, Mascalchi M, et al. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. *Lung cancer (Amsterdam, Netherlands)* 2009; **64**(1): 34-40.

75. Lopes Pegna A, Picozzi G, Falaschi F, et al. Four-year results of low-dose CT screening and nodule management in the ITALUNG trial. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2013; **8**(7): 866-75.

76. Pedersen JH, Ashraf H, Dirksen A, et al. The Danish randomized lung cancer CT screening trial--overall design and results of the prevalence round. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2009; **4**(5): 608-14.

77. Horeweg N, Scholten ET, de Jong PA, et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. *The Lancet Oncology*; **15**(12): 1342-50.

78. Becker N, Motsch E, Gross ML, et al. Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round. *Journal of cancer research and clinical oncology* 2012; **138**(9): 1475-86.

79. Becker N, Motsch E, Gross ML, et al. Randomized Study on Early Detection of Lung Cancer with MSCT in Germany: Results of the First 3 Years of Follow-up After Randomization. *Journal of Thoracic Oncology* 2015; **10**(6): 890-6.

80. Baldwin DR, Duffy SW, Wald NJ, Page R, Hansell DM, Field JK. UK Lung Screen (UKLS) nodule management protocol: Modelling of a single screen randomised controlled trial of low-dose CT screening for lung cancer. *Thorax* 2011; **66**(4): 308-13.

81. UK Lung Screening Trial Protocol. Available at: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0018/54612/PRO-09-61-01.pdf. Last accsesed: 03.04.2016.

82. de Koning HJ, Meza R, Plevritis SK, et al. Benefits and Harms of Computed Tomography Lung Cancer Screening Strategies: A Comparative Modeling Study for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* 2014; **160**(5): 311-20.

83. Brodersen J, Jørgensen KJ, Gøtzsche PC. The benefits and harms of screening for cancer with a focus on breast screening. *Polskie Archiwum Medycyny Wewnetrznej* 2010; **120**(3): 89-94.

84. Harris RP, Sheridan SL, Lewis CL, et al. The harms of screening : A proposed taxonomy and application to lung cancer screening. *JAMA Internal Medicine* 2014; **174**(2): 281-5.

85. Patz EF, Jr., Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med* 2014; **174**(2): 269-74.

86. Humphrey LL, Deffebach M, Pappas M, et al. Screening for lung cancer with low-dose computed tomography: A systematic review to update the U.S. preventive services task force recommendation. *Annals of Internal Medicine* 2013; **159**(6): 411-20.

87. Patz EF, Jr, Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Internal Medicine* 2014; **174**(2): 269-74.

88. Byrne MM, Weissfeld J, Roberts MS. Anxiety, fear of cancer, and perceived risk of cancer following lung cancer screening. *Medical Decision Making* 2008; **28**(6): 917-25.

89. van den Bergh KA, Essink-Bot ML, Borsboom GJ, Scholten ET, van Klaveren RJ, de Koning HJ. Long-term effects of lung cancer computed tomography screening on health-related quality of life: the NELSON trial. *Eur Respir J* 2011; **38**(1): 154-61.

90. van den Bergh KA, Essink-Bot ML, Borsboom GJ, et al. Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON). *Br J Cancer* 2010; **102**(1): 27-34.

91. Sinicrope PS, Rabe KG, Brockman TA, et al. Perceptions of Lung Cancer Risk and Beliefs in Screening Accuracy of Spiral Computed Tomography among High-Risk Lung Cancer Family Members. *Academic Radiology* 2010; **17**(8): 1012-25.

92. Field JK, Oudkerk M, Pedersen JH, Duffy SW. Prospects for population screening and diagnosis of lung cancer. *The Lancet*; **382**(9893): 732-41.

93. Black WC, Gareen IF, Soneji SS, et al. Cost-Effectiveness of CT Screening in the National Lung Screening Trial. *New England Journal of Medicine* 2014; **371**(19): 1793-802.

94. Whynes DK. Could CT screening for lung cancer ever be cost effective in the United Kingdom? *Cost effectiveness and resource allocation : C/E* 2008; **6**: 5-.

95. Field JK, Devaraj A, Duffy SW, Baldwin DR. CT screening for lung cancer: Is the evidence strong enough? *Lung cancer (Amsterdam, Netherlands)* 2016; **91**: 29-35.

96. Boyle P, Chapman CJ, Holdenrieder S, et al. Clinical validation of an autoantibody test for lung cancer. *Annals of Oncology* 2010.

97. Jett JR, Peek LJ, Fredericks L, Jewell W, Pingleton WW, Robertson JFR. Audit of the autoantibody test, EarlyCDT®-Lung, in 1600 patients: An evaluation of its performance in routine clinical practice. *Lung cancer (Amsterdam, Netherlands)* 2014; **83**(1): 51-5.

98. Chapman CJ, Healey GF, Murray A, et al. EarlyCDT(R)-Lung test: improved clinical utility through additional autoantibody assays. *Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine* 2012; **33**(5): 1319-26.

99. Sullivan, F. M. et al. Detection in blood of autoantibodies to tumour antigens as a case-finding method in lung cancer using the EarlyCDT®-Lung Test (ECLS): study protocol for a randomized controlled trial. *Journal paper in preparation*.

100. Sullivan FM, Farmer E, Mair FS, et al. Detection in blood of autoantibodies to tumour antigens as a case-finding method in lung cancer using the EarlyCDT(R)-Lung Test (ECLS): study protocol for a randomized controlled trial. *BMC Cancer* 2017; **17**(1): 187.

101. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American journal of clinical oncology* 1982; **5**(6): 649-55.

102. das Nair R, Orr KS, Vedhara K, Kendrick D. Exploring recruitment barriers and facilitators in early cancer detection trials: the use of pre-trial focus groups. *Trials* 2014; **15**: 98.

103. Welch HG. Should I Be Tested for Cancer? Maybe Not and Here's Why. Berkeley, CA, United States of America: University of California Press; 2004.

104. Detterbeck FC, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; **143**(5 Suppl): e78S-92S.

105. DeFrank J, Barclay C, Sheridan S, et al. The Psychological Harms of Screening: the Evidence We Have Versus the Evidence We Need. *J GEN INTERN MED* 2015; **30**(2): 242-8.

106. Bunge EM, van den Bergh KA, Essink-Bot ML, van Klaveren RJ, de Koning HJ. High affective risk perception is associated with more lung cancer-specific distress in CT screening for lung cancer. *Lung cancer (Amsterdam, Netherlands)* 2008; **62**(3): 385-90.

107. van den Bergh KAM, Essink-Bot M-L, van Klaveren RJ, de Koning HJ. Informed decision making does not affect health-related quality of life in lung cancer screening (NELSON trial). *European Journal of Cancer* 2010; **46**(18): 3300-6.

108. Hestbech MS, Siersma V, Dirksen A, Pedersen JH, Brodersen J. Participation bias in a randomised trial of screening for lung cancer. *Lung cancer (Amsterdam, Netherlands)* 2011; **73**(3): 325-31.

109. Wu GX, Raz DJ, Brown L, Sun V. Psychological Burden Associated With Lung Cancer Screening: A Systematic Review. *Clin Lung Cancer* 2016.

110. Slatore CG, Sullivan DR, Pappas M, Humphrey LL. Patient-centered outcomes among lung cancer screening recipients with computed tomography: a systematic review. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2014; **9**(7): 927-34.

111. Field JK, Duffy SW, Baldwin DR, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. *Health technology assessment (Winchester, England)* 2016; **20**(40): 1-146.

112. Aggestrup LM, Hestbech MS, Siersma V, Pedersen JH, Brodersen J. Psychosocial consequences of allocation to lung cancer screening: a randomised controlled trial. *BMJ Open* 2012; **2**(2).

113. Kaerlev L, Iachina M, Pedersen JH, Green A, Nørgård BM. CT-Screening for lung cancer does not increase the use of anxiolytic or antidepressant medication. *BMC Cancer* 2012; **12**.

114. van den Bergh KA, Essink-Bot ML, Bunge EM, et al. Impact of computed tomography screening for lung cancer on participants in a randomized controlled trial (NELSON trial). *Cancer* 2008; **113**(2): 396-404.

115. Rasmussen JF, Siersma V, Pedersen JH, Brodersen J. Psychosocial consequences in the Danish randomised controlled lung cancer screening trial (DLCST). *Lung cancer (Amsterdam, Netherlands)* 2015; **87**(1): 65-72.

116. Gareen IF, Duan F, Greco EM, et al. Impact of lung cancer screening results on participant health-related quality of life and state anxiety in the National Lung Screening Trial. *Cancer* 2014; **120**(21): 3401-9.

117. Vierikko T, Kivisto S, Jarvenpaa R, et al. Psychological impact of computed tomography screening for lung cancer and occupational pulmonary disease among asbestos-exposed workers. *Eur J Cancer Prev* 2009; **18**(3): 203-6.

118. Brain K, Lifford KJ, Carter B, et al. Long-term psychosocial outcomes of low-dose CT screening: results of the UK Lung Cancer Screening randomised controlled trial. *Thorax* 2016.

119. Ali N, Lifford KJ, Carter B, et al. Barriers to uptake among high-risk individuals declining participation in lung cancer screening: a mixed methods analysis of the UK Lung Cancer Screening (UKLS) trial. *BMJ Open* 2015; **5**(7).

120. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. *Psychosomatic medicine* 1979; **41**(3): 209-18.

121. McCaffery KJ, Barratt AL. Assessing psychosocial/quality of life outcomes in screening: how do we do it better? *Journal of epidemiology and community health* 2004; **58**(12): 968-70.

122. Lazarus RS, Folkman S. Stress, appraisal, and coping: Springer publishing company; 1984.

123. Folkman S. The case for positive emotions in the stress process. *Anxiety, stress, and coping* 2008; **21**(1): 3-14.

124. Folkman S. Stress, coping, and hope. *Psychooncology* 2010; **19**(9): 901-8.

125. Folkman S, Lazarus RS. If it changes it must be a process: study of emotion and coping during three stages of a college examination. *Journal of personality and social psychology* 1985; **48**(1): 150-70.

126. Folkman S. Positive psychological states and coping with severe stress. *Social science & medicine (1982)* 1997; **45**(8): 1207-21.

127. Brain K, Henderson BJ, Tyndel S, et al. Predictors of breast cancer-related distress following mammography screening in younger women on a family history breast screening programme. *Psychooncology* 2008; **17**(12): 1180-8.

128. Leventhal H, Benyamini Y, Brownlee S, et al. Illness representations: Theoretical foundations. Perceptions of health and illness: Current research and applications. Amsterdam, Netherlands: Harwood Academic Publishers; 1997: 19-45.

129. Lancastle D, Brain K, Phelps C. Illness representations and distress in women undergoing screening for familial ovarian cancer. *Psychol Health* 2011; **26**(12): 1659-77.

130. Rees G, Fry A, Cull A, Sutton S. Illness perceptions and distress in women at increased risk of breast cancer. *Psychology & Health* 2004; **19**(6): 749-65.

131. Hagger MS, Orbell S. Illness representations and emotion in people with abnormal screening results. *Psychol Health* 2006; **21**(2): 183-209.

132. Hagger MS, Orbell S. A Meta-Analytic Review of the Common-Sense Model of Illness Representations. *Psychology & Health* 2003; **18**(2): 141-84.

133. Andrykowski MA, Pavlik EJ. Response to an abnormal ovarian cancer-screening test result: test of the social cognitive processing and cognitive social health information processing models. *Psychol Health* 2011; **26**(4): 383-97.

134. Brett J, Bankhead C, Henderson B, Watson E, Austoker J. The psychological impact of mammographic screening. A systematic review. *Psycho-Oncology* 2005; **14**(11): 917-38.

135. Tinmouth J, Raboud J, Ali M, et al. The psychological impact of being screened for anal cancer in HIV-infected men who have sex with men. *Diseases of the colon and rectum* 2011; **54**(3): 352-9.

136. Hensley ML, Robson ME, Kauff ND, et al. Pre- and postmenopausal high-risk women undergoing screening for ovarian cancer: anxiety, risk perceptions, and quality of life. *Gynecol Oncol* 2003; **89**(3): 440-6.

137. Sharp L, Cotton SC, Cruickshank ME, et al. Long-Term Worries after Colposcopy: Which Women Are at Increased Risk? *Women's Health Issues* 2015; **25**(5): 517-27.

138. Miles A, Wardle J. Adverse psychological outcomes in colorectal cancer screening: Does health anxiety play a role? *Behaviour Research and Therapy* 2006; **44**(8): 1117-27.

139. French DP, Maissi E, Marteau TM. The psychological costs of inadequate cervical smear test results: three-month follow-up. *Psychooncology* 2006; **15**(6): 498-508.

140. French DP, Maissi E, Marteau TM. Psychological costs of inadequate cervical smear test results. *Br J Cancer* 2004; **91**(11): 1887-92.

141. O'Connor D, Green S, Higgins JPT. (2011). Chapter 5: Defining the review question and developing criteria for including studies. In: Higgins, JPT., Green, S. (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Date accessed: 28/05/2013.

142. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of epidemiology and community health* 1998; **52**(6): 377-84.

143. Joseph S. Psychometric evaluation of Horowitz's Impact of Event Scale: a review. *Journal of traumatic stress* 2000; **13**(1): 101-13.

144. Park ER, Ostroff JS, Rakowski W, et al. Risk perceptions among participants undergoing lung cancer screening: baseline results from the National Lung Screening Trial. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine* 2009; **37**(3): 268-79.

145. Park ER, Streck JM, Gareen IF, et al. A qualitative study of lung cancer risk perceptions and smoking beliefs among national lung screening trial participants. *Nicotine and Tobacco Research* 2014; **16**(2): 166-73.

146. McRonald FE, Yadegarfar G, Baldwin DR, et al. The UK Lung Screen (UKLS): demographic profile of first 88,897 approaches provides recommendations for population screening. *Cancer Prev Res (Phila)* 2014; **7**(3): 362-71.

147. Patel D, Akporobaro A, Chinyanganya N, et al. Attitudes to participation in a lung cancer screening trial: a qualitative study. *Thorax* 2012; **67**(5): 418-25.

148. Vrinten C, van Jaarsveld CHM, Waller J, von Wagner C, Wardle J. The structure and demographic correlates of cancer fear. *BMC Cancer* 2014; **14**(1): 597.

149. McQueen A, Vernon SW, Meissner HI, Rakowski W. Risk perceptions and worry about cancer: does gender make a difference? *J Health Commun* 2008; **13**.

150. Eisinger F, Moatti JP, Beja V, Obadia Y, Alias F, Dressen C. Attitude of the French female population to cancer screening. *Bull Cancer* 1994; **81**.

151. Young B, Bedford L, Kendrick D, Vedhara K, Robertson JFR, das Nair R. Factors influencing the decision to attend screening for cancer in the UK: a meta-ethnography of qualitative research. *Journal of public health (Oxford, England)* 2017: 1-25.

152. Vrinten C, Wardle J, Marlow LAV. Cancer fear and fatalism among ethnic minority women in the United Kingdom. *Br J Cancer* 2016; **114**(5): 597-604.

153. Licqurish S, Phillipson L, Chiang P, Walker J, Walter F, Emery J. Cancer beliefs in ethnic minority populations: a review and meta-synthesis of qualitative studies. *European journal of cancer care* 2017; **26**(1).

154. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org. Last accessed: 19.01.2017.

155. Quaife SL, Marlow LA, McEwen A, Janes SM, Wardle J. Attitudes towards lung cancer screening in socioeconomically deprived and heavy smoking communities: informing screening communication. *Health expectations : an international journal of public participation in health care and health policy* 2016.

156. Glasgow Centre for Population Health. Asset based approaches for health improvement: redressing the balance. Available at: http://www.gcph.co.uk/work_themes/theme_4_assets_and_resilience/health_improvement_asset_based_approaches. Last accessed: 17.05.2017.

157. Norman GR, Sloan JA, Wyrwich KW. Interpretation of Changes in Health-related Quality of Life: The Remarkable Universality of Half a Standard Deviation. *Medical Care* 2003; **41**(5): 582-92.

158. Watson EK, Henderson BJ, Brett J, Bankhead C, Austoker J. The psychological impact of mammographic screening on women with a family history of breast cancer--a systematic review. *Psychooncology* 2005; **14**(11): 939-48.

159. Reade CJ, Riva JJ, Busse JW, Goldsmith CH, Elit L. Risks and benefits of screening asymptomatic women for ovarian cancer: A systematic review and meta-analysis. *Gynecologic Oncology* 2013; **130**(3): 674-81.

160. Metsälä E, Pajukari A, Aro AR. Breast cancer worry in further examination of mammography screening - a systematic review. *Scandinavian Journal of Caring Sciences* 2012; **26**(4): 773-86.

161. Gaugler JE, Pavlik E, Salsman JM, Andrykowski MA. Psychological and behavioral impact of receipt of a "normal" ovarian cancer screening test. *Preventive medicine* 2006; **42**(6): 463-70.

162. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of personality and social psychology* 1988; **54**(6): 1063-70.

163. Crawford JR, Henry JD. The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample. *The British journal of clinical psychology* 2004; **43**(Pt 3): 245-65.

164. Lerman C, Trock B, Rimer BK, Jepson C, Brody D, Boyce A. Psychological side effects of breast cancer screening. *Health Psychol* 1991; **10**(4): 259-67.

165. Macefield RC, Metcalfe C, Lane JA, et al. Impact of prostate cancer testing: an evaluation of the emotional consequences of a negative biopsy result. *Br J Cancer* 2010; **102**(9): 1335-40.

166. Ost D, Fein AM, Feinsilver SH. The Solitary Pulmonary Nodule. *New England Journal of Medicine* 2003; **348**(25): 2535-42.

167. Sullivan DR, Golden SE, Ganzini L, Hansen L, Slatore CG. 'I still don't know diddly': a longitudinal qualitative study of patients' knowledge and distress while undergoing evaluation of incidental pulmonary nodules. *NPJ Primary Care Respiratory Medicine* 2015; **25**: 15028.

168. Slatore CG, Press N, Au DH, Curtis JR, Wiener RS, Ganzini L. What the heck is a "nodule"?: A qualitative study of Veterans with pulmonary nodules. *Annals of the American Thoracic Society* 2013; **10**(4): 330-5.

169. Wiener RS, Gould MK, Woloshin S, Schwartz LM, Clark JA. 'The thing is not knowing': patients' perspectives on surveillance of an indeterminate pulmonary nodule. *Health expectations : an international journal of public participation in health care and health policy* 2015; **18**(3): 355-65.

170. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta psychiatrica Scandinavica* 1983; **67**(6): 361-70.

171. Folkman S, Lazarus RS. Stress-processes and depressive symptomatology. *J Abnorm Psychol* 1986; **95**(2): 107-13.

172. Bell ML, Fairclough DL, Fiero MH, Butow PN. Handling missing items in the Hospital Anxiety and Depression Scale (HADS): a simulation study. *BMC Res Notes* 2016; **9**(1): 479.

173. StataCorp. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

174. Bland JM, Altman DG. Statistics notes: Transformations, means, and confidence intervals. *BMJ* 1996; **312**(7038): 1079.

175. Bland JM, Altman DG. Statistics Notes: The use of transformation when comparing two means. *BMJ* 1996; **312**(7039): 1153.

176. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. *Journal of Psychosomatic Research* 2002; **52**(2): 69-77.

177. Ioannidis JP. Why most published research findings are false. *PLoS medicine* 2005; **2**(8): e124.

178. Delgado-Rodríguez M, Llorca J. Bias. *Journal of epidemiology and community health* 2004; **58**(8): 635-41.

179. Labott SM, Johnson TP, Fendrich M, Feeny NC. Emotional Risks to Respondents in Survey Research: Some Empirical Evidence. *Journal of empirical research on human research ethics : JERHRE* 2013; **8**(4): 53-66.

180. Grimes DA, Schulz KF. Bias and causal associations in observational research. *The Lancet*; **359**(9302): 248-52.

181. Merz EL, Roesch SC. Modeling trait and state variation using multilevel factor analysis with PANAS daily diary data. *Journal of research in personality* 2011; **45**(1): 2-9.

182. Kercher K. Assessing Subjective Well-Being in the Old-Old. *Research on Aging* 1992; **14**(2): 131-68.

183. Mackinnon A, Jorm AF, Christensen H, Korten AE, Jacomb PA, Rodgers B. A short form of the Positive and Negative Affect Schedule: evaluation of factorial validity and invariance across demographic variables in a community sample. *Personality and Individual Differences* 1999; **27**(3): 405-16.

184. Rolstad S, Adler J, Rydén A. Response Burden and Questionnaire Length: Is Shorter Better? A Review and Meta-analysis. *Value in Health* 2011; **14**(8): 1101-8.

185. Orbell S, O'Sullivan I, Parker R, Steele B, Campbell C, Weller D. Illness representations and coping following an abnormal colorectal cancer screening result. *Social science & medicine (1982)* 2008; **67**(9): 1465-74.

186. Carver CS, Scheier MF, Weintraub JK. Assessing coping strategies: a theoretically based approach. *Journal of personality and social psychology* 1989; **56**(2): 267-83.

187. Fernandez-Feito A, Lana A, Baldonedo-Cernuda R, Mosteiro-Diaz MP. A brief nursing intervention reduces anxiety before breast cancer screening mammography. *Psicothema* 2015; **27**(2): 128-33.

188. Nakash RA, Hutton JL, Lamb SE, Gates S, Fisher J. Response and non-response to postal questionnaire follow-up in a clinical trial--a qualitative study of the patient's perspective. *Journal of evaluation in clinical practice* 2008; **14**(2): 226-35.

189. Young JM, O'Halloran A, McAulay C, et al. Unconditional and conditional incentives differentially improved general practitioners' participation in an online survey: randomized controlled trial. *J Clin Epidemiol* 2015; **68**(6): 693-7.

190. Robinson KA, Dennison CR, Wayman DM, Pronovost PJ, Needham DM. Systematic review identifies number of strategies important for retaining study participants. *Journal of Clinical Epidemiology* 2007; **60**(8): 757.e1-.e19.

191. Brueton V, Tierney J, Stenning S, Harding S, Meredith S, Nazareth I. Strategies to improve retention in randomized trials. *Cochrane Database Syst Rev* 2013; **12**.

192. Brueton VC, Tierney JF, Stenning S, et al. Strategies to improve retention in randomised trials: a Cochrane systematic review and meta-analysis. *BMJ Open* 2014; **4**(2).

193. Edwards L, Salisbury C, Horspool K, Foster A, Garner K, Montgomery AA. Increasing follow-up questionnaire response rates in a randomized controlled trial of telehealth for depression: three embedded controlled studies. *Trials* 2016; **17**(1): 1-13.

194. Sutherland H, Beaton M, Mazer R, Kriukov V, Boyd N. A randomized trial of the total design method for the postal follow-up of women in a cancer prevention trial. *Eur J Cancer Prev* 1996; **5**.

195. Brueton V, Stevenson F, Vale C, Stenning S, Tierney J, Harding S. Use of strategies to improve retention in primary care randomised trials: a qualitative study with in-depth interviews. *BMJ Open* 2014; **4**.

196. Gates S, Williams M, Withers E, Williamson E, Mt-Isa S, Lamb S. Does a monetary incentive improve the response to a postal questionnaire in a randomised controlled trial? The MINT incentive study. *Trials* 2009; **10**(1): 1-7.

197. Kenyon S, Pike K, Jones D, et al. The effect of a monetary incentive on return of a postal health and development questionnaire: a randomised trial [ISRCTN53994660]. *BMC Health Serv Res* 2005; **5**: 55.

198. Kenton L, Dennis CL, Weston J, et al. Abstracts from the 28th Meeting of the Society of Clinical Trials, Montreal, May 20−23, 2007: the effect of incentives and high priority mailing on postal questionnaire response rates: A Mini-RCT. Clinical Trials 2007;4:371–455.

199. Bauer JE, Rezaishiraz H, Head K, et al. Obtaining DNA from a geographically dispersed cohort of current and former smokers: use of mail-based mouthwash collection and monetary incentives. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2004; **6**(3): 439-46.

200. Edwards PJ, Roberts I, Clarke MJ, et al. Methods to increase response to postal and electronic questionnaires. *The Cochrane database of systematic reviews* 2009; (3): MR000008.

201. Edwards P, Roberts I, Clarke M, DiGuiseppi C, Wentz R, Kwan I. Methods to increase response to postal and electronic questionnaires. *Cochrane Database Syst Rev* 2009; **3**.

202. Singer E, Ye C. The Use and Effects of Incentives in Surveys. *The ANNALS of the American Academy of Political and Social Science* 2013; **645**(1): 112-41.

203. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010; **152**(11): 726-32.

204. Groves RM, Presser S, Dipko S. The Role of Topic Interest in Survey Participation Decisions. *Public Opinion Quarterly* 2004; **68**(1): 2-31.

205. Groves RM, Singer E, Corning A. Leverage-saliency theory of survey participation: description and an illustration. *Public Opin Q* 2000; **64**(3): 299-308.

206. Bower P, Brueton V, Gamble C, Treweek S, Smith C, Young B. Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities. *Trials* 2014; **15**.

Appendices

Appendix 1. Permission to republish figures depicting the Stress and Coping Model



Copyright Clearance Center RightsLink®

Home | Create Account | Help

Routledge Taylor & Francis Group

Title: The case for positive emotions in the stress process
Author: Susan Folkman
Publication: Anxiety, Stress and Coping
Publisher: Taylor & Francis
Date: Jan 1, 2008
Copyright © 2008 Routledge

LOGIN

If you're a copyright.com user, you can login to RightsLink using your copyright.com credentials. Already **a RightsLink user** or want to learn more?

Thesis/Dissertation Reuse Request

Taylor & Francis is pleased to offer reuses of its content for a thesis or dissertation free of charge contingent on resubmission of permission request if work is published.

BACK | CLOSE WINDOW

Copyright © 2017 Copyright Clearance Center, Inc. All Rights Reserved. Privacy statement. Terms and Conditions.
Comments? We would like to hear from you. E-mail us at customercare@copyright.com

Appendix 2. Permission to republish a figure illustrating the Self-Regulation Model of illness beliefs



https://s100.copyright.com/AppDispatchServlet#formTop

Copyright Clearance Center RightsLink®

Home | Create Account | Help

Routledge
Taylor & Francis Group

Title: A Meta-Analytic Review of the Common-Sense Model of Illness Representations
Author: Martin S. Hagger, Sheina Orbell
Publication: Psychology and Health
Publisher: Taylor & Francis
Date: Jan 1, 2003
Copyright © 2003 Routledge

LOGIN
If you're a copyright.com user, you can login to RightsLink using your copyright.com credentials. Already a RightsLink user or want to learn more?

Thesis/Dissertation Reuse Request

Taylor & Francis is pleased to offer reuses of its content for a thesis or dissertation free of charge contingent on resubmission of permission request if work is published.

BACK | CLOSE WINDOW

Copyright © 2017 Copyright Clearance Center, Inc. All Rights Reserved. Privacy statement. Terms and Conditions.
Comments? We would like to hear from you. E-mail us at customercare@copyright.com

Appendix 3. Systematic review data extraction form

General information	
1. Study reference	
2. Country	
3. Aim	
Intervention details	
4. Cancer being screened for	
5. Type of screening test (*e.g., chest x-ray*)	
6. Any additional information on the intervention (Provide further details on screening test here and describe any other interventions that were provided in addition to screening, such as risk counselling)	
Participants	
7. Gender	
8. Age	
9. Additional demographic/clinical information (*e.g., ethnicity, socioeconomic status, screening history*)	
10. Test result groups (n)	
11. Controls?	
Study design details	
12. Type of study	☐ Randomised controlled trials (RCTs) ☐ Quasi-randomized controlled trial ☐ Nonrandomized trial ☐ Controlled before-and-after study ☐ Before-and-after comparison ☐ Nested case control study ☐ Case control study ☐ Cohort study ☐ Prospective longitudinal design

13. Randomisation (if applicable)	☐ Yes – blind ☐ Yes – known ☐ No ☐ NA
Emotional outcomes	
14. Emotional impact focus?	Primary ☐ Secondary ☐
15. Emotional outcomes reported (and how they were measured)	
16. How were emotional outcomes assessed? (e.g., postal questionnaires)	
17. When were emotional outcomes measured? (e.g., before screening test, one-month post test-result)	
Predictor factors (and how they were measured, if applicable)	
18. Demographic factors?	
19. Clinical factors? (*e.g., screening history, family history of disease being screened for*)	
20. Psychosocial factors? (*e.g., perceived susceptibility)*	
21. Understanding of screening test results?	
22. Factors related to the screening process? (*e.g., method of invitation, information provided on test, invasiveness of test, communication of test results*)	

Analysis	
23. Description of analysis employed to measure the impact of predictor factors on emotional outcomes	
Results	
24. Results of the analysis (*narrative description, including data*)	
25. Final number of participants included in analysis	
26. Follow-up response rates (*state reasons for non-response, if reported*)	
27. Cases excluded from analysis	
Conclusions	
Discusses clinical significance?	
Clinical implications?	
Other comments (e.g., strengths and limitations)	

Appendix 4. Systematic review quality assessment results

				Publications reporting on the NELSON trial			
	Byrne et al. 2008 [88]	Sinicrope et al. 2010 [91]	Vierikko et al. 2009 [117]	Bunge et al. 2008 [106]	Van den Berg et al. 2008 [114]	Van den Berg et al. 2010 [90]	Van den Berg et al. 2011 [89]
Subscale 1. Reporting (N = 10)							
1. Is the hypothesis/aim/objective of the study clearly described? (Yes = 1, No = 0)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
2. Are the main outcomes to be measured clearly described in the introduction or method section? (Yes = 1, No = 0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
3. Are the characteristics of the patients included in	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)

the study clearly described? (Yes = 1, No = 0)							
4. Are the interventions of interest clearly described? (Yes = 1, No = 0)	Yes (1)	No (0)	No (0)	No (0)	Yes (1)	Yes (1)	Yes (1)
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described? (Yes = 2, Partially = 1, No = 0)	Yes (2)	No (0)	No (0)	Yes (2)	No (0)	Yes (2)	Yes (2)
6. Are the main findings of the study clearly described? (Yes = 1, No = 0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
7. Does the study provide estimates of the random variability in the data for the main outcomes? (Yes = 1, No = 0)	Yes (1)	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
8. Have all important adverse events that may	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)

be a consequence of the intervention been reported? (Yes = 1, No = 0)							
9. Have the characteristics of patients lost to follow-up been described? (Yes = 1, No = 0)	No (1)	No (0)	Yes (1)	Yes (1)	No (0)	Yes (1)	No (0)
10. Have actual probability values been reported (e.g. 0.035 rather than < 0.05) for the main outcomes except where the probability value is less than 0.01? (Yes = 1, No = 0)	No (1)	No (0)	Yes (1)	No (0)	No (0)	No (0)	No (0)
Total subscale score (11)	**9**	**5**	**6**	**9**	**7**	**9**	**9**

Subscale 2. External validity (N = 3)							
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited? (Yes = 1, No = 0, Unable to determine = 0)	Unable to determine (0)	Yes (1)	Yes (1)	Yes (1)	No (0)	Yes (1)	Unable to determine (0)
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited? (Yes = 1, No = 0, Unable to determine = 0)	Yes (1)	Unable to determine (0)	Unable to determine (0)	Unable to determine (0)	No (0)	Unable to determine (0)	Unable to determine (0)
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Yes (1)	Unable to determine (0)	Unable to determine (0)	Unable to determine (0)	Unable to determine (0)	Yes (1)	Yes (1)

(Yes = 1, No = 0, Unable to determine = 0)							
Total subscale score (3)	**2**	**1**	**1**	**1**	**0**	**2**	**1**
Subscale 3. Internal validity – bias (N = 7)							
14. Was an attempt made to blind study subjects to the intervention they received? (Yes = 1, No = 0, Unable to determine = 0)	N/A	N/A	N/A	N/A	N/A	N/A	No (0)
15. Was an attempt made to blind those measuring the main outcomes of the intervention? (Yes = 1, No = 0, Unable to determine = 0)	N/A	N/A	N/A	N/A	N/A	N/A	Unable to determine (0)
16. If any of the results of the study were based on "data dredging," was this made clear? (Yes = 1, No = 0, Unable to determine = 0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? (Yes = 1, No = 0, Unable to determine = 0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
18. Were the statistical tests used to assess the main outcomes appropriate? (Yes = 1, No = 0, Unable to determine = 0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
19. Was compliance with the intervention/s reliable? (Yes = 1, No = 0, Unable to determine = 0)	Yes (1)	Unable to determine (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
20. Were the main outcome measures used accurate (valid and reliable)?	No (0)	No (0)	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)

(Yes = 1, No = 0, Unable to determine = 0)							
Total subscale score (7)	**4 (5)**	**3 (5)**	**4 (5)**	**5 (5)**	**5 (5)**	**5 (5)**	**5 (7)**
Subscale 4. Internal validity - confounding (selection bias) (N = 6)							
21. Were the patients in different intervention group (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? (Yes = 1, No = 0, Unable to determine = 0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? (Yes = 1, No = 0, Unable to determine = 0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)

23. Were study subjects randomised to intervention groups? (Yes = 1, No = 0, Unable to determine = 0)	N/A	N/A	N/A	N/A	N/A	N/A	Yes (1)
24. Was the randomised intervention assignment concealed from both parties and health care staff until recruitment was complete and irrevocable? (Yes = 1, No = 0, Unable to determine = 0)	N/A	N/A	N/A	N/A	N/A	N/A	Unable to determine (0)
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? (Yes = 1, No = 0, Unable to determine = 0)	Yes (1)	No (0)	Yes (1)	No (0)	No (0)	Yes (1)	Yes (1)
26. Were losses of patients to follow-up taken into account?	Unable to determine (0)	Unable to determine (0)	No	Yes (1)	Yes (1)	Yes (1)	No (0)

Total subscale score (6)	**3 (4)**	**2 (4)**	**3 (4)**	**3 (4)**	**3 (4)**	**4 (4)**	**4 (6)**
Subscale 5. power (N = 1)							
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? (<n_1 = 0, n_1–n_2 = 1, n_3–n_4 = 2, n_5–n_6 = 3, n_7–n_8 = 4, n_8+ = 5)	Power calculation not reported (0)	Power calculation not reported (0)	Power calculation not reported (0)	Power calculation not reported (0)	Power calculation not reported (0)	Power calculation not reported (0)	Power calculation not reported (0)
Total subscale score (5)	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Total checklist score (%)	18/28 (64.3%)	11/28 (39.3%)	14/28 (50%)	18/28 (64.3%)	15/28 (53.6%)	20/28 (71.4%)	19/32 (59.4%)
Number of disagreements between reviewers	6	6	6	5	5	1	5

Item(s) disagreed on	8, 9, 13, 20, 22, 26	4, 7, 8, 10, 18, 19	1, 12, 13, 20, 22, 26	4, 8, 13, 19, 21	7, 9 , 13, 25, 26	13	13, 14, 22, 23, 24

Appendix 5. Ethical approval documents

EoSRES

NHS SCOTLAND
Research Ethics Service

East of Scotland Research Ethics Service (EoSRES) REC 1
Tayside Medical Sciences Centre (TASC)
Residency Block C, Level 3
Ninewells Hospital & Medical School
George Pirie Way
Dundee DD1 9SY

Professor Frank M Sullivan
NHS Professor of R&D in General Practice
University of Dundee
Division of Population Health Sciences
Mackenzie Building
Kirsty Semple Way
DUNDEE, DD2 4BF

Date: 26 November 2013
Your Ref:
Our Ref: LR/13/ES/0024
Enquiries to: Mrs Lorraine Reilly
Extension: Ninewells extension: 83878
Direct Line: 01382 383878
Email: eosres.tayside@nhs.net

Dear Professor Sullivan

Study title: **Detection in blood of autoantibodies to tumour antigens as a case-finding method in lung cancer using the EarlyCDT-Lung test**
REC reference: **13/ES/0024**
Amendment number: **AM05 (For REC Reference Only)**
Amendment date: **19 November 2013**
IRAS project ID: **111984**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

There were no ethical issues noted.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
ECLS Invalid Result Letter RB	1	11 September 2013
Questionnaire: ECLS Study - Participant Questionnaire 3S	1.3	06 August 2013
Protocol	2	11 October 2013
Participant Information Sheet: ECLS Sub study 2	1	11 September 2013
Letter of invitation to participant	1	11 September 2013
ECLS Appointment Letter	1.1	11 September 2013
Questionnaire: ECLS Study - Participant Questionnaire 3C	1.3	06 August 2013
ECLS Study CT Scan Nodule Result Letter	1.1	11 September 2013
Letter of invitation to participant	1	11 September 2013
Letter of invitation to participant	1	11 September 2013

Questionnaire: ECLS Study - Participant Questionnaire 1S	1.3	06 August 2013
Questionnaire: ECLS Study - Participant Questionnaire H	1.3	06 August 2013
Letter of invitation to participant	1	11 September 2013
Participant Information Sheet: ECLS Sub study 3	1	11 September 2013
ECLS Reminder Postcard	1	10 October 2013
Questionnaire: ECLS Study - Participant Questionnaire 6S	1.3	06 August 2013
Participant Information Sheet: ECLS Sub study 1	1	11 September 2013
Letter of invitation to participant	1	11 September 2013
Notice of Substantial Amendment (non-CTIMPs)	AM05	19 November 2013
ECLS Invalid Result Letter NO RB	1	11 September 2013
Questionnaire: ECLS Study - Participant Questionnaire 6C	1.3	06 August 2013
Participant Consent Form: ECLS Sub study 1	1	11 September 2013
Participant Consent Form: ECLS Sub study 3	1	11 September 2013
GP/Consultant Information Sheets	1	11 September 2013
Questionnaire: ECLS Study - Participant Questionnaire 1C.	1.3	06 August 2013
Questionnaire: ECLS Study - Participant Questionnaire 12C	1.3	06 August 2013
Participant Consent Form: ECLS Sub study 2	1	11 September 2013
Letter of invitation to participant	1	11 September 2013

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

13/ES/0024:	**Please quote this number on all correspondence**

Yours sincerely

pp
Dr Lynda Cochrane
Alternate Vice-chair

Email: eosres.tayside@nhs.net

Enclosures: List of names and professions of members who took part in the review

Copy to: NHS Tayside R&D Office

East of Scotland Research Ethics Service REC 1

Attendance at Sub-Committee of the REC meeting on 26 November 2013

Also in attendance:

Name	Position (or reason for attending)
Mrs Lorraine Reilly	Senior Co-ordinator

Written comments received from:

Name	Position
Dr Lynda Cochrane	Professional Statistician, Alternate Vice-chair
Mrs Shona Carson	Clinical Trials Pharmacist

NHS Tayside

10 January 2014

Professor Frank Sullivan
NHS Professor of R&D in General Practice
University of Dundee
Division of Population Health Sciences
Mackenzie Building
Kirsty Semple Way
DUNDEE
DD2 4BF

Dear Professor Sullivan,

ACCEPTANCE OF AMENDMENT LETTER

Title: Detection in blood of autoantibodies to tumour antigens as a case-finding method in lung cancer using the EarlyCDT-Lung test.

Chief Investigator: Professor Frank Sullivan **Principal Investigator: Professor Frank Sullivan**

Tayside Ref: 2013ON07 **NRS Ref: NRS13/ON400**

REC Ref: 13/ES/0024

Sponsors: University of Dundee and NHS Tayside

Funders: Chief Scientist Office and Oncimmune Ltd

Amendment Number: 05 **Amendment Date: 19/11/13**

Thank you for submitting the above amendment for review by the R&D Office here in NHS Tayside. Following my assessment of the proposed changes I am pleased to confirm that NHS Tayside has no objection to these being implemented locally.

Approved Documents

Document	Version	Date
Ethics – Favourable Ethical Opinion of Amendment Letter		26/11/13
Notice of Amendment		19/11/13
Participant Information Leaflet (Sub Study 1)	1	11/09/13
Participant Information Leaflet (Sub Study 2)	1	11/09/13
Participant Information Leaflet (Sub Study 3)	1	11/09/13
Participant Consent Form (Sub Study 1)	1	11/09/13
Participant Consent Form (Sub Study 2)	1	11/09/13

Participant Consent Form (Sub Study 3)	**1**	**11/09/13**
Participant Invitation Letter (Sub Study 1)	**1**	**11/09/13**
Participant Invitation Letter (Sub Study 2)	**1**	**11/09/13**
Participant Invitation Letter (Sub Study 3)	**1**	**11/09/13**
Participant Reminder Letter (Sub Study 1)	**1**	**11/09/13**
Participant Reminder Letter (Sub Study 2)	**1**	**11/09/13**
Participant Reminder Letter (Sub Study 3)	**1**	**11/09/13**
Participant Appointment Letter	**1.1**	**11/09/13**
CT Scan Nodule Result Letter	**1.1**	**11/09/13**
Invalid Test Letter RB	**1**	**11/09/13**
Invalid Test Letter NO RB	**1**	**11/09/13**
GP Invitation Reminder Letter	**1**	**11/09/13**
Reminder Postcard	**1.0**	**10/10/13**
Participant Questionnaire 1S	**1.3**	**06/08/13**
Participant Questionnaire 3S	**1.3**	**06/08/13**
Participant Questionnaire 6S	**1.3**	**06/08/13**
Participant Questionnaire 1C	**1.3**	**06/08/13**
Participant Questionnaire 3C	**1.3**	**06/08/13**
Participant Questionnaire 6C	**1.3**	**06/08/13**
Participant Questionnaire 12C	**1.3**	**06/08/13**
Participant Questionnaire H	**1.3**	**06/08/13**
Protocol	**2**	**11/10/13**

I thank you for keeping the R&D Office informed of the study progress.

Please note all minor/substantial amendments and end of trial notifications must be reported to the R&D Office.

Yours Sincerely



Elizabeth Coote
R&D Manager

TAyside medical Science Centre (TASC)
Ninewells Hospital & Medical School
TASC Research & Development Office
Residency Block, Level 3
George Pirie Way
Dundee DD1 9SY
Email: liz.coote@nhs.net
Tel: 01382 383876 Fax: 013812 740122

c.c. Dr Roberta Littleford
Ms Stephanie Gallant

Appendix 6. Sample questionnaire cover letter



TASC, R&D Office
Residency Block, Level 3
George Pirie Way
Ninewells Hospital
DD1 9SY

Date:

Dear [patient name here],

Lung Cancer Screening Scotland Study: £5 gift voucher enclosed

When you gave your blood sample the nurse said we might send you some more surveys to fill in. You are one of a small group chosen from the 10,000 people taking part in the ECLS study to do this. Completing the surveys is very important as we need to find out about the full impact of the new screening test.

Please complete the enclosed survey and return it to us in the freepost envelope provided **within the next 7 days**. We have also enclosed a £5 gift voucher to thank you for doing this. There is a list of places where you can spend the voucher on the back of this letter.

We will send you three more surveys over the next year as we would like to see how your thoughts change. A £5 voucher will be available for each survey we send to you. Once we have all the surveys back from you, we will be happy to send you a copy of our findings.

Everything you say in the survey will be kept confidential.

If you have any questions about the survey, or would like some help to fill it in, you can call us on 0115 823 1260. We will be happy to help.

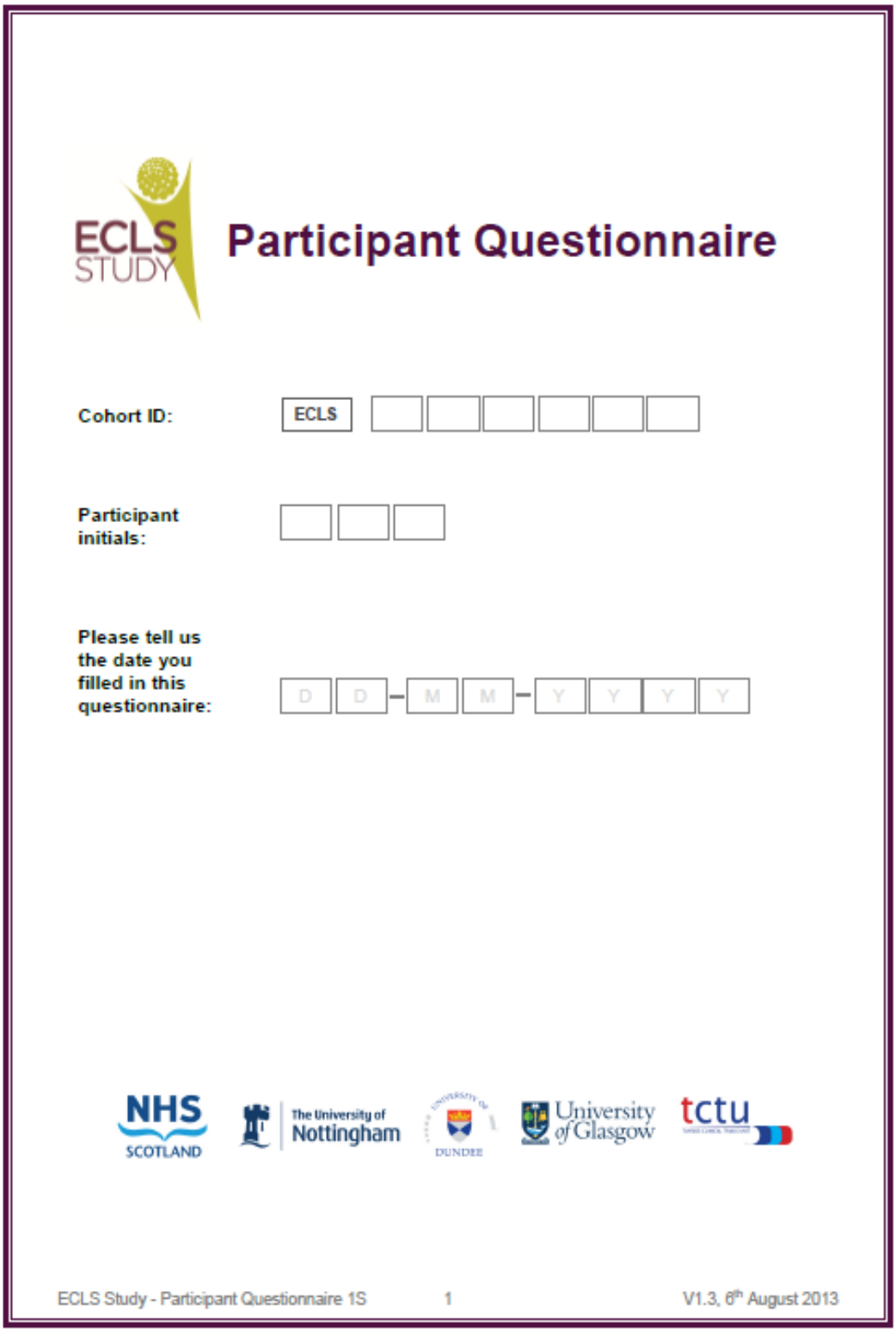
Yours sincerely,

Laura Bedford Ben Young

ECLS Research Team

ECLS 1m Questionnaire letter NC-V, v1, 1st May 2013

Appendix 7. Sample study questionnaire



ECLS STUDY

Participant Questionnaire

Cohort ID: ECLS

Participant initials:

Please tell us the date you filled in this questionnaire: D D – M M – Y Y Y Y

NHS SCOTLAND · The University of Nottingham · University of Dundee · University of Glasgow · tctu

ECLS Study - Participant Questionnaire 1S 1 V1.3, 6th August 2013

PART A

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐

Self-Care

I have no problems with self-care	☐
I have some problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities	☐
I have some problems with performing my usual activities	☐
I am unable to perform my usual activities	☐

Pain/Discomfort

I have no pain or discomfort	☐
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐

Anxiety/Depression

I am not anxious or depressed	☐
I am moderately anxious or depressed	☐
I am extremely anxious or depressed	☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



PART B

This questionnaire lists a number of words that people often use to describe different feelings and emotions. Read each item and then tick the appropriate answer in the space next to the word. **Indicate the extent you have felt this way over the past week.**

		Very slightly or not at all	A little	Moderately	Quite a bit	Extremely
1)	Interested	☐	☐	☐	☐	☐
2)	Distressed	☐	☐	☐	☐	☐
3)	Excited	☐	☐	☐	☐	☐
4)	Upset	☐	☐	☐	☐	☐
5)	Strong	☐	☐	☐	☐	☐
6)	Guilty	☐	☐	☐	☐	☐
7)	Scared	☐	☐	☐	☐	☐
8)	Hostile	☐	☐	☐	☐	☐
9)	Enthusiastic	☐	☐	☐	☐	☐
10)	Proud	☐	☐	☐	☐	☐
11)	Irritable	☐	☐	☐	☐	☐
12)	Alert	☐	☐	☐	☐	☐
13)	Ashamed	☐	☐	☐	☐	☐
14)	Inspired	☐	☐	☐	☐	☐
15)	Nervous	☐	☐	☐	☐	☐
16)	Determined	☐	☐	☐	☐	☐
17)	Attentive	☐	☐	☐	☐	☐
18)	Jittery	☐	☐	☐	☐	☐
19)	Active	☐	☐	☐	☐	☐
20)	Afraid	☐	☐	☐	☐	☐

From "Development and validation of brief measures of positive and negative affect: The PANAS scales," by D. Watson, L. A. Clark, and A. Tellegen, 1988, Journal of Personality and Social Psychology, 54, 1063-1070. Copyright © 1988 by the American Psychological Association. Reproduced with permission. No further reproduction or distribution is permitted without written permission from the American Psychological Association.

PART C

We are interested in your personal views about lung cancer.

Please indicate how much you agree or disagree with the statements below by ticking the box that best describes your views.

	VIEWS ABOUT LUNG CANCER	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
1	What I do can affect my risk of getting lung cancer					
2	When I think about my risk of getting lung cancer I get upset					
3	I do not know how likely it is that I might get lung cancer					
4	Finding lung cancer early can improve my chances of survival					
5	Lung cancer would have a big impact on my life					
6	Lung cancer lasts for a long time					
7	A blood screening test can accurately detect lung cancer					
8.	Please list in rank-order the three most important factors that you believe cause lung cancer. The most important causes for me are:- 1. ..... 2. ..... 3.					

PART D

1. What are the chances that you will develop lung cancer over the next five years? (Please tick one box)

- Approximately 1 in 1000 (0.1%) ☐
- Approximately 1 in 500 (0.2%) ☐
- Approximately 1 in 250 (0.4%) ☐
- Approximately 1 in 100 (1%) ☐
- Approximately 1 in 20 (5%) ☐
- Approximately 1 in 10 (10%), or greater ☐
- Don't know ☐

2. Compared to other people of your age and sex, how likely are you to develop lung cancer over the next 5 years? (Please tick one box)

- A lot less likely than other people ☐
- Less likely than other people ☐
- About as likely as other people ☐
- More likely than other people ☐
- Much more likely than other people ☐
- Don't know ☐

PART E

Please read the following statements carefully and decide to what extent it is a characteristic of you at the moment.

Please tick one of the responses to each statement.

		Not at all	Slightly	Somewhat	Moderately	Very
1)	I feel anxious when I think about my health	☐	☐	☐	☐	☐
2)	I'm worried about how healthy my body is	☐	☐	☐	☐	☐
3)	Thinking about my health leaves me with an uneasy feeling	☐	☐	☐	☐	☐
4)	I usually worry about whether I am in good health	☐	☐	☐	☐	☐
5)	I feel nervous when I think about the status of my physical health	☐	☐	☐	☐	☐

Below are four questions asking you about how worried you are about lung cancer at the moment.

Please tick one of the responses to each question.

How worried are you about getting lung cancer someday?

- Not at all worried ☐
- Rarely worried ☐
- Sometimes worried ☐
- Often worried ☐
- Worried almost all the time ☐

How much does your worry affect your mood?

- Not at all ☐
- A little ☐
- Somewhat ☐
- A lot ☐
- Almost all the time ☐

How much does your worry affect your ability to perform your daily activities?

- Not at all ☐
- A little ☐
- Sometimes ☐
- A lot ☐
- Almost all the time ☐

What is your current level of anxiety about the results of future tests/treatments?

- Not at all anxious ☐
- A little anxious ☐
- Somewhat anxious ☐
- Anxious a lot ☐
- Anxious almost all the time ☐

PART F

Below is a list of comments that people have made about their feelings upon being tested for an illness. Please place a tick against each item to indicate how often you had these feelings **during the PAST WEEK including today**. If you did not have these feelings during that time, please tick the 'not at all' column. **Please tick only one box in each section.**

		Not at all	Rarely	Sometimes	Often
1)	I thought about being tested for lung cancer when I did not mean to.				
2)	I avoided letting myself get upset when I thought about being tested for lung cancer or was reminded of it.				
3)	I tried to remove being tested for lung cancer from memory.				
4)	I had trouble falling asleep, because of pictures or thoughts about being tested for lung cancer that came into my mind.				
5)	I had waves of strong feelings about being tested for lung cancer.				
6)	I had dreams about being tested for lung cancer.				
7)	I stayed away from reminders of being tested for lung cancer.				
8)	I felt as if being tested for lung cancer wasn't happening to me, or wasn't real.				
9)	I tried not to talk about being tested for lung cancer.				
10)	Pictures about being tested for lung cancer popped into my mind.				
11)	Other things kept making me think about being tested for lung cancer.				
12)	I was aware that I still had a lot of feelings about being tested for lung cancer but I didn't deal with them.				
13)	I tried not to think about being tested for lung cancer.				
14)	Any reminder brought back feelings about being tested for lung cancer.				
15)	My feelings about being tested for lung cancer were kind of numb.				

PART G

In the past month, how many times have you seen the people below because of <u>any of these symptoms</u>:

	Persistent cough Coughing up blood Shortness of breath Weight loss Loss of appetite	Any other symptoms
1. Seen the GP	Number of times: ☐	Number of times: ☐
2. Seen the Practice/ Community Nurse	Number of times: ☐	Number of times: ☐
3. Seen other health or social care workers	Number of times: ☐ Who did you see? --- --- --- ---	Number of times: ☐ Who did you see? --- --- --- ---
4. Been a hospital in-patient	Number of times: ☐ Total no. of days: ☐	Number of times: ☐ Total no. of days: ☐

Are you currently taking any tablets or medicines on prescription? **YES / NO**

(circle one)

If YES, please list the names here:

.....

.....

.....

.....

.....

.....

.....

.....

.....

.....

Has your prescription for tablets/medicines changed in the last month? **YES / NO**
(circle one)

If YES, please list tablets/medicines that have changed on your prescription:

New tablets/medicines started within the last month:	Tablets/medicines stopped within the last month:

Part H

This study is not about trying to encourage people to stop smoking but we are still interested in your smoking behaviour and your views about smoking.

1) Not counting the last week, have you smoked any cigarettes or tobacco in the LAST MONTH?

Yes ☐ No ☐

---

2) Have you smoked any cigarettes or tobacco in the last seven days / week?

Yes ☐ No ☐

If YES, please go to **Question 3**
If NO, please go to the end of the questionnaire

---

3) How soon after you wake up do you smoke your first cigarette or tobacco? (Tick one box)

After 60 minutes ☐

31 to 60 minutes ☐

6 to 30 minutes ☐

Within 5 minutes ☐

---

4) On average, how many cigarettes do you smoke each day?
(Enter a number)

☐

5) Do you have any intention of giving up smoking in the next four weeks? (Tick one box)

- Yes, definitely ☐
- Yes, probably ☐
- Don't know ☐
- Probably not ☐
- Definitely not ☐

---

6) How sure or confident are you that if you tried, you could give up smoking for good? (Tick one box)

- Very certain ☐
- Fairly certain ☐
- Don't know ☐
- Fairly uncertain ☐
- Very uncertain ☐

---

7) Which one of these statements do you most strongly agree with? (Tick one box)

- I would like to keep on smoking ☐
- I don't really want to stop smoking ☐
- I don't know whether I want to stop smoking or not ☐
- I don't really want to carry on smoking ☐
- I would like to stop smoking ☐

8) Which one of these statements do you most strongly agree with? (Tick one box)

I never think about stopping smoking ☐

One day I will need to think about stopping smoking ☐

I should stop smoking but I don't think I'm ready ☐

I am starting to think about how I can smoke less ☐

I am trying to stop smoking ☐

---

9) How strongly do you agree or disagree with the statement "My health will improve if I stop smoking." (Tick one box)

Disagree strongly ☐

Disagree ☐

Don't know ☐

Agree ☐

Agree strongly ☐

---

10) How strongly do you agree or disagree with the statement "People who are important to me want me to stop smoking." (Tick one box)

Disagree strongly ☐

Disagree ☐

Don't know ☐

Agree ☐

Agree strongly ☐

11) In the LAST MONTH have you tried to cut down the number of cigarettes you smoke?

Yes ☐ No ☐

12) In the LAST MONTH have you tried to stop smoking?

Yes ☐ No ☐

Thank you for completing this questionnaire.

Appendix 8. Chapter four model checking results

Appendix seven contains the results from the model checks conducted for negative affect as part of the analyses presented in chapter 4. For each adjusted linear regression model for negative affect, histograms, P-P plots, Q-Q plots and scatterplots are presented for both the original scale and on the logarithmic scale.

1.1. Negative affect scores within screening groups over time

1.1.1. Model 1 (adjusted for ECLS minimisation variables)

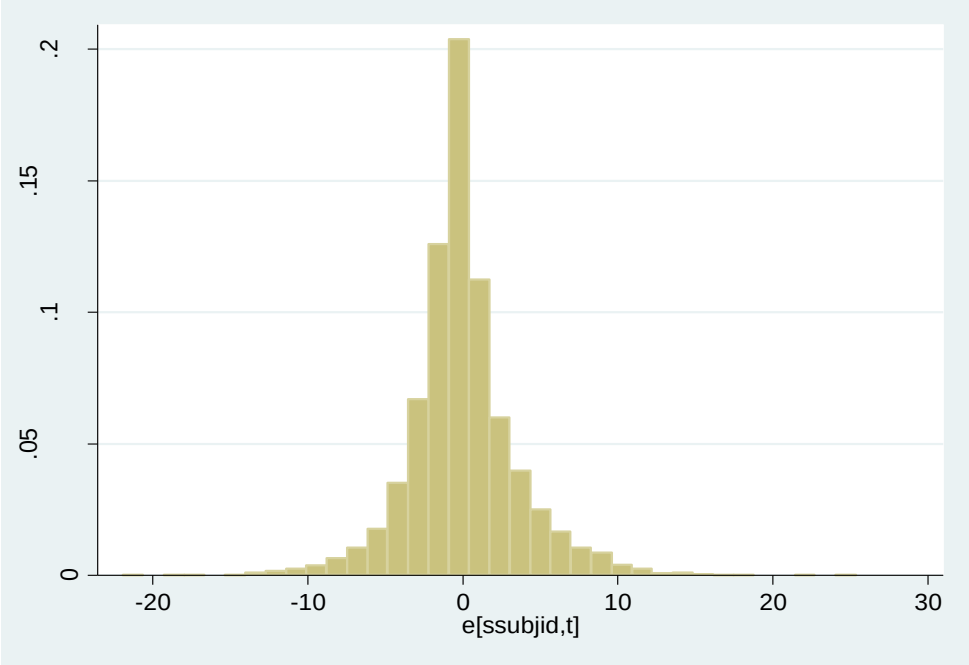


Figure 1. Histogram for level one residuals with negative affect as the outcome variable

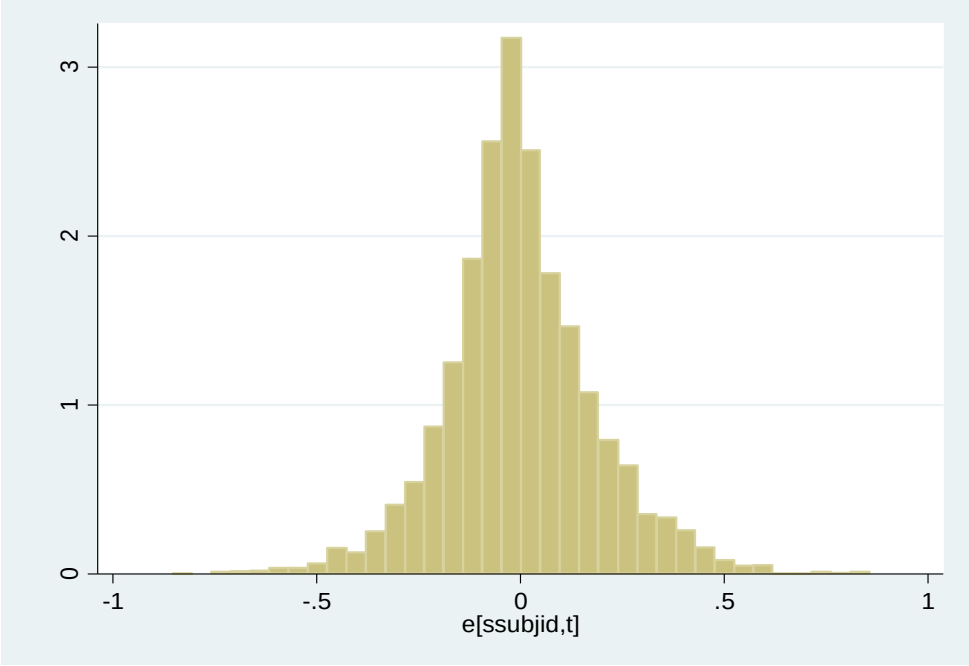


Figure 2. Histogram for level one residuals with logarithmic transformed negative affect scores as the outcome variable

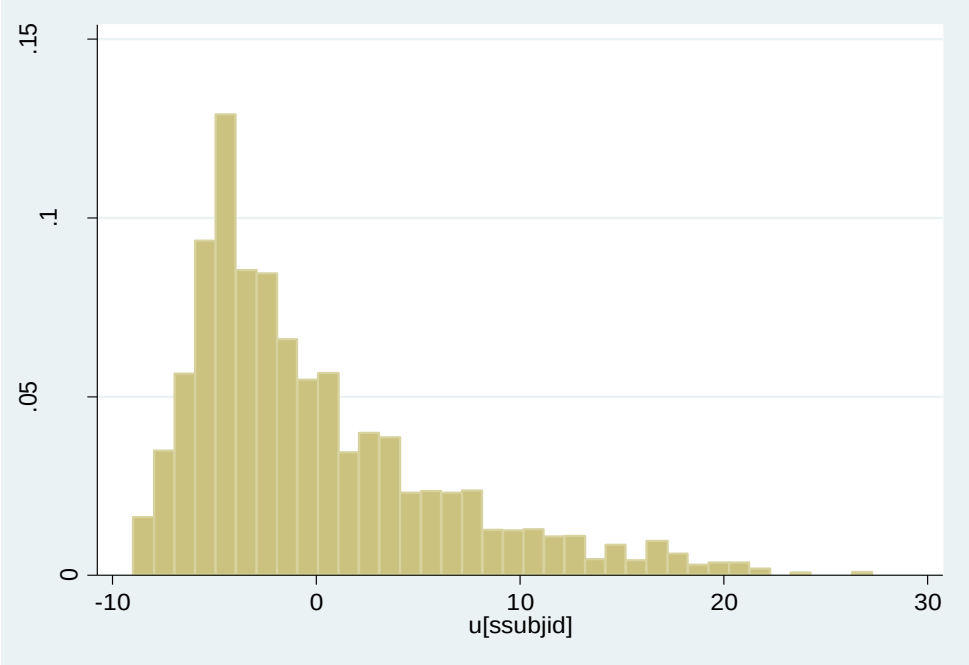


Figure 3. Histogram for level two residuals with negative affect as the outcome variable

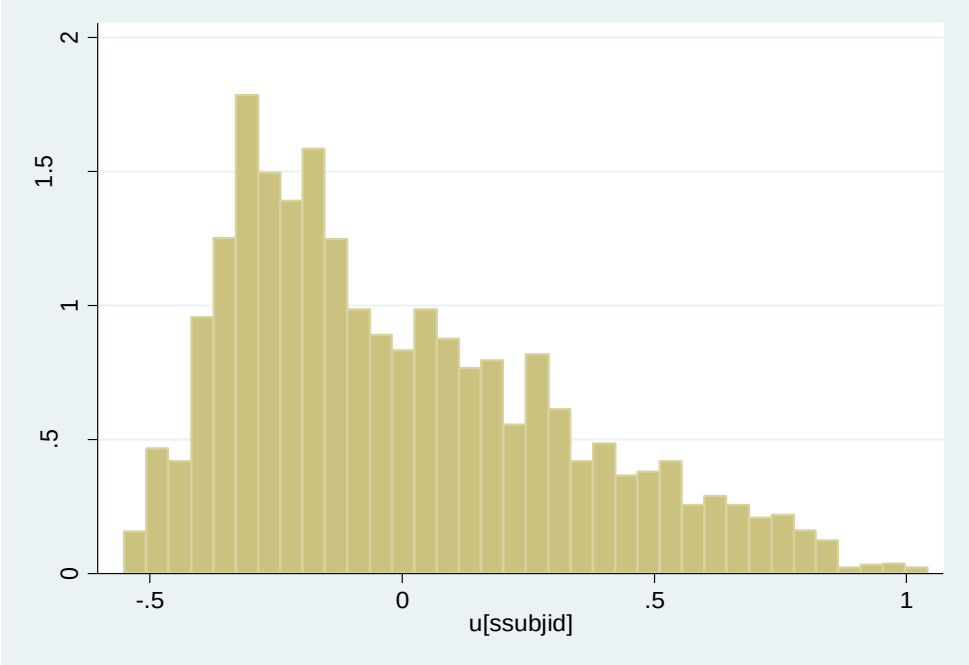


Figure 4. Histogram for level two residuals with logarithmic transformed negative affect scores as the outcome variable

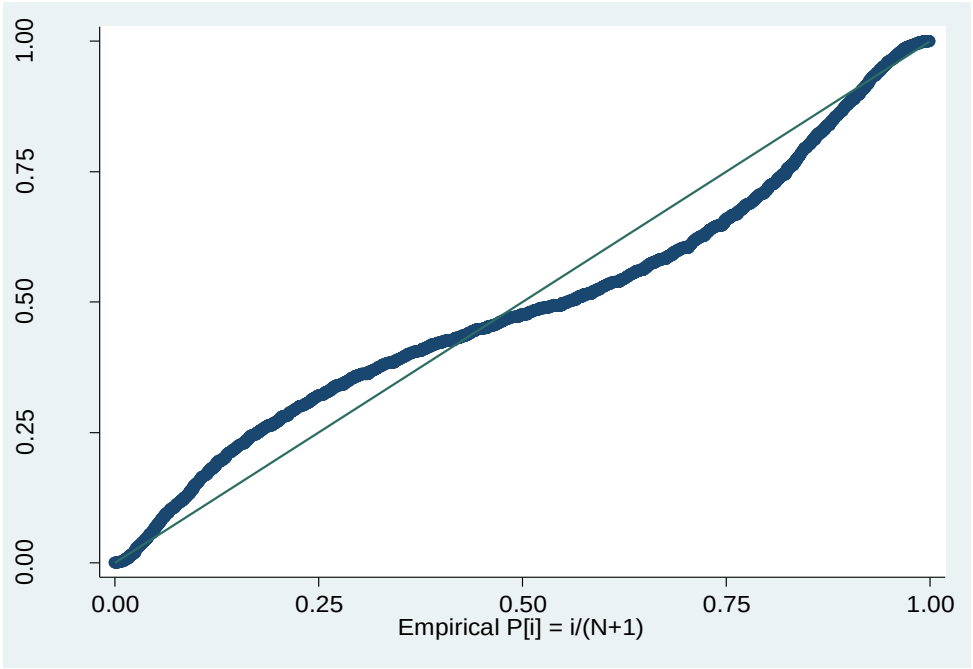


Figure 5. P-P plot for level one residuals with negative affect as the outcome variable

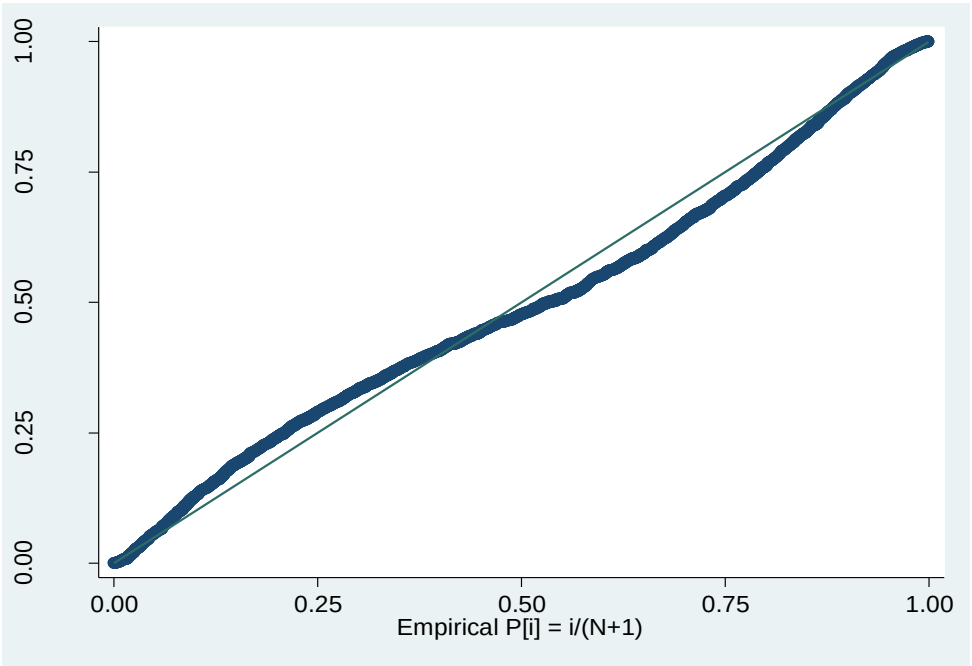


Figure 6. P-P plot for level one residuals with logarithmic transformed negative affect scores as the outcome variable

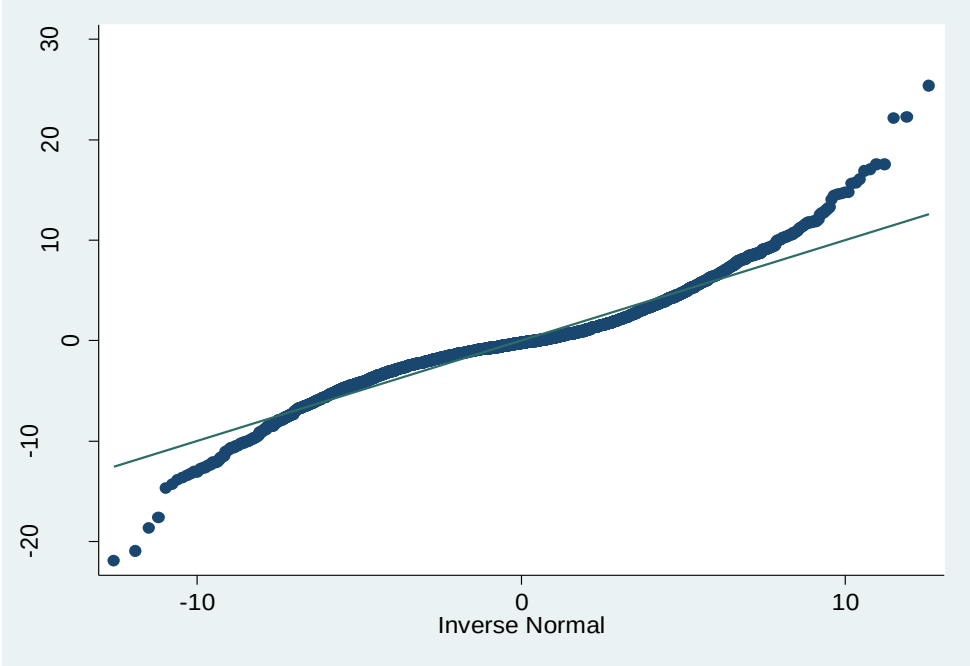


Figure 7. Q-Q plot for level one residuals with negative affect as the outcome variable

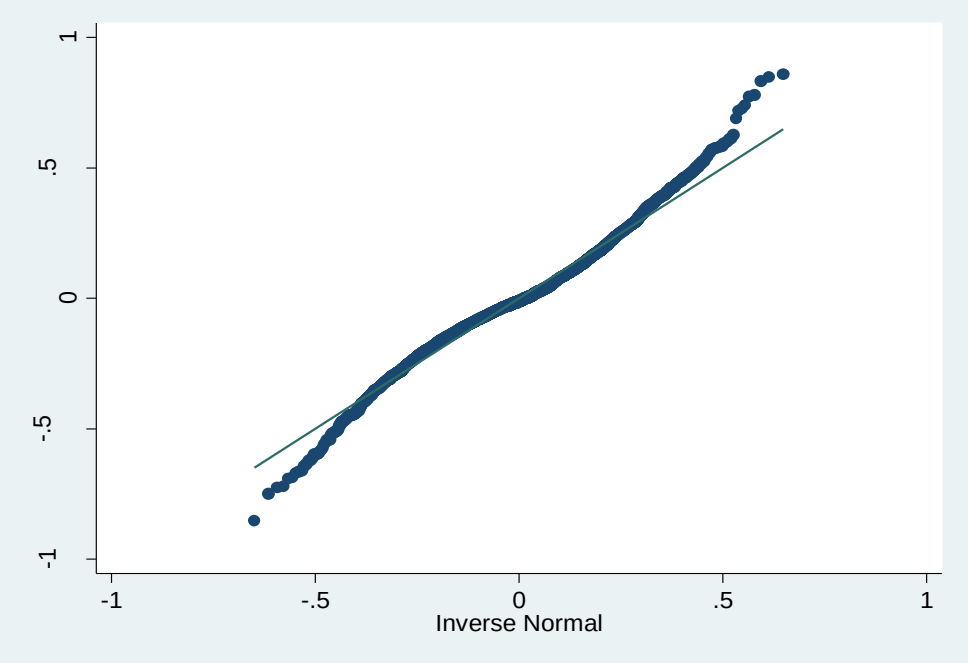


Figure 8. Q-Q plot for level one residuals with logarithmic transformed negative affect scores as the outcome variable

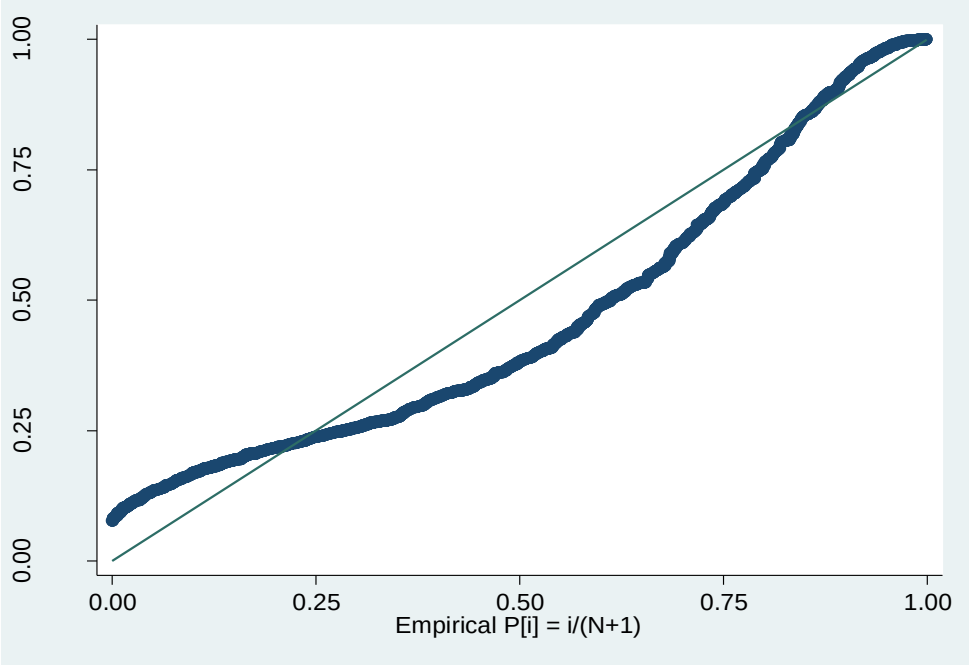


Figure 9. P-P plot for level two residuals with negative affect as the outcome variable

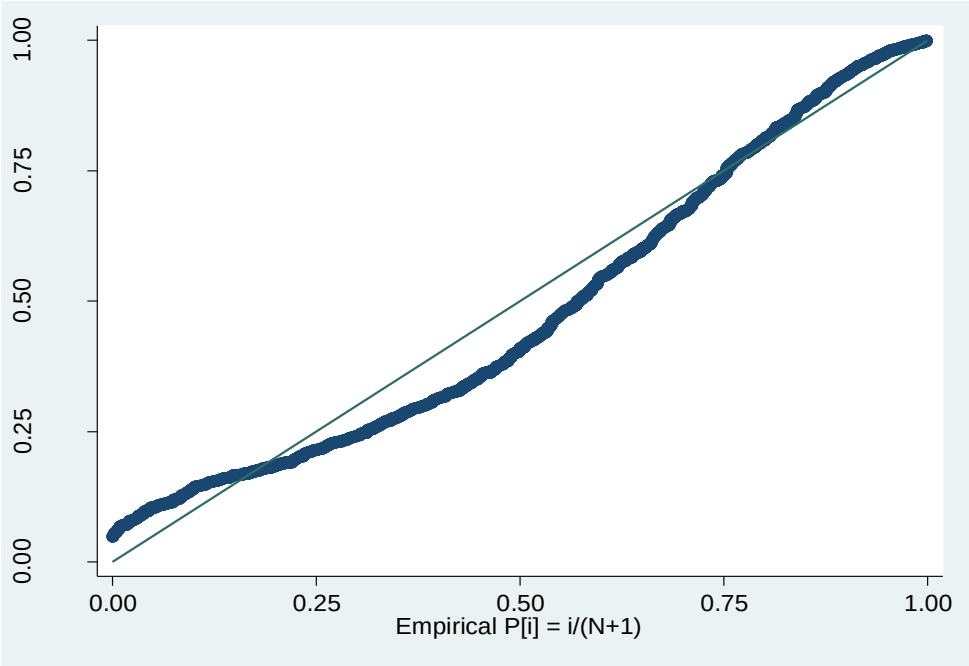


Figure 10. P-P plot for level two residuals with logarithmic transformed negative affect scores as the outcome variable

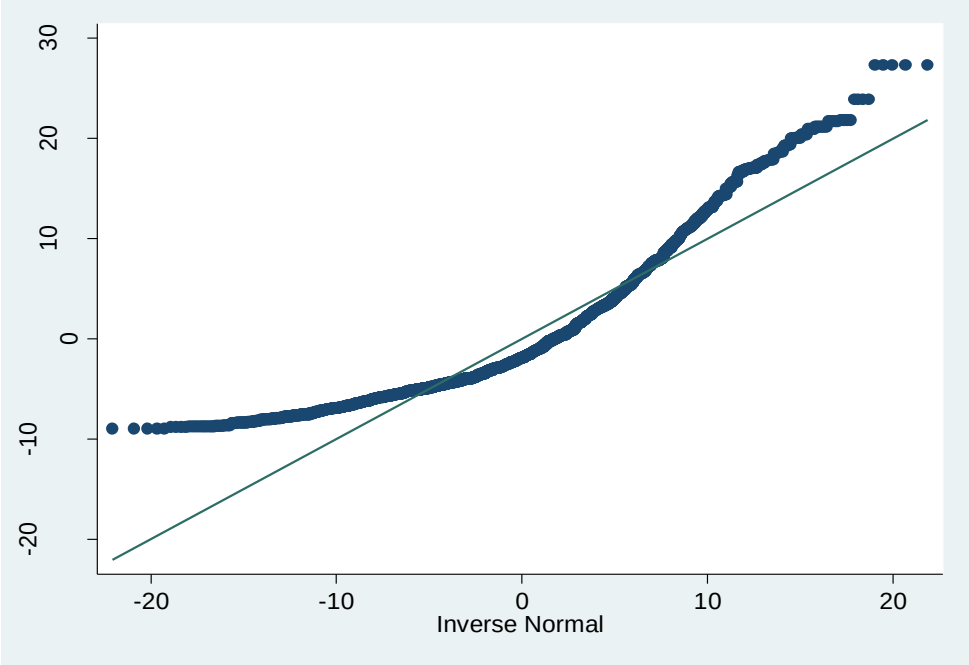


Figure 11. Q-Q plot for level two residuals with negative affect as the outcome variable

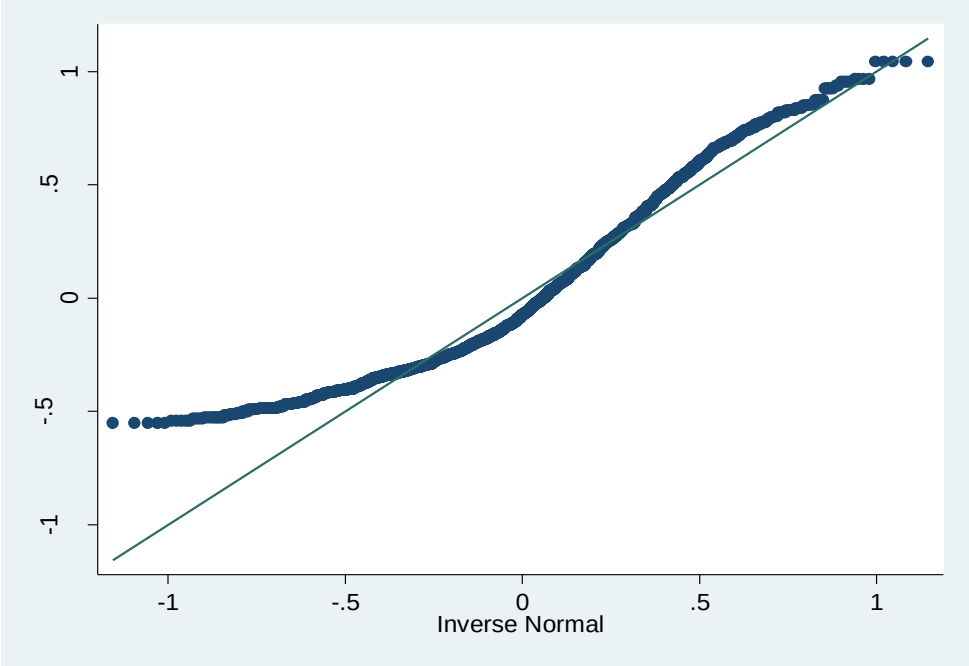


Figure 12. Q-Q plot for level two residuals with logarithmic transformed negative affect scores as the outcome variable

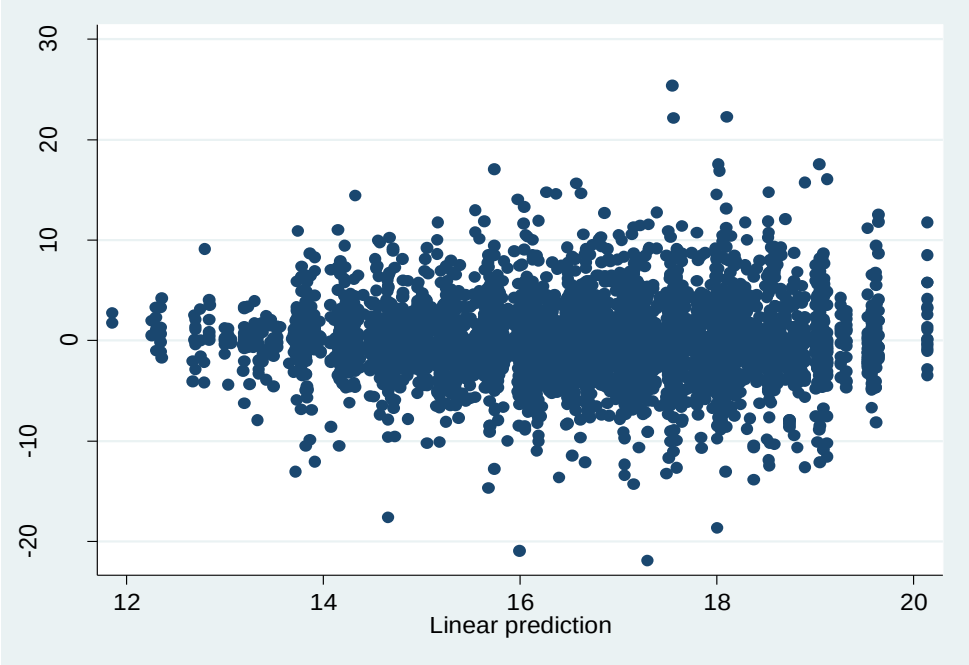


Figure 13. Scatterplot for level one residuals with negative affect as the outcome variable

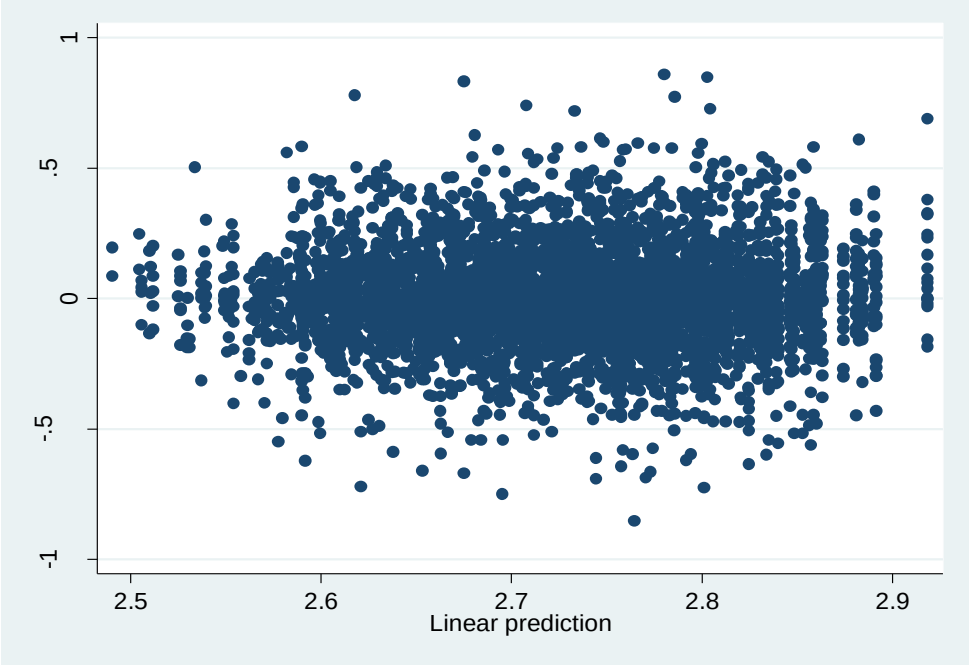


Figure 14. Scatterplot for level one residuals with logarithmic transformed negative affect scores as the outcome variable

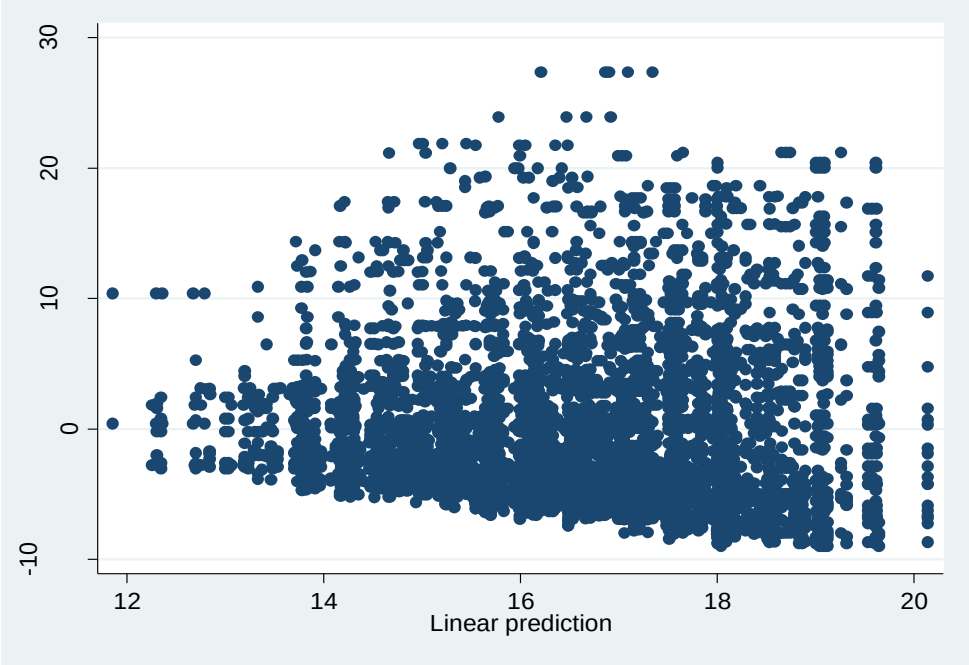


Figure 15. Scatterplot for level two residuals with negative affect as the outcome variable

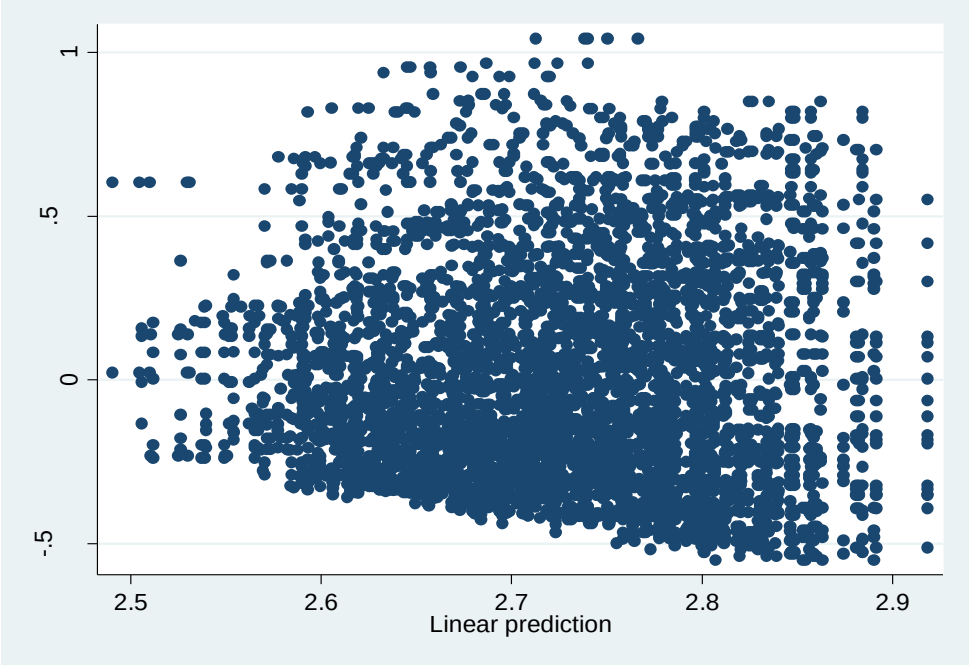


Figure 16. Scatterplot for level two residuals with logarithmic transformed negative affect scores as the outcome variable

1.1.2. Model 2 (Adjusted for ECLS minimisation variables and additional variables)

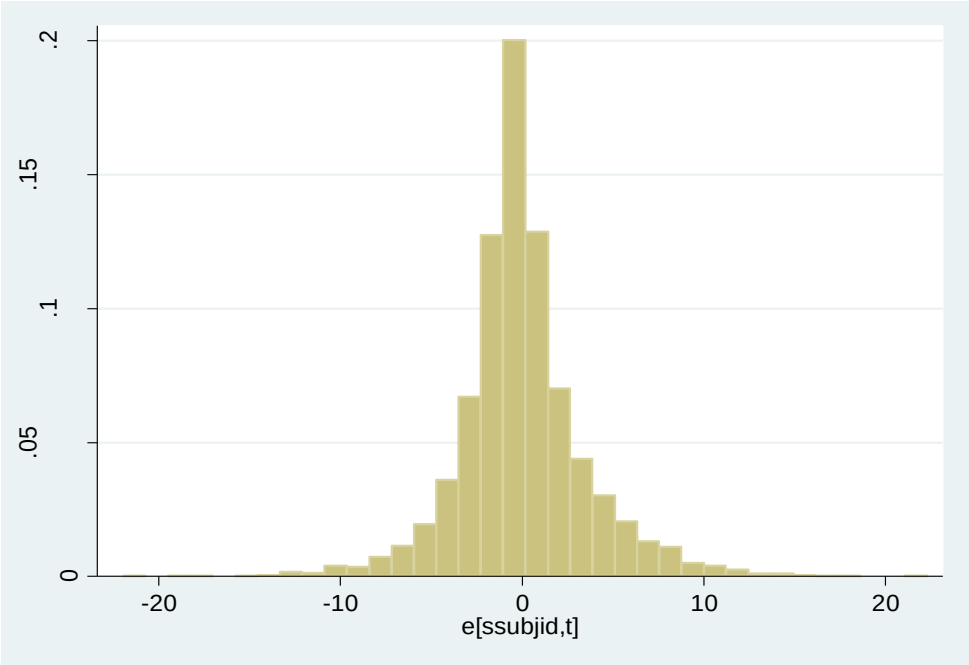


Figure 17. Histogram for level one residuals with negative affect as the outcome variable

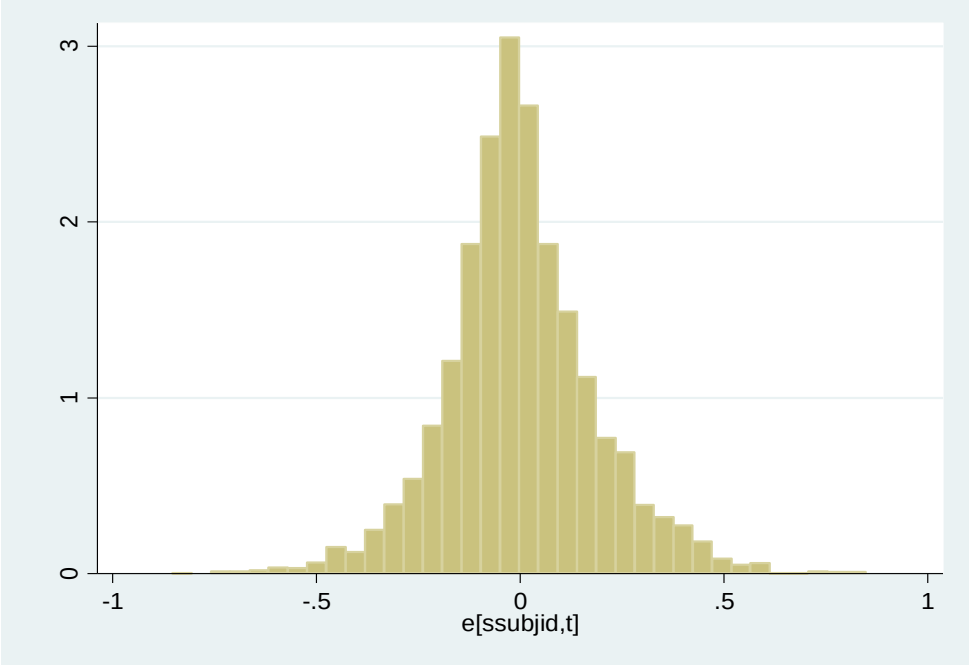


Figure 18. Histogram for level one residuals with logarithmic transformed negative affect scores as the outcome variable

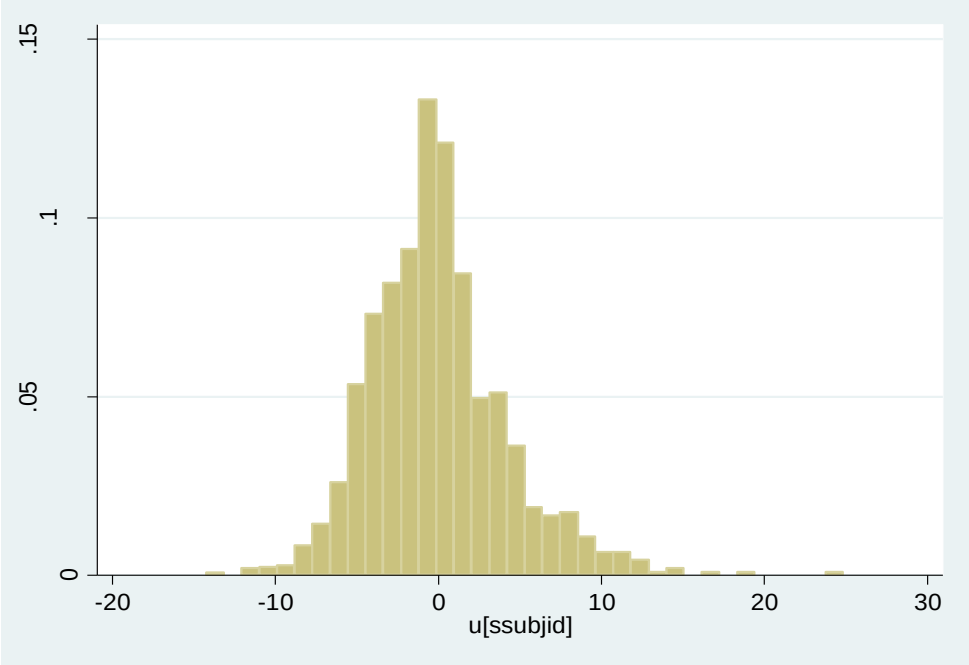


Figure 19. Histogram for level two residuals with negative affect as the outcome variable

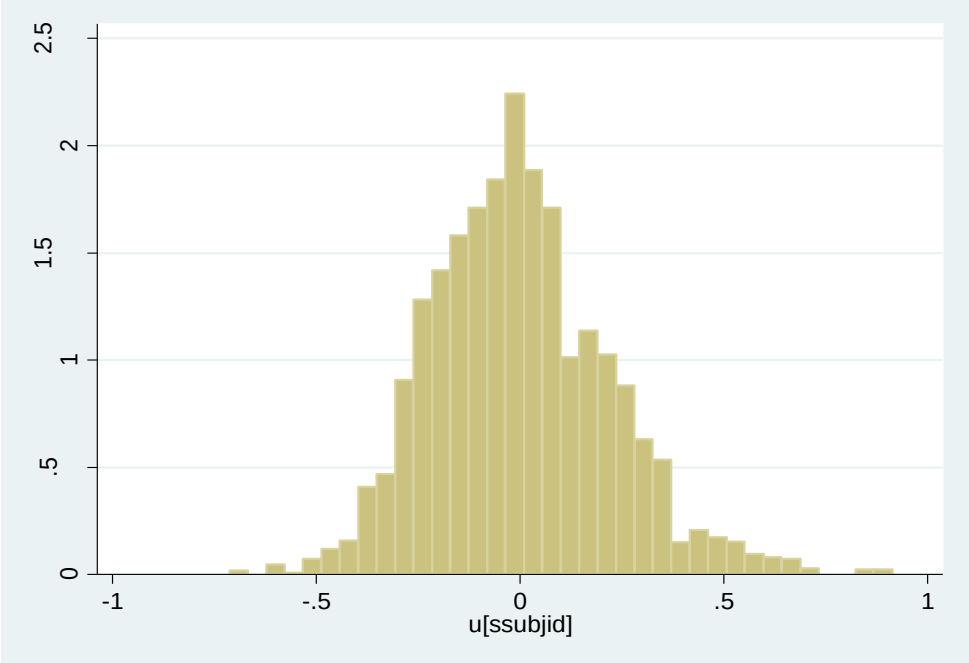


Figure 20. Histogram for level two residuals with logarithmic transformed negative affect scores as the outcome variable

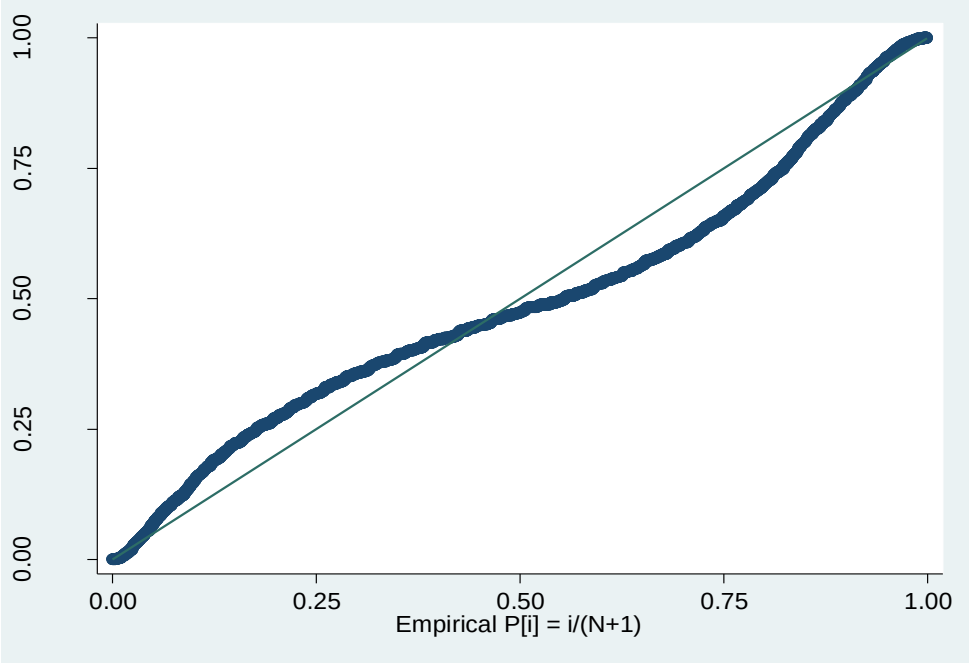


Figure 21. P-P plot for level one residuals with negative affect as the outcome variable

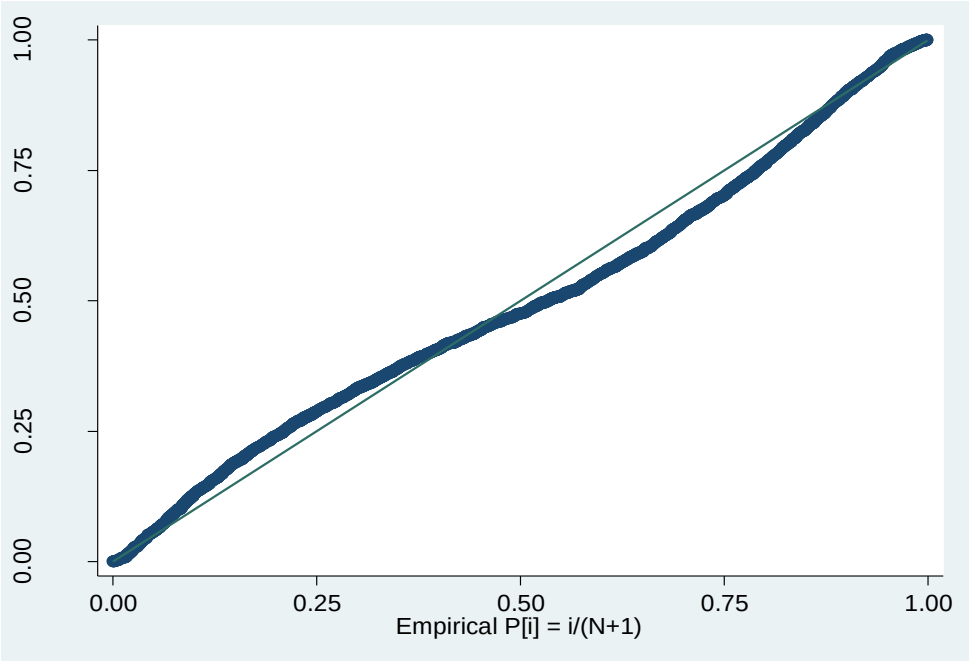


Figure 22. P-P plot for level one residuals with logarithmic transformed negative affect scores as the outcome variable

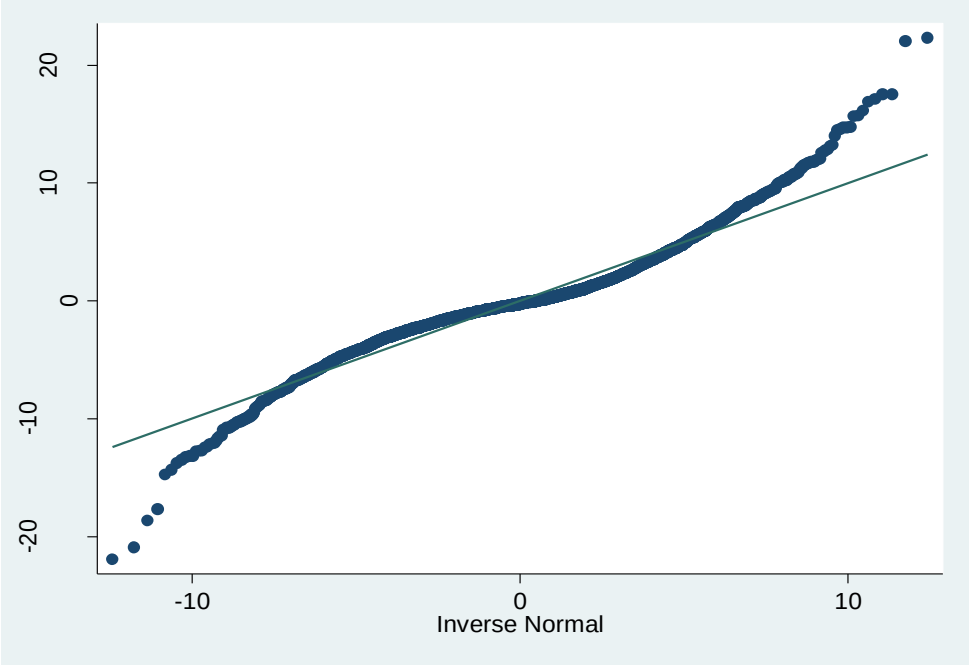


Figure 23. Q-Q plot for level one residuals with negative affect as the outcome variable

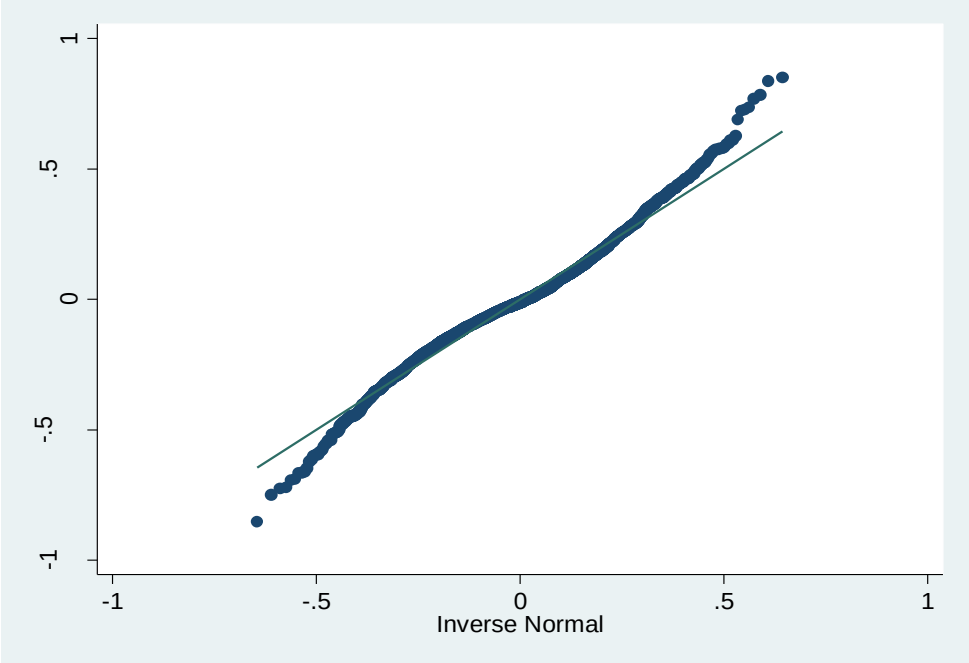


Figure 24. Q-Q plot for level one residuals with logarithmic transformed negative affect scores as the outcome variable

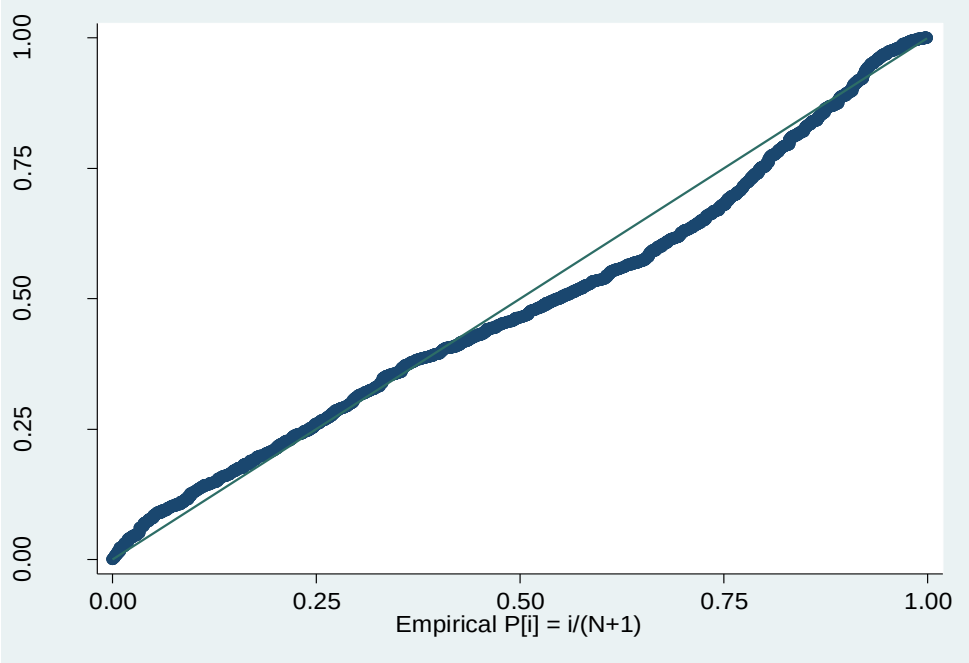


Figure 25. P-P plot for level two residuals with negative affect as the outcome variable

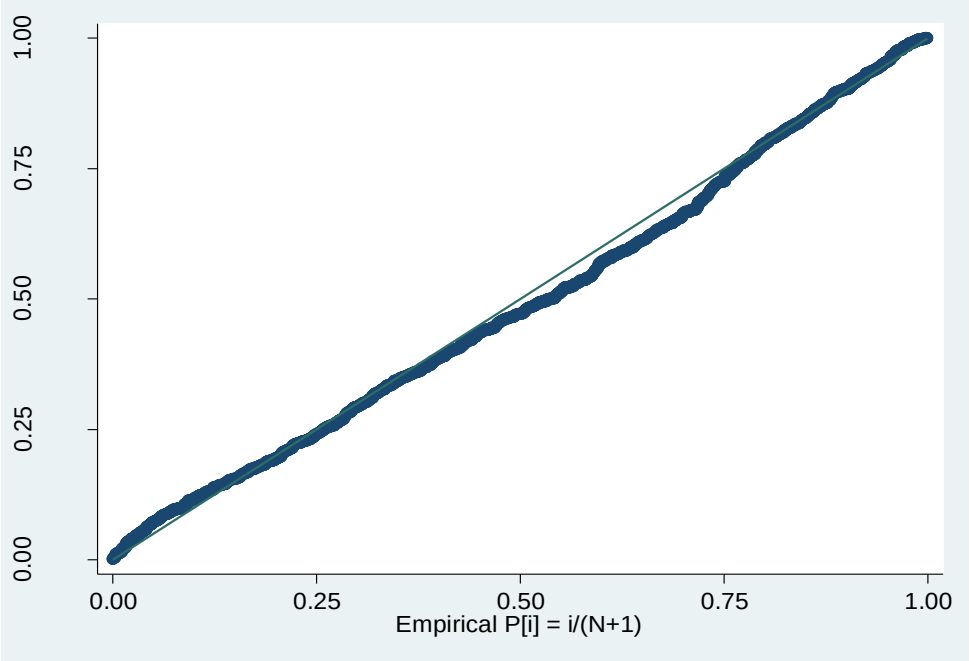


Figure 26. P-P plot for level two residuals with logarithmic transformed negative affect scores as the outcome variable

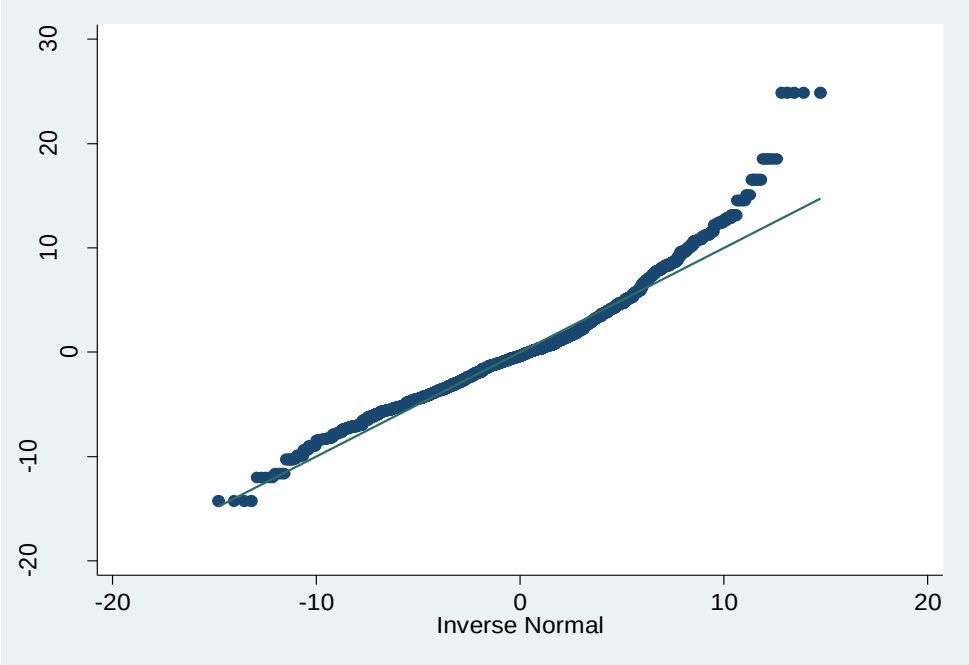


Figure 27. Q-Q plot for level two residuals with negative affect as the outcome variable

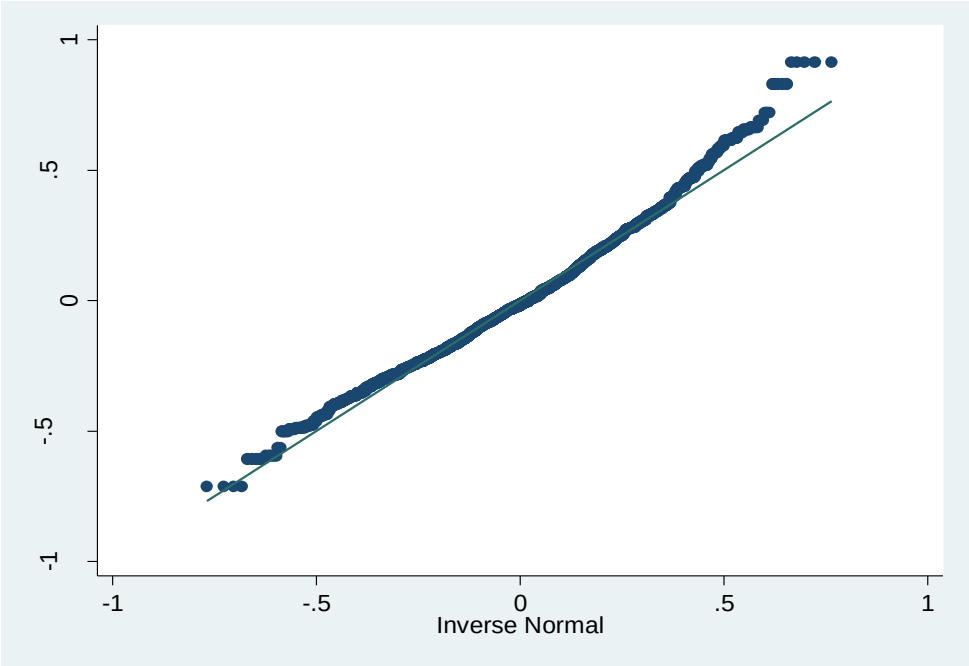


Figure 28. Q-Q plot for level two residuals with logarithmic transformed negative affect scores as the outcome variable

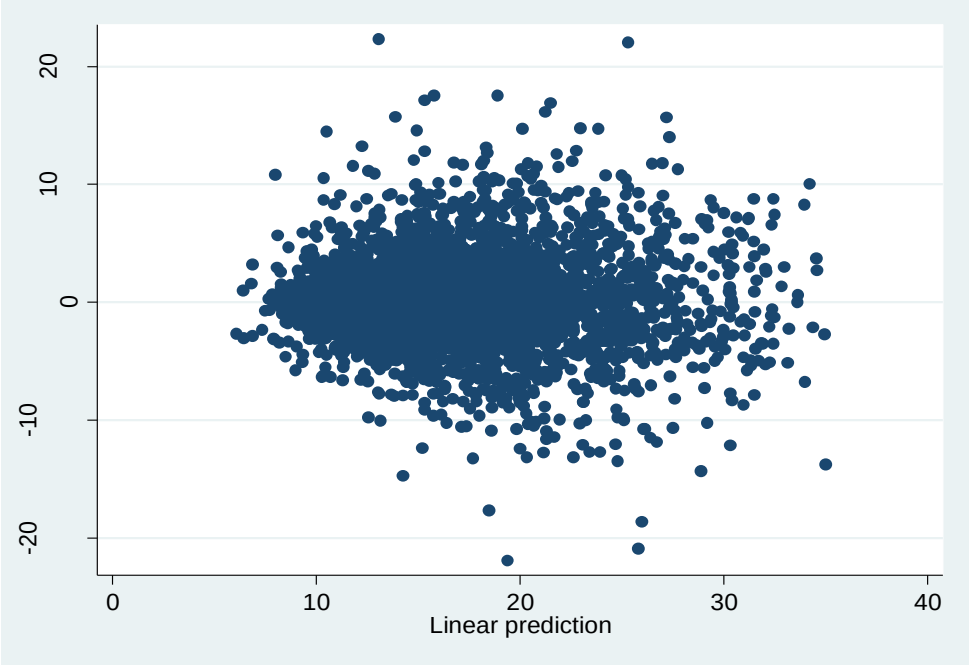


Figure 29. Scatterplot for level one residuals with negative affect as the outcome variable

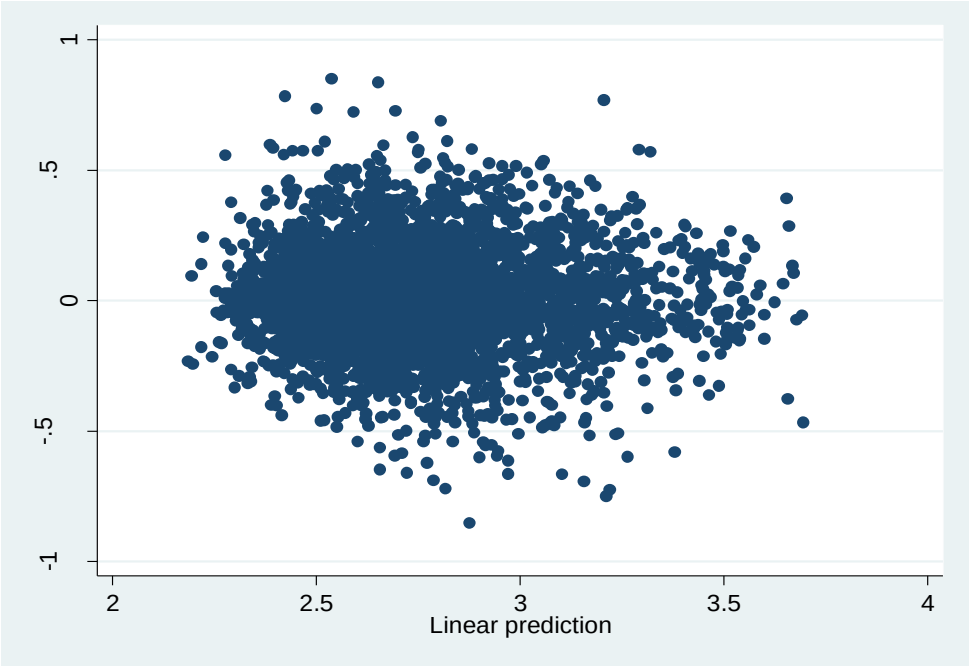


Figure 30. Scatterplot for level one residuals with logarithmic transformed negative affect scores as the outcome variable

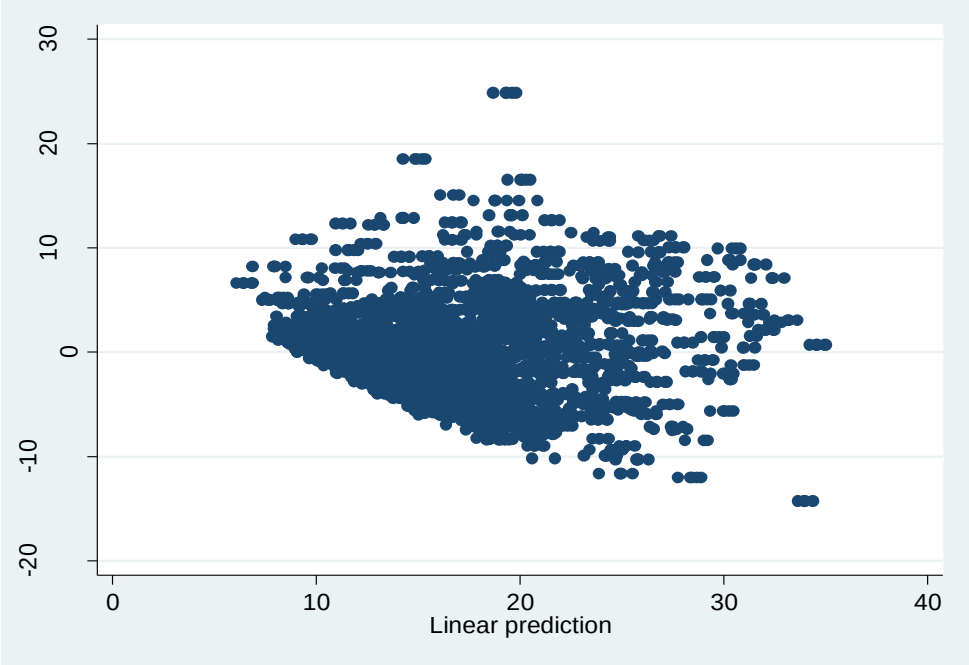


Figure 31. Scatterplot for level two residuals with negative affect as the outcome variable

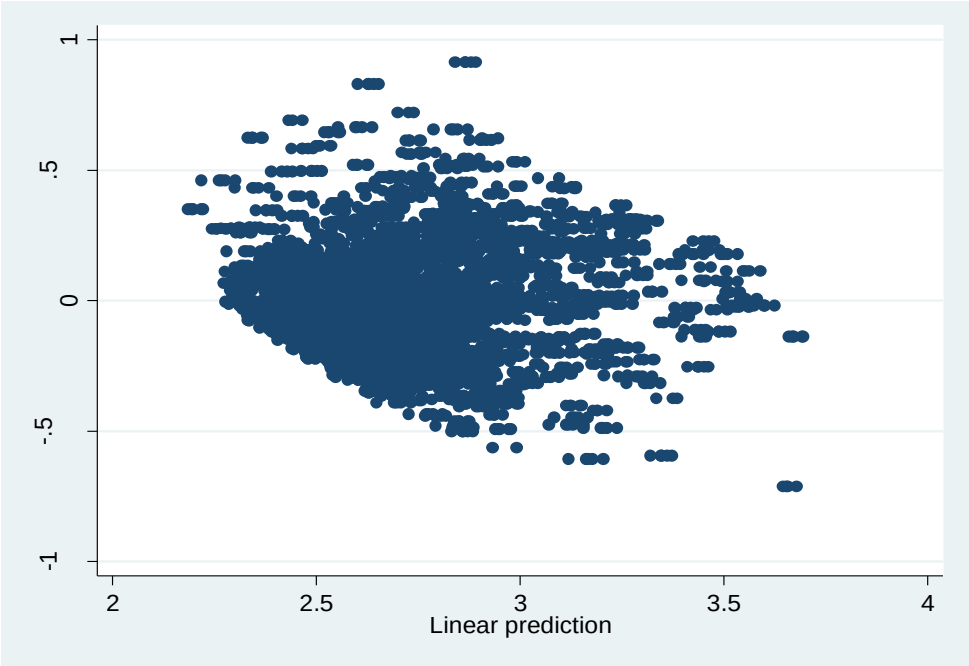


Figure 32. Scatterplot for level two residuals with logarithmic transformed negative affect scores as the outcome variable

1.2. Adjusted analyses comparing negative affect scores between screening groups over time

1.2.1. **Model 1** (Adjusted for ECLS minimisation variables)

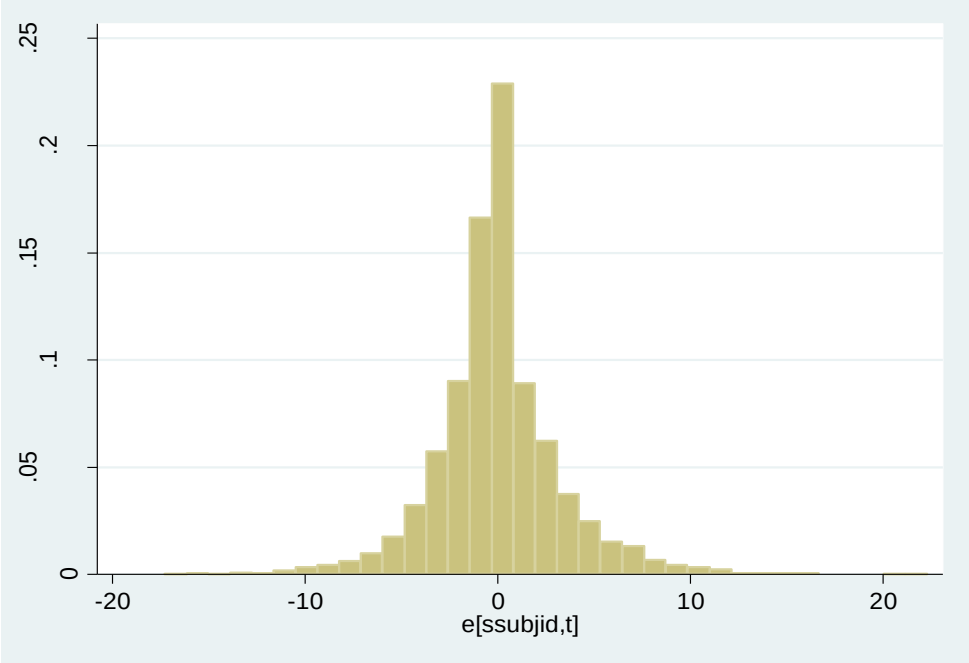


Figure 33. Histogram for level one residuals with negative affect as the outcome variable

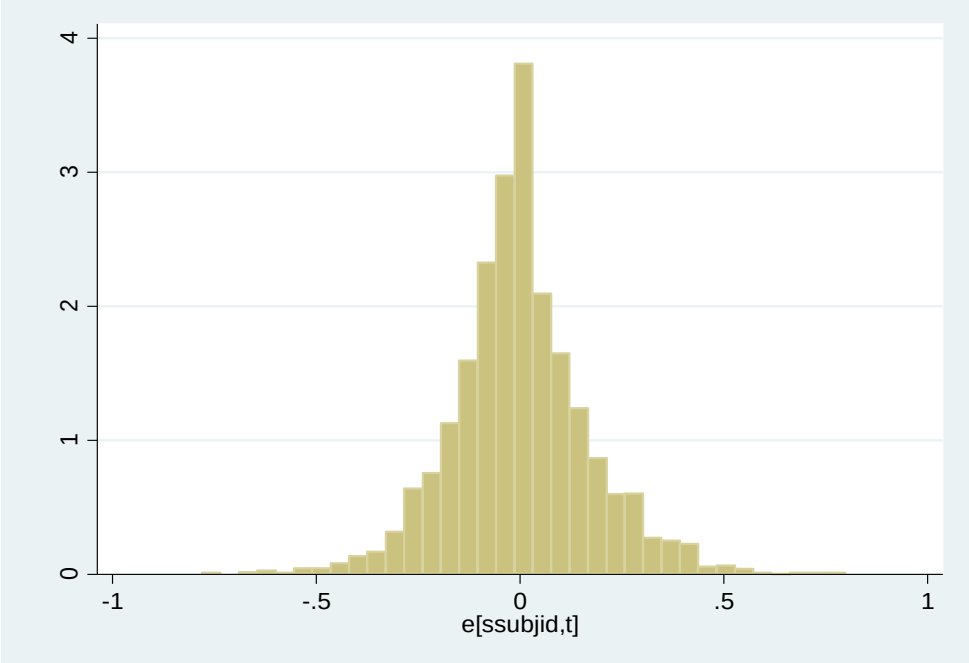


Figure 34. Histogram for level one residuals with logarithmic transformed negative affect scores as the outcome variable

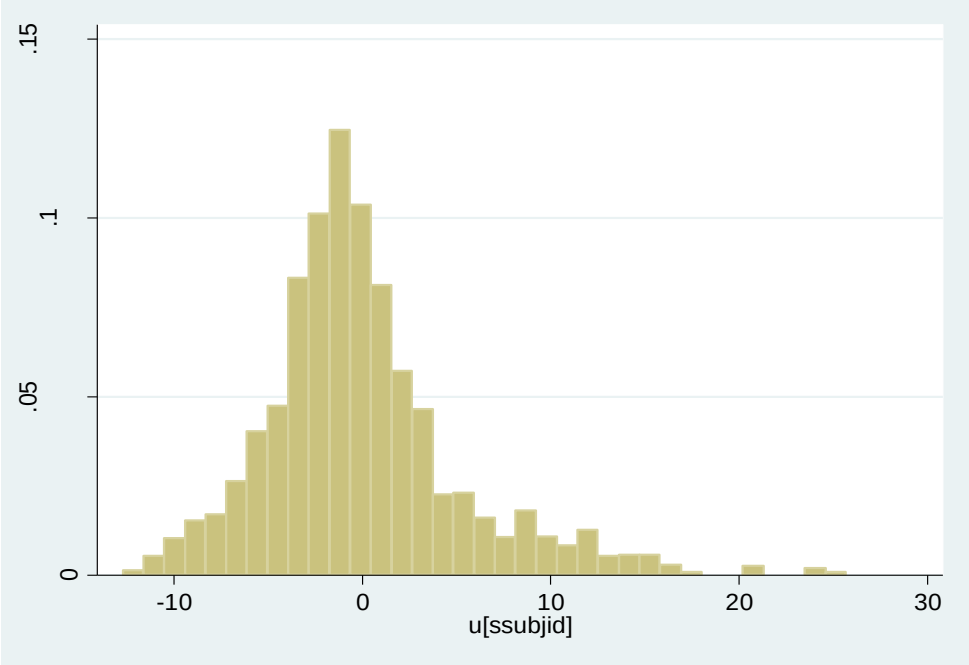


Figure 35. Histogram for level two residuals with negative affect as the outcome variable

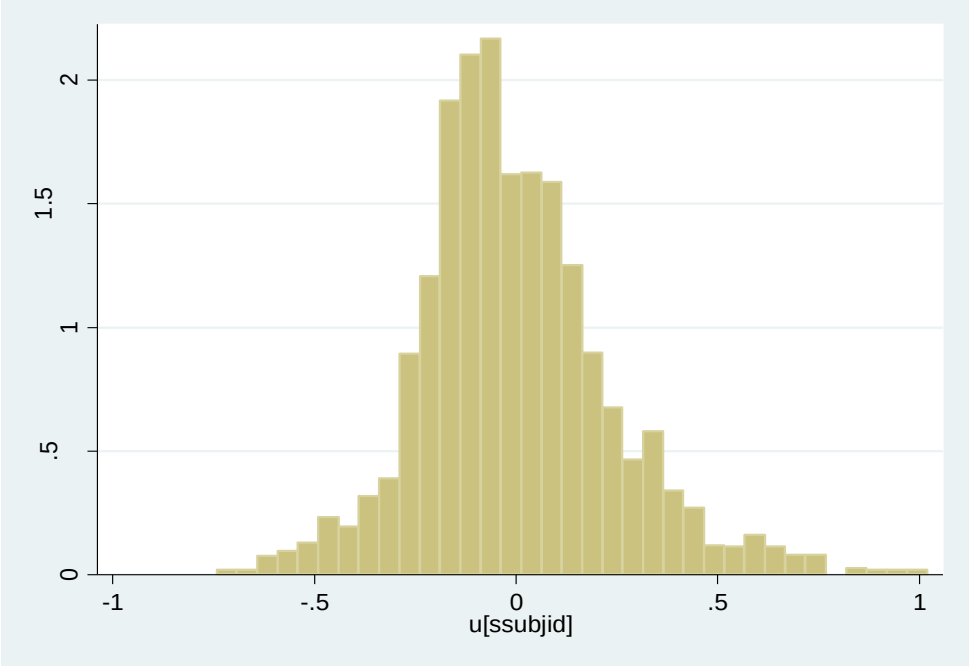


Figure 36. Histogram for level two residuals with logarithmic transformed negative affect scores as the outcome variable

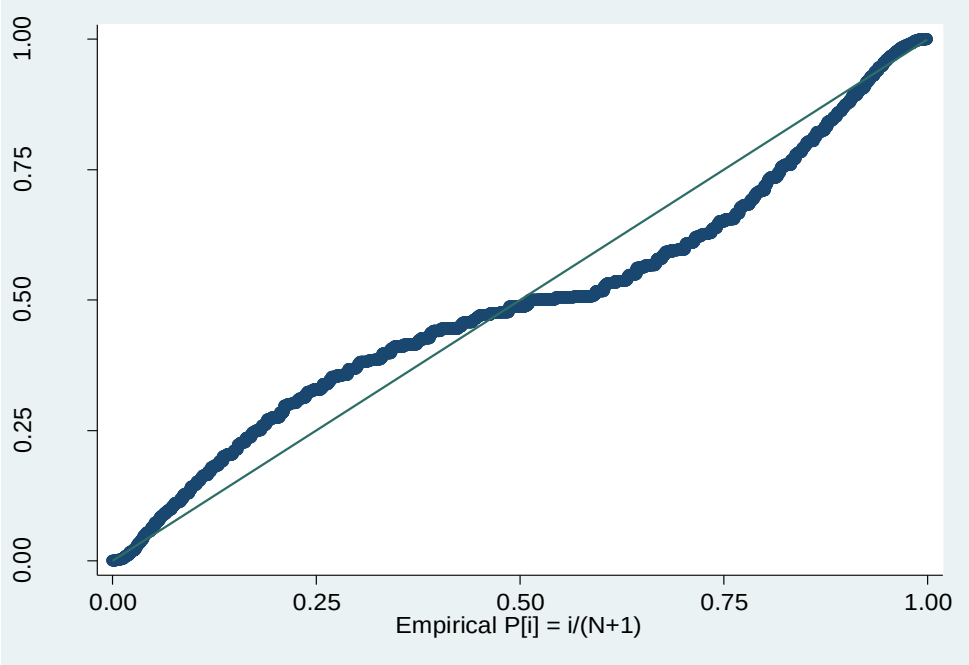


Figure 37. P-P plot for level one residuals with negative affect as the outcome variable

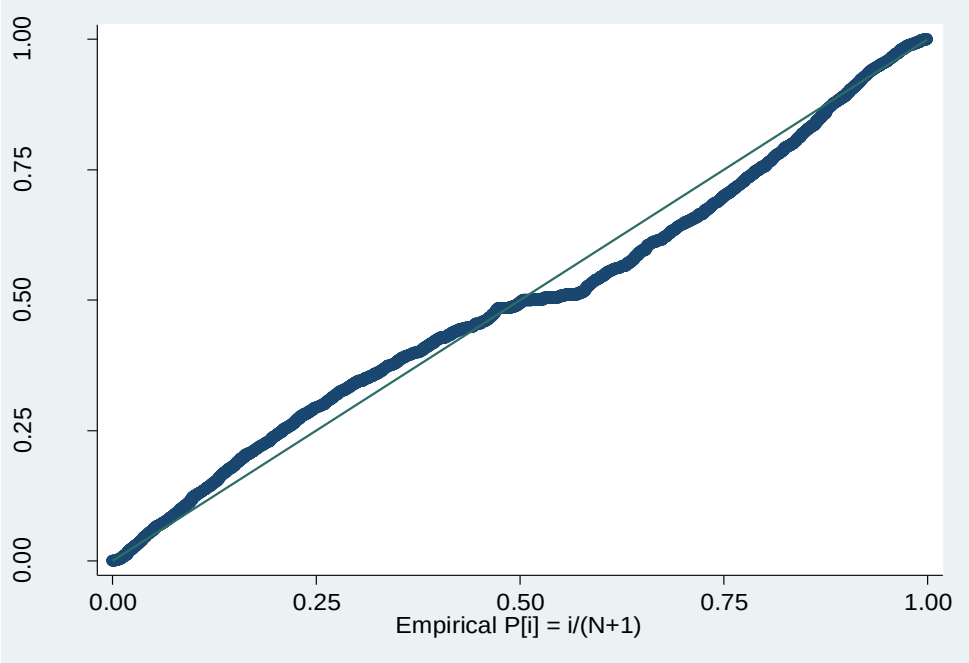


Figure 38. P-P plot for level one residuals with logarithmic transformed negative affect scores as the outcome variable

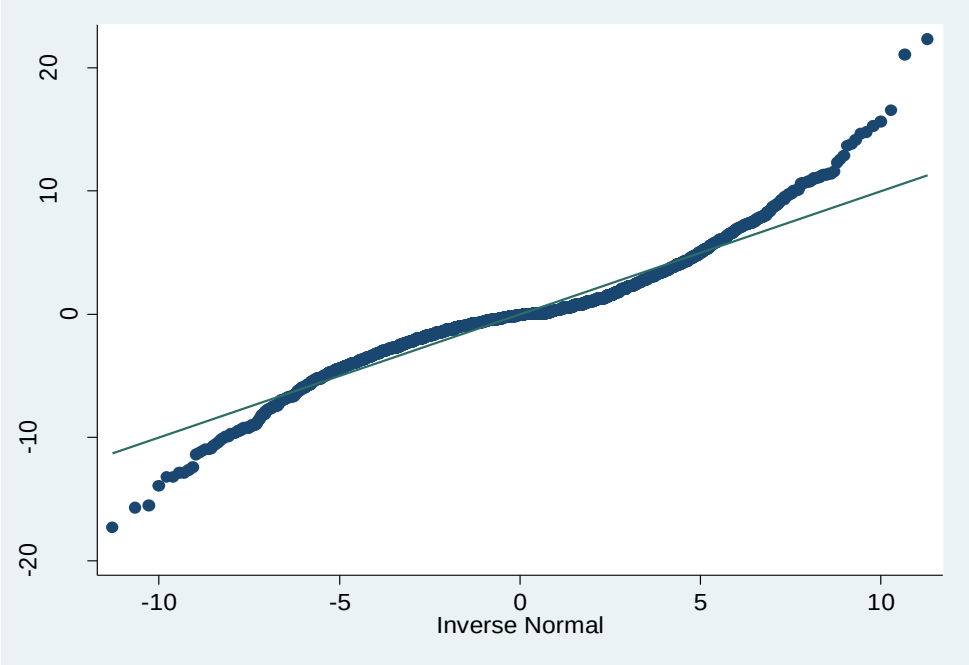


Figure 39. Q-Q plot for level one residuals with negative affect as the outcome variable

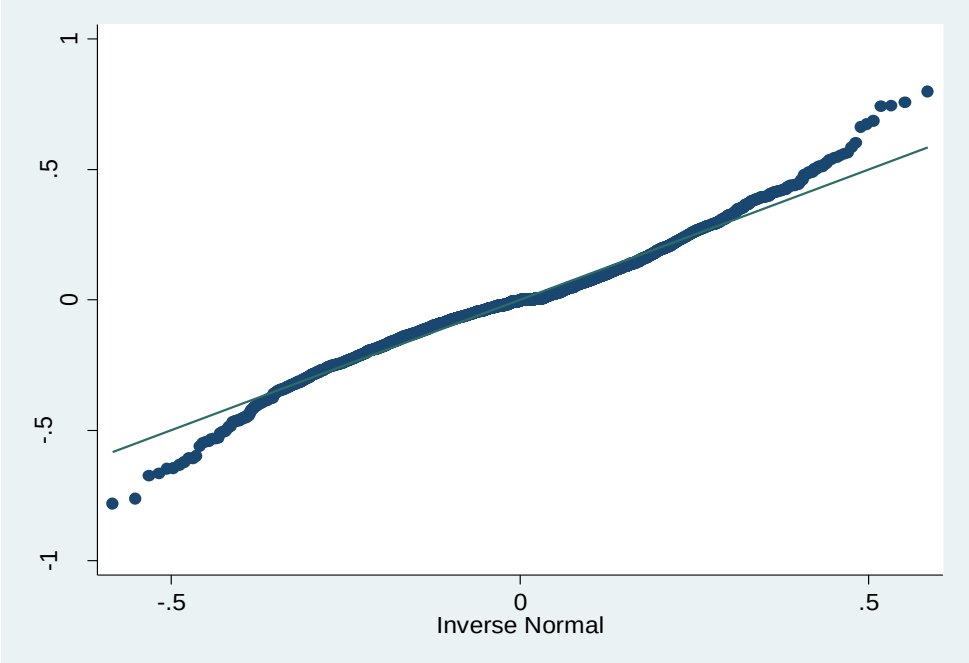


Figure 40. Q-Q plot for level one residuals with logarithmic transformed negative affect scores as the outcome variable

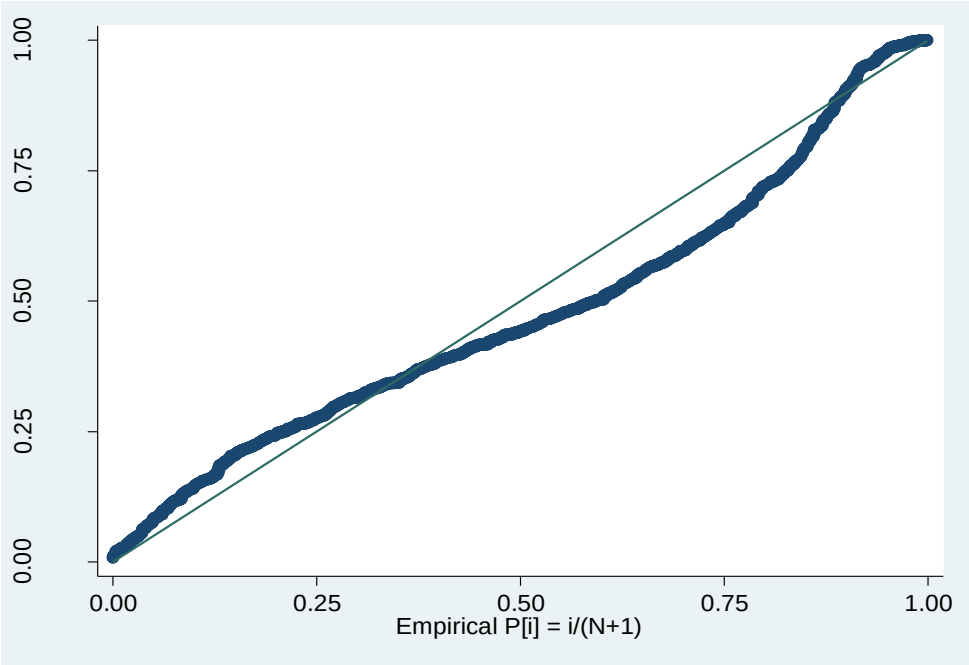


Figure 41. P-P plot for level two residuals with negative affect as the outcome variable

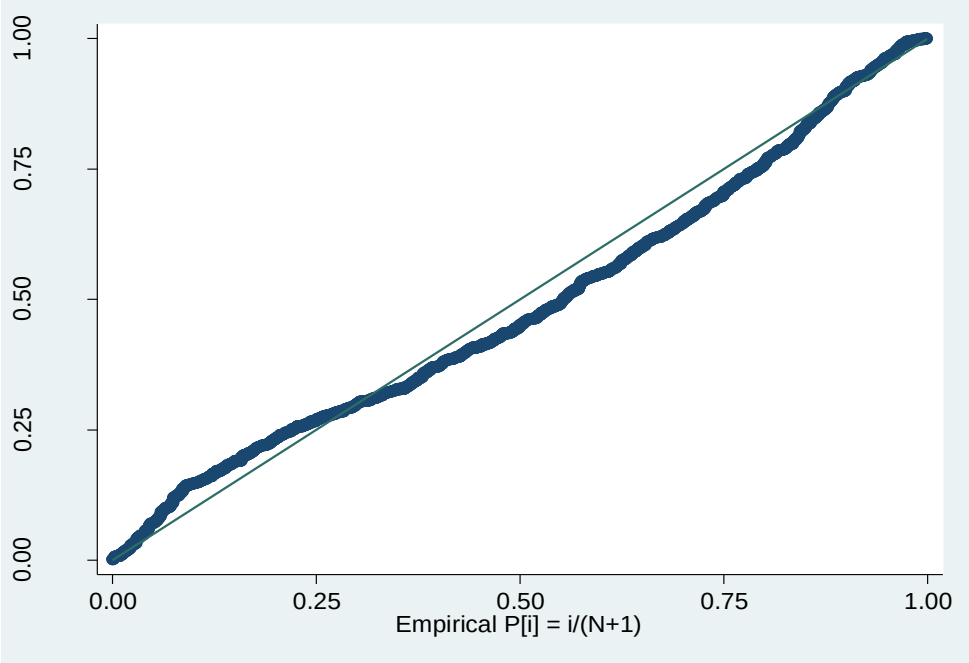


Figure 42. P-P plot for level two residuals with logarithmic transformed negative affect scores as the outcome variable

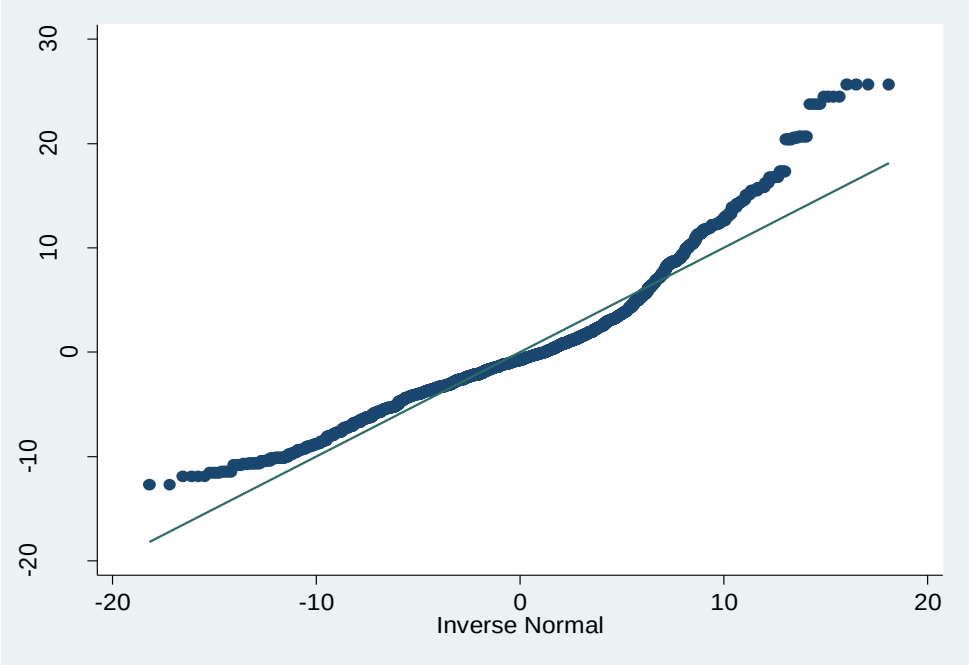


Figure 43. Q-Q plot for level two residuals with negative affect as the outcome variable

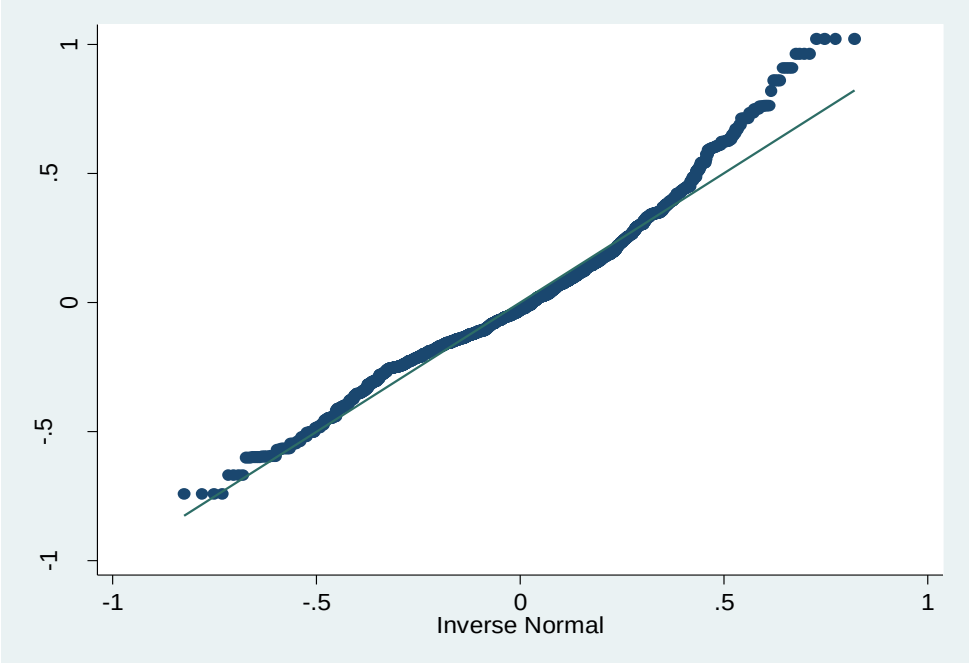


Figure 44. Q-Q plot for level two residuals with logarithmic transformed negative affect scores as the outcome variable

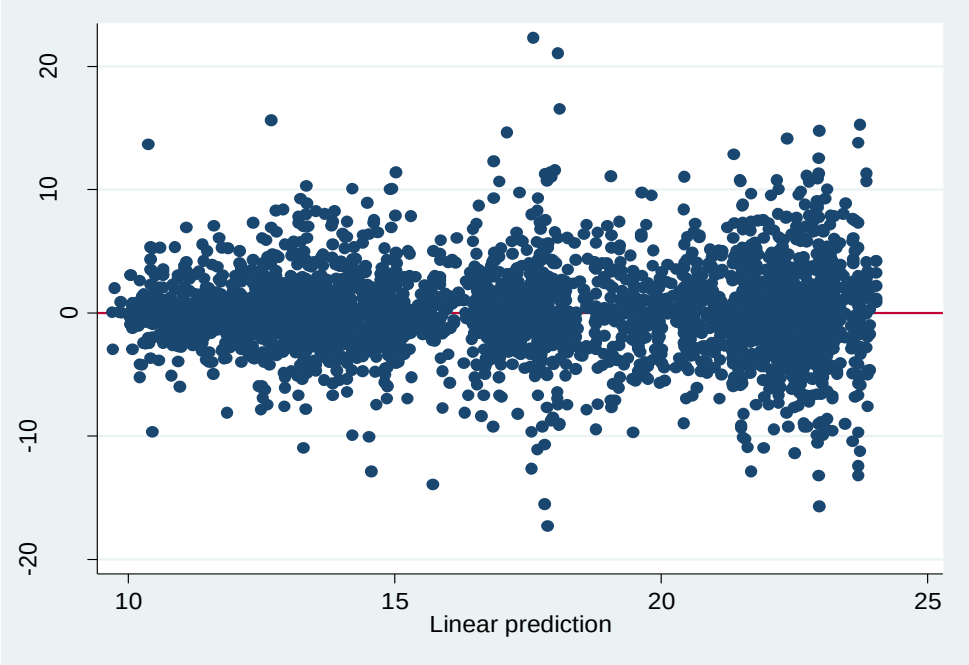


Figure 45. Scatterplot for level one residuals with negative affect as the outcome variable

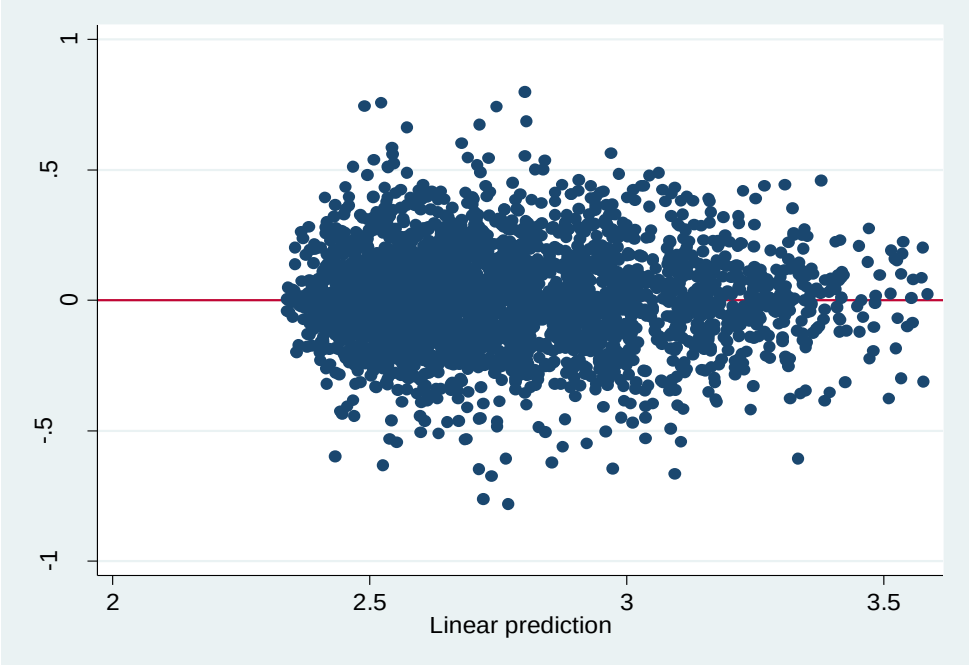


Figure 46. Scatterplot for level one residuals with logarithmic transformed negative affect scores as the outcome variable

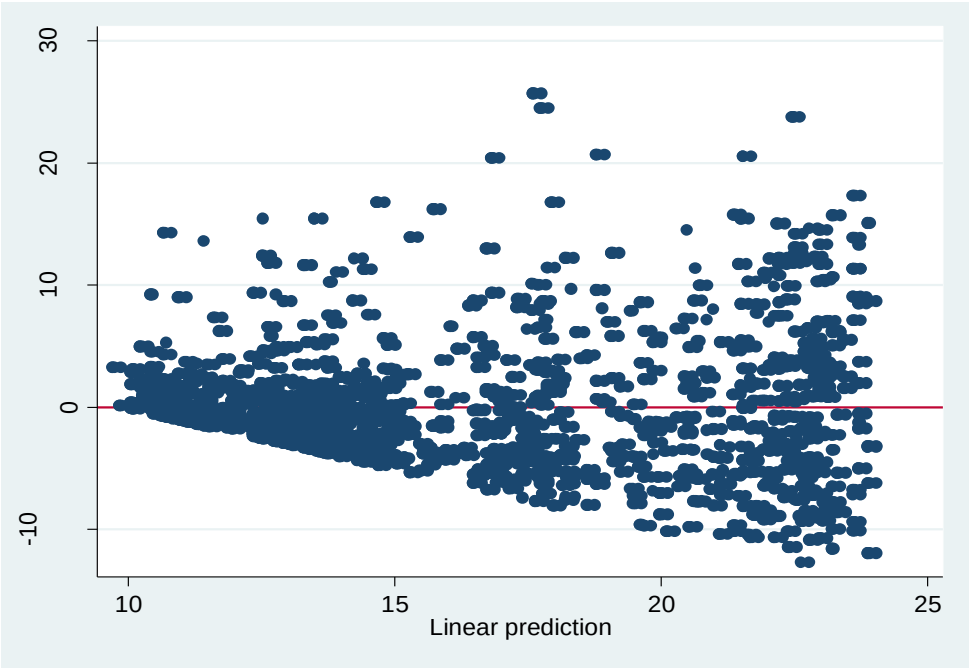


Figure 47. Scatterplot for level two residuals with negative affect as the outcome variable

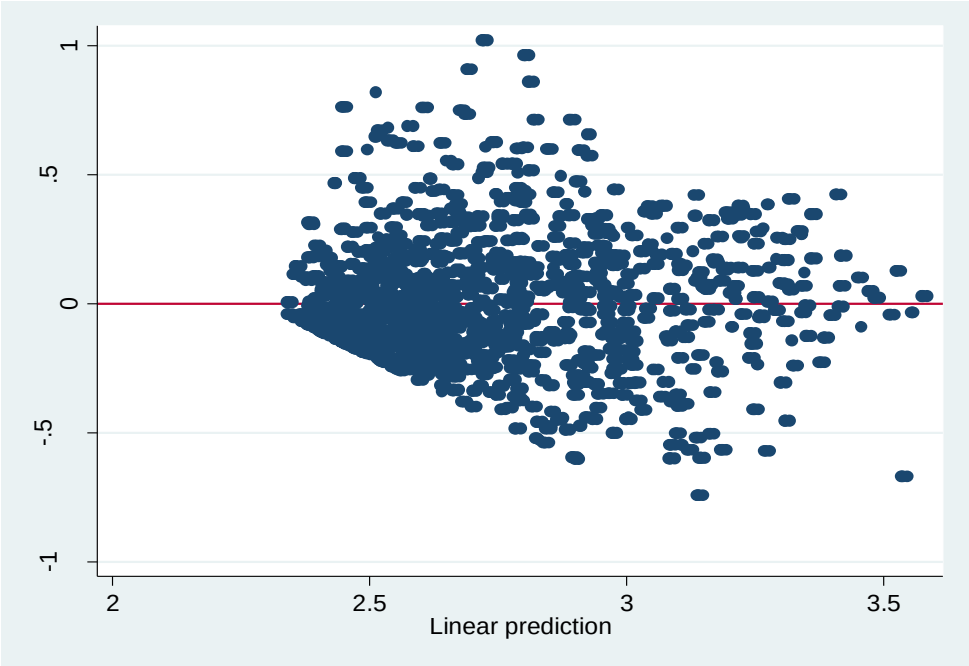


Figure 48. Scatterplot for level two residuals with logarithmic transformed negative affect scores as the outcome variable

1.2.2. Model 2 (Adjusted for ECLS minimisation variables and additional variables)

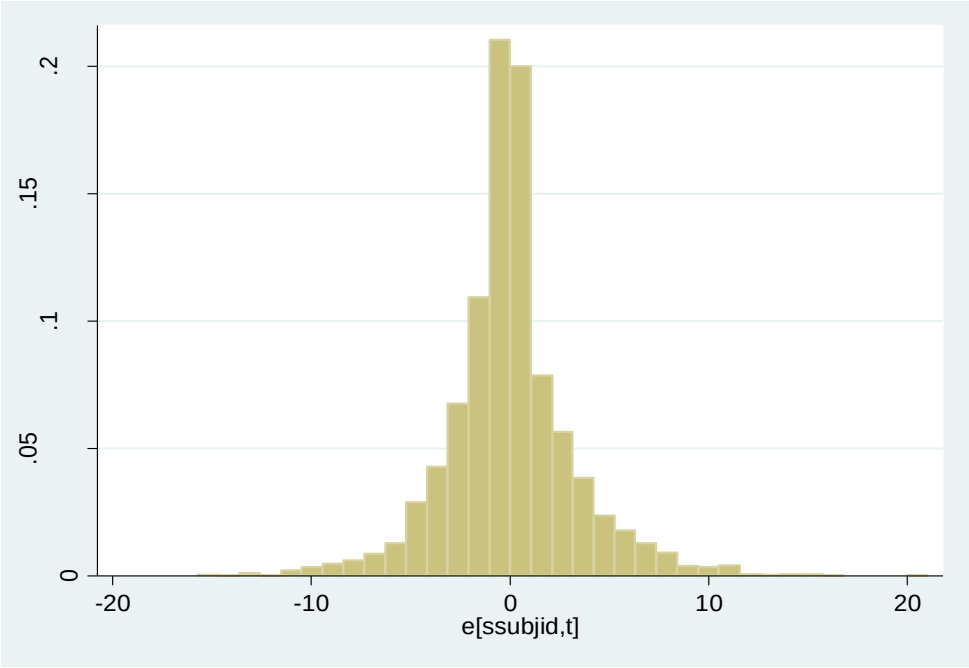


Figure 49. Histogram for level one residuals with negative affect as the outcome variable

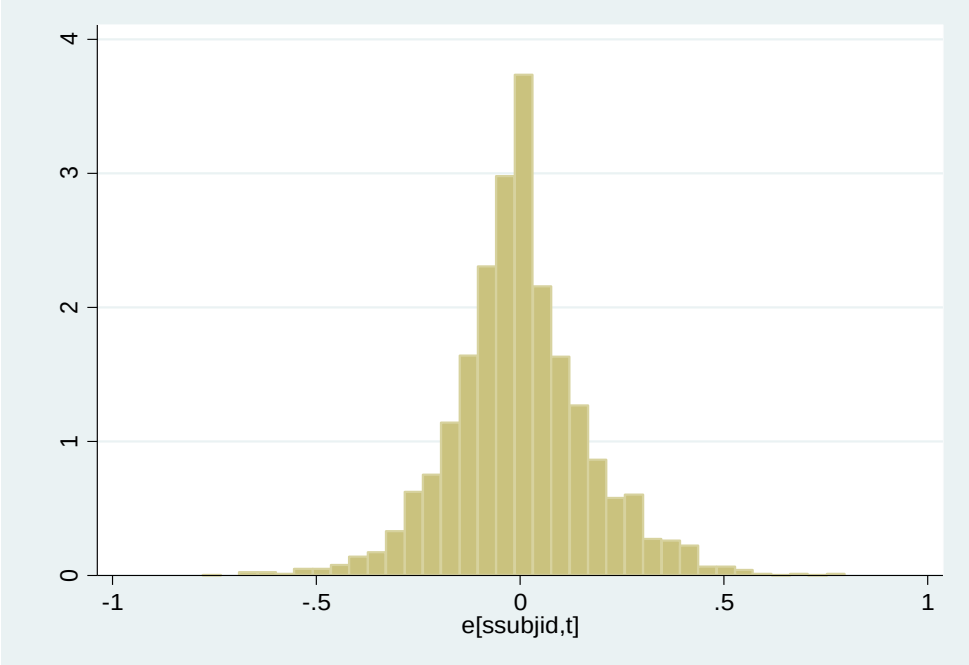


Figure 50. Histogram for level one residuals with logarithmic transformed negative affect scores as the outcome variable

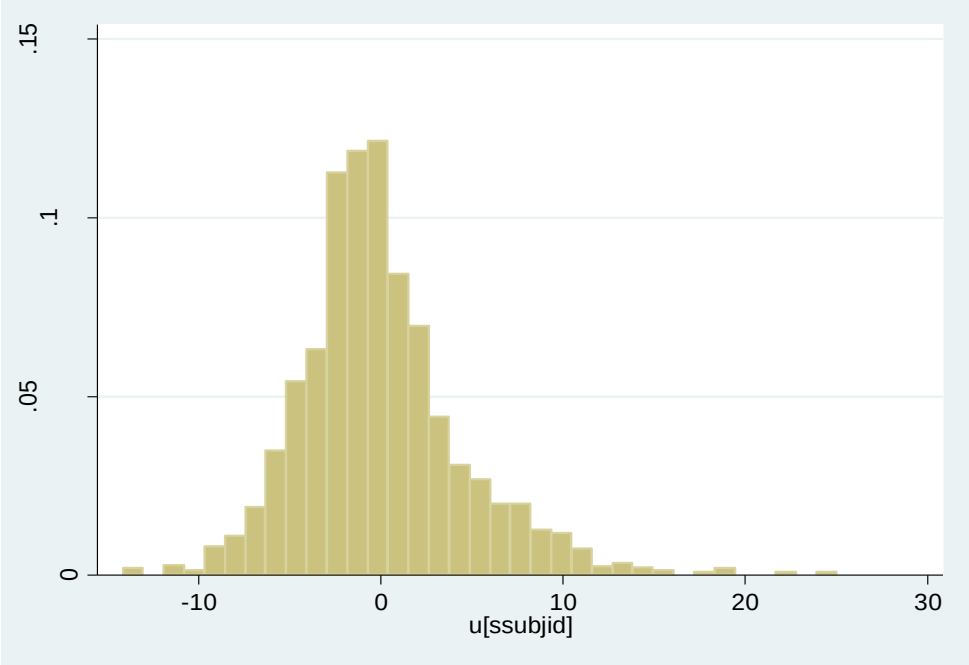


Figure 51. Histogram for level two residuals with negative affect as the outcome variable

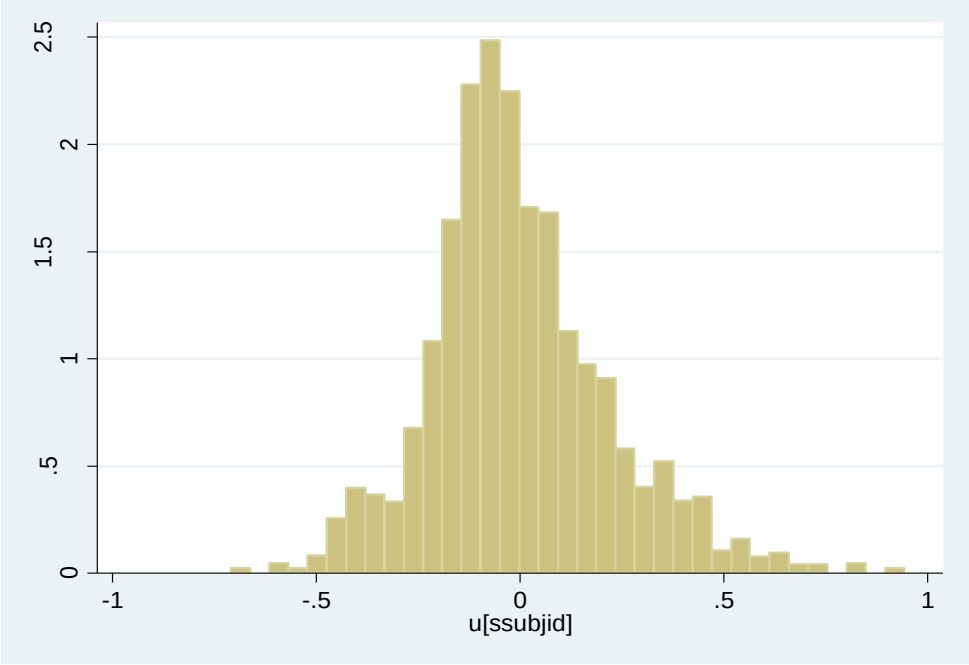


Figure 52. Histogram for level two residuals with logarithmic transformed negative affect scores as the outcome variable

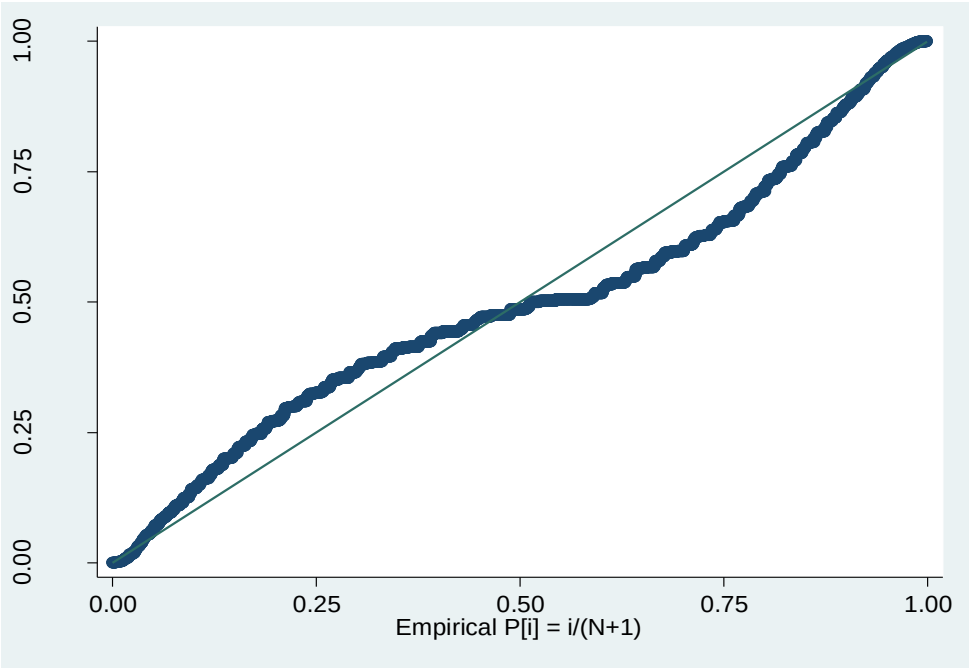


Figure 53. P-P plot for level one residuals with negative affect as the outcome variable

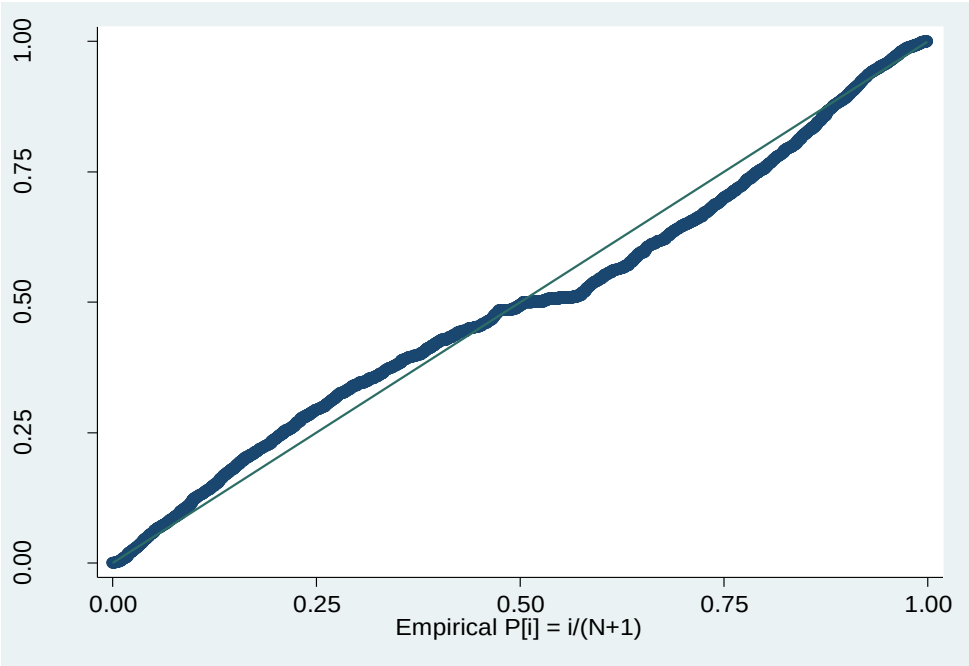


Figure 54. P-P plot for level one residuals with logarithmic transformed negative affect scores as the outcome variable

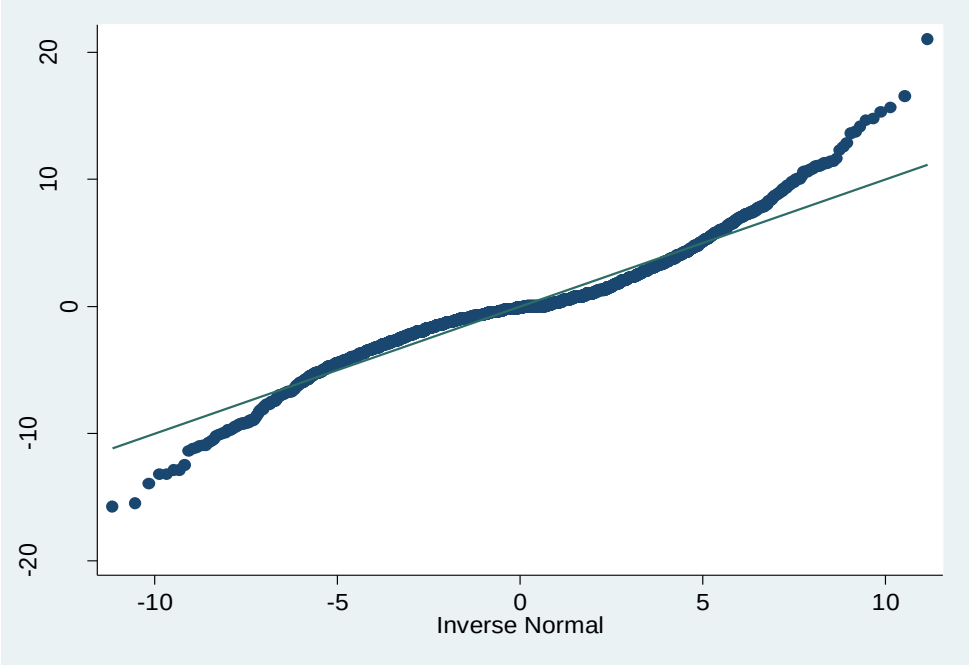


Figure 55. Q-Q plot for level one residuals with negative affect as the outcome variable

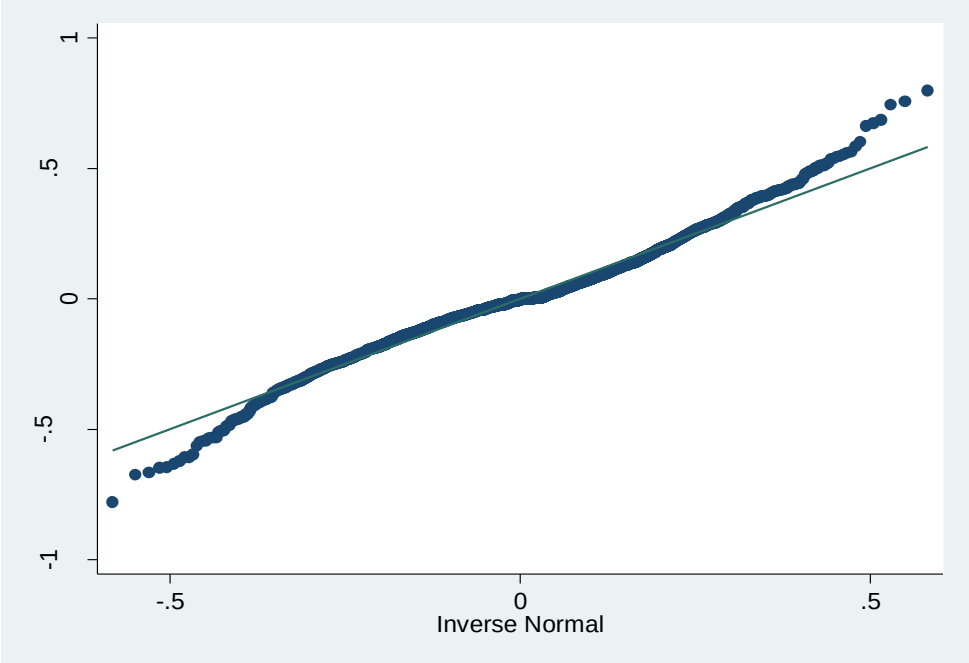


Figure 56. Q-Q plot for level one residuals with logarithmic transformed negative affect scores as the outcome variable

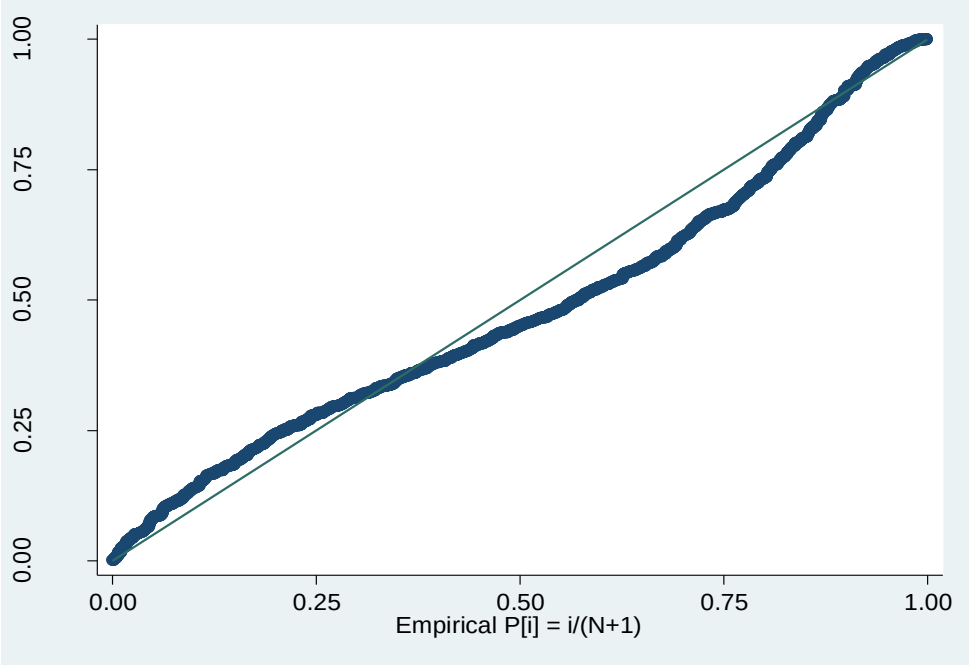


Figure 57. P-P plot for level two residuals with negative affect as the outcome variable

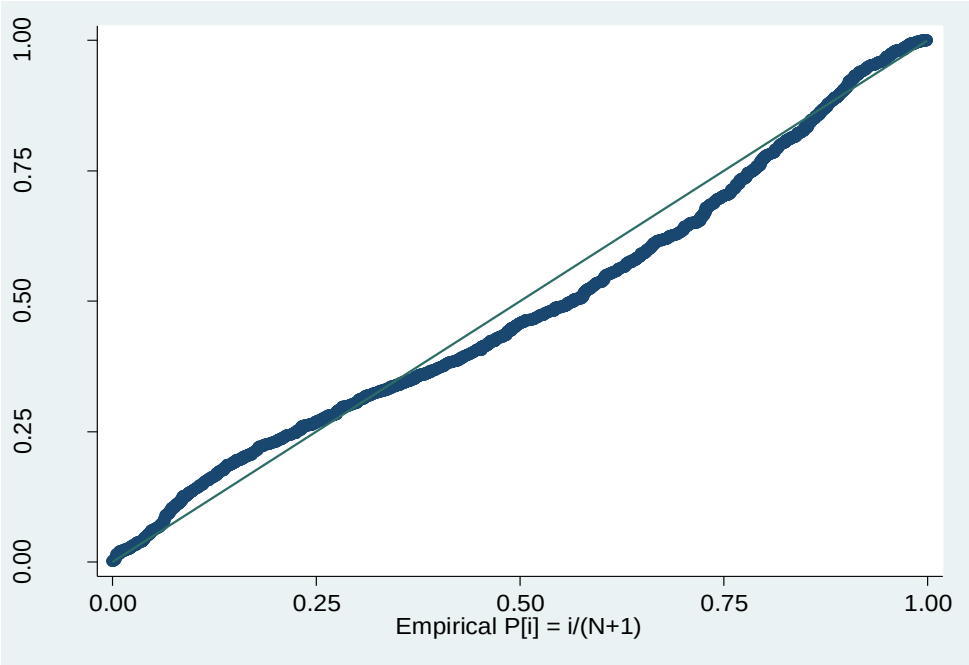


Figure 58. P-P plot for level two residuals with logarithmic transformed negative affect scores as the outcome variable

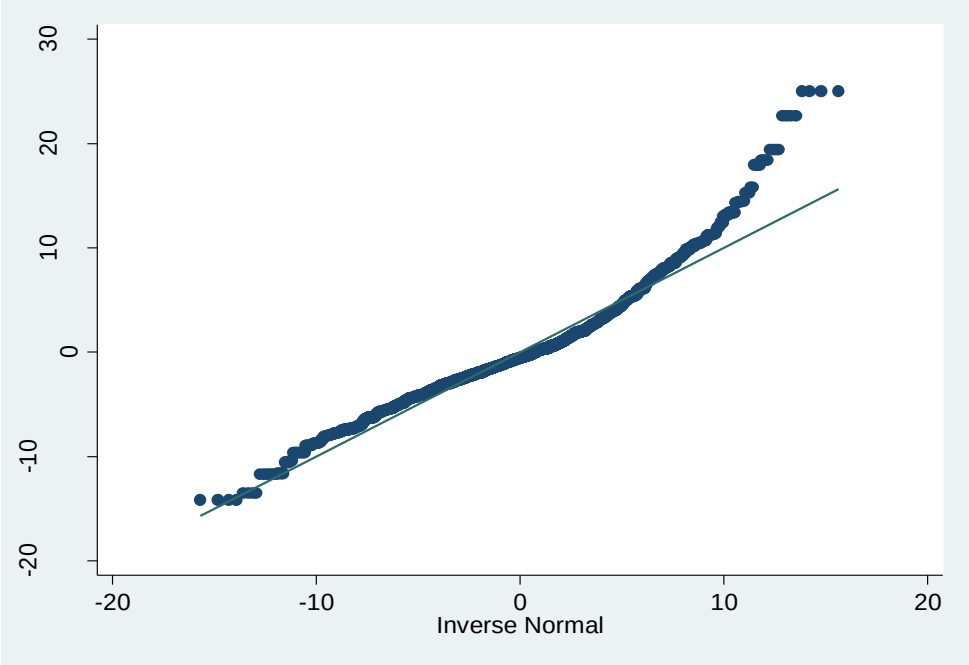


Figure 59. Q-Q plot for level two residuals with negative affect as the outcome variable

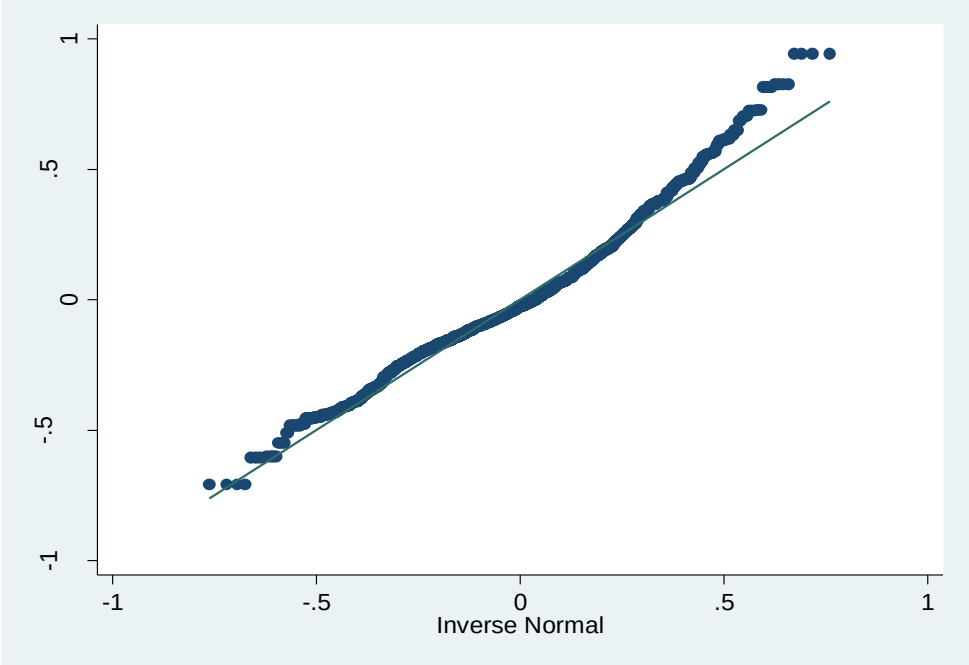


Figure 60. Q-Q plot for level two residuals with logarithmic transformed negative affect scores as the outcome variable

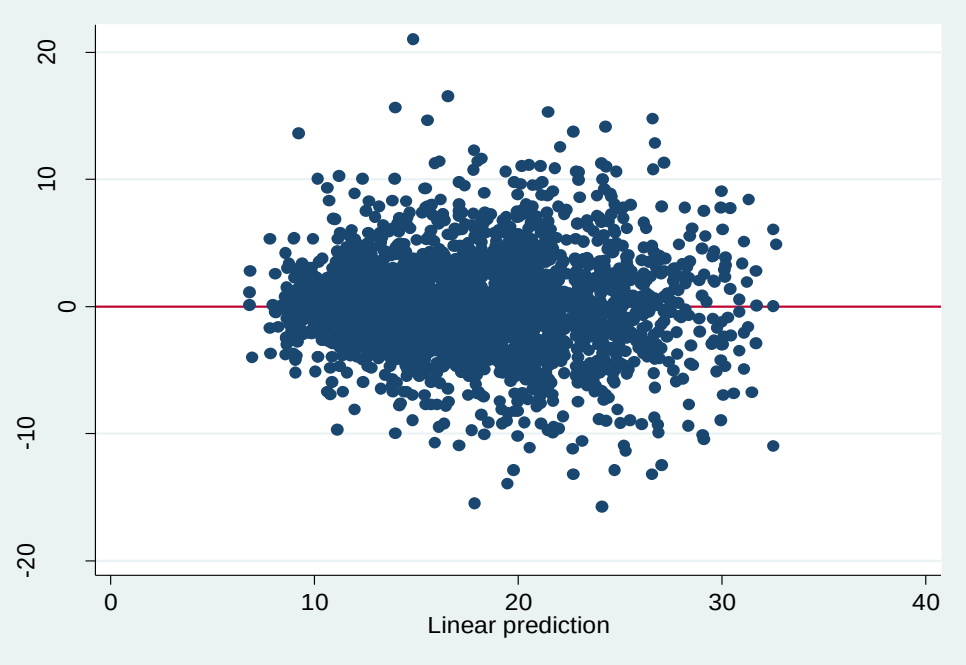


Figure 61. Scatterplot for level one residuals with negative affect as the outcome variable

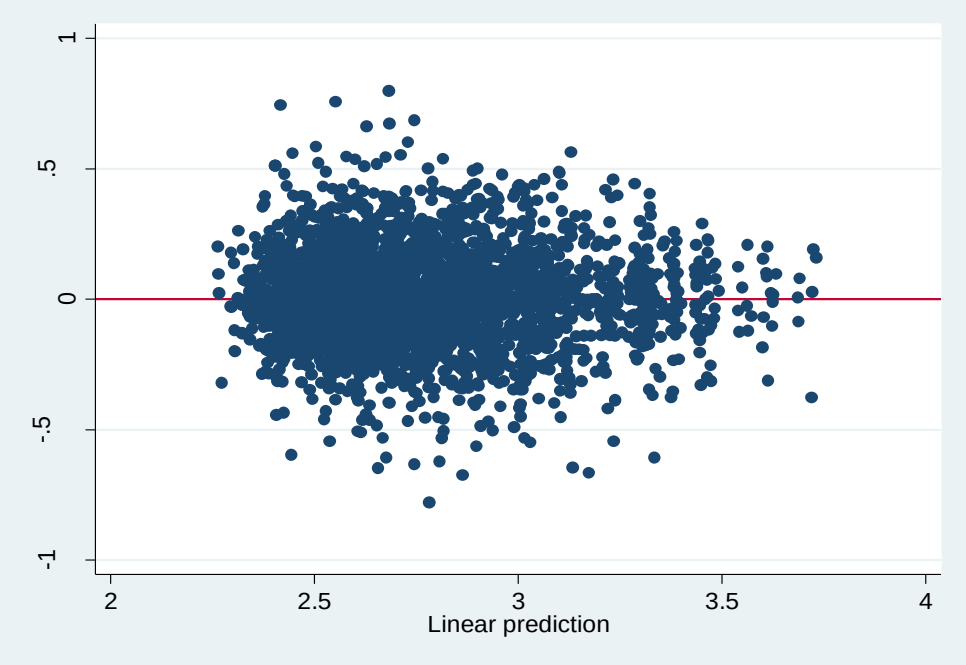


Figure 62. Scatterplot for level one residuals with logarithmic transformed negative affect scores as the outcome variable

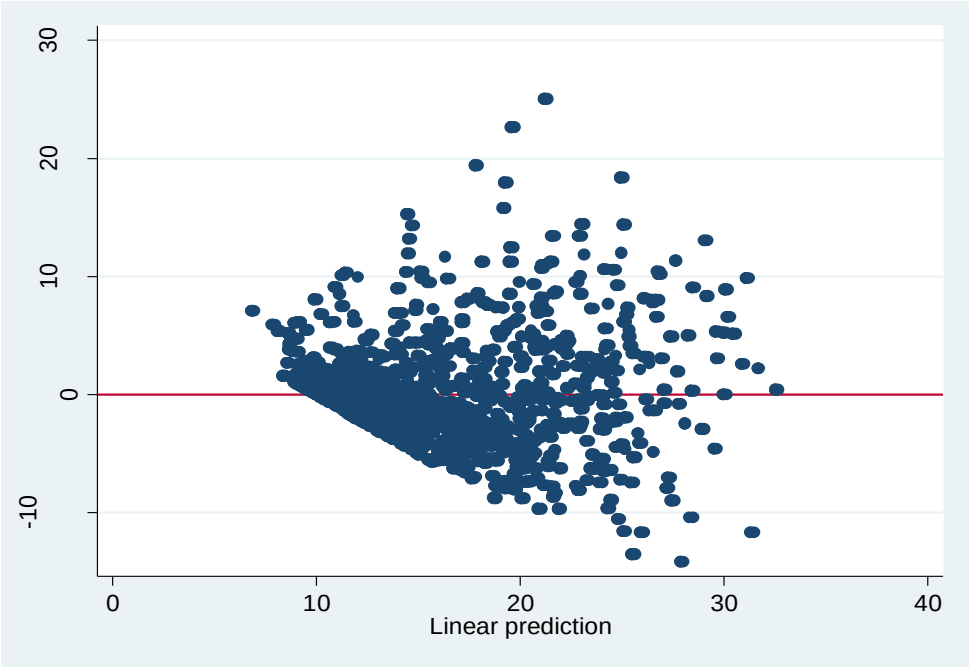


Figure 63. Scatterplot for level two residuals with negative affect as the outcome variable

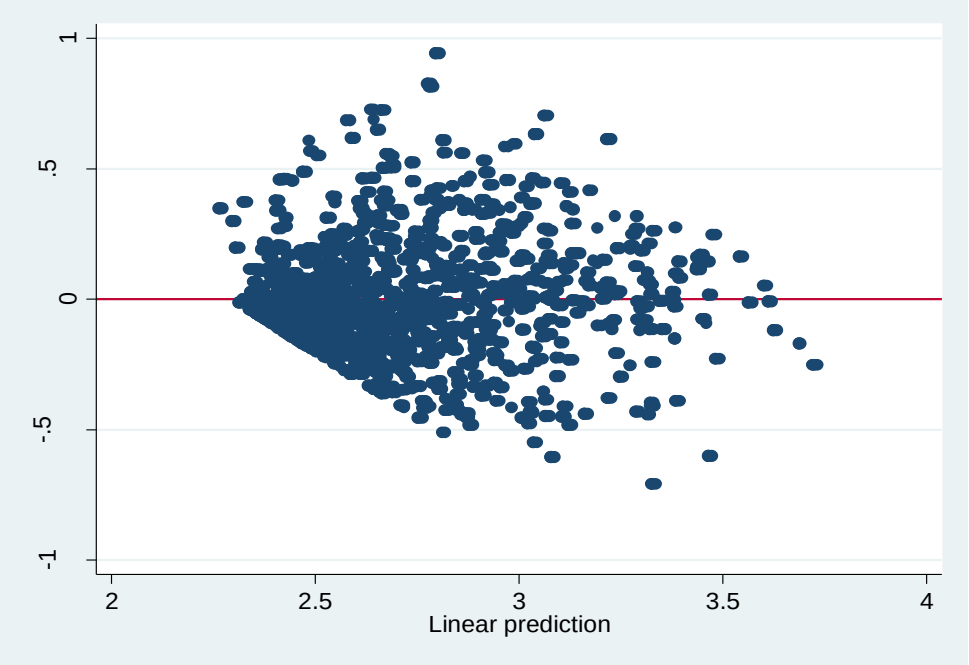


Figure 64. Scatterplot for level two residuals with logarithmic transformed negative affect scores as the outcome variable

Appendix 9. Power calculation output for chapter 6

sampsi 0.65 0.75, alpha(0.05) n1(279) n2(279) onesided

Estimated power for two-sample comparison of proportions

Test Ho: p1 = p2, where p1 is the proportion in population 1 and p2 is the proportion in population 2

Assumptions:

alpha = 0.0500 (one-sided)
p1 = 0.6500
p2 = 0.7500
Sample size n1 = 279 and n2 = 279
n2/n1 = 1.00

Estimated power: 0.8010