Modifiable Lifestyle Risk factors of Frailty among Community-Dwelling Older People

Thesis submitted to University College London
for the Degree of Doctor of Philosophy

Gotaro Kojima, MD

Department of Primary Care and Population Health
University College London
2019

Supervisors: Prof Kate Walters, Prof Steve Iliffe, Dr Stephen Jivraj

Funding: University College London Overseas Research Scholarship
The Great Britain Sasakawa Foundation Butterfield Award

DECLARATION OF AUTHORSHIP

I, Gotaro Kojima, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature: ……

Gotaro Kojima

Date: ……

ACKNOWLEDGEMENTS

I would like to express my sincere appreciation to my supervisors, Prof Kate Walters, Prof Steve Iliffe and Dr Stephen Jivraj. I also thank Dr Milena Falcaro for her support especially in statistical analyses and Dr Ann Liljas and Dr Christina Avgerinou for their help in the systematic reviews and data analyses.

ABSTRACT

BACKGROUND:

Frailty is common as people age and is associated with multiple adverse health outcomes. With an increasing number of older people worldwide, preventing frailty is recognised as a major public priority. The aims of this thesis are to examine associations between three potential modifiable lifestyle risk factors, smoking, alcohol and fruit and vegetable consumption, and frailty risks among community-dwelling older people.

METHODS:

This thesis used data on community-dwelling older men and women aged ≥60 from the English Longitudinal Study of Ageing (ELSA), an ongoing prospective panel study of a nationally representative population in England. Frailty was defined by modified frailty phenotype criteria. Information on smoking, alcohol and fruit and vegetable consumption was self-reported. Subsequent frailty risks over 4 years according to the three modifiable lifestyle risk factors at baseline were examined using logistic regression models controlling for potentially confounding factors.

RESULTS:

Current smokers had a significantly higher odds of frailty risk compared with non-smokers (never and past smokers). Non-drinkers had significantly worse health profiles at baseline and had a significantly increased risk of developing frailty compared with low drinkers (>0-7 UK units per week). This association was fully attenuated after adjusting for self-reported general health. Among drinkers, alcohol use (of any amount) was not associated with frailty. Consumption of 5-10 portions of fruit and vegetables a day was associated with reduced odds of pre-frailty and frailty combined compared to those with low consumption (0-2.5portions); however those eating high amounts (>10 portions per day) had a similar risk of frailty as those with low consumption.

CONCLUSIONS:

The findings suggest that smoking cessation and moderate-high consumption of fruit and vegetables (5-10 portions a day) have potential to reduce risk of frailty, however they do not support reducing alcohol consumption to prevent frailty over a short period of 4 years.

IMPACT STATEMENT

Frailty, a multisystem dysregulation of overall health status due to age-related deficit accumulation, has been attracted increasing scientific attention, especially in the last two decades. With tremendous impacts on older people and ongoing global population ageing, frailty has been recognized as an emerging public health priority by researchers, clinicians and policy makers. With limited evidence on effective treatments against frailty, it may plausible to proactively identify and address modifiable risk factors of frailty.

In this thesis, three modifiable lifestyle risk factors of frailty, specifically smoking, alcohol and fruit and vegetable consumption, were focused on.

Given that current smoking was shown to be associated with frailty, likely through chronic obstructive pulmonary disease and inflammation and it is feasibly possible to quit smoking in old age, smoking cessation may be an effective measure decreasing frailty risk among current smokers. Smoking cessation can be recommended for older people through public health campaigns as well as by clinicians to older patients who smoke. Although high alcohol consumption in old age was not shown to be associated with frailty in this thesis, non-drinkers were found to have increased frailty risks due to a generally poor health status. As alcohol consumption patterns may change over time, future research should use life-course history of alcohol use rather than one-time information, especially for those classified as non-drinkers in old age. These data are rarely collected and missing in the secondary data source used in this study, ELSA investigators could consider retrospective tools for life history alcohol consumption data collection. My analysis suggests that 5-10 portions of fruit and vegetable consumption per day was associated with lower frailty risk only among robust participants. At least of 5 portions of fruit and vegetables may be encouraged for those with insufficient intake or be included as a part of lifestyle interventions. Public health campaigns should include the potential benefit of higher levels of fruit and vegetables in preventing frailty. A note of caution should be given however that the same benefit was not seen for very high (>10 portions of fruit and vegetables). Future research should include other macro- and micro-nutrients and total calories and use valid measurement tools.

Although there is uncertainty due to the observational nature of the findings, clinicians could potentially decease risk of frailty by advising patients to stop smoking and increase fruit and vegetable consumption. These recommendations add to similar findings for other health outcomes of major public health importance such as the prevalence of cardiovascular disease, and could be easily provided and reinforced during regular primary care visits.

These impacts have been and will continue to be achieved through dissemination of the 8 papers related to the thesis, some of which are published in high impact journals, such as Age and Ageing, and 3 conference papers at scientific meetings, such as the British Geriatrics Society meetings or the Society of Social Medicine Annual Scientific Meeting. The article of the smoking analysis has been picked up as a press release and covered by multiple media, which contributed to significant impacts both inside and outside academia.

DISSEMINATION

Peer-reviewed publications

Smoking

Kojima G, Iliffe S, Walters K. Smoking as a predictor of frailty: a systematic review. BMC Geriatrics. 2015;15:131. DOI: 10.1186/s12877-015-0134-9

Kojima G, Iliffe S, Jivraj S, Liljas A, Walters K. Does current smoking predict future frailty in older people? the English Longitudinal Study of Ageing. Age and Ageing. 1;47(1):126-131. DOI: 10.1093/ageing/afx136

Alcohol

Kojima G, Liljas A, Iliffe S, Jivraj S, Walters K. A Systematic Review and Meta-analysis of Prospective Associations between Alcohol Consumption and Incident Frailty. Age and Ageing. 14(12):1256-1263. DOI: 10.1093/ageing/afx086

Kojima G, Iliffe S, Liljas A, Walters K. Non-linear association between alcohol and incident frailty among community-dwelling older people: A dose-response meta-analysis. BioScience Trends. 20;11(5):600-602. DOI: 10.5582/bst.2017.01237

Kojima G, Jivraj S, Iliffe S, Liljas A, Walters K. Alcohol consumption and risk of incident frailty: the English Longitudinal Study of Ageing. Journal of American Medical Directors Association DOI: 10.1016/j.jamda.2018.10.011

Fruit and vegetables

Kojima G, Avgerinou C, Iliffe S, Jivraj S, Sekiguchi K, Walters K. Fruit and Vegetable Consumption and Frailty: A Systematic Review. Journal of Nutrition, Health and Aging. 2018;22(8):1010-1017. DOI: 10.1007/s12603-018-1069-6

Kojima G, Iliffe S, Jivraj S, Walters K.
Fruit and vegetable consumption and incident prefrailty and frailty risk in community-dwelling older people: the English Longitudinal Study of Ageing. Under review.

Kojima G, Avgerinou C, Iliffe S, Walters K. Adherence to Mediterranean Diet Reduces Incident Frailty Risk: Systematic Review and Meta-Analysis. Journal of American Geriatrics Society. 2018;66(4):783-788. DOI: 10.1111/jgs.15251

Poster presentations

Smoking

Kojima G, Iliffe S, K Walters. Smoking as a Predictor of Frailty: A Systematic Review.

- British Geriatrics Society Autumn Meeting, Oct 2015, Brighton, UK

Alcohol

Kojima G, Jivraj S, Iliffe S, Liljas A, Walters K.
Alcohol consumption and risk of incident frailty: the English Longitudinal Study of Ageing

- Society for Social Medicine Annual Scientific Meeting, Sept 2018, Glasgow, UK
- University College London Institute of Epidemiology & Health Care PhD Poster Competition, November 2018, London, UK

Fruit and vegetables

Kojima G, Avgerinou C, Iliffe S, Jivraj S, Sekiguchi K, Walters K.
Fruit and Vegetable Consumption and Frailty: A Systematic Review.

- British Geriatrics Society Spring Meeting, Apr 2018, Nottingham, UK

LIST OF ABBREVIATIONS

ADL	Activities of daily living
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
BMI	Body mass index
CAPI	Computer-assisted personal interview
CES-D	Center for Epidemiologic Studies Depression Scale
CHS	Cardiovascular Health Study
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CSHA CFS	Canadian Study of Health and Ageing Clinical Frailty Scale
CVD	Cardiovascular disease
eFI	electronic Frailty Index
ELSA	English Longitudinal Study of Ageing
EU	European Union
FIT	Frailty Intervention Trial
IADL	Instrumental activities of daily living
ICHOM	International Consortium for Health Outcomes Measurement
HRS	Health Retirement Study
HSE	Health Survey for England
MeSH	Medical Subject Heading terms
MFGM	Milk fat globule membrane
MICE	Multiple imputation by chained equations
NIAAA	The National Institute of Alcohol Abuse and Alcoholism
NRES	National Research and Ethics Service
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
SHARE	Survey of Health, Ageing and Retirement in Europe

LIST OF TABLES

Table 2. 1. ELSA Fieldwork response rates by wave 41

Table 2. 2. Main interview questionnaire modules (from User Guide to the Main Interview Datasets Waves 1 to 8). 43

Table 2. 3. Comparison of five components from the modified Cardiovascular Health Study criteria at wave 2 and the original criteria. 51

Table 2. 4. Summary of fruit and vegetable categories data (portion/day) 59

Table 3. 1. Methodological quality assessment using the Newcastle-Ottawa Quality Assessment Scale for cohort studies. 78

Table 3. 2. Summary of included studies on associations between smoking and subsequent frailty status change among community-dwelling older people. 81

Table 3. 3. Comparisons between those included in the analyses (n=2,542) and those excluded due to missing data (n=1,376). 90

Table 3. 4. Baseline characteristics of ELSA participants in smoking and incident frailty analysis. (N=2,542) 92

Table 3. 5. Multivariable logistic regression models examining associations between smoking status and 4-year incident frailty. (N=2,542). 94

Table 3. 6. Odds ratios of incident frailty for current smoking and its changes when adding COPD, CVD, cancers, CRP and fibrinogen to Model 5. 96

Table 3. 7. Odds ratios of incident frailty for current and past smoking compared with never smoking. (N=2542)* 97

Table 3. 8. Numbers of participants missing data of covariates used for adjustments. (N=2,542) 98

Table 3. 9. Comparison between Model 5 (complete case analysis) and Model 5 with missing data imputed using multiple imputation by chained equations (MICE). 98

Table 4. 1. Methodological quality assessment using the Newcastle-Ottawa Quality Assessment Scale for cohort studies. 109

Table 4. 2. Summary of included studies on alcohol consumption associated with subsequent frailty status change among community-dwelling older people. 112

Table 4. 3. Comparisons between those included in the analyses (n=2,544) and those excluded due to missing data (n=1,376). 126

Table 4. 4. Baseline characteristics of ELSA participants in alcohol consumption and incident frailty analysis. (N=2,544) 129

Table 4. 5. Multivariable logistic regression models examining associations between alcohol consumption groups and 4-year incident frailty. (N=2,544). 131

Table 4. 6. Odds ratios of incident frailty for alcohol consumption and its changes when adding COPD, CVD, cancers, CRP and fibrinogen to Model 5. 133

Table 4. 7. Multivariable logistic regression models examining associations between alcohol consumption (quantity on the heaviest day) groups and 4-year incident frailty. (N=2,298)..... 135

Table 4. 8. Multivariable logistic regression models examining associations between frequency of alcohol consumption and 4-year incident frailty. (N=2,382)..... 138

Table 4. 9. Numbers of participants missing data of covariates used for adjustments. (N=2,544) 140

Table 4. 10. Comparison between Model 4 (complete case analysis) and Model 4 imputed using multiple imputation by chained equations (MICE). 141

Table 4. 11. Multivariable logistic regression models with restricted cubic spline function predicting incident frailty over 4 years according to alcohol consumption (N=2,325 drinkers). 142

Table 5. 1. Methodological quality assessment using the Newcastle-Ottawa Quality Assessment Scale for cohort studies..... 154

Table 5. 2. Summary of included studies on associations between fruit and vegetable consumption and frailty among community-dwelling older people. 158

Table 5. 3. Comparisons between those included in the analyses (n=2,634) and those excluded due to missing data (n=812). 170

Table 5. 4. Baseline characteristics of ELSA participants in fruit and vegetable consumption and incident frailty analysis. (N=2,634) 173

Table 5. 5. Multivariable logistic regression models examining associations between fruit and vegetable consumption groups and 4-year incident frailty among 2,634 non-frail community-dwelling older people in England. 176

Table 5. 6. Multivariable logistic regression models examining associations between fruit and vegetable consumption groups and 4-year incident pre-frailty/frailty among 1,577 robust community-dwelling older people in England..... 178

Table 5. 7. Multivariable logistic regression models examining associations between consumption of fruit and vegetable, respectively, and 4-year incident frailty among 2,634 non-frail community-dwelling older people in England..... 181

Table 5. 8. Multivariable logistic regression models examining associations between consumption of fruit and vegetable, respectively, and 4-year incident pre-frailty/frailty among 1,577 robust community-dwelling older people in England. 182

Table 5. 9 Fully adjusted logistic regression models for incident frailty with implausibly high values treated as 0 (Model 5a), treated as were (Model 5b) and with missing covariates imputed by multiple imputation by chained equations (MICE)..... 183

Table 5. 10 Fully adjusted logistic regression models for incident pre-frailty/frailty with implausibly high values treated as 0 (Model 5a), treated as were (Model 5b) and with missing covariates imputed by multiple imputation by chained equations (MICE). 184

LIST OF FIGURES

Figure 1. 1. Weighted prevalence of frailty stratified by age and gender. Reused from Collard and colleagues 2012[47] with permission. 23

Figure 2. 1. Timeline showing the number of core member participants at each wave in the English Longitudinal Study of Ageing. 40

Figure 2. 2. Self-completion questionnaire for fruit and vegetable consumption at English Longitudinal Study of Ageing wave 4,[163] and conversion rates into portions. 57

Figure 2. 3. Probability of history of cardiovascular diseases according to fruit and vegetable consumption groups at ELSA wave 4. 61

Figure 3. 1. PRISMA Flowchart (Smoking and frailty) 76

Figure 3. 2. ELSA final analytic population for smoking analyses. 86

Figure 4. 1. PRISMA Flowchart (Alcohol and frailty) 108

Figure 4. 2. Forest plots of odds ratio of incident frailty risk according highest alcohol use (quantity and frequency) compared with no alcohol use. 115

Figure 4. 3. Dose-response linear and non-linear relationships between alcohol consumption and incident frailty risk. CI: confidence interval. (The same figure used in a paper, Non-linear association between alcohol and incident frailty among community-dwelling older people: A dose-response meta-analysis. Kojima G, Iliffe S, Liljas A, Walters K. Biosci Trends 2017 (Open access)) 116

Figure 4. 4. ELSA final analytic population for alcohol analyses. 121

Figure 4. 5. Distribution of alcohol consumption per week in UK units. 128

Figure 4. 6. Distribution of alcohol consumption on the heaviest drinking day in UK units. 133

Figure 4. 7. Fully adjusted odds ratio (solid line) with 95% confidence interval (dash line) for association between alcohol consumption and incident frailty in restricted cubic spline regression model. 144

Figure 5. 1. PRISMA Flowchart (Fruit and vegetable consumption and frailty) 153

Figure 5. 2. ELSA final analytic population for fruit and vegetable consumption analyses. 166

Figure 5. 3. Distribution of fruit and vegetable consumption (portions/day) 172

Figure 6. 1. Self-completion questionnaire for fruit and vegetable consumption at English Longitudinal Study of Ageing wave 8. 194

CONTENTS

DECLARATION OF AUTHORSHIP **2**
ACKNOWLEDGEMENTS **2**
ABSTRACT **3**
IMPACT STATEMENT **5**
DISSEMINATION **7**
LIST OF ABBREVIATIONS **9**
LIST OF TABLES **10**
LIST OF FIGURES **12**
CONTENTS **13**
1 INTRODUCTION **16**
1.1 Ageing Population 16
1.2 Frailty in Older People 17
1.3 Frailty Measurements 18
1.4 Prevalence of Frailty 22
1.5 Implementation and Challenges for Frailty 23
1.5.1 Exercise Interventions 25
1.5.2 Nutritional Interventions 26
1.5.3 Integrated Care 29
1.5.4 Future Directions 31
1.6 Modifiable Lifestyle Risk Factors of Frailty 33
1.7 Research Objectives 36
2 METHODS **37**
2.1 Introduction 37
2.2 English Longitudinal Study of Ageing (ELSA) 37
2.2.1 Description of the Cohort 37
2.2.2 Follow-Up 40
2.2.3 Measurements 41
2.2.4 Ethical Approval and Funding 45
2.3 Definition of Frailty 46
2.3.1 Weight loss or ‘shrinking’ 46
2.3.2 Self-reported exhaustion 47
2.3.3 Weakness 48
2.3.4 Slow walking speed 48
2.3.5 Low physical activity 49
2.4 Definition of Smoking 52
2.5 Definitions of Alcohol Consumption 53
2.5.1 Quantity of Alcohol Consumption Per Week 54
2.5.2 Quantity of Alcohol Consumption on the Heaviest Drinking Day of the Last Week 55
2.5.3 Frequency of Alcohol Consumption 56
2.6 Definitions of Fruit and Vegetable Consumption 56
2.7 Definitions of Covariates 61
2.7.1 Age 62
2.7.2 Gender 62
2.7.3 Education 62
2.7.4 Wealth 64
2.7.5 Living Alone 65
2.7.6 Cognitive Function 65
2.7.7 Depressed Mood 67
2.7.8 Loneliness 67
2.7.9 Chronic Diseases 67
2.7.10 Self-reported General Health 68
2.7.11 Blood Tests 69
2.8 Statistical analysis 69
2.8.1 Main analysis 69
2.8.2 Weighting 70
2.8.3 Multiple imputation by chained equations 71
3 SMOKING **72**

3.1 Introduction 72
3.2 Systematic Literature Review 73
3.2.1 Objective 73
3.2.2 Methods 74
3.2.3 Results 75
3.2.4 Discussion 83
3.3 Smoking and Incident Frailty (ELSA) 85
3.3.1 Objective 85
3.3.2 Study Population 85
3.3.3 Predictor Variable − Smoking 87
3.3.4 Outcome Variable − Incident Frailty 87
3.3.5 Covariates 87
3.3.6 Statistical Analyses 87
3.3.7 Results 89
3.3.8 Discussion 99
4 ALCOHOL 102
4.1 Introduction 102
4.2 Systematic Review and Meta-Analysis 105
4.2.1 Objectives 105
4.2.2 Methods 105
4.2.3 Results 107
4.2.4 Discussion 117
4.3 Alcohol Consumption and Incident Frailty (ELSA) 119
4.3.1 Objective 119
4.3.2 Study Population 119
4.3.3 Predictor Variable - Alcohol 122
4.3.4 Outcome Variable - Incident Frailty 122
4.3.5 Covariates 122
4.3.6 Statistical Analyses 123
4.3.7 Results 125
4.3.8 Discussion 145
5 FRUIT AND VEGETABLE CONSUMPTION 148
5.1 Introduction 148
5.2 Systematic Literature Review 150
5.2.1 Objective 150
5.2.2 Methods 150
5.2.3 Results 152
5.2.4 Discussion 162
5.3 Fruit and Vegetable Consumption and Incident Pre-frailty/Frailty (ELSA) 164
5.3.1 Objective 164
5.3.2 Study population 164
5.3.3 Predictor variable - Fruit and vegetable consumption 167
5.3.4 Outcome variable - Incident frailty and incident pre-frailty/frailty 167
5.3.5 Covariates 167
5.3.6 Statistical Analyses 168
5.3.7 Results 169
5.3.8 Discussion 184
6 OVERALL DISCUSSION 187
6.1 Key Findings 187
6.1.1 Systematic reviews 187
6.1.2 Smoking 188
6.1.3 Alcohol 189
6.1.4 Fruit and vegetable consumption 189
6.2 Frailty as an Outcome Measure 190
6.3 Strengths 191
6.4 Limitations 192
6.4.1 Systematic reviews and meta-analyses 192
6.4.2 ELSA analyses 192
6.5 Implications 198
6.5.1 Smoking 198
6.5.2 Alcohol 198
6.5.3 Fruit and vegetable consumption 199

6.5.4 Lead Time 199
6.6 Future Directions 200
6.6.1 Smoking 200
6.6.2 Alcohol 200
6.6.3 Fruit and vegetable consumption 201
6.7 Conclusions 201
7 REFERENCES 202
8 APPENDICES 230
8.1 Related publications 246
8.1.1 Smoking 246
8.1.2 Alcohol 268
8.1.3 Fruit and vegetable 295

1 INTRODUCTION

This chapter presents an overview of this thesis and its contents.

1.1 Ageing Population

Life expectancy has markedly increased worldwide over the past century largely due to public health improvements.[1] This global population transformation has resulted in growing numbers of older people in both developing and developed countries.[2] The proportion of older people is projected to increase, in part, due to the lower mortality at the oldest age.[2] Between 2000 and 2050, the proportion of the population aged 60 years or older in the world is forecast to double from about 11% to 22%, and the number of older people is forecast to increase from 605 million to 2 billion.[1] During the same period, the number of people aged 80 years or older is expected to almost quadruple to 395 million.[1]

Japan is one of the countries with the most rapidly ageing population.[3] In Japan, due to the world's highest life expectancy and a persistently low birth rate, the proportion of people aged 65 years and older has increased from 10% in 1985 up to 26.7% in 2015,[4] which is much higher than in other developed countries: 22% in Italy, 21% in Germany, 19% in France, 16% in Canada, 14% in the United States and 9% in China.[5] The United Kingdom is no exception. The proportion of people aged 65 years and over increased from 15% in 1985 to 17% in 2010, and is expected to increase up to 23% by 2035.[6] The age group increasing at the fastest rate is the "oldest old" who are those aged 85 years and over. The proportion of this oldest old group was 2% in 2010 and is forecast to be 5% in 2035.[6] The similar population changes are expected in other European countries.[6]

People generally develop health problems and become frailer as they age. The increasing life expectancy brings with it development of chronic diseases and physical and cognitive functional decline, leading to disability or dependency.[7] Care for older patients accounts for the majority of healthcare costs[8] and global-scale ongoing population ageing has just started to have a powerful

demographic impact on current healthcare systems. The unprecedented growth in the number and proportions of older people requires transformation of healthcare and creates the need for effective and sustainable long-term care services to meet their demands. Older people are a highly heterogeneous population and the trajectories and rates of changes in their health and functional status may vary substantially depending on genetic, biological and environmental backgrounds. The life course of health status is also influenced by other factors, including physical, psychological and social factors. Therefore, persons with the same chronological age can have different physiological ages.[9] It is thus challenging to explain the heterogeneity of the ageing process in older people and critical to ensure all enjoy as long as healthy life expectancy as possible.[10]

1.2 Frailty in Older People

One of the potential concepts that can be used to describe the overall health diversity of older people is frailty.[11] Frailty as a term was once used interchangeably with ageing, comorbidity or disability, partly because of their similarities and partly because of their co-existence.[12] Advanced age does not always mean vulnerability to negative health outcomes.[13] Some people live into their 90's in excellent health with preserved physical and cognitive functions and independence in activities of daily living (ADL), while others suffer from chronic medical conditions with comorbidities, disabilities, decline functionally and mentally and die much earlier in life. Disability is usually defined as difficulty or dependency in performing activities necessary to live independently and often described as ADL (e.g. bathing, dressing, eating, toileting, continence, transferring[14]) and instrumental activities of daily living (IADL: e.g. shopping, telephone use, meal preparation, housekeeping, laundry, transportation, medication, finances[15]). Multi-morbidity is generally used to describe having two or more medically diagnosed diseases in a single person. Multi-morbidity is rather crudely defined and while it increases frailty risk overall, a person can be multi-morbid and 'healthy' in the sense of being robust, active with good quality of life and no functional impairment. Frailty has now been conceptualised more clearly as a state of decreased physiological reserve and compromised capacity to maintain homeostasis as a consequence of age-related multiple accumulated

deficits.[11] Common clinical presentations of frailty include fatigue, unexplained weight loss, sarcopenia, frequent infection, delirium, fluctuating disability, loss of resilience and inability to recover from acute stressors.[11, 16] Therefore frail older people are predisposed to significant health declines and are highly vulnerable to adverse health outcomes when exposed to an internal or external stressor.[11] The adverse health outcomes associated with frailty include but are not limited to: falls,[17, 18] fractures,[19, 20] disability,[21, 22] emergency department visits,[23] hospitalisation,[24] institutionalisation[25] and mortality.[26-28] Frailty is also shown to be associated with worse psychological or cognitive outcomes, such as poor quality of life,[29, 30] depression[31] and dementia.[32] These outcomes can further exacerbate frailty, causing a vicious cycle. As a result, the level of frailty as a whole tends to progress with age.[33, 34] Frailty is not an irreversible one-way process to disability or death, but a dynamic process involving improvement as well as natural progression.[35, 36] Although all entities are closely related to each other and become more common as people age, often co-existing and overlapping, the frailty concept is clearly distinguishable from ageing, disability or multi-morbidity. In fact, among 368 frail older people in the Cardiovascular Health Study (CHS) cohort, 21 participants (5.7%) had 1 or more ADL disability, 170 participants (46.2%) had multi-morbidity and 79 (21.5%) had all (frailty, disability and comorbidity).[12] However approximately one fourth (n=98, 26.6%) were found to have only frailty, without disability or comorbidity. In this regard frailty can be considered a distinct entity, different from the other two.[12]

1.3 Frailty Measurements

Multiple tools to measure frailty have been developed and validated in population-based studies,[37] including the CHS criteria, (also known as the 'frailty phenotype'),[16] the Frailty Index,[10] the Edmonton Frail Scale,[38] the Groningen Frailty Indicator,[39] the Tilburg Frailty Indicator,[40] the FRAIL scale[41] or the Kihon Check-list.[42] Although the concept of frailty has now been widely accepted and agreed, its definition is still controversial and a consensus regarding the best definition to operationalise frailty has not been reached.[11] This ongoing controversy on the definition of frailty may be due to its complex nature and heterogeneous presentations.[43] Lack of standardised definitions to operationalise frailty against the other conditions may be another reason why

frailty was defined arbitrarily and sometimes confused with disability or comorbidity,[12, 16, 44] especially until around 2001 when two major frailty conceptualisations were articulated, the frailty phenotype and the Frailty Index. Among a number of proposed definitions and criteria to operationalise frailty,[45] the most frequently used definition in the literature is the frailty phenotype first described by Fried and colleagues using the CHS cohort in 2001.[16] They use a combination of five physical frailty components: (1) unintentional weight loss, (2) self-reported exhaustion, (3) weakness, (4) slow walking speed and (5) low physical activity, to define frailty as having three or more of the five criteria.[16] An individual who meet one or two criteria is classified as pre-frail and an individual with no criteria is classified as robust.[16] These components used to operationalise frailty in the CHS were modified in various ways from study to study as a result of the availability of data in different contexts.[46]

The Frailty Index based on a cumulative deficit model is another operationalisation commonly used to define frailty, proposed by Rockwood and colleagues in 2001.[10] In contrast to the frailty phenotype, this approach regards frailty as a state caused by the accumulation of health deficits during the life course.[10] Therefore the more deficits an individual has, the more likely the individual is to be frail.[10] The Frailty Index can be calculated as a ratio of the number of deficits present to the number of total deficits considered.[47] The deficits can be symptoms, signs, diseases, disabilities, laboratory, radiographic, or electrocardiographic abnormalities and social characteristics.[47] Frailty defined by the Frailty Index was superior in predicting mortality and other health outcome risks to frailty defined by the frailty phenotype.[48] Since these frailty definitions were published and framed as distinct entities on scientific and theoretical bases, frailty has been more clearly recognised as an important issue for older people by clinicians, researchers and policymakers,[49] and an exponentially increasing amount of research has been conducted based on these definitions (as well as others) over the past few decades.

Some also argue that the most commonly used two frailty definitions, the frailty phenotype and the Frailty Index, may be rather impractical or unfeasible as tools especially in a busy clinical setting.[50] The frailty phenotype requires special equipment for handgrip measurement, space for gait speed

measurement, and calculations for population-based lowest 20% of handgrip strength, gait speed and low physical activity.[16]

In contrast, the Frailty Index requires collecting a number of deficits, typically more than 30-40,[47] and summing and dividing the number of present and absent deficits, which may take 20-30 minutes.[51] However it may be possible to shorten the time to (or automatically) calculate the Frailty Index. A recent study demonstrated that an electronic Frailty Index (eFI) can be calculated using routinely available primary care health record data and effectively discriminated risks of hospitalization, nursing home admission and mortality.[52]

There are some criticisms however of both the frailty phenotype and the Frailty Index. The main concern regarding the frailty phenotype model is that this does not adequately cover cognitive and psycho-social elements of frailty in light of multidimensionality of frailty.[53, 54] In contrast, the Frailty Index consists of a wide range of deficits, including disease, disabilities, signs, symptoms, laboratory abnormalities, cognitive impairment.[47] However, this model does not directly measure frailty but only measures risk of frailty, and there are concerns that by measuring cumulative deficits, it does not adequately allow for the measurement of frailty improvement.

According to the International Association of Nutrition and Aging Task Force, a frailty tool should be quick, inexpensive, reliable, and easy to use in clinical settings because the identification of frail older people at risk is the important initial step, leading to appropriate preventive and/or treatment interventions and ultimately to high quality care for this vulnerable population.[50] In 2008, based on a systematic review of the literature as well as input from a panel of geriatric experts, this organisation's working group advocated a new frailty tool, the FRAIL scale.[50] This is a simple tool consisting of five yes/no questions: ***F***atigue, ***R***esistance (inability to climb stairs), ***A***mbulation (inability to walk a certain distance), ***I***llnesses, and ***L***oss of weight.[55] A recent meta-analysis study showed frailty defined by the FRAIL scale is a significant predictor of mortality.[27] The Kihon Checklist is also among relatively new frailty tools.[56] The Kihon Checklist is a self-reported comprehensive questionnaire consisting of 25 simple yes/no questions covering multiple domains of instrumental ADL, physical function, oral

function, nutrition status, cognition, social activity, and depressive mood.[3] Although this tool was originally developed by the Japanese Ministry of Health, Labour and Welfare in 2005-2006 as a screening tool to identify vulnerable older people who are at high risk of dependency,[3] it has increasingly been recognized as a frailty assessment tool.[42] The validation study showed that the Kihon Checklist score was highly correlated to frailty status defined by the frailty phenotype criteria.[42] If the 25 items are considered as deficits, a total score of the Kihon Checklist can be treated as a fixed set of the Frailty Index. In a prospective cohort study of 1,023 Japanese community-dwelling older people aged ≥65 years, the Kihon Checklist treated as a Frailty Index was validated to be consistent with 32-item and 68-item Frailty Indexes in predicting loss of independence (composite outcome of either long-term care insurance certification or mortality) over 3 years.[28] The Canadian Study of Health and Aging Clinical Frailty Scale (CSHA CFS) was developed as a frailty tool, which is based on clinical judgement and easy to use by practicing clinicians.[57] CSHA CFS stratified individuals into 7 classes: 1 Very fit, 2. Well, 3. Well, with treated comorbid disease, 4. Apparently vulnerably, 5. Mildly frail, 6. Moderately frailty and 7. Severely frail.[57] This scale has good criterion and construct validity and good inter-rater reliability, and can predict mortality.[57] These frailty tools are brief, simple, and quick, as well as cost-effective as they do not require any training, special equipment and such calculations as lowest 20% of the population or summing and dividing the number of the deficits, and they take less than 10 minutes to complete.[51] These newer frailty scales can be easily incorporated into comprehensive geriatric assessment or primary care in a busy clinical setting to identify frail older individuals. In light of the short lists of simple questions, both tools can be administered via phone, mail, or email, and by not only physicians but also other healthcare professionals.

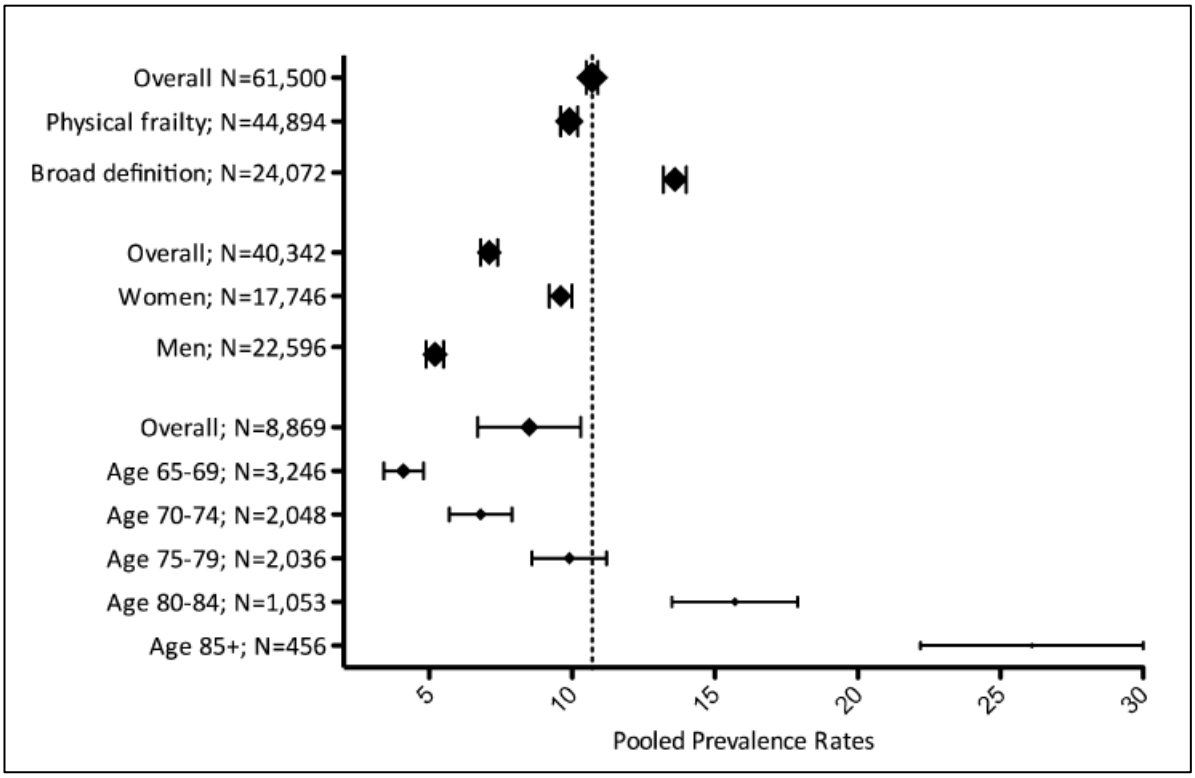
Among these frailty definitions, the frailty phenotype was selected for this thesis. The frailty phenotype considers frailty as a specific clinical syndrome with the typical phenotypic presentations, thus is useful for investigating the underlying mechanisms, pathophysiology, and risk factors. This robust foundation of biological theory of the frailty phenotype is particularly important when examining potential predictors of incident frailty and exploring how lifestyle-related diseases, such as chronic obstructive pulmonary disease (COPD)

caused by smoking, are related to the association between the target lifestyle factor and frailty. It uses five components including objective measures and has ability to predict adverse outcomes. It has been shown to have good validity and reliability in various populations and settings. These features have led to its widespread use as the most dominant method of measuring frailty today.[58]

1.4 Prevalence of Frailty

According to previous systematic review articles, prevalence of frailty globally based on various frailty criteria varies widely, ranging from 4.0% to 59.1%, among community-dwelling older people aged 65 and older.[34, 59] The overall weighted prevalence of frailty and pre-frailty is 10.7% and 41.6%, respectively, based on multidimensional frailty definitions, such as the Frailty Index[10] or FRAIL scale,[41] and 9.9% and 44.2%, respectively, based on physical frailty criteria.[34] Female gender and advanced age were associated with higher prevalence of frailty: women were almost twice as frail as men, and frailty prevalence was less than 5% among those aged 65-69 while it was over 25% among those aged 85 or older (**Figure 1.1**).[34] These factors may have contributed the large difference in prevalence of frailty.

Figure 1. 1. Weighted prevalence of frailty stratified by age and gender. Reused from Collard and colleagues 2012[47] with permission.



Higher prevalence of frailty is observed in selected populations of patients with a specific disease or medical condition, such as cancer patients[60] (median prevalence 42% for frailty and 43% for pre-frailty), patients with end-stage renal disease[61] (pooled prevalence 36.8% by objectively measured CHS frailty criteria and 67.0% by self-reported CHS criteria), patients with heart failure (overall estimated prevalence of frailty 44.5%),[62] patients with depression (pooled prevalence 40.4%), patients with COPD (pooled prevalence 19%)[63] and patients with Alzheimer's disease[64] (pooled prevalence 31.9% for frailty). Given frailty as a significant predictor of nursing home placement,[25] prevalence of frailty is extremely high among nursing home patients:[65] More than 90% of them are pre-frail or frail (pooled prevalence 52.3% for frailty and 40.2% for pre-frailty).[65]

1.5 Implementation and Challenges for Frailty

Frailty places a huge burden on patients, their families, society and healthcare systems in various ways and is significantly associated with increased

healthcare resource utilisation.[66] Compared with non-frail robust individuals, frail older people are 1.9 times more likely to have hospital admissions (pooled odds ratio (OR)=1.90)[24] and 5.6 times more likely to be placed at nursing homes (pooled OR=5.58).[25] Co-occurrence of frailty, comorbidities and disabilities is common,[67] and they may make each other worse.[30] Frailty itself is shown to be a significant predictor of disability by a recent systematic review and meta-analysis study, in which frail older people have 2 to 4 times higher risks of developing or worsening disabilities in ADL (pooled OR=2.76 and pooled hazard ratio=2.23) and in IADL (pooled OR=3.62, pooled hazard ratio=4.23).[21] Furthermore, muscle weakness, poor physical balance and impaired gait are among major components of frailty,[16] and all of them contribute to an increased risk of falling. Falling is a leading cause of mortality among older people,[68] and is associated with serious trauma such as fractures and head injury, disabilities, fear of falling and healthcare utilisation.[68] Frailty is a significant predictor of falling (pooled OR=1.84)[18] and fractures (pooled OR=1.70).[19] Dementia is another major cause of disabilities and dependence in older people.[69] Frailty is associated with dementia in cross-sectional studies[64] and is shown to be a significant predictor of dementia, including Alzheimer disease and vascular dementia.[32] As such, frailty itself and the related secondary and tertiary consequences further increase the complexity of care for frail older people and the burden on healthcare systems.

It is to be expected that frailty is associated with higher healthcare costs.[70-74] Two longitudinal studies showed that progression from non-frailty to frailty was associated with approximately a two-fold increase in total healthcare costs during the study periods.[70, 71] Once frailty is developed, healthcare costs apparently jump up several fold according to a cross-sectional study of German older people, which showed the mean total 3-month healthcare costs of a frail (defined as having 4 or 5 out of 5 phenotype criteria) individual to be €3659, compared with €642 for a non-frail (defined as having none of the phenotype criteria) individual.[72] Another cross-sectional study of 2,150 community-dwelling older women from the Study of Osteoporotic Fractures demonstrated the mean total annualised costs were $16,589, $6,632 and $3,781 for frail, pre-frail and robust individuals.[73] In light of the growing number of older populations worldwide and a wide range of devastating impacts of frailty on the healthcare

systems, frailty is one of the major public health challenges for all related parties of researchers, clinicians and policy makers.[75]

Although there is no consensus on the standard treatments of choice specifically for frailty, high quality cost-effective sustainable healthcare interventions against frailty are urgently needed.[76] Their successful implementation, which would require multidisciplinary contribution from researchers, clinicians and policy makers, would have substantial public health importance.[77] Researchers will need to explore pathophysiology, aetiology and risk factors of frailty and develop the best care and treatment models, clinicians will need to screen frail patients and directly deliver care and policy makers will need to create healthcare systems prepared for upcoming population ageing and allocate healthcare resources effectively and efficiently. To date various types of intervention models have been proposed and investigated, but with inconclusive findings. The major types of interventions that have been studied and evaluated so far include (1) exercise interventions, (2) nutritional interventions (and combined with exercise and nutrition) and (3) integrated care models, which are discussed below.

1.5.1 Exercise Interventions

Five exercise studies that examined frailty status change as an outcome were identified. All of these 5 intervention studies employed multicomponent exercise and examined frailty status change or frailty reversal rate as intervention outcomes.[78-82] The number of participants ranged from 100[81] to 610,[82] with the intervention periods from 3 months[79] to 12 months.[78] Most of the study populations were pre-frail or frail defined by the frailty phenotype criteria, except for one study in Japan using the Kihon Checklist.[82] All studies consistently showed improvement in frailty status, suggesting strong and robust evidence of multicomponent exercise intervention for frailty.[78-82] In two studies, some small additive effects of nutritional supplementation[79] and a combination of cognitive and nutritional interventions[80] to exercise were observed. A multicomponent exercise seems the most effective single intervention for frailty and may play an important role in treatment.[83] Especially the ones combining multicomponent exercise and other types of interventions, for example nutritional

supplementation, seem plausible.[84] A recent systematic review with a focus on multi-domain interventions for frailty identified five intervention studies examined the impact of multi-domain intervention on frailty status, all of which included at least both exercise and nutritional intervention components.[85] Four of the five studies showed significantly larger improvement in frailty status compared with mono-domain or control interventions.[85] The authors concluded that physical exercise seems to play an essential role in the multi-domain intervention and that additional interventions, such as nutritional intervention, may provide further improvement.[85] None of these intervention studies focused on optimising lifestyle factors, such as smoking, alcohol or dietary patterns.

1.5.2 Nutritional Interventions

Nutrition is a fundamental important factor for healthy ageing but risk of malnutrition increases as people age.[86] Malnutrition is associated with weight loss, which may lead to exhaustion, weakness and slow gait speed, and eventually the development of frailty.[84] A cross-sectional study of 206 community-dwelling older men and women in Germany examined associations between frailty defined by the frailty phenotype and nutritional status based on the Mini Nutritional Assessment tool, and showed that 47% of frail individuals were at risk of malnutrition (17-23.5 points on Mini Nutritional Assessment) and that as high as 93% of individuals at risk of malnutrition were either pre-frail or frail.[87]

Among various types of macro- and micro-nutrients, adequate intake of dietary protein is an essential factor of maintaining muscle mass and function.[88] In older people, one of the major causes of loss of muscle mass is inadequate amount of protein in their diet,[89] and amino acid supplementation has been shown to increase muscle synthesis in older people.[90] Vitamin D deficiency is also common among older people and associated with various negative health outcomes,[91-96] including frailty.[97, 98] Vitamin D supplementation was suggested to have beneficial effects on muscle strength by systematic review and meta-analysis studies,[99, 100] and may be used as a potential treatment for frailty especially among vitamin D deficient individuals.[101] Supplementation of caloric, protein, and vitamin D is recommended as potential treatments for frailty by the

consensus report of major international societies.[102] The main focus of nutritional interventions has been oral supplementation, which is expensive and generally not very palatable. There has been little research that has examined benefits of dietary patterns (e.g. Mediterranean diet[103]) or fortifying normal diets to optimise protein and calorie intake. Although nutrition education interventions may have potential to improve malnutrition-related outcomes in older people,[104] there is limited evidence for potential benefit of nutrition education on frailty.[105]

Many cross-sectional and prospective cohort studies have shown significant relationships between frailty and dietary factors.[106] However, there is limited evidence about the value of nutritional interventions for frailty and most of such interventions were oral nutritional supplements combined with exercise and their outcomes were often individual frailty components or physical functions, but not frailty status changes.[106] There are few studies that examined effects of nutritional interventions alone on frailty status, with mixed results.[107]

In the two trials described in the previous section on exercise interventions, the effectiveness of nutritional intervention alone (without exercise) was also examined. The Japanese study's nutritional-only intervention arm received 1g of milk fat globule membrane (MFGM) in a pill form (21.5% protein, 44.0% fat, 26.5% carbohydrate, 6.4% ash, 1.6% moisture) daily.[79] There was no significant difference observed in the frailty reversal rates between MFGM and placebo arms at both 3-month and 7-months follow-up points (28.1% vs 25.0%, 30.2% vs 15.2%, respectively).[79] The nutritional intervention arm of the Singapore Frailty Intervention Trial provided a commercially-available formula (300 kcal, 12g of protein, 36.8g of carbohydrate, 11.6g of fat) and supplements (iron, folate, vitamins B6, B12 and D, calcium) to be taken daily for 24 weeks. Frailty status of the intervention arm improved significantly more than that of control group (frailty reduction rate 35.6% vs 15.2%, OR=2.89, 95% confidence interval (CI)=1.07-7.82).[80] The treatment effect of the nutrition was smaller than that of the multicomponent exercise (frailty reduction rate 41.3% vs 15.2%, OR=4.05, 95%CI=1.50-10.8).[80] However, no nutrition intervention studies using fruit and vegetables to protect against frailty are found in the literature. Associations between fruit and vegetable consumption and frailty risk among community-

dwelling older people will be examined using the English Longitudinal Study of Ageing (ELSA) sample in **Chapter 5**.

A randomised controlled trial in Australia examined the effects of oral testosterone with a high calorie supplement (2108-2416 kJ/day) vs placebo with a low calorie supplement control group, on frailty status defined by 3 types of the Frailty Index (based on self-report data, lab data and combined data) and the frailty phenotype in 53 community-dwelling undernourished older people aged 65 or over.[108] There was a significant improvement in frailty status in the Frailty Index based on the combined self-report and lab data deficits, but not by the other Frailty Indices or the frailty phenotype.[108]

The effects of L-carnitine (naturally occurring amino acid derivative) supplementation (1.5g/day for 10 weeks) on frailty status changes were examined in a Malaysian randomised double-blind placebo-controlled trial with 50 men and women who were at least 60 years old and were defined as pre-frail by the frailty phenotype.[109] Frailty status at follow up based on the phenotype and the Frailty Index was improved in the L-carnitine supplementation group compared with control: 3 participants improved to robust in L-carnitine group (11.5%) while only 1 (4.2%) did in control.[109] On average the Frailty Index decreased (i.e. participants became less frail) by 34.3% in L-carnitine group while only by 2.1% in control.[109]

Fish oil supplementation (1.2 g of eicosapentaenoic acid and docosahexaenoic acid per day for 6 months) failed to improve frailty status defined by the frailty phenotype in a US randomised double-blind placebo study including 126 postmenopausal women (3% frail, 80% pre-frail, 17% robust at baseline based on the frailty phenotype criteria).[110]

As well as the limited number of studies, a high degree of heterogeneity was observed in types of nutritional supplementation, study population (especially in terms of nutritional status at baseline), design, setting and frailty definition, and the findings were inconsistent. It should also be noted that most of the nutritional interventions did not optimise normal diets but used supplementation.

More well-designed randomised controlled trials are needed in order to elucidate the effects of nutritional interventions on frailty.

1.5.3 Integrated Care

Frail older people tend to suffer from multiple diseases and medical conditions, along with physical, psychological and social problems. Therefore traditional organ-specific or disease-specific healthcare delivery models without coordination cannot adequately meet multidimensional needs and problems of frail older people.[111, 112] It is a complex task to adequately address their problems and may require a comprehensive care approach with a holistic view in order to provide optimal care.[113] Integrated care is characterised by organisational efforts for sustained holistic care tailored to individual demands by coordinating multidisciplinary professionals and services.[114-116] This patient-centred approach has recently been recognised as a potential solution to postpone health decline, extend the duration of healthy ageing and improve quality of life for frail older people.[116, 117] The World Health Organization has started the development of evidence-based guidelines on integrated care for older people with support from experts in Geriatric medicine.[118] According to recent systematic reviews on integrated care for community-dwelling frail older people, the previous studies employed a various range of interventional components and outcomes.[113, 116, 117] The interventions used included but were not limited to case management, interdisciplinary team assessment (including comprehensive geriatric assessment) and care, periodic reassessment, physical activity, rehabilitation, referrals and coordination of home-/community-based health and social services, periodical follow-ups by home visits/phone calls/geriatric clinic, caregiver support and health education.[113, 116, 117] The major outcomes were healthcare utilisation (hospital admission, emergency department visit, home service use etc.), disability, physical function, cognition, perceived health, satisfaction, medication, depression, quality of life and mortality.[113, 116, 117] Contrary to the high expectation, only a small number of studies demonstrated that integrated care is effective for frail older people compared with normal care, while a majority showed no clear benefits on patient satisfaction, depressive symptoms, health-related quality of life, physical function or healthcare utilisation.[113, 116, 117] Only two integrated care trials had a

primary outcome of reversing frailty, both of which improved frailty status as described below.[119]

The Frailty Intervention Trial (FIT) was a 12-month prospective assessor-blind randomised controlled multifactorial interdisciplinary interventional trial, with 216 Australian older people with frailty defined by the phenotype criteria.[120] The intervention was tailored to the participants depending on which of the five frailty phenotype criteria they met at baseline: (1) for weight loss, clinical evaluation of nutritional intake at home, followed by recommendation of home delivered meals and high every high protein nutritional supplementation if necessary, (2) for exhaustion, referral to a psychiatrist or psychologist, and greater social engagement encouraged if socially isolated, (3) for weakness, slow gait or low physical activity, physiotherapist-led home-based physiotherapy sessions and home exercise programme. Multidisciplinary delivery of these intervention components was facilitated by case management and weekly case conferences.[120] This intervention successfully decreased prevalence of frailty (between-group difference in frailty 14.7%, p=0.02).[119] Although this programme was resource intensive and costly, employing multiple interdisciplinary interventions, it was shown to be cost-effective.[121] The unique features of this intervention are that all the participants were frail defined by the phenotype criteria and that each of the present phenotype criteria components was addressed by appropriate measures,[119, 120] which may have led to the significant effects against frailty.

Another randomised controlled trial study examined the effects of comprehensive geriatric assessment and subsequent integrated care, including medication adjustment, exercise instruction, nutrition support, physical rehabilitation, social worker consultation and specialty referral, in 310 community-dwelling Taiwanese people aged 65 years or older who were pre-frail or frail based on the frailty phenotype criteria.[122] In the intervention group, 3.9% became robust and the percentage of frailty remained almost the same (from 17.1% to 17.8%) at 6-month follow-up, while 2.1% became robust and more participants were frail (from 19.6% to 24.3%) at 6-month follow-up in the control group.[122]

Similar features of these two successful integrated care intervention studies were (1) pre-frail or frail older people were recruited, excluding the robust, (2) exercise and nutritional components were included, (3) frailty was defined by the frailty phenotype, which mainly focuses physical aspects and (4) the degree of frailty status improvement was somewhat smaller than that of multicomponent exercise interventions. Although the exercise interventions used by these two studies (physiotherapy and home exercise,[120] exercise instruction and physical rehabilitation.[122]) seem less intensive than multicomponent exercise interventions, it is possible exercise was the main driver of the intervention, not the integrated care per se, which may explain the smaller improvement. However, the physically oriented frailty phenotype criteria used by the two studies possibly could not fully evaluate the effect of integrated care models and detect multidimensional frailty changes. Taking these into account, the potentials of the integrated care model should be examined by well-designed intervention studies. These multicomponent integrated care models did not include lifestyle interventions, such as smoking cessation, alcohol reduction or dietary optimization. How smoking and alcohol consumption are associated with frailty risk among community-dwelling older people will be examined using ELSA sample in **Chapters 3 and 4**, respectively.

1.5.4 Future Directions

Frailty will most likely continue to attract scientific attention and will become more and more important to public health. However there are still some challenges hampering further progress in frailty research and its public health implementation.

First of all, gold standard criteria to define frailty are currently lacking. This affects all aspects and process of translation from frailty research into practice. It may be why a significant number of published papers used “frailty” or “frail older adults” in their titles, but they were vague in defining frailty or used non-valid frailty definitions. The absence of standard criteria means that it remains difficult to identify frail individuals, to be followed by prompt management decisions or interventions. For the same reason, feasibility or necessity of frailty screening cannot be assessed properly, although some experts recommend

frailty screening for selected at-risk subgroups of older people, such as those aged 80 years or older with subjective fatigue,[50] those with some risk factors (living alone, memory complaints, history of falls, weight loss, low walking speed or sensory dysfunction),[50] those aged 70 years or older[102] or those with significant weight loss (5% or more over the past year) due to chronic illnesses.[102] In a UK consensus best practice guidance published in 2014 for the management of frailty in community and outpatient settings, “Fit for Frailty” produced by the British Geriatrics Society in association with Age UK and the Royal College of General Practitioners (available online at http://www.bgs.org.uk/campaigns/fff/fff_full.pdf and http://www.bgs.org.uk/campaigns/fff/fff2_full.pdf), population-level screening for frailty was not recommended since it would be expensive and would not result in better outcomes or be cost-effective with frailty instruments available at that time.[123] However later on the eFI was developed in the UK and published in 2016.[52] This index is automatically populated from routinely collected data stored in the existing GP primary care electronic health record.[52] The eFI can quantitatively assess risk of frailty and predict negative health outcomes, such as mortality, hospitalization and nursing home admission.[52] In 2017 NHS England started to require GPs to identify patients aged 65 years or older with moderate and severe frailty using validated frailty instruments including eFI For initial population screening, supplemented by more detailed assessment in high risk groups (moderate and severe frailty) on the eFI. The eFI is now freely available at most of GP practices.[124, 125] This is probably the first attempt of nation-wide population-based frailty risk stratification and healthcare system utilisation.[126]

Second, although various interventions have been developed and evaluated for their effectiveness among frail older people as discussed above, it is still unclear what the optimal frailty intervention is, due to a great heterogeneity among the studies regarding intervention (for example, frequency, intensity and duration if exercise intervention) as well as sample size, population, setting, frailty status, frailty definition use and outcome. Based on the currently available literature, it appears that physical exercise, especially multicomponent exercise intervention including resistance training, has the strongest evidence as a single intervention component for frail older people.[127] Additive benefits may be

expected by the multi-domain interdisciplinary interventions, such as nutritional supplementation, cognitive intervention and/or integrated care, but the evidence base for these is mixed.

Lastly, it is not known when the best time to initiate frailty interventions is. For example, frailty interventions may be most effective if initiated proactively while the individuals are still non-frail, or should be started on patients who are found to be pre-frail or frail at screening. The interventions may have to be tailored according to patients' frailty status as well as health status and abilities. If these concerns are addressed in the future research, widespread application of public health approaches would be possible and may result in better care and healthier ageing for older people.

1.6 Modifiable Lifestyle Risk Factors of Frailty

Reflecting the urgent need to develop effective interventions against frailty given ongoing global-scale population ageing, numerous interventional studies have been conducted targeting frail older people as discussed above. Some models or intervention components seem promising but still the majority of the intervention studies, except for the multicomponent exercise intervention, yield small or no significant effects. Given limited evidence on what the best interventions or treatments are against frailty and the fact the natural course of frailty transition is mostly progression to worse frailty status rather than improvement,[35] addressing risk factors of frailty may be a plausible approach to proactively prevent frailty.[128]

Previous observational studies have revealed a number of factors have been revealed to be associated with risk of frailty. According to a mounting body of evidence, the factors associated with frailty in late life include (but are not limited to) advanced age, female gender, some ethnicity minorities (black, Hispanic), poor socioeconomic circumstances, less education, reduced cognitive function, comorbidities such as depression, diabetes, osteoarthritis, chronic lung diseases, stroke, fracture and cardiovascular diseases (CVD), low physical activity, low body mass index (BMI)/underweight, polypharmacy, poor quality of life, low self-rated health and poor neighbourhood characteristics

(such as lack of security, social cohesion or sense of belonging).[129-137] A systematic review published in 2017 of longitudinal studies searched for risk factors and protective factors associated with incident or increase of frailty among community-dwelling older people and found that advanced age, obesity, depressive symptoms and cognitive impairment were consistently shown by multiple studies to predict frailty, while the other factors predicted frailty in few studies or in not all studies.[138] It should be noted that the included studies used different definitions of frailty and methodological approaches and their results may have been biased.[138] While majority of the included studies (nine out of 23, 39%) were from the US, only one UK study was included in this review.[139]

There are fewer studies examining mid-life factors associated with elevated frailty risk in later life. One study from Australia of 5,462 middle-aged women showed that high or increasing patterns of sedentary time were significantly associated with higher risk of frailty defined by FRAIL scale in older age.[140] Studies using two Finnish cohorts, the Helsinki Businessmen Study and Mini-Finland Health Examination Survey, showed that lower self-rated health, lower leisure-time physical activity, overweight (BMI 25-30), obese (BMI>=30) and a higher composite risk score for coronary artery disease that takes into account age, systolic blood pressure, cholesterol, high alcohol consumption (>196g of alcohol/week), but not being abstinent, compared with light consumption (1-98g of alcohol/week), smoking and BMI in mid-life significantly predicted frailty risk defined by CHS criteria in old age.[141-145] In a UK study using the Whitehall II cohort, consisting of 6,233 British civil servants, mid-life predictors of frailty defined by the CHS criteria in late life were abstinence or high consumption of alcohol, current smoking, low daily fruit and vegetable consumption, moderate or no physical activity, low lung function measured by Forced Expiratory Volume, overweight/obese, depressive symptoms, hypertension and CVD, low HDL cholesterol, low ratio of total to HDL cholesterol and high concentrations of interleukin-6 and C-reactive protein (CRP).[146]

Many of these mid-life and late life frailty risk factors are known as well-established risk factors for CVD and dementia as well. Traditional cardiovascular risk factors that also increase frailty risk are advanced age, hypertension, diabetes, smoking, high alcohol use, overweight/obesity, low

physical activity, ethnicity and poor quality diet.[147] According to the summary report of the Alzheimer's Association in 2014, strong or moderate risk factors of dementia that are common with frailty risk factors include advanced age, current smoking, diabetes, low education and low physical activity in late life and obesity and hypertension in mid-life.

Although information on the characteristics of these frailty risk factors and their relationships is important fundamental groundwork for future frailty research and public health policy making, not all of these risk factors are modifiable or amendable. However lifestyle factors, such as smoking, alcohol use, exercise or diet, can be theoretically modified, started or stopped even in old age. There is a wealth of evidence on the links between exercise and frailty,[127] but far less is known on smoking, alcohol and diet.

Tobacco is the leading cause of preventable death in the world and kills more than 7 million people each year.[148] In England the prevalence of smoking has been gradually decreasing, however 15.1% of adults aged 18 or older are still smoking.[149] As people age the smoking prevalence decreases and 8.1% of older people ≥65 years smoked in 2017.[149] Generally alcohol consumption decreases with age and the proportion of non-drinkers increases.[150, 151] Compared with younger populations, those who are 65 years and older tend to drink less amount of alcohol and less frequently, and are less likely to have high risk drinking behaviours.[150, 151] However, in surveys many older people aged 65 years and older self-report drinking in the last week in the UK: approximately 60% of men and 40% of women aged 65 and older, according to the General Lifestyle Survey between 2005 and 2011.[152] Diet quality of adults (18-75 years) in the UK was moderate to relatively high compared with other EU countries, depending on diet quality scores used,[153] and another study showed that a diet quality score increases as people age in the UK. However, malnutrition is common in over 10% of older people aged 65 or over, due to various causes including underlying diseases, loss of appetite, decreased mobility and social factors.[154]

If modifying smoking, alcohol an diet eventually lead to decreasing risk of developing frailty or mitigating its progression, they are a good target of

interventions.[155] This could easily be translated into clinical practice for better care for older people or incorporated into a multidisciplinary intervention as one of the interventional components,[155] or could be targeted by educational programmes, campaigns or consultation services.[156]

1.7 Research Objectives

Rationale: In terms of frailty prevention or intervention, exercise, supplementation of protein or calorie or integrated care models have been studies in clinical trials and have already contributed to the evidence base of frailty research (see above).[157] However, other potentially modifiable factors, such as smoking, alcohol and fruit and vegetable consumption, were relatively under-studied and their potential for reducing the risk of frailty is not yet established. Therefore, in this thesis I have decided to focus on these three modifiable lifestyle factors for frailty.

The aims of this thesis are to examine associations between the potential modifiable lifestyle risk factors and subsequent changes in frailty status among community-dwelling older people using the data from ELSA. The specific research objectives are:

1. To systematically review the existing evidence on modifiable risk factors for frailty in three key areas: i) smoking, ii) alcohol consumption and iii) fruit and vegetable consumption, and to conduct a meta-analysis if possible.

2. To determine if i) smoking, ii) alcohol consumption and iii) fruit and vegetable consumption predict frailty status changes in community-dwelling older people in the UK, independent of important confounders.

2 METHODS

2.1 Introduction

This thesis consists of systematic reviews and epidemiological analyses for each of three modifiable lifestyle factors (alcohol, smoking and fruit and vegetable consumption) as potential predictors of incident frailty. ELSA is a longitudinal panel study of community-dwelling middle-aged and older people in England, and was used for the epidemiological analyses.

In this chapter I describe the overarching methods employed in my three main analyses, including details of ELSA from which I drew study samples, the definitions of the key measurements, statistical approaches to analysis and handling issues such as missing data and attrition. More detailed information regarding the analytical samples, including the number of participants, how they were included or the reasons why they were excluded, will be presented in each chapter since it was different for the three main analyses. The methods of systematic reviews and meta-analysis will be described later in each respective chapter.

2.2 English Longitudinal Study of Ageing (ELSA)

2.2.1 Description of the Cohort

ELSA is a multi-centre longitudinal panel study of a nationally representative cohort consisting of community-dwelling men and women aged 50 years and older in England.[158] ELSA was launched in 2002/2003 and designed to investigate a broad range of research areas relevant to understanding the ageing process.[158] The topics covered include physical and mental health, cognitive function, social and economic circumstances, social relationships and relationships between these factors.[158] The initial participants of ELSA were recruited from private households that participated in the Health Survey for England (HSE) in 1998, 1999 and 2001 (=wave 0). HSE is an annual cross-sectional survey to collect detailed information on mental and physical health, health-related behaviour, and objective physical and biological measures in relation to sociodemographic characteristics of people aged 16 years and older (the lower age limit was removed later) at private residential addresses.[159] In

HSE the sample was drawn by postcode sector and stratified by proportion of households headed by someone in a non-manual occupation in the last census.

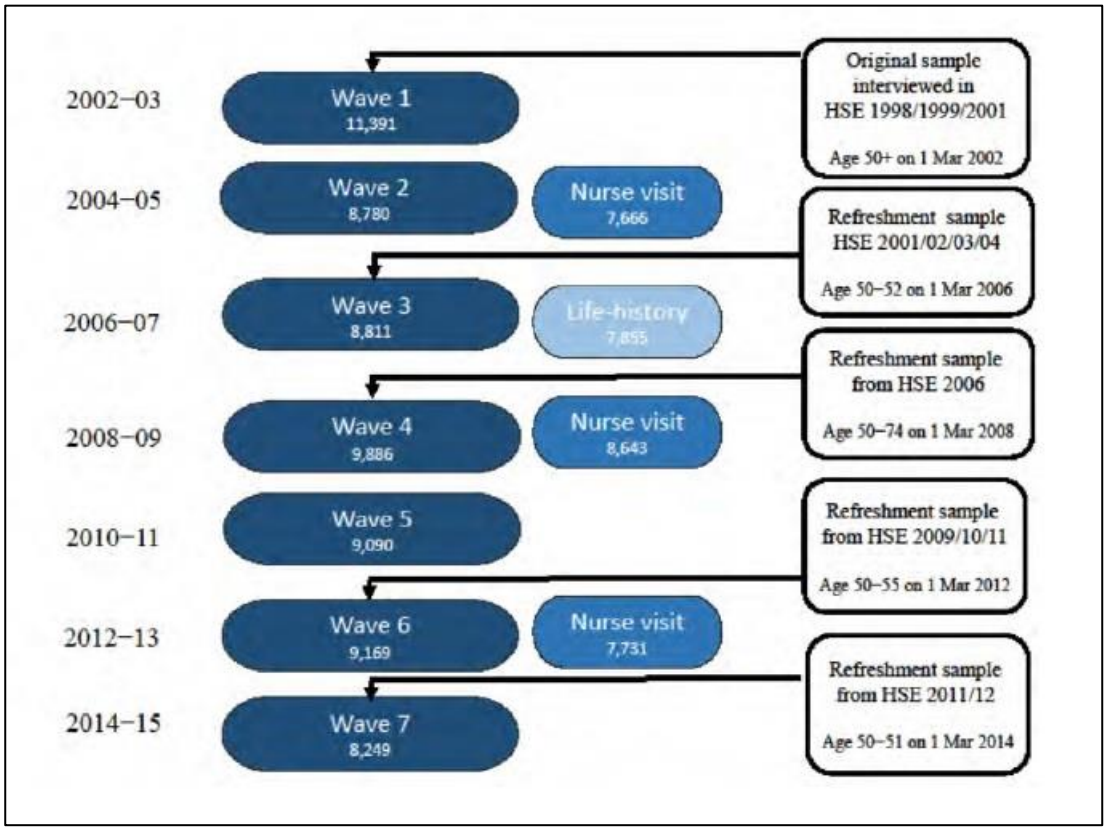
Criteria for eligibility for ELSA were membership of a participating household from HSE in which at least one individual had agreed to be re-contacted in the future, born before 1 March 1952 and living in a private household in England at the time of wave 1 fieldwork. In addition to the target individuals, their partners who were aged less than 50 years and those who had joined the household since HSE were also invited for interview. The initial sample size was chosen to have an adequate number of men and women in 5-year age bands.

The total sample at wave 1 consisted of 11,391 core members, 636 partners aged less than 50 years and 72 new partners aged 50 year or older. The household response rates of households and individuals were 70% and 67%, respectively. ELSA included mostly white British individuals and underrepresented black and minority ethnic populations.[158] The socio-demographic characteristics of the ELSA participants were compared with the results from the national census, and it was found that the sample was broadly representative of the English population aged 50 and over.[158]

Core members have remained eligible for ELSA interview over the waves as long as they have not died or moved out of Great Britain or moved into an institution within Great Britain from their original residential address. New participants have been recruited as refreshment samples from HSE in order to maintain the cohort size and representativeness at waves 3, 4, 6 and 7, in 2006, 2008, 2012 and 2014, respectively. The refreshment samples at waves 3, 4, 6 and 7 were aged 50-52 years recruited from HSE in 2001, 2002, 2003 and 2004, aged 50-74 years recruited from HSE 2006, aged 50-55 years recruited from HSE 2009, 2010 and 2011, aged 50-51 recruited from HSE 2011 and 2012, respectively. The number of core member participants at each wave was shown in **Figure 2.1**. The wave 8 data have recently been published, however, they were not available when this thesis was started and therefore were not used for this thesis. Core members from wave 1 were used for smoking and alcohol analyses while core members and refreshment sample at wave 4 were

used for fruit and vegetable consumption analysis. The details of the analytical samples will be described in each chapter.

Figure 2. 1. Timeline showing the number of core member participants at each wave in the English Longitudinal Study of Ageing.



Derived from the English Longitudinal Study of Ageing wave 7 report, available at https://www.ifs.org.uk/uploads/elsa/docs_w7/ELSA%20Wave%207%20report.pdf

2.2.2 Follow-Up

The cohort has been followed up every two years. To minimise sample attrition it attempted to track participants who had changed their address between waves. If participant had consented to be re-contacted in the future waves, interviewers attempted either to telephone the participant, find a follow-up address, approach the present occupant, neighbours or friends to obtain the new address or consider phone books, the electoral register, local shops, letting agencies, estate agents or the post office. From wave 3, interviewers also attempted to approach the person(s) living at the ‘stable address’ provided by the participant previously. At wave 3 the Department of Work and Pensions assisted with tracing core members using their state pension databases. At

waves 3-6 the National Health Service Central Register was also used for the tracing.[160]

Attrition is a common issue for most panel studies and can potentially cause a bias due to individuals dropping out of the study non-randomly over time.[161] In ELSA those lost to follow-up were more likely to be older, less wealthy, less educated, in a non-managerial occupation and with a limiting long-standing illness than those who stayed in the study.[158] **Table 2.1** shows the fieldwork response rates from waves 1 to 6. In order to reduce any bias caused by attrition, weighting was used in all logistic regression models. Please see **Chapter 2.8.2 Weighting** for detail.

Table 2. 1. ELSA Fieldwork response rates by wave

Type of field response rate		Response rates					
		Wave 1	Wave 2	Wave 3	Wave 4	Wave 5	Wave 6
		%	%	%	%	%	%
Household contact rate	Cohort 1	95	97	97	97	97	98
	Cohort 3	N/A	N/A	83	97	94	97
	Cohort 4	N/A	N/A	N/A	92	98	98
	Cohort 6	N/A	N/A	N/A	N/A	N/A	89
Fieldwork cooperation rate	Cohort 1	70	84	83	77	80	86
	Cohort 3	N/A	N/A	74	81	81	84
	Cohort 4	N/A	N/A	N/A	69	87	85
	Cohort 6	N/A	N/A	N/A	N/A	N/A	62

2.2.3 Measurements

Although it was overall intended to collect data on the same topics at each wave in ELSA, there were inconsistencies between certain waves. At some waves additional data were collected to respond to new areas of enquiry, or at certain waves questions were omitted as it was considered not necessary to ask them at every wave. In addition, some questions or questionnaires were amended to take account of responses provided at the previous waves. Many of the questionnaires used in ELSA have been designed to be comparable with those

used in the Health Retirement Study (HRS) in the US and the Survey of Health, Ageing and Retirement in Europe (SHARE).[160]

2.2.3.1 Interview questionnaire

All participants were asked to have a personal face-to-face computer-assisted personal interview (CAPI) and to complete a self-completion questionnaire at all waves (the main interview). The interviews were generally started in February or March of the designated year and completed in January or February the following year. A participant was interviewed individually in their home. If there were more than one eligible participant a concurrent interview was offered. A proxy interview was conducted if an eligible participant was physically or cognitively impaired, hospitalised or temporarily in care for the whole of the fieldwork period. Those who refused to participate in person but agreed that someone else could take the interview on their behalf were eligible for a proxy interview with a responsible adult aged 16 years or older who knew enough about the participant's circumstances to be able to provide information about them.

The face-to-face interviews were based on a structured questionnaire on individual and household demographics, health (including self-reported general health, longstanding illness or disability, specific diagnoses and symptoms, pain and ADL), health behaviours (including smoking, alcohol use and physical activity), social participation, work and pensions, income and assets, housing, expectations of the future, psychosocial health (including **depressed mood**), cognitive function (including memory, speed, mental flexibility and numeracy), final questions and consents. Data provided at previous waves were fed forward to aid recall and improve consistency of responses across interviews. **Gait speed** was measured by timed walking test only for those aged 60 years or older as a part of the interview at any time after the Health module. Five 'private modules': Cognitive function, Expectations, Effort and Reward, Psychosocial health and Final questions, were conducted without the presence of other household members wherever possible. **Table 2.2** summarises the main interview questionnaire modules.

Table 2. 2. Main interview questionnaire modules (from User Guide to the Main Interview Datasets Waves 1 to 8).

Code	Module	Description
HD	Household demographics	Basic demographic information on all in the household.
ID	Individual Demographics	Legal marital status, living children (including adopted, fostered or stepchildren), grandchildren and great-grandchildren, number of siblings, childhood circumstances, information on parents.
HE	Health	Self-reported general health, long-standing illness or disability, eye sight and hearing, specific diagnoses and symptoms, pain, difficulties with activities and instruments of daily living, health behaviours. Falls and fractures for those aged 60 or older. Receipt of and payment for social care from wave 6.
SP	Social participation	Public transport, use of services, such as transport provided by hospitals or day centres and meals on wheels.
WP	Work and pensions	Current work activities, current or past pensions. Details of pension if retired and receiving a pension.
IA	Income and assets	Wages, state and private pensions, annuity income, state benefits, financial and non-financial assets, income from these assets, regular and one-off transfers from non-household members and life insurance.
HO	Housing	Current housing situation, housing-related expenses, ownership of durables, cars and pets, expenditure on food, clothes, gifts and leisure activities.
CF	Cognitive function	Cognitive function.
EX	Expectation	Expectations about certainty of future events and financial decision-making.
ER	Effort and reward	Motivations for voluntary work, caring for others, relationship between effort and reward and provision of care and use of respite care services.
PS	Psychosocial health	Views on their life across a variety of dimensions.
FQ	Final questions and consents	Demographic information and stable address contact, consent for nurse visit at waves 2, 4, 6 and 8, verbal reminder of data linkage consent if already given, otherwise asked for consent to obtain health and economic data from administrative sources.
MM	Measurement Modules	Walking speed for those aged 60 years or older, weight for those aged 51 years or older at wave 8 only.
SC	Self-completion questionnaire	Quality of life, social participation, control at work, life satisfaction, social networks, alcohol, fruit and vegetable consumption and wellbeing. Work and health questionnaires with vignettes at wave 3. Sexual activity at waves 6 and 8.

2.2.3.2 Self-completion questionnaire

After the face-to-face interview, a self-completion questionnaire paper was provided to a participant. The questionnaire was designed to collect data on social circumstances (including participation, network and relationships), wellbeing, quality of life, life satisfaction and consumption of **alcohol**, **fruit and vegetables.** The questionnaire was completed and returned to the interviewer on the day of the interview or later by post.

2.2.3.3 Nurse visit

A participant who completed the main interview in waves 2, 4, 6 and 8 were invited to have a follow-up visit by a qualified nurse.[162] The nurse visit collected physical examination and performance data and also collected biological samples for analysis. Additional consent was obtained from a participant who underwent the nurse visit. A participant who had the nurse visit had been informed in advance about the examinations and asked not to eat, smoke, drink alcohol or do any vigorous exercise during 30 minutes before the nurse visit.

The physical examinations included standing and sitting height, **weight**, waist and hip measurement, blood pressure, lung function, drug coding, balance, leg raise, chair rise and **grip strength**. The grip strength measure was taken from SHARE. For biological examinations blood (waves 2, 4, 6 and 8), saliva (waves 2 and 4) and hair sample (wave 6) were obtained.

All participants who gave consent were eligible for blood sampling except for those with clotting or bleeding disorders, a history of fits or convulsions or consumption of anticoagulant drugs, such as warfarin, protamine or acenocoumarol or pregnant.[158, 163] In addition, participants under 80 years old were asked to fast before the nurse visit for at least 5 hours before the blood test so that a fasting blood sample could be obtained. Participants who were expected to be fasting for the blood collection were asked not to eat or drink anything apart from water on that day if the nurse visit was before 1pm, were told that they were allowed to have a light breakfast before 8am but not to eat or drink anything apart from water after 1pm if the nurse visit was between 1pm

and 6pm and were told that they were allowed to have a usual breakfast and a light lunch before 1pm but not to eat or drink anything apart from water after 1pm if the nurse visit was after 6pm.[163] Participants were not eligible to fast if they were aged 80 or over, diabetic and on treatment malnourished or unfit to fast in nurse's judgement.[163] The blood tests results used as a covariate in this thesis were CRP and fibrinogen. Blood pressure, blood test results and lung function were shared with their general practitioners. Blood tests that were done at one wave or more included total and high-density lipoprotein cholesterol, low density lipoprotein cholesterol, CRP, fibrinogen, haemoglobin, ferritin, white blood cell count, mean corpuscular haemoglobin, fasting lipids, glucose, glycated haemoglobin, immunoglobulin E, insulin-like growth factor 1, dehydroepiandrosterone and vitamin D.

2.2.3.4 Life history questionnaire (wave 3)

A subset of ELSA participants was invited to complete 'Life History' interview, which was to collect retrospective information on a range of areas regarding their whole life including important events that have occurred in their lives and what their childhood was like. The collected data included were regarding children, fertility, cohabiting and important non-cohabiting relationships, housing and geographical mobility, living situation when participants were 10 years old, jobs and earnings, health including injuries, childhood health, smoking (including **year first smoked or frequency of smoking**) and gynaecological history, relationship with parents when they were a child and other important and difficult events in their lives.

2.2.4 Ethical Approval and Funding

Ethical approval for all the ELSA waves was obtained from NHS Research Ethics Committees under the National Research and Ethics Service (NRES), and informed consent was obtained from all participants.[160] ELSA has been funded by the National Institute of Aging in the United States and a consortium of UK government departments, including Department of Health, Department of Transport, Department for Work and Pensions, Communities and Local Government (formerly Office of the Deputy Prime Minister), HM Treasury,

Department of Environment, Food and Rural Affairs, HMRC (formerly Inland Revenue and HM Customs and Excise and Office for National Statistics.[160] The data are available through the UK Data Service (https://www.ukdataservice.ac.uk/).

Analytical sample

In this thesis, for smoking and alcohol analyses baseline was wave 2 and follow-up was wave 4, and the analytical samples were those who had been participating since wave 1. For fruit and vegetable consumption analysis baseline was wave 4 and follow-up was wave 6 because data on fruit and vegetable consumption were available from wave 3 onwards, and the analytical sample was those who had been participating since wave 1 and those who participated since wave 4 as a refreshment sample from HSE 2006. There was another refreshment sample (aged 50-52 in 2006) at wave 3, however, they could not be included in analysis because they were younger than 60 years old at the time of wave 4 thus not eligible for nurse visit.

2.3 Definition of Frailty

In this thesis, frailty is defined using the CHS criteria,[16] which were described in detail in the previous **Chapter 1.3 Frailty measurements**. Among data necessary to define the frailty status, data on weight, height and handgrip strength were measured only during nurse visits, which took place every other wave from wave 2. Therefore, the frailty phenotype was able to be composed only at wave 2, 4 and 6. In this thesis, the five components are slightly modified according availability of the data and are described below. Using these five criteria, an individual who met 0, 1-2 and 3-5 criteria was classified as robust, pre-frail and frail, respectively.[16]

2.3.1 Weight loss or ‘shrinking’

Anthropometric measures including height and weight were measured during the nurse visit. Height and weight were measured while a participant was standing, and were not measured the participant was chair-bound, too unsteady on their feet or found standing painful. When measuring height a participant was

asked to remove their shoes. A portable stadiometer with a sliding head plate, a base plate and four connecting rods marked with a measuring scale was used to measure height, which was recorded in centimetres and millimetre units (0.1cm). When measuring weight a participant was asked to remove their shoes, heavy outer garments such as jackets and cardigans, heavy jewellery, loose change and keys. Weight was measured using a Soehnle scale at wave 0, a Tanita THD-305 scale at waves 2 and 4, a Soehnle scale, Seca 850, Seca 870 or Tanita THD-305 at HSE 2006 and a calibrated Tanita Body Fat Scale at wave 6, and recorded in kilograms and 100 gram units (0.1kg). BMI was calculated the body weight in kilograms divided by the square of the height in meters.

For smoking and alcohol analyses, weight loss at wave 2 (baseline) was defined as loss of 5% or more of body weight since wave 0 or BMI of less than 18.5 kg/m^2, and weight loss at wave 4 (follow-up) was defined as loss of 5% or more of body weight since wave 2 or BMI of less than 18.5 kg/m^2. For fruit and vegetable analysis, weight loss at wave 4 (baseline) was defined as loss of 5% or more of body weight since wave 2 or BMI of less than 18.5 kg/m^2 for those who had been involved since wave 1, and loss of 5% or more of body weight since HSE 2006 or BMI of less than 18.5 kg/m^2 for those who were newly recruited at wave 4 as a refreshment sample from HSE, and weight loss at wave 6 (follow-up) was defined as loss of 5% or more of body weight since wave 4 or BMI of less than 18.5 kg/m^2 for both those who had been participating since wave 1 and those who were newly recruited from HSE 2006.

2.3.2 Self-reported exhaustion

During the main interview using CAPI at waves 2, 4 and 6, depressed mood during the last week was measured using the 8-item Center for Epidemiologic Studies Depression Scale (CES-D).[164] A participant was asked to answer ‘yes’ if the sentences were true ‘much of the time in the past week’ and ‘no’ if the sentences were not true ‘much of the time in the past week’. Exhaustion was defined based on responses to two questions, ‘you felt everything you did was an effort?’ and ‘you could not get going?’. Exhaustion was considered to be present if the participant responded ‘yes’ to one or both of the questions.

2.3.3 Weakness

Grip strength was measured during nurse visit at waves 2, 4 and 6. Those with swelling or inflammation, severe pain or recent injury and those with surgery to the hand in the last six months were excluded. If there was a problem with one of the participant's hands, grip strength was measured on the other hand only. Grip strength measurement procedure was explained and demonstrated and a participant was allowed to have a practice with one hand. A participant was asked to remove large rings. Grip strength was measured preferably while standing but if not possible while sitting in an upright chair. After adjusting the lever of the gripometer (Smedley's dynamo meter) and positioning, a participant was asked to squeeze as hard as they could for a couple of seconds. The measurement was done up to three times for each hand, with the non-dominant hand first and alternating between hands. The value on the scale to the nearest whole number was recorded. The highest value of the six measurements was used to define weakness.

The sample was initially divided into female and male groups then further divided into four groups each by BMI quartiles. Weakness was defined having the grip strength values in the lowest 20% in each of the eight groups. Grip strength has been shown to be a reliable measure for upper body strength[165] and validated against ADL, IADL and functional abilities.[166]

2.3.4 Slow walking speed

Gait speed was measured by interviewers during the personal interview at waves 2, 4 and 6. All participants who underwent the main interview and were aged 60 or older were eligible. Those who had any problems from recent surgery, injury or other health conditions that might prevent them from walking were excluded. If the participant was wearing slippers or high-heeled shoes or was not wearing shoes, they were asked to change into a pair of low-heeled shoes or trainers.

Time walk was conducted by measuring the time taken by a participant to walk a distance of 8 feet (244cm) at their usual pace on a floor that is level, not carpeted and not slippery. Any walking aids, such as a stick or Zimmer frame, used were allowed and recorded, but the participant should not rely on the support of another person. After demonstration by the interviewer the time was measured using a stopwatch and recorded in hundredths of a second. The participant was asked to walk the course twice. Criteria for an acceptable test were (i) the participant began with both feet together at the beginning of the course, (ii) timing was started when either food was placed down on the floor across the start line, (iii) the participant walked and did not race, (iv) the participant walked all the way past the end of the tape ruler and (v) the interviewer stopped timing when either foot was placed down on the floor across the finish line. Gait speed used for the frailty phenotype was based on the mean of the time taken for the two trials, or the time if one measurement was available.

The sample was divided into female and male groups, and then further divided into two groups each at the gender-specific height median, creating a total of four groups. Those who were in the lowest 20% of gait speed distribution in each of the four groups were defined as having slow walking speed. Those who were in a wheelchair, who were bedbound or unable to walk without assistance were also considered to have slow walking speed. Gait speed at usual pace has been shown to have acceptable reliability and validity for estimating physical function in older people.[167, 168]

2.3.5 Low physical activity

Information about physical activity in daily life was collected during the main interview at waves 2, 4 and 6. A participant was asked about frequency for each of three different levels of sport and activity participation: vigorous, moderate and mild. Four options for the frequency were ‘more than once a week’, ‘once a week’, ‘one to three times a month’ and ‘hardly ever, or never’. The questions were derived from a validated physical activity interview employed in HSE.[169] Physical activity was ranked based on a combination of the intensity and frequency of daily life physical activity. A participant who hardly ever or never

engaged in vigorous, moderate and mild activity was classified as sedentary. Engaging in mild activity one to three times a month, once a week or more than once a week, or engaging in moderate activity one to three times a month was classified as low activity. Engaging in moderate activity once a week or more than once a week or vigorous activity one to three times a month was classified as moderate activity. Engaging in vigorous activity once a week or more than once a week was classified as high activity. Low activity for the frailty phenotype criterion was defined as being sedentary or low activity. This physical activity scoring has been validated against muscle strength, inflammatory markers and depressive symptoms in older people.[170, 171]

Individual components of the modified CHS criteria at ELSA wave 2 were compared with ones of the original CHS criteria in **Table 2.3**.

Table 2. 3. Comparison of five components from the modified Cardiovascular Health Study criteria at wave 2 and the original criteria.

Component	Original version by Fried and colleagues	Modified version at wave 2
1. Weight Loss or shrinking	Answering YES to "In the last year, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?" or more than 5% of unintentional weight loss since last year.	Loss of 5% or more of body weight since wave 0 or BMI of less than 18.5 kg/m^2.
2. Exhaustion	Reporting "a moderate amount of the time (3–4 days)" or "most of the time" in the last week to either of two questions from the Center for Epidemiological Studies-Depression Scale: "I felt that everything I did was an effort" or "I could not get going".	Answering YES to either of two questions from Center for Epidemiological Studies-Depression Scale: "(Much of the time during the past week), you felt that everything you did was an effort?" or "(Much of the time during the past week), you could not get going?".
3. Weakness	Lowest 20% of handgrip strength stratified by gender and BMI quartiles (Cutoff for men: ≤29kg for BMI≤ 24, ≤30kg for BMI 24.1-26, ≤30kg for BMI 26.1-28, ≤32kg for BMI>28, For women: ≤17kg for BMI≤23, ≤17.3kg for BMI 23.1-26, ≤18kg for BMI 26.1-29, ≤21kg for BMI>29)	Lowest 20% of handgrip strength stratified by gender and BMI quartiles (Cut-off for men: <29kg for BMI< 25.04, <31kg for BMI 25.04-27.20, <32kg for BMI 27.20-30.02, <32kg for BMI>30.02, For women: <17kg for BMI<24.19, <18kg for BMI 24.19-27.11, <18kg for BMI 27.11-30.94, <18kg for BMI>30.94)
4. Slowness	Slowest 20% of usual walk speed stratified by gender and medium height (Cutoff time to walk 15 feet for men: ≥7 seconds for height≤173 cm, ≥6 seconds for height>173 cm, For women: ≥7 seconds for height≤159 cm, ≥6 seconds for height>159 cm)	Slowest 20% of gait speed at usual pace stratified by gender and medium height (Cut-off time to walk 8 feet for men: >4.11 seconds for height<171.6 cm, >3.51 seconds for height>171.6 cm, For women: >4.90 seconds for height<158.4 cm, >3.81 seconds for height>158.4 cm)
5. Low Physical Activity	Lowest 20% kilocalorie based on the short version of the Minnesota Leisure Time Activity questionnaire stratified by gender (Cutoff for men: <383 Kcal per week, For women: <270 Kcal per week)	Sedentary or low activity based on intensity and frequency of physical activity in daily life involved.

2.4 Definition of Smoking

For the smoking analysis the baseline was wave 2 and follow-up was wave 4. Smoking status was classified based on two questions in the main interview into two groups: current smokers and non-smokers. A participant was first asked 'Have you ever smoked cigarettes?' Those who answered no to the first question were classified as non-smokers. If answered yes, they were further asked 'Do you smoke cigarettes at all nowadays?' Those who answered yes to the second question were classified as current smokers, and those answered no to the same question were classified as current non-smokers.

Self-reported smoking history has been shown to be reliable,[172, 173] and its validity has been described against biochemical measures, such as cotinine, nicotine, thiocyanate or carbon monoxide.[174] At ELSA wave 0, salivary cotinine level was measured and smoking status was measured using the same question 'Do you smoke cigarettes at all nowadays?'. Salivary cotinine level is considered to be one of gold standard measurements of smoking status and those with salivary cotinine levels of 15 ng/ml or more are considered to be current smokers as recommended by the Society for Nicotine and Tobacco Research.[175] Among 5376 core member participants who self-reported themselves as non-current smokers and had salivary cotinine levels measured at wave 0, only 229 (4.3%) had $\geq$15 ng/ml of salivary cotinine levels and more than 95% of them reported their smoking status accurately. The same question, 'Do you smoke cigarettes at all nowadays', has been used in the Annual Population Survey,[176] the Opinion and Lifestyle Survey[177] (formerly known as Office for National Statistics (ONS) Opinions Survey or ONS Omnibus Survey), the General Household Survey[178] and HSE.[159]

It was possible to classify three smoking groups: current smokers, past smokers and never smokers, using these two questions. However, if those who answered yes to the first question 'Have you ever smoked cigarettes?' and then answered no to the second question 'Do you smoke cigarettes at all nowadays?' would be classified past smokers, the number of the past smokers would be overestimated because a participant who had never smoked regularly but smoked just once in the past may be classified as a past smoker, although

they should be classified as a never smoker instead.[179] Thus the sample was divided into two groups; current smokers and current non-smokers. In a previous study, current smokers compared with non-smokers had a significantly higher risk of non-fatal myocardial infarction.[180]

However, past smokers may be a different group from never smokers in that they may carry higher risks of frailty than never smokers due to accumulated effects of smoking even after quitting. To take this matter into account, as a supplementary analysis, non-smokers were further divided into two groups: past smokers and never smokers, using data on when they quit smoking available from life history interview data at wave 3 (please see **Chapter 2.2.3.4 Life history questionnaire (wave 3)**). Those who were not smoking at wave 2 (non-smokers) and found to have quitted smoking before wave 2 based on the data from the life history interview at wave 3 were defined as past smokers, and the remainder of the non-smokers were defined as never smokers. The past smokers were further divided into another 2 groups: those who quit smoking within the last 10 years and those who quit smoking more than 10 years ago.

When smoking was used as a covariate for adjustment, a binary smoking status (current smokers and non-smokers) at baseline waves (wave 2 for alcohol consumption and wave 4 for fruit and vegetable consumption) was used.

2.5 Definitions of Alcohol Consumption

Alcohol consumption was described in three ways in this thesis as (1) quantity per week, (2) quantity on the heaviest drinking day and (3) frequency of alcohol use. As the average amount of alcohol consumption (quantity) has been a standard in alcohol epidemiology and has been associated with multiple disease conditions,[181] the (1) quantitative amount of alcohol consumption per week was used in the main analysis. Although (2) quantity of alcohol consumption on the heaviest drinking day and (3) frequency of alcohol use cannot accurately calculate the overall quantity of alcohol, the patterns of alcohol consumption are known to have impacts on health outcomes regardless of the total amount of alcohol consumed.[182-184] These measures were therefore used in supplementary analyses.

Binge drinking usually refers to drinking high amounts of alcohol in a short period of time or drinking to get drunk; UK researchers commonly define binge drinking as consuming 6 units of alcohol in a single session for men and women.[185] Binge drinking often occurs in young people at weekends and the acute consequences are traffic accidents, injuries, homicide, violence, suicide attempts, sexual assault, risky sexual behaviours or vandalism.[181, 186] Binge drinking also affects older people. A US study showed drinking as small as 3.5 UK units (=2 US units) or more on the heaviest day was significantly associated with alcohol-related problems, based on 12 items from the Drinking Problems Index,[187] among US community-dwelling older people aged 55 to 65 years.[188]

Frequency of alcohol consumption has been examined in previous studies, including ELSA studies.[163] The same questionnaire on frequency of alcohol consumption in ELSA has been used in other population-based studies, including HSE,[159] the UK Household Longitudinal Study,[189] the Cognitive Function and Ageing Studies and the Scottish Health Survey.[190] One US prospective study showed that those drinking 3 times a week had the lowest and those drinking daily had the highest mortality risks, even though the amount of alcohol per occasion was moderate at 1 to 2 drinks, in 90,000 community-dwelling population aged from 18 to 85 years (the National Health Interview Survey).[191]

2.5.1 Quantity of Alcohol Consumption Per Week

Data on alcohol consumption quantity per week were only available from wave 0. Quantity of alcohol consumption per week was calculated based on frequency over the last 12 months and usual quantity on any one day for different types of alcoholic beverage obtained from the main interview. Options for frequency were (i) almost every day, (ii) five or six days a week, (iii) three or four days a week, (iv) once or twice a week, (v) once or twice a month, (vi) once every couple of months, (vii) once or twice in last 12 months and (viii) never in last 12 months. The types of alcohol considered were normal strength beer, lager, stout, cider or shandy (less than 6% alcohol) excluding bottles\cans of shandy, strong beer, lager, stout, cider (6% alcohol or more, such as Tennants

Extra, Special Brew, Diamond White), spirits or liqueurs, such as gin, whisky, rum, brandy, vodka or cocktails, sherry or martini (including port, vermouth, cinzano or dubonnet), wine (including babycham and champagne) and alcoholic soft drinks or 'alcopops' (such as Hooch, Two Dogs or Alcola). Options for quantity consumed on any one day were; a combination of the number of pints, large cans or bottles or small cans or bottles for normal strength beer, lager, stout, cider or shandy and strong beer, lager, stout, cider; the number of glasses for spirits or liqueurs, sherry or martini and wine; and the number of small cans or bottles for alcoholic soft drinks or alcopops. For spirits or liqueurs and sherry or martini, the number of glasses were counted doubles as 2 singles. The amount of alcohol consumption from all the types was added and converted into the number of UK units (1 UK unit = 8g of pure alcohol). The cohort was divided into five groups: (i) 0 (non-drinkers), (ii) >0, <=7 units (low drinkers), (iii) >7, <=14 units (moderate drinkers), (iv) >14, <=21 units (high drinkers) and (v) >21 units (very high drinkers). The cut-points were decided according to the current UK alcohol guidelines that recommend that both men and women should not drink more than 14 units per week[192] and the fact that older people are generally more likely to be affected by alcohol than younger people.[193]

2.5.2 Quantity of Alcohol Consumption on the Heaviest Drinking Day of the Last Week

Quantity of alcohol consumption on the heaviest drinking day of the last week was calculated as a sum of consumption of different types of alcoholic beverages. On the self-completion questionnaire at wave 2, a participant was asked to select all types of alcoholic beverages and the amount consumed on the day in the last week on which the participant drank the most. The types of beverages were the same as **2.5.1 Quantity of alcohol consumption per week** above. The cohort was divided into five groups: (i) 0, (ii) >0, <=3 units, (iii) >3, <=6 units and (iv) >6 units. The cut-points were decided according to the first report of the Older Persons' Substance Misuse Working Group of the Royal College of Psychiatrists in the UK, which states that more than 3 units of alcohol per day for older men and women are associated with alcohol-related problems.[194]

2.5.3 Frequency of Alcohol Consumption

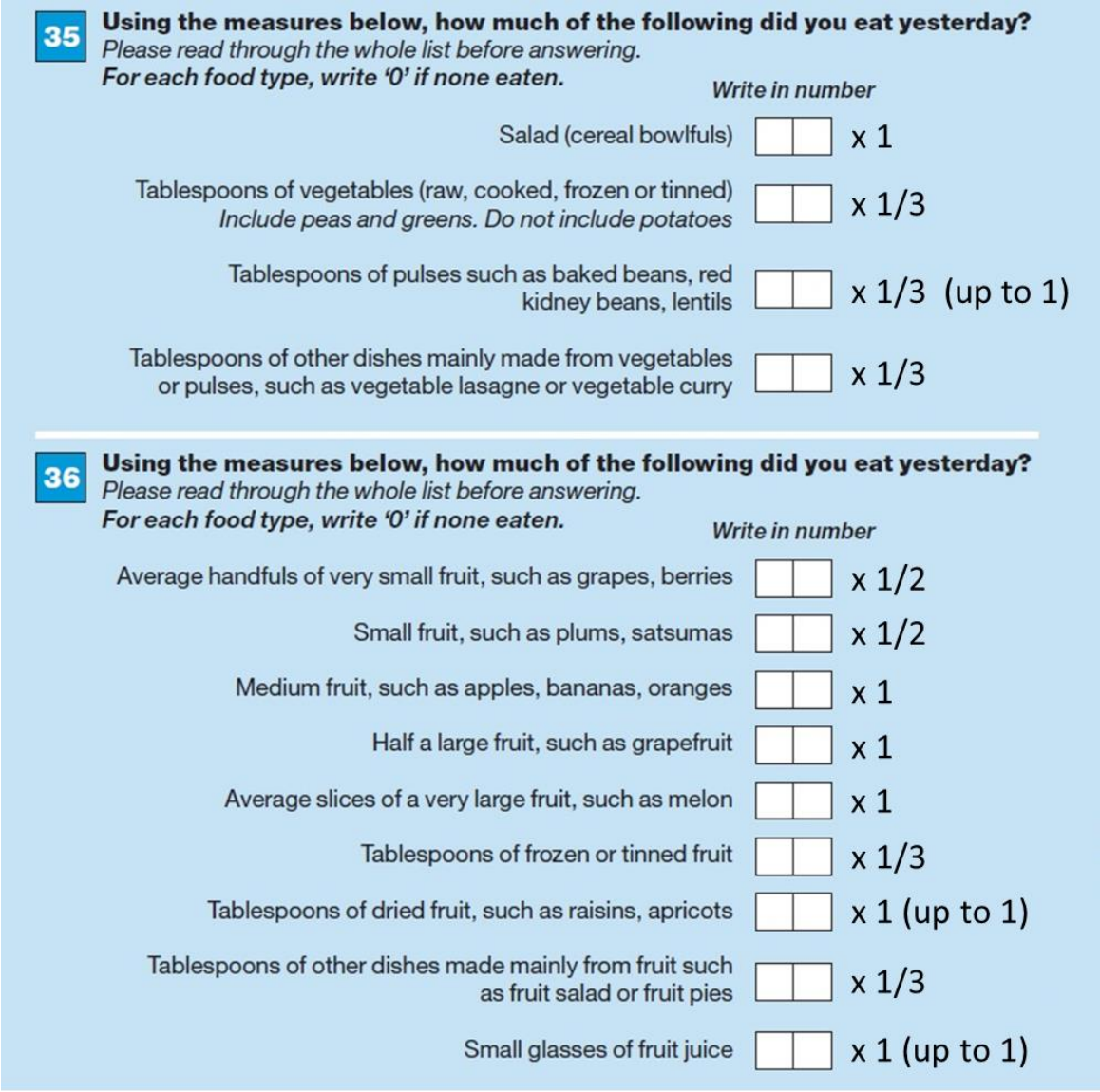
Frequency of alcohol consumption was measured at waves 2 and 4 by the self-completion questionnaire, in which a participant was asked to choose one of eight options regarding frequency of alcohol use during the last 12 months: (i) almost every day, (ii) five or six days a week, (iii) three or four days a week, (iv) once or twice a week, (v) once or twice a month, (vi) once every couple of months, (vii) once or twice a year and (viii) not at all in the last 12 months.[163] These responses were classified into four groups: (1) None (viii), (2) once a year to once every couple of months (vi, vii), (3) once a month to four times a week (iii, iv, v) and (4) five times a week or more (i, ii).

This categorical variable based on frequency of alcohol consumption was used for adjustment of alcohol consumption in smoking and fruit and vegetable consumption analyses as it was available at both of their baselines, waves 2 and 4, while quantity of alcohol consumption was not available at waves 2 and 4 and quantity of alcohol consumption on the heaviest day was not available at wave 4.

2.6 Definitions of Fruit and Vegetable Consumption

Consumption of fruit and vegetables was measured at wave 4 by a self-completion questionnaire (**Figure 2.2**), which was derived from the Welsh Health Survey.[195] The questionnaire asked the number of each kind of fruit and vegetables consumed on the previous day. The data of fruit and vegetable consumption were converted into portions in accordance with the NHS 5-A day campaign.[196] Conversion rates are available in **Figure 2.2.** For example, the number of ‘Salad (cereal bowlfuls)’ was multiplied by ‘1’ and the number of ‘Tablespoons of vegetables (raw, cooked, frozen or tinned)’ was multiplied by ‘1/3’. The portion of pulses, dried fruit and fruit juice was counted as 1 at most even if consuming more than 1 portion, according to the Welsh Health Survey.[195]

Figure 2. 2. Self-completion questionnaire for fruit and vegetable consumption at English Longitudinal Study of Ageing wave 4,[163] and conversion rates into portions.



35 **Using the measures below, how much of the following did you eat yesterday?**
Please read through the whole list before answering.
For each food type, write '0' if none eaten.

	Write in number	
Salad (cereal bowlfuls)	☐☐	x 1
Tablespoons of vegetables (raw, cooked, frozen or tinned) *Include peas and greens. Do not include potatoes*	☐☐	x 1/3
Tablespoons of pulses such as baked beans, red kidney beans, lentils	☐☐	x 1/3 (up to 1)
Tablespoons of other dishes mainly made from vegetables or pulses, such as vegetable lasagne or vegetable curry	☐☐	x 1/3

36 **Using the measures below, how much of the following did you eat yesterday?**
Please read through the whole list before answering.
For each food type, write '0' if none eaten.

	Write in number	
Average handfuls of very small fruit, such as grapes, berries	☐☐	x 1/2
Small fruit, such as plums, satsumas	☐☐	x 1/2
Medium fruit, such as apples, bananas, oranges	☐☐	x 1
Half a large fruit, such as grapefruit	☐☐	x 1
Average slices of a very large fruit, such as melon	☐☐	x 1
Tablespoons of frozen or tinned fruit	☐☐	x 1/3
Tablespoons of dried fruit, such as raisins, apricots	☐☐	x 1 (up to 1)
Tablespoons of other dishes made mainly from fruit such as fruit salad or fruit pies	☐☐	x 1/3
Small glasses of fruit juice	☐☐	x 1 (up to 1)

When a distribution of each fruit and vegetable category was observed, there were some implausibly high values as consumption of fruit or vegetables for one day, for example 31 bowlfuls of salad, 95 tablespoons of vegetables, 40 handfuls of very small fruit, such as grapes or berries, or 50 medium fruit, such as apples, bananas or oranges. Implausibly high values were defined as values more than mean of the population plus 3 standard deviations in this thesis and participants who had one or more implausibly high values were excluded for the main analysis. Range, mean and median of fruit and vegetable categories and cut-point for implausibly high value are summarized in **Table 2.4**.

Supplementary analyses were conducted to evaluate the impact of excluding these participants (see **Chapter 5.3 Fruit and Vegetable Consumption and Incident Pre-frailty/Frailty (ELSA)**).

Table 2. 4. Summary of fruit and vegetable categories data (portion/day)

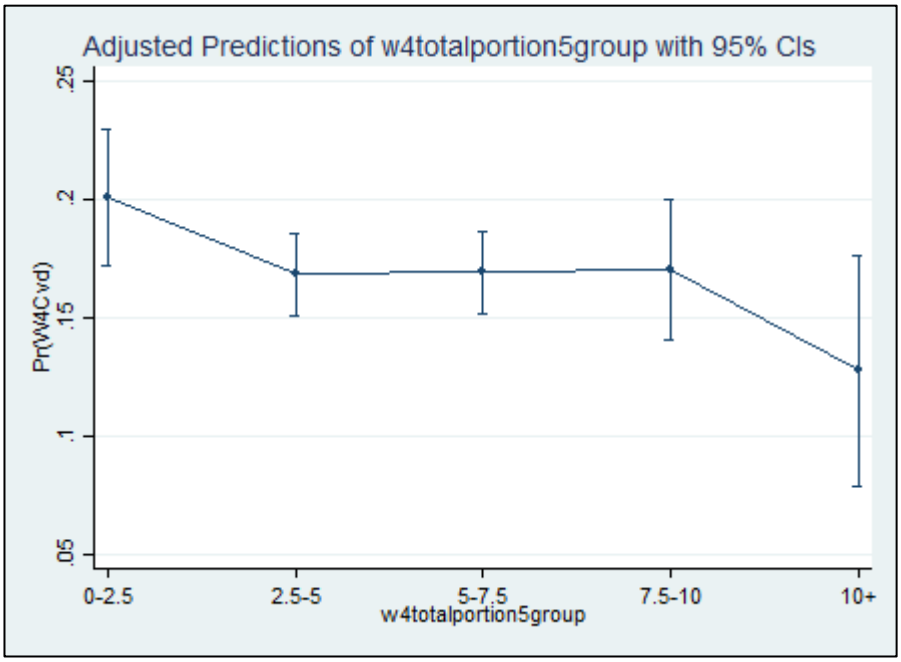
	Min	Max	Mean	Median	Cut-point for implausibly high value
Very small fruit	0	20	0.5	0.9	3.1
Small fruit	0	16	0.3	0.6	2.1
Medium fruit	0	50	1.2	1.3	5.2
Large fruit	0	20	0.1	0.5	1.6
Very large fruit	0	11	0.2	0.7	2.3
Frozen or tinned fruit	0	4	0.1	0.4	1.2
Dried fruit	0	1	0.3	0.5	n/a
Other fruit	0	7.7	0.2	0.4	1.4
Fruit juice	0	1	0.6	0.5	n/a
Salad	0	31	0.8	1.2	4.5
Raw, cooked, frozen or tinned vegetables	0	31.7	1.1	1.1	4.4
Pulse	0	1	0.2	0.3	n/a
Other vegetables	0	13.3	0.3	0.8	2.6

A total portion of fruit and vegetable consumption was divided into 5 groups (>0 - 2.5 portions, >2.5 - 5, >5 - 7.5, >7.5 - 10 and >10 portions per day). The cut-points were chosen based on the 5 A Day campaign and the recent findings on beneficial effects of fruit and vegetables with a higher amount than 5 portions.[196, 197]

This questionnaire was also used in HSE, in which higher fruit and vegetable consumption was shown to be associated with significantly lower all-cause, cancer and cardiovascular mortality.[198] However, to the best of my knowledge, no study was found in the literature that has examined psychometric properties of this questionnaire. Based on the well-known fact that fruit and vegetable consumption is negatively associated with CVD,[199] I explore the criterion validity (concurrent validity) of the questionnaire by examining a cross-sectional association between fruit and vegetable consumption and prevalence of CVD at wave 4 among 5060 participants who were aged 60 or older and had valid data of fruit and vegetable consumption (without implausibly high values) and history of CVD. CVD was defined as having either angina, a heart attack, congestive heart failure or a stroke. Please see **Chapter 2.7.9 Chronic Diseases** for detail.

Three types of fruit and vegetable consumption were considered; (1) five fruit and vegetable consumption groups as a categorical variable, (2) five fruit and vegetable consumption groups as a continuous variable and (3) portions of fruit and vegetables per day as a continuous variable, and separately entered into an unadjusted logistic regression model with a history of CVD. Compared with the lowest consumption group, the second and third groups had almost significantly lower probability of CVD (OR=0.81, 95%CI=0.65-1.00, p=0.051; OR=0.81, 95%CI=0.65-1.01, p=0.057, respectively) and the highest group had significant and the lowest risk of probability of CVD (OR=0.58, 95%CI=0.36-0.93, p=0.02), while there was not significant difference in probability of CVD between the lowest and the third group (OR=0.82, 95%CI=0.36-0.93, p=0.15). **Figure 2.3** shows probability of history of CVD according to the five fruit and vegetable consumption groups.

Figure 2. 3. Probability of history of cardiovascular diseases according to fruit and vegetable consumption groups at ELSA wave 4.



When fruit and vegetable consumption group as a continuous variable and fruit and vegetable consumption in portions were separately entered in the model, both variables of fruit and vegetable consumption were inversely associated with history of CVD (OR=0.93 per 1 group increase, 95%CI=0.86-1.00, p=0.046; OR=0.96 per 1 portion increase, 95%CI=0.94-0.99, p=0.01, respectively). It was potentially possible to assess test-retest reliability as fruit and vegetable consumption had been measured using the same questionnaire with the same individuals at wave 3, 2 years before wave 4. However, the interval of 2 years was felt to be too long and the test-retest reliability assessment was not conducted.

2.7 Definitions of Covariates

Various variables can potentially confound the association between smoking, alcohol and fruit and vegetable consumption, respectively, and frailty risk. These variables were used as covariates for adjustment to assess independent associations. The covariates covered a wide range of socio-demographic and health characteristics relevant to the associations between each of three lifestyle factors and frailty risk. Each of the covariates is described especially

focusing on how the original data were collected in ELSA, definitions, reliability and validity.

2.7.1 Age

When a participant entered the study date of birth was recorded. Age was computed from data of birth and date of ELSA interview. Age of those aged over 90 years old were not available for confidentiality reasons due to the small number of people in this category. Therefore, instead of using age itself as a continuous variable, 5 age groups were created: 60-64 years, 65-69 years, 70-74 years, 75-79 years and 80 years or older, and used as categorical variables in analyses. This 5-year grouping has been used in other ELSA papers[163] and other international studies such as the Global Burden of Disease Study, which showed those in older age groups had a significantly higher mortality risk than younger age groups.[200]

2.7.2 Gender

Information on self-reported definitive gender (male or female) was obtained in the main interview. If it was not available, information from the household demographics module was used. Women have consistently been found to be more frail than men in previous studies, using different frailty instruments.[11, 34, 201, 202]

2.7.3 Education

Education was measured as the highest education qualification achieved by the main interview. During the main interview a participant was asked to choose their highest educational qualifications obtained from as follows:

i. degree/degree level qualification (including higher degree)
ii. teaching qualification
iii. nursing qualification (State Registered Nurse (SRN), Sate Certified Midwife (SCM), State Enrolled Nurse (SEN), Registered General Nurse

(RGN), Registered Midwife (RM), Registered Health Visitor (RHV), Midwife)

iv. Higher National Certificate (HNC)/ Higher National Diploma (HND), Business Education Council (BEC)/ Technology Education Council (TEC) higher, Business & Technology Education Council (BTEC) higher/Scottish Technical Education Council (SCOTECH) higher

v. Ordinary National Certificate (ONC) /Ordinary National Diploma (OND) / BEC / TEC / BTEC not higher

vi. City and Guilds Full Technology Certificate

vii. City and Guilds Advanced/Final Level

viii. City and Guilds Craft/Ordinary Level

ix. A-levels/Higher School Certificate

x. Advanced Subsidiary (AS) level

xi. Scottish Leaving Certificate (SLC) / Scottish Certificate of Education (SCE) / Scottish University Preliminary Examination (SUPE) at Higher Grade or Certificate or Sixth Year

xii. O-level passes taken in 1975 or earlier

xiii. O-level passes taken after 1975 GARDES A-C

xiv. O-level passes taken after 1975 GARDES D-E

xv. General Certificate of Secondary Education (GCSE) GRADES A-C

xvi. GCSE GRADES D-G

xvii. (Certificate of Secondary Education) CSE GRADE 1 / SCE BANDS A-C / Standard Grade LEVEL 1-3

xviii. CSE GRADES 2-5 / SCE Ordinary BANDS D-E

xix. CSE Ungraded

xx. SLC Lower

xxi. SUPE Lower or Ordinary

xxii. School Certificate of Matric

xxiii. National Vocational Qualification (NVQ) Level 5

xxiv. NVQ Level 4

xxv. NVQ Level 3 / Advanced level General National Vocational Qualification (GNVQ)

xxvi. NVQ Level 2 / Intermediate level GNVQ, (xxvii) NVQ Level 1 / Foundation level GNVQ

xxvii. Recognised Trade Apprenticeship completed

xxviii. Clerical or Commercial Qualification (e.g. typing/book-keeping/commerce)

xxix. other qualification

xxx. None of these

These educational categories were divided into 3 groups: (1) higher education (i, xxiii, xxiv), (2) intermediate education (ii, iii, iv, v, vi, vii, viii, ix, x, xi, xii, xiii, xiv, xv, xvi, xvii, xviii, xx, xxi, xxii, xxv, xxvi, xxvii, xxviii, xxix) and (3) no qualification (xix, xxx). Higher education has been shown to be associated with lower frailty risk.[135]

2.7.4 Wealth

Detailed information regarding income and financial and physical assets of the household over the last 12 months was obtained during the interview from one participant from each household. Wealth was represented as quintiles of total net primary housing non-pension wealth (housing value minus housing debts), net physical wealth (values of farm property, business property, business, second home and other property) and net financial wealth (savings, Individual Saving Account savings, Tax-exempt special savings account savings, joint assets, Premium Bonds, National Savings account savings, Personal Equity Plan values, shares, trusts, bonds, gilts and life insurance savings components) deducting financial debt (credit card debt, other loans and debt and amount owed to friends, relatives or other private individuals) and mortgage debt for the household, excluding pension wealth. Wealth was used as a socioeconomic measure instead of income, as income in old age is often low but those with high wealth may still be able to keep high living standards. Higher wealth has been shown to be negatively associated with frailty risks.[135] This total non-pension wealth measure has been used by other ELSA papers,[203, 204] and was shown to be the most robust indicator of socioeconomic circumstances in ELSA and to be more strongly associated with mortality than other socioeconomic indicators at old age.[205] Each missing value was imputed by the ELSA team using the conditional hot-deck imputation procedure, which chooses a random observation from all observations with matching characteristics in a number of conditioning variables.[163] The conditioning variables at the benefit unit level

were broad age bands (50 to state pension age, state pension age to 75 and 75+; for couples the age of the male was used or for single-sex couples, the age of the older was used) and benefit unit type (couple, single man or single woman). The conditioning variables at the individual level were age and gender.

2.7.5 Living Alone

Living status was defined based on the number of people in a household, which was obtained during the main interview. If the number of people in the household was one the participant was considered to be living alone, and if the number was two or more the participant was considered to not live alone. This variable was used in analysis of fruit and vegetable consumption. Previous research has identified associations between living alone and multiple adverse health outcomes, such as social isolation, functional impairment and mortality.[206] Dietary behaviours are also affected by living alone and older people who live alone are shown to have a lower consumption of fruit and vegetables.[206] Marital status could have been used, however marital status may not reflect actual living arrangements, for example a participant could live alone even if in a marital relationship or a participant could live with a partner but not in a marital relationship.

2.7.6 Cognitive Function

Cognitive function has been argued to be one of the important components of frailty and been shown to be negatively associated with frailty risks.[207] In this thesis cognitive function was represented as a composite score of four cognitive function tests conducted during the main interview (Verbal-fluency task, letter-cancellation task, immediate word-recall task and delayed word-recall task) [158] as these tests cover three important key domains of cognitive functioning (executive function, processing speed and memory).[208] All four scores in ELSA were normally distributed with no evidence of floor and ceiling effect.[209] The higher score indicates better cognitive function. This composite score has been used by a previous ELSA paper and was validated in association with mortality.[208] The details of four cognitive function tests are described below.

2.7.6.1 Verbal-fluency task

This is a test of how quickly a participant can think of words from a certain category. In ELSA, the participant was asked to name as many different kinds of animal as possible in 1 minute. The score is the number of animals named. The reliability and validity of the animal-naming test are well documented.[210]

2.7.6.2 Letter-cancellation task

This test examines attention, visual search and mental speed. The participant was asked to cross out as many target alphabet letters (P and W) from a total of 65 random alphabets written on a page. The score is the number of alphabets correctly assessed (theoretical range: 0-65). This test was shown to have good reliability and validity.[211]

2.7.6.3 Immediate word-recall task

This and the following tests examine verbal learning and recall. Initially ten common words were aurally presented by a computer using a taped voice to a participant. Four different versions of word lists, originally developed for the HRS, were used. A word list was assigned at random by the computer, excluding the list that the participant had heard in wave 1. The participant was immediately asked to recall all words. The score is the number of words recalled (theoretical range: 0-10).

2.7.6.4 Delayed word-recall task

Five minutes after the immediate word-recall task, the participant was again asked to recall all words. The participant did other cognitive tests during the delay. The score is the number of words recalled (theoretical range: 0-10).

Immediate and delayed recall tests have been shown to have good consistency and construct validity.[212]

2.7.7 Depressed Mood

During the main interview a participant was asked to answer 8-item CES-D questionnaire. As described in **Chapter 2.3 Definition of frailty 2. Self-reported exhaustion**, two items were used to construct the frailty phenotype. Among the remainder of six items, five items representing depressed affect were used to create a depressed mood subscale.[213] Questions for the five items are (Much of the time during the past week), 'you felt depressed?', 'you were happy?', 'you felt lonely?', 'you enjoyed life?' and 'you felt sad?' (the question that was not used is 'your sleep was restless?'). Although 8-item CES-D has been shown to be a reliable and valid instrument of depression among older people,[214] the 5-item depressed mood subscale has yet to be validated.

2.7.8 Loneliness

Loneliness was assessed using a 3-item short version questionnaire of the Revised UCLA Loneliness Scale.[215] The 3 questions were (1) How often the respondent feels they lack companionship, (2) How often the respondent feels left out and (3) How often the respondent feels isolated from others. A participant was asked to choose from 3 options: 'Hardly ever or never' (1 point), 'Some of the time' (2 points) and 'Often' (3 points) to answer. One to three points were given accordingly, and the total score ranged from 3 (the least lonely) to 9 (the most lonely). The 3-item UCLA Loneliness Scale showed satisfactory reliability and both concurrent and discriminant validity in middle-aged and older people from HRS and the Chicago Health, Aging and Social Relations Study.[215] Higher loneliness measured by the 3-item UCLA Loneliness Scale was associated with a higher frailty risk in English community-dwelling older people from ELSA.[216]

2.7.9 Chronic Diseases

During the interview at wave 1, a participant was asked if he or she had had or had been told by a doctor that he or she had any of the following chronic diseases:

(1) high blood pressure or hypertension

(2) angina
(3) heart attack (including myocardial infarction or coronary thrombosis)
(4) congestive heart failure
(5) heart murmur
(6) abnormal heart rhythm
(7) diabetes or high blood sugar
(8) stroke (cerebral vascular disease)
(9) chronic lung disease such as chronic bronchitis or emphysema
(10) asthma
(11) arthritis (including osteoarthritis or rheumatism)
(12) Osteoporosis or thin or brittle bones
(13) cancer or a malignant tumour (excluding minor skin cancers)
(14) Parkinson's disease
(15) Any emotional, nervous or psychiatric problems

The information was fed forward at later waves. (16) High cholesterol was first added to the list at wave 3 and the information was fed forward at later waves as the other chronic diseases. Those who were taking medication for diabetes or using insulin were considered to have diabetes. (17) CVD was defined as having either one or more of (2) angina, (3) a heart attack, (4) congestive heart failure or (8) a stroke. A comorbidity index was calculated as the number of any comorbidity present in a participant out of the 15 comorbidities. This list of chronic diseases seems to have been created for ELSA and does not include multiple potentially relevant chronic diseases, such as liver, gastro-intestinal diseases, kidney or autoimmune diseases. Previous studies of older people showed that self-reported diagnosis of the chronic diseases listed here had moderate to good agreement with information from medical records, which is considered as the gold standard for diagnosis of chronic diseases.[217-219]

2.7.10 Self-reported General Health

A participant was asked to choose one of five options; excellent, very good, good, fair and poor, to describe their health during the main interview. Self-reported general health is a good proxy measure for morbidity and mortality and

has been used in various large population-based studies or surveys.[220] It has been shown to have good reliability and validity.[220]

2.7.11 Blood Tests

Blood samples were drawn during the nurse visit from participants who gave written consent. Details of blood test procedures were described in the precious section **2.2.2.3 Nurse visit**. CRP and fibrinogen were used as covariates in the ELSA smoking analysis.

2.8 Statistical analysis

StataSE 14 (StataCorp LP, College Station, Texas, USA) was used to analyse ELSA dataset. Statistical analysis for a meta-analysis on alcohol and frailty will be explained later in the alcohol chapter. All statistical analyses were conducted based on 2-tailed significance with the level of significance set at $p<0.05$. Data of analytical samples were explored by checking the lowest five and high five values, mean, median, skewness and the number of missing values. Distribution was examined by visually inspecting a histogram.

2.8.1 Main analysis

In order to examine selection bias, those who were included in the analytical samples were compared with those who were excluded from analyses due to loss to follow-up or missing data. The reasons for exclusions were classified as either (1) death, (2) being ill, (3) refusal by participants or proxies, (4) being unable to be contacted, (5) missing data for frailty at follow-up wave or (6) other reasons. Variables compared between the included and excluded participants were age, gender, smoking, alcohol, wealth, education, baseline frailty status and other variables used in analyses using t-test for continuous variables and chi-square test for categorical variables.

The main statistical analysis for each of three modifiable lifestyle risk factors of frailty, smoking, alcohol and fruit and vegetable consumption, was multivariable logistic regression models. Outcome variables were either incident frailty,

defined as those who were robust or pre-frail at baseline and became frail at follow-up, or incident pre-frailty/frailty, defined as those as those who were robust at baseline and became pre-frail or frail at follow-up, or both. Predictor variables were smoking, alcohol and fruit and vegetable consumption, the details of which were described in each of their chapters. Covariates used for adjustment in this thesis were age, gender, smoking, alcohol, wealth, education, cognition, depressed mood, loneliness, comorbidities, CRP and fibrinogen. Appropriate covariates were chosen a priori with reference to literature on known potential confounders and entered in the models separately for smoking, alcohol and fruit and vegetable analyses. The details of covariates, including which covariates were selected, and other statistical methodologies used specifically for each of smoking, alcohol and fruit and vegetable analyses are described in detail in each chapter. While logistic regression models consider cumulative incidence in a given time period, proportional hazards regression models consider incidence rate per unit time and might have been used in this thesis. However the frailty status was only measured at the waves of data collection in set four year intervals, and the information on when frailty was newly developed between the waves was not available. Therefore the proportional hazards regression models, which require this time to an event data, could not be used.

2.8.2 Weighting

Several weighting codes are available for ELSA to reduce any bias caused by non-response and to ensure representativeness.[221] The weights available at waves 4 and 6 are cross-sectional weight, longitudinal weight, self-completion weight, weight for nurse data and weight for blood sample analyses.[163] Given that all the analytic samples for this thesis had nurse visits, where necessary data for constructing frailty (weight, height and handgrip strength) were measured, weights for nurse visit (the weight for nurse visit at wave 4 ‘w4nurwt’ for smoking and alcohol analyses, and the one at wave 6 ‘w6nurwt’ for fruit and vegetable analysis) were used.

2.8.3 Multiple imputation by chained equations

Since there were missing data in the majority of the covariates and given that complete case analysis may decrease power and result in biased results,[222] multiple imputation by chained equations (MICE) was used to address this issue based on the assumption of missing at random where the probability of missing data does not depend on unobserved data but on observed data. MICE imputes missing values based on the observed values for a given individual and the relationships observed in the data for other individuals, generating multiple complete datasets.[223] MICE was chosen for several reasons. First, compared with single imputations MICE can account for the statistical uncertainty in the imputation and calculate accurate standard errors, by creating multiple predictions for each missing value.[223] Second, MICE can flexibly impute various types of variables, such as continuous, binary and ordinal variables.[223] Third, MICE can include auxiliary variables, which can reduce estimation bias due to missing not at random and can partially restore lost power due to missingness.[224] Auxiliary variables are variables that are not part of the model but are highly correlated with the variables in the model. Fourth, while other imputation methods were only available in special software, MICE is available in StataSE 14, which was used for all ELSA data analyses in this thesis.

When MICE was used, continuous variables were imputed using predictive mean matching, binary variables were imputed using logistic regression, ordinal variables were imputed using ordinal logistic regression and nominal variables were imputed using multinomial logistic regression. Twenty sets of data with imputation were generated. In this thesis, auxiliary variables were the same covariates in the previous wave, for example in the smoking analysis, an auxiliary variable for the imputation of the wealth quintile at wave 2 was the wealth quintile at wave 1.

3 SMOKING

This is the first of three chapters exploring modifiable lifestyle risk factors for frailty. In each chapter I introduce the topic, then report my systematic review of the literature followed by my empirical analysis, including the topic specific methods, my findings and a brief discussion of their interpretation with reference to other literature. This chapter focuses on smoking as a risk factor for frailty. The findings from this chapter have been published[225, 226] and presented.[227] (Please see **8 Appendices** for details)

3.1 Introduction

Smoking increases the risk of developing a number of diseases, such as COPD, cancers, coronary heart disease, stroke and peripheral vascular disease, all of which can potentially have negative effects on the physical, psychological and social health of smokers and contribute to mortality.[228] When national surveys on smoking started in the UK in 1974, 51% of men and 41% of women were smokers.[229] Although the overall prevalence of smoking has been declining since then, smoking is still common with the latest prevalence of 17.7% for men and 14.1% for women in 2016,[229] and is the single most preventable cause of morbidity and mortality in the UK.[230] In light of the negative health impacts, smoking may be a risk factor of frailty.

Smoking has been examined in relation to frailty in population-based studies as an important modifiable lifestyle factor.[226] However, in many studies, smoking was used as a covariate for adjustment in order to examine independent risks of target outcomes, and only a limited number of studies have focused on associations between smoking and frailty.[226] Findings of previous cross-sectional studies that examined associations between smoking and frailty were mixed, and some unexpectedly showed that smoking was associated with being less frail.[132, 231] A cross-sectional study design limits causal interpretation, whereas prospective observational studies appropriately controlling for confounding factors are required to assess the direction of the relationship.

A previous systematic review reported the evidence on the association between frailty and various health-related and socio-demographic factors including

smoking.[135] This review was limited to only studies using the Fried phenotype criteria[16] and did not include other studies using different criteria.[135] It is important to include studies using frailty criteria other than Fried's given that no consensus has been reached on how best to operationalise frailty.[207] Although ten articles examining smoking and frailty were identified,[135] most of them had a cross-sectional study design and only two articles examined smoking longitudinally as a predictor of frailty changes.[232, 233] One of them showed that current and past smoking were both significantly associated with increased risks of incident frailty over three years compared with never smoking, however the effect measures were unadjusted. The other study showed that those who had "ever smoked" had a higher number of the five CHS criteria, in a linear regression model adjusted for age, gender, education, marital status, financial strain, comorbidities, BMI and the number of positive CHS criteria at baseline, but did not examine incident frailty. Therefore, the independent association of smoking with incident frailty has not been convincingly established. This chapter pursues the possibility that smoking is a risk factor of frailty by reporting a systematic review of the literature and a prospective analysis using ELSA data.

3.2 Systematic Literature Review

3.2.1 Objective

The objective of this section of the chapter is to systematically review the literature for evidence on smoking as a predictor of subsequent frailty status changes in longitudinal studies of the community-dwelling elderly population.

The 'PICO' for the systematic review is as follows:
Population: community-dwelling older people
Intervention/exposure: current smoking
Comparison: never or past smoking
Outcome: Frailty status changes

3.2.2 Methods

3.2.2.1 Data source and search strategy

This systematic review was conducted according to a protocol developed with adherence to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement (**Appendix 1a**).[234] A systematic search of the literature was conducted in May 2015 using three electronic databases (MEDLINE, Embase and Scopus) without language restriction using an explosion function and Medical Subject Heading terms (MeSH) if available from 2000 through May 2015. Validated definitions of frailty were not generally used prior to 2000, and the two most widely accepted definitions and measurements for frailty, the CHS criteria[16] and the FI[10] were first published in 2001. The search terms included ("Smoking (MeSH)" OR "Smoking cessation (MeSH)" OR "Smoking cessation program (MeSH)" OR "Smoking habit (MeSH)" OR "Tobacco (MeSH)" OR "Smokeless Tobacco (MeSH)" OR "Tobacco products (MeSH)" OR "Tobacco Consumption (MeSH)" OR "Tobacco dependence (MeSH)" OR "Tobacco smoker (MeSH)" OR "Nicotine (MeSH)" OR "Nicotine derivative (MeSH)" OR "Nicotine gum (MeSH)" OR "Nicotine lozenge (MeSH)" OR "Nicotine Patch (MeSH)" OR "Nicotine replacement therapy (MeSH)" OR "Cotinine (MeSH)" OR "Smok*" OR "Tobacc*" OR "Nicotin*" OR "Cotinin*" OR "Cigarett*") AND "Frail*". Additional sources included reference lists of relevant articles and included studies, articles shown as related citations in PubMed of the included studies and articles citing the included studies displayed under Cited by in Google Scholar.

3.2.2.2 Study selection and data extraction

Studies were considered to be potentially eligible for inclusion if they were prospective observational studies investigating smoking status as a predictor and subsequent frailty status as an outcome in the community-dwelling population aged 50 or older. In addition, in order to be considered for inclusion, frailty must have been defined using criteria originally designed to measure frailty and validated in population-based studies or its modified versions, such as CHS criteria or FI. Studies were excluded if they substituted other measures, such as disability or nursing home placement, to define frailty or used selected samples with specific diseases or conditions. All potentially eligible studies identified were searched for duplicates using the Endnote duplicate finding

function and manually, followed by title, abstract and full-text reviews. Data extracted from eligible studies were first author, publication year, location, sample size, proportion of women, age (mean or range), smoking measure, frailty criteria, follow-up period and findings.

3.2.2.3 Methodological quality assessment

Methodological quality of the eligible studies were examined using the Newcastle-Ottawa Scale for cohort studies (**Appendix 3**).[235] This scale is designed to evaluate the methodological quality of a cohort study based on nine items over three domains: Selection (representativeness of the exposed cohort; selection of the non-exposed cohort; ascertainment of exposure; and demonstration that outcome of interest was not present at start of study), Comparability (comparability of cohorts on the basis of the design or analysis) and Outcome (assessment of outcome; was follow-up long enough for outcomes to occur; and adequacy of follow-up of cohorts). Each of the included studies was assessed using this scale and considered to have adequate quality if it met five or more of the nine items.

3.2.2.4 Data analysis

It was planned to assess heterogeneity of the study findings and to perform meta-analysis to synthesise pooled estimates from the included studies if possible, otherwise a narrative review would be pursued.

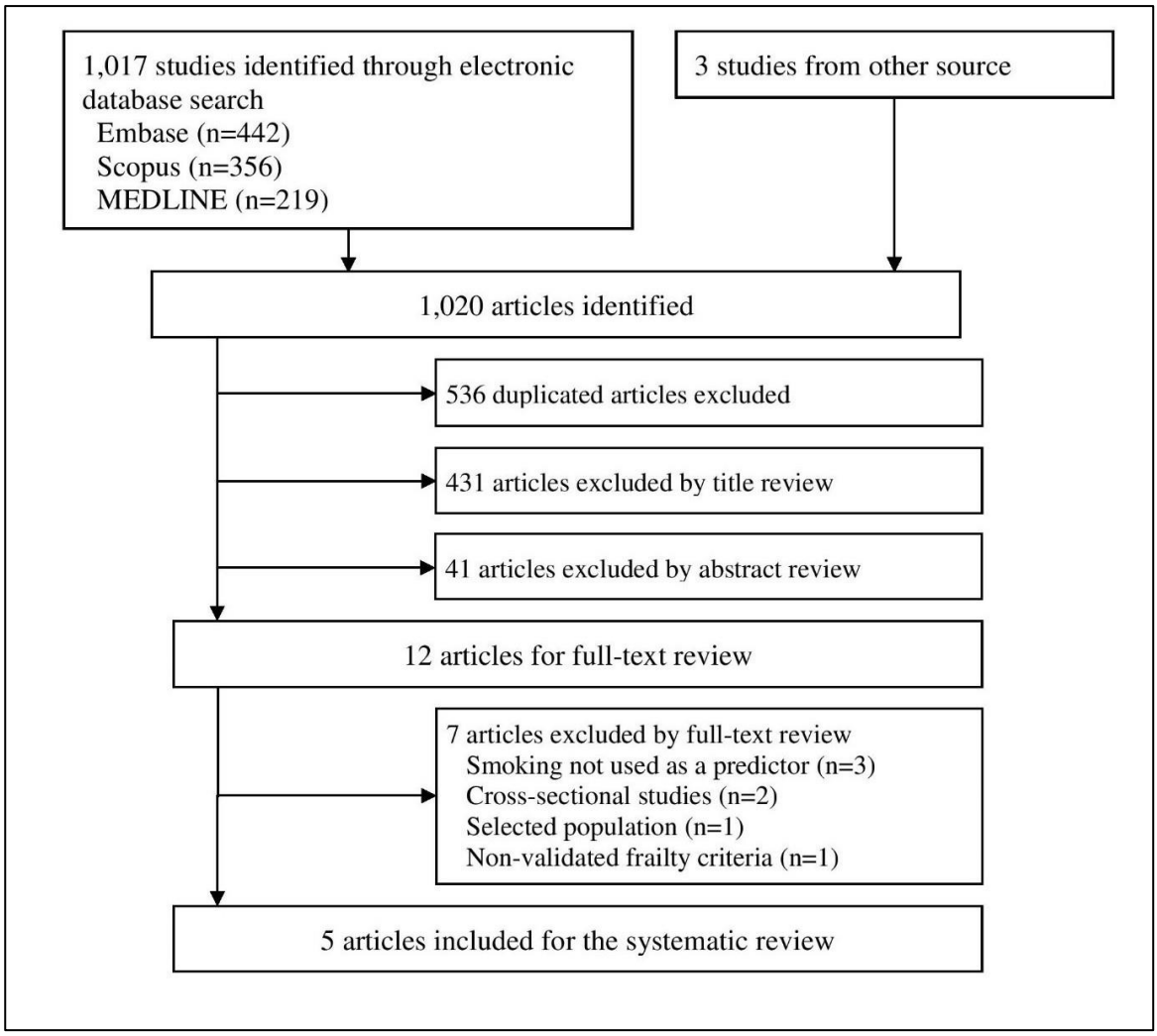
3.2.3 Results

3.2.3.1 Selection processes

A PRISMA flowchart of the literature search and study selection with the number of studies at each stage is presented in **Figure 3.1**. Of the 1,020 citations identified from the literature search using three electronic databases and other sources, 536 duplicate studies were excluded, and 431 and 41 studies were also excluded through title and abstract review, respectively, leaving 12 studies for potential inclusion. Full-texts of these 12 studies were assessed and seven studies were further excluded because smoking status was not used as a predictor (n = 3), study designs were cross-sectional (n = 2), a selected population was used (n = 1) or non-validated frailty criteria were used

(n = 1). Five studies[130, 232, 233, 236, 237] were confirmed to meet the inclusion criteria and were included in this systematic review.

Figure 3. 1. PRISMA Flowchart (Smoking and frailty)



3.2.3.2 Study characteristics

The included studies were assessed for methodological quality using the Newcastle-Ottawa quality assessment scale for cohort studies. All five studies met at least five criteria and were considered to have adequate methodological quality (**Table 3.1**). Characteristics of the five studies are summarised in **Table 3.2**. Two studies were from the US[232, 233] and China,[130, 236] respectively, and one study used populations from 11 European countries.[129] The largest study involved 28,181 women from the Women's Health Initiative Observational Study, which was conducted in the US in 1990's.[233] The other studies used

cohorts consisting of almost half men and half women.[130, 232, 236, 237] Three studies defined three smoking status categories: ‘never’, ‘past’ and ‘current’ smoking[130, 233, 237] and two studies defined two categories: ‘never/past’ versus ‘current’ smoking[232] and ‘never’ versus ‘past/current smoking’,[236] respectively. Four studies used the Fried phenotype frailty criteria;[130, 232, 233, 237] one study used the Frailty Index.[236] Although only two types of criteria were used, how the changes in frailty status were measured as outcomes at follow-up were different across the included studies. The outcomes used were the development of frailty,[233] follow-up frailty status scores based on the frailty phenotype criteria[232] and the Frailty Index[236] and changes in frailty categories based on the frailty phenotype.[129, 130] The follow-up periods ranged widely from two years to 15 years. In terms of statistical analysis, three studies used logistic regression models[130, 233, 237] and two studies used linear regression models.[232, 236] As the included studies used different methodology in terms of predictors, outcomes and statistical analyses, a meta-analysis was not possible. Four studies conducted multivariable regression models controlling for at least age and gender,[130, 232, 236, 237] which are important confounding factors for both smoking and frailty, and one study showed only the results of unadjusted models.[233]

Table 3. 1. Methodological quality assessment using the Newcastle-Ottawa Quality Assessment Scale for cohort studies.

The Newcastle-Ottawa Quality Assessment Scale for cohort studies										
	Selection				Comparability		Outcome			
	1	2	3	4	1a	1b	1	2	3	tota
Woods 2005	1	1	0	1	0	0	1	1	0	5/9
Ottenbacher 2009	1	1	0	n/a	1	1	1	1	0	6/8
Wang 2013	1	1	0	n/a	1	1	1	1	0	6/8
Lee 2014	1	1	0	n/a	1	0	1	1	0	5/8
Etman 2015	1	1	0	n/a	1	1	1	1	0	6/8

Appendix 3 for detail.

3.2.3.3 Study findings

As described above, due to the considerable heterogeneity between studies, findings of the included studies are reported in narrative form (**Table 3.2**).

Etman 2014

Etman and colleagues investigated associations between smoking status (never, former and current) at baseline and frailty status at two-year follow-up using a large cohort of 14,082 middle-aged and older community-dwelling men and women from 11 European countries using SHARE.[237] Using modified Fried phenotype criteria (either from robust to pre-frail/frail or from pre-frail to frail), the authors showed that current smokers had a 16 % increased risk of worsening frailty status two years after baseline, compared to those who never smoked; multivariable logistic regression models were adjusted for age, gender, educational level, baseline frailty state and country (OR = 1.16, 95 % CI = 1.02–1.32, $p < 0.05$).

Ottenbacher 2009

In the Hispanic Established Populations for Epidemiologic Studies of the Elderly, among 777 Hispanic Americans aged 65 or older, those who ever smoked were significantly more likely to have a worse frailty status at follow-up than those who never smoked.[232] In this study, a summary frailty score, defined as the total number of five components of Fried phenotype criteria ranging from

0 to 5, was created and used as a continuous variable in multivariable linear regression models adjusted for age, gender, BMI, education, marital status, financial strain, chronic diseases and baseline frailty score to examine frailty status changes over 10 years (unstandardised coefficient = 0.36, standard error = 0.15, $p < 0.05$).

Lee 2014

A Chinese study of 3,018 community-dwelling older people examining changes in frailty status over two years according to smoking status is the only study that failed to show significant findings.[130] Although not reaching statistical significance, directions of the associations between smoking and frailty appear consistent with the other included studies in that frailty status of (male) current smokers were more likely to worsen and less likely to improve than it was for those who never smoked in age-adjusted logistic regression models (OR = 1.53, 95 % CI = 0.73–3.23 for pre-frail worsening; OR = 1.29, 95 % = 0.75–2.23 for robust worsening; OR = 0.63, 95 % = 0.33–1.21 for pre-frail improvement; OR = 0.21, 95 % = 0.02–1.80 for frail improvement). No trends were observed among women. There is a possibility that the statistical power may have been lost as a result of dividing the cohort by gender and further by three Fried frailty categories (robust, pre-frail and frail) at baseline as well as using three smoking statuses as predictors (never, past and current) and using four different frailty transition states (pre-frail worsening, pre-frail improvement, robust worsening and frail improvement).

Woods 2005

A US study involving 28,181 women aged 65 to 79 from the Women's Health Initiative Observational Study who were free from frailty at baseline examined risk of newly developing frailty and pre-frailty with modified Fried phenotype criteria over three years according to baseline smoking status and using unadjusted multinomial logistic regression models.[233] Past smoking was associated with significantly higher odds of frailty (OR = 1.12, 95 % = 1.02–1.23), but not of pre-frailty (OR = 0.95, 95 % CI = 0.89–1.02), and current smoking was significantly associated with higher odds of frailty (OR = 2.90, 95 % CI = 2.35–3.57) and pre-frailty (OR = 1.76, 95 % CI = 1.49–2.09). The findings of this study need to be interpreted cautiously because important

confounding factors including age, socioeconomic status, education and alcohol use, were not controlled for in the models.

Wang 2013

Only one study employed a frailty index and assessed frailty status among 3,257 Chinese community-dwellers aged ≥ 55. Men and women were analysed separately using multivariable linear regression models adjusted for age, education and baseline frailty index.[236] Current and past male smokers showed a worsening in their frailty status over the 15-year follow-up, significantly more than men who never smoked (standardised coefficient = 3.643, standard error = 1.621, p = 0.026) while there was no such difference observed in women (p = 0.529). In this study, the frailty index was constructed based on 28 variables excluding respiratory health deficits such as chronic tracheitis or cough, which are directly related to smoking. The analyses were also repeated with a frailty index using 25 variables without three non-respiratory smoking-related variables (hypertension, CVD and cerebrovascular disease), providing similar results.

In summary, most studies demonstrated current, past (or both) smoking status at baseline predicted subsequent incident or worsening of frailty status at follow-up.[232, 233, 236, 237] One study failed to show any significant associations between baseline smoking status and frailty trajectories.[130] It is of note however that most of the estimate measures were either unadjusted or only adjusted for a limited number of important covariates. A meta-analysis was not possible due to the methodological diversity of the included studies.

Table 3. 2. Summary of included studies on associations between smoking and subsequent frailty status change among community-dwelling older people.

Author, year Location N*	female (%)*	age**	smoking definition	Frailty outcome	Follow-up	Findings (unadjusted)	Findings (adjusted)
Woods 2005 USA 28,181	100%	65-79	never, past, current smoking	Incident frailty by modified frailty phenotype	3 years	Unadjusted multinomial logistic regression models for incident frailty. OR=1.12, 95%CI=1.02-1.23 for past smokers OR=2.90, 95%CI=2.35-3.57 for current smokers Unadjusted multinomial logistic regressions for incident pre-frailty OR=0.95, 95%CI=0.89-1.02 for past smokers OR=1.76, 95%CI=1.49-2.09 for current smokers	Not reported
Ottenbacher 2009 USA 777	56.4%	82.5	never, past, current smoking	Frailty phenotype score (range: 0-5)	10 years	Not reported	Linear regression model adjusted for age, gender, education, married, financial strain, diabetes, hip fracture, cancer, stroke, cardiac diseases, arthritis, body mass index and base frailty. “Ever smoked” was associated with increase in frailty score (beta=0.36, SE=0.15, p<0.05).

Author, year Location N*	female (%)*	age**	smoking definition	Frailty outcome	Follow-up	Findings (unadjusted)	Findings (adjusted)
Wang 2013 China 3,257	51.1%	70.1	never, current/past smoking	Frailty Index	15 years	Not reported	Linear regression adjusted for age, education, base Frailty Index. Current/past smoking was associated with increase in frailty index (beta=3.64, SE=1.62, p=0.03) in men. No such association was observed in women.
Lee 2014 China 3,018	49.7%	73.6	never, past, current smoking	Change in frailty Category change by frailty phenotype	2 years	Not reported	Gender-stratified age-adjusted logistic regression models for frailty status changes. No significant association was observed.
Etman 2015 11 European countries 14,082	54.3%	>55	never, past, current smoking	Worsening in frailty by frailty phenotype (robust>pre-frail/frail or pre-frail>frail)	2 years	Not reported	Logistic regression adjusted for age, gender, education, base frail and country. Current smoking was associated with worsening of frailty status (adjOR=1.16 95%CI=1.02-1.32, p<0.05). Past smoking was not significantly associated with worsening of frailty status (adjOR=1.07, 95%CI=0.96-1.19).

* Cohort used for analysis of interest, or entire cohort.

** Mean age, age range, or age for inclusion.

95%CI: 95% confidence interval, OR: Odds ratio, SE: Standard error.

3.2.4 Discussion

This systematic review identified five prospective cohort studies that examined associations between smoking and subsequent frailty changes. Although the studies employed different methodology and frailty criteria, most studies demonstrated that baseline smoking predicted significant worsening of frailty status at follow-up.

Some further studies have examined cross-sectional associations between smoking and frailty status. In a large older female sample from the Women's Health Initiative Observational Study from the US, prevalence of frailty, defined by the frailty phenotype criteria, of never, past and current smokers was 15.7%, 16.4% and 21.9%, respectively.[233] A previous study using the ELSA data showed that 12.0% of non-smokers and 13.9% of current smokers were frail based on the frailty phenotype.[132] Three studies using the Frailty Index showed inconsistent findings. A German study showed never smokers had the lowest frailty index (the least frail) of 0.205 and past and current smokers had higher values of 0.258 and 0.239 (more frail), respectively,[238] while little or no difference in the Frailty Index was observed across smoking categories in two studies from China (0.12 in both male smokers and non-smokers and 0.14 in both female smokers and non-smokers)[236] and Canada (0.14 in heavy smokers, 0.14 in light smokers and 0.15 in never smokers). One large European study showing cross-sectional associations between smoking and frailty by age groups.[231] In those in their 50's current smoking status was associated with a higher frailty risk, but, on the contrary, associated with a lower frailty risk for those in their 70's.[231] Given the higher morbidity and mortality risks in smokers, these paradoxical findings may have resulted from reverse causality (frailty leads to an older person quitting smoking) or a healthy survivor effect; frail smokers having died early, therefore smoking may diminish in the very old.

Although It is well known that smoking increases risks of death,[148] some other outcomes, such as quality of life, disabilities and functional decline, were also shown to be associated with smoking. In a review paper of 54 relevant studies on smoking and quality of life, smoking was associated with lower quality of life and the magnitude of the association was related to the number of cigarettes smoked.[239] This review also showed a possibility that smoking cessation improves quality of

life.[239] Smoking has been shown to be a risk factor of increased risks of disabilities and functional decline in a number of previous studies.[240]

As this systematic review was originally completed in 2015, an update search has been conducted in March 2019 by using PubMed with search terms “smoking” and “frailty” and reading relevant papers. Six new papers examining smoking at baseline and subsequent frailty changes were identified, which broadly confirm the findings of the papers in my original review. Three studies examined transitions of frailty status defined by modified frailty phenotype criteria.[130, 241, 242] Two of them showed that current smokers were more likely to worsen and less likely to improve their frailty status compared with never smokers,[241, 242] while one study showed no significant association.[130] Two studies examined frailty trajectories using the Frailty Index and showed that smokers were shown to have significantly higher degree of frailty compared with their counterparts.[243, 244] A study using data from the Whitehall II study examined midlife smoking status at the age of 45-55 years and subsequent frailty status approximately 18 years later at a mean age of 69 among 6233 British civil servants.[146] Compared with never smokers, current smokers were significantly more likely to be frail at follow-up (OR=1.69, 95%CI=1.27-2.25) while there was no significant difference in frailty risk in past smokers (OR=0.85, 95%CI=0.67-1.07).[146]

My systematic review has some limitations. First, the systematic literature search, study selection, data extraction and methodological quality assessment were conducted by one researcher (Gotaro Kojima), therefore there may have been a possibility that relevant studies would have been missed. Second, a relatively limited number of studies were identified, and some studies may have been missed that were not referenced on the three main data sources searched, were published earlier than in 2000, or if unpublished were in the grey literature. Nonetheless, four out of the five included studies consistently showed evidence that smoking was a predictor of frailty status. Third, partly because an accepted standard definition of frailty has not yet been achieved, the study designs and methodologies of the included studies varied widely therefore meta-analysis was not possible. Fourth, a protocol of the systematic review was not registered on PROSPERO prior to the review.

This systematic review demonstrated that only limited amounts of evidence existed in the literature on smoking as a predictor of frailty among community-dwelling people.[226] Although most of the included studies suggest smoking predicts worsening or incident frailty, not all of them were originally designed to examine the associations between smoking[232, 233] and frailty and some studies failed to adjust for important confounding factors, such as age, gender, alcohol use, education or socioeconomic status.[130, 233, 237] This review demonstrated a need for further research, in particular a longitudinal study designed to explore the relationship between smoking and incident frailty, controlling for important confounders.

3.3 Smoking and Incident Frailty (ELSA)

3.3.1 Objective

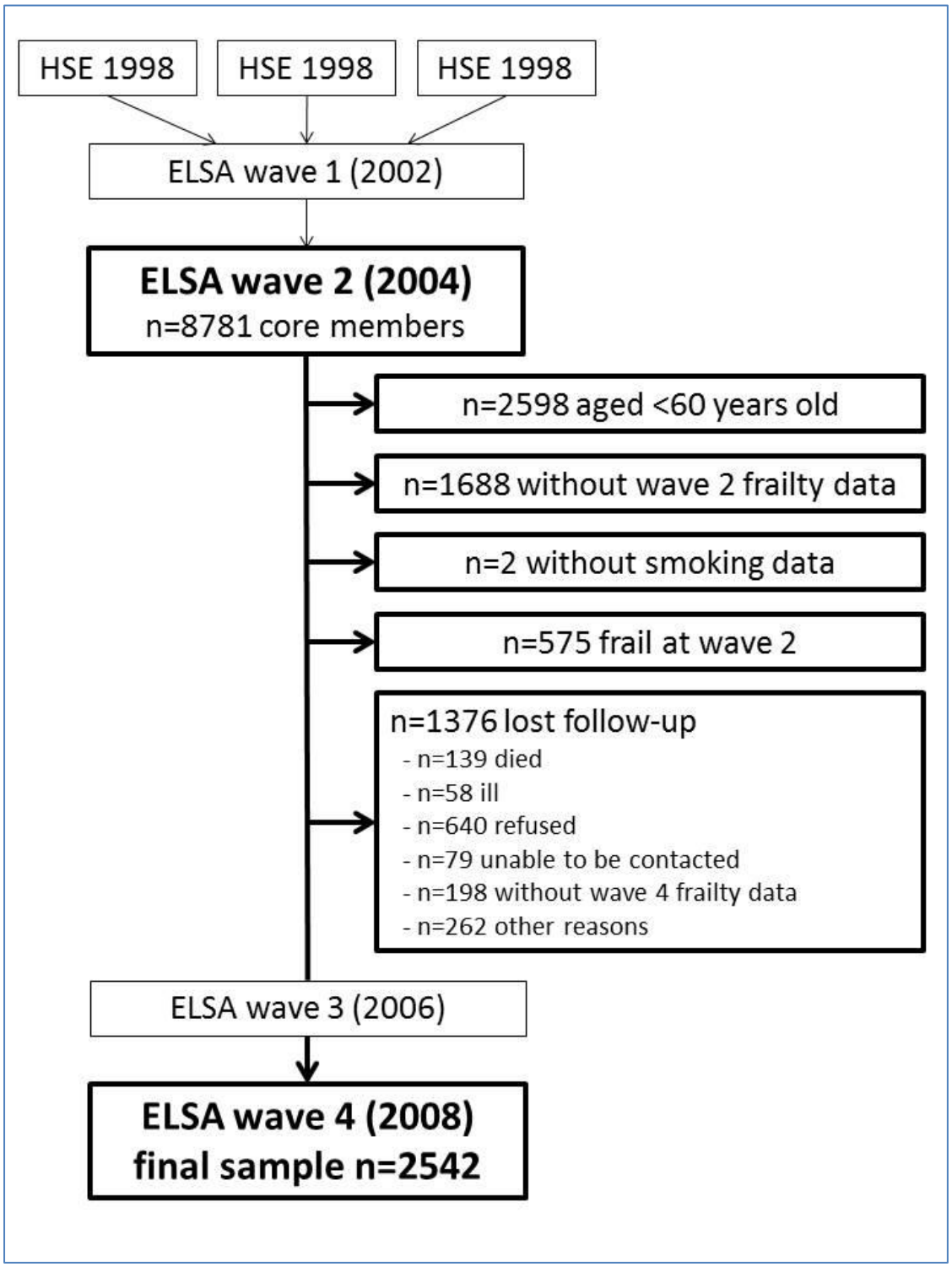
The objective of the second section of the chapter is to examine if smoking is associated with increased risk of incident frailty in community-dwelling older people.

3.3.2 Study Population

The ELSA population is described in detail in **Chapter 2.1 English Longitudinal Study of Ageing (ELSA)**. The participants who were aged 60 years or older at wave 2 (baseline) and with information regarding frailty at waves 2 and 4 and smoking status at wave 2 were used for the smoking and incident frailty analyses in this chapter.

A total of 8,781 core members had an interview at wave 2, among which 2,598 were younger than 60 years old and were excluded. Among 6,183 participants aged 60 or older, 1,688 and 2 were excluded due to missing data at wave 2 for frailty and smoking status, respectively. In order to examine incident frailty risk, 575 participants who were frail at wave 2 were also excluded. Between waves 2 and 4, 1,376 were loss to follow-up for various reasons, including death (n=139), being ill (n=58), refusal (n=640), being unable to contact (n=79), no frailty data at wave 4 (n=198) and other (unspecified) reasons (n=262). Therefore, the final analytic sample for this chapter was 2,542 participants (**Figure 3.2**)

Figure 3. 2. ELSA final analytic population for smoking analyses.



3.3.3 Predictor Variable − Smoking

Self-reported smoking status (current smokers versus non-smokers) was used as a predictor variable in the main analysis. Please see **Chapter 2.4 Definition of Smoking** for detail.

3.3.4 Outcome Variable − Incident Frailty

The outcome variable in the main analysis was incident frailty, which was defined as development of frailty (the frailty phenotype score $\geq$3) in those who were pre-frail or robust (the frailty phenotype score 0-2) at baseline. Frailty was defined by the frailty phenotype including the five characteristics of weight loss or 'shrinking', exhaustion, weakness, slow walking speed and low physical activity.[16] Please see **Chapter 2.3 Definition of Frailty** for detail.

3.3.5 Covariates

Baseline covariates considered for the main analyses in this chapter were age, gender, alcohol, education, wealth, depressive mood, cognitive function and loneliness. These factors were chosen because they are closely related to both smoking and frailty but are not on the causal pathways. For supplementary analyses, COPD, CVD, cancers, CRP and fibrinogen were used (see rationale below). Please see **Chapter 2.6 Definitions of Covariates** for detail.

3.3.6 Statistical Analyses

3.3.6.1 Main analysis

In order to examine selection bias, the participants who were included in analyses and the participants who were excluded due to loss to follow-up and missing data were compared for frailty status, smoking status, age, gender, alcohol, wealth, education, COPD, CVD and cancers at wave 2 using a chi-square test, and cognition, depressed mood and loneliness using a t-test.

Baseline characteristics were compared according to smoking status (current smoker versus non-smoker) using a t-test for continuous variables and a chi square test for categorical variables.

Multivariable logistic regression models were then used to examine risks of incident frailty for those currently smoking compared with non-smoking (past smokers and non-smokers combined). Please see **Chapter 2.8 ELSA Statistical Analysis** for detail.

3.3.6.2 Supplementary analysis - smoking-related diseases and inflammatory markers

Supplementary analyses were conducted in order to explore the degrees to which smoking-related diseases and inflammatory markers explained the association between current smoking and subsequent incident frailty risk. The smoking-related diseases considered were COPD, CVD (angina, myocardial infarction, congestive heart failure or stroke) and cancers. The inflammatory makers were CRP and fibrinogen. Smoking is known to increase risks of these diseases and inflammation,[245-247] which may increase frailty risk. These diseases and inflammatory markers were separately added to the final fully-adjusted model and changes in the OR and p values before and after the additions were compared.

3.3.6.3 Supplementary analysis - three smoking groups

In order to explore whether there is a difference between past smoker and never smokers (exploring for a ‘sick quitter’ effect), the multivariable logistic regression models were repeated using three smoking groups, which were classified based on data from waves 1 and 2. Those who were classified as non-smokers at wave 2 were further divided into past smokers, if at wave 1 they were current smokers or said that they had ever smoked in the past, and never smokers if otherwise. Multivariable logistic regression models were used to examine incident frailty risks for current and past smokers compared with never smokers.

3.3.6.4 Supplementary analysis - multiple imputation by chained equations

My main analysis was a complete case analysis. There were some limited missing data on some covariates, and as a supplementary analysis I used multiple imputation to impute these and conducted a further analysis using the imputed datasets. Please see **Chapter 2.8 ELSA Statistical Analysis** for detail.

3.3.7 Results

3.3.7.1 Main analysis

Among 3,918 participants who were aged 60 or older, with data on frailty and smoking and non-frail (robust or pre-frail, but not frail) at wave 2, 2,542 participants had frailty data at wave 4 and were included in the analyses. The remainder of 1,376 participants were not included due to various reasons. Please see **Chapter 3.3.2 Study Population** above and **Figure 3.2** for detail.

On comparison, those who were excluded were found to have overall worse health profile in the majority of the variables. Those who were excluded were significantly more likely than those who were included to be frailer, current smokers, older, and to have lower wealth, lower education, lower cognitive function score, higher prevalence of COPD, CVD and cancers, higher CRP and higher fibrinogen. There were no significant associations between those included and excluded for gender, alcohol, depressive mood subscale and loneliness score (**Table 3.3**)

Table 3. 3. Comparisons between those included in the analyses (n=2,542) and those excluded due to missing data (n=1,376).

Variables at wave 2*	Included n=2,452	Excluded n=1,376	P value
Frailty status			
Robust	1,430 (56.3%)	624 (45.4%)	<0.001
Pre-frail	1,112 (43.8%)	752 (54.7%)	
smoking status			
Non-smoker	2,281 (89.7%)	1,188 (86.3%)	0.001
Current smoker	261 (10.3%)	188 (13.7%)	
Age group			
60-64	611 (24.0%)	264 (19.2%)	<0.001
65-69	825 (32.5%)	377 (27.4%)	
70-74	542 (13.9%)	284 (20.6%)	
75-79	354 (21.3%)	229 (16.6%)	
80+	210 (8.3%)	222 (16.1%)	
Gender			
Male	1,150 (45.2%)	640 (46.5%)	0.45
Female	1,392 (54.8%)	736 (53.5%)	
Alcohol			
None	223 (9.4%)	140 (11.5%)	0.26
1/y-2/m	690 (29.0%)	344 (28.2%)	
1/w-4/w	877 (36.8%)	445 (36.5%)	
5/w-daily	592 (24.9%)	292 (23.9%)	
Wealth quintile			
Richest	661 (26.3%)	251 (18.4%)	<0.001
2nd	569 (22.7%)	309 (22.6%)	
3rd	523 (20.8%)	301 (22.0%)	
4th	446 (17.8%)	260 (19.0%)	
Poorest	312 (12.4%)	245 (17.9%)	
Education			
Higher education	322 (12.7%)	115 (8.4%)	<0.001
Intermediate	1,314 (51.7%)	623 (45.3%)	
No qualification	906 (35.6%)	637 (46.3%)	

Variables at wave 2*	Included n=2,452	Excluded n=1,376	P value
Depressive mood subscale	0.5 ± 1.1	0.6 ± 1.1	0.11
Cognitive function score	48.9 ± 10.4	45.0 ± 11.8	<0.001
Loneliness score	3.9 ± 1.4	4.0 ± 1.5	0.11
COPD	153 (6.0%)	117 (8.5%)	<0.01
CVD	406 (16.0%)	273 (19.8%)	<0.01
Cancers	213 (8.4%)	146 (10.6%)	0.02
CRP (mg/L)	3.5 ± 5.8	5.0 ± 10.2	<0.001
Fibrinogen (g/L)	3.2 ± 0.7	3.4 ± 0.8	<0.001

*t-test and chi-square test were used for continuous and categorical variables, respectively. Percentages may not sum up to 100% due to rounding. Mean ± standard deviation or n (%).

COPD: Chronic obstructive pulmonary disease

CRP: C-reactive protein

CVD: Cardiovascular diseases (angina, myocardial infarction, congestive heart failure or stroke)

Table 3.4 presents the baseline characteristics of 2,542 participants, comparing variables according to smoking status. At baseline, 2281 participants were non-smokers and 261 were current smokers. Current smokers were significantly frailer, younger, less educated, less wealthy, more depressed, with lower cognitive function scores and lonelier compared with non-smokers. There were no significant associations between current smokers and non-smokers in gender, ethnicity and alcohol use between these two groups. As for chronic diseases, only COPD was more prevalent in current smokers than in non-smokers. Both inflammatory markers of CRP and fibrinogen were significantly higher in current smokers than in non-smokers.

Table 3. 4. Baseline characteristics of ELSA participants in smoking and incident frailty analysis. (N=2,542)

Variable*	Entire cohort	Non-smoker	Current smoker	P value
Number of participants (%)	2,542	2,281 (89.7%)	261 (10.3%)	
Incident frailty, n (%)	271 (10.7%)	232 (10.2%)	39 (14.9%)	
Frailty status				
Robust	1,430 (56.3%)	1,319 (57.8%)	111 (42.5%)	<0.001
Pre-frail	1,112 (43.7%)	962 (42.2%)	150 (57.5%)	
Age group				
60-64	611 (24.0%)	526 (23.1%)	85 (32.6%)	<0.01
65-69	825 (32.5%)	739 (32.4%)	86 (33.0%)	
70-74	542 (21.3%)	498 (21.8%)	44 (16.9%)	
70-79	354 (13.9%)	320 (14.0%)	34 (13.0%)	
80+	210 (8.3%)	198 (8.7%)	12 (4.6%)	
Gender				0.02
Male	1,150 (45.2%)	1,032 (45.2%)	118 (45.2%)	
Female	1,392 (54.8%)	1,249 (54.8%)	143 (54.8%)	
Alcohol				
None	223 (9.4%)	192 (9.0%)	31 (13.0%)	0.15
1/y-2/m	690 (29.0%)	617 (28.8%)	73 (30.5%)	
1/w-4/w	877 (36.8%)	794 (37.1%)	83 (36.8%)	
5/w-daily	592 (24.9%)	541 (25.2%)	52 (21.8%)	
Education				
Higher education	322 (12.7%)	306 (13.4%)	16 (6.1%)	<0.001
Intermediate	1,314 (51.7%)	1,201 (52.7%)	113 (43.3%)	
No qualification	906 (35.6%)	774 (33.9%)	132 (50.6%)	
Wealth quintile				
Richest	661 (26.3%)	619 (27.5%)	42 (16.3%)	<0.001
2nd	569 (22.7%)	528 (23.4%)	41 (16.0%)	
3rd	523 (20.8%)	474 (21.0%)	49 (19.1%)	
4th	446 (17.7%)	393 (17.4%)	53 (20.6%)	
Poorest	312 (12.4%)	240 (10.7%)	72 (28.0%)	
Depressive mood subscale	0.5 $\pm$ 1.1	0.5 $\pm$ 1.0	0.7 $\pm$ 1.3	<0.01

Variable*	Entire cohort	Non-smoker	Current smoker	P value
Cognitive function score	48.9 ± 10.4	49.2 ± 10.3	46.9 ± 10.8	<0.001
Loneliness score	3.9 ± 1.4	3.9 ± 1.3	4.3 ± 1.6	<0.001
COPD	153 (6.0%)	113 (5.0%)	40 (15.3%)	<0.001
CVD	406 (16.0%)	365 (16.0%)	41 (15.7%)	0.90
Cancers	213 (8.4%)	191 (8.4%)	22 (8.4%)	0.98
CRP (mg/L)	3.5 ± 5.8	3.3 ± 5.8	4.9 ± 5.9	<0.001
Fibrinogen (g/L)	3.3 ± 0.7	3.2 ± 0.7	3.5 ± 0.8	<0.001

*t-test and chi-square test were used for continuous and categorical variables, respectively. Percentages may not sum up to 100% due to rounding. Mean ± standard deviation or n (%).

COPD: Chronic obstructive pulmonary disease

CRP: C-reactive protein

CVD: Cardiovascular diseases (angina, myocardial infarction, congestive heart failure or stroke)

Table 3.5 shows the results of multivariable logistic regression models. In Model 1 adjusting for age and gender, current smokers were twice more likely to develop frailty at follow-up 4 years later than non-smokers (OR=2.11, 95%CI=1.35-3.29, p=0.001). Further adjusting for alcohol use made almost no change in OR (OR=2.17, 95%CI=1.33-3.36, p<0.01). Although adding wealth and education for adjustment in Models 3 and 4, respectively, decreased ORs of frailty risk, the association between current smoking and increased frailty risks remained significant (Model 3: OR=1.71, 95%CI=1.08-2.71, p=0.02. Model 4: OR=1.62, 95%CI=1.05-2.52, p=0.03). Depressive mood, cognition and loneliness were added for adjustment in Model 5, which made little change in the association (OR=1.58, 95%CI=1.00-2.50, p=0.05).

Table 3. 5. Multivariable logistic regression models examining associations between smoking status and 4-year incident frailty. (N=2,542).

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value
Smoking										
Non-smoker	ref		ref		ref		ref		ref	
Current smoker	2.11 (1.35-3.29)	0.001	2.11 (1.33-3.36)	<0.01	1.71 (1.08-2.71)	0.02	1.62 (1.05-2.52)	0.03	1.58 (1.00-2.50)	0.05
Age group										
60-64	ref		ref		ref		ref		ref	
65-69	1.26 (0.72-2.19)	0.42	1.23 (0.70-2.18)	0.47	1.16 (0.66-2.05)	0.60	0.97 (0.56-1.68)	0.90	0.87 (0.48-1.59)	0.66
70-74	3.08 (1.84-5.16)	<0.001	3.00 (1.76-5.10)	<0.001	2.63 (1.54-4.48)	<0.001	2.34 (1.38-3.94)	0.001	2.22 (1.28-3.88)	<0.01
75-79	5.48 (3.26-9.22)	<0.001	5.59 (3.25-9.60)	<0.001	4.76 (2.78-8.16)	<0.001	4.23 (2.50-7.15)	<0.001	3.83 (2.17-6.75)	<0.001
80+	13.92 (8.07-24.03)	<0.001	13.30 (7.53-23.48)	<0.001	10.76 (6.03-19.18)	<0.001	9.16 (5.22-16.07)	<0.001	7.33 (3.99-13.45)	<0.001
Female	1.65 (1.23-2.21)	0.001	1.76 (1.28-2.43)	0.001	1.72 (1.24-2.39)	0.001	1.68 (1.21-2.33)	<0.01	1.87 (1.32-2.64)	<0.001
Alcohol										
None	-		ref		ref		ref		ref	
1/year-2/month	-		0.56 (0.35-0.89)	0.02	0.56 (0.34-0.91)	0.02	0.54 (0.34-0.87)	0.01	0.59 (0.36-0.97)	0.04
1/week-4/week	-		0.61 (0.38-0.97)	0.04	0.64 (0.40-1.05)	0.08	0.63 (0.39-1.01)	0.06	0.71 (0.43-1.19)	0.20
5-7 times/week	-		0.41 (0.24-0.69)	0.001	0.50 (0.29-0.87)	0.01	0.49 (0.28-0.85)	0.01	0.54 (0.30-0.96)	0.04
Wealth quintile										
Richest	-		-		ref		ref		ref	
2nd	-		-		1.56 (0.95-2.57)	0.08	1.39 (0.85-2.27)	0.20	1.28 (0.77-2.14)	0.34
3rd	-		-		1.35 (0.80-2.29)	0.26	1.25 (0.74-2.11)	0.41	1.06 (0.62-1.83)	0.82
4th	-		-		1.79 (1.07-2.99)	0.03	1.61 (0.96-2.69)	0.07	1.26 (0.73-2.16)	0.40
Poorest	-		-		3.09 (1.79-5.33)	<0.001	2.79 (1.62-4.81)	<0.001	2.20 (1.25-3.87)	<0.01

Education										
Higher education	-		-		-		ref		ref	
Intermediate	-		-		-		1.20 (0.63-2.31)	0.58	1.24 (0.61-2.53)	0.55
No qualification	-		-		-		1.97 (1.01-3.85)	0.05	1.78 (0.85-3.71)	0.13
Depressive mood	-		-		-		-		1.17 (1.02-1.36)	0.03
Cognition	-		-		-		-		0.97 (0.95-0.99)	0.001
Loneliness	-		-		-		-		1.13 (1.00-1.28)	0.05

Model 1: Adjusted for age and gender.

Model 2: Further adjusted for alcohol.

Model 3: Further adjusted for wealth.

Model 4: Further adjusted for education.

Model 5: Further adjusted for depressive mood, cognition and loneliness.

3.3.7.2 Supplementary analysis - smoking-related diseases and inflammatory markers

COPD, CVD, cancers, CRP and fibrinogen were separately added to the final model (Model 5, adjusted for age, gender, alcohol, wealth, education, depressive mood, cognition and loneliness).

When COPD, CRP and fibrinogen were separately added to the final model, current smoking was no longer significantly associated with frailty and ORs decreased by 13.3%, 13.3% and 5.7%, respectively. Adding CVD and cancers made little difference in OR of current smoking. In each of the models, COPD and CRP were significantly associated with higher odds of frailty (COPD: OR=2.58, 95%CI=1.59-4.20, p<0.001. CRP: OR=1.02 (95%CI=1.00-1.04, p=0.04), while CVD, cancers and fibrinogen were not (**Table 3. 6**)

Table 3. 6. Odds ratios of incident frailty for current smoking and its changes when adding COPD, CVD, cancers, CRP and fibrinogen to Model 5.

	Odds Ratio (95%CI)	P value	Change
Model 5	1.58 (1.00-2.50)	0.05	-
Model 5 + COPD	1.37 (0.85-2.20)	0.19	-13.3%
Model 5 + CVD	1.60 (1.02-2.51)	0.04	+0.6%
Model 5 + cancers	1.59 (1.01-2.50)	0.05	±0.0%
Model 5 + CRP	1.37 (0.80-2.34)	0.25	-13.3%
Model 5 + Fibrinogen	1.49 (0.87-2.55)	0.15	-5.7%

COPD: Chronic obstructive pulmonary disease

CRP: C-reactive protein

CVD: Cardiovascular diseases (angina, myocardial infarction, congestive heart failure or stroke)

3.3.7.3 Supplementary analysis - three smoking groups

At wave 2, 2,281 participants were classified as non-smokers and 261 were classified as current smokers. Non-smokers were re-classified into past smokers

(n=1271) if they stated at wave 2 that they had stopped smoking between waves 1 and 2, or stated at wave 1 that they had ever smoked cigarettes in the past or that were currently smoking. The remainder of non-smokers was re-classified into never smokers (n=1,010).

The multivariable logistic regression models were repeated for OR of frailty for current and past smokers with never smokers as reference. Current smokers were significantly more likely to develop frailty compared with never smokers in Models 1 and 2, but the association became non-significant in Models 3, 4 and 5. There was no significantly association between past smoking and frailty risk in all Models compared with never smoking. (**Table 3.7**)

Table 3. 7. Odds ratios of incident frailty for current and past smoking compared with never smoking. (N=2542)*

	Never smokers (n=1,010)	Past smokers (n=1,271)		Current smokers (n=261)	
Model 1	ref	0.74 (0.54-1.02)	0.07	1.80 (1.12-2.88)	0.01
Model 2	ref	0.79 (0.56-1.13)	0.20	1.87 (1.15-3.06)	0.01
Model 3	ref	0.80 (0.56-1.14)	0.21	1.52 (0.93-2.48)	0.10
Model 4	ref	0.79 (0.56-1.12)	0.19	1.43 (0.90-2.29)	0.13
Model 5	ref	0.79 (0.55-1.14)	0.21	1.40 (0.86-2.28)	0.18

*Odds ratio (95% confidence interval) and p value

Model 1: Adjusted for age and gender.

Model 2: Further adjusted for alcohol.

Model 3: Further adjusted for wealth.

Model 4: Further adjusted for education.

Model 5: Further adjusted for depressive mood, cognition and loneliness.

3.3.7.4 Supplementary analysis - multiple imputation by chained equations

Table 3.8 shows the numbers of participants who had missing data of covariates used for adjustments in the multivariable logistic regression models. While there

were no missing data for age, gender and education, up to 6% of missing data were found in other covariates: alcohol, wealth, depressive mood, cognition and loneliness.

Table 3. 8. Numbers of participants missing data of covariates used for adjustments. (N=2,542)

	Number of participants with missing data at wave 2
Age group	0 (0.0%)
Gender	0 (0.0%)
Alcohol	160 (6.3%)
Wealth	31 (1.2%)
Education	0 (0.0%)
Depressive mood	6 (0.2%)
Cognition	29 (1.1%)
Loneliness	163 (6.4%)

Missing data for alcohol, wealth, depressive mood, cognition and loneliness were imputed using MICE. Auxiliary variables were the same from wave 1 except for alcohol and loneliness, for which auxiliary variables were obtained from wave 3. The alcohol variable at wave 1 was different from the ones at waves 2 and 3, and the loneliness was not measured at wave 1 but at waves 2 and 3. Results of Model 5 with the imputation were essentially the same as those of Model 5. (**Table 3.9**)

Table 3. 9. Comparison between Model 5 (complete case analysis) and Model 5 with missing data imputed using multiple imputation by chained equations (MICE).

	Odds Ratio (95%CI)	P value
Model 5	1.58 (1.00-2.50)	0.05
Model 5 (MICE)	1.57 (1.01-2.43)	0.05

3.3.8 Discussion

The analyses using 2,542 English community-dwelling men and women aged 60 years or older free of frailty at baseline showed that current smokers were 1.6 times more likely to develop frailty than non-smokers over 4 years and that the risk was independent of a wide range of potential confounders; age, gender, alcohol, wealth, education, depressive mood, cognition and loneliness.

The association between current smoking and an increased risk of incident frailty suggests that smoking may play a role in the pathogenesis of frailty. The underlying mechanism by which smokers are predisposed to frailty is not clear but is likely to be multifactorial given the detrimental effects of smoking on a wide range of organs and tissues.[245] Smoking is associated with COPD, CVD and cancers,[245] all of which could cause morbidities and disabilities (both physical and mental), and potentially contribute to increased risks of frailty status. Another possibility is inflammation. Cigarette smoke contains various toxic chemicals and has been shown to be associated with increased levels of inflammatory mediators.[248] Chronic inflammation causes muscle wasting[249] and leads to weight loss, exhaustion, weakness or slow walking speed; these are all major components of frailty.[16] This possible link between smoking and frailty via inflammation is further supported by population-based studies reporting that elevated inflammatory markers are associated with a higher prevalence and incidence of frailty.[250-252]

Therefore, COPD, CVD, cancers and inflammation were considered to be on the causal pathway from smoking to the development of frailty, and to explain at least partially the increased risk of incident frailty in smokers. When COPD, CVD, cancers and two inflammatory markers were separately added to the final models, the significant association between smoking and incident frailty risk was attenuated and became non-significant for COPD, CRP and fibrinogen. The results with CVD or cancers did not show significant changes, which suggests that CVD and cancers were not related to the associations between current smoking and development of frailty.

The analysis was repeated using three smoking groups (never, past and current smoking) using the data from a previous wave in addition to baseline wave data, and showed that using this further categorisation neither current nor past smoking was associated with increased risk of incident frailty compared with never smoking. The lack of association of past smokers and frailty does not support a 'sick quitter' effect that people who are becoming frailty quit smoking. The discrepancy of findings between two and three smoking groups may be due to imprecise measurement of smoking in ELSA into crude categories at both waves. For example, current smokers can range from a person who smokes a few cigarettes a day to a person who has been smoking two packs per day for five decades, and past smokers can be a fit person who temporarily smoked when he/she was a teenager or can be a frail person who had to quit smoking recently because of severe COPD due to life-long heavy smoking. It may also be attributed to the nature of self-reporting, which is subject to response bias and could lead to misclassification.[253] However, as the self-reported smoking history in the ELSA has been validated against salivary cotinine level in **Chapter 2.4 Definition of Smoking**, this bias should have had a minimal effect on this analysis. It would have contributed to more precise analysis if the smoking exposure was quantified over time by pack-years of smoking (a quantitative measurement of exposure to tobacco calculated by multiplying the number of packs of cigarettes smoked per day by the number of years that person has smoked.), however this information is not available in the data source. Given ORs of past smoking for frailty compared with never smoking in all logistic regression models ranged from 0.74 to 0.80 without statistical significance, it was speculated that most of the past smokers were those who smoked temporarily and quit a long time ago, without any current significant smoking-related risks to frailty. Therefore, past smokers and never smokers were combined and treated as one group in the analyses.

Fifteen data sets were newly generated, imputing missing values of alcohol, wealth, depressive mood, cognition and loneliness using MICE, and the final model was repeated. The results with imputed data were almost identical to the complete case analysis.

In conclusion, among community-dwelling older people in England, current smokers compared with non-smokers were significantly more likely to develop frailty over four years.[225] This result is in line with the findings of the systematic review.[226] Given smoking is a modifiable lifestyle factor, smoking cessation may potentially prevent developing frailty or improve frailty status even in old age.

I discuss the strengths and limitations of this analysis and further discuss the meaning and implications of the findings in my final **Chapter 6 OVERALL DISCUSSION**.

4 ALCOHOL

This is the second of three chapters exploring modifiable lifestyle risk factors for frailty. This chapter explores associations between alcohol consumption and risk of frailty. Here I introduce the topic and report my systematic review of the literature. My empirical analysis, findings and a discussion of the interpretation with reference to other literature follow. The findings from this chapter have been published[254, 255] and presented as a poster.[256] (Please see **8 Appendices** for details)

4.1 Introduction

Alcohol consumption, especially in large quantities, is known to have immediate and long term negative effects on the human body and has been shown to be a cause of more than 200 diseases, particularly, liver cirrhosis, CVD and various cancers.[257] Health risks associated with alcohol use also include alcohol dependence, potential alcohol-drug interactions, falls and related injuries.[257] Its harmful use has been reported to result in 3.3 million deaths over the world each year.[257] In older people alcohol consumption may be more harmful, even at a low level, compared with a younger population, especially when they take certain medications, have health problems or drink heavily.[258] Older people can have higher blood alcohol concentration and experience the effects of alcohol more seriously than when they were younger, which predisposes older people at higher risks for falls, car accidents and other unintentional injuries due to drinking.[258] Heaving drinking can worsen existing health problems, including diabetes, hypertension, congestive heart failure, liver disease, cognitive and mood disorders.[258] Many older people take medications for their health problems, and alcohol use can potentially cause alcohol-drug interactions and be hazardous.[258]

The Low Risk Drinking Guidelines issued by the UK Chief Medical Officer state that it is safest for adults (both men and women) not to drink more than 14 units a week on a regular basis .[192] Drinking a large amount of alcohol on one occasion increases immediate risks of harm, injury, accident and even death.[192] Although they don't provide a specific threshold of alcohol quantity for safe drinking on a single occasion, it is recommended to drink slowly with food and limit the total amount of alcohol on

any single occasion.[192] The National Institute of Alcohol Abuse and Alcoholism (NIAAA) shows drinking guidelines for older people recommending that people aged 65 or older who are healthy and do not take medications should not have more than 3 drinks on a given day and 7 drinks in a week and that older people with a health problem or taking certain medications should drink less or should not drink at all.[258]

A number of observational cohort studies have examined the association between alcohol consumption and health outcomes including all-cause mortality, and many of these have shown U- or J-shaped relationships in which light-to-moderate drinkers have the lowest risk compared with non-drinkers and heavy drinkers.[259, 260] This protective effect has been long debated and is still controversial.[261] Although the mechanisms underlying this potential beneficial effect of light-to-moderate alcohol consumption are not clear and lack underpinning robust scientific evidence, it has been speculated that light-to-moderate alcohol intake may improve insulin sensitivity, increase high-density lipoprotein cholesterol, decrease inflammation and increase adiponectin.[262] Some recent studies attributed the lower mortality in light-to-moderate drinkers to various biases. Such biases include (1) misclassification as abstainers of former drinkers who reduce alcohol consumption when they were ill, known as the 'sick quitters' effect, (2) inappropriate selection of reference group, and (3) poor study designs or inadequate adjustment for important confounders.[263-265] Some argued that low-to-moderate drinkers appear to have health benefits because they are compared with non-drinkers, who can include 'sick quitters' and are more likely to have worse socio-demographic and health related factors than drinkers.[259, 264, 265]

Controlling for these factors attenuates or eliminates the apparent protective effect of alcohol.[263-265] However, it is difficult to determine causal inferences using conventional statistical methods. A recent Mendelian randomisation analysis using 261,991 European individuals concluded that increased alcohol consumption is associated with increased risk for coronary heart disease among drinkers of any alcohol quantity, including light-to-moderate drinkers.[266] This suggests that there are no such protective effects for coronary heart disease.

Alcohol consumption may potentially contribute to the development of frailty by accumulating health deficits due to alcohol-related medical conditions. Conversely, alcohol may exert protective effects as described above to prevent developing frailty. Habitual alcohol consumption is one of the most common modifiable lifestyle factors, even in older populations.[267] Therefore it is beneficial to know the relationships between alcohol consumption and frailty as alcohol may be a modifiable risk factor for frailty and an important target in preventative frailty interventions.

There has been little research on prospective associations between alcohol use and frailty. The earlier systematic review[135] mentioned in the smoking chapter found only one prospective study[233] on this topic based on their search for publications between 2001 and 2013. In this study[233] that examined incident frailty defined by the CHS criteria according to self-reported alcohol consumption among 28 thousand women from the Women's Health Initiative Observational Study, women who consumed <1 drink (14g of pure alcohol)/week and 1-14 drinks (14-196g)/week were significantly less likely to develop frailty over three years (OR=0.87, 95%CI=0.77-0.79, OR=0.69, 95%CI=0.61-0.77, respectively) compared with non-drinkers. My thesis therefore aimed to address this gap in knowledge by conducting a more extensive systematic review with meta-analysis and analyzing the nationally representative cohort of older people in England for prospective associations between alcohol consumption and incident frailty.

In this chapter, a systematic review was performed of currently available evidence on the associations of alcohol consumption with subsequent frailty risk, and effect measures obtained from the original studies included in the systematic review were pooled in a meta-analysis. A prospective analysis using the ELSA data was conducted to investigate how alcohol consumption was related to the development of frailty. The findings of both the systematic review[255] and ELSA analysis[254] have been published and are reproduced in **8 Appendices**.

4.2 Systematic Review and Meta-Analysis

4.2.1 Objectives

The objective of this section of the chapter is to conduct a systematic review of the literature for prospective associations between alcohol consumption and subsequent changes in frailty status, and to perform a meta-analysis to synthesise pooled estimates among the community-dwelling older population.

The 'PICO' for the systematic review is as follows:
Population: community-dwelling older people
Intervention/exposure: any alcohol consumption
Comparison: no or low alcohol consumption
Outcome: Frailty status changes

4.2.2 Methods

4.2.2.1 Data source and search strategy

This systematic review was conducted according to a protocol developed with adherence to PRISMA statement[234] (**Appendix 1b**). Five electronic databases (Embase, Scopus, MEDLINE, CINAHL Plus and PsycINFO) were searched for studies published between 2000 and July 2016. Validated definitions of frailty were not generally used prior to 2000, and the two most widely accepted definitions and measurements for frailty, the CHS criteria[16] and the FI[10] were first published in 2001. The search was performed with an explosion function when available and without language restriction, using a combination of MeSH terms and text keywords as follows: ("Alcohols (MeSH)" OR "Alcohol drinking (MeSH)" OR "Drinking behavior (MeSH)" OR "Alcohol consumption (MeSH)" OR "Alcohol drinking patterns (MeSH)" OR "Ethanol (MeSH)" OR "alcohol*" OR "drink*" OR "ethanol") AND ("frailty syndrome (MeSH)" OR "frail*"). A full search results using Medline is summarised in **Appendix 4a**. Reference lists of the relevant articles were also hand searched for additional studies. Forward citation search of the included studies was performed using Google scholar in December 2016. Authors of potentially eligible studies were

contacted for additional data necessary for a meta-analysis. The protocol was registered with PROSPERO (Registration number: CRD42016045445).

4.2.2.2 Study selection and data extraction

Any prospective studies were considered potentially eligible if they examined baseline alcohol use, including both quantity or frequency, and subsequent changes in frailty status among general population in the community. Randomised controlled trials, reviews, conference abstracts, editorials and comments were not considered. When the same cohort was used by two or more studies, the study with the largest size was included. Titles, abstracts and full-texts of the studies identified by the systematic literature search were independently screened for eligibility by myself and the second reviewer (Dr Ann Liljas). Any disagreement was solved by discussion. The data extracted from each eligible study were; first author, study cohort name if any, publication year, location, sample size, proportion of women, age (mean and range), alcohol measure, frailty criteria, follow-up period and findings, which included effect measures and covariates for adjustment.

4.2.2.3 Methodological quality assessment

Methodological quality of the eligible studies were examined using the Newcastle-Ottawa Scale for cohort studies,[235] as in the previous chapter. Please see **Chapter 3.2.2.3 Methodological Quality Assessment** for detail.

4.2.2.4 Data analysis

When two or more studies provided the same or equivalent effect measures, such as ORs or hazard ratios, alcohol variables and frailty outcomes, it was attempted to combine the effect measures to calculate pooled risk estimates. Necessary data were enquired for by contacting authors of the original studies. The presence and degree of heterogeneity across the studies were examined using the chi-square test and I^2 statistic, respectively. The I^2 values of 25%, 50% and 75% were considered as low, moderate and high heterogeneity, respectively.[268] A random-effects model if heterogeneity was present, or a fixed-effects model if heterogeneity was absent, were used to calculate pooled risk estimates using the generic inverse variance

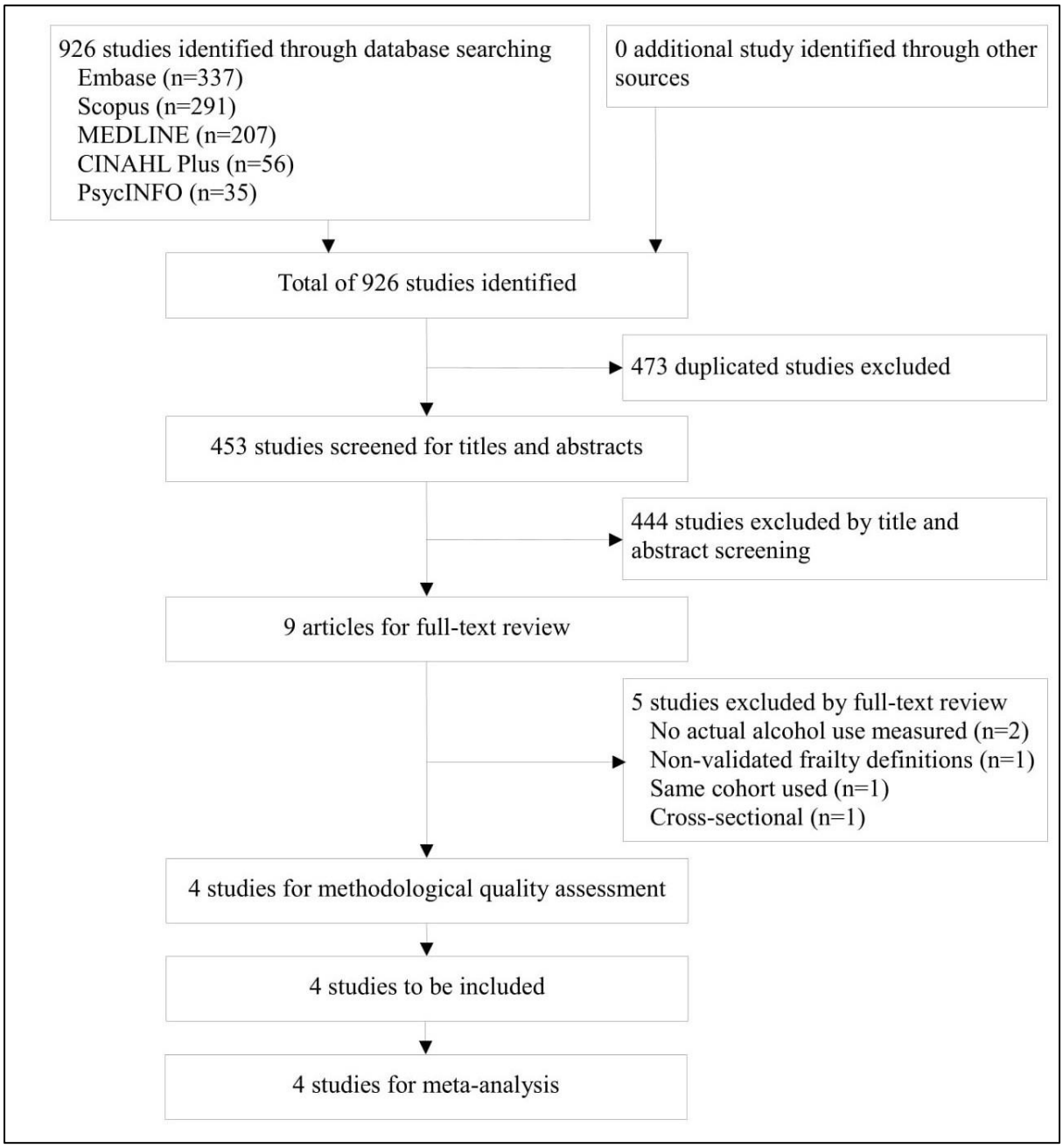
method. Publication bias was examined using Begg-Mazumdar's[269] and Egger's[270] tests. All meta-analyses were conducted using Review Manager 5 (version 5.2, The Cochrane Collaboration, Copenhagen, Denmark). $p<0.05$ was considered as statistically significant.

4.2.3 Results

4.2.3.1 Selection processes

Figure 4.1 is a PRISMA flowchart showing study selection with the number of studies at each stage. The systematic search of the five databases yielded 926 studies. Of these studies, 473 duplicates were excluded and 444 studies were excluded by title and abstract screening, leaving nine studies for full-text review. Five of the nine studies were further excluded because they did not use measured alcohol consumption (n=2), or used a non-validated frailty definition (n=1), or used the same cohort with a smaller number of participants (n=1) or was cross-sectional (n=1). Four studies[233, 237, 271, 272] remained and were included in this review.

Figure 4. 1. PRISMA Flowchart (Alcohol and frailty)



4.2.3.2 Study characteristics

All four studies were considered to have adequate methodological quality based on the Newcastle-Ottawa Quality Assessment Scale. The scores ranged from 5 to 8, with a mean of 6.5. (**Table 4.1**) **Table 4.2** presents the characteristics and findings of interest of the four studies included in this systematic review. Three studies[237, 271, 272] were published recently (2014-16) and one study[233] was published in 2005. One

study was from the US[233] and three studies[237, 271, 272] were from European countries. The study size ranged from 840[272] to 28,003.[233] One study[233] included only female participants from the Women's Health Initiative Observational Study and the other three studies[237, 271, 272] used mixed cohorts with a female proportion of 52.2-57.3%. Age ranges of the participants were >55 years,[237] >60 years,[271] 65-70 years[272] and 65-79 years.[233] Follow-up periods ranged from 2[237] to 3.3 years.[271] All four studies[233, 237, 271, 272] used modified versions of the CHS criteria[16] to define frailty. One study[271] provided adjusted OR of frailty for alcohol quantity, and three studies[233, 237, 272] provided sufficient data, in the text or from the authors on request, to calculate crude OR of frailty for alcohol quantity[233, 272] or frequency.[237]

Table 4. 1. Methodological quality assessment using the Newcastle-Ottawa Quality Assessment Scale for cohort studies.

The Newcastle-Ottawa Quality Assessment Scale for cohort studies										
	Selection				Comparability		Outcome			
	1	2	3	4	1a	1b	1	2	3	total
Ortola 2016	1	1	0	1	1	1	1	1	1	8/9
Etman 2014	1	1	0	n/a	1	1	1	1	0	6/8
Seematter-Bagnoud 2014	1	1	0	1	1	1	1	1	0	7/9
Woods 2005	1	1	0	1	0	0	1	1	0	5/9

Appendix 3 for detail.

4.2.3.3 Study findings

Ortola 2016

Ortola and colleagues used data of 2,086 Spanish community-dwelling men and women aged 60 and older to examine incident frailty risk according to alcohol consumption.[271] Compared with non-drinkers, heavy drinkers (defined as consuming alcohol >40g/day for men and >24g/day for women) had a significantly lower risk of developing frailty over 3.3 years (adjusted OR=0.24, 95%CI=0.10-0.56. See **Table 4.2** for covariates for adjustment).[271] Odds of frailty for moderate drinkers (defined as consuming alcohol <40g/day for men and <24g/day for women) and past drinkers

compared with non-drinkers were non-significant (OR=0.90, 95%CI=0.65-1.25; OR=1.04, 95%CI=0.64-1.68, respectively).[271]

Etman 2014

A large multinational study from 11 European countries including nationally representative samples aged 55 and older classified participants as frail, pre-frail and non-frail according to modified CHS criteria and examined the risk of worsening in frailty status (from non-frail to pre-frail or frail, or from pre-frail to frail) over two years.[237] Compared with hardly ever/never alcohol consumption, consuming alcohol for 1-2 days, 3-4 days and 5-7 days per week was associated with 12-21% decreased risk of worsening frailty status (adjusted OR=0.84, 95%CI=0.73-0.96; adjusted OR=0.88, 95%CI=0.73-1.06; and adjusted OR=0.79, 95%CI=0.71-0.88, respectively. See **Table 4.2** for covariates for adjustment) although drinking for 3-4 days per week did not reach statistical significance.[237]

Woods 2005

The Women's Health Initiative Observational Study from the US followed 28,003 women aged 65-79 free of frailty at baseline for three years for incident frailty using a nominal multinomial logistic regression models.[233] Compared with non-drinkers, decreased risk was observed in women who consumed less than 1 drink per week (unadjusted OR=0.87, 95%CI=0.77-0.97) and 1-14 drinks per week (unadjusted OR=0.69, 95%CI=0.61-0.77) while the risk of incident frailty was not significantly different in women who consumed more than 14 drinks per week (unadjusted OR=0.93, 95%CI=0.74-1.16).[233]

Seematter-Bagnoud 2014

In a prospective study from Switzerland, 840 robust community-dwelling older people in a narrow age range of 65-70 years without any of the five Fried's phenotype components at baseline were observed three years later for new development of any of the five components.[272] Non-drinkers were found to have twice the risk of developing any of the five components (adjusted OR=2.00, 95%CI=1.02-3.91, p=0.04) and heavy drinkers, defined as consuming >20 drinks for men and >12 drinks for women per week, had non-significant risk (adjusted OR=0.73, 95%CI=0.34-1.58, p=0.43), compared with light-to-moderate drinkers, defined as

consuming up to 14 drinks for men and 7 drink for women per week, controlling for potential confounders, including age, gender, education, smoking, self-rated health, comorbidity, cognitive impairment, functional status, previous alcohol-related problem and significant changes in alcohol during the follow-up.[272]

Table 4. 2. Summary of included studies on alcohol consumption associated with subsequent frailty status change among community-dwelling older people.

Author, Year Location N*	Female (%)*	Age**	Follow-up period	Findings (unadjusted)	Findings (adjusted)
Ortola 2016 Spain 2,086	52.2%†	68.5†	3.3 years	Unadjusted logistic regression models for incident frailty (nondrinkers as reference) OR=1.10, 95%CI=0.72-1.68 for ex-drinker OR=0.65, 95%CI=0.50-0.85 for <40g (men) or <24g (women) of alcohol/day OR=0.19, 95%CI=0.09-0.42 for ≥40g (men) or ≥24g (women) of alcohol/day	Logistic regression models for incident frailty adjusted for age, gender, education, smoking, time watching TV, leisure-time physical activity, household physical activity, Trichopoulou index, BMI, cardiovascular disease, diabetes, respiratory disease, musculoskeletal disease, depression, IADL, SF-12 physical and mental component summary scores (nondrinker as reference) adjOR=1.04, 95%CI=0.64-1.68 for ex-drinker adjOR=0.90, 95%CI=0.65-1.25 for <40g (men) or <24g (women) of alcohol/day adjOR=0.24, 95%CI=0.10-0.56 for ≥40g (men) or ≥24g (women) of alcohol/day

Author, Year Location N*	Female (%)*	Age**	Follow-up period	Findings (unadjusted)	Findings (adjusted)
Etman 2014 11 European countries‡ 14,082	54.3%	≥55	2 years	Not reported	Logistic regression models for worsening frailty compared with no change in frailty status adjusted for age, gender, education, baseline frailty and country (hardly ever/never drinker as reference) adjOR=0.84, 95%CI=0.73-0.96 for drinking for 1-2 days/week adjOR=0.88, 95%CI=0.73-1.06 for drinking for 3-4 days/week adjOR=0.79, 95%CI=0.71-0.88 for drinking for ≥5 days/week Unadjusted logistic regression models for incident frailty (calculated, no drinker as reference, N=12,905) OR=0.45, 95%CI=0.37-0.55 for drinking for 1-2 days/week OR=0.35, 95%CI=0.25-0.49 for drinking for 3-4 days/week OR=0.63, 95%CI=0.54-0.75 for drinking for ≥5 days/week
Seematter-Bagnoud 2014 Switzerland 840	57.3%	65-70	3 years	Unadjusted logistic regression models for incident frailty (calculated, no drinker as reference) OR=0.72, 95%CI=0.15-3.37 for 1-14 drinks (men) or 1-7 drinks (women)/week OR=0.33, 95%CI=0.05-2.35 for >14 drinks (men) or >7 drinks (women)/week	Not reported

Author, Year Location N*	Female (%)*	Age**	Follow-up period	Findings (unadjusted)	Findings (adjusted)
Woods 2005 USA 28,003	100.0%	65-79	3 years	Unadjusted multinomial logistic regression models (no drinker as reference) OR=0.87, 95%CI=0.77-0.97 for <1 drink/week OR=0.69, 95%CI=0.61-0.77 for 1-14 drinks/week OR=0.93, 95%CI=0.74-1.16 for >14 drinks/week Unadjusted logistic regression models for incident frailty (calculated, no drinker as reference) OR=0.80, 95%CI=0.74-0.78 for <1 drink/week OR=0.54, 95%CI=0.49-0.58 for 1-14 drinks/week OR=0.69, 95%CI=0.58-0.81 for >14 drinks/week	Not reported

All studies used modified frailty phenotype criteria.

* Cohort used for analysis of interest, or entire cohort.

** Mean age, age range, or age for inclusion.

95%CI: 95% confidence interval, adjOR: Adjusted odds ratio.

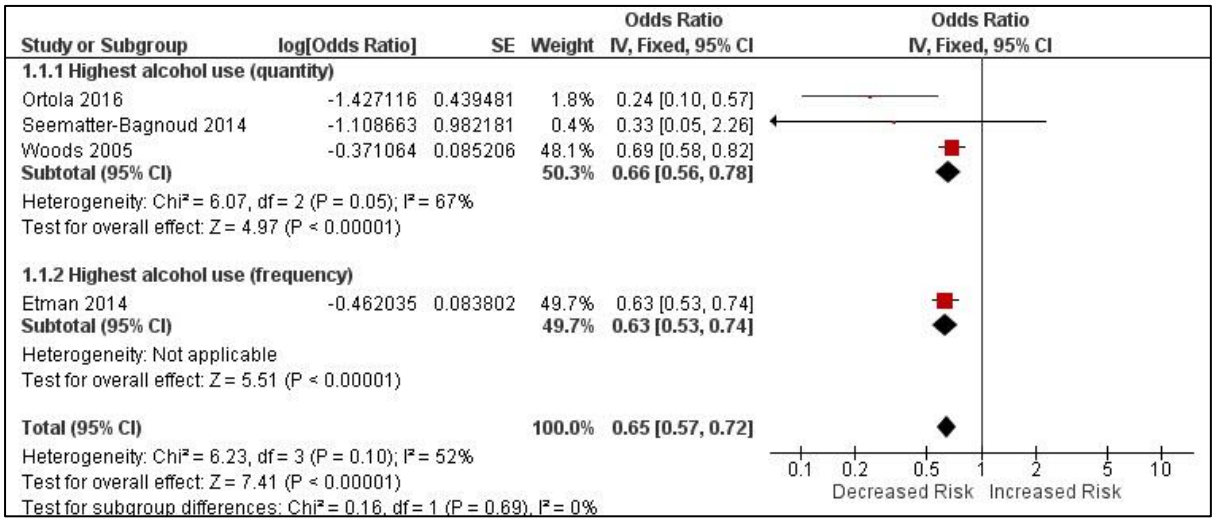
† Calculated from available data

‡ Sweden, Denmark, Germany, the Netherlands, Belgium, Switzerland, Austria, France, Italy, Spain and Greece

4.2.3.4 Alcohol consumption and incident frailty risk

Three studies[233, 271, 272] measured quantity of alcohol consumption and one study[237] used a frequency measurement according to the number of days they were consuming alcohol drinks. Adjusted and unadjusted OR of frailty for the highest or the most frequent alcohol use categories compared with no drinking were used for a meta-analysis. ORs of the three studies with quantity of alcohol measurements[233, 271, 272] were pooled using a fixed-effects model due to the absence of high heterogeneity (I^2=67%, p=0.05), and showed a 34% reduced odds of frailty for the highest alcohol use (3 studies: pooled OR=0.66, 95%CI=0.56-0.78, p<0.001). Adding the other study using frequency of alcohol use did not change the result significantly (4 studies: pooled OR=0.63, 95%CI=0.53-0.74, p<0.001). (**Figure 4.2**) Begg-Mazumdar's and Egger's tests were able to assess publication bias only for the latter study group including four studies, which showed no evidence of publication bias (p value>0.10 for both tests), but not for the former group including three studies due to the small number of the included studies.

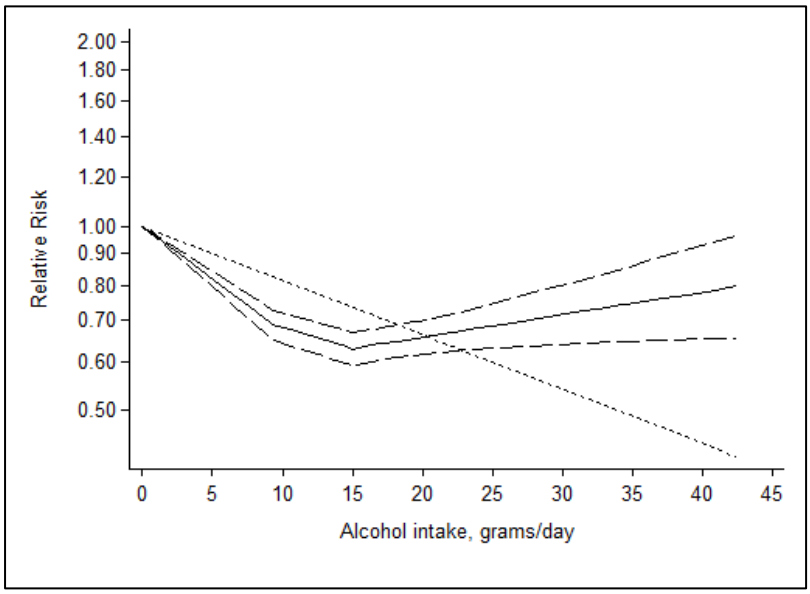
Figure 4. 2. Forest plots of odds ratio of incident frailty risk according highest alcohol use (quantity and frequency) compared with no alcohol use.



Permission for this figure obtained from Oxford Academic.

I conducted a further dose-response meta-analysis[273] using ORs of frailty according to quantitative alcohol consumption provided by the three studies,[233, 237, 272] which showed a significant non-linear association. **Figure 4.3** presents the U-shaped curve showing that the frailty risk decreased until around 15 g/day of alcohol consumption (corresponding to approximately 13 UK units/week) and increased thereafter.

Figure 4. 3. Dose-response linear and non-linear relationships between alcohol consumption and incident frailty risk. CI: confidence interval. (The same figure used in a paper, Non-linear association between alcohol and incident frailty among community-dwelling older people: A dose-response meta-analysis. Kojima G, Iliffe S, Liljas A, Walters K. Biosci Trends 2017 (Open access))



Another very recent study involving older business executives in Finland examined 3-year incident frailty defined by the frailty phenotype according to alcohol consumption groups and showed that non-drinkers had a non-significant 41% higher odds of frailty (OR=1.41, 95%CI=0.62-3.21) compared with those drinking 1-98g of alcohol/week (>0-7 UK units/week, as in this thesis), which supports the findings of this thesis.

4.2.4 Discussion

This systematic review identified four prospective cohort studies examining associations between alcohol consumption according to quantity and frequency and subsequent frailty risk. The findings of the included studies were mixed, showing high alcohol consumption was significantly associated with decreased risk of incident frailty compared with abstinence in two studies, however this association was not found in the remaining study. None of the included studies showed alcohol consumption significantly *increased* risk of incident frailty, compared with abstinence. The pooled estimates suggested that the highest alcohol use was associated with lower risk of incident frailty compared with no alcohol use. All included studies used non-drinkers as their reference group.

The significantly lower risk of incident frailty among drinkers in the highest alcohol use categories compared with non-drinkers could be due to possible protective effects of alcohol against frailty. However it is more likely to be due to the 'sick quitters' effect, which artificially generated lower frailty risks among drinkers by using non-drinkers as a reference group, who might have quit drinking because of ill health.[274, 275] Another possibility is healthy survivors effect, where those with high alcohol consumption injuries to their health had died early and those who drinking healthily (or in some other way protected from the effects of high alcohol consumption) survived. More in-depth interpretations of the findings will follow in the **Discussion chapter**.

Possible U- or J-shaped associations were observed in two studies.[233, 237] One study created four groups based on the number of drinks per week, and moderate drinkers (1-14 drinks/week) had a lower risk of frailty than non-drinkers, light drinkers (<1 drink/week) or heavy drinkers (>14 drinks/week).[233] Another study used the number of drinking days per week to create four groups (hardly ever/never, 1-2 days/week, 3-4 days/week and 5-7days/week) and showed that those drinking 1-2 days a week had the lowest risk of worsening frailty and those drinking 3-4 days a week had the lowest risk of incident frailty.[237]

In my current review studies measuring alcohol consumption in quantity or frequency were included and examined, however the nature or patterns of alcohol consumption may also affect subsequent frailty status.[276] One of the included studies examined two drinking patterns: a Mediterranean drinking pattern defined as moderate alcohol intake with >80% wine, and a pattern of drinking alcohol only with meals, and showed both patterns were significantly associated with lower incident risk of frailty adjusting for multiple confounders (OR=0.68, 95%CI=0.47-0.99; OR=0.53, 95%CI=0.31-0.92, respectively).[271] A further study not included in my review has examined trajectories of frailty status over eight years using the Frailty Index in 12270 older people.[243] While this study did not measure alcohol quantity or frequency, it showed that those reporting concerns about alcohol use themselves or reported by relatives/friends were more likely to have worse frailty status at baseline and to belong to the worse frailty trajectory pattern.[243] In this context, alcohol use may potentially increase risks of frailty.

Although alcohol consumption may have some theoretical benefits against frailty, in general, the evidence is limited and with some methodological concerns. First, non-drinkers were used as a reference group by all included studies, which may be problematic due to the 'sick quitters' effect.[274, 275] Second, the pooled estimate was based on the mostly unadjusted risk estimates and there were likely to be important confounders, such as age, gender, education, socioeconomic status, smoking, depressive symptoms and cognitive function. Third, alcohol quantity cut-points used by the included studies for defining the highest alcohol consumption groups were >280g/week (men) and >168g/week (women),[271] and >196g (=14 drinks)/week.[233, 272] Therefore extreme drinkers or binge drinkers, who may be at high risk of incident frailty, were not well delineated, leading to the apparently protective effect of alcohol against frailty. The other limitations include that a relatively small number of studies (four) were found by the systematic review, probably because the association between alcohol consumption and frailty has not yet been extensively studied. In addition, due to different cut-points or types of alcohol measurements employed by the studies, it was not possible to examine using a simple meta-analysis if there were U- or J-shaped associations between alcohol use and frailty, as those found between alcohol use and mortality.

Although alcohol consumption may have some theoretical benefits against frailty, the evidence is limited and with some methodological concerns. There is no clear evidence to support therapeutic use of alcohol for non-drinkers and it cannot be advocated that non-drinkers should start drinking, especially given the potential harms from alcohol. The decreased risk of incident frailty with heavier consumption suggested in the meta-analysis of the current review may not be a true finding, for methodological reasons mentioned above. A well-designed study that addresses these methodological concerns is therefore needed.

4.3 Alcohol Consumption and Incident Frailty (ELSA)

The systematic review demonstrated that few studies had been conducted which had methodological limitations and no studies were identified conducted in a UK setting.

4.3.1 Objective

The objective of the second section of this chapter is therefore to examine the association of alcohol consumption with the risk of incident frailty in community-dwelling older people, controlling for important confounders and addressing methodological limitations of an appropriate comparator group.

4.3.2 Study Population

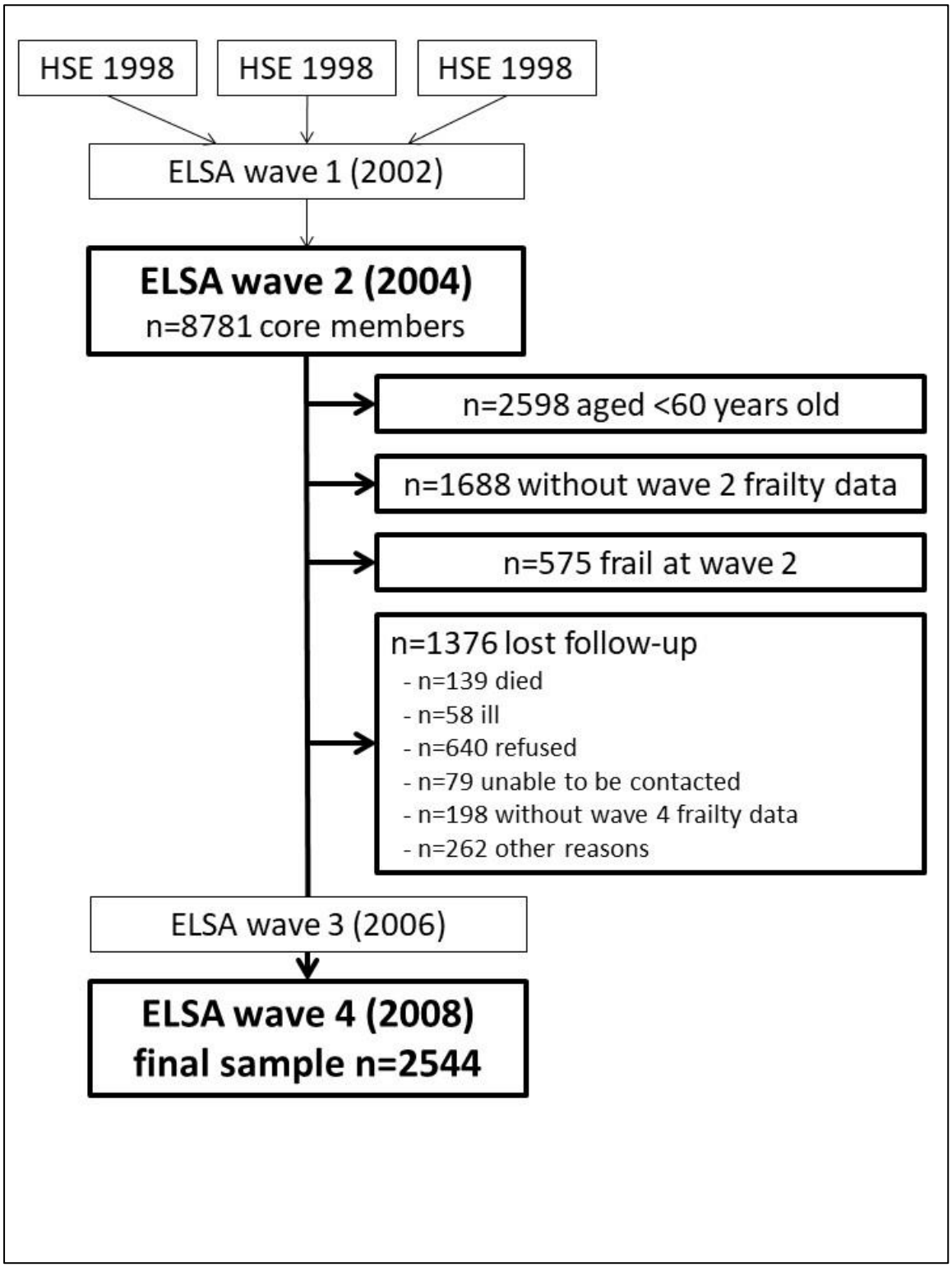
The ELSA population is described in detail in **Chapter 2.1 English Longitudinal Study of Ageing (ELSA)**. The population used for the alcohol and incident frailty analyses in this chapter was the participants who were aged 60 years or older at wave 2 (baseline) and with information on frailty status at waves 2 and 4 and alcohol consumption at waves 0 or 2.

A total of 8,781 core members had an interview at wave 2, among which 2,598 were younger than 60 years old and were excluded. Among 6,183 participants aged 60 or

older, 1,688 who did not have valid data for frailty at wave 2 and 575 who were frail at wave 2 were excluded.

Between waves 2 and 4, a total of 1,376 dropped out: n=139 for death, n=58 being ill, n=640 for refusal, n=79 for being unable to contact, N=198 for no available data for frailty at wave 4 and other reasons (n=262), leaving the final analytic sample of 2,544 participants. (**Figure 4.4**)

Figure 4. 4. ELSA final analytic population for alcohol analyses.



4.3.3 Predictor Variable - Alcohol

Predictor variable of the main analysis was quantity of alcohol consumption per week in UK units. Quantity of alcohol consumption on the heaviest drinking day of the last week and frequency of alcohol consumption were also used in supplementary analysis. Please see **Chapter 2.5 Definition of Alcohol Consumption** for detail.

4.3.4 Outcome Variable - Incident Frailty

Outcome variable in the main analysis was incident frailty, which was defined as new development of frailty (the frailty phenotype score $\geq$3) in those who were pre-frail or robust (the frailty phenotype score 0-2) at baseline. Frailty was defined by the frailty phenotype including the five characteristics of weight loss or 'shrinking', exhaustion, weakness, slow walking speed and low physical activity.[16] Please see **Chapter 2.3 Definition of Frailty** for detail.

4.3.5 Covariates

In this chapter, baseline covariates for adjustment in the main analyses were age, gender, smoking, education and wealth. These variables influence both alcohol consumption and frailty and are therefore chosen as covariates for adjustment, a priori based on evidence from the literature[11, 135, 193] and discussion with my supervisors. In addition, cognitive function, depressed mood, self-reported general health and comorbidities were also considered as potential confounders. However, these four factors were considered to be potentially in the causal pathway from alcohol consumption to development of frailty and thus were not used in the main analysis because alcohol can cause cognitive impairment, depressed mood, comorbidity, and poor health status[267] which in turn can cause frailty.[138] In supplementary analyses, baseline self-reported general health and a comorbidity index were additionally added in the fully adjusted model in order to explore 'sick quitters' effect, where non-drinkers may be those who had quit drinking due to health reasons, such as ill-health due to multi-comorbidity. Please see **Chapter 2.6 Definitions of Covariates** for detail of how each covariate was measured.

4.3.6 Statistical Analyses

4.3.6.1 Main analyses

As in the smoking chapter the participants who were included in the alcohol analyses and the participants who were excluded due to loss to follow-up and missing data were compared for frailty status, alcohol-related variables, age, gender, smoking, wealth, education and self-reported general health using a chi-square test and for comorbidity index using a t-test.

Baseline characteristics were compared across five groups based on quantity of alcohol consumption per week as described in **Chapter 2.5.1. Quantity of Alcohol Consumption Per Week**.

Multivariable logistic regression models were used to examine risks of incident frailty for the alcohol consumption groups. Although a non-drinker group has been used as a reference group in many studies in the past, this group is known to have a worse health profile than drinkers and may not be or have quit drinking due to ill health, known as the 'sick quitters' effect'.[274, 275] Therefore, in order to avoid this problem, low drinkers (>0, <=7 units) were used as a reference. Please see **Chapter 2.8.1 Main Analysis** for detail.

4.3.6.2 Supplementary analysis

I conducted a series of supplementary analyses to explore how comorbidity and self-reported general health mediated associations between alcohol consumption and incident frailty, and if quantity of alcohol consumption on the heaviest drinking day and frequency of alcohol consumption were associated with incident frailty risks. I also explored possible non-linear associations between alcohol consumption and incident frailty using restricted cubic spline.

4.3.6.2.1 Comorbidity index and self-reported general health

Non-drinkers have been shown to have worse health profile than drinkers, which may be due to 'sick quitters' effects.[274, 275] I explored the possibility of confounding resulting from a worse baseline health profile of non-drinkers than drinkers by adding the comorbidity index and self-reported general health separately to the final multivariable logistic regression model because comorbidity index and self-reported general health can be a good marker of overall health status.

4.3.6.2.2 Quantity of alcohol consumption on the heaviest drinking day

Instead of quantity of alcohol consumption per week, quantity of alcohol consumption on the heaviest day was used as a predictor of incident frailty. The multivariable logistic regression models were the same as the main analysis. Among 2544 participants in the main analysis, 246 (9.7%) had missing data for the alcohol consumption on the heaviest drinking day, leaving 2298 participants for this supplementary analysis. For the same reason in **Chapter 4.3.6.1 Main analyses**, those who drank >0, ≤3 units/day were used as a reference group. Please see **Chapter 2.5.2 Quantity of Alcohol Consumption on the Heaviest Drinking Day of the Last Week** for detail.

4.3.6.2.3 Frequency of alcohol consumption

Frequency of alcohol consumption was used as a predictor variable to predict risk of incident frailty in the same multivariable logistic regression models as the main analysis. Among 2544 participants used in the main analysis, 162 (6.4%) had missing data for the frequency of alcohol consumption and were removed, leaving 2382 for this supplementary analysis. Those who drank alcohol 'once a year to once every couple of months' (one category above a group drinking 'none') were used as a reference. Please see **Chapter 2.5.3 Frequency of Alcohol Consumption** for detail.

4.3.6.2.4 Multiple imputation by chained equations

Please see **Chapter 2.8 ELSA Statistical Analysis** for detail.

4.3.6.2.5 Restricted cubic spline

In order to explore the potential of non-linear associations between alcohol consumption and incident frailty, fully multivariable logistic regression models with restricted cubic spline function with 5 knots were conducted for quantity of alcohol consumption per week and incident frailty. The locations of the knots were determined by 5%, 27.5%, 50%, 72.5% and 95% percentiles of the cohort, recommended by Harrell.[277] Given non-drinkers (n=219) were found to have different socio-demographic and health-related characteristics from drinkers, only drinkers (n=2,325) were included in this analysis.

4.3.7 Results

4.3.7.1 Main analyses

There were 3,920 non-frail participants who were 60 years old or over at wave 2 and had data on frailty and alcohol quantity per week, among which 2,544 participants with data on frailty status at wave 4 were included as an analytical sample, and 1,376 were excluded for reasons described in **Chapter 4.3.2 Study Population** and **Figure 4.3**.

There were significant differences between those who were excluded and included. Those who were excluded were significantly frailer, older, likely to be current smokers and more likely to have lower wealth, education and self-reported general health and higher comorbidity index. This may generate a bias and cause the findings towards no effects of alcohol on incident frailty risk. No statistically significant differences were observed in gender and alcohol consumption. (**Table 4.3**)

Table 4. 3. Comparisons between those included in the analyses (n=2,544) and those excluded due to missing data (n=1,376).

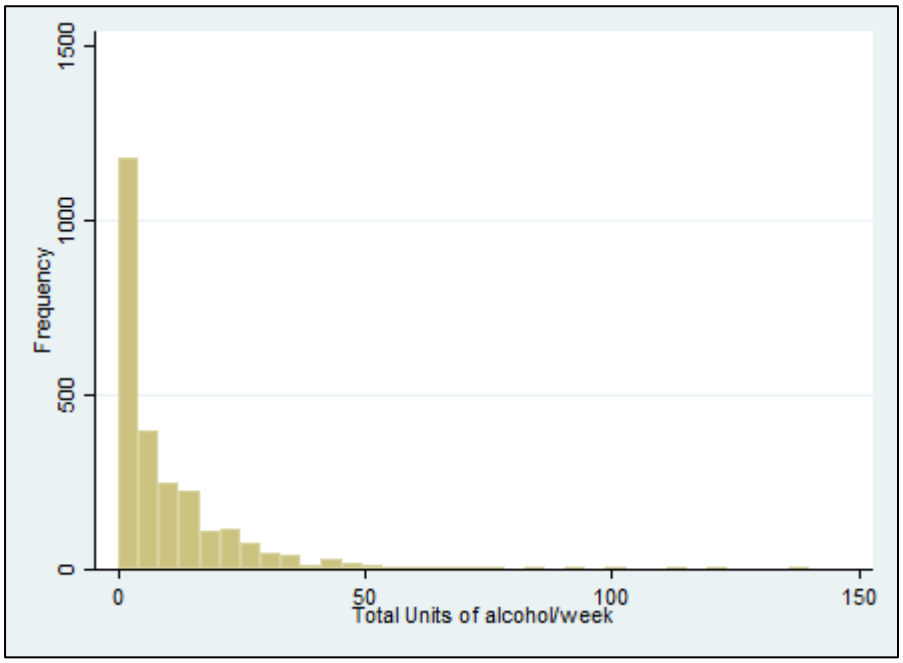
Variables at wave 2*	Included n=2,454	Excluded n=1,376	P value
Frailty status			
Robust	1,431 (56.3%)	624 (45.4%)	<0.001
Pre-frail	1,113 (43.8%)	752 (54.7%)	
Alcohol (wave 0)			
non-drinkers	219 (8.6%)	131 (9.5%)	0.61
>0, <=7 units/week	1,225 (48.2%)	673 (48.9%)	
>7, <=14 units/week	467 (18.4%)	258 (18.8%)	
>14, <=21 units/week	268 (10.5%)	129 (9.4%)	
>21 units/week	365 (14.4%)	185 (13.4%)	
Age group			
60-64	611 (24.0%)	264 (19.2%)	<0.001
65-69	826 (32.5%)	377 (27.4%)	
70-74	543 (21.3%)	284 (20.6%)	
75-79	354 (13.9%)	229 (16.6%)	
80+	210 (8.3%)	222 (16.1%)	
Gender			
Male	1,150 (45.2%)	640 (46.5%)	0.43
Female	1,394 (54.8%)	736 (53.5%)	
smoking status			
Never/past	2,281 (89.7%)	1,188 (86.3%)	0.001
Current	261 (10.3%)	188 (13.7%)	
Wealth quintile			
Richest	662 (26.3%)	251 (18.4%)	<0.001
2nd	570 (22.7%)	309 (22.6%)	
3rd	523 (20.8%)	301 (22.0%)	
4th	446 (17.8%)	260 (19.0%)	
Poorest	312 (12.4%)	245 (17.9%)	
Education			
Higher education	322 (12.7%)	115 (8.4%)	<0.001
Intermediate	1314 (51.7%)	623 (45.3%)	
No qualification	908 (35.7%)	637 (46.3%)	

Variables at wave 2*	Included n=2,454	Excluded n=1,376	P value
Comorbidity index	1.6 (1.3)	1.8 (1.4)	<0.001
Self-reported general health			
Excellent	366 (14.4%)	148 (10.8%)	<0.001
Very good	838 (33.0%)	346 (25.2%)	
Good	873 (34.3%)	507 (36.9%)	
Fair	394 (15.5%)	306 (22.2%)	
Poor	72 (2.8%)	69 (5.0%)	

*t-test and chi-square test were used for continuous and categorical variables, respectively. Percentages may not sum up to 100% due to rounding. Mean ± standard deviation or n (%).

The distribution of alcohol consumption per week was skewed to the right with the maximum value of 140 units (**Figure 4.5**), with 219 non-drinkers. The mean and median were 9.5 and 4.9 units of alcohol consumed per week (standard deviation=12.6, interquartile range=13.3).

Figure 4. 5. Distribution of alcohol consumption per week in UK units.



The baseline characteristics of 2,544 participants are shown in **Table 4.4**, compared across the alcohol consumption groups. The number of non-drinkers, low drinkers, moderate drinkers, high drinkers and very high drinkers were 219 (8.6%), 1,225 (66.5%), 467 (16.4%), 268 (5.4%) and 365 (2.2%), respectively. Two-thirds of the cohort consumed 7 units of alcohol or less per week (n=1,225, 66.5%). Approximately a quarter (633, 24.9%) consumed more than 14 units of alcohol per week, the threshold for low-risk drinking recommended in the recently published guidelines of the UK Chief Medical Officer.[192] At baseline non-drinkers were more likely to be pre-frail rather than robust, older, women, current smokers, with no educational qualification, in the lowest wealth quintile and to have a higher comorbidity index.

Table 4. 4. Baseline characteristics of ELSA participants in alcohol consumption and incident frailty analysis. (N=2,544)

Variable*	Entire sample	Non-drinker	>0 - 7 units/week (low drinkers)	>7 - 14 units/week (moderate drinkers)	>14 - 21 units/week (high drinkers)	>21 units/week (very high drinkers)
Number of participants (%)	2,544	219 (8.6%)	1,225 (66.5%)	467 (16.4%)	268 (5.4%)	365 (2.2%)
Incident frailty, n (%)	271 (10.7%)	43 (19.6%)	140 (11.4%)	41 (8.8%)	26 (9.7%)	21 (5.8%)
Frailty status						
Robust	1,431 (56.3%)	101 (7.1%)	686 (47.9%)	261 (18.2%)	161 (11.3%)	222 (15.5%)
Pre-frail	1,113 (43.8%)	118 (10.6%)	539 (48.4%)	206 (18.5%)	107 (9.6%)	143 (12.9%)
Age group						
60-64	611 (24.0%)	40 (6.6%)	270 (44.2%)	133 (21.8%)	52 (8.5%)	116 (19.0%)
65-69	826 (32.5%)	69 (8.4%)	406 (49.2%)	132 (16.0%)	99 (12.0%)	120 (14.5%)
70-74	543 (21.3%)	54 (9.9%)	266 (49.0%)	94 (17.3%)	60 (11.1%)	69 (12.7%)
75-79	354 (13.9%)	34 (9.6%)	179 (50.6%)	66 (18.6%)	37 (10.5%)	38 (10.7%)
80+	210 (8.3%)	22 (10.5%)	104 (49.5%)	42 (20.0%)	20 (9.5%)	22 (10.5%)
Gender						
Male	1,150 (45.2%)	73 (6.4%)	412 (35.8%)	233 (20.3%)	155 (13.5%)	277 (24.1%)
Female	1,394 (54.8%)	146 (10.5%)	813 (58.3%)	234 (16.8%)	113 (8.1%)	88 (6.3%)
BMI, median (IQR)	27.1 (24.7-30.1)	27.4 (24.3-31.5)	27.1 (24.5-30.3)	26.7 (24.5-29.5)	26.8 (25.0-29.2)	27.1 (25.1-30.0)
Smoking						
Non-smoker	2,281 (89.7%)	188 (8.2%)	1,110 (48.7%)	424 (18.6%)	239 (10.5%)	320 (14.0%)
Current smoker	261 (10.3%)	31 (11.9%)	114 (43.7%)	43 (16.5%)	28 (10.7%)	45 (17.2%)
Wealth quintile						
Richest	662 (26.3%)	24 (3.6%)	267 (40.3%)	146 (22.1%)	94 (14.2%)	131 (19.8%)
2nd	570 (22.7%)	51 (9.0%)	275 (48.3%)	107 (18.8%)	69 (12.1%)	68 (11.9%)
3rd	523 (20.8%)	39 (7.5%)	284 (54.3%)	90 (17.2%)	43 (8.2%)	67 (12.8%)
4th	446 (17.7%)	56 (12.6%)	219 (49.1%)	75 (16.8%)	37 (8.3%)	59 (13.2%)
Poorest	312 (12.4%)	46 (14.7%)	168 (53.9%)	41 (13.1%)	23 (7.4%)	34 (10.9%)
Education						
Higher education	322 (12.7%)	9 (2.8%)	113 (35.1%)	67 (20.8%)	45 (14.0%)	88 (27.3%)
Intermediate	1,314 (51.7%)	91 (6.9%)	617 (47.0%)	258 (19.6%)	159 (12.1%)	189 (14.4%)
No qualification	908 (35.7%)	119 (13.1%)	495 (54.5%)	142 (15.6%)	64 (7.1%)	88 (9.7%)
Cognition, mean (SD)	13.9 (1.3)	13.3 (3.2)	13.9 (3.2)	14.2 (3.2)	13.8 (3.3)	13.9 (3.3)
Comorbidity index	1.6 (1.3)	1.8 (1.4)	1.6 (1.3)	1.6 (1.3)	1.5 (1.3)	1.5 (1.2)
Self-reported general health						
Excellent	366 (14.4%)	21 (5.7%)	159 (43.4%)	82 (22.4%)	39 (10.7%)	65 (17.8%)
Very good	838 (33.0%)	51 (6.1%)	436 (52.0%)	145 (17.3%)	95 (11.3%)	111 (13.3%)
Good	873 (34.3%)	92 (10.5%)	402 (46.1%)	156 (17.9%)	96 (11.0%)	127 (14.6%)
Fair	394 (15.5%)	46 (11.7%)	194 (49.2%)	74 (18.8%)	28 (7.1%)	52 (13.2%)
Poor	72 (2.8%)	9 (12.5%)	33 (45.8%)	10 (13.9%)	10 (13.9%)	10 (13.9%)

BMI: body mass index, IQR: Interquartile range, SD: standard deviation

* Median + interquartile range, mean (standard deviation) or n (%).

The first column reports column percentages and the rest report row percentages. The percentages may not sum up to 100% due to rounding.

Table 4.5 shows the results of multivariable logistic regression models examining incident frailty risks according to alcohol consumption group with a low drinker group (>0 - 7 units/week) as the reference group. In age- and gender-adjusted model (Model 1) non-drinkers were significantly more likely to develop frailty compared with low drinkers (OR=1.88, 95%CI=1.25-2.84, p<0.01) while risks of incident frailty among moderate drinkers (>7 - 14 units/week), heavy drinkers (>14 - 21 units/week) and very heavy drinkers (>21 units/week) were not significantly different from those of low drinkers (ORs=0.62-0.89, all p>0.08). The elevated incident frailty risk for non-drinkers remained significant after further adjusting for smoking, wealth and education in Models 2 to 4, respectively. The risks of moderate, heavy and very heavy drinkers did not change significantly in Models 2 to 4.

Table 4. 5. Multivariable logistic regression models examining associations between alcohol consumption groups and 4-year incident frailty. (N=2,544).

	Model 1		Model 2		Model 3		Model 4	
Variable	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value
Alcohol								
Non-drinkers	1.88 (1.25-2.84)	<0.01	1.79 (1.19-2.69)	<0.01	1.76 (1.16-2.67)	<0.01	1.71 (1.12-2.60)	0.01
>0 – 7 units/week	ref		ref		ref		ref	
>7 – 14 units/week	0.89 (0.60-1.33)	0.57	0.88 (0.59-1.33)	0.55	0.97 (0.63-1.49)	0.89	0.97 (0.64-1.49)	0.90
>14 – 21 units/week	0.83 (0.50-1.39)	0.48	0.81 (0.49-1.36)	0.43	0.95 (0.57-1.60)	0.85	1.01 (0.60-1.70)	0.98
>21 units/week	0.62 (0.36-1.06)	0.08	0.59 (0.34-1.03)	0.07	0.62 (0.36-1.10)	0.10	0.64 (0.37-1.13)	0.12
Age group								
60-64	ref		ref		ref		ref	
65-69	1.16 (0.67-2.02)	0.60	1.21 (0.70-2.12)	0.49	1.23 (0.70-2.15)	0.47	1.16 (0.66-2.03)	0.60
70-74	2.73 (1.64-4.56)	<0.001	2.93 (1.75-4.93)	<0.001	2.80 (1.65-4.74)	<0.001	2.64 (1.56-4.47)	<0.001
75-79	4.98 (2.96-8.39)	<0.001	5.28 (3.11-8.96)	<0.001	4.80 (2.81-8.21)	<0.001	4.43 (2.59-7.58)	<0.001
80+	12.15 (7.12-20.71)	<0.001	13.47 (7.81-23.25)	<0.001	12.05 (6.88-21.11)	<0.001	11.26 (6.43-19.70)	<0.001
Female	1.52 (1.18-2.06)	<0.01	1.51 (1.11-2.05)	<0.01	1.46 (1.07-2.01)	0.02	1.41 (1.03-1.94)	0.03
Smoking								
Non-smoker	-		ref		ref		ref	
Current smoker	-		2.08 (1.35-3.20)	0.001	1.72 (1.11-2.66)	0.01	1.67 (1.08-2.56)	0.02
Wealth quintile								
Richest	-		-		ref		ref	
2nd	-		-		1.60 (0.99-2.59)	0.05	1.51 (0.93-2.43)	0.09
3rd	-		-		1.49 (0.91-2.44)	0.12	1.35 (0.81-2.24)	0.25
4th	-		-		1.91 (1.18-3.10)	<0.01	1.70 (1.04-2.80)	0.04

Poorest	-		-		3.07 (1.85-5.08)	<0.001	2.54 (1.50-4.29)	0.001
Education								
Higher education	-		-		-		ref	
Intermediate	-		-		-		0.99 (0.54-1.82)	0.99
No qualification	-		-		-		1.60 (0.86-2.98)	0.14

Model 1: Adjusted for age and gender.

Model 2: Further adjusted for smoking.

Model 3: Further adjusted for wealth.

Model 4: Further adjusted for education.

CI: Confidence interval

4.3.7.2 Supplementary analysis – comorbidity index and self-reported general health

Non-drinkers consist of those who have never drunk (never drinkers) and those who have quit drinking (past drinkers) and are known to have worse health profile.[265] In order to examine how the elevated incident frailty risk among non-drinkers changes, Model 4 adjusting for age, gender, smoking, wealth and education were further adjusted for comorbidity index and self-reported general health (**Table 4.6**). When comorbidity index was added in Model 4, OR of incident frailty risk slightly decreased by 2.3% but remained significant. However, in Model 4 with self-reported general health, ORs decreased by 13.5% and became non-significant (p value = 0.09). Comorbidity index and self-reported general health were significant in the models. No significant changes were observed in incident frailty risks of moderate, heavy and very heavy drinkers in any models in this supplementary analysis.

Table 4. 6. Odds ratios of incident frailty for alcohol consumption and its changes when adding COPD, CVD, cancers, CRP and fibrinogen to Model 5.

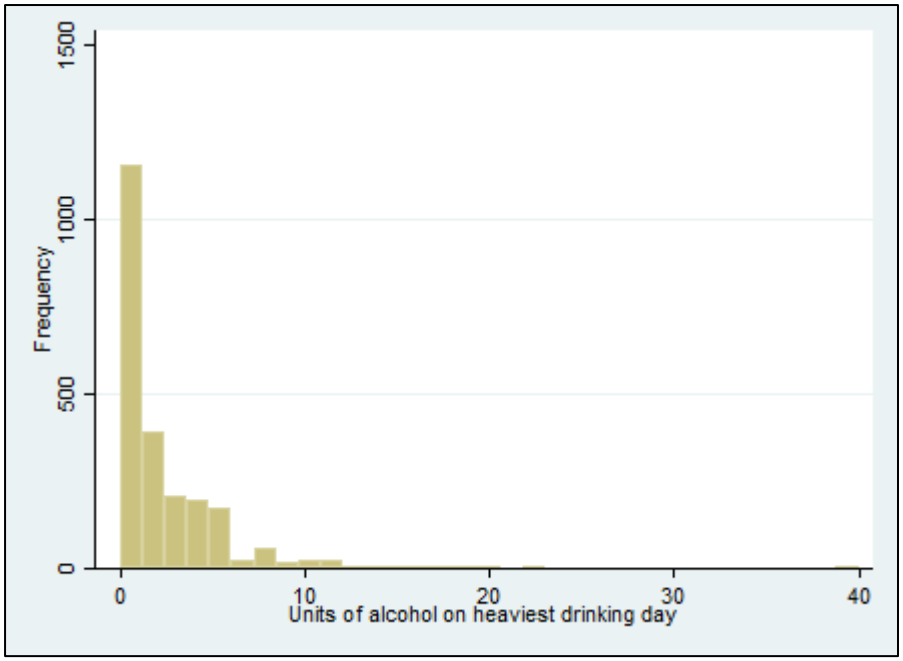
	Odds Ratio (95%CI)	P value	Change
Model 4	1.71 (1.12-2.60)	0.01	-
Model 4 + comorbidity index	1.67 (1.08-2.58)	0.02	-2.3%
Model 4 + self-reported health	1.48 (0.95-2.30)	0.09	-13.5%

CI: Confidence interval

4.3.7.3 Supplementary analysis - quantity of alcohol consumption on the heaviest drinking day

The distribution of alcohol consumption on the heaviest drinking day was skewed to the right with the maximum value of 40 units (**Figure 4.6**), with 890 participants reporting zero. The mean and median were 2.2 and 1.0 units (standard deviation=3.02, interquartile range=3.0).

Figure 4. 6. Distribution of alcohol consumption on the heaviest drinking day in UK units.



The same set of multivariable logistic regression models as used in the main alcohol analysis (Models 1 to 4) calculated ORs of incident frailty risks according to alcohol consumption on the heaviest drinking day (**Table 4.7**). The odds of frailty for non-drinkers and those who drank >3 – 6 units on the heaviest day were significantly higher than that of those who drank >0 – 3 units on the heaviest day in Models 1 and 2 (ORs=1.66-1.71) but became non-significant in Models 3 and 4 with further adjustment for wealth and education, respectively. There were no significant difference between the risks of those who drank more than 6 units on the heaviest day and those who drank >0 – 3 units on the heaviest day in any models.

Table 4. 7. Multivariable logistic regression models examining associations between alcohol consumption (quantity on the heaviest day) groups and 4-year incident frailty. (N=2,298).

	Model 1		Model 2		Model 3		Model 4	
Variable	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value
Alcohol consumption on the heaviest day								
0 units/occasion	1.71 (1.21-2.42)	<0.01	1.66 (1.16-2.36)	<0.01	1.41 (0.98-2.05)	0.07	1.32 (0.91-1.93)	0.15
>0 – 3 units/occasion	ref		ref		ref		ref	
>3 – 6 units/occasion	1.70 (1.02-2.82)	0.04	1.66 (1.00-2.77)	0.05	1.57 (0.95-2.62)	0.08	1.62 (0.97-2.70)	0.07
>6 units/occasion	1.22 (0.58-2.57)	0.60	1.14 (0.55-2.36)	0.73	1.07 (0.50-2.30)	0.85	1.08 (0.51-2.28)	0.84
Age group								
60-64	ref		ref		ref		ref	
65-69	1.37 (0.76-2.46)	0.29	1.45 (0.81-2.62)	0.21	1.45 (0.80-2.61)	0.22	1.33 (0.74-2.40)	0.34
70-74	3.10 (1.79-5.39)	<0.001	3.39 (1.94-5.92)	<0.001	3.19 (1.81-5.63)	<0.001	2.93 (1.66-5.18)	<0.001
75-79	5.96 (3.37-10.52)	<0.001	6.37 (3.60-11.28)	<0.001	5.75 (3.23-10.24)	<0.001	5.24 (2.93-9.37)	<0.001
80+	13.73 (7.65-24.62)	<0.001	15.36 (8.47-27.86)	<0.001	13.39 (7.27-24.66)	<0.001	12.34 (6.69-22.77)	<0.001
Female	1.54 (1.11-2.13)	0.01	1.52 (1.10-2.11)	0.01	1.48 (1.06-2.06)	0.02	1.41 (1.01-1.96)	0.05
Smoking								
Non-smoker	-		ref		ref		ref	
Current smoker	-		2.15 (1.37-3.39)	0.001	1.81 (1.15-2.85)	0.01	1.73 (1.11-2.70)	0.02
Wealth quintile								
Richest	-		-		ref		ref	
2nd	-		-		2.00 (1.20-3.34)	<0.01	1.51 (0.93-2.43)	0.02
3rd	-		-		1.65 (0.98-2.79)	0.06	1.41 (0.82-2.44)	0.21
4th	-		-		2.17 (1.29-3.67)	<0.01	1.82 (1.06-3.14)	0.03

Poorest	-		-		3.52 (2.05-6.04)	<0.001	2.68 (1.52-4.71)	0.001
Education								
Higher education	-		-		-		ref	
Intermediate	-		-		-		1.14 (0.59-2.20)	0.70
No qualification	-		-		-		2.09 (1.05-4.15)	0.04

Model 1: Adjusted for age and gender.

Model 2: Further adjusted for smoking.

Model 3: Further adjusted for wealth.

Model 4: Further adjusted for education.

CI: Confidence interval

4.3.7.4 Supplementary analysis - frequency of alcohol consumption

The number of participants who drank no alcohol, once a year to once every couple of months, once a month to four times a week and five times a week or more were 223 (9.4%), 690 (29.0%), 877 (26.8%) and 592 (24.9%), respectively.

Compared with those drinking once a year to twice a month, those who had not consumed alcohol had a significantly elevated odds of frailty in Model 1 (OR=1.81, 95%CI=1.21-2.42, p=0.01), which slightly decreased as further adjusting for smoking, wealth and education in Models 2 to 4, respectively, but remained statistically significant (OR=1.73, 95%CI=1.06-2.82, p=0.03) in Model 4. There were no significantly increased odds of frailty in those who consumed alcohol 1-4 days a week and those who consumed 5-7 days a week in any model. (**Table 4.8**)

Table 4. 8. Multivariable logistic regression models examining associations between frequency of alcohol consumption and 4-year incident frailty. (N=2,382).

	Model 1		Model 2		Model 3		Model 4	
Variable	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value
Frequency of alcohol consumption								
Not at all	1.81 (1.21-2.42)	0.01	1.79 (1.12-2.86)	0.02	1.79 (1.10-2.90)	0.02	1.73 (1.06-2.82)	0.03
once/year - twice/ month	ref		ref		ref		ref	
1-4 days/week	1.06 (0.73-1.53)	0.78	1.09 (0.75-1.59)	0.66	1.15 (0.78-1.70)	0.48	1.14 (0.77-1.68)	0.52
5-7days/week	0.73 (0.46-1.14)	0.17	0.73 (0.46-1.16)	0.18	0.89 (0.55-1.44)	0.63	0.96 (0.59-1.55)	0.86
Age group								
60-64	ref		ref		ref		ref	
65-69	1.17 (0.66-2.07)	0.58	1.23 (0.70-2.18)	0.47	1.16 (0.66-2.05)	0.60	1.09 (0.62-1.92)	0.76
70-74	2.77 (1.64-4.67)	<0.001	3.00 (1.76-5.10)	<0.001	2.63 (1.54-4.48)	<0.001	2.43 (1.42-4.16)	0.001
75-79	5.17 (3.03-8.81)	<0.001	5.59 (3.25-9.60)	<0.001	4.76 (2.78-8.16)	<0.001	4.38 (2.55-7.50)	<0.001
80+	11.87 (6.81-20.67)	<0.001	13.30 (7.53-23.48)	<0.001	10.76 (6.03-19.18)	<0.001	9.77 (5.49-17.38)	<0.001
Female	1.76 (1.27-2.42)	0.001	1.76 (1.28-2.43)	0.001	1.72 (1.24-2.39)	0.001	1.61 (1.16-2.24)	<0.01
Smoking								
Non-smoker	-		ref		ref		ref	
Current smoker	-		2.11 (1.33-3.36)	<0.01	1.71 (1.08-2.71)	0.02	1.64 (1.04-2.59)	0.03
Wealth quintile								
Richest	-		-		ref		ref	
2nd	-		-		1.56 (0.94-2.57)	0.08	1.44 (0.88-2.36)	0.15
3rd	-		-		1.35 (0.80-2.29)	0.26	1.19 (0.70-2.02)	0.53
4th	-		-		1.79 (1.07-2.99)	0.03	1.52 (0.90-2.56)	0.11

Poorest	-		-		3.09 (1.79-5.33)	<0.001	2.47 (1.42-4.32)	0.001
Education								
Higher education	-		-		-		ref	
Intermediate	-		-		-		1.30 (0.67-2.52)	0.44
No qualification	-		-		-		2.15 (1.09-4.26)	0.03

Model 1: Adjusted for age and gender.

Model 2: Further adjusted for smoking.

Model 3: Further adjusted for wealth.

Model 4: Further adjusted for education.

CI: Confidence interval

4.3.7.5 Supplementary analysis - multiple imputation by chained equations

The number of participants who had missing data in covariates used for adjustments in the main analysis is summarised in **Table 4.9**. Although age, gender and education had no missing data, smoking and wealth had 2 and 31 missing values, respectively.

Table 4. 9. Numbers of participants missing data of covariates used for adjustments. (N=2,544)

	Number of participants with missing data at wave 2
Age group	0 (0.0%)
Gender	0 (0.0%)
Smoking	2 (0.1%)
Wealth	31 (1.2%)
Education	0 (0.0%)

Missing data for smoking and wealth were imputed using MICE and Model 4 of the main analysis was repeated. Auxiliary variables were smoking (current vs non-smokers) and wealth quintiles at wave 1. **Table 4.10** compares the results of Model 4 (left column) and Model 4 repeated with MICE (right column) and the associations between alcohol consumption and frailty risks essentially did not change by the imputation.

Table 4. 10. Comparison between Model 4 (complete case analysis) and Model 4 imputed using multiple imputation by chained equations (MICE).

	Model 4		Model 4 (MICE)	
Variable	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value
Alcohol				
Non-drinkers	1.71 (1.12-2.60)	0.01	1.63 (1.08-2.45)	0.02
>0 – 7 units/week	ref		ref	
>7 – 14 units/week	0.97 (0.64-1.49)	0.90	0.88 (0.59-1.30)	0.51
>14 – 21 units/week	1.01 (0.60-1.70)	0.98	1.12 (0.69-1.80)	0.65
>21 units/week	0.64 (0.37-1.13)	0.12	0.74 (0.44-1.23)	0.25

MICE: Multiple imputation by chained equations.

4.3.7.6 Supplementary analysis - restricted cubic spline

The values of alcohol consumption at the five knots were 0.06, 1.58, 6.26, 14 and 35 units per week. **Table 4.11** shows multivariable logistic regression models with restricted cubic spline function predicting incident frailty over 4 years according to alcohol consumption. In any of Models 1 to 4, alcohol consumption was not significantly associated with incident frailty. No significant non-linear association was observed between alcohol consumption and odds of incident frailty in Models 1 to 4. **Figure 4.7** presents the fully adjusted restricted cubic spline regression curve (Model 4) of associations between alcohol consumption and incident frailty. There were wide 95% CIs, suggesting no significant association between alcohol consumption and incident frailty. There were few participants who drank more than 35 units per week, and the findings beyond this point should be treated with caution.

Table 4. 11. Multivariable logistic regression models with restricted cubic spline function predicting incident frailty over 4 years according to alcohol consumption (N=2,325 drinkers).

	Model 1		Model 2		Model 3		Model 4	
Variable	Coefficient (95%CI)	p value	Coefficient (95%CI)	p value	Coefficient (95%CI)	p value	Coefficient (95%CI)	p value
Alcohol units per week								
First segment	ref		ref		ref		ref	
Second segment	-0.26 (-0.57, 0.04)	0.09	-0.25 (-0.56, 0.05)	0.10	-0.24 (-0.55, 0.06)	0.12	-0.22 (-0.54, 0.09)	0.16
Third segment	15.18 (-6.24, 36.59)	0.17	14.45 (-7.00, 35.90)	0.19	14.19 (-7.29, 35.65)	0.20	14.59 (-7.23, 36.41)	0.19
Fourth segment	-20.91 (-51.04, 9.23)	0.17	-19.91 (-50.11, 10.30)	0.20	-19.54 (-49.77, 10.68)	0.21	-20.35 (-51.04, 10.35)	0.19
Fifth segment	6.25 (-3.78, 16.29)	0.22	5.96 (-4.13, 16.04)	0.25	5.84 (-4.24, 15.92)	0.26	6.42 (-3.80, 16.63)	0.22
Overall significance	-	0.09	-	0.08	-	0.20	-	0.36
P for non-linearity	-	0.39	-	0.43	-	0.50	-	0.61
Age group								
60-64	ref		ref		ref		ref	
65-69	0.12 (-0.46, 0.72)	0.67	0.16 (-0.43, 0.74)	0.60	0.08 (-0.51, 0.67)	0.79	0.14 (-0.46, 0.73)	0.65
70-74	1.00 (0.45, 1.54)	<0.001	1.04 (0.50, 1.59)	<0.001	0.92 (0.36, 1.47)	0.001	0.92 (0.35, 1.48)	0.001
75-79	1.63 (1.08, 2.19)	<0.001	1.66 (1.11, 2.22)	<0.001	1.52 (0.96, 2.08)	<0.001	1.49 (0.93, 2.06)	<0.001
80+	2.37 (1.79, 2.94)	<0.001	2.43 (1.86, 3.01)	<0.001	2.29 (1.70, 2.87)	<0.001	2.22 (1.62, 2.82)	<0.001
Female	0.38 (0.06, 0.71)	<0.001	0.38 (0.05, 0.70)	0.02	0.32 (-0.01, 0.65)	0.06	0.35 (0.01, 0.69)	0.04
Smoking status	-							
Never/ex-smoker	-		ref		ref		ref	
Current smoker	-		0.63 (0.16, 1.11)	0.01	0.53 (0.07, 1.00)	0.03	0.38 (-0.10, 0.85)	0.12
Education								
Higher education	-		-		ref		ref	

Intermediate	-		-		0.06 (-0.51, 0.64)	0.83	-0.11 (-0.71, 0.49)	0.72
No qualification	-		-		0.78 (0.20, 1.36)	<0.01	0.45 (-0.16, 1.07)	0.15
Wealth quintile								
Richest	-		-		-		ref	
2nd	-		-		-		0.45 (-0.07, 0.96)	0.09
3rd	-		-		-		0.48 (-0.06, 1.01)	0.08
4th	-		-		-		0.69 (0.16, 1.21)	0.01
Poorest	-		-		-		1.08 (0.52, 1.64)	<0.001

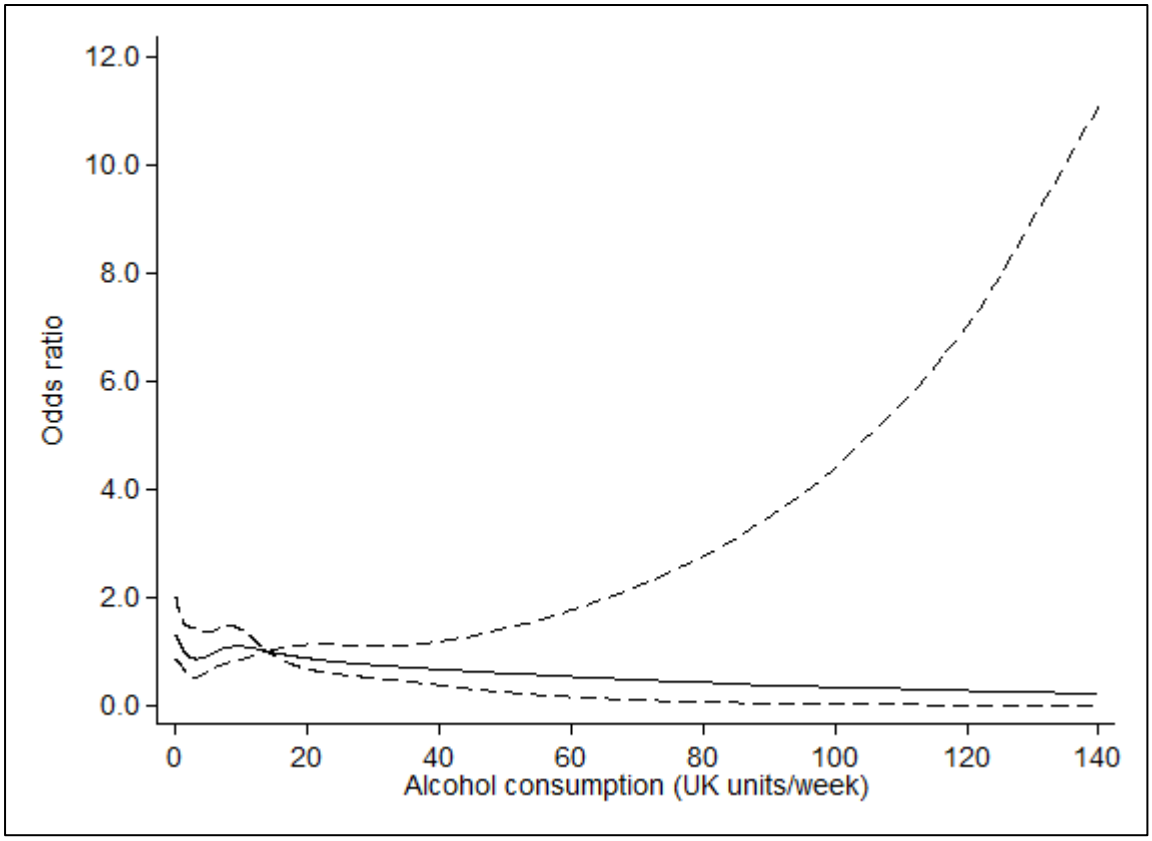
Model 1: Adjusted for age and gender.

Model 2: Further adjusted for smoking.

Model 3: Further adjusted for wealth.

Model 4: Further adjusted for education.

Figure 4. 7. Fully adjusted odds ratio (solid line) with 95% confidence interval (dash line) for association between alcohol consumption and incident frailty in restricted cubic spline regression model.



4.3.8 Discussion

The main analysis of this chapter involving 2,544 English non-frail community-dwelling men and women aged 60 or older showed that non-drinkers had overall worse health profile and worse socioeconomic status and were associated with an increased odds of frailty over 4 years than low drinkers, after controlling for various potential confounders. The odds of frailty for moderate (>7 - ≤14 units/week), heavy (>14 - ≤21 units/week) and very heavy (>21 units/week) drinkers were not significantly different from that of low drinkers in the fully adjusted model.

The worse health profile and increased frailty risk observed in non-drinkers in this chapter is in line with previous studies.[145, 255, 278] The non-drinkers category is likely to include those who have never consumed alcohol[274] or who had quit drinking for health reasons, for example cognitive decline or ill-health due to multi-morbidity ('sick quitters'),[275] and this may affect the alcohol-frailty association.[255] The supplementary analysis using frequency of alcohol consumption also showed that non-drinkers (never in the last 12 months) had a significantly higher odds of frailty compared with those who consumed alcohol rarely (once a year to twice a month). This is the reason that the low drinker category (>0 - 7 units/week) was used as a reference to address this issue. The raised risk in non-drinkers decreased and became statistically non-significant when further adjusting for self-reported general health. While non-drinking was no longer significantly associated with frailty in the model, lower self-reported general health was significantly associated with higher odds of frailty. Adding comorbidity index score to the fully adjusted model also attenuated the association between alcohol and frailty. Given these findings, it is suggested that the elevated odds of frailty risk among non-drinkers compared with low drinkers may be in part explained by non-drinkers' worse health status.

As a supplementary analysis, two different measurements of alcohol use, quantity on the heaviest drinking day and frequency, were examined to explore the impact of drinking patterns on frailty risk. In both analyses, as in the main analysis non-drinking was associated with significantly increased odds of frailty in models adjusted for age, gender and smoking (Models 1 and 2). In fully adjusted models (Model 4), while the increased odds of frailty for non-drinking remained statistically significant in the

frequency analysis, it attenuated and became non-significant in the analysis of quantity on the heaviest drinking day. There were no apparent harmful effects on frailty risk from both binge drinking (>6 units per occasion) and almost daily drinking (5-7 days of drinking per week) in old age. In another supplementary analysis, a possible non-linear association between alcohol consumption and frailty was explored, however no significant association was observed.

Most of the previous studies on alcohol and frailty used non-drinkers as the reference group.[255] There is only one study in the literature not using such a reference.[145] This study examined associations between alcohol intake in midlife and frailty in old age by following male businessmen in Finland for almost 30 years, and found that heavy alcohol intake (>196g/week) in mid-life (mean age 49 years) was associated with a significantly higher risk of developing frailty and pre-frailty 26 years later, compared with light intake (1-98g/week), while heavy use in old age (mean age 74 years) was not associated with frailty risk three years later, [145] as in my analysis. This study's findings support 'sick quitter' effects. It should be noted that some important factors, such as education and socioeconomic status, were not adjusted for and a rather selected population (male businessmen) was used in Strandberg's study.[145]

There is a similarity between the findings of alcohol and frailty in this alcohol chapter and that of alcohol and mortality. Multiple epidemiological studies have shown mortality benefit with moderate alcohol use until recently,[265] when more studies have revealed that the supposed benefit disappears when potential biases are avoided.[263-265] Similarly in frailty research, initial studies showed alcohol's beneficial effects against frailty.[255] However recent studies that took potential biases into consideration, including my paper written based on the analysis in this chapter (please see **8 Appendices**), have negated it.[145, 254]

Fifteen data sets were newly generated with missing values of smoking and wealth imputed using MICE, and the fully adjusted model was repeated, which did not change the results significantly. The essentially same results by the multiple imputation, which can decrease biases and loss of power and precision due to missing data, underpins the findings of the main (complete case) analysis.

In conclusion, non-drinkers were more likely than low drinkers to develop frailty after adjusting for socio-demographic factors among community-dwelling older people in England. In a supplementary analysis, however, this relationship attenuated and became non-significant after accounting for baseline self-reported general health. No evidence was found of an association between becoming frail and high levels of alcohol consumption at old age.[254]

I discuss the strengths and limitations of this analysis and further discuss the meaning and implications of the findings in my final **Chapter 6 OVERALL DISCUSSION**.

5 FRUIT AND VEGETABLE CONSUMPTION

This is the last of three chapters exploring modifiable lifestyle risk factors for frailty. This chapter examines associations between fruit and vegetable consumption and risk of frailty. In this chapter I describe the background of this topic and the findings of my systematic review of the literature. Then I report my empirical analysis, findings and discussion regarding their interpretation. The findings reported in this chapter have been published[279] and presented as a poster.[280] (Please see **8 Appendices** for details)

5.1 Introduction

There has been growing evidence on relationships between frailty and diet.[88, 281] Healthy dietary patterns (e.g. the Mediterranean diet), high-quality diet measured by the Diet Quality Index-International and some nutrients (e.g. protein or vitamin D) are associated with lower frailty risks.[88, 102, 103, 282, 283] A balanced diet is one of the most important factors for maintaining good health, and poor dietary patterns may lead to malnutrition, obesity and chronic diseases, such as diabetes, CVD and cancers.[196, 284]

Among various dietary components, fruit and vegetables have been recognised as key to a healthy diet due to their high concentrations of nutrients, including vitamins, antioxidants, dietary fibre and minerals.[285] The World Health Organization and the Food and Agriculture Organization of the United Nations launched a joint initiative in 2003 to recommend that people should eat at least 400g of fruit and vegetables per day to promote good health.[199] In the UK, the US, France, Germany and many other countries, consumption of at least five portions of fruit and vegetables (approximately 80g/portion) per day has been recommended by “5 A Day” campaigns. In some countries, consumption even higher than 400g/day of fruit and vegetable is recommended. A recent dose-response meta-analysis revealed that fruit and vegetable consumption higher than 400g/day is associated with health benefits; consumption up to 600g (7.5 portions) per day is associated with decreased risk for cancer, and consumption up to 800g (10 portions) per day is associated with decreased risks for coronary heart disease, stroke, CVD and all-cause mortality.[197] However most of the studies used in the dose-response meta-analysis included

young and middle-aged populations and only a few studies focused on only older people, and the authors did not stratify by age or examine an interaction with age.[197] Therefore, lack of evidence relevant to older people is a limitation of this review.

Based on the most recent data from the European Health Interview Survey, which is a survey providing information on health status, health determinants and healthcare activities of general population aged at least 15 and living in private households in 28 member countries of the European Union (EU),[286] on average 14.1% of the population aged ≥15 years consumed more than 5 portions of fruit and vegetables a day while 51.4% consumed 1 to 4 portions a day and 34.4% did not consume fruit or vegetables daily.[287] In the UK approximately one third (33.1%) of the population consumed more than 5 portions of fruit and vegetable, which was the highest percentage among the EU countries followed by 25.9% in Denmark and 25.0% in the Netherlands, and 45.6% and 21.3% consumed 1 to 4 portions a day and did not consume fruit and vegetables daily, respectively.[287] Among older people aged 65 years or above in the UK, slightly more people consumed 5 portions or more (36.5%) and less people did not consume daily (14.9%).[287]

In light of the possible beneficial effects of fruit and vegetable consumption on health in later life, fruit and vegetable consumption may be associated with a lower risk of frailty.[106] However, there is limited evidence regarding associations between fruit and vegetable consumption and frailty with mixed findings reported in the literature.[138] A recent systematic review on risk factors of frailty found only two papers on this topic and therefore could not draw a clear conclusion.[138] For this chapter I investigated the association between fruit and vegetable consumption and incident frailty among community-dwelling older people by conducting a systematic review on the currently available evidence and prospectively analysing ELSA data.

5.2 Systematic Literature Review

5.2.1 Objective

The objective of this section of the chapter was to conduct a systematic review of the literature searching for evidence on fruit and vegetable consumption and risk of incident frailty among community-dwelling older people.

The 'PICO' for the systematic review is as follows:
Population: community-dwelling older people
Intervention/exposure: fruit and vegetable consumption
Comparison: no or low fruit and vegetable consumption
Outcome: Incident frailty

5.2.2 Methods

5.2.2.1 Data source and search strategy

This systematic review was conducted in August 2017 based on a protocol (PROSPERO registration number: CRD42017057165) generated according to the PRISMA statement (**Appendix 1c**).[234] Ms Sophie Pattison, a clinical support librarian at the Royal Free Hospital Medical Library, kindly supported the development of the systematic review search strategy. Four electronic databases (Embase, MEDLINE, CINAHL Plus and PsycINFO) were systematically searched with explosion functions if available between 2000 and August 2017. Validated definitions of frailty were not generally used prior to 2000, and the two most widely accepted definitions and measurements for frailty, the CHS criteria[16] and the FI[10] were first published in 2001. No language restriction was imposed. A combination of MeSH terms and text keywords were used: "Fruit (MeSH)" OR "Vegetables (MeSH)" OR "Fruit Vegetable(s) (MeSH)" OR "Fruit and Vegetable Juice(s) (MeSH)" OR "Fruit Juice(s) (MeSH)" OR "Vegetable Juice (MeSH)" OR "Antioxidant(s) (MeSH)" OR "Diet(s) (MeSH)" OR "Diet Therapy (MeSH)" OR "Nutrition (MeSH)" OR "Nutrition Therapy (MeSH)" OR "fruit*" OR "vegetable*" OR "anti-oxidant*" OR "antioxidant*" OR "diet*" OR "nutrition*" AND frailty related terms, including "Frail Elderly (MeSH)" OR "Frailty Syndrome (MeSH)" OR "frail*". A full search results using Medline is summarised in

Appendix 4b. The reference lists of related papers and included studies were manually searched for additional studies. Forward citation-tracking of the included studies was conducted using Google Scholar (http://scholar.google.com/).

5.2.2.2 Study selection and data extraction

Any original observational population-based studies allowing analysis of cross-sectional or prospective associations between fruit and vegetable consumption and frailty were considered. Studies with selective samples unrepresentative of community-dwelling people in general, such as patients with diabetes or hospitalised patients, were excluded. Studies that reported fruit and vegetable consumption as a quantity or the consumption frequency of fruits alone, vegetables alone or fruits and vegetables combined were included. Studies including a specific type of fruit or vegetable only, or studies concerned with dietary patterns including fruit and vegetable consumption as part of a wider diet including other nutrients (e.g. the Mediterranean diet) were excluded unless the studies separately reported the associations between fruit and vegetable consumption and frailty. Studies had to define frailty by using original or modified version of validated criteria designed to measure frailty in order to be included. Randomised controlled trials, reviews, conference abstracts, editorials and comments were not considered. All study titles, abstract and full texts were screened for eligibility by me. Another researcher (Dr Christina Avgerinou) independently screened the full-texts for eligibility, as a second reviewer. We solved any disagreement by discussion. First author, study cohort name if any, publication year, location, sample size, proportion of women, age (mean and range), frailty criteria, follow-up period, fruit and vegetable measurement method and findings were extracted from each of the eligible studies.

5.2.2.3 Methodological quality assessment

Methodological quality of the eligible prospective studies were examined independently by me and a second reviewer (Dr Kenji Sekiguchi) using the Newcastle-Ottawa Scale for cohort studies,[235] as described in the previous chapters. Please see **Chapter 3.2.2.3 Methodological Quality Assessment** for detail.

5.2.2.4 Data analysis

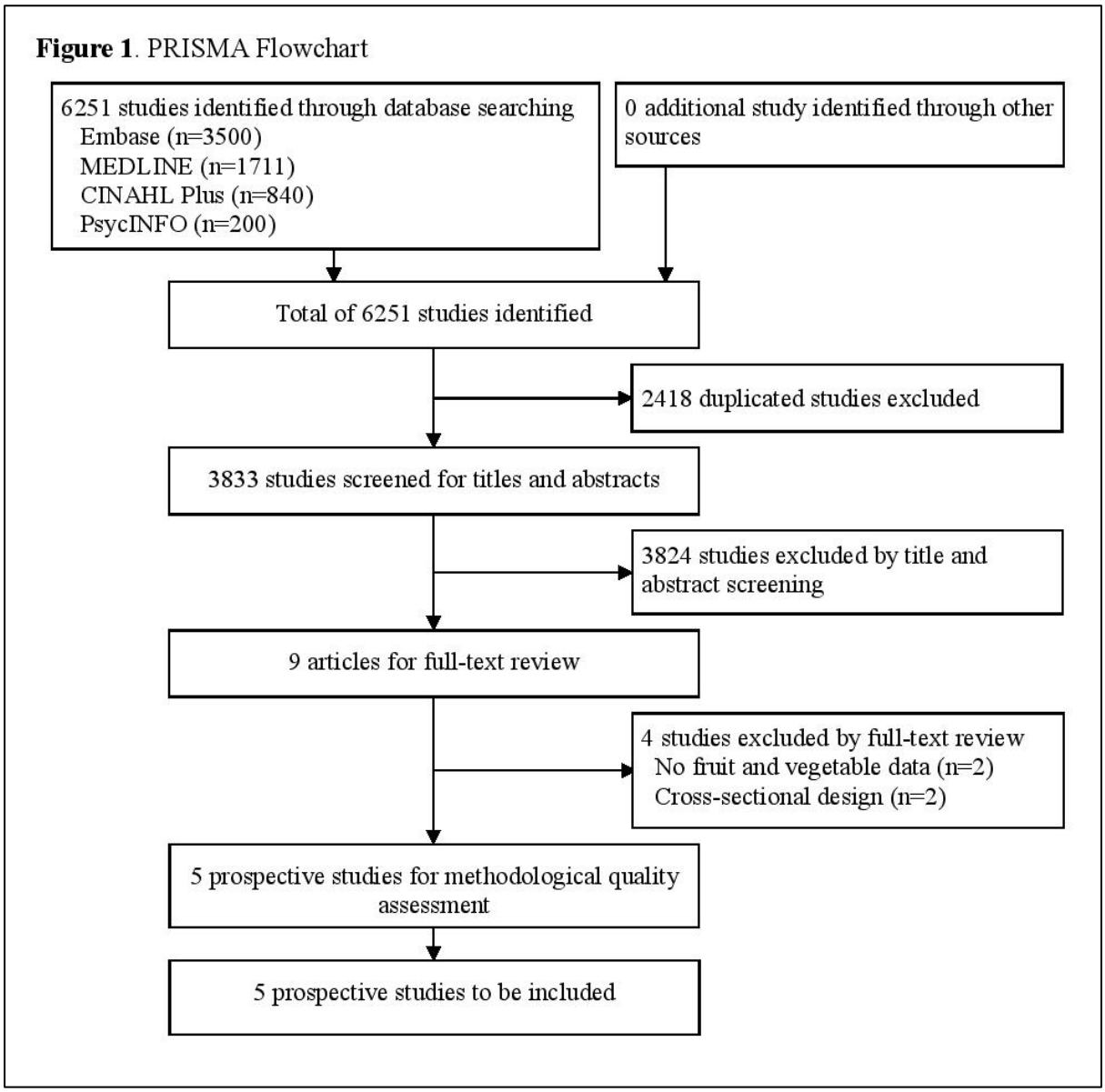
I planned to conduct a meta-analysis to combine findings of the included studies if possible; otherwise however, I would conduct a narrative review.

5.2.3 Results

5.2.3.1 Selection processes

Results of the literature search and study selection processes, with the number of studies at each stage, are shown in a PRISMA flowchart in **Figure 5.1**. The electronic search using the four databases identified a total of 6251 studies. After excluding duplicates and studies that were considered not eligible through screening of the titles and abstracts, full-texts of nine studies were reviewed. Two of them were excluded because these studies did not examine fruit and vegetable consumption but dietary patterns, leaving seven studies[288-292] to be included in this review.

Figure 5. 1. PRISMA Flowchart (Fruit and vegetable consumption and frailty)



5.2.3.2 Study characteristics

The five included studies were assessed for methodological quality using the Newcastle-Ottawa quality assessment scale for cohort studies. Three studies were considered to have adequate methodological quality.[289-291] The remaining two studies were considered to have suboptimal quality.[288, 292] (**Table 5.1**) **Table 5.2** shows the characteristics of the five included studies.[288-292] One study each was from Spain,[290] France,[291] the US[292] and the UK.[288] One study used a combination of three cohorts (Three-City Study, the Senior-ENRICA and the integrated multidisciplinary

approach cohorts).[289] The Three-City Study and the Senior-ENRICA cohorts were also used individually by Rahi and Leon-Munoz, respectively.[290, 291] The sample sizes ranged from 432[292] to 2,926.[289] The proportion of female participants was from 27.9%[288] to 63.2%.[291] All studies used middle-aged and elderly populations; the mean age varied considerably from 50's to 80's. The modified versions of the CHS frailty criteria[16] were used in four studies[288-291] to define frailty, while FRAIL scale was used in one study.[292] The data collection methods of fruit and vegetable consumption were based on questionnaires, either self-reported [288, 291, 292] or given by a research personnel.[289, 290] Different measurements of fruit and vegetable consumption were employed: the number of times per day,[291, 292] quantity in grams per day,[290] whether consuming daily or not (YES/NO)[288] or the number of portions per day.[289] Due to the various measurements of fruit and vegetable consumption and the definitions of frailty as well as differing statistical methodologies, a meta-analysis was judged not to be possible, and a narrative synthesis was conducted.

Table 5. 1. Methodological quality assessment using the Newcastle-Ottawa Quality Assessment Scale for cohort studies.

The Newcastle-Ottawa Quality Assessment Scale for cohort studies										
	Selection				Comparability		Outcome			
	1	2	3	4	1a	1b	1	2	3	total
Rahi 2017	1	1	1	1	1	1	1	1	1	9/9
Garcia- 2016	1	1	1	1	1	1	1	1	0	8/9
Ribeiro 2016	1	1	0	n/a	0	0	0	1	0	3/8
Leon-Munoz 2014	1	1	0	1	1	1	1	1	1	8/9
Bouillon 2013	0	1	0	0	0	0	1	1	1	4/9

Appendix 3 for detail.

5.2.3.3 Study findings

Prospective studies (adequate methodological quality)

Leon-Munoz 2014

In a supplementary analysis of a study using 1,815 Spanish older people from the Seniors-ENRICA study, consuming the median amount of fruits and nuts or more

was associated with lower incident frailty risk over a 3.5-year period (OR=0.59, 95%CI=0.39-0.91) compared with less than the median. However consuming three or more servings of fruit per day was not (OR=0.73, 95%CI=0.45-1.16). Neither consuming two servings of vegetables or more per day (OR=0.82, 95%CI=0.44-1.50) nor consuming the median amount of vegetables or more (OR=0.73, 95%CI=0.48-1.11) were associated significantly with frailty risk. The median amounts of fruit and nuts and vegetables were not shown in this paper. All models were adjusted for age, gender, education, smoking, BMI, energy intake, CVD, diabetes, cancer, asthma/chronic bronchitis, musculoskeletal disease, depression, number of medications and the other components of the Mediterranean Diet Score or Mediterranean Diet Adherence Screener Score.

Rahi 2017

This study followed 560 non-frail French older people from the Three-City study and found that higher Mediterranean diet adherence based on Mediterranean Diet Score at baseline was associated with lower risks of incident frailty during 2-year follow-up. As a supplementary analysis, baseline values of nine components of the Mediterranean Diet Score at baseline, namely mean numbers of weekly servings of (1) “legumes”, (2) cereals, (3) seafood, (4) meat, (5) dairy products, (6) fruits (7) and vegetables, “frequent” or “all the time” use of (8) olive oil and “mild-to-moderate” consumption of (9) alcohol, were retrospectively examined according to follow-up frailty status (frail versus non-frail) using t-test or chi-square tests. There were no statistical differences in mean numbers of weekly servings for fruit (Men: those who developed frailty 12.0 servings versus those who did not 13.4 servings, Women: those who developed frailty 14.4 servings versus those who did not 13.8 servings) and vegetables (Men: those who developed frailty 9.8 servings versus those who did not 9.6 servings, Women: those who developed frailty 8.5 servings versus those who did not 9.6 servings). Legumes were significantly more frequently consumed by non-frail men than by frail men while no such associations were observed in women. (Men: those who developed frailty 0.5 versus those who did not 0.9, Women: those who developed frailty 0.6 versus those who did not 0.6). It should be noted that statistical power may have been lowered by dividing the cohort into smaller four groups: 19 men and 60 women who developed frailty and 187 men and 294 women who did not.

Garcia-Esquinas 2016

Risks of Incident frailty according to fruit and vegetable consumption at baseline were investigated in 2,926 non-frail older men and women from three different cohorts (Three-City Bordeaux cohort and the Integrated Multidisciplinary Approach cohort from France and Seniors-ENRICA cohort from Spain). The Senior-ENRICA and the Three-City cohorts were used by Leon-Munoz and Rahi above, respectively, although fruit and vegetable consumption measurements were all different. Frailty was defined using the modified CHS frailty criteria. Those who consumed higher amounts of fruit, vegetables and both combined had a significantly lower risk of developing frailty over 2.5 years. OR of frailty controlled for age, gender, education, BMI, smoking, CVD, diabetes, cancer, asthma or chronic bronchitis, musculoskeletal disease, cognition, depression, number of medications, modified Mediterranean Diet Score and energy intake were: for those consuming 1, 2 or >3 portions of fruit/day (1 portion=120g of fruits), compared with those consuming <1 portion/day, 0.59 (95%CI=0.27-0.90), 0.58 (95%CI=0.29-0.86) and 0.48 (95%CI=0.20-0.75), respectively (p for trend=0.04); for those consuming 1, 2 or >3 portions of vegetables/day (1 portion=150g of vegetables), compared with those consuming <1 portion/day, 0.69 (95%CI=0.42-0.97), 0.56 (95%CI=0.35-0.77) and 0.52 (95%CI=0.13-0.92), respectively (p for trend<0.01); and for those consuming 2, 3, 4 and >=5 portions of fruits and vegetables combined/day, compared with those consuming <=1 portion, 0.41 (95%CI=0.21-0.60), 0.47 (95%CI=0.25-0.68), 0.36 (95%CI=0.18-0.53) and 0.31 (95%CI=0.13-0.48), respectively. The effects were dose-dependent (p for trend<0.01).

Prospective studies (suboptimal methodological quality)

Ribeiro 2016

A US study by Ribeiro and colleagues examined fruit and vegetable consumption at baseline and changes in frailty status measured by the FRAIL scale over a 6-year period between 2004 and 2010 in 432 middle-aged and older African American men and women. The reasons for suboptimal quality were lack of objective measurement of fruit and vegetable consumption, adjustment for important confounders, clear description of frailty measurements and details of those who were lost for follow-up. Frequencies of five categories of fruit and vegetable intakes (average number of

times eaten per day) were measured in 2006 based on a questionnaire: (1) fruit juices such as orange, grapefruit or tomato, (2) fruit, (3) green salad, (4) carrots and (5) vegetable different from carrots, potatoes or salad (defined as “other non-potato vegetables”). All these fruit and vegetable variables, physical activity levels, age, gender and baseline FRAIL scale were initially entered into a multivariable residual-change score linear regression model to predict FRAIL scale score at follow-up. After backward stepwise elimination of non-significant variables, the final model included other non-potato vegetables, fruit juices, leisurely walking, sitting and baseline FRAIL scale score (adjusted R^2=0.33). Higher intake of other non-potato vegetables was significantly associated with lower risk of frailty (B=-0.20 (standard error=0.08), Beta=-0.12 (standard error=0.04), p=0.01) while higher consumption of fruit juices was significantly associated with higher risk of frailty (B=0.15 (standard error=0.07), Beta=0.09 (standard error=0.04), p=0.04). Important confounding factors, such as education or socioeconomic status, were not considered in the models.

Bouillon 2013

Bouillon and colleagues used the Whitehall II study cohort consisting of 2,707 middle-aged and older civil servants aged 45-69 in the UK to examine the frailty risk over a long follow-up period of 10.5 years. Those who answered that they did not consume fruits and vegetables daily in a self-reported questionnaire at baseline were more likely to be pre-frail/frail at follow-up, compared with those who reported that they did daily (adjusted OR=1.51, 95%CI=1.26-1.82). There are some limitations to be noted. First, the cohort used was a selected sample of civil servants, and may not be generalisable to the overall population. Second, frailty was measured at follow-up but not at baseline. Baseline frailty status should have been considered in the analysis, or frail participants at baseline should have been excluded if incident frailty had been examined, otherwise there is potential for reverse causality. Lastly, the presence or absence of daily fruit and vegetable consumption is limited as a predictor variable.

Table 5. 2. Summary of included studies on associations between fruit and vegetable consumption and frailty among community-dwelling older people.

Author, Year Location N*	Female (%)*	Age**	Frailty criteria	Follow-up	Fruit and vegetable measure	Findings (unadjusted)	Findings (adjusted)
adequate quality							
Leon-Munoz 2014 Spain 1,815	-	≥60	mCHS	3.5 years	Gram per day and number of servings per day, by computerized diet history or semiquantitative food-frequency questionnaire by a trained research assistant	Not reported	Logistic regression models for Incident frailty adjusted for age, gender, education, smoking, BMI, energy intake, cardiovascular disease, diabetes mellitus, cancer, asthma or chronic bronchitis, musculoskeletal disease, depression, number of medications, and remaining of MDS or MEDAS components. adjOR=0.59 (95%CI=0.39-0.91) for fruits and nuts ≥ median consumption (gram/day) adjOR=0.73 (95%CI=0.45-1.16) for fruit ≥ 3 servings per day adjOR=1.06 (95%CI=0.67-1.68) for nuts ≥ 3 times a week adjOR=0.73 (95%CI=0.48-1.11) for vegetables ≥ median consumption adjOR=0.82 (95%CI=0.44-1.50) for vegetables ≥ 2 servings per day adjOR=0.80 (95%CI=0.54-1.18) for legumes ≥ median consumption adjOR=0.85 (95%CI=0.49-1.46) for legumes ≥ 3 times a week

Author, Year Location N*	Female (%)*	Age**	Frailty criteria	Follow-up	Fruit and vegetable measure	Findings (unadjusted)	Findings (adjusted)
Rahi 2017 France 560	63.2%	81.7	mCHS	2 years	semi-quantitative food-frequency questionnaire	T-tests to compare each consumption between those who developed frailty 2 years later and those who did not, there were no significant differences in mean number of servings per week at baseline for fruit (Men: those who became frail 12.0 vs. those who did not 13.4, Women: those who became frail 14.4 vs. those who did not 13.8) and vegetable (Men: incident frailty 9.8 vs. non-frailty 9.6, Women: incident frailty 8.5 vs. non-frailty 9.6). Men who became frail had consumed significantly lower number of legume servings per week than men who did not become frail (0.5 vs. 0.9), but no association was observed in women (0.6 vs 0.6).	Not reported

Author, Year Location N*	Female (%)*	Age**	Frailty criteria	Follow-up	Fruit and vegetable measure	Findings (unadjusted)	Findings (adjusted)
Garcia-Esquinas 2016 Spain France 2,926	37.8-63.5%	68.7-81.8	mCHS	2.5 years	Number of portions per day (120g for fruit, 150g for veg), by computerized diet history or semi-quantitative food-frequency questionnaire by a trained research assistant.	Not reported	Logistic regression models for Incident frailty adjusted for age, gender, education, BMI, smoking, cardiovascular disease, DM, cancer, asthma or chronic bronchitis, musculoskeletal disease, MMSE, depression, number of meds, modified Trichopoulou index and energy intake. - Fruit: compared with fruit <1 portion/day adjOR=0.59 (95%CI=0.27-0.90) for fruit 1 portion/day adjOR=0.58 (95%CI=0.29-0.86) for fruit 2 portions/day adjOR=0.48 (95%CI=0.20-0.75) for fruit ≥3 portions/day p for trend=0.04 - Vegetable: compared with vegetable <1 portion/day adjOR=0.69 (95%CI=0.42-0.97) for vegetable 1 portion/day adjOR=0.56 (95%CI=0.35-0.77) for vegetable 2 portions/day adjOR=0.52 (95%CI=0.13-0.92) for vegetable ≥3 portions/day p for trend <0.01 - Fruit and vegetable: compared with fruit+ vegetable ≤1 portion/day adjOR=0.41 (95%CI=0.21-0.60) for fruit + vegetable 2 portions/day adjOR=0.47 (95%CI=0.25-0.68) for fruit + vegetable 3 portions/day adjOR=0.36 (95%CI=0.18-0.53) for fruit + vegetable 4 portions/day adjOR=0.31 (95%CI=0.13-0.48) for fruit + vegetable ≥5 portions/day p for trend <0.01
suboptimal quality							

Author, Year Location N*	Female (%)*	Age**	Frailty criteria	Follow-up	Fruit and vegetable measure	Findings (unadjusted)	Findings (adjusted)
Ribeiro 2016 US 432	63%	59.2	FRAIL	6 years	Average number of times consuming per day, by 2005 Behavioral Risk Factor Surveillance System questions at wave 8 (approximately 4 years after baseline)	Not reported	A multivariable residual-change score linear regression model, including FRAIL scale at wave 4 (baseline), Leisurely walking and sitting, showed that other non-potato vegetables was negatively (B(SE)=-0.20 (0.08), Beta(SE)=-0.12 (0.04), p=0.01) and fruit juices was positively (B(SE)=0.15 (0.07), Beta(SE)=0.09 (0.04), p=0.04) related to FRAIL scale at wave 10 (follow-up) (adjusted R^2=0.33).
Bouillon 2013 UK 2,797 civil servants	27.9%	55.0	mCHS	10.5 years	Whether consuming fruits and vegetables daily (YES/NO), by self-reported questionnaire	Not reported	Multivariable logistic regression model for being pre-frail/frail at follow-up adjusted for age, gender and physical activity. adjOR=1.51 (1.26-1.82) for not consuming fruits and vegetables daily.

* Cohort used for analysis of interest, or entire cohort.

** Mean age, age range, or age for inclusion.

95%CI: 95% confidence interval, adjOR: Adjusted odds ratio, FRAIL: FRAIL Scale, mCHS: Modified Cardiovascular Health Study criteria, OR: Odds ratio, SE: Standard error, TFI: Tilburg Frailty Indicator.

5.2.4 Discussion

The systematic review identified five studies that examined prospective associations between fruit and vegetable consumption and frailty in middle-aged and older people. Among three prospective studies with adequate methodological quality, only one study primarily examined fruits and vegetables and showed that higher intakes of fruits, vegetables and fruit and vegetable combined were significantly associated with lower odds of frailty in a dose-response manner.[289] The main focus of the other two studies was a Mediterranean diet,[290, 291] and fruit and vegetable consumption was examined only as supplementary analysis, which showed only fruit and nuts consumption greater than the median amount was associated with lower odds of frailty in one study.[290] The findings of two prospective studies with suboptimal quality were consistent: one study showed a higher non-potato vegetable intake was associated with lower frailty risks,[292] and the other one showed that those who consumed fruits and vegetables daily had lower frailty risks at follow-up compared with those who did not.[288] The study by Ribeiro and colleagues[292] also showed fruit juice intake at baseline was associated with worse frailty status at follow-up. This could be because “fruit juice” in this study was not restricted to 100% pure fruit juice but could refer to drinks with lower fruit content or with added sugar.

Although not included in this systematic review, one study that did not examine fruit and vegetable consumption specifically but instead examined dietary patterns including fruits and vegetables in their association with frailty. This is a cross-sectional study of 923 elderly Taiwanese aged 65 or older, which explored a dietary pattern associated with frailty using reduced rank regression analysis and found that fresh fruit had the highest factor loading value (-0.48) and vegetables had the fourth highest one (-0.33), both suggesting strong inverse associations with frailty.[293]

This systematic review has some limitations. The research area of diet, especially fruit and vegetable consumption, in relation to frailty is relatively new, and only a limited number of studies were found through the systematic review. In addition, because the included studies used different measures of fruit and vegetable consumption and different statistical methods, a meta-analysis was not possible. All included studies used self-report measures of fruit and vegetables, which could be

subject to recall bias. It should also be noted that all included studies did not take into account important potential confounders, including socioeconomic status or education. I did not explore the grey literature, such as conference abstracts, as methodological quality could not be assessed properly due to missing details of methods used.

In conclusion, the overall evidence regarding the associations between fruit and vegetable consumption and frailty is limited in the literature. In addition, the study settings, statistical methods and findings were heterogeneous and some of the effect measures were not adjusting for important confounders. Nonetheless there is some suggestion from limited evidence that higher fruit and vegetable consumption may be associated with a lower risk of frailty. There were no studies showing that fruits or vegetables worsen frailty. More high-quality research is needed to further enhance our understanding of the association between fruit and vegetable consumption and frailty risks.

5.3 Fruit and Vegetable Consumption and Incident Pre-frailty/Frailty (ELSA)

5.3.1 Objective

The objective of the second section of the chapter was to examine association between fruit and vegetable consumption and risks of incident pre-frailty/frailty in community-dwelling older people in England.

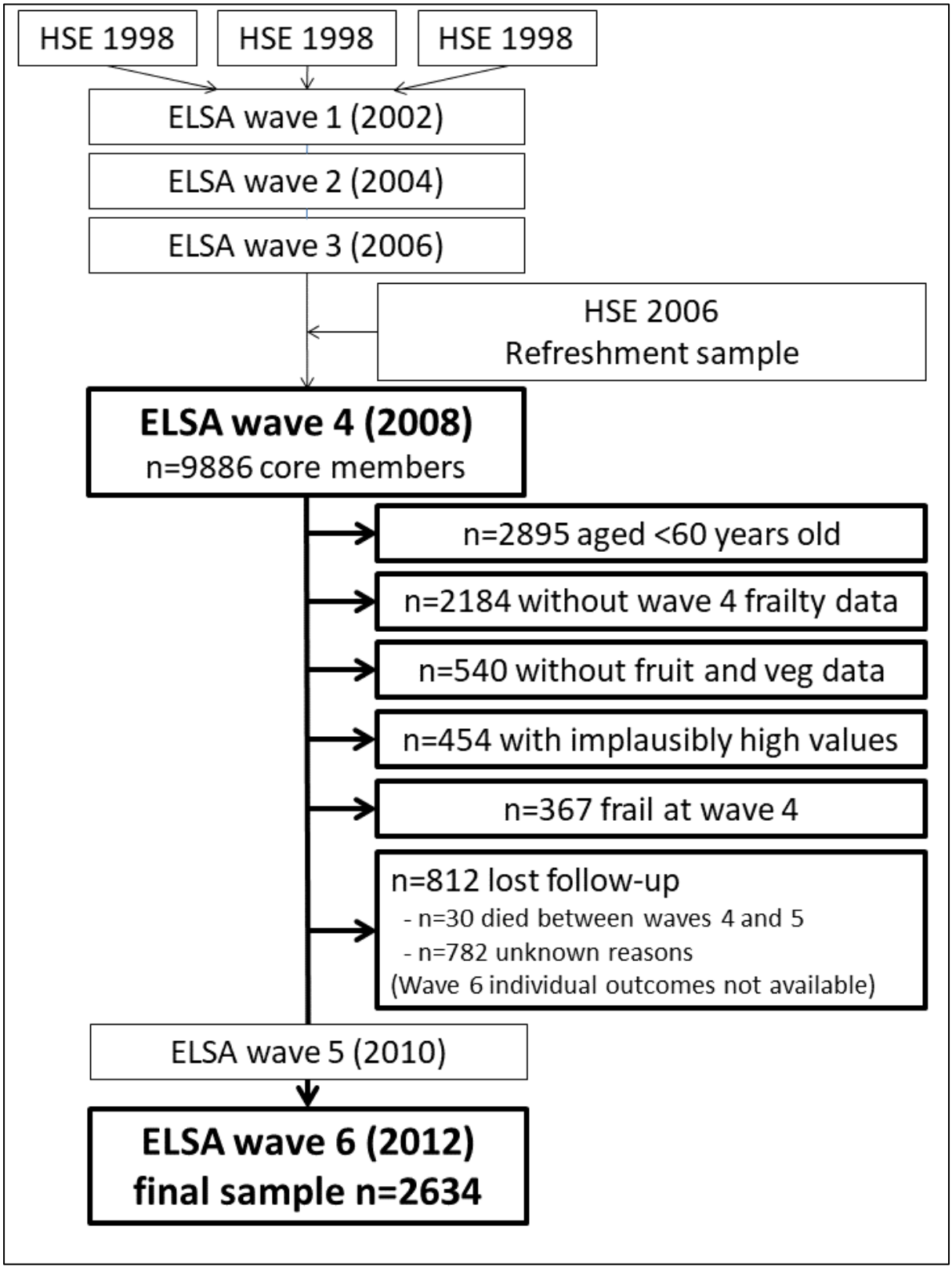
5.3.2 Study population

The ELSA population is described in detail in **Chapter 2.1 English Longitudinal Study of Ageing (ELSA)**. The population used for the fruit and vegetable consumption analyses in this chapter included ELSA participants who were aged 60 years or older at wave 4 (baseline) and with information on frailty status at waves 4 and 6 and fruit and vegetable consumption at waves 4. Fruit and vegetable consumption was measured at waves 3, 4, 5, 6 and 7 but not at wave 2. Therefore, baseline was wave 4 and follow-up was wave 6 for fruit and vegetable consumption analysis.

At wave 4, 9,886 core members had a main interview, of which 7,595 were from ELSA wave 3 and 2,291 were from HSE 2006 as a refreshment sample. There was another refreshment sample recruitment at wave 3 from HSE 2001/2002/2003/2004. Those participants were aged 50-52 on 1 March 2006, were still aged less than 60 at wave 4 in 2008, therefore, were not included in this fruit and vegetable consumption analysis. A total of 2,895 participants were aged 59 or younger and were excluded. Among 6,991 participants who were 60 years or older at wave 4, 2,184 participants who had missing data for frailty at wave 4, 540 participants who had missing data for fruit and vegetable consumption and 454 participants who had one or more implausibly high values of fruit or vegetable consumption were excluded. The implausibly high values were defined as values of > three standard deviations from mean values. The cut-points for the implausibly high values were described in detail in **Chapter 2.6 Definitions of Fruit and Vegetable Consumption.** A supplementary analysis was done including those with the implausibly high values. A further 367 participants who were frailty at wave 4 were excluded, in order to examine incident

frailty at wave 6. Between waves 4 and 6, 812 were loss to follow-up. The reasons for loss to follow-up at wave 6 were not known at the time of analysis, except for except for 30 participants who died between waves 4 and 5. The final analytic sample for fruit and vegetable consumption analysis was 2,634 participants (**Figure 5.2**).

Figure 5. 2. ELSA final analytic population for fruit and vegetable consumption analyses.



5.3.3 Predictor variable - Fruit and vegetable consumption

In the main analysis, a categorical variable of fruit and vegetable consumption was used as a predictor variable. The fruit and vegetable consumption was calculated as a sum in portions per day and was divided into five categories with cut-points of 2.5, 5, 7.5 and 10 portions. Categorical variable was chosen based on possible non-linear associations between fruit and vegetable consumption and frailty risk.[197] Please see **Chapter 2.6 Definitions of Fruit and Vegetable Consumption** for detail.

5.3.4 Outcome variable - Incident frailty and incident pre-frailty/frailty

The outcome variable in the main analysis was incident frailty and incident pre-frailty/frailty, which were defined as new development of frailty (the frailty phenotype score $\geq$3) in those who were pre-frail or robust (the frailty phenotype score 0-2) and new development of pre-frailty or frailty (the frailty phenotype score $\geq$1) in those who were robust (the frailty phenotype score=0), respectively. Frailty was defined by the frailty phenotype including the five characteristics of weight loss or 'shrinking', exhaustion, weakness, slow walking speed and low physical activity.[16] Please see **Chapter 2.3 Definition of Frailty** for detail.

5.3.5 Covariates

Covariates that were used for adjustment in this chapter were age, gender, smoking, alcohol, wealth, education, living alone, cognitive function, depressed mood, diabetes and hyperlipidemia.

These variables influence both fruit and vegetable consumption and frailty and are therefore chosen as covariates for adjustment, a priori based on evidence on independent associations with frailty from the literature[11, 135, 193] and discussion with my supervisors. Please see **Chapter 2.7 Definitions of Covariates** for detail.

5.3.6 Statistical Analyses

5.3.6.1 Main analysis

Participants who were included in the fruit and vegetable consumption analysis and participants who were excluded due to loss to follow-up and missing data were compared for frailty status, fruit and vegetable consumption, age, gender, smoking, alcohol, wealth, education, living alone, cognitive function, depressed mood, diabetes and hyperlipidemia, using chi-square tests or t-tests.

Baseline characteristics were compared across five fruit and vegetable consumption groups as described in **Chapter 2.6 Definition of Fruit and Vegetable Consumption**.

Multivariable logistic regression models were used to examine risks of incident frailty and incident pre-frailty/frailty for the fruit and vegetable consumption groups with the lowest consumption group (0-2.5 portions/day) as a reference. P for trend was calculated by entering the five fruit and vegetable consumption groups into models as a continuous variable. Please see **Chapter 2.8.1 Main Analysis** for detail.

5.3.6.2 Supplementary analysis - separate consumption of fruit and vegetables

The fully adjusted model was repeated with fruit consumption and vegetable consumption one at a time as a predictor variable to examine how consumption of fruit and vegetables separately affects subsequent risks of incident frailty and incident pre-frailty/frailty. Cut-points for fruit and vegetable consumption were 1.5, 3, 4.5 and 6, and 1, 2, 3 and 4, respectively.

5.3.6.3 Supplementary analysis - implausibly high values

In the main analysis implausibly high values of fruit or vegetable consumption were excluded from the main analysis (please see **Chapter 2.6 Definitions of Fruit and Vegetable Consumption** for definitions). To explore the impact of excluding these values, in a supplementary analysis the final model was repeated with a ‘worse case’

and ‘best case’ scenario: with implausibly high values treated as 0, and with the implausibly high values retained, assuming that the values were still true.

5.3.6.4 Supplementary analysis - multiple imputation by chained equations

Please see **Chapter 2.8 ELSA Statistical Analysis** for detail.

5.3.7 Results

5.3.7.1 Main analysis

There were 3,446 participants who were aged 60 or older at wave 4, were non-frail (robust or pre-frail) and had complete data on fruit and vegetable consumption. Among them 812 participants were excluded due to lost for follow-up (including 30 deaths) and 2,634 participants were in the analytic sample.

Several variables were different between those who were included and excluded. Those who were excluded were significantly frailer, older, current smoker, non-drinkers and more likely to be male, living alone, depressed, have lower wealth, lower education and lower cognitive function. There were no significant differences in fruit and vegetable consumption, prevalence of diabetes and hyperlipidemia. (**Table 5.3**)

Table 5. 3. Comparisons between those included in the analyses (n=2,634) and those excluded due to missing data (n=812).

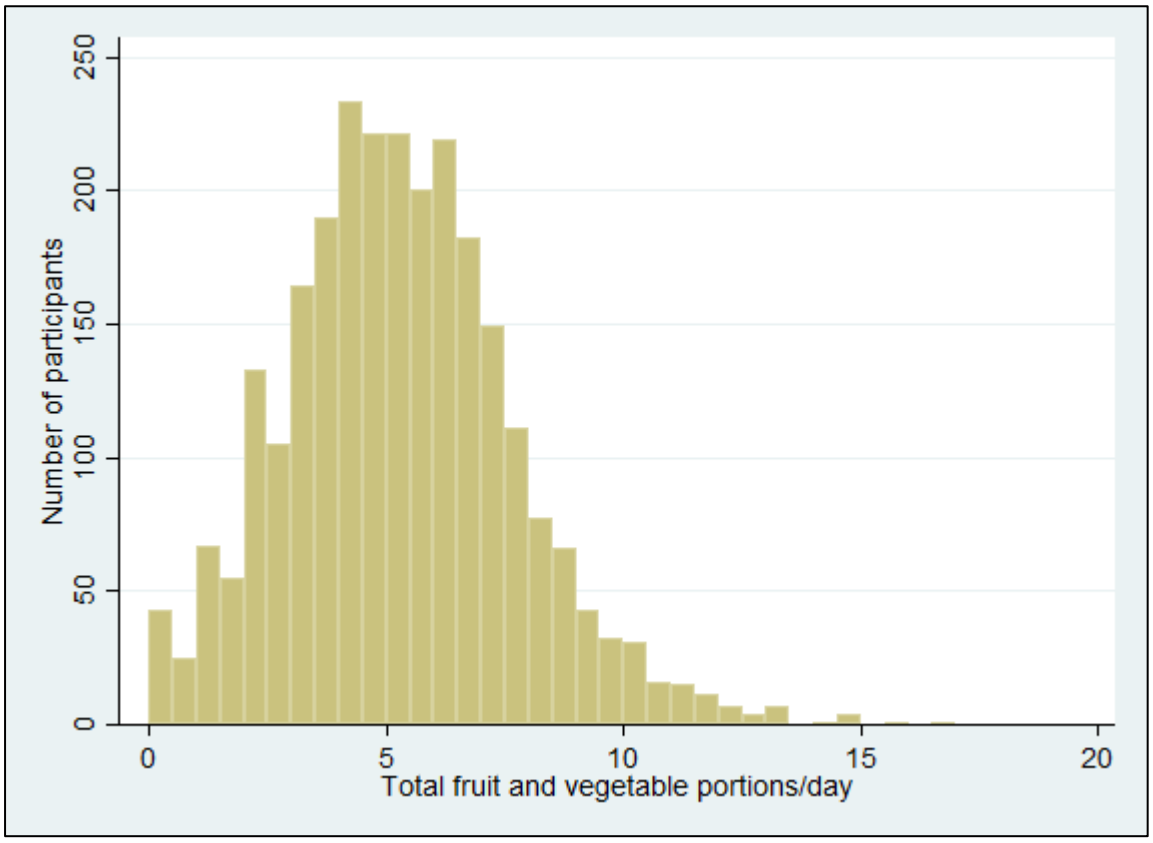
Variables at wave 4*	Included n=2,634	Excluded n=812	P value
Frailty status			
Robust	1,577 (59.9%)	383 (47.2%)	<0.001
Pre-frail	1,057 (40.1%)	429 (52.8%)	
Fruit	3.1 ± 1.7	3.1 ± 1.8	0.92
Vegetable	2.1 ± 1.3	2.1 ± 1.3	0.53
Fruit and veg combined	5.2 ± 2.4	5.2 ± 2.6	0.69
Age group			
60-64	941 (35.7%)	200 (24.6%)	<0.001
65-69	645 (24.5%)	188 (23.2%)	
70-74	606 (23.0%)	163 (20.1%)	
75-79	275 (10.4%)	124 (15.3%)	
80+	167 (6.3%)	137 (16.9%)	
Gender			
Male	1,163 (44.2%)	398 (49.0%)	0.02
Female	1,471 (55.9%)	414 (51.0%)	
smoking status			
Never/past	2,398 (91.7%)	706 (87.6%)	<0.001
Current	218 (8.3%)	100 (12.4%)	
Alcohol			
None	205 (7.8%)	94 (11.7%)	<0.01
1/y-2/m	694 (26.5%)	218 (27.1%)	
1/w-4/w	1,043 (39.9%)	280 (34.7%)	
5/w-daily	673 (25.7%)	214 (26.6%)	
Wealth quintile			
Richest	702 (27.2%)	177 (22.4%)	<0.01
2nd	620 (24.0%)	184 (23.3%)	
3rd	568 (22.0%)	168 (21.3%)	
4th	423 (16.4%)	150 (19.0%)	
Poorest	273 (10.6%)	110 (13.9%)	
Education			
Higher education	468 (17.8%)	132 (16.3%)	<0.001

Variables at wave 4*	Included n=2,634	Excluded n=812	P value
Intermediate	1,524 (57.9%)	422 (52.0%)	
No qualification	642 (24.4%)	258 (31.8%)	
Living alone	610 (23.2%)	216 (26.6%)	0.05
Cognitive function score	51.8 ± 10.5	47.8 ± 11.4	<0.001
Depressed mood	0.5 ± 1.0	0.6 ± 1.1	0.01
Diabetes	239 (9.1%)	89 (11.0%)	0.11
Hyperlipidemia	1,077 (40.9%)	303 (37.3%)	0.07

*t-test and chi-square test were used for continuous and categorical variables, respectively. Percentages may not sum up to 100% due to rounding. Mean ± standard deviation or n (%).

The distribution of consumption of fruit and vegetable combined was depicted in **Figure 5.3**, ranging from 0 to 17 portions per day. The mean and median were 5.2 and 5.0 portions per day, respectively (standard deviation=2.4, interquartile range=3.0).

Figure 5. 3. Distribution of fruit and vegetable consumption (portions/day)



The baseline characteristics of 2,634 participants are shown in **Table 5.4** and variables were compared across the fruit and vegetable consumption groups. The number of participants were 323 (0 - <2.5 portions/day), 913 (2.5 - <5 portions/day), 971 (5 - <7.5 portions/day), 329 (7.5 - <10 portions/day) and 98 (10 or more portions/day). Approximately a half of the sample (51.0%) consumed 5 or more portions of fruit and vegetables per day. The lower fruit and vegetable consumption group tended to have higher prevalence of current smokers and non-drinkers, lower prevalence of being in the highest wealth quintile group and the highest education group and lower cognitive function scores.

Table 5. 4. Baseline characteristics of ELSA participants in fruit and vegetable consumption and incident frailty analysis. (N=2,634)

Variable*	Entire cohort N=2,634	0 - <2.5 portions	2.5 - <5 portions	5 - <7.5 portions	7.5 - <10 portions	≥10 - 17 portions
Number of participants (%)		323 (12.3%)	913 (34.7%)	971 (36.9%)	329 (12.5%)	98 (3.7%)
Frailty status						
Robust	1,577 (59.9%)	174 (53.9)	556 (60.9)	581 (59.8)	212 (64.4)	54 (55.1)
Pre-frail	1,057 (40.1%)	149 (46.1)	357 (39.1)	390 (40.2)	117 (35.6)	44 (44.9)
Incident frailty, case/total (%)	189/2,634 (7.2%)	31/323 (9.6%)	72/913 (7.9%)	60/971 (6.2%)	20/329 (6.1%)	6/98 (6.1%)
Incident pre-frailty/frailty, case/total (%)	500/1,577 (31.7%)	68/174 (39.1%)	187/556 (33.6%)	169/581 (29.1%)	54/212 (25.5%)	22/54 (40.7%)
Age group						
60-64	941 (35.7%)	129 (39.9%)	345 (37.8%)	319 (32.9%)	121 (36.8%)	27 (27.6%)
65-69	645 (24.5%)	82 (25.4%)	211 (23.1%)	236 (24.3%)	89 (27.1%)	27 (27.6%)
70-74	606 (23.1%)	60 (18.6%)	206 (22.6%)	248 (25.5%)	72 (21.9%)	20 (20.4%)
75-79	275 (10.4%)	33 (10.2%)	95 (10.4%)	110 (11.3%)	24 (7.3%)	13 (13.3%)
80+	167 (6.3%)	19 (5.9%)	56 (6.1%)	58 (6.0%)	23 (7.0%)	11 (11.2%)
Gender						
Male	1,163 (44.1%)	166 (51.4%)	423 (46.3%)	386 (39.7%)	138 (41.9%)	50 (51.0%)
Female	1,471 (55.9%)	157 (48.6%)	490 (53.7%)	585 (60.3%)	191 (58.1%)	48 (49.0%)
BMI, median (IQR)	27.4 (24.9-30.5)	27.7 (25.3-31.7)	27.4 (24.9-30.5)	27.4 (24.8-30.3)	27.3 (24.9-30.5)	27.3 (24.9-29.7)
Smoking						
Non-smoker	2,398 (91.7%)	265 (82.6%)	814 (89.8%)	913 (94.5%)	317 (97.5%)	89 (91.8%)
Current smoker	218 (8.3%)	56 (17.5%)	93 (10.3%)	53 (5.5%)	8 (2.5%)	8 (8.3%)
Alcohol						
None	205 (7.8%)	39 (12.2%)	70 (7.7%)	73 (7.6%)	17 (5.2%)	6 (6.2%)
1/y-2/m	694 (26.5%)	82 (25.6%)	247 (27.3%)	248 (25.7%)	90 (27.5%)	27 (27.8%)
1/w-4/w	1,043 (39.9%)	117 (36.6%)	352 (38.8%)	386 (40.0%)	143 (43.7%)	45 (46.4%)
5/w-daily	673 (25.7%)	82 (25.6%)	238 (26.2%)	257 (26.7%)	77 (23.6%)	19 (19.6%)
Living alone	610 (23.2%)	84 (26.1%)	183 (20.0%)	235 (24.2%)	83 (25.2%)	25 (25.5%)
Wealth quintile						
Richest	702 (27.2%)	52 (16.5%)	219 (24.4%)	295 (31.0%)	109 (33.8%)	27 (28.1%)
2nd	620 (24.0%)	52 (16.5%)	233 (26.0%)	246 (25.8%)	77 (23.8%)	12 (12.5%)
3rd	568 (22.0%)	73 (23.1%)	207 (23.1%)	194 (20.4%)	71 (22.0%)	23 (24.0%)
4th	423 (16.4%)	80 (25.3%)	143 (15.9%)	141 (14.8%)	38 (11.8%)	21 (21.9%)
Poorest	273 (10.6%)	59 (18.7%)	96 (10.7%)	77 (8.1%)	28 (8.7%)	13 (13.5%)
Education						

Variable*	Entire cohort N=2,634	0 - <2.5 portions	2.5 - <5 portions	5 - <7.5 portions	7.5 - <10 portions	≥10 - 17 portions
Higher education	468 (17.8%)	30 (9.3%)	160 (17.5%)	183 (18.9%)	75 (22.8%)	20 (20.4%)
Intermediate	1,524 (57.9%)	169 (52.3%)	539 (59.0%)	578 (59.5%)	182 (55.3%)	56 (57.1%)
No qualification	642 (24.4%)	124 (38.4%)	214 (23.4%)	210 (21.6%)	72 (21.9%)	22 (22.5%)
Depressive mood	0.5 ± 1.0	0.6 ± 1.2	0.4 ± 0.9	0.5 ± 1.0	0.5 ± 1.1	0.6 ± 1.3
Cognitive function	51.8 ± 12.3	50.1 ± 10.6	51.6 ± 10.4	52.2 ± 10.0	52.8 ± 11.1	50.9 ± 12.3
Diabetes	239 (9.1%)	40 (12.4%)	87 (9.5%)	75 (7.7%)	26 (7.9%)	11 (11.2%)
Hyperlipidemia	1,077 (40.9%)	132 (40.9%)	387 (42.4%)	401 (41.3%)	119 (36.2%)	38 (38.8%)

BMI: body mass index, IQR: Interquartile range, SD: standard deviation

* Median + interquartile range, mean (standard deviation) or n (%).

The first column reports column percentages and the rest report row percentages.

The percentages may not sum up to 100% due to rounding.

Table 5.5 shows associations between fruit and vegetable consumption and incident frailty risks using multivariable logistic regression models among 2,634 participants who were robust or pre-frail at baseline, with the lowest consumption group as a reference. In Model 1 adjusted for age and gender, higher consumption of fruit and vegetables was associated with lower odds of frailty (p for trend=0.02) although only a group of 5-7.5 portions per day reached a statistical significance (OR=0.58, 95%CI=0.35-0.98, p=0.04). However, there were no significant associations between any fruit and vegetable consumption groups and frailty risks in Models 2-5 with further adjustments.

The same multivariable logistic regression models were used to examine incident pre-frailty/frailty risks according to fruit and vegetable consumption among 1577 robust participants at baseline (**Table 5.6**). There are dose-response associations between higher consumption of fruit and vegetables and lower risk of pre-frailty/frailty among the lower four consumption groups, where ORs decreased with higher fruit and vegetable consumption in all Models. In Model 5 with full adjustments, ORs for groups consuming 2.5 - <5 portions, 5 - <7.5 portions and 7.5 - <10 portions were 0.77 (955CI=0.52-1.15, p=0.21), 0.56 (95%CI=0.37-0.85, p<0.01) and 0.46 (95%CI=0.27-0.77, p<0.01), respectively, compared with those consuming 0 - <2.5 portions. The highest consumption group of 10-17 portions, however, had odds of pre-frailty/frailty not significantly different from the lowest (0 - <2.5 portions)

consumption group’s in all Models (OR=0.89-1.16, p=0.66-0.84). Although p for trend was calculated and was shown in **Table 5.6**, the shape of the association between fruit and vegetable consumption and pre-frailty/frailty risks was clearly not linear but seemed J-shaped, so p for trend was not interpreted.

Table 5. 5. Multivariable logistic regression models examining associations between fruit and vegetable consumption groups and 4-year incident frailty among 2,634 non-frail community-dwelling older people in England.

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	Odds Ratio (95%CI)	P value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value
Fruit and vegetable										
0 - <2.5 portions	ref		ref		ref		ref		ref	
2.5 - <5 portions	0.77 (0.46-1.28)	0.32	0.94 (0.57-1.56)	0.82	1.06 (0.63-1.79)	0.82	1.06 (0.63-1.80)	0.83	1.22 (0.68-2.17)	0.50
5 - <7.5 portions	0.58 (0.35-0.98)	0.04	0.73 (0.44-1.22)	0.23	0.88 (0.51-1.50)	0.63	0.87 (0.51-1.50)	0.62	1.03 (0.58-1.84)	0.91
7.5 - <10 portions	0.56 (0.28-1.12)	0.10	0.75 (0.37-1.51)	0.42	0.93 (0.45-1.96)	0.86	0.93 (0.44-1.96)	0.86	1.19 (0.54-2.65)	0.67
10 - 17 portions	0.44 (0.17-1.17)	0.10	0.46 (0.17-1.22)	0.12	0.53 (0.19-1.47)	0.22	0.51 (0.18-1.42)	0.20	0.60 (0.21-1.77)	0.36
P for trend		0.02		0.06		0.23		0.22		0.56
Age group										
60-64	ref		ref		ref		ref		ref	
65-69	2.03 (1.14-3.64)	0.02	2.05 (1.15-3.68)	0.02	2.23 (1.23-4.04)	<0.01	2.21 (1.22-4.01)	<0.01	1.68 (0.89-3.18)	0.11
70-74	3.68 (2.17-6.23)	<0.001	3.38 (1.96-5.83)	<0.001	3.57 (2.03-6.28)	<0.001	3.46 (1.96-6.11)	<0.001	2.91 (1.58-5.37)	0.001
75-79	6.60 (3.69-11.79)	<0.001	6.69 (3.67-12.17)	<0.001	6.55 (3.53-12.17)	<0.001	6.38 (3.43-11.89)	<0.001	5.25 (2.71-10.15)	<0.001
80+	18.02 (10.38-31.28)	<0.001	19.05 (10.77-33.70)	<0.001	18.67 (10.26-33.98)	<0.001	18.73 (12.24-34.28)	<0.001	14.91 (7.58-29.35)	<0.001
Female	1.65 (1.23-2.21)	0.001	0.96 (0.69-1.35)	0.83	0.88 (0.62-1.25)	0.48	0.85 (0.60-1.21)	0.37	0.96 (0.65-1.41)	0.84
Smoking										
Non-smoker	ref		ref		ref		ref		ref	
Current smoker	1.13 (0.81-1.58)	0.48	2.24 (1.32-3.79)	<0.01	1.94 (1.13-3.34)	0.02	1.90 (1.10-3.28)	0.02	1.54 (0.85-2.76)	0.15
Alcohol										
None	-		ref		ref		ref		ref	
1/year-2/month	-		0.37 (0.22-0.63)	<0.001	0.39 (0.23-0.67)	0.001	0.39 (0.23-0.67)	0.001	0.44 (0.24-0.78)	<0.01
1/week-4/week	-		0.40 (0.24-0.66)	<0.001	0.46 (0.28-0.77)	<0.01	0.46 (0.28-0.77)	<0.01	0.52 (0.30-0.92)	0.03
5-7 times/week	-		0.34 (0.20-0.59)	<0.001	0.46 (0.26-0.82)	<0.01	0.47 (0.27-0.85)	0.01	0.61 (0.33-1.16)	0.13

Wealth quintile										
Richest	-		-		ref		ref		ref	
2nd	-		-		1.05 (0.60-1.85)	0.85	0.94 (0.53-1.67)	0.84	0.85 (0.46-1.58)	0.61
3rd	-		-		1.54 (0.89-2.69)	0.13	1.35 (0.77-2.38)	0.29	1.13 (0.62-2.08)	0.68
4th	-		-		1.77 (0.98-3.20)	0.06	1.52 (0.82-2.82)	0.18	1.52 (0.79-2.93)	0.21
Poorest	-		-		3.33 (1.84-6.02)	<0.001	2.88 (1.58-5.27)	0.001	2.43 (1.26-4.67)	<0.01
Education										
Higher education	-		-		-		ref		ref	
Intermediate	-		-		-		2.20 (1.10-4.38)	0.03	2.29 (1.07-4.89)	0.03
No qualification	-		-		-		1.95 (0.91-4.16)	0.09	1.87 (0.80-4.37)	0.15
Living alone	-		-		-		-		0.99 (0.64-1.51)	0.95
Cognition	-		-		-		-		0.96 (0.94-0.98)	<0.001
Depressive mood	-		-		-		-		1.32 (1.15-1.52)	<0.001
Diabetes	-		-		-		-		1.57 (0.90-2.74)	0.11
Hyperlipidemia	-		-		-		-		1.20 (0.82-1.75)	0.35

Model 1: Adjusted for age and gender.

Model 2: Further adjusted for smoking and alcohol

Model 3: Further adjusted for wealth.

Model 4: Further adjusted for education.

Model 5: Further adjusted for living alone, cognition, depressed mood, diabetes and hyperlipidemia

CI: Confidence interval

Table 5. 6. Multivariable logistic regression models examining associations between fruit and vegetable consumption groups and 4-year incident pre-frailty/frailty among 1,577 robust community-dwelling older people in England.

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	Odds Ratio (95%CI)	P value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value
Fruit and vegetable										
0 - <2.5 portions	ref		ref		ref		ref		ref	
2.5 - <5 portions	0.76 (0.52-1.11)	0.20	0.78 (0.53-1.15)	0.21	0.86 (0.58-1.27)	0.45	0.89 (0.60-1.33)	0.58	0.77 (0.52-1.15)	0.21
5 - <7.5 portions	0.54 (0.37-0.79)	<0.01	0.56 (0.38-0.83)	<0.01	0.64 (0.43-0.95)	0.03	0.66 (0.44-0.99)	0.04	0.56 (0.37-0.85)	<0.01
7.5 - <10 portions	0.43 (0.27-0.68)	<0.001	0.46 (0.28-0.73)	0.001	0.52 (0.32-0.86)	0.01	0.55 (0.34-0.91)	0.02	0.46 (0.27-0.77)	<0.01
10 - 17 portions	0.93 (0.47-1.84)	0.84	0.89 (0.46-1.75)	0.74	1.08 (0.55-2.11)	0.82	1.16 (0.59-2.29)	0.66	1.10 (0.54-2.26)	0.79
P for trend		<0.01		<0.01		0.03		0.05		0.02
Age group										
60-64	ref		ref		ref		ref		ref	
65-69	1.36 (1.01-1.84)	0.04	1.32 (0.98-1.79)	0.07	1.31 (0.97-1.78)	0.08	1.28 (0.94-1.74)	0.12	1.23 (0.89-1.69)	0.22
70-74	1.88 (1.38-2.54)	<0.001	1.85 (1.36-2.53)	<0.001	1.85 (1.35-2.52)	<0.001	1.77 (1.29-2.42)	<0.001	1.65 (1.19-2.28)	<0.01
75-79	3.25 (2.17-4.85)	<0.001	3.38 (2.23-5.11)	<0.001	3.23 (2.13-4.90)	<0.001	3.07 (2.02-4.68)	<0.001	2.91 (1.86-4.56)	<0.001
80+	7.46 (3.97-1.4.02)	<0.001	8.08 (4.22-15.48)	<0.001	8.19 (4.14-16.20)	<0.001	7.94 (4.01-15.72)	<0.001	7.00 (3.37-14.55)	<0.001
Female	1.66 (1.31-2.10)	<0.001	1.57 (1.23-1.99)	<0.001	1.54 (1.20-1.96)	0.001	1.45 (1.13-1.87)	<0.01	1.59 (1.22-2.08)	0.001
Smoking										
Non-smoker	-		ref		ref		ref		ref	
Current smoker	-		1.46 (0.95-2.23)	0.08	1.44 (0.93-2.22)	0.10	1.34 (0.87-2.09)	0.19	1.43 (0.91-2.26)	0.13
Alcohol										
None	-		ref		ref		ref		ref	
1/year-2/month	-		0.61 (0.37-1.03)	0.06	0.68 (0.40-1.14)	0.15	0.68 (0.41-1.15)	0.15	0.77 (0.45-1.31)	0.33
1/week-4/week	-		0.63 (0.39-1.04)	0.07	0.73 (0.44-1.21)	0.22	0.77 (0.46-1.26)	0.30	0.87 (0.52-1.45)	0.59
5-7 times/week	-		0.47 (0.28-0.78)	<0.01	0.60 (0.35-1.01)	0.05	0.64 (0.38-1.07)	0.09	0.71 (0.41-1.21)	0.21

Wealth quintile										
Richest	-		-		ref		ref		ref	
2nd	-		-		1.11 (0.80-1.53)	0.54	1.05 (0.76-1.46)	0.78	1.11 (0.79-1.56)	0.54
3rd	-		-		1.40 (1.01-1.95)	0.05	1.27 (0.90-1.79)	0.17	1.34 (0.93-1.91)	0.11
4th	-		-		1.65 (1.12-2.44)	0.01	1.46 (0.98-2.17)	0.06	1.38 (0.90-2.10)	0.14
Poorest	-		-		1.73 (1.05-2.86)	0.03	1.50 (0.89-2.52)	0.12	1.52 (0.90-2.57)	0.12
Education										
Higher education	-		-		-		ref		ref	
Intermediate	-		-		-		1.18 (0.84-1.66)	0.34	1.08 (0.75-1.54)	0.69
No qualification	-		-		-		1.67 (1.10-2.54)	0.02	1.20 (0.77-1.88)	0.42
Living alone	-		-		-		-		0.98 (0.71-1.34)	0.90
Cognition	-		-		-		-		0.98 (0.96-0.99)	0.001
Depressive mood	-		-		-		-		1.20 (1.00-1.44)	0.05
Diabetes	-		-		-		-		1.51 (0.95-2.40)	0.08
Hyperlipidemia	-		-		-		-		1.18 (0.92-1.52)	0.19

Model 1: Adjusted for age and gender.

Model 2: Further adjusted for smoking and alcohol

Model 3: Further adjusted for wealth.

Model 4: Further adjusted for education.

Model 5: Further adjusted for living alone, cognition, depressed mood, diabetes and hyperlipidemia

CI: Confidence interval

5.3.7.2 Supplementary analysis - separate consumption of fruit and vegetables

Models 1-5 were repeated with consumption of fruit and vegetables separately as a predictor variable for risks of frailty and pre-frailty/frailty. Fruit consumption ranged from 0 to 11 portions per day with mean and median of 3.1 and 3 portions, respectively. Vegetable consumption ranged from 0 to 9 portions per day with mean and median of 2.1 and 2 portions, respectively. Please see **Chapter 5.3.6.2 Supplementary analysis - separate consumption of fruit and vegetables** for detail.

Table 5.7 shows results of multivariable logistic regression models for incident frailty according to consumption of fruit and vegetable, respectively. In all Models there were no significant associations between fruit and vegetable consumption, respectively, and incident frailty, except those consuming 3 - <4.5 portions and 4.5 - <6 portions of fruit had significantly lower risks of incident frailty compared with those consuming 0 - <1.5 portions of fruit (OR=0.56, 95%CI=0.23-0.92, p=0.02; OR=0.56, 95%CI=0.31-0.99, p=0.05, respectively). This association became non-significant in later Models with further adjustments.

Results of multivariable logistic regression models examining risks of incident pre-frailty/frailty according to fruit and vegetable consumption separately are summarised in **Table 5.8**. For fruit consumption, 3 - <4.5 and 4.5 - <6 portions per day were significantly associated with lower odds of pre-frailty/frailty compared with 0 - <1.5 portions per day in all Models. 1.5 - <3 portions and 6 - 11 portions were not associated with pre-frailty/frailty in any Models. For vegetable consumption, 1 - <2 portions of vegetable was significantly associated with lower odds of pre-frailty/frailty in all Models. 2 - <3 portions, 3 - <4 portions and 4 - 9 portions were all significantly associated with lower odds of pre-frailty/frailty compared with 0 - <1 portion in Model 1, and in the final Model 5 2 - <3 portions and 4 - 9 portions remained significant while 3 - <4 portions became non-significant.

Table 5. 7. Multivariable logistic regression models examining associations between consumption of fruit and vegetable, respectively, and 4-year incident frailty among 2,634 non-frail community-dwelling older people in England.

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	Odds Ratio (95%CI)	P value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value
Fruit										
0 - <1.5 portions (n=423)	ref		ref		ref		ref		ref	
1.5 - <3 portions (n=727)	0.71 (0.44-1.15)	0.16	0.88 (0.55-1.42)	0.60	0.94 (0.57-1.54)	0.81	0.94 (0.57-1.54)	0.81	1.07 (0.63-1.82)	0.79
3 - <4.5 portions (n=917)	0.56 (0.23-0.92)	0.02	0.69 (0.42-1.14)	0.15	0.76 (0.45-1.29)	0.31	0.77 (0.45-1.31)	0.33	0.93 (0.53-1.65)	0.81
4.5 - <6 portions (n=402)	0.56 (0.31-0.99)	0.05	0.68 (0.38-1.22)	0.19	0.77 (0.42-1.40)	0.38	0.77 (0.42-1.40)	0.39	1.05 (0.55-2.01)	0.87
6 - 11 portions (n=165)	0.92 (0.47-1.80)	0.80	1.21 (0.60-2.43)	0.59	1.40 (0.69-2.82)	0.35	1.42 (0.69-2.92)	0.34	1.98 (0.93-4.22)	0.08
Vegetable										
0 - <1 portion	ref		ref		ref		ref		ref	
1 - <2 portions	0.79 (0.47-1.32)	0.37	0.96 (0.56-1.66)	0.90	1.10 (0.63-1.93)	0.74	1.10 (0.63-1.92)	0.75	1.24 (0.67-2.28)	0.49
2 - <3 portions	0.97 (0.58-1.63)	0.92	1.15 (0.67-1.98)	0.60	1.34 (0.76-2.35)	0.31	1.33 (0.76-2.34)	0.32	1.54 (0.84-2.84)	0.16
3 - <4 portions	0.65 (0.34-1.24)	0.19	0.81 (0.41-1.59)	0.54	0.97 (0.48-1.94)	0.93	0.95 (0.47-1.90)	0.88	1.05 (0.49-2.22)	0.90
4 - 9 portions	0.46 (0.20-1.04)	0.06	0.51 (0.22-1.18)	0.12	0.58 (0.24-1.39)	0.22	0.57 (0.24-1.36)	0.20	0.53 (0.20-1.36)	0.19

Model 1: Adjusted for age and gender.

Model 2: Further adjusted for smoking and alcohol

Model 3: Further adjusted for wealth.

Model 4: Further adjusted for education.

Model 5: Further adjusted for living alone, cognition, depressed mood, diabetes and hyperlipidemia

CI: Confidence interval

Table 5. 8. Multivariable logistic regression models examining associations between consumption of fruit and vegetable, respectively, and 4-year incident pre-frailty/frailty among 1,577 robust community-dwelling older people in England.

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	Odds Ratio (95%CI)	P value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value
Fruit										
0 - <1.5 portions (n=423)	ref		ref		ref		ref		ref	
1.5 - <3 portions (n=727)	0.82 (0.58-1.18)	0.28	0.83 (0.58-1.19)	0.31	0.93 (0.65-1.34)	0.70	0.96 (0.67-1.38)	0.83	0.86 (0.59-1.26)	0.45
3 - <4.5 portions (n=917)	0.55 (0.39-0.78)	0.001	0.56 (0.39-0.80)	<0.01	0.64 (0.45-0.92)	0.02	0.66 (0.46-0.95)	0.02	0.58 (0.40-0.84)	<0.01
4.5 - <6 portions (n=402)	0.56 (0.37-0.83)	<0.01	0.54 (0.36-0.82)	<0.01	0.61 (0.40-0.94)	0.02	0.64 (0.42-0.98)	0.04	0.52 (0.33-0.81)	<0.01
6 - 11 portions (n=165)	0.82 (0.48-1.39)	0.46	0.86 (0.51-1.46)	0.58	1.04 (0.62-1.75)	0.89	1.12 (0.66-1.90)	0.67	1.17 (0.67-2.02)	0.58
Vegetable										
0 - <1 portion	ref		ref		ref		ref		ref	
1 - <2 portions	0.57 (0.39-0.84)	<0.01	0.58 (0.39-0.85)	<0.01	0.62 (0.42-0.92)	0.02	0.64 (0.43-0.95)	0.03	0.57 (0.38-0.86)	<0.01
2 - <3 portions	0.57 (0.39-0.84)	<0.01	0.60 (0.41-0.89)	0.01	0.70 (0.47-1.03)	0.07	0.71 (0.48-1.05)	0.09	0.64 (0.43-0.96)	0.03
3 - <4 portions	0.64 (0.41-0.99)	0.05	0.67 (0.43-1.05)	0.08	0.74 (0.47-1.17)	0.20	0.75 (0.48-1.18)	0.21	0.70 (0.44-1.11)	0.13
4 - 9 portions	0.52 (0.31-0.87)	0.01	0.53 (0.31-0.89)	0.02	0.60 (0.25-1.01)	0.06	0.62 (0.37-1.06)	0.08	0.53 (0.30-0.93)	0.03

Model 1: Adjusted for age and gender.

Model 2: Further adjusted for smoking and alcohol

Model 3: Further adjusted for wealth.

Model 4: Further adjusted for education.

Model 5: Further adjusted for living alone, cognition, depressed mood, diabetes and hyperlipidemia

CI: Confidence interval

5.3.7.3 Supplementary analysis - implausibly high values

Implausibly high values were excluded from the main analysis. In this supplementary analysis, the fully adjusted Model 5 was repeated with implausibly high values treated as 0 (Model 5a) and treated as were without being changed or excluded (Model 5b). Results of Models 5a and 5b are not significantly different from those of Model 5 (**Tables 5.9** and **5.10**).

5.3.7.4 Supplementary analysis - multiple imputation by chained equations

There were missing values for some covariates, including smoking (n=18), alcohol (n=19), wealth (n=48), cognitive function score (n=183) and depressed mood (n=11) while all analytic sample had complete data for the rest of the covariates of age, gender, education, living alone, diabetes and hyperlipidemia. Models 5 for incident frailty and incident pre-frailty/frailty were repeated imputing the missing values of covariates using MICE. Imputing missing covariates did not significantly change the results of Model 5 (**Tables 5.9** and **5.10**).

Table 5. 9 Fully adjusted logistic regression models for incident frailty with implausibly high values treated as 0 (Model 5a), treated as were (Model 5b) and with missing covariates imputed by multiple imputation by chained equations (MICE).

Total	Model 5		Model 5a		Model 5b		MICE	
Variable	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value
Fruit and vegetable								
0 - <2.5 portions	ref							
2.5 - <5 portions	1.22 (0.68-2.17)	0.50	1.25 (0.73-2.16)	0.42	1.22 (0.69-2.17)	0.49	1.10 (0.66-1.85)	0.71
5 - <7.5 portions	1.03 (0.58-1.84)	0.91	1.09 (0.63-1.89)	0.76	1.05 (0.60-1.86)	0.86	0.94 (0.56-1.60)	0.83
7.5 - <10 portions	1.19 (0.54-2.65)	0.67	1.08 (0.51-2.30)	0.84	0.98 (0.45-2.11)	0.96	0.94 (0.45-1.97)	0.87
10 - 17 portions	0.60 (0.21-1.77)	0.36	0.59 (0.21-1.62)	0.31	0.96 (0.46-2.03)	0.92	0.54 (0.20-1.47)	0.23

CI: Confidence interval.

MICE: Multiple imputation by chained equations.

Table 5. 10 Fully adjusted logistic regression models for incident pre-frailty/frailty with implausibly high values treated as 0 (Model 5a), treated as were (Model 5b) and with missing covariates imputed by multiple imputation by chained equations (MICE).

Total	Model 5		Model 5a		Model 5b		MICE	
Variable	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value
Fruit and vegetable								
0 - <2.5 portions	ref							
2.5 - <5 portions	0.77 (0.52-1.15)	0.21	0.69 (0.48-1.01)	0.06	0.80 (0.53-1.19)	0.26	0.86 (0.58-1.27)	0.44
5 - <7.5 portions	0.56 (0.37-0.85)	<0.01	0.55 (0.38-0.81)	<0.01	0.59 (0.40-0.89)	0.01	0.66 (0.44-0.98)	0.04
7.5 - <10 portions	0.46 (0.27-0.77)	<0.01	0.48 (0.30-0.77)	<0.01	0.55 (0.33-0.90)	0.02	0.53 (0.32-0.87)	0.01
10 - 17 portions	1.10 (0.54-2.26)	0.79	0.80 (0.42-1.54)	0.50	0.97 (0.58-1.63)	0.91	1.12 (0.55-2.27)	0.75

CI: Confidence interval.

MICE: Multiple imputation by chained equations.

5.3.8 Discussion

In this chapter, risks of 4-year incident frailty and incident pre-frailty/frailty according to fruit and vegetable consumption were examined among 2,634 non-frail (robust or pre-frail) and 1,577 robust English community-dwelling men and women aged 60 or older, respectively. There were no significant association between fruit and vegetable consumption and incidence of frailty among robust or pre-frail participants, after adjusting for potential confounding factors. Interestingly, however, consuming 5-10 portions of fruit and vegetables per day was associated with approximately half the odds of pre-frailty/frailty compared with 0-2.5 portions per day among robust participants. No potential protective effect for incident pre-frailty/frailty were observed among participants consuming 10 or more portions per day; the incidence of pre-frailty/frailty was similar in this very high consuming group, as those with very low consumption (0 - <2.5 portions).

The reason why fruit and vegetable consumption was associated with incident pre-frailty/frailty but not with incident frailty is not clear. This may suggest that fruit and vegetable consumption is beneficial more for preventing the development of pre-frailty/frailty than for delaying or reversing changes in already pre-frail individuals.

Another interesting finding is that the potentially beneficial effects of consuming 5 to 10 portions disappeared for those consuming 10 or more portions. This may be attributable to a possible ceiling effect of health benefits from consumption of fruit and vegetables, or unmeasured characteristics of those who consumed that high amount of fruit and vegetables. The dose-response meta-analysis study described in **Chapter 5.1 Introduction** showed that more than 10 portions of fruit and vegetable consumption failed to show additional benefits against mortality and CVD.[197] Another possible explanation is that a very high amount of fruit and vegetable consumption may hinder consuming sufficient calories or other important nutrients, such as protein, and result in an unbalanced poor quality diet. Fruit and vegetables contain multiple micro-nutrients, but are not high calorie or protein-rich food, except for legumes. Low intake of calories or protein has been shown to be associated with increased risks of frailty.[282, 283, 294]

Adequate consumption of fruits and vegetables may be protective against frailty. One of the possible mechanisms is anti-oxidative effects. A recent systematic review has shown that frailty appears to be associated with higher oxidative stress and lower anti-oxidant-related measurements.[295] Fruits and vegetables are rich in natural anti-oxidants, such as vitamin C, vitamin E, carotenoids and selenium and may prevent frailty by decreasing reactive oxygen species, which cause damage to DNA, lipids and proteins and induce mitochondrial dysfunction and apoptosis.[88] Another explanation is that legumes and beans are potential source of proteins. Adequate dietary protein intake is essential to increase muscle protein synthesis and improve physical function, and counteract sarcopenia, which is the age-related loss of muscle mass and strength and a core feature of frailty. Therefore those with adequate, but not too large, intakes of fruits and vegetables may obtain more plant-based proteins and have lower frailty risk than those with low intake.[84] Another possible explanation is that a high fruit and vegetable consumption may be a marker of healthy characteristics that were unmeasured or accounted for. Those who consumed a sufficient amount of fruit and vegetable may be more health conscious and motivated for healthy behaviours, such as physical exercise or trying to have a balanced diet.

Supplementary analyses examined individual consumption of fruit and vegetable and showed similar findings to the main analyses with fruit and vegetable combined: moderate consumption was associated with lower odds of pre-frailty/frailty but higher consumption was not. The other supplementary analyses imputing missing values of covariates and keeping implausibly high values of fruit and vegetable consumption or treating them as 0 did not change the findings significantly.

In conclusion, moderate consumption of fruit and vegetable (5 to 10 portions per day) was significantly associated with lower risks of developing pre-frailty/frailty among robust older people in England. Older people, especially those who are robust, can be advised that it may be beneficial to consume sufficient amounts of fruit and vegetables for frailty prevention as well as for health in general. In light of scarce information available on this topic in the literature, more high-quality studies are warranted, in particular to further examine our findings of reduced benefit for those eating more than 10 portions of fruit and vegetables per day.

I discuss the strengths and limitations of this analysis and further discuss the meaning and implications of the findings in my final **Chapter 6 OVERALL DISCUSSION**.

6 OVERALL DISCUSSION

This thesis considers the potential of three modifiable lifestyle factors, (i) smoking, (ii) alcohol and (iii) fruit and vegetable consumption, as risk factors for frailty by reviewing the evidence and examining the prospective associations between them, at baseline and subsequent frailty risks over 4 years using a representative sample of community-dwelling older people in England (ELSA).

In this chapter the key findings are summarised and discussed in comparison with previous studies, followed by a discussion of the strengths and limitations of the methods used. Clinical and research implications of the findings and directions for future research are also highlighted before the conclusion.

6.1 Key Findings

6.1.1 Systematic reviews

Three systematic reviews on smoking, alcohol consumption and fruit and vegetable consumption as risk factors of incident frailty revealed that there was only limited evidence in the literature. The number of eligible prospective studies identified by the systematic reviews was small, ranging from 4 to 5. Some of the included studies were not originally designed to examine the three factors of my thesis's interest as risk factors of frailty, and others had suboptimal methodological quality. A meta-analysis was conducted only for alcohol analysis but this was not possible for smoking and fruit and vegetable consumption due to different methodologies regarding predictors, outcomes and statistical analyses. For smoking, most of the included studies showed that current smoking at baseline predicted worsening of frailty status at follow-up. For alcohol, a meta-analysis suggested a significantly lower odds of frailty in the highest amount of alcohol consumption. However, this finding was questioned mainly because non-drinkers were used as a reference. For fruit and vegetable consumption, two of three studies with adequate methodological quality showed associations between higher fruit and vegetable consumption and lower frailty risks.

6.1.2 Smoking

Chapter 3 demonstrated that current smokers had 58% higher odds of frailty compared with non-smokers (OR=1.58, 95%CI=1.00-2.50, p=0.05) controlling for potential confounders. This association was attenuated and became non-significant after further adjusting for COPD, CRP and fibrinogen, respectively, which suggests that these three factors may partially explain the association between smoking and frailty. Smoking is the main risk factor for COPD and is responsible for 40-70% of the cases.[296] Typical symptoms of COPD include cough, wheezing, shortness of breath, especially with exercise, which could cause fatigue, low physical activity and function, including slow walking speed, and predispose patients with COPD to developing frailty. The OR for Model 5 decreased by 13.3% to 1.37 and p values changed from 0.05 to 0.19 when COPD was added to the model. Toxic compounds included in cigarette smoke cause inflammatory reactions through a number of inflammatory mediators.[248] Chronic inflammation can cause muscle wasting,[249] which is a core component of frailty. When CRP and fibrinogen were added separately, ORs decreased from 1.58 to 1.37 and 1.49, respectively, and p values changed from 0.05 to 0.25 and 0.15, respectively.

Based on the systematic review of the literature (**Chapter 3.2**),[226] only one previous study examined risks of 3-year incident frailty defined by the frailty phenotype according to baseline smoking status, in American older women from the Women's Health Initiative Observational Study.[233] Past smokers and current smokers had 12% and 76% higher risks of developing frailty compared with never smokers in a multinomial logistic regression model. According to my calculation using available data in the paper, the unadjusted OR of frailty for current smokers compared with non-smokers (never and past smokers combined) was 1.80 (95%CI=1.56-2.08, p<0.001), which is smaller than but comparable to findings of this thesis's age- and gender adjusted model (OR=2.11, 95%CI=1.35-3.29, p=0.001). Another comparable study examining smoking and incident frailty was found in the updated literature search.[146] This study showed that current smoking at mid-life (45-55 years old) was significantly associated with a higher odd of frailty at old age (mean age=69).[146] Their OR adjusted for age, age-squared, gender, time of frailty measure and ethnic origin was 1.69 (95%CI=1.27-2.25) was similar to the age- and gender- adjusted OR for

current smokers (OR=1.80, 95%CI=1.12-2.88) in the supplementary analysis using three smoking groups.

6.1.3 Alcohol

In Chapter 4 non-drinkers had a 73% higher risk of developing frailty over 4 years compared with low drinkers who drank >0 - 7 units of alcohol per week (OR=1.71, 95%CI=1.12-2.60, p=0.01) in the fully adjusted model controlling for age, gender, smoking, wealth and education. The odds of frailty of moderate, heavy and very heavy drinkers who consumed >7 - 14, >14 - 21 and >21 units per week, respectively, were not significantly different from that of low drinkers (ORs=0.64-1.01, all p>0.12). When the model was further adjusted for self-reported general health, the OR for non-drinkers decreased from 1.71 to 1.48 by 13.5% and became non-significant with the p value changing from 0.01 to 0.09. This suggests that non-drinkers' increased incident frailty risk can partially attributable to their worse health status at baseline. Non-drinkers may have included 'sick quitters', who had quit drinking due to ill health from alcohol and other diseases.[275] At baseline non-drinkers had worse health profiles, such as worse baseline frailty status, advanced age, current smoking, lower wealth and lower education.

6.1.4 Fruit and vegetable consumption

Chapter 5 analysed the associations between fruit and vegetable consumption and frailty risks. Fruit and vegetable consumption of ELSA participants (mean 5 portions) was found to be higher than that of general and older populations (mean around 3 portions).[198, 287] Prospective associations between fruit and vegetable consumption at baseline and risk of incident frailty and incident pre-frailty/frailty over 4 years were examined. Although there was no significant association with incident frailty among robust and pre-frail participants, consumption of 5-10 portions of fruit and vegetable per day was significantly associated with 44-54% decreased odds of pre-frailty/frailty among robust participants (OR=0.56, 95%CI=0.37-0.85, p<0.01 for 5-7.5 portions per day; OR=0.46, 95%CI=0.27-0.77, p<0.01 for 7.5-10 portions per day). However, consuming more than 10 portions of fruit and vegetables showed no potential

protective effects against incident pre-frailty/frailty compared with consuming fewer than 2.5 portions/day.

Only one study was found by the systematic review (**Chapter 5.2**) that focused mainly on the association between fruit and vegetable consumption and incident frailty.[279] This study by Garcia-Esquinas and colleagues examined 2926 non-frail community-dwelling older people from three cohorts (two from France and one from Spain) and showed that consumption of fruit, vegetables and fruit and vegetables combined was inversely associated with incident frailty over 2.5 years in a dose-response manner.[289] Although 1 portion of both fruit and vegetable was defined as 80g according to WHO[199] in this thesis, Garcia-Esquinas's study defined 1 portion as 120g for fruit and 150g for vegetables.[289] Therefore it is not possible to compare the findings precisely because of the different amount of fruit and vegetables per portion. Garcia-Esquinas's study showed significant associations with incident frailty controlling for age, gender, education, BMI, smoking, comorbidities, cognition, depression, number of medications, modified Mediterranean Diet Score and energy intake, while significant associations were observed not with incident frailty but only with incident pre-frailty/frailty in this thesis. Garcia-Esquinas's study showed a dose-response inverse relationship between fruit and vegetable consumption and incident frailty risk, while this thesis's analysis showed a dose-response decrease in incident pre-frailty/frailty risks as fruit and vegetable consumption increases until 10 portions per day, after which there was no significant association compared with consuming fewer than 2.5 portions. Garcia-Esquinas's study's highest category is '5 portions' or more. Their '5 portions' can range from 600g to 750g of fruit and vegetables, which is lower than this thesis's highest category of 800g, therefore they may have failed to categorise the very high end of consumption. Alternatively, dietary choices in terms of what types of fruit and vegetable were eaten might be different in different countries.

6.2 Frailty as an Outcome Measure

Frailty has been chosen as the main outcome measure in this thesis over the wide range of other possible outcome measures because it is an important issue for older

people and is associated with a range of adverse health consequences and increased health and social costs.[74, 157] The International Consortium for Health Outcomes Measurement (ICHOM) organised the Older Person Working Group, consisting patient representatives, measurement experts, clinical, social and psychological researchers, and the Group agreed with a standard set of important outcome measures that matter to older people. The set includes frailty and the other outcomes are participation in decision making, autonomy and control, mood and emotional health, loneliness and isolation, pain, activities of daily living, frailty, time spent in hospital, overall survival, carer burden, polypharmacy, falls and place of death.[297] Although there are various important outcome measures for older people included in the set, such as disability, frailty is important in that it is a reversible process[35, 36] and can potentially be prevented or improved by interventions (please see **Chapter 1.5**) Frailty has been shown to be closely related to most of the included outcome measures,[11, 216, 298-303] and to predict some of them, including disability,[21, 22] falls,[18] hospitalisation[24] and mortality.[26, 27] It is also noted that frailty has not been studied extensively until recently thus there is relatively less evidence on frailty than the other outcome measures, especially regarding modifiable lifestyle risk factors. One of other important outcome measures for older people is physical performance, which is closely related to frailty. However, it was not chosen because there was no good validated performance battery in ELSA.

6.3 Strengths

Major strengths of the use of ELSA include that the data are from a large nationally representative cohort of community-dwelling older men and women in England. Furthermore, risks of incident frailty and incident pre-frailty/frailty over 4 years were prospectively examined controlling for a wide range of important confounders, including socio-demographic and lifestyle and health variables. The longitudinal weights were used to address biases caused by attrition. Although the main analyses were all complete case analyses, which included participants with complete data, the models were repeated, in supplementary analyses with missing values of covariates imputed using MICE. For all three modifiable lifestyle risk factors of frailty,

systematic reviews were performed to search for currently available evidence and a meta-analysis was conducted for the alcohol analysis.

6.4 Limitations

There are several limitations that should be considered when interpreting the findings of systematic reviews, meta-analyses and analyses using ELSA data.

6.4.1 Systematic reviews and meta-analyses

A MeaSurement Tool to Assess systematic Reviews (AMSTAR) checklist was used to assess methodological quality of the three systematic reviews.[304] This instrument was developed to assess methodological quality of systematic reviews and has good face and content validity.[304] According to the AMSTAR checklist, all three systematic reviews had moderate quality (**Appendices 2a-c**). Methodological limitations suggested by the checklist included: 1. only one investigator, but not two, extracted data; 2. I did not report the source of funding of the included studies; 3. I did not search trial/study registries, did not consult experts in the field and did not pursue grey literature; and 4. a protocol was not registered (only for smoking review). However, all three reviews were conducted with robust methodology in accordance with the PRISMA statement, including comprehensive and extensive search using a combination of MeSH and text terms in multiple electronic databases.

6.4.2 ELSA analyses

6.4.2.1 Selection bias

Participants of the ELSA cohort were recruited from HSE rather than directly from general population. Although the ELSA cohort is considered to be a representative sample of community-dwelling men and women in England,[158] they may not be in that they had elected to participate twice, first in HSE then in ELSA. This may have led to selection bias and the ELSA participants may be healthier and more health conscious due to a healthy user effect,[305] which could be further amplified in older populations,[306] as well as attrition over time. It should also be noted that the non-

responders from the ELSA cohort were sicker than the responders therefore my ELSA analytic sample might be healthier than the total ELSA population. This may explain why fruit and vegetable consumption in the ELSA cohort than average UK population (**Chapter 5.3 5.3 Fruit and Vegetable Consumption and incident Pre-frailty/Frailty (ELSA)**).

Non-respondents in ELSA tended to be older with worse health profiles,[307] and those who could not be followed in all the analyses in this thesis were also more likely to be older, frailer, current smokers, non-drinkers and have lower education, wealth and cognitive function (see results sections of each analysis). This may generate a selection bias towards the null hypothesis (i.e. no significant association between each of three modifiable lifestyle risk factors and frailty) The reasons for loss to follow-up were available between waves 2 and 4 for the smoking and alcohol analyses, but reasons were not available those between waves 4 and 6 in the fruit and vegetable consumption analysis. The main analyses of this thesis were based on complete case analysis, therefore, those who were excluded may be at a higher risk of incident frailty, which may have attenuated the population incident frailty risks.

The ELSA cohort does not represent the ethnic minority population of England, including few non-white British respondents. Therefore, the findings may not be generalizable to other populations. However, the ELSA sample was broadly representative of the English population based on comparisons of the sociodemographic characteristics of the ELSA participants against results from the national census.[158]

6.4.2.2 Measurement bias

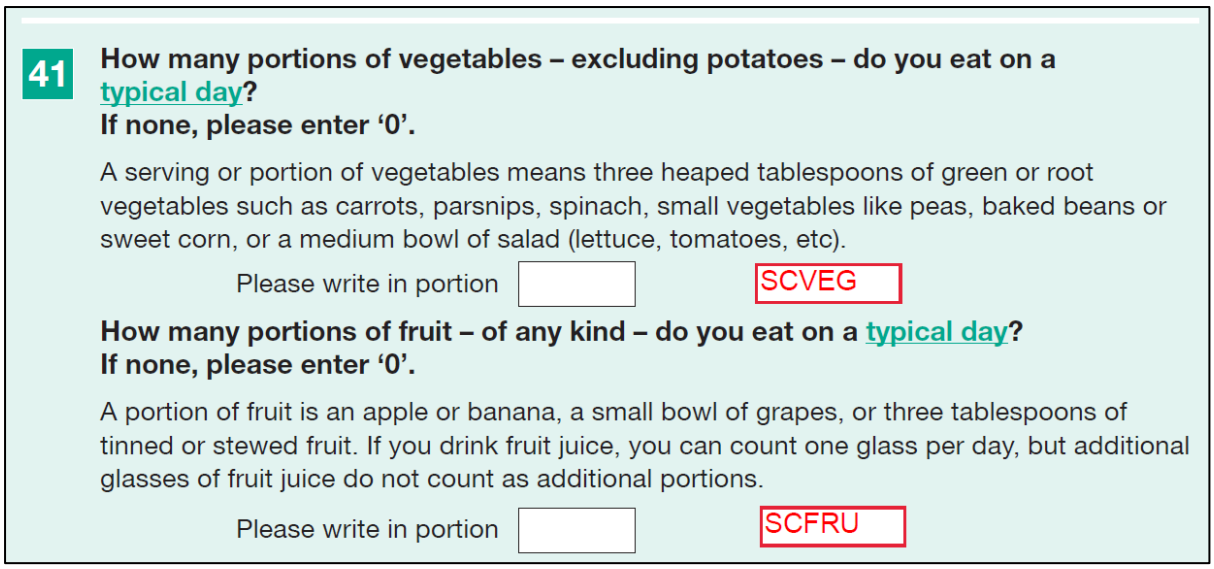
The three modifiable lifestyle risk factors - smoking, alcohol consumption and fruit and vegetable consumption - were all self-reported and may be subject to recall bias to varying degrees. There is a tendency of underestimation when smoking prevalence is based on self-reported information compared with that based on cotinine measurement,[308] which may bias the findings towards the null hypothesis (no effect of smoking on risk of incident frailty). Alcohol consumption and fruit and vegetable consumption were more likely to be subject to the recall bias, because

participants needed to recall detail on types and amounts for fruit and vegetables and on types, amounts, frequency over the last 12 months for alcohol consumption, while participants needed to answer their current status for smoking. All the three alcohol measures used in this thesis are self-reported. A recent systematic review showed that self-reported alcohol consumption in both quantity and frequency demonstrated good\adequate test-retest reliability, criterion validity, hypothesis validity and convergent validity.[309]

Self-reported smoking history has been validated[172-174] and the ELSA questionnaire of smoking status was shown to accurately distinguish more than 95% of non-current smokers at wave 0 against salivary cotinine levels (**Chapter 2.5 Definition of Alcohol Consumption**).

The ELSA wave 4 cohort was used for the fruit and vegetable analysis, and it was shown that mean and median fruit and vegetable consumption were 5.2 and 5.0 portions, respectively, and with 51.0% of participants consuming 5 or more portions per day. Data of fruit and vegetable consumption were collected through a self-completion questionnaire (**Figure 2.2**). The same questionnaire was used at wave 3. However, in waves 5, 6, 7 and 8 the questionnaire had been changed to two simple self-completion questions: ‘How many portions of vegetables - excluding potatoes - do you eat on a typical day?’ and ‘How may portions of fruit - of any kind - do you eat on a typical day?’ (**Figure 6.1**).

Figure 6. 1. Self-completion questionnaire for fruit and vegetable consumption at English Longitudinal Study of Ageing wave 8.



41 **How many portions of vegetables – excluding potatoes – do you eat on a typical day?**
If none, please enter '0'.

A serving or portion of vegetables means three heaped tablespoons of green or root vegetables such as carrots, parsnips, spinach, small vegetables like peas, baked beans or sweet corn, or a medium bowl of salad (lettuce, tomatoes, etc).

Please write in portion [ ] SCVEG

How many portions of fruit – of any kind – do you eat on a typical day?
If none, please enter '0'.

A portion of fruit is an apple or banana, a small bowl of grapes, or three tablespoons of tinned or stewed fruit. If you drink fruit juice, you can count one glass per day, but additional glasses of fruit juice do not count as additional portions.

Please write in portion [ ] SCFRU

A previous study using the ELSA cohort aged 52 or older showed that median portions of fruit and vegetable consumption were 4.3, 5.3, 5.0, 5.0 and 5.0 portions per day at waves 3, 4, 5, 6 and 7,[310] using the different method of ascertainment, which are compatible with this thesis's findings.

These values are higher than those of the general population in the UK, derived from other sources. According to data from the Eurostat (the statistical office of the EU) in 2014,[287] 36.5% of British people aged 65 or older living in private households consumed 5 or more portions of fruit and vegetables. Although the questionnaire at wave 4 might be over-reporting the intake of fruit and vegetables, a study using the HSE 2001 cohort (≥35 years old, mean age=56.6) showed that mean daily portion of fruit and vegetable consumption was 3.8 portions based on the same questionnaire as used at ELSA wave 4 (**Figure 2. 2**),[198] which was lower than the mean of fruit and vegetable consumption in this thesis. Moreover, fruit and vegetable consumption was shown to be linearly associated with CVD risks cross-sectionally at ELSA wave 4 (**Chapter 2.7 Definition of Fruit and Vegetable Consumption**). Therefore, the higher fruit and vegetable consumption than the general population in the UK may be attributable to the specific population characteristics of the ELSA cohort.

It was not possible to confirm reliability or validity of the quantity of alcohol consumption at wave 0, which was used in this thesis, due to lack of data such as blood alcohol concentration. In addition, the alcohol quantity was calculated based

on participants' responses to multiple questions regarding amount and frequency of different alcoholic beverages, and studies using the same methodology to quantify alcohol consumption could not be identified, while the same methodologies of smoking and fruit and vegetable consumption were used by previous studies.[176, 177, 195] Amount of alcohol consumption was not available at baseline wave 2 but measured only at one time point at wave 0 (HSE 1998, 1999 and 2001) 3-7 years before wave 2. (**Chapter 2 METHODS**). These measurement error in the three modifiable lifestyle factors may lead to underestimation of the true effects.

It should also be noted that the three modifiable lifestyle risk factors were measured once at baseline, and changes during follow-up periods or past history during mid-life were not considered in this thesis. Given cumulative effects on health during life course and possible 'sick quitter' effects in alcohol consumption,[311] it would have been ideal to take a life-long history of the three lifestyle risk factors into account. In smoking analysis, data on reasons for smoking cessation among past smokers were not available. In alcohol analysis, non-drinkers included never drinkers and past drinkers. Those who are in poor health tend to avoid drinking, decrease alcohol consumption or quit drinking.[274, 275] However, no data were available regarding never drinkers and past drinkers or reasons for abstaining from alcohol intake. For fruit and vegetable consumption, data on the consumption in mid-life were not available. Amount of fruit and vegetable consumption may have changed over time as people tend to eat more fruit and vegetables when they age.[287, 312]

This thesis adopted the frailty phenotype criteria[16] to define frailty. Currently this is the most commonly used frailty definition in the literature and has been well validated in various populations and settings.[11, 51] A potential limitation of this model is that it includes only physical components. Some experts argue that the multidimensional approaches, including social, psychological, and cognitive factors rather than only physical components, should be included to define frailty.[207, 313] It was demonstrated that adding cognitive impairment to the frailty phenotype criteria improved predictive ability for different adverse health outcomes, including incident disability, hospitalisation, dementia and mortality over 4 years in a prospective study of more than 6000 French older people.[53] The Frailty Index, a multidimensional approach to define frailty, was shown to have a better discriminative ability for mortality than the

frailty phenotype.[3,14] However, the Frailty Index model does not directly measure frailty but risk of frailty, while the frailty phenotype presents frailty as a specific clinical syndrome and enables to investigate the underlying mechanisms, pathophysiology, and risk factors.

A slightly modified version of the frailty phenotype criteria was used due to availability of ELSA data (**Table 2.4. Comparison of five components from the modified Cardiovascular Health Study criteria at wave 2 and the original criteria**). There were some important differences in weight loss and low physical activity criteria while the criteria of exhaustion, weakness and slowness were almost identical to the original ones. The original version defined unintentional weight loss by asking participants, however the ELSA version defined weight loss by calculating actual changes in weight or BMI and did not confirm whether it was unintentional or not. Low physical activity was defined based on kilocalorie consumption in the original version but was defined by intensity and frequency of physical activity in daily life in the ELSA version. Although such modifications are common in other previous studies, they may have affected the comparability to existing findings.[4,6] In this thesis, regardless of these differences, prevalence of frailty in the ELSA cohort is compatible with that of the original version.[16]

6.4.2.3 Chance and multiple testing

There are multiple ways of classifying alcohol consumption. In this thesis, three alcohol consumption measurements were used (quantity per week, quantity on the heaviest drinking day and frequency) and there is a risk of multiple testing. This risk was addressed by choosing the standard of alcohol epidemiology (quantity per week)[181] as a primary predictor and using the others as supplementary supportive analyses. Similarly, consumption of combined fruit and vegetables was used in the main analysis, and fruit and vegetables were examined separately in the supplementary analysis.

6.4.2.4 Unmeasured confounders

As is always the case with observational studies like ELSA, there may be unmeasured confounding factors which I could not account for in my analysis. Lifespan history regarding quantity and frequency of smoking and alcohol consumption was not available in ELSA and may have affected this thesis's findings. In particular, a 'sick quitters' effect could have influenced the smoking and alcohol analyses. Regarding fruit and vegetable analysis, their consumption may be a marker of an overall healthier lifestyle, which may be beneficial against frailty, independently of fruit and vegetable consumption. It is also of note that data on total calorie or intake of other nutrients, such as protein or fat, were not available and that only a small range of co-morbidities were recorded.

6.5 Implications

This thesis has demonstrated that there are modifiable lifestyle factors that are associated with an increased risk of frailty and addressing these might potentially prevent or delay the onset of frailty.

6.5.1 Smoking

It was shown in the ELSA analysis that COPD and inflammation may at least partially explain the association between current smoking and increased incident frailty risk. Smoking cessation can decrease risk of COPD[315] and reduce systemic inflammation.[316] Therefore, although no study was found in the literature regarding effects of smoking cessation on frailty, smoking cessation may be recommended for current smokers for alleviating risk of developing frailty as well as for general health.

6.5.2 Alcohol

This thesis's analysis did not show evidence that high alcohol consumption in old age is a risk factor of frailty. Although alcohol consumption is a modifiable lifestyle factor, from a clinical point of view, the findings do not currently support targeting reduction in alcohol consumption in older people as a key factor aiming to reduce the

development of frailty over the short-medium term (4 years). It did not show evidence that alcohol consumption is beneficial for frailty, either, and does not support the view that non-drinkers should start drinking alcohol in order to prevent the development of frailty. Non-drinkers may have increased incident frailty due to a generally poor health status.

6.5.3 Fruit and vegetable consumption

There is currently limited evidence regarding effects of fruit and vegetable consumption on frailty.[279] If fruit and vegetables are beneficial in preventing or reversing frailty, it may be a promising target for intervention against frailty as fruit and vegetable consumption is a modifiable lifestyle factor that can be relatively easily addressed without significant side effects or costs, especially for those who were robust. However, a possible ceiling effect was observed for 10 or more portions of fruit and vegetable per day. From a clinical perspective, therefore, those with insufficient intake of fruit and vegetables can be encouraged to have a balanced diet with at least 5 portions of fruit and vegetables per day. For those who are consuming 10 or more of fruit and vegetables, it should be confirmed that they also consume other nutrients and sufficient calories.

6.5.4 Lead Time

These analyses showed that modification of lifestyle factors, such as smoking and fruit and vegetable consumption, may potentially be beneficial even in old age of 60 years or older. Whether a lead time exists regarding the associations between frailty and these lifestyle factors is not known, and this thesis evaluates the associations over a relatively short time period in later life (four years). Further research should explore if these relationships remain over longer time periods. As the findings of this thesis are based on the secondary data analysis of an observational cohort study (ELSA), it cannot be inferred that changing the lifestyle factors is causal in decreasing the risk of incident frailty in later life. A randomised controlled trial of smoking cessation or increasing fruit and vegetable consumption would provide further insights on whether the lifestyle modification in old age would be effective. In

addition, age stratification of the randomised controlled trial would elucidate when it is too late to change the lifestyle factors to gain health benefits against frailty.

6.6 Future Directions

Based on the currently available evidence in the literature found through the systematic reviews and this thesis's findings by analysing the ELSA cohort, there are some suggestions for future research.

6.6.1 Smoking

Given that smoking cessation can be feasibly and effectively implemented in old age,[317] the findings of this thesis highlights the potential of smoking cessation as a plausible intervention against frailty for older smokers. Future research could be designed to evaluate the effectiveness of smoking cessation in preventing the onset of frailty or delaying progression to frailty.

6.6.2 Alcohol

Alcohol consumption patterns and frailty status change over time,[11, 275, 318] and these associations seem complex and possibly bidirectional. They are also affected by various factors. For example, alcohol consumption patterns in old age may not be the same as in mid-life, and current non-drinkers or light drinkers may have been heavy drinkers in the past. Those who are in the process of developing frailty due to alcohol-related or other health issues may be reducing their intake or may no longer tolerate alcohol. Such changes in people's drinking behaviours are likely to mask the harmful effects of alcohol on frailty. In contrast to the findings that alcohol consumption in old age was not associated with increased frailty risks shown in this thesis and previous studies,[251, 252] alcohol consumption in mid-life significantly increased risk of incident frailty in old age in one study.[145] In this regard, future studies with information on life-course history of alcohol use rather than one-time alcohol use information, especially for those classified as non-drinkers in old age, are warranted.

6.6.3 Fruit and vegetable consumption

As described in **Chapter 5**, a very high amount of fruit and vegetable consumption, 10 portions per day or more, may not be as effective as moderate amount of 5-10 portions per day, possibly because it hinders sufficient intake of other nutrients or calories. Future research on fruit and vegetable consumption and frailty should take into consideration other macro- and micro-nutrients and total calories rather than fruit and vegetables alone. More studies are needed to assess benefits of dietary patterns and changing diet as a part of multi-domain intervention against frailty.

6.7 Conclusions

With global population ageing and extended life expectancy, there are a growing number of older people worldwide as well as in the UK. Frailty, one of the geriatric syndromes, has increasingly been gaining scientific attention and recognised as a public health priority. This thesis has examined associations of three modifiable lifestyle factors, smoking, alcohol and fruit and vegetable consumption, respectively, with incident frailty risks. The findings of the thesis demonstrated that in the ELSA sample (i) current smoking was a significant risk factor for incident frailty, (ii) alcohol consumption in old age was not associated with incident frailty except for non-drinkers who had poor health profile and a higher risk of incident frailty and (iii) moderate amount of fruit and vegetable consumption (5-10 portions per day) was associated with lower incident pre-frailty/frailty while 10 portions or more per day were not as potentially beneficial. These findings highlight the importance of current smoking and low fruit and vegetable consumption in old age as risk factors for frailty and the possibility that modifying these lifestyle factors may decrease the risk of developing frailty as well as subsequent negative health outcomes related to frailty, thereby promoting of healthy ageing and enhancing the quality of life of older people.

7 REFERENCES

1. World Health Organization, World Health Day 2012, Are you ready? What you need to know about ageing; 2012. http://www.who.int/world-health-day/2012/toolkit/background/en/. Accessed 19 February 2019.
2. United Nations, World Population Ageing: 1950-2050; 2002. http://www.un.org/esa/population/publications/worldageing19502050/. Accessed 6 February 2018.
3. Kojima, G, Iliffe, S, Taniguchi, Y, et al. Prevalence of frailty in Japan: A systematic review and meta-analysis. Journal of epidemiology / Japan Epidemiological Association 2016;27(8):347-353.
4. Ministry of Internal Affairs and Communications (Japan), Statistics Bureau, Provisional Estimates (in Japanese); 2016. http://www.stat.go.jp/data/jinsui/pdf/201603.pdf. Accessed.
5. The World Bank, Paaa. https://data.worldbank.org/indicator/SP.POP.65UP.TO.ZS. Accessed 13 April 2016.
6. Office for National Statistics, Population Ageing in the United Kingdom, its Constituent Countries and the European Union; 2012. http://www.ons.gov.uk/ons/dcp171776_258607.pdf. Accessed 2 March 2016.
7. Gaugler, JE, Duval, S, Anderson, KA, et al. Predicting nursing home admission in the U.S: a meta-analysis. BMC geriatrics 2007;7:13.
8. Alemayehu, B, Warner, KE. The lifetime distribution of health care costs. Health services research 2004;39(3):627-642.
9. Mitnitski, AB, Graham, JE, Mogilner, AJ, et al. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC geriatrics 2002;2:1.
10. Mitnitski, AB, Mogilner, AJ, Rockwood, K. Accumulation of deficits as a proxy measure of aging. TheScientificWorldJournal 2001;1:323-336.
11. Clegg, A, Young, J, Iliffe, S, et al. Frailty in elderly people. Lancet (London, England) 2013;381(9868):752-762.
12. Fried, LP, Ferrucci, L, Darer, J, et al. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. The journals of gerontology Series A, Biological sciences and medical sciences 2004;59(3):255-263.

13. Schuurmans, H, Steverink, N, Lindenberg, S, et al. Old or frail: what tells us more? The journals of gerontology Series A, Biological sciences and medical sciences 2004;59(9):M962-965.
14. Katz, S, Downs, TD, Cash, HR, et al. Progress in development of the index of ADL. Gerontologist 1970;10(1):20-30.
15. Lawton, MP, Brody, EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9(3):179-186.
16. Fried, LP, Tangen, CM, Walston, J, et al. Frailty in older adults: evidence for a phenotype. The journals of gerontology Series A, Biological sciences and medical sciences 2001;56(3):M146-156.
17. Kojima, G, Kendrick, D, Skelton, DA, et al. Frailty predicts short-term incidence of future falls among British community-dwelling older people: a prospective cohort study nested within a randomised controlled trial. BMC geriatrics 2015;15:155.
18. Kojima, G. Frailty as a Predictor of Future Falls Among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. Journal of the American Medical Directors Association 2015;16(12):1027-1033.
19. Kojima, G. Frailty as a predictor of fractures among community-dwelling older people: A systematic review and meta-analysis. Bone 2016;90:116-122.
20. Kojima, G. Frailty significantly increases the risk of fractures among middle-aged and older people. Evidence-based nursing 2017;20(4):119-120.
21. Kojima, G. Frailty as a predictor of disabilities among community-dwelling older people: a systematic review and meta-analysis. Disability and Rehabilitation 2017;39(19):1897-1908.
22. Kojima, G. Quick and Simple FRAIL Scale Predicts Incident Activities of Daily Living (ADL) and Instrumental ADL (IADL) Disabilities: A Systematic Review and Meta-analysis. Journal of the American Medical Directors Association 2018;19(12):1063-1068.
23. Kojima, G. Frailty as a Predictor of Emergency Department Utilization among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. Journal of the American Medical Directors Association 2019;20(1):103-105.
24. Kojima, G. Frailty as a predictor of hospitalisation among community-dwelling older people: a systematic review and meta-analysis. Journal of epidemiology and community health 2016;70(7):722-729.

25. Kojima, G. Frailty as a Predictor of Nursing Home Placement among Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. Journal of Geriatric Physical Therapy 2018;41(1):42-48.
26. Kojima, G, Iliffe, S, Walters, K. Frailty index as a predictor of mortality: a systematic review and meta-analysis. Age and ageing 2018;47(2):193-200.
27. Kojima, G. Frailty Defined by FRAIL Scale as a Predictor of Mortality: A Systematic Review and Meta-analysis. Journal of the American Medical Directors Association 2018;19(6):480-483.
28. Kojima, G, Taniguchi, Y, Kitamura, A, et al. Are the Kihon Checklist and the Kaigo-Yobo Checklist compatible with the Frailty Index? Journal of the American Medical Directors Association 2018;19(9):797-800.
29. Kojima, G, Iliffe, S, Morris, RW, et al. Frailty predicts trajectories of quality of life over time among British community-dwelling older people. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2016;25(7):1743-1750.
30. Kojima, G, Iliffe, S, Jivraj, S, et al. Association between frailty and quality of life among community-dwelling older people: a systematic review and meta-analysis. Journal of epidemiology and community health 2016;70(7):716-721.
31. Vaughan, L, Corbin, AL, Goveas, JS. Depression and frailty in later life: a systematic review. Clinical interventions in aging 2015;10:1947-1958.
32. Kojima, G, Taniguchi, Y, Iliffe, S, et al. Frailty as a Predictor of Alzheimer Disease, Vascular Dementia, and All Dementia Among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. Journal of the American Medical Directors Association 2016;17(10):881-888.
33. Marshall, A, Nazroo, J, Tampubolon, G, et al. Cohort differences in the levels and trajectories of frailty among older people in England. Journal of epidemiology and community health 2015;69(4):316-321.
34. Collard, RM, Boter, H, Schoevers, RA, et al. Prevalence of frailty in community-dwelling older persons: a systematic review. Journal of the American Geriatrics Society 2012;60(8):1487-1492.
35. Kojima, G, Taniguchi, Y, Iliffe, S, et al. Transitions between frailty states among community-dwelling older people: A systematic review and meta-analysis. Ageing research reviews 2019;50:81-88.

36. Kojima, G, Taniguchi, Y, Iliffe, S, et al. Factors Associated With Improvement in Frailty Status Defined Using the Frailty Phenotype: A Systematic Review and Meta-analysis. Journal of the American Medical Directors Association 2019.
37. de Vries, NM, Staal, JB, van Ravensberg, CD, et al. Outcome instruments to measure frailty: a systematic review. Ageing research reviews 2011;10(1):104-114.
38. Rolfson, DB, Majumdar, SR, Tsuyuki, RT, et al. Validity and reliability of the Edmonton Frail Scale. Age and ageing 2006;35(5):526-529.
39. Steverink, N, Slaets, J, Schuurmans, H, et al. Measuring frailty: development and testing of the Groningen Frailty Indicator (GFI). Gerontologist 2001;41(1):236.
40. Gobbens, RJ, van Assen, MA, Luijkx, KG, et al. The Tilburg Frailty Indicator: psychometric properties. Journal of the American Medical Directors Association 2010;11(5):344-355.
41. Morley, JE, Malmstrom, TK, Miller, DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. The journal of nutrition, health & aging 2012;16(7):601-608.
42. Satake, S, Senda, K, Hong, YJ, et al. Validity of the Kihon Checklist for assessing frailty status. Geriatrics & gerontology international 2016;16(6):709-715.
43. Bergman, H, Ferrucci, L, Guralnik, J, et al. Frailty: an emerging research and clinical paradigm--issues and controversies. The journals of gerontology Series A, Biological sciences and medical sciences 2007;62(7):731-737.
44. Bandeen-Roche, K, Xue, QL, Ferrucci, L, et al. Phenotype of frailty: characterization in the women's health and aging studies. The journals of gerontology Series A, Biological sciences and medical sciences 2006;61(3):262-266.
45. Bouillon, K, Kivimaki, M, Hamer, M, et al. Measures of frailty in population-based studies: an overview. BMC geriatrics 2013;13:64.
46. Theou, O, Cann, L, Blodgett, J, et al. Modifications to the frailty phenotype criteria: Systematic review of the current literature and investigation of 262 frailty phenotypes in the Survey of Health, Ageing, and Retirement in Europe. Ageing research reviews 2015;21:78-94.
47. Searle, SD, Mitnitski, A, Gahbauer, EA, et al. A standard procedure for creating a frailty index. BMC geriatrics 2008;8:24.
48. Rockwood, K, Andrew, M, Mitnitski, A. A comparison of two approaches to measuring frailty in elderly people. The journals of gerontology Series A, Biological sciences and medical sciences 2007;62(7):738-743.

49. Wu, S, Leff, B. Frailty measurement and its contribution to clinical care and health services: a commentary. Israel journal of health policy research 2018;7(1):27.
50. Abellan van Kan, G, Rolland, Y, Bergman, H, et al. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. The journal of nutrition, health & aging 2008;12(1):29-37.
51. Dent, E, Kowal, P, Hoogendijk, EO. Frailty measurement in research and clinical practice: A review. European journal of internal medicine 2016;31:3-10.
52. Clegg, A, Bates, C, Young, J, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age and ageing 2016;45(3):353-360.
53. Avila-Funes, JA, Amieva, H, Barberger-Gateau, P, et al. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: the three-city study. Journal of the American Geriatrics Society 2009;57(3):453-461.
54. Gobbens, RJ, Luijkx, KG, Wijnen-Sponselee, MT, et al. Toward a conceptual definition of frail community dwelling older people. Nursing outlook 2010;58(2):76-86.
55. Abellan van Kan, G, Rolland, YM, Morley, JE, et al. Frailty: toward a clinical definition. Journal of the American Medical Directors Association 2008;9(2):71-72.
56. Sewo Sampaio, PY, Sampaio, RA, Yamada, M, et al. Systematic review of the Kihon Checklist: Is it a reliable assessment of frailty? Geriatrics & gerontology international 2016;16(8):893-902.
57. Rockwood, K, Song, X, MacKnight, C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2005;173(5):489-495.
58. Buta, BJ, Walston, JD, Godino, JG, et al. Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments. Ageing research reviews 2016;26:53-61.
59. Choi, J, Ahn, A, Kim, S, et al. Global Prevalence of Physical Frailty by Fried's Criteria in Community-Dwelling Elderly With National Population-Based Surveys. Journal of the American Medical Directors Association 2015;16(7):548-550.
60. Handforth, C, Clegg, A, Young, C, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2015;26(6):1091-1101.

61. Kojima, G. Prevalence of frailty in end-stage renal disease: a systematic review and meta-analysis. International urology and nephrology 2017;49(11):1989-1997.
62. Denfeld, QE, Winters-Stone, K, Mudd, JO, et al. The prevalence of frailty in heart failure: A systematic review and meta-analysis. International journal of cardiology 2017;236:283-289.
63. Marengoni, A, Vetrano, DL, Manes-Gravina, E, et al. The Relationship Between COPD and Frailty: A Systematic Review and Meta-Analysis of Observational Studies. Chest 2018.
64. Kojima, G, Liljas, A, Iliffe, S, et al. Prevalence of Frailty in Mild to Moderate Alzheimer's Disease: A Systematic Review and Meta-analysis. Current Alzheimer research 2017.
65. Kojima, G. Prevalence of Frailty in Nursing Homes: A Systematic Review and Meta-Analysis. Journal of the American Medical Directors Association 2015;16(11):940-945.
66. Rochat, S, Cumming, RG, Blyth, F, et al. Frailty and use of health and community services by community-dwelling older men: the Concord Health and Ageing in Men Project. Age and ageing 2010;39(2):228-233.
67. Theou, O, Rockwood, MR, Mitnitski, A, et al. Disability and co-morbidity in relation to frailty: how much do they overlap? Archives of gerontology and geriatrics 2012;55(2):e1-8.
68. Centers for Disease Control and Prevention (US). Falls Among Older Adults: An Overview; 2017. http://www.cdc.gov/homeandrecreationalsafety/falls/adultfalls.html. Accessed 17 June 2018.
69. Prince, M, Bryce, R, Albanese, E, et al. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimer's & dementia : the journal of the Alzheimer's Association 2013;9(1):63-75 e62.
70. Simpson, KN, Seamon, BA, Hand, BN, et al. Effect of frailty on resource use and cost for Medicare patients. Journal of comparative effectiveness research 2018.
71. Hajek, A, Bock, JO, Saum, KU, et al. Frailty and healthcare costs-longitudinal results of a prospective cohort study. Age and ageing 2018;47(2):233-241.
72. Bock, JO, Konig, HH, Brenner, H, et al. Associations of frailty with health care costs--results of the ESTHER cohort study. BMC health services research 2016;16:128.
73. Ensrud, KE, Kats, AM, Schousboe, JT, et al. Frailty Phenotype and Healthcare Costs and Utilization in Older Women. Journal of the American Geriatrics Society 2018.

74. Kojima, G. Increased healthcare costs associated with frailty among community-dwelling older people: A systematic review and meta-analysis. Archives of gerontology and geriatrics 2019.
75. Cesari, M, Prince, M, Thiyagarajan, JA, et al. Frailty: An Emerging Public Health Priority. Journal of the American Medical Directors Association 2016;17(3):188-192.
76. Walston, J. Frailty Research Moves Beyond Risk Assessment. The journals of gerontology Series A, Biological sciences and medical sciences 2017;72(7):915-916.
77. Ferrucci, L, Guralnik, JM, Studenski, S, et al. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: a consensus report. Journal of the American Geriatrics Society 2004;52(4):625-634.
78. Cesari, M, Vellas, B, Hsu, FC, et al. A physical activity intervention to treat the frailty syndrome in older persons-results from the LIFE-P study. The journals of gerontology Series A, Biological sciences and medical sciences 2015;70(2):216-222.
79. Kim, H, Suzuki, T, Kim, M, et al. Effects of exercise and milk fat globule membrane (MFGM) supplementation on body composition, physical function, and hematological parameters in community-dwelling frail Japanese women: a randomized double blind, placebo-controlled, follow-up trial. PloS one 2015;10(2):e0116256.
80. Ng, TP, Feng, L, Nyunt, MS, et al. Nutritional, Physical, Cognitive, and Combination Interventions and Frailty Reversal Among Older Adults: A Randomized Controlled Trial. The American journal of medicine 2015;128(11):1225-1236 e1221.
81. Tarazona-Santabalbina, FJ, Gomez-Cabrera, MC, Perez-Ros, P, et al. A Multicomponent Exercise Intervention that Reverses Frailty and Improves Cognition, Emotion, and Social Networking in the Community-Dwelling Frail Elderly: A Randomized Clinical Trial. Journal of the American Medical Directors Association 2016;17(5):426-433.
82. Yamada, M, Arai, H, Sonoda, T, et al. Community-based exercise program is cost-effective by preventing care and disability in Japanese frail older adults. Journal of the American Medical Directors Association 2012;13(6):507-511.
83. Cadore, EL, Rodriguez-Manas, L, Sinclair, A, et al. Effects of different exercise interventions on risk of falls, gait ability, and balance in physically frail older adults: a systematic review. Rejuvenation research 2013;16(2):105-114.
84. Artaza-Artabe, I, Saez-Lopez, P, Sanchez-Hernandez, N, et al. The relationship between nutrition and frailty: Effects of protein intake, nutritional supplementation,

vitamin D and exercise on muscle metabolism in the elderly. A systematic review. Maturitas 2016;93:89-99.

85. Dedeyne, L, Deschodt, M, Verschueren, S, et al. Effects of multi-domain interventions in (pre)frail elderly on frailty, functional, and cognitive status: a systematic review. Clinical interventions in aging 2017;12:873-896.
86. Guyonnet, S, Rolland, Y. Screening for Malnutrition in Older People. Clinics in geriatric medicine 2015;31(3):429-437.
87. Bollwein, J, Volkert, D, Diekmann, R, et al. Nutritional status according to the mini nutritional assessment (MNA(R)) and frailty in community dwelling older persons: a close relationship. The journal of nutrition, health & aging 2013;17(4):351-356.
88. Bonnefoy, M, Berrut, G, Lesourd, B, et al. Frailty and nutrition: searching for evidence. The journal of nutrition, health & aging 2015;19(3):250-257.
89. Yannakoulia, M, Mamalaki, E, Anastasiou, CA, et al. Eating habits and behaviors of older people: Where are we now and where should we go? Maturitas 2018;114:14-21.
90. Malafarina, V, Uriz-Otano, F, Iniesta, R, et al. Effectiveness of nutritional supplementation on muscle mass in treatment of sarcopenia in old age: a systematic review. Journal of the American Medical Directors Association 2013;14(1):10-17.
91. Holick, MF. Vitamin D deficiency. The New England journal of medicine 2007;357(3):266-281.
92. Kojima, G, Bell, C, Abbott, RD, et al. Low dietary vitamin D predicts 34-year incident stroke: the Honolulu Heart Program. Stroke 2012;43(8):2163-2167.
93. Kojima, G, Bell, CL, Chen, R, et al. Low dietary vitamin D in mid-life predicts total mortality in men with hypertension: the Honolulu heart program. Journal of the American College of Nutrition 2014;33(2):129-135.
94. Kojima, G, Iliffe, S, Tanabe, M. Vitamin D supplementation as a potential cause of U-shaped associations between vitamin D levels and negative health outcomes: a decision tree analysis for risk of frailty. BMC geriatrics 2017;17(1):236.
95. Kojima, G, Tamai, A, Masaki, K, et al. Prevalence of vitamin D deficiency and association with functional status in newly admitted male veteran nursing home residents. Journal of the American Geriatrics Society 2013;61(11):1953-1957.
96. Kojima, G, Tanabe, M, Masaki, K, et al. Association Between Depressive Symptoms and Vitamin D Deficiency in Recently Admitted Nursing Home Residents. Journal of the American Geriatrics Society 2016;64(4):893-895.

97. Zhou, J, Huang, P, Liu, P, et al. Association of vitamin D deficiency and frailty: A systematic review and meta-analysis. Maturitas 2016;94:70-76.
98. Kojima, G, Tanabe, M. Frailty is Highly Prevalent and Associated with Vitamin D Deficiency in Male Nursing Home Residents. Journal of the American Geriatrics Society 2016.
99. Muir, SW, Montero-Odasso, M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. Journal of the American Geriatrics Society 2011;59(12):2291-2300.
100. Beaudart, C, Buckinx, F, Rabenda, V, et al. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. The Journal of clinical endocrinology and metabolism 2014;99(11):4336-4345.
101. Bruyere, O, Cavalier, E, Buckinx, F, et al. Relevance of vitamin D in the pathogenesis and therapy of frailty. Current opinion in clinical nutrition and metabolic care 2017;20(1):26-29.
102. Morley, JE, Vellas, B, van Kan, GA, et al. Frailty consensus: a call to action. Journal of the American Medical Directors Association 2013;14(6):392-397.
103. Kojima, G, Avgerinou, C, Iliffe, S, et al. Adherence to Mediterranean Diet Reduces Incident Frailty Risk: Systematic Review and Meta-Analysis. Journal of the American Geriatrics Society 2018;66(4):783-788.
104. Rea, J, Walters, K, Avgerinou, C. How effective is nutrition education aiming to prevent or treat malnutrition in community-dwelling older adults? A systematic review. European Geriatric Medicine 2019:1-20.
105. Wu, SY, Hsu, LL, Hsu, CC, et al. Dietary education with customised dishware and food supplements can reduce frailty and improve mental well-being in elderly people: A single-blind randomized controlled study. Asia Pacific journal of clinical nutrition 2018;27(5):1018-1030.
106. Yannakoulia, M, Ntanasi, E, Anastasiou, CA, et al. Frailty and nutrition: From epidemiological and clinical evidence to potential mechanisms. Metabolism: clinical and experimental 2017;68:64-76.
107. Walston, J, Buta, B, Xue, QL. Frailty Screening and Interventions: Considerations for Clinical Practice. Clinics in geriatric medicine 2018;34(1):25-38.

108. Theou, O, Chapman, I, Wijeyaratne, L, et al. Can an Intervention with Testosterone and Nutritional Supplement Improve the Frailty Level of Under-Nourished Older People? The Journal of frailty & aging 2016;5(4):247-252.
109. Badrasawi, M, Shahar, S, Zahara, AM, et al. Efficacy of L-carnitine supplementation on frailty status and its biomarkers, nutritional status, and physical and cognitive function among prefrail older adults: a double-blind, randomized, placebo-controlled clinical trial. Clinical interventions in aging 2016;11:1675-1686.
110. Hutchins-Wiese, HL, Kleppinger, A, Annis, K, et al. The impact of supplemental n-3 long chain polyunsaturated fatty acids and dietary antioxidants on physical performance in postmenopausal women. The journal of nutrition, health & aging 2013;17(1):76-80.
111. Boyd, CM, Darer, J, Boult, C, et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. Jama 2005;294(6):716-724.
112. Cesari, M, Marzetti, E, Thiem, U, et al. The geriatric management of frailty as paradigm of "The end of the disease era". European journal of internal medicine 2016;31:11-14.
113. Hopman, P, de Bruin, SR, Forjaz, MJ, et al. Effectiveness of comprehensive care programs for patients with multiple chronic conditions or frailty: A systematic literature review. Health policy (Amsterdam, Netherlands) 2016;120(7):818-832.
114. Grone, O, Garcia-Barbero, M. Integrated care: a position paper of the WHO European Office for Integrated Health Care Services. International journal of integrated care 2001;1:e21.
115. Mur-Veeman, I, Hardy, B, Steenbergen, M, et al. Development of integrated care in England and the Netherlands: managing across public-private boundaries. Health policy (Amsterdam, Netherlands) 2003;65(3):227-241.
116. Looman, WM, Huijsman, R, Fabbricotti, IN. The (cost-)effectiveness of preventive, integrated care for community-dwelling frail older people: A systematic review. Health & social care in the community 2018.
117. Eklund, K, Wilhelmson, K. Outcomes of coordinated and integrated interventions targeting frail elderly people: a systematic review of randomised controlled trials. Health & social care in the community 2009;17(5):447-458.
118. Integrated care for older people, World Health Organization; 2016. http://www.who.int/ageing/health-systems/integrated-care/en/. Accessed.

119. Cameron, ID, Fairhall, N, Langron, C, et al. A multifactorial interdisciplinary intervention reduces frailty in older people: randomized trial. BMC medicine 2013;11:65.
120. Fairhall, N, Aggar, C, Kurrle, SE, et al. Frailty Intervention Trial (FIT). BMC geriatrics 2008;8:27.
121. Fairhall, N, Sherrington, C, Kurrle, SE, et al. Economic evaluation of a multifactorial, interdisciplinary intervention versus usual care to reduce frailty in frail older people. Journal of the American Medical Directors Association 2015;16(1):41-48.
122. Li, CM, Chen, CY, Li, CY, et al. The effectiveness of a comprehensive geriatric assessment intervention program for frailty in community-dwelling older people: a randomized, controlled trial. Archives of gerontology and geriatrics 2010;50 Suppl 1:S39-42.
123. Turner, G, Clegg, A. Best practice guidelines for the management of frailty: a British Geriatrics Society, Age UK and Royal College of General Practitioners report. Age and ageing 2014;43(6):744-747.
124. Updated guidance on supporting routine frailty identification and frailty care through the GP Contract 2017/2018, NHS England; 2017. https://www.england.nhs.uk/wp-content/

uploads/2017/04/supporting-guidance-on-frailty-update-sept-2017.pdf. Accessed 13 November 2018.
125. Supporting routine frailty identification and frailty through the GP Contract 2017/2018, NHS England; 2017. https://www.england.nhs.uk/publication/supporting-routine-frailty-identification-and-frailty-through-the-gp-contract-20172018/. Accessed 14 March, 2019.
126. Reeves, D, Pye, S, Ashcroft, DM, et al. The challenge of ageing populations and patient frailty: can primary care adapt? BMJ (Clinical research ed) 2018;362:k3349.
127. de Labra, C, Guimaraes-Pinheiro, C, Maseda, A, et al. Effects of physical exercise interventions in frail older adults: a systematic review of randomized controlled trials. BMC geriatrics 2015;15:154.
128. De Lepeleire, J, Illiffe, S, Mann, E, et al. Frailty: an emerging concept for general practice. The British journal of general practice : the journal of the Royal College of General Practitioners 2009;59(562):e177-182.

129. Etman, A, Burdorf, A, Van der Cammen, TJ, et al. Socio-demographic determinants of worsening in frailty among community-dwelling older people in 11 European countries. Journal of epidemiology and community health 2012;66(12):1116-1121.
130. Lee, JS, Auyeung, TW, Leung, J, et al. Transitions in frailty states among community-living older adults and their associated factors. Journal of the American Medical Directors Association 2014;15(4):281-286.
131. Peterson, MJ, Giuliani, C, Morey, MC, et al. Physical activity as a preventative factor for frailty: the health, aging, and body composition study. The journals of gerontology Series A, Biological sciences and medical sciences 2009;64(1):61-68.
132. Gale, CR, Cooper, C, Deary, IJ, et al. Psychological well-being and incident frailty in men and women: the English Longitudinal Study of Ageing. Psychological medicine 2014;44(4):697-706.
133. Lakey, SL, LaCroix, AZ, Gray, SL, et al. Antidepressant use, depressive symptoms, and incident frailty in women aged 65 and older from the Women's Health Initiative Observational Study. Journal of the American Geriatrics Society 2012;60(5):854-861.
134. Gobbens, RJ, van Assen, MA. Explaining frailty by lifestyle. Archives of gerontology and geriatrics 2016;66:49-53.
135. Mello Ade, C, Engstrom, EM, Alves, LC. Health-related and socio-demographic factors associated with frailty in the elderly: a systematic literature review. Cadernos de saude publica 2014;30(6):1143-1168.
136. Diez-Ruiz, A, Bueno-Errandonea, A, Nunez-Barrio, J, et al. Factors associated with frailty in primary care: a prospective cohort study. BMC geriatrics 2016;16:91.
137. Cramm, JM, Nieboer, AP. Relationships between frailty, neighborhood security, social cohesion and sense of belonging among community-dwelling older people. Geriatrics & gerontology international 2013;13(3):759-763.
138. Feng, Z, Lugtenberg, M, Franse, C, et al. Risk factors and protective factors associated with incident or increase of frailty among community-dwelling older adults: A systematic review of longitudinal studies. PloS one 2017;12(6):e0178383.
139. Baylis, D, Bartlett, DB, Syddall, HE, et al. Immune-endocrine biomarkers as predictors of frailty and mortality: a 10-year longitudinal study in community-dwelling older people. Age (Dordrecht, Netherlands) 2013;35(3):963-971.
140. Susanto, M, Hubbard, RE, Gardiner, PA. Twelve-Year Trajectories of Sitting Time are Associated With Frailty in Middle-Aged Women. American journal of epidemiology 2018.

141. Huohvanainen, E, Strandberg, AY, Stenholm, S, et al. Association of Self-Rated Health in Midlife With Mortality and Old Age Frailty: A 26-Year Follow-Up of Initially Healthy Men. The journals of gerontology Series A, Biological sciences and medical sciences 2016;71(7):923-928.
142. Savela, SL, Koistinen, P, Stenholm, S, et al. Leisure-time physical activity in midlife is related to old age frailty. The journals of gerontology Series A, Biological sciences and medical sciences 2013;68(11):1433-1438.
143. Stenholm, S, Strandberg, TE, Pitkala, K, et al. Midlife obesity and risk of frailty in old age during a 22-year follow-up in men and women: the Mini-Finland Follow-up Survey. The journals of gerontology Series A, Biological sciences and medical sciences 2014;69(1):73-78.
144. Strandberg, TE, Sirola, J, Pitkala, KH, et al. Association of midlife obesity and cardiovascular risk with old age frailty: a 26-year follow-up of initially healthy men. International journal of obesity (2005) 2012;36(9):1153-1157.
145. Strandberg, AY, Trygg, T, Pitkala, KH, et al. Alcohol consumption in midlife and old age and risk of frailty: Alcohol paradox in a 30-year follow-up study. Age and ageing 2017:1-7.
146. Brunner, EJ, Shipley, MJ, Ahmadi-Abhari, S, et al. Midlife contributors to socioeconomic differences in frailty during later life: a prospective cohort study. The Lancet Public health 2018;3(7):e313-e322.
147. Risk Factors for Cardiovascular Disease (CVD), heart UK; https://heartuk.org.uk/files/uploads/documents/huk_fs_mfsI_riskfactorsforchd_v2.pdf. Accessed 29 September 2018.
148. Tobacco, World Health Organization; 2018. https://www.who.int/en/news-room/fact-sheets/detail/tobacco. Accessed 26 March 2019.
149. Adult smoking habits in the UK: 2017, Office of National statistics; 2018. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2017. Accessed 27 March 2019.
150. Statistics on Alcohol, England, 2018, NHS; 2018. https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-alcohol/2018/part-4. Accessed 24 January 2019.

151. Older people's drinking habits, Institute of Alcohol Studies; http://www.ias.org.uk/Alcohol-knowledge-centre/Alcohol-and-older-people/Factsheets/Older-peoples-drinking-habits.aspx. Accessed 24 January 2019.
152. Older people and alcohol Factsheet, Institute of Alcohol Studies; http://www.ias.org.uk/uploads/pdf/Factsheets/Alcohol%20and%20older%20people%20FS%20May%202013.pdf. Accessed.
153. Fallaize, R, Livingstone, KM, Celis-Morales, C, et al. Association between Diet-Quality Scores, Adiposity, Total Cholesterol and Markers of Nutritional Status in European Adults: Findings from the Food4Me Study. Nutrients 2018;10(1).
154. Malnutrition, NHS; 2017. https://www.nhs.uk/conditions/malnutrition/. Accessed.
155. Younge, JO, Kouwenhoven-Pasmooij, TA, Freak-Poli, R, et al. Randomized study designs for lifestyle interventions: a tutorial. International journal of epidemiology 2015;44(6):2006-2019.
156. Shaikh, W, Nugawela, MD, Szatkowski, L. What are the main sources of smoking cessation support used by adolescent smokers in England? A cross-sectional study. BMC public health 2015;15:562.
157. Kojima, G, Liljas, A, Iliffe, S. Frailty Syndrome: implications and challenges for healthcare policy. Risk Manag Healthc Policy 2019;12:23-30.
158. Steptoe, A, Breeze, E, Banks, J, et al. Cohort profile: the English longitudinal study of ageing. International journal of epidemiology 2013;42(6):1640-1648.
159. Mindell, J, Biddulph, JP, Hirani, V, et al. Cohort profile: the health survey for England. International journal of epidemiology 2012;41(6):1585-1593.
160. User Guide to the Main Interview Datasets Waves 1 to 8, NatCen Social Research.; 2018. http://doc.ukdataservice.ac.uk/doc/5050/mrdoc/pdf/5050_waves_1-8_interviewer_data_user_guide_v01.pdf. Accessed 8 November 2018.
161. Banks, J, Muriel, A, Smith, JP. Attrition and health in ageing studies: Evidence from ELSA and HRS. Longitudinal and life course studies 2011;2(2).
162. User Guide to the Nurse Visit Datasets - Waves 2, 4, 6, 8., NatCen Social Research.; 2018. http://doc.ukdataservice.ac.uk/doc/5050/mrdoc/pdf/5050_waves_1-8_interviewer_data_user_guide_v01.pdf. Accessed 9 November 2018.
163. English Longitudinal Study of Ageing; http://www.elsa-project.ac.uk/. Accessed 18 September 2018.
164. Radloff, LS. The CES-D scale a self-report depression scale for research in the general population. Applied psychological measurement 1977;1(3):385-401.

165. Bohannon, RW. Test-Retest Reliability of Measurements of Hand-Grip Strength Obtained by Dynamometry from Older Adults: A Systematic Review of Research in the PubMed Database. The Journal of frailty & aging 2017;6(2):83-87.
166. Abizanda, P, Navarro, JL, Garcia-Tomas, MI, et al. Validity and usefulness of hand-held dynamometry for measuring muscle strength in community-dwelling older persons. Archives of gerontology and geriatrics 2012;54(1):21-27.
167. Kim, HJ, Park, I, Lee, HJ, et al. The reliability and validity of gait speed with different walking pace and distances against general health, physical function, and chronic disease in aged adults. Journal of exercise nutrition & biochemistry 2016;20(3):46-50.
168. Higueras-Fresnillo, S, de la Camara, MA, Esteban-Cornejo, I, et al. Concurrent Criterion Validity of a Test of Usual Gait Speed in Older Adults. Perceptual and motor skills 2018;125(5):908-922.
169. Unit, JHS. Health Survey for England Physical Activity Validation Study: Substantive Report. Information Centre for Health and Social Care Leeds; 2007.
170. Hamer, M, Molloy, GJ, de Oliveira, C, et al. Leisure time physical activity, risk of depressive symptoms, and inflammatory mediators: the English Longitudinal Study of Ageing. Psychoneuroendocrinology 2009;34(7):1050-1055.
171. Hamer, M, Stamatakis, E. Screen-based sedentary behavior, physical activity, and muscle strength in the English longitudinal study of ageing. PloS one 2013;8(6):e66222.
172. Soulakova, JN, Hartman, AM, Liu, B, et al. Reliability of adult self-reported smoking history: data from the tobacco use supplement to the current population survey 2002-2003 cohort. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 2012;14(8):952-960.
173. Hatziandreu, EJ, Pierce, JP, Fiore, MC, et al. The reliability of self-reported cigarette consumption in the United States. American journal of public health 1989;79(8):1020-1023.
174. Patrick, DL, Cheadle, A, Thompson, DC, et al. The validity of self-reported smoking: a review and meta-analysis. American journal of public health 1994;84(7):1086-1093.
175. Biochemical verification of tobacco use and cessation. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 2002;4(2):149-159.

176. Annual population survey (APS) QMI, The Office for National Statistics; 2012. https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/employmentandemployeetypes/methodologies/annualpopulationsurveyapsqmi. Accessed 19 November 2018.
177. Opinions and Lifestyle Survey, The Office for National Statistics https://www.ons.gov.uk/surveys/informationforhouseholdsandindividuals/householdandindividualsurveys/opinionsandlifestylesurvey. Accessed 19 November 2018.
178. General Household Survey, The Office for National Statistics; https://data.gov.uk/dataset/138ca035-a90c-4e37-80f5-4c73eeb6ae04/general-household-survey. Accessed 19 November 2018.
179. Adult smoking habits in the UK: 2016, Office for National Statistics; 2017. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2016. Accessed 10 November 2018.
180. Mahonen, MS, McElduff, P, Dobson, AJ, et al. Current smoking and the risk of non-fatal myocardial infarction in the WHO MONICA Project populations. Tobacco control 2004;13(3):244-250.
181. Li, TK, Hewitt, BG, Grant, BF. Is there a future for quantifying drinking in the diagnosis, treatment, and prevention of alcohol use disorders? Alcohol and alcoholism (Oxford, Oxfordshire) 2007;42(2):57-63.
182. Graff-Iversen, S, Jansen, MD, Hoff, DA, et al. Divergent associations of drinking frequency and binge consumption of alcohol with mortality within the same cohort. Journal of epidemiology and community health 2013;67(4):350-357.
183. Heckley, G, Jarl, J, Gerdtham, UG. Frequency and intensity of alcohol consumption: new evidence from Sweden. The European journal of health economics : HEPAC : health economics in prevention and care 2017;18(4):495-517.
184. Horvat, P, Stefler, D, Murphy, M, et al. Alcohol, pattern of drinking and all-cause mortality in Russia, Belarus and Hungary: a retrospective indirect cohort study based on mortality of relatives. Addiction (Abingdon, England) 2018;113(7):1252-1263.
185. Binge drinking, Alcohol support, NHS; 2016. https://www.nhs.uk/live-well/alcohol-support/binge-drinking-effects/. Accessed 19 November 2018.
186. Kuntsche, E, Kuntsche, S, Thrul, J, et al. Binge drinking: Health impact, prevalence, correlates and interventions. Psychology & health 2017;32(8):976-1017.

187. Finney, JW, Moos, RH, Brennan, PL. The Drinking Problems Index: a measure to assess alcohol-related problems among older adults. Journal of substance abuse 1991;3(4):395-404.
188. Moos, RH, Schutte, KK, Brennan, PL, et al. Older adults' alcohol consumption and late-life drinking problems: a 20-year perspective. Addiction (Abingdon, England) 2009;104(8):1293-1302.
189. The UK Household Longitudinal Study; https://www.understandingsociety.ac.uk/. Accessed 5 December 2018.
190. Scottish Health Survey, Scottish Government; https://www2.gov.scot/scottishhealthsurvey. Accessed 5 December 2018.
191. Hartz, SM, Oehlert, M, Horton, AC, et al. Daily Drinking Is Associated with Increased Mortality. Alcoholism, clinical and experimental research 2018;42(11):2246-2255.
192. UK Chief Medical Officers' Low Risk Drinking Guidelines, Department of Health; 2016. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/545937/UK_CMOs__report.pdf. Accessed 8 February 2018.
193. Heuberger, RA. Alcohol and the older adult: a comprehensive review. Journal of nutrition for the elderly 2009;28(3):203-235.
194. Our invisible addicts, First Report of the Older Persons' Substance Misuse Working Group of the Royal College of Psychiatrists, the Royal College of Psychiatrists; 2011. https://www.nationalelfservice.net/cms/wp-content/uploads/2011/06/CR165-Our-Invisible-Addicts.pdf. Accessed 30 September 2018.
195. Welsh Health Survey, Welsh Government; 2016. https://gov.wales/statistics-and-research/welsh-health-survey/?lang=en. Accessed 26 October 2018.
196. Eat Well, 5 A Day portion sizes, NHS; 2015. https://www.nhs.uk/live-well/eat-well/5-a-day-portion-sizes/. Accessed 18 September 2018.
197. Aune, D, Giovannucci, E, Boffetta, P, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies. International journal of epidemiology 2017;46(3):1029-1056.
198. Oyebode, O, Gordon-Dseagu, V, Walker, A, et al. Fruit and vegetable consumption and all-cause, cancer and CVD mortality: analysis of Health Survey for England data. Journal of epidemiology and community health 2014;68(9):856-862.

199. Promoting fruit and vegetable consumption around the world, World Health Organization; http://www.who.int/dietphysicalactivity/fruit/en/. Accessed 18 September 2018.
200. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet (London, England) 2016;388(10053):1459-1544.
201. Gordon, EH, Peel, NM, Samanta, M, et al. Sex differences in frailty: A systematic review and meta-analysis. Experimental gerontology 2017;89:30-40.
202. Hubbard, RE. Sex Differences in Frailty. Interdisciplinary topics in gerontology and geriatrics 2015;41:41-53.
203. de Oliveira, C, Biddulph, JP, Hirani, V, et al. Vitamin D and inflammatory markers: cross-sectional analyses using data from the English Longitudinal Study of Ageing (ELSA). Journal of nutritional science 2017;6:e1.
204. Solmi, F, Von Wagner, C, Kobayashi, LC, et al. Decomposing socio-economic inequality in colorectal cancer screening uptake in England. Social science & medicine (1982) 2015;134:76-86.
205. Demakakos, P, Biddulph, JP, Bobak, M, et al. Wealth and mortality at older ages: a prospective cohort study. Journal of epidemiology and community health 2016;70(4):346-353.
206. Hanna, KL, Collins, PF. Relationship between living alone and food and nutrient intake. Nutrition reviews 2015;73(9):594-611.
207. Rodriguez-Manas, L, Feart, C, Mann, G, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. The journals of gerontology Series A, Biological sciences and medical sciences 2013;68(1):62-67.
208. Batty, GD, Deary, IJ, Zaninotto, P. Association of Cognitive Function With Cause-Specific Mortality in Middle and Older Age: Follow-up of Participants in the English Longitudinal Study of Ageing. American journal of epidemiology 2016;183(3):183-190.
209. Zaninotto, P, Batty, GD, Allerhand, M, et al. Cognitive function trajectories and their determinants in older people: 8 years of follow-up in the English Longitudinal Study of Ageing. Journal of epidemiology and community health 2018;72(8):685-694.

210. Herzog, AR, Wallace, RB. Measures of cognitive functioning in the AHEAD Study. The journals of gerontology Series B, Psychological sciences and social sciences 1997;52 Spec No:37-48.
211. Uttl, B, Pilkenton-Taylor, C. Letter cancellation performance across the adult life span. The Clinical neuropsychologist 2001;15(4):521-530.
212. Baars, MA, van Boxtel, MP, Dijkstra, JB, et al. Predictive value of mild cognitive impairment for dementia. The influence of case definition and age. Dementia and geriatric cognitive disorders 2009;27(2):173-181.
213. Vanhoutte, B. The Multidimensional Structure of Subjective Well-Being In Later Life. Journal of population ageing 2014;7(1):1-20.
214. Karim, J, Weisz, R, Bibi, Z, et al. Validation of the eight-item center for epidemiologic studies depression scale (CES-D) among older adults. 2015;34(4):681-692.
215. Hughes, ME, Waite, LJ, Hawkley, LC, et al. A Short Scale for Measuring Loneliness in Large Surveys: Results From Two Population-Based Studies. Research on aging 2004;26(6):655-672.
216. Gale, CR, Westbury, L, Cooper, C. Social isolation and loneliness as risk factors for the progression of frailty: the English Longitudinal Study of Ageing. Age and ageing 2018;47(3):392-397.
217. Hansen, H, Pohontsch, N, van den Bussche, H, et al. Reasons for disagreement regarding illnesses between older patients with multimorbidity and their GPs - a qualitative study. BMC family practice 2015;16:68.
218. Hansen, H, Schafer, I, Schon, G, et al. Agreement between self-reported and general practitioner-reported chronic conditions among multimorbid patients in primary care - results of the MultiCare Cohort Study. BMC family practice 2014;15:39.
219. Kriegsman, DM, Penninx, BW, van Eijk, JT, et al. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. Journal of clinical epidemiology 1996;49(12):1407-1417.
220. Shields, M, Shooshtari, S. Determinants of self-perceived health. Health reports 2001;13(1):35-52.
221. Cheshire, H, Hussey, D, Media, J, et al. Financial circumstances, health and well-being of the older population in England: The 2008 English Longitudinal Study of

Ageing Technical Report; 2012. http://www.ifs.org.uk/elsa/report10/w4_tech.pdf. Accessed 18 April 2016.

222. Graham, JW. Missing data analysis: making it work in the real world. Annual review of psychology 2009;60:549-576.

223. Azur, MJ, Stuart, EA, Frangakis, C, et al. Multiple imputation by chained equations: what is it and how does it work? International journal of methods in psychiatric research 2011;20(1):40-49.

224. Collins, LM, Schafer, JL, Kam, CM. A comparison of inclusive and restrictive strategies in modern missing data procedures. Psychological methods 2001;6(4):330-351.

225. Kojima, G, Iliffe, S, Jivraj, S, et al. Does current smoking predict future frailty? The English longitudinal study of ageing. Age and ageing 2018;47(1):126-131.

226. Kojima, G, Iliffe, S, Walters, K. Smoking as a predictor of frailty: a systematic review. BMC geriatrics 2015;15:131.

227. Kojima, G, Iliffe, S, Walters, K. 61SMOKING AS A PREDICTOR OF FRAILTY: A SYSTEMATIC REVIEW. Age and ageing 2016;45(Suppl 1):i18.

228. What are the health risks of smoking? NHS; 2015. https://www.nhs.uk/common-health-questions/lifestyle/what-are-the-health-risks-of-smoking/. Accessed 14 October 2018.

229. Smoking Statistics, Action on Smoking and Health (ASH); 2016. http://ash.org.uk/information-and-resources/fact-sheets/smoking-statistics-who-smokes-and-how-much/. Accessed 14 October 2018.

230. Statistics on Smoking - England , 2018, NHS; 2018. https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-smoking/statistics-on-smoking-england-2018/part-1-smoking-related-ill-health-and-mortality. Accessed 14 October 2018.

231. Romero-Ortuno, R. Frailty Index in Europeans: association with determinants of health. Geriatrics & gerontology international 2014;14(2):420-429.

232. Ottenbacher, KJ, Graham, JE, Al Snih, S, et al. Mexican Americans and frailty: findings from the Hispanic established populations epidemiologic studies of the elderly. American journal of public health 2009;99(4):673-679.

233. Woods, NF, LaCroix, AZ, Gray, SL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. Journal of the American Geriatrics Society 2005;53(8):1321-1330.

234. Moher, D, Liberati, A, Tetzlaff, J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clinical research ed) 2009;339:b2535.
235. Wells, GA, Shea, D, O'Connell, D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses; http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 23 February 2019.
236. Wang, C, Song, X, Mitnitski, A, et al. Gender differences in the relationship between smoking and frailty: results from the Beijing Longitudinal Study of Aging. The journals of gerontology Series A, Biological sciences and medical sciences 2013;68(3):338-346.
237. Etman, A, Kamphuis, CB, van der Cammen, TJ, et al. Do lifestyle, health and social participation mediate educational inequalities in frailty worsening? European journal of public health 2015;25(2):345-350.
238. Gao, X, Zhang, Y, Saum, KU, et al. Tobacco smoking and smoking-related DNA methylation are associated with the development of frailty among older adults. Epigenetics 2017;12(2):149-156.
239. Goldenberg, M, Danovitch, I, IsHak, WW. Quality of life and smoking. The American journal on addictions 2014;23(6):540-562.
240. Takashima, N, Miura, K, Hozawa, A, et al. Cigarette smoking in middle age and a long-term risk of impaired activities of daily living: NIPPON DATA80. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 2010;12(9):944-949.
241. Pollack, LR, Litwack-Harrison, S, Cawthon, PM, et al. Patterns and Predictors of Frailty Transitions in Older Men: The Osteoporotic Fractures in Men Study. Journal of the American Geriatrics Society 2017;65(11):2473-2479.
242. Trevisan, C, Veronese, N, Maggi, S, et al. Factors Influencing Transitions Between Frailty States in Elderly Adults: The Progetto Veneto Anziani Longitudinal Study. Journal of the American Geriatrics Society 2017;65(1):179-184.
243. Chamberlain, AM, St Sauver, JL, Jacobson, DJ, et al. Social and behavioural factors associated with frailty trajectories in a population-based cohort of older adults. BMJ open 2016;6(5):e011410.

244. Yu, R, Wong, M, Chong, KC, et al. Trajectories of frailty among Chinese older people in Hong Kong between 2001 and 2012: an age-period-cohort analysis. Age and ageing 2018;47(2):254-261.
245. Centers for Disease Control and Prevention, Smoking & Tobacco Use, Health Effects of Cigarette Smoking; 2015. http://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/effects_cig_smoking/. Accessed 27 March, 2016.
246. What are the health risks of smoking? NHS choices; 2015. http://www.nhs.uk/chq/Pages/2344.aspx?CategoryID=53. Accessed.
247. Smoking statistics, Illness and death, Acton on Smoking and Health (ASH); 2015. http://ash.org.uk/files/documents/ASH_107.pdf. Accessed.
248. Goncalves, RB, Coletta, RD, Silverio, KG, et al. Impact of smoking on inflammation: overview of molecular mechanisms. Inflammation research : official journal of the European Histamine Research Society [et al] 2011;60(5):409-424.
249. Kanapuru, B, Ershler, WB. Inflammation, coagulation, and the pathway to frailty. The American journal of medicine 2009;122(7):605-613.
250. Gale, CR, Baylis, D, Cooper, C, et al. Inflammatory markers and incident frailty in men and women: the English Longitudinal Study of Ageing. Age (Dordrecht, Netherlands) 2013;35(6):2493-2501.
251. Barzilay, JI, Blaum, C, Moore, T, et al. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. Archives of internal medicine 2007;167(7):635-641.
252. Puts, MT, Visser, M, Twisk, JW, et al. Endocrine and inflammatory markers as predictors of frailty. Clinical endocrinology 2005;63(4):403-411.
253. Marston, L, Carpenter, JR, Walters, KR, et al. Smoker, ex-smoker or non-smoker? The validity of routinely recorded smoking status in UK primary care: a cross-sectional study. BMJ open 2014;4(4):e004958.
254. Kojima, G, Jivraj, S, Iliffe, S, et al. Alcohol Consumption and Risk of Incident Frailty: The English Longitudinal Study of Aging. Journal of the American Medical Directors Association 2018.
255. Kojima, G, Liljas, A, Iliffe, S, et al. A systematic review and meta-analysis of prospective associations between alcohol consumption and incident frailty. Age and ageing 2018;47(1):26-34.

256. Kojima, G, Jivraj, S, Iliffe, S, et al. P60 Alcohol consumption and risk of incident frailty: the english longitudinal study of ageing. BMJ Publishing Group Ltd; 2018.
257. Management of substance abuse, World Health Organization.; http://www.who.int/substance_abuse/en/. Accessed 14 October 2018.
258. Older Adults, National Institute of Alcohol Abuse and Alcoholism; https://www.niaaa.nih.gov/alcohol-health/special-populations-co-occurring-disorders/older-adults. Accessed 26 March, 2019.
259. Fekjaer, HO. Alcohol-a universal preventive agent? A critical analysis. Addiction (Abingdon, England) 2013;108(12):2051-2057.
260. Jayasekara, H, English, DR, Room, R, et al. Alcohol consumption over time and risk of death: a systematic review and meta-analysis. American journal of epidemiology 2014;179(9):1049-1059.
261. Nova, E, Baccan, GC, Veses, A, et al. Potential health benefits of moderate alcohol consumption: current perspectives in research. The Proceedings of the Nutrition Society 2012;71(2):307-315.
262. O'Keefe, JH, Bhatti, SK, Bajwa, A, et al. Alcohol and cardiovascular health: the dose makes the poison...or the remedy. Mayo Clinic proceedings 2014;89(3):382-393.
263. Knott, CS, Coombs, N, Stamatakis, E, et al. All cause mortality and the case for age specific alcohol consumption guidelines: pooled analyses of up to 10 population based cohorts. BMJ (Clinical research ed) 2015;350:h384.
264. Naimi, TS, Brown, DW, Brewer, RD, et al. Cardiovascular risk factors and confounders among nondrinking and moderate-drinking U.S. adults. American journal of preventive medicine 2005;28(4):369-373.
265. Stockwell, T, Zhao, J, Panwar, S, et al. Do "Moderate" Drinkers Have Reduced Mortality Risk? A Systematic Review and Meta-Analysis of Alcohol Consumption and All-Cause Mortality. Journal of studies on alcohol and drugs 2016;77(2):185-198.
266. Holmes, MV, Dale, CE, Zuccolo, L, et al. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. BMJ (Clinical research ed) 2014;349:g4164.
267. Global status report on alcohol and health 2018, World Health Organization; 2018. https://www.who.int/substance_abuse/publications/global_alcohol_report/en/. Accessed 24 January 2019.
268. Higgins, JP, Thompson, SG, Deeks, JJ, et al. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed) 2003;327(7414):557-560.

269. Begg, CB, Mazumdar, M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50(4):1088-1101.
270. Egger, M, Davey Smith, G, Schneider, M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed) 1997;315(7109):629-634.
271. Ortola, R, Garcia-Esquinas, E, Leon-Munoz, LM, et al. Patterns of Alcohol Consumption and Risk of Frailty in Community-dwelling Older Adults. The journals of gerontology Series A, Biological sciences and medical sciences 2016;71(2):251-258.
272. Seematter-Bagnoud, L, Spagnoli, J, Bula, C, et al. Alcohol Use and Frailty in Community-Dwelling Older Persons Aged 65 to 70 Years. The Journal of frailty & aging 2014;3(1):9-14.
273. Kojima, G, Iliffe, S, Liljas, A, et al. Non-linear association between alcohol and incident frailty among community-dwelling older people: A dose-response meta-analysis. Bioscience trends 2017;11(5):600-602.
274. Ng Fat, L, Cable, N, Marmot, MG, et al. Persistent long-standing illness and non-drinking over time, implications for the use of lifetime abstainers as a control group. Journal of epidemiology and community health 2014;68(1):71-77.
275. Ng Fat, L, Cable, N, Shelton, N. Worsening of health and a cessation or reduction in alcohol consumption to special occasion drinking across three decades of the life course. Alcoholism, clinical and experimental research 2015;39(1):166-174.
276. Khadjesari, Z, Marston, L, Petersen, I, et al. Alcohol consumption screening of newly-registered patients in primary care: a cross-sectional analysis. The British journal of general practice : the journal of the Royal College of General Practitioners 2013;63(615):e706-712.
277. Harrell, FE. Regression modeling strategies, with applications to linear models, survival analysis and logistic regression. New York, NY: Springer: Springer 2001.
278. Shah, M, Paulson, D, Nguyen, V. Alcohol Use and Frailty Risk among Older Adults over 12 Years: The Health and Retirement Study. Clinical gerontologist 2017:1-11.
279. Kojima, G, Avgerinou, C, Iliffe, S, et al. Fruit and Vegetable Consumption and Frailty: A Systematic Review. The journal of nutrition, health & aging 2018:1-8.
280. Kojima, G, Avgerinou, C, Iliffe, S, et al. 15FRUIT AND VEGETABLE CONSUMPTION AND FRAILTY: A SYSTEMATIC REVIEW. Age and ageing 2018;47(Suppl 3):iii6.

281. Gabrovec, B, Veninsek, G, Samaniego, LL, et al. The role of nutrition in ageing: A narrative review from the perspective of the European joint action on frailty - ADVANTAGE JA. European journal of internal medicine 2018.
282. Coelho-Junior, HJ, Rodrigues, B, Uchida, M, et al. Low Protein Intake Is Associated with Frailty in Older Adults: A Systematic Review and Meta-Analysis of Observational Studies. Nutrients 2018;10(9).
283. Lorenzo-Lopez, L, Maseda, A, de Labra, C, et al. Nutritional determinants of frailty in older adults: A systematic review. BMC geriatrics 2017;17(1):108.
284. 2015-2020 Dietary guidelines for Americans, 8th Edition, U.S. Department of Health and Human Services and U.S. Department of Agriculture.; 2015. http://health.gov/dietaryguidelines/2015/guidelines/. Accessed 17 September 2018.
285. Slavin, JL, Lloyd, B. Health benefits of fruits and vegetables. Advances in nutrition (Bethesda, Md) 2012;3(4):506-516.
286. European health interview survey - methodology, eurostat; 2018. https://ec.europa.eu/eurostat/statistics-explained/index.php/European_health_interview_survey_-_methodology. Accessed 25 March, 2019.
287. The fruit and vegetable sector in the EU - a statistical overview, eurostat; https://ec.europa.eu/eurostat/statistics-explained/index.php/The_fruit_and_vegetable_sector_in_the_EU_-_a_statistical_overview#Consumption. Accessed 15 December 2018.
288. Bouillon, K, Kivimaki, M, Hamer, M, et al. Diabetes risk factors, diabetes risk algorithms, and the prediction of future frailty: the Whitehall II prospective cohort study. Journal of the American Medical Directors Association 2013;14(11):851 e851-856.
289. Garcia-Esquinas, E, Rahi, B, Peres, K, et al. Consumption of fruit and vegetables and risk of frailty: a dose-response analysis of 3 prospective cohorts of community-dwelling older adults. The American journal of clinical nutrition 2016;104(1):132-142.
290. Leon-Munoz, LM, Guallar-Castillon, P, Lopez-Garcia, E, et al. Mediterranean diet and risk of frailty in community-dwelling older adults. Journal of the American Medical Directors Association 2014;15(12):899-903.

291. Rahi, B, Ajana, S, Tabue-Teguo, M, et al. High adherence to a Mediterranean diet and lower risk of frailty among French older adults community-dwellers: Results from the Three-City-Bordeaux Study. Clinical nutrition (Edinburgh, Scotland) 2017.
292. Ribeiro, SM, Morley, JE, Malmstrom, TK, et al. Fruit and Vegetable Intake and Physical Activity as Predictors of Disability Risk Factors in African-American Middle-Aged Individuals. The journal of nutrition, health & aging 2016;20(9):891-896.
293. Lo, YL, Hsieh, YT, Hsu, LL, et al. Dietary Pattern Associated with Frailty: Results from Nutrition and Health Survey in Taiwan. Journal of the American Geriatrics Society 2017;65(9):2009-2015.
294. Bartali, B, Frongillo, EA, Bandinelli, S, et al. Low nutrient intake is an essential component of frailty in older persons. The journals of gerontology Series A, Biological sciences and medical sciences 2006;61(6):589-593.
295. Soysal, P, Isik, AT, Carvalho, AF, et al. Oxidative stress and frailty: A systematic review and synthesis of the best evidence. Maturitas 2017;99:66-72.
296. Sharifabad, MA. COPD, BMJ Best Practice; 2018. https://bestpractice.bmj.com/topics/en-gb/7. Accessed 24 December 2018.
297. Akpan, A, Roberts, C, Bandeen-Roche, K, et al. Standard set of health outcome measures for older persons. BMC geriatrics 2018;18(1):36.
298. Soysal, P, Veronese, N, Thompson, T, et al. Relationship between depression and frailty in older adults: A systematic review and meta-analysis. Ageing research reviews 2017;36:78-87.
299. Gutierrez-Valencia, M, Izquierdo, M, Cesari, M, et al. The relationship between frailty and polypharmacy in older people: A systematic review. Br J Clin Pharmacol 2018;84(7):1432-1444.
300. Saraiva, MD, Suzuki, GS, Lin, SM, et al. Persistent pain is a risk factor for frailty: a systematic review and meta-analysis from prospective longitudinal studies. Age and ageing 2018;47(6):785-793.
301. Oldenkamp, M, Hagedoorn, M, Wittek, R, et al. The impact of older person's frailty on the care-related quality of life of their informal caregiver over time: results from the TOPICS-MDS project. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2017;26(10):2705-2716.

302. Stow, D, Spiers, G, Matthews, FE, et al. What is the evidence that people with frailty have needs for palliative care at the end of life? A systematic review and narrative synthesis. Palliat Med 2019;33(4):399-414.
303. Becker, G. The oldest old; autonomy in the face of frailty. Journal of aging studies 1994;8(1):59-76.
304. Shea, BJ, Grimshaw, JM, Wells, GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC medical research methodology 2007;7:10.
305. Shrank, WH, Patrick, AR, Brookhart, MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. Journal of general internal medicine 2011;26(5):546-550.
306. Golomb, BA, Chan, VT, Evans, MA, et al. The older the better: are elderly study participants more non-representative? A cross-sectional analysis of clinical trial and observational study samples. BMJ open 2012;2(6).
307. Banks, J, Breeze, E, Lessof, C, et al. Retirement, health and relationships of the older population in England: The 2004 English Longitudinal Study of Ageing (Wave 2). Institute for Fiscal Studies; 2006.
308. Connor Gorber, S, Schofield-Hurwitz, S, Hardt, J, et al. The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 2009;11(1):12-24.
309. McKenna, H, Treanor, C, O'Reilly, D, et al. Evaluation of the psychometric properties of self-reported measures of alcohol consumption: a COSMIN systematic review. Substance abuse treatment, prevention, and policy 2018;13(1):6.
310. Kobayashi, LC, Steptoe, A. Social Isolation, Loneliness, and Health Behaviors at Older Ages: Longitudinal Cohort Study. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine 2018;52(7):582-593.
311. Holdsworth, C, Mendonca, M, Pikhart, H, et al. Is regular drinking in later life an indicator of good health? Evidence from the English Longitudinal Study of Ageing. Journal of epidemiology and community health 2016;70(8):764-770.
312. Nicklett, EJ, Kadell, AR. Fruit and vegetable intake among older adults: a scoping review. Maturitas 2013;75(4):305-312.
313. Walston, J, Hadley, EC, Ferrucci, L, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the

American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. Journal of the American Geriatrics Society 2006;54(6):991-1001.

314. Garcia-Gonzalez, JJ, Garcia-Pena, C, Franco-Marina, F, et al. A frailty index to predict the mortality risk in a population of senior Mexican adults. BMC geriatrics 2009;9:47.

315. Lee, PN, Fry, JS, Forey, BA. Estimating the decline in excess risk of chronic obstructive pulmonary disease following quitting smoking - a systematic review based on the negative exponential model. Regulatory toxicology and pharmacology : RTP 2014;68(2):231-239.

316. Colak, Y, Afzal, S, Lange, P, et al. Smoking, Systemic Inflammation, and Airflow Limitation: A Mendelian Randomization Analysis of 98 085 Individuals from the General Population. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 2018.

317. Bratzler, DW, Oehlert, WH, Austelle, A. Smoking in the elderly--it's never too late to quit. The Journal of the Oklahoma State Medical Association 2002;95(3):185-191; quiz 192-183.

318. Britton, A, Ben-Shlomo, Y, Benzeval, M, et al. Life course trajectories of alcohol consumption in the United Kingdom using longitudinal data from nine cohort studies. BMC medicine 2015;13:47.

8 APPENDICES

Appendix 1a. PRISMA checklist (smoking)

Section/topic	#	Checklist item	Reported on page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	✓
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	✓
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	✓
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	✓
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	✓
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	✓
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	✓
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	✓
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	✓
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	✓
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	✓
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	✓
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	✓
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	✓
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	✓
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	✓
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	✓
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	✓
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	✓
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	n/a

Appendix 1b. PRISMA checklist (alcohol)

Section/topic	#	Checklist item	Reported on page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	✓
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	✓
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	✓
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	✓
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	✓
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	✓
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	✓
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	✓
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	✓
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	✓
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	✓
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	✓
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	✓
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	✓

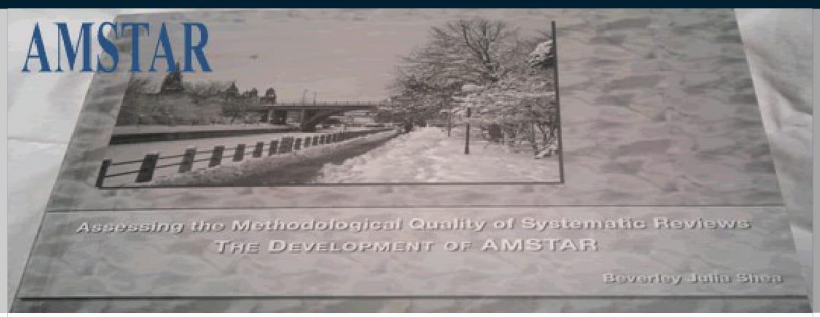
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	✓
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	✓
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	✓
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	✓
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	✓
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	✓
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	✓
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	✓
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	✓
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	✓
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	n/a

Appendix 1c. PRISMA checklist (fruit and vegetable consumption)

Section/topic	#	Checklist item	Reported on page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	✓
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	✓
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	✓
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	✓
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	✓
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	✓
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	✓
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	✓
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	✓
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	✓
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	✓
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	✓
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	✓
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	✓
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	✓
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	✓
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	✓
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	✓
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	✓
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	n/a

Appendix 2a. AMSTAR checklist (smoking)



Home | About Us | Publications | Checklist | FAQs | Contact Us

AMSTAR 2 Results

Article Name: Alcohol

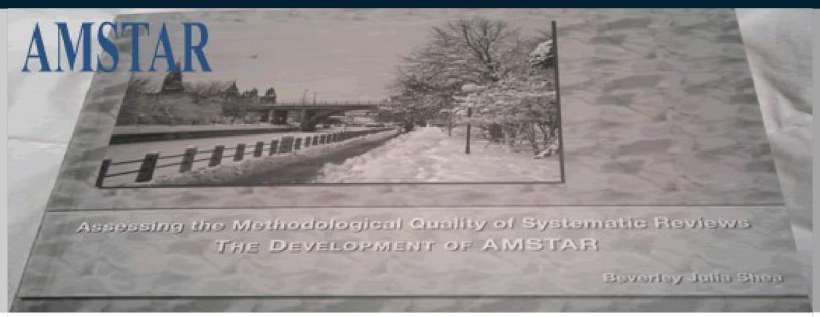
Alcohol is a Moderate quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	YesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes Yes
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes Yes Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes Yes Yes
8. Did the review authors describe the included studies in adequate detail?	Yes

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	
RCT	
NRSI	Yes Yes Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	
RCT	
NRSI	Yes Yes Yes Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Appendix 2b. AMSTAR checklist (alcohol)



Home | About Us | Publications | Checklist | FAQs | Contact Us

AMSTAR 2 Results

Article Name:

Alcohol

You are currently logged on as Guest. You need to be logged on as a member to submit your score.
Log On

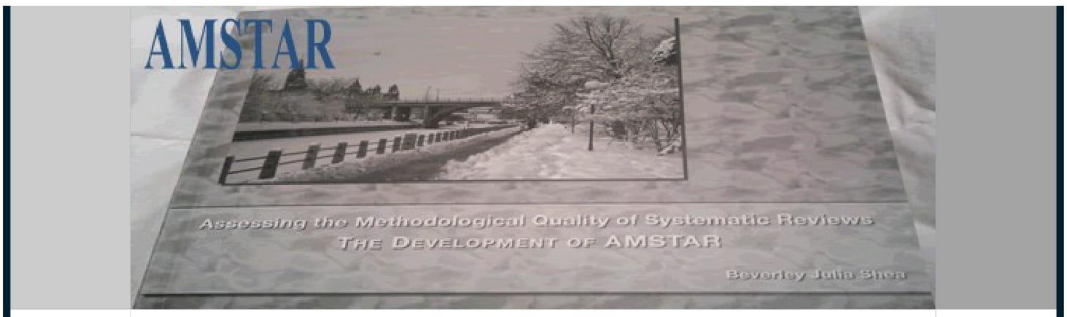
Alcohol is a Moderate quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	YesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes Yes
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes Yes Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	No
7. Did the review authors provide a list of excluded studies and justify the	Yes

exclusions?	Yes Yes
8. Did the review authors describe the included studies in adequate detail?	Yes Yes Yes Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? **RCT**	
NRSI	Yes Yes Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **RCT**	
NRSI	Yes Yes Yes Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Appendix 2c. AMSTAR checklist (fruit and vegetable consumption)



Home | About Us | Publications | Checklist | FAQs | Contact Us

AMSTAR 2 Results

Article Name:

Fruit and vegetable

You are currently logged on as Guest. You need to be logged on as a member to submit your score.
Log On

Fruit and vegetable is a Moderate quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	YesYesYesYesYesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes Yes
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes Yes Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes Yes Yes
8. Did the review authors describe the included studies in adequate detail?	Yes

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	
RCT	
NRSI	Yes Yes Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	
RCT	
NRSI	0
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	0
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	0
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Appendix 3. Newcastle-Ottawa quality assessment scale for cohort studies

(available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✵
   b) somewhat representative of the average _____ in the community ✵
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✵
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✵
   b) structured interview ✵
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✵
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✵
   b) study controls for any additional factor ✵ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✵
   b) record linkage ✵
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✵
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✵
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✵
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Appendix 4a. A full search result of systematic review for alcohol and frailty using Medline.

1	exp Alcohols/	593997
2	limit 1 to yr="2001 -Current"	207206
3	exp Ethanol/	99290
4	limit 3 to yr="2001 -Current"	40305
5	exp Drinking Behavior/ or exp Alcohol Drinking/	64315
6	limit 5 to yr="2001 -Current"	35523
7	alcohol*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	352743
8	limit 7 to yr="2001 -Current"	188750
9	ethanol.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	133484
10	limit 9 to yr="2001 -Current"	67701
11	drink*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	158175
12	limit 11 to yr="2001 -Current"	94512
13	2 or 4 or 6 or 8 or 10 or 12	433503
14	frail*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	16422
15	limit 14 to yr="2001 -Current"	13191
16	13 and 15	207

Appendix 4b. A full search result of systematic review for fruit and vegetable consumption and frailty using Medline.

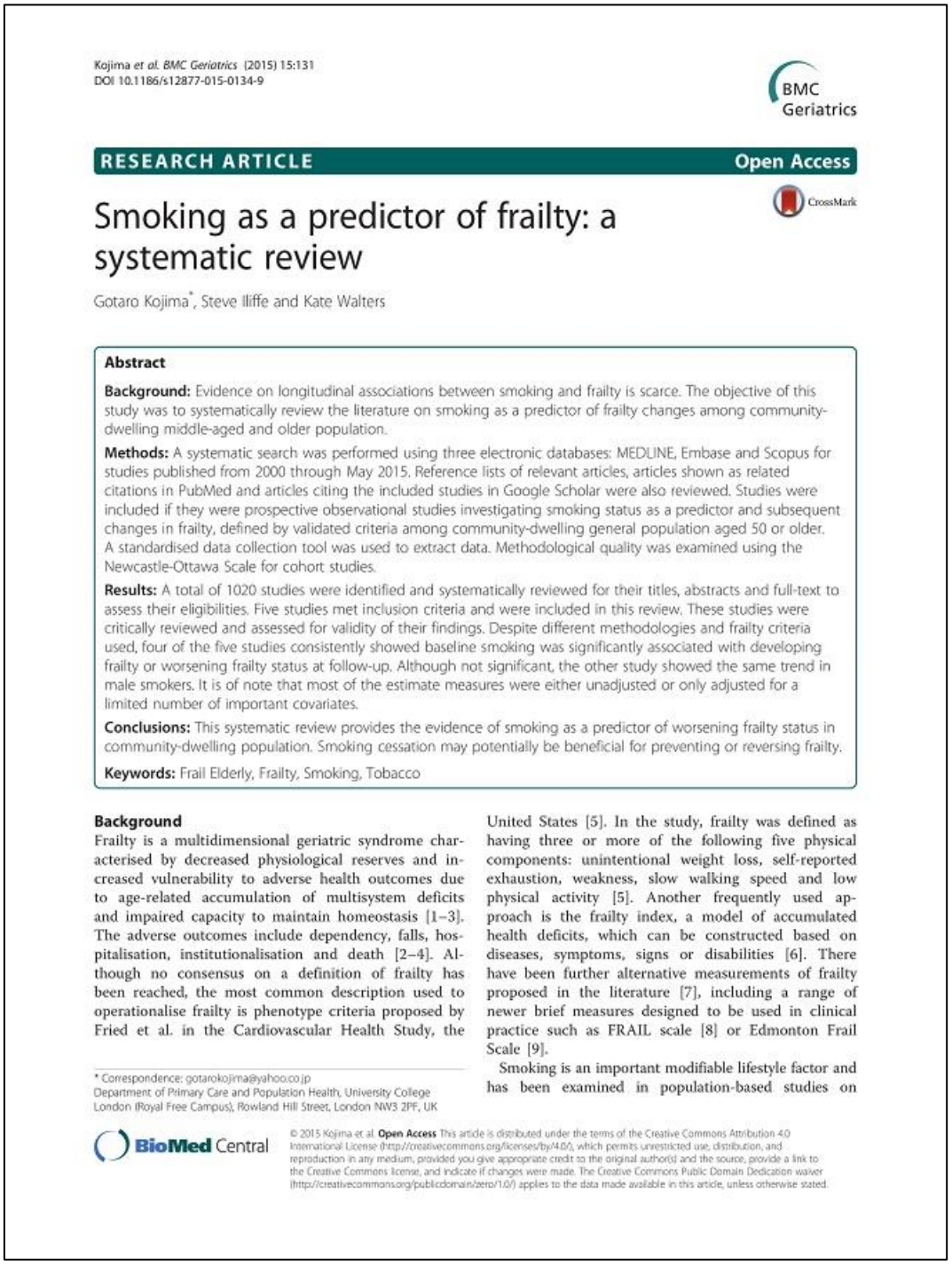
	Searches	Results	Type
1	exp Diet/	249198	Advanced
2	limit 1 to yr="2000 -Current"	136999	Advanced
3	exp Enteral Nutrition/ or exp Nutrition Therapy/	95577	Advanced
4	limit 3 to yr="2000 -Current"	45908	Advanced
5	exp "Fruit and Vegetable Juices"/ or exp Antioxidants/ or exp Fruit/ or exp Vegetables/	514989	Advanced
6	limit 5 to yr="2000 -Current"	315466	Advanced
7	diet*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	657217	Advanced
8	limit 7 to yr="2000 -Current"	379354	Advanced
9	nutrition*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	338583	Advanced
10	limit 9 to yr="2000 -Current"	195385	Advanced
11	fruit*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	97850	Advanced
12	limit 11 to yr="2000 -Current"	78833	Advanced
13	vegetable*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	55788	Advanced
14	limit 13 to yr="2000 -Current"	39254	Advanced
15	antioxidant*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol	187207	Advanced

	supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]		
16	limit 15 to yr="2000 -Current"	160650	Advanced
17	anti-oxidant*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	8817	Advanced
18	limit 17 to yr="2000 -Current"	7859	Advanced
19	2 or 4 or 6 or 8 or 10 or 12 or 14 or 16 or 18	869652	Advanced
20	frail*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	19144	Advanced
21	limit 20 to yr="2000 -Current"	16174	Advanced
22	exp Frail Elderly/	9272	Advanced
23	limit 22 to yr="2000 -Current"	7501	Advanced
24	21 or 23	16174	Advanced
25	19 and 24	1711	Advanced

8.1 Related publications

8.1.1 Smoking

8.1.1.1 Smoking systematic review (Open access)



Kojima et al. BMC Geriatrics (2015) 15:131
DOI 10.1186/s12877-015-0134-9

BMC Geriatrics

RESEARCH ARTICLE Open Access

Smoking as a predictor of frailty: a systematic review

Gotaro Kojima*, Steve Iliffe and Kate Walters

Abstract

Background: Evidence on longitudinal associations between smoking and frailty is scarce. The objective of this study was to systematically review the literature on smoking as a predictor of frailty changes among community-dwelling middle-aged and older population.

Methods: A systematic search was performed using three electronic databases: MEDLINE, Embase and Scopus for studies published from 2000 through May 2015. Reference lists of relevant articles, articles shown as related citations in PubMed and articles citing the included studies in Google Scholar were also reviewed. Studies were included if they were prospective observational studies investigating smoking status as a predictor and subsequent changes in frailty, defined by validated criteria among community-dwelling general population aged 50 or older. A standardised data collection tool was used to extract data. Methodological quality was examined using the Newcastle-Ottawa Scale for cohort studies.

Results: A total of 1020 studies were identified and systematically reviewed for their titles, abstracts and full-text to assess their eligibilities. Five studies met inclusion criteria and were included in this review. These studies were critically reviewed and assessed for validity of their findings. Despite different methodologies and frailty criteria used, four of the five studies consistently showed baseline smoking was significantly associated with developing frailty or worsening frailty status at follow-up. Although not significant, the other study showed the same trend in male smokers. It is of note that most of the estimate measures were either unadjusted or only adjusted for a limited number of important covariates.

Conclusions: This systematic review provides the evidence of smoking as a predictor of worsening frailty status in community-dwelling population. Smoking cessation may potentially be beneficial for preventing or reversing frailty.

Keywords: Frail Elderly, Frailty, Smoking, Tobacco

Background

Frailty is a multidimensional geriatric syndrome characterised by decreased physiological reserves and increased vulnerability to adverse health outcomes due to age-related accumulation of multisystem deficits and impaired capacity to maintain homeostasis [1–3]. The adverse outcomes include dependency, falls, hospitalisation, institutionalisation and death [2–4]. Although no consensus on a definition of frailty has been reached, the most common description used to operationalise frailty is phenotype criteria proposed by Fried et al. in the Cardiovascular Health Study, the United States [5]. In the study, frailty was defined as having three or more of the following five physical components: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed and low physical activity [5]. Another frequently used approach is the frailty index, a model of accumulated health deficits, which can be constructed based on diseases, symptoms, signs or disabilities [6]. There have been further alternative measurements of frailty proposed in the literature [7], including a range of newer brief measures designed to be used in clinical practice such as FRAIL scale [8] or Edmonton Frail Scale [9].

Smoking is an important modifiable lifestyle factor and has been examined in population-based studies on

* Correspondence: gotarokojima@yahoo.co.jp
Department of Primary Care and Population Health, University College London (Royal Free Campus), Rowland Hill Street, London NW3 2PF, UK

frailty. However in many studies, smoking has been used for adjustment as a confounding covariate to examine independent risks of target outcomes, and only a limited number of studies have focused on associations between smoking and frailty. Given that tobacco use is a major cause of preventable death and is associated with various negative health outcomes [10, 11], it is hypothesised that smokers are more likely to be frail than non-smokers. Unexpectedly, however, cross-sectional studies show mixed results and in some studies, smoking is associated with being less frail [12–15]. A large European study showed cross-sectional associations between smoking and frailty by age groups [12]. In those in their 50's current smoking status was positively associated with frailty but negatively associated with frailty for those in their 70's [15]. In light of higher morbidity and mortality risks in smokers, these paradoxical findings may have resulted from the survivor effect; frail smokers having died early or becoming too frail to smoke, therefore smoking habit as a contributor to frailty may diminish in the very old. In any case, a cross-sectional study design does not allow causal relationships to be inferred and prospective observational studies appropriately controlling for confounding factors are required to assess the causality.

There has been one systematic review paper on the association between frailty and various health-related and socio-demographic factors including smoking [16]. Although ten articles examining smoking and frailty were identified, most of them had a cross-sectional study design and only two articles longitudinally examined smoking as a predictor of frailty changes in the general population [17, 18]. In addition, the review was limited to only studies using Fried phenotype criteria and did not include other important studies using different criteria.

The objective of the current study was to systematically review the literature for evidence on smoking as a predictor of subsequent frailty status changes in longitudinal studies among the general population.

Methods

Data sources and search strategy

This systematic review was conducted according to a protocol developed with adherence to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [19]. One investigator (GK) performed a systematic search of the literature in May 2015 using MEDLINE, Embase and Scopus without language restriction using an explosion function and Medical Subject Heading terms if available from 2000 through current. Validated definitions of frailty were not generally used prior to 2000, and the two most widely accepted definitions and measurements for frailty, the frailty phenotype [5] and the frailty index [6] were first published in 2001. The search terms included ("Smoking" OR "Smoking cessation" OR "Smoking cessation program" OR "Smoking habit" OR "Tobacco" OR "Smokeless Tobacco" OR "Tobacco products" OR "Tobacco consumption" OR "Tobacco dependence" OR "Tobacco smoker" OR "Nicotine" OR "Nicotine derivative" OR "Nicotine gum" OR "Nicotine lozenge" OR "Nicotine Patch" OR "Nicotine replacement therapy" OR "Cotinine" OR "Smok*" OR "Tobacc*" OR "Nicotin*" OR "Cotinin*" OR "Cigarett*") AND "Frail*". Additional sources included reference lists of relevant articles, articles shown as related citations in PubMed of the included studies and articles citing the included studies displayed under Cited by in Google Scholar.

Study selection and data extraction

Studies were considered to be potentially eligible for inclusion if they were prospective observational studies investigating smoking status as a predictor and subsequent frailty status as an outcome among the community-dwelling general population aged 50 or older. In addition, in order to be considered for inclusion, frailty must have been defined criteria originally designed to measure frailty and validated in population-based studies or its modified versions, such as Fried phenotype criteria or the frailty index [5, 6]. Studies were excluded if they substituted other measures, such as disability or nursing home placement [20], to define frailty or used selected samples with certain diseases or conditions [21]. All potentially eligible studies identified were searched for duplicates using the Endnote duplicate finding function and manually, followed by title, abstract and full-text reviews. A standardised data collection tool was used to collect data from the eligible studies.

Methodological quality assessment

Methodological quality of the eligible studies were examined using the Newcastle-Ottawa Scale for cohort studies [22]. This scale has nine criteria to examine the methodological quality of cohort studies. Each of the included studies was assessed using this scale and considered to have adequate quality if it met five or more of the nine items.

Data analysis

It was planned to perform meta-analysis to synthesise pooled estimates from the included studies if possible, otherwise a narrative review would be pursued.

Results

Selection processes

A PRISMA flowchart [19] of the literature search and study selection with the number of studies at each stage is presented in Fig. 1. Of the 1020 citations identified

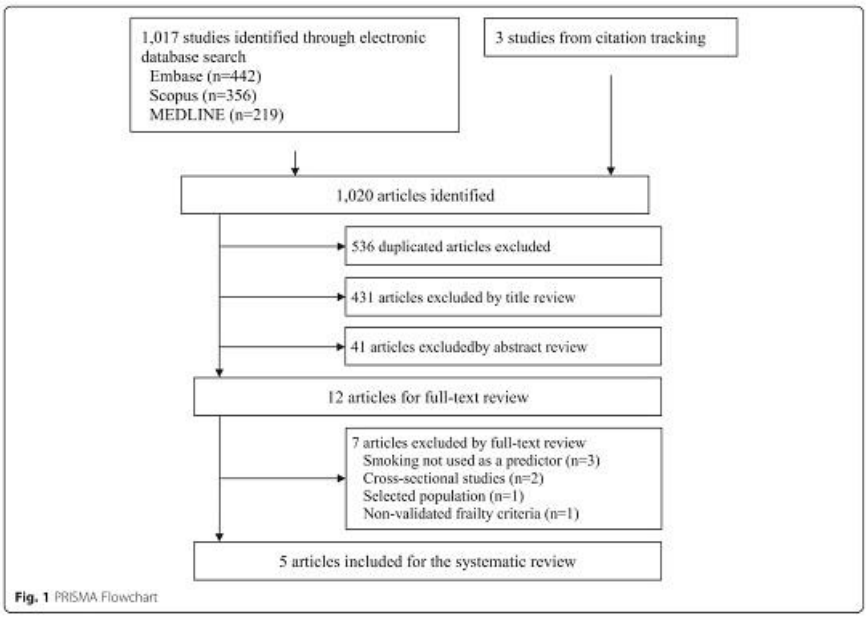


Fig. 1 PRISMA Flowchart

from the literature search using three electronic databases and other sources, 536 duplicated studies were excluded, and 431 and 41 studies were also excluded through title and abstract review, respectively, leaving 12 studies for potential inclusion. Full-texts of these 12 studies were assessed and seven studies were further excluded because smoking status was not used as a predictor ($n = 3$), study designs were cross-sectional ($n = 2$), a selected population was used ($n = 1$) or non-validated frailty criteria were used ($n = 1$). Five studies [17, 18, 23–25] were confirmed to meet the inclusion criteria and were included in this systematic review.

Study characteristics

Characteristics of the five studies are summarised in Table 1. Two studies were from the US [17, 18] and China [23, 24], respectively, and one study used populations from 11 European countries [25]. The largest study involved 28,181 women from the Women's Health Initiative Observational Study [18]. The other studies used cohorts consisting of almost half men and half women [17, 23–25]. Three studies defined three smoking status categories: 'never,' 'past' and 'current' smoking [18, 24, 25] and two studies defined two categories: 'never/past' versus 'current' smoking [17] and 'never' versus 'past/current smoking' [23], respectively. Four studies used the Fried phenotype frailty criteria [17, 18, 24, 25]; one study used the frailty index [23]. Although only two kinds of criteria were used, measures of changes in frailty status as outcomes at follow-up varied across the included studies. The follow-up periods ranged widely from two years to 15 years. In terms of statistical analysis, three studies used logistic regression models [18, 24, 25] and two studies used linear regression models [17, 23]. Four studies conducted multivariate regression models controlling for at least age and gender [17, 23–25], which are important confounding factors for both smoking and frailty, and one study showed only the results of unadjusted models [18].

The included studies were assessed for methodological quality using the Newcastle-Ottawa quality assessment scale for cohort studies. All five studies met at least five criteria and were considered to have adequate methodological quality (Table 2).

Etman et al. investigated associations between smoking status (never, former and current) at baseline and frailty status at two-year follow-up using a large cohort of 14,082 middle-aged and older community-dwelling men and women from the Survey on Health, Ageing, and

Table 1 Summary of included studies on smoking associated with subsequent frailty status change among community-dwelling older people

Author, year	Location	N	Age*	Female (%)	Smoking definition	Frailty outcome	Follow-up	Finding
Woods et al., 2005 [18]	USA	28,181	65–79	100 %	never, past, current smoking	Incident frailty by modified Fried criteria	3 years	- Past smoking was associated with incident frailty (OR = 1.12 95 % CI = 1.02–1.23), but not prefrailty (OR = 0.95 95 % CI = 0.89–1.02). - Current smoking was associated with both incidence frailty (OR = 1.76 95 % CI = 1.49–2.09) and prefrailty (OR = 2.90 95 % CI = 2.35–3.57) - Unadjusted multinomial logistic regression.
Ortenbacher et al., 2009 [17]	USA	777	82.5	56.4 %	never, past, current smoking	Fried frailty score (range: 0–5)	10 years	- "Ever smoked" was associated with increase in frailty score at follow-up (beta = 0.36, SE = 0.15, $p < 0.05$) - Linear regression adjusted for age, gender, education, married, financial strain, diabetes, hip fracture, cancer, stroke, cardiac diseases, arthritis, body mass index and baseline frailty.
Wang et al., 2013 [23]	China	3257	70.1	51.1 %	never, current/past smoking	Frailty index	15 years	- Current/past smoking was associated with increase in frailty at follow-up (beta = 3.64, SE = 1.62, $p = 0.03$) in men. - No such association was observed in women. - Linear regression adjusted for age, education, baseline frailty index.
Lee et al., 2014 [24]	China	3018	73.6	49.7 %	never, past, current smoking	Change in frailty Category change by Fried criteria	2 years	- No significant association was observed. - Gender-stratified age-adjusted logistic regression
Ernan et al., 2015 [25]	11 European countries	14,082	>55	54.3 %	never, past, current smoking	Worsening in frailty by Fried criteria (robust > prefrail/frail or prefrail > frail)	2 years	- Current smoking was associated with worsening of frailty status at follow-up (OR = 1.16, 95 % CI = 1.02–1.32, $p < 0.05$) - Logistic regression adjusted for age, gender, education, baseline frailty and country.

*Mean age, age range, or age for inclusion
95 % CI: 95 % confidence interval; OR: Odds ratio, SE: Standard error

Table 2 Methodological quality assessment using the Newcastle-Ottawa Quality Assessment Scale for cohort studies

Author	Selection 1	Selection 2	Selection 3	Selection 4	Comparability 1	Comparability 2	Outcome 1	Outcome 2	Outcome 3	Total
Woods et al., 2005 [18]	1	1	0	1	0	0	1	1	0	5/9
Ottenbacher et al., 2009 [17]	1	1	0	n/a	1	1	1	1	0	6/8
Wang et al., 2013 [23]	1	1	0	n/a	1	1	1	1	0	6/8
Lee et al., 2014 [24]	1	1	0	n/a	1	0	1	1	0	5/8
Etman et al., 2015 [25]	1	1	0	n/a	1	1	1	1	0	6/8

Retirement in Europe (SHARE) [25]. Using modified Fried phenotype criteria (either from robust to prefrail/frail or from prefrail to frail), the authors showed that current smokers had a 16 % increased risk of worsening frailty status two years after baseline, compared to those who never smoked; multivariate logistic regression models were adjusted for age, gender, educational level, baseline frailty state and country (OR = 1.16, 95 % CI = 1.02–1.32, $p < 0.05$).

In the Hispanic Established Populations for Epidemiologic Studies of the Elderly (EPESE), among 777 Hispanic Americans aged 65 or older, those who ever smoked were significantly more likely to have a higher frailty status at follow-up than those who never smoked [17]. In this study, a summary frailty score, defined as the total number of five components of Fried phenotype criteria ranging from 0 to 5, was created and used as a continuous variable in multivariate linear regression models adjusted for age, gender, body mass index, education, marital status, financial strain, chronic diseases and baseline frailty score to examine frailty status changes over 10 years (unstandardised coefficient = 0.36, standard error = 0.15, $p < 0.05$).

A Chinese study of 3018 community-dwelling older people examining changes in frailty status over two years according to smoking status is the only study that failed to show significant findings [24]. Although not reaching statistical significance, directions of the associations between smoking and frailty appear consistent with the other included studies in that frailty status of (male) current smokers were more likely to worsen and less likely to improve than it was for those who never smoked in age-adjusted logistic regression models (OR = 1.53, 95 % CI = 0.73–3.23 for prefrail worsening; OR = 1.29, 95 % = 0.75–2.23 for robust worsening; OR = 0.63, 95 % = 0.33–1.21 for prefrail improvement; OR = 0.21, 95 % = 0.02–1.80 for frail improvement). No trends were observed among women. There is a possibility that the statistical power may have been lost as a result of dividing the cohort by gender and further by three Fried frailty categories (robust, prefrail and frail) at baseline as well as using three smoking statuses as predictors (never, past and current) and using four different frailty transition states (prefrail worsening, prefrail improvement, robust worsening and frail improvement).

A US study involving 28,181 women aged 65 to 79 from the Women's Health Initiative Observational Study who were free from frailty at baseline examined risk of newly developing frailty and prefrailty with modified Fried phenotype criteria over three years according to baseline smoking status and using unadjusted multinomial logistic regression models [18]. Past smoking predicted incident frailty (OR = 1.12, 95 % = 1.02–1.23), but not prefrailty (OR = 0.95, 95 % CI = 0.89–1.02), and current smoking predicted incident frailty (OR = 2.90, 95 % CI = 2.35–3.57) and prefrailty (OR = 1.76, 95 % CI = 1.49–2.09). The findings of this study need to be interpreted cautiously because important confounding factors including age, socioeconomic status, education and alcohol use, were not controlled for in the models.

Only one study employed a frailty index and assessed frailty status among 3257 Chinese community-dwellers aged ≥ 55. Men and women were analysed separately using multivariate linear regression models adjusted for age, education and baseline frailty index [23]. Current and past male smokers showed a worsening in their frailty status over the 15-year follow-up, significantly more than men who never smoked (standardised coefficient = 3.643, standard error = 1.621, $p = 0.026$) while there was no such difference observed in women ($p = 0.529$). In this study, the frailty index was constructed based on 28 variables excluding respiratory health deficits such as chronic tracheitis or cough, which are directly related to smoking. The analyses were also repeated with a frailty index using 25 variables without three non-respiratory smoking-related variables (hypertension, cardiovascular disease and cerebrovascular disease), providing similar results.

Most studies demonstrated current, past (or both) smoking status at baseline predicted subsequent incident or worsening of frailty status at follow-up [17, 18, 23,

25]. One study failed to show any significant associations between baseline smoking status and frailty trajectories [24]. It is of note however that most of the estimate measures were either unadjusted or only adjusted for a limited number of important covariates. We were unable to perform a meta-analysis due to methodological diversity of the included studies.

Discussion

This systematic review identified five prospective cohort studies on smoking and frailty. Although the studies employed different methodology and frailty criteria, most studies demonstrated that baseline smoking significantly predicted worsening of frailty status at follow-up. All studies at best only adjusted for a very limited range of potential confounding factors.

The association between smoking and subsequently developing or worsening frailty demonstrated by the included studies suggests that smoking may play a role in the pathogenesis of frailty. The underlying mechanism by which smokers are predisposed to frailty is not clear but is likely to be multifactorial given the detrimental effects of smoking on a wide range of organs and tissues [11]. Smoking is associated with cardiovascular diseases, respiratory diseases and cancers [11], all of which could cause morbidities and disabilities (both physical and mental), and potentially contribute to increased risks of frailty status.

The association between smoking and frailty may be explained by inflammation. Cigarette smoke contains various toxic chemicals and has been shown to be associated with increased levels of various inflammatory mediators [26]. Chronic inflammation causes muscle wasting [27] and leads to weight loss, exhaustion, weakness or slow gait speed; these are all major components of frailty [5]. This possible link between smoking and frailty via inflammation is further supported by population-based studies reporting that elevated inflammatory markers were associated with a higher prevalence and incidence of frailty [28–30].

The current systematic review has some limitations. First, the systematic literature search, study selection, data extraction and methodological quality assessment were conducted by one researcher; involving at least two researchers would have been more appropriate. Second, a relatively limited number of studies were identified, and some studies may have been missed that were not referenced on the three main data sources searched. Nonetheless, four out of the five included studies consistently showed evidence that smoking was a predictor of frailty status. Third, partly because a uniform definition of frailty has not yet been identified, study designs and methodologies of the included studies varied widely therefore meta-analysis was not possible.

"Currently smokers" can range from a person who smokes a few cigarettes a day to a person who has been smoking two packs per day for five decades, and "former smokers" can be a fit person who temporarily smoked when he/she was a teenager or can be a frail person who had to quit smoking recently because of severe emphysema due to life-long heavy smoking. All of the included studies examined only current status of smoking, however the amount of smoking history, such as by pack-years, is an important factor to examine impacts of smoking, and none of the studies in this review examined this. Therefore, the magnitude of the contribution of smoking to the development of frailty was not clear from the evidence identified by the current review. One study cross-sectionally investigated severity of frailty across three groups created based on amount and length of smoking history: 1) heavy smokers defined as one pack a day for 20 years or more, 2) light smokers defined as less than one pack a day or 1 pack per day for less than 20 years and 3) never smokers, and showed a dose-response association between smoking and frailty: heavy smokers had the highest degree of frailty and never smoker the lowest [15].

Although some of the included studies were not originally designed to examine the associations between smoking and frailty, it is important to note that some studies did not adjust or only adjusted for a limited number of confounding factors [18, 24, 25]. The important variables which should be considered for the link between smoking and frailty may include but not limited to age, gender, education, socioeconomic status and alcohol use.

In the future research, therefore, detailed smoking history information in addition to current smoking status, rather than just current, past and never smoking, and controlling for the abovementioned confounding variables should be taken into account to enable more accurate analysis and to provide more relevant results on the association between smoking and frailty.

Conclusion

In summary, this systematic review provides evidence suggesting smoking can be a predictor of worsening frailty status among community-dwelling people. Smoking cessation may potentially be beneficial for preventing or reversing frailty.

Abbreviations

EPESE: Established Populations for Epidemiologic Studies of the Elderly; SHARE: the Survey on Health, Ageing, and Retirement in Europe.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions
GK, SI and KW contributed to the conception and design. GK performed systematic review and drafted the manuscript. All authors contributed to interpretation of the data, revised the manuscript critically for important intellectual content, read and approved the final manuscript.

Acknowledgements
GK is funded by a University College London (UCL) Overseas Research Scholarship; SI is Emeritus Professor at UCL; KW is Director of Centre for Aging & Population Studies at UCL. UCL did not have any involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Received: 30 July 2015 Accepted: 15 October 2015
Published online: 22 October 2015

References

1. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci. 2004;59(3):255–63.
2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752–62.
3. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14(6):392–7.
4. Kojima G. Frailty as a predictor of future falls among community-dwelling older people: a systematic review and meta-analysis. J Am Med Dir Assoc. 2015.
5. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–156.
6. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal. 2001;1:323–36.
7. Rodriguez-Manas L, Feart C, Mann G, Vina J, Chatterji S, Chodzko-Zajko W, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci. 2013;68(1):62–7.
8. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging. 2012;16(7):601–8.
9. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing. 2006;35(5):526–9.
10. Tobacco. Media centre. WHO [www.who.int/mediacentre/factsheets/fs339/en/]. Accessed 19 May 2015.
11. Centers for Disease Control and Prevention (USA). Smoking & Tobacco Use. Health Effects of Cigarette Smoking. 2014. http://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/effects_cig_smoking/index.htm. Accessed 19 May 2015.
12. Romero-Ortuno R. Frailty Index in Europeans: association with determinants of health. Geriatr Gerontol Int. 2014;14(2):420–9.
13. Gale CR, Cooper C, Deary IJ, Aihie Sayer A. Psychological well-being and incident frailty in men and women: the English Longitudinal Study of Ageing. Psychol Med. 2014;44(4):697–706.
14. Leng SX, Hung W, Cappola AR, Yu Q, Xue QL, Fried LP. White blood cell counts, insulin-like growth factor-1 levels, and frailty in community-dwelling older women. J Gerontol A Biol Sci Med Sci. 2009;64(4):499–502.
15. Hubbard RE, Searle SD, Mitnitski A, Rockwood K. Effect of smoking on the accumulation of deficits, frailty and survival in older adults: a secondary analysis from the Canadian Study of Health and Aging. J Nutr Health Aging. 2009;13(5):468–72.
16. Mello Ade C, Engstrom EM, Alves LC. Health-related and socio-demographic factors associated with frailty in the elderly: a systematic literature review. Cad Saude Publica. 2014;30(6):1143–68.
17. Ottenbacher KJ, Graham JE, Al Snih S, Raji M, Samper-Ternent R, Ostir GV, et al. Mexican Americans and frailty: findings from the Hispanic established populations epidemiologic studies of the elderly. Am J Public Health. 2009;99(4):673–9.
18. Woods NF, LaCroix AZ, Gray SL, Aragaki A, Cochrane BB, Brunner RL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. J Am Geriatr Soc. 2005;53(8):1321–30.
19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clinical research ed). 2009;339:b2535.
20. Fushiki Y, Ohnishi H, Sakauchi F, Oura A, Mori M. Relationship of hobby activities with mortality and frailty among community-dwelling elderly adults: results of a follow-up study in Japan. J Epidemiol. 2012;22(4):340–7.
21. Semba RD, Bartali B, Zhou J, Blaum C, Ko CW, Fried LP. Low serum micronutrient concentrations predict frailty among older women living in the community. J Gerontol A Biol Sci Med Sci. 2006;61(6):594–9.
22. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 17 May 2015.
23. Wang C, Song X, Mitnitski A, Yu P, Fang X, Tang Z, et al. Gender differences in the relationship between smoking and frailty: results from the Beijing Longitudinal Study of Aging. J Gerontol A Biol Sci Med Sci. 2013;68(3):338–46.
24. Lee JS, Auyeung TW, Leung J, Kwok T, Woo J. Transitions in frailty states among community-living older adults and their associated factors. J Am Med Dir Assoc. 2014;15(4):281–6.
25. Etman A, Kamphuis CB, van der Cammen TJ, Burdorf A, van Lenthe FJ. Do lifestyle, health and social participation mediate educational inequalities in frailty worsening? Eur J Public Health. 2015;25(2):345–50.
26. Goncalves RB, Coletta RD, Silverio KG, Benevides L, Casati MZ, da Silva JS, et al. Impact of smoking on inflammation: overview of molecular mechanisms. Inflamm Res. 2011;60(5):409–24.
27. Kanapuru B, Ershler WB. Inflammation, coagulation, and the pathway to frailty. Am J Med. 2009;122(7):605–13.
28. Gale CR, Baylis D, Cooper C, Sayer AA. Inflammatory markers and incident frailty in men and women: the English Longitudinal Study of Ageing. Age (Dordr). 2013;35(6):2493–501.
29. Barzilay JI, Blaum C, Moore T, Xue QL, Hirsch CH, Walston JD, et al. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. Arch Intern Med. 2007;167(7):635–41.
30. Puts MT, Visser M, Twisk JW, Deeg DJ, Lips P. Endocrine and inflammatory markers as predictors of frailty. Clin Endocrinol (Oxf). 2005;63(4):403–11.

8.1.1.2 Smoking ELSA analysis

This is a pre-copyedited, author-produced version of an article accepted for publication in Age and Ageing following peer review. The version of record (Kojima G, Iliffe S, Jivraj S, Liljas A, Walters K. Does current smoking predict future frailty? The English longitudinal study of ageing. Age and ageing. 2017 Aug 17;47(1):126-31. doi: 10.1093/ageing/afx136) is available online at: https://academic.oup.com/ageing/article-abstract/47/1/126/4062212?redirectedFrom=fulltext.

Does current smoking predict future frailty? the English Longitudinal Study of Ageing

Gotaro Kojima, MD[1]; Steve Iliffe, FRCGP[1]; Stephen Jivraj, PhD[2];
Ann Liljas, MPH[1]; Kate Walters, PhD[1].

[1] Department of Primary Care and Population Health, University College London, London, UK
[2] Department of Epidemiology and Public Health, University College London, London, UK

ABSTRACT

Background:
Smoking is the single most preventable cause of morbidity and mortality. The evidence on independent associations between smoking in later life and incident frailty is scarce.

Objectives:
To examine the effect of current smoking in older people on the risk of developing frailty, controlling for important confounders.

Methods:
We used data of 2,542 community-dwelling older people aged ≥60 years in England. Participants were classified as current smokers or non-smokers. Frailty was defined using modified Fried criteria. Multivariable logistic regression models were used to examine risk of four-year incident frailty in current smokers compared with non-smokers, adjusted for demographic, socioeconomic and health variables.

Results:
Of 2,542 participants, 261 and 2,281 were current smokers and non-smokers, respectively. The current smokers were significantly frailer, younger, with lower BMI, less educated, less wealthy and lonelier compared with non-smokers at baseline. In multivariable logistic regression models adjusting for age and gender, current smokers were twice as likely to develop frailty compared with non-smokers (OR=2.07, 95%CI=1.39-3.39, p=0.001). The association is attenuated largely by controlling for socioeconomic status. Smoking remains significantly associated with incident frailty in fully adjusted models including age, gender, socioeconomic status, alcohol use, education, wealth, cognitive function and loneliness (OR=1.60, 95%CI=1.02-2.51, p=0.04). The relationship is however attenuated when taking account of non-response bias through multiple imputation.

Conclusions:
Current smokers compared with non-smokers were significantly more likely to develop frailty over four years among community-dwelling older people. Given that smoking is a modifiable lifestyle factor, smoking cessation may potentially prevent or delay developing frailty, even in old age.

INTRODUCTION

When national surveys on smoking started in the UK in 1974, 41% of women and 51% of men were smokers.[1] The overall prevalence of smoking has been declining since then, down to 17% for women and 20% for men in 2014.[1] Tobacco smoking is the single most preventable cause of morbidity and mortality in the UK.[2] The National Health Service (NHS) spent £5.2 billion (approximately $7.5 billion) in treating smoking-related health conditions in 2005/06.[3]

Smoking also increases the risk of developing a number of other diseases, such as chronic obstructive pulmonary disease (COPD), coronary heart disease, stroke and peripheral vascular disease,[4] all of which can potentially have negative effects on the physical, psychological and social health of smokers. Disability itself limits autonomy, increases the risk of dependence, reduces quality of life and contributes to mortality.[5]

Frailty is considered a precursor to, but a distinct state from, disability.[6] Frailty has been described as a condition associated with decreased physiological reserve and increased vulnerability to adverse health outcomes with exposure to a stressor.[7] The outcomes include falls,[8] fractures,[9] disability,[10] hospitalisation[11] and institutionalisation.[12] Frailty has also been shown to be linked to worse psychological or cognitive outcomes, such as poor quality of life[13] and dementia.[14] Due to the potential for reversibility of frailty,[15] identifying potentially modifiable risk factors of frailty may help to develop strategies to prevent or slow progression of adverse health outcomes associated with both frailty and smoking. As maintaining independence is a key priority for older people, demonstrating links with smoking and frailty might provide additional motivation for older smokers to quit. A previous systematic review showed that only a few studies have examined longitudinal associations between smoking and risk of incident frailty.[16] Although most of these studies demonstrated that smokers were more likely to develop frailty, they provided effect measures that were unadjusted or adjusted for a limited number of confounders.[16] Therefore, the independent association of smoking with incident frailty has not been convincingly established. We thus aimed to examine the association of smoking with the risk of developing frailty, controlling for important confounding variables and using data from a nationally representative sample of community-dwelling older men and women living in England.

METHODS

Study Setting and Population

The English Longitudinal Study of Ageing (ELSA) is a multi-centre longitudinal panel study of a nationally representative sample of community-dwelling men and women aged 50 years and older in England and its detail has been published elsewhere.[17] The initial participants (n=11,391) at wave 1 in 2002 were recruited from households that participated in the Health Survey for England (HSE). The panel has been followed up with every two years. Ethical approval for all of the ELSA waves was obtained from the National Research and Ethics Committee and informed consent was obtained from all participants.

The current study used data of participants who were aged 60 years or older at wave 2 (baseline), since the gait speed was not measured for those aged less than 60 years, and who also participated at wave 4 (follow-up). Of 6,183 men and women aged 60 years or older who were interviewed at wave 2, those who missed any data regarding smoking status at wave 2 (n=3) and frailty components at waves 2 (n=1,688) were excluded. Those who were frail at wave 2 (n=575) were also excluded in order to examine the risk of incident frailty. Among 3,918 participants left, 1,376 could not participate at the follow-up wave due to ill health

(n=44), death (n=139), refusal (n=547), being unable to contact (n=132) or other reasons (n=514). The final analytic sample for this study was 2,542 participants.

Predictor Variable − Smoking

Participants were classified as 'current smoker' or 'non-smoker' based on answers to the question 'Do you smoke cigarettes at all nowadays?' during the interview at wave 2. To examine effects of smoking cessation on frailty, the non-smokers were divided, based on data of when they quit smoking available from wave 3 (2 years after wave 2), into two groups: past smokers and never smoker. The past smokers were further divided into another two groups: those who quit within the last 10 years and those who quit more than 10 years ago.[18]

Outcome Variable − Incident frailty

Frailty was defined using the frailty phenotype criteria that Fried et al. described in the Cardiovascular Health Study (CHS).[6] In CHS, frailty is defined using a combination of five physical frailty components: (1) unintentional weight loss, (2) self-reported exhaustion, (3) weakness, (4) slow walking speed and (5) low physical activity. Frailty is classified as having three or more of the five criteria. An individual who meets one or two criteria is classified as prefrail, and an individual with no criterion is classified as robust. Please see **Appendix 1** for detail of definitions of the CHS criteria components, covariates and statistical analysis.

RESULTS

Table 1 and **Appendix 2** present the baseline characteristics of the final analytic sample of 2,542 participants according to smoking status as well as 1,376 who were excluded at follow-up according to reasons for lost follow-up. Among the analytic sample at baseline, 2,281 participants were non-smokers (1,168 never smokers and 1,113past smokers) and 261 were current smokers. Current smokers were significantly frailer, younger, with lower BMI, less educated, less wealthy and lonelier compared with non-smokers. There were no significant differences in gender, alcohol use and cognitive function between these two groups.

In the univariate logistic regression models, various factors were significantly associated with a higher risk of incident frailty over four years. Current smoking was associated with an approximately 50% increased risk of developing frailty (OR=1.56, 95% confidence interval (CI)=1.06-2.29, p=0.02). Other factors associated with an increased risk of incident frailty were belonging to the older age group, being a female, having a higher BMI, consuming alcohol less frequently, having completed a lower level of education, having a lower level of wealth, having a lower cognitive function and having more loneliness. (**Table 2**)

Table 3 shows the results of the multivariable logistic regression models. In Model 1 adjusting for age and gender, current smokers were twice as likely to develop frailty at the time of follow-up compared with non-smokers (OR=2.07, 95%CI=1.34-3.19, p=0.001). Further adjusting for alcohol use did not change the odds ratio drastically (OR=2.17, 95%CI=1.39-3.39, p=0.001). Although adding education and wealth for adjustment in Model 3 decreased the odds ratio, current smoking remained a significant predictor of incident frailty (OR=1.62, 95%CI=1.05-2.52, p=0.03). In Model 4, cognitive function and loneliness were further adjusted for, which made little change in the association (OR=1.60, 95%CI=1.02-2.51, p=0.04). We repeated the final model (Model 4) with multiple imputation by chained equations, and this attenuated the association (OR=1.48, 95%CI=0.97-2.28, p=0.07).

When COPD was added to the Model 4, current smoking was no longer a significant predictor of incident frailty and the OR decreased by 14.4% (OR=1.37, p=0.19). In this model, COPD was strongly associated with incident frailty (OR=2.58, 95%CI=1.59-4.20, p<0.001). These findings suggest that current smokers are more likely to develop frailty due to COPD, rather than smoking itself. Adding CVD or cancers to Model 4 made little changes in the results, which suggest that CVD and cancers are not a modulator in the associations between current smoking and development of frailty.

In supplementary analyses, incident frailty risk for current and past smokers compared with never smokers was calculated. Compared with never smokers, current smokers were significantly more likely to develop frailty in Models 1 and 2, which became non-significant in Models 3 and 4. There was no significant association between past smoking and incident frailty in any models. (**Appendix 3**) Among 1,113 past smokers, 157 quit smoking within the last 10 years and 956 quit smoking for more than 10 years ago. Incident frailty risks of these two groups were not significantly different to that of non-smokers in all models. (**Appendix 4**)

DISCUSSION

This prospective panel study of 2,542 British community-dwelling men and women aged 60 years or older who were free of frailty at baseline showed that current older smokers were 60% more likely to develop frailty than non-smokers over four years, controlling for a wide range of potential confounders including age, gender, alcohol use, education, wealth, cognitive function and loneliness.

Our findings are consistent with the limited previous longitudinal research, which has shown in the majority of studies that smoking worsened subsequent frailty status,[19-23] except for one study.[15]

Mechanisms by which current smokers are more likely to develop frailty are unknown, but may be multifactorial given that tobacco smoke is a mixture of numerous kinds of toxic chemicals and compounds and can affect every organ in the body. Smoking has been shown to be associated with various physical and mental illnesses,[4] any of which can contribute to the development of frailty. These health risks can be reduced substantially by smoking cessation, according mostly to findings from studies among middle aged adults.[24] Although scarce, the evidence supports that one is never too old to quit smoking and older smokers can still benefit from quitting.[25] One study showed that the risks of myocardial infarction and stroke were reduced by 40% within five years of smoking cessation in German older people aged 50 and over.[26] Smoking cessation can potentially be an effective strategy to prevent or delay developing frailty among older smokers. This possible benefit of smoking cessation is supported by our findings that past smokers did not have higher risk of incident frailty than never smokers. Evidence suggests that older people may be less motivated by preventing disease such as heart attacks than younger people.[27] However it is their priority to remain independent, able to look after themselves and engaged socially.[28] Therefore knowledge that continued smoking in later life may increase the risk of frailty, which itself is strongly associated with increased dependency and increased risk of moving into care home settings, may provide additional motivation to encourage older smokers to quit.

In the multivariable logistic regression models, the odds ratio of developing frailty in current smokers compared with non-smokers decreased from 2.17 to 1.62 (-25.3%) when further adjusted for education and wealth, which suggests that the association between smoking and

incident frailty can partially be explained by socioeconomic status. Lower socioeconomic status has been shown to be associated with a higher prevalence of smoking[3] and a higher level and faster progression of frailty.[29] Socioeconomically disadvantaged smokers typically are found to have developed their smoking habit earlier in their lives, and are likely to be more nicotine dependent, to have less social support for smoking cessation and to be less likely to succeed in smoking cessation attempts.[30] In order to reduce the smoking-related health inequalities, smoking cessation measures should be effective on these hard-core smokers with low socioeconomic status.[30] In our supplementary analysis using multiple imputation of covariates the relationship of smoking with frailty was attenuated further and becomes non-significant.

COPD, CVD and cancers were separately added to the final multivariable logistic regression model to see if these smoking-related diseases fully explained the association between current smoking and incident frailty, or if there appeared to be a further independent effect of smoking on frailty. Only COPD changed the results significantly and current smoking no longer predicted incident frailty in that model, which suggests that the association appears to be explained by COPD. Finally our supplementary analysis suggests that the harmful effects of smoking on frailty are largely restricted to those who were currently smoking at baseline, as with even those who had more recently quit (within the last 10 years), showed no increased risk of frailty compared to never-smokers.

There are some limitations and strengths of this study. First, due to the limited availability of data at the baseline wave, only current smokers and non-smokers were defined. We had to retrieve data from a later wave to create past and never smoker groups. We had no information on the extent of smoking exposure (quantity of cigarettes consumed or length of exposure) and we were therefore unable to explore a 'dose-response' relationship. It should be noted that the information on smoking status was self-reported and potentially subject to response bias. Second, our sample was restricted to those who had completed measurements of frailty status (e.g. gait speed, handgrip strength) in nurse interviews at two time points in ELSA. Those who were excluded due to missing data at follow-up were significantly frailer and more likely to be current smokers compared with those who were included, which suggests that those excluded were missing data that were not random. Therefore, this exclusion is likely to attenuate an association between smoking status and incident frailty. Whilst we attempted to account for attrition bias by using non-response weights, this differential loss to follow-up may have underestimated the associations between frailty and smoking. Third, the ELSA cohort only includes the English population and may not be generalisable to other populations. Fourth, as in other studies, components of CHS criteria were slightly modified according to availability of ELSA data, which may have affected the findings.[31] Fifth, we used to only two time points four years apart to assess incident frailty risk according to smoking. Given that COPD may be an important mediator in the association between smoking and frailty, over many years, a study with a longer follow-up period and multiple data collection time points would be justified.

The major strengths of this analysis are a large sample size, a prospective study design and the use of a wide range of potential confounders for adjustment.

In conclusion, current smokers compared with non-smokers were significantly more likely to develop frailty over four years among British community-dwelling older people. This result is in line with findings of a recent systematic review.[16] Given that smoking is a modifiable

lifestyle factor, smoking cessation may potentially prevent or delay developing frailty, even in old age.

ACKNOWLEDGEMENT

ELSA has been funded by the National Institute of Aging in the United States and a consortium of UK government departments coordinated by the Office for the National Statistics, and the data are available through the UK Data Archive (http://data-archive.ac.uk).

REFERENCES

1. Smoking statistics, who smokes and how much, Action on Smoking and Health (ASH). 2016; http://ash.org.uk/files/documents/ASH_106.pdf. Accessed 23 May 2016.
2. Smoking statistics, Illness and death, Acton on Smoking and Health (ASH). 2015; http://ash.org.uk/files/documents/ASH_107.pdf.
3. Adult smoking habits in Great Britain: 2014, Office for National Statistics. 2016; http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2014. Accessed 26 May 2016.
4. What are the health risks of smoking? NHS choices. 2015; http://www.nhs.uk/chq/Pages/2344.aspx?CategoryID=53.
5. Van Oyen H, Berger N, Nusselder W, et al. The effect of smoking on the duration of life with and without disability, Belgium 1997-2011. BMC public health 2014;14:723.
6. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. The journals of gerontology. Series A, Biological sciences and medical sciences 2001;56:M146-156.
7. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet (London, England) 2013;381:752-762.
8. Kojima G. Frailty as a Predictor of Future Falls Among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. Journal of the American Medical Directors Association 2015;16:1027-1033.
9. Kojima G. Frailty as a predictor of fractures among community-dwelling older people: A systematic review and meta-analysis. Bone 2016;90:116-122.
10. Kojima G. Frailty as a Predictor of Disabilities among Community-Dwelling Older People: A Systematic Review and Meta-analysis. Disability and Rehabilitation 2016;
11. Kojima G. Frailty as a predictor of hospitalisation among community-dwelling older people: a systematic review and meta-analysis. Journal of epidemiology and community health 2016;70:722-729.
12. Kojima G. Frailty as a Predictor of Nursing Home Placement among Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. Journal of Geriatric Physical Therapy 2016;
13. Kojima G, Iliffe S, Jivraj S, Walters K. Association between frailty and quality of life among community-dwelling older people: a systematic review and meta-analysis. Journal of epidemiology and community health 2016;70:716-721.
14. Kojima G, Taniguchi Y, Iliffe S, Walters K. Frailty as a Predictor of Alzheimer Disease, Vascular Dementia, and All Dementia Among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. Journal of the American Medical Directors Association 2016;17:881-888.
15. Lee JS, Auyeung TW, Leung J, et al. Transitions in frailty states among community-living older adults and their associated factors. Journal of the American Medical Directors Association 2014;15:281-286.

16. Kojima G, Iliffe S, Walters K. Smoking as a predictor of frailty: a systematic review. BMC geriatrics 2015;15:131.
17. Steptoe A, Breeze E, Banks J, Nazroo J. Cohort profile: the English longitudinal study of ageing. International journal of epidemiology 2013;42:1640-1648.
18. Lee PN, Fry JS, Forey BA. Estimating the decline in excess risk of chronic obstructive pulmonary disease following quitting smoking - a systematic review based on the negative exponential model. Regulatory toxicology and pharmacology : RTP 2014;68:231-239.
19. Chamberlain AM, St Sauver JL, Jacobson DJ, et al. Social and behavioural factors associated with frailty trajectories in a population-based cohort of older adults. BMJ open 2016;6:e011410.
20. Etman A, Kamphuis CB, van der Cammen TJ, et al. Do lifestyle, health and social participation mediate educational inequalities in frailty worsening? European journal of public health 2015;25:345-350.
21. Ottenbacher KJ, Graham JE, Al Snih S, et al. Mexican Americans and frailty: findings from the Hispanic established populations epidemiologic studies of the elderly. American journal of public health 2009;99:673-679.
22. Wang C, Song X, Mitnitski A, et al. Gender differences in the relationship between smoking and frailty: results from the Beijing Longitudinal Study of Aging. The journals of gerontology. Series A, Biological sciences and medical sciences 2013;68:338-346.
23. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. Journal of the American Geriatrics Society 2005;53:1321-1330.
24. Stop smoking, The benefits and adis to quitting, Action on Smoking and Health (ASH). http://ash.org.uk/files/documents/ASH_116.pdf.
25. Bratzler DW, Oehlert WH, Austelle A. Smoking in the elderly--it's never too late to quit. The Journal of the Oklahoma State Medical Association 2002;95:185-191; quiz 192-183.
26. Gellert C, Schottker B, Muller H, et al. Impact of smoking and quitting on cardiovascular outcomes and risk advancement periods among older adults. European journal of epidemiology 2013;28:649-658.
27. Kviz FJ, Clark MA, Crittenden KS, et al. Age and readiness to quit smoking. Preventive medicine 1994;23:211-222.
28. Anton SD, Woods AJ, Ashizawa T, et al. Successful aging: Advancing the science of physical independence in older adults. Ageing research reviews 2015;24:304-327.
29. Herr M, Robine JM, Aegerter P, et al. Contribution of socioeconomic position over life to frailty differences in old age: comparison of life-course models in a French sample of 2350 old people. Annals of epidemiology 2015;25:674-680 e671.
30. ASH Briefing: Health inequalities and smoking, Action on Smoking and Health (ASH). 2016; http://ash.org.uk/files/documents/ASH_1017.pdf.
31. Theou O, Cann L, Blodgett J, et al. Modifications to the frailty phenotype criteria: Systematic review of the current literature and investigation of 262 frailty phenotypes in the Survey of Health, Ageing, and Retirement in Europe. Ageing research reviews 2015;21:78-94.

Table 1. Summary of the baseline characteristics of analytic sample (N=2,542)

Variable*	Entire sample	Non-smoker			Current smoker
	N=2,542	Total non-smoker n=2,281	Never smoker n=1,168 (51.2%)	Past smoker n=1,113 (48.8%)	n=261
Frailty status					
Robust	1,430 (56.3%)	1,319 (57.8%)	698 (59.8%)	621 (55.8%)	111 (42.5%)
Prefrail	1,112 (43.7%)	962 (42.2%)	470 (40.2%)	492 (44.2%)	150 (57.5%)
Age group					
60-64	611 (24.0%)	526 (23.1%)	276 (23.6%)	250 (22.5%)	85 (32.6%)
65-65	825 (32.5%)	739 (32.4%)	409 (35.0%)	330 (29.6%)	86 (33.0%)
70-74	542 (21.3%)	498 (21.8%)	257 (22.0%)	241 (21.7%)	44 (16.9%)
75-79	354 (13.9%)	320 (14.0%)	140 (12.0%)	180 (16.2%)	34 (13.0%)
80+	210 (8.3%)	198 (8.7%)	86 (7.4%)	112 (10.1%)	12 (46%)
Gender					
Male	1,150 (45.2%)	1,032 (45.2%)	421 (36.0%)	611 (54.9%)	118 (45.2%)
Female	1,392 (54.8%)	1,249 (54.8%)	747 (64.0%)	502 (45.1%)	143 (54.8%)
BMI	27.6 ± 4.4	27.7 ± 4.4	27.5 ± 4.5	28.0 ± 4.4	26.8 ± 4.3
<=25	706 (27.8%)	613 (26.9%)	353 (30.2%)	260 (23.4%)	93 (35.6%)
25<, <=30	1180 (46.4%)	1071 (47.0%)	541 (46.3%)	530 (47.6%)	109 (41.8%)
>30	656 (25.8%)	597 (26.2%)	274 (23.5%)	323 (29.0%)	59 (22.6%)
Alcohol					
None	223 (9.4%)	192 (9.0%)	123 (11.1%)	69 (6.7%)	31 (13.0%)
1/year - 2/month	690 (29.0%)	617 (28.8%)	363 (32.6%)	254 (24.7%)	73 (30.5%)
1/month - 4/week	877 (36.8%)	794 (37.1%)	409 (36.7%)	385 (37.4%)	83 (36.8%)
5/week or more	592 (24.9%)	541 (25.2%)	218 (19.6%)	322 (31.3%)	52 (21.8%)
Education					
Higher education	322 (12.7%)	306 (13.4%)	164 (14.0%)	142 (12.8%)	16 (6.1%)
Intermediate	1,314 (51.7%)	1,201 (52.7%)	610 (52.2%)	591 (53.1%)	113 (43.3%)
No qualification	906 (35.6%)	774 (33.9%)	394 (33.7%)	380 (34.1%)	132 (50.6%)
Wealth quintile					
Richest	661 (26.3%)	619 (27.5%)	327 (28.3%)	292 (26.6%)	42 (16.3%)
2nd	569 (22.7%)	528 (23.4%)	258 (22.3%)	270 (24.6%)	41 (16.0%)
3rd	523 (20.8%)	474 (21.0%)	261 (22.6%)	213 (19.4%)	49 (19.1%)
4th	446 (17.7%)	393 (17.4%)	187 (16.2%)	206 (18.7%)	53 (20.6%)
Poorest	312 (12.4%)	240 (10.7%)	122 (10.6%)	118 (10.7%)	72 (28.0%)
Cognitive function score	48.9 ± 10.4	49.2 ± 10.3	49.5 ± 10.2	48.8 ± 10.4	46.9 ± 10.8
Loneliness score	3.9 ± 1.4	3.9 ± 1.3	3.9 ± 1.3	3.9 ± 1.3	4.3 ± 1.6
COPD	153 (6.0%)	113 (5.0%)	53 (4.5%)	60 (5.4%)	40 (15.3%)

* Mean + standard deviation or n (%), COPD: chronic obstructive pulmonary disease

Table 2. Risk factors of incident frailty by univariate logistic regression models (N=2,542).
* ref: reference group

Variable	Odds ratio (95%CI)	p value
Smoking Status		
Never/past	ref*	
Current	1.56 (1.06-2.29)	0.02
Age group		
60-64	ref*	
65-69	1.07 (0.63-1.83)	0.80
70-74	2.70 (1.64-4.44)	<0.001
75-79	5.16 (3.13-8.51)	<0.001
80+	11.88 (7.09-19.92)	<0.001
Gender		
Male	ref*	
Female	1.69 (1.28-2.23)	<0.001
BMI	1.08 (1.04-1.11)	<0.001
<=25	ref	
25<, <=30	0.90 (0.63-1.27)	0.53
>30	1.64 (1.16-2.34)	<0.01
Alcohol		
None	ref*	
1/year - 2/month	0.57 (0.37-0.88)	0.01
1/month - 4/week	0.46 (0.30-0.70)	<0.001
5/week or more	0.31 (0.19-0.51)	<0.001
Education		
Higher education	ref*	
Intermediate	1.48 (0.88-2.51)	0.14
No qualification	3.73 (2.23-6.25)	<0.001
Wealth quintile		
Richest	ref*	
2nd	1.92 (1.20-3.07)	<0.01
3rd	1.96 (1.23-3.14)	<0.01
4th	2.65 (1.68-4.18)	<0.001
Poorest	5.96 (3.81-9.34)	<0.001
Cognitive function score	0.94 (0.92-0.95)	<0.001
Loneliness score	1.27 (1.17-1.38)	<0.001

Table 3. Incident frailty risk of current smoking by multivariable logistic regression models (N=2,542).

	Odds Ratio (95%CI)	p value
Model 1	2.07 (1.34-3.19)	0.001
Model 2	2.17 (1.39-3.39)	0.001
Model 3	1.62 (1.05-2.52)	0.03
Model 4	1.60 (1.02-2.51)	0.04

Model 1: Adjusted for age and gender
Model 2: Further adjusted for alcohol
Model 3: Further adjusted for education and wealth
Model 4: Further adjusted for cognitive function and loneliness

Appendix 1. Methods

Outcome Variable – Incident frailty

In the current study, the five phenotype components are slightly modified according to data availability. At baseline, weight loss was defined as loss of 5% or more of body weight since HSE in 1998, 1999 or 2001, or body mass index (BMI) of less than 18.5 kg/m^2. At follow-up, weight loss was defined as loss of 5% or more of body weight since baseline or BMI of less than 18.5 kg/m^2. Exhaustion was defined based on responses to two questions from the eight-item Center for Epidemiologic Studies Depression Scale (CES-D) on whether much of the time during the past week (1) they felt that everything they did was an effort and (2) they could not get going. Exhaustion was considered to be present if the participant answered YES to either or both of these questions. Handgrip strength was measured three times on each hand using a dynamometer and the highest measurement was used for this criterion. Weakness was defined as having the handgrip measurement in the lowest 20%, stratified by gender and BMI quartiles. Gait speed was calculated according to the average time taken to walk eight feet at a usual pace following two attempts. Slow walking speed was defined as having gait speed in the lowest 20%, stratified by gender and median height. Those who were in wheelchair, were bed-bound or were unable to walk without assistance were considered to have slow walking speed. Physical activity was ranked based on a combination of intensity (vigorous; moderate; mild exercise) and frequency (more than once a week; once a week; one to three times a month; hardly ever or never) of usual exercise involved. Low physical activity was defined as being in the lower two ranks out of the possible four.

Covariates

Baseline covariates that could potentially have a confounding effect on the associations between smoking and frailty available in ELSA, include age, gender, BMI, alcohol consumption, education, wealth, cognitive function, and loneliness. ELSA participants were asked if they were ever told by a doctor that they had or had had COPD, cardiovascular diseases (CVD) (angina, myocardial infarction, congestive heart failure or stroke) and cancers.

Participants were classified into five age groups based on their age at baseline:(1) 60-64 years old, (2) 65-69 years old, (3) 70-74 years old (4) 75-79 years old and (5) 80 years or older. BMI was calculated as weight in kilograms divided by the square of height in metres. Alcohol use was categorised into four groups based on frequency of alcohol consumption: (1) not at all, (2) once a year to twice a month, (3) once a week to four days a week and (4) five days a week or more. Education was classified into three groups: (1) higher education, (2) intermediate and (3) no qualification. The quintiles of the net total wealth, which was calculated as the sum of savings, investments, physical wealth and housing wealth deducting financial debt and mortgage debt, were used. Cognitive function was assessed using a composite score, summing up scores of four tests covering three domains of cognitive function: (1) executive function (animal naming task, distribution range: 0-57), (2) processing speed (letter cancellation task, distribution range: 0-64) and (3) memory (immediate and delayed recall tasks, distribution range: both 0-10, together 0-20), with a higher score suggestive of better cognitive function.[17] Loneliness was assessed using a three-item short form of the Revised UCLA Loneliness Scale, with the score ranging from three to nine.

Statistical Analyses

Baseline characteristics were compared according to smoking status (current smoker or non-smoker) using a t-test for continuous variables and a chi square test for categorical variables. Univariate logistic regression models were used to examine the risk of incident frailty for baseline characteristics. Multivariable logistic regression models were used to examine the risk of incident frailty for being a current smoker compared with a non-smoker, adjusted for age, gender and other variables that were significantly associated with a risk of incident frailty in the univariate analyses. The longitudinal weighting was used for all analyses to reduce any bias caused by non-response. The longitudinal weights are created sequentially on top of the previous wave's weights for the core members who have participated in all the previous waves, in order to minimize bias from sample loss due to attrition and be representative of those living in England (i.e. 2002).[17]

We conducted several supplementary analyses. The fully adjusted model was repeated using multiple imputation by chained equations for missing value of the covariates used for adjustment. It is based on the assumption of missing at random where the probability of missing data does not depend on unobserved data but on observed data. We also repeated the main analysis in order to explore the degrees to which smoking-related diseases explained the association between current smoking and subsequent incident frailty. Three diseases: COPD, CVD and cancers, were chosen because smoking is known to increase the risk of these diseases and they can increase the risk of frailty. These diseases were separately added to the final model and changes in the odds ratios before and after the addition were compared. We conducted a further supplementary analysis to explore if the relationships change when non-smokers were reclassified as either 'never smokers' or 'past smokers' using data of when they quit smoking from another wave two years later (these data were not available for our main cohort at baseline). The past smokers were further divided into two groups: those who quit within 10 years and those who quit more than 10 years ago. The multivariable logistic regression models were repeated using these three and four smoking groups.

All statistical analyses were conducted using StataSE 14 (StataCorp LP, College Station, Texas, USA) based on 2-tailed significance. The level of significance was set at $p<0.05$.

Appendix 2. The full version of baseline characteristics of analytic sample (N=2,542) and those who lost follow-up (N=1,376)

Variable*	Entire cohort	Analytic sample	Non-smoker			Current smoker	Lost f/u			
	N=3,918	N=2,542	Total non-smoker n=2,281	Never smoker n=1,168 (51.2%)	Past smoker n=1,113 (48.8%)	n=261	Total lost f/u N=1,376	Died n=139 (10.1%)	Ill health n=44 (3.2%)	Other reasons n=1,193 (86.7%)
Frailty status										
Robust	2054 (52.4%)	1,430 (56.3%)	1,319 (57.8%)	698 (59.8%)	621 (55.8%)	111 (42.5%)	624 (45.4%)	40 (28.8%)	17 (38.6%)	567 (47.5%)
Prefrail	1864 (47.6%)	1,112 (43.7%)	962 (42.2%)	470 (40.2%)	492 (44.2%)	150 (57.5%)	752 (54.7%)	99 (71.2%)	27 (61.4%)	626 (52.5%)
Age group										
60-64	875 (22.3%)	611 (24.0%)	526 (23.1%)	276 (23.6%)	250 (22.5%)	85 (32.6%)	264 (19.2%)	15 (10.8%)	2 (4.5%)	247 (20.7%)
65-65	1202 (30.7%)	825 (32.5%)	739 (32.4%)	409 (35.0%)	330 (29.6%)	86 (33.0%)	377 (27.4%)	19 (13.7)	11 (25.0%)	347 (29.1%)
70-74	826 (21.1%)	542 (21.3%)	498 (21.8%)	257 (22.0%)	241 (21.7%)	44 (16.9%)	284 (20.6%)	37 (26.6%)	14 (31.8%)	233 (19.5%)
75-79	583 (14.9%)	354 (13.9%)	320 (14.0%)	140 (12.0%)	180 (16.2%)	34 (13.0%)	229 (16.6%)	30 (21.6%)	10 (22.7%)	189 (15.8%)
80+	432 (11.0%)	210 (8.3%)	198 (8.7%)	86 (7.4%)	112 (10.1%)	12 (46%)	222 (16.1%)	38 (27.3%)	7 (15.9%)	177 (14.8%)
Gender										
Male	1790 (45.7%)	1,150 (45.2%)	1,032 (45.2%)	421 (36.0%)	611 (54.9%)	118 (45.2%)	640 (46.5%)	75 (54.0%)	15 (34.1%)	550 (46.1%)
Female	2128 (54.3%)	1,392 (54.8%)	1,249 (54.8%)	747 (64.0%)	502 (45.1%)	143 (54.8%)	736 (53.5%)	64 (46.0%)	29 (65.9%)	643 (53.9%)
BMI	27.7 ± 4.5	27.6 ± 4.4	27.7 ± 4.4	27.5 ± 4.5	28.0 ± 4.4	26.8 ± 4.3	27.8 ± 4.5	26.9 ± 4.4	27.8 ± 5.3	27.9 ± 4.5
<=25	1099 (28.0%)	706 (27.8%)	613 (26.9%)	353 (30.2%)	260 (23.4%)	93 (35.6%)	393 (28.6%)	51 (36.7%)	16 (36.4%)	326 (27.3%)
25<, <=30	1761 (45.0%)	1180 (46.4%)	1071 (47.0%)	541 (46.3%)	530 (47.6%)	109 (41.8%)	581 (42.2%)	56 (40.3%)	13 (29.6%)	512 (42.9%)
>30	1058 (27.0%)	656 (25.8%)	597 (26.2%)	274 (23.5%)	323 (29.0%)	59 (22.6%)	402 (29.2%)	32 (23.0%)	15 (34.1%)	355 (29.8%)
Alcohol										
None	363 (9.3%)	223 (9.4%)	192 (9.0%)	123 (11.1%)	69 (6.7%)	31 (13.0%)	140 (10.2%)	22 (19.5%)	9 (23.7%)	109 (10.2%)
1/year - 2/month	1034 (26.4%)	690 (29.0%)	617 (28.8%)	363 (32.6%)	254 (24.7%)	73 (30.5%)	344 (25.0%)	27 (23.9%)	5 (13.2 %)	312 (29.2%)
1/month - 4/week	1322 (33.7%)	877 (36.8%)	794 (37.1%)	409 (36.7%)	385 (37.4%)	83 (36.8%)	445 (32.3%)	34 (30.1%)	14 (36.8%)	397 (37.1%)
5/week or more	884 (22.6%)	592 (24.9%)	541 (25.2%)	218 (19.6%)	322 (31.3%)	52 (21.8%)	292 (21.2%)	30 (26.5%)	10 (26.3%)	252 (23.6%)
Education										
Higher education	437 (11.2%)	322 (12.7%)	306 (13.4%)	164 (14.0%)	142 (12.8%)	16 (6.1%)	637 (46.3%)	70 (50.4%)	21 (47.7%)	546 (45.8%)
Intermediate	1937 (49.4%)	1,314 (51.7%)	1,201 (52.7%)	610 (52.2%)	591 (53.1%)	113 (43.3%)	623 (45.3%)	54 (38.8%)	18 (40.9%)	551 (46.2%)
No qualification	1543 (39.4%)	906 (35.6%)	774 (33.9%)	394 (33.7%)	380 (34.1%)	132 (50.6%)	115 (8.4%)	15 (10.8%)	5 (11.4%)	95 (8.0%)
Wealth quintile										
Richest	912 (23.3%)	661 (26.3%)	619 (27.5%)	327 (28.3%)	292 (26.6%)	42 (16.3%)	251 (18.2%)	26 (18.7%)	8 (19.0%)	217 (18.3%)
2nd	878 (22.4%)	569 (22.7%)	528 (23.4%)	258 (22.3%)	270 (24.6%)	41 (16.0%)	309 (22.5%)	26 (18.7%)	11 (26.2%)	272 (23.0%)
3rd	824 (21.0%)	523 (20.8%)	474 (21.0%)	261 (22.6%)	213 (19.4%)	49 (19.1%)	301 (21.9%)	31 (22.3%)	5 (11.9%)	265 (22.4%)
4th	706 (18.0%)	446 (17.7%)	393 (17.4%)	187 (16.2%)	206 (18.7%)	53 (20.6%)	260 (18.9%)	27 (19.4%)	6 (14.3%)	227 (19.2%)
Poorest	557 (14.2%)	312 (12.4%)	240 (10.7%)	122 (10.6%)	118 (10.7%)	72 (28.0%)	245 (17.8%)	29 (20.9%)	12 (28.6%)	204 (17.2%)
Cognitive function score	47.6 ± 11.0	48.9 ± 10.4	49.2 ± 10.3	49.5 ± 10.2	48.8 ± 10.4	46.9 ± 10.8	45.0 ± 11.8	41.8 ± 12.7	44.8 ± 11.5	45.4 ± 11.6
Loneliness score	4.0 ± 1.4	3.9 ± 1.4	3.9 ± 1.3	3.9 ± 1.3	3.9 ± 1.3	4.3 ± 1.6	4.0 ± 1.5	4.2 ± 1.6	3.8 ± 1.4	4.0 ± 1.5
COPD	270 (6.9%)	153 (6.0%)	113 (5.0%)	53 (4.5%)	60 (5.4%)	40 (15.3%)	117 (8.5%)	20 (14.4%)	9 (20.5%)	88 (7.4%)

* Mean + standard deviation or n (%), COPD: chronic obstructive pulmonary disease

Appendix 3. Incident frailty risk for current and past smokers by multivariable logistic regression models (N=2,542).*

	Current smoker n=261		Past smoker n=1,113	
	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value
Model 1	1.93 (1.22-3.04)	0.005	0.86 (0.63-1.18)	0.35
Model 2	2.11 (1.32-3.37)	0.002	0.94 (0.67-1.31)	0.71
Model 3	1.56 (0.97-2.49)	0.06	0.92 (0.64-1.30)	0.62
Model 4	1.55 (0.96-2.50)	0.08	0.94 (0.65-1.35)	0.72

* Never smoker (n=1,168) as reference group
Model 1: Adjusted for age and gender
Model 2: Further adjusted for alcohol
Model 3: Further adjusted for education and wealth
Model 4: Further adjusted for cognitive function and loneliness

Appendix 4. Incident frailty risk for past smokers who quit within the last 10 years and who quit more than 10 years ago by multivariable logistic regression models (N=2,542).*

	Quit <= 10 years ago n=157		Quit > 10 years ago n=956	
	Odds Ratio (95%CI)	p value	Odds Ratio (95%CI)	p value
Model 1	0.88 (0.46-1.69)	0.70	0.86 (0.62-1.19)	0.36
Model 2	1.01 (0.51-2.00)	0.97	0.93 (0.65-1.32)	0.67
Model 3	0.85 (0.43-1.69)	0.64	0.93 (0.64-1.33)	0.68
Model 4	0.88 (0.43-1.79)	0.73	0.95 (0.65-1.38)	0.77

* Never smoker (n=1,168) as reference group
Model 1: Adjusted for age and gender
Model 2: Further adjusted for alcohol
Model 3: Further adjusted for education and wealth
Model 4: Further adjusted for cognitive function and loneliness

8.1.2 Alcohol

8.1.2.1 Alcohol systematic review 1

This is a pre-copyedited, author-produced version of an article accepted for publication in Age and Ageing following peer review. The version of record (Kojima G, Liljas A, Iliffe S, Jivraj S, Walters K. A systematic review and meta-analysis of prospective associations between alcohol consumption and incident frailty. Age and ageing. 2017 May 25;47(1):26-34. doi: 10.1093/ageing/afx086) is available online at: https://academic.oup.com/ageing/article-abstract/47/1/26/3854659?redirectedFrom=fulltext.

A Systematic Review and Meta-analysis of Prospective Associations between Alcohol Consumption and Incident Frailty.

Gotaro Kojima, MD[1]; Ann Liljas, MPH[1]; Steve Iliffe, FRCGP[1]; Stephen Jivraj, PhD[2]; Kate Walters, PhD[1].

[1] Department of Primary Care and Population Health, University College London, London, UK
[2] Department of Epidemiology and Public Health, University College London, London, UK

ABSTRACT

Background: Light-to-moderate alcohol consumption is protective against all-cause mortality and cardiovascular diseases. There is limited evidence in the literature on how alcohol consumption is related to frailty.

Methods: Five databases (Embase, Scopus, MEDLINE, CINAHL, PsycINFO) were systematically searched in July 2016 for prospective studies published between 2000 and 2016 examining baseline alcohol consumption and subsequent frailty risk among middle-aged or older community-dwelling population. Odds ratios (OR) for incident frailty were pooled using a random-effects model. Heterogeneity, methodological quality and publication bias were assessed.

Results: Of 926 studies identified by the systematic search, four studies were included (total n=44051,>=55years,66.2% alcohol users). OR of incident frailty for the highest (at least 24g of alcohol/day for men, 12g of alcohol/day for women) or the most frequent (≥5 days of drinking/week) alcohol consumption compared with no drinking were used for a meta-analysis. Pooled OR among three studies measuring alcohol consumption quantitatively showed that the highest alcohol consumption was associated with lower frailty risk (3studies:pooled OR=0.44,95%CI=0.19-1.00,p=0.05). Adding the other study measuring frequency of alcohol consumption made little change (4studies:pooled OR=0.61,95%CI=0.44-0.77,p<0.001). Two of the included studies suggested a possible U-shaped association with lowest risks for moderate drinkers. Heterogeneity was moderate in both analyses (I^2=52-67%). There was no evidence of publication bias.

Conclusions: This systematic review and meta-analysis study provides the first pooled evidence suggesting that heavier alcohol consumption is associated with lower incident frailty compared with no alcohol consumption among community-dwelling middle-aged and older people. However, this association may be due to unadjusted effect measures, residual confounding, 'sick quitter' effect or survival bias.

Key Points

- Some epidemiological studies showed health benefit in moderate alcohol use.
- The relationship of alcohol use to frailty is not clear.
- A systematic review identified four studies examining alcohol consumption and subsequent frailty risk in community-dwellers.
- The highest alcohol use was associated with lower incident frailty risk than no drinking (OR=0.61, 95%CI=0.49-0.77, p<0.001).
- Important limitations, such as unadjusted or residual confounding, 'sick-quitters' effect or survival bias, should be noted.

INTRODUCTION

Alcohol consumption has been shown to be a cause of more than 200 diseases, particularly, liver cirrhosis, cardiovascular diseases and various cancers.[1] Health risks associated with alcohol use also include alcohol dependence, potential alcohol-drug interactions, falls and related injuries.[1] Its harmful use has been reported to result in 3.3 million deaths worldwide each year.[1] However, some epidemiological studies have shown U-shaped or J-shaped associations between alcohol and all-cause mortality, with decreased mortality risks in light-to-moderate drinkers compared with non- and heavy drinkers.[2] This protective effect of alcohol consumption has been long debated and controversial, lacking underpinning robust scientific evidence.[3] Some recent studies attributed the lower mortality in low-to-moderate drinkers to various biases. Such biases include misclassification as abstainers of former drinkers who reduce alcohol consumption when ill known as the 'sick quitters' effect, inappropriate selection of reference group, and poor study designs or inadequate adjustment for important confounders. Controlling for these factors attenuated or eliminated the apparent protective effect of alcohol.[4-6] However, it is difficult to determine causal inferences using conventional statistical methods. A recent Mendelian randomisation analysis using 261,991 European individuals concluded that increased alcohol consumption is associated with increased risk for coronary heart disease (CHD) among drinkers of any alcohol amount, including light to moderate drinkers.[7] This suggests that there are no such protective effects for CHD. Moreover, in older people alcohol consumption may be more harmful even at a low level compared with younger population. This is because of higher blood alcohol concentration due to age-related decreased proportion of water compartment to total body mass or potential alcohol-drug interactions.[8]

Frailty is an age-related condition with increased vulnerability to adverse health outcomes,[9] such as falls, fracture, disability, hospitalization or institutionalisation,[10-14] as a consequence of depleted physiological reserve.[9] Alcohol consumption may potentially contribute to the development of frailty by accumulating health deficits due to alcohol-related medical conditions. Conversely, alcohol may exert such protective effects as in lowering risks of mortality[2] and prevent developing frailty. Therefore it is beneficial to know relationships between frailty and alcohol as alcohol may be a modifiable risk factor for frailty and an important target in preventative frailty interventions.

There has been little research on prospective associations between alcohol use and frailty. An earlier systematic review[15] searched for publications between 2001 and 2013 and found only one prospective study on this topic.[16] However since this time it is expected that there have been more related publications as frailty has been extensively studied in recent years. We thus aimed to systematically search the literature for currently available evidence on the associations of alcohol consumption with subsequent frailty risk and to conduct a meta-analysis to synthesise a pooled estimate of alcohol consumption for risk of frailty.

METHOD

Search strategy and selection criteria

We conducted a systematic review in July 2016 according to a protocol developed based on Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement.[17] The protocol has been registered with PROSPERO (Registration number: CRD42016045445). We searched five electronic databases (Embase, Scopus, MEDLINE, CINAHL Plus and PsycINFO) for studies published between 2000 and 2016. The publication period was decided based on the fact that the most widely used definition of frailty, so-called Fried phenotype, was published by Fried et al. using the Cardiovascular Health Study (CHS)

cohort in 2001.[18] Before then validated measurements of frailty were not generally used. The search was performed with an explosion function when available and without language restriction, using a combination of Medical Subject Heading (MeSH) terms and text (see **Appendix 1** in the supplementary data, available at *Age and Ageing* online). Reference lists of the relevant articles were also hand searched for additional studies. The forward citation search of the included studies was performed using Google scholar in December 2016. Authors of potentially eligible studies were contacted for additional data necessary for a meta-analysis.

Any prospective studies were considered potentially eligible if they examined baseline alcohol consumption, including quantity or frequency, and subsequent frailty risk among middle-aged or older population in the community. Randomised controlled trials, reviews, conference abstracts, editorials and comments were excluded. When the same cohort was used by multiple studies, the study with the largest size was included. Titles, abstracts and full-texts of the studies identified by the systematic literature search were screened by two researchers of the review team (GK and AL) independently for eligibility. We solved any disagreement by discussion.

Data Extraction

The data extracted from each eligible study were first author, study cohort name if any, publication year, location, sample size, proportion of women, age (mean and range), alcohol measure, frailty criteria, follow-up period and findings, including an effect measure and covariates for adjustment. Alcohol consumption was calculated and converted to amount of pure alcohol in grams.

Methodological Quality Assessment

The studies considered as eligible through title, abstract and title screening were assessed for methodological quality using 9 items of the Newcastle-Ottawa scale for cohort studies.[19] This scale is designed to evaluate methodological quality of a cohort study based on nine items over three domains: Selection (representativeness of the exposed cohort; selection of the non-exposed cohort; ascertainment of exposure; and demonstration that outcome of interest was not present at start of study), Comparability (comparability of cohorts on the basis of the design or analysis) and Outcome (assessment of outcome; was follow-up long enough for outcomes to occur; and adequacy of follow-up of cohorts). Although this scale has been widely used, it should be noted its inter-rater reliability has been questioned[20] and its external validation has yet to be examined.[21] A study meeting five items or more was considered to have adequate quality of methodology and was included in this review.

Statistical Analysis

When two or more studies provided the same or equivalent effect measures, such as odds ratio (OR) or hazard ratio, alcohol variables and frailty outcomes, it was attempted to combine the effect measures to calculate pooled risk estimates. Necessary data were enquired for by contacting authors. The presence and degree of heterogeneity across the studies were examined using the chi-square test and I^2 statistic, respectively. The I^2 values of 25%, 50% and 75% were considered as low, moderate and high heterogeneity, respectively. The fixed-effects model assumes that there is one true effect size among all the included studies while the random-effects model assumes that the true effect size may vary from study to study. We used a random-effects model to calculated pooled risk estimates using the generic inverse variance method because included studies were expected to have different alcohol measurements, frailty definitions, populations, follow-up periods and covariates for

adjustment. Publication bias was examined using Begg-Mazumdar's and Egger's tests.

The odds ratios of incident frailty were calculated based on the additional data provided by the authors of the original studies using StataSE 14 (StataCorp LP, College Station, Texas, USA). All meta-analyses were conducted using Review Manager 5 (version 5.2, The Cochrane Collaboration, Copenhagen, Denmark). $p<0.05$ was considered as statistically significant.

RESULTS

Selection Process

The systematic search of the five databases yielded 926 citations. Of these studies, 473 duplicates were excluded and 444 studies were excluded by screening title and abstract, leaving nine studies for full-text review. Five of the nine studies were further excluded because they did not use measured alcohol consumption (n=2), used a non-validated frailty definition (n=1), used the same cohort with a smaller number of participants (n=1) and was cross-sectional (n=1). All four studies used the CHS criteria [18] to define frailty with some modifications (see **Appendix 2** in the supplementary data, available at *Age and Ageing* online). Each study was considered to have adequate methodological quality based on the Newcastle-Ottawa Quality Assessment Scale (mean score=6.5, range=5-8).[16, 22-24] The selection and follow-up were considered to be the most important indicators for this review and were met by all the studies. (see **Appendix 3** in the supplementary data, available at *Age and Ageing* online)

Study Characteristics

Table 1 presents the characteristics of the included studies, including 44,051 community-dwelling people aged at least 55 years, and findings of interest. Three studies[22-24] were published in recent years of 2014-16 and one study[16] was published in 2005. Three studies[22-24] were from European countries and one was from the US.[16] The study size ranged from 1057[24] to 28,003.[16] One study[16] included only women from the Women's Health Initiative Observational Study and the other three studies[22-24] used mixed cohorts with a female proportion of 52.2-57.3%. Age ranges of the participants were ≥55 years,[23] >60 years,[22] 65-70 years[24] and 65-79 years.[16] All four studies[16, 22-24] used modified versions of CHS criteria. Follow-up periods ranged from 2[23] to 3.3 years.[22] One study[22] showed adjusted OR of incident frailty for alcohol quantity, and three studies[16, 23, 24] provided sufficient data, in the text or from the authors on request, to calculate crude OR of incident frailty for alcohol quantity[16, 24] or frequency.[23]

Ortola et al. used data of 2,086 community-dwelling men and women aged 60 and older in Spain to examine risk of incident frailty according to alcohol consumption.[22] Compared with non-drinkers, heavy drinkers (defined as consuming alcohol ≥40g/day for men and ≥24g/day for women) had a significantly lower risk of developing frailty over 3.3 years (OR=0.24, 95%CI=0.10-0.56).[22] Incident frailty risks of moderate drinkers (defined as consuming alcohol <40g/day for men and <24g/day for women) and ex-drinkers compared with non-drinkers were non-significant (OR=0.90, 95%CI=0.65-1.25; OR=1.04, 95%CI=0.64-1.68, respectively).[22]

A large multinational study involving nationally representative samples aged 55 and older from 11 European countries classified the participants as frail, pre-frail and non-frail according to modified CHS criteria and examined risk of worsening in frailty status (from non-frail to pre-frail or frail, or from pre-frail to frail) over two years.[23] Compared with

hardly ever/never alcohol use, consuming alcohol for 1-2 days, 3-4 days and 5-7 days per week was associated with 12-21% decreased risk of worsening frailty status (adjusted OR=0.84, 95%CI=0.73-0.96; adjusted OR=0.88, 95%CI=0.73-1.06; and adjusted OR=0.79, 95%CI=0.71-0.88, respectively) although drinking for 3-4 days per week did not reach statistical significance.[23]

The Women's Health Initiative Observational Study in the US followed 28,003 women aged 65-79 free of frailty at baseline for three years for incident frailty using a nominal multinomial logistic regression model.[16] Decreased risk was observed in women who consumed less than 1 drink per week (<2g of alcohol/day) (OR=0.87, 95%CI=0.77-0.97) and 1-14 drinks per week (2-28g of alcohol/day) (OR=0.69, 95%CI=0.61-0.77) while the risk of incident frailty was not significantly different in women who consumed more than 14 drinks per week (>28g of alcohol/day) (OR=0.93, 95%CI=0.74-1.16), compared with non drinkers.[16]

In a prospective study from Switzerland, 840 robust community-dwelling older people in a narrow age range of 65-70 years without any of the five CHS criteria components at baseline were observed three years later for newly developing any of the five components.[24] Non-drinkers were found to have twice the risk of developing any of the five components (adjusted OR=2.00, 95%CI=1.02-3.91, p=0.04) compared with light-to-moderate drinkers (men who consumed 12-168g of alcohol per week and women who consumed 12-84g of alcohol per week)).[24] Heavy drinkers, defined as consuming ≥144g of alcohol per week for women and ≥240g of alcohol per week for men, had no statistically significant lower risk (adjusted OR=0.73, 95%CI=0.34-1.58, p=0.43), compared with the light-to-moderate drinkers.[24] These ORs were adjusted for a number of potential confounders, including age, gender, education, smoking, self-rated health, comorbidity, cognitive impairment, functional status, previous alcohol-related problem and significant changes in alcohol during the follow-up, which may have been over-adjustment and resulted in the non-significant association for the heavy drinkers.[24]

Alcohol Use and Incident Frailty Risk

Three studies[16, 22, 24] measured alcohol consumption quantity and one study[23] used frequency measurement according to the number of days they were consuming alcohol. OR of incident frailty for the highest quantity of alcohol consumption or the most frequent alcohol use categories compared with no drinking was used for a meta-analysis. We initially pooled the OR of the three studies with the quantity alcohol measurements[16, 22, 24] using a random-effects model to show an almost significant reduced risk of incident frailty for the highest alcohol consumption (3 studies: pooled OR=0.44, 95%CI=0.19-1.00, p=0.05). Adding another study[23] using frequency of alcohol use increased the OR from 0.44 to 0.61 and the association became statistically significant (4 studies: pooled OR=0.61, 95%CI=0.49-0.77, p<0.001). (**Figure 2**)

Begg-Mazumdar's and Egger's tests assessed publication bias among the four studies[16, 22-24] and showed no evidence of publication bias (p value>0.10 for both tests).

DISCUSSION

The current study has systematically searched the literature for currently available evidence and combined risk of incident frailty according to the alcohol consumption in community-dwelling middle-aged and older population (55 years and above). The findings of the included studies were mixed, showing that heavy alcohol consumption was significantly

associated in three studies with decreased risk of incident frailty compared with those abstaining.[16, 22, 23] In contrast, heavy alcohol consumption was not associated with decreased risk of incident frailty in the remaining one study.[24] None of the included studies showed alcohol consumption significantly *increased* risk of incident frailty. The meta-analysis suggested that the highest quantity of alcohol consumption among the three studies[16, 22, 24] was associated with decreased risk of incident frailty with marginal statistical significance. After adding another study with alcohol drinking frequency,[23] although the heaviest drinking groups defined by quantity and frequency may not be the same, the association changed to statistically significant. This change may be due to the large sample size of the forth study (n=12,905).[23]

Possible U- or J-shaped associations were observed in two studies.[16, 23] One study created four groups based on the number of drinks per week, and moderate drinkers (1-14 drinks/week) had a lower frailty risk than non drinkers, light drinkers (<1 drink/week) or heavy drinkers (>14 drinks/week).[16] Another study used the number of days of drinking per week (hardly ever/never, 1-2 days/week, 3-4 days/week and 5-7days/week) and showed that those drinking 1-2 days a week had the lowest risk of worsening frailty and those drinking 3-4 days a week had the lowest risk of incident frailty.[23] **(Table 1)**

We included studies measuring alcohol consumption in quantity or frequency, however nature or patterns of alcohol consumption may also affect subsequent frailty status.[25] One of the included studies showed that a Mediterranean drinking pattern, defined as moderate alcohol intake (but no binge drinking) only with meals with ≥80% wine preference was significantly associated with lower incident frailty risks controlling for multiple confounders (OR=0.68, 95%CI=0.47-0.99).[22] Another study examined trajectories of frailty over eight years using the Frailty Index in 12,270 older people.[26] While this study did not measure alcohol quantity or frequency, it showed that those reporting concerns about alcohol use themselves or from relatives/friends were more likely to have worse frailty status at baseline and to belong to the worse frailty trajectory.[26]

Alcohol consumption may have some theoretical benefits against frailty however, in general, there has been no evidence to support therapeutic use of alcohol for non-drinkers and it cannot be advocated that non-drinkers should start drinking, especially given the potential harms from alcohol.[1] The decreased risk of incident frailty with heavier consumption suggested in the meta-analysis of this study may be a biased finding as for methodological reasons the pooled estimate was based on the mostly unadjusted risk estimates. The important confounders would include age, gender, education, socioeconomic status, smoking, depressive symptoms and cognitive function. In addition, alcohol quantity cut-points used by the included studies to define the highest alcohol consumption groups varied: ≥40g/day (men) and ≥24g/day (women),[22] and >27g/day.[16, 24] Binge drinkers, who may be at high risk of incident frailty and likely to be in the highest alcohol consumption categories, were not identified separately in any of the included studies. We therefore cannot draw any definite conclusions regarding the relationship of binge drinking to incident frailty, and this should be addressed in further research.

The underlying mechanisms for lower risk of incident frailty among the highest drinkers compared with non/past drinkers are not clear. Social components have been included in some multidimensional frailty criteria,[27] and social vulnerability can negatively affect both mental and physical health, contributing to the development of frailty.[28] Alcohol is often consumed socially and moderate consumption was shown to facilitate social bonding,[29]

and may possibly help construct or reinforce social support or network and prevent social isolation. Another possibility is a 'sick quitters' effect that sick individuals who quit drinking or would not start drinking were classified as non drinkers and healthier drinkers who continued to consume alcohol were classified as current drinkers, leading to an apparent lower risk of frailty among drinkers.[24] Other potential reasons would include residual confounding or survival bias. It should be also noted that the included studies are heterogeneous in terms of study populations, inclusion criteria and frailty assessment, therefore the results should be interpreted with caution. Casual analysis techniques of observational data, such as Mendelian randomisation analysis would be able to address at least some of these confounding factors and the issue of reverse causation (i.e. sick quitter hypothesis).

In terms of clinical implications, our findings would not support the reduction of alcohol consumption as an approach to reduce frailty risk. The research implications in light out of the findings of this review and the included studies are that further research in this area should both better define non-drinkers and heavy drinkers (e.g. those with harmful drinking levels) to tackle the potential heterogeneity of these two categories and explore reverse causality.

This study has some potential limitations. First, a relatively small number of studies were identified, probably because the association between alcohol and frailty has not yet been extensively studied. Especially given that we used a random-effect model, estimates of between-study variance may be less reliable based on the small number of studies.[30] Second, due to different cut-points or types of measurements of alcohol consumption employed by the studies, it was not possible to examine using a meta-analysis if there were U- or J-shaped associations between alcohol use and frailty like those between alcohol use and mortality. Third, while one study provided adjusted OR for incident frailty,[22] the other three studies did not, therefore unadjusted OR was calculated and used in the meta-analysis.[16, 23, 24] The adjustment for potential confounders would attenuate the association and could even change the direction of the effect. Fourth, 'non-drinkers' were used as a reference group in the included studies. This group may include people who have stopped drinking for health reasons. Therefore there remains potential for a 'sick-quitters' effect. Fifth, the follow-up periods of the included studies were short, between 2 to 3.3 years. It may need longer time to observe the development of frailty among the drinkers. Due to these important limitations, especially the unadjusted OR and 'sick-quitters' effect, the results of this review must be interpreted with caution. Further research should address these points, by adjusting for important confounding factors, including better definition of 'non-drinking' group and using a different reference group.

The robust methodology in accordance with the PRISMA statement is a strength to the study. The systematic review of the literature was furthermore comprehensive and extensive and included searching five databases, screening of title, abstract and full-text by two independent researchers, assessments of heterogeneity, methodological quality and publication bias of the included studies. Furthermore, the meta-analysis was conducted to provide the pooled evidence.

CONCLUSION

This systematic review and meta-analysis study provides the first pooled evidence suggesting that heavier alcohol consumption is associated with lower incident frailty compared with no alcohol use among community-dwelling middle-aged and older people. This might be

explained by reverse causality ('sick quitters', with individuals reducing/stopping alcohol consumption as they start to become more frail) or omitted variables hypothesis (uncontrolled confounding variables that explain the relationship). Future research should both fully adjust for potential confounding factors and examine various measures of alcohol intake, such as quantity, frequency, type or patterns (including harmful drinking), in relation to frailty.

CONFLICTS OF INTEREST

None.

ACKNOWLEDGEMENT

We are grateful to the authors for sharing the data.[23, 24]

Declaration of Sources of Funding

GK is funded by a University College London (UCL) Overseas Research Scholarship, which did not have any influence on the study design, the collection, analysis, and interpretation of data, the writing of the article or the decision to submit it for publication.

REFERENCES

1. World Health Organization, Management of substance abuse. [31 July 2016]; Available from: http://www.who.int/substance_abuse/en/.
2. Jayasekara H, English DR, Room R, MacInnis RJ. Alcohol consumption over time and risk of death: a systematic review and meta-analysis. Am J Epidemiol. 2014; 179: 1049-59.
3. Nova E, Baccan GC, Veses A, Zapatera B, Marcos A. Potential health benefits of moderate alcohol consumption: current perspectives in research. Proc Nutr Soc. 2012; 71: 307-15.
4. Stockwell T, Zhao J, Panwar S, et al. Do "Moderate" Drinkers Have Reduced Mortality Risk? A Systematic Review and Meta-Analysis of Alcohol Consumption and All-Cause Mortality. J Stud Alcohol Drugs. 2016; 77: 185-98.
5. Knott CS, Coombs N, Stamatakis E, Biddulph JP. All cause mortality and the case for age specific alcohol consumption guidelines: pooled analyses of up to 10 population based cohorts. BMJ. 2015; 350: h384.
6. Naimi TS, Brown DW, Brewer RD, et al. Cardiovascular risk factors and confounders among nondrinking and moderate-drinking U.S. adults. Am J Prev Med. 2005; 28: 369-73.
7. Holmes MV, Dale CE, Zuccolo L, et al. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. BMJ. 2014; 349: g4164.
8. Heuberger RA. Alcohol and the older adult: a comprehensive review. J Nutr Elder. 2009; 28: 203-35.
9. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013; 381: 752-62.
10. Kojima G. Frailty as a Predictor of Future Falls Among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. J Am Med Dir Assoc. 2015; 16: 1027-33.
11. Kojima G. Frailty as a predictor of fractures among community-dwelling older people: A systematic review and meta-analysis. Bone. 2016; 90: 116-22.
12. Kojima G. Frailty as a predictor of hospitalisation among community-dwelling older people: a systematic review and meta-analysis. J Epidemiol Community Health. 2016; 70: 722-9.
13. Kojima G. Frailty as a Predictor of Nursing Home Placement Among Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. J Geriatr Phys Ther. 2016.

14. Kojima G. Frailty as a Predictor of Disabilities among Community-Dwelling Older People: A Systematic Review and Meta-analysis. Disabil Rehabil. 2016.
15. Mello Ade C, Engstrom EM, Alves LC. Health-related and socio-demographic factors associated with frailty in the elderly: a systematic literature review. Cad Saude Publica. 2014; 30: 1143-68.
16. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. J Am Geriatr Soc. 2005; 53: 1321-30.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009; 339: b2535.
18. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56: M146-56.
19. Wells GA, Shea D, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [31 July, 2016]; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
20. Hartling L, Milne A, Hamm MP, et al. Testing the Newcastle Ottawa Scale showed low reliability between individual reviewers. J Clin Epidemiol. 2013; 66: 982-93.
21. Harrison JK, Reid J, Quinn TJ, Shenkin SD. Using quality assessment tools to critically appraise ageing research: a guide for clinicians. Age Ageing. 2016.
22. Ortola R, Garcia-Esquinas E, Leon-Munoz LM, et al. Patterns of Alcohol Consumption and Risk of Frailty in Community-dwelling Older Adults. J Gerontol A Biol Sci Med Sci. 2016; 71: 251-8.
23. Etman A, Kamphuis CB, van der Cammen TJ, Burdorf A, van Lenthe FJ. Do lifestyle, health and social participation mediate educational inequalities in frailty worsening? Eur J Public Health. 2015; 25: 345-50.
24. Seematter-Bagnoud L, Spagnoli J, Bula C, Santos-Eggimann B. Alcohol Use and Frailty in Community-Dwelling Older Persons Aged 65 to 70 Years. J Frailty Aging. 2014; 3: 9-14.
25. Khadjesari Z, Marston L, Petersen I, Nazareth I, Walters K. Alcohol consumption screening of newly-registered patients in primary care: a cross-sectional analysis. Br J Gen Pract. 2013; 63: e706-12.
26. Chamberlain AM, St Sauver JL, Jacobson DJ, et al. Social and behavioural factors associated with frailty trajectories in a population-based cohort of older adults. BMJ Open. 2016; 6: e011410.
27. Gobbens RJ, van Assen MA, Luijkx KG, Wijnen-Sponselee MT, Schols JM. Determinants of frailty. J Am Med Dir Assoc. 2010; 11: 356-64.
28. Peek MK, Howrey BT, Ternent RS, Ray LA, Ottenbacher KJ. Social support, stressors, and frailty among older Mexican American adults. J Gerontol B Psychol Sci Soc Sci. 2012; 67: 755-64.
29. Sayette MA, Creswell KG, Dimoff JD, et al. Alcohol and group formation: a multimodal investigation of the effects of alcohol on emotion and social bonding. Psychol Sci. 2012; 23: 869-78.
30. Guolo A. Higher-order likelihood inference in meta-analysis and meta-regression. Stat Med. 2012; 31: 313-27.

Figure 1. PRISMA Flowchart

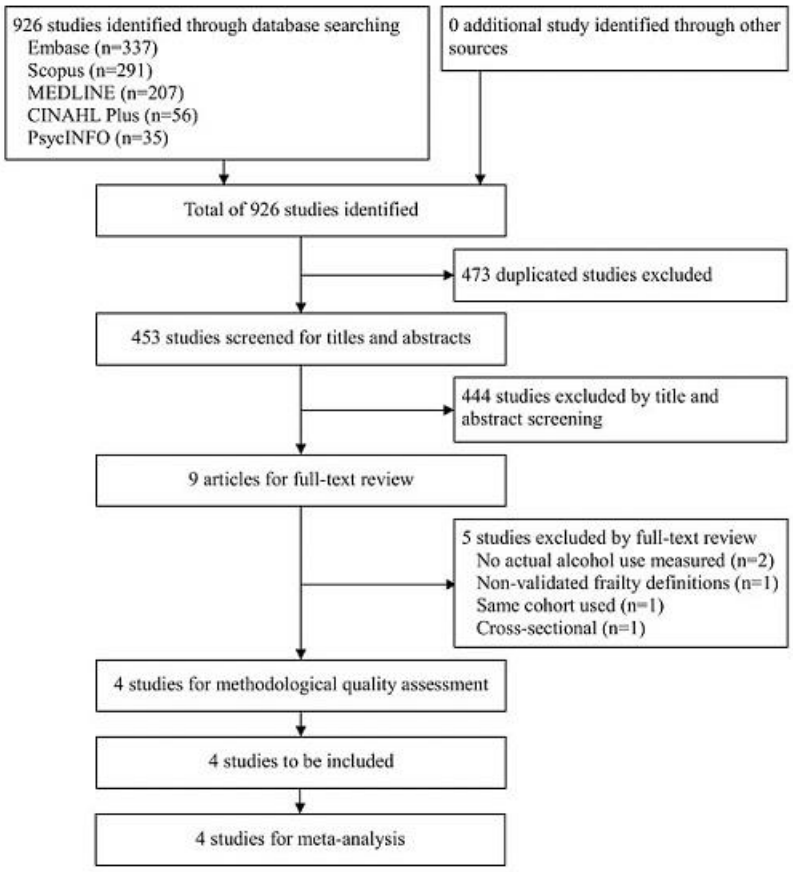


Table 1. Summary of studies examining associations between alcohol and frailty.

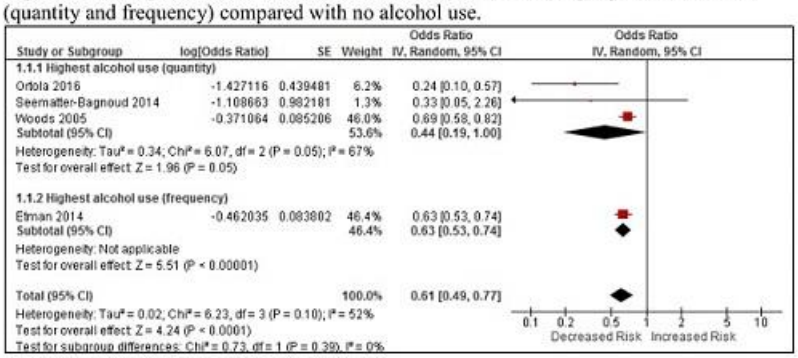
Author/Study	Year	Location	Sample size*	Female (%)*	Age (range)*	Frailty criteria	Follow-up period	Alcohol measure	findings
Ortola et al. ENRICA	2016	Spain	2,086	52.2%†	68.5† (≥60)	mCHS	3.3 years	Usual consumption of alcoholic beverages in the previous year estimated with validated diet history	Logistic regression models for incident frailty adjusted for age, gender, education, smoking, time watching TV, leisure-time physical activity, household physical activity, Trichopoulou index, BMI, cardiovascular disease, diabetes, respiratory disease, osteomuscular disease, depression, IADL, SF-12 physical and mental component summary scores (nondrinker as reference) aOR=1.04, 95%CI=0.64-1.68 for ex-drinker aOR=0.90, 95%CI=0.65-1.25 for <40g (men) or <24g (women) of alcohol/day aOR=0.24, 95%CI=0.10-0.56 for ≥40g (men) or ≥24g (women) of alcohol/day
Etman et al. SHARE	2014	11 European countries‡	12,905	54.3%	67.6 (≥55)	mCHS	2 years	The number of days per week when participants were drinking alcohol during the last six months	Logistic regression models for worsening frailty compared with no change in frailty status adjusted for age, gender, education, baseline frailty and country (hardly ever/never drinker as reference, N=14,082) aOR=0.84, 95%CI=0.73-0.96 for drinking for 1-2 days per week aOR=0.88, 95%CI=0.73-1.06 for drinking for 3-4 days per week aOR=0.79, 95%CI=0.71-0.88 for drinking for ≥5 days per week Unadjusted logistic regression models for incident frailty (calculated, non drinker as reference, N=12,905) OR=0.45, 95%CI=0.37-0.55 for drinking for 1-2 days per week OR=0.35, 95%CI=0.25-0.49 for drinking for 3-4 days per week OR=0.63, 95%CI=0.54-0.75 for drinking for ≥5 days per week
Seematter-Bagnoud et al. Lausanne cohort 65+	2014	Switzerland	1057	57.3%	67.0 (65-70)	mCHS	3 years	The average number of standard drinks (wine, beer, spirits) consumed per week was estimated using the AUDIT-C questionnaire.	Unadjusted logistic regression models for incident frailty (calculated, non drinker as reference) OR=0.72, 95%CI=0.15-3.37 for 1-14 drinks (men) or 1-7 drinks (women)/week (or 1.7-24g (men) or 1.7-12g (women) of alcohol/day) OR=0.33, 95%CI=0.05-2.35 for >14 drinks (men) or >7 drinks (women)/week (or >24g (men) or >12g (women) of alcohol/day)
Woods et al. WHI-OS	2005	USA	28,003	100.0%	- (65-79)	mCHS	3 years	Self-report at baseline	Multinomial logistic regression models (non drinker as reference) OR=0.87, 95%CI=0.77-0.97 for <1 drink/week (or <2g of alcohol/day) OR=0.69, 95%CI=0.61-0.77 for 1-14 drinks/week (or 2-28g of alcohol/day) OR=0.93, 95%CI=0.74-1.16 for >14 drinks/week (or >28g of alcohol/day) Unadjusted logistic regression models for incident frailty (calculated, non drinker as reference) OR=0.80, 95%CI=0.74-0.78 for <1 drink/week (or <2g of alcohol/day) OR=0.54, 95%CI=0.49-0.58 for 1-14 drinks/week (or 2-28g of alcohol/day) OR=0.69, 95%CI=0.58-0.81 for >14 drinks/week (or >28g of alcohol/day)

* Cohort used for analysis of interest, or entire cohort.
† Calculated from available data
‡ Sweden, Denmark, Germany, the Netherlands, Belgium, Switzerland, Austria, France, Italy, Spain and Greece

95%CI= 95% confidence interval
aOR: Adjusted odds ratio
ENRICA: El Estudio de Nutrición y Riesgo Cardiovascular en España
mCHS: Modified Cardiovascular Health Study criteria
OR: Unadjusted odds ratio

SHARE: Survey on Health, Ageing, and Retirement in Europe
WHI-OS: Women's Health Initiative Observational Study

Figure 2. Forest plots of odds ratio of incident frailty risk according highest alcohol use (quantity and frequency) compared with no alcohol use.



Appendix 1. Search strategy.

	Medline
1	exp Alcohols/
2	exp Ethanol/
3	exp Drinking Behavior/
4	exp Alcohol Drinking/
5	alcohol*.mp.
6	ethanol.mp.
7	drink*.mp.
8	frail*.mp.
9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
10	8 AND 9
	Embase
1	exp alcohol consumption/
2	exp alcohol/
3	exp drinking behavior/
4	alcohol*.mp.
5	ethanol.mp.
6	drink*.mp.
7	frail*.mp.
8	1 OR 2 OR 3 OR 4 OR 5 OR 6
9	7 AND 8
	PsycINFO
1	exp ALCOHOLS/
2	exp ETHANOL/
3	exp ALCOHOL DRINKING PATTERNS/
4	exp DRINKING BEHAVIOR/
5	alcohol*.mp.
6	ethanol.mp.
7	drink*.mp.
8	frail*.mp.
9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
10	7 AND 8
	CINAHL
1	Ethanol+
2	Alcohol Drinking+
3	Drinking Behavior+
4	Alcohol Drinking+
5	alcohol*
6	ethanol
7	drink*
8	Frailty Syndrome
9	frail*
10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
11	8 OR 9
12	10 AND 11
	Scopus
1	alcohol*
2	ethanol
3	drink*
4	frail*
5	1 OR 2 OR 3
6	4 AND 5

Appendix 2. Modifications of Cardiovascular Health Study criteria.

	Weight loss	Exhaustion	Weakness	Slowness	Low Physical Activity
Original by Fried et al.	Answering YES to "In the last year, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?" or more than 5% of unintentional weight loss since last year.	Reporting "a moderate amount of the time (3–4 days)" or "most of the time" in the last week to either of two questions from the Center for Epidemiological Studies-Depression Scale: "I felt that everything I did was an effort" or "I could not get going".	Lowest 20% of handgrip strength stratified by gender and BMI quartiles (Cutoff for men: <29kg for BMI< 24, <30kg for BMI 24.1-26, <30kg for BMI 26.1-28, <32kg for BMI>28, For women: <17kg for BMI<23, <17.3kg for BMI 23.1-26, <18kg for BMI 26.1-29, <21kg for BMI>29).	Slowest 20% of usual walk speed stratified by gender and medium height (Cutoff time to walk 15 feet for men: >7 seconds for height<173 cm, >6 seconds for height>173 cm, For women: >7 seconds for height<159 cm, >6 seconds for height>159 cm).	Lowest 20% kilocalorie based on the short version of the Minnesota Leisure Time Activity questionnaire stratified by gender (Cutoff for men: <383 Kcal per week, For women: <270 Kcal per week).
Ortola et al.	Not included	Same as original.	Same as original.	Slowest 20% of 3-meter walking speed test stratified by gender and height (Cutoff walking speed for men: <0.47 m/s for height<=173cm, <0.45 m/s for height>173cm, For women: <0.37 m/s for height<=159cm, <0.40 m/s for height>159cm).	Walking <=2.5 hours per week for men and <=2 hours per week for women.
Etman et al.	Answers 'less' or 'diminution in desire for food' to 'what has your appetite been like?' or answering 'less' to 'So you have been eating more, or less than usual?'.	Answering 'yes' to 'In the last month, have you had too little energy to do the things you wanted to do?'.	Same as original.	Having difficulty walking 100 meters or climbing one flight of stairs.	Answering 'one to three times a month' or 'hardly ever or never' to 'How often do you engage in activities that require a low or moderate state of energy, such as walking, gardening, cleaning the car, or doing a walk?'
Seematter-Bagnoud et al.	Self-reported unintentional weight loss during the last 12 months.	Self-reported lack of energy and fatigue during the last 4 weeks.	Same as original.	Same as original.	Doing less than 20 minutes of sports per week and walking less than 90 minutes per week, unless doing a high amount of daily usual physical activity such as climbing stairs or lifting weights.
Woods et al.	Unintentional weight loss of more than 5% of body weight in the previous 2 years.	Lowest 25% of the Rand-36 vitality scale.	For both weakness and slowness, lowest 25% of the Rand-36 physical function scale.		Lowest 25% of kilocalorie of energy expended in a week on leisure time activity.

Appendix 3. Methodological quality assessment using the Newcastle-Ottawa Quality Assessment Scale for cohort studies.

Author/year	Selection 1	Selection 2	Selection 3	Selection 4	Comparability 1	Comparability 2	Outcome 1	Outcome 2	Outcome 3	total
Ortola et al.	1	1	0	1	1	1	1	1	1	8/9
Etman et al.	1	1	0	n/a	1	1	1	1	0	6/8
Seematter-Bagnoud et al..	1	1	0	1	1	1	1	1	0	7/9
Woods et al.	1	1	0	1	0	0	1	1	0	5/9

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average middle-aged or older population in the community *
   b) somewhat representative of the average middle-aged or older population in the community *
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort *
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) *
   b) structured interview *
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes *
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for age and gender *
   b) study controls for any additional factor * (such as education, socioeconomic status and smoking)

Outcome

1) Assessment of outcome
    a) independent blind assessment *
    b) record linkage *
    c) self report
    d) no description
2) Was follow-up long enough for outcomes to occur
    a) yes (select an adequate follow up period for outcome of interest) *
    b) no
3) Adequacy of follow up of cohorts
    a) complete follow up - all subjects accounted for *
    b) subjects lost to follow up unlikely to introduce bias - small number lost - > 10 % follow up, or description provided of those lost) *
    c) follow up rate < 10% and no description of those lost
    d) no statement

8.1.2.2 Alcohol systematic review 2 (Open access)

Letter

DOI: 10.5582/bst.2017.01237

Non-linear association between alcohol and incident frailty among community-dwelling older people: A dose-response meta-analysis

Gotaro Kojima*, Steve Iliffe, Ann Liljas, Kate Walters

Department of Primary Care and Population Health, University College London, London, UK.

Summary **A recent systematic review and meta-analysis study suggested that higher alcohol consumption is associated with lower risks for frailty. However the apparent protective effect may not be true because of some limitations. Therefore we further explored potential linear and non-linear associations using a two-stage dose-response meta-analysis. Restricted cubic splines were applied with three fixed knots at percentiles (10%, 50%, and 90%). A two-stage dose-response meta-analysis showed a significant non-linear association (*p* for non-linearity < 0.001); incident frailty risk decreased until around 15 g/day of alcohol consumption and increased thereafter. This suggests that while moderate alcohol consumption is associated with a lower risk of frailty, at higher consumption levels this apparent protect effect is lost. Given these findings, non-linear associations should be considered in future research on alcohol and frailty.**

Keywords: Frailty, alcohol, dose-response meta-analysis, older people

Beneficial effects of light-to-moderate alcohol consumption against various diseases suggested by numerous population-based studies have been controversial and debated in the literature (*1*). There has been limited evidence regarding whether light-to-moderate alcohol consumption is also protective against frailty (*2*). Frailty is a state characterized by decreased physiological reserve resulting from age-related accumulated deficits across multiple systems, with increased risks of various negative health outcomes (*3*). Although a few prospective cohort studies have examined associations between alcohol and risk of frailty, the results are mixed and inconclusive (*4-6*). Our recent systematic review and meta-analysis study suggested that alcohol consumption is associated with lower risks for frailty (pooled odds ratio (OR) of incident frailty among the highest alcohol use categories compared with non-drinkers = 0.44, 95% confidence interval (CI) = 0.19-1.00, $p = 0.05$) (*2*). However, only data of the heaviest drinkers were used in the main meta-analysis and the association of intermediate alcohol use categories with incident frailty has not been investigated (*2*). Therefore, to further explore potential linear and non-linear associations between alcohol consumption and incident frailty risk, we conducted a two-stage dose-response meta-analysis using the data from the same longitudinal cohort studies.

The data used come from three prospective studies examining associations between quantity of alcohol consumption and incident frailty (*4-6*), identified in our previous systematic review and meta-analysis study, that provided data on frailty risk according to quantity of alcohol consumption (*2*). A value (in grams of alcohol per day) assigned to each alcohol consumption category was based on a mid-point of the upper and lower boundary values of the category. When the ranges of the alcohol consumption were different by gender in the same category, the assigned value was modified based on the gender proportion in the category. For the highest alcohol consumption category with only the lower boundary value, the boundary value multiplied by 1.2 was assigned (*7*). All three studies included had defined frailty according to the Fried phenotype (*8*). Crude relative risk (RR) and 95% CI of incident frailty for each alcohol consumption category compared with non-drinking category were calculated and used for the meta-

Released online in J-STAGE as advance publication October 11, 2017.

*Address correspondence to:
Dr. Gotaro Kojima, Department of Primary Care and Population Health, University College London (Royal Free Campus), Rowland Hill Street, London, NW3 2PF, UK.
E-mail: gotarokojima@yahoo.co.jp

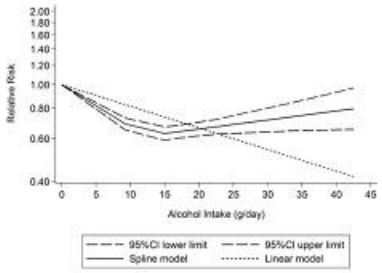


Figure 1. Dose-response linear and non-linear relationships between alcohol consumption and incident frailty risk. CI: confidence interval.

analyses.

Potential linear and non-linear dose-response associations between alcohol consumption and incident frailty were estimated using a two-stage dose-response meta-analysis (*9*). A random-effect model was used when heterogeneity was detected using the chi-square test, and a fixed-effect model was used otherwise. For the non-linear association, in the first stage, the restricted cubic spline method was applied with three fixed knots at percentiles (10%, 50%, and 90%) of the alcohol consumption distribution. In the second stage, the regression coefficients and the variance/covariance matrix were combined. Non-linearity was examined by the null hypothesis that the coefficient of the second spline is equal to zero. All statistical analyses were conducted using StataSE 14 (StataCorp LP, College Station, Texas, USA).

We included three studies examining incident frailty risks according to alcohol consumption among a total of 30,929 community-dwelling older people (age ≥ 60 years old) with 4,433 incident frailty cases (*4-6*). These studies categorized alcohol consumption into three or four categories with various cut-points (*4-6*).

For the linear association, a two-stage fixed-effect dose-response meta-analysis was conducted because of absence of significant heterogeneity ($p = 0.27$). There was a significant inverse linear association (pooled RR = 0.83 per 10 g/day increase in alcohol, 95% CI = 0.80-0.85, $p < 0.001$). However there was also a significant non-linear association between alcohol consumption and incident frailty risk (p for non-linearity < 0.001). In the model, the incident frailty risk by alcohol consumption showed a U-shaped association. The frailty risk decreased until around 15 g/day of alcohol consumption and increased thereafter. Predicted linear and non-linear incident frailty risk estimates by alcohol consumption are depicted in Figure 1. The non-linear model had a better fit, based on Akaike's information criterion (AIC) and Bayesian information criterion (BIC); AIC and BIC of the linear model were 82.6 and 81.7, respectively, while AIC and BIC of the non-linear model were 21.5 and 21.4, respectively.

We found a significant non-linear dose-response association between alcohol consumption and incident frailty among community-dwelling older people. Our analysis showed a U-shaped association, with the lowest risk with drinking around 15 g of alcohol per day (equivalent to approximately 2 UK units of alcohol or approximately 1 standard drink in the US). The incident frailty risk slowly increased at consumption above 15 g/day, however remained below that of non-drinkers until the highest alcohol value in our dataset (40 g/day).

These results should be interpreted with caution because of some limitations. First, only three studies were included in the analysis. The small number of the included studies also limited us in undertaking flexible non-linear dose-response analysis with more knots. Second, the highest alcohol consumption category was approximately 40 g/day (*4*) and it was not possible to examine frailty risk above that limit. Alcohol consumption less than 40 g/day may be too low to cause any clinically meaningful worsening of frailty even in older people (*10*). Third, all RRs used in the dose-response meta-analyses were unadjusted since they were calculated based on data from the included studies. Therefore our findings may be confounded by important factors like age, gender, smoking and socioeconomic status.

More research on the associations between alcohol consumption and frailty is needed. Future research should consider using higher cut-points to categorize alcohol consumption than 40 g/day, and use such statistical methods to examine potential dose-response non-linear associations. It is also vital to that future studies control for potential confounders.

Acknowledgements

We are grateful to the authors of the original study for sharing the data (*5*).

Funding

GK is funded by a University College London (UCL) Overseas Research Scholarship, which did not have any influence on the study design, the collection, analysis, and interpretation of data, the writing of the article or the decision to submit it for publication.

References

1. Nova E, Baccan GC, Veses A, Zapatera B, Marcos A. Potential health benefits of moderate alcohol consumption: Current perspectives in research. Proc Nutr Soc. 2012; 71:307-315.
2. Kojima G, Liljas A, Iliffe S, Jivraj S, Walters K. A systematic review and meta-analysis of prospective associations between alcohol consumption and incident

frailty. Age Ageing. 2017;1-9.
3. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013; 381:752-762.
4. Ortola R, Garcia-Esquinas E, Leon-Munoz LM, Guallar-Castillon P, Valencia-Martin JL, Galan I, Rodriguez-Artalejo F. Patterns of alcohol consumption and risk of frailty in community-dwelling older adults. J Gerontol A Biol Sci Med Sci. 2016; 71:251-258.
5. Seematter-Bagnoud L, Spagnoli J, Bula C, Santos-Eggimann B. Alcohol use and frailty in community-dwelling older persons aged 65 to 70 years. J Frailty Aging. 2014; 3:9-14.
6. Woods NF, LaCroix AZ, Gray SL, Aragaki A, Cochrane BB, Brunner RL, Masaki K, Murray A, Newman AB; Women's Health Initiative. Frailty: Emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. J Am Geriatr Soc. 2005; 53:1321-1330.
7. Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. Epidemiology. 1993; 4:218-228.
8. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56:M146-156.
9. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: Examples, an evaluation of approximations, and software. Am J Epidemiol. 2012; 175:66-73.
10. Crome I, Li TK, Rao R, Wu LT. Alcohol limits in older people. Addiction. 2012; 107:1541-1543.

(Received September 23, 2017; Revised October 3, 2017; Accepted October 5, 2017

8.1.2.3 Alcohol ELSA analysis

This is an epubed version of an article accepted for publication in Journal of American Medical Directors Association following peer review (Kojima G, Jivraj S, Iliffe S, Falcaro M, Liljas A, Walters K. Alcohol Consumption and Risk of Incident Frailty: The English Longitudinal Study of Aging. 2018 2018 Nov 28. pii: S1525-8610(18)30584-X. doi: 10.1016/j.jamda.2018.10.011) available online at: https://www.jamda.com/article/S1525-8610(18)30584-X/fulltext

I retain the right to include in a thesis provided not published commercially as per Elesvier's policies on journal author rights.

8.1.3 Fruit and vegetable

8.1.3.1 Fruit and vegetable systematic review (Open access)

J Nutr Health Aging. 2018;

FRUIT AND VEGETABLE CONSUMPTION AND FRAILTY: A SYSTEMATIC REVIEW

G. KOJIMA[1], C. AVGERINOU[1], S. ILIFFE[1], S. JIVRAJ[2], K. SEKIGUCHI[3], K. WALTERS[1]

1. Department of Primary Care and Population Health, University College London, London, UK; 2. Department of Epidemiology and Public Health, University College London, London, UK; 3. Department of General Medicine, Shinshu University School of Medicine, Matsumoto, Nagano, Japan. Corresponding author: Gotaro Kojima, MD, Department of Primary Care and Population Health, University College London (Royal Free Campus), Rowland Hill Street, London, NW3 2PF, UK, Phone: +44 (0)20 7794 0500, Fax: +44 (0)20 7472 6871, Email: gotarokojima@yahoo.co.jp

Abstract: *Objective:* To identify currently available evidence on fruit and vegetable consumption in association with frailty by conducting a systematic review of the literature and to summarise and critically evaluate it. *Design:* Systematic review. *Setting:* Four electronic databases (Embase, MEDLINE, CINAHL and PsycINFO) were systematically searched in August 2017 for observational cohort studies providing cross-sectional or prospective associations between fruit and vegetable consumption and frailty risks. Additional studies were searched by manually reviewing the reference lists of the included studies and related review papers and conducting forward citation tracking of the included studies. The methodological quality of prospective studies was assessed using the Newcastle-Ottawa scale. *Participants:* Community-dwelling general populations. *Results:* A total of 6251 studies were identified, of which five prospective studies with follow-up periods of 2-10.5 years and two cross-sectional studies were included. Among the five prospective studies, three had adequate methodological quality. Because of different measurements and statistical methodologies, a meta-analysis was not possible. The two studies of good quality showed that fruit and vegetable consumption was mostly associated with lower risk of incident frailty. The other study as a sub-analysis retrospectively examined baseline fruit and vegetable consumption of those who developed frailty and those who did not at follow-up and showed no significant associations. *Conclusions:* Although good quality studies on this topic are scarce, there is some suggestion that higher fruit and vegetable consumption may be associated with lower frailty risk. More high quality research is needed.

Key words: Frailty, fruits, vegetables, nutrition, diet.

Introduction

Frailty, a geriatric syndrome characterised by an age-related decrease in physiological reserve and an increase in vulnerability to stressors, commonly affects older people (1). Approximately 10% of persons aged 65 years or older and at least a quarter of those aged over 85 years are frail (2). Frailty is associated with various negative health outcomes, including falls, fractures, hospitalization, nursing home placement, disability, dementia, impaired quality of life and mortality (1). Due to the ageing world population, the number of frail older people is projected to increase (1). In light of the serious consequences of frailty, it is a priority of all healthcare professionals to prevent the development of frailty and delay its progression. For these purposes, an effective strategy is required to identify significant risk factors for frailty, which would lead to effective interventions or treatments.

In recent years, different aspects of diet have been studied in frailty research (3). Intakes of various macro- and micronutrients as well as healthy dietary patterns, such as Mediterranean diet, have been found to be associated with lower frailty risks (4, 5). However it is not well-established what components within these broad dietary patterns contribute to this association. Fruits and vegetables are recognised as an important part of a healthy diet for all ages. Fruits and vegetables are important sources of vitamins, mineral, fibre, anti-oxidants and anti-inflammatory agents, and guidelines recommend adequate amount should be consumed (6). Increased fruit and vegetable intakes are associated with a lower risk of cardiovascular diseases (7, 8), various types of cancer (9, 10), and mortality (11). Although it can be hypothesised that fruit and vegetable intake is also beneficial against frailty, the body of knowledge on the association between fruit and vegetable intake and frailty in the literature is conflicting and not well synthesised (3). Therefore, we aimed to identify currently available evidence on fruit and vegetable consumption in association with frailty by conducting a systematic review of the literature and to summarise and critically evaluate it.

Method

Data source and search strategy

A systematic review of the literature was performed in August 2017 based on a protocol (PROSPERO registration number: CRD42017057165) developed a priori according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement (12). Four electronic databases (Embase, MEDLINE, CINAHL Plus and PsycINFO were systematically searched with explosion functions if available between 2000 and August 2017. The beginning of the search period, 2000, was chosen because the Cardiovascular Health Study frailty criteria, the most widely used frailty criteria, were published in 2001 (13). No language restriction was

Received March 15, 2018
Accepted for publication March 16, 2018
Published online June 26, 2018. http://dx.doi.org/10.1007/s12603-018-1069-6

imposed. We used a combination of Medical Subject Heading (MeSH) terms and text keywords as follows: Fruit (MeSH) OR Vegetables (MeSH) OR Fruit Vegetable(s) (MeSH) OR Fruit and Vegetable Juice(s) (MeSH) Fruit Juice(s) (MeSH) OR Vegetable Juice (MeSH) OR Antioxidant(s) (MeSH) OR Diet(s) (MeSH) OR Diet Therapy (MeSH) OR Nutrition (MeSH) OR Nutrition Therapy (MeSH) OR fruit* OR vegetable* OR anti-oxidant* OR antioxidant* OR diet* OR nutrition* AND frailty related terms, including Frail Elderly (MeSH) OR Frailty Syndrome (MeSH) OR frail*. The reference lists of the included studies and related review papers were manually searched for additional studies. The forward citation tracking of the included studies was conducted using Google Scholar (http://scholar.google.com/).

Study selection

Any original papers of observational cohorts providing cross-sectional or prospective associations between fruit and vegetable consumption and frailty were considered. Selective samples unrepresentative of community-dwelling people in general, such as hospitalised patients or those with heart failure, were excluded. Studies reporting fruit and vegetable consumption as a quantity or the consumption frequency of fruits alone, vegetables alone or fruits and vegetables combined were included. Those including a specific type of fruit or vegetable only, or those concerned with dietary patterns including fruit and vegetable consumption as part of a wider diet including other nutrients (e.g. the Mediterranean diet) were excluded unless they reported on the associations between fruit and/or vegetable consumption and frailty separately. To be included, studies had to define frailty by original or modified version of validated criteria designed to measure frailty. Randomised controlled trials, reviews, conference abstracts, editorials, comments and letters were excluded. One author (GK) first screened for eligibility all study titles and then the abstracts and full texts of the studies identified by the systematic review. The second author (CA) independently screened the full-texts for eligibility. We solved any disagreement by discussion.

Data extraction

A standardised data collection form was used to extract data including first author, publication year, cohort name, location, sample size, proportion of women, age, frailty criteria, follow-up period, fruit and vegetable measurement method and findings.

Methodological quality assessment

The methodological quality of prospective studies was assessed by two authors (GK and KS) independently using the Newcastle-Ottawa scale for cohort studies (14), which consists of nine items covering three domains: Selection (representativeness of the exposed cohort; selection of the non-exposed cohort; ascertainment of exposure; and demonstration that outcome of interest was not present at start of study), Comparability (comparability of cohorts on the basis of the design or analysis) and Outcome (assessment of outcome; was follow-up long enough for outcomes to occur; and adequacy of follow-up of cohorts). A study meeting five items or more was considered to have adequate methodological quality. Disagreements were solved by discussion.

Data analysis

We aimed to conduct a meta-analysis to combine findings of the included studies if it was possible, otherwise, however, we would pursue a narrative review.

Results

Selection process

Supplementary Figure is the PRISMA flowchart showing the study selection process and results of the systematic review. The search of the four databases identified a total of 6251 studies. After excluding duplicates and studies that were considered not eligible through screening of the titles and abstracts, full-texts of nine potentially eligible studies were reviewed. Two studies were excluded because these studies did not examine fruit and vegetable consumption but dietary patterns, leaving seven studies for this review.

Study characteristics

Table 1 shows the characteristics of the seven included studies (15-21). Five studies were prospective with follow-up periods of 2-10.5 years (15-19) and two studies were cross-sectional (20, 21). One study each was from France (16), Spain (15) the US (18), the UK (19), Netherlands (20) and Japan. (21) One study used a combination of three cohorts (Three-City Study, the Senior-ENRICA and the Integrated Multidisciplinary Approach cohorts) (17). The Three-City Study and the Senior-ENRICA cohorts were also used individually by Rahi et al. and Leon-Munoz et al., respectively (15, 16). The sample sizes ranged from 432 (18) to 2926 (17). The proportion of female participants ranged from 27.9% (19) to 100% (21). All studies used middle-aged and elderly populations; the mean age varied considerably from 50's to 80's. The modified versions of the Cardiovascular Health Study frailty criteria (13) were used by five studies (15-17, 19, 21) to define frailty while one study (18) used FRAIL scale and another study (20) used Tilburg Frailty Indicator. The data collection methods of fruit and vegetable consumption were based on questionnaires (16, 18-21), either self-reported or by a research personnel (15, 17). Different measurements of fruit and vegetable consumption were employed: the number of portions per day (17), the number of times per day (16, 1), quantity in grams per day (15, 21) and whether consuming daily or not (YES/NO) (19, 20). Due to the various measurements of fruit and vegetable consumption and the definitions of frailty as well as differing statistical methodologies (logistic regression, linear regression,

Table 1
Summary of studies examining associations between fruit and vegetable consumption and frailty

Author/Year/Cohort	Location	Sample size	Female (%)	Age (range)	Frailty criteria	Follow-up period	Fruit and vegetable measure	findings
longitudinal studies (adequate quality)								
Leon-Munoz 2014 Senior-ENRICA cohort	Spain	1815	-	- (>60)	mCHS	3.5 years	Gram per day and number of servings per day, by computerized diet history or semi-quantitative food-frequency questionnaire by a trained research assistant	Incident frailty adjusted for age, gender, education, smoking, BMI, energy intake, cardiovascular disease, diabetes mellitus, cancer, asthma or chronic bronchitis, musculoskeletal disease, depression, number of medication, and remaining of MDS or MEDAS components. aOR=0.59 (95%CI=0.39-0.91) for fruits and nuts > median consumption (gram/day) aOR=0.73 (95%CI=0.45-1.16) for fruit > 3 servings per day aOR=1.06 (95%CI=0.67-1.68) for nuts > 3 times a week aOR=0.73 (95%CI=0.48-1.11) for vegetables > median consumption aOR=0.82 (95%CI=0.44-1.50) for vegetables > 2 servings per day aOR=0.80 (95%CI=0.54-1.18) for legumes > median consumption aOR=0.85 (95%CI=0.49-1.46) for legumes > 3 times a week
Rahi 2017 3C Bordeaux cohort	France	560	63.2%	81.7(>75)	mCHS	2 years	semi-quantitative food-frequency questionnaire	Between those who developed frailty 2 years later and those who did not, there were no significant differences in mean number of servings per week at baseline for fruit (Men: those who became frail 12.0 vs. those who did not 13.4, Women: those who became frail 14.4 vs. those who did not 13.8) and vegetable (Men: incident frailty 9.8 vs. non-frailty 9.6, Women: incident frailty 8.5 vs. non-frailty 9.6). Men who became frail had consumed significantly lower number of legume servings per week than men who did not become frail (0.5 vs. 0.9), but no association was observed in women (0.6 vs 0.6).
Garcia-Esquinas 2016 Senior-ENRICA cohort 3C, Bordeaux cohort, AMI cohort	Spain France	1872 581 473 (total 2926)	37.8-63.5%	68.7-81.8	mCHS	2.5 years	Number of portions per day (120g for fruit, 150g for veg), by computerized diet history or semi-quantitative food-frequency questionnaire by a trained research assistant.	Incident frailty adjusted for age, gender, education, BMI, smoking, cardiovascular disease, DM, cancer, asthma or chronic bronchitis, musculoskeletal disease, MMSE, depression, number of meds, modified Trichopoulou index and energy intake. - Fruit: compared with fruit <1 portion/day aOR=0.59 (95%CI=0.27-0.90) for fruit 1 portion/day aOR=0.58 (95%CI=0.29-0.86) for fruit 2 portions/day aOR=0.48 (95%CI=0.20-0.75) for fruit >3 portions/day p for trend=0.04 - Vegetable: compared with vegetable <1 portion/day aOR=0.69 (95%CI=0.42-0.97) for vegetable 1 portion/day aOR=0.56 (95%CI=0.35-0.77) for vegetable 2 portions/day aOR=0.52 (95%CI=0.13-0.92) for vegetable >3 portions/day p for trend <0.01 - Fruit and vegetable: compared with fruit+ vegetable <1 portion/day aOR=0.41 (95%CI=0.21-0.60) for fruit + vegetable 2 portions/day aOR=0.47 (95%CI=0.25-0.68) for fruit + vegetable 3 portions/day aOR=0.36 (95%CI=0.18-0.53) for fruit + vegetable 4 portions/day aOR=0.31 (95%CI=0.13-0.48) for fruit + vegetable >5 portions/day p for trend <0.01

Table 1 (Continued)
Summary of studies examining associations between fruit and vegetable consumption and frailty

Author/Year/Cohort	Location	Sample size	Female (%)	Age (range)	Frailty criteria	Follow-up period	Fruit and vegetable measure	findings
Ribeiro 2016 African American Health study	US	432	63%	59.2	FRAIL	6 years	Average times consuming per day, by 2005 Behavioral Risk Factor Surveillance System questions at wave 8 (approximately 4 years after baseline)	A multivariable residual-change score linear regression model, including FRAIL scale at wave 4 (baseline), Leisurely walking and sitting, showed that other non-potato vegetables was negatively (B(SE)=-0.20 (0.08), Beta(SE)= -0.12 (0.04), p=0.01) and fruit juices was positively (B(SE)=0.15 (0.07), Beta(SE)=0.09 (0.04), p=0.04) related to FRAIL scale at wave 10 (follow-up) (adjusted R^2=0.33).
Bouillon 2013 Whitehall II civil servants	UK	2707	27.9%	55.0 (45-69)	mCHS	10.5 years	Whether consuming fruits and vegetables daily (YES/NO), by self-reported questionnaire	Daily consumption of fruits and vegetables at baseline was associated with being not frail at follow-up: 37.8% (755/1998) of those with the daily consumption and 47.4% (336/709) of those with NO daily consumption were prefrail or frail (p<0.0001)
cross-sectional studies								
Gobbens 2016	Netherlands	610	38.4%	70.6 (52-89)	TFI	-	Whether consuming fruit 7 days a week (YES/NO) and whether consuming vegetables 7 days a week (YES/NO), based on web-based questionnaire	Multiple linear regression models to explain frailty scores at follow-up adjusted for age, gender, education, income satisfaction, marital status and multimorbidity. - Not consuming fruit 7 days a week was significantly associated only with psychological frailty score (B=0.266, SE=0.123, p=0.03) but not with total frailty score, physical frailty score and social frailty score. - Not consuming vegetable 7 days a week was associated with none of total frailty score, physical frailty score, psychological frailty score and social frailty score.
Kobayashi 2014	Japan	2121 (dietetic students' mother and grandmothers)	100%	74.7	mCHS	-	Grams per day, by self-administered diet history questionnaire	Mutlivariate logistic regression adjusted for age, body mass index, residential region, size of residential area, living alone, smoking, alcohol, dietary supplement use, chronic disease, depressive symptoms and energy intake. - Fruit: compared with 1st (lowest) quintile (<47.1 g/day) aOR=0.86 (95%CI=0.60-1.22) for 2nd quintile (47.1-78.8 g/day) aOR=0.88 (95%CI=0.62-1.25) for 3rd quintile (18.9-116 g/day) aOR=0.61 (95%CI=0.42-0.88) for 4th quintile (116-167 g/day) aOR=0.71 (95%CI=0.49-1.03) for 5th (highest) quintile (>167 g/day) p for trend=0.02 - Vegetable: compared with 1st (lowest) quintile (<208 g/day) aOR=0.71 (95%CI=0.50-1.00) for 2nd quintile (208-266 g/day) aOR=0.57 (95%CI=0.40-0.81) for 3rd quintile (267-328 g/day) aOR=0.55 (95%CI=0.40-0.81) for 4th quintile (328-412 g/day) aOR=0.47 (95%CI=0.33-0.69) for 5th (highest) quintile (>412 g/day) p for trend<0.0001

3C Bordeaux cohort: Three-City Bordeaux cohort. 95%CI: 95% confidence interval. AMI cohort: integrated multidisciplinary approach cohort. aOR: Adjusted odds ratio. mCHS: Modified Cardiovascular Health Study criteria. MEDAS: Mediterranean Diet Adherence Screener. MDS: Mediterranean Diet Score Senior-ENRICA cohort: Study on Nutrition and Cardiovascular Risk Factors in Spain cohort. SE: Standard error. TFI: Tilburg Frailty Indicator

t-test), a meta-analysis was not possible, and a narrative synthesis was performed.

Methodological quality assessment of prospective studies

Three studies of incident frailty were both considered to have adequate methodological quality (15-17). The remaining two studies were considered to have suboptimal quality (18, 19). (Supplementary Table)

Prospective studies (adequate methodological quality)

Leon-Munoz et al. (15)

Among 1,815 Spanish older people from the Seniors-ENRICA study, consuming the median amount or more of fruits and nuts was associated with lower risk of incident frailty over a 3.5-year period Odds ratio (OR)=0.59, 95% confidence interval (CI)=0.39-0.91) compared with comsuming less than the median. However consuming three servings or more of fruit per day was not (OR=0.73, 95%CI=0.45-1.16). Neither consuming two servings or more of vegetables per day (OR=0.82, 95%CI=0.44-1.50) nor consuming the median amount or more of vegetables (OR=0.73, 95%CI=0.48-1.11) were associated significantly with frailty risk. The median amounts of fruit and nuts and vegetables were not provided in this paper. All models were adjusted for age, gender, education, smoking, body mass index, energy intake, cardiovascular disease, diabetes, cancer, asthma or chronic bronchitis, musculoskeletal disease, depression, number of medications and the other components of the Mediterranean Diet Score or Mediterranean Diet Adherence Screener Score.

Rahi et al. (16)

This study followed 560 non-frail French older people from the Three-City study and found that higher Mediterranean diet adherence based on Mediterranean Diet Score at baseline was associated with lower incident frailty risk over 2-year follow-up. As a sub-analysis, baseline values of nine components of the Mediterranean Diet Score, namely mean numbers of weekly servings of (1) legumes, (2) cereals, (3) seafood, (4) meat, (5) dairy products, (6) fruits (7) and vegetables, "frequent" or "all the time" use of (8) olive oil and "mild-to-moderate" consumption of (9) alcohol, were retrospectively examined according to follow-up frailty status (frail vs. non-frail) using t-test or chi-square tests. There were no statistical differences in mean numbers of weekly servings for fruit (Men: those who developed frailty 12.0 vs. those who did not 13.4, Women: those who developed frailty 14.4 vs. those who did not 13.8) and vegetable (Men: those who developed frailty 9.8 vs. those who did not 9.6, Women: those who developed frailty 8.5 vs. those who did not 9.6). Legumes were significantly more frequently consumed by non-frail men than frail men while no such associations were observed in women. (Men: those who developed frailty 0.5 vs. those who did not 0.9, Women: those who developed frailty 0.6 vs. those who did not 0.6). It should be noted that statistical power may have been lowered by dividing the cohort into smaller groups: 19 men and 60 women who developed frailty and 187 men and 294 women who did not.

Garcia-Esquinas et al. (17)

Incident frailty risks according to fruit and vegetable consumption at baseline were investigated in a total of 2,926 older men and women who were free of frailty at baseline from three different cohorts (Three-City Bordeaux cohort and the Integrated Multidisciplinary Approach cohort from France and Seniors-ENRICA cohort from Spain). The modified Cardiovascular Health Study frailty criteria were used to define frailty. Those who consumed higher amounts of fruit, vegetables and both combined had a significantly lower risk of developing frailty over 2.5 years. The effects were dose-dependent and ORs of incident frailty controlled for age, gender, education, body mass index, smoking, cardiovascular disease, diabetes, cancer, asthma or chronic bronchitis, musculoskeletal disease, cognition, depression, number of medications, modified Mediterranean Diet Score and energy intake were: for those who consumed 1, 2 or >3 portions of fruit/day (1 portion=120g of fruits), compared with those who consumed <1 portion/day, 0.59 (95%CI=0.27-0.90), 0.58 (95%CI=0.29-0.86) and 0.48 (95%CI=0.20-0.75), respectively (p for trend=0.04); for those who consumed 1, 2 or >3 portions of vegetables/day (1 portion=150g of vegetables), compared with those who consumed <1 portion/day, 0.69 (95%CI=0.42-0.97), 0.56 (95%CI=0.35-0.77) and 0.52 (95%CI=0.13-0.92), respectively (p for trend<0.01); and for those consumed 2, 3, 4 and >=5 portions of fruits and vegetables combined/day, compared with those who consumed <=1 portion, 0.41 (95%CI=0.21-0.60), 0.47 (95%CI=0.25-0.68), 0.36 (95%CI=0.18-0.53) and 0.31 (95%CI=0.13-0.48), respectively (p for trend<0.01).

Prospective studies (suboptimal methodological quality)

Ribeiro et al. (18)

A US study by Ribeiro et al. examined baseline fruit and vegetable consumption and changes in frailty status measured by the FRAIL scale over a 6-year period between 2004 and 2010 in 432 middle-aged and older African American men and women. Frequencies of five types of fruit and vegetable intakes (average times taken per day) were measured in 2006 based on a questionnaire: (1) fruit juices such as orange, grapefruit or tomato, (2) fruit, (3) green salad, (4) carrots and (5) vegetable different from carrots, potatoes or salad (defined as "other non-potato vegetables"). All these variables, physical activity levels, age, gender and baseline FRAIL scale were initially entered into a multivariable residual-change score linear regression model to predict FRAIL scale at follow-up. After backward stepwise elimination of non-significant variables, the final model included other non-potato vegetables, fruit juices,

leisurely walking, sitting and baseline FRAIL scale (adjusted R^2=0.33). The intake of other non-potato vegetables was negatively (B(SE)=-0.20 (0.08), Beta(SE)=-0.12 (0.04), p=0.01) but consumption of fruit juices was positively (B(SE)=0.15 (0.07), Beta(SE)=0.09 (0.04), p=0.04) associated with FRAIL scale. Important confounding factors, such as education or socioeconomic factors, were not considered in the model.

Bouillon et al. (19)

Bouillon et al. used the Whitehall II study cohort consisting of 2,707 middle-aged and older civil servants aged 45-69 in the UK to examine the frailty risk over a long follow-up period of 10.5 years. Those who answered that they consumed fruits and vegetables daily in a self-reported questionnaire at baseline were less likely to be frail (37.8%, 755/1998) than those who reported not consuming fruits and vegetables daily (47.4%, 336/709) (p<0.0001). There are some important limitations to be noted. First, the cohort used was a selected sample of civil servants. Second, frailty was measured at follow-up but not at baseline. Baseline frailty status should have been considered in the analysis, or frail participants at baseline should have been excluded if incident frailty had been examined, otherwise reverse causality cannot be denied. Lastly, the presence or absence of daily fruit and vegetable consumption is a rather crude predictor variable.

Cross-sectional studies

Gobbens et al. (20)

A cross-sectional study of 610 middle-aged and older men and women aged 52-89 years (mean age 70.6) in the Netherlands examined associations of fruit and vegetable consumption with frailty, measured by the Tilburg Frailty Indicator. The information was collected via a web-based questionnaire. Multiple linear regression models adjusted for age, gender, education, income satisfaction, marital status and multimorbidity showed that consuming fruits on fewer than 7 days a week was significantly associated only with higher psychological frailty score (B=0.266, SE=0.123, p=0.03) but not with the total, physical and social frailty scores, compared with consuming fruits on 7 days per week. Consuming vegetables on fewer than 7 days per week was associated with none of the frailty scores, compared with consuming vegetables on 7 days per week. As the authors acknowledged, the major limitations included restriction of the sample to those who had internet access and were able to complete the online questionnaire and the crude measurement of fruit and vegetable consumption as a dichotomous variable instead of quantitatively or in a dose-response manner.

Kobayashi et al. (21)

Another cross-sectional study used a selected cohort of 2,121 Japanese older women with mean age of 74.7 years old, who were mothers or grandmothers of dietetic students, to examine associations between consumption of fruits and vegetables and frailty. The consumption of fruits and vegetables was measured using a self-administered diet history questionnaire, and frailty was defined by the Cardiovascular Health Study criteria (13)with Woods' modification (22). Multivariable logistic regression models controlled for age, body mass index, residential region, size of residential area, living alone, smoking, alcohol, dietary supplement use, chronic disease, depressive symptoms and energy intake showed higher intakes of fruits (compared with 1st quintile (lowest), adjusted OR=0.86, 0.88, 0.61 and 0.71 for 2nd-5th (highest) quintiles, respectively) and vegetables (compared with 1st quintile (lowest), adjusted OR=0.71, 0.57, 0.55 and 0.47 for 2nd-5th (highest) quintiles, respectively) were associated with lower frailty risks in a graded manner (p for trend=0.02 and <0.0001, respectively).

Discussion

This systematic review has identified a total of seven studies examining middle-aged and older populations for associations between fruit and vegetable consumption and frailty. Among three studies with adequate methodological quality, only one study primarily examined fruits and vegetables and showed that higher intakes of fruits, vegetables and both combined were significantly associated with lower incident frailty risks in a dose-response manner (17). The main focus of the other two studies was a Mediterranean diet (15, 16) and fruits and vegetables were examined only in sub-analyses, which showed only fruits and nuts of more than median amount was associated with lower incident frailty risk in one study (15).

The findings of two prospective studies with suboptimal quality were consistent: a higher non-potato vegetable intake was associated with lower frailty risks (18), and those who consumed fruits and vegetables daily had lower frailty risks compared with those who did not (19). The former study (18) also showed fruit juice intake at baseline was associated with worse frailty at follow-up. This could be because "fruit juice" described in this study was not restricted to 100% pure fruit juice but could refer to drinks with a lower fruit content or with added sugar. In addition, this "fruit juice" may be replacing real fruit intake and therefore underestimate the true fruit consumption.

One cross-sectional study showed significant dose-response reverse association between higher intakes of fruits and vegetables and prevalent frailty (21). Another cross-sectional study showed not consuming fruit 7 days/week was associated with significantly higher psychological frailty score than consuming fruit 7 days/week, while there were no significant associations between not consuming vegetables 7 days/week and frailty scores (20). Due to cross-sectional nature of these two studies, reverse causality may be possible, for example, loss of appetite can be a feature of frailty leading to lower intake of fruit and vegetables.

Although not included in this review, we identified a further study that did not investigate fruit and vegetable consumption specifically but instead examined dietary patterns including fruits and vegetables in association with frailty. A cross-sectional study of 923 elderly Taiwanese aged 65 or older explored a dietary pattern associated with frailty using reduced rank regression analysis and found that fresh fruit had the highest factor loading value (-0.48) and vegetables had the fourth highest one (-0.33), both suggesting strong inverse associations with frailty (23).

Fruits and vegetables are important part of the Mediterranean diet, which is traditionally consumed in the countries surrounding the Mediterranean and is characterised by high intakes of plant-based foods, such as fruits, vegetables, legumes, whole grains and nuts, and low-to-moderate consumption of red meat and wine (24). A few cross-sectional and prospective studies have suggested inverse associations between higher adherence to the Mediterranean diet and lower frailty risks (5, 24). This protective effect of the Mediterranean diet against frailty is not necessarily attributed only to high consumption of fruits and vegetables, but could also be due to the other characteristics of Mediterranean diet, including consumption of more olive oil or canola oil than butter, more nuts and legumes (containing protein) and more spices other than salt, as well as limited intake of red meats, or all of these features combined (24).

Fruits and vegetables are well known to benefit human health and may also protect against frailty. One of the possible mechanisms is through anti-oxidative effects. A recent systematic review has shown that frailty appears to be associated with higher oxidative stress and possibly lower anti-oxidant-related measurements (25). Fruits and vegetables are natural sources of anti-oxidants, such as vitamin C, vitamin E, carotenoids and selenium (26). These anti-oxidants may reduce or prevent frailty by decreasing reactive oxygen species, which cause damage to DNA, lipids and proteins and induce mitochondrial dysfunction and apoptosis (26). Another explanation is that fruits and vegetables including legumes are potential source of proteins against frailty. Adequate dietary protein intake is essential to increase muscle protein synthesis and improve physical function, and counteract sarcopenia, the age-related loss of muscle mass and strength, a core feature of frailty. Given some fruits and vegetables, such as legumes and nuts, are rich in protein, those with high intakes of fruits and vegetables may obtain more plant-based proteins than those with low intakes of fruits and vegetables (27).

This study has some limitations. The area of diet, especially fruit and vegetable consumption, in relation to frailty is relatively new, and only a limited number of studies were found through the searches. In addition, because the included studies used different measurements of fruit and vegetable consumption and statistical methodologies, a meta-analysis could not be conducted. It was also not possible to know exactly how fruits and vegetables were defined in all studies: some studies separated legumes or nuts from fruits and vegetables (15, 16) while others did not specify the definitions of fruits and vegetables (17-21). Furthermore, it should be noted that not all studies took into account important potential confounders, including socioeconomic status, education and IQ.

The robust methodology employed in accordance with PRISMA statements was the major strength of this review. The systematic literature search was conducted using four electronic databases with a comprehensive and reproducible search strategy using a combination of MeSH and text terms. The identified studies were screened by two independent investigators with a standardised protocol and were assessed for methodological quality.

Conclusion

The overall evidence regarding the associations between fruit and vegetable consumption and frailty is scarce in the literature and the study settings, statistical methods and findings were heterogeneous. More high quality research is needed in order to elucidate these associations, especially research to confirm the causal relationships. There is some suggestion from limited evidence that higher fruit and vegetable consumption may be associated with a lower risk of frailty. There were no studies showing fruits or vegetables worsen frailty. If intake of fruits and vegetables is beneficial in preventing or reversing frailty, this might be a good target for intervention against frailty given increasing fruits and vegetables consumption is relatively easy and without significant side effects. Future research should also investigate how much of fruits and vegetables is enough to give protection against frailty among older people.

The original version of this article was revised.

Funding: This study was supported by the Sasakawa Foundation Butterfield Awards for UK-Japan collaboration in medicine and health (Application number B111). GK is funded by a University College London (UCL) Overseas Research Scholarship. Neither funder had any influence on the study design, the collection, analysis, and interpretation of data, the writing of the article or the decision to submit it for publication.

Acknowledgment: We thank Ms Sophie Pattison, a clinical support librarian at the Royal Free Hospital Medical Library, for supporting the systematic review.

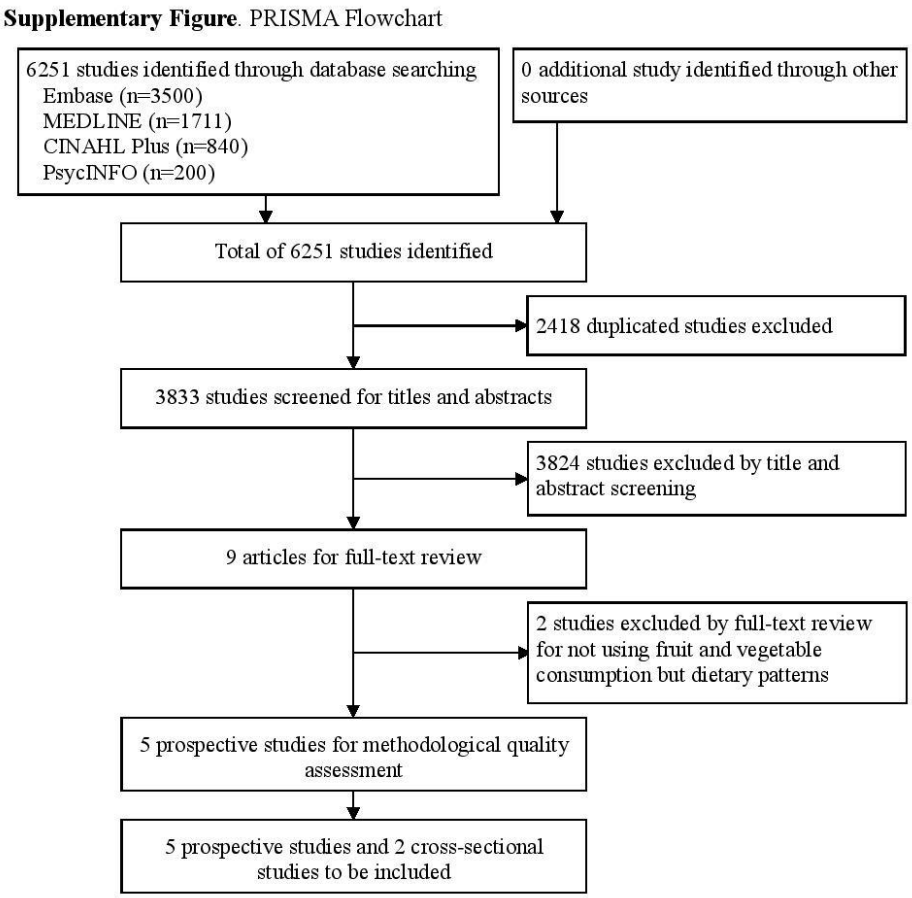
Conflict of interest: None.

References

1. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet. 2013;381:752-62.
2. Collard RM, Boter H, Schoevers RA, et al. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc. 2012;60:1487-92.
3. Yannakoulia M, Ntanasi E, Anastasiou CA, et al. Frailty and nutrition: From epidemiological and clinical evidence to potential mechanisms. Metabolism. 2017;68:64-76.
4. Lorenzo-Lopez L, Maseda A, de Labra C, et al. Nutritional determinants of frailty in older adults: A systematic review. BMC Geriatr. 2017;17:108.
5. Kojima G, Avgerinou C, Iliffe S, et al. Adherence to Mediterranean diet reduces incident frailty risk: A systematic review and meta-analysis. J Am Geriatr Soc. 2018;66:703-8

6. Slavin JL, Lloyd B. Health benefits of fruits and vegetables. Adv Nutr. 2012;3:506-16.
7. Zhan J, Liu YJ, Cai LB, et al. Fruit and vegetable consumption and risk of cardiovascular disease: A meta-analysis of prospective cohort studies. Crit Rev Food Sci Nutr. 2017;57:1650-63.
8. Gan Y, Tong X, Li L, et al. Consumption of fruit and vegetable and risk of coronary heart disease: a meta-analysis of prospective cohort studies. Int J Cardiol. 2015;183:129-37.
9. Lunet N, Lacerda-Vieira A, Barros H. Fruit and vegetables consumption and gastric cancer: a systematic review and meta-analysis of cohort studies. Nutr Cancer. 2005;53:1-10.
10. Aune D, Giovannucci E, Boffetta P, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies. Int J Epidemiol. 2017;46:1029-56.
11. Wang X, Ouyang Y, Liu J, et al. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. BMJ. 2014;349:g4490.
12. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
13. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146-56.
14. Wells GA, Shea D, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [20th August, 2017]; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
15. Leon-Munoz LM, Guallar-Castillon P, Lopez-Garcia E, et al. Mediterranean diet and risk of frailty in community-dwelling older adults. J Am Med Dir Assoc. 2014;15:899-903.
16. Rahi B, Ajana S, Tabue-Teguo M, et al. High adherence to a Mediterranean diet and lower risk of frailty among French older adults community-dwellers: Results from the Three-City-Bordeaux Study. Clin Nutr 2017.
17. Garcia-Esquinas E, Rahi B, Peres K, et al. Consumption of fruit and vegetables and risk of frailty: a dose-response analysis of 3 prospective cohorts of community-dwelling older adults. Am J Clin Nutr. 2016;104:132-42.
18. Ribeiro SM, Morley JE, Malmstrom 2016TK, et al. Fruit and Vegetable Intake and Physical Activity as Predictors of Disability Risk Factors in African-American Middle-Aged Individuals. J Nutr Health Aging. 2016;20:891-6.
19. Bouillon K, Kivimaki M, Hamer M, et al. Diabetes risk factors, diabetes risk algorithms, and the prediction of future frailty: the Whitehall II prospective cohort study. J Am Med Dir Assoc. 2013;14:851 e1-6.
20. Gobbens RJ, van Assen MA. Explaining frailty by lifestyle. Arch Gerontol Geriatr. 2016;66:49-53.
21. Kobayashi S, Asakura K, Suga H, et al. Inverse association between dietary habits with high total antioxidant capacity and prevalence of frailty among elderly Japanese women: a multicenter cross-sectional study. J Nutr Health Aging. 2014;18:827-39.
22. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. J Am Geriatr Soc. 2005;53:1321-30.
23. Lo YL, Hsieh YT, Hsu LL, et al. Dietary Pattern Associated with Frailty: Results from Nutrition and Health Survey in Taiwan. J Am Geriatr Soc. 2017;65:2009-15.
24. MacDonell SO, Miller JC, Waters DL, et al. Dietary Patterns in the Frail Elderly. Current Nutrition Reports. 2016;5:68-75.
25. Soysal P, Isik AT, Carvalho AF, et al. Oxidative stress and frailty: A systematic review and synthesis of the best evidence. Maturitas. 2017;99:66-72.
26. Bonnefoy M, Berrut G, Lesourd B, et al. Frailty and nutrition: searching for evidence. J Nutr Health Aging. 2015;19:250-7.
27. Artaza-Artabe I, Saez-Lopez P, Sanchez-Hernandez N, et al. The relationship between nutrition and frailty: Effects of protein intake, nutritional supplementation, vitamin D and exercise on muscle metabolism in the elderly. A systematic review. Maturitas.2016; 93:89-99.

Supplementary Figure



1

Supplementary Table

Supplementary Table. Methodological quality assessment using the Newcastle-Ottawa Quality Assessment Scale (cohort studies)

Author/year	Selection 1	Selection 2	Selection 3	Selection 4	Comparability 1	Comparability 2	Outcome 1	Outcome 2	Outcome 3	total
Rahi 2017	1	1	1	1	1	1	1	1	1	9/9
Garcia-Esquinas 2016	1	1	1	1	1	1	1	1	0	8/9
Ribeiro 2016	1	1	0	n/a	0	0	0	1	0	3/8
Leon-Munoz 2014	1	1	0	1	1	1	1	1	1	8/9
Botillon 2013	0	1	0	0	0	0	1	1	1	4/9
Cross-sectional										
Gobbens 2016	-	-	-	-	-	-	-	-	-	-
Kobayashi 2014	-	-	-	-	-	-	-	-	-	-

1

PRISMA Checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3-4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3-4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a

Page 1 of 2

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4,10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4-6,11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6,13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	4-6,11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	7

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Page 2 of 2

8.1.3.2 Fruit and vegetable ELSA analysis

Manuscript is currently under review.