



Risk of Frailty and Cardiovascular Disease in the China Kadoorie Biobank

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Abstract

Background: Frailty and cardiovascular disease (CVD) are an increasing burden in rapidly ageing societies like China. While frailty and CVD commonly coexist, there is substantial uncertainty about their relationships particularly about the relevance of modifiable CVD risk factors (RFs) for frailty and frailty for CVD. Moreover, frailty research is constrained by a lack of consensus on the optimum definition for frailty with limited evidence on their relative performance. This thesis first compared the measurement properties of the most widely used frailty models, the frailty index (FI) and frailty phenotype (FP), to guide selection of a frailty instrument, and second investigated the associations of CVD RFs with frailty and of frailty with CVD in Chinese adults.

Methods: The validity and reliability of the FI and FP were compared using a systematic review of the predictive accuracy for all-cause mortality and a prospective analysis of repeat frailty assessments from the Irish Longitudinal Study on Ageing (TILDA), respectively. The China Kadoorie Biobank, involving 0.5 million adults aged 30-79 years recruited between 2004-08 from 10 diverse regions, was used to assess the associations of CVD RFs (systolic blood pressure [SBP], random plasma glucose [RPG], alcohol consumption, smoking, fat mass, and lean body mass) with incident frailty and frailty with incident CVD (stroke and ischaemic heart disease [IHD]) among participants without prevalent CVD. Logistic and Cox regression yielded adjusted odds (ORs) and hazard ratios (HRs), respectively. Frailty and CVD associations were corrected for regression dilution bias. Modifications of the FI (excluding relevant cardiovascular items) assessed the presence of circularity in relationships.

Results: The comparative analyses of the measurement properties of the main frailty instruments found that continuous instruments were more accurate predictors of all-cause mortality and FI was more reliable than FP (kappa statistic [95%CI]) 0.60 [0.58-0.62] vs. 0.37 [0.35-0.40]), supporting the selection of FI for subsequent analyses in CKB. Among ~20,000 CKB participants without prevalent frailty or CVD, positive associations were found between SBP, RPG, fat mass, and incident frailty after adjustment for confounders, but associations

were substantially attenuated after accounting for circularity. During 13-years' follow-up, 54,193 incident stroke events (46,043 ischaemic [IS] and 10,535 haemorrhagic [HS] stroke) and 49,937 IHD events (7,749 myocardial infarction [MI] and 10,193 major coronary event [MCE]) were recorded. Among ~0.5M CKB participants without prevalent CVD, there were positive log-linear associations between frailty and incident stroke and IHD (and their subtypes) after adjustment for confounders, which became stronger with correction for regression dilution bias. Each 1 SD higher usual FI was associated with HRs (95%CI) of 1.31 (1.29-1.33) and 1.37 (1.35-1.40) for incident stroke and IHD, respectively, which attenuated to 1.13 (1.11-1.15) and 1.34 (1.31-1.36), respectively, after accounting for circularity. Associations were stronger for fatal than overall events, amounting to nearly 2-fold differences, and there were some differences in the strength of associations by subtypes of stroke (IS: 1.28 [1.25-1.30] and HS: 1.46 [1.41-1.51]) and IHD (MI: 1.44 [1.38-1.50] and MCE: 1.51 [1.46-1.57]).

Conclusions: Among Chinese adults without prior CVD, there was no clear association between the modifiable CVD RFs and risk of frailty after accounting for circularity in the relationships. However, frailty was associated with significantly increased risk of major CVDs, which was stronger for IHD than for stroke and fatal events, and largely similar within each type.

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Statement of contribution to work

The overall idea for this thesis was proposed by Robert Clarke. I developed the initial proposal into the present thesis with constant advice and supervision from my supervisors, Robert Clarke, Derrick Bennett, and Sofia Massa. All protocols for the analyses conducted in **Chapters 2 to 8** were developed by myself with guidance from my supervisors. I conducted all the analyses producing most of the code for the analyses in thesis with some technical support provided within CTSU. The tables, figures, and writing presented in the thesis are all my own, unless otherwise stated, and have been refined by my supervisors through comments and edits. Therefore, the work presented in this thesis, including any errors, is my own. I was not involved in the design and collection of data from The Irish Longitudinal Study on Ageing (TILDA) or the China Kadoorie Biobank (CKB).

In **Chapter 1**, I included several figures from previously published work, which have all been appropriately referenced. The research presented in **Chapter 2** has been published in the Systematic Reviews journal (listed in **Publications**). I designed the review, conducted the analysis with a second reviewer, and wrote the first draft of the paper. My supervisors and an expert in psychometric research, Caroline Potter, provided advice on the analysis and contributed to the revision of the manuscript. The research presented in **Chapter 3** has been published in the Scientific Reports journal (listed in **Publications**). I designed and conducted the analysis and wrote the first draft of the paper. Access to the TILDA dataset was supported by the research team at TILDA (Siobhan Scarlett, Aisling O'Halloran, and Rose Anne Kenny), who along with my supervisors provided advice on the analysis and contributed to the revision of the manuscript.

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Publications

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Kim DJ, Massa MS, Clarke R, et al. Variability and agreement of frailty measures and risk of falls, hospital admissions and mortality in TILDA. *Sci Rep.* 2022;12(1):4878. doi:[10.1038/s41598-022-08959-7](https://doi.org/10.1038/s41598-022-08959-7) (**Chapter 3**)

List of Abbreviations

Abbreviations	Definition	Abbreviations	Definition
AF	Atrial fibrillation	IV	Instrumental variable
AMI	Acute myocardial infarction	IPAQ-SF	International Physical Activity Questionnaire - Short Form
ANOVA	Analysis of variance	IQR	Interquartile range
AUC	Area under the ROC curve	IS	Ischaemic stroke
AUDIT-C	Alcohol use disorders identification test for consumption	IT	Information technology
BA	Bland-Altman	KYCL	Kaigo-Yobo Checklist
BF	Body fat	LMIC	Low- and middle-income countries
BMI	Body mass index	LVMI	Left ventricular mass index
BP	Blood pressure	M	Million
CAD	Coronary artery disease	MAR	Missing at random
CAPI	Computer-aided personal interview	MCAR	Missing completely at random
CART	Classification and regression trees	MCE	Major coronary event
CDC	Centre for Disease Control	MDC	Minimally detectable change
CES-D	Centre for Epidemiologic Studies Depression Scale	MeSH	Medical Subject Heading
CHD	Coronary heart disease	MET	Metabolic equivalent of task
CI	Confidence interval	mFI	Modified frailty index
CKB	China Kadoorie Biobank	MI	Myocardial infarction
CO	Carbon monoxide	MIC	Minimal important change
COPD	Chronic obstructive pulmonary disorder	MICE	Multiple Imputation by Chained Equations
CRP	C-reactive protein	MMSE	Mini mental state examination
CRT	Creatinine	MR	Mendelian randomisation
CTSU	Clinical Trial Service Unit	OR	Odds ratio
CVD	Cardiovascular disease	PLFI	Paulson-Lichtenberg Frailty Index
DSP	Disease Surveillance Point	PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
EHR	Electronic health records	RDB	Regression dilution bias
FAR	Floating absolute risk	RDR	Regression dilution ratio
FEV	Forced expiratory volume	RF	Risk factor
FI	Frailty index	ROC	Receiver operating characteristic curve
FP	Frailty phenotype	RPG	Random plasma glucose
FRAIL	Fatigue, Resistance, Ambulation, Illness, and Loss	SAH	Subarachnoid haemorrhage
FVC	Forced vital capacity	SBP	Systolic blood pressure
GBD	Global Burden of Disease	SCQ	Self-Completion Questionnaire
HC	Hip circumference	SD	Standard deviation
HF	Heart failure	SEM	Standard error of the mean
HI	Health insurance	SIGN	Scottish Intercollegiate Guidelines Network
HR	Hazard ratio	SWiM	Synthesis without Meta-analysis
HS	Haemorrhagic stroke	TIA	Transient ischaemic attack
ICC	Intraclass correlation coefficient	TILDA	The Irish Longitudinal Study on Ageing
ICD-10	International Classification of Diseases 10th Revision	TUG	Timed up and go
ICH	Intracerebral haemorrhage	WC	Waist circumference
IHD	Ischaemic heart disease	WHO	World Health Organisation
IL	Interleukin	WHR	Waist hip ratio

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1 Introduction

Frailty is a common condition in older people that affects approximately 24% of people aged over 50 years.¹ It is a major cause of morbidity and premature mortality and accounts for approximately one-third of deaths in older people.² The prevalence of frailty is expected to increase substantially, particularly in low- and middle-income countries (LMICs) such as China, where the population is ageing rapidly. Despite its high prevalence, our understanding of the causes of frailty and their relevance for the development of other diseases is uncertain. The World Health Organisation (WHO) Clinical Consortium on Healthy Ageing recognised the importance of the detection and treatment for frailty,³ but given the limited evidence and guidance on its prevention or alleviation, the relevance of public health and medical policies for prevention of frailty is uncertain.

Cardiovascular disease (CVD) frequently co-occurs with frailty and is another highly prevalent disease and the leading cause of mortality in older people. The coexistence of frailty and CVD is supported by the presence of shared, modifiable cardiovascular risk factors (CVD RFs), but there is significant uncertainty about the shape, strength, and causal relevance of these relationships. In particular, there is substantial uncertainty about the relevance of individual CVD RFs for the development of frailty. Likewise, there is uncertainty about whether frailty increases the likelihood of developing CVD. Understanding these relationships may provide insights into the mechanisms of frailty and have important implications for public health policies.

However, designing population studies to investigate frailty is challenging. First, frailty lacks a standard definition – several, very different, conceptualisations of frailty exist. The different frailty models classify different sets of individuals as frail and have variable abilities to predict adverse health outcomes. Despite this, the selection of a frailty instrument for research or clinical practice is typically based on availability or preference rather than comparative evidence of their performance.⁴ There is a general lack of high-quality and reliable evidence comparing the measurement properties of the existing frailty instruments to guide selection.⁵ Second, frailty and CVD (RF) relationships are inherently difficult to study. The inclusion of

cardiovascular components in the frailty definition is common depending on the frailty definition, which can result in significant circularity when estimating these relationships and add to the uncertainty about their true associations. In addition, frailty is believed to develop over several years and result in an increased risk of mortality. Thus, observational studies of frailty are constrained by bias from reverse causation (a form of confounding), which implies that the frailty-outcome relation is biased by the progression of frailty due to pre-existing illness or that the exposure-frailty relation is biased by the change in the exposure due to underlying frailty. Thus, elucidation of the causal relevance of associations involving frailty is challenging. This thesis conducted a critical review of the available evidence from population studies of CVD RFs, frailty, and CVD associations with an appraisal of the potential biases.

This chapter overviews the epidemiology of frailty and CVD, including a description of terminology, diagnostic criteria, and the main types of CVD and frailty models. The hypothesised relationships between frailty and CVD are also discussed, highlighting their shared RFs and the challenges to investigating these relationships. This is followed by a discussion of the limitations of the existing frailty instruments and their implications for this thesis. Finally, the chapter outlines the overall aims and objectives of the thesis.

1.1 Epidemiology of frailty and cardiovascular disease (CVD)

1.1.1 *Frailty*

Frailty is defined as an increased vulnerability to external stressors due to an age-related decline in biological reserves and function across multiple physiological systems.⁶ It is strongly associated with all-cause mortality,⁷ unplanned hospitalisations,⁸ disability,⁹ falls,¹⁰ multimorbidity,¹¹ and poor outcomes following the onset of a range of diseases and medical procedures.^{12,13} Despite this, a standard definition of frailty does not exist and its global prevalence is uncertain. Recent estimates of the global prevalence of frailty in 240 population-based studies varied from 12% to 24% in adults aged ≥ 50 years; but there was a 2-fold difference depending on the definitions of frailty used. In China, the range of the prevalence of frailty was lower, between 8% and 12%, among adults aged ≥ 65 years based on 14

population-based studies.¹⁴ Frailty prevalence reached 50% in even older populations (>80 years).¹⁵

The prevalence of frailty is projected to increase in the future due to rapid ageing of the worldwide population, a phenomenon arising from increasing life expectancy and reductions in fertility rates.¹⁶ Accordingly, the number of older people (≥ 60 years) is predicted to increase by 38% – from 1 billion to 1.4 billion between 2019 and 2030,¹⁷ and the global prevalence of frailty has already increased since an earlier estimate of 10.7% in 2012 (although this increase may reflect higher availability of data than a true increase in frailty over time).¹⁵ It is also likely that in the next few decades, there will be major regional disparities in frailty prevalence, where LMICs will be disproportionately affected. For example, 80% of adults aged ≥ 60 years are predicted to live in LMICs by 2050.¹⁶

Ageing populations have greater demands for healthcare reflecting their clinical complexity and requirement for physical and social support. Thus, frailty has been recognised as an emerging public health priority worldwide.^{5,18} The United Nations Decade of Healthy Ageing (2021-2030) advocated the need to improve the lives of older people,¹⁷ though precisely how this will be achieved is uncertain. While frailty appears to be modifiable, there is limited reliable evidence on the efficacy of specific interventions to alleviate frailty in older adults.^{19,20}

1.1.2 Cardiovascular disease (CVD)

CVD is the leading cause of death and disability worldwide.²¹ In 2019, about 18 million people died from CVD, which is approximately one-third of all deaths worldwide.²² Most CVD deaths were due to stroke or ischaemic heart disease (IHD), accounting for 7 million²¹ and 9 million²³ deaths, respectively.

Global trends in the number of CVD deaths and prevalence demonstrated a substantial increase. According to the Global Burden of Disease (GBD) study, CVD deaths increased by 54% from 1990 to 2019, from 12.1 million to 18.6 million, respectively, and CVD prevalence doubled, from 271 million to 523 million, respectively.²¹ In contrast, the global age-standardised rates of CVD decreased or stabilised²⁴ (mortality rates of stroke²⁵ and IHD²⁶ decreased), suggesting that the absolute increases in CVD may reflect population growth and ageing. Other reasons for the decrease in the rates of CVD include lifestyle and behavioural changes, public health interventions, and advances in therapies. For example, the increased awareness about the risks of smoking, poor diet, and sedentary lifestyle, and the effect of CVD prevention strategies, such as implementing smoking bans and control of dietary salt, have led to a decline in the incidence rates of the major RFs of heart disease in most countries.^{27–29} In addition, advances in therapies like medications for lowering cholesterol, controlling blood pressure, and preventing blood clots has contributed to better management of CVD and its risk factors.³⁰ However, substantial heterogeneity in CVD mortality rates exists geographically – over three-quarters of all CVD deaths now occur in LMICs.³¹ This disparity reflects differences in the prevalence of major RFs and inequalities in access to health services and CVD prevention strategies.³² Hence, CVD remains a major cause of premature death in both high- and LMICs.

In China, CVD is also the leading cause of mortality, accounting for more than 40% of all deaths.³³ Consistent with worldwide patterns, CVD mortality rates increased in recent years, from 2.5 million in 1990 to 4.0 million in 2016, while age-standardised rates decreased by 28.7%.³³ Similarly, the two leading causes of CVD deaths were stroke and IHD, each

accounting for 1.7 million deaths.²¹ In contrast with global patterns, the age-standardised mortality from IHD in China increased by about 25% over this period. However, stroke accounted for more cases in China despite the increase in IHD cases.³³ The incidence rate of ischaemic stroke, a subtype of stroke, in China is 36% higher than the global average,³⁴ but the mortality-to-incidence ratio is lower (0.19 versus 0.24).³² The reasons for the geographical differences in CVD patterns are not fully understood and may reflect differences in economic development and levels of established CVD RFs. China is currently at an earlier stage of urbanisation than Western countries and Chinese men have the highest prevalence of cigarette smoking³⁵ in addition to increasing rates of diabetes, hypertension, dyslipidaemia, obesity, and physical inactivity.³⁶

The epidemiology of CVD varies substantially across China.³⁷ In general, the Northern provinces have higher prevalence, incidence, and mortality rate from stroke and IHD compared to Southern provinces.^{34,37} IHD mortality rates were typically higher in urban than in rural areas, while stroke mortality rates were lower in urban than in rural areas.³⁵ These differences may reflect varying levels of CVD RFs, such as the higher prevalence of hypertension in Northern and rural areas,³⁷ and differential effects of RFs on CVD risk (e.g. the effect of smoking on CVD was over 2.5-fold greater in urban male smokers versus those living in rural areas).³⁸ Furthermore, cohort effects, such as the changing distribution and severity of RFs over time, are likely to affect temporal trends in CVD mortality,³⁸ which, in addition to the ageing population, may increase CVD burden and mortality in future years.

1.2 An overview of the main types of CVD

CVD refers to a group of diseases affecting the blood supply to the heart or brain or other major vessels.²² The present thesis focused on the main causes of premature death and morbidity, stroke and IHD.²¹

1.2.1 Stroke

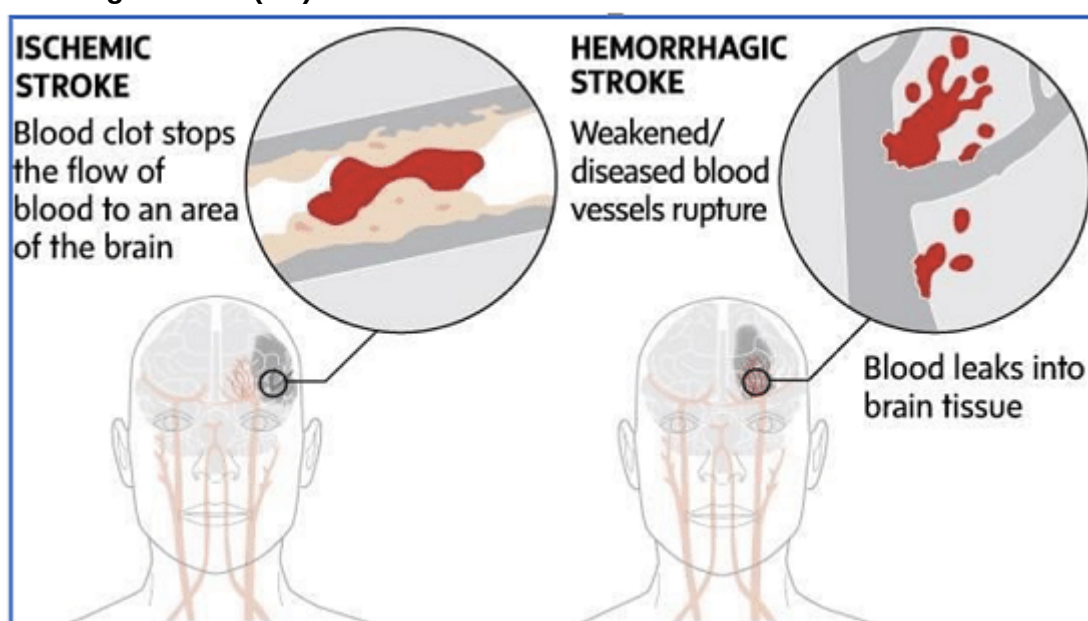
WHO defines stroke as a “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin”.³⁹ Hence, stroke is a neurological disorder caused by blockage of the blood supply to the brain.

Types of stroke

The two main types of stroke are ischaemic stroke (IS), caused by a blockage in the arteries supplying the brain, and haemorrhagic stroke (HS), caused by bleeding or haemorrhage into the brain tissues or surrounding spaces. IS and HS account for approximately 62% and 37% of all stroke cases, respectively, worldwide.⁴⁰

Figure 1.1 shows a schematic representation of the pathology of stroke. The subtypes of IS (e.g. thrombotic and embolic IS) reflect differences in aetiology. Thrombotic IS occurs due to a blood clot within the carotid arteries and embolic IS due to a clot fragment that blocks a carotid artery. The subtypes of HS include intracerebral haemorrhage (ICH), characterised by bleeding directly into the parenchyma of the brain, and subarachnoid haemorrhage (SAH), by bleeding into the subarachnoid space around the brain.

Figure 1.1 Schematic representation of the pathology of ischaemic stroke (IS) and haemorrhagic stroke (HS)

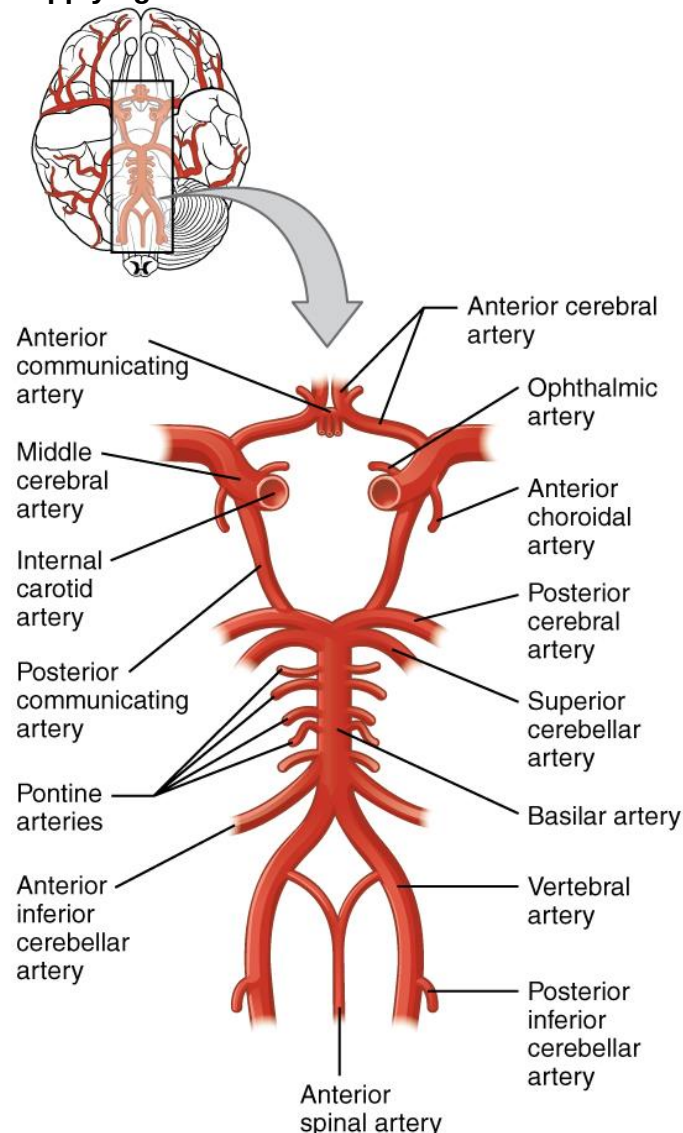


In ischaemic stroke (IS), arteries may be blocked by a blood clot in carotid arteries (thrombosis) or a fragment of a clot may break off and travel through the bloodstream, which may then block an artery that supplies blood to the brain, e.g. cerebral arteries (embolism). In haemorrhagic stroke (HS), bleeding may occur within the parenchyma of the brain (intracerebral haemorrhage) or in the subarachnoid space (subarachnoid haemorrhage). Image was reprinted from Qureshi *et al.* (2018).⁴¹ Permission to make digital or hard copies of all or part of this work for personal or classroom use is granted without fee provided that copies bear this notice and the full citation on the first page.

Pathogenesis of stroke

Four major arteries supply blood to the brain: the two internal carotid arteries and two vertebral arteries (the arteries supplying the brain are depicted in **Figure 1.2**).⁴² IS is chiefly caused by the occlusion of one of these main arteries from a physiological process called atherosclerosis.^{42,43} Conversely, HS results from rupture of the arteries and bleeding into the brain tissues (ICH) or the subarachnoid space (SAH). ICH is chiefly caused by hypertension, disrupted vasculature, and excessive use of anticoagulants.⁴³ SAH is usually caused by rupture or cerebral aneurysm⁴³ and typically occurs in the circle of Willis that is supplied by the vertebral arteries.⁴²

Figure 1.2 Arteries supplying blood to the brain



The blood supply to the brain enters via the internal carotid and vertebral arteries, which comprise the circle of Willis. The circle of Willis is a group of arteries that ensures constant blood supply to the brain. Image was reprinted from: <http://cnx.org/content/col11496/1.6/> and licensed under a Creative Commons Attribution 4.0 International License.

1.2.2 Ischaemic heart disease (IHD)

IHD is a heart condition caused by ischaemia or the narrowing of the coronary arteries that supply blood to the heart muscle.⁴⁴ Accordingly, the terminology used to describe IHD, coronary artery disease (CAD), and coronary heart disease (CHD) is used interchangeably. The narrowing of the coronary artery is caused by the accumulation of fatty deposits and the development of atherosclerotic plaques, a process referred to as atherosclerosis (**Figure 1.3**).^{23,44}

Figure 1.3 Schematic representation of the progression of atherosclerosis

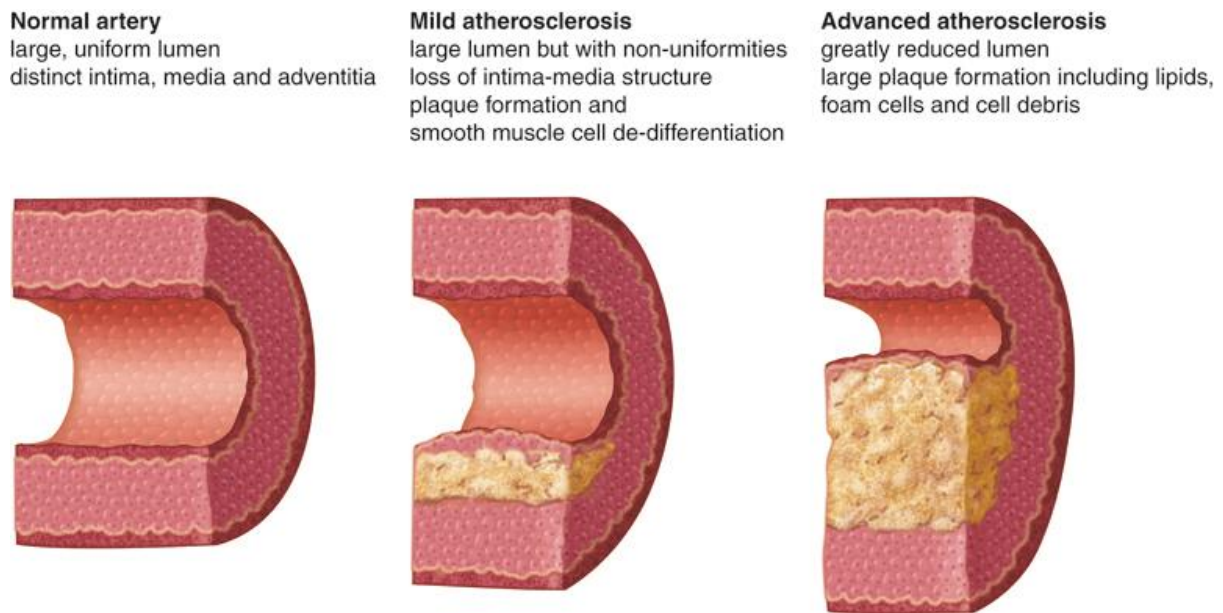


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Types of IHD

Depending on the severity of atherosclerosis, the symptoms of ischaemia manifest as (in order of severity) stable or unstable angina, myocardial infarction (MI), heart failure (HF), or cardiac arrest.²³ Minor ischaemia of the blood supply to the heart can result in stable angina, which causes chest pain on exertion, and poor management of angina can result in MI or heart attack.²³ MI occurs when there is a complete blockage of a coronary artery supplying the heart. Complete occlusion of the coronary arteries exacerbates ischaemia, which causes cell death that manifests clinically as a heart attack.²³ A large or repeated heart attack can cause irreversible damage to the heart muscle and reduce its ability to pump blood around the body, resulting in HF. A single and massive heart attack can cause fatal cardiac arrest, which completely stops the heart.²³ Lastly, myocardial ischaemia or a heart attack can result in an increased risk of atrial fibrillation (AF), characterised by an abnormally fast and irregular cardiac rhythm.

Pathogenesis of IHD

A schematic representation of atherosclerosis is shown in **Figure 1.4**. Atherosclerosis occurs in the coronary arteries that supply blood to the heart muscle. When the endothelium, a thin layer on the inner surface of arterial vessels, is damaged, it responds by triggering an immune response.^{45,46} Monocytes are first attracted to the damaged arterial intima, the innermost layer of the blood vessel,^{45,46} and subsequently mature into macrophages. As the macrophages accumulate cholesterol particles, they transform into lipid-rich foam cells, a characteristic constituent of atherosclerotic lesions or plaques.⁴⁷ These foam cells sustain the localised inflammation and promote local intimal thickening,^{45,47} which results in a progressive reduction in the supply of blood to the surrounding tissue and ischaemia. Advanced plaques with major lipid deposits are susceptible to rupture, which can initiate thrombosis and activation of the clotting cascade, resulting in complete occlusion of the underlying vessel.^{45,46}

Figure 1.4 Pathogenesis of atherosclerosis

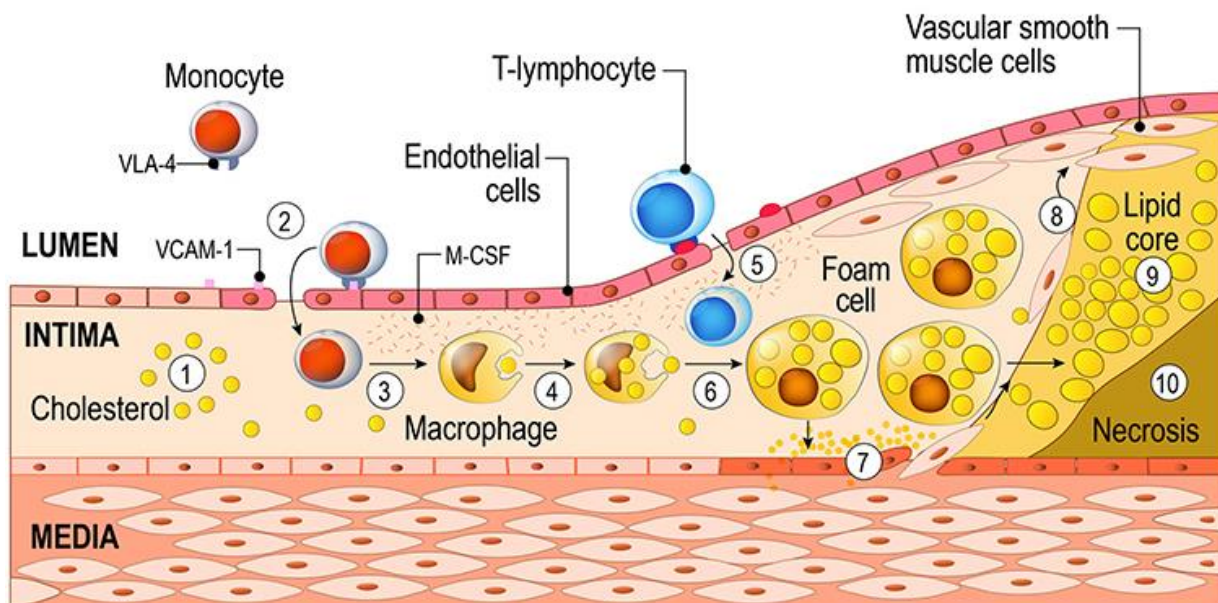


Image was reprinted from Minelli and Montinari (2019).⁴⁶ This work is published and licensed by Dove Medical Press Limited under the Creative Commons Attribution – Non Commercial (unported, v3.0) License. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed.

1.3 Frailty: conceptualisation and instruments to assess frailty

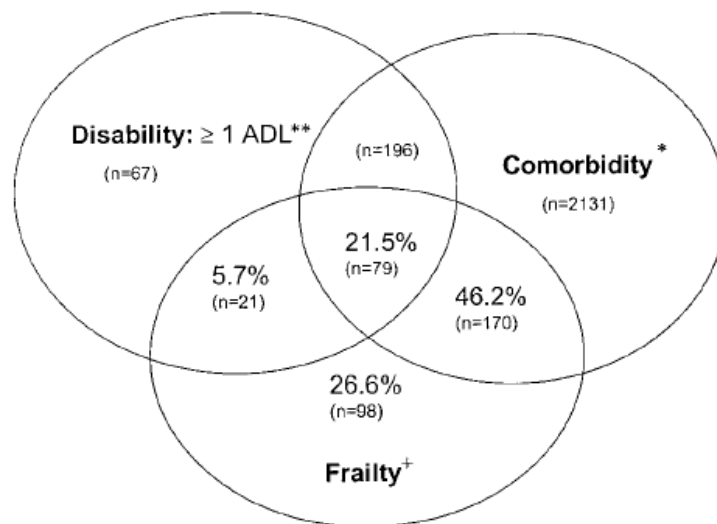
One of the major challenges of frailty research is the absence of a uniform definition. Instead, several models of frailty have been developed. Although the different frailty models often state the same general definition of frailty (that frailty is a state of vulnerability to external stressors),

the precise conceptualisation and operationalisation of the frailty models differ, which have implications for subsequent research and clinical practice. For example, the different conceptualisations affect which components are included in the frailty instruments, which subsequently impact who is defined as being frail or non-frail. In addition, the composition of frailty instruments may influence the strength of associations with risk factors and disease outcomes. The next section provides an overview of the major frailty models and compares the main frailty instruments widely used in clinical practice and research.

1.3.1 Conceptualisation and overview of frailty instruments

Frailty is a state of vulnerability to internal and external stressors. It is a phenomenon that accounts for the substantial variation in the health of older people, whereby a single stressor, such as an infection, may have different consequences in individuals. Whilst believed to be a distinct entity, frailty is strongly associated with chronological age and other common geriatric conditions, including falls, multimorbidity (the presence of two or more diseases), and disability (difficulty carrying out activities essential to independent living).⁴⁸ The overlap in the prevalence, construct, and multifactorial origin of these conditions have influenced the diverse conceptualisations of frailty.⁴⁹ For example, initial research on this topic used the terms ageing, frailty, disability, and comorbidities synonymously owing to their overlapping prevalence (**Figure 1.5**). However, the growing evidence on the inter-relationships between these concepts suggests that they are distinct entities.⁵⁰ Frailty increases with age but is considered to be an extreme consequence of ageing⁵ as not all older people are frail. Similarly, not all individuals with frailty are disabled or vice versa.⁵⁰ In contrast, comorbidity is present in most people with frailty among the 2,762 Cardiovascular Health Study participants, but fewer comorbid people were frail (**Figure 1.5**).⁵⁰ This suggests that frailty may contribute to the development or progression of several chronic diseases, but the mechanisms by which these occur (e.g. through lower activity levels or biological mechanisms) are uncertain.

Figure 1.5 Venn diagram displaying the extent of overlap of frailty with disability and comorbidity



Total number of participants with frailty (n=368). Abbreviations: ADL=activity of daily living. Image was reprinted from The Journal of Gerontology – Series A: Biological Sciences and Medical Sciences, Vol. 56A, Fried *et al.*, Frailty in Older Adults: Evidence for a Phenotype, Pages M151, Copyright (2001), with permission from Oxford University Press. License number: 5303821471840.

Frailty is believed to be caused by the accumulation of age-related molecular and cellular damage that reduces biological (e.g. body reserves like fat, protein, and nutrients) and functional (e.g. the capacity to fulfil functional activities) reserves. Declines in these reserves lead to cumulative decline in function across multiple physiologic systems (e.g. immune, skeletal muscle, cardiovascular) and increase an individual's vulnerability to stressors, i.e. frailty. A schematic representation of the onset of frailty is shown in **Figure 1.6**.⁶ Therefore, central to the definition of frailty is the concept that multiple systems are involved and no single disrupted system defines it (a concept that also distinguishes it from disability and disease). A consensus-building effort using a Delphi process concluded that the definition of frailty should be multidimensional.⁵¹

Figure 1.6 A schematic representation of the origin of frailty

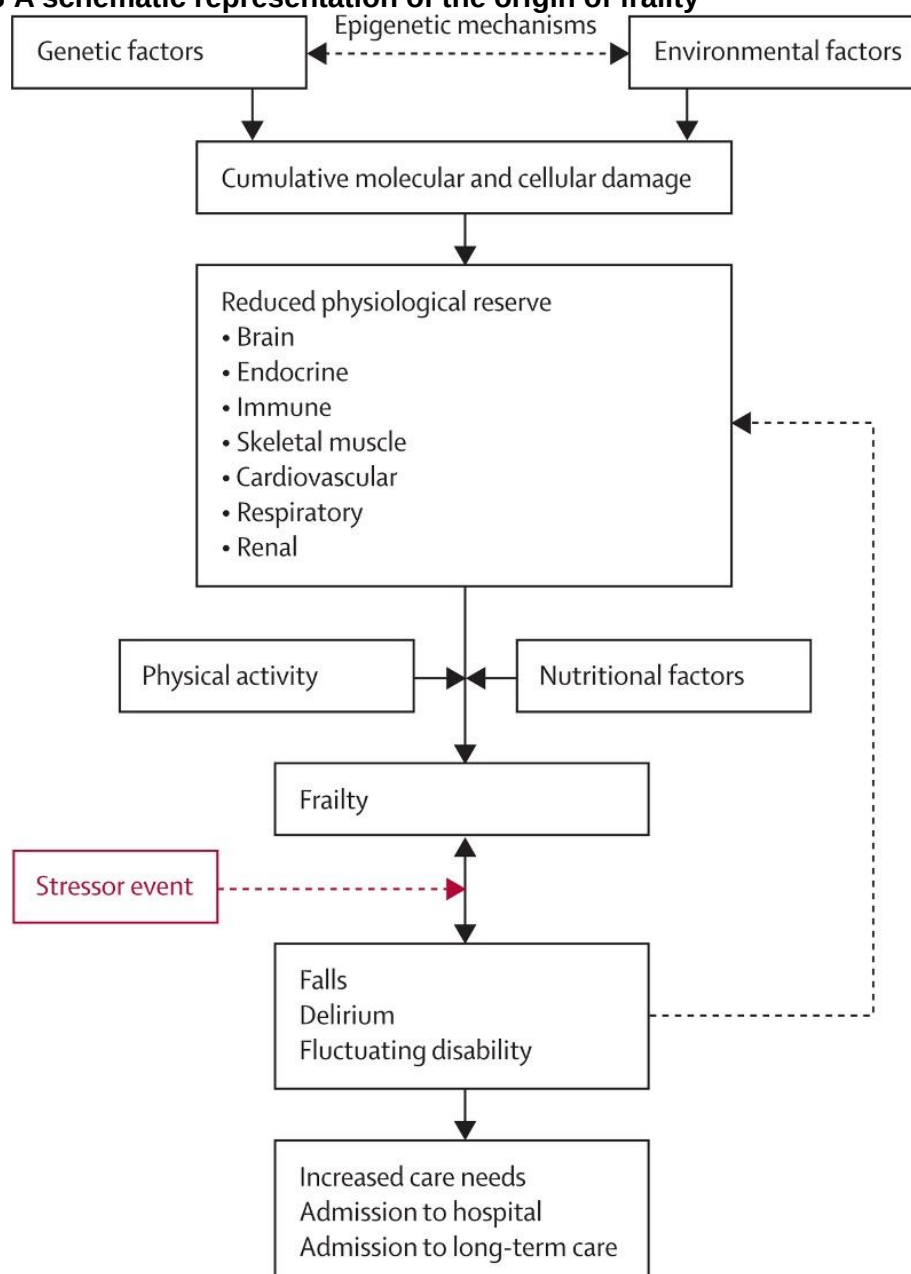


Image was reprinted from The Lancet, Vol. number 381, Clegg A., Young J., Iliffe S., Rikkert M. O., and Rockwood K., Frailty in elderly people, 752-762,⁶ Copyright (2013), with permission from Elsevier. License number: 5560871484322.

Operationalising this definition, however, is challenging. Two systematic reviews identified 51-61 frailty instruments in the literature,^{52,53} but only nine of the existing instruments are widely used.⁵³ **Table 1.1** summarises the characteristics of the 9 most widely used frailty instruments and **Table 1.2** lists the domains included in each instrument. The instruments vary substantially in the number of included items, domains, level of data, expertise, and time required. For example, the Clinical Frailty Scale is a broad assessment of functional capacity

and general health, operationalised through a simple but relatively subjective assessment by clinicians from “very fit” to “very severely frail”. The frailty phenotype (FP)⁵⁴ is an instrument based on 5 physical criteria involving a combination of subjective (e.g. self-reported exhaustion) and objective measurements (e.g. grip strength). The FRAIL scale is a close modification of the FP with a simpler application using 5 binary questions. Conversely, the frailty index (FI)⁵⁵ is a multidimensional measure involving 20-30 or more items based on self-reported, objective, or diagnostic data, and needs a data analyst or software to compute it. In addition to the 9 most highly-cited instruments, other forms of frailty instruments include single-domain measures (e.g. gait speed), biological-based measures,^{56–58} and electronic health records (EHR)-based measures (e.g. electronic frailty index⁵⁹ and Hospital Frailty Risk Score).⁶⁰

Table 1.1 Characteristics of the most widely used frailty instruments

Tool	Requires data	Survey	Self-assessment	No. of items	Domain type	Expertise	Time rating 1-5
Frailty Phenotype	√			5	Physical	Clinical	5
Frailty Index	√			20-30+	Multidim.	Data analyst	5
Gill Frailty Measure		√	√	8	Disability	n/a	1
Frailty/Vigor Assessment	√			9	Multidim.	Data analyst	2
Clinical Frailty Scale	√			9	Multidim.	Clinical	1
Brief Frailty Instrument	√			4	Multidim.	Clinical	2
Vulnerable Elders Survey		√	√	12	Multidim.	n/a	1
FRAIL Scale		√	√	5	Physical	General	1
Winograd Screening Instrument	√			15	Multidim.	Clinical	2

Table was inspired by The Improvement Hub (2017),⁶¹ which is licensed under the Creative Commons Attribution-Noncommercial-NoDerivatives 4.0 International Licence.

Table 1.2 Summary of the domains included in widely used frailty instruments

	Nutritional	Physical activity	Mobility	Strength	Energy	Cognition	Mood	Social aspect	Disability	Disease, medication	General health	Balance
Frailty Phenotype	✓	✓	✓	✓	✓							
Frailty Index	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Gill Frailty Measure			✓						✓			✓
Frailty/Vigor Assessment		✓		✓			✓		✓	✓		✓
Clinical Frailty Scale		✓	✓		✓	✓		✓	✓	✓	✓	
Brief Frailty Instrument						✓			✓	✓		
Vulnerable Elders Survey		✓	✓	✓		✓		✓	✓		✓	✓
FRAIL Scale	✓		✓	✓	✓				✓			
Winograd Screening Instrument	✓		✓			✓	✓	✓	✓	✓		

Table was adapted from Chung *et al.* (2020).⁶² This work is open access under the CC-BY-NC 4.0 License which allows users to copy, redistribute and make derivative works for non-commercial purposes, provided the original work is cited correctly.

1.3.2 Two schools of thought: the frailty phenotype (FP) and frailty index (FI)

Despite multiple instruments to assess frailty, the published literature on this topic is dominated by one of two frailty models, the FP and FI. Most of the available frailty instruments are adaptations of these two and have emerged largely due to the availability of specific data rather than any distinct differences in the conceptualisation of frailty.⁶³ It is common to see a preference for one model, which has resulted in these two ‘schools of thought’. The main characteristics and differences in the two frailty models are presented in **Table 1.3**.

Table 1.3 Summary of the main differences in the FP and FI models

Frailty phenotype	Frailty index
➤ Considered to be a medical syndrome ➤ Clear biological framework; distinct from disability but often considered a “pre-disability” disability ➤ Based on signs and symptoms ➤ Has 5 components ➤ Can be completely self-reported, but is usually a combination of self-reported and objective measures ➤ Includes mostly physical components ➤ Uses a pre-defined set of criteria ➤ Possible before a clinical assessment ➤ Not (realistically) possible using routine electronic health records without modifications ➤ Ordinal variable with range 0-5 or categorical variable with 3 levels	➤ Considered to be a measure of overall biological age ➤ No biological framework; no clear differentiation from disability (disability often included in the definition) ➤ Based on diseases, activities of daily living, results of a clinical evaluation, signs, and symptoms ➤ Has 20-30 or more components, but not fixed ➤ Can be completely self-reported, but is usually a combination of self-reported and objective measures, and medical records ➤ Includes multidimensional components ➤ Uses an unspecified set of criteria ➤ Only possible after a comprehensive clinical assessment ➤ Possible using routine electronic health records ➤ Continuous variable with range 0-1 or categorical variable with 3 levels

Table was adapted from Cesari, M., Giovanni, G., Abellan van Kan, G., and Vellas, B., The frailty phenotype and the frailty index: different instruments for different purposes, *Age and Ageing*, 2014, 43, 10-12,⁶⁴ by permission of Oxford University Press. License: number 5560880963343.

Frailty phenotype (FP)

The FP was developed by Fried and colleagues^{53,54} and views frailty as a medical syndrome – the occurrence of a set of physical symptoms suggests the presence of frailty. The core frailty symptoms were identified as wasting (loss of muscle and strength and weight loss), loss of endurance (exhaustion), reduced balance and slow mobility, and reduced physical activity. These symptoms are related and can be unified into a re-enforcing cycle of declining energy and reserve termed the ‘frailty cycle’ (**Figure 1.7**).⁶⁵ The authors hypothesise that insults at any point of the cycle, such as age-related cellular dysregulation and diseases, can initiate the frailty cycle and result in the FP symptoms.

Figure 1.7 Cycle of frailty: the hypothesised FP model

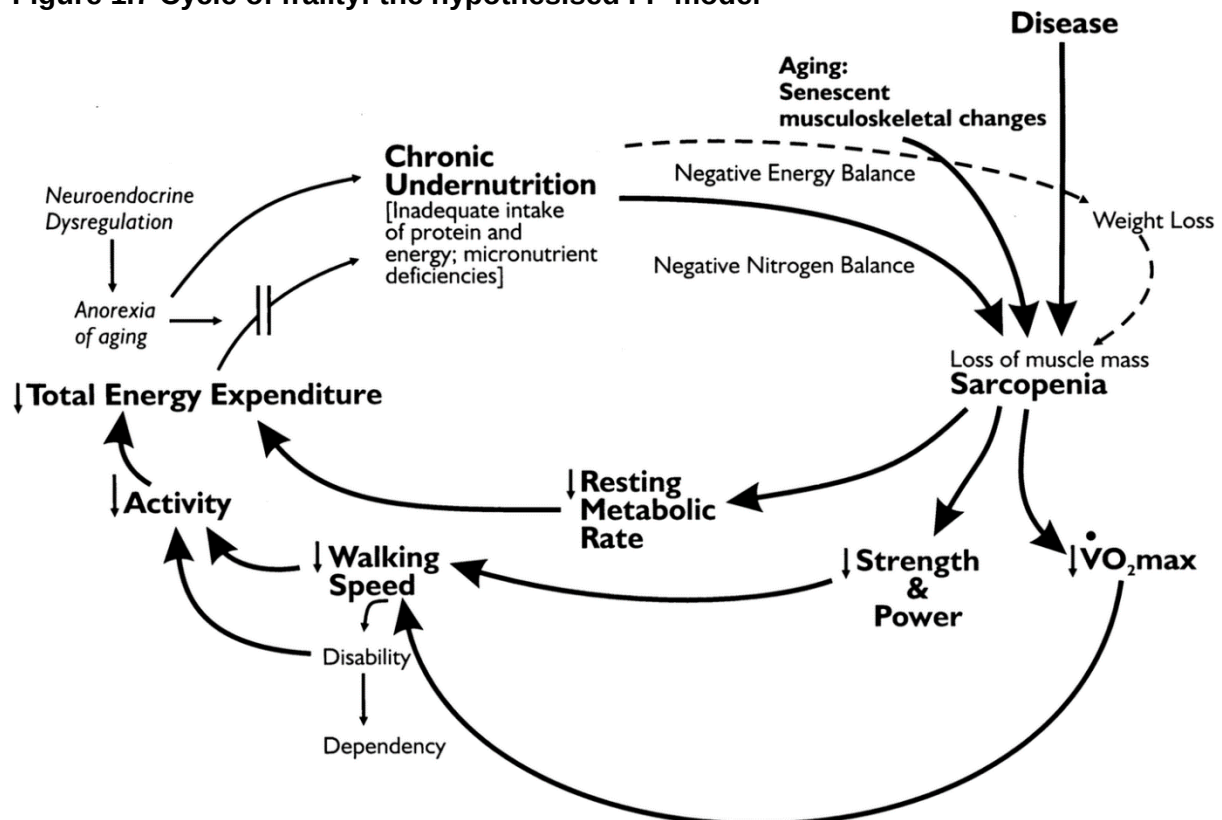


Image was reprinted from Negm *et al.* (2018).⁶⁶ This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>).

To operationalise this frailty model, the authors identified a set of frailty symptoms that were ranked by geriatricians and defined a criteria for each component.⁵⁰ Five physical components were identified: weakness, slow gait speed, low physical activity, exhaustion, and unintentional weight loss. The criteria used are shown in **Figure 1.8**. Individuals that presented with 1 or 2 criteria were identified as pre-frail and those with three or more as frail. The original authors have rigorously validated their hypothesised model. FP is associated with frailty-related outcomes⁵⁴ and the symptoms occur in aggregation in a hierarchical order,⁶⁵ which conforms to the definition of a medical syndrome.

Figure 1.8 Operationalisation of the FP and FI models

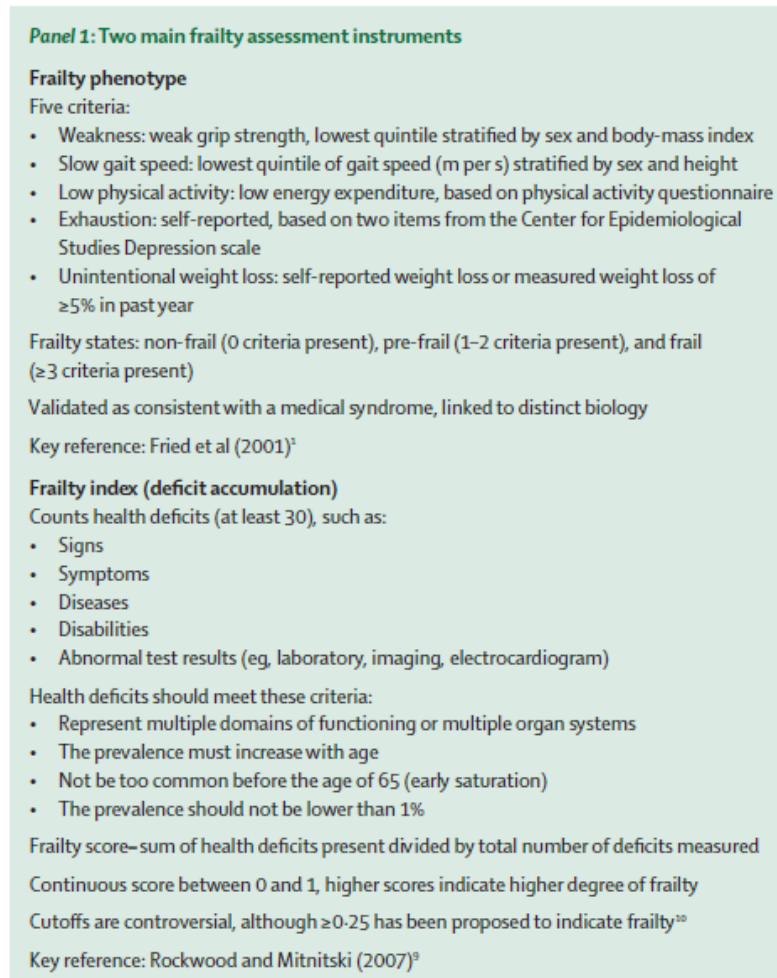


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Frailty index (FI)

The FI (or “deficit accumulation”) model was developed by Rockwood and Mitnitski as a proxy marker of biological ageing.⁵⁵ This model suggests that “the more individuals have wrong with them, the more likely they are to be frail”.⁶⁷ A key concept of the model is that being frail depends on the number of deficits (symptoms, signs, diseases, disabilities, or laboratory anomalies) an individual has rather than their nature, reflecting the inter-dependent nature of health variables owing to a shared underlying relationship. This interdependency means that the accumulation of deficits follows a distinct pattern: deficits accumulate exponentially with age and FI has a gamma distribution – the increase in frailty has a limit (around a score of 0.7) beyond which further deficit accumulation appears to be biologically impossible.⁶⁸ The

properties of FI were reproducible and consistent across many different populations regardless of the included deficits.^{59,69–71}

To operationalise FI, 20-30 or more (and even up to 70) signs, symptoms, diseases, disabilities, and abnormal test results are required (examples of deficits included are presented in **Figure 1.9**). Importantly, it is common to include cardiovascular (e.g. hypertension, history of stroke, or MI) and adiposity (e.g. abnormal BMI) deficits in the FI. The individual deficits have several criteria for inclusion: they should (1) represent multiple domains of functioning or organ systems; (2) increase in prevalence with age; (3) not be too common before older age; and (4) not be too rare (prevalence > 1%).⁷² Each deficit is given a score of 1 (present) or 0 (absent) when dichotomised and equally weighted given their hypothesised inter-dependent relationship. FI is expressed as a ratio score between 0 to 1 (sum of deficits present over the total number of deficits measured), which can be categorised using the following cut-offs: ≥ 0.25 (frailty) and ≥ 0.10 and < 0.25 (pre-frailty).⁷²

Figure 1.9 Example of a list of variables used to construct the FI

Appendix A: List of variables used to construct the Frailty Index

1	memory changes	2	general mental functioning changes	3	everyday activities changes
4	clouding/delirium	5	history of depressed mood	6	sleep changes
7	paranoid features	8	cerebrovascular problems	9	mobility impairment
10	past history relevant to cognitive impairment/ loss	11	other past history	12	family history relevant to cognitive impairment/ loss
13	other family history of degenerative disease	14	short-term memory impairment	15	long-term memory impairment
16	mood problem	17	problem in going out alone	18	problem in cooking
19	problem in getting dressed	20	problem in grooming	21	problem in bathing
22	problem in toileting	23	incontinence (urine)	24	onset of cognitive symptoms
25	feels sad, blue, depressed	26	tired all the time	27	moving all the time
28	depression – clinical impression	29	seizures, partial complex	30	seizures, generalized
31	syncope or blackouts	32	falls	33	Parkinson's disease
34	history of stroke	35	headaches	36	hypertension
37	myocardial infarction	38	arrhythmia	39	congestive heart failure
40	respiratory	41	malignancy	42	gastro-intestinal
43	history of thyroid disease	44	history of diabetes mellitus	45	head and neck
46	thyroid abnormality	47	breasts	48	lungs
49	cardiac	50	peripheral pulses	51	abdomen
52	rectal	53	skin	54	musculoskeletal
55	sucking	56	snout	57	palmomentalis R
58	bulk	59	tone/neck	60	tone/limbs
61	tremor/rest	62	tremor/postural	63	tremor/intention
64	bradykinesia/face	65	bradykinesia/limbs	66	coordination/limbs
67	coordination/trunk	68	posture/standing	69	gait pattern
70	vibration sense				

Image was reprinted from Rockwood and Mitnitski (2007).⁷³ License not required – permission is granted at no cost for use of content in a Master's Thesis and/or Doctoral Dissertation.

The FP and FI are different (**Table 1.3**). There is a growing consensus that the two frailty models are not equal but complementary.⁶⁴ Extensive research has been carried out to compare the utility of both models to predict adverse outcomes. The FP is preferred by their proponents due to its distinct biological conceptualisation and evidence of a syndrome, which lends to identifying potential targets for intervention. The main criticism of the FP model is that the definition only includes physical symptoms and therefore contradicts the growing consensus that frailty is a multidimensional concept. However, the original authors advocate that the FP syndrome reflects a cumulative decline across multiple physiological systems.⁶⁵ The FI is preferred for its flexibility (e.g. the number or type of deficits included is not fixed) and finer grading of frailty. However, the FI construct for frailty lacks a clear biological framework from which potential targets can be identified and its operationalisation is labour- and data-intensive (but easy to compute with established EHRs) compared to other frailty instruments.

1.4 The hypothesised relationships between CVD RFs, CVD, and frailty

Frailty and CVD commonly coexist.⁷⁴ A meta-analysis of over 54,000 older adults reported that CVD was associated with 2.7- to 4.1-fold higher odds of frailty⁷⁵ and linear associations of frailty and CVD risk scores have been previously reported.⁷⁶ The coexistence of frailty and CVD is supported by substantial overlap in RFs that may contribute to their pathogenesis.⁷⁷ Therefore, a bidirectional relationship between frailty and CVD has been hypothesised (depicted in **Figure 1.10**), which is driven by common lifestyle RFs and mediated by biological processes.

Figure 1.10 Hypothesised relationship between frailty and CVD

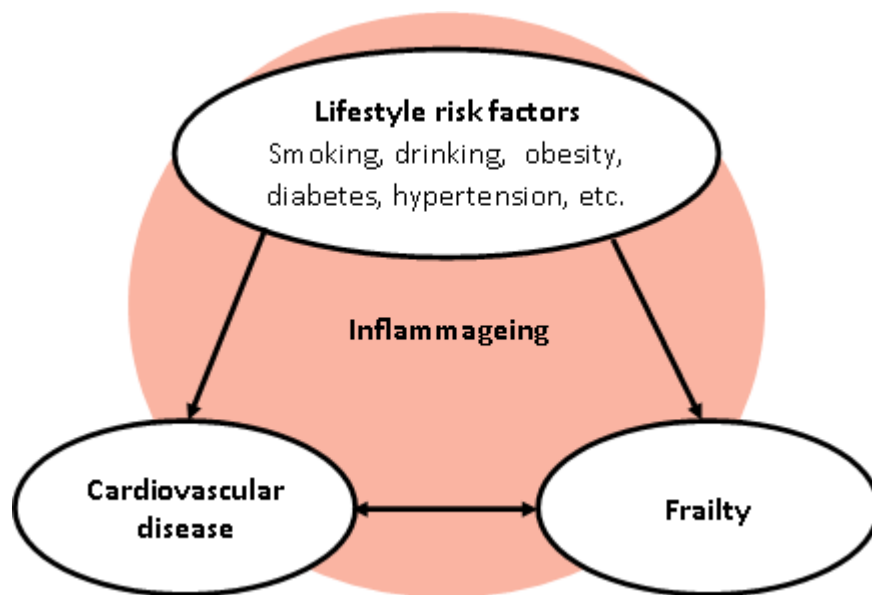
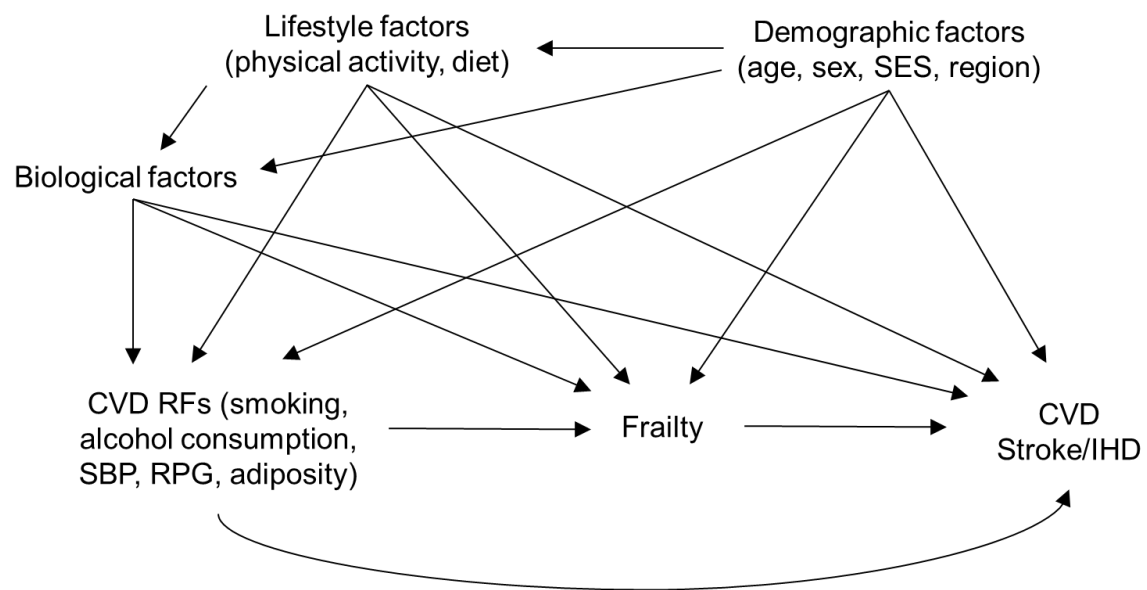


Figure was inspired by Stewart (2019).⁷⁸

The common lifestyle RFs, e.g. smoking, alcohol consumption, and obesity, are established RFs for CVD. Most CVD RFs have been reported to be causally related to CVD^{79,80} and their pathophysiology is understood well. Conversely, the available evidence supporting the relevance of individual CVD RFs and frailty is much smaller and weaker. Similarly, while it is well known that CVD is associated with a higher risk of frailty (e.g. a diagnosis of CVD is often followed by reductions in physical activity, leading to muscle wasting and frailty),⁷⁴ evidence suggesting the reverse association – that frailty predicts CVD – is less common.⁸¹ A directed acyclic graph, which depicts the hypothesised relationships between a set of variables, is shown for the relationships studied in this thesis (**Figure 1.11**).

Figure 1.11 Directed acyclic graph of the hypothesised relationships between CVD RFs, frailty, and CVD and confounders



1.4.1 Shared risk factors and aetiology

Frailty, stroke, and IHD share several common RFs, including sociodemographic, clinical, and biological factors. The major RFs for frailty are modifiable: smoking, excessive alcohol consumption, diabetes, hypertension, physical inactivity, obesity, and poor diet. Frailty and CVD also share non-modifiable RFs including age, sex, ethnicity, and family history of CVD. Being male is a stronger risk factor for CVD and being female is strongly associated with frailty. The different pathological types of CVD share the same RFs, but some are more specific for certain types. IHD and IS share similar RFs due to their common aetiology of atherosclerosis. Hypertension is the most important RF for ICH, and SAH, whilst sharing many of these RFs, is chiefly caused by a vascular deformation.⁸²

The biological pathways connecting CVD RFs to CVD have been extensively studied, but exactly how CVD RFs are related to frailty is less certain. The pathophysiology of frailty is believed to involve ageing processes.⁸³ For example, age-related accumulation of molecular and cellular damage and deterioration of tissue function can lead to a progressive decline in health by increased risk of disease and death. The causes of ageing include chronic inflammation, endocrine dysregulation, immune dysfunction, metabolic imbalance, oxidative

stress, epigenetic modifications, and proteostasis.⁸⁴ One of the most likely mechanisms linking between CVD RFs and frailty is believed to include ‘inflammageing’. Inflammageing refers to the chronic, low-grade inflammation that occurs during ageing and involves pro-inflammatory markers like interleukin-6 (IL-6) and C-reactive protein (CRP), which have been associated with frailty and its various markers.⁸⁵ Inflammageing is a pathogenic mechanism underlying frailty and atherosclerosis.

The development of frailty through inflammageing can occur by several mechanisms. For example, multiple morbidities from chronic inflammation can be detected using the FI model. In the FP model, inflammatory cytokines can cause mitochondrial dysfunction and damage the skeletal muscle, resulting in sarcopenia. Inflammation also promotes protein degradation, directly reducing biological reserve.⁷⁷ The individual CVD RFs may also be related to frailty via inflammation. Smoking and the metabolism of alcohol directly trigger an inflammatory response, which can exacerbate the effects described above.^{86,87} In obesity, fat cells or adipocytes secrete inflammatory mediators that recruit and activate immune cells.⁸⁸ The same inflammatory mechanisms may be involved in the pathways by which frailty contribute to the development of atherosclerosis and risk of CVD.

The bi-directional associations between frailty and CVD are challenging when studying these associations. First, the shared RFs and biological processes suggest that substantial unmeasured confounding is likely when studying these associations. Second, both frailty and CVD develop over a long latent period and subclinical phase, which means that the directionality of the associations is difficult to assess in observational studies (due to their reliance on reported symptoms) and the associations may be modified partly by reverse causation. Rather than frailty being a unique risk factor for CVD, their co-existence may simply reflect an advanced disease state and a consequence of CVD.⁸⁹ Finally, the FI model commonly includes deficits related to CVD, such as hypertension and BMI, which are problematic when interpreting the independent effects of CVD RFs for frailty and frailty in CVD. Therefore, substantial uncertainty about the associations involving frailty and CVD (RFs) exist.

1.5 Gaps in knowledge about measurement of existing frailty instruments

The requirement for long-term management of frailty is becoming more evident, such as improved detection following interventions or deterioration in hospital care. Ideal frailty instruments for this purpose should be simple to use and provide valid and reproducible measures.⁸⁹ Observational studies assessing frailty will also benefit from valid and reliable instruments to provide more accurate estimation of associations. Accordingly, several criteria for frailty instruments were suggested by Clegg *et al.*⁶ (listed in **Box 1.1**), but whether most frailty instruments fulfil these criteria is uncertain.

Box 1.1 Criteria for the optimum instrument to assess frailty

- Ability to reliably predict adverse clinical outcomes
- Ability to reliably predict patient response to potential therapies
- To be supported by a biological causative theory
- Be simple to apply

Criteria are from Clegg *et al.* (2013).⁶

The criteria suggest that frailty instruments should reliably predict adverse clinical outcomes and patient response to potential therapies. This means that in terms of psychometrics – a field of study devoted to testing and measuring human responses – frailty instruments should be valid (measure what it purports to measure) and reliable (measurement is consistent when taken on different occasions or by different observers).⁹⁰ The taxonomy of measurement properties to assess the quality of health-related outcomes measures proposed by Mokkink *et al.* is shown in **Figure 1.12**.⁹¹ The validity of frailty instruments is often assessed by their consistency with known frailty constructs (construct validity), their ability to predict adverse outcomes (criterion or predictive validity), and by their reproducibility or degree of measurement error or within-person variability over time (reliability).⁹² Currently, there is limited reliable evidence of these measurement properties.⁵ In general, the predictive performance of instruments is highly variable⁹³ and the degree of reliability or measurement error of frailty measurements is largely unknown. With few frailty instruments appearing to fulfil

Clegg's criteria, the selection of instruments is frequently based on pragmatism rather than evidence,⁹⁴ creating fragmented research that uses different frailty instruments.

Figure 1.12 Taxonomy of measurement properties



Abbreviations: HR-PRO=health-related patient-reported outcome. Reprinted from Journal of Clinical Epidemiology, 63(7), Lidwine B. Mokkink, Caroline B. Terwee, Donald L. Patrick, Jordi Alonso, Paul W. Stratford, Dirk L. Knol, Lex M. Bouter, Henrica C.W. de Vet, The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes, Pages 9, Copyright (2010), with permission from Elsevier. License Number: 5620650255874.

The lack of a “gold standard” for frailty is controversial.⁵ Many consider different frailty models to be complementary⁶⁴ due to the accumulating evidence that they are not interchangeable and may measure different constructs (agreement between the frailty instruments is variable: Cohen’s kappa range 0.10-0.83).⁹⁵ Conversely, the consequences of not having a standardised instrument are significant. First, there is no consensus on the global prevalence of frailty and estimates vary from 4% to 59% between studies.¹⁵ Second, the results of

observational studies are not directly comparable, which limits the power of systematic reviews and their ability to inform clinical practice. In addition, the absence of a gold standard means that frailty instruments are often validated by their ability to predict other frailty models, which may not be comparable, or all-cause mortality, which leads to concerns that frailty has been reduced to predicting mortality rather than the frailty construct itself.⁹⁶

Standardisation of a frailty definition has important implications for clinical practice, research, and policy.⁴⁹ Exactly which individuals are defined as frail determines who ultimately receives or is rejected for appropriate treatment. For example, it is increasingly recognised that older adults with frailty benefit from higher blood pressure (BP) targets when managing BP⁹⁷ and older stroke patients, who are at greater risk of frailty, are often withheld thrombolytic therapy due to concerns of adverse prognosis and higher risk of complications.⁹⁸ Also, the types of management strategies differ according to the hypothesised frailty models. Definitions based on the physical frailty model may involve interventions based on physical activity whilst those based on multidimensional definitions may require integrated care. Policy-makers require a reliable definition of frailty to be able to measure the prevalence of frailty, predict the future burden of frailty, and allocate limited resources effectively. Hence, comparative studies are needed to assess the criteria suggested by Clegg *et al.* (2013),⁶ including validity and reliability of different frailty measures.

1.6 Aims and objectives

Frailty and CVD in older people are major public health concerns worldwide. Rapidly ageing populations, particularly in LMICs like China, are likely to be accompanied by an increased burden of frailty and CVD.¹⁷ Understanding the associations between frailty and CVD can inform public health policies to mitigate the socioeconomic impacts of population ageing.

Frailty and CVD share common RFs and are hypothesised to have bidirectional associations that are mediated by shared biological processes. However, the directionality of the associations and their precise shape and strength are uncertain. Therefore, the relevance of modifiable CVD RFs in the risk of frailty and frailty of CVD is uncertain. In addition, frailty

instruments vary in their measurement properties, but there is a major gap in the existing evidence on the validity and reliability of frailty instruments. A valid and reliable instrument is required to enable an accurate assessment of frailty and its associations with disease outcomes.

The main aims of the thesis are to investigate the associations of frailty with CVD, particularly the relevance of modifiable CVD RFs for the risk of frailty and frailty in the risk of the major CVDs using a prospective study of 0.5 million adults in the China Kadoorie Biobank (CKB).⁹⁹ An additional aim of the thesis was to compare the measurement properties of widely used frailty instruments, which will contribute to the evidence-based selection of frailty instruments.

The specific objectives of the thesis are to:

1. Conduct a systematic review to compare the utility of widely used frailty instruments to predict all-cause mortality. (Chapter 2)
2. Compare the reliability and magnitude of within-person variability of the most widely used frailty instruments in studies with repeat measurements of frailty. (Chapter 3)
3. Conduct a literature review on the observational evidence of prospective associations of key modifiable CVD RFs with risk of frailty and frailty with risk of the main CVD types. (Chapter 4)
4. Examine the prevalence, correlates, validity, and reliability of frailty in the CKB population. (Chapter 6)
5. Characterise the cross-sectional and prospective associations of CVD RFs (alcohol consumption, smoking, systolic blood pressure, glucose, fat mass, and lean body mass) with risk of frailty. (Chapter 7)
6. Characterise the prospective associations of frailty with incident stroke and IHD (and subtypes) and fatal and overall events. Examine how the associations are modified by age, sex, and other factors, and assess the effects of reverse causation bias. (Chapter 8)

2 Systematic review of the utility of the major frailty measures for prediction of all-cause mortality in older people

2.1 Introduction

Frailty is a well-established risk factor for all-cause mortality and widely used to guide decisions in clinical practice. Nevertheless, there is considerable heterogeneity in the performance of the available frailty instruments,^{100–102} including modest utility for prediction of adverse outcomes.^{103–105} This suggests that many instruments do not fulfil the criteria for an optimum frailty instrument as suggested by Clegg *et al.* (2013)⁶ and whether instruments can reliably predict adverse clinical outcomes is uncertain. To assess Clegg's criteria to promote an evidence-based selection of instruments in clinical practice and research, reliable comparisons of the measurement properties, such as validity and reliability,^{90,92,106} of frailty instruments is needed.

One way to assess the validity of health measurement tools is to compare how well the instruments agree with or predict the gold standard, also known as criterion or predictive validity.^{107,108} The criterion validity of an instrument is usually determined by the association between the instrument and a gold standard. In the absence of a gold standard, the criterion validity of the frailty instruments is typically assessed by their ability to predict adverse outcomes like all-cause mortality.¹⁰⁰ Previous systematic reviews that assessed this property have “catalogued” a wide range of available frailty instruments, but heterogeneity across studies limits the ability to perform a meta-analysis of such studies. Two previous systematic reviews^{109,110} that compared the FP and FI suggested that the FI may be a better predictor of mortality than FP, but the latter was based on a single FI study.¹¹⁰ One review concluded that the FI was the most appropriate instrument to assess frailty,⁹⁴ but their assessment was qualitative. In most cases, comparisons were limited because of the heterogeneity in frailty instruments and the baseline risks in the different populations studied.

The aim of the present chapter is to assess the criterion validity of the FP and FI by comparing their predictive accuracy for all-cause mortality in older people via a systematic review. Importantly, the review is limited to studies where both instruments were directly compared in the same study population to avoid confounding by differences in absolute risks between populations.

2.2 Methods

2.2.1 Data sources

A systematic literature search was conducted to identify population studies of frailty and all-cause mortality in older people in Ovid Medline, Embase, Scopus, Web of Science, and CINAHL databases between 1 January 2000 (shortly before the initial reports of each frailty instrument) and 21 September 2021. Two updated searches were conducted on 27 July 2022 and 24 August 2023, but did not identify any eligible studies.

2.2.2 Search strategy and selection criteria

The search strategy (described in **Table S2.1**) included key terms and Medical Subject Heading (MeSH) terms that were related to study design and frailty models. MeSH terms are a list of subject headings used to index articles according to their content, so using these search terms enabled a more focussed search. Inclusion criteria were: (1) population-based prospective studies of older people (aged ≥ 65 years) excluding individuals recruited from long-term care facilities or hospital settings (these individuals were excluded because of their higher baseline risk for mortality compared to non-institutionalised or -hospitalised populations, which means the predictive accuracy of frailty instruments are also likely to differ); (2) studied both FP and FI; (3) reported receiver operating characteristics (ROC) curves; and (4) articles in English. Study selection was conducted by the author, and data extraction and quality assessment were conducted independently by the author and another reviewer.

2.2.3 Data extraction, synthesis, and analysis

Data were extracted using a standardised extraction form (**Table S2.2**). The area under the ROC curve (AUC) and 95% confidence intervals (95%CI) were extracted for the associations of each frailty instrument with all-cause mortality. Since the frailty instruments involved both categorical (non-frail, pre-frail, or frail) and continuous (ratio or ordinal score) formats, the extracted AUCs were grouped by the format. When multiple adjustments for confounders were used, AUC estimates based on the most comprehensive adjustment were extracted. If results for multiple follow-up periods were reported, data were extracted for the most frequently used duration of follow-up in the included studies. In addition, details of how each frailty instrument was estimated (e.g. the list of items and domains included in the FI-based instruments and the criteria used to define each FP component) were recorded. Finally, the authors were contacted for further information if needed.

The methodological quality of the studies was assessed using the Scottish Intercollegiate Guidelines Network's (SIGN) Methodology checklist^{111–113} (**Table S2.3**). The SIGN checklist is one of several tools currently in use to assess the risk of bias in cohort studies.¹¹³ A systematic review by Sanderson *et al.* (2007)¹¹⁴ reported that the SIGN checklist has similar characteristics to other scales, such as the Joanna Briggs Institute critical checklist¹¹⁵ and Newcastle-Ottawa Scale for cohort study,¹¹⁶ which provides justification for its use in the present thesis. The checklist included standardised statements to assess possible risks of bias in individual studies, including the selection of participants, the definition of exposure and outcomes, confounding, and statistical analyses. All studies were graded as having either a High (++), Acceptable (+) or Low (0) quality rating.

The systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (**Table S2.4**) and Synthesis Without Meta-analysis (SWiM), which is a 9-item checklist that provides a standardised approach to reporting alternative synthesis methods.¹¹⁷ A formal meta-analysis was not considered because of the substantial methodological heterogeneity between the individual studies.¹⁰⁶ A descriptive

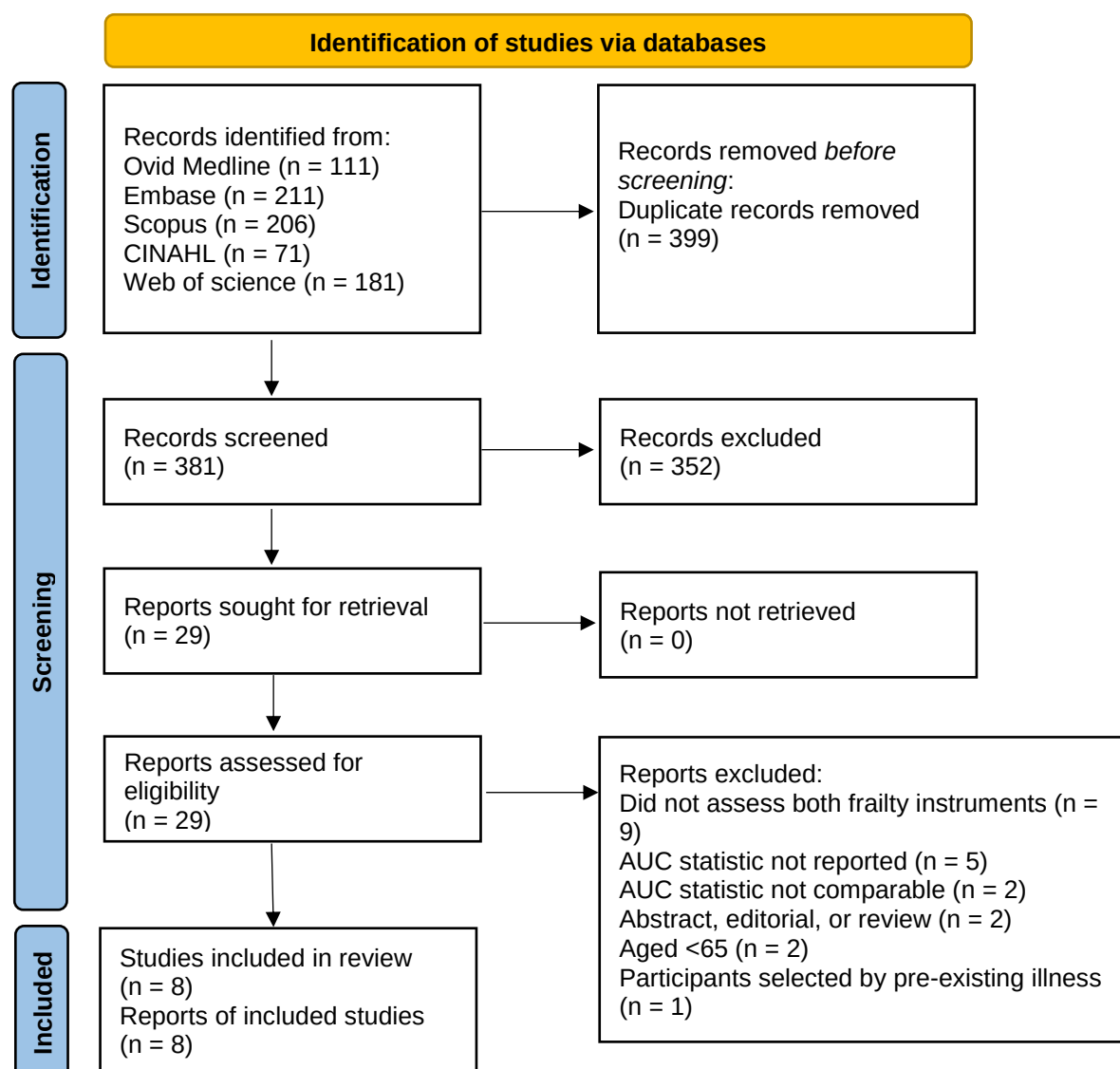
comparison of the extracted data is provided instead. AUCs were displayed using a forest plot by frailty model and instrument type. The proportion of results that met the criteria of having acceptable discriminatory power ($AUC \geq 0.7$), indicating that there was a 70% chance that the frailty instrument could rank a person who died with a higher frailty score than a person who survived, was also calculated. To investigate the sources of heterogeneity, AUCs were plotted using funnel and forest plots to visualise patterns by the number of deaths, study quality, and the number of domains and items in the FI.

2.3 Results

2.3.1 Study selection and characteristics

The PRISMA flow diagram is shown in **Figure 2.1**. The search identified 780 reports, which included 399 duplicates. Review of titles and abstracts left 29 studies for a detailed assessment of eligibility. Of the 10 community-based prospective cohort studies that were eligible for analysis, two studies were subsequently excluded because they omitted participants without frailty from the analysis¹⁰⁵ or combined the pre-frail and frail categories,¹¹⁸ leaving 8 studies for inclusion in the review.

Figure 2.1 PRISMA flow diagram of included studies



Databases were searched between 1 January 2000 and 21 September 2021. Update searches were carried out on 26 July 2022 and 24 August 2023, but did not identify any additional eligible studies.

Table 2.1 shows selected characteristics of the 8 included studies. The number of participants in the individual studies varied from 909 to 7,713 and their mean age ranged from 69.4 to 81.1 years. The duration of follow-up of studies ranged from 2 to 7 years. Most studies involved participants living in Europe (n=3)^{119–121} or Australia (n=2),^{122,123} and the remaining 3 studies were in the United States,¹²⁴ China,¹²⁵ or multiple diverse countries in Europe, North America or Australia.¹²⁶ According to the SIGN checklist, 3 reports had ‘High (++)’,^{119,123,126} 3 had ‘Acceptable (+)’,^{121,124,125} and 2 had ‘Low (0)’ quality.^{120,122} The risk of bias chiefly reflected uncertainty about the response rates and loss to follow-up by levels of frailty (**Table S2.5**).

Table 2.1 Characteristics of the included studies by study size

Author, (year)	Country (Name of Study) ^a	No. of participants (% female)	Age, years mean (SD)	Follow- up (yrs)	Study quality (SIGN ^b checklist)	Details of the frailty index used in individual studies						
						No. of items	Domains included					No. of other domains ^e
							Energy	Physical activity	Weight loss or BMI	Strength ^c	Gait ^d	
Chao (2018)	USA (HRS)	FP: 1642 (n/s); FI: 7713 (n/s)	n/s (aged ≥65)	7	+	24	✓					8
Romero-Ortuno and Soraghan (2014)	Europe - various (SHARE)	7058 (56.7%)	M: 80.4 (4.6); F: 81.1 (4.9)	5	++	70	✓	✓		✓	✓	12
Ding (2017)	England (ELSA)	4638 (55.4%)	74.0 (6.3)	2	0	30	✓			✓	✓	6
Woo (2012)	China	4000 (50%)	n/s (aged ≥65)	4	+	47		✓	✓	✓	✓	8
Li (2015)	Europe, North America and Australia (GLOW)	3985 (100%)	69.4 (8.9)	3	++	34	✓	✓	✓	✓	✓	7
Zucchelli (2019)	Sweden (SNSACK)	3363 (64.9%)	74.7 (11.2)	3 to 5	+	45					✓	10
Widagdo (2015)	Australia (ALSA)	2087 (n/s)	n/s (aged ≥65)	3	0	39				✓	✓	8
Thompson (2019)	Australia (NWAHS)	909 (55%)	74.4 (6.2)	1 to 10	++	34	✓	✓	✓	✓	✓	8

^aStudy names are: HRS=The Health and Retirement Study; SHARE=The Survey of Health, Ageing and Retirement in Europe; ELSA=The English Longitudinal Study of Ageing; GLOW=The Global Longitudinal Study of Osteoporosis; SNSACK=The Swedish National Study on Ageing and Care in Kungsholmen; ALSA=The Australian Longitudinal Study of Ageing; and NWAHS=The North West Adelaide Health Study.

^bSIGN, Scottish Intercollegiate Guidelines Network. Quality ratings: ++ all or most of the criteria fulfilled, + some of the criteria fulfilled, 0 few or no criteria fulfilled.

^cItems like grip strength and difficulty lifting weights over 10 lbs.

^dItems like gait speed, can you walk 100m, difficulty with moving around, and usage of a walking stick.

^eTable S2.9 lists all domains.

2.3.2 Comparative ability of the FP and FI to predict all-cause mortality

Data on the utility of frailty to predict all-cause mortality are presented separately for the FP (Table 2.2) and FI (Table 2.3). Among the 8 studies, 3 studies assessed frailty using a continuous format, 1 used a categorical format, and 4 used both formats (Table S2.6). Two studies reported AUCs separately by sex^{119,125} and one study was restricted to females.¹²⁶

Table 2.2 Key findings and study quality of FP studies

Author (year)	Continuous or categorical	Statistic reported	No. deaths	Results	AUC≥0.7 (Max 1)	Study quality (SIGN)
Romero-Ortuno and Soraghan (2014)	Continuous	AUC ²¹	M: 239 F: 132	0.69 (0.65-0.73) 0.65 (0.61-0.70)	No No	++
Ding (2017)	Continuous ^a	C-statistic ^{*1}	278	0.75 (0.72-0.78) ^b	Yes	0
Li (2015)	Continuous	AUC ^{†1}	107	0.79 (0.74-0.84)	Yes	++
Zucchelli (2019)	Continuous	AUC ^{*3}	477	0.80 (0.78-0.82)	Yes	+
Widagdo (2015)	Continuous	AUC ^{*1}	205	0.63 (0.59-0.67) ^b	No	0
Chao (2018)	Continuous	AUC ^{†1}	754	0.77 (0.75-0.78)	Yes	+
Thompson (2019)	Continuous	AUC ^{†1}	86	0.73 (0.68-0.79)	Yes	++
Woo (2012)	Categorical	AUC ^{*1}	M: 350 F: 137	0.64 (0.61-0.67) 0.60 (0.55-0.65)	No No	+
Li (2015)	Categorical	AUC ^{†1}	107	0.79 (0.74-0.83)	Yes	+
Widagdo (2015)	Categorical	AUC ^{*1}	205	0.57 (0.53-0.61) ^b	No	0
Chao (2018)	Categorical	AUC ^{†1}	754	0.75 (0.74-0.77)	Yes	+
Thompson (2019)	Categorical	AUC ^{†1}	86	0.71 (0.66-0.78)	Yes	++

^aUsed factor score from confirmatory factor analysis.

^bNo confidence interval was provided so estimated standard error using formula (3) page 2771 from Debray *et al.* (2019)¹²⁷

Model adjustment: †: age and sex; ‡: age and/or sex plus other confounders; *: none specified; and ?: undetermined.

Models used to generate ROC: ¹: logistic regression; ²: Cox regression; and ³: not specified.

*AUC approximated using sensitivity and specificity: (sensitivity + specificity)/2

Abbreviations: AUC=area under the ROC curve; ROC=receiver operating characteristics; SIGN=Scottish Intercollegiate Guidelines Network

Table 2.3 Key findings and study quality of FI studies

Author (year)	Continuous or categorical	Statistic reported	No. deaths	Results	AUC≥0.7 (Max 1)	Study quality (SIGN)
Chao (2018)	Continuous	AUC ^{†1}	4140	0.73 (0.72-0.74)	Yes	+
Romero-Ortuno and Soraghan (2014)	Continuous	AUC ^{‡1}	M: 239 F: 132	0.70 (0.66-0.74) 0.65 (0.61-0.70)	Yes No	++
Ding (2017)	Continuous	C-statistic ^{*1}	278	0.75 (0.72-0.78) ^b	Yes	0
Li (2015)	Continuous ^a	AUC ^{†1}	107	0.80 (0.76-0.85)	Yes	++
Zucchelli (2019)	Continuous	AUC ^{*3}	477	0.84 (0.82-0.86)	Yes	+
Widagdo (2015)	Continuous	AUC ^{*1}	346	0.66 (0.63-0.69) ^b	No	0
Thompson (2019)	Continuous	AUC ^{†1}	86	0.73 (0.67-0.79)	Yes	++
Chao (2018)	Categorical	AUC ^{†1}	4140	0.72 (0.71-0.73)	Yes	+
Woo (2012)	Categorical	AUC ^{*1}	M: 350 F: 137	0.63 (0.60-0.66) 0.61 (0.56-0.66)	No No	+
Li (2015)	Categorical	AUC ^{†1}	107	0.80 (0.75-0.84)	Yes	+
Widagdo (2015)	Categorical	AUC ^{*1}	346	0.60 (0.57-0.63) ^b	No	0
Thompson (2019)	Categorical	AUC ^{†1}	86	0.73 (0.68-0.79)	Yes	++

^aUsed quintiles rather than items.

^bNo confidence interval was provided so estimated standard error using formula (3) page 2771 from Debray *et al.* (2019)¹²⁷
Model adjustment: [†]: age and sex; [‡]: age and/or sex plus other confounders; ^{*}: none specified; and [?]: undetermined.

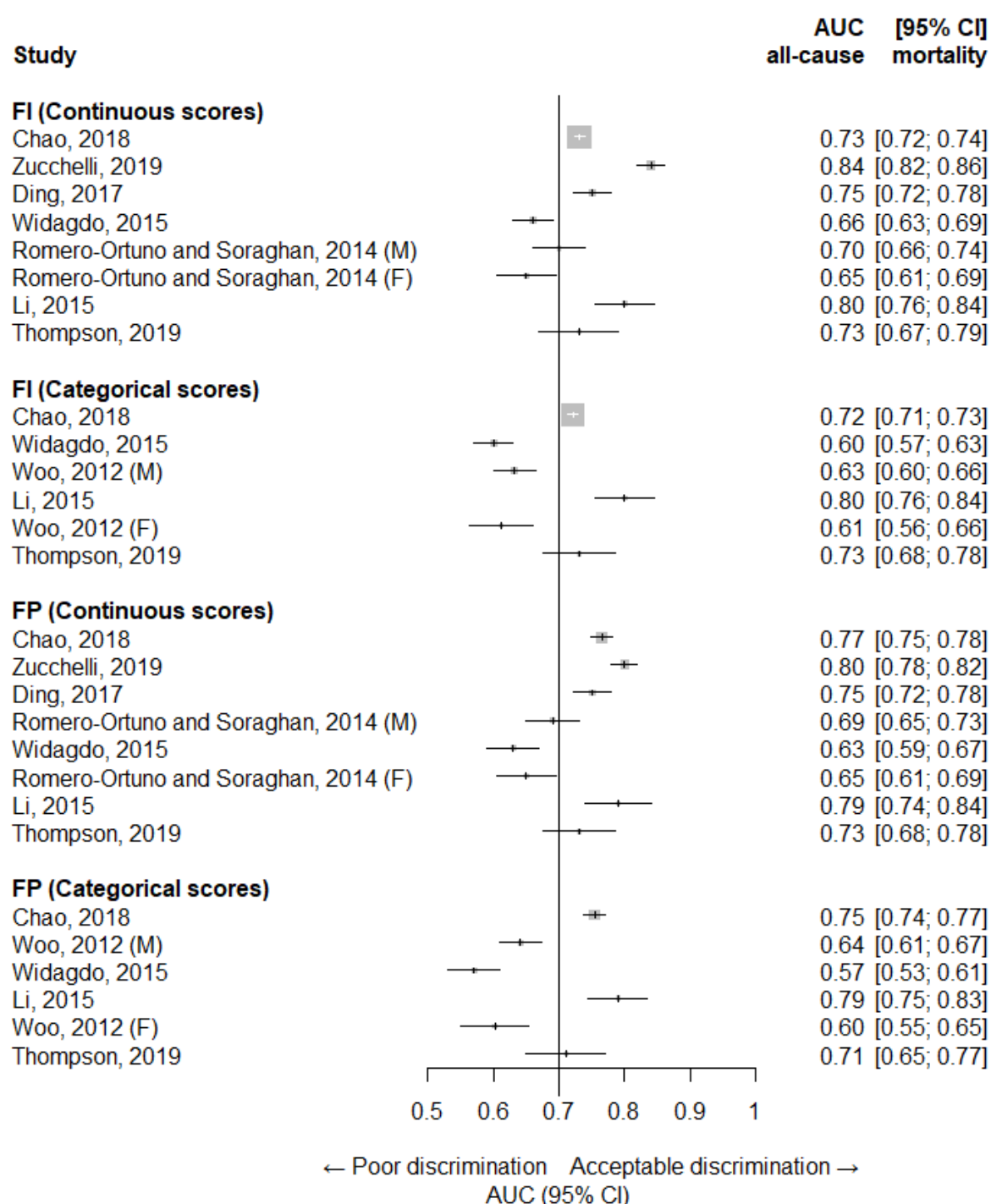
Models used to generate ROC: ¹: logistic regression; ²: Cox regression; ³: other; and ⁴: not specified.

*AUC approximated using sensitivity and specificity: (sensitivity + specificity)/2

Abbreviations: AUC=area under the ROC curve; ROC=receiver operating characteristics; SIGN=Scottish Intercollegiate Guidelines Network

AUCs were displayed using a forest plot (**Figure 2.2**). The range of AUC (95%CI) for the FI continuous, FI categorical, FP continuous, and FP categorical scores was 0.65 (0.61-0.70) to 0.84 (0.82-0.86), 0.60 (0.57-0.63) to 0.80 (0.75-0.84), 0.63 (0.59-0.67) to 0.80 (0.78-0.82), and 0.57 (0.53-0.61) to 0.79 (0.75-0.83), respectively. Likewise, the proportions of study results exceeding an AUC threshold of 0.7 were 75% (6/8), 50% (3/6), 63% (5/8), and 50% (3/6), respectively.

Figure 2.2 Forest plot of AUCs for prediction of all-cause mortality by the FI and FP



2.3.3 Assessment of heterogeneity

There was substantial methodological heterogeneity across individual studies. The methods used to ascertain deaths included proxy-reported^{120,124,126} or linkage to national death registers.^{121–123} The definition of frailty instruments also differed among studies. No two FP-

based instruments were identical and all the FP instruments included in the review were modifications of the original approach⁵⁴ (**Table S2.7**). For the FI, the number of items (range: 24 - 70) and domains included in the FI instruments also varied (**Table S2.8** and **Table S2.9**). Most instruments were constructed using the standard procedure developed by the original authors⁷² and were multi-dimensional. The thresholds used to detect frailty, the statistical methods used to derive the AUC, and the level of adjustment for confounders also varied between studies (legends under **Table 2.2** and **Table 2.3** describe the statistical methods used). The limited overlap in the 95% CI for the AUCs reflects the substantial statistical heterogeneity in the results between individual studies.

The sources of heterogeneity in AUCs were investigated using funnel and forest plots. Neither the power of the study nor the quality of the studies appeared to influence the AUC. In the Figure of the AUCs against the number of deaths indicating the power of the study (**Figure 2.3** and **Figure 2.4** showing the same figure restricting the y-axis to 1000), AUCs were equally distributed regardless of study power. However, 4 out of 5 low quality studies had lower than the acceptable threshold compared to a majority of studies involving higher quality studies. Thus, study quality may account for some of the heterogeneity in AUCs between individual studies.

Figure 2.3 Plot of discriminative ability (AUC) against the number of events by SIGN quality rating

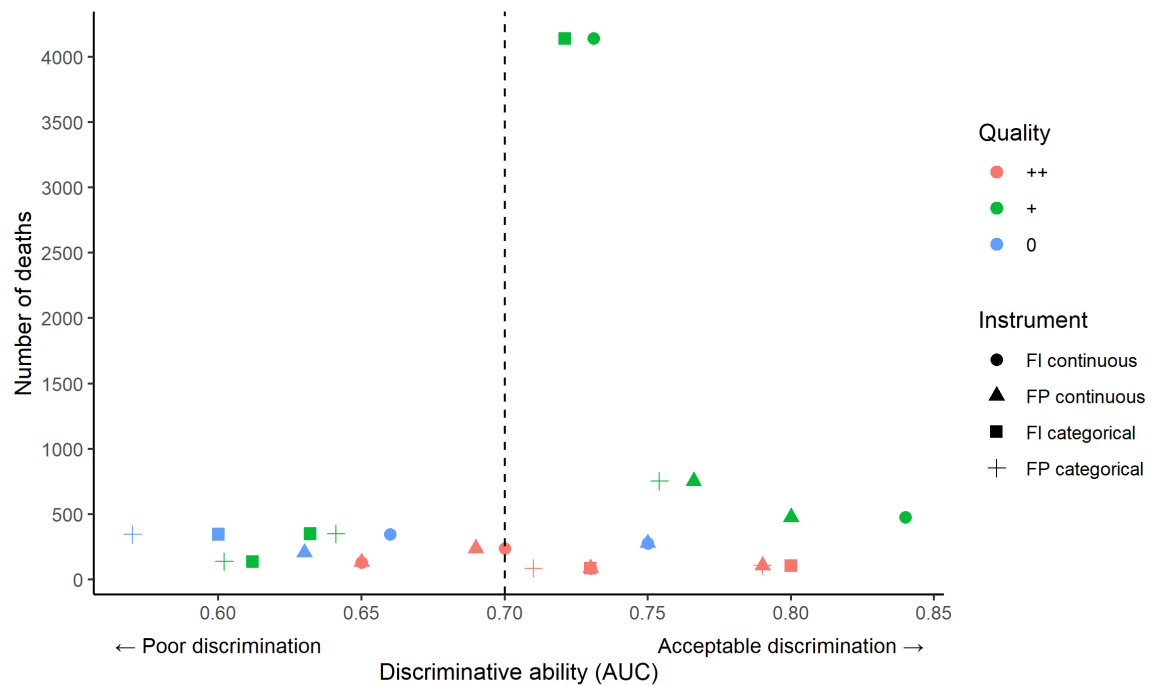
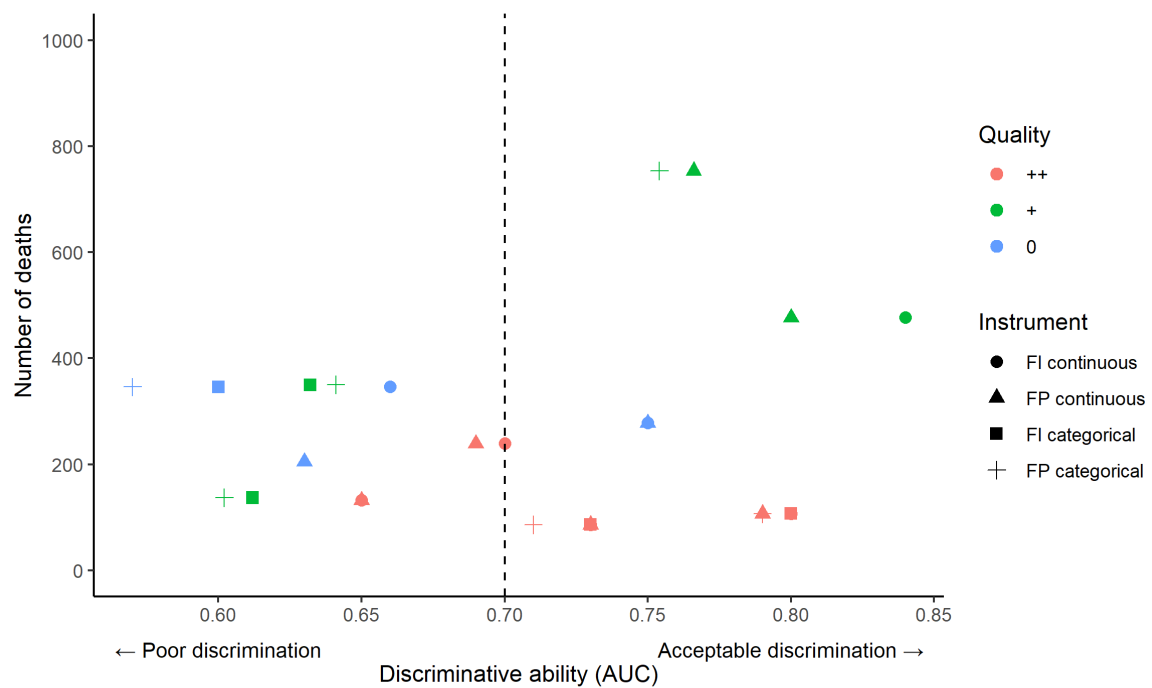
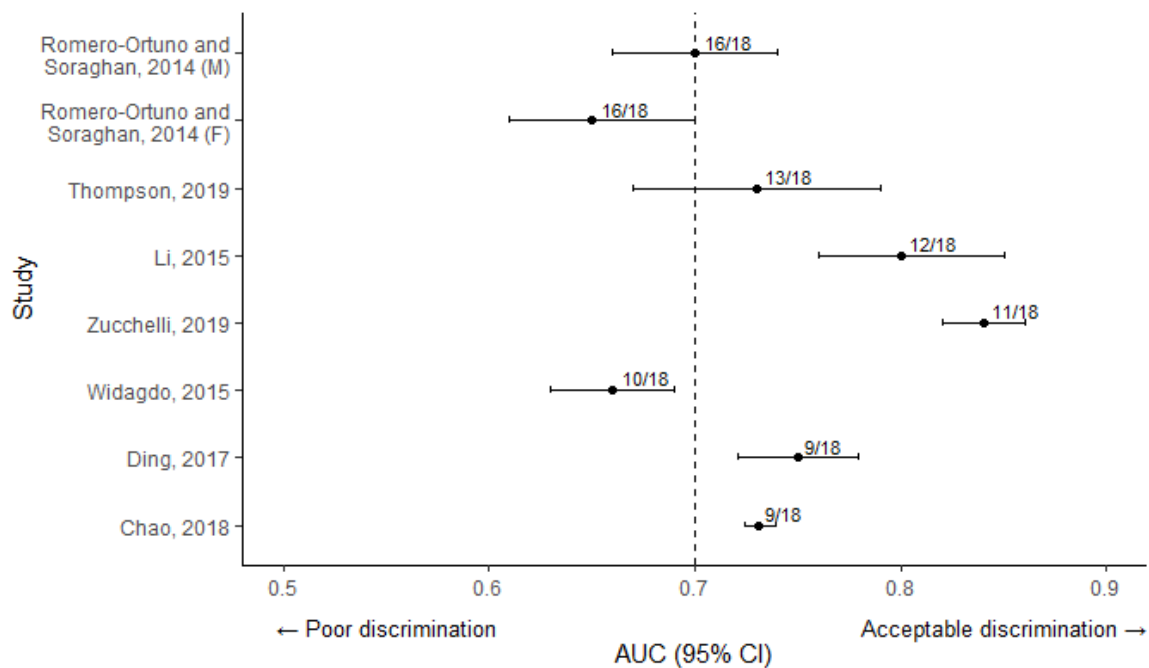


Figure 2.4 Plot of discriminative ability (AUC) against the number of events (restricted to 1000) by SIGN quality rating



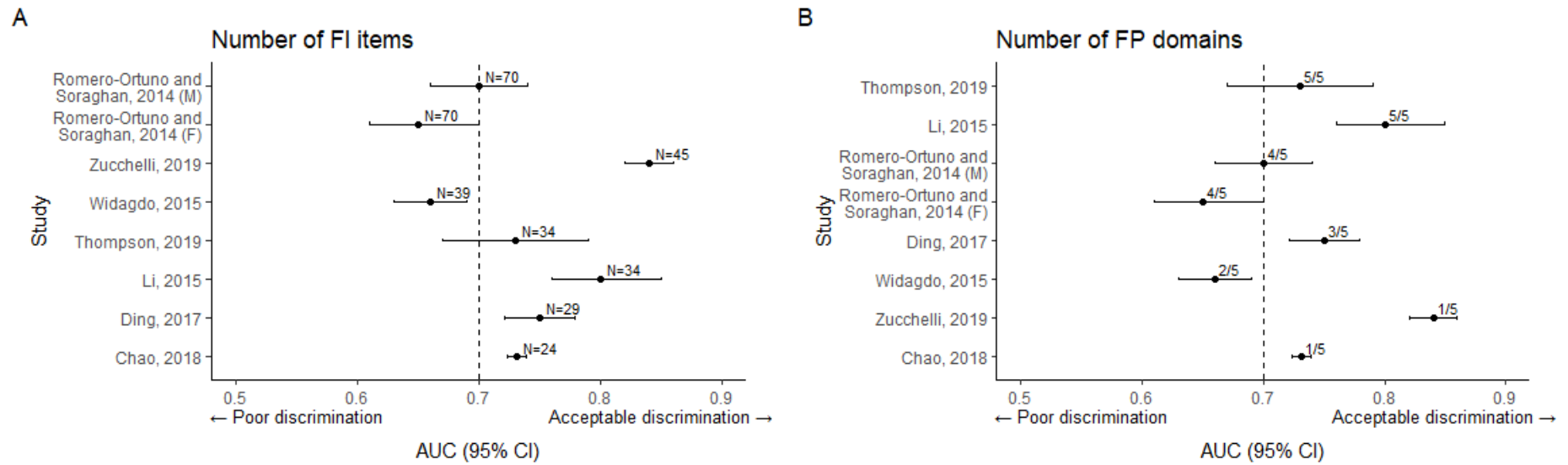
The AUCs were also explored by characteristics of the FI (continuous) instrument. First, AUCs were ordered by the total number of domains included in the continuous FI instrument (**Figure 2.5**), which ranged from 9 to 16 out of 18 considered. The AUCs appeared to be distributed randomly around the 0.7 threshold regardless of the number of domains included.

Figure 2.5 Discriminative ability (AUC) for FI continuous instruments arranged by the total number of domains included



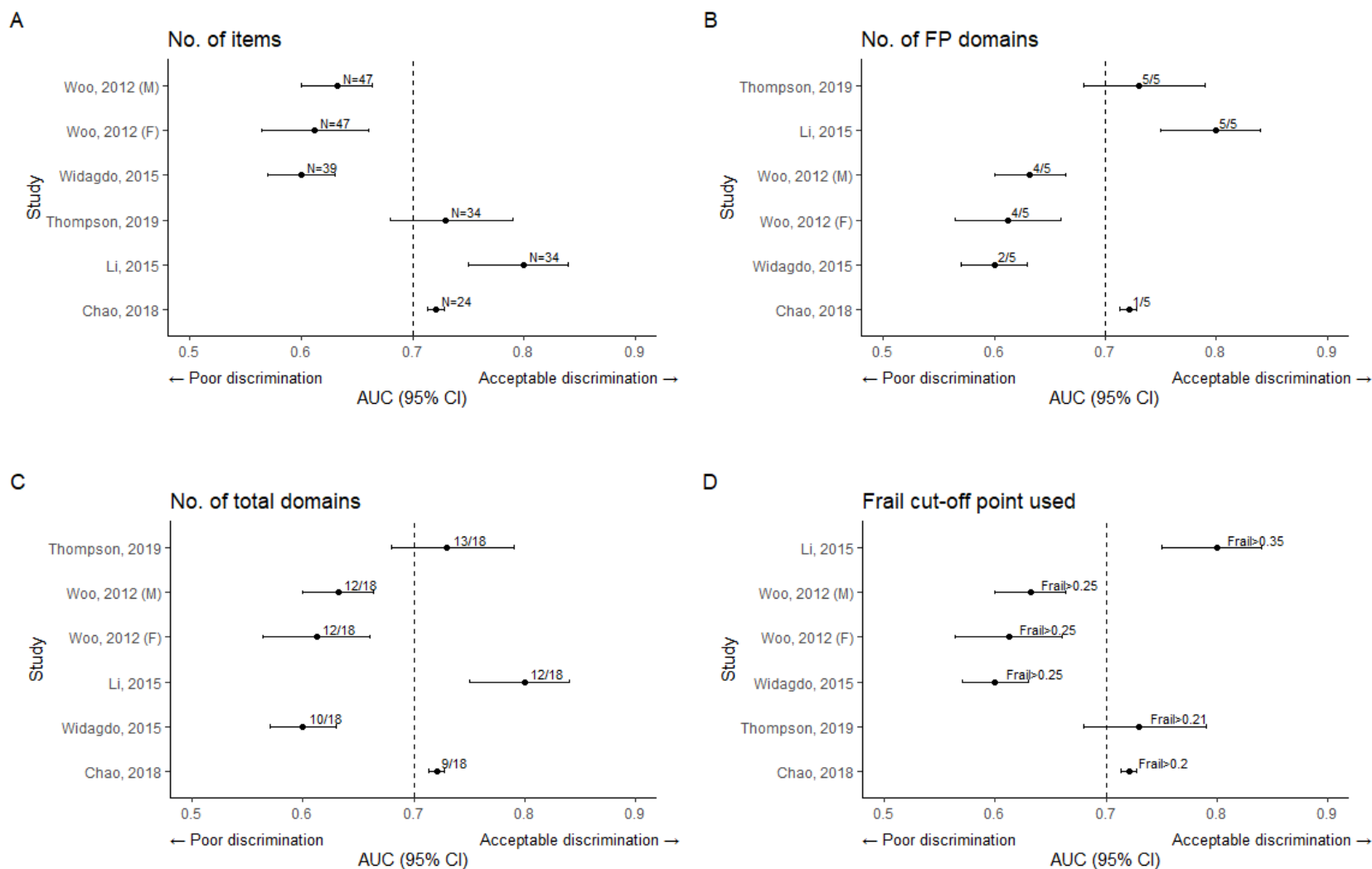
Second, AUCs were also ordered by the total number of items and the number of FP domains included in the continuous FI instruments (**Figure 2.6**). The total number of FI items ranged from 24 to 70 and the number of FP domains from 1 to 5. AUCs were equally distributed regardless of the number of items or FP domains included.

Figure 2.6 Discrimination ability (AUC) for FI continuous instruments by (A) no. of items and (B) no. of FP domains included



A similar assessment for categorical FI instruments showed no obvious sources of heterogeneity (**Figure 2.7**). The number of items, number of FP domains, or the number of total domains included in the categorical FI instruments did not appear to affect AUC. AUCs also did not show any trend by the different thresholds used to categorise frailty in the FI score (0.2, 0.21, 0.25, and 0.35). The above sensitivity analysis suggests the characteristics of the FI instrument does not explain the heterogeneity in AUCs observed in the present systematic review. However, the relative differences were unclear and the results were difficult to interpret due to the low number of included studies.

Figure 2.7 Discriminative ability (AUC) for FI categorical instruments by (A) no. of items, (B) no. of FP domains, (C) no. of total domains, and (D) frail cut-off point used



2.4 Discussion

The proportion of studies that reached the acceptable threshold for discriminatory ability was similar for the FI and FP and higher for continuous versus categorical frailty instruments. The distribution of AUC values was also slightly higher for instruments that used continuous rather than categorical formats.

2.4.1 Comparison with existing literature

Previous systematic reviews have suggested that the FI may be a superior predictor of mortality.^{4,94,109,110} The potential reason for this superiority, suggested by the present systematic review, is the continuous nature of the FI – categorisations of continuous scores may lead to loss of information and reduction in their predictive ability.¹²⁸ This review also demonstrated that both FP and FI had generally comparable (despite large differences in content) and suboptimal ability to predict mortality, as reported previously.^{103–105} This suboptimal ability may be explained by poor reliability of frailty instruments. Unreliable exposures are characterised by wide within-person variability from random measurement errors, which may result in the underestimation of associations with outcomes.^{129,130} However, the reliability of existing frailty instruments has yet to be established.

A novel aspect of this review was the direct comparison of the frailty models within studies that compared the performance of these instruments in the same participants (i.e. with comparable selection biases and absolute risks for all-cause mortality). This approach should have enhanced the validity of the comparisons evaluated in the present study than previous studies.^{4,94,109,110,131,132}

2.4.2 Strengths and limitations

The main strengths of the review were the synthesised results based on reports involving a large number of participants that were mainly of high methodological quality. The methodological quality of reports was assessed using a standardised checklist and used to explore inconsistencies in the results. Nevertheless, the review had several limitations.

Despite efforts to enhance comparability, substantial methodological heterogeneity persisted between studies, which may have obscured true differences. Second, the decision to include only studies that compared two frailty instruments in the same population may have been overly restrictive. Third, the study selection was undertaken by the thesis author only and the review was restricted to English language articles, which means that relevant articles may have been missed out during the screening process. Finally, the small number of studies evaluated means that any comparative analyses of subgroups should be interpreted with caution.

2.5 Summary

The two most widely used frailty models are the FP and FI. Despite their differing properties and moderate agreement, the selection between these two instruments in research and clinical practice is generally based on their availability or personal preference. For instance, the FP is often preferred for having a clear biological framework whilst the FI is preferred for its flexibility. Additionally, the FP only requires 5 components, whilst the FI usually requires at least 20 items; thus, the availability of data may determine which frailty measure can be used.

According to Clegg *et al.* (2013),⁶ the ideal frailty instrument should be able to reliably predict adverse clinical outcomes. However, evidence-based selection of frailty instruments based on the above criteria is not common practice due to a lack of comprehensive evidence on the comparison of the measurement properties of frailty instruments. Comparing the predictive ability of the FP and FI, however, is not straight forward. The existing evidence that compares the predictive validity of different frailty instruments is mainly limited by the comparison of results from different populations with varied baseline risks. Therefore, the present systematic review evaluated the validity of the FP and FI, restricting to studies that used both instruments.

The present chapter found that the two major frailty models had limited and comparable ability to predict all-cause mortality, but continuous formats of frailty instruments had slightly superior discrimination compared to categorical formats. This suggests that continuous frailty instruments like the FI may provide a more accurate estimation of associations of CVD RFs

with frailty, and of frailty with CVD. While the findings of the present chapter provide relevant evidence for the subsequent chapters of this thesis, the suboptimal predictive ability of frailty instruments reinforce the ongoing uncertainty about the optimum instruments to assess frailty and highlight the need to evaluate other, understudied measurement properties, such as reliability, to aid evidence-based selection of a frailty instruments. Frailty measurements that are more reliable may provide more accurate estimation of frailty and CVD (RF) associations, but there is a gap in the evidence on the reliability of frailty instruments.⁵ Therefore, the subsequent chapter compares the reliability of the most widely used frailty instruments using repeat assessments of frailty measures in a prospective cohort.

3 Reliability and within-person variability of the major frailty measures

3.1 Introduction

The criteria for optimum frailty instruments to assess the associations of CVD RFs with frailty were previously suggested by Clegg *et al.*⁶ The criteria includes that instruments should reliably predict adverse clinical outcomes and patient responses to potential therapies.⁶ However, whether existing frailty instruments fulfil this criteria is uncertain⁹⁴ and previous investigations of the thesis found suboptimal validity of the existing frailty instruments (**Chapter 2**). Also, there is limited available evidence on other measurement properties, particularly reliability, to compare the performance of different frailty instruments.⁵

Most observational studies of frailty rely on measurements recorded at a single visit and examine the associations of frailty with outcomes after several years or decades. This assumes that a single assessment of frailty is reliable, measured consistently, and reflective of one's long-term frailty status. However, the degree of agreement between repeat frailty assessments and the magnitude of within-person variability, the extent to which a single measurement represents a stable measure of frailty over several years, are unknown. If variability is present, it is uncertain whether this can affect the predictive ability of frailty instruments. Frailty is likely to vary within individuals due to fluctuations in severity or random variability. Hence, a comparison of the reliability in different frailty measures over time could be particularly informative about the selection of the optimum instruments to assess frailty.

This chapter will compare two different measures of reliability, agreement and within-person variability, of the FP and FI, and assess the potential effect of this variability on the prediction of outcomes. Repeat measurements of frailty on separate occasions will be used to assess the reliability of frailty measures.¹³³ These analyses should provide novel evidence on the reliability of widely used frailty instruments and guide the selection of the optimum instrument for subsequent analyses. The specific objectives are to (1) compare the agreement and magnitude of within-person variability of frailty scores in the FP and FI and (2) compare the

strength of the associations of falls, hospitalisation, or death with frailty measured at single versus multiple visits.

3.2 Methods

3.2.1 Data source and participants

The Irish Longitudinal Study on Ageing (TILDA)¹³⁴ is a prospective cohort of older people that included repeat assessments of both the FP and FI and follow-up for adverse outcomes. TILDA included 8,175 community-dwelling participants aged ≥ 50 years and their younger spouses or partners ($n=329$) at Wave 1 (October 2009 – February 2011).^{134,135} Repeat assessment was conducted approximately 2 years later (February 2012 – March 2013) with 8,469 eligible participants including 170 new participants. Of these, 7,455 were included in Wave 2 after exclusion of soft refusals ($n=732$) (i.e. did not participate in this particular wave but were contacted again at subsequent waves),¹³⁴ withdrawals ($n=118$), participants who moved abroad ($n=30$), lost to follow-up ($n=114$), and other reasons ($n=20$).¹³⁴ Data on medical history and lifestyle, social, and economic factors were collected in each survey by trained interviewers using a computer-assisted personal interview (CAPI) and a self-completion questionnaire (SCQ).¹³⁴ Data collected from the CAPI and SCQ are shown in **Figure S3.1**. At Wave 1, participants were invited to undertake a nurse-led comprehensive health assessment at a dedicated centre (or in their own homes) during which participants' measurements of anthropometry, physical, cognitive, cardiovascular, and visual function were recorded, and a blood sample was collected for long-term storage.^{134,135} Tests included in the TILDA health assessments are shown in **Figure S3.2**.

3.2.2 Definition of exposure, covariates, and outcomes

Frailty was classified using the FP⁵⁴ and FI⁵⁵ models. The definition of the 5 FP components (weakness, physical inactivity, slow walking speed, unintentional weight loss, and exhaustion) is outlined in **Table 3.1**. Participants with 0, 1-2, and ≥ 3 of these criteria were defined as non-frail, pre-frail, and frail, respectively. Importantly, there were minor differences in the

measurement of variables between Wave 1 (home and/or health assessment centre) and Wave 2 (home assessment only). Wave 1 contains objective height and weight data compared to self-reported data in Wave 2. Additionally, Wave 1 took two measurements of grip strength, which were then used to compute mean grip strength; Wave 2 took one measurement only.

Table 3.1 Operationalisation of the FP model in TILDA

FP component	Definition using TILDA variables	Criteria
Weakness	Sex- and BMI-adjusted grip strength were measured on the dominant hand using a dynamometer. Weight and height were measured using standardised procedures during home and health centre assessments.	Lowest quintile
Physical activity	Sex-adjusted kilocalories (kcal) from the International Physical Activity Questionnaire – Short Form [IPAQ-SF]).	Lowest quintile
Slow walking speed	Sex- and height-adjusted time taken in seconds to perform the Timed-Up-and-Go (TUG) task.	Slowest quintile
Unintended weight loss	Ascertained by the question “In the past year have you lost 10 pounds (4.5kg) or more in weight when you were not trying to.”	Answer “Yes”
Exhaustion	Ascertained using two items from the 20-item Centre for Epidemiological Studies Depression (CES-D) scale. Participants were asked how often they felt that “I could not get going” and “I felt that everything I did was an effort”.	A response of “moderate amount/all of the time” to either question

Table contents derived from Fried *et al.* (2001) and O'Halloran *et al.* (2019)^{54,136}

A 40-item FI was computed according to the standard procedure,⁷² including self-reported variables from the CAPI questionnaire. The coding of the 40 deficits is shown in **Table 3.2**. Binary deficits were coded as present (1) or absent (0) and ordered categorical deficits as a fraction proportional to the number of responses. The FI score, a ratio of the sum of variables by 40, was classified as non-frail (<0.10), pre-frail (≥0.10 to <0.25), and frail (≥0.25).

Table 3.2 Components and coding of the 40-item FI

Variables in TILDA	Cut-points
1. Difficulty walking 100 m	Yes=1; No=0
2. Difficulty jogging 1.5 km	Yes=1; No=0
3. Difficulty rising from chair	Yes=1; No=0
4. Difficulty climbing several flights of stairs	Yes=1; No=0
5. Difficulty climbing one flight of stairs	Yes=1; No=0
6. Difficulty stooping, kneeling, or crouching	Yes=1; No=0
7. Difficulty reaching above shoulder height	Yes=1; No=0
8. Difficulty pushing/pulling large objects	Yes=1; No=0
9. Difficulty lifting/carrying weights ≥ 10 lb	Yes=1; No=0
10. Difficulty picking up coin from table	Yes=1; No=0
11. Difficulty preparing a hot meal	Yes=1; No=0
12. Difficulty with household chores	Yes=1; No=0
13. Difficulty shopping for groceries	Yes=1; No=0
14. Feeling lonely	Rarely or none of the time=0; Some or a little of the time=0.33; Occasionally or a moderate amount of time=0.66; All of the time (5-7 days)=1
15. Poor self-rated physical health	Excellent=0; Very good=0.25; Good=0.5; Fair=0.75; Poor=1
16. Poor self-rated vision	Excellent=0; Very good=0.25; Good=0.5; Fair=0.75; Poor=1
17. Poor self-rated hearing	Excellent=0; Very good=0.25; Good=0.5; Fair=0.75; Poor=1
18. Difficulty following a conversation with one person	None=0; Some=0.5; Much/Impossible=1
19. Daytime sleepiness	Would never doze=0; Slight chance of dozing=0.33; Moderate chance of dozing=0.66; High chance of dozing=1
20. Polypharmacy (≥ 5 medications)	Yes=1; No=0
21. Intrusive pain	Yes=1; No=0
22. Knee pain	Yes=1; No=0
23. Urinary incontinence	Yes=1; No=0
24. Hypertension or high blood pressure	Yes=1; No=0
25. Angina	Yes=1; No=0
26. Heart attack	Yes=1; No=0
27. Diabetes	Yes=1; No=0
28. Stroke	Yes=1; No=0
29. Transient ischemic attack	Yes=1; No=0
30. High cholesterol	Yes=1; No=0
31. Irregular heart rhythm	Yes=1; No=0
32. Other cardiovascular disease	Yes=1; No=0
33. Cataracts	Yes=1; No=0
34. Glaucoma	Yes=1; No=0
35. Age related macular degeneration	Yes=1; No=0
36. Chronic lung disease	Yes=1; No=0
37. Arthritis	Yes=1; No=0
38. Osteoporosis	Yes=1; No=0
39. Cancer	Yes=1; No=0
40. Varicose ulcer	Yes=1; No=0

Table from supplementary material in Wong *et al.* (2018)⁶⁸

Repeat assessments of the FP and FI were measured in Waves 1 and 2, which were also used to calculate mean frailty scores. Frailty was studied as an ordinal score [0-5] for FP or a ratio [0-1] for FI and as categorical variables (non-frail, pre-frail, or frail) using the specified

thresholds above. Covariates included were: sex (male or female), highest education level (some primary, primary, intermediate/junior/group certificate, leaving certificate, diploma/certificate, graduate degree, postgraduate degree, or none), social class (professional workers, managerial and technical, non-manual, skilled manual, semi-skilled, unskilled, or unknown/refused), marital status (married, living with a partner as if married, single (never married), separated, divorced or widowed), smoker (if they had ever smoked daily for a period of at least one year), and drinker (if their alcohol consumption exceeded the weekly limit of standard drinks defined by the government guidelines).¹³⁷

Outcomes studied were: (1) overnight hospital admissions reported in both waves (recurrent overnight hospital admissions); (2) falls reported in both waves (recurrent falls); and (3) all-cause mortality. Self-reported falls and overnight hospital admissions in the past 12 months were obtained from the CAPI questionnaire. Data on mortality were obtained from the Irish General Register Office up to March 2018.¹³⁸

3.2.3 Statistical analyses

Within-person variability and agreement of frailty

The within- and between-person standard deviation (SD)¹³⁹ in frailty scores were estimated using one-way analysis of variance (ANOVA) with higher SDs indicating less consistency in scores. Agreement in the classification of frailty status ($FP \geq 3$ or $FI \geq 0.25$) within individuals was assessed using intra-class kappa scores, overall and in age-specific groups (<60, 60-69, and ≥ 70 years).^{140,141} Bland-Altman (BA) plots, which are plots of the difference of the paired continuous measurements against the mean of the two measurements and describe the agreement between the two measurements, were plotted to demonstrate the strength and pattern of the agreement for continuous scores (FI only).^{139,142,143}

To enhance the interpretation of the findings, other estimates related to precision and variability were reported. This included the standard errors of measurement (SEM),^{144,145} minimal detectable change (MDC),¹⁴⁶ and minimally importance change (MIC)¹⁴⁷ in frailty measures. Their definition, estimation method, and interpretation are described in **Table 3.3**.

Table 3.3 Definition, estimation method, and interpretation of precision and variability measures

Measure of precision and variability	Estimation method	Interpretation
Standard errors of measurement (SEM) ^{144,145} represents the variability of measurement in an individual around their “true” score.	SEM was calculated as $SD \text{ of frailty} \times \sqrt{1 - \text{correlation coefficient}}$, where the correlation coefficient of the repeat frailty measures for the FP and FI was determined using Kendall’s W and Lin’s concordance correlation coefficients, respectively.	Since the units of SEM and the original test scores were identical, SEM was used to assess the precision of single measurements of frailty scores. A higher SEM estimate indicates a higher level of within-person variability and poor precision.
Minimal detectable change (MDC) ¹⁴⁶ is the minimal change required to distinguish a true change in performance from a change due to errors in measurement.	MDC ₉₅ was calculated using the equation: $1.96 \times \sqrt{2} \times SEM$.	The MDC ₉₅ provides an estimate of error around repeated measures. Overall, 95% of the observed differences between pairs of observations will be smaller than the MDC ₉₅ values (given that there are no true differences) indicating any changes greater than MDC ₉₅ can be confidently attributed to real change.
Minimally important change (MIC) ¹⁴⁷ reflects the smallest change in test scores detectable as clinically meaningful change (improvement or deterioration) in health by individuals or clinicians.	MIC was estimated using the anchor method, which uses an external indicator or “anchor” that correlates with the health instrument under study, to determine the magnitude of clinically important change in the health instrument. ^{92,146,148} The anchor may be an objective or subjective measure. In the present analysis, self-reported health status was used as the anchor. Clinically meaningful change was defined as two or more units of decline in self-reported health status (5-levels in total: Excellent, Very good, Good, Fair, and Poor). MIC was calculated using the change difference method: the difference between the average frailty score change of those reporting a transition in the anchor status (a deterioration in self-reported health) and those reporting no change. ^{148,149} Bootstrapping was used to calculate 95% confidence intervals using 1000 samples. ¹⁵⁰	Whether any clinically meaningful changes could be distinguished from within-person variability was determined by comparing the magnitude of the MIC and MDC (i.e. $MIC > MDC$). ¹⁰⁶

Imputation of missing data

The degree of missingness in the frailty variables may affect reliability estimates and associations with adverse outcomes. The missingness of FP variables was far greater than FI (no missing data), which could have significant implications on the validity of the comparison. Therefore, missing data was imputed using MICE (Multiple Imputation by Chained Equations).¹⁵¹

Missing data may be handled in various ways, such as using complete cases, creating a missing category, replacing missing values with the mean or mode value, or single imputations.¹⁵¹ These approaches are suitable when data are Missing Completely-at-Random (MCAR, there is no relationship between the missingness of the data and any observed or missing data), but this assumption is rarely met¹⁵² and they do not account for the uncertainty of missing values. Multiple imputation is considered to be the most appropriate approach for dealing with missing data. It creates multiple imputations of a complete dataset and estimates multiple results of the same analysis, which are averaged to produce a single estimate with the appropriate standard errors that reflect uncertainty about the missing value.¹⁵³ In principle, more imputations will result in a more precise estimated result but may be computationally intensive. The number of imputations recommended is the percentages of cases that are incomplete.¹⁵⁴

MICE is the process by which the multiply imputed datasets are created.¹⁵⁵ In MICE, the variable with the least missingness is first imputed by a model, such as classical regression models or machine learning algorithms, conditioned on all non-missing variables.¹⁵² This process is repeated, cycling through the next least missing variable until there is no missing data. Ten “iterations”, referring to a complete cycle through all missing variables, is recommended for each imputation.¹⁵⁶

In the present analysis, the number of participants with missing frailty-related variables was recorded. Overall, 20 imputations¹⁵⁷ with 10 iterations were carried out using the classification and regression trees (CART) method.¹⁵⁸ CART, a class of machine learning algorithm, was

used for their robustness against outliers and ability to model interactions and non-linear relationships, and deal with skewed distributions.^{158,159} The following variables were imputed: age, sex, smoker, area of residence, social class, education level, living arrangement, marital status, medical history, disability information, hospital use, cognition, number of falls, attendance of health assessment centre at baseline, and the FP variables.

MICE operates under the Missing-at-Random (MAR) assumption that the missingness of data is related to the observed data but unrelated to missing data.¹⁵⁶ Missing data was visualised using margin plots, which are scatter plots between two continuous variables that display non-missing and missing values. The distributions of the values are also displayed as box plots by whether the other variable is observed or unobserved. If data are MCAR, the distribution of the box plots would be similar. Conversely, the MAR assumption is plausible if distributions of values differ by whether data are missing or not.

Associations with recurrent falls, hospital admission and all-cause mortality

Logistic regression was used to estimate the associations between frailty (categorical and continuous) and adverse outcomes (recurrent falls, recurrent hospital admission, and all-cause mortality) after adjustment for age, sex, education level, social class, marital status, smoking status, and alcohol consumption. Odds ratios (ORs) for categorical levels of frailty were used to compare associations using a single frailty measurement versus the mean of two repeated measures. AUCs were estimated for logistic regression models using continuous frailty scores;¹⁶⁰ $AUC \geq 0.7$ was used as an indication of good discriminatory power.¹⁰⁶

All analyses were conducted using R version 4.0.2.

3.3 Results

3.3.1 Baseline characteristics

The flow diagram of participants is shown in **Figure 3.1** and selected characteristics of study participants are reported in **Table 3.4**. Among 8,504 participants included in Wave 1, 7,455 were followed up, 1,011 were lost to follow-up, and 208 had died at Wave 2. At baseline,

participants had a mean (SD) age of 63.1 (10.2) years; 55.6% were female; 70% were married; and over one-quarter were manual workers. Overall, demographic factors, lifestyle or medical history variables did not change appreciably within 2 years. The median frailty level also remained constant over 2 years regardless of the definition. **Table S3.1** shows the baseline characteristics of participants by whether they were followed up at Wave 2. While most baseline characteristics were similar, participants who were lost to follow-up were more likely to be current smokers ($p<0.001$), depressed ($p=0.01$), have lower socioeconomic status ($p<0.001$), lower Mini-Mental State Examination (MMSE) score ($p<0.001$), slower walking speed ($p=0.02$), and lower physical activity ($p=0.03$) at baseline than those who were followed-up.

Figure 3.1 Flow diagram of TILDA participants selected for this chapter

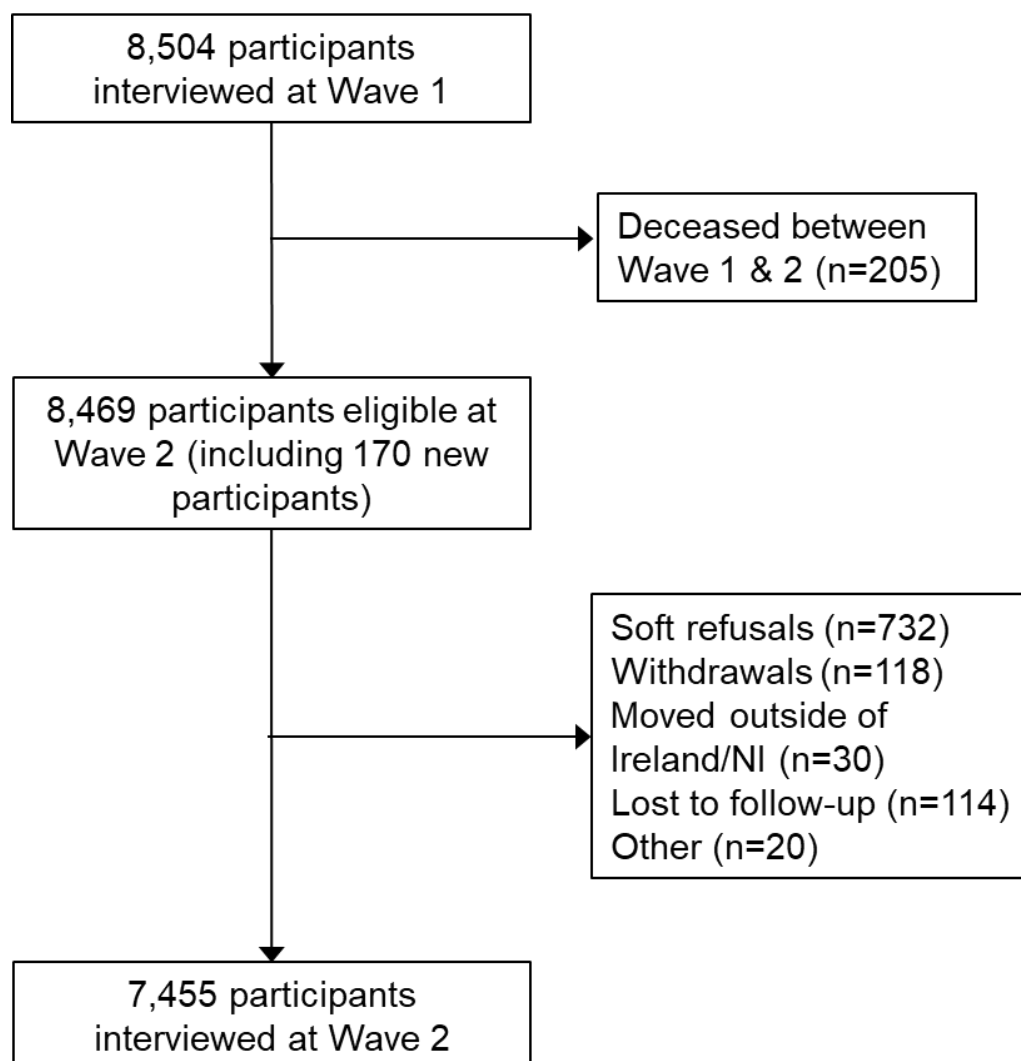


Table 3.4 Selected characteristics of study participants at Waves 1 and 2

Mean (SD), median (IQR) or N (%)	Wave 1 (N=8504)	Wave 2 (N=7455)	Lost to follow-up or death (N=1219)
Demographic			
Age, years	63.1 (10.2)	64.7 (9.9)	65.4 (11.4)
Sex (female)	4724 (55.6 %)	4149 (55.7 %)	670 (55 %)
Education			
Primary	2975 (35 %)	2469 (33.9 %)	506 (41.5 %)
Secondary	3431 (40.3 %)	2983 (40.9 %)	448 (36.8 %)
Tertiary	1818 (21.4 %)	1617 (22.2 %)	201 (16.5 %)
Married	5966 (70.2 %)	5220 (70 %)	796 (65.3 %)
Lives alone	1822 (21.4 %)	1510 (20.7 %)	312 (25.6 %)
Occupation			
Manual worker	2341 (27.5 %)	2665 (35.7 %)	410 (33.6 %)
Non-manual worker	6163 (72.5 %)	4790 (64.3 %)	809 (66.4 %)
Lifestyle/medical history			
BMI, kg/m ²	28.7 (5.1)	27.1 (4.8)	28.6 (5.1)
Smoker	1564 (18.4 %)	1168 (15.7 %)	300 (24.6 %)
Drinker ^a	453 (5.3 %)	402 (5.5 %)	51 (4.2 %)
Depressed	809 (9.5 %)	638 (8.6 %)	135 (11.1 %)
MMSE errors	1.7 (2.2)	1.5 (2.2)	2.7 (3)
Baseline health assessment			
Health centre	5275 (62 %)	4927 (67.6 %)	348 (28.5 %)
Home	875 (10.3 %)	721 (9.9 %)	154 (12.6 %)
Missing	2354 (27.7 %)	1637 (22.5 %)	717 (58.8 %)
Prior CVD ^b	1704 (20 %)	1584 (21.2 %)	255 (20.9 %)
Prior cancer	522 (6.1 %)	566 (7.6 %)	97 (8 %)
Diabetes	641 (7.5 %)	610 (8.2 %)	116 (9.5 %)
Polypharmacy (≥5 medications)	1703 (20 %)	2065 (27.7 %)	260 (21.3 %)
Falls in the past year (ever)	1640 (19.3 %)	1652 (22.2 %)	231 (18.9 %)
Overnight hospitalisation in the past year (ever)	1085 (12.8 %)	1047 (14 %)	180 (14.8 %)
Frailty measurements			
Grip strength, kg	26 (9.9)	29.4 (10.8)	25.3 (10)
TUG, seconds	9.1 (3.7)	9.5 (3.8)	10.3 (4.6)
IPAQ-SF, kcal/week	2274 (796.1-5488.1)	2079 (716.1-5196.8)	1716.9 (492.2-4299)
Frailty Phenotype (FP, 0-5)			
Count	0 (0-1)	0 (0-1)	1 (0-2)
Non-frail	3087 (36.3 %)	3308 (44.4 %)	204 (16.7 %)
Pre-frail	2492 (29.3 %)	2829 (37.9 %)	206 (16.9 %)
Frail	374 (4.4 %)	476 (6.4 %)	64 (5.3 %)
Missing	2551 (30 %)	842 (11.3 %)	745 (61.1 %)
Frailty Index (FI, 0-1)			
Score	0.12 (0.06-0.2)	0.13 (0.07-0.22)	0.13 (0.07-0.22)
Non-frail	3576 (42.1 %)	2803 (37.6 %)	479 (39.3 %)
Pre-frail	3517 (41.4 %)	3265 (43.8 %)	490 (40.2 %)
Frail	1411 (16.6 %)	1387 (18.6 %)	250 (20.5 %)

Continuous data presented as mean (SD) for age, BMI, grip strength and TUG, or median (IQR) for MMSE errors, frailty scores/count and IPAQkcal.

Baseline data was reported for lives alone, education level, and prior CVD for all groups due to data availability.

^aDrinkers consuming levels above the weekly limit on standard drinks (1/2 pint of beer or a glass of wine) according to the government guidelines (>21 for men; >14 for women).

^bCVD defined as any of the following diagnosis present: angina, heart attack, diabetes, stroke, transient ischaemic attack, or heart murmur.

Abbreviations: BMI=body mass index; CVD=cardiovascular diseases; FI=frailty index; FP=frailty phenotype; IPAQ-SF=International Physical Activity Questionnaire-Short Form; MMSE=Mini-Mental State Examination; TUG=Timed-Up-and-Go.

3.3.2 Missing data

Table 3.5 shows the proportion of participants with missing FP-related data. Over one-quarter of participants were missing variables required to define the FP (except for the exhaustion component). None of the FI deficits was missing.

Table 3.5 Number of missing values in FP-related variables

Variables	% missing in Wave 1 (N=8504)	% missing in Wave 2 (N=7455)
Height	27.9	2.2
Weight	27.9	3.5
Grip strength	28.7	6.5
Physical activity	28.5	4.3
Energy	-	1.1
Timed-up-and-go (TUG)	28.5	3.8

Missing data was visualised to assess the MAR assumption. Margin plots between grip strength, Timed-Up-and-Go (TUG) time, and physical activity with other participant characteristics (age, TUG time, grip strength, BMI, MMSE errors, creatinine [CRT], FI score, and the number of comorbidities present, where appropriate) are shown. Additionally, the difference in the distributions of other participant characteristics by whether participants were missing the grip strength, TUG time or physical activity was tested using the t-test or Wilcoxon test. Missingness patterns are only shown for Wave 1 but patterns were similar for Wave 2.

At Wave 1, 2,442 participants were missing grip strength. The distribution of grip strength was significantly lower for participants with values missing on TUG time, BMI, MMSE errors, and CRT (left red boxes) compared to participants where these variables were present (left blue boxes) (**Figure S3.3**). Those with missing grip strength were also older ($p<0.001$), slower ($p=0.02$), less active ($p<0.001$), and had poorer cognitive scores ($p=0.03$).

At Wave 1, 2,421 participants were missing TUG time. The distribution of TUG time was significantly higher for participants with values missing on the MMSE errors and CRT (left red boxes) compared to participants where these variables were present (left blue boxes) (**Figure S3.4**). Individuals with missing TUG time were also older ($p<0.001$), less active ($p<0.001$), had

lower grip strength ($p<0.001$), poorer cognitive score ($p<0.001$), and higher CRT values ($p<0.001$).

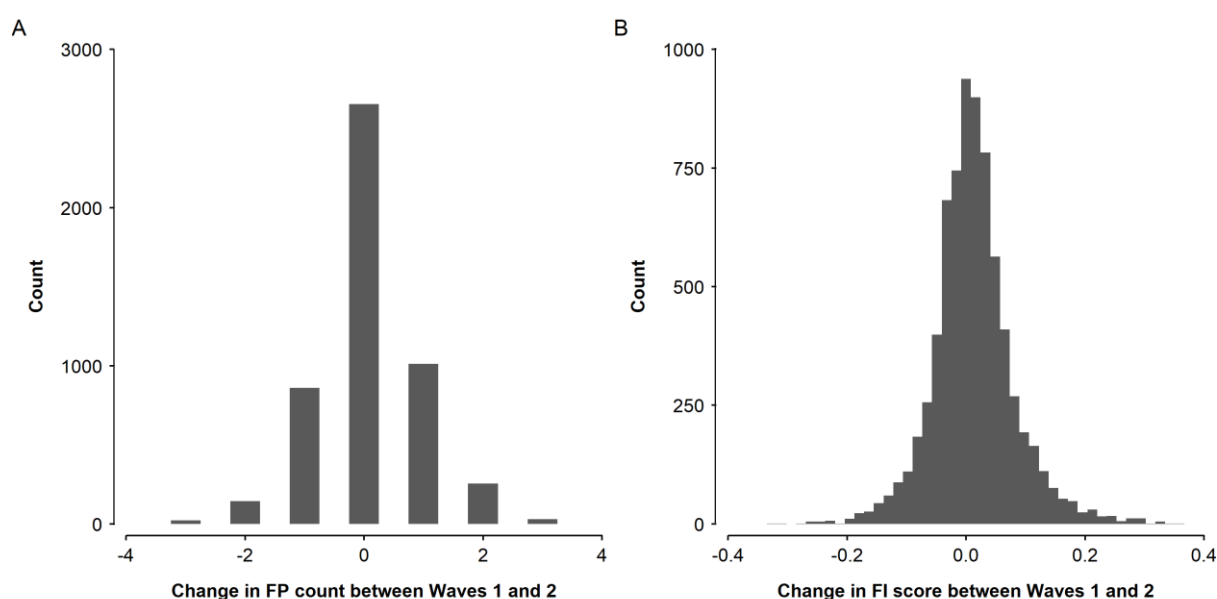
At Wave 1, 2,424 participants were missing physical activity data. The distribution of physical activity was significantly lower for participants with values missing on TUG time, BMI, grip strength, MMSE errors, and mean CRT (left red boxes) compared to participants where these variables were present (left blue boxes) (**Figure S3.5**). Individuals with missing physical activity data were also older ($p<0.001$).

Overall, the distribution of several observed variables, such as the number of MMSE errors and CRT, appeared to differ by whether grip strength, TUG time, and physical activity data were missing, which suggest that the missingness in these data is related to the observed data. Thus, the margin plots support the MAR assumption and the use of MICE to impute data.

3.3.3 Within-person variability and agreement of frailty

Figure 3.2 shows the distribution of the changes in frailty scores between Waves 1 and 2. Most participants experienced minimal changes in frailty status over time.

Figure 3.2 Distribution of the change in FP count (A) and FI score (B) between Waves 1 and 2



Data on the variability in frailty measurements are shown in **Table 3.6**. At baseline, the mean (SD) scores of FP and FI were 0.756 (0.969) and 0.145 (0.108), respectively. The within-person SD (95%CI) in frailty was 0.664 (0.654-0.671) and 0.050 (0.048-0.051), respectively, and SEM (95%CI) was 0.473 (0.470-0.478) and 0.048 (0.047-0.050), respectively. Thus, an individual's observed scores on a single administration were within $\pm 0.5/0.7$ units (FP) or 2 (2/40=0.05) deficits (FI) of their true values. The MDC₉₅ and MIC values and their 95% CI were 1.310 (1.301-1.324) and 0.099 (0.035-0.154) for FP and 0.134 (0.131-0.138) and 0.044 (0.036-0.054) for FI, respectively. These results suggest that any differences less than 1.31 (FP) and 0.13 (or 5 deficits, FI) between two assessments could be expected by chance alone, so while an increase in scores by 0.10 (FP) and 2 deficits (FI) from Wave 1 and Wave 2 might represent a detectable deterioration in self-rated health, it cannot be distinguished from chance alone.

Table 3.6 Within-person variability in the FP and FI

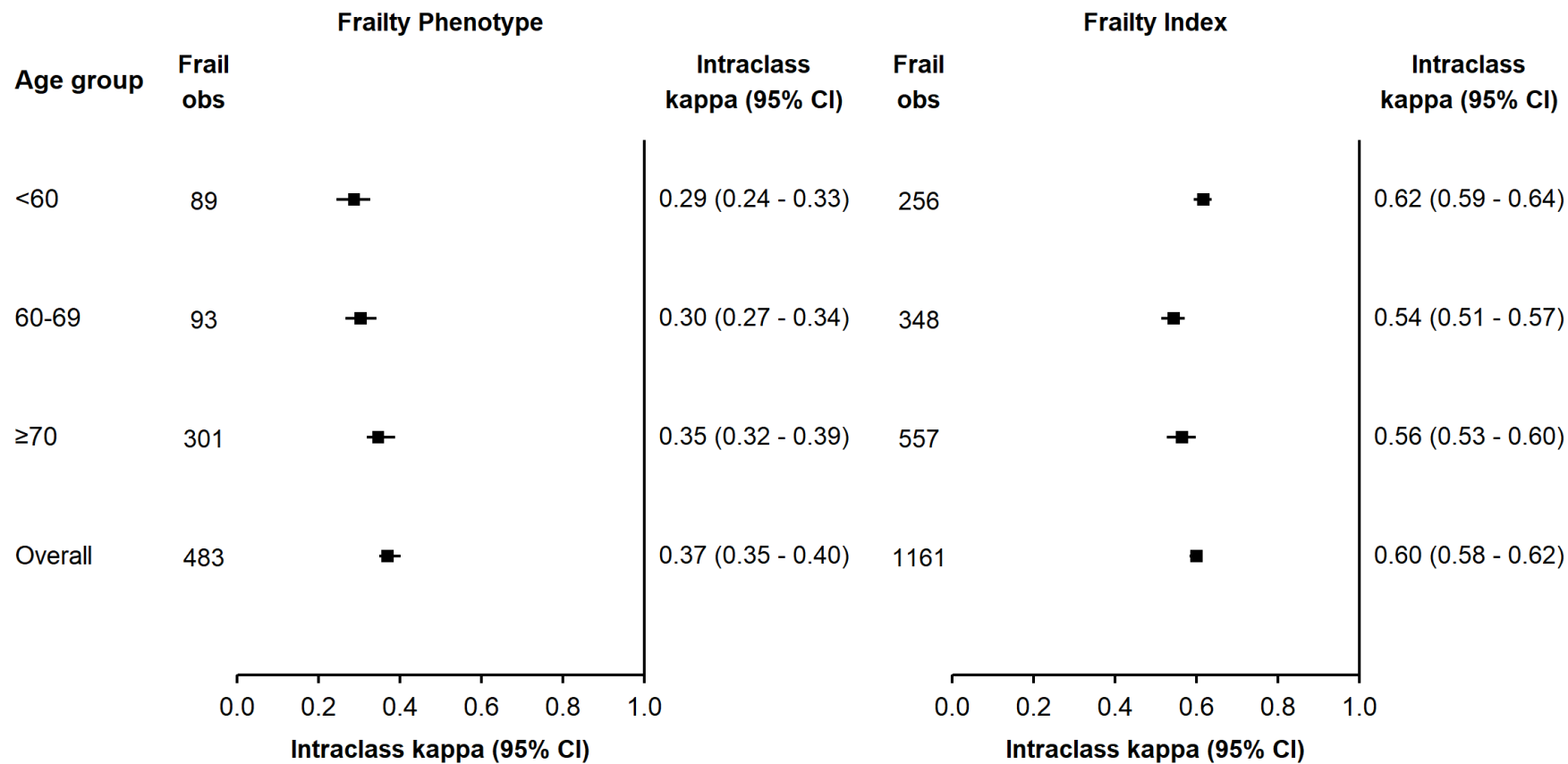
	Frailty Phenotype	Frailty Index
Mean (SD)		
Wave 1	0.756 (0.969)	0.145 (0.108)
Wave 2	0.825 (1.433)	0.159 (0.112)
Waves 1 and 2	0.791 (1.212)	0.152 (0.111)
Reliability estimates using Waves 1 and 2 data		
Within-person SD ^a	0.664 (0.654-0.671)	0.050 (0.048-0.051)
Between-person SD ^a	1.247 (1.243-1.257)	0.148 (0.145-0.151)
Correlation coefficient ^b	0.752 (0.748-0.755)	0.800 (0.791-0.808)
Standard error of measurement	0.473 (0.470-0.478)	0.048 (0.047-0.050)
Minimally detectable change	1.310 (1.301-1.324)	0.134 (0.131-0.138)
Minimally important change	0.099 (0.035-0.154)	0.044 (0.036-0.054)

^aWithin- and between-person variance was calculated using the one-way analysis of variance method.¹³⁹

^bCorrelation coefficients are Kendall's W and Lin's concordance correlation coefficient for FP and FI, respectively.

Figure 3.3 demonstrates a higher level of agreement in frailty status over 2 years by FI over FP (kappa statistic [95%CI]: 0.60 [0.58-0.62] vs. 0.37 [0.35-0.40], respectively). Agreement was higher in older age groups for FP but lower for FI.

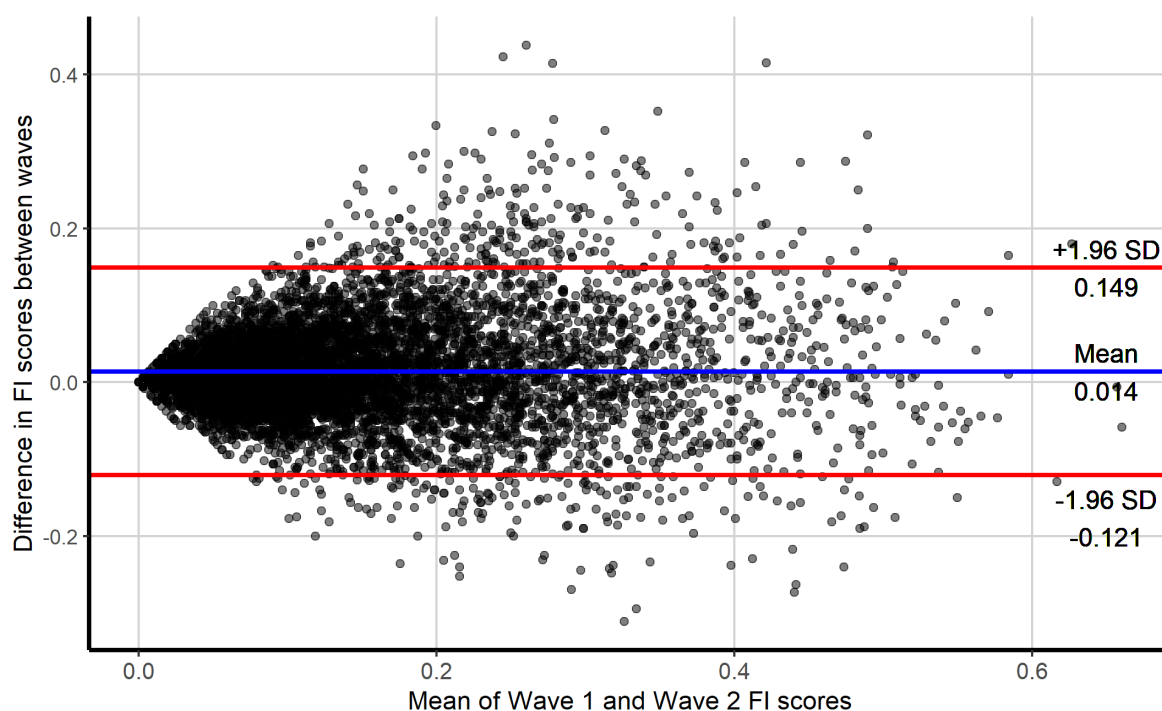
Figure 3.3 Agreement in the classification of frailty over 2 years using the FP and FI, overall and by age group



Frail obs refer to the number of participants with frailty at Wave 1. Total participants at Wave 1 by age group were 3154 (<60), 2265 (60-69), and 1866 (≥70).

The Bland-Altman plot for FI (**Figure 3.4**) shows that most of the data points lie within ± 2 SD of the mean difference (red lines), but indicates some heterogeneity in agreement by the severity of FI scores. Participants with higher average FI scores tended to improve over time.

Figure 3.4 Bland-Altman plot for the FI score

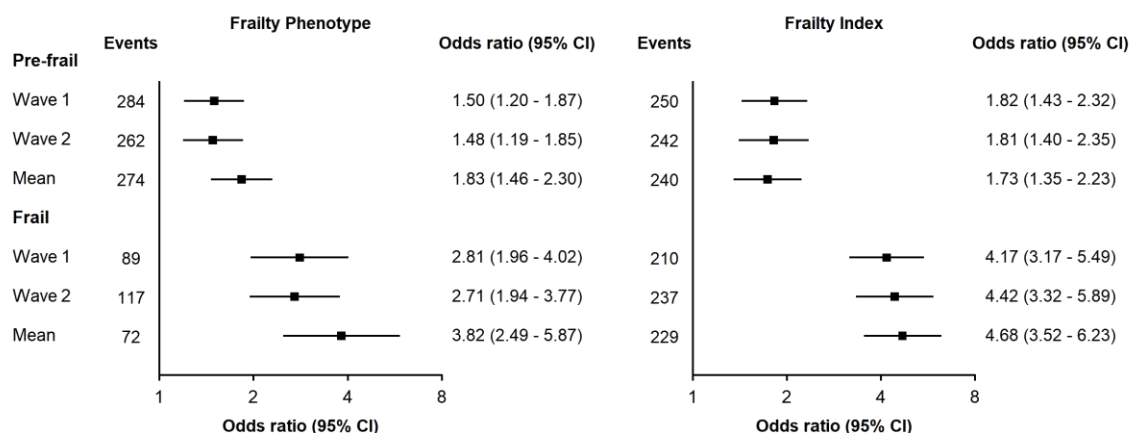


3.3.4 Associations of frailty with adverse outcomes

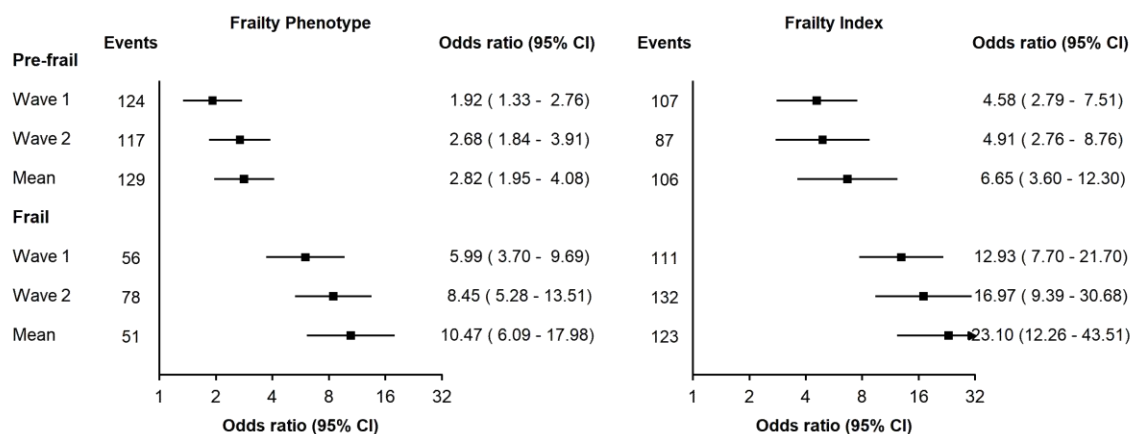
Both frailty measures were strongly associated with higher risks of adverse outcomes (**Figure 3.5**). The ORs associated with frailty classified by the FI were greater than those by FP for recurrent falls and hospital, but not all-cause mortality. For both measures, frailty classification based on the mean of repeat frailty measurements was generally more strongly associated with adverse outcomes than those based on single measurements. For FP and FI, the strength of associations of frailty with recurrent hospitalisation was nearly 2-fold greater using the mean scores versus scores from a single visit.

Figure 3.5 Associations of the FP and FI with recurrent falls (A), recurrent overnight hospital stay (B) and all-cause mortality (C)

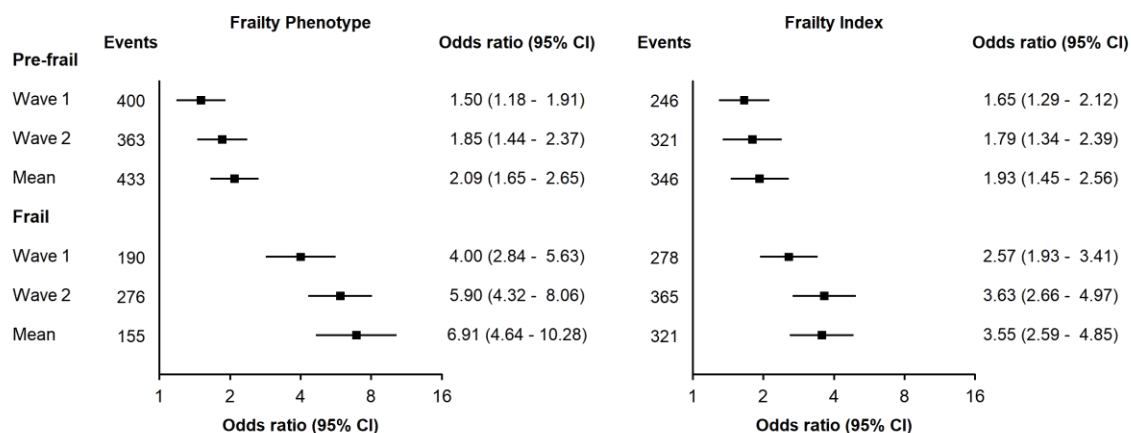
A



B



C



Odds ratios (OR) were adjusted for age, sex, education level, social class, marital status, smoking status, and alcohol drinking frequency at baseline. The reference level was the non-frail group for each frailty definition. Recurrent outcomes were defined as experiencing a disease outcome at Waves 1 and 2.

The AUCs were higher for FI than FP and comparable irrespective of the number of frailty measurements used (single versus mean) (**Table 3.7**).

Table 3.7 Discrimination of the FP and FI for recurrent falls, recurrent overnight hospital stay, and all-cause mortality

	Frailty Phenotype AUC (95% CI)	Frailty Index AUC (95% CI)
Falls		
Wave 1	0.646 (0.642 - 0.650)	0.687 (0.662 - 0.711)
Wave 2	0.643 (0.641 - 0.646)	0.686 (0.662 - 0.711)
Mean of Waves 1 and 2	0.651 (0.648 - 0.654)	0.693 (0.669 - 0.718)
Hospitalisation		
Wave 1	0.700 (0.692 - 0.708)	0.764 (0.732 - 0.796)
Wave 2	0.726 (0.723 - 0.731)	0.778 (0.747 - 0.809)
Mean of Waves 1 and 2	0.734 (0.729 - 0.739)	0.784 (0.753 - 0.814)
Mortality		
Wave 1	0.840 (0.838 - 0.841)	0.840 (0.823 - 0.857)
Wave 2	0.850 (0.848 - 0.851)	0.847 (0.830 - 0.863)
Mean of Waves 1 and 2	0.849 (0.847 - 0.849)	0.844 (0.828 - 0.861)

AUCs were computed using logistic regression models of the association between the predictors (continuous FI and ordinal FP separately) and outcomes adjusted for age, sex, education level, social class, marital status, smoking status, and alcohol drinking frequency at baseline.

Abbreviation: AUC=area under the receiver operating characteristic curve

3.4 Discussion

Frailty scores for individuals based on a single measurement were associated with high within-person variability. Over 2 years, frailty scores were associated with a within-person variability of about 0.7 units for FP and 2 deficits for FI. Also, the agreement of frailty status was modest, but stronger for FI than FP reflected by the nearly 2-fold difference in the kappa statistic. Importantly, the strengths of the associations for adverse outcomes based on repeat frailty measurements were almost 2-fold greater than those based on the single, baseline visit.

3.4.1 Comparison with existing literature

The findings of the present chapter were consistent with recent literature on the reliability of frailty instruments. Stolz *et al.* (2020)¹⁶¹ reported a similar magnitude of intra-individual variability for FI (0.04/0.05). The FI also showed better reliability than FP in a study of 243 acutely hospitalised medical patients aged ≥ 70 years: at 12 months, the intraclass correlation coefficient (ICC) (95%CI) was 0.84 (0.77-0.90) for the FI and 0.77 (0.65-0.84) for the FP.¹⁶² Widagdo *et al.* (2015)¹⁰³ found that the FI had superior accuracy predicting adverse outcomes (AUC range: 0.59-0.70) among the four frailty instruments compared (FI, FP, simplified FP, and prognostic frailty score) in ~2,000 Australian older men. Similarly, in 749 Chinese older

adults, FI generally had higher predictive accuracy than 6 other frailty instruments (including FP) for incident disability, falls, hospitalisation, or combined after 1 year.¹⁰⁴ The authors also found that the multidimensional instruments (including FI) had higher sensitivity (21-50% versus 4-12%) than the 3 purely physical instruments (including FP).

Potential reasons for the lower reliability and poorer predictive accuracy in FP and other physical frailty instruments could be that measurements like gait speed and TUG test, which have been shown to have moderate to excellent reliability,¹⁶³ may be subject to greater within-person variability due to variability in the individual's condition and the administrator on the day of the test. Additionally, FI is commonly composed of mostly self-reported items, which have shown to have higher reliability.¹⁰⁴

Consistent with Thompson *et al.* (2019),¹²³ the present analyses demonstrated that more recent measurements of FI had stronger association with adverse outcomes compared to baseline measurements. The present chapter further demonstrated that combining the baseline and repeat measurements yielded stronger associations than single measurements. The apparent increase in the strength of associations may reflect some correction for the within-person variability associated with single measurements in frailty and the persistence of frailty over time. For FI, it was the most recent value that was most strongly associated with all-cause mortality, which may reflect the cumulative nature of deficits in FI.

Jang *et al.* (2020)¹⁶⁴ estimated MIC in 925 Korean older adults using 1-year follow-up: 0.097 and 0.028 for the FP and FI, respectively. While the magnitude of MIC was similar to those found in the present chapter, they are not directly comparable as a different anchor was used (decline of -0.1 to -0.2 in health-related quality of life measure, EuroQol-5D). Thompson *et al.* (2021)¹⁶⁵ reported a much higher magnitude of MIC (SD) – 0.59 (0.31) for FP and 0.11 (0.05) for FI – using another self-reported health measure (SF-36: Excellent, Very good, Good, or Fair).

3.4.2 Strengths and limitations

The analyses of the TILDA study had several strengths, including longitudinal data from a large cohort study, a comprehensive comparison of an understudied measurement property of frailty (reliability),^{5,52,110,166} and multiple imputation to minimise the impact of missing data on the validity of comparisons. However, the study had several limitations. First, some differences in the way FP variables were measured across TILDA waves meant more accurate measurements at baseline versus the second wave, which may have resulted in an overestimation of the variability of FP.¹⁶⁷ Second, the large number of participants lost to follow-up could have differed from those that completed the study, and this is likely to underestimate the associations of frailty with adverse outcomes. Third, residual confounding is likely to be present. For example, multimorbidity (a person with frailty may also have cancer and osteoporosis, each of which can independently contribute to hospitalisation and all-cause mortality) was not adjusted for, which means that associations between frailty and outcomes may be biased. Fourth, TILDA is a predominantly Caucasian population; therefore, whether the findings can be translated to non-white populations is uncertain. Fifth, interventions for frailty could have occurred during the interim, but this information was unavailable and could not be accounted for. Finally, a limitation of the anchor method (used to estimate MIC) is that it is dependent on the distribution of frailty and the anchor in the population studied, which are likely to vary between studies.

3.5 Summary

Chapter 1 outlined the various frailty models and instruments in existence, illustrating their extensive differences. Despite their widespread use, there is still a lack of consensus about the optimum instruments to measure frailty and whether these instruments can accurately and reliably monitor frailty. Also, the comparative evidence of the key measurement properties is lacking in the literature, which limit evidence-based selection of instruments by clinicians and researchers.⁵ Accordingly, the present thesis compared the validity and reliability of the two major frailty models prior to conducting the main analyses of the thesis.

In **Chapter 2**, the validity of the FP and FI was investigated by comparing their predictive ability for all-cause mortality among populations with the same baseline risks for mortality. Both instruments had suboptimal predictive ability, re-enforcing the uncertainty about the suitability of existing frailty tools. However, the analysis suggested that continuous instruments had slightly superior ability. In the present chapter, the reliability of the FP and FI was investigated by comparing the agreement and magnitude of within-person variability in a population of older adults with repeat measurements of the FP and FI. The low agreement and wide within-person variability of frailty scores over time suggested limited ability of the existing frailty instruments to reliably measure frailty, but the FI appears to produce more consistent frailty measurements than FP.

Overall, the findings provide novel evidence for the frailty literature, providing higher quality evidence on the comparative validity of the major instruments and a comprehensive analysis of a previously understudied measurement property, reliability. The findings suggest that the FI may be a more appropriate and superior frailty tool, which allows better prediction of adverse outcomes and more reliable monitoring of changes in frailty over time. The evidence thus far supports the selection of FI over FP for subsequent analyses of the thesis. However, the findings also highlighted suboptimal ability of the existing frailty instruments regarding these key measurement properties, suggesting that exploring approaches to improve existing instruments is warranted. In addition, the analysis included in the present chapter was conducted in a European population and there is limited available evidence on the reliability of frailty instruments in Chinese populations.

The subsequent chapters will conduct analyses of frailty using the FI in the China Kadoorie Biobank (CKB). The FI's validity and reliability will be assessed in Chinese adults using similar approaches to those conducted in Europeans. Subsequently, the main aims of the thesis, to examine the associations of frailty and CVD (RFs), will be explored. The literature on the prospective associations of CVD RFs with frailty and frailty with CVD will be reviewed and appraised next.

4 Literature review of the prospective associations of cardiovascular risk factors, frailty, and CVD

4.1 Introduction

Frailty and the co-occurrence of diseases like CVD are a growing public health problem. While the importance of frailty is well recognised, there is little reliable evidence on modifiable risk factors for frailty to guide policy-makers or geriatricians on treatment or prevention of frailty in older people. Thus, there is an urgent need to understand how frailty develops and the mechanisms that link frailty with CVD. Understanding of the determinants and consequences of frailty is relevant for strategies to manage frailty and attenuate its adverse effects on disease outcomes in older people.

The background to the epidemiology of the relationship between frailty and CVD was described in **Chapter 1**. Frailty and CVD typically occur together in older people and are hypothesised to involve bidirectional associations involving shared CVD RFs. The shared RFs include alcohol drinking, smoking, blood pressure (BP), diabetes, and adiposity. While strong cross-sectional associations have been reported between CVD RFs and frailty, and separately between frailty with CVD, it is unclear if these cross-sectional associations have been replicated in prospective studies. Moreover, the causal relevance of CVD RFs for CVD is well-established, but the role of individual CVD RFs in the development of frailty is less certain. Likewise, there is reliable evidence suggesting that frailty predicts CVD, but evaluating the magnitude and directionality of these associations is challenging.

This chapter examined the published reports on the prospective associations of CVD RFs with frailty and frailty with CVD. The objectives were to summarise the available evidence from previously published prospective studies on: (1) the associations of the modifiable CVD RFs (adiposity, lean body mass, alcohol consumption, smoking, diabetes, and hypertension) and risk of incident frailty and (2) the associations of frailty and risk of incident stroke and ischaemic heart disease (IHD), after adjustment for confounding factors.

4.2 Prospective associations of cardiovascular risk factors (CVD RFs) with incident frailty

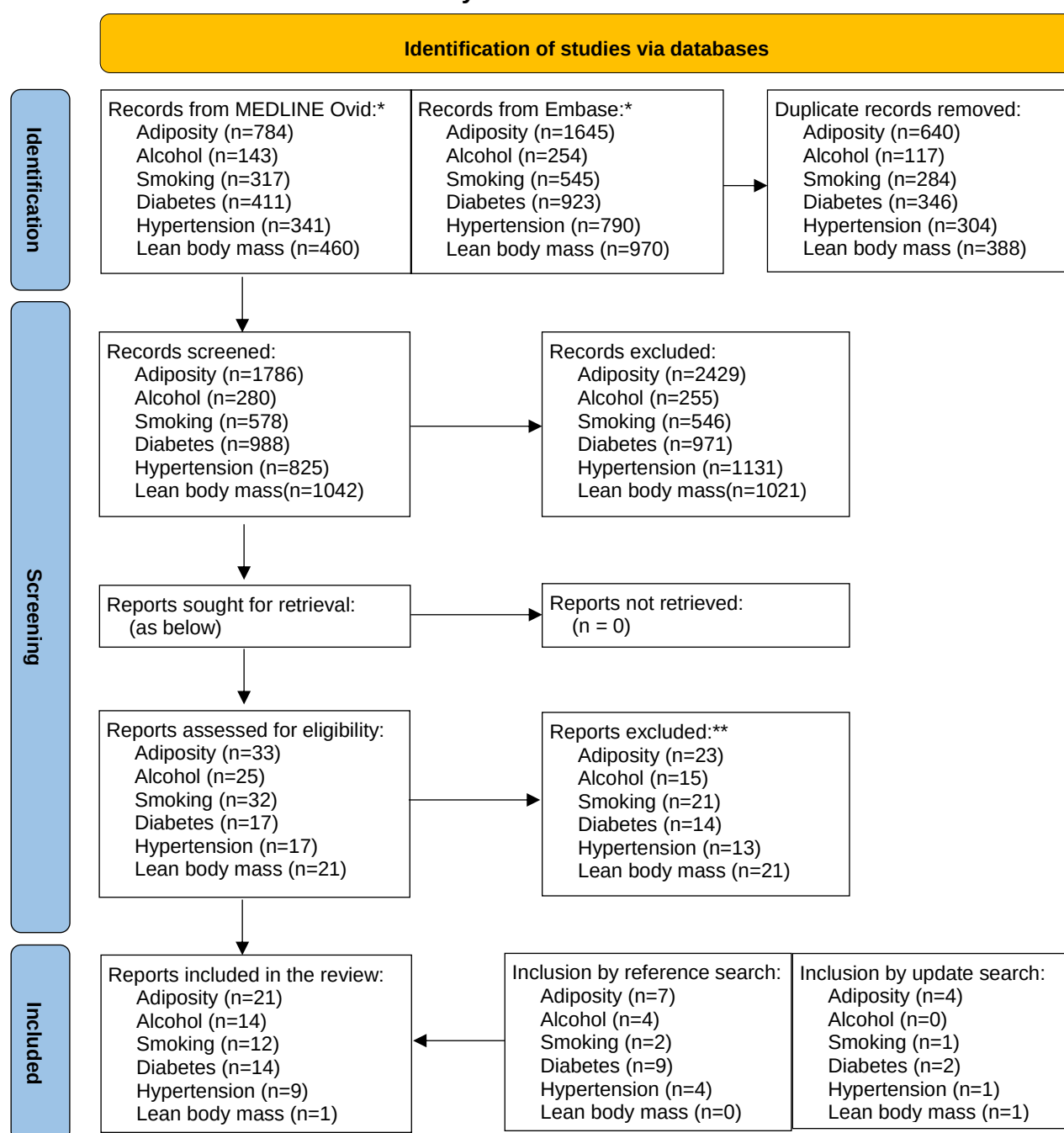
4.2.1 Methods

Six literature searches were conducted to identify studies investigating each CVD RF (adiposity, lean body mass, alcohol consumption, smoking, diabetes, and hypertension) with incident frailty. The reports were identified using Ovid Medline and Embase databases from their inception to 9 December 2021. Two update searches were conducted on 22 August 2022 and 24 August 2023, which identified one and 3 additional studies for inclusion, respectively. The inclusion criteria for the review were: (1) prospective observational studies; (2) included community-based participants; and (3) investigated CVD RFs as exposures and incident frailty as an outcome. The keywords and MeSH terms used to identify articles are summarised in **Table S4.1**. Although studies were limited to those reported in the English language, one Japanese study was identified and data were extracted with some assistance for translation. Studies were excluded if participants with frailty were not excluded at baseline, but those with long follow-up (>20 years) were included as the level of frailty at baseline was likely to be minimal. For the assessment of alcohol consumption, measurements involving the amount of alcohol consumed were required (i.e. measurements based solely on the frequency of alcohol intake were not considered). When duplicate studies were identified, reports with the longest duration of follow-up were included. The references of identified reports were also screened manually by the author to identify articles missed by the search strategy.

Data were extracted on study characteristics (name of study, year of baseline study, geographical location, and duration of follow-up), population characteristics (size, mean age, percentage of females, and exclusion criteria), exposure definition, outcome definition, number of events, statistical analyses performed, and summary results of the associations reported. Additionally, details of subgroup analyses or investigations of reverse causation bias were recorded.

The selection process for included reports was summarised using a flowchart (**Figure 4.1**). A total of 21 reports for prospective studies assessing the associations between adiposity and frailty risk; 14 reports of alcohol consumption and frailty risk; 12 reports of smoking and frailty risk; 14 reports of diabetes and frailty risk; 9 reports of hypertension and frailty risk; and 1 for lean body mass and frailty risk.

Figure 4.1 Flow diagram of article selection for prospective studies reporting the association between CVD RFs and frailty



*Search was carried out on 9 December 2021. Update searches carried out on 22 August 2022 and 24 August 2023 identified 1 and 3 additional reports that met the inclusion criteria, respectively.

**Reasons for exclusions were:

- Adiposity: 23 exclusions due to incorrect exposure (n=5), outcome (n=6), study design (n=6), CKB study (n=1), and article type (n=5). 7 articles¹⁶⁸⁻¹⁷⁴ were found manually.
- Alcohol: 15 exclusions due to incorrect exposure (n=3), outcome (n=4), study design (n=2), population (n=1), duplicate cohort (n=1), CKB study (n=1), and article type (n=3). 4 articles^{173,175-177} were found manually.
- Smoking: 21 exclusions due to incorrect exposure (n=2), outcome (n=10), study design (n=2), population (n=1), duplicate cohort (n=2), CKB study (n=1), and article type (n=3). 2 articles^{178,179} were found manually.
- Diabetes: 14 exclusions due to incorrect exposure (n=3), outcome (n=7), study design (n=3) and duplicate cohort (n=1). 9 articles^{171-173,178,180-184} were found manually.
- Hypertension: 13 exclusions due to incorrect exposure (n=2), outcome (n=5), study design (n=1), population (n=3), article type (n=1), and relative risk not reported (n=1). 4 articles^{172,178,181,182} were found manually.
- Lean body mass: 21 exclusions due to incorrect exposure (n=5), outcome (n=3), study design (n=6), population (n=1), article type (n=4), and relative risk not reported (n=2).

4.2.2 Results

Study selection and characteristics

Twenty-seven distinct prospective studies (30 reports) of RFs with frailty were identified. **Table 4.1** summarises the study characteristics of the included reports ordered by the duration of follow-up. Several reports used duplicate cohorts but were included as they either provided sex-specific risk estimates,¹⁷¹ were included in a meta-analysis with another study,¹⁸⁵ or had studied multiple CVD RF associations with frailty.^{178–180,186–188}

The mean age of participants varied from 47 to 81.2 years at baseline and the duration of follow-up from 1 to 30 years. The size of the individual studies varied from 334 to 68,416 participants. Six reports provided sex-specific estimates.^{171,172,174,178,188,189}

Table 4.1 Summary of prospective studies identified in the literature review, by the length of follow-up

First author's name, study name, year of the baseline study	Country (ethnicity)	No. of participants (% female)	Mean age [range], (years)	Follow-up (years)	Exposures studied	Definition of frailty	Were participants with frailty excluded at baseline?	No. of participants with frailty at follow-up
Chhetri, Beijing Longitudinal Study of Aging II (BLSA-II), 2009 ¹⁹⁰	Beijing, China (East Asian)	6293 (61%)	71 [≥55]	1	Diabetes	FI (≥0.25)	n/s	527
Jazbar, Survey of Health, Ageing and Retirement in Europe (SHARE), 2013 ¹⁸¹	European countries and Israel (White)	8133 (48%)	72 [≥65]	2	Alcohol consumption, diabetes, hypertension	FP (≥3 criteria); FI (≥0.21)	Yes (non-frail at baseline)	247 (FP); 1800 (FI)
Yoshida, 2005 ¹⁹¹	Japan (East Asian)	334 (58%)	76 [≥70]	2	Hypertension	FI-J (≥4)	Yes	45
Woods, Women's Health Initiative Observational Study (WHI-OS), 1993-1998 ¹⁷²	US (White)	28181 (100%)	[65-79]	3	Alcohol consumption, BMI, diabetes, hypertension, smoking	FP (≥3 criteria)	Yes	4158
Borda, Mexican Health and Aging Study (MHAS) ¹⁹²	Mexico (Hispanic)	6087 (45%)	62 [≥50]	3	Smoking	FI (≥0.21)	Yes	2301
Seematter-Bagnoud, Lausanne cohort 65+, 2004-2005 ¹⁹³	Switzerland (White)	1057 (57%)	67 [65-70]	3	Alcohol consumption	FP (≥1 criteria)	Yes (non-frail at baseline, i.e. FP<1)	220
Garcia-Esquinas, Study on Cardiovascular Health, Nutrition and Frailty in Older Adults in Spain (Seniors-ENRICA), 2008-2010 & Toledo Study for Healthy Ageing (TSHA), 2006-2009 ¹⁸⁵	Spain (Hispanic)	Seniors-ENRICA 1801; TSHA 1289	Seniors-ENRICA 69 [≥60]; TSHA 74 [≥65]	3.5	BMI, WC	FP (≥3 criteria)	Yes	287
Soler-Vila, Seniors-ENRICA, 2008-2010 ¹⁷¹	Spain (Hispanic)	1857 (0%; 100%)	n/s [≥60]	3.5	Alcohol consumption, BMI, WC, diabetes, smoking	FP (≥3 criteria)	Yes	133
Garcia-Esquinas, Seniors-ENRICA, 2008-2010 ¹⁷⁵	Spain (Hispanic)	1750 (51%)	68 [≥60]	3.5	Alcohol consumption, diabetes (and HbA1c)	FP (≥3 criteria)	Yes	115
Graciani, Seniors-ENRICA, 2008-2010 ¹⁹⁴	Spain (Hispanic)	1745 (52%)	69 [≥60]	3.5	Hypertension, smoking	FP (≥3 criteria)	Yes	
Dai, Chinese Longitudinal Healthy Longevity Survey (CLHLS), 2014 ¹⁹⁵	China	2359 (47%)	80 [≥65]	4	WC, calf circumference	FI (>0.21)	Yes	668
Doi, Obu Study of Health Promotion for the Elderly (OSHPE), 2011-2012 ¹⁸²	Japan (East Asian)	4322 (50%)	72 [≥65]	4	BMI, diabetes, hypertension	FP (≥3 criteria)	Yes	333

First author's name, study name, year of the baseline study	Country (ethnicity)	No. of participants (% female)	Mean age [range], (years)	Follow-up (years)	Exposures studied	Definition of frailty	Were participants with frailty excluded at baseline?	No. of participants with frailty at follow-up
Kojima, English Longitudinal Study of Ageing (ELSA), 2004 ¹⁸⁶	England (White)	2544 (55%)	n/s [≥60]	4	Alcohol consumption	FP (≥3 criteria)	Yes	271
Trevisan, the Progetto Veneto Anziani (Pro.V.A.), 1995-1998 ¹⁷³	Italy (White)	2925 (60%)	74 [≥65]	4.4	BMI, diabetes, smoking	FP (≥3 criteria)	Yes	Pre-frail and frail 416
Thompson, North West Adelaide Health Study (NWAHS), 2004-2006 ¹⁹⁶	Australia (White)	696 (53%)	73 [≥65]	4.5	WC	FP (≥3 criteria); FI (≥0.21)	Yes (non-frail at baseline)	Worsening state (incl. death) FP (40.1%) FI (39.5%)
Cheong, Singapore Longitudinal Ageing Study-2 (SLAS-2), 2009-2011 ¹⁶⁸	Singapore (Asian)	1297 (64%)	66 [≥55]	4.5	BMI, diabetes	FP (≥3 criteria)	Yes	204
Zaslavsky, The Adult Changes in Thought (ACT) study, 1994-1996 ¹⁹⁷	US (White)	1848 (58%)	Median 76 [≥65]	Median 4.8	Diabetes (inc. HbA1c)	FP (≥3 criteria)	Yes	578
Ting, The Western Australian Health In Men Study (HIMS), 2001-2004 ¹⁸⁹	Australia (White)	1743 (0%)	77 [≥65]	4-8	BMI, diabetes, smoking	FRAIL (≥3 criteria)	Yes	444
Abe, Yabu Cohort Study, 2012 ¹⁹⁸	Japan (East Asian)	2633 (52%)	75 [≥65]	5	Smoking	KYCL [0-15] [≥4]	Yes	441
Rodriguez-Laso, The Toledo Study of Healthy Ageing (TSHA), 2006-2009 ¹⁸³	Spain (Hispanic)	1748 (56%)	75 [≥65]	Median 5.2	Alcohol consumption, BMI, diabetes	FP (≥1 criteria)	Yes (non-frail at baseline, i.e. FP<1)	232 (26 frail; 206 pre-frail)
Ho, Taiwan Longitudinal Study on Ageing (TLA), 1999 ¹⁷⁶	Taiwan (East Asian)	1609 (48%)	61 [50-69]	8	Alcohol consumption, BMI	FP (≥3 criteria)	Yes	?
Barzilay, Cardiovascular Health Study (CHS), 1989-1990 ¹⁸⁴	US (White)	2926 (64%)	[69-74]	9	SBP	FP (≥3 criteria)	Yes	234
Wang, Chinese Longitudinal Healthy Longevity Survey (CLHLS), 2008-2018 ¹⁹⁹	China (East Asian)	3327 (49%)	81 [65-116]	10	Alcohol consumption, smoking	FP (≥3 criteria)	Yes (non-frail at baseline, i.e. FP<1)	1249
Bouillon, Whitehall II Prospective Cohort Study, 1997-1999 ¹⁸⁰	England (White)	2702 (28%)	55 [35-55]	10.5	BMI, WC, glucose, hypertension, smoking	FP (≥3 criteria)	No	2.80%
Niederstrasser, English Longitudinal Study of Ageing (ELSA), 2004-2005 ¹⁸⁷	England (White)	7420 (55%)	67 [≥50]	12	BMI, WHR, smoking	FI (≥0.25)	Yes	2241
Shah, Health and Retirement Study (HRS), 2000 ¹⁷⁰	US (White)	6073 (59%)	74 [≥65]	12	Alcohol consumption, BMI	PLFI (≥3 criteria)	Yes	2030

First author's name, study name, year of the baseline study	Country (ethnicity)	No. of participants (% female)	Mean age [range], (years)	Follow-up (years)	Exposures studied	Definition of frailty	Were participants with frailty excluded at baseline?	No. of participants with frailty at follow-up
Rutherford, Hispanic Established Population for the Epidemiologic Study of the Elderly (EPESE), 1993-1994 ²⁰⁰	Mexico (Hispanic)	1638 (58%)	74 [≥67]	18	BMI, diabetes, hypertension	FP (≥3 criteria)	Yes	?
Gil-Salcedo, Whitehall II cohort, 1985-1988 ¹⁷⁹	England (White)	6357 (29%)	50 [35-55]	20	Alcohol consumption, smoking	FP (≥3 criteria)	Yes	445
Uchai, Tromso study, 1994-1995 ²⁰¹	Norway (White)	1534-4509 (52%)	52 [≥45]	21	BMI, WC	FP (≥1 criteria)	No	1330
Stenholm, Mini-Finland Health Examination Survey (MFHES), 1978-1980 ²⁰²	Finland (White)	1119 (58%)	44 [30-75]	22	BMI	FP (≥3 criteria)	Yes	56
Sotos-Prieto, Nurses' Health Study (NHS), 1992 ¹⁷⁴	US (White)	68416 (100%)	63 [≥60]	22	Alcohol consumption, BMI, smoking	FRAIL (≥3 criteria)	Yes	11041
Strandberg, Helsinki Businessmen Study (HBS), 1974	Finland (White)	1815-2360 (0%)	47-49	26-30	Alcohol consumption, ¹⁸⁸ BMI, ¹⁷⁸ glucose, ¹⁷⁸ SBP, ¹⁷⁸ smoking ¹⁷⁸	FP (≥3 criteria)	No	108-135

Abbreviations: BMI=body mass index; CI=confidence interval; FI=frailty index; FRAIL= Fatigue, Resistance, Ambulation, Illness, and Loss of weight scale; FP=frailty phenotype; KYCL=Kaigo-Yobo Checklist; PLFI= Paulson-Lichtenberg Frailty Index; SBP=systolic blood pressure; WC=waist circumference; WHR=waist-to-hip ratio

Adiposity

Central adiposity

Six studies and one meta-analysis reported the associations between central adiposity and incident frailty, of which 5 were conducted in Western populations and 1 in China. Central adiposity was measured using waist circumference (WC) or waist-to-hip ratio (WHR) and definitions of obesity were consistent across studies. In men and women, obesity was defined as WC>102 cm and WC>88 cm, respectively, and WHR>0.9/0.95 and WHR>0.85/0.9, respectively. Two studies categorised WC into 3 categories: low (<95cm in men; <81cm in women), intermediate (95-102cm in men; 81-88cm in women), and high (>102cm in men; 88cm in women).^{180,201} Frailty was defined using the FP and FI. The key findings are shown in **Table 4.2**. All studies reported positive associations between central obesity and incident frailty, but associations were generally significant in studies that used the FI or in women.

Table 4.2 Key findings of studies investigating the associations between central adiposity and incident frailty

First author name, Study name	Region (ethnicity)	No. of participants / duration of follow-up	Exposure	Odds ratio (95% CI) for incident frailty	Adjustments [†] / reported association
Soler-Vila, Seniors-ENRICA ¹⁷¹	Europe (Hispanic)	1857 3.5 years	WC ^a Non-obese obese	FP (men): reference 1.50 (0.73 to 3.05) FP (women): reference 3.62 (1.86 to 7.05)	+ plus baseline frailty / Positive (women only)
Garcia-Esquinas, Seniors-ENRICA & TSHA ¹⁸⁵	Europe (Hispanic)	3090 3.5 years	WC ^a Non-obese obese	FP: reference 1.61 (0.95-2.26)	+++ / None
Dai, CLHLS ¹⁹⁵	Asia (East Asian)	2359 4 years	WC (cm) ≤74.0 74.0-≤80.0 80.0-≤84.0 84.8-≤90.0 >90.0	FI: reference 1.22 (0.97-1.53)* 1.31 (1.00-1.72)* 1.39 (1.07-1.79)* 1.69 (1.27-2.24)*	+++ / Positive
Thompson, NWAHS ¹⁹⁶	Australia (White)	696 4.5 years	WC ^a Non-obese obese	FP: reference 1.50 (0.81-2.78)	+++ / Positive (FI only)
Bouillon, Whitehall II ¹⁸⁰	Europe (White)	2702 10.5 years	WC ^b Low Intermediate High	FI: reference 2.24 (1.06-4.76) FP: reference 0.99 (0.79-1.17) 1.25 (0.76-1.58)	++++ / None
Niederstrasser, ELSA ¹⁸⁷	Europe (White)	7420 12 years	WHR ^c Non-obese obese	FI: reference 1.25 (1.13-1.38)*	n/s / Positive
Uchai, Tromso ²⁰¹	Europe (White)	1534 21 years	WC ^d Normal Moderate High	FP: reference 1.57 (1.21-2.03) 2.14 (1.59-2.87)	+++ / Positive

^aWC was categorised into a binary variable where obese was defined as WC>102cm in men and WC>88cm in women

^bWC was categorised into 3 levels where 'low', 'intermediate', and 'high' levels were defined as <94, 94-102, ≥102cm for men, and <80, 80-88, ≥88cm for women, respectively.

^cWHR was categorised into a binary variable where obese was defined as WHR>0.9 in men and WHR>0.85 in women

^dWC was categorised into 3 levels where 'normal', 'moderate' and 'high' levels were defined as <95, 95-102, >102cm for men, and <81, 81-88, and >88cm for women, respectively.

[†]Adjustments: + age and/or sex; ++ plus cardiovascular risk factors (smoking, body mass index, alcohol consumption, diabetes, hypertension, family history of heart disease, etc.); +++ plus demographic variables (education, income, ethnicity, etc.) and other disease and medications; ++++ plus biomarkers.

*Hazard ratio (95% CI)

Abbreviations: CI=confidence interval; FI=frailty index; FP=frailty phenotype; WC=waist circumference; WHR=waist-to-hip ratio

General adiposity

Seventeen studies examined the associations between general adiposity and incident frailty; 14 were conducted in Western populations (European or US), 3 in Asian populations, and 1 in Latin America. All studies measured general adiposity using body mass index (BMI), which was categorised into 2 to 5 levels or used as a continuous variable. In most studies, identical

BMI thresholds (underweight $<18.5 \text{ kg/m}^2$, normal $18.5\text{-}24.9 \text{ kg/m}^2$, overweight $25.0\text{-}29.0 \text{ kg/m}^2$, and obese $\geq 30 \text{ kg/m}^2$) were used, but some studies combined the underweight and normal categories, divided the obese categories into obese and morbidly obese categories, or created binary variables (e.g. obese or not obese). Frailty was defined using the FP, FI, FRAIL (Fatigue, Resistance, Ambulation, Illness, and Loss of weight) scale, or the PLFI (Paulson-Lichtenberg Frailty Index). The key findings are shown in **Table 4.3**. Overall, a positive, potentially U- or J-shaped association between general adiposity and incident frailty was reported in studies with duration up to 21 years, but only the highest BMI group was significantly associated with frailty after adjustment for confounders. In contrast, the two Finnish studies with very long follow-up (22-26 years) (the Mini-Finland Follow-up Survey²⁰² and Helsinki Businessmen Study¹⁷⁸) reported positive associations between BMI and incident frailty (rather than a J-shaped association), but fewer BMI categories were used. The studies involving Asian populations – Japan,¹⁸² Singapore,¹⁶⁸ and Taiwan¹⁷⁶ – reported associations that were generally consistent with those reported in Western populations.

Table 4.3 Key findings of studies investigating the association between general adiposity and incident frailty

First author name, Study name	Region (ethnicity)	No. of participants / duration of follow-up	Exposure	Odds ratio (95% CI) for incident frailty	Adjustments [†] / reported association
Woods, WHI-OS ¹⁷²	US (White)	28181 3 years	BMI <18.5 18.5-24.9 25.0-29.9 ≥30.0	FP: 1.65 (1.11–2.45) (reference) 1.92 (1.73–2.13) 3.95 (3.50–4.47)	n/s / Positive (J-shape)
Soler-Vila, Seniors-ENRICA ¹⁷¹	Europe (Hispanic)	1857 3.5 years	BMI <25.0 25.0-29.9 ≥30.0	FP (men): (reference) 0.82 (0.28 to 2.40) 2.29 (0.79 to 6.68)	+ plus baseline frailty / Positive (female only)
Garcia-Esquinas, Seniors-ENRICA, & TSHA ¹⁸⁵	Europe (Hispanic)	3090 3.5 years	BMI <25.0 25.0-29.9 ≥30.0	FP: 1.36 (0.62-2.09) (reference) 1.51 (1.00-2.01)	+++ / Positive (J-shape)
Doi, OSHPE ¹⁸²	Asia (East Asian)	4322 4 years	BMI per kg/m ²	FP: 1.06 (1.01-1.12)	+++ / Positive (linear)
Trevisan, Pro.V.A. ¹⁷³	Europe (White)	2925 4.4 years	BMI <20 20-25.0 25-29.9 ≥30	FP: ? (reference) 1.24 (1.12-1.38) 1.76 (1.66-1.98)	++++ / Positive
Cheong, SLAS-2 ¹⁶⁸	Asia (Asian)	1297 4.5 years	BMI per kg/m ² >30	FP: 0.98 (0.94-1.02) 1.13 (0.63-2.01)	n/a / None
Ting, HIMS ¹⁸⁹	Australia (White)	1743 4-8 years	BMI <18.5 18.5-24.9 25-29.9 ≥30.0	FRAIL: 0.69 (0.08-5.95) (reference) 1.29 (0.96-1.73) 1.91 (1.28-2.87)	++ / Positive
Rodriguez-Laso, TSHA ¹⁸³	Europe (Hispanic)	1748 5.2 years	BMI per kg/m ² ≤29 >29	FP: 0.90 (0.80-1.01) 1.07 (0.98-1.17)	++++ / None
Ho, TLSA ¹⁷⁶	Asia (East Asian)	1609 8 years	BMI trajectory Group 1 Group 2 Group 3 Group 5	FP: 1.79 (1.05-3.07) (reference) 0.96 (0.56-1.64) 2.01 (1.01-4.00)	+++ / Positive (J-shape)
Bouillon, Whitehall II ¹⁸⁰	Europe (White)	2702 10.5 years	BMI <25.0 25.0-29.9 ≥30.0	FP: (reference) 0.94 (0.76-1.17) 1.10 (0.76-1.58)	++++ / None
Shah, HRS ¹⁷⁰	US (White)	6073 12 years	BMI per kg/m ²	PLFI (men): 1.01 (0.99-1.03)*	n/a / Positive (linear) in females only
Niederstrasser, ELSA ¹⁸⁷	Europe (White)	7420 12 years	BMI per kg/m ² <18.5 18.5-24.9 25.0-29.9 ≥30.0	PLFI (women): 1.03 (1.02-1.04)* FI: 1.43 (0.97-2.11)* (reference) 1.01 (0.91-1.50)* 1.33 (1.18-1.50)*	n/a / Positive (U-shape)
Rutherford, EPESE ²⁰⁰	Latin America	1648 18 years	BMI	FP:	+++ /

First author name, Study name	Region (ethnicity)	No. of participants / duration of follow-up	Exposure	Odds ratio (95% CI) for incident frailty	Adjustments [†] / reported association
	(Hispanic)		<18.5 18.5-24.9 25.0-29.9 30.0-34.9 ≥35.0	2.40 (1.29-4.46) reference 0.86 (0.65-1.13) 1.09 (0.80-1.50) 1.62 (1.07-2.44)	Positive (U-shape)
Uchai, Tromso ²⁰¹	Europe (White)	4509 21 years	BMI <18.5 18.5-24.9 25.0-29.9 ≥30.0	FP: 1.32 (0.49-3.54) reference 1.19 (1.02-1.39) 2.41 (1.93-3.02)	+++ / Positive (J-shape)
Stenholm, MFHES ²⁰²	Europe (White)	1119 22 years	BMI <25.0 25.0-29.9 ≥30.0	FP: (reference) 2.49 (1.22-5.06) 5.02 (1.89-13.33)	+++ / Positive
Sotos-Prieto, NHS ¹⁷⁴	US (White)	68416 22 years	BMI >25 ≥25	FRAIL: (reference) 1.79 (1.72-1.86)*	+++ / Positive
Strandberg, HBS ¹⁷⁸	Europe (White)	1815 26 years	BMI <25.0 25.0-29.9 ≥30.0	FP: (reference) 2.06 (1.21-3.52) 5.41 (1.94-15.11)	++ plus biomarkers / Positive

[†]Adjustments: + age and/or sex; ++ plus cardiovascular risk factors (smoking, body mass index, alcohol consumption, diabetes, hypertension, family history of heart disease, etc.); +++ plus demographic variables (education, income, ethnicity, etc.) and other disease and medications; ++++ plus biomarkers.

*Hazard ratio (95% CI)

Abbreviations: BMI=body mass index; CI=confidence interval; FI=frailty index; FP=frailty phenotype; FRAIL=Fatigue, Resistance, Ambulation, Illness, and Loss of weight scale; PLFI=Paulson-Lichtenberg Frailty Index

Lean body mass

Only one study in China met the eligibility criteria (**Table 4.4**).¹⁹⁵ Lean body mass was assessed using calf circumference (CC), which was measured at its widest point with minimal pressure. The association between CC and incident frailty was inverse and J-shaped. Those with higher CC had lower risk of frailty and those in the fourth quintile of CC had a lower likelihood of developing frailty compared to those in the first quintile (HR [95%CI]: 0.67 [0.50-0.89]).

Table 4.4 Key findings of studies investigating the association between lean body mass and incident frailty

First author name, Study name	Region (ethnicity)	No. of participants / duration of follow-up	Exposure	Hazard ratio (95% CI) for incident frailty	Adjustments [†] / reported association
Dai, CLHLS ¹⁹⁵	Asia (East Asian)	2359 4 years	CC (cm): ≤28.0 28.0-≤30.0 30.0-≤33.0 33.0-≤35.0 >35.0	FI: reference 1.02 (0.82-1.27) 0.89 (0.71-1.11) 0.67 (0.50-0.89) 0.78 (0.58-1.05)	+++ / J-shaped

Alcohol Consumption

Twelve studies (13 reports) evaluated the prospective association between alcohol consumption and the risk of incident frailty. Alcohol consumption was estimated by the first 3 questions of the Alcohol Use Disorders Identification Test (AUDIT) questionnaire (AUDIT-C, a screening test for hazardous alcohol consumption that has been validated and extensively used in many countries),^{203–205} validated diet questionnaires, or other unspecified self-reported measures, and categorised into 2 to 5 levels by the amount and frequency of drinking (see ‘Exposure’ column of **Table 4.5** for the exact levels). Importantly, many of the definitions combined never and ex-drinkers into a single category. Frailty was mostly defined using the FP, but also the FI, FRAIL, and PLFI. The key findings are shown in **Table 4.5**. In the 10 Western cohorts, alcohol consumption had an inverse or U-shape relationship with incident frailty. For instance, hazardous alcohol use (based on a high score from the AUDIT-C questionnaire, ≥ 4 pts in women and ≥ 5 pts in men) was associated with a lower risk of incident frailty than non-drinkers using different definitions of frailty (OR [95%CI] FI: 0.68 [0.60-0.77] & FP: 0.66 [0.47-0.93]).¹⁸¹ Compared to never drinkers, light-to-moderate drinkers had lower risk of frailty (0.53 [0.31-0.91]) while heavy drinkers had comparable risk (0.87 [0.44-1.69]).¹⁷⁵ Studies with longer follow-up (>5 years) showed a similar pattern – light-to-moderate drinking was inversely associated with frailty risk,^{170,174,179,188} but heavy alcohol use was now positively, albeit non-significantly, associated with frailty. The association between alcohol consumption and incident frailty was evaluated in two Asian populations: China¹⁹⁹ and Taiwan.¹⁷⁶ In both cohorts, alcohol consumption versus non-consumption was inversely associated with frailty, but associations were either not statistically significant¹⁹⁹ or their strength attenuated after adjustment for confounders.¹⁷⁶

Table 4.5 Key findings of studies investigating the association between alcohol consumption and incident frailty

First author name, Study name	Region (ethnicity)	No. of participants / duration of follow-up	Exposure	Odds ratio (95% CI) for incident frailty	Adjustments [†] / reported association
Jazbar, SHARE ¹⁸¹	Europe (White)	8133 2 years	Drinker: ^a Non- Non-hazard Hazardous	FP: (reference) 0.66 (0.47–0.93) 0.88 (0.58–1.32)	+++./ Inverse
Seematter-Bagnoud, Lausanne cohort 65+ ¹⁹³	Europe (White)	1057 3 years	Drinker: ^a Non- Non-hazard Hazardous	FI: (reference) 0.68 (0.60–0.77) 0.80 (0.68–0.93)	+++ / Inverse
Woods, WHI-OS ¹⁷²	US (White)	28181 3 years	Drinker: ^b Non- Light-mod At-risk Heavy	FP: (reference) 2.00 (1.02-3.91) (reference) 1.49 (0.98-2.26) 0.73 (0.34-1.58)	n/a / None
Garcia-Esquinas, Seniors-ENRICA ¹⁷⁵	Europe (Hispanic)	1750 3.5 years	Drinks/wk: 0/ex-drinker <1 1-14 ≥14	FP: (reference) 0.87 (0.77-0.97) 0.69 (0.61-0.77) 0.93 (0.74-1.16)	+ plus education / Inverse or J- shape
Soler-Vila, Seniors-ENRICA ¹⁷¹	Europe (Hispanic)	1857 3.5 years	Drinker: ^c Never Ex- Moderate Heavy	FP (men): (reference) 0.86 (0.25–2.95) 0.81 (0.34-1.92) 0.64 (0.16–2.58)	+ plus baseline frailty / Inverse or J- shape
Kojima, ELSA ¹⁸⁶	Europe (White)	2544 4 years	Drinker: ^c Non- Ex- Light-mod Heavy	FP (women): (reference) 0.68 (0.31 to 1.50) 0.49 (0.28 to 0.86) 0.44 (0.10 to 1.96)	+++ / None
Rodriguez-Laso, TSHA ¹⁸³	Europe (Hispanic)	1748 5.2 years	Units/wk: ^d Non- >0-7 >7-14 >14-21 >21	FP: (reference) 1.39 (0.88-2.19) (reference) 0.98 (0.62-1.55) 1.01 (0.60-1.71) 0.63 (0.34-1.18)	++++ / J-shape
Ho, TLISA ¹⁷⁶	Asia (East Asian)	1609 8 years	Drinker: ^e Teetotaler Ex- Not at risk At risk Undeclared	FP: (reference) 1.42 (0.59-3.41) 0.69 (0.34-1.39) 1.52 (0.34-6.71) 2.12 (1.10-4.11)	+++ / None
Wang, CLHLS ¹⁹⁹	Asia (East Asian)	3327 10 years	Drinking ^e	FP: (reference) 1.025 (0.585-1.794)	+ plus multi- morbidity / None
Shah, HRS ¹⁷⁰	US (White)	6073 12 years	Drinker: ^f Never Ex- Low risk High risk	FP: (reference) 0.86 (0.57–1.29) 0.88 (0.49–1.58) 0.81 (0.53–1.24)	n/s / J-shape
			Drinks/wk: ^g 0 1-7 8-14 ≥15	PLFI (men): (reference) 0.78 (0.63–0.96)* 0.95 (0.70–1.28)* 1.30 (0.90–1.88)*	

First author name, Study name	Region (ethnicity)	No. of participants / duration of follow-up	Exposure	Odds ratio (95% CI) for incident frailty	Adjustments [†] / reported association
			Drinks/wk: ^g 0 1-7 8-14 ≥15	PLFI (women): (reference) 0.81 (0.69–0.96)* 1.08 (0.77–1.52)* 1.65 (0.93–2.94)*	
Gil-Salcedo, Whitehall II ¹⁷⁹	Europe (White)	6357 20 years	Drinker: ^h None Moderate High	FP: 1.15 (0.85–1.57)* 0.76 (0.59–0.98)* (reference)	+++ / U-shape or inverse J- shape
Sotos-Prieto, NHS ¹⁷⁴	US (White)	68416 22 years	Drinker: Moderate/non-drinker Not moderate drinker	FRAIL: (reference) 1.43 (1.37–1.49)*	+++ / Positive
Strandberg, HBS ¹⁸⁸	Europe (White)	2360 30 years	Drinker: ⁱ None Light Moderate High	FP: 1.14 (0.48–2.73) (reference) 0.86 (0.52–1.44) 1.61 (1.01–2.56)	++ / J-shape

^aAlcohol use was categorised into 3 levels: no use (0), non-hazardous use (1–3pts in women and 1–4pts in men), and hazardous use (≥4pts in women and ≥5 pts in men) based on 3 questions (0–4 points) from the AUDIT-C test regarding the amount and frequency of drinking in the last 3 months.

^bAlcohol use was categorised into 4 levels: non-, light-to-moderate, at-risk, and heavy based on the average number of standard drinks consumed per week using the AUDIT-C test. Threshold separating light-to-moderate and at-risk drinking is 1–7 drinks/week for women and 1–14 for men, and for at-risk and heavy drinking is ≥12 for women and ≥20 for men. Ex-drinkers were identified at a later follow-up in 2011.

^cAlcohol use was categorised into 4 levels: non-drinkers, ex-drinkers, light-moderate drinkers, and heavy drinkers based on alcohol consumption in the preceding 12 months collected with a validated diet history. Threshold separating light-moderate and heavy drinkers is ≥40 g/day in men and ≥24 g/day in women.

^dAlcohol use was categorised into 5 levels: non-drinkers, >0–7, >7–14, <14–21, and >21 units/week based on self-reported alcohol consumption. UK units (1 unit = 8 g of pure alcohol) was calculated based on drinking frequency over the past 12 months and the average amount of alcoholic beverages.

^eDefinitions were not specified.

^fAlcohol use was categorised into 4 levels: never, past, low-risk drinking, and high-risk drinking, where the threshold separating low and high-risk drinking is 25g for men and 15g for women.

^gAlcohol use was categorised into 4 levels: 0, 1–7, 8–14, and ≥15 based on self-reported typical number of drinks per week (multiplied the average number of drinks per day by the average number of drinking days per week in the past 3 months).

^hAlcohol use was categorised into 3 levels: none, moderate (1–14 units/week), and high (>14 units/week) based on the number of units of alcohol consumed last week.

ⁱAlcohol use was categorised into 4 levels: none, light (1–98g/week), moderate (99–196 g/week) and high (>196 g/week) based on self-reported alcohol consumption as the weekly number of drinks during the past year.

[†]Adjustments: + age and/or sex; ++ plus cardiovascular risk factors (smoking, body mass index, alcohol consumption, diabetes, hypertension, family history of heart disease, etc.); +++ plus demographic variables (education, income, ethnicity, etc.) and other disease and medications; ++++ plus biomarkers.

*Hazard ratio (95% CI)

Abbreviations: CI=confidence interval; FI=frailty index; FP=frailty phenotype; FRAIL=Fatigue, Resistance, Ambulation, Illness, and Loss of weight scale, PLFI=Paul-Lichtenberg Frailty Index

Smoking

Twelve studies described the prospective associations between smoking and incident frailty, of which 9 were conducted in Western populations and the remaining 3 in Mexico, Japan, and China. Smoking status was self-reported and analysed as a binary (ever or never) or 3-level (never, past, or current) variable. Frailty was defined mostly using the FP, but also the FI,

FRAIL, and Kaigo-Yobo Checklist (KYCL).²⁰⁶ The KYCL is a checklist consisting of 15 questions related to falls, physical abilities, social activities, and nutritional status, and has been shown to be highly correlated with the FI.²⁰⁷ The key findings of individual studies are summarised in **Table 4.6**. In general, positive associations between smoking and incident frailty were found. Among 6 studies reporting a positive association, current smoking was associated with 1.38- to 2.90-fold higher risk of frailty compared to never smokers. Similarly, never smoking was associated with a 22% (95%CI: 15%-29%)¹⁸⁷ or 32% (11%-47%)¹⁷⁹ lower risk of incident frailty than ever smokers. The remaining studies reported statistically non-significant associations, but the risk estimates were directionally consistent.

Table 4.6 Key findings of studies investigating the association between smoking and incident frailty

First author name, Study name	Region (ethnicity)	No. of participants / duration of follow-up	Exposure	Odds ratio (95% CI) for incident frailty	Adjustments [†] / reported association
Borda, MHAS ¹⁹²	Mexico (Hispanic)	6087 3 years	Smoker: ^a Non-current Current	FI: 1.1 (0.9-1.3) (reference)	+ plus demographic variables / None
Woods, WHI-OS ¹⁷²	US (White)	28181 3 years	Smoker: ^b Never Past Current	FP: (reference) 1.12 (1.02-1.23) 2.90 (2.35-3.57)	None / Positive
Graciani, Seniors-ENRICA ¹⁹⁴	Europe (Hispanic)	1745 3.5 years	Smoker: ^b Never Past Current	FP: (reference) 1.04 (0.41-2.63) 0.96 (0.39-2.35)	++++ / None
Trevisan, Pro.V.A. ¹⁷³	Europe (White)	2925 4.4 years	Smoker: ^b Never Past Current	FP: ^d (reference) n/s 1.18 (1.03-1.37)	++++ / Positive
Abe, Yabu Cohort ¹⁹⁸	Asia (East Asian)	2633 5 years	Smoking: ^b Never Past Current	KYCL: (reference) 1.07 (0.84-1.37) 1.36 (0.88-2.12)	+++ / None
Rodriguez-Laso, TSHA ¹⁸³	Europe (Hispanic)	1748 5.2 years	Smoker: ^b Never Past Current	FP: ^d (reference) 0.98 (0.53-1.83) 1.96 (0.95-4.03)	++++ / None
Ting, HIMS ¹⁸⁹	Australia (White)	1743 4-8 years	Smoking: ^b Never Past Current	FRAIL: (reference) 1.51 (1.14-2.00) 2.02 (0.95-4.27)	++
Wang, CLHLS ¹⁹⁹	Asia (East Asian)	3327 10 years	Smoker: ^b Never Past Current	FP: (reference) 1.33 (0.89-1.98) 1.34 (0.90-1.98)	+ plus multi-morbidity / None (positive in males only)
Niederstrasser, ELSA ¹⁸⁷	Europe (White)	7420 12 years	Smoker: ^c Never Ever	FI: 0.78 (0.71-0.85)* (reference)	None / Positive
Gil-Salcedo, Whitehall II ¹⁷⁹	Europe (White)	6347 20 years	Smoker: ^b Never Past Current	FP: 0.68 (0.52-0.89) 0.53 (0.40-0.71) (reference)	+++ / Positive
Sotos-Prieto, NHS ¹⁷⁴	US (White)	68416 22 years	Smoker: ^c Never Ever	FRAIL: (reference) 1.38 (1.33-1.43)*	+++ / Positive
Strandberg, HBS ¹⁷⁸	Europe (White)	1815 26 years	Smoker: No Yes	FP: (reference) 1.34 (0.79-2.26)	++ plus biomarkers / None

^aSmoking definition self-reported 2 levels: current or not current smoker ("Did you smoke in the last two years").

^bSmoking definition self-reported 3 levels: never, past, and current.

^cSmoking definition self-reported 2 levels: never and ever.

^dOutcome is incident pre-frailty or frailty.

[†]Adjustments: + age and/or sex; ++ plus cardiovascular risk factors (smoking, body mass index, alcohol consumption, diabetes, hypertension, family history of heart disease, etc.); +++ plus demographic variables (education, income, ethnicity, etc.) and other disease and medications; ++++ plus biomarkers.

*Hazard ratio (95% CI)

Abbreviations: CI=confidence interval; FI=frailty index; FP=frailty phenotype; FRAIL=Fatigue, Resistance, Ambulation, Illness, and Loss of weight scale; KYCL=Kaigo-Yobo Checklist

Diabetes or elevated plasma glucose levels

Thirteen studies (14 reports) describing the prospective associations between diabetes or plasma glucose levels and incident frailty were identified. Diabetes was defined using self-reported doctor-diagnosis of diabetes, current treatment for diabetes, fasting glucose levels (≥ 7 mmol/L, ≥ 126 mg/dl, or 100-126 mg/dl), a combination of the above, or undefined.¹⁸² Frailty was defined using the FP or FI. The key findings are shown in **Table 4.7**. Most of the studies from Western cohorts reported a positive association between diabetes and risk of incident frailty. Diabetes was associated with 1.4- to 1.8-fold higher risk of frailty after adjustment for several confounders including demographic or other CVD RFs. The magnitude of association was also similar regardless of the frailty definition used (OR [95%CI] FI: 1.69 [1.46-1.96] & FP: 1.62 [1.11-2.37]).¹⁸¹ The two male cohort studies^{178,180} involving prolonged duration of follow-up (10-26 years), however, reported no significant associations between glucose and incident frailty. The three studies conducted in Asian populations (China,¹⁹⁰ Singapore,¹⁶⁸ and Japan¹⁸²) reported comparable results to those conducted in Western populations. Diabetes was associated with a 44%-56% higher risk for incident frailty after adjustment for confounders (albeit not statistically significant in the Japanese study¹⁸²).

Table 4.7 Key findings of studies investigating the association between diabetes and incident frailty

First author name, Study name	Region (ethnicity)	No. of participants / duration of follow-up	Exposure	Odds ratio (95% CI) for incident frailty	Adjustments [†] / reported association
Chhetri, BLSA-II ¹⁹⁰	Asia (East Asian)	6293 1 year	Diabetes ^a	FI: 1.56 (1.32-1.85)	+ plus residency and comorbidity / Positive
Jazbar, SHARE ¹⁸¹	Europe (White)	8133 2 years	Diabetes treatment	FP: 1.62 (1.11–2.37) FI: 1.69 (1.46–1.96)	+++ / Positive
Woods, WHI-OS ¹⁷²	US (White)	28181 3 years	Diabetes treatment	FP: 1.40 (1.11–1.76)	n/s / Positive
Garcia-Esquinas, Seniors-ENRICA ¹⁷⁵	Europe (Hispanic)	1750 3.5 years	Diabetes ^b	FP: 1.76 (1.10-2.82)	+++ / Positive
Soler-Vila, Seniors-ENRICA ¹⁷¹	Europe (Hispanic)	1857 3.5 years	Self-reported physician-diagnosed diabetes	FP (men): 1.53 (0.66-3.54) FP (women): 1.78 (0.96-3.31)	+ plus baseline frailty / None
Doi, OSHPE ¹⁸²	Asia (East Asian)	4322 4 years	Diabetes (undefined)	FP: 1.44 (0.92-2.24)	+++ / None
Trevisan, Pro.V.A. ¹⁷³	Europe (White)	2925 4.4 years	Diabetes	FP: 1.44 (1.28-1.68)	++++ / Positive
Cheong, SLAS-2 ¹⁶⁸	Asia (Asian)	1297 4.5 years	Self-reported physician-diagnosed diabetes	FP: 1.51 (1.03-2.22)	+ plus education/ Positive
Zaslavsky, ACT ¹⁹⁷	US (n/s)	1848 4.8 years	Diabetes treatment	FP: 1.52 (1.19-1.94)*	+++ / Positive
Ting, HIMS ¹⁸⁹	Australia (White)	1743 4-8 years	Diabetes ^c	FRAIL: 1.53 (1.09-2.15)	++ / Positive
Rodriguez-Laso, TSHA ¹⁸³	Europe (Hispanic)	1748 5.2 years	Diabetes ^d	FP: 1 (1-1.01)	n/a / Positive
Bouillon, Whitehall II ¹⁸⁰	Europe (White)	2702 10 years	Fasting glucose 100-126 mg/dL	FP: 0.99 (0.79-1.24)	++++ / None
Rutherford, EPESE ²⁰⁰	Latin America (Hispanic)	1648 18 years	Self-reported diabetes	FP: 1.20 (0.94-1.55)	+++ / None
Strandberg, HBS ¹⁷⁸	Europe (White)	1815 26 years	Fasting glucose (log 1-h glucose) per 1 unit increase	FP: 6.61 (0.82-53.10)	++ plus biomarkers / None

^aDiabetes was defined as WHO criteria of fasting plasma glucose ≥ 7 mmol/L or self-reported doctor diagnosis of diabetes and taking anti-diabetic medications.

^bDiabetes was defined as fasting serum glucose ≥ 126 mg/dL or physician-diagnosed diabetes.

^cDiabetes was defined as self-reported diabetes, use of glucose-lowering medication using insulin or had fasting or non-fasting glucose concentration of ≥ 7 mmol/L or ≥ 11.1 mmol/L, respectively.

^dDiabetes was defined as hyperglycemia (fasting glucose > 126 mg/dL).

[†]Adjustments: + age and/or sex; ++ plus cardiovascular risk factors (smoking, body mass index, alcohol consumption, diabetes, hypertension, family history of heart disease, etc.); +++ plus demographic variables (education, income, ethnicity, etc.) and other disease and medications; ++++ plus biomarkers.

*Hazard ratio (95% CI)

Abbreviations: CI=confidence interval; FI=frailty index; FP=frailty phenotype

Hypertension or systolic blood pressure

Nine studies described the prospective associations between hypertension or BP levels and incident frailty. Hypertension was defined using self-reported history of hypertension, current use of BP-lowering medications, BP (continuous or $\geq 130/85$ mmHg), or a combination of these. Frailty was defined using the FP or FI. **Table 4.8** shows the key findings of each study. Overall, hypertension was associated with 1.09- to 1.37-fold higher risk of incident frailty in Western populations, but associations were only significant in studies with a shorter duration of follow-up (≤ 3 years) or for crude associations.¹⁷² The magnitude of associations of hypertension and frailty risk was similar using the FP (OR [95%CI]: 1.37 [1.21-1.51]) and FI (1.35 [1.21-1.51]).¹⁸¹ Two studies described the associations between hypertension and incident frailty in Japanese older adults over 2-4 years of follow-up,^{182,191} which were of comparable strength to those from studies conducted in Western populations.

Table 4.8 Key findings of studies investigating the association between hypertension and incident frailty, ordered by length of follow-up

First author name, Study name	Region (ethnicity)	No. of participants / duration of follow-up	Exposure	Odds ratio (95% CI) for incident frailty	Adjustments [†] / reported association
Yoshida ¹⁹¹	Asia (East Asian)	334 2 years	Hypertension ^a	FI: 2.55 (1.24–5.25)	n/s / Positive
Jazbar, SHARE ¹⁸¹	Europe (White)	8133 2 years	Hypertensive medication	FP: 1.37 (1.02–1.84) FI: 1.35 (1.21–1.51)	+++./ Positive
Woods, WHI-OS ¹⁷²	US (White)	28181 3 years	Hypertension (undefined) or hypertensive medication	FP: 1.18 (1.08–1.29)	n/s / Positive
Graciani, Seniors-ENRICA ¹⁹⁴	Europe (Hispanic)	1745 3.5 years	BP: ^b Ideal Intermediate Poor	FP: 1.48 (0.92–2.36)* 0.99 (0.58–1.70)* (reference)	++++ / None
Doi, OSHPE ¹⁸²	Asia (East Asian)	4322 4 years	Hypertension (undefined)	FP: 1.19 (0.84–1.69)	+++ / None
Barzilay, CHS ¹⁸⁴	US (White)	2926 9 years	SBP per SD increase	FP: 1.01 (0.88–1.17)	+++ / None
Bouillon, Whitehall II ¹⁸⁰	Europe (White)	2702 10 years	Hypertension ^c	FP: 1.09 (0.92–1.29)	++++ / None
Rutherford, EPESE ²⁰⁰	Latin America (Hispanic)	1648 18 years	Hypertension ^a	FP: 0.96 (0.76–1.21)	+++ / None
Strandberg, HBS ¹⁷⁸	Europe (White)	1815 26 years	SBP per 10 mmHg increase	FP: 1.06 (0.93–1.21)	++ plus biomarkers / None

^aSelf-reported history of hypertension.

^bBP was categorised into 3 levels: poor $\geq 140/90$, intermediate $\geq 140/90$, treated and ideal $< 140/90$, untreated.

^cHypertension was defined as BP $\geq 130/85$ mmHg or hypertension therapy use.

[†]Adjustments: + age and/or sex; ++ plus cardiovascular risk factors (smoking, body mass index, alcohol consumption, diabetes, hypertension, family history of heart disease, etc.); +++ plus demographic variables (education, income, ethnicity, etc.) and other disease and medications; ++++ plus biomarkers.

*Hazard ratio (95% CI)

Abbreviations: CI=confidence interval; FI=frailty index; FP=frailty phenotype; SBP=systolic blood pressure

4.2.3 Discussion

Adiposity

The available evidence suggests that higher levels of adiposity were associated with higher risks of frailty, but some uncertainties exist. Central obesity was positively associated with incident frailty but most of the associations were statistically non-significant, which may reflect a lack of power to detect such associations, truly null associations, or bias. There is a relatively high risk of misclassification bias arising from using measurement tapes to manually measure WHR. Previous studies have shown that waist and hip measurements are less precise than BMI even when measured by medical professionals²⁰⁸ and that measurements are particularly

imprecise when trying to assess overweight and obese people.²⁰⁹ Since the anatomical landmarks are less clear in overweight and obese people, their waist and hip measurements are more difficult to take than leaner people. Thus, differential misclassification of WHR may occur, which can under- or over-estimate the association between WHR and frailty. Additionally, only studies that used the FI^{180,196} (including one study that compared the FI versus FP in the same study)¹⁹⁶ tended to report significant associations between central adiposity with frailty, which suggests that central adiposity may not be associated with the FP model or physical wasting symptoms. However, the inclusion of CVD in the FI (e.g. FI included hypertension, diabetes, heart disease, and stroke/TIA in the CLHLS study)¹⁹⁵ may have inflated the association between central adiposity and the FI model.

The association between general obesity and risk of frailty was also inconsistent in the literature. A J-shaped association was reported for BMI and frailty in studies with a shorter duration of follow-up, suggesting that lower BMI levels (e.g. underweight) was associated with higher risk of frailty compared to normal or overweight BMI but the highest risk of frailty was in the obese category. That some body fat and adipose tissue is beneficial to human survival and function is well known. For instance, adiposity is related to important physiological processes like energy expenditure, reproduction, insulation, bone health, and immune function.²¹⁰ However, this inverse effect attenuated with a longer duration of follow-up (>20 years). Also, many associations crossed the null value, so it is possible that there is no association between obesity and frailty or a lack of power to detect associations. Additionally, information bias may be present in the measurement of BMI. It is unclear whether weight and height measurements were taken objectively or self-reported in many of the included studies. If self-reported, weight and height measurements are likely to be susceptible to under- and over-reporting, respectively, leading to an underestimation of overweight and obesity.²¹¹ This may explain the lack of association between BMI and frailty. Importantly, associations differed by the length of follow-up – the inverse effect in shorter studies may be an artefact of reverse causation bias or protopathic bias whereby the exposure is influenced by early (subclinical)

stages of disease.²¹² Participants with subclinical frailty at baseline may exhibit muscle wasting after a short follow-up, which may explain the higher risk of frailty among individuals with lower BMI. An investigation of reverse causation by the ELSA study (excluding participants who became frail within 2 years of follow-up) found no such evidence,¹⁸⁰ but the exclusion of 2 years may be insufficient to exclude risks of reverse causality given the long latent period of frailty.

Alcohol consumption

The literature review identified substantial uncertainty about the strength and shape of the associations between alcohol consumption and frailty. Studies reported both inverse and U-shaped associations – typically an inverse association between light-to-moderate, and even heavy, drinking with frailty risk was seen. While a true protective effect of alcohol consumption on frailty may be possible, differences in the definition of alcohol use may account for the conflicting results. Alcohol consumption was chiefly estimated using validated questionnaires, but their validity may vary – estimations using the amount of alcohol (e.g. g/week) may be more accurate than those based on the number of drinks (e.g. drinks/week). In addition, the arbitrary and varied categorisation of alcohol consumption may have influenced the shape of the association reported. For instance, thresholds to define the high drinking category ranged from 112 g/week¹⁷⁹ to 280 g/week.¹⁷⁵ Such differences influence the strength of associations of heavy drinkers with frailty and the shape of the overall relationship. Several studies also combined never and ex-drinkers into a single category (non-drinkers). The latter group were likely to have a higher level of risk, particularly by the time since and reason for quitting, which may explain the higher frailty risk in the non-drinkers in the review. Additionally, the length of studies may explain some of the inconsistencies. In studies with very long follow-up, such as the Nurses' Healthy Study¹⁷⁴ and Helsinki Businessmen Study,¹⁸⁸ the opposing evidence was found. Rather than an inverse association, heavy alcohol consumption was associated with a greater risk of frailty compared to non- or light drinkers. This may be explained by differences in the age of enrolment – younger cohorts followed up to older age may have had greater opportunity for the effects of alcohol on frailty to take place, whilst older cohorts excluded

premature deaths such as individuals with heavy drinking patterns who die before old age, which may explain the inverse association between alcohol consumption on frailty risk. Lastly, similar findings were reported regardless of the frailty definition used (FP, FI, or FRAIL).

Smoking

Current smoking at baseline was associated with higher risks of incident frailty, but most of the reported associations were non-significant. Also, there was substantial risk of misclassification bias in the classification of smoking exposures and residual confounding. Methods seldom reported the questions used to obtain smoking status; when reported, they appeared to vary significantly across studies. For instance, the questions “did you smoke in the last 2 years” or “do you smoke nowadays” will capture different smoking patterns. Moreover, most studies differentiated between never and former smokers, but none were able to distinguish between former smokers who had quit by choice or due to illness. The inclusion of the latter group (i.e. smokers who had quit due to illness) in the former smoking category may explain why many former smokers had greater or comparable risk of frailty to current smokers. Conversely, one study reported an inverse association between past smoking for risk of frailty,¹⁷⁹ which may be explained by residual confounding. Former smokers may exhibit or have taken up other healthy lifestyle behaviours, which over the course of the 20 years of study follow-up manifested a lower risk of frailty. Lastly, similar findings were reported regardless of the frailty definitions used (FP, FI, FRAIL, and KYCL).

Diabetes

The literature review found strong positive associations between baseline diabetes and higher risks of incident frailty (apart from two studies with more than 20 years of follow-up that found no association between glucose and incident frailty). The strength of associations was comparable across studies, despite the different study protocols used. However, the presence of biases may undermine these findings, namely the differences in the definition of diabetes used across the different studies. Self-reported diagnoses may be less specific than physician diagnoses, while screen-detected diabetes involving glucose measurements may be more sensitive but exclude those with well-controlled diabetes. Also, those taking diabetes

medications may be at more advanced stages of the disease. Thus, the reported associations were of similar magnitude, but the differences in exposure definition may have introduced misclassification bias and clouded any real variation in the results. The inconsistent results by the length of follow-up may be explained by attrition in longitudinal studies, which can be non-random.²¹³ Those who drop out may be more likely to exhibit unfavourable risk factors like poor glucose control and increased dependency, which may explain the lack of association between glucose and incident frailty in studies with longer follow-up. Lastly, similar findings were reported regardless of the frailty definitions used – a study that compared the FP and FI reported similar magnitude of association between diabetes and incident frailty.¹⁸¹

Hypertension

There was conflicting evidence about the associations between hypertension and the risk of frailty. Like diabetes, the definition of hypertension varied across studies and may have resulted in some misclassification biases outlined above. Attrition bias is also likely to be present, which may explain the fact that only studies with shorter follow-up (≤ 3 years) reported significant positive associations – these attenuated with a longer duration of follow-up (3.5-26 years). Another potential explanation for the conflicting results is the differences in the populations studied. Many of the studies that reported no significant associations between hypertension and frailty had applied certain inclusion criteria at baseline. For instance, the Seniors-ENRICA,¹⁹⁴ Whitehall II Prospective Cohort Study,¹⁸⁰ and HBS¹⁷⁸ excluded men with a history of CVD. This suggests effect modification of the relationship between hypertension and frailty may be possible by the presence of CVD. Lastly, similar findings were reported regardless of the frailty definitions used – a study that compared the FP and FI reported similar magnitude of association between hypertension and incident frailty.¹⁸¹

4.3 Prospective associations of frailty with stroke and ischaemic heart disease

4.3.1 Methods

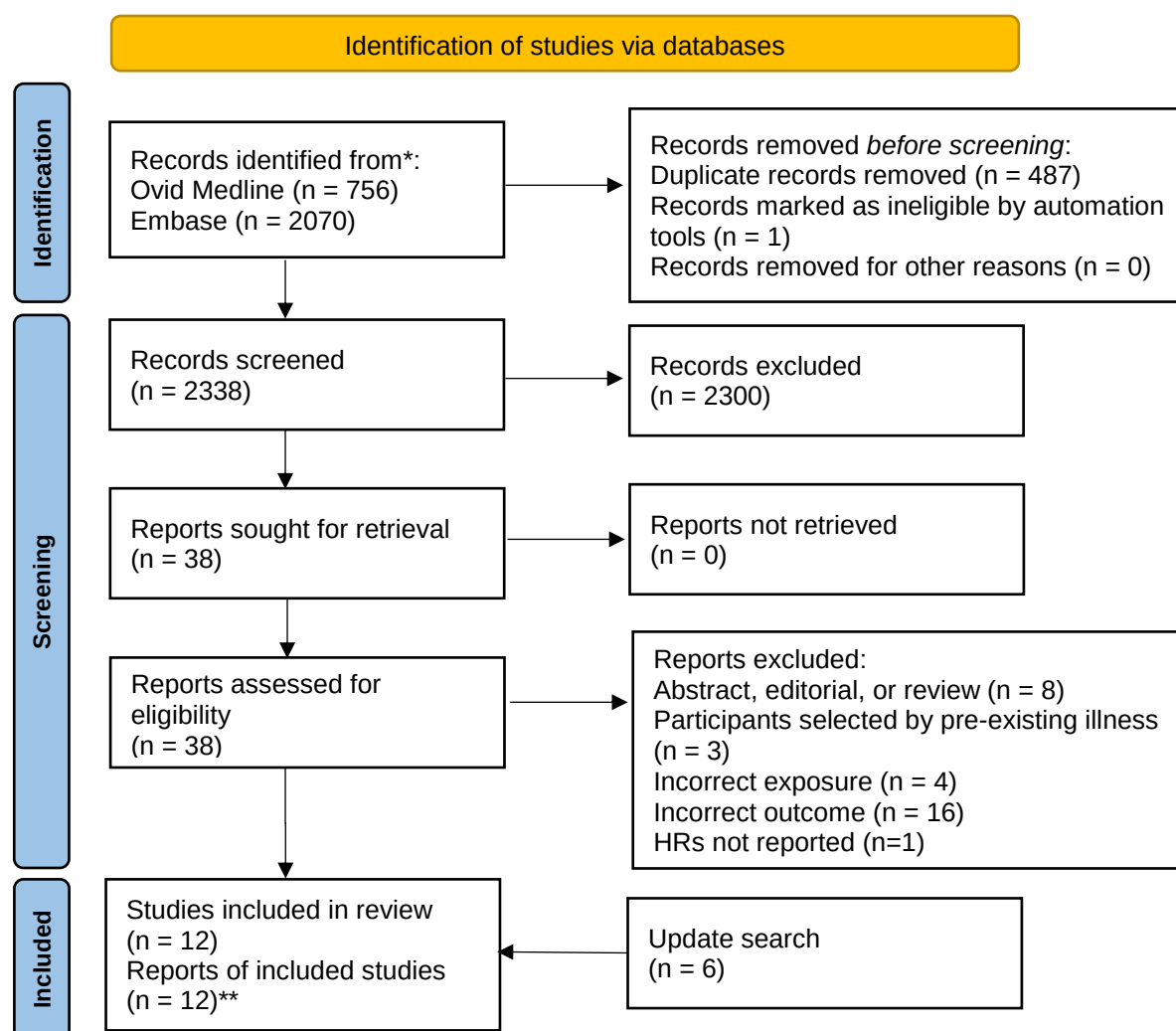
The articles were identified using Ovid Medline and Embase databases from January 1, 2001 (shortly after the inception of frailty models) to 3 March 2022. Two update searches carried out on 22 August 2022 and 24 August 2023 identified zero and 6 additional eligible studies, respectively. The inclusion criteria for the review were: (1) prospective observational studies; included community-based participants; (2) measured frailty at baseline (and frailty or related terms appeared in the title as the main focus of the article); and (3) studied incident stroke or IHD as the outcome. The keywords, MeSH terms, and search strategy are summarised in **Table S4.2**. Studies were excluded when participants were selected on the basis of pre-existing diseases, did not report original research (i.e. review articles), or did not report associations using hazard ratios (HR) from Cox proportional hazards models. Studies were limited to published reports using the English language. References were screened manually to identify additional articles missed by the database search. Data were extracted for information previously listed (**page 80**).

4.3.2 Results

Study selection and characteristics

The selection process for included studies was summarised using a flow chart (**Figure 4.2**). In brief, 2,825 articles were identified by the database searches, which included 487 duplicates. 2,340 articles were screened for eligibility, after which 6 articles were identified for inclusion. An additional 6 studies were identified in an update search, resulting in 12 studies for inclusion.

Figure 4.2 Flow diagram of article selection for prospective studies reporting the association between frailty and stroke and ischaemic heart disease



*Search was carried out on 21 March 2022. Update searches were carried out on 22 August 2022 and 24 August 2023, which identified zero and 6 additional eligible studies, respectively.

**Of these, 9 reports studied stroke and 12 reports studied IHD as outcomes.

The literature review included 12 prospective studies investigating the associations between frailty and incident stroke or IHD. Nine studies investigated the associations of frailty with stroke and 12 of frailty with IHD. **Table 4.9** summarises the study characteristics and the main findings are presented in **Table 4.10** (incident stroke) and **Table 4.11** (incident IHD).

Table 4.9 Prospective studies of frailty and risk of stroke and IHD

First author's name, study name, year of baseline study	Region (ethnicity)	No. of participants (% female)	Mean age [range] (years)	Duration of follow-up (years)	Definition of frailty	Definition of outcome	Were participants with CVD excluded at baseline?	No. of events
Stroke and IHD								
Chen, UK Biobank, 2006-2010 ²¹⁴	UK (White)	314093 (53%)	56 [38-73]	11	FP	Stroke (ICD-9 430, 431, 434, 4340, 4341, 4349, 436; ICD-10 I60-I61, I63-I64; OPCS-4 A052-A054, L351, L353, L343; Self-reported field IDs 6150, 4056, 20002) CHD (ICD-9 410, 411, 412, 413, 414; ICD-10 I20-I25; OPCS-4 K40-K46, K49, K50, K75; Self-reported field IDs 6150, 3894, 3627, 20002, 20004)	Excluded prevalent CVD	Stroke: 5359 CHD: 20454
Damulji, The National Health and Aging Trends (NHAT) study, 2011 ²¹⁵	US (White)	3259 (61%)	78 [≥65]	6	FP	Stroke (unspecified) Acute MI (unspecified)	Excluded participants with a history of CHD and stroke Excluded prevalent CVD, cognitive impairment, persistent physical disability, or known life-limiting illness.	Stroke: 24.2% AMI: 9%
Ekram, The ASPirin in Reducing Events in the Elderly (ASPREE) clinical trial, 2010-2017 ²¹⁶	US and Australia (White)	19114 (56%)	74 [≥65]	Median 4.7	FP & FI	Stroke (fatal and non-fatal) defined using medical records and death certificates		403 MI 355
Grabovac, Survey on Health, Aging and Retirement in Europe (SHARE), 2004 ²¹⁷	11 European countries (White)	24634 (54%)	64 [≥50]	Median 9	FP	Stroke mortality (unspecified) Heart attack mortality (unspecified)	No	Stroke: 255 Heart attack: 384
Shrauner, Veterans Health Administration (VHA), 2002 ²¹⁸	US (White)	1606703 (1.8%)	74 [≥65]	2	FI	Stroke (fatal and non-fatal) (ICD-9 443.x1, 434, 436, 437.0, 437.7; ICD-10 I63.20, I63.22, I63.30, I63.40, I64.50, I63.59, I67.2, I67.6, I67.89, I63.xx9) MI (fatal and non-fatal) (ICD-9 410.x, 411.x; ICD-10 I20.0, I21, I24.1, I24.8)	No Excluded participants with heart disease, stroke, cancer, COPD or diabetes in a sensitivity analysis	Stroke: 8.8% MI: 14.1 % Cerebrovascular disease : 10933 IHD: 7288
Fan, China Kadoorie Biobank (CKB), 2004-2008 ²¹⁹	China (East Asian)	512723 (59%)	52 [30-79]	Median 10.8	FI	Cerebrovascular disease mortality (ICD-10 I60-I69) IHD mortality (ICD-10 I20-I25)		

First author's name, study name, year of baseline study	Region (ethnicity)	No. of participants (% female)	Mean age [range] (years)	Duration of follow-up (years)	Definition of frailty	Definition of outcome	Were participants with CVD excluded at baseline?	No. of events
Jang, The Korean National Health Insurance database (KNHI), 2007-2017 ²²⁰	South Korea (East Asian)	Stroke: 870175 CAD: 885131 (53%)	66 [66]	10	FI	Stroke: G45-G46, I60-I69 CAD: I20-I25	No	Stroke: 102848 CAD: 63347
Liu, The China Health and Retirement and Longitudinal Study (CHARLS), 2011-2018 ²²¹	China (East Asian)	13580 (50%)	58 [≥45]	7	FI	Stroke: "Have you been told by a doctor that you have been diagnosed with a stroke?" Heart disease: "Have you been diagnosed with heart disease (including heart attack, angina, coronary heart disease, heart failure, or other heart problems)?"	Excluded participants with stroke at baseline	Stroke: 680 Heart dis: 1617
Liu, The Singapore Longitudinal Ageing Study (SLAS), 2003-2004 & 2009-2013 ²²²	Singapore (Asian)	5015 (65%)	66 [≥55]	10	FP	Non-fatal stroke obtained from Singapore Stroke Registry Non-fatal MI obtained from Singapore Myocardial Infarction Registry	Excluded confirmed diagnosis of AMI and stroke, and self-reported AF, heart attack and HF	Stroke: 164 MI: 145
IHD only								
McKechnie, British Regional Heart Study (BRHS), 2010-2012 ²²³	UK (White)	1445 (0%)	78 [40-59]	6	FP, Gill Index, HABC battery	HF was based on confirmed doctors' diagnoses from primary care records and verified where possible using primary and secondary care records and death certificates	Excluded prevalent HF	99
Khan, Health ABC (HABC) study, 1997-1999 ²²⁴	US (40% African American)	2825 (52%)	74 [70-79]	Median 11	Gill Index, HABC battery	HF based on medical records, self-reported dx adjudicated by relevant history, physical examination, or use of medication; physician diagnosis with HF symptoms or signs or X-ray evidence or HF treatment	Excluded prevalent CHD	466
Orkaby, The Framingham Heart Study (FHS) Offspring cohort, 2005-2008 ²²⁵	US (White)	2053 (56%)	70 [≥60]	9	FP, FI	AF or atrial flutter diagnosed on ECG or Holter monitoring at FHS research visit, during examination by an outside clinician or in-patient admission to hospital	Excluded prevalent AF	306

Abbreviations: AF=atrial fibrillation; CAD=coronary artery disease; CHD=coronary heart disease; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease; ECG=electrocardiogram; FHS=Framingham Heart Study; FI=frailty index; FP=frailty phenotype; FRAIL=Fatigue, Resistance, Ambulation, Illness, and Loss of weight; GP=general practice; HABC battery=Health ABC Short Physical Performance Battery; HF=heart failure; ICD=international classification of diseases; IHD=ischaeemic heart disease; MI=myocardial infarction; OPCS=Office of Population, Censuses and Surveys: Classification of interventions and Procedures; TIA=transient ischaemic attack

Stroke

Nine studies describing the prospective associations of frailty with stroke were identified: 5 from Western and 4 from Asian cohorts. The included studies suggested an approximate 1.4-3.4 fold higher risk of stroke associated with frailty, which was potentially stronger in younger people.

Table 4.10 Key findings of studies investigating the association of frailty with incident stroke

First author name, Study name (region, ethnicity)	No. of participants / duration of follow-up	Hazard ratios (95% CI) minimal adjustment [†]	Hazard ratios (95% CI) extensive adjustment	Adjustment [‡]
Chen, UKB ²¹⁴ (Europe, White)	314093 11 years	n/a	FP & stroke: (reference = non-frail) 1.09 (1.03-1.15) for pre-frail 1.36 (1.20-1.55) for frail	+++
Damulji, NHAT ²¹⁵ (US, White)	3259 6 years	FP & stroke: (reference = non-frail) 1.32 (1.12-1.57) for pre-frail 2.00 (1.62-2.46) for frail	FP & stroke: (reference = non-frail) 1.25 (1.05-1.49) for pre-frail 1.71 (1.34-2.17) for frail	+++
Ekram, ASPREE ²¹⁶ (US & Australia, White)	19114 4.7 years	FP & stroke: ^a (reference = non-frail) 1.46 (1.20-1.78) for pre-frail 1.79 (1.00-3.20) for frail FI & stroke: ^a (reference = non-frail) 1.68 (1.36-2.07) for pre-frail 2.33 (1.70-3.20) for frail	FP & stroke: (reference = non-frail) 1.19 (0.97-1.46) for pre-frail 1.10 (0.61-2.00) for frail FI & stroke: (reference = non-frail) 1.47 (1.18-1.84) for pre-frail 1.84 (1.31-2.58) for frail	++++
Grabovac, SHARE ²¹⁷ (Europe, White)	24634 9 years	FP & fatal stroke: (reference = non-frail) 2.50 (1.84-3.39) for pre-frail 6.83 (5.01-9.32) for frail	FP & fatal stroke: (reference = non-frail) 1.31 (0.93-1.85) for pre-frail 2.06 (1.37-3.10) for frail	+++
Shrauner, VHA ²¹⁸ (US, White)	1606703 2 years	n/a	FI & total stroke: (reference = non-frail) 1.4 (1.4-1.5) for pre-frail 1.9 (1.8-1.9) for mild frailty 2.2 (2.1-2.3) for moderate frailty 2.6 (2.4-2.7) for severe frailty FI & fatal cerebrovascular disease:	+++
Fan, CKB ²¹⁹ (Asia, East Asian)	512723 11 years	n/a	1.84 (1.79-1.89) per 0.1 unit (reference = non-frail) 2.07 (1.97-2.17) for pre-frail 3.37 (3.42-3.93) for frail	+++
Jang, KNHI ²²⁰ (Asia, East Asian)	870175 10 years	n/a	FI & stroke: ^b 1.34 (1.33-1.35) per 0.1 unit (reference = non-frail) 1.35 (1.33-1.37) for pre-frail 1.66 (1.62-1.70) for mild frailty 2.06 (1.94-2.17) for moderate to severe frailty	+++
Liu, CHARLS ²²¹ (Asia, East Asian)	13580 7 years	FI & stroke: 1.31 (1.23-1.41) per 0.1 unit (reference = non-frail) 1.23 (1.07-1.50) for pre-frail 2.26 (1.79-2.86) for frail	FI & stroke: 1.28 (1.20-1.37) per 0.1 unit (reference = non-frail) 1.23 (1.03-1.46) for pre-frail 2.06 (1.62-2.63) for frail	+++

First author name, Study name (region, ethnicity)	No. of participants / duration of follow-up	Hazard ratios (95% CI) minimal adjustment [†]	Hazard ratios (95% CI) extensive adjustment	Adjustment [‡]
Liu, SLAS ²²² (Asia, Asian)	5015 10 years	FI & non-fatal stroke: ^b (reference = non-frail) 1.28 (0.93-1.78) for pre-frail 1.55 (0.74-3.26) for frail	FI & non-fatal stroke: ^b (reference = non-frail) 1.25 (0.87-1.79) for pre-frail 1.43 (0.61-3.38) for frail	++++

[†]Adjusted for age and/or sex.

[‡]Adjustments: + age and/or sex and smoking; ++ plus cardiovascular variables (body mass index, alcohol consumption, diabetes, hypertension, family history of heart disease, etc.); +++ plus demographic variables (education, income, ethnicity, etc.) and other disease; ++++ plus biomarkers.

^aCrude HRs

^bSubdistribution hazard models

Abbreviations: CI=confidence interval; FI=frailty index; FP=frailty phenotype

In the National Health and Aging Trends (NHAT) study²¹⁵ of 3,259 adults (>50 years) without history of CHD or stroke at baseline, pre-frailty and frailty were associated with HRs (95%CI) of 1.25 (1.05-1.49) and 1.71 (1.34-2.17), respectively (**Table 4.10**). In the SHARE study of around 24,000 older adults (>65 years; no exclusion by pre-existing disease),²¹⁷ pre-frailty and frailty were associated with HRs (95%CI) of 1.31 (0.93-1.85) and 2.06 (1.37-3.10), respectively, for fatal stroke. In the predominantly male VHA study involving over 1 million older adults (>65 years), frailty was similarly associated with over 2-fold higher risk of total stroke.²¹⁸ In the relatively younger cohort of UKB (age 40-75), pre-frailty and frailty were associated with HRs (95%CI) of 1.09 (1.03-1.15) and 1.36 (1.20-1.55), respectively.²¹⁴ All studies applied extensive adjustment of confounders in the Cox model. In NHAT,²¹⁵ similar results were found when stratified Cox models allowing baseline hazard function to vary by age and sex groups were used. In SHARE,²¹⁷ stratified analyses by age group suggested that associations are stronger in younger age groups (<69 versus ≥70 years), but a heterogeneity test was not performed. Only one study assessed both FP and FI and found that FI had a stronger association with stroke than FP: frailty was associated with HRs (95%CI) of 1.84 (1.31-2.58) and 1.10 (0.61-2.00) for stroke, respectively.²¹⁶

A previous study using the CKB data reported the association between frailty and fatal stroke (ICD-10 codes: I60-I69).²¹⁹ Of the 512,723 participants at baseline (mean [SD] age: 52.0 [10.7] years), 10,933 experienced stroke mortality after a median 10.8 years follow-up. Frailty (a 28-item FI) was associated with adjusted HRs (95%CI) of 1.84 (1.79-1.89) per 0.1 unit of FI for

fatal stroke, assuming a linear association. Using categorical definitions of FI, pre-frailty, and frailty (versus non-frail) were associated with HRs (95%CI) of 2.07 (1.97-2.17) and 3.37 (3.42-3.93), respectively. Stratified analyses by age group suggested more than doubling in the risk of stroke mortality associated with frailty in younger (<50 years; 6.41 [4.57-8.99]) than older (≥ 65 years; 2.78 [2.54-3.05]) participants ($P_{\text{interaction}} < 0.0001$). Reverse causation bias was explored by the exclusion of participants who had died during the first five years of follow-up, which found minor attenuation in risk estimates. The magnitude of associations were smaller in the 3 other Asian studies,^{220–222} but stroke was either non-fatal or total events rather than fatal.

Ischaemic heart disease

Twelve studies describing the prospective associations of frailty with IHD were identified: 8 from Western and 4 from Asian cohorts. Each study reported various IHD endpoints: IHD, MI, acute MI, heart attack, HF, and AF. Overall, a positive association between frailty and risk of IHD (except AF) was reported (**Table 4.11**).

Table 4.11 Key findings of studies investigating the associations of frailty with incident IHD

First author name, Study name (region, ethnicity)	No. of participants / duration of follow-up	Hazard ratios (95% CI) minimal adjustment [†]	Hazard ratios (95% CI) extensive adjustment	Adjustment [‡]
Chen, UKB ²¹⁴ (Europe, White)	314093 11 years	n/a	FP & CHD: (reference = non-frail) 1.15 (1.12-1.19) for pre-frail 1.44 (1.35-1.53) for frail	+++
Damluji, NHAT ²¹⁵ (US, White)	3259 6 years	FP & acute MI: (reference = non-frail) 1.51 (1.14-2.01) for pre-frail 2.35 (1.65-3.33) for frail	FP & acute MI: (reference = non-frail) 1.36 (1.01-1.82) for pre-frail 1.95 (1.31-2.90) for frail	+++
Ekram, ASPREE ²¹⁶ (US & Australia, White)	19114 4.7 years	FP & MI: ^a (reference = non-frail) 1.36 (1.10-1.68) for pre-frail 2.29 (1.33-3.95) for frail FI & MI: ^a (reference = non-frail) 1.92 (1.53-2.40) for pre-frail 2.30 (1.62-3.26) for frail	FP & MI: (reference = non-frail) 1.25 (1.01-1.56) for pre-frail 1.92 (1.10-3.36) for frail FI & MI: (reference = non-frail) 1.91 (1.51-2.42) for pre-frail 2.52 (1.74-3.65) for frail	++++
Grabovac, SHARE ²¹⁷ (Europe, White)	24634 9 years	FP & fatal heart attack: (reference = non-frail) 2.41 (1.89-3.08) for pre-frail 5.30 (4.05-6.94) for frail	FP & fatal heart attack: (reference = non-frail) 1.31 (1.01-1.72) for pre-frail 1.67 (1.19-2.34) for frail	+++
Khan, HABC ²²⁴ (US, 40% African American)	2825 11 years	HABC battery & HF: 1.36 (1.24-1.48) per 1SD Gill index & HF: (reference = non-frail) 1.36 (1.08-1.71) ^a for moderate 1.88 (1.02-3.47) ^a for severe	HABC battery & HF: 1.24 (1.13-1.36) per 1SD	++
McKechnie, BRHS ²²³ (Europe, White)	1445 6 years	FP & HF: 1.38 (1.01-1.89) per 1 unit (reference = non-frail) 1.68 (0.99-2.97) for pre-frail 1.92 (0.99-3.73) for frail Gill index & HF: 1.36 (0.91-2.03) per 1 unit (reference = mild/non-frail) 1.29 (0.64-2.58) for moderate 1.93 (0.77-4.80) for severe HABC battery & HF: 1.41 (1.13-1.76) per 1 unit (reference = 0) 1.51 (0.94-2.41) for 1 1.89 (0.92-3.89) for 2 2.77 (1.25-6.15) for 3	FP & HF: 1.23 (0.87-1.72) per 1 unit (reference = non-frail) 1.47 (0.85-2.57) for pre-frail 1.51 (0.74-3.07) for frail Gill index & HF: 1.19 (0.77-1.84) per 1 unit (reference = mild/non-frail) 1.36 (0.66-2.81) for moderate 1.33 (0.47-3.76) for severe HABC battery & HF: 1.37 (1.07-1.76) per 1 unit (reference = 0) 1.22 (0.73-2.02) for 1 1.58 (0.72-3.42) for 2 3.14 (1.25-7.31) for 3	++++ (but no demographic variables)
Orkaby, FHS Offspring ²²⁵ (US, White)	2053 9 years	FP & AF/flutter: (reference = non-frail) 1.22 (0.96-1.55) for pre-frail 0.93 (0.58-1.48) for frail FI & AF/flutter: (reference = non-frail) 1.31 (1.01-1.72) for pre-frail 1.32 (0.96-1.82) for frail	FP & AF/flutter: (reference = non-frail) 1.09 (0.84-1.42) for pre-frail 0.64 (0.37-1.12) for frail FI & AF/flutter: (reference = non-frail) 1.16 (0.86-1.56) for pre-frail 0.94 (0.64-1.39) for frail FI & total MI: (reference = non-frail) 1.5 (1.5-1.6) for pre-frail 2.0 (2.0-2.1) for mild frailty 2.4 (2.3-2.5) for moderate frailty 2.9 (2.8-3.0) for severe frailty	+++
Shrauner, VHA ²¹⁸ (US, White)	1606703 2 years	n/a		+++

First author name, Study name (region, ethnicity)	No. of participants / duration of follow-up	Hazard ratios (95% CI) minimal adjustment [†]	Hazard ratios (95% CI) extensive adjustment	Adjustment [‡]
Fan, CKB ²¹⁹ (Asia, East Asian)	512723 11 years	n/a	FI & fatal IHD: 1.89 (1.83-1.94) per 0.1 unit (reference = non-frail) 1.98 (1.87-2.10) for pre-frail 4.02 (3.70-4.36) for frail FI & CAD: ^b 1.40 (1.38-1.41) per 0.1 unit (reference = non-frail) 1.49 (1.47-1.52) for pre-frail 1.82 (1.77-1.88) for mild frailty 1.78 (1.66-1.91) for moderate to severe frailty	+++
Jang, KNHI ²²⁰ (Asia, East Asian)	885131 10 years	n/a	FI & heart disease: 1.28 (1.23-1.34) per 0.1 unit (reference = non-frail) 1.61 (1.44-1.79) for pre-frail 2.14 (1.82-2.52) for frail	+++
Liu, CHARLS ²²¹ (Asia, East Asian)	13580 7 years	FI & non-fatal MI: ^b (reference = non-frail) 1.37 (0.98-1.91) for pre-frail 1.52 (0.73-3.18) for frail	FI & heart disease: 1.28 (1.22-1.34) per 0.1 unit (reference = non-frail) 1.62 (1.45-1.81) for pre-frail 2.16 (1.83-2.56) for frail	+++
Liu, SLAS ²²² (Asia, Asian)	5015 10 years	FI & non-fatal MI: ^b (reference = non-frail) 1.37 (0.98-1.91) for pre-frail 1.52 (0.73-3.18) for frail	FI & non-fatal MI: ^b (reference = non-frail) 1.16 (0.81-1.67) for pre-frail 0.77 (0.32-1.86) for frail	++++

[†]Adjusted for age and/or sex.

[‡]Adjustments: + age and/or sex and smoking; ++ plus cardiovascular variables (body mass index, alcohol consumption, diabetes, hypertension, family history of heart disease, etc.); +++ plus demographic variables (education, income, ethnicity, etc.) and other disease; ++++ plus biomarkers.

^aCrude HRs

^bSubdistribution hazard models

Abbreviations: AF=atrial fibrillation; CI=confidence interval; CAD=coronary artery disease; FI=frailty index; FP=frailty phenotype; FRAIL=Fatigue, Resistance, Ambulation, Illness, and Loss of weight; HABC battery=Health ABC Short Physical Performance Battery; HF=heart failure; IHD=ischemic heart disease

In US Medicare beneficiaries without a history of CHD at baseline (NHAT study),²¹⁵ frailty (FP) was associated with incident IHD and AMI after 6 years. Pre-frailty and frailty (versus non-frail) were associated with HRs (95%CI) of 1.17 (1.02-1.35) and 1.35 (1.11-1.65), respectively, for IHD, and 1.36 (1.01-1.82) and 1.95 (1.31-2.90), respectively, for AMI. (**Table 4.11**). The UKB study²¹⁴ reported a similar magnitude of association between frailty and CHD using the FP. The corresponding HRs were 1.15 (1.12-1.19) and 1.44 (1.35-1.53), respectively. In the ASPREE study,²¹⁶ Ekram *et al.* also found a similar magnitude of association between frailty and MI for FP (1.92 [1.10-3.36]), but a stronger association using the FI model (2.52 [1.74-3.65]). The VHA study also reported more than 2-fold higher risk of total MI among frail US veterans using the FI.²¹⁸ HRs were adjusted for various demographic factors, CVD RFs, and relevant comorbidities.

In a previous report using the CKB,²¹⁹ 7,288 participants experienced IHD mortality (ICD-10 codes: I20-I25) after approximately 10 years of follow-up. Frailty was associated with adjusted HRs (95%CI) of 1.89 (1.83-1.94) per 0.1 unit for IHD mortality, and pre-frailty and frailty (versus non-frail) were associated with HRs (95%CI) of 1.98 (1.87-2.10) and 4.02 (3.70-4.36), respectively. Similar to stroke mortality, a doubling in the risk of IHD mortality associated with frailty was observed in younger (<50 years; 7.57 [5.30-10.8]) than in older (≥65 years; 3.23 [2.91-3.58]) participants ($P_{\text{interaction}} < 0.0001$). The exclusion of participants who died during the first 5 years of follow-up attenuated the HRs slightly. The magnitude of associations were smaller in the 3 other Asian studies,^{220–222} but heart disease was either non-fatal or total events rather than fatal.

4.3.3 Discussion

This literature review demonstrated limited but consistent evidence for positive, prospective associations of frailty with risk of stroke and IHD in mainly Western populations. Given that few studies were identified, uncertainties about the available evidence persist, including: (1) the exact shape and strength of the associations of frailty with CVD; (2) whether such associations differ by CVD subtypes; (3) the comprehensive assessment of effect modification; and (4) the potential for reverse causation. Additionally, the risk of residual and unmeasured confounding in the context of frailty and CVD, such as health behaviours, environmental exposures and genetic factors that were not fully accounted for in the included studies, exacerbates the uncertainty about the existing evidence.

Shape and strength of associations

The shape and strength of the reported associations may be affected by differences in the definition of outcomes, exposures, or populations studied. First, many studies did not report the specific ICD-10 codes used to define outcomes,^{215,217} which may have resulted in some misclassification of outcomes. Second, associations may truly vary by the frailty model used. For instance, a positive association between frailty and HF was found using the HABC battery test but not the FP or Gill index, although they are all based on similar physical function tests.

The ASPREE study²¹⁶ that studied both FP and FI reported stronger associations between frailty with stroke and MI using the FI, but this may reflect circularity in the association as the FI included several cardiovascular factors and the outcome itself (diabetes, hospitalisation for heart failure, hypertension, smoking, dyslipidemia, obesity, stroke, and MI). Similarly, the FI in the VHA study²¹⁸ also included AF, CAD, diabetes, heart failure, hypertension, and stroke/TIA and the KNHI study²²⁰ included CAD, diabetes, hypertension, HF, and stroke. Only the CHARLS study²²¹ explicitly excluded relevant deficits (hypertension, diabetes, dyslipidemia, and BMI) from the FI. Thus, the inclusion of CVD- and adiposity-related deficits in the FI in some studies is likely to have inflated the association between frailty and CVD. This variability in the strength of associations for different frailty scores was previously reported,⁹³ which may be explained by the differing predictive performance and reliability of frailty measures. Importantly, all studies included in the literature review had assessed frailty at baseline only, implicitly assuming that this single assessment of frailty was measured reliably and without error. Third, different population exclusion criteria may have influenced the strength of associations. The inclusion of individuals with prevalent CVD could inflate the associations of frailty with CVD^{217,219} if the relationship is mediated by biological processes involved in CVD. Also, the apparent inverse association between frailty and AF (although non-significant)²²⁵ could reflect the exclusion of 65 participants with incomplete frailty data (i.e. exclusion of participants with frailty as a result of their inability to complete tests could result in an inverse effect). Finally, many studies assumed a linear relationship between frailty and CVD, but it is unclear whether healthy adults have similar relative risks as those who are clinically considered to be frail.

Investigation of CVD subtypes

CVD subtypes (e.g. ischaemic or haemorrhagic stroke) were not always distinguished. Consequently, associations may differ with these CVD subtypes, which may be relevant for guiding future policy and clinical practice.

Effect modification

The limited power of the studies precluded stratified analyses, so the investigation of effect modification was typically limited to age^{215,217,219,226,227} and sex.^{215,219,226,228,229} Overall, the investigations identified more extreme relative risks of CVD in younger than in older participants^{217,219,226,227} and in females than in males.^{226,228,229} The relative importance of frailty in younger populations^{230–233} and the ‘male-female health-survival paradox’, in which females have a higher burden of frailty and morbidity but a lower risk of mortality, has been widely reported. However, the reasons for such differences are unclear. Whether this paradox reflects true physiological differences^{234,235} or external causes (e.g. differential access to healthcare) and the relevance of this phenomenon with different CVD subtypes require further investigation. One study in China additionally explored effect modification by residence (urban or rural), BMI levels (<25 or ≥25), hypertension, diabetes, and dyslipidemia.²²¹ Stronger associations were observed in participants with BMI≥25, rural community-dwellers, and without hypertension and dyslipidemia. Whether these patterns are replicated in other cohorts is unknown and more extensive analysis of effect modification of these subgroups (e.g. quintile groups of SBP) could provide a better understanding of the underlying pathways involved in the relationships.

Reverse causation bias

The potential for reverse causation bias is significant in the relationship between frailty and CVD – the presence of subclinical CVD could result in frailty rather than the converse association. Despite this, few studies investigated this bias. Those that did either excluded participants with pre-existing illness or CVD at baseline,^{215,219,223,225,226,228,236–239} or excluded participants who died early,²¹⁹ or adjusted for prior CVD in the Cox models.²²⁹ None of the studies carried out a rigorous investigation of reverse causality through simultaneous exclusions of the above, in addition to ensuring that the frailty instrument used did not include CVD RFs as components. This suggests that the reported associations of frailty with CVD may be an overestimation of the true relationships.

4.4 Summary

The present chapter reviewed the available evidence in prospective studies on the associations between key modifiable CVD RFs with frailty (**Section 4.2**) and frailty with stroke and IHD (**Section 4.3**). The literature review identified few prospective associations, which were mainly conducted in Western populations, despite many reports indicating strong cross-sectional associations of CVD RFs or CVD with frailty.⁷⁴

The prospective evidence of individual CVD RFs with frailty was conflicting and only one study investigated the effect of lean body mass on incident frailty. Almost all the CVD RFs had inconsistent findings about the shape and strength of associations with incident frailty, reflecting misclassification of exposure due to varying definitions (apart from adiposity measures), application of different exclusion criteria in study populations, and risk of attrition bias. Additionally, there was limited assessment of the shape of the associations using continuous exposures, such as blood pressure and glucose, which could have resolved some of these uncertainties. The use of different population exclusion criteria also suggests that the exposure-frailty associations may be mediated differently across studies. For instance, few studies had excluded individuals with pre-existing CVD (the presence of CVD affects blood pressure, adiposity, and glucose levels), so whether associations persist independently of pre-existing CVD is unknown. Also, most studies employed the FP model of frailty, but the varying definitions of frailty instruments are likely to impact the strength of associations with CVD RFs – those that include cardiovascular components or domains may inflate associations. Finally, associations reported for individual CVD RFs typically differed by the duration of follow-up, suggesting the risk of attrition bias but also the presence of reverse causation bias. Hence, the prospective relationship between CVD RFs and frailty remains uncertain.

Evidence on the associations between frailty and incident stroke and IHD suggested a positive association, but few studies were identified. Most studies also used the FP model to define frailty and use of other frailty models may influence the strength of the reported associations. Furthermore, the included studies had limited assessments of the associations with specific

CVD subtypes, the effect modification of these relationships, and the potential for reverse causation bias. Thus, the precise association between frailty and CVD outcomes remain unclear and more detailed investigation is warranted to better understand the effects of frailty.

Overall, this review highlights limitations in the current evidence and the need for further large, well-powered studies with long follow-up to better characterise the relationships between frailty and CVD and their RFs in LMIC populations. The remainder of this thesis will investigate the cross-sectional and prospective relationships of frailty and CVD (and their RFs) in the China Kadoorie Biobank (CKB) population and attempt to address some of these limitations. The subsequent chapter will introduce and describe the CKB dataset, including its study design, population, and the relevant exposures and outcomes.

5 China Kadoorie Biobank: study design and methods

The aetiology of frailty is poorly understood, which hampers efforts to prevent and treat frailty. The thesis therefore aims to investigate the correlates and consequences of frailty, focussing on the associations of CVD RFs with risk of frailty and frailty with risk of CVD. The literature review of these associations (**Chapter 4**) showed that most frailty research has been conducted in Western, high-income countries. The epidemiology of frailty and CVD (RFs) is different in China, the prevalence of frailty appears to be lower and the prevalence of CVD (and RFs) is increasing rapidly, thus the reported associations in the literature review may differ in China.

The China Kadoorie Biobank (CKB) is a prospective study of over 0.5 million Chinese adults. CKB is a unique resource with access to large populations, prolonged follow-up, and a wide range of events that can be used to explore the main aims of this thesis while addressing some of the limitations found in the current literature.

The present chapter provides a detailed introduction of the CKB dataset and describes the rationale, study design, characteristics of the CKB population, the content and procedures of the surveys, and the follow-up of disease outcomes. In addition, the exposure and confounders used in the thesis and the baseline characteristics of the cohort will be described.

5.1 Study rationale and design

CKB is a large prospective study of over 500,000 middle-aged and older adults recruited from 10 diverse regions in China.^{99,240} The study was established in 2004 by the Clinical Trial Unit and Epidemiological Studies Unit (CTSU) at the University of Oxford and the China National Centre for Disease Control and Prevention (CDC).^{241,242} The main aim of the study was to investigate the major causes of common chronic diseases in China. The CKB study recorded both established and novel risk factors, including physical measurements, blood biochemistry, genetic markers, and a wide range of disease outcomes. All participants were followed-up for

incident disease outcomes. Ethical approval was granted by the University of Oxford, the China National CDC, and the institutional research boards at the local CDCs.

5.2 Study population

Participants were recruited from 10 regions (five urban and five rural) (**Figure 5.1**) between June 2004 and July 2008.⁹⁹ Eligible participants, permanent residents aged 35-74 years, were identified using official residential records in each of the 100-150 administrative units (rural villages or urban residential committees) within each study region.^{99,240} Eligible people were invited to participate using hand-delivered letters and information leaflets, which were delivered after an extensive publicity campaign to raise awareness of the study among the local residents.^{99,240} Eligible participants were recruited if they were able to confirm their identity via unique national identity cards.^{99,240} Individuals who were slightly outside of the target age range (35-74 years) were also included to maximise study participation. The recruitment process resulted in a participation response rate of about 30% (26-38% in the five rural regions and 16-50% in the five urban regions).^{99,240} The main reasons for non-participation were reluctance to spend time visiting the screening centre and not being at home.²⁴³ Overall, 512,891 individuals were recruited to the study.⁹⁹

Figure 5.1 Geographical locations of the CKB study regions

Map produced by Dr Hongchao Pan, CTSU University of Oxford.



The 10 study regions were selected to maximise geographic and socioeconomic diversity rather than being representative of the Chinese population. Additional criteria for selection included the quality of mortality and disease registries, local commitment and capacity, and population stability. Importantly, local disease patterns and exposures to certain RFs were considered to maximise the ability of the study to investigate the determinants of major chronic diseases in the Chinese population.²⁴⁰

5.3 Baseline survey

All participants provided written informed consent to participate in the study. The consent included permission to access their medical records and other official disease registration systems, and for long-term storage of blood samples for non-specified medical research.

Anonymity of the data was assured. Following informed consent, participants were invited to attend their local CKB assessment centre.²⁴⁴

For the baseline assessment, participants completed interviewer-administered electronic questionnaires,²⁴⁵ which took approximately 60-75 minutes to complete. The questionnaires collected information on general demographic and socio-economic status (such as occupation, highest education level, and household income level), dietary and other lifestyle habits (such as smoking and alcohol drinking), medical history, mental status, and reproductive history for women. Physical measurements included height, weight, hip and waist circumference, bio-impedance, lung function, blood pressure, and pulse, and these were recorded using calibrated instruments and standard operating procedures. The questionnaires and systems used to collect data were developed specifically for the study by CKB's Information Technology (IT) team.²⁴⁶ The software was designed to highlight any missing data, logic errors, and inconsistencies in responses to the interviewer to maximise data quality.

5.3.1 Self-reported disease and symptoms

Participants were asked about doctor diagnoses of medical conditions and various clinical symptoms (a copy of the questionnaire on self-reported diseases is shown in **Figure S5.1**). Self-reported doctor diagnoses of disease were obtained using the following question, "Has a doctor ever told you that you had [disease]?" (yes/no). Examples of self-reported symptoms collected via the questionnaire are listed in **Table 5.1**.

Table 5.1 Assessment of self-reported symptoms in CKB

Self-reported symptoms	Question and response or information obtained
Frequency of bowel movement	Frequency of bowel movement per week (more than once on most days; about daily; once every 2-3 days; and less than 3 times a week)
Body pain	Continuous body pain was recorded using the following question: "During the past 12 months, have you experienced a pain or discomfort in your body lasting ≥ 3 months that interfered with your life?" (yes/no)
Frequent cough	Frequent cough was reported using the question: "During the past 12 months, do you usually cough frequently?" (No; Yes, for <3 months; or Yes, for ≥ 3 months)
Being sad or depressed	Being sad or depressed was reported by asking: "During the past 12 months, was there ever a time when you felt sad, blue, or depressed for two weeks or more in a row?" (yes/no)
Self-rated health	Participants were asked to rate their current self-rated health status, to which they answered: excellent, good, fair, or poor.
Sleep problems	Questions related to sleep included: "During the past month, did you have difficulty staying alert while at work, eating or meeting people during daytime for 3 or more days each week?" (yes/no), "During the past month, did you take >30 minutes to fall asleep after going to bed or wake up in the middle of the night for 3 or days each week?" (yes/no), and "During the past month, did you wake up early and not be able to go back to sleep for 3 or more days each week?" (yes/no)
Weight loss	Self-reported weight loss was reported by asking: "During the past 12 months, has your weight changed significantly" (yes, lost ≥ 2.5 kg; yes, gained ≥ 2.5 kg; or about the same as before). Whether this weight change was intentional could be determined by the following question: "Have you tried to reduce weight in the past 12 months" (yes/no)
Walking difficulties	Walking difficulties were gauged by the questions: "If you were walking on level ground with other healthy people of the same age, would you usually become short of breath?" (yes/no) or "If you were walking on level ground with other healthy people of the same age, would you usually slow down due to chest discomfort?" (yes/no)

5.3.2 Lifestyle behaviours

Alcohol consumption

Details of participants' alcohol consumption patterns were obtained using the questions in **Table 5.2.**²⁴³ All participants were asked about their alcohol consumption in the past 12 months. Non-weekly drinkers were asked whether they were ever drinkers, and, if yes, how long ago they stopped. Current weekly drinkers were asked about the frequency of drinking, type of beverage, and amount of alcohol drunk, which was used to estimate the average grams of pure alcohol consumed in a typical week.²⁴⁷ The following alcohol content by volume (v/v)

was assumed: beer 4%, grape wine 12%, rice wine 15%, weak spirits 38%, and strong spirits 53%.

Table 5.2 Assessment of alcohol consumption in CKB

Question or information obtained		Response
Everyone	During the past 12 months, how often did you drink any alcohol?	1. Never or almost never
		2. Occasionally
Non-weekly drinkers	In the past, did you ever have a period of at least 1 year, during which you usually drank some alcohol?	3. Only at certain seasons
		4. Every month but less than weekly
	How long ago did you stop drinking alcohol at least once per week?	5. Usually at least once a week
	Frequency of drinking (days per week)	1. 1-2
	Types of beverage	2. 3-5
		3. 6-7
		1. Beer
		2. Grape wine
		3. Rice wine
	Amount of alcohol drunk	4. Weak spirits <40% alcohol content
		5. Strong spirits ≥40% alcohol content
		Reported by number of small (250ml) or large (640ml) bottles for beer, and number of liang (50g) for wines and spirits on a typical day, on special occasions, and at the last time of drinking.
		1. Drinking in the morning
		2. Unable to work or do anything due to drinking
Weekly drinkers	Experience of problem drinking indicators in the past month	3. Depressed
		4. Irritated or loss of control due to drinking
		5. Unable to stop drinking
		6. Shakes when stopping drinking
	Time of drinking in relation to meals Age of starting drinking weekly Whether consumption had changed significantly in the past few years Experience of flushing or dizziness after drinking	

Table was produced using information from Millwood *et al.* (2013)²⁴³

Dietary intake of major food groups

CKB recorded the dietary intake of 12 major food groups: rice, wheat, other staple food, red meat, poultry, fish or seafood, eggs, fresh fruit, fresh vegetables, soybean products, preserved vegetables, and dairy products. Participants reported their habitual consumption frequency (daily, 4-6 days per week, 1-3 days per week, monthly, or never/rarely) in the past year with

reasonably good validity and reproducibility.²⁴⁸ In 432 participants selected from 4 study regions, the reproducibility of the dietary responses exceeded 0.60 (weighted kappa coefficients) for most food groups.²⁴⁸

Physical activity

A detailed physical activity questionnaire was used, which was adapted from validated questionnaires like the European Prospective Investigation into Cancer and Nutrition²⁴⁹ and the Shanghai Women's Health study.²⁵⁰ Although not separately validated, some modifications to the initial questionnaire were made following a CKB pilot study. Participants were asked about their usual type and duration of activities related to occupation, commuting, housework, and leisure in the past year. Leisure-type activity included active but not sedentary activities (such as watching TV) performed during leisure-time.²⁵¹ Questions related to occupation and commuting were tailored by occupation type (farmers and non-farmers).²⁵²

Physical activity was expressed in metabolic equivalent of task hours performed per day (MET-hours/day)²⁵³ on average over the last year. MET values for a particular type of activity represent an individual's energy expenditure relative to their resting metabolic rate (i.e. the ratio of energy spent per kilogram of body weight per hour of activity to that spent while resting). Therefore, 1 MET equals 1 hour of sitting quietly. To estimate MET-hours/day, the MET value for a particular activity was multiplied by the average duration of the activity performed per day. The sum of the MET-hours/day for all activities related to occupation, commuting, housework, and non-sedentary leisure-time represent the participant's daily level of total physical activity. MET values of individual activities were obtained from the 2011 update of a major compendium of physical activities (example of MET values for activities are listed in **Table S5.1**)²⁵³ and were matched to activities in China as closely as possible.

Smoking

Data on smoking patterns were collected using the following questions: "Have you smoked any tobacco today?", "How many cigarettes have you smoked today?", "How often do you smoke tobacco now?", "In the past, how frequently did you smoke?", and "In your lifetime,

have you smoked a total of at least 100 cigarettes or equivalent?”. Details on the type, age first began, age stopped, and the main reason for smoking cessation (ill health or stopped by choice) were also recorded. Cigarette equivalents smoked per day were estimated using the following derivation rule: No. filter cigarettes/day + No. non-filter cigarettes/day + 2*(Liang of cigars/month) + 5/3*No. of roll-up cigarettes/day + 5/3*Liang of pipe tobacco/month.²⁵⁴

5.3.3 Physical measurements

Adiposity measures

Trained health workers measured standing height, body weight, waist circumference (WC), hip circumference (HC), and body fat percentage while participants wore light indoor clothing without shoes. Standing height was measured using a portable stadiometer to the nearest 0.1cm. Weight was measured using the TBF-300 Body Composition Analyzer (TANITA-TBF-300GS, Tanita Corp., Tokyo, Japan) to the nearest 0.1kg. Weight of clothing (estimated as summer 0.5kg; spring/autumn 1.0kg; winter 2.0-2.5kg) was subtracted from measurements.^{251,255,256} WC (measured midway between the lowest rib and the iliac crest at the end of a normal expiration) and HC (measured around the maximum circumference of the buttocks) were recorded to the nearest 0.1cm using a non-stretchable measuring tape. Measurements were deducted to account for clothing: 1-2 cm (undergarments) from WC readings and 1 (skirt) and 2.5 cm (trousers) from HC readings. Waist-to-hip ratio (WHR) was calculated as the ratio of WC to HC.^{251,255,256} Body composition was estimated using the TBF-300 Body Composition Analyzer, which carried out foot-to-foot bioelectrical impedance analysis using its built-in proprietary algorithm. Body fat percentage (BF%) was the proportion of total weight due to fat weight.^{251,255,256} Fat mass was calculated as the product of BF% divided by 100 and weight. Lean body mass was calculated by subtracting fat body mass from the weight.

Blood pressure and heart rate

Resting blood pressure (BP) and heart rate were measured using the UA-779 digital sphygmomanometer (A&D Instruments, Abingdon, UK) after participants had been seated for

at least 5 minutes. Trained fieldworkers measured the right brachia BP and heart rate at the level of the heart twice.²⁵⁷ The mean of two measurements was calculated. For BP, if measurements had a difference greater than 10 mmHg, a third measurement was conducted and the last two readings were recorded. The sphygmomanometers were supplied centrally and calibrated daily by the fieldworkers.²⁵⁸

Blood glucose

A 10-ml non-fasting blood sample (with the time since the participant last ate recorded) was collected for each participant, except in Zhejiang where participants were asked to have a fasting blood sample collected. Samples were stored in cool boxes (to maintain their temperature at 0-4°C) and taken to a local study laboratory for immediate processing.²⁴⁰ Random plasma glucose (RPG) level was measured using the SureStep Plus meters (LifeScan, Milpitas, CA, USA). These devices were regularly calibrated using the manufacturer's quality control solution.²⁵⁹ Participants with RPG ≥ 7.8 mmol/L and < 11.1 mmol/L were invited to have measurements of fasting plasma glucose (FPG) levels on the following day. RPG data is unavailable for 8,306 participants without self-reported diabetes due to a delay in the availability of on-site testing in certain regions.^{259,260}

5.3.4 Quality assurance procedures

Several measures were undertaken to ensure high quality of the data collection. All standard operating procedures were tested in a pilot study and equipment was supplied centrally. Field survey staff undertaking the interviews received extensive training.²⁴⁰ This included training on data collection using the electronic questionnaire, recording physical measurements using standard protocols, appropriate maintenance of equipment, and communication with participants. Additional quality control measures included regular monitoring of central data and blood processing times, and site visits by the regional CDC, the China CDC, and CTSU staff to overview procedures.²⁶¹

In total, 354 local staff were involved in the baseline data collection. Each staff member's entries were monitored throughout the survey via their unique study identification number. The

number of staff who completed 95% of the data for the whole study was 21 for initial registration and consenting, 20 for anthropometry measurements, 24 for blood pressure measurements and blood collection, 23 for lung function and carbon monoxide measurement, and 113 for the main questionnaire.^{99,240}

A quality control (QC) survey was carried out within 2-6 weeks of the baseline survey comprising randomly selected participants (n=15,728, around 3% of CKB).²⁶² This involved repeating the baseline survey questionnaire and some physical measurements to assess the reliability and consistency of the data. The mean (SD) length of time between the baseline and QC survey was 17 (36) days.²⁴⁰ Most physical measurements had good agreement between the baseline and QC surveys: the within-person Spearman correlation coefficients for height, weight, and BMI were 0.99, 0.96, and 0.93, respectively.²⁴⁰ For SBP, the agreement was 0.70 without any adjustment for season.²⁴⁰ There was also good agreement between the baseline and QC survey for alcohol drinking and tobacco use: the weighted kappa coefficients were 0.79 and 0.94, respectively.²⁴⁰

5.4 Resurveys

A random subset (around 5%) of surviving participants were invited to participate in two resurveys. These participants were randomly selected from each study region using cluster random sampling with the administrative unit as the basic sampling unit. The resurveys collected identical data to those collected in the baseline questionnaire with a few additional questions, such as recent hospitalisation.^{263,264}

The 1st resurvey was undertaken between August and October 2008 and the 2nd between 2013 and 2014. This meant that repeat measurements were collected approximately every 5 years. For the 1st resurvey, 24,760 participants were invited to participate and a 79.9% participation rate was achieved (n=19,788). For the 2nd resurvey, 33,073 participants were invited and a 75.6% participation rate was achieved (n=25,011).

5.5 Follow-up of events and outcome adjudication

5.5.1 Outcome ascertainment

All study participants were followed up for cause-specific mortality. Mortality data were obtained from China's Disease Surveillance Points (DSP) system²⁶⁵ and supplemented by reviewing medical records, annual reviews of residential records, and visits to local communities to minimise under-reporting. For the few deaths with unidentified cause of death (<5%), verbal autopsies were carried out using a validated instrument to determine the probable cause of death.²⁶⁶ The annual review of residential records and visits to local communities also identified participants who had permanently moved out of the study region.

Study participants were also followed-up for cause-specific morbidity. Incident disease events were obtained using disease registries and national health insurance (HI) databases. Eight study regions had established disease registries, which provided information on stroke, IHD, diabetes, and cancer incidence.²⁴⁰ The national HI databases were available and established in all study regions, and provided information on coded hospitalisations and examination and treatment procedures through electronic linkage via a unique national ID. Almost all CKB participants (>98%) are covered by this HI system.

The causes of death and disease were coded using the 10th International Classification of Diseases (ICD-10)²⁶⁷ by trained, regional CDC staff who were blinded to participants' baseline information. Information entered from the death certificates was regularly cross-checked by local CKB staff. Additionally, outcome validation was conducted within CKB to collect additional medical records to enable reliable classification of the major diseases (stroke, IHD, cancer and chronic kidney disease) (**Section 5.5.2**).

5.5.2 Outcome definition

The main CVD outcomes in this thesis were stroke, ischaemic heart disease, and fatal cardiovascular disease events (**Table 5.3**). The subtypes investigated were ischaemic stroke (IS), haemorrhagic stroke (HS), myocardial infarction (MI), and major coronary event (MCE,

defined as acute myocardial infarction or fatal IHD). Incident events, fatal or non-fatal, were investigated in the prospective analyses conducted in the thesis. Of these events, fatal events were investigated separately for each outcome (apart from MCE, CVD and all-cause mortality). Fatal events were events followed by death from any cause within 28 days of the event date.

Table 5.3 Main outcomes of the thesis

Outcome	ICD-10 codes
Stroke	I60-I61, I63-I64
Ischaemic stroke	I63
Haemorrhagic stroke	I61
Ischaemic heart disease	I20-I25
Myocardial infarction	I21-I23
Major coronary event	I21-I23, I20-I25
Fatal cardiovascular event	I00-I99

5.5.3 Verification and adjudication of outcomes

Detailed verification and adjudication of outcomes were not possible for all the outcomes collected in CKB; thus validation of selected diseases was prioritised. Several pilot studies were conducted to verify and adjudicate approximately 1,000 first, incident cases of stroke, IHD, cancer, diabetes, and COPD.^{261,268} This process involved: (1) the ascertainment of outcomes; (2) verification of the diagnosis by qualified specialists blinded to the original diagnosis on a randomly selected subset using medical records; and (3) adjudicating the correct phenotype using additional data from medical records, such as those relevant to classifying diseases into different aetiological subtypes, after which events can be confirmed, reclassified, or refuted.²⁶¹ The outcome verification and adjudication process of incident IHD and stroke cases began in 2014.²⁶⁹ Over 12,000 incident IHD cases were adjudicated by 2015 and diagnosis was confirmed in 82.4%.²⁶⁹ For stroke, the verification was conducted by Chinese neurologists who adjudicated stroke outcomes by careful review of medical records, such as information on presenting symptoms and results of examinations, diagnostic tests or procedures, and neuroimaging.²⁶¹ Their adjudication was further checked centrally by the CKB team.²⁶¹ As of 2019, over 22,000 IS cases and 3,278 ICH cases had been adjudicated with a confirmation rate (95%CI) of 79.6% (79.1%-80.0%) and 98.2% (98.1%-98.4%), respectively.²⁶¹ This process of adjudication has shown to improve relative risk estimates involving individual stroke types.²⁶¹

5.6 Exposure and confounder definitions

Potential variables that may confound the association between frailty and CVD outcomes were identified using background knowledge (**Chapter 1**). The variables used in the thesis were: age, sex, study region, the highest level of education received, income level, marital status, occupation, general adiposity measure (BMI or fat mass), WHR, lean body mass, alcohol consumption, smoking status, frequency of fresh fruit, fresh vegetables, and meat consumption, physical activity (MET-hours/day), SBP, RPG, hypertension, and diabetes. Categorisation of study variables is shown in **Table 5.4**.

Table 5.4 Categorisation of study variables

Variable	Categorisation
BMI	Underweight, normal, overweight, and obese using the following thresholds: <18.5, 18.5-23.9, 24.0-27.9, and ≥ 28 kg/m ² , respectively. ²¹⁹
WHR	Normal, overweight, and obese using the following thresholds: <0.90, 0.90-<0.95, and ≥ 0.95 for men and <0.85, 0.85-<0.90, and ≥ 0.90 for women, respectively. ²¹⁹
Abnormal adiposity	Binary variable: being underweight (BMI<18.5 kg/m ²) or obese (BMI ≥ 28 kg/m ² , WHR ≥ 0.95 in men or ≥ 0.9 in women).
Alcohol consumption ^a	Never-regular (never or almost never drinkers in the past 12 months and had not drunk weekly in the past), Ex-regular drinkers (never or almost never drinkers in the past 12 months but had drunk weekly in the past), Reduced-intake (drunk alcohol occasionally, at certain seasons, or every month in the past 12 months but had drunk weekly in the past), Occasional (drunk alcohol occasionally, at certain seasons, or every month in the past 12 months, but had not drunk weekly in the past), and Current weekly drinkers. ²⁷⁰
Smoking status	Never-smokers (those who were not current smokers and had smoked <100 cigarettes in their lifetime), Ex-smokers by choice (those who smoked ≥ 100 cigarettes or equivalents in their lifetime but had quit smoking by choice ≥ 6 months), Ever-regular smokers ^b (ever smoked 1 or more cigarettes or equivalents daily for at least 6 months and participants who stopped smoking ≥ 6 months due to ill health), ²⁷¹ and Occasional smokers (participants who did not meet the criteria for never- or ever-regular smokers, and had not stopped smoking completely for at least 6 months before recruitment). ²⁵⁴
Poor diet	Binary variable: not eating fruit and vegetables daily and eating red meat on most days (daily or 4-6 days/week).
SBP	<120, 120-139, ≥ 140 mmHg
RPG	<5.8, 5.8-7.7, 7.8-11, ≥ 11 mmol/L

^aThe drinking categories broadly represent those used to monitor alcohol consumption as per WHO guidance.²⁷²

^bAmong regular smokers, the amount of smoking was categorised as <20, 20-25, and ≥ 25 cigarettes per day.^{38,273}

5.7 Baseline characteristics

The main analyses for the present thesis will involve CKB participants at baseline and participants who were followed up at the 2nd resurvey questionnaire. Their baseline characteristics are displayed separately.

5.7.1 Baseline characteristics of CKB participants

Overall, 512,726 participants (210,204 men and 302,522 women) were recruited to the study and completed the baseline questionnaire. Among study participants, 59% (302,522) were women and 44% (226,193) were resident in urban regions. The number of participants recruited from each of the 10 study regions ranged from 29,686 (Haikou) to 63,356 (Henan) (**Table 5.5** shows the number and proportion of participants recruited from each study region).

Table 5.5 Number and proportion of participants recruited in study regions, by sex

Study region	Male (N=210204)	Female (N=302522)
Urban regions		
Qingdao	15624 (7.4)	19884 (6.6)
Harbin	23252 (11.1)	34304 (11.3)
Haikou	10794 (5.1)	18892 (6.2)
Suzhou	22366 (10.6)	30903 (10.2)
Liuzhou	19321 (9.2)	30853 (10.2)
Rural regions		
Sichuan	21315 (10.1)	34371 (11.4)
Gansu	19298 (9.2)	30589 (10.1)
Henan	27841 (13.2)	35515 (11.7)
Zhejiang	24027 (11.4)	33677 (11.1)
Hunan	26366 (12.5)	33534 (11.1)

The baseline characteristics of the whole CKB cohort are presented in **Table 5.6**. The mean (SD) age of the participants was 52 (11) years (53 [11] years for men and 51 [10] years for women). Most of the participants were married (91%) and around one-fifth had no formal education: 8.9% of men and 25% of women had no formal education ($p<0.001$). There were marked sex difference in smoking patterns, whereby the prevalence of smokers was 65% in men and 2.5% in women ($p<0.001$), and alcohol consumption, whereby 33% of men reported weekly consumption of alcohol compared to 2.1% of women ($p<0.001$). While daily consumption of vegetables was almost universal (95%) among men and women, daily

consumption of meat was higher in men (33%) than in women (27%) ($p < 0.001$). Men reported median (IQR) daily physical activity (MET-hours/day) of 18.72 (9.6-32.45), whilst women reported 16.80 (10.67-28.21) ($p < 0.001$). Men were more likely to report having 'Excellent' self-rated health than women (20.0% versus 16.0%) ($p < 0.001$). The most common self-reported physician-diagnosed diseases at baseline were hypertension (12%), COPD (7.6%), fracture (6.9%), and prior history of gallstones (6.0%), but the prevalence of other diseases was low ($< 3\%$).

Table 5.6 Baseline demographic and lifestyle characteristics of recruited participants, overall and by sex

N (%), mean (SD) or median (IQR)	Overall (N=512726)	Male (N=210204)	Female (N=302522)
Age (years)			
Mean (SD)	52.03 (10.68)	52.85 (10.91)	51.46 (10.48)
Urban region	226193 (44.1)	91357 (43.5)	134836 (44.6)
Married	464475 (90.6)	195298 (92.9)	269177 (89.0)
No formal education	95179 (18.6)	18661 (8.9)	76518 (25.3)
Smoking status			
Never smoker	317495 (61.9)	30303 (14.4)	287192 (94.9)
Occasional smoker	29147 (5.7)	23614 (11.2)	5533 (1.8)
Ex regular smoker	22979 (4.5)	20763 (9.9)	2216 (0.7)
Smoker	143105 (27.9)	135524 (64.5)	7581 (2.5)
Drinking status			
Never regular	235113 (45.9)	42779 (20.4)	192334 (63.6)
Ex-regular	9256 (1.8)	7924 (3.8)	1332 (0.4)
Occasional	163132 (31.8)	66073 (31.4)	97059 (32.1)
Monthly	17385 (3.4)	13158 (6.3)	4227 (1.4)
Reduced intake	11696 (2.3)	10371 (4.9)	1325 (0.4)
Weekly	76144 (14.9)	69899 (33.3)	6245 (2.1)
Daily fresh fruit consumption	96588 (18.8)	30504 (14.5)	66084 (21.8)
Daily fresh vegetable consumption	485950 (94.8)	199532 (94.9)	286418 (94.7)
Daily meat consumption	150023 (29.3)	69103 (32.9)	80920 (26.7)
Physical activity (MET-hours/day)	17.47	18.72	16.80
(Median [IQR])	[10.31, 30.01]	[9.60, 32.45]	[10.67, 28.21]
Self-rated health			
Excellent	90401 (17.6)	42018 (20.0)	48383 (16.0)
Good	144211 (28.1)	61469 (29.2)	82742 (27.4)
Fair	225023 (43.9)	87976 (41.9)	137047 (45.3)
Poor	53091 (10.4)	18741 (8.9)	34350 (11.4)
Self-reported prevalent disease			
Asthma	2806 (0.5)	1214 (0.6)	1592 (0.5)
Cancer	2578 (0.5)	968 (0.5)	1610 (0.5)
Ischaemic heart disease	15472 (3.0)	5717 (2.7)	9755 (3.2)
Cirrhosis	6193 (1.2)	3641 (1.7)	2552 (0.8)
COPD	37057 (7.2)	18446 (8.8)	18611 (6.2)
Emphysema or bronchitis	13288 (2.6)	6542 (3.1)	6746 (2.2)
Fracture	35445 (6.9)	18509 (8.8)	16936 (5.6)
Gallstone disease	30997 (6.0)	8168 (3.9)	22829 (7.5)
Hypertension	59703 (11.6)	23768 (11.3)	35935 (11.9)
Kidney disease	7575 (1.5)	2663 (1.3)	4912 (1.6)
Neurasthenia	5699 (1.1)	1542 (0.7)	4157 (1.4)
Peptic ulcer	20015 (3.9)	11189 (5.3)	8826 (2.9)
Rheumatoid arthritis	10624 (2.1)	3048 (1.5)	7576 (2.5)
Rheumatoid heart disease	937 (0.2)	210 (0.1)	727 (0.2)
Stroke or TIA	8884 (1.7)	4911 (2.3)	3973 (1.3)
Tuberculosis	7659 (1.5)	4236 (2.0)	3423 (1.1)

Abbreviations: MET=metabolic equivalent of tasks; SD=standard deviation; TIA= transient ischaemic attack
None of the above demographic and health variables had missing data.

The participants' physical measurements and glucose levels are summarised in **Table 5.7**.

BMI was similar across sexes: mean (SD) BMI (kg/m²) was 23 (3) in men and 24 (3) in women (p<0.001). Men had slightly higher WHR (SD) than women (0.90 [0.06] vs 0.87 [0.07], p<0.001), but women had higher fat mass (% , SD) than men (18.72 [4.13] vs 14.60 [6.17],

p<0.001). Hence, lean body mass was higher in men than women. Overall, mean (SD) SBP (mmHg) was 131 (21) (men: 133 [20]; women: 130 [22]) and mean (SD) RPG (mmol/L) was 6.07 (2.34) (men: 5.97 [2.33]; women: 6.14 [2.34]).

Table 5.7 Mean values and distributions of physical measurements and random plasma glucose of recruited participants, overall and by sex

N (%) or mean (SD)	Overall (N=512726)	Male (N=210204)	Female (N=302522)
Body mass index (kg/m ²)			
Mean (SD)	23.66 (3.38)	23.43 (3.25)	23.82 (3.46)
<18.5	22361 (4.4)	9425 (4.5)	12936 (4.3)
18.5-23.9	265882 (51.9)	113249 (53.9)	152633 (50.5)
24.0-27.9	170140 (33.2)	68823 (32.7)	101317 (33.5)
≥28.0	54341 (10.6)	18706 (8.9)	35635 (11.8)
Missing	2 (0.0)	1 (0.0)	1 (0.0)
Waist-to-hip ratio			
Mean (SD)	0.88 (0.07)	0.90 (0.06)	0.87 (0.07)
Normal	213457 (41.6)	94704 (45.1)	118753 (39.3)
Overweight	144117 (28.1)	60593 (28.8)	83524 (27.6)
Obese	155152 (30.3)	54907 (26.1)	100245 (33.1)
Fat body mass (kg)			
Mean (SD)	17.03 (6.92)	14.60 (6.17)	18.72 (6.91)
...Missing	240 (0.0)	124 (0.0)	116 (0.0)
Lean body mass (kg)			
Mean (SD)	42.73 (7.63)	49.58 (6.15)	37.98 (4.13)
Missing	240 (0.0)	124 (0.0)	116 (0.0)
SBP (mmHg)			
Mean (SD)	131.08 (21.26)	132.83 (20.04)	129.87 (21.99)
<120	163175 (31.8)	54853 (26.1)	108322 (35.8)
120-139	201560 (39.3)	90855 (43.2)	110705 (36.6)
≥140	147991 (28.9)	64496 (30.7)	83495 (27.6)
RPG (mmol/L)			
Mean (SD)	6.07 (2.34)	5.97 (2.33)	6.14 (2.34)
<5.8	285907 (55.8)	124715 (59.3)	161192 (53.3)
5.8-7.7	173444 (33.8)	63808 (30.4)	109636 (36.2)
7.8-11.0	29406 (5.7)	11916 (5.7)	17490 (5.8)
≥11.0	23969 (4.7)	9765 (4.6)	14204 (4.7)
Missing	8341 (1.6)	3410 (1.6)	4931 (1.6)

Abbreviations: RPG=random plasma glucose; SBP=systolic blood pressure; SD=standard deviation

5.7.2 Baseline characteristics of CKB 2nd resurvey participants

Participants who attended the 2nd resurvey had similar demographic characteristics at baseline to those who were not followed up (**Table 5.8**). Although there were statistically significant differences in the distribution of age, region, marital status, education level, smoking and drinking status, dietary patterns, physical activity levels, self-reported health, and self-reported diseases, these differences were small.

Table 5.8 Baseline demographic and lifestyle characteristics of recruited participants by 2nd resurvey follow-up status

N (%), mean (SD) or median (IQR)	Not followed-up (N=487487)	Followed-up (N=25239)
Age (years)		
Mean (SD)	52.05 (10.71)	51.55 (10.15)
Urban region	215253 (44.2)	10940 (43.3)
Married	441224 (90.5)	23251 (92.1)
No formal education	90431 (18.6)	4748 (18.8)
Smoking status		
Never smoker	301250 (61.8)	16245 (64.4)
Occasional smoker	27753 (5.7)	1394 (5.5)
Ex regular smoker	21969 (4.5)	1010 (4.0)
Smoker	136515 (28.0)	6590 (26.1)
Drinking status		
Never regular	223176 (45.8)	11937 (47.3)
Ex-regular	8856 (1.8)	400 (1.6)
Occasional	155270 (31.9)	7862 (31.2)
Monthly	16569 (3.4)	816 (3.2)
Reduced intake	11166 (2.3)	530 (2.1)
Weekly	72450 (14.9)	3694 (14.6)
Daily fresh fruit consumption	92213 (18.9)	4375 (17.3)
Daily fresh vegetable consumption	461814 (94.7)	24136 (95.6)
Daily meat consumption	142299 (29.2)	7724 (30.6)
Physical activity (MET-hours/day) Median [IQR]	17.45 [10.31, 30.00]	17.70 [10.67, 30.21]
Self-rated health		
Excellent	85858 (17.6)	4543 (18.0)
Good	136777 (28.1)	7434 (29.5)
Fair	214253 (44.0)	10770 (42.7)
Poor	50599 (10.4)	2492 (9.9)
Self-reported prevalent disease		
Asthma	2672 (0.5)	134 (0.5)
Cancer	2468 (0.5)	110 (0.4)
Ischaemic heart disease	14751 (3.0)	721 (2.9)
Cirrhosis	5940 (1.2)	253 (1.0)
COPD	35266 (7.2)	1791 (7.1)
Emphysema or bronchitis	15498 (3.2)	664 (2.6)
Fracture	12673 (2.6)	615 (2.4)
Gallstone disease	33652 (6.9)	1793 (7.1)
Hypertension	29542 (6.1)	1455 (5.8)
Kidney disease	57061 (11.7)	2642 (10.5)
Neurasthenia	7263 (1.5)	312 (1.2)
Peptic ulcer	5381 (1.1)	318 (1.3)
Rheumatoid arthritis	18961 (3.9)	1054 (4.2)
Rheumatoid heart disease	10034 (2.1)	590 (2.3)
Stroke or TIA	897 (0.2)	40 (0.2)
Tuberculosis	8618 (1.8)	266 (1.1)

Abbreviations: MET=metabolic equivalent of tasks; SD=standard deviation; TIA= transient ischaemic attack
None of the above demographic and health variables had missing data.

Similarly, there were minimal (albeit statistically significant) differences in the distribution of baseline physical measurements and glucose levels between participants who were followed up at the 2nd resurvey versus those who weren't (**Table 5.9**).

Table 5.9 Mean values and distributions of physical measurements and random plasma glucose of recruited participants by 2nd resurvey follow-up status

N (%) or mean (SD)	Not followed-up (N=487487)	Followed-up (N=25239)
Body mass index (kg/m ²)		
Mean (SD)	23.65 (3.38)	23.74 (3.36)
<18.5	21379 (4.4)	982 (3.9)
18.5-23.9	252854 (51.9)	13028 (51.6)
24.0-27.9	161673 (33.2)	8467 (33.5)
≥28.0	51580 (10.6)	2761 (10.9)
...Missing	1 (0.0)	1 (0.0)
Waist-to-hip ratio		
Mean (SD)	0.88 (0.07)	0.88 (0.07)
Normal	203009 (41.6)	10448 (41.4)
Overweight	136887 (28.1)	7230 (28.6)
Obese	147591 (30.3)	7561 (30.0)
Fat body mass (kg)		
Mean (SD)	203009 (41.6)	10448 (41.4)
...Missing	234 (0.0)	6 (0.0)
Lean body mass (kg)		
Mean (SD)	42.75 (7.63)	42.42 (7.49)
...Missing	234 (0.0)	6 (0.0)
Systolic blood pressure (mmHg)		
Mean (SD)	131.09 (21.29)	131.01 (20.81)
<120	155253 (31.8)	7922 (31.4)
120-139	191538 (39.3)	10022 (39.7)
≥140	140696 (28.9)	7295 (28.9)
Random plasma glucose (mmol/L)		
Mean (SD)	6.08 (2.35)	5.87 (2.16)
<5.8	270536 (55.5)	15371 (60.9)
5.8-7.7	165795 (34.0)	7649 (30.3)
7.8-11.0	28131 (5.8)	1275 (5.1)
≥11.0	23025 (4.7)	944 (3.7)
...Missing	8010 (1.6)	331 (1.3)

Abbreviations: SD=standard deviation

Lastly, the level of missingness in CKB data at baseline is very low (<1%). The highest level of missingness was in RPG (1.6%), which was due to a delay in the availability of on-site testing in certain regions.^{259,260}

5.8 Summary

The CKB is one of the largest prospective cohort studies conducted in China with several features that are highly advantageous for observational epidemiological studies. CKB included over half a million participants at baseline and an average duration of follow-up exceeds 13 years with incident diseases recorded via ICD-10 codes through linkage to national hospital and health insurance claims records. This has resulted in a large number of events with more

than 100,000 incident cardiovascular events recorded in CKB. In addition, detailed standardised surveys have been carried at baseline and two subsequent resurveys, which have enabled repeat measurements of a wide range of sociodemographic and health information.

This rich detailed resource provides a unique opportunity to investigate the main aims of the thesis in greater detail than previous studies. First, a wide range of CVD RFs were recorded at baseline including SBP, RPG, fat mass, lean body mass, cigarette smoking, and alcohol drinking habits. For the latter RFs, information on reasons for quitting were recorded, which can be used to amend exposure data accordingly to limit misclassification.

Second, the large study size and diverse population (wide age range and regional differences) means that various subgroup and sensitivity analyses can be performed without the loss of power. Thus, the thesis can explore whether the relationship between frailty and incident CVD differs by age group, ranging from 35 to 80 years, the 10 study regions, and other demographic and clinical groups. The exclusion of specific subgroup, such as participants who died shortly after follow-up or those who were ever smokers, means that healthier cohorts can be investigated to assess the presence of reverse causality. In addition, the minimal amount of missing data and loss to follow-up in CKB suggests that the associations of interest should be less susceptible to various biases. Furthermore, the detailed events recorded in CKB mean that a wider range of disease outcomes can be investigated. The investigation of the associations between frailty and CVD will not be restricted to total CVD outcomes but include fatal events and CVD subtypes (e.g. ischaemic and haemorrhagic stroke). Comparison of the associations by CVD types should allow a broad assessment of whether the mechanism of effect between frailty and CVD differ by differences in disease pathophysiology or whether the effect is more general to everyone in the population.

Lastly, the systematic review of the utility of the major frailty instruments for prediction of all-cause mortality reported superior ability of continuous frailty measures (**Chapter 2**) and the prospective analysis of TILDA reported higher reproducibility of the FI than FP (**Chapter 3**),

supporting the selection of FI for subsequent analyses in this thesis. The FI is a more reliable and valid instrument and should provide more accurate estimations of the determinants and consequences of frailty in Chinese adults. While previous studies have evaluated the prevalence, correlates, and consequences of frailty in China, none, to my knowledge, have conducted a large-scale assessment of the validity and reliability of frailty instruments using prospective data. In the subsequent chapter, the large number of covariates recorded in CKB will be used to estimate the prevalence and correlates of FI and the repeat surveys of CKB will be used to determine its reliability in a Chinese population.

6 Prevalence, correlates, validity, and reliability of the frailty index in the China Kadoorie Biobank

6.1 Introduction

A major challenge in frailty research using the FI is the potential interplay of the frailty instrument with RFs and disease. The FI is a composite indicator consisting of 20-30 or more items that are closely related to ageing. Accordingly, CVD and related RFs, such as hypertension and BMI are routinely included in the FI, which means that the associations of FI with CVD (or associated RFs) may be inflated. Therefore, the present thesis will use modified versions of the FI that exclude cardiovascular deficits. It is common practice to exclude traditional CVD RFs while studying associations between CVD and FI, but the modified index is often not validated at all²²¹ or authors simply compare the associations of interest between the original and modified FI.²¹⁸ For example, Shrauner *et al.* (2022)²¹⁸ reported that the association between FI and CVD mortality was similar between the original and modified FI, suggesting that the modified FI is therefore valid. However, how modifications of the FI affect its validity and reliability and subsequently on its associations with other outcomes is unknown. For example, excluding certain deficits may affect the properties of the FI in a way that changes its association with age and sex (i.e. construct validity), its ability to predict adverse outcomes (i.e. criterion validity), or the degree of error associated with measurements (i.e. reliability), meaning that simple comparisons between the original and modified FI may not be appropriate.

In addition, whether the FI provides a reliable assessment of frailty in Chinese populations is uncertain. Previous studies have reported good reliability of other frailty instruments but in generally smaller populations.^{274–277} As outlined previously, frailty measurements may be associated with random measurement error and within-person variation over time (**Chapter 3**), in which case a single assessment of frailty in participants may not reflect their true or “usual” levels. Failure to take account for this measurement error in the predictor in subsequent analyses of disease associations may result in a systematic underestimation of

associations, a phenomenon called “regression dilution bias”.¹²⁹ Thus, correction for this bias is appropriate when the aim of the study, like the present thesis, is to estimate the magnitude of hypothesised relationships. One approach to correct for this bias is the MacMahon-Peto method,¹²⁹ which adjusts the estimated coefficient using correction factors obtained from reliability studies¹³⁰ with repeat measurements of the covariate obtained for a random sample of participants. Thus, the repeat surveys in CKB, which allow repeat assessments of frailty, can be used to quantify the within-person variation associated with the FI and correct for regression dilution bias in subsequent analyses.

The aim of the present chapter is to estimate the FI and assess its validity and reliability in a Chinese population. The objectives of the present chapter are to: (1) assess the distribution and prevalence of frailty in CKB; (2) examine the association of frailty with other relevant demographic and CVD RFs (construct validity) and all-cause mortality (criterion validity); (3) quantify the extent of reliability and within-person variability of the FI; and (4) estimate the correction factor to correct for regression dilution bias in subsequent analysis. In addition, different modifications of the FI – the exclusion of CVD or adiposity deficits – will be compared for each objective. This chapter will also explore whether further modifications of the FI could improve its validity.

6.2 Methods

6.2.1 Participants

Baseline participants were used to examine the prevalence, correlates, and validity of frailty. Participants who were followed up at both resurveys were used to examine the reliability and within-person variability of the FI. Participants were excluded from the analyses if they were missing BMI. At baseline, 512,728 participants were eligible for analysis. Of these, 14,901 were also followed-up at the 1st and 2nd resurveys.

6.2.2 Definition of FI

FI is composed of deficits, which refer to particular aspects of an individual's health status that are *in deficit* or poor form, such as diabetes and poor self-rated health.⁵⁵ The FI was previously operationalised in CKB as a 28-item index by Fan *et al.* (2020).²¹⁹ The present thesis reproduced the same 28 deficits with minor modifications described below. Fan *et al.* selected the deficits according to the standard procedure.⁷² Potential deficits in the baseline questionnaire were considered for inclusion in the FI if they met the following criteria: (1) involves multiple body systems; (2) prevalence generally increases with age but is not universal at older age (e.g. grey hair); (3) baseline prevalence $\geq 0.5\%$ in CKB; and (4) $< 5\%$ missing data. If deficits were highly correlated (i.e. Spearman's rank correlation coefficient was > 0.4), the deficit with a higher correlation with age was included.²¹⁹ The original standard procedure do not give a rationale for each criterion. Ideally, variables should be selected based on their relevance to the construct of interest, analytical soundness, accessibility, and so on, but no fixed method exists to build a composite indicator.²⁷⁸ The standard procedure, however, is consistent with the general consensus that frailty is a multidimensional construct (Criteria 1),⁵¹ support an important role of the FI which is to differentiate risks for various adverse outcomes among individuals (a deficit that is universal among the older population would be counterproductive to this) (Criteria 2), and accessibility of variables (Criteria 3).

Measurement of frailty deficits

Twenty-eight self-reported or objective variables from the CKB questionnaire were included in the FI. These were self-reported doctor diagnosis of medical conditions (asthma, cancer, chronic kidney disease, COPD, diabetes, emphysema/bronchitis, fracture, gallstone disease, heart disease, hypertension, neurasthenia, peptic ulcer, rheumatoid arthritis, stroke/TIA, and tuberculosis), self-reported symptoms (abnormal bowel movement, continuous pain, dental problems, frequent cough, being sad or depressed, self-rated health, sleep problems, unintentional weight loss, and walking difficulties), self-reported levels of physical activity, and measured anthropometry and physiology (BMI, WHR, heart rate, and lung function). The diabetes diagnosis was supplemented by fasting (≥ 0.7 mmol/L) and random (≥ 11.1 mmol/L)

glucose measurements, and hypertension diagnosis by SBP (≥ 140 mmHg), DBP (≥ 90 mmHg), and self-reported use of antihypertension drugs. Recording of these variables was described in **Chapter 5**. Of the 28 deficits previously identified by Fan *et al.*,²¹⁹ the present thesis modified one deficit (lung capacity deficit) by replacing FEV1:FVC with the COPD diagnosis because of minor differences in the measurement of FEV1:FVC across CKB study surveys.

Definition of FI

The 28 deficits were coded as either a binary or as ordinal variables with values ranging from 0 to 1 (shown in **Table S6.1**).⁷² Zero indicates absence of deficit (the healthiest status) and 1 indicates full expression of the deficit (the unhealthiest status). For example, for variables with binary values like self-reported diagnosis of heart disease (yes/no), participants without heart disease were coded as '0' and those with a diagnosis of heart disease was coded as '1'. Ordinal variables were mapped to a value between 0 and 1 with equal intervals. For example, self-reported health status (excellent, good, fair, poor) was re-coded as 0.00, 0.25, 0.50, and 1.00, respectively. Continuous variables, such as BMI, waist circumference, and heart rate, were first categorised, which was based on published thresholds or in relation to some clinically relevant hazard. Afterwards, variables were mapped into values between 0 and 1 like ordinal variables. The FI score was calculated as the ratio of the sum of deficits over the number of deficits considered and categorised into non-frail, pre-frail, and frail status using the following thresholds: <0.10 , ≥ 0.10 - <0.25 ; and ≥ 0.25 , respectively. The frail threshold value is recognised as the score at which individuals approach a frail state⁷² and was originally determined by identifying the point at which the distribution of FI for people classified by the Fried phenotypic definition of pre-frail and frail crossed.²⁷⁹

The present thesis made modifications to the FI by excluding certain deficits (described in **Table 6.1**). These modifications were made to assess the presence of circularity in the associations between frailty and CVD (RFs).

Table 6.1 Definition of FI studied in the thesis

Frailty index	Definition
Original FI	28-item FI
Modified FI-1 (mFI-1)	Four cardiovascular deficits (heart disease, stroke/TIA, diabetes, and hypertension) were excluded from the original FI, leaving a 24-item FI.
Modified FI-2 (mFI-2)	Three adiposity deficits (abnormal BMI, abnormal WHR, and unintentional weight loss) were excluded from the original FI, leaving a 25-item FI.
Modified FI-3 (mFI-3)	The final modification is a 21-item FI that excludes all cardiovascular and adiposity deficits mentioned above from the original FI.

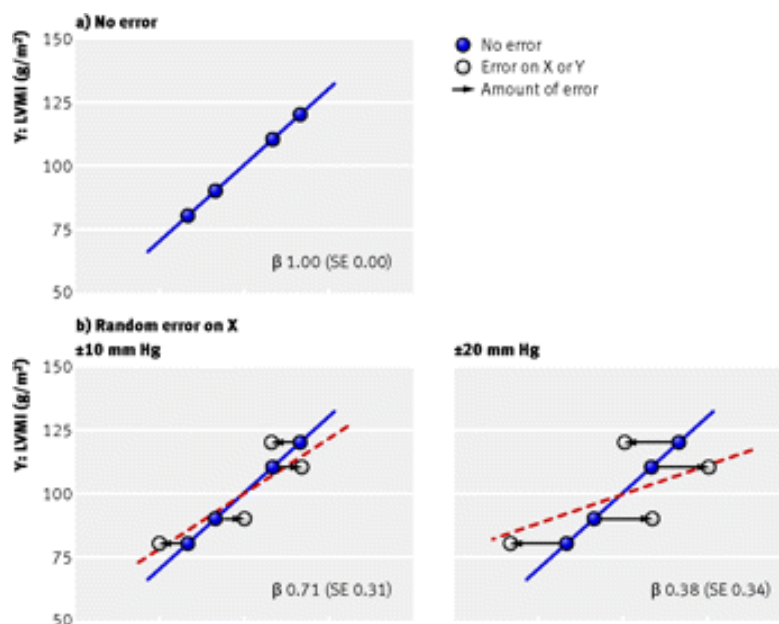
6.2.3 Regression dilution bias and correction methods

In an ideal situation, all exposure measurements undertaken during epidemiological studies would be measured perfectly and without random error. This means that exposure measurements do not randomly change or vary throughout the day or in different environments. However, random measurement error is pervasive in epidemiological research and can introduce bias. The impact of random measurement error was described by Hutcheon and colleagues²⁸⁰ using the linear relationship between SBP (exposure) and left ventricular mass index (LVMI) (outcome),²⁸¹ which is illustrated in **Figure 6.1**.

In scenario 1 (**Figure 6.1**, panel a), Hutcheon *et al.* (2010)²⁸⁰ illustrate a scenario in which random measurement error is absent. Since there are no random errors in SBP measurement, the true relation of the “usual” (or the long-term average levels of) SBP and LVMI risk can be estimated. However, when random measurement error of the exposure is introduced in scenario 2 (**Figure 6.1**, panel b), such as due to technical errors like imprecise measurement devices or biological variation over time, the SBP values will no longer represent a participant’s true, “usual” values. Instead, error-prone measurements around the true value, either higher or lower (reflected by variability of the x-axis measurements), will be recorded. As shown by the change in slope, this random error results in the systematic attenuation of the true association towards the null (or “regression dilution bias”) and the magnitude of error will determine the degree of this bias. Thus, correcting for regression dilution bias in epidemiological studies will provide more accurate estimation of RF and disease associations.

While this example illustrates regression dilution bias in linear regression models, this bias also occurs with logistic and survival regression models.²⁸²

Figure 6.1 Illustration of the effect of random measurement error on the linear relationship between SBP (exposure) and left ventricular mass index (outcome)



Panel a shows a scenario in which there is no random measurement error, thus the slope (β) describes the true association between SBP (x-axis) and left ventricular mass index (LVMI) (y-axis). Panel b shows a scenario in which SBP is measured with random measurement error ($\pm 10/20$ mmHg), which attenuates the association. Reproduced from [Random measurement error and regression dilution bias, Jennifer A Hutcheon, Arnaud Chiolero, James A Hanley, 340, c2289, 2010] with permission from BMJ Publishing Group Ltd (License Number: 5582421305348).

The importance of regression dilution bias was highlighted by MacMahon *et al.* (1990) when they showed a systematic underestimation in the risk of stroke due to the random measurement error in DBP in the Framingham study.¹²⁹ Given that the aim of the present thesis is to accurately estimate the magnitude of association between frailty and CVD outcomes (**Chapter 8**), rather than solely hypothesis testing, correction of regression dilution bias is warranted. Various methods to correct for regression dilution bias exist.²⁸³ **Figure 6.1** shows that multiplying a correction factor to the slope of the association between exposure and outcome would correct for this bias. Thus, existing methods in the literature involve estimating this correction factor, which can be divided into two approaches: regression- and correlation-based methods.²⁸³ This correction factor represents the size of the measurement error and, regardless of the approaches to estimate it, is usually obtained from reliability

studies.²⁸⁴ Reliability studies are generally a random subset of the main study and involve at least one repeated measurement of the exposure.²⁸⁴

The MacMahon-Peto method¹²⁹ and regression-based methods, namely Rosner's regression method,²⁸² are based on the assumption that the relationship between the 2nd and 1st measurements of the exposure can be used to correct for regression dilution bias. Importantly, both approaches regress the 2nd measurement on the 1st to calculate the correction factor. The MacMahon-Peto method¹²⁹ can be understood by the phenomena of "regression to the mean", that extreme measurements of the exposure will tend to be closer to the mean of its distribution on reassessment. Fluctuations in the exposure will lead to values regressing to the mean at re-measurement, so the degree of this change can be thought of as the correction factor. The MacMahon-Peto method divides the exposure data for both the 1st and 2nd measurements into quintile groups based on the 1st measurement. The correction factor is obtained as the ratio of the differences in the mean values of the exposure from the top and bottom quintile groups in the 2nd and 1st measurements (i.e. the "ratio of range"). In Rosner's regression method,²⁸² the correction factor is the regression coefficient obtained by regressing the 2nd exposure measurement on the 1st. The difference between the MacMahon-Peto and Rosner's regression method is that the latter does not arbitrarily split the data into quintiles, which can affect the value of the correction factor, and utilises all the available exposure data in the estimation of the correction factor. Thus, Rosner's method is usually considered superior given that the parametric assumptions are met. However, a general limitation of regression methods is the arbitrary ordering of the repeat measurements (i.e. regressing 2nd on the 1st) to obtain the correction factor and the restriction of using two measurements only. The alternative method is correlation-based approaches, such as the intraclass correlation coefficient method and Rosner's components-of-variance method,²⁸⁵ where the correction factor is the correlation coefficient itself.²⁸³ Correlation-based approaches do not depend on the ordering of the exposure measurements and can be used in situations where more than two repeat measurements are available. While Frost and Thompson (2000)²⁸³ argue that

correlation-based methods are superior to regression-based methods due to the higher precision of the correction factor, the use of these approaches involve assumptions that are not always met, e.g. that the repeat measurements have similar variances, that they are normally distributed, and that their errors are not correlated.^{280,283} These assumptions of parametric methods however can be violated by changes in population parameters due to increasing age or changes in lifestyle. Violation of such assumptions will limit the validity of the “de-attenuated” regression coefficients. For instance, Davey-Smith and Phillips (1997)²⁸⁶ argued that the authors of the Intersalt study may have over-corrected associations between sodium excretion and BP.^{287–289} They argued that fluctuations in sodium excretion and BP were correlated over the study interval, which would violate the assumption of their correction method and provide misleading findings.

In light of this background, the MacMahon-Peto method was chosen to correct for regression dilution bias in the present thesis (**Chapter 8**). The MacMahon-Peto method is a non-parametric method with no assumptions about the distribution of exposures.¹²⁹ This means that this method is suitable when distributions of repeated measurements are not equal, which is likely for cohort studies with long intervals between measurements. Additionally, the method is simple and intuitive. Correction for regression dilution bias is carried out by dividing the observed estimate and its standard errors by the correction factor.²⁸⁴ Thus, this approach does not make non-statistically significant results statistically significant and vice versa. However, a limitation of the MacMahon-Peto method is that a precision level of the correction factor is not given.¹²⁹ The reliability analysis of the present chapter will be used to estimate the correction factor to correct for regression dilution bias in subsequent analyses (**Chapter 8**).

Lastly, other types of measurement error in exposures exist, which can bias the estimation of exposure-disease associations by imprecise measurement of the exposure variable. For instance, systematic measurement error can attenuate or exaggerate the association depending on the nature of the error in the exposure, which can be systematically over- or under-estimated. Within-person variability, as described above, introduces random error into

the exposure measurement and results in the attenuation of associations.^{129,130} The approach to correct for each type of error is different. While random error can generally be addressed using replicate exposure measurements, systematic error must be addressed using a reference instrument, which is assumed to be free of systematic error.²⁹⁰ Thus, systematic error is more difficult to measure and much of the statistical approaches to correct measurement error has been developed for random error.²⁹⁰ The present thesis focuses on the correction of within-person variability in exposure measurement.

6.2.4 Statistical analyses

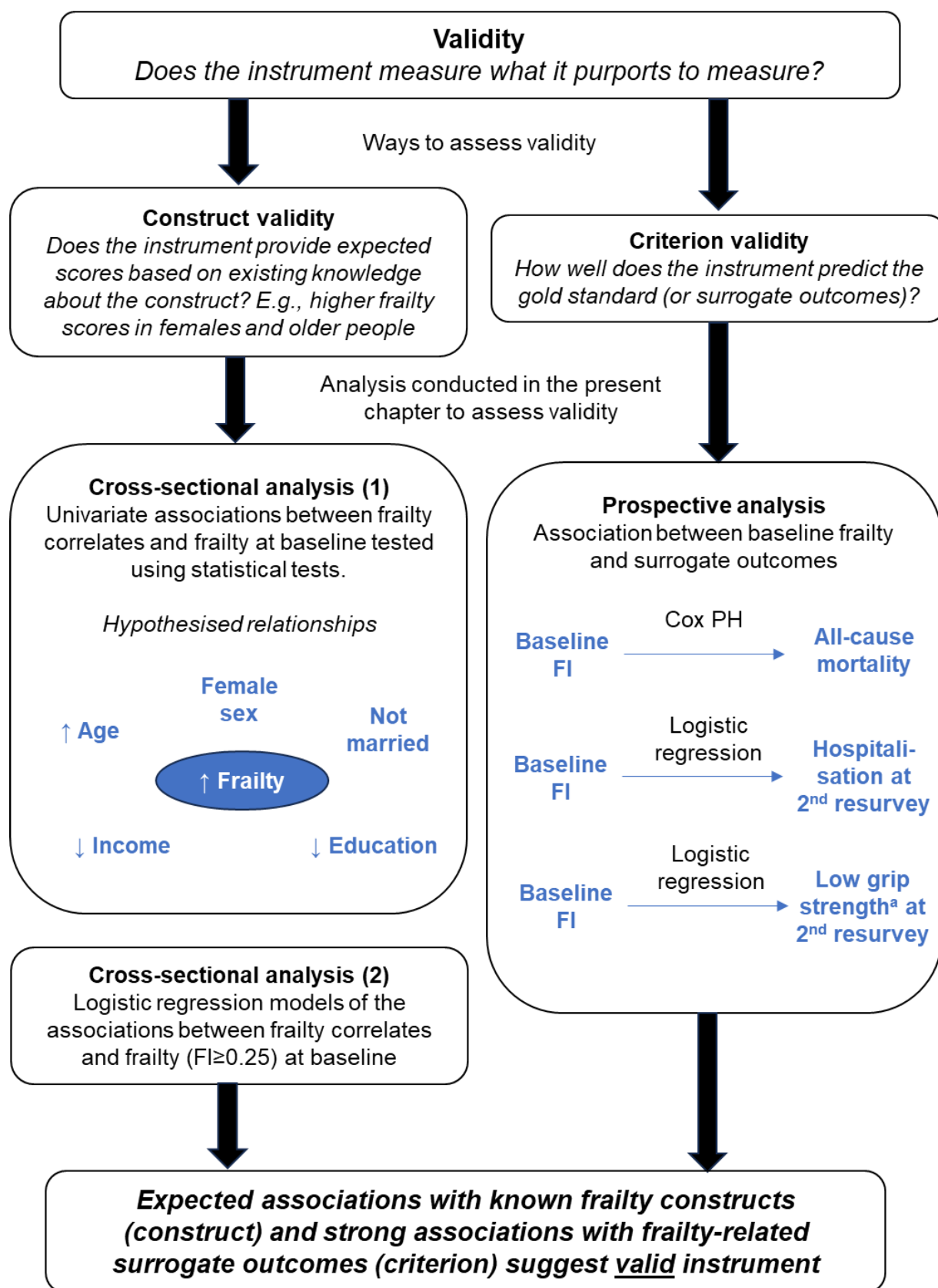
Descriptive analyses

Standard descriptive statistics were used to summarise the individual deficits and FI. The correlation of individual frailty deficits with age was visualised by plotting the prevalence of deficits by age group. Continuous variables were summarised using mean (SD) or median (IQR) and their distributions were plotted using histograms. Categorical variables were summarised using counts, percentages, and bar plots.

Construct and criterion validity of FI

The present chapter assessed the validity¹³³ of the FI in CKB. A schematic representation of this assessment is shown in **Figure 6.2**. In brief, construct and criterion validity were assessed.¹⁰⁷ Construct validity was assessed by whether the FI was associated with known correlates of frailty, such as female sex and older age, via cross-sectional associations. Criterion validity was assessed by the prospective association between FI and the gold standard. In the absence of a gold standard for frailty, all-cause mortality, self-reported hospitalisation in the past year (2nd resurvey), and objectively measured grip strength (2nd resurvey) were considered as surrogate outcomes.

Figure 6.2 Schematic representation of the assessment of validity in the present chapter



^aLow grip strength was defined as being in the sex-adjusted lowest quintile of grip strength.

To examine construct validity, univariate associations between frailty and frailty correlates were assessed. The distribution of frailty was compared across levels of other baseline variables: age group, sex, region, highest education, household income, marital status, alcohol consumption, and smoking status. The specific tests used to detect differences in frailty distribution across these subgroups and the hypothesised associations are shown in **Figure 6.2** and **Table 6.2**. The independent effects of correlates with frailty (defined as FI $\geq$ 0.25) were assessed via logistic regression models, which were adjusted for age, sex, and region, and additionally for education level, income level, marital status, alcohol consumption, and smoking status (where appropriate). Associations of alcohol consumption and smoking were restricted to men due to the low prevalence of drinking and smoking in women.

Table 6.2 Statistical tests used to detect significant differences in the distribution FI by frailty correlates

Univariate association		
Frailty index	Frailty correlates	Statistical test used to detect significance
Categorical	Categorical	Chi-square test of independence ²⁹¹ to compare the prevalence of frailty categories across groups.
Continuous	Binary variables e.g. sex	Wilcoxon Rank Sum test, a non-parametric alternative of the two-sample t-test, to test whether the medians of the FI in two populations were equal.
	Nominal variables e.g. smoking status	Kruskal-Wallis test to compare the distribution of frailty in nominal variables with 2 or more levels.
	Ordinal variables e.g. education level	Jonckheere-Terpstra test to determine whether there were statistically significant differences in the distribution between ordinal variables with 2 or more levels; it additionally tested for ordered differences in the medians. ²⁹²

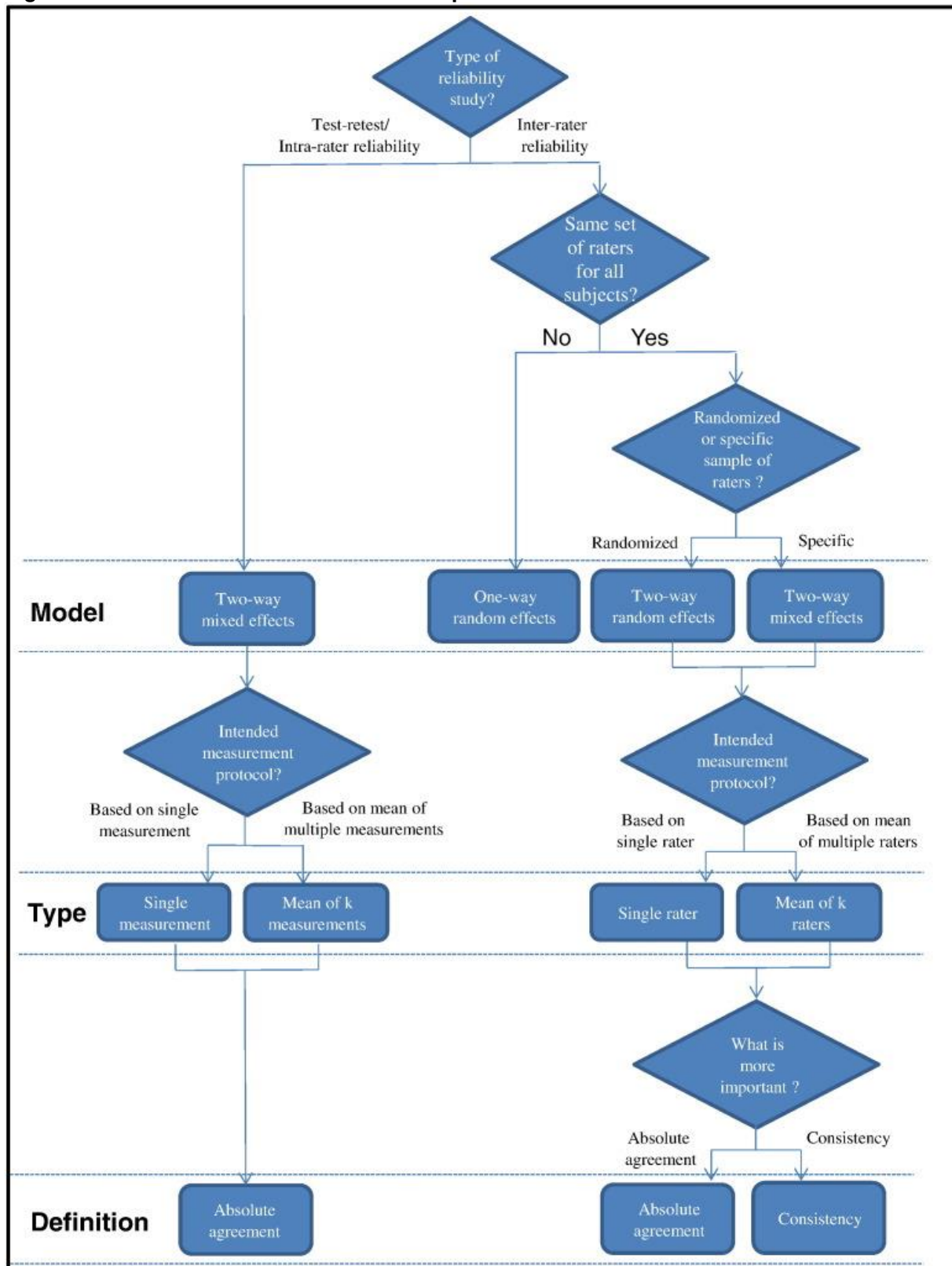
For the assessment of criterion validity, the associations between frailty and outcomes were assessed using logistic regression models (as above) and Cox proportional hazards models (for all-cause mortality), which were stratified by age-at-risk, sex, and region. Associations were reported for categorical frailty levels and 1 SD increase in the FI score at baseline, which equated to approximately: 0.065 (~2 deficit) for the original FI, 0.065 (~1.5 deficit) for mFI-1, 0.062 (~1.5 deficit) for mFI-2, and 0.063 (~1.5 deficit) for mFI-3.

Reliability and within-person variability of FI

The methods used to examine the reliability and within-person variability of FI were similar to those used in **Chapter 3**. In the present chapter, the weighted kappa statistic was used to estimate within-person agreement in frailty categorisation ($FI \geq 0.25$) and the anchor used to calculate the MIC was 1 unit or more decline in self-rated health. Additionally, the intraclass correlation coefficient (ICC) was used to estimate the agreement in continuous FI scores across the 3 measurements (baseline, 1st resurvey, and 2nd resurvey).²⁹³ McGraw and Wong defined 10 ICC statistics based on the model, unit, and type of reliability of interest.²⁹⁴ The flowchart depicting the selection process of the ICC is shown in **Figure 6.3**.

The present analysis involves a test-retest design, which determines reliability based on measurements taken for identical subjects at different time-points and typically assume that rater effects are negligible (FI score of individuals at different time-points were considered to be rated by the same set of raters i.e. standardised methods).²⁹³ Thus, the '2-way mixed effects' model, which treats individuals as a random effect and raters as fixed, was selected.²⁹⁵ The type or unit of analysis (i.e. whether the agreement is measured between individual or an average of measurements) was 'single' as single frailty measurements were taken. Finally, 'absolute agreement', the extent to which repeat frailty measurements were equal, was the definition of interest.²⁹³ Therefore, the ICC model for test-retest design, a 2-way mixed effects model (single rater, absolute agreement), was used.²⁹³ Higher ICC suggests lower random measurement error.

Figure 6.3 A flowchart of the ICC selection process



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Estimation of the correction factor for regression dilution bias

The MacMahon-Peto method¹²⁹ will be used to correct for the degree of regression dilution bias in the frailty-outcome associations (**Chapter 8**). Repeat FI measures (baseline and 1st or 2nd resurvey) in CKB were used to calculate the correction factor, the regression dilution ratio (RDR). The magnitude of regression dilution bias in FI scores was visualised. Based on five equally sized categories of FI at baseline, the mean FI for each group was plotted at baseline and the 1st or 2nd resurvey.^{283,284} RDR was calculated using the ratio of the ranges of the mean FI (top vs bottom quintile defined by baseline FI) at resurvey to the range of such measurements at baseline.¹²⁹

Exploratory analysis: improving the FI

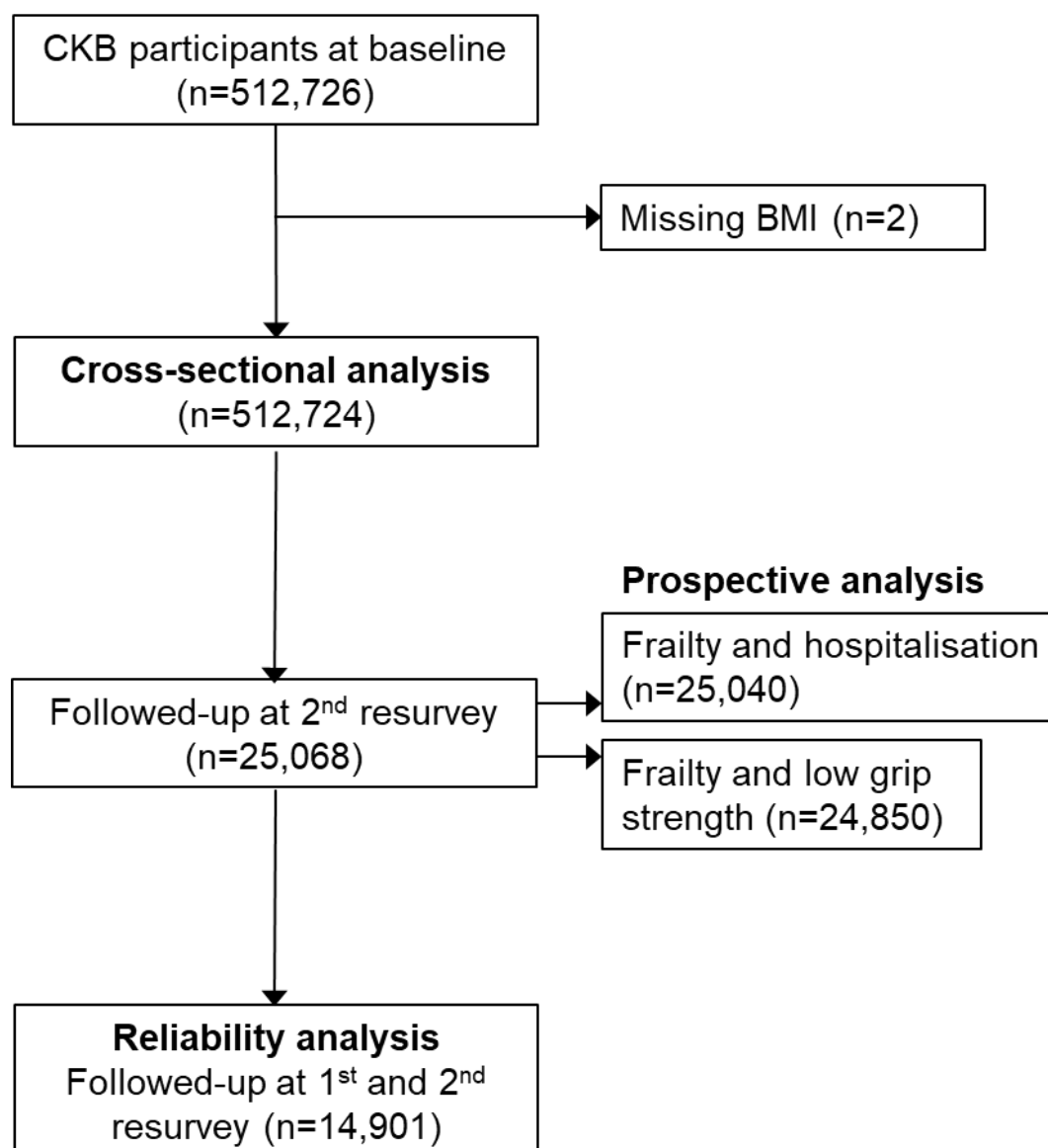
The analyses in **Chapter 3** reported large within-person variability in the FI and suggested that repeat or recent assessments may improve the predictive accuracy of the FI. Thus, I attempted to improve the FI by using the available follow-up data in CKB. Repeat FI measurements were computed based on ICD-10 codes from CKB's incidence data. The definitions of the 28 individual frailty deficits were mapped to ICD-10 codes with the help of a clinician (**Table S6.1**). The presence of an ICD-10 code was considered as having a deficit. Using the incidence data, repeat FI scores based on ICD-10 codes were calculated for individuals every year between the study baseline and resurvey.

All statistical analyses were conducted using R version 4.2.1.

6.3 Results

The flow diagram of participants is shown in **Figure 6.4**. The construct and criterion validity analysis of frailty involved 512,726 participants excluding those missing BMI at baseline (n=2). As part of the assessment of criterion validity of frailty, the prospective analysis of the associations between frailty and hospitalisation (n=25,404) and low grip strength (n=24,850) included participants who were followed-up at the 2nd resurvey. The reliability analysis involved 14,901 participants who were followed up at the 1st and 2nd resurvey.

Figure 6.4 Flow diagram CKB participants selected for this chapter

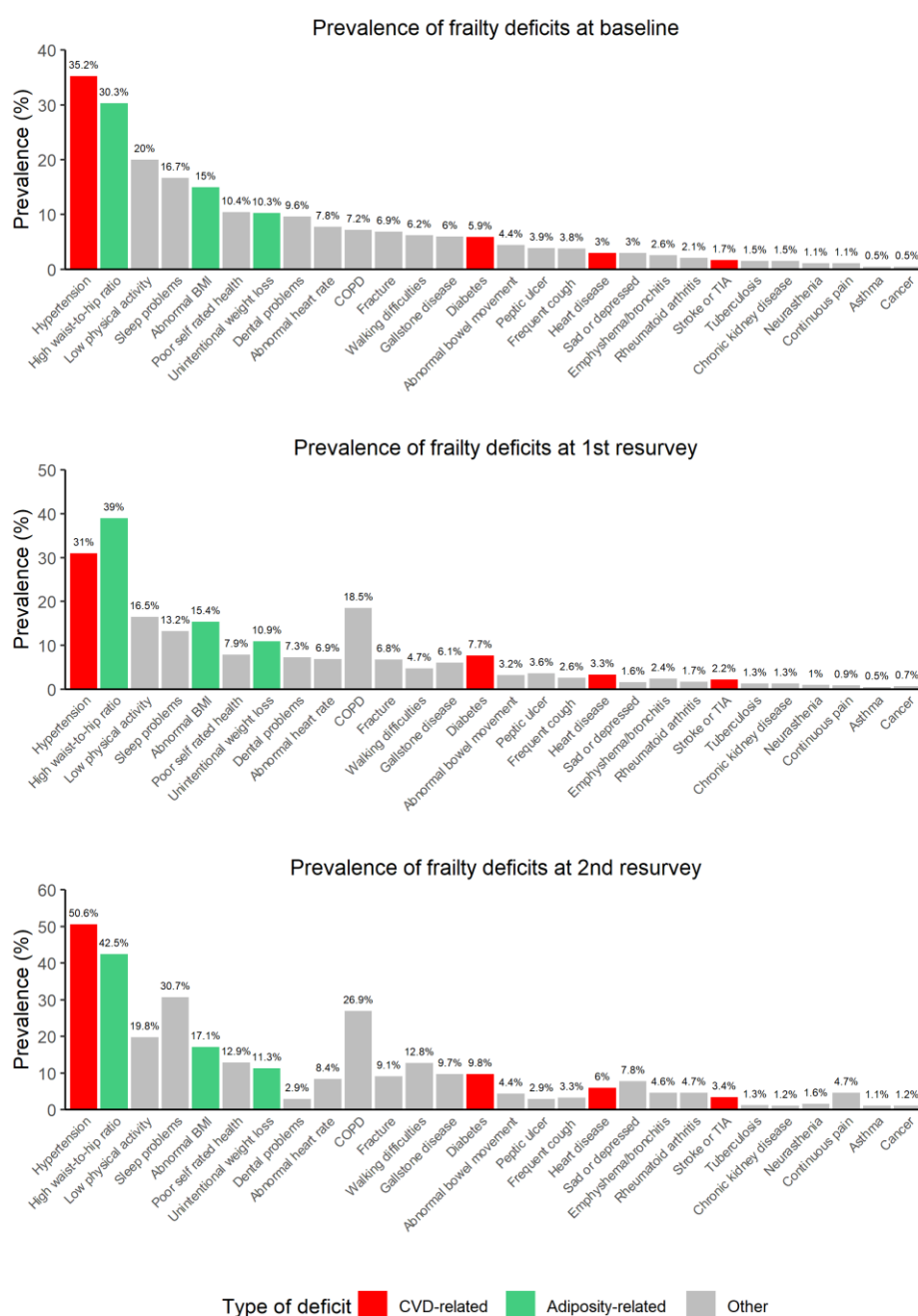


6.3.1 Distribution and prevalence of frailty

Distribution and prevalence of frailty deficits

The prevalence of individual frailty deficits is shown in **Figure 6.5** (full deficits only) and **Figure S6.1** (full and partial deficits). At baseline, frailty deficits had a minimum prevalence of 0.5%. The most prevalent frailty deficits were hypertension (35%), high WHR (30%), and low physical activity (20%) and the least common were cancer (0.5%), asthma (0.5%), continuous pain (1%), and neurasthenia (1%).

Figure 6.5 Prevalence of individual frailty deficits



After an average follow-up of approximately 2.5 years (1st resurvey) and 8 years (2nd resurvey), hypertension and high WHR remained the top two most prevalent deficits. While low physical activity, sleep problems, and abnormal BMI also remained highly prevalent, the prevalence of COPD increased sharply between baseline (7%) and resurveys (19% and 27). Deficits with low prevalence (<5%) were largely unaltered at successive surveys. Over time, the prevalence

of deficits generally increased, but the following deficits declined consistently: dental problems, low physical activity, peptic ulcer, frequent cough, tuberculosis, and chronic kidney disease.

All deficits were strongly correlated with increasing age, shown by correlation coefficients between the prevalence of deficits and age group (**Figure S6.2**). In general, a positive, linear associations were found except for unintentional weight loss, abnormal bowel movement, and continuous pain. These deficits were still included in the FI because of their relevance in the frailty construct or ageing.

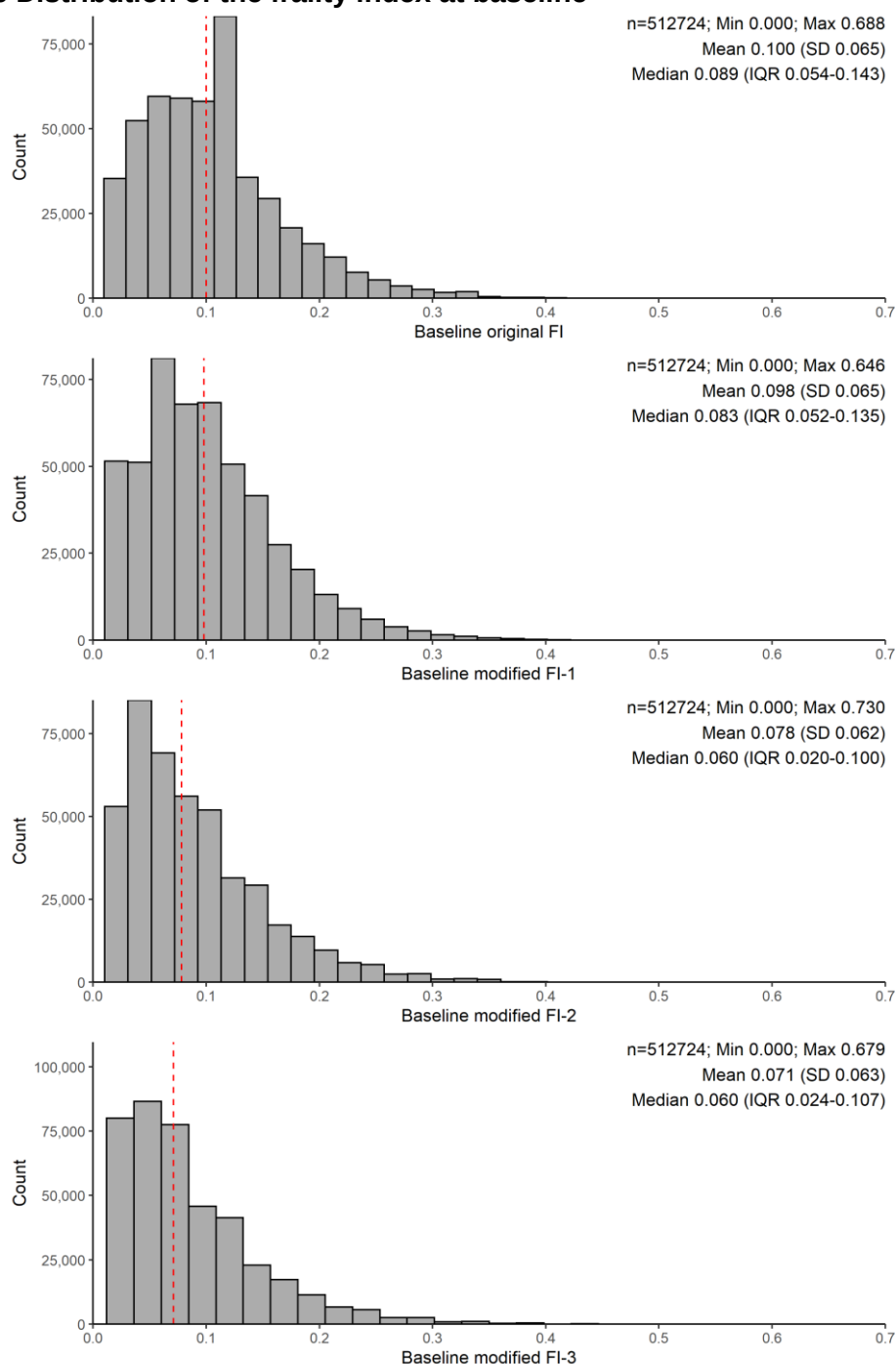
At baseline, the prevalence of deficits differed by sex (**Figure S6.3**). The prevalence of abnormal adiposity (high WHR and abnormal BMI), diseases (gallstone disease, diabetes, heart disease, abnormal bowel movement, rheumatoid arthritis, and chronic kidney disease), and general self-reported health deficits (sleep problems, poor self-rated health, walking difficulties, neurasthenia, and continuous pain) were higher in females than in males ($p < 0.001$ for all). Conversely, the prevalence of hypertension, stroke/TIA, respiratory deficits (COPD, frequent cough, emphysema/bronchitis, tuberculosis, and asthma), dental problems, abnormal heart rate, fracture, peptic ulcer, low physical activity, and unintentional weight loss were higher in males than in females ($p < 0.001$ for all). The difference in the prevalence of cancer between males and females, while statistically significant ($p < 0.001$), was negligible.

There were large differences in the prevalence of individual deficits by study region (**Figure S6.4**) and between rural and urban regions ($p < 0.001$ for all). For example, heart disease, stroke/TIA, and diabetes had about 2-fold greater prevalence in urban (especially Harbin and Liuzhou) than in rural regions.

Distribution and prevalence of frailty

At baseline, the FI was highly right-skewed (**Figure 6.6**). Participants defined according to the original FI had slightly higher levels of frailty than the modified FIs. Mean (SD) frailty levels for the FI, mFI-1, mFI-2, and mFI-3 were 0.100 (0.065), 0.098 (0.065), 0.078 (0.062), and 0.071 (0.063), respectively. The correlation between the original and mFI-1 was high ($R^2 = 0.89$).

Figure 6.6 Distribution of the frailty index at baseline



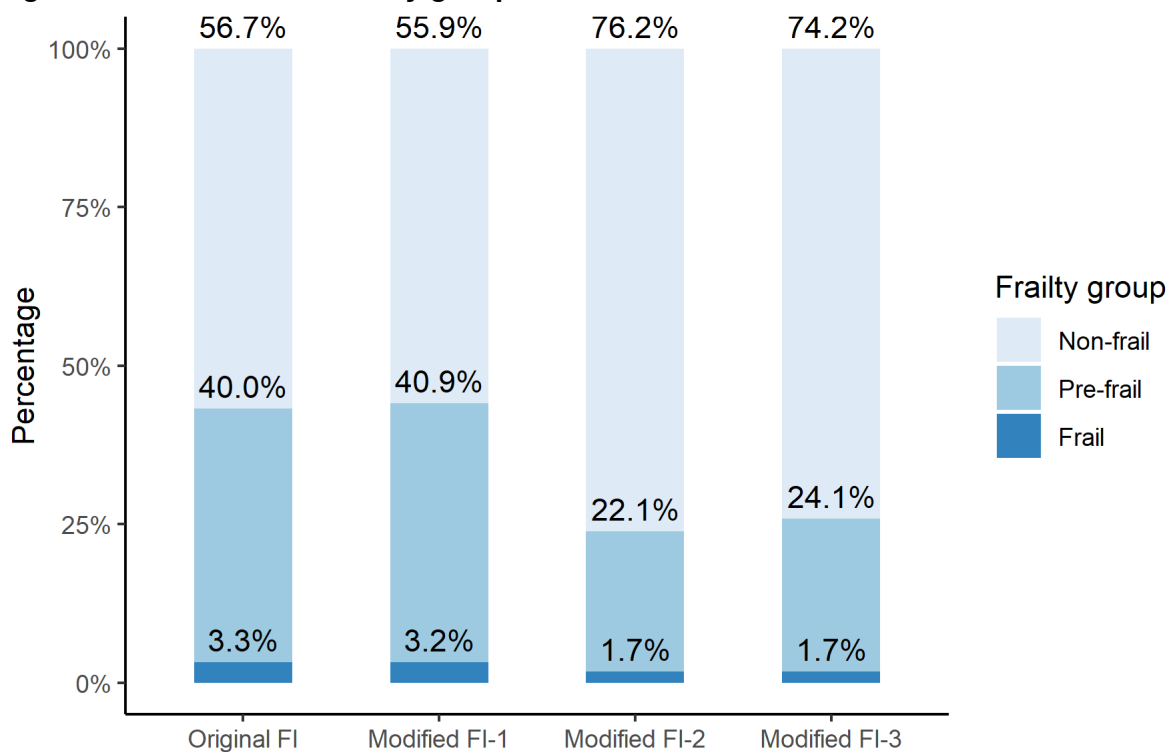
FI definitions: Original FI = 28-item FI; Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits); Modified FI-2 = 25-item FI (original FI excluding adiposity deficits); Modified FI-3 = 21-item FI (original FI excluding cardiovascular and adiposity deficits)

According to mFI-1, 3% and 41% of participants were defined as frail and pre-frail, respectively, at baseline (**Figure 6.7**). Women had a slightly higher prevalence of frailty (3.4% vs 2.8%) and pre-frailty (42% vs 39%) than men. These sex differences in prevalence also differed by age (**Figure S6.5**) and region (**Figure S6.6**). The prevalence of frailty was higher in men <40 years,

women ≥ 50 years, men from Haikou (urban), Liuzhou (urban), and Henan (rural), and women from all other study sites. The prevalence of frailty was slightly higher in rural than urban regions (2.3% vs 2.7%) with large differences by study region. The highest prevalence of frailty was found in Sichuan (rural) (6%) with approximately 4-fold higher than regions with the lowest frailty level, Hunan (rural) (1.5%) and Haikou (Urban) (1.3%). Although Sichuan had the highest prevalence of frailty ($FI \geq 0.25$), vastly higher levels of pre-frailty in Henan (rural) than the average (55% vs 41%) resulted in the average frailty score being highest in Henan (rural) (mean mFI-1 [SD]: Henan 0.123 [0.065]; Sichuan 0.116 [0.072]).

Similar patterns were seen for the original FI, which generally had slightly higher distributions and frailty prevalence than mFI-1. Conversely, the prevalence of frailty and pre-frailty were much lower (nearly half) using the modified FIs that excluded adiposity deficits (mFI-2 or -3) than those that included these deficits (**Figure 6.7**).

Figure 6.7 Prevalence of frailty groups at baseline



FI definitions: Original FI = 28-item FI; Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits); Modified FI-2 = 25-item FI (original FI excluding adiposity deficits); Modified FI-3 = 21-item FI (original FI excluding cardiovascular and adiposity deficits)

6.3.2 Construct and criterion validity of FI

Construct validity of frailty: cross-sectional associations with frailty correlates

Table 6.3 shows the cross-sectional associations of mFI-1 with other baseline variables. Mean (SD) mFI-1 scores were higher in females than males (females 0.100 [0.066]; males 0.095 [0.063]) ($p<0.001$). The prevalence of frailty was strongly and positively associated with age, ranging from 0.7% in 30-39 years to 8% in 65-80 years ($p<0.001$). In contrast, the prevalence of frailty declined with increasing levels of education ($p<0.001$) and household income ($p<0.001$). Frailty prevalence in participants who were widowed, separated or divorced was also 2-fold greater than those of their married counterparts (6.6% vs 2.9%) ($p<0.001$). Ex-regular drinkers and smokers had the highest prevalence of frailty compared with other drinking and smoking categories ($p<0.001$ for both), respectively. Similar patterns were found using the original FI, mFI-2, and mFI-3.

Table 6.3 Distribution and prevalence of frailty (mFI-1) at baseline by demographic factors

Variable	N	Modified FI-1 Mean (SD)	Non-frail (%)	Pre-frail (%)	Frail (%)
Sex					
Male	210203	0.095 (0.063)	57.7	39.5	2.8
Female	302521	0.100 (0.066)	54.6	41.9	3.5
Age group (years)					
30-39	77622	0.072 (0.052)	73.3	25.9	0.8
40-49	152769	0.083 (0.056)	66	32.6	1.5
50-54	87562	0.097 (0.061)	55.6	41.9	2.5
55-59	70054	0.107 (0.064)	48.9	47.3	3.8
60-64	49897	0.118 (0.069)	42.1	52.4	5.5
65-80	74820	0.133 (0.072)	33.5	58.5	8
Region					
Rural	286531	0.099 (0.066)	55.9	40.6	3.5
Urban	226193	0.096 (0.063)	55.9	41.2	2.9
Education level					
No formal school	95178	0.114 (0.071)	46.7	47.6	5.7
Primary School	165187	0.102 (0.065)	52.7	43.8	3.6
Middle School	144874	0.091 (0.060)	60	37.9	2.1
High School	77509	0.086 (0.059)	62.7	35.5	1.9
Technical school/college	18265	0.082 (0.060)	66.1	32	1.9
University	11711	0.083 (0.060)	65	33.1	1.9
Income level (yuan)					
<2,500	15539	0.145 (0.077)	28.6	60.1	11.3
2,500-4,999	34627	0.116 (0.073)	45	48.7	6.3
5,000-9,999	94569	0.103 (0.067)	52.3	43.8	4
10,000-19,999	148958	0.099 (0.063)	54.5	42.6	2.9
20,000-34,999	126704	0.089 (0.060)	61.4	36.5	2.1
≥35,000	92327	0.087 (0.059)	63	35.1	1.9
Marital status					
Married	464474	0.095 (0.063)	57.4	39.8	2.9
Widowed, separated or divorced	44499	0.122 (0.072)	40.6	52.8	6.6

Variable	N	Modified FI-1 Mean (SD)	Non-frail (%)	Pre-frail (%)	Frail (%)
Never married	3751	0.098 (0.070)	56	39.8	4.2
Alcohol consumption					
Never regular	235112	0.100 (0.067)	54.7	41.5	3.8
Ex-regular	9256	0.130 (0.078)	37.8	53.1	9.1
Occasional	163132	0.095 (0.062)	57.2	40.2	2.6
Monthly	17385	0.089 (0.059)	61.3	36.9	1.8
Reduced intake	11696	0.118 (0.068)	42.1	52.4	5.5
Weekly	76143	0.091 (0.059)	59.8	38.1	2.1
Smoking status					
Never	317494	0.098 (0.064)	55.8	41	3.1
Occasional	29147	0.098 (0.063)	55.8	41.2	3
Ex regular	22979	0.124 (0.075)	41.1	51.1	7.7
Smoker	143104	0.094 (0.063)	58.4	38.9	2.7

FI definition: Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits)

The independent associations of the demographic factors with frailty are reported in **Table 6.4**, which were similar to the crude associations. After adjustment for age, sex (where appropriate), and region, ORs of frailty were higher in females, increasing age group, ex-drinkers and ex-smokers (in men only), and lower with increasing levels of education and income. Individuals that had never married were more likely to be frail than those who were married, divorced, or widowed. Further adjustment for levels of education, income level, marital status, alcohol consumption, and smoking status showed similar patterns (**Table S6.2**).

Table 6.4 Odds ratios (95% CI) of associations between demographic factors and frailty measures at baseline

	Original FI OR (95% CI)	Modified FI-1 OR (95% CI)	Modified FI-2 OR (95% CI)	Modified FI-3 OR (95% CI)
Highest education				
No formal school	1.00 (0.96-1.04)	1.00 (0.96-1.04)	1.00 (0.94-1.06)	1.00 (0.95-1.05)
Primary School	0.84 (0.81-0.86)	0.81 (0.79-0.83)	0.80 (0.76-0.83)	0.78 (0.75-0.81)
Middle School	0.79 (0.75-0.83)	0.76 (0.73-0.79)	0.81 (0.75-0.87)	0.74 (0.70-0.79)
High School	0.65 (0.61-0.70)	0.66 (0.62-0.70)	0.67 (0.60-0.75)	0.68 (0.62-0.74)
Technical school/college	0.67 (0.58-0.77)	0.65 (0.58-0.75)	0.81 (0.66-0.99)	0.77 (0.65-0.91)
University	0.47 (0.39-0.57)	0.49 (0.41-0.58)	0.55 (0.42-0.71)	0.57 (0.46-0.70)
Household income (yuan)				
<2,500	1.00 (0.94-1.06)	1.00 (0.95-1.06)	1.00 (0.92-1.09)	1.00 (0.93-1.07)
2,500-4,999	0.85 (0.80-0.89)	0.83 (0.79-0.87)	0.77 (0.72-0.83)	0.78 (0.73-0.83)
5,000-9,999	0.72 (0.70-0.75)	0.70 (0.68-0.73)	0.70 (0.66-0.74)	0.66 (0.63-0.69)
10,000-19,999	0.62 (0.59-0.64)	0.56 (0.54-0.58)	0.58 (0.54-0.61)	0.50 (0.48-0.53)
20,000-34,999	0.53 (0.51-0.56)	0.48 (0.46-0.50)	0.50 (0.47-0.54)	0.45 (0.42-0.48)
≥35,000	0.49 (0.46-0.52)	0.42 (0.40-0.45)	0.42 (0.39-0.46)	0.37 (0.34-0.40)
Marital status				
Married	1.00 (0.98-1.02)	1.00 (0.98-1.02)	1.00 (0.98-1.03)	1.00 (0.98-1.02)
Widowed, separated or divorced	1.16 (1.10-1.21)	1.21 (1.16-1.27)	1.20 (1.12-1.28)	1.25 (1.18-1.32)
Never married	1.93 (1.59-2.34)	2.00 (1.69-2.36)	2.02 (1.57-2.61)	2.12 (1.72-2.61)
Alcohol consumption (men only)				
Never regular	1.00 (0.94-1.07)	1.00 (0.94-1.06)	1.00 (0.92-1.08)	1.00 (0.93-1.07)
Ex-regular	1.87 (1.70-2.06)	1.76 (1.61-1.92)	1.79 (1.58-2.02)	1.72 (1.54-1.91)

	Original FI OR (95% CI)	Modified FI-1 OR (95% CI)	Modified FI-2 OR (95% CI)	Modified FI-3 OR (95% CI)
Occasional	0.53 (0.50-0.57)	0.55 (0.52-0.58)	0.47 (0.43-0.52)	0.50 (0.47-0.55)
Monthly	0.52 (0.44-0.62)	0.50 (0.44-0.58)	0.40 (0.31-0.52)	0.42 (0.34-0.52)
Reduced intake	1.27 (1.15-1.41)	1.17 (1.07-1.28)	1.12 (0.97-1.29)	1.05 (0.93-1.19)
Weekly	0.58 (0.54-0.62)	0.55 (0.52-0.59)	0.51 (0.46-0.56)	0.51 (0.47-0.55)
Smoking status (men only)				
Never	1.00 (0.91-1.09)	1.00 (0.92-1.09)	1.00 (0.89-1.13)	1.00 (0.90-1.11)
Occasional	1.01 (0.91-1.12)	0.97 (0.88-1.07)	0.97 (0.83-1.12)	0.97 (0.86-1.10)
Ex regular	2.47 (2.32-2.64)	2.44 (2.30-2.59)	2.60 (2.39-2.82)	2.51 (2.34-2.70)
Smoker	1.06 (1.02-1.11)	1.10 (1.05-1.14)	1.04 (0.98-1.10)	1.05 (1.00-1.11)

Logistic regression models were adjusted for age, sex, and region.
FI definitions: Original FI = 28-item FI; Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits); Modified FI-2 = 25-item FI (original FI excluding adiposity deficits); Modified FI-3 = 21-item FI (original FI excluding cardiovascular and adiposity deficits)

Criterion validity of frailty: prospective association with adverse outcomes

All FI measures were strongly associated with hospitalisation and having low grip strength at the 2nd resurvey and all-cause mortality (**Table 6.5**). ORs (95%CI) for hospitalisation per 1 SD increase for the original FI, mFI-1, mFI-2, and mFI-3 were 1.34 (1.26-1.42), 1.27 (1.22-1.31), 1.30 (1.25-1.35), and 1.21 (1.17-1.26), respectively; ORs (95%CI) for low grip strength were 1.25 (1.19-1.31), 1.22 (1.16-1.27), 1.23 (1.18-1.29), and 1.19 (1.14-1.24), respectively, and Hazard ratios (HR) (95%CI) for all-cause mortality were 1.44 (1.43-1.45), 1.34 (1.33-1.35), 1.42 (1.41-1.43), and 1.31 (1.30-1.32), respectively. Additional adjustment for levels of education, income level, marital status, alcohol consumption, and smoking status showed similar patterns (**Table S6.3**).

Table 6.5 Relative risks (95% CI) of associations between baseline frailty measures and adverse outcomes

	Hospitalisation		Low grip strength		All-cause mortality	
	Cases / non-cases	OR (95% CI)	Cases / non-cases	OR (95% CI)	Cases / non-cases	HR (95% CI)
Original FI						
Non-frail	1660 / 12833	1.00 (0.94-1.06)	1025 / 13399	1.00 (0.93-1.08)	15136 / 275819	1.00 (0.98-1.02)
Pre-frail	1811 / 8094	1.48 (1.41-1.55)	1517 / 8286	1.28 (1.20-1.36)	28584 / 176458	1.70 (1.68-1.72)
Frail	199 / 443	2.60 (2.18-3.09)	189 / 434	2.30 (1.89-2.79)	5738 / 10989	3.46 (3.36-3.56)
Per 1 SD	3670 / 21370	1.34 (1.29-1.39)	2731 / 22119	1.25 (1.19-1.31)	49458 / 463266	1.44 (1.43-1.45)
Modified FI-1						
Non-frail	1670 / 12506	1.00 (0.94-1.06)	1053 / 13046	1.00 (0.93-1.07)	16942 / 269658	1.00 (0.98-1.02)
Pre-frail	1804 / 8378	1.40 (1.33-1.47)	1504 / 8581	1.30 (1.23-1.38)	27463 / 182176	1.52 (1.50-1.54)
Frail	196 / 486	2.37 (2.00-2.82)	174 / 492	2.04 (1.67-2.49)	5053 / 11432	2.90 (2.81-2.99)
Per 1 SD	3670 / 21370	1.27 (1.22-1.31)	2731 / 22119	1.22 (1.16-1.27)	49458 / 463266	1.34 (1.33-1.35)
Modified FI-2						
Non-frail	2477 / 16964	1.00 (0.95-1.05)	1639 / 17701	1.00 (0.94-1.06)	24144 / 366483	1.00 (0.98-1.02)
Pre-frail	1082 / 4177	1.52 (1.42-1.62)	987 / 4194	1.35 (1.25-1.46)	21862 / 91527	1.87 (1.85-1.90)
Frail	111 / 229	2.49 (1.97-3.15)	105 / 224	2.23 (1.71-2.90)	3452 / 5256	3.36 (3.24-3.49)
Per 1 SD	3670 / 21370	1.30 (1.25-1.35)	2731 / 22119	1.23 (1.18-1.29)	49458 / 463266	1.42 (1.41-1.43)
Modified FI-3						

Non-frail	2472 / 16285	1.00 (0.95-1.05)	1635 / 17016	1.00 (0.94-1.06)	25941 / 354276	1.00 (0.99-1.01)
Pre-frail	1094 / 4835	1.33 (1.25-1.42)	1008 / 4844	1.31 (1.21-1.41)	20450 / 103354	1.52 (1.50-1.54)
Frail	104 / 250	2.18 (1.72-2.77)	88 / 259	1.62 (1.23-2.14)	3067 / 5636	2.81 (2.70-2.92)
Per 1 SD	3670 / 21370	1.21 (1.17-1.26)	2731 / 22119	1.19 (1.14-1.24)	49458 / 463266	1.31 (1.30-1.32)

Logistic regression models were adjusted for age, sex, and region; Cox proportional hazard regression models were stratified by age-at-risk, sex, and region.

FI definitions: Original FI = 28-item FI; Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits); Modified FI-2 = 25-item FI (original FI excluding adiposity deficits); Modified FI-3 = 21-item FI (original FI excluding cardiovascular and adiposity deficits)

6.3.3 Reliability and within-person variability of frailty

Among 512,724 participants included at baseline, 19,785 were followed-up at 1st resurvey, 25,068 at 2nd resurvey, and 14,901 at both resurveys. The transitions in frailty status across study waves are shown in **Table 6.6**. Among the participants included in both resurveys (n=14,901), most non-frail participants at baseline either remained non-frail (51%-70%) or became pre-frail (29%-46%) at resurveys. Few participants became frail at the 1st (0.5%) or 2nd (2.9%) resurvey. Similarly, most pre-frail participants at baseline remained pre-frail at 1st (59%) or 2nd (65%) resurveys, with approximately a third (38%) and quarter (25%) regressing to non-frail at the 1st and 2nd resurveys, respectively. In contrast, most participants with frailty at baseline regressed to a less frail state at subsequent resurveys. Of the 372 participants with frailty at baseline, 63% and 57% became pre-frail and 16% and 6% became non-frail in the 1st and 2nd resurveys, respectively.

The reliability estimates of the FI are reported in **Table 6.7**. Using the original FI, the agreement in frailty categorisation across all study waves was modest (ICC [95%CI]: 0.48 [0.39-0.56]). The agreement in frailty was highest (albeit still modest) for analyses using the original FI and lowest for analyses using the mFI-3 as reflected by the weighted kappa scores (0.45 [0.33-0.47] vs 0.31 [0.29-0.33]) and ICC (0.48 [0.39-0.56] vs 0.36 [0.31-0.41]). Consequently, the magnitude of within-person variability was smallest using the original FI and largest using the mFI-3 as reflected by the within-person SD (0.049 [0.049-0.050] vs 0.053 [0.053-0.054]), SEM (0.045 [0.044-0.045] vs 0.049 [0.048-0.050]) and MDC (0.124 [0.122-0.126] vs 0.135 [0.133-0.138]), respectively. For all of the FI versions, the magnitude of MIC

was smaller than MDC e.g. MIC (95%CI) and MDC (95%CI) for the original FI were 0.019 (0.017-0.021) and 0.124 (0.122-0.126), respectively.

Table 6.6 Categorisation of frailty (mFI-1) at baseline and resurvey among participants included in both resurveys (n=14881)

Frailty status at baseline	N	Frailty status at 1 st resurvey				Frailty status at 2 nd resurvey			
		Non-frail	Pre-frail	Frail	Weighted kappa	Non-frail	Pre-frail	Frail	Weighted kappa
Non-frail	8401	5924 (70.5%)	2436 (29.0%)	41 (0.5%)	0.37 (0.35-0.38)	4203 (50.0%)	3909 (46.5%)	289 (3.4%)	0.30 (0.29-0.32)
Pre-frail	6070	2300 (37.9%)	3586 (59.1%)	184 (3.0%)		1447 (23.8%)	3919 (64.6%)	704 (11.6%)	
Frail	410	66 (16.1%)	255 (62.2%)	89 (21.7%)		21 (5.1%)	231 (56.3%)	158 (38.5%)	

FI definition: Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits)

Table 6.7 Agreement and variability estimates (95% CI) of frailty measures between study waves among participants included in 1st and 2nd resurvey (n=14881)

	Original FI	Modified FI-1	Modified FI-2	Modified FI-3
Weighted kappa				
Baseline and 1 st resurvey	0.453 (0.439-0.468)	0.367 (0.352-0.382)	0.377 (0.358-0.396)	0.306 (0.288-0.325)
Baseline and 1 st resurvey	0.356 (0.343-0.370)	0.301 (0.287-0.315)	0.304 (0.289-0.320)	0.262 (0.246-0.278)
1 st and 2 nd resurvey	0.362 (0.349-0.375)	0.302 (0.288-0.316)	0.294 (0.279-0.308)	0.265 (0.249-0.280)
Intraclass correlation coefficient (ICC)				
ICC	0.484 (0.388-0.562)	0.417 (0.356-0.471)	0.427 (0.343-0.499)	0.360 (0.312-0.405)
Within- and between-person variability				
Within-person SD	0.049 (0.049-0.050)	0.052 (0.051-0.052)	0.051 (0.050-0.052)	0.053 (0.053-0.054)
Between-person SD	0.077 (0.076-0.078)	0.073 (0.072-0.074)	0.073 (0.072-0.074)	0.070 (0.069-0.071)
SEM	0.045 (0.044-0.045)	0.048 (0.047-0.049)	0.045 (0.044-0.046)	0.049 (0.048-0.050)
MDC	0.124 (0.122-0.126)	0.133 (0.131-0.135)	0.125 (0.123-0.127)	0.135 (0.133-0.138)
MIC	0.019 (0.017-0.021)	0.021 (0.019-0.023)	0.021 (0.018-0.023)	0.024 (0.021-0.026)

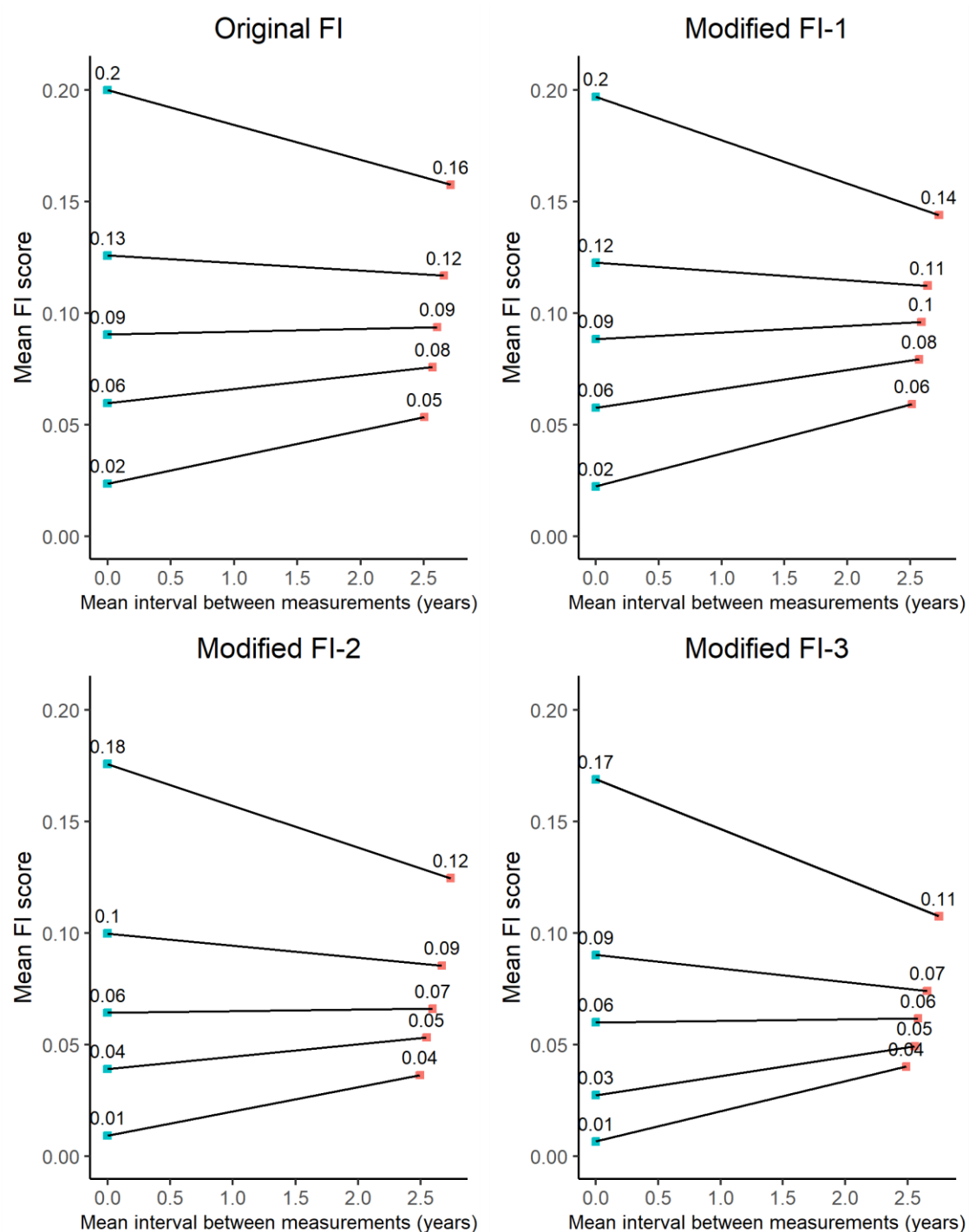
ICC model for the test-retest design used a single-measurement, absolute agreement, 2-way mixed effects model.²⁹³

Abbreviations: ICC=intraclass correlation coefficient; MDC=minimally detectable change; MIC=minimally important change; SD=standard deviation; SEM=standard error of measurement
FI definitions: Original FI = 28-item FI; Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits); Modified FI-2 = 25-item FI (original FI excluding adiposity deficits); Modified FI-3 = 21-item FI (original FI excluding cardiovascular and adiposity deficits)

6.3.4 Estimation of the regression dilution ratio (RDR)

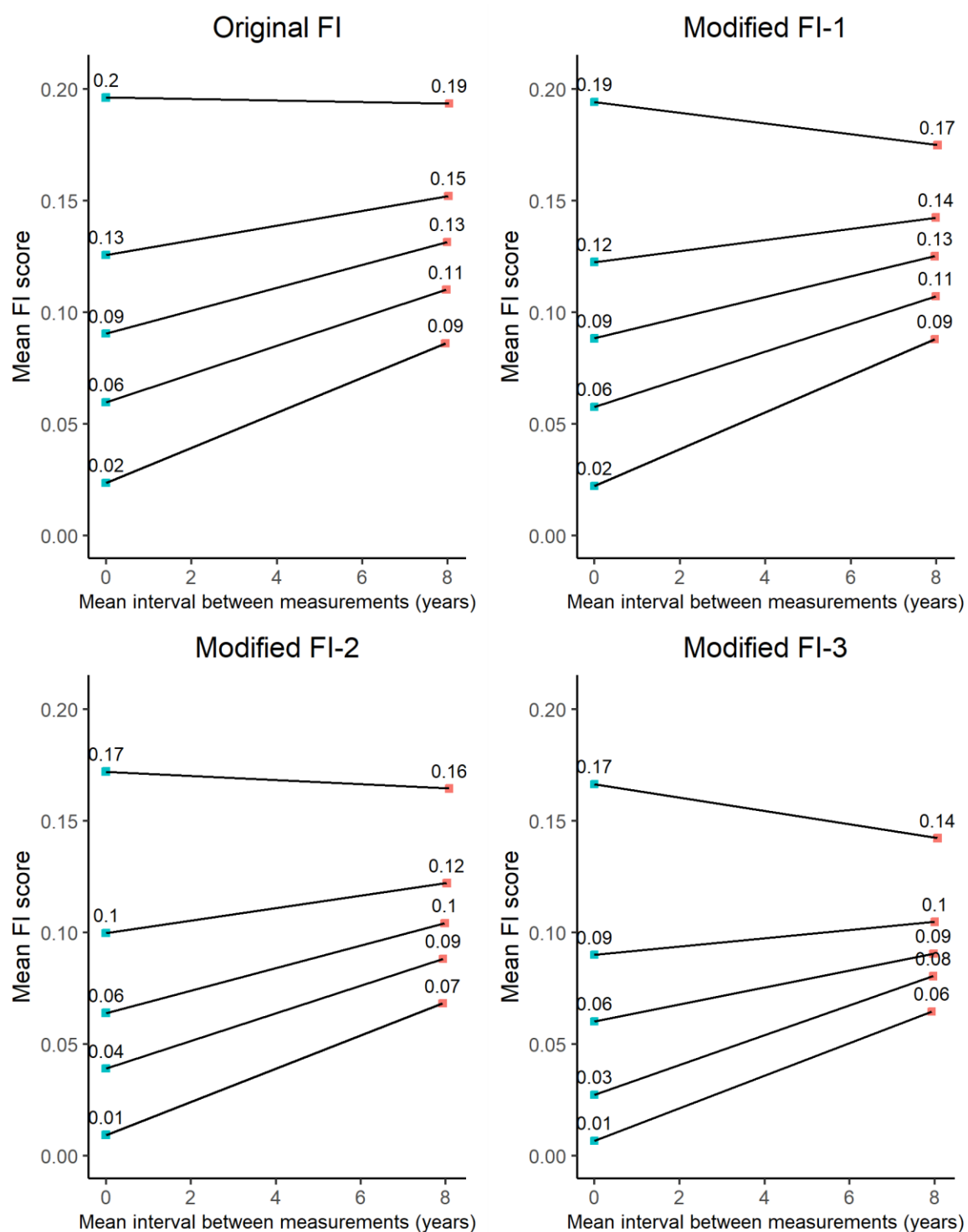
The range of the FI scores (according to quintile groups of baseline FI) is illustrated in **Figure 6.8** at baseline and the 1st resurvey. At baseline, mean original FI score ranged from 0.02 in the lowest quintile group to 0.20 in the highest quintile group. At the 1st resurvey, around 2.5 years later, the corresponding means were 0.05 and 0.16, respectively. The range of the mean FI between the top and bottom quintile groups decreased from 0.18 at baseline to 0.11 at the 1st resurvey, resulting in a RDR of 0.61. The RDRs for the mFI-1, mFI-2, and mFI-3 were 0.44, 0.47, and 0.44, respectively. Using the 2nd resurvey (corresponding plot shown in **Figure 6.9**), the RDRs for the original FI, mFI-1, mFI-2, and mFI-3 were 0.56, 0.47, 0.56, and 0.50, respectively.

Figure 6.8 Mean FI scores at baseline and 1st resurvey by baseline quintile groups of FI



FI definitions: Original FI = 28-item FI; Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits); Modified FI-2 = 25-item FI (original FI excluding adiposity deficits); Modified FI-3 = 21-item FI (original FI excluding cardiovascular and adiposity deficits)

Figure 6.9 Mean FI scores at baseline and 2nd resurvey by baseline quintile groups of FI



FI definitions: Original FI = 28-item FI; Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits); Modified FI-2 = 25-item FI (original FI excluding adiposity deficits); Modified FI-3 = 21-item FI (original FI excluding cardiovascular and adiposity deficits)

6.3.5 Exploratory analysis: improving the FI

Chapter 3 showed that FI scores based on repeat or recent assessments may improve the predictive accuracy of the FI. Hence, whether repeat FI measurements based on ICD-10 codes from CKB's incidence data could improve the accuracy of the FI was explored. However, significant differences in the prevalence of deficits were found between the CKB questionnaire and incidence data. For instance, the prevalence of cancer was 0.5-1.2% in the questionnaire (**Figure 6.5**), but 6.2% in the incidence data (**Figure S6.7**). Also, deficits based on physical measurements, such as BMI, and self-reported symptoms, such as sleep problems, were poorly recorded using ICD-10 codes (prevalence: 0-0.4%). Although hypertension was the most prevalent deficit recorded using either data source, its prevalence using in the questionnaire was much higher than the incidence data (51% vs 16%). Additionally, the recording of these ICD-10 codes throughout the whole follow-up was generally low. Most participants had none of the ICD-10 recorded each year of follow-up (**Figure S6.8**). This meant that repeat FI scores based on ICD-10 codes could not be calculated and would not be comparable to the baseline scores from the questionnaire. Therefore, the attempt to improve the FI through more frequent repeat measurements was not possible.

6.4 Discussion

Data from approximately 0.5M Chinese adults were used for a detailed assessment of the distribution, correlates, and predictive validity of frailty using the FI. Analyses of resurveys in a subset of the available population allowed investigation of the reliability and within-person variability of frailty and estimation of the correction factor to correct for regression dilution bias in subsequent analyses.

6.4.1 Distribution and prevalence of frailty

The most prevalent frailty deficits were related to CVD and adiposity. This was particularly evident when taking into account partial deficits – more than half of the CKB participants were considered to have abnormal BMI or WHR – and explained the lower frailty distribution by the

mFI-2 and mFI-3 that excluded adiposity deficits. The prevalence of individual frailty deficits was generally strongly correlated with age and varied significantly by sex, which was consistent with existing knowledge of higher levels of adiposity in females^{296,297} and higher prevalence of CVD in men.²⁹⁷ The FI had a highly right-skewed distribution with a limit of 0.68, which was consistent with previous studies of Chinese²⁹⁸ and Western cohorts.²⁹⁹ This apparent limit to the number of health deficits that people can tolerate supports the concept of physiological redundancy³⁰⁰ and interrelation of deficits that the FI is based on – “any system with a large amount of accumulated damage can only tolerate a finite amount of additional damage without failure.”²⁹⁹

The prevalence of frailty, however, was less consistent across existing Chinese cohorts mainly due to differences in the populations used. In the relatively young CKB (30-79 years), the prevalence of frailty and pre-frailty according were 3% and 41%, respectively. In the Rugao Longevity and Ageing Study (RuLAS), the prevalence of frailty was much higher at 28% (FI>0.21) in 788 older adults (70-84 years) recruited from rural communities.³⁰¹ Previous systematic reviews of community-dwelling Chinese populations identified a pooled prevalence (95%CI) of 13% (11%-15%)³⁰² and a range of 6% to 17% between individual studies.¹⁴ Differences in the pooled prevalence by the frailty model was also observed, which was 8%, 12%, and 15% for FP, FI, and FRAIL scale, respectively.¹⁴

6.4.2 Construct and criterion validity of frailty

Higher levels of frailty with increasing age are observed universally, regardless of the population or frailty model. In CKB, females had higher levels of frailty than males, which is consistent with previous reports and systematic reviews conducted in China.^{14,302–304} In previous studies, the pooled prevalence of frailty in females versus males was 13% vs 9%³⁰² and 11% vs 8%.¹⁴ It has been widely reported that females live longer than males, but are considered to be frailer, a phenomenon termed the ‘sex-frailty paradox’.³⁰⁵ While the reasons for this phenomenon are uncertain, several biological, behavioural, and social explanations are possible.³⁰⁵ For instance, males appear to be more likely to acquire ‘lethal’ conditions,

such as stroke and MI, and may be less willing to identify and report health issues than females.³⁰⁵ However, a slightly higher prevalence of frailty was observed in men than in women among CKB participants aged <40 years, which could reflect a survivorship bias in men.

Previous studies reported substantial heterogeneity in frailty levels across China. In CKB, while the prevalence of frailty was similar between rural and urban regions overall, significant variations were observed across the 10 study regions. Previous studies have reported conflicting results, reporting a higher prevalence of frailty in urban than in rural regions (11% vs 4%)^{14,304} and vice versa.^{306,307} The conflicting results may reflect real geographical heterogeneity in frailty and differences in the definitions of frailty and rural and urban residents. Another study found specific regional differences, such as ~2-fold higher incidence of frailty in the Northwest (inland areas) versus Southeast (generally coastal areas) of China.^{306,307} In CKB, no such geographical pattern was found. However, the regions with the highest and lowest frailty levels were all rural regions suggesting substantial heterogeneity even within the regions classified as rural.

Increasing levels of education and income were both strongly and inversely associated with frailty in CKB. This likely represents some residual confounding where more affluent participants may have lifestyles that are protective of frailty, including better access to healthcare and better nutritional status and lifestyle. A similar explanation can be given for the lower frailty prevalence in married than in unmarried participants.

Among alcohol consumption and smoking groups, the frailty levels were highest in participants who had quit drinking or smoking. Reverse causality is the most likely explanation for these observed associations as participants with frailty are more likely to quit such behaviours and it is this behaviour change that explains the higher prevalence of frailty in quitters than current drinkers and smokers (as opposed to current drinking and smoking having a protective effect). The potential for reverse causation bias was observed despite excluding participants who had

quit drinking and smoking due to health reasons from the 'ex-regular' categories, suggesting that underlying, subclinical frailty may still influence behaviour.

Frailty was strongly associated with higher risks of adverse outcomes in CKB. The graded associations of frailty with all-cause mortality, hospitalisations, and low grip strength have been reported previously, regardless of the frailty definition used. Similar risks were also reported in Chinese populations. Frailty was associated with 2-fold higher risks of readmission to hospital (OR [95%CI]: 2.03 [1.48-2.79])³⁰⁸ and a 2.31-fold (1.16-4.6) higher risk of all-cause mortality compared to non-frail individuals.³⁰¹

Overall, the patterns of demographic factors and magnitude of associations with adverse outcomes were similar regardless of the definition of FI used in the analyses. However, the magnitude of associations with adverse outcomes attenuated when FI modifications were used. The largest attenuations were observed when cardiovascular deficits were excluded (mFI-1 and mFI-3), which is expected given that IHD and stroke/TIA are lethal diagnoses.

6.4.3 Reliability and within-person variability of frailty

The present chapter found that frailty scores measured by the FI were highly variable within individuals and had poor reliability in CKB. FI scores were associated with within-person variability of around 0.05 or 1½ (1.5/28 = 0.05) deficits. In addition, clinically meaningful changes in frailty equated to approximately ½ (0.5/28 = 0.017) deficit.

The findings of the present study are consistent with recent estimations of within-person variability of the FI. Stolz *et al.* (2019)³⁰⁹ estimated variability of 0.04/0.05 (~2 deficits) from 4,514 older adults in the SHARE study and the present thesis estimated 0.05 (~2 deficits) from 7,455 older adults in TILDA (**Chapter 3**). Although few studies are available, the consistent results with previously reported findings suggest that a single assessment of FI is associated with variability of ~2 deficits within individuals. Given that the threshold for the definition of pre-frail and frail are around 3 and 7.5 deficits, respectively, variability in the score by 2 deficits creates sufficient margin of error in the classification of frailty status. Accordingly, the

agreement in the classification of frailty and FI score was poor (Kappa & ICC <0.5) and regression to the mean in FI scores was observed, particularly in the extremes of the distributions. The reasons for the poor reliability in FI are uncertain. The disease deficits, such as a past diagnosis of stroke or TIA, which do not change with time are likely to be recorded with high reproducibility, but others, such as those related to sleep quality and bowel movements, are inherently variable and individuals may experience different symptoms at different time points. The use of standardised questionnaires, equipment and software to obtain the baseline and resurvey data is likely to have minimised measurement error. Therefore, the variability in FI scores may reflect true fluctuations in frailty state and variability in the participants' self-reported answers to the questionnaire on the day of the assessment.

The reliability of FI was poor irrespective of the FI definition but differed by the number of included deficits in the FI – the reliability of the FI improved with an increasing number of deficits. While this was not hypothesised in the present study, the finding is consistent with a recent simulation analysis that hypothesised that the number of items in the FI may impact its reliability.³¹⁰ Through simulation of 12,000 studies using 70 candidate deficits in 12,080 community-dwelling participants, Nguyen *et al.* (2021)³¹⁰ found that the number of items in FI strongly influenced its reliability; with 5-item FIs having the lowest (ICC=0.19) and 45-item FIs having the highest (ICC=0.84) reliability.

6.4.4 Strengths and limitations

The present chapter reports one of the largest assessments of validity and reliability of FI in China involving approximately 0.5M and 15,000 participants, respectively. In addition, the validity and reliability of different modifications of the FI were compared, providing useful evidence prior to their use in subsequent analyses. Several limitations exist. First, multimorbidity is an important confounder that was not accounted for in the present thesis. As the FI includes several long-term conditions, its adjustment is likely to have resulted in an overadjustment. Thus, whether the increased risks in adverse outcomes associated with frailty (validity assessment) remain after the adjustment of multimorbidity is unknown. Second, the

reliability of frailty scores was assessed using intervals that were longer than typical periods (7-15 days) used in a test-retest design. Consequently, the estimates were not directly comparable to previous reliability studies in Chinese populations. Previous studies have reported high levels of reliability of frailty instruments, including the Groningen Frailty Indicator (ICC=0.87),²⁷⁴ Chinese Comprehensive Frailty Assessment Instrument (ICC=0.90),²⁷⁵ Chinese Tilburg Frailty Indicator ($r=0.88$),²⁷⁶ and Chinese FRAIL scale (ICC=0.708).²⁷⁷ These studies were based on a much smaller number of participants (77-1,235) and a shorter duration of follow-up (7-15 days). However, longer intervals between measurements are likely associated with lower reliability and wider within-person variability, so the estimates of the present chapter are likely an underestimation of reliability. Third, as discussed in **Chapter 3**, the use of different anchors, and differences in the distribution of the anchor and frailty will influence the magnitude of MIC, which also complicate comparisons between studies. While the comparisons of the magnitude of MIC against MDC (within the same study) were useful to assess whether clinically important changes can be distinguished from measurement error, the selection of anchor was somewhat arbitrary and dependent on the availability of an appropriate anchor in the dataset.

6.5 Summary

The present chapter reports one of the largest assessments of the validity and reliability of FI in Chinese adults. The properties of the FI were consistent with the existing literature. FI was a valid frailty measure but had poor reliability and was associated with wide within-person variability, amounting to 1.5 deficits or 0.05 FI score. Analyses also showed regression to the mean in frailty scores over time. In addition, the validity and reliability were compared for different FI modifications, providing useful evidence prior to their use in subsequent analyses. Overall, the different modifications of the FI had good validity showing expected associations with frailty-related constructs and adverse outcomes. Modified FIs has similar overall patterns of associations with demographic factors, but resulted in changes in the strength of associations with covariates and outcomes. For instance, associations with adverse outcomes

attenuated with modifications. Also, modifying the FI had a distinct and noticeable impact on the reliability of instruments, with a smaller the number of items in the FI being associated with lower reliability. Therefore, changes in the FI may have small but noticeable impact on the validity and reliability of the index.

In the following chapters, the prospective associations between CVD RFs and frailty (**Chapter 7**) and frailty and CVD (**Chapter 8**) will be examined. The different modifications of the FI will be used to investigate the presence of circularity in the relationship between frailty and CVD (RFs) and account for some of this circularity in order to estimate more accurate associations. While the modifications of the FI have resulted in valid instruments, the subtle differences in their validity and reliability should be considered when interpreting subsequent analyses. While the FI appears to be a valid frailty instrument and appropriate for use in subsequent analyses, the low reliability and wide within-person variability of the FI is likely to affect the magnitude of subsequent associations of frailty as a predictor variable with disease outcomes (regression dilution bias) (**Chapter 8**). Thus, within-person variability in frailty measurements will be taken account of in subsequent analyses for using the methods introduced in this chapter.

7 Cardiovascular risk factors and risk of frailty

7.1 Introduction

Frailty is an increasing public health burden worldwide. Despite this, there is little reliable evidence on the role of modifiable RFs for frailty. The frequent co-occurrence of frailty and CVD in older people has led to the suggestion that CVD RFs may be potential modifiable RFs for frailty. In China, the prevalence of CVD and associated RFs have increased rapidly in recent decades,³¹¹ reflecting the widespread adoption of Western dietary patterns and sedentary lifestyles. Coupled with a rapidly ageing population, there is an urgent need to clarify the longitudinal effects of CVD RFs on frailty risk.

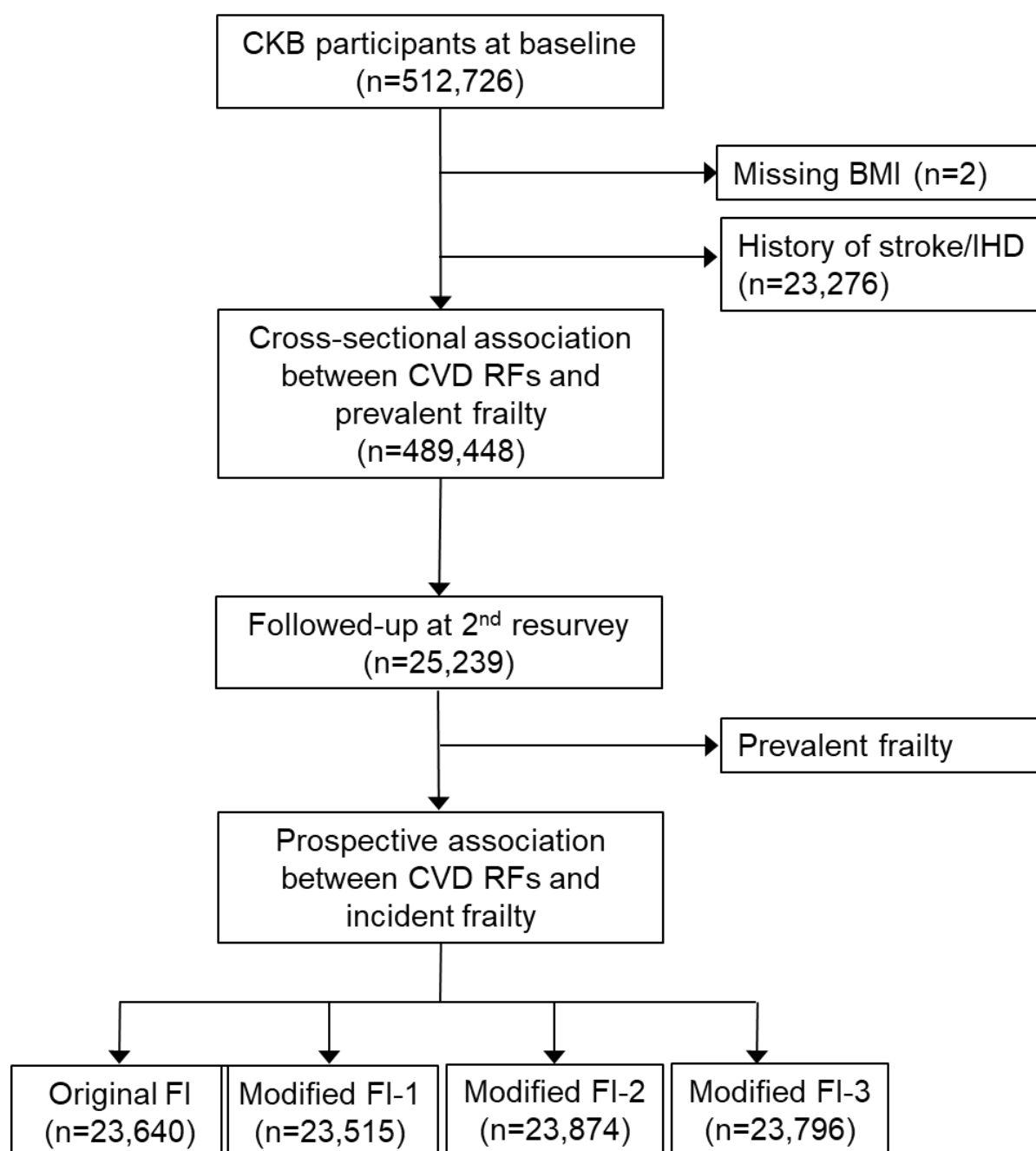
A literature review of the prospective associations of CVD RFs and incident frailty (**Chapter 4**) found that the available evidence is constrained by relatively short durations of follow-up and measurement error in exposures, including misclassification of drinking and smoking status and self-reported diabetes and hypertension. Moreover, much of the available evidence was based on the FP model, so additional evidence replicating the associations using other frailty models is warranted. However, the presence of relevant cardiovascular deficits in the FI raises the risk of circularity in the associations between CVD RF and frailty, which adds to the uncertainty in the evidence.

The objectives of the present chapter are to: (1) investigate the associations of modifiable CVD RFs with risk of frailty using cross-sectional (i.e. prevalent frailty) and prospective (i.e. incident frailty) data; and (2) assess the presence of circularity in these associations from the inclusion of cardiovascular deficits in the FI.

7.2 Methods

The flow diagram of CKB participants selected for this chapter is shown in **Figure 7.1**. The cross-sectional analyses included 489,448 participants and the prospective analyses included 23,650 (9,070 men), 23,515 (9,021 men), 23,874 (9,130 men), and 23,796 (9,106 men) participants involving the original FI, mFI-1, mFI-2, and mFI-3, respectively.

Figure 7.1 Flow diagram of CKB participants selected for this chapter



7.2.1 Definition of CVD RFs and frailty

The definition of individual CVD RFs were described in **Chapter 5**. The CVD RFs studied were alcohol consumption (never-regular, occasional intake, monthly, reduced intake, ex-regular, weekly intake), smoking status (never-regular, occasional, ex-regular, current regular [further divided into <20 cig/d, 20-25 cig/d, ≥25 cig/d]), SBP (mmHg), RPG (mmol/L), lean body mass

(kg), and fat mass (kg). More common adiposity measures like BMI (kg/m^2) and WHR were not studied as these were included as deficits in the FI. Associations of alcohol consumption and smoking status with frailty were reported for men only due to the very low levels of drinking and smoking in Chinese women.

The definition of the FI was described in **Chapter 6**. The inclusion of cardiovascular and adiposity deficits in the FI results in circularity between the exposure (CVD RFs) and outcome (frailty), which means the observed associations between each CVD RF and FI may be inflated due to the inclusion of these deficits rather than a specific effect of the exposure. Therefore, both original (28 deficits) and modified versions of the FI were used to assess the presence of circularity and potential inflation of the associations. These modifications were mFI-1 (24 deficits excluding cardiovascular deficits: IHD, stroke/TIA, diabetes, and hypertension), mFI-2 (25 deficits excluding adiposity deficits: BMI, WHR, and unintentional weight loss), and mFI-3 (21 deficits excluding both cardiovascular and adiposity deficits).

7.2.2 Statistical analyses

Cross-sectional associations

Mean FI scores were compared across levels of alcohol consumption and smoking status and quintiles of SBP, RPG, lean body mass, and fat mass at baseline. The cross-sectional associations between continuous CVD RFs (SBP, RPG, lean body mass, and fat mass) and frailty were visualised to assess the shape of the associations. While positive associations were hypothesised for most factors, an inverse association was expected for lean body mass and a potential U-shaped association for fat mass. To compare the distribution of FI score across groups, the Kruskal-Wallis (for variables with 2 or more levels e.g. smoking status) and Jonckheere-Terpstra (to test for trend across ordinal variables) tests were used. The distribution of frailty categories across groups was tested by the Chi-square test of independence. Logistic regression models were used to estimate the association of each CVD RF with frailty ($\text{FI} \geq 0.25$). The floating absolute risk (FAR) method was used to calculate ORs and group-specific 95% CIs for each OR.³¹² In epidemiological studies, risk estimates are

usually reported with respect to a single reference category (e.g. baseline exposure level). This means that comparing the association between any two groups other than the reference category is difficult. The FAR method provides standard errors and confidence intervals across all pairs of exposure categories, including the reference group, which enables comparisons between any two exposure categories (as opposed to pairwise comparisons with the reference group).³¹²

Prospective associations

Logistic regression was used to assess the associations between each CVD RF at baseline and incident frailty at the 2nd resurvey. ORs (95%CI) were estimated using the FAR method.³¹² All models were adjusted for age, sex, and region, and additionally for income level, education level, marital status, and other CVD RFs (where appropriate). The adjusted estimates were plotted on a log scale against categories or mean levels of the CVD RF.

Sensitivity analysis

The CVD RF and frailty associations were stratified by the 10 study regions (given the large regional differences in the frailty, **Chapter 6**) and displayed in a forest plot to visualise any heterogeneity.

The literature review suggested potential for reverse causation bias in the associations involving CVD RFs and risk of frailty (**Chapter 4**). To explore the potential for this bias, analyses for the prospective associations were restricted to participants who did not die within 2 years of the 2nd resurvey date and to participants who did not report unintentional weight loss and poor self-rated health at baseline.

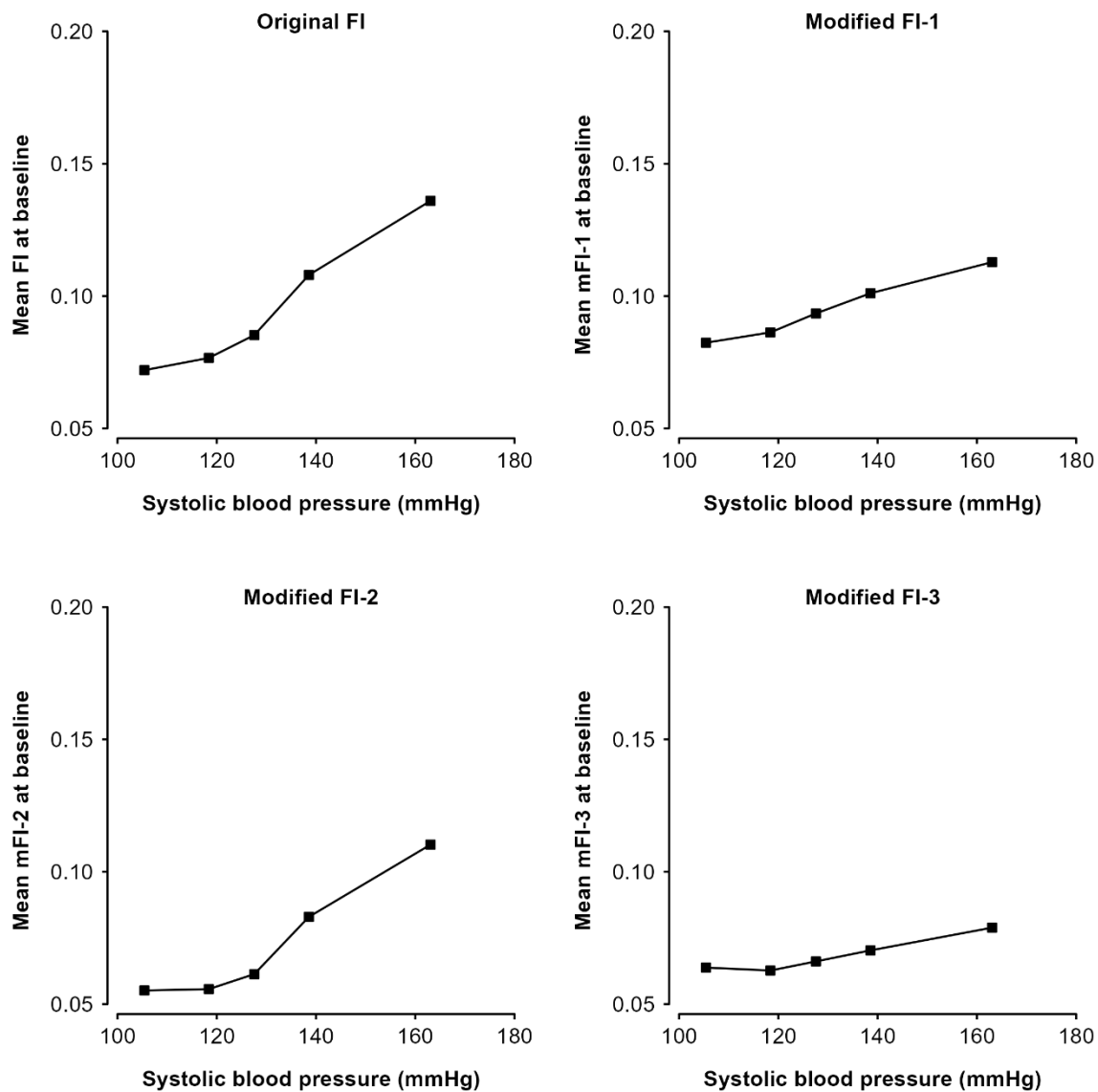
7.3 Results

7.3.1 Cross-sectional associations

The crude, cross-sectional associations between quintiles of CVD RFs (SBP, RPG, fat mass, and lean body mass) and mean FI scores are shown for the original and modified FIs. SBP was strongly and positively associated with mean FI score at baseline (p for trend < 0.001) using the original FI and mFI-2 (albeit on lower average FI levels) (**Figure 7.2**). The positive

associations of SBP and frailty attenuated in magnitude significantly when cardiovascular deficits were excluded from the FI (mFI-1) and attenuated even further when both cardiovascular and adiposity deficits were excluded (mFI-3). However, a positive association remained.

Figure 7.2 Mean FI at baseline by quintiles of systolic blood pressure in 489,448 participants

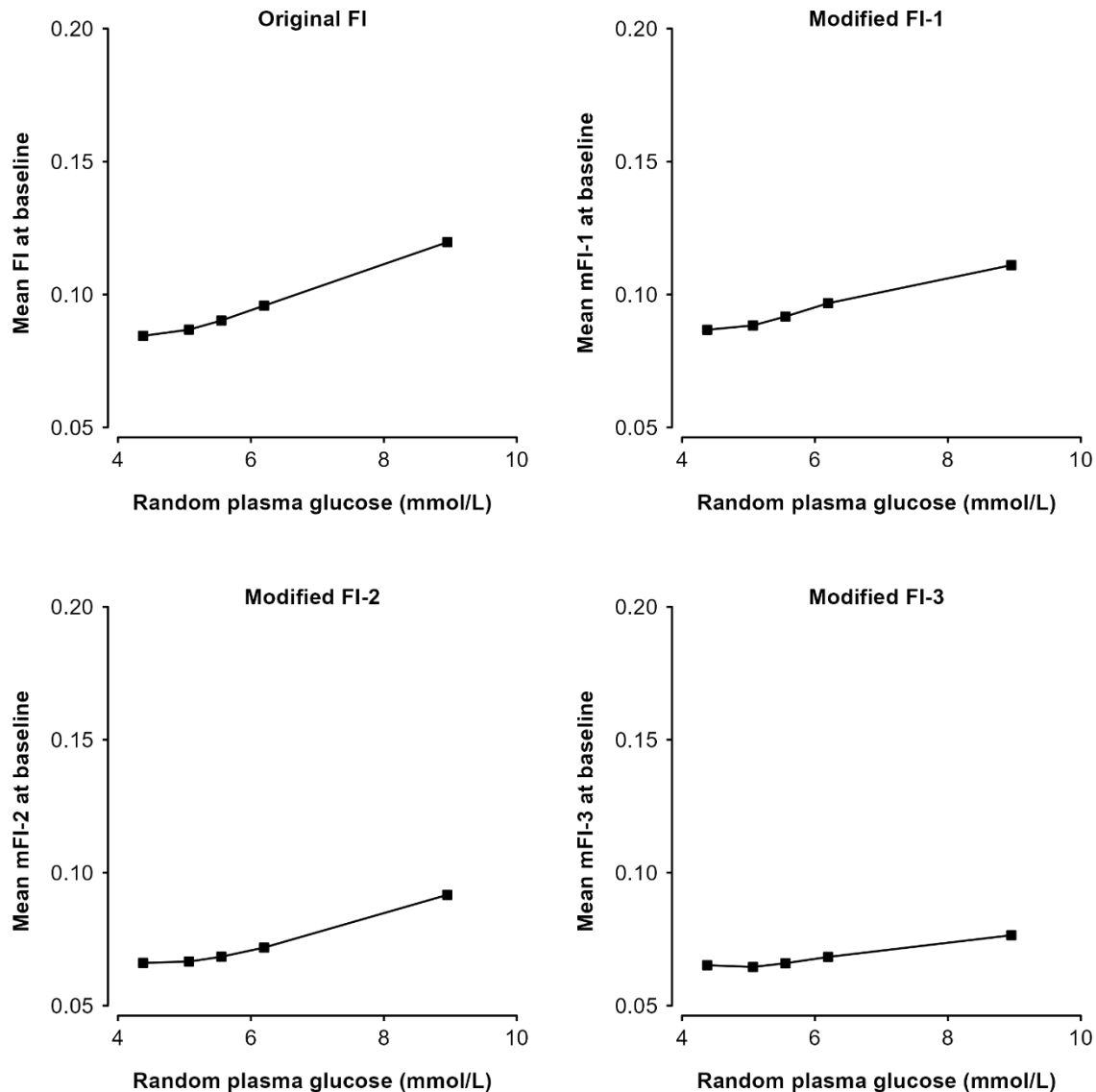


Original FI: 28-item FI; Modified FI-1: 24-item FI (excluding cardiovascular deficits); Modified FI-2: 25-item FI (excluding adiposity deficits); Modified FI-3: 21-item FI (excluding cardiovascular and adiposity deficits)

A similar pattern was found between RPG and frailty at baseline (**Figure 7.3**). The strongest positive association was present between RPG and the original FI (p for trend < 0.001), which

decreased in magnitude after excluding (in approximately increasing order of magnitude) cardiovascular (mFI-1), adiposity (mFI-2), and cardiovascular and adiposity (mFI-3) deficits.

Figure 7.3 Mean FI at baseline by quintiles of random plasma glucose in 489,448 participants

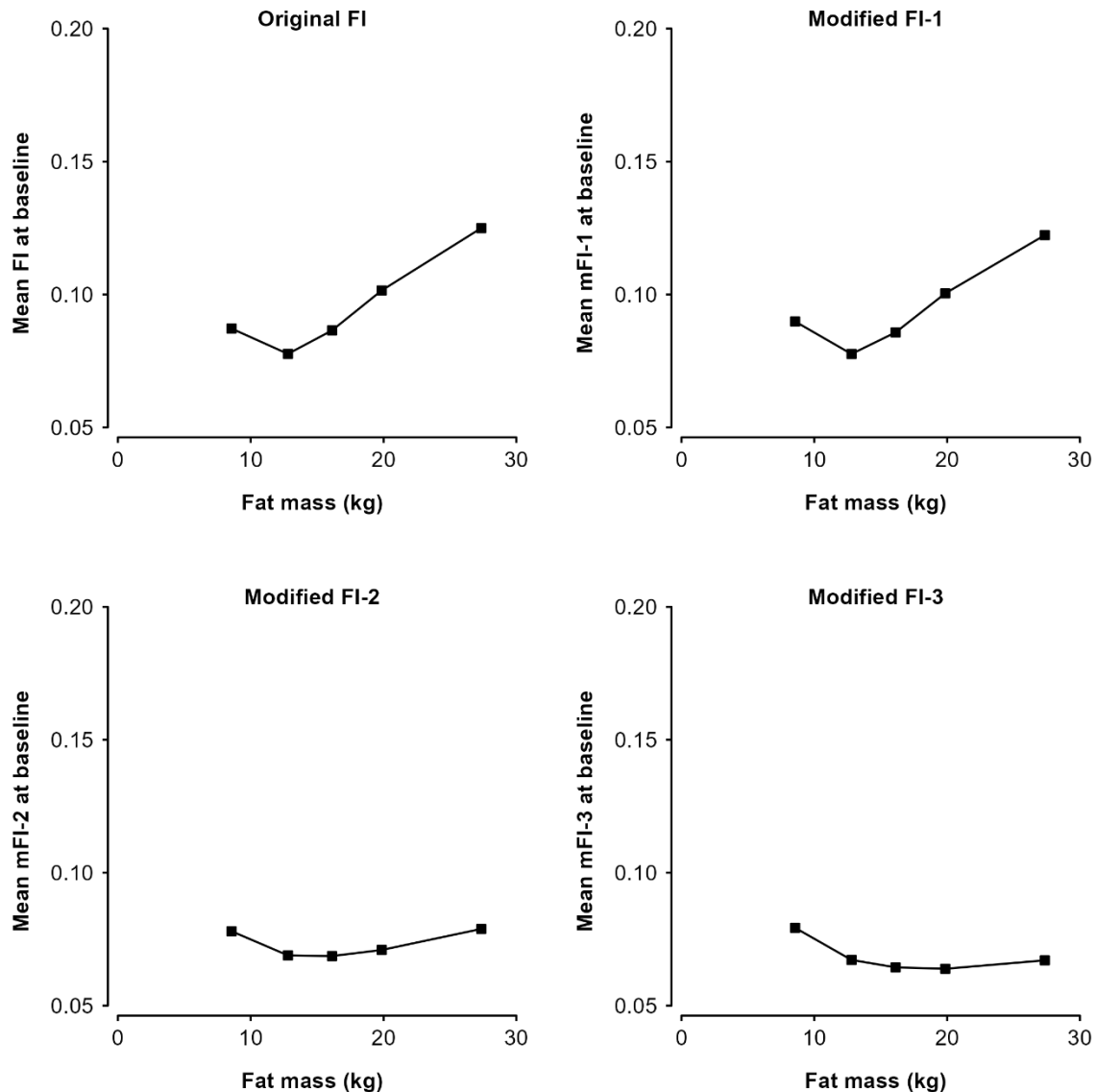


Original FI: 28-item FI; Modified FI-1: 24-item FI (excluding cardiovascular deficits); Modified FI-2: 25-item FI (excluding adiposity deficits); Modified FI-3: 21-item FI (excluding cardiovascular and adiposity deficits)

Using the original FI and mFI-1 definitions, fat mass had a U-shaped association with mean FI score at baseline (**Figure 7.4**): individuals with lower and higher fat mass had higher levels of mean FI scores than those with intermediate fat mass. After excluding adiposity deficits

(mFI-2 and mFI-3), the association between fat mass and frailty attenuated significantly resulting in no clear relationship.

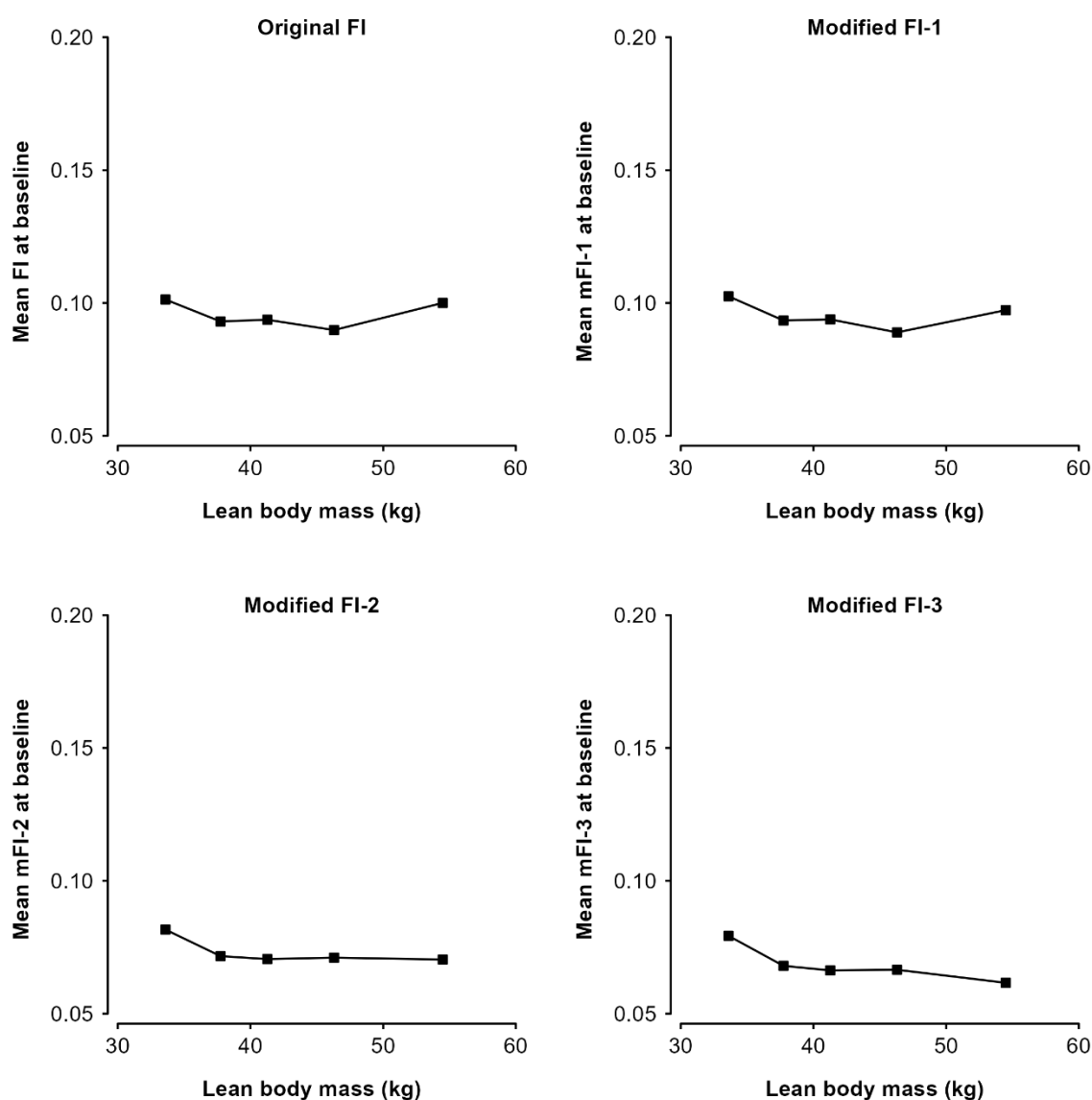
Figure 7.4 Mean FI at baseline by quintiles of fat mass in 489,448 participants



Original FI: 28-item FI; Modified FI-1: 24-item FI (excluding cardiovascular deficits); Modified FI-2: 25-item FI (excluding adiposity deficits); Modified FI-3: 21-item FI (excluding cardiovascular and adiposity deficits)

Weak U-shaped associations were observed between lean body mass and mean FI levels using the original FI and mFI-1, which attenuated in magnitude, becoming flat or inverse, after excluding adiposity deficits (mFI-2 and mFI-3) (**Figure 7.5**).

Figure 7.5 Mean FI at baseline by quintiles of lean body mass in 489,448 participants



Original FI: 28-item FI; Modified FI-1: 24-item FI (excluding cardiovascular deficits); Modified FI-2: 25-item FI (excluding adiposity deficits); Modified FI-3: 21-item FI (excluding cardiovascular and adiposity deficits)

The distributions of FI scores by alcohol consumption and smoking status at baseline are described in **Chapter 6**. A similar pattern was found using the present CKB subset without prior CVD. **Table 7.1** shows that mean FI levels were higher among ex-regular and reduced-intake drinkers and highest in ex-regular smokers than other categories regardless of the FI definition. However, modification of the FI by exclusion of deficits resulted in lower average frailty scores.

Table 7.1 Distribution of the FI at baseline by alcohol consumption and smoking status in 199,576 male participants without history of CVD

	Original FI Mean (SD)	Modified FI-1 Mean (SD)	Modified FI-2 Mean (SD)	Modified FI-3 Mean (SD)
Alcohol consumption (men only)				
Never regular	0.099 (0.063)	0.097 (0.065)	0.076 (0.060)	0.071 (0.063)
Ex-regular	0.127 (0.071)	0.125 (0.077)	0.107 (0.071)	0.101 (0.078)
Occasional	0.091 (0.059)	0.092 (0.061)	0.068 (0.055)	0.066 (0.058)
Monthly	0.086 (0.056)	0.087 (0.058)	0.063 (0.052)	0.061 (0.055)
Reduced-intake	0.117 (0.064)	0.116 (0.067)	0.091 (0.062)	0.084 (0.068)
Weekly	0.092 (0.057)	0.090 (0.059)	0.070 (0.053)	0.063 (0.056)
Never regular	0.099 (0.063)	0.097 (0.065)	0.076 (0.060)	0.071 (0.063)
Smoking status (men only)				
Never smoker	0.095 (0.061)	0.095 (0.063)	0.072 (0.058)	0.067 (0.060)
Occasional	0.096 (0.060)	0.096 (0.062)	0.073 (0.057)	0.068 (0.061)
Ex-regular	0.122 (0.069)	0.119 (0.074)	0.099 (0.070)	0.091 (0.077)
Smoker	0.092 (0.059)	0.092 (0.062)	0.072 (0.056)	0.068 (0.060)

P-values for the Kruskal-Wallis test were all <0.001.

Original FI: 28-item FI; Modified FI-1: 24-item FI (excluding cardiovascular deficits); Modified FI-2: 25-item FI (excluding adiposity deficits); Modified FI-3: 21-item FI (excluding cardiovascular and adiposity deficits)

Table 7.2 shows the ORs of between CVD RFs and frailty at baseline after adjustment for age, sex, and study region. Using the original FI, the positive associations of SBP and RPG with frailty and the U-shaped association of fat mass with frailty were similar to the univariate associations reported above. Higher SBP was associated with frailty: ORs (95%CI) were 1.17 (1.13-1.21) and 2.54 (2.47-2.61) for individuals with 120-139 mmHg and ≥ 140 mmHg, respectively, versus <120 mmHg. Higher RPG was also associated with frailty: ORs (95%CI) were 1.15 (1.11-1.19), 2.11 (1.99-2.24), and 4.68 (4.45-4.91) for individuals with 5.8-7.7 mmol/L, 7.8-11 mmol/L, and ≥ 11 mmol/L, respectively, compared to the baseline group. Having intermediate levels (11.0kg-17.8kg) of fat mass was associated with lower levels of frailty: ORs (95%CI) were 0.64 (0.60-0.67) and 0.84 (0.80-0.89) for individuals in the second (11.0kg-14.5 kg) and third (14.5kg-17.8 kg) quintile of fat mass, respectively, whilst ORs were 1.27 (1.22-1.33) and 2.39 (2.30-2.48) for individuals in the fourth (17.8kg-22.2 kg) and highest (≥ 22 kg) quintiles, respectively. There was no clear association between lean body mass and the original FI. Similar to the univariate associations, higher odds of frailty were observed among ex-regular (OR [95%CI]: 1.92 [1.74-2.13]) and reduced-intake (1.28 [1.15-1.42]) drinkers in men. Additionally, men who were occasional (0.52 [0.49-0.56]), monthly (0.52 [0.44-0.61]), and weekly (0.57 [0.53-0.61]) drinkers had lower odds of being frail than other

categories. Similarly, ex-regular male smokers (2.54 [2.37-2.71]) and men with the highest smoking level (≥ 25 cig/d) (1.22 [1.10-1.34]) had the highest odds of frailty versus other categories.

The associations between alcohol consumption, smoking status with frailty remained similar regardless of the FI modification. Conversely, the strong, positive associations between SBP and RPG with frailty were attenuated substantially after removing cardiovascular deficits from the FI (mFI-1), but remained relatively strong when only the adiposity deficits were excluded (mFI-2). Using the mFI-3, the associations of SBP with frailty reversed in direction – higher levels of SBP were associated with a lower odds of frailty. Similarly, the U-shaped associations of fat mass and frailty attenuated significantly and became inverse using FI modifications. Lastly, excluding cardiovascular and/or adiposity deficits resulted in a clear inverse association between lean body mass and frailty – individuals with higher lean body mass had lower odds of frailty after adjustment for age, sex, and study region. Logistic regression models adjusted for further demographic and CVD RFs found similar patterns (**Table S7.1**).

Table 7.2 Odds ratios (95% CI) of cross-sectional associations between CVD RFs and frailty at baseline in 489,448 participants

	Original FI OR (95% CI)	Modified FI-1 OR (95% CI)	Modified FI-2 OR (95% CI)	Modified FI-3 OR (95% CI)
Alcohol consumption (men only)				
Never regular	1.00 (0.94-1.07)	1.00 (0.94-1.06)	1.00 (0.92-1.08)	1.00 (0.93-1.07)
Ex-regular	1.92 (1.74-2.13)	1.82 (1.66-2.00)	1.82 (1.61-2.07)	1.76 (1.57-1.96)
Occasional	0.52 (0.49-0.56)	0.54 (0.51-0.58)	0.47 (0.42-0.51)	0.50 (0.46-0.54)
Monthly	0.52 (0.44-0.61)	0.50 (0.43-0.58)	0.40 (0.31-0.52)	0.41 (0.34-0.51)
Reduced-intake	1.28 (1.15-1.42)	1.18 (1.07-1.30)	1.12 (0.97-1.29)	1.05 (0.93-1.19)
Weekly	0.57 (0.53-0.61)	0.55 (0.51-0.58)	0.50 (0.46-0.55)	0.50 (0.47-0.55)
Smoking status (men only)				
Never smoker	1.00 (0.91-1.10)	1.00 (0.92-1.09)	1.00 (0.88-1.13)	1.00 (0.90-1.11)
Occasional	1.01 (0.90-1.12)	0.97 (0.88-1.07)	0.96 (0.83-1.12)	0.97 (0.86-1.10)
Ex-regular	2.54 (2.37-2.71)	2.51 (2.35-2.67)	2.65 (2.44-2.89)	2.57 (2.38-2.77)
<20 cig/d	1.03 (0.97-1.10)	1.05 (1.00-1.11)	1.02 (0.94-1.11)	1.04 (0.97-1.11)
20-25 cig/d	1.04 (0.95-1.12)	1.08 (1.01-1.16)	1.00 (0.89-1.12)	1.05 (0.96-1.15)
≥25 cig/d	1.22 (1.10-1.34)	1.26 (1.16-1.37)	1.14 (0.99-1.30)	1.11 (0.99-1.24)
Systolic blood pressure (mmHg)				
<120	1.00 (0.95-1.05)	1.00 (0.96-1.04)	1.00 (0.93-1.07)	1.00 (0.95-1.05)
120-139	1.17 (1.13-1.21)	0.95 (0.92-0.98)	0.94 (0.90-0.99)	0.79 (0.76-0.82)
≥140	2.54 (2.47-2.61)	1.02 (0.99-1.05)	1.85 (1.78-1.93)	0.70 (0.67-0.73)
Random plasma glucose (mmol/L)				
<5.8	1.00 (0.97-1.03)	1.00 (0.97-1.03)	1.00 (0.96-1.04)	1.00 (0.97-1.03)
5.8-7.7	1.15 (1.11-1.19)	1.05 (1.02-1.08)	0.97 (0.93-1.02)	0.90 (0.87-0.94)
7.8-11	2.11 (1.99-2.24)	1.38 (1.30-1.47)	1.54 (1.41-1.68)	0.97 (0.89-1.06)
≥11	4.68 (4.45-4.91)	2.12 (2.00-2.24)	3.38 (3.15-3.63)	1.51 (1.39-1.64)
Fat mass (kg) quintile				
1 (<11.0)	1.00 (0.96-1.05)	1.00 (0.96-1.04)	1.00 (0.95-1.06)	1.00 (0.96-1.05)
2 (11.0-14.5)	0.64 (0.60-0.67)	0.54 (0.51-0.57)	0.70 (0.66-0.75)	0.60 (0.57-0.63)
3 (14.5-17.8)	0.84 (0.80-0.89)	0.65 (0.62-0.68)	0.69 (0.64-0.74)	0.52 (0.49-0.55)
4 (17.8-22.2)	1.27 (1.22-1.33)	0.91 (0.87-0.94)	0.79 (0.73-0.84)	0.54 (0.51-0.57)
5 (≥22.2)	2.39 (2.30-2.48)	1.48 (1.43-1.53)	0.99 (0.93-1.06)	0.61 (0.57-0.64)
Lean body mass (kg) quintile				
1 (<36.1)	1.00 (0.95-1.05)	1.00 (0.96-1.04)	1.00 (0.93-1.07)	1.00 (0.94-1.06)
2 (36.1-39.4)	0.90 (0.86-0.94)	0.83 (0.80-0.87)	0.76 (0.71-0.81)	0.68 (0.64-0.72)
3 (39.4-43.4)	1.00 (0.96-1.04)	0.85 (0.82-0.88)	0.70 (0.66-0.74)	0.59 (0.56-0.62)
4 (43.4-49.5)	0.95 (0.89-1.00)	0.71 (0.67-0.75)	0.58 (0.53-0.63)	0.43 (0.40-0.46)
5 (≥49.5)	1.30 (1.22-1.40)	0.79 (0.75-0.85)	0.52 (0.47-0.57)	0.33 (0.30-0.36)

Logistic regression models were adjusted for age, sex, and region.

Original FI: 28-item FI; Modified FI-1: 24-item FI (excluding cardiovascular deficits); Modified FI-2: 25-item FI (excluding adiposity deficits); Modified FI-3: 21-item FI (excluding cardiovascular and adiposity deficits)

Given the diversity within CKB, the ORs (95%CI) of the cross-sectional associations between CVD RFs and frailty at baseline were shown by the 10 CKB study regions (**Figure 7.6**). There were only modest differences in the patterns of the associations between each CVD RF and frailty (original FI) by study region. Across all 10 study regions, ex-regular drinkers and smokers had the highest odds of frailty; SBP and RPG had strong positive associations with frailty; fat mass had a U-shaped association with frailty; but there was no clear association between lean body mass and frailty. However, there was some differences in the strength of

associations by study region. For instance, the positive association between ex-regular drinking (vs never drinkers) and prevalent frailty was strongest in Haikou (urban) with an age and sex adjusted OR (95%CI) of 6.44 (4.24-9.78) compared to the weakest in Henan (rural) where there was no association (1.19 [0.69-2.06]). The strength of associations between ex-regular smoking or smoking ≥ 25 cig/d (vs never smoking) with prevalent frailty also differed by region. The associations were strongest in Qingdao (urban) (ex-regular smoker 5.09 [3.69-7.00] & ≥ 25 cig/d 5.52 [3.53-8.63]); weakest in Zhejiang (rural) (ex-regular smoker 1.77 [1.46-2.14] & ≥ 25 cig/d 0.73 [0.51-1.05]); but similar in other regions. Similarly, the associations of baseline SBP (≥ 140 mmHg vs < 120 mmHg) and frailty were strongest in Qingdao (urban) (4.65 [4.02-5.38]) and weakest in Zhejiang (rural) (1.87 [1.72-2.03]). In addition, these associations were generally stronger in urban (OR range: 2.17-4.65) versus rural (OR range: 1.87-3.20) regions. For RPG (≥ 11 mmol/L vs < 5.8 mmol/L), the strongest association was seen in Hunan (rural) (7.43 [6.14-8.99]) and the weakest in Sichuan (rural) (2.97 [2.70-3.27]). The association between fat mass varied to a lesser degree and the lack of association between lean body mass and frailty was consistent across all study regions. The patterns of associations by region were broadly similar irrespective of whether frailty was measured using the modified FI-1 (**Figure S7.1**), modified-FI-2 (**Figure S7.2**), or modified FI-3 (**Figure S7.3**).

Figure 7.6 Odds ratios (95% CI) of cross-sectional associations between CVD RFs and frailty (original FI) at baseline in 489,448 participants by the 10 CKB study regions

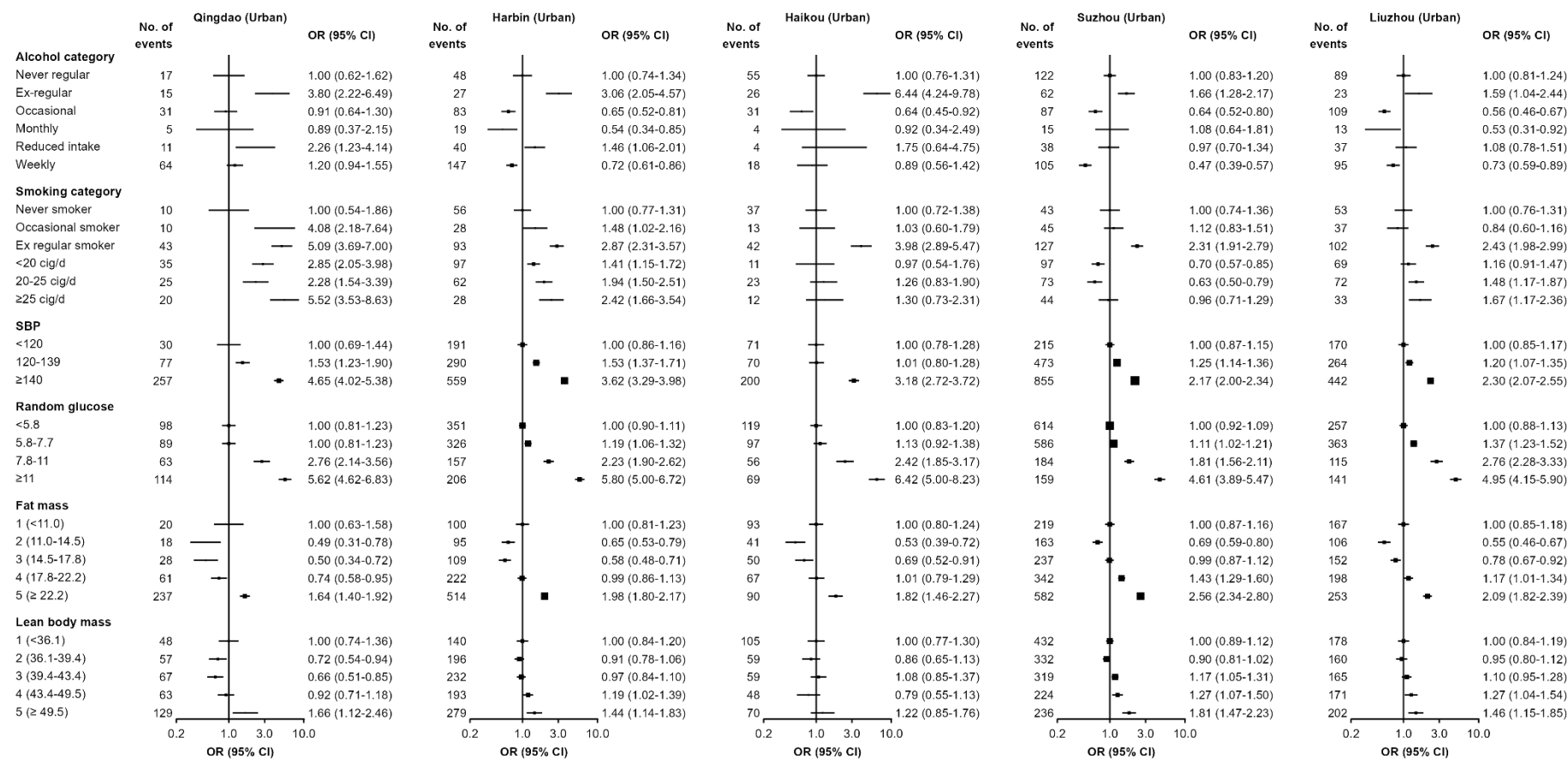
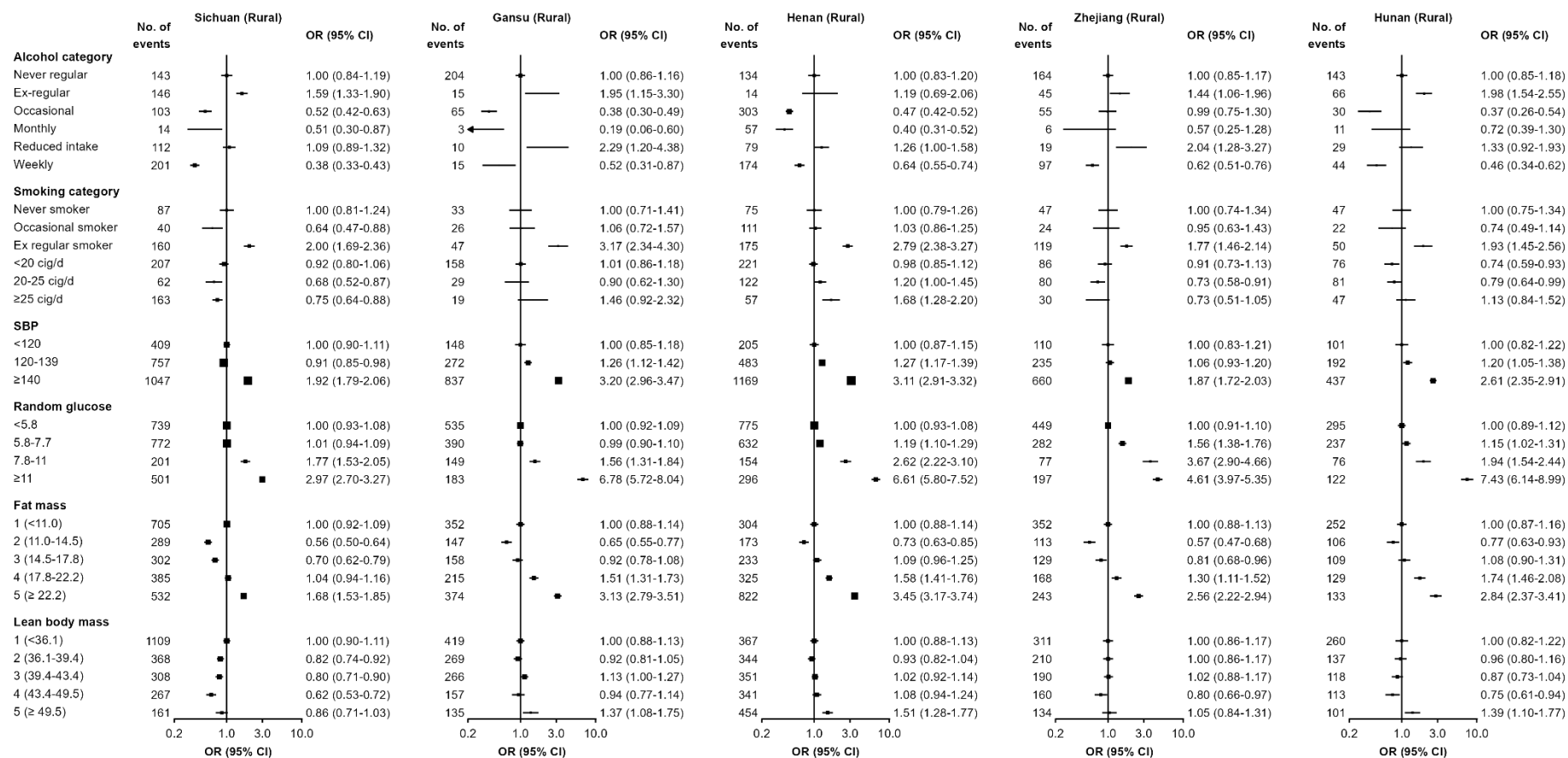


Figure 7.6 continued



Logistic regression models were adjusted for age and sex.

7.3.2 Prospective associations

Among 23,874 participants without prior frailty and CVD at baseline, 1,674 participants became frail at the 2nd resurvey (mean 8 years follow-up). The ORs (95%CI) of the adjusted associations between CVD RFs and incident frailty were presented in **Table 7.3** and illustrated as figures separately for each of the CVD RFs.

Table 7.3 Odds ratios (95% CI) of prospective associations between baseline CVD RFs and incident frailty at 2nd resurvey in ~24,000 participants

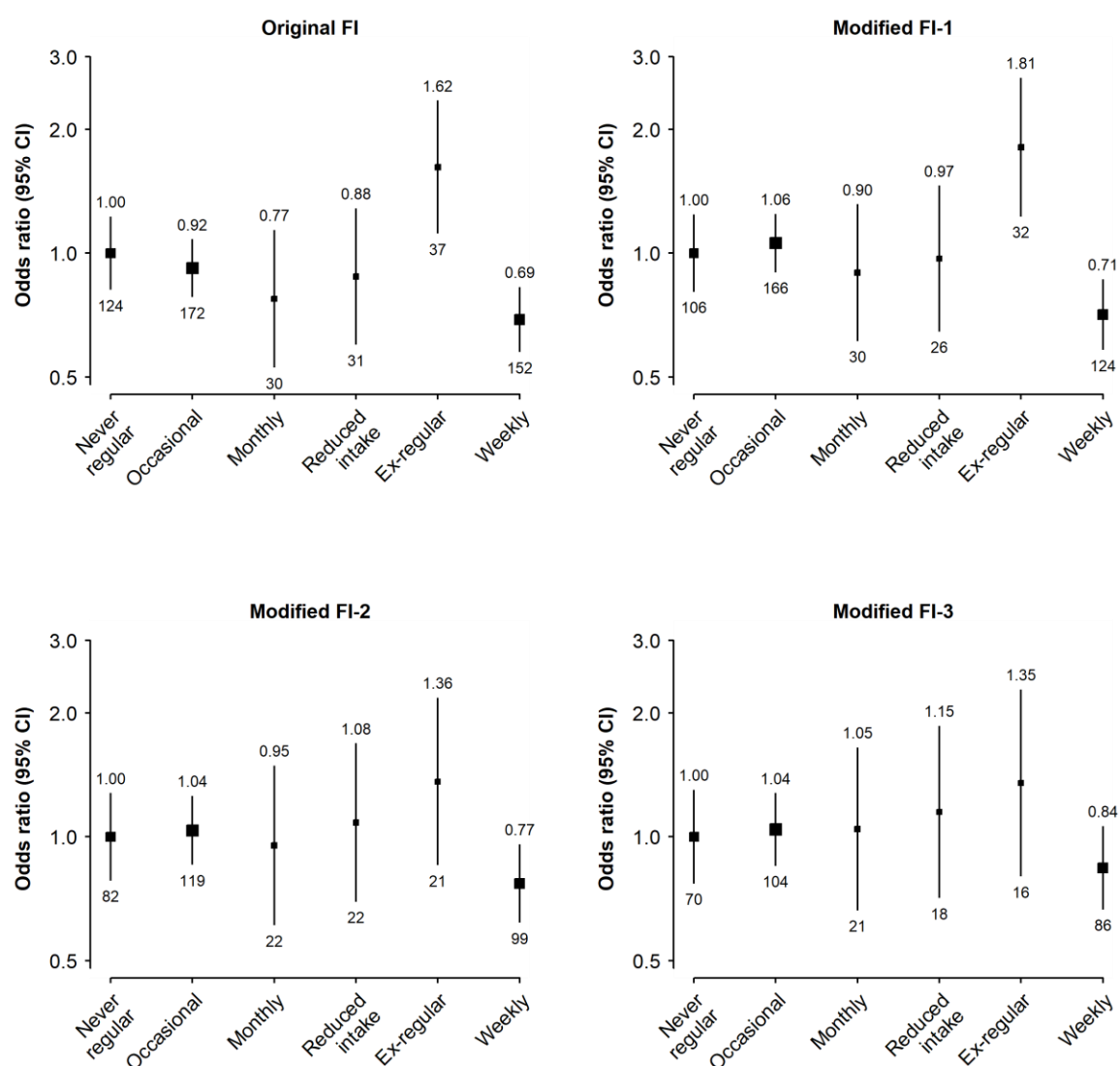
	Original FI		Modified FI-1		Modified FI-2		Modified FI-3	
	No. frail	OR (95% CI)	No. frail	OR (95% CI)	No. frail	OR (95% CI)	No. frail	OR (95% CI)
Alcohol consumption (men only)								
Never	124	1.00 (0.81-1.23)	106	1.00 (0.81-1.24)	82	1.00 (0.78-1.28)	70	1.00 (0.77-1.30)
regular								
Ex-regular	37	1.62 (1.12-2.35)	32	1.81 (1.23-2.67)	21	1.36 (0.85-2.18)	16	1.35 (0.80-2.28)
Occasional	172	0.92 (0.78-1.08)	166	1.06 (0.90-1.25)	119	1.04 (0.85-1.26)	104	1.04 (0.85-1.28)
Monthly	30	0.77 (0.53-1.14)	30	0.90 (0.61-1.32)	22	0.95 (0.61-1.49)	21	1.05 (0.66-1.65)
Reduced intake	31	0.88 (0.60-1.29)	26	0.97 (0.64-1.46)	22	1.08 (0.69-1.69)	18	1.15 (0.71-1.86)
Weekly	152	0.69 (0.57-0.83)	124	0.71 (0.58-0.86)	99	0.77 (0.62-0.96)	86	0.84 (0.67-1.06)
Smoking status (men only)								
Never	84	1.00 (0.79-1.27)	70	1.00 (0.78-1.29)	52	1.00 (0.75-1.34)	45	1.00 (0.73-1.37)
Occasional	51	0.93 (0.69-1.24)	44	0.90 (0.66-1.23)	28	0.81 (0.55-1.18)	25	0.74 (0.49-1.11)
Ex-regular	93	1.71 (1.36-2.17)	73	1.59 (1.23-2.06)	64	1.84 (1.40-2.42)	45	1.51 (1.10-2.07)
<20 cig/d	141	1.05 (0.88-1.26)	131	1.07 (0.89-1.28)	104	1.17 (0.95-1.44)	90	1.01 (0.81-1.26)
20-25 cig/d	103	1.05 (0.86-1.29)	104	1.17 (0.95-1.43)	72	1.14 (0.89-1.45)	70	1.10 (0.86-1.41)
≥25 cig/d	74	1.55 (1.21-2.00)	62	1.42 (1.09-1.86)	45	1.54 (1.13-2.11)	40	1.29 (0.93-1.80)
Systolic blood pressure (mmHg)								
<120	286	1.00 (0.88-1.14)	392	1.00 (0.89-1.12)	194	1.00 (0.86-1.17)	259	1.00 (0.87-1.15)
120-139	622	1.44 (1.33-1.56)	580	0.98 (0.90-1.06)	373	1.31 (1.18-1.44)	328	0.89 (0.80-0.99)
≥140	766	1.92 (1.76-2.10)	582	1.03 (0.94-1.14)	462	1.68 (1.51-1.88)	330	0.96 (0.84-1.09)
Random plasma glucose (mmol/L)								
<5.8	845	1.00 (0.93-1.08)	854	1.00 (0.93-1.08)	539	1.00 (0.91-1.10)	527	1.00 (0.91-1.10)
5.8-7.7	574	1.11 (1.02-1.21)	524	1.03 (0.94-1.12)	334	1.02 (0.91-1.13)	295	0.96 (0.85-1.08)
7.8-11	147	1.49 (1.25-1.79)	106	1.12 (0.91-1.37)	91	1.43 (1.15-1.79)	60	1.06 (0.81-1.39)
≥11	108	2.06 (1.65-2.56)	70	1.18 (0.91-1.53)	65	1.82 (1.39-2.37)	35	0.95 (0.67-1.35)
Fat mass (kg) quintile (mean of quintile group)								
1 (9)	219	1.00 (0.85-1.18)	235	1.00 (0.85-1.17)	175	1.00 (0.83-1.21)	201	1.00 (0.84-1.19)
2 (13)	227	1.08 (0.94-1.25)	232	1.07 (0.93-1.22)	177	1.07 (0.91-1.25)	180	0.93 (0.79-1.08)
3 (16)	275	1.29 (1.14-1.46)	273	1.29 (1.14-1.46)	181	1.06 (0.91-1.23)	167	0.85 (0.73-0.99)
4 (20)	351	1.70 (1.52-1.90)	305	1.49 (1.32-1.67)	201	1.19 (1.03-1.38)	159	0.84 (0.71-0.99)
5 (27)	600	2.89 (2.60-3.21)	507	2.49 (2.23-2.78)	293	1.63 (1.42-1.89)	208	1.08 (0.92-1.28)
Lean body mass (kg) quintile (mean of quintile group)								
1 (34)	356	1.00 (0.87-1.15)	347	1.00 (0.87-1.15)	230	1.00 (0.84-1.19)	230	1.00 (0.84-1.20)
2 (38)	369	1.04 (0.92-1.17)	349	1.02 (0.91-1.15)	214	1.03 (0.89-1.20)	205	1.05 (0.90-1.22)
3 (41)	363	1.10 (0.99-1.22)	353	1.09 (0.98-1.22)	221	1.18 (1.03-1.35)	185	1.02 (0.88-1.17)
4 (46)	265	1.01 (0.86-1.17)	253	0.96 (0.82-1.13)	165	0.99 (0.81-1.20)	141	0.83 (0.68-1.03)
5 (54)	319	1.18 (0.95-1.45)	250	0.96 (0.77-1.20)	197	1.17 (0.91-1.51)	154	1.00 (0.77-1.32)

Logistic regression models were adjusted for age, sex, region, income level, education level, alcohol consumption, smoking status, systolic blood pressure, random plasma glucose, fat mass, and lean body mass, where appropriate.

Original FI: 28-item FI; Modified FI-1: 24-item FI (excluding cardiovascular deficits); Modified FI-2: 25-item FI (excluding adiposity deficits); Modified FI-3: 21-item FI (excluding cardiovascular and adiposity deficits)

In men, the pattern of the association between baseline alcohol consumption and risk of incident frailty was similar across FI definitions (**Figure 7.7**). Using the original FI, weekly consumption of alcohol was associated with lower risk of frailty (OR [95%CI]: 0.69 [0.57-0.83]) and ex-regular drinkers had higher risk of incident frailty (1.62 [1.12-2.35]). Using the modified FI definitions, these associations attenuated slightly but remained directionally consistent with the above results.

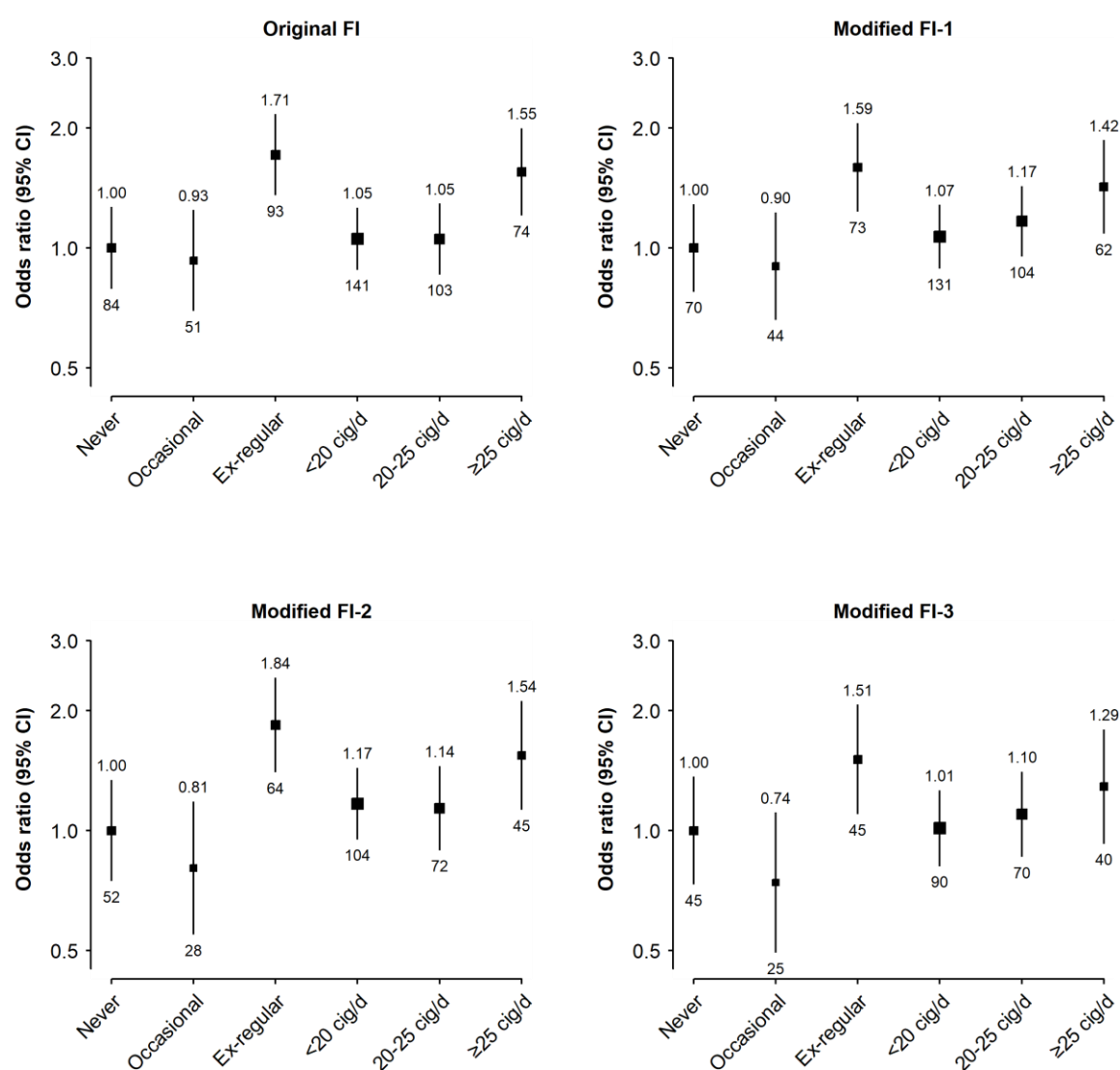
Figure 7.7 Odds ratios (95% CI) of prospective associations between baseline alcohol consumption and incident frailty at 2nd resurvey in ~9,000 male participants by FI type



Original FI: 28-item FI; Modified FI-1: 24-item FI (excluding cardiovascular deficits); Modified FI-2: 25-item FI (excluding adiposity deficits); Modified FI-3: 21-item FI (excluding cardiovascular and adiposity deficits)

In men, the pattern of the association between smoking status and incident frailty was similar across frailty definitions (**Figure 7.8**). Using the original FI, only ex-regular smokers (OR [95%CI]: 1.71 [1.36-2.17]) and smokers of ≥ 25 cig/d (1.55 [1.21-2.00]) were associated with incident frailty. Associations became stronger when only adiposity deficits were excluded (mFI-2): the corresponding ORs (95%CI) were 1.84 (1.40-2.42), and 1.54 (1.13-2.11), respectively. Conversely, the associations attenuated when cardiovascular deficits were excluded from the FI (mFI-1 or mFI-3): the corresponding ORs (95%CI) were 1.51 (1.10-2.07) and 1.29 (0.93-1.80), respectively.

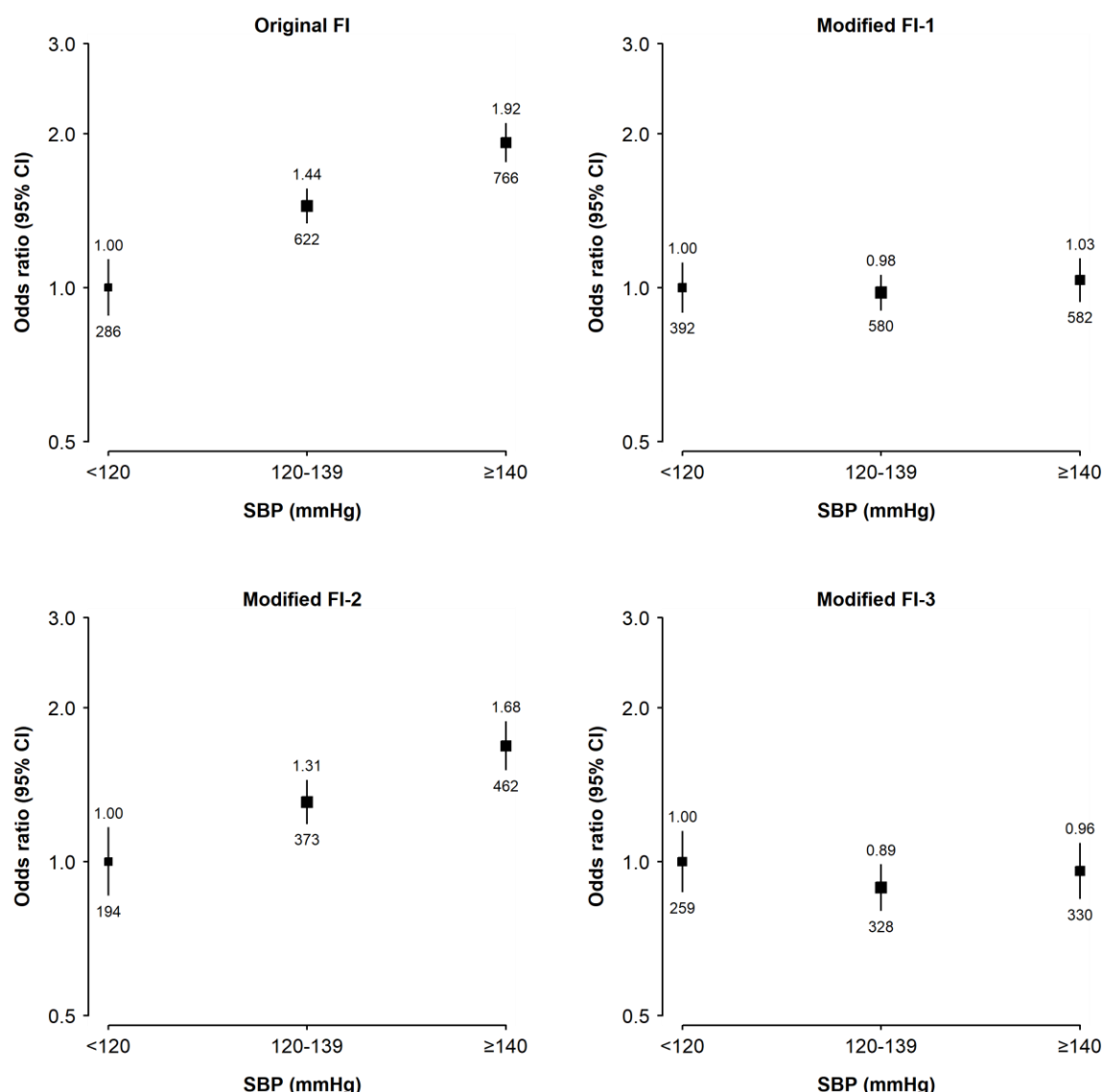
Figure 7.8 Odds ratios (95% CI) of prospective associations between baseline smoking status and incident frailty at 2nd resurvey in ~9,000 male participants by FI type



Original FI: 28-item FI; Modified FI-1: 24-item FI (excluding cardiovascular deficits); Modified FI-2: 25-item FI (excluding adiposity deficits); Modified FI-3: 21-item FI (excluding cardiovascular and adiposity deficits)

The associations between baseline SBP and incident frailty differed markedly depending on which version of the FI was utilised (**Figure 7.9**). Using the original FI, SBP had positive, log-linear associations with incident frailty at the 2nd resurvey. Compared to the SBP <120 mmHg group, those with 120-139 mmHg and $\geq$ 140 mmHg had 44% (33%-56%) and 92% (76%-210%), respectively, higher risk of incident frailty. The log-linear association attenuated only slightly when the adiposity deficits were excluded (mFI-2), but disappeared when cardiovascular deficits were removed (mFI-1 or mFI-3). Using mFI-3, the corresponding ORs (95%CI) were 0.89 (0.80-0.99) and 0.96 (0.84-1.09) for 120-139 mmHg and $\geq$ 140 mmHg groups, respectively, compared to the <120 mmHg group.

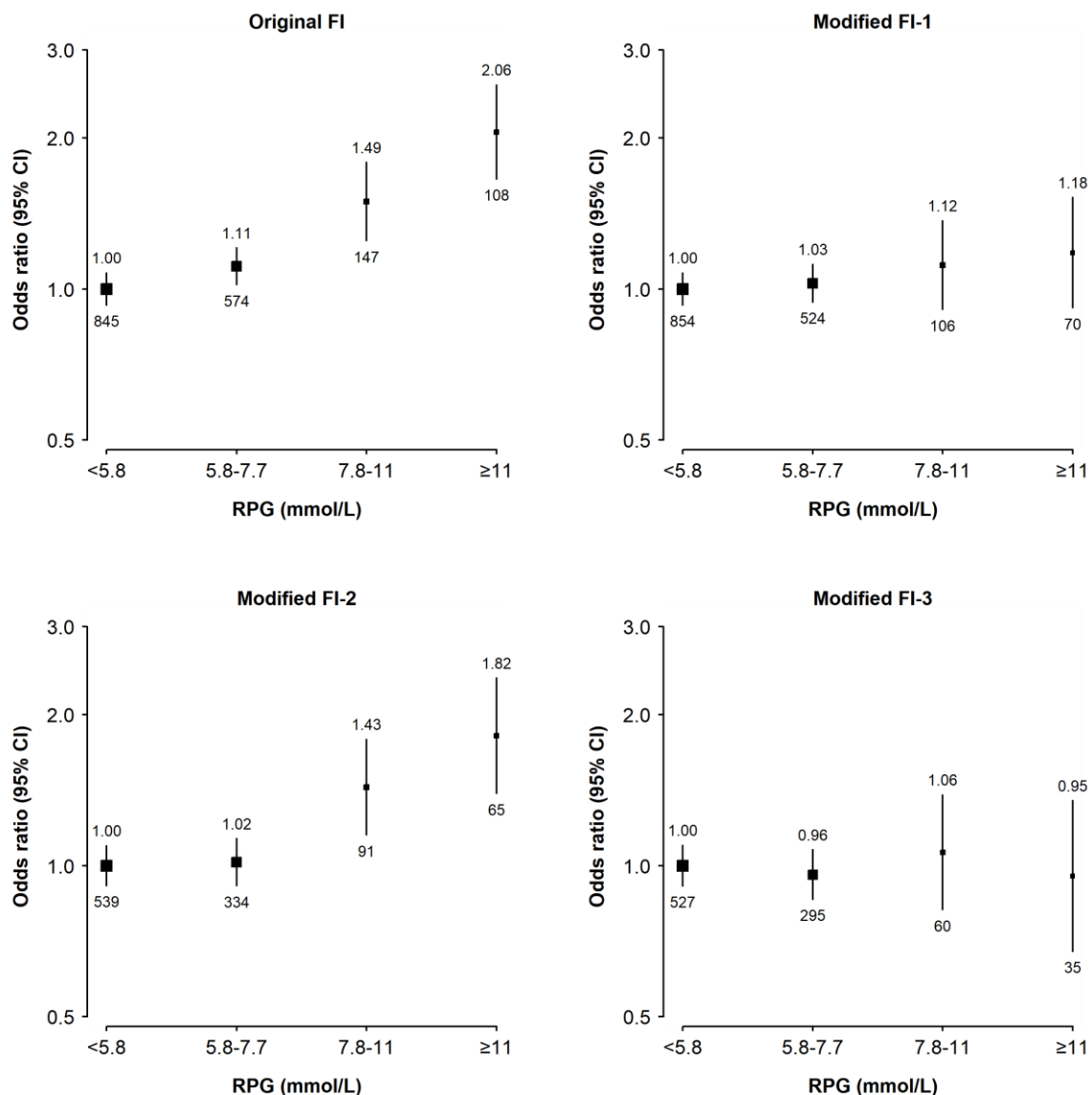
Figure 7.9 Odds ratios (95% CI) of prospective associations between baseline systolic blood pressure and incident frailty at 2nd resurvey in ~24,000 participants by FI type



Original FI: 28-item FI; Modified FI-1: 24-item FI (excluding cardiovascular deficits); Modified FI-2: 25-item FI (excluding adiposity deficits); Modified FI-3: 21-item FI (excluding cardiovascular and adiposity deficits)

Similarly, the association between baseline RPG and incident frailty differed by the FI definition (**Figure 7.10**). Using the original FI, RPG had a positive, log-linear association with incident frailty. Compared to individuals with low RPG (<5.8 mmol/L), those in the 5.8-7.7 mmol/L, 7.8-11 mmol/L and ≥11 mmol/L groups had ORs (95%CI) of 1.11 (1.02-1.21), 1.49 (1.25-1.79), and 2.06 (1.65-2.56) for incident frailty. These associations were similar using the mFI-2 definition but attenuated to the null using the mFI-1 or mFI-3 definition.

Figure 7.10 Odds ratios (95% CI) of prospective associations between baseline random plasma glucose and incident frailty at 2nd resurvey in ~24,000 participants by FI type

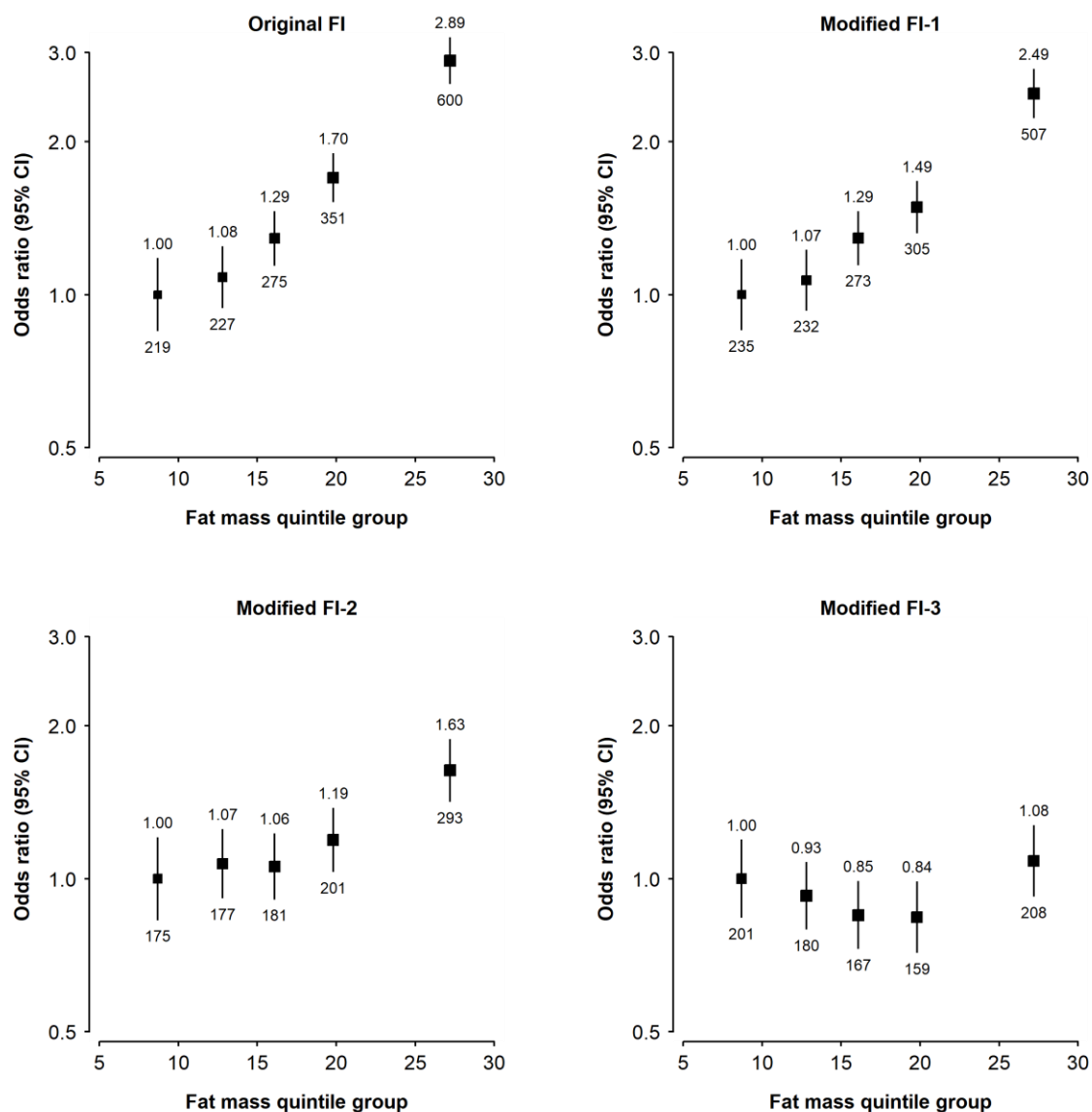


Original FI: 28-item FI; Modified FI-1: 24-item FI (excluding cardiovascular deficits); Modified FI-2: 25-item FI (excluding adiposity deficits); Modified FI-3: 21-item FI (excluding cardiovascular and adiposity deficits)

The association between baseline fat mass and incident frailty also differed by definition (**Figure 7.11**). Using the original FI, fat mass had a positive, log-linear association with incident frailty. Compared to the lowest fat mass quintile, each consecutive increase in the quintile group was associated with a significantly higher risk of incident frailty. Those in the highest fat mass quintile had nearly 3-fold (OR [95%CI]: 2.89 [2.60-3.21]) higher odds of incident frailty compared with the lowest quintile. The association remained similar using the mFI-1 definition

excluding cardiovascular deficits (2.49 [2.23-2.79]), but attenuated further when adiposity deficits were excluded (mFI-2) (1.63 [1.42-1.89]). Lastly, when both cardiovascular and adiposity deficits were removed from the definition (mFI-3), fat mass no longer had a significant positive linear association with incident frailty. Instead, an inverse association was observed (except for the highest quintile group). Those in the intermediate fat mass groups had slightly lower risk of incident frailty: ORs (95%CI) for the third and fourth quintile groups were 0.85 (0.73-0.99) and 0.84 (0.71-0.99), respectively.

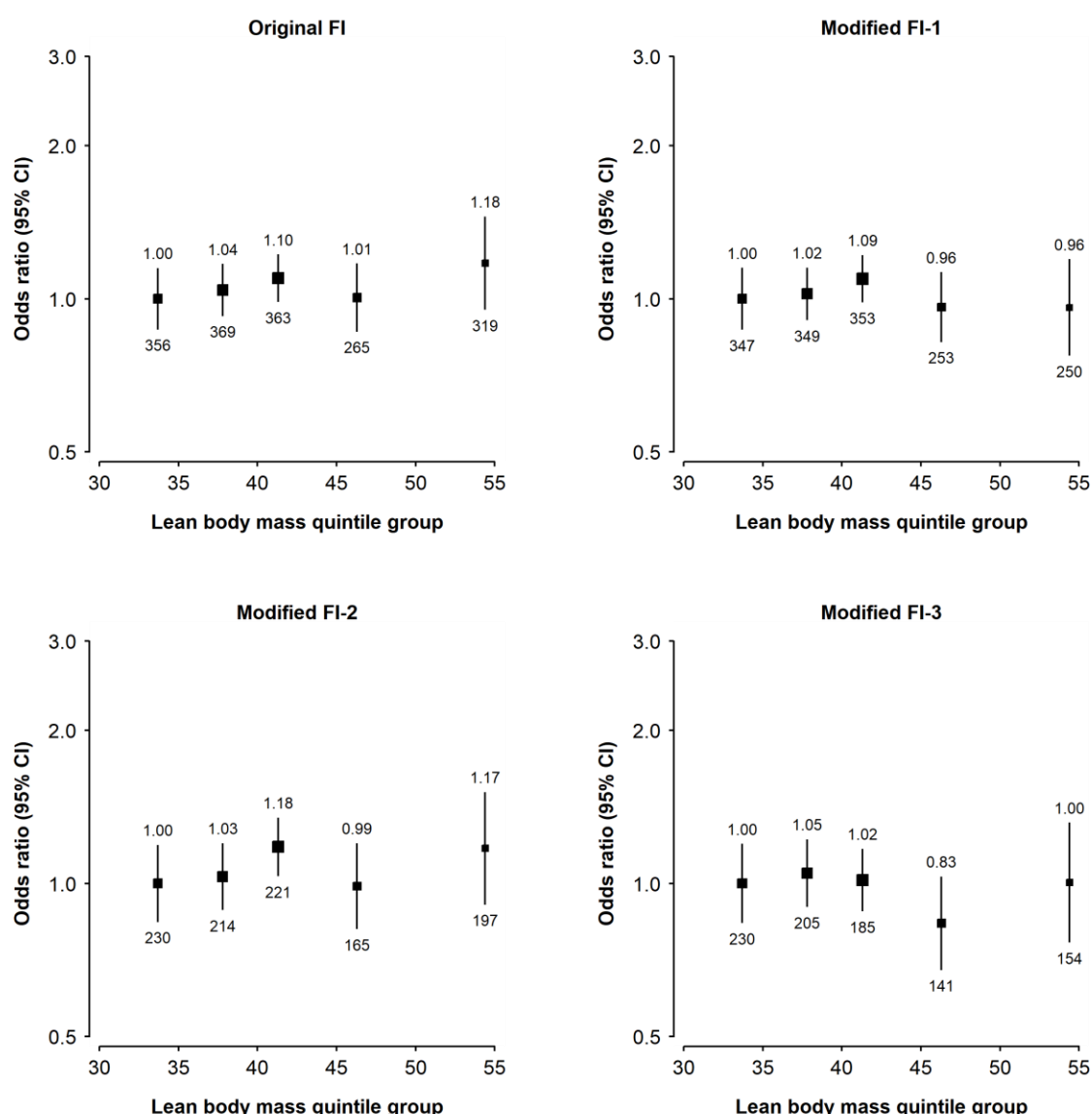
Figure 7.11 Odds ratios (95% CI) of prospective associations between fat mass and incident frailty at 2nd resurvey in ~24,000 participants by FI type



Original FI: 28-item FI; Modified FI-1: 24-item FI (excluding cardiovascular deficits); Modified FI-2: 25-item FI (excluding adiposity deficits); Modified FI-3: 21-item FI (excluding cardiovascular and adiposity deficits)

Finally, irrespective of the definition of FI, there was no association between baseline lean body mass and incident frailty (**Figure 7.12**).

Figure 7.12 Odds ratios (95% CI) of prospective associations between baseline lean body mass and incident frailty at 2nd resurvey in ~24,000 participants by FI type



Original FI: 28-item FI; Modified FI-1: 24-item FI (excluding cardiovascular deficits); Modified FI-2: 25-item FI (excluding adiposity deficits); Modified FI-3: 21-item FI (excluding cardiovascular and adiposity deficits)

Similar to the cross-sectional analyses, the ORs (95%CI) of the prospective associations between CVD RFs and incident frailty were shown by the 10 CKB study regions (**Figure 7.13**). The associations between alcohol consumption and smoking groups and incident frailty (original FI) were difficult to compare by region due to the wide confidence intervals (analyses

included men only). The positive log-linear associations between SBP, RPG, or fat mass and incident frailty were generally consistent across the 10 study regions. The magnitude of the association between SBP (≥ 140 mmHg vs < 120 mmHg) and incident frailty varied somewhat: the strongest association was seen in Sichuan (rural) (OR [95%CI]: 2.51 [1.75-3.62]) and the weakest in Suzhou (urban) (1.11 [0.81-1.52]). The strongest association between RPG (≥ 11 mmol/L vs < 5.8 mmol/L) and incident frailty was seen in Suzhou (urban) (3.76 [2.60-5.43]) and the weakest in Qingdao (urban) (0.89 [0.45-1.70]) where the log-linear association was not observed. The association between fat mass (Q5 vs Q1) and incident frailty was strongest in Liuzhou (urban) (4.13 [3.09-5.51]) and weakest in Harbin (urban) (1.60 [1.21-2.12]) but were generally similar across the remaining regions (respective OR range: 2.47-4.11). Finally, the lack of association between lean body mass and incident frailty was consistent across study regions, but potential positive (Suzhou) and negative (Sichuan) associations were observed. Similar regional differences in the prospective associations between each CVD RF and incident frailty were observed for the mFI-1 (**Figure S7.4**), mFI-2 (**Figure S7.5**), and mFI-3 (**Figure S7.6**).

Figure 7.13 Odds ratios (95% CI) of prospective associations between CVD RFs and incident frailty (original FI) 2nd resurvey in ~24,000 participants by the 10 CKB study regions

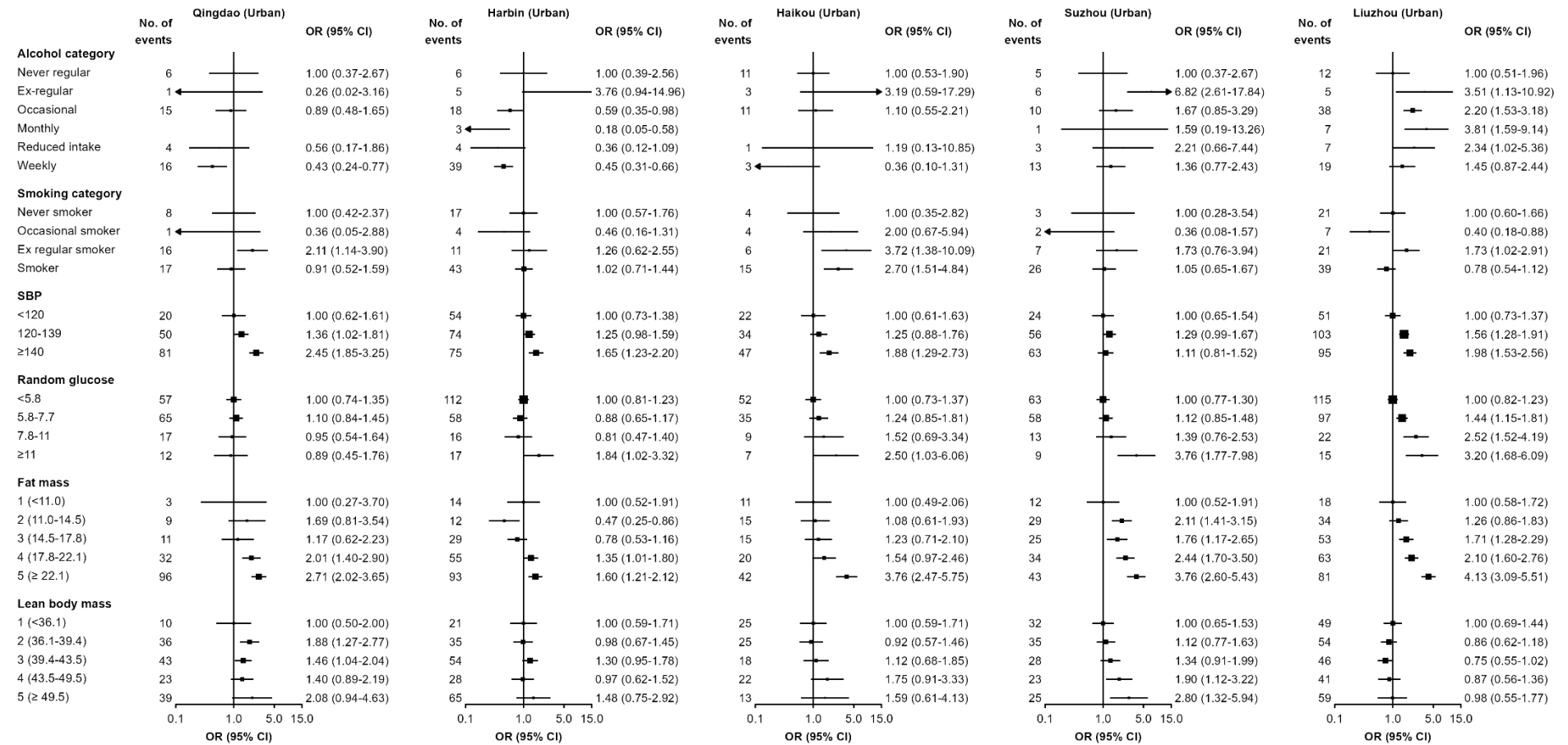
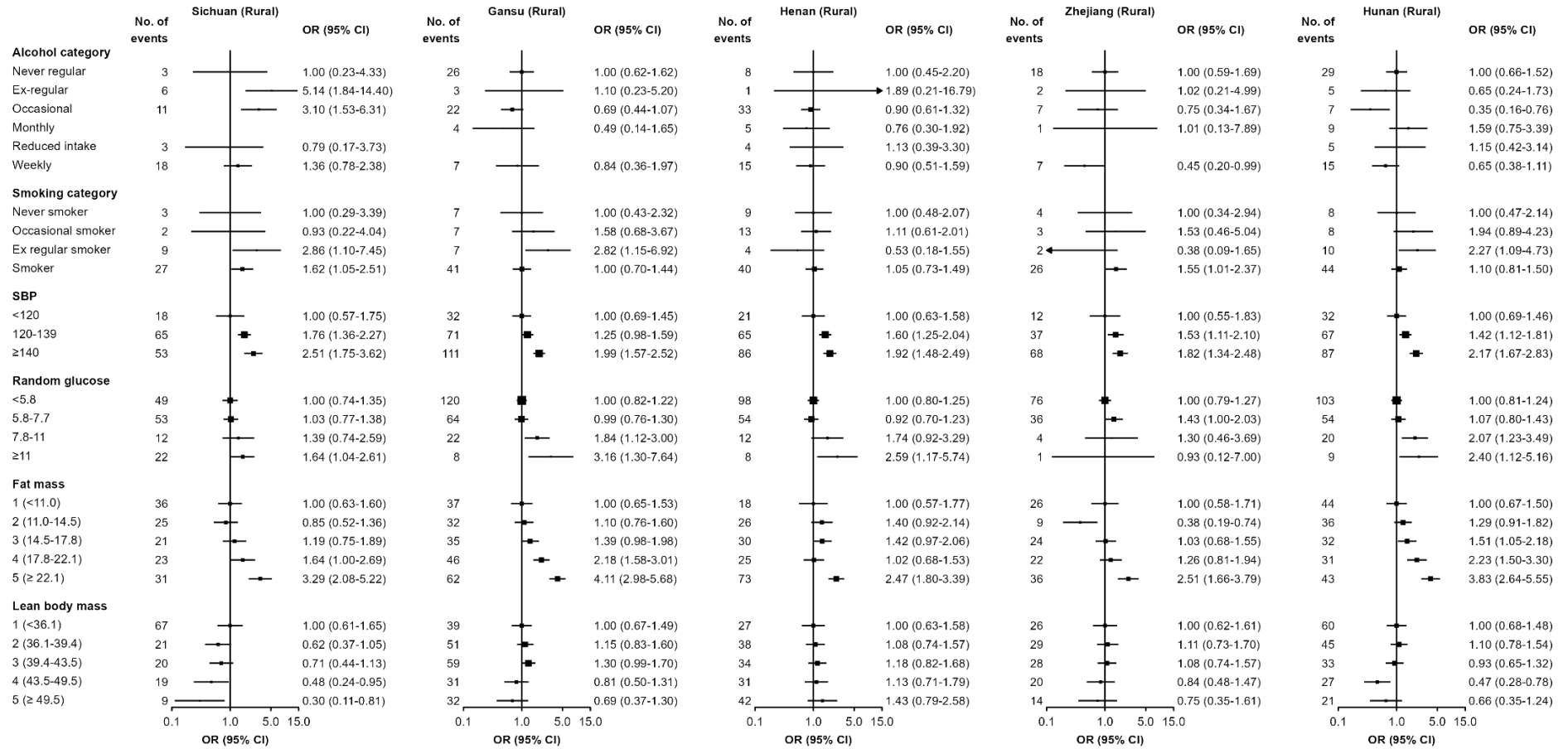


Figure 7.13 continued



Logistic regression models were adjusted for age and sex.

Sensitivity analyses were conducted to explore the potential for reverse causation bias in the association between fat mass and incident frailty (**Figure S7.7**). The analyses were repeated by excluding participants who reported unintentional weight loss and poor self-rated health status at baseline and participants who died shortly (2 years) after the 2nd resurvey. After excluding participants with potentially undetected frailty, the positive associations between fat mass and incident frailty (mFI-2) became more extreme, while no clear changes were seen in the inverse association between fat mass and incident frailty (mFI-3).

A post-hoc sensitivity analysis was carried out after detecting a potential association between fat mass and incident frailty. Analyses were repeated by the participants' baseline unintentional weight loss status and physical activity levels (to assess whether the association was modified by weight loss or physical activity), and whether participants reported CVD during the 2nd resurvey (to assess whether observed associations were independent of the presence of CVD) using the mFI-2 (**Figure S7.8**) and mFI-3 (**Figure S7.9**). The associations were broadly similar by unintentional weight loss status, levels of physical activity, and CVD status regardless of the FI definition.

7.4 Discussion

7.4.1 Summary of findings

Alcohol consumption

The findings of the present chapter were consistent with previous studies reporting an inverse association between alcohol consumption and frailty.³¹³ Using data from ~24,000 Chinese adults aged 30-79 years, drinking (especially weekly consumption) was associated with a lower risk of frailty cross-sectionally and prospectively.

A true inverse relationship between alcohol and frailty may be possible. For example, light-to-moderate drinking has shown cardioprotective effects³¹⁴ via high-density lipoprotein (HDL) cholesterol and lowering blood coagulation factors,³¹⁵ which may reduce the progression of frailty. This is supported by a recent genetic study using CKB, which found that genotype-predicted alcohol intake was associated with increased SBP and HDL cholesterol in men.⁷⁹

While increased SBP is “bad” for many outcomes, it could be that the increased HDL (“good”) cholesterol and its cardioprotective effects (removing excess cholesterol in the blood thereby limiting atherogenesis and inflammation) outweigh the negative effects of alcohol consumption (e.g. increased SBP) and results in lower frailty. Another possible explanation for these associations is the presence of unmeasured characteristics associated with alcohol consumption and frailty. For example, non-drinkers may be more likely to exhibit confounders associated with increased frailty, such as unfavourable deficits related to sociodemographic, behavioural, clinical, and biological factors, which could not be accounted for completely.³¹⁶ Misclassification of alcohol consumption, which was self-reported, is another potential explanation.³¹⁷ People with high alcohol intake may under-report to a greater extent than those with lower intake, which could bias the association away from the null. Conversely, random misclassification or systematic underestimation of alcohol consumption, which might mean that fewer cases are considered to be exposed, would bias the association to the null. Thus, the apparent inverse association between moderate alcohol consumption and the risk of frailty is likely to reflect effects of residual confounding and misclassification bias.

Smoking

Previous studies have reported conflicting results for the effect of smoking on risk of frailty. Current smoking is associated with both higher^{172,173,187} and lower^{179,194} risks of frailty compared to non-smokers in prospective cohort studies. In the present chapter, former and current smokers (vs non-smokers) had higher risks of frailty. Smoking may increase the risk of frailty directly (such as inflammation from cigarette smoke may exacerbate biological processes involved in frailty) or indirectly (such as via increased risk of other diseases). However, like alcohol consumption, there is some potential for misclassification of smoking status. Although the present analysis attempted to reduce this bias by reclassifying former smokers who had quit due to previous illness as current smokers, the self-reported nature of the data means that misclassification may persist. For example, current smokers may have reported themselves to be non-smokers and the inclusion of these individuals in the non-smoking category may have underestimated the association between smokers and frailty.

In CKB, the current smoking group was further divided by the number of cigarettes smoked per day. Based on this definition, higher number of cigarettes smoked per day was associated with higher risks of frailty. However, associations were attenuated to the null when using the mFI-3, suggesting that the positive association between current smoking and FI may reflect the association between smoking and the inclusion of relevant frailty deficits (i.e. IHD, hypertension, stroke/TIA, or poor adiposity) in the FI rather than the frailty itself. Overall, the findings of the present chapter suggest that the previously reported inverse association between smoking and frailty are partly explained by misclassification of smoking status. In addition, while a positive association between the amount of cigarettes smoked and incident frailty may exist, it may be explained partly by circularity in the exposure and outcome.

Systolic blood pressure and random plasma glucose

Previous studies on the associations between SBP and RPG with incident frailty have also reported conflicting results. While studies with a shorter duration of follow-up suggested a positive association between SBP or RPG and frailty, those with longer follow-ups reported no association. The findings of the present chapter are consistent with previous studies. Cross-sectionally, SBP and RPG were positively associated with frailty (even after adjustment for age and excluding cardiovascular and adiposity deficits in the FI), but associations were attenuated to the null in the prospective analyses. The likelihood of misclassification bias is low as both SBP and RPG were measured objectively using standardised methods across study regions. Random measurement error of SBP and RPG, however, is possible in which case random fluctuations in SBP and RPG may have resulted in an underestimation of their association with incident frailty. Additionally, sampling bias could explain the attenuation of associations. The resurveys conducted on a random subset of 5% of CKB population had a response rate of 80%.³¹⁸ Participants who refused to participate in the resurvey may have been more likely to have unfavourable RFs like high BP, high BMI, physical inactivity, and frailty.²¹³ Thus, exclusion of these non-responders in the analyses may explain the attenuation in associations using longitudinal data.

The ORs of the cross-sectional and prospective associations between SBP and RPG with frailty also attenuated with the exclusion of adiposity or cardiovascular deficits (i.e. using the modified FIs). For the cross-sectional associations, the positive associations found using the original FI reversed and became inverse using the mFI-3. The reason for this reversal in ORs is unclear and may be partly explained by the exclusion of related deficits (i.e. accounting for circularity). In addition, sampling bias may be present. Those with severe frailty are not detected using the modified FIs that exclude deficits like stroke and CHD; thus, they are under-represented in the highest categories of SBP and RPG, which may explain the apparent inverse relationship.

Fat mass

Previous studies reported U-shaped associations between BMI and incident frailty, suggesting that adiposity is inversely related to frailty. Among 0.5M Chinese older adults, cross-sectional analyses suggested a U-shaped association between fat mass and prevalent frailty, but the prospective analyses were less clear. There was a positive log-linear association between fat mass and incident frailty using the original FI, but the association became inverse when cardiovascular and adiposity deficits were excluded. The apparent inverse association suggests that some general adiposity may be associated with lower frailty risk, which may be possible as body fat is beneficial for normal function.²¹⁰ However, another potential explanation is reverse causation bias – individuals with undiagnosed frailty may experience unintentional weight loss, a marker of physical frailty, which explains the higher risk among the underweight group.

To investigate the potential for reverse causation, associations were repeated by excluding participants who reported unintentional weight loss and poor self-rated health at baseline or died within two years of the 2nd resurvey. Using the mFI-2, the positive association between fat mass and incident frailty became stronger after excluding these participants with potentially undiagnosed frailty, suggesting that higher levels of adiposity may predict risk of frailty even after accounting for some degree of reverse causation bias. The sensitivity analyses using the

mFI-3 did not show any clear patterns. Additionally, the associations were similar by baseline unintentional weight loss status and physical activity level and whether participants reported CVD in the 2nd resurvey, suggesting that the effect of fat mass on incident frailty is independent of these factors.

Lean body mass

The literature on the association between lean body mass and frailty was limited. In the present study, a strong inverse association between lean body mass and prevalent frailty was observed cross-sectionally – participants with higher lean body mass had lower levels of frailty. Despite a strong cross-sectional relationship and muscle wasting being an important theme of frailty, there was no association between lean body mass and incident frailty in the prospective analyses. This suggests that reductions in lean body mass may simply reflect a consequence of frailty or muscle wasting in individuals who are closer to death rather than being an independent predictor of frailty.

7.4.2 Strengths and limitations

The main strengths of the present chapter include the measurement of a wide range of CVD RFs and frailty in a large population study. The data collection procedures employed by CKB (described in **Chapter 5**) are likely to have mitigated the introduction of systematic error, measurement error, and misclassification in the exposures and thus have a minimal effect on the observed associations. Another strength of the present analysis is the comparison of several FI modifications to explore the issue of circularity between the exposures and FI. This highlighted dramatic differences in the shape and strength of associations between CVD RFs and frailty depending on the composition of the FI.

However, there are several limitations that may undermine the findings of the present chapter. Even though CKB is one of the largest cohort studies of Chinese adults, the prospective analysis of this chapter was limited to only ~5% of the total cohort due to the requirement of repeat frailty measures, which limited the ability to conduct sensitivity analyses and interpret findings. Also, several CVD RFs relied on self-reported measures (alcohol consumption and

smoking status) that are subject to recall and social desirability bias and affected by residual confounding. Both recall and social desirability biases are likely to lead to under-reporting of alcohol and smoking consumption, thus non-drinkers or -smokers may be heavier drinkers or smokers than reported, which may explain the null associations and the small relative risks between the different categories of smoking and drinking. These lifestyle behaviours are also associated with unmeasured confounders, i.e. non-drinkers and non-smokers are more likely to exhibit other healthy behaviours, thus true associations may have been clouded by residual confounding. However, the remaining CVD RFs (SBP, glucose, adiposity, and lean body mass) were measured objectively and are less susceptible to these biases. Another important limitation is that the number of items included in the FI is fewer than recommended (21-28 versus 30-40+ items),⁷² Thus, whether the FI used in the present thesis adequately represents the frailty index and its multidimensional nature is uncertain. Including fewer deficits and excluding deficits from specific domains in the FI may lead to reduced sensitivity to detect subtle differences in frailty, limited variability in frailty scores, and a reduction in their predictive accuracy.³¹⁹ This may partly explain the lack of clear patterns and associations found in the present chapter.

7.5 Summary

Strong cross-sectional associations between CVD RFs and frailty have been reported in previous studies. Thus, CVD RFs have been proposed as potential modifiable RFs of frailty. However, there is little evidence on the shape and strength of CVD RFs and frailty in prospective studies. Evidence on the prospective association between CVD RFs and frailty is limited and mainly restricted to analyses using the FP model (**Chapter 4**). In the present chapter, the relationship between six CVD RFs and prevalent and incident frailty were assessed using the FI. Additionally, several modifications of the FI were used to assess the presence of circularity between the exposure (CVD RFs) and outcome (FI).

The present chapter identified conflicting results for the associations between CVD RFs and frailty, including discrepant associations between cross-sectional and longitudinal analyses.

Cross-sectionally, strong associations between the CVD RFs and FI were found among approximately 0.5M CKB participants without prevalent CVD, even after accounting for some of the circularity in the relationship. Importantly, many of the positive associations observed in the cross-sectional analysis were attenuated to the null in the prospective analysis, namely SBP, RPG, fat mass, and lean body mass. These attenuations may be explained partly by random measurement error in exposures, but other sources of biases may also be present. The sensitivity analyses suggested that the association between fat mass and frailty may be confounded by reverse causation.

The findings of the chapter also showed the presence of circularity in the associations between CVD RFs and the FI. The shape and strength of associations between CVD RFs and FI depended on the type of deficits included. Importantly, many of the positive associations, both cross-sectional and longitudinal, between individual CVD RFs and frailty were almost completely attenuated when cardiovascular and adiposity deficits were excluded. In addition, the shape of the associations, notably between fat mass and frailty, changed remarkably when certain deficits were excluded. This conflicting shape of the association between CVD RFs and frailty challenges the interpretation of the associations and suggests associations may simply reflect circularity between the CVD RFs and FI. Thus, the definition of frailty had a considerable impact on the nature of the associations between CVD RFs and frailty and given the large heterogeneity in the definition of frailty measures used in practice it may partly explain the conflicting results in the literature review of these associations (**Chapter 4**).

The findings of this chapter have important implications for public health practitioners and policy-makers trying to mitigate frailty levels in older people. First, the potential for several biases in the associations of CVD RFs and frailty raises substantial uncertainty about the relevance of individual CVD RFs in frailty risk, hence whether they can be considered as modifiable RFs of frailty is unclear. Second, the conflicting results regarding the shape and strength of associations arising from different frailty definitions, which mirrors the inconsistent evidence in the literature due to a wide range of frailty models, are likely to challenge policy-

makers on making informed, evidence-based decisions for the allocation of resources and development of specific policies. In the next chapter, the relevance of frailty for the risk of major CVD types, stroke and IHD, will be examined and whether similar issues identified in this chapter are present will be investigated and discussed.

8 Frailty and risk of incident stroke and ischaemic heart disease

8.1 Introduction

Over the next few decades, the prevalence of frailty is expected to increase worldwide particularly in countries like China where the demographic structure is transitioning rapidly. Frailty has been associated with a wide range of adverse health outcomes, but there is little reliable evidence on the associations of frailty with the risk of CVD types. A literature review identified just 12 prospective studies of frailty and risk of stroke or IHD (**Chapter 4**); while these studies suggested a positive association, there was considerable uncertainty about the shape and strength of these associations.

One of the studies identified was an earlier analysis of CKB data reporting the associations between FI and fatal outcomes: IHD and cerebrovascular disease mortality, and all-cause mortality (Fan *et al.*, 2020).²¹⁹ This study found significant and positive associations between FI and fatal IHD (HR [95%CI]: 1.89 [1.83-1.94] per 0.1 FI unit increment), fatal cerebrovascular disease (1.84 [1.79-1.89] per 0.1 FI increment), and all-cause mortality (1.36 [1.34-1.38] per 0.1 FI increment).²¹⁹ The findings of the thesis so far have raised important issues that question the accuracy of their findings.

First, the investigations conducted in the present thesis showed that frailty scores were associated with wide within-person variability (**Chapters 3 and 6**). Random measurement error in frailty is possible due to variability in health status of the individual study participant or the observer recording the assessments. However, epidemiological studies involving frailty, including those identified in the literature review, typically assessed frailty once at baseline and assumed that a single measurement is a reliable estimate of its long-term, usual levels. However, the variability of exposures within individuals due to random measurement error results in an underestimation of the true or 'usual' levels of exposure over the course of follow-up, which can substantially underestimate the magnitude of frailty-disease associations

(‘regression dilution bias’).^{129,130} Correcting this bias should result in more reliable estimates of frailty-disease associations.

Second, **Chapter 7** of the thesis showed that the inclusion of cardiovascular and adiposity deficits in the FI may result in circularity between the FI and CVD relationships, thus inflating the associations. Fan *et al.* (2020)²¹⁹ also accounted for this circularity but to a minimum extent, only excluding heart disease or stroke deficits from the FI but not other strong CVD RFs like hypertension and obesity. Whether the positive associations persist after fully accounting for such circularity is uncertain.

Third, the literature review (**Chapter 4**) showed that there were few investigations of the association between frailty and CVD with respect to different subtypes, different endpoints, and effect modification. In previous studies,^{215,217,219,223} the investigation of effect modification has been limited to age or sex due to the limited power of studies. Investigation of whether the association differs by other demographic or clinical groups may provide unique insights into the underlying mechanisms. Likewise, few studies have distinguished effects of frailty on different CVD subtypes (such as IS, HS, or MI) or endpoints (like fatal outcomes). Understanding how relationships differ by the precise outcomes may be relevant when assessing implications for future policy and clinical practice.

Therefore, the aims of the present chapter are to: (1) examine the shape and strength of the associations of ‘usual’ frailty with the risks of incident stroke and IHD among ~0.5M CKB participants by subtype and endpoint; (2) assess the presence of circularity in the associations from the inclusion of cardiovascular deficits in the FI; (3) explore the effect modifiers of these associations; and (4) assess the potential for reverse causation bias.

8.2 Methods

8.2.1 Data source and participants

Analyses of the prospective analyses of frailty and incident CVD involved ~0.5M participants from the CKB study. Participants with a prior history of CVD (self-reported history of doctor-

diagnosed IHD or stroke/TIA) (n=23,276) and missing BMI (n=2) at baseline were excluded, leaving 489,448 participants. Information on participants' self-reported disease and symptoms, lifestyle behaviours, and physical measurements from CKB's baseline survey data was used to estimate participants' frailty levels. CVD outcomes were obtained from the follow-up of events in disease and mortality registries, national health insurance databases, and disease surveillance systems.

8.2.2 Definition of frailty, confounders, and outcomes

The definition of FI using the data collected in the CKB questionnaire was previously described in **Chapter 6**. To assess the presence of circularity between the exposure (FI) and outcome (CVD), both original (28 deficits) and modified versions of the FI were used. Two FI modifications were used: mFI-1 (24 deficits that excluded cardiovascular deficits: IHD, stroke/TIA, diabetes, and hypertension) and mFI-3 (21 deficits that exclude both cardiovascular and adiposity deficits: abnormal BMI, abnormal WHR, and unintentional weight loss).

The primary disease outcomes investigated in this chapter were total stroke (ICD-10 codes: I60-I61, I63-I64), total IHD (ICD-10: I20-I25), CVD mortality (ICD-10: I00-I99), and all-cause mortality. The subtypes of stroke and IHD studied were IS (ICD-10: I63) and HS (ICD-10: I61), and MI (ICD-10: I21-I23) and MCE (acute myocardial infarction [ICD-10: I21-I23] or fatal IHD [ICD-10: I20-I25]), respectively. Outcomes were obtained from national disease registries, mortality records, and health insurance databases, supplemented by reviewing medical and residential records, and have been described previously (**Chapter 5**). Outcomes were analysed for incident and fatal (died within 28 days of the event) events. Participants were censored at the time of the first event, date of death or loss to follow-up, or at the final censoring date (31 December 2017), or at 80 years of age.

8.2.3 Statistical analyses

Associations of usual frailty with incident CVD and all-cause mortality

Analyses from **Chapters 3 and 6** suggested wide within-person variability of the FI, which may result in regression dilution bias in the associations of frailty and disease outcomes. The MacMahon-Peto method was used to correct for this bias and the associations between “usual” FI values and outcomes are reported. In **Chapter 6**, repeat FI measures in CKB were used to calculate the regression dilution ratios (RDR) for the MacMahon-Peto method.¹²⁹ The associations between baseline frailty and outcomes were calculated and the RDRs were used to correct the risk estimates and standard errors (1/RDR times the “uncorrected” estimates). The RDRs obtained from **Chapter 6** were 0.44 for mFI-1 and mFI-3.

Cox proportional hazards models were used to estimate HRs and associated 95% CIs for the associations of baseline frailty with outcomes. Associations were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day). These confounders were selected based on their associations with frailty and CVD.

In prospective cohort studies, the timescale typically used in Cox proportional hazards models is follow-up time and age at entry is included as a covariate. This assumes that changes in the rate of disease are the same for all ages in any follow-up period, but in reality, the rate of chronic diseases can vary significantly in the young versus the old – e.g. occurrence of CVD rapidly increase at later ages, which violates assumptions of the proportional hazards model. Also, age is likely to be an important confounder of the associations between frailty and CVD and may reflect important unmeasured confounders like accumulation of cell mutations and tissue damage. Thus, lack of appropriate adjustment for age may fail to remove important confounding biases. To mitigate this, “age-at-risk” analysis was carried out in the Cox model, which assesses risk within each stratum of the participants’ age and does not pre-define the distribution of the baseline hazard.³²⁰ By analysing risk within age strata, this approach

enables the Cox models to accommodate different baseline hazard functions and variable strengths of associations across age bands. Thus, by rigorously controlling for one of the most important confounders between RF and disease (age), more reliable estimation of such associations is possible.

Frailty was assessed as categorical and continuous variables in the Cox models. FI was categorised into five equally sized groups (quintiles) and 3 levels (non-frail, pre-frail, and frail) using previously defined thresholds for comparison with existing studies. The FAR method was used to estimate HRs and group-specific 95% CIs for each HR,³¹² which were plotted on a log scale against categories of FI. Continuous FI scores were standardised to allow comparison of effect estimates between different FI modifications. Therefore, interpretation of the resulting HRs from the models were HRs per 1 SD higher FI score, which is equivalent to approximately: 0.061, 0.063, and 0.061 for the original FI, mFI-1, and mFI-3, respectively. Additionally, associations per 0.1 unit increase of FI score were reported to permit comparisons with previous studies.

Investigation of effect modification

Subgroup analyses were carried out to investigate effect modification of the association between continuous FI (mFI-1 and mFI-3) and outcomes by key demographic (age, sex, region, and education) and CVD RFs (alcohol consumption, smoking, fat mass, SBP, RPG, and physical activity) at baseline. The subgroup analyses were also stratified by age-at-risk, sex, and study region, and adjusted simultaneously for the confounders except when the confounder of interest was the variable being examined for effect modification. Chi-square tests for trend and heterogeneity in the associations were carried out by comparing the effect estimates and associated standard errors from regressions across strata.³²¹

Investigation of reverse causation bias

Sensitivity analyses were also conducted to investigate the likelihood of reverse causality in the observed associations. Investigations involved the exclusion of participants with suspected underlying disease and the comparison of HRs by the duration of follow-up. In the exclusion

approach, associations of frailty with outcomes were reported for subsets of the CKB population: (1) no early deaths (exclusion of deaths within the first 5 years of follow-up); (2) no unintentional weight loss (exclusion of participants reporting unintentional weight loss at baseline); (3) no poor self-rated health (exclusion of participants reporting poor self-rated health at baseline); and (4) a healthy subset (exclusion of current or former smokers, participants reporting unintentional weight loss or poor self-rated health at baseline, and early deaths). In the second approach, HRs of associations of frailty with outcomes were compared using different lengths of the follow-up periods (1, 3, 5, 8, and 13 years) using the full cohort. Both approaches used the mFI-1 and mFI-3 definitions.

All statistical analyses were conducted in R version 4.2.1. R codes developed within CTSU were also used to undertake Cox proportional hazards regression. All plots were produced using ckbplotr, an R package developed within CKB.³²²

8.3 Results

After following 489,448 cardiovascular disease-free CKB participants for a mean (SD) duration of 11 (2) years, 54,193 first stroke events (16% fatal), 49,937 first IHD events (14% fatal), 20,610 CVD deaths, and 43,239 all-cause mortality outcomes were recorded. For stroke events, 46,043 IS events (7% fatal) and 10,525 HS events (53% fatal) were recorded. For IHD, 7,749 MI events (51% fatal) and 10,193 MCE (64% fatal) were recorded. **Table 8.1** shows the baseline characteristics of the CKB participants included in the present analysis, overall and by frailty levels according to the mFI-1. Compared to their non-frail counterparts, participants with frailty tended to be older (mean [SD]: 59 [10] vs 49 [10] years), less likely to live in urban regions (35% vs 44%), less likely to be married (93% vs 81%), have no formal education (16% vs 35%), ex-smokers (3% vs 10%), ex-regular drinkers (1.1% vs 5%), consume less fresh fruit (20% vs 13%), report lower physical activity (median [IQR] MET-hours/day: 21 [14, 33] vs 9 [6, 19]), and have poor self-rated health (3% vs 57%). Additionally, participants with frailty had higher rates of all CVD outcomes and mortality than pre-frail and non-frail participants during the follow-up period.

Table 8.1 Baseline characteristics of included participants by mFI-1 levels

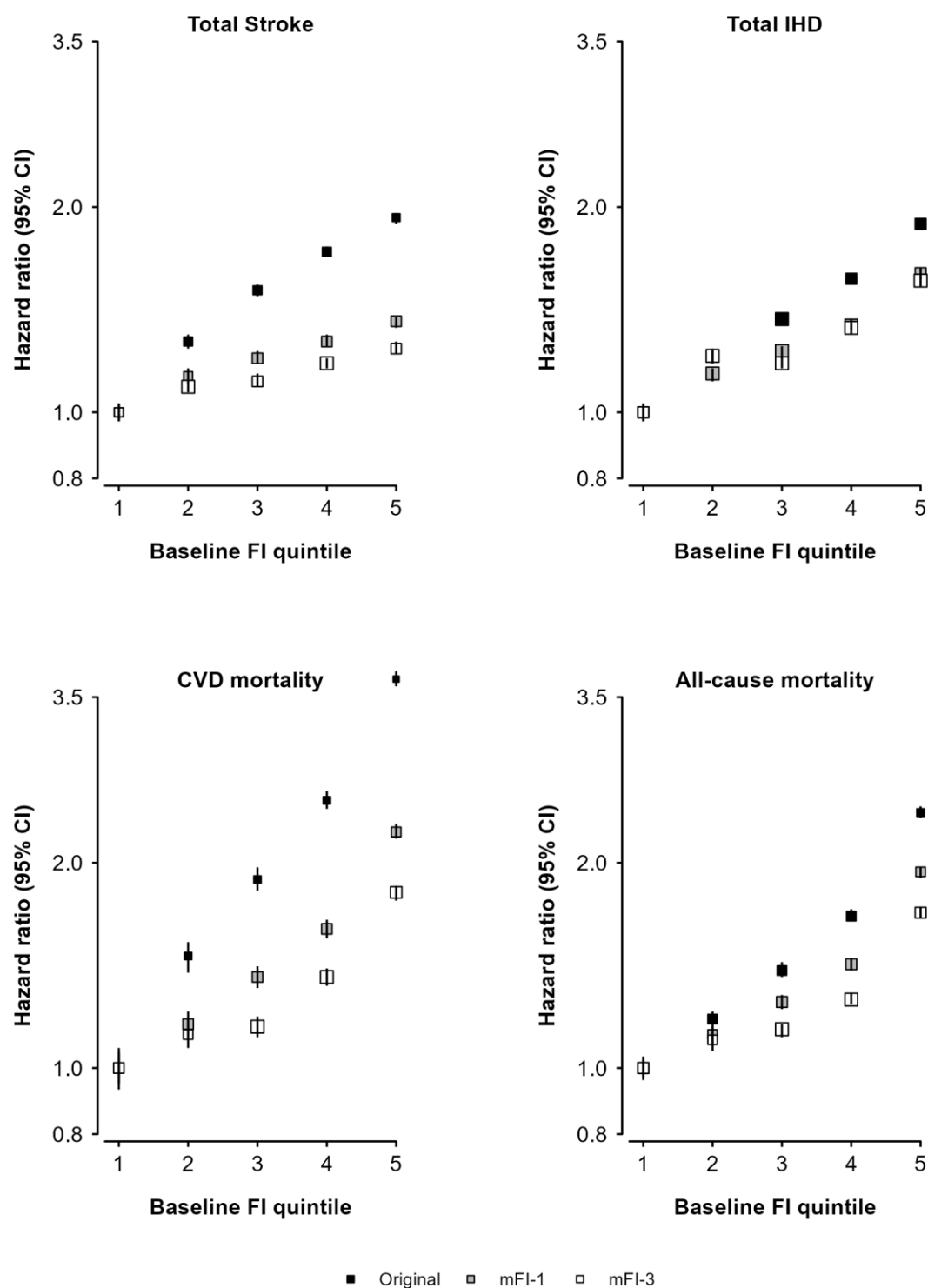
N (%), mean (SD) or median (IQR)	Overall (N=489448)	Non-frail (N=280775)	Pre-frail (N=194823)	Frail (N=13850)
Age (years)	51.57 (10.55)	49.24 (9.84)	54.38 (10.61)	59.08 (10.32)
Urban region	211358 (43.2)	122820 (43.7)	83671 (42.9)	4867 (35.1)
Marital status				
Married	444768 (90.9)	261301 (93.1)	172177 (88.4)	11290 (81.5)
Highest education				
No formal school	91369 (18.7)	43748 (15.6)	42783 (22.0)	4838 (34.9)
Smoking status				
Never smoker	303557 (62.0)	173896 (61.9)	121294 (62.3)	8367 (60.4)
Occasional smoker	27996 (5.7)	15929 (5.7)	11314 (5.8)	753 (5.4)
Ex regular smoker	20221 (4.1)	8896 (3.2)	9912 (5.1)	1413 (10.2)
Smoker	137674 (28.1)	82054 (29.2)	52303 (26.8)	3317 (23.9)
Drinking status				
Never regular	223753 (45.7)	125903 (44.8)	90387 (46.4)	7463 (53.9)
Ex-regular	7935 (1.6)	3198 (1.1)	4077 (2.1)	660 (4.8)
Occasional	156459 (32.0)	91658 (32.6)	61277 (31.5)	3524 (25.4)
Monthly	16914 (3.5)	10533 (3.8)	6108 (3.1)	273 (2.0)
Reduced intake	10593 (2.2)	4655 (1.7)	5395 (2.8)	543 (3.9)
Weekly	73794 (15.1)	44828 (16.0)	27579 (14.2)	1387 (10.0)
Daily fresh fruit consumption	89542 (18.3)	54698 (19.5)	33024 (17.0)	1820 (13.1)
Daily fresh vegetable consumption	463493 (94.7)	265942 (94.7)	184583 (94.7)	12968 (93.6)
Daily meat consumption	142180 (29.0)	85244 (30.4)	54080 (27.8)	2856 (20.6)
Physical activity (MET-hours/day) (Median [IQR])	18.02 [10.71, 30.53]	21.40 [13.61, 33.30]	14.00 [8.40, 25.87]	8.80 [5.60, 19.18]
Self-rated health				
Excellent	88525 (18.1)	67769 (24.1)	20498 (10.5)	258 (1.9)
Good	141392 (28.9)	102553 (36.5)	38127 (19.6)	712 (5.1)
Fair	213504 (43.6)	102740 (36.6)	105804 (54.3)	4960 (35.8)
Poor	46027 (9.4)	7713 (2.7)	30394 (15.6)	7920 (57.2)

Abbreviations: FI=frailty index; HS=haemorrhagic stroke; IHD=ischaeemic heart disease; IS=ischaeemic heart disease; MCE=major coronary event; MET=metabolic equivalent tasks; MI=myocardial infarction

8.3.1 Frailty and risk of cardiovascular disease

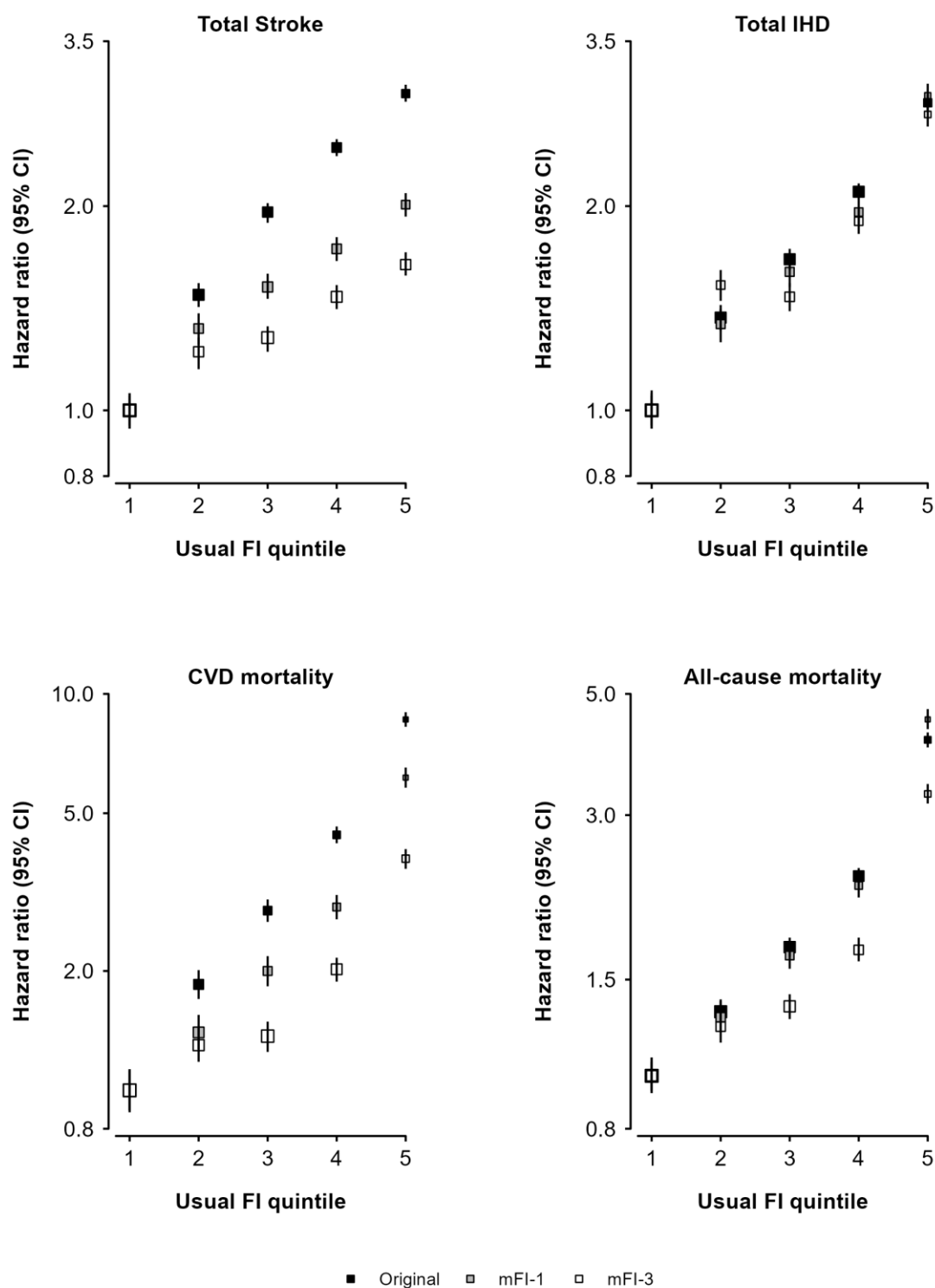
Among the ~0.5M participants without previously diagnosed IHD or stroke/TIA, increasing severity of frailty status and increments of FI score were associated with higher risks of major CVDs and all-cause mortality. A log-linear association between baseline (**Figure 8.1**) and usual FI (**Figure 8.2**) and the primary CVD outcomes and all-cause mortality was found according to the original FI, mFI-1 (excluding cardiovascular deficits), and mFI-3 (excluding cardiovascular and adiposity deficits). The strongest association was found using the original FI definition, which attenuated further with each level of modification made to the FI.

Figure 8.1 Adjusted hazard ratios (95% CI) for the association between baseline FI quintile and incident stroke, IHD, CVD and all-cause mortality



Original FI: 28-item FI; mFI-1: 24-item FI (excluding cardiovascular deficits); mFI-3 = 21-item FI (excluding cardiovascular and adiposity deficits).
Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day).

Figure 8.2 Adjusted hazard ratios (95% CI) for the association between usual FI quintile and incident stroke, IHD, CVD and all-cause mortality



Original FI: 28-item FI; mFI-1: 24-item FI (excluding cardiovascular deficits); mFI-3 = 21-item FI (excluding cardiovascular and adiposity deficits).
Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day).

Table 8.2 shows the corresponding adjusted HRs (95%CI) using categorical frailty levels and continuous FI scores. Correction for regression dilution bias, as illustrated by the associations of usual FI and outcomes, resulted in more extreme strength of such associations with disease outcomes. The strongest associations with disease outcomes were detected using the original FI and the weakest using mFI-3, with differences in risks varying by almost 2-fold. For incident stroke, each 1 SD higher “usual” score of original FI, mFI-1, and mFI-3 were associated adjusted HRs (95%CI) of 1.31 (1.29-1.33), 1.19 (1.17-1.22), and 1.13 (1.11-1.15), respectively. The corresponding HRs were: for incident IHD 1.37 (1.35-1.40), 1.40 (1.37-1.43), and 1.34 (1.31-1.36), respectively; for CVD mortality 1.84 (1.80-1.88), 1.86 (1.80-1.91), and 1.68 (1.63-1.73), respectively; and for all-cause mortality 1.67 (1.65-1.70), 1.76 (1.72-1.80), and 1.60 (1.57-1.63), respectively. The associations were independent of key demographic and CVD RFs at baseline.

Table 8.2 Adjusted hazard ratios (95% CI) for associations between baseline and usual frailty and incident stroke, IHD, CVD and all-cause mortality

	Original FI			Modified FI-1			Modified FI-3		
	No. events	Baseline FI HR (95% CI)	Usual FI HR (95% CI)	No. events	Baseline FI HR (95% CI)	Usual FI HR (95% CI)	No. events	Baseline FI HR (95% CI)	Usual FI HR (95% CI)
Total stroke									
Non-frail	20712	1.00 (0.98-1.02)	-	22798	1.00 (0.98-1.02)	-	35045	1.00 (0.99-1.01)	-
Pre-frail	30939	1.39 (1.38-1.40)	-	28810	1.17 (1.16-1.18)	-	17811	1.09 (1.08-1.11)	-
Frail	2542	1.45 (1.39-1.51)	-	2585	1.18 (1.13-1.23)	-	1337	1.08 (1.02-1.15)	-
Per 1 SD	54193	1.18 (1.17-1.19)	1.31 (1.29-1.33)	54193	1.08 (1.07-1.09)	1.19 (1.17-1.22)	54193	1.06 (1.05-1.06)	1.13 (1.11-1.15)
Per 0.1 unit		1.31 (1.29-1.33)	1.55 (1.52-1.59)		1.13 (1.11-1.15)	1.32 (1.28-1.37)		1.09 (1.08-1.11)	1.22 (1.18-1.26)
Total IHD									
Non-frail	19508	1.00 (0.98-1.02)	-	20552	1.00 (0.98-1.02)	-	31836	1.00 (0.99-1.01)	-
Pre-frail	27856	1.38 (1.37-1.39)	-	26629	1.28 (1.26-1.29)	-	16626	1.23 (1.21-1.25)	-
Frail	2573	1.71 (1.64-1.78)	-	2756	1.59 (1.52-1.65)	-	1475	1.49 (1.41-1.57)	-
Per 1 SD	49937	1.21 (1.20-1.23)	1.37 (1.35-1.40)	49937	1.16 (1.15-1.17)	1.40 (1.37-1.43)	49937	1.14 (1.13-1.15)	1.34 (1.31-1.36)
Per 0.1 unit		1.37 (1.35-1.40)	1.68 (1.64-1.73)		1.27 (1.25-1.29)	1.71 (1.65-1.77)		1.23 (1.22-1.25)	1.61 (1.56-1.66)
CVD mortality									
Non-frail	5583	1.00 (0.97-1.03)	-	6537	1.00 (0.97-1.03)	-	10324	1.00 (0.97-1.03)	-
Pre-frail	12863	1.90 (1.87-1.93)	-	11755	1.50 (1.48-1.53)	-	8793	1.37 (1.34-1.40)	-
Frail	2164	3.47 (3.30-3.64)	-	2318	2.70 (2.58-2.83)	-	1493	2.54 (2.40-2.69)	-
Per 1 SD	20610	1.45 (1.43-1.47)	1.84 (1.80-1.88)	20610	1.31 (1.30-1.33)	1.86 (1.80-1.91)	20610	1.26 (1.24-1.27)	1.68 (1.63-1.73)
Per 0.1 unit		1.84 (1.79-1.88)	2.71 (2.61-2.81)		1.54 (1.51-1.57)	2.67 (2.55-2.80)		1.45 (1.43-1.48)	2.34 (2.24-2.45)
All-cause mortality									
Non-frail	14882	1.00 (0.98-1.02)	-	15867	1.00 (0.98-1.02)	-	23578	1.00 (0.98-1.02)	-
Pre-frail	24687	1.57 (1.55-1.58)	-	23327	1.40 (1.38-1.41)	-	17108	1.34 (1.32-1.36)	-
Frail	3670	2.89 (2.78-2.99)	-	4045	2.51 (2.43-2.60)	-	2553	2.40 (2.30-2.51)	-
Per 1 SD	43239	1.37 (1.36-1.38)	1.67 (1.65-1.70)	43239	1.28 (1.27-1.29)	1.76 (1.72-1.80)	43239	1.23 (1.22-1.24)	1.60 (1.57-1.63)
Per 0.1 unit		1.67 (1.64-1.70)	2.32 (2.26-2.38)		1.48 (1.46-1.51)	2.45 (2.37-2.53)		1.40 (1.38-1.42)	2.16 (2.09-2.23)

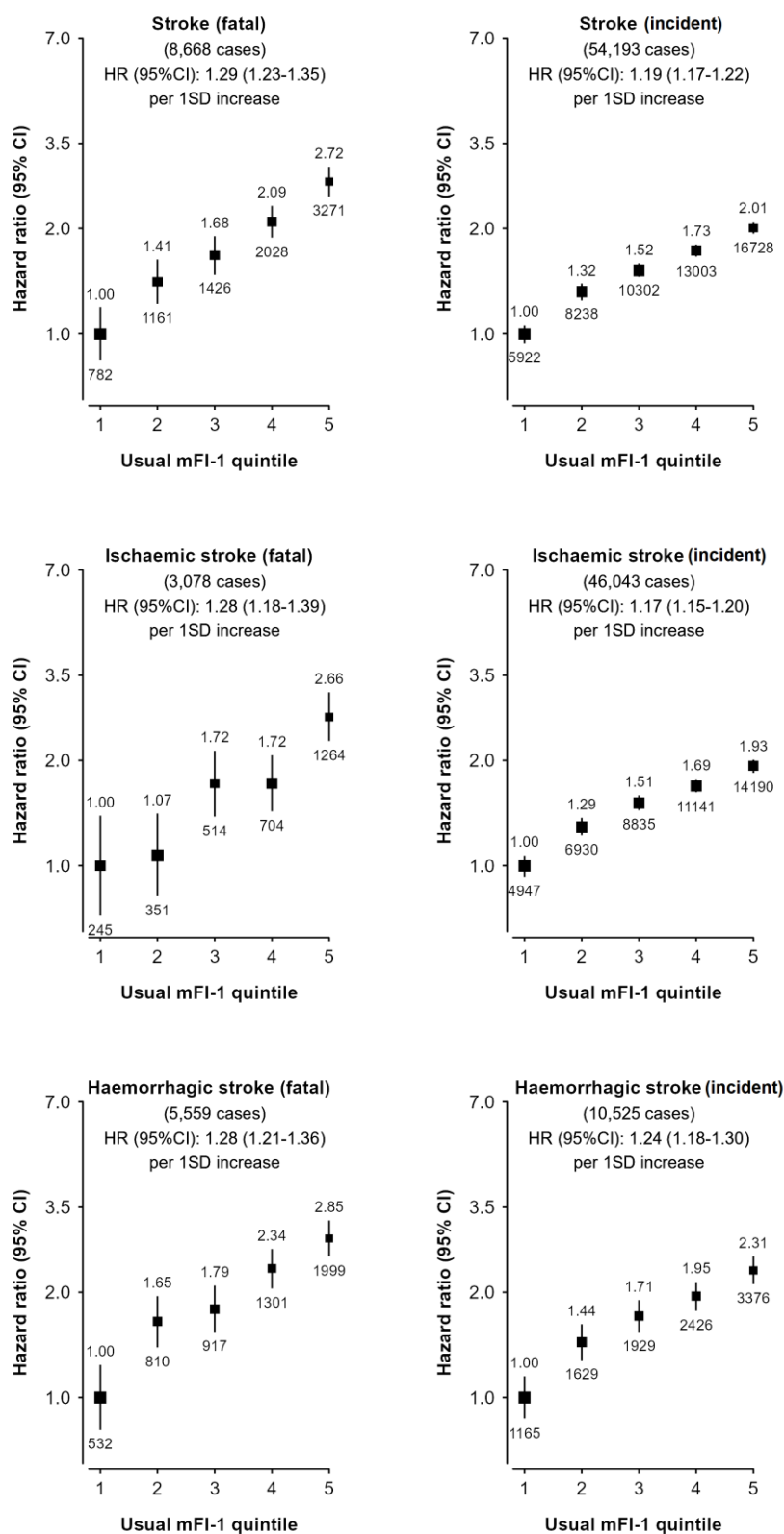
Original FI: 28-item FI; mFI-1: 24-item FI (excluding cardiovascular deficits); mFI-3 = 21-item FI (excluding cardiovascular and adiposity deficits).

Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day).

Stroke and subtypes

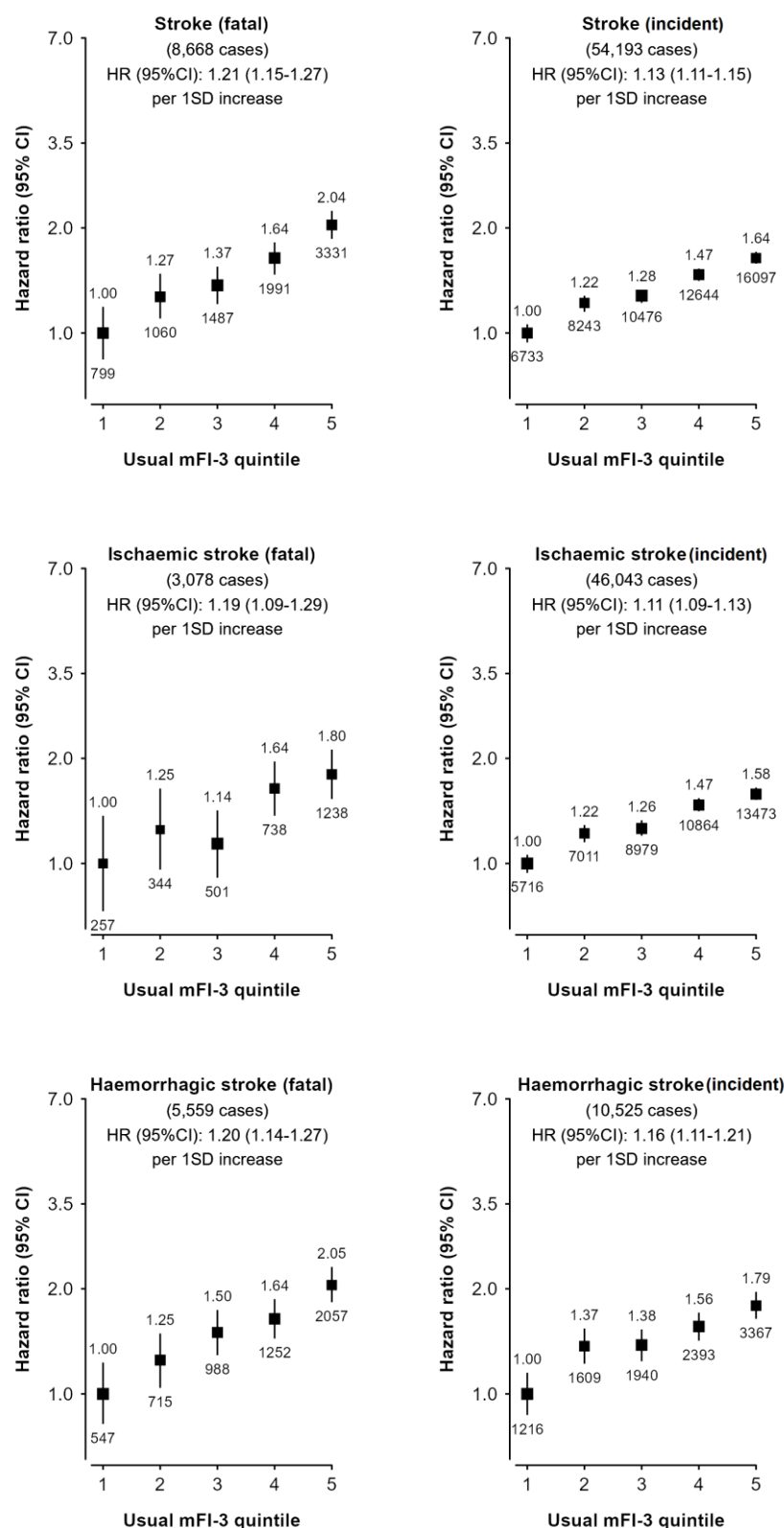
Figure 8.3 shows the associations between usual mFI-1 quintiles with risk of stroke, IS, and HS (fatal or incident event). Risks for stroke increased progressively with higher levels of usual mFI-1, consistent with a linear association with no evidence of a threshold below which risks for stroke diminish or increase. Compared to the reference group (lowest mFI-1 quintile), the risk of incident stroke was approximately 2-fold higher in the highest quintile. The differences in relative risks were more extreme for fatal versus incident stroke events, 2.7-fold and 2.0-fold, respectively. The magnitude of associations were similar when the analyses were restricted to specific stroke sub-types, with slightly stronger associations for HS than IS. For 1 SD increase in usual mFI-1, the risk of total stroke, IS, and HS events were: HRs (95%CI) 1.19 (1.17-1.22), 1.17 (1.15-1.20), and 1.24 (1.18-1.30), respectively. The patterns of associations using usual mFI-3 quintiles (**Figure 8.4**) were similar to those observed with mFI-1, but the magnitude of associations was smaller.

Figure 8.3 Adjusted hazard ratios (95% CI) for the association between usual mFI-1 quintile and incident stroke (total stroke, IS, and HS)



Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day).

Figure 8.4 Adjusted hazard ratios (95% CI) for the association between usual mFI-3 quintile and incident stroke (total stroke, IS, and HS)

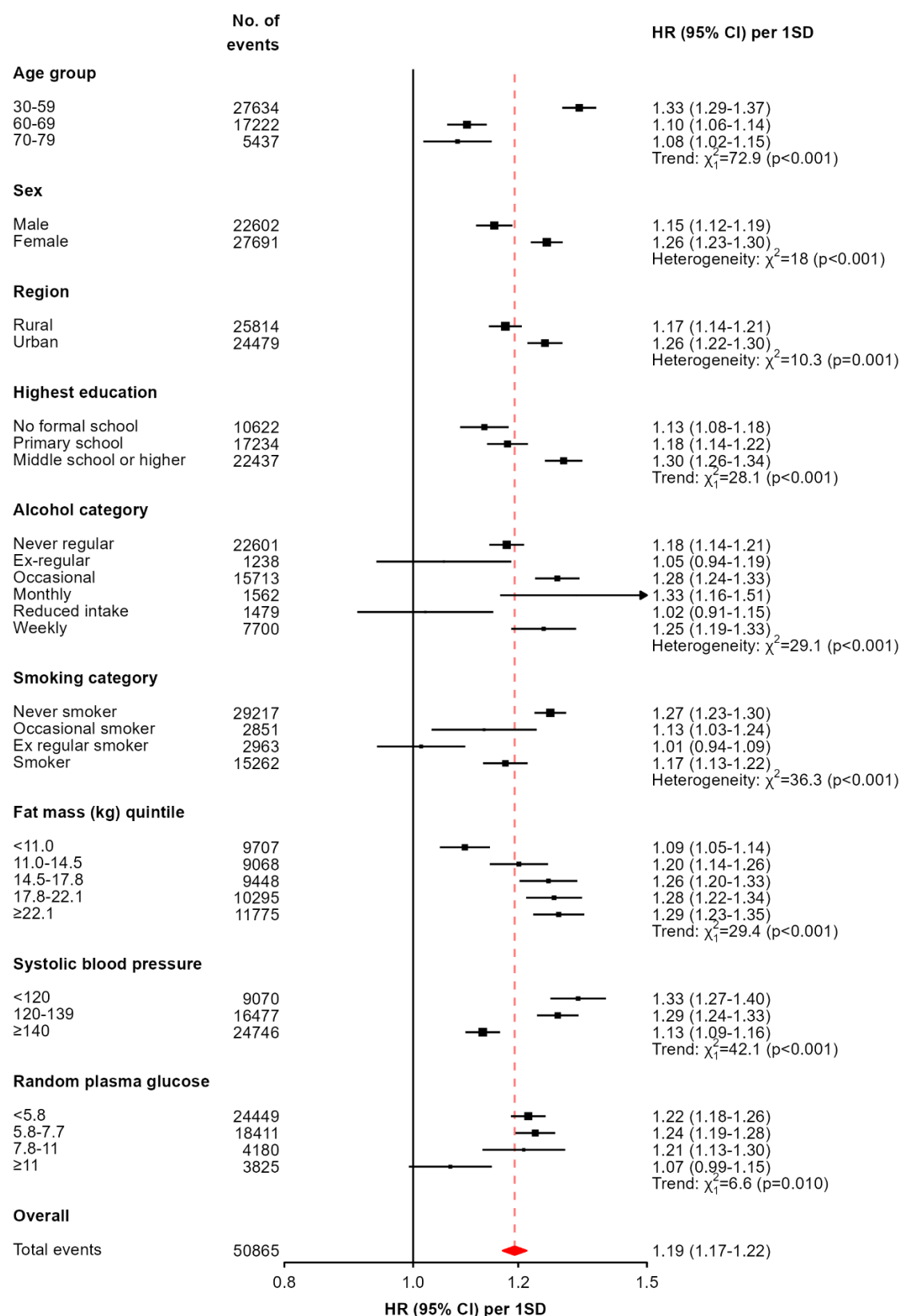


Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day).

The associations of usual frailty with incident stroke by subgroups are shown in **Figure 8.5** (usual mFI-1) and **Figure 8.6** (usual mFI-3). Using the mFI-1, associations were stronger in the following groups: younger age groups (baseline age 30-59 years, $p_{\text{trend}} < 0.001$), females ($p_{\text{heterogeneity}} < 0.001$), those living in urban regions ($p_{\text{heterogeneity}} = 0.001$), those with middle or higher education ($p_{\text{trend}} < 0.001$), drinkers ($p_{\text{heterogeneity}} < 0.001$), and never smokers ($p_{\text{heterogeneity}} < 0.001$). Associations were also stronger in individuals with higher fat mass ($p_{\text{trend}} < 0.001$), lower SBP ($p_{\text{trend}} < 0.001$), and lower RPG ($p_{\text{trend}} = 0.010$) levels at baseline. Similar patterns were found when different levels of the effect modifiers were used (**Figure S8.1**). Additionally, associations were stronger among participants without hypertension ($p_{\text{heterogeneity}} = 0.001$) but did not differ by diabetes status ($p_{\text{heterogeneity}} = 0.099$) or RPG quintiles ($p_{\text{trend}} = 0.569$). The same trends were observed using the mFI-3 definition for either categorical definitions of the effect modifiers (**Figure 8.6** and **Figure S8.2**).

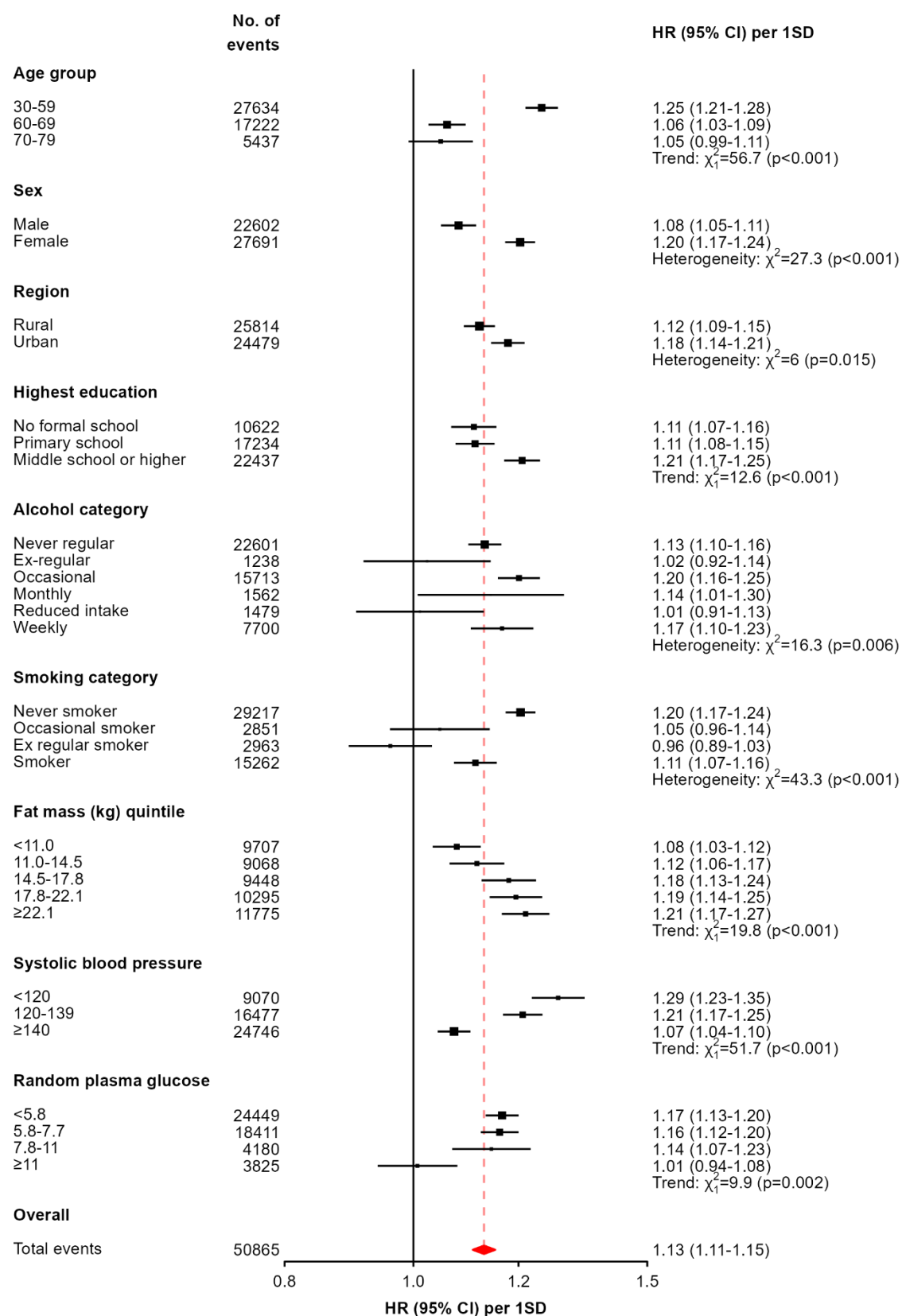
When the associations were stratified by region, they were significantly higher among urban than rural residents and different between the 10 study regions ($p_{\text{heterogeneity}} < 0.001$), with the highest associations in 2 urban regions, Qingdao (HR [95%CI]: 1.42 [1.25-1.63]) and Liuzhou (1.42 [1.32-1.52]), and the weakest in 2 rural regions, Gansu (1.10 [1.03-1.17]) and Hunan (1.08 [1.01-1.15]) (**Figure S8.9**). The pattern was similar using the mFI-3 (**Figure S8.10**).

Figure 8.5 Adjusted hazard ratios (95% CI) for the association between usual m-FI and incident stroke in subgroups



Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day) where appropriate.

Figure 8.6 Adjusted hazard ratios (95% CI) for the association between usual mFI-3 and incident stroke in subgroups

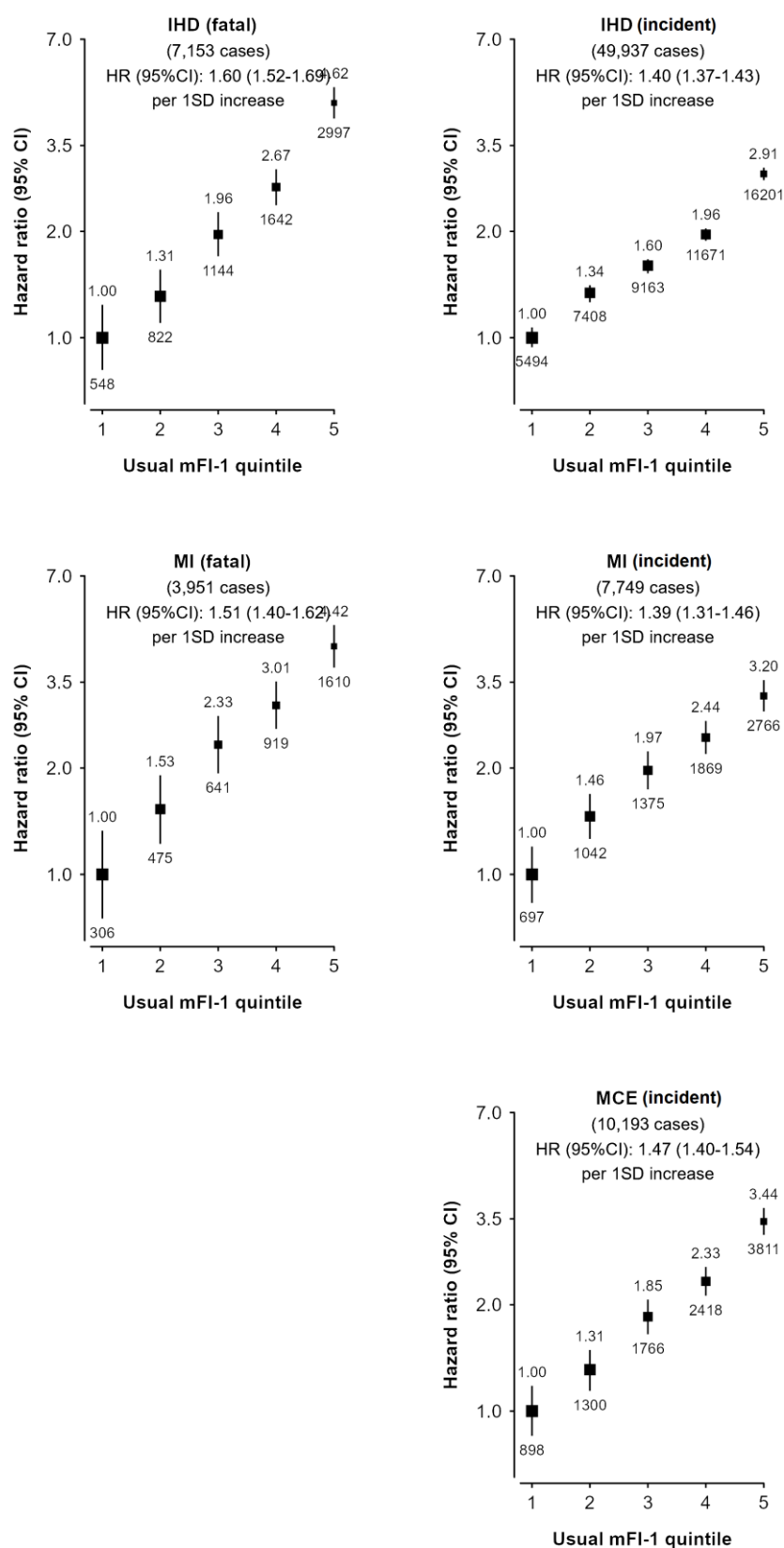


Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day) where appropriate.

IHD and subtypes

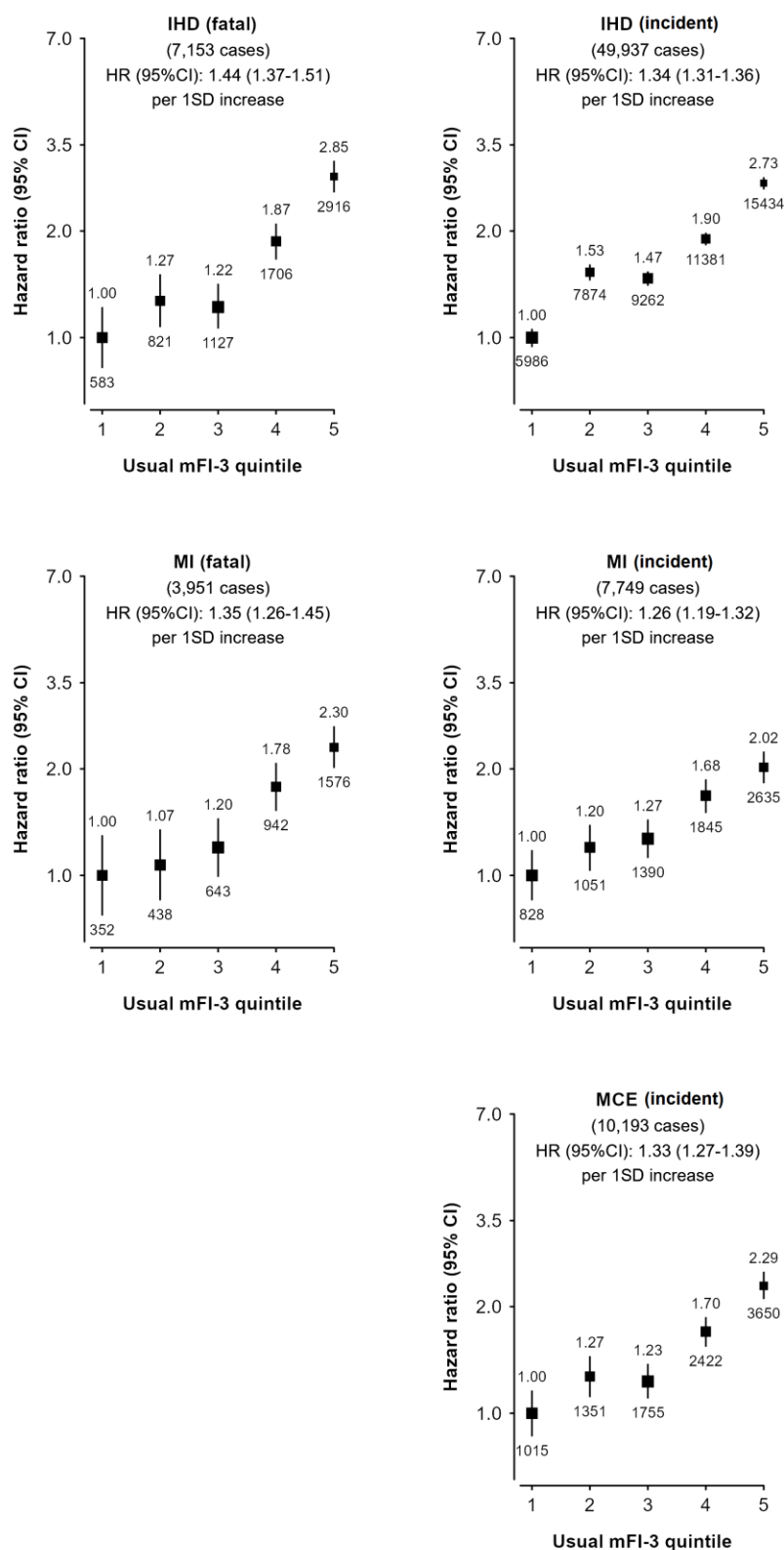
Figure 8.7 shows the association between usual mFI-1 quintile and IHD, MI (fatal or incident event), and MCE (incident event). A log-linear positive association was also found between usual mFI-1 and the risk of IHD, MI, and MCE. Compared to the reference group (lowest mFI-1 quintile), the risk of incident IHD was 2.9-fold higher in the highest quintile, and this difference in risk was more extreme for fatal versus incident IHD outcomes, 4.6-fold and 2.9-fold, respectively. The strength of the associations was similar when the analyses were restricted to specific endpoints, with slightly stronger associations for MCE than MI outcomes, HRs (95%CI) per 1 SD increase in usual mFI-1 for total IHD, MI, and MCE events were 1.40 (1.37-1.43), 1.39 (1.31-1.46), and 1.47 (1.40-1.54), respectively. The patterns of associations using usual mFI-3 quintiles (**Figure 8.8**) were similar to those observed with mFI-1, but the strength of associations was attenuated.

Figure 8.7 Adjusted hazard ratios (95% CI) for the association between usual mFI-1 quintile and incident IHD (total IHD, MI, and MCE)



Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day).

Figure 8.8 Adjusted hazard ratios (95% CI) for the association between usual mFI-3 quintile and incident IHD (total IHD, MI, and MCE)

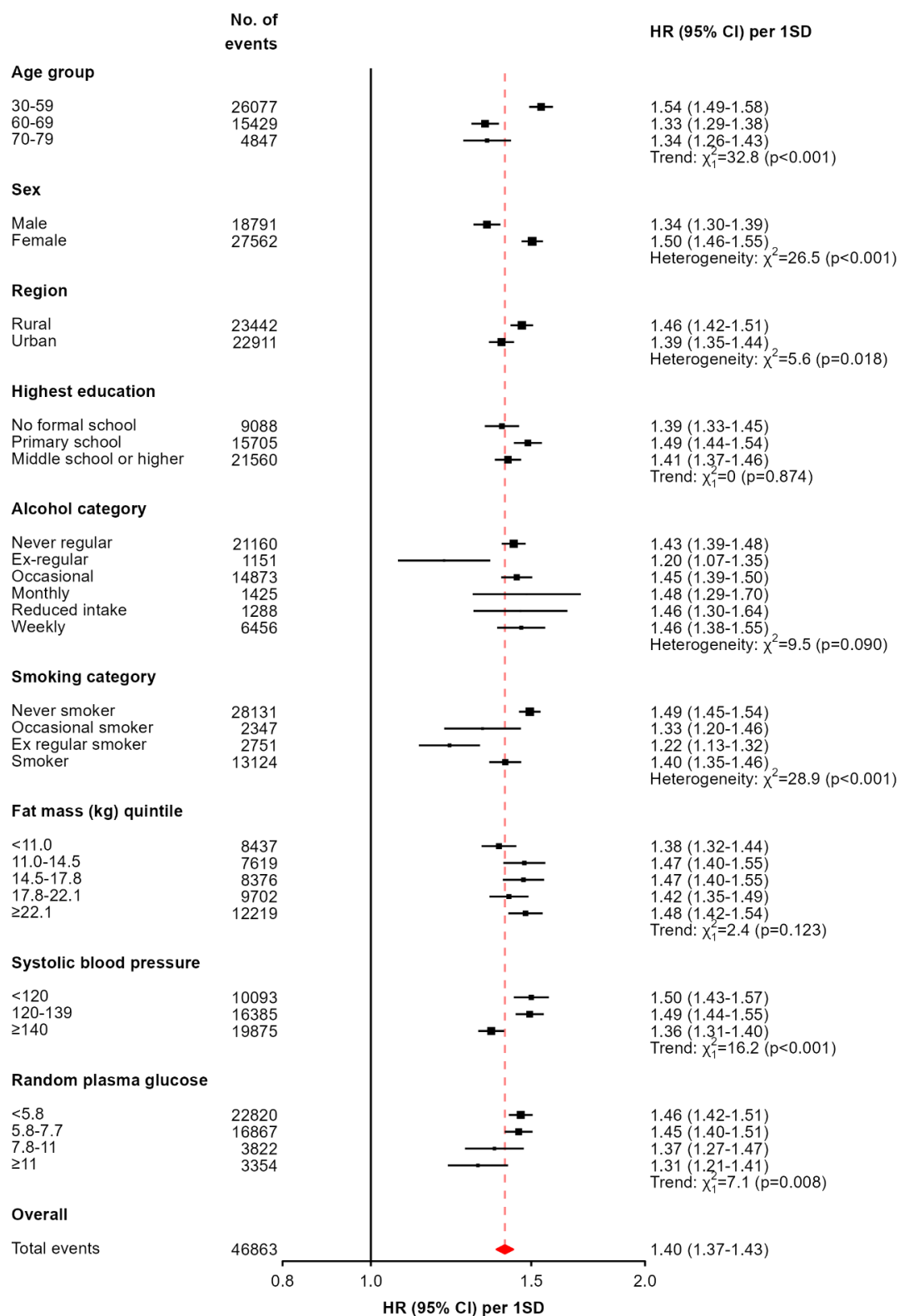


Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day).

The associations of usual frailty and incident IHD by subgroups are shown in **Figure 8.9** (usual mFI-1) and **Figure 8.10** (usual mFI-3). Using the mFI-1, associations were stronger in the following groups: younger age groups (baseline age 30-59, $p_{\text{trend}} < 0.001$), females ($p_{\text{heterogeneity}} < 0.001$), those living in rural regions ($p_{\text{heterogeneity}} = 0.018$), and never smokers ($p_{\text{heterogeneity}} < 0.001$). Associations were also stronger in individuals with lower levels of SBP ($p_{\text{trend}} < 0.001$) and lower RPG ($p_{\text{trend}} = 0.008$) levels at baseline (**Figure 8.9**). Conversely, associations did not differ by levels of education ($p_{\text{trend}} = 0.874$), alcohol consumption ($p_{\text{heterogeneity}} = 0.090$), or fat mass ($p_{\text{trend}} = 0.123$) levels. Similar patterns were found when different levels of the effect modifiers were used (**Figure S8.3**). Additionally, associations were stronger among individuals without hypertension ($p_{\text{heterogeneity}} < 0.001$) or diabetes ($p_{\text{heterogeneity}} < 0.001$). Similar trends were observed using the mFI-3 definition for either categorical definitions of the effect modifiers (**Figure 8.10** and **Figure S8.4**).

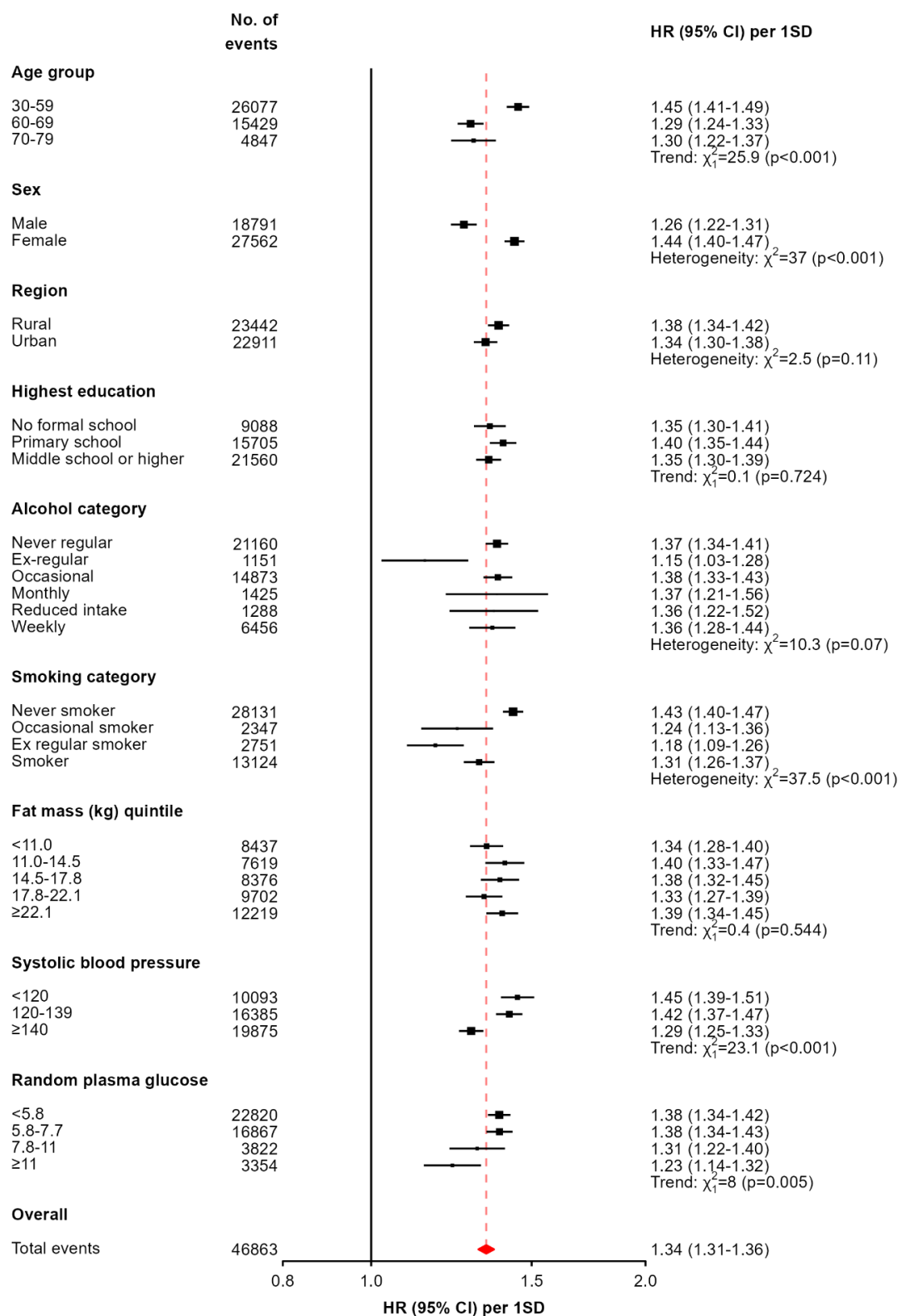
Associations also varied significantly across the 10 study regions ($p_{\text{heterogeneity}} < 0.001$), which were strongest in Qingdao (HR [95%CI]: 1.59 [1.46-1.74]) and Sichuan (1.61 [1.52-1.71]), and weakest in Haikou (1.18 [1.05-1.33]) and Gansu (1.29 [1.21-1.37]) (**Figure S8.11**). The patterns were similar using the mFI-3 (**Figure S8.12**).

Figure 8.9 Adjusted hazard ratios (95% CI) for the association between usual mFI-1 and incident IHD in subgroups



Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day) where appropriate.

Figure 8.10 Adjusted hazard ratios (95% CI) for the association between mFI-3 and incident IHD in subgroups

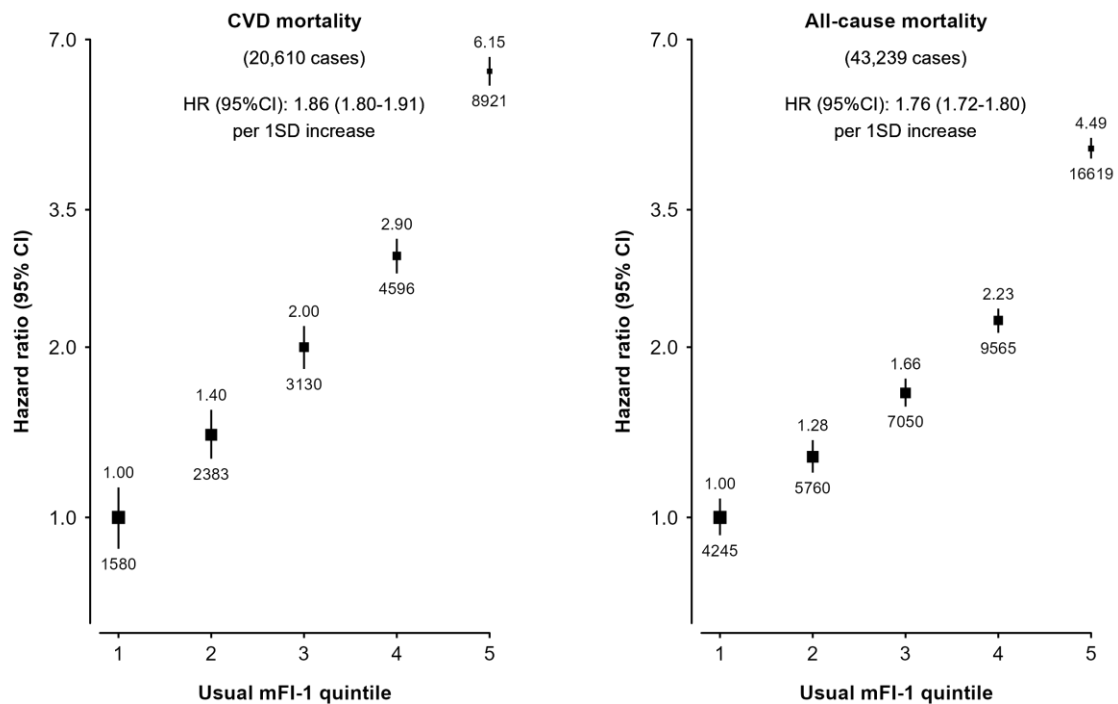


Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day) where appropriate.

CVD- and all-cause mortality

Figure 8.11 shows a log-linear relationship between usual mFI-1 and CVD and all-cause mortality with 86% (80%-91%) higher risk of CVD mortality and 76% (72%-80%) higher risk of all-cause mortality per 1 SD increase in usual mFI-1.

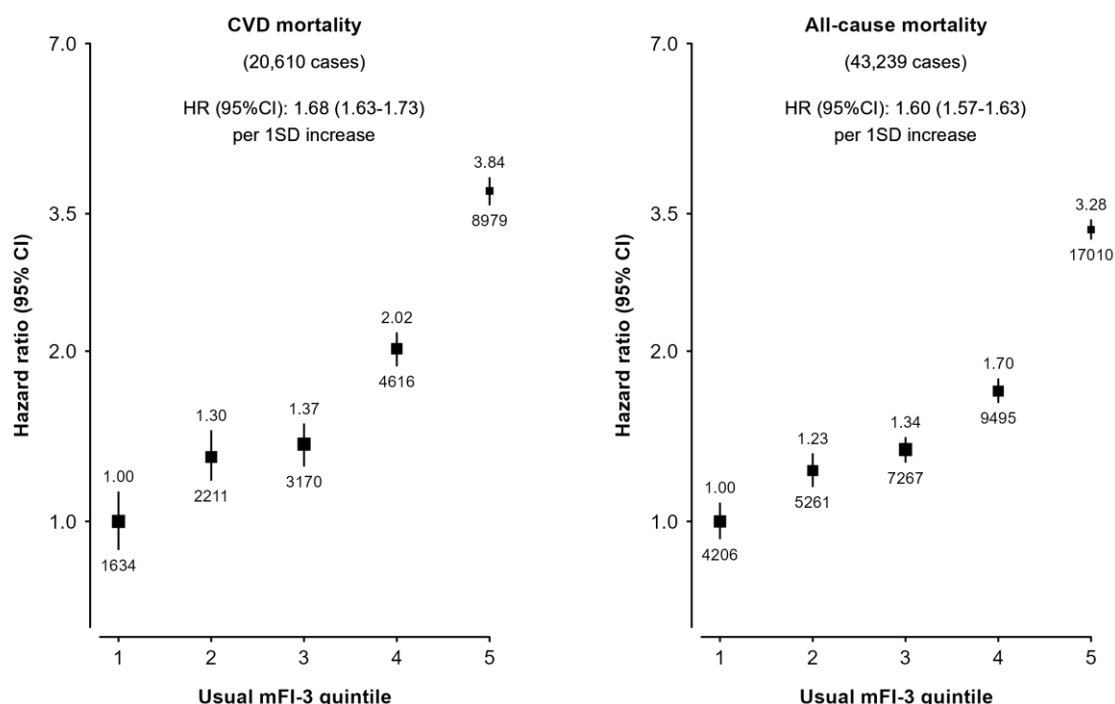
Figure 8.11 Adjusted hazard ratios (95% CI) for the associations between usual mFI-1 quintile and CVD- and all-cause mortality



Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day).

These associations were slightly attenuated using the mFI-3, but there was a similar linear association between usual mFI-3 and CVD and all-cause mortality (**Figure 8.12**).

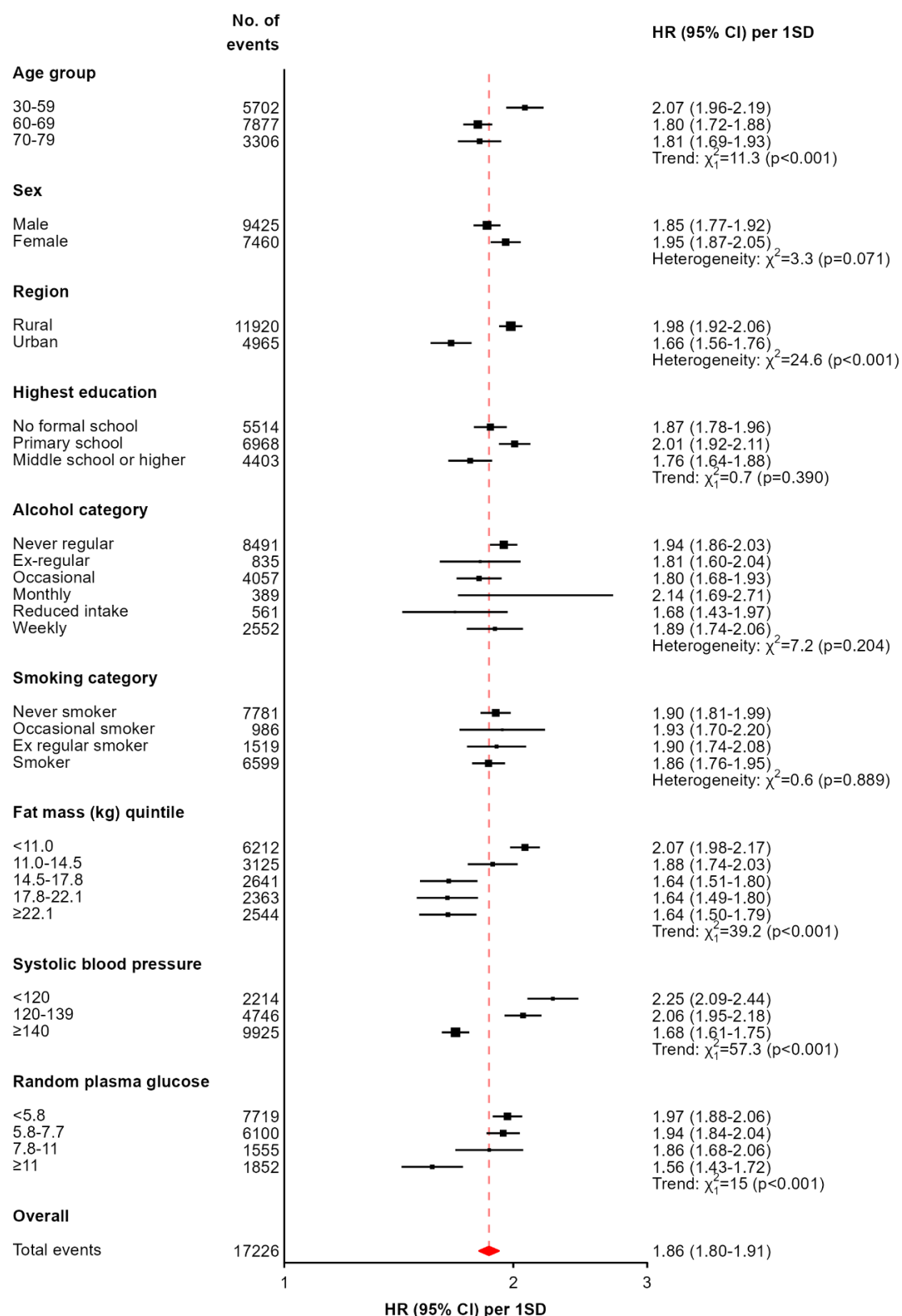
Figure 8.12 Adjusted hazard ratios (95% CI) for the associations between usual mFI-3 quintile and CVD- and all-cause mortality



Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day).

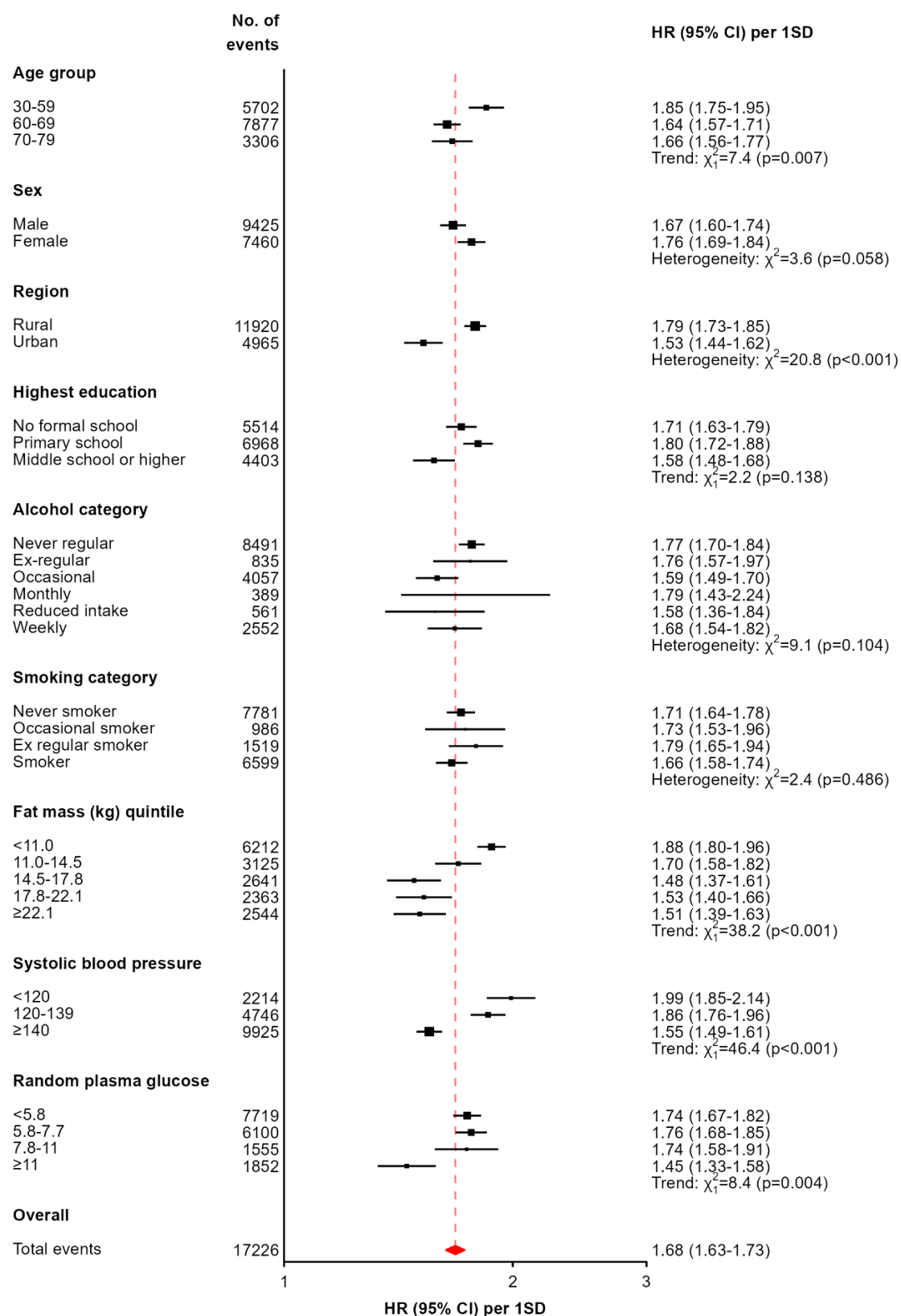
In the subgroup analysis of the associations between usual mFI-1 and CVD mortality, associations were stronger in younger age groups ($p_{\text{trend}} < 0.001$), rural residents ($p_{\text{heterogeneity}} < 0.001$), and in individuals with lower fat mass ($p_{\text{trend}} < 0.001$), lower SBP ($p_{\text{trend}} < 0.001$), lower RPG ($p_{\text{trend}} < 0.001$) levels (**Figure 8.13**), without hypertension ($p_{\text{heterogeneity}} < 0.001$), and without diabetes ($p_{\text{heterogeneity}} < 0.001$) (**Figure S8.5**). CVD mortality did not differ by sex ($p_{\text{heterogeneity}} = 0.071$), highest education ($p_{\text{trend}} = 0.390$), alcohol consumption ($p_{\text{heterogeneity}} = 0.204$), and smoking status ($p_{\text{heterogeneity}} = 0.889$). Similar patterns were found using the mFI-3 (**Figure 8.14** and **Figure S8.6**).

Figure 8.13 Adjusted hazard ratios (95% CI) for the association between usual mFI-1 and CVD mortality in subgroups



Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day) where appropriate.

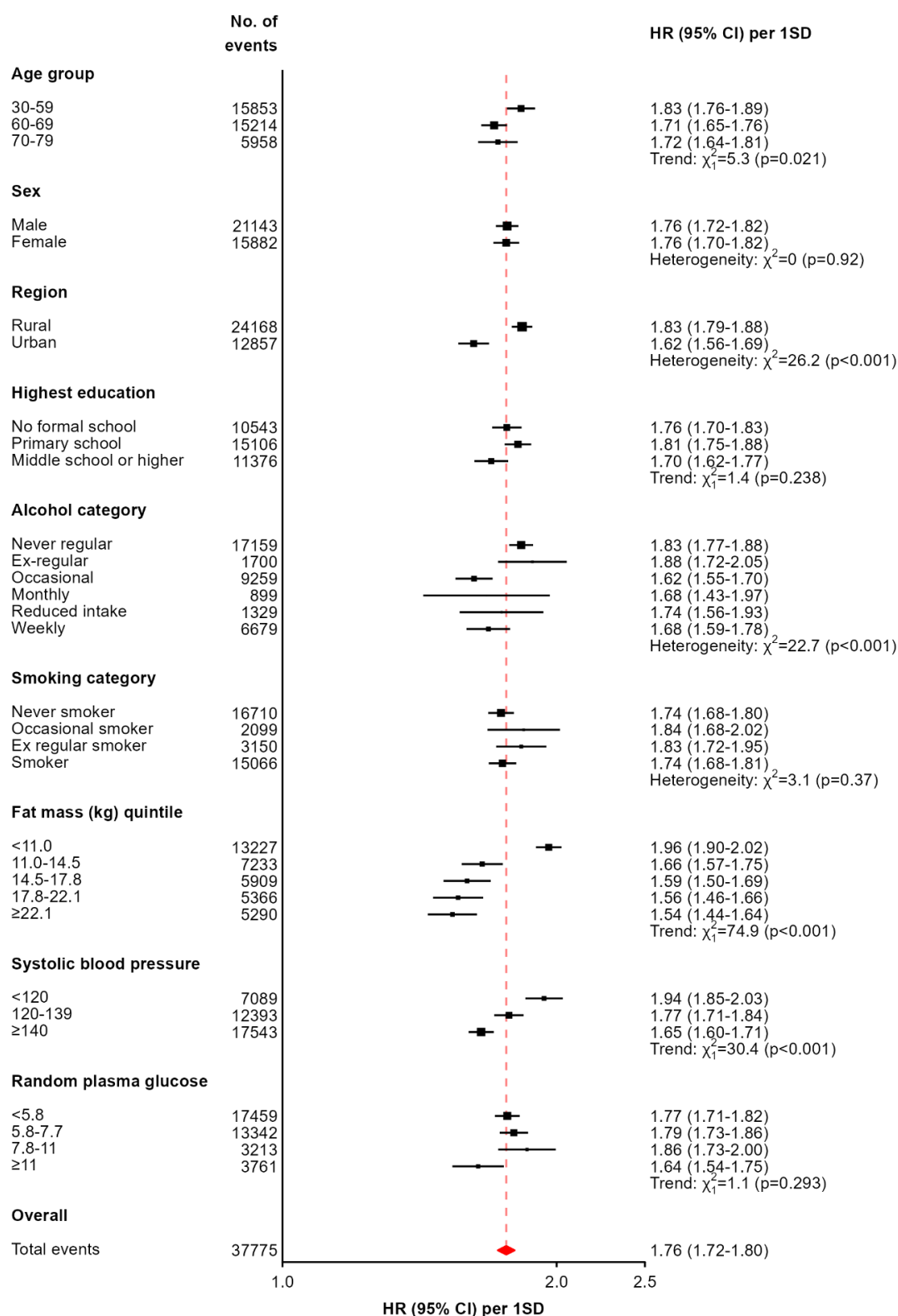
Figure 8.14 Adjusted hazard ratios (95% CI) for the association between usual mFI-3 and CVD mortality in subgroups



Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day) where appropriate.

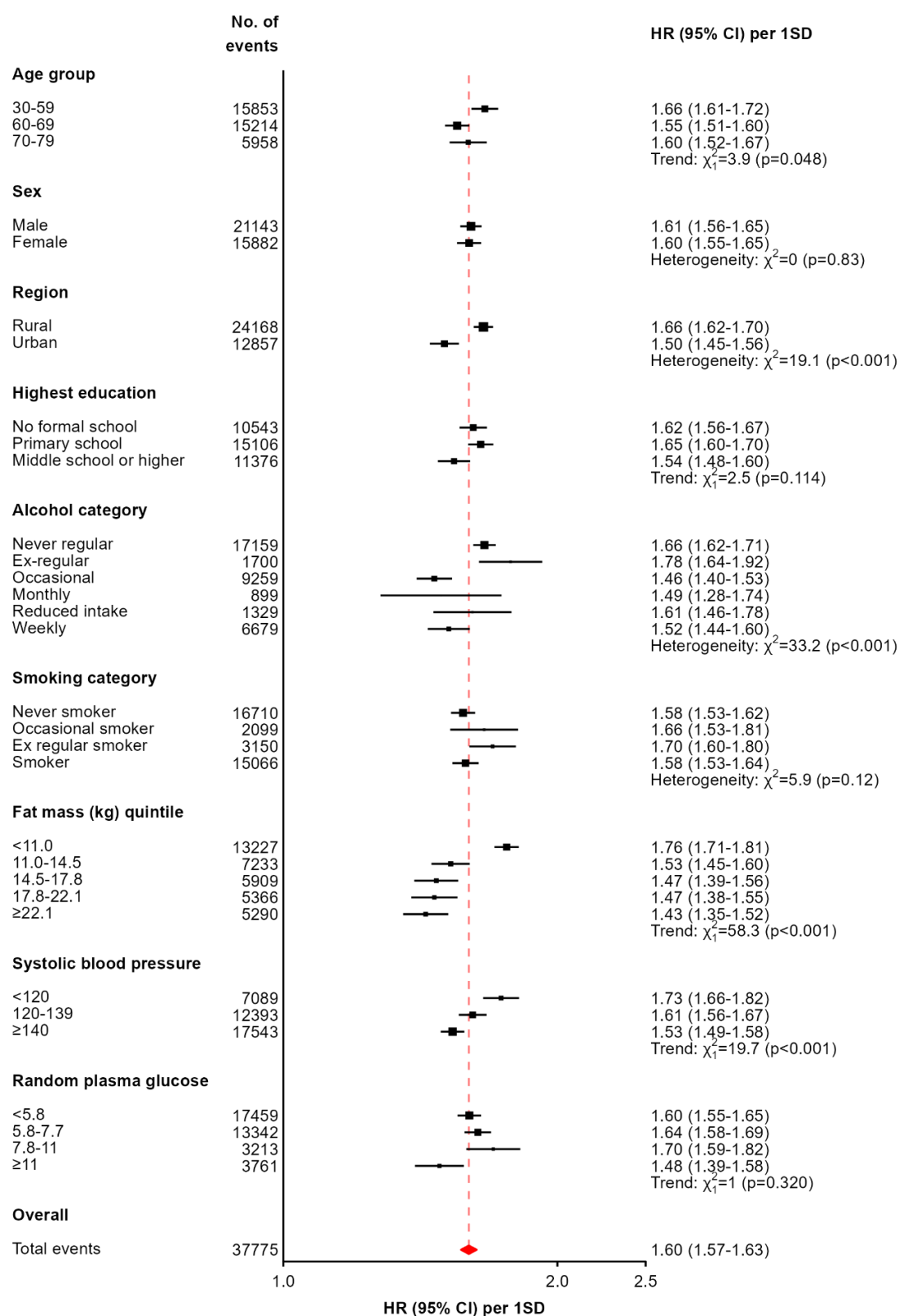
In the subgroup analysis of the associations between usual mFI-1 and all-cause mortality, associations were also stronger in younger age groups ($p_{\text{trend}}=0.021$), rural residents ($p_{\text{heterogeneity}}<0.001$), never or ex-regular drinkers ($p_{\text{heterogeneity}}<0.001$), and individuals with lower fat mass ($p_{\text{trend}}<0.001$), lower SBP ($p_{\text{trend}}<0.001$) (**Figure 8.15**), without hypertension ($p_{\text{heterogeneity}}<0.001$), and without diabetes ($p_{\text{heterogeneity}}=0.04$) (**Figure S8.7**). Risk of all-cause mortality did not differ by sex ($p_{\text{heterogeneity}}=0.92$), education level ($p_{\text{trend}}=0.238$), smoking status ($p_{\text{heterogeneity}}=0.37$), and RPG levels ($p_{\text{trend}}=0.293$). Similar patterns were found using the mFI-3 (**Figure 8.16** and **Figure S8.8**).

Figure 8.15 Adjusted hazard ratios (95% CI) for the association between usual mFI-1 and all-cause mortality in subgroups



Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day) where appropriate.

Figure 8.16 Adjusted hazard ratios (95% CI) for the association between usual mFI-3 and all-cause mortality in subgroups



Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day) where appropriate.

8.3.2 Assessment of reverse causation bias

Exclusion of participants with underlying illness

Several 'healthier' subsets of the CKB population were selected by excluding individuals with underlying illnesses and used to examine the potential for reverse causation bias in relation to frailty-associated incident CVD outcomes and all-cause mortality. The subsets were: (1) participants who did not report unintentional weight loss at baseline (n=439,636); (2) participants who did not die within the first 5 years of follow-up (n=475,034), (3) participants who did not report poor self-rated health status at baseline (n=443,421); and (4) participants who were never smokers, did not report unintentional weight loss or poor self-rated health at baseline, and did not die within first 5 years (n=297,387). **Table 8.3** shows the adjusted HRs (95%CI) for associations between baseline mFI-1 and mFI-3 (per 1 SD increase) and incident stroke, incident IHD, CVD mortality, and all-cause mortality in each subset.

For CVD- and all-cause mortality, most of the different participant exclusions resulted in an attenuation of associations between frailty (mFI-1) and outcomes. The largest attenuation of associations was seen in the 'healthy' subset that excluded participants who died within 5 years of follow-up, were ever smokers, and reported unintentional weight loss or poor self-rated health at baseline. In the total cohort, 1 SD higher mFI-1 was associated with 31% (30%-33%) and 28% (27%-29%) higher risk of CVD- and all-cause mortality, respectively. In the 'healthy' subset, this attenuated to 25% (20%-29%) and 18% (15%-21%), respectively. Other subsets ('no early deaths' and 'no poor self-rated health' subsets) had smaller attenuations in the associations between frailty and CVD or all-cause mortality, whilst the exclusion of participants with unintentional weight loss did not attenuate or change these associations. A similar pattern was observed using the mFI-3.

For the association between baseline frailty (mFI-1) and incident stroke, the exclusion of different population subsets resulted in very small changes in the strength of the association between frailty and incident stroke. The exclusion of participants who reported unintentional weight loss, poor self-rated health, or early deaths did not significantly change the strength of

the association. Conversely, the associations became stronger in the 'healthy cohort'. In the total cohort, 1 SD higher mFI-1 was associated with 8% (7%-9%) higher risk of stroke; after excluding early deaths, ever smokers, and those reporting unintentional weight loss and poor self-rated health (i.e. the 'healthy' cohort), this association increased to 10% (9%-12%). A similar pattern was observed using the mFI-3.

For the association between baseline frailty (mFI-1 or mFI-3) and incident IHD, the exclusion of different population subsets resulted in largely no change in the strength of the association between frailty and incident IHD. Only the exclusion of participants reporting poor self-rated health at baseline resulted in a small attenuation in the strength of association. In the total cohort, 1 SD higher mFI-1 was associated with 16% (15%-17%) higher risk of IHD; after excluding individuals reporting poor self-rated health at baseline, this association attenuated to 14% (13%-16%). A similar pattern was observed using the mFI-3.

Table 8.3 Adjusted hazard ratios (95% CI) for the associations between baseline FI and incident stroke, IHD, CVD mortality, and all-cause mortality in healthier subsets of the CKB population

	Stroke		IHD		CVD mortality		All-cause mortality	
	No. events	HR (95% CI) per 1 SD	No. events	HR (95% CI) per 1 SD	No. events	HR (95% CI) per 1 SD	No. events	HR (95% CI) per 1 SD
Modified FI-1								
Total	54193	1.08 (1.07-1.09)	49937	1.16 (1.15-1.17)	20610	1.31 (1.30-1.33)	43239	1.28 (1.27-1.29)
No unintentional weight loss	48234	1.08 (1.07-1.10)	44296	1.17 (1.16-1.18)	18104	1.33 (1.31-1.35)	37786	1.28 (1.27-1.29)
No early deaths	50872	1.09 (1.08-1.10)	47491	1.17 (1.16-1.18)	14568	1.29 (1.27-1.31)	28825	1.24 (1.23-1.26)
No poor self-rated health	47351	1.08 (1.07-1.09)	43055	1.14 (1.13-1.16)	16406	1.26 (1.24-1.28)	35489	1.23 (1.21-1.24)
No early deaths, never smokers, no unintentional weight loss & no poor self-rated health	23464	1.10 (1.08-1.12)	22529	1.17 (1.15-1.19)	5042	1.25 (1.20-1.29)	10068	1.18 (1.15-1.21)
Modified FI-3								
Total	54193	1.06 (1.05-1.06)	49937	1.14 (1.13-1.15)	20610	1.26 (1.24-1.27)	43239	1.23 (1.22-1.24)
No unintentional weight loss	48234	1.06 (1.05-1.07)	44296	1.14 (1.13-1.15)	18104	1.26 (1.24-1.28)	37786	1.22 (1.21-1.23)
No early deaths	50872	1.06 (1.05-1.07)	47491	1.14 (1.13-1.15)	14568	1.23 (1.21-1.25)	28825	1.20 (1.18-1.21)
No poor self-rated health	47351	1.05 (1.04-1.06)	43055	1.12 (1.10-1.13)	16406	1.19 (1.17-1.21)	35489	1.17 (1.16-1.18)
No early deaths, never smokers, no unintentional weight loss & no poor self-rated health	23464	1.07 (1.05-1.09)	22529	1.14 (1.13-1.16)	5042	1.17 (1.13-1.21)	10068	1.13 (1.11-1.16)

Original FI: 28-item FI; mFI-1: 24-item FI (excluding cardiovascular deficits); mFI-3 = 21-item FI (excluding cardiovascular and adiposity deficits).

Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day).

Comparison of associations by the length of follow-up

The potential for reverse causation bias was also explored by comparing the strength of associations by different lengths of follow-up (1, 3, 5, 8, and 13 [total follow-up] years). **Table 8.4** shows the adjusted HRs (95%CI) for associations per 1 SD increase in baseline FI and outcomes by the length of follow-up.

The association between baseline mFI-1 and all-cause mortality was strongest in the first year of follow-up (HR [95%CI]: 1.46 [1.41-1.51]), which decreased progressively with each incremental increase in duration of follow-up. The strength of associations attenuated by 39% (1.28 [1.27-1.29]) at the longest duration of follow-up (13 years) and by 48% (1.24 [1.23-1.26]) after the additional exclusion of early deaths. A similar pattern was observed for the association between frailty and CVD mortality: the strength of association in the first year of follow-up (1.49 [1.41-1.57]) decreased by 36% (1.31 [1.30-1.33]) and 41% (1.29 [1.27-1.31]), respectively. For incident stroke and IHD, similar attenuations in the strength of associations with baseline mFI-1 were observed (-30-38%) between the first year and longest follow-up, but the additional exclusion of early deaths did not attenuate the associations further. The pattern was equivalent using the mFI-3.

Table 8.4 Adjusted hazard ratios (95% CI) for the associations between baseline FI and incident stroke, IHD, CVD mortality, and all-cause mortality by length of follow-up

Length of follow-up	Stroke		IHD		CVD mortality		All-cause mortality	
	No. events	HR (95% CI) per 1 SD	No. events	HR (95% CI) per 1 SD	No. events	HR (95% CI) per 1 SD	No. events	HR (95% CI) per 1 SD
Modified FI-1								
1 year	2159	1.13 (1.09-1.18)	2607	1.23 (1.19-1.28)	769	1.49 (1.41-1.57)	1926	1.46 (1.41-1.51)
3 years	8705	1.10 (1.08-1.13)	9039	1.19 (1.17-1.22)	3025	1.42 (1.38-1.46)	7562	1.38 (1.35-1.40)
5 years	17410	1.09 (1.08-1.11)	16762	1.18 (1.16-1.20)	6049	1.38 (1.35-1.41)	14431	1.34 (1.32-1.35)
8 years	33830	1.09 (1.07-1.10)	31632	1.17 (1.16-1.18)	11856	1.35 (1.33-1.37)	26601	1.30 (1.29-1.32)
Total (13 years)	54193	1.08 (1.07-1.09)	49937	1.16 (1.15-1.17)	20610	1.31 (1.30-1.33)	43239	1.28 (1.27-1.29)
Total (excluding early deaths)	50872	1.09 (1.08-1.10)	47491	1.17 (1.16-1.18)	14568	1.29 (1.27-1.31)	28825	1.24 (1.23-1.26)
Modified FI-3								
1 year	2159	1.10 (1.05-1.14)	2607	1.21 (1.17-1.25)	769	1.41 (1.33-1.48)	1926	1.36 (1.31-1.40)
3 years	8705	1.07 (1.05-1.09)	9039	1.17 (1.14-1.19)	3025	1.35 (1.32-1.39)	7562	1.30 (1.28-1.33)
5 years	17410	1.06 (1.05-1.08)	16762	1.15 (1.14-1.17)	6049	1.32 (1.30-1.35)	14431	1.27 (1.25-1.29)
8 years	33830	1.06 (1.05-1.07)	31632	1.14 (1.13-1.16)	11856	1.29 (1.27-1.31)	26601	1.25 (1.23-1.26)
Total (13 years)	54193	1.06 (1.05-1.06)	49937	1.14 (1.13-1.15)	20610	1.26 (1.24-1.27)	43239	1.23 (1.22-1.24)
Total (excluding early deaths)	50872	1.06 (1.05-1.07)	47491	1.14 (1.13-1.15)	14568	1.23 (1.21-1.25)	28825	1.20 (1.18-1.21)

Original FI: 28-item FI; mFI-1: 24-item FI (excluding cardiovascular deficits); mFI-3 = 21-item FI (excluding cardiovascular and adiposity deficits).

Cox PH models were stratified by 5-year age-at-risk groups, sex, and study region, and adjusted for education level, income level, marital status, alcohol consumption, smoking status, SBP (mmHg), RPG (mmol/L), poor diet, and physical activity (MET-hours/day).

8.4 Discussion

The present chapter includes a detailed analysis of the associations between frailty and the major CVD types in Chinese older adults without a previous CVD diagnosis. Frailty is an increasing public health burden in an ageing population, but its aetiology and consequences are still not well understood. The initial chapters of this thesis identified several gaps in the current research including few studies investigating the risk of stroke or IHD from frailty with limited investigation on how associations differed by the CVD subtypes and in subpopulations (**Chapter 4**). Also, high within-person variability in the measurement of the main frailty instruments was detected (**Chapter 3**) but few studies in the literature accounted for this. Lastly, analyses of **Chapter 7** suggested strong potential for circularity between the exposure (FI) and outcome (CVD) and the inclusion of cardiovascular deficits in the FI may inflate the association. Therefore, the present chapter aimed to study the associations between frailty and CVD types, correcting for regression dilution bias, and investigated how the associations differed by the main subtypes and among various population subgroups. Additionally, the potential for circularity in the associations were investigated by comparing different definitions of the FI. The analyses found strong positive log-linear associations of frailty with stroke, IHD, CVD mortality, and all-cause mortality among Chinese adults aged 30-79 years old without prior CVD.

8.4.1 *Frailty and risk of incident stroke*

In **Chapter 4**, a literature review of studies investigating the association of frailty with incident stroke identified 9 studies. The studies reported that frailty was associated with a greater risk of incident stroke compared to being non-frail, with varied magnitude of relative risks. Being frail (vs non-frail) at baseline was associated with 43% (SLAS)²²² to over 200% (VHA)²¹⁸ higher risk for incident stroke according to the FI model and 10% (ASPREE)²¹⁶ to 200% (SHARE)²¹⁷ according to the FP model. The corresponding risk estimates from the present chapter ranged from 8% to 45% depending on the FI definition (which strengthened to 20% to 84% after correction for regression dilution bias). However, these risk estimates are not directly

comparable for several reasons. First, the studies were conducted in different populations. The studies in the literature review generally involved older populations and may have included individuals with prior history of heart disease or stroke (SHARE).²¹⁷ Thus, the stronger associations found in the literature review may be attributed to these differences in the population studied that had greater baseline risks for CVD. Second, the studies used different stroke definitions (e.g. fatal and non-fatal stroke). Also, the precise definition of stroke was not stated in certain studies (e.g. NHAT²¹⁵ and SHARE).²¹⁷ Thus, the misclassification and uncertain ascertainment methods of the outcomes in some studies may have under- or over-estimated the associations. Lastly, the included studies used different definitions of frailty. For instance, FP may have a stronger association with stroke than the FI: the components of the FP cycle, such as physical inactivity, muscle wasting, and poor nutrition, may lead to build-up of fatty material in the arteries supplying the brain and subsequently stroke. Conversely, the inclusion of cardiovascular deficits in the FI (e.g. VHA)²¹⁸ may have resulted in an overestimation of the relationship between FI and stroke. Thus, the degree of circularity likely to be present in any frailty model may have also influenced its association with stroke.

8.4.2 Frailty and risk of incident IHD

The literature review identified 12 studies reporting the prospective association between frailty and incident IHD (**Chapter 4**). However, the definition of IHD varied significantly between the studies making comparisons difficult. In studies that reported (acute) MI, frailty (vs non-frail) at baseline was associated with HRs (95%CI) of 1.95 (1.31-2.90) (NHAT),²¹⁵ 2.52 (1.74-3.65) (ASPREE),²¹⁶ and 2.9 (2.8-3.0) (VHA).²¹⁸ The corresponding HRs (95%CI) for MI found in the present chapter were 1.95 (1.77-2.15), 1.58 (1.43-1.74), and 1.33 (1.17-1.52) for the original FI, mFI-1, and mFI-3, respectively. These associations were more extreme after adjustment for regression dilution bias: 3.00 (2.55-3.52), 2.83 (2.27-3.52) and 1.93 (1.42-2.61), respectively. Although a similar magnitude of association was found, the differences in the definition of frailty, outcomes, and population between the studies found in the literature review

and the present chapter are the same as those described for incident stroke (**Section 8.4.1**), which limit the comparability of the risk estimates.

8.4.3 Comparison with prior CKB analysis

The literature review of the prospective associations between frailty and stroke or IHD (**Chapter 4**) identified a previous study that used CKB data (Fan *et al.*, 2020).²¹⁹ This study aimed to test the predictive value of the FI in Chinese middle-aged and older adults by examining the associations between FI and fatal outcomes, including IHD and all-cause mortality. While some overlap exists with the analyses conducted in the present chapter, the distinct aims of this thesis and its findings have resulted in more accurate and reliable estimation of the strength of the associations between the FI and CVD outcomes in Chinese adults. This section will compare the methods and findings of the two analyses.

The two studies used similar methodology. Both studies applied similar participant exclusions and used the same approach define the FI and ascertain outcomes. While some differences in the specification of the Cox proportional hazards models were present, both studies used appropriate methods to account for the confounding effect of age and adjusted for the major confounders of the frailty and CVD relationship. There were several notable differences that distinguish the two studies. First, the present chapter used several modified versions of the FI, which showed substantial differences in the strength of associations depending on the FI definition used. This illustrates the presence of circularity in the association between FI and CVD outcomes and suggests that previous studies may have overestimated these associations. Another important difference is the outcomes studied. Fan *et al.* investigated fatal CVD outcomes (IHD and cerebrovascular mortality) only, while the present chapter explored a wider range of outcomes including different types of CVD (stroke and IHD) and their subtypes. Importantly, these individual outcomes were investigated by fatal events. Thus, the findings of the present chapter could inform whether there are any differential effects of frailty on individual CVD outcomes. A key aim of this thesis was to investigate the measurement properties of the major frailty instruments, including the reliability of FI scores,

the findings of which prompted the author to correct for regression dilution bias. The findings of this chapter showed that adjusting for this bias resulted in much stronger and reliable FI-CVD associations, suggesting that previous estimations may be under-estimated. According to Fan *et al.* (2020),²¹⁹ 0.1 increment in baseline FI was associated with HR (95%CI) of 1.81 (1.75-1.88) for IHD mortality in CKB participants without prior heart disease. In the present chapter, the corresponding HRs (95%CI) after correction for regression dilution bias were 2.22 (2.07-2.37), 2.11 (1.94-2.25), and 1.18 (1.67-1.97) for the original FI, mFI-1, and mFI-3, respectively. Other differences between the studies included the assessment of the shape of associations (the present chapter showed a log-linear relationship between FI and CVD outcomes) and more detailed investigation of effect modification and reverse causation bias in the present chapter. Fan *et al.* investigated effect modification by age and sex (described further in the next **Section 8.4.4**) and the presence of reverse causation bias by removing deaths during the first 5 years of follow-up. The present chapter also demonstrated evidence of reverse causation bias by comparing varying durations of follow-up (1, 3, 5, 8, and 13 years) and by repeating analyses in healthy participants.

8.4.4 Investigation of effect modification

Previous studies of frailty with CVD (**Chapter 4**) investigated effect modification by age group and sex. In addition to these variables, the present chapter also assessed effect modification by other demographic (education, income level, region) and cardiovascular (alcohol, smoking, fat mass, SBP, hypertension, glucose, diabetes) RFs.

Previous studies found that frailty was a stronger predictor of CVD mortality in younger versus older age groups. For instance, Fan *et al.* (2020)²¹⁹ found that 0.1 increment in baseline FI was associated with 2.45-fold higher risk of IHD mortality in Chinese adults aged <50 years and 1.71-fold higher risk in ≥65 years. The same pattern was found in the present chapter. There was a clear attenuation in the magnitude of the association between (usual) FI and incident IHD by age: the corresponding HRs were 1.66, 1.53, 1.42, 1.39, 1.29, and 1.34 for Chinese adults aged 30-49, 50-54, 55-59, 60-64, 65-69, and 70-80 years, respectively. A

similar pattern was found for the association between FI and incident stroke, CVD mortality, and all-cause mortality. The diminishing predictive ability of frailty for mortality with increasing age has been reported previously.²³⁰ Several explanations for this exist. First, frailty is much more common at older age so the distribution of frailty may be narrower among older people. Rockwood *et al.* (2004) showed that the distribution of FI changes with age becoming less skewed and reducing the relative heterogeneity in FI scores,³²³ which may limit the ability of the FI to discriminate older individuals with adverse outcomes. Second, use of healthcare services in older people is complex. Older people are affected by multiple morbidities but their access to healthcare may be lower than younger people. Previous studies in China reported that women older than 75 years were 10-14% less likely to be medically insured,³²⁴ which means that early identification of new diseases may be delayed or challenging at older ages.^{325,326} Conversely, younger people may be more driven to investigate new illnesses aggressively and may have greater access to healthcare.³²⁷ This difference in healthcare-seeking behaviour and accessibility may not only explain the mechanism of effect modification by age group but also other factors like education level, household income, and urban or rural region.

Stronger associations were found in females than males for frailty and incident stroke, incident IHD, and CVD mortality, but for not all-cause mortality. This phenomenon, whereby women experience higher levels of frailty and greater burden of disease but survive longer than men, is the well-described 'male-female health-survival paradox'.²³⁴ Several explanations for this paradox have been proposed. Biologically, there may be sex differences in physiological reserves, inflammageing, hormone systems, and genetic factors that contribute to greater susceptibility to frailty and diseases (but also longevity) in women than men. As mentioned previously, social and behavioural factors, such as sex differences in preventative- and healthcare-seeking behaviour promoting female survival are also likely to be involved.³²⁷ While the exact reason for the paradox cannot be defined, it likely involves a complex interplay between the hypothesised biological and social factors.

The associations between frailty and outcomes (except for stroke) were stronger in rural than urban regions, which have been reported previous in Western cohorts and in China.^{328,329} This phenomenon has been attributed to rural populations having poorer cardiovascular risk profile and access to healthcare and higher level of deprivation.³³⁰

Associations between frailty and risks of incident stroke, IHD, CVD and all-cause mortality were stronger among those without hypertension or with lower blood pressure. Previous observational studies have also reported associations between lower SBP with risk of mortality in a very old English population³³¹ and with cardiovascular events in treated hypertensive patients.³³² People who are at the final stages of life or advanced disease state may have lower BP levels and tight BP control may be associated with CVD by the inability to meet myocardial oxygen demands. Similarly, associations between frailty and risks of CVD (but not all-cause mortality) were stronger among those without diabetes or with lower glucose levels. While the reasons for this are unclear, similar patterns were found previously.^{333,334} Wei *et al.* (2000) hypothesised that long-term exposure to low glucose may contribute to abnormal cardiac activity and thrombosis, which in turn contributes to CVD incidence and mortality.³³³

Individuals with the lowest fat mass at baseline experienced the highest risks of CVD- and all-cause mortality but the lowest risk of incident stroke from frailty. A higher risk of mortality in those with lower fat mass may be explained by reverse causation and potential confounding by pre-existing illnesses that led to recent weight loss³³⁵ or the loss of beneficial fat associated with a protective glycolipid profile (CVD mortality risk). The former may also explain the lower risk of incident stroke and IHD in former smokers in the present study. Underlying illness in former smokers may have led to changes in health behaviour, which conferred the lower risk of incident stroke/IHD, or participants in this subgroup may have already experienced stroke/IHD previous and were thus excluded from the study. A higher risk of stroke in those with higher fat mass suggests that a potential mechanistic link between frailty and stroke may be increased fat accumulation – the build-up of fat is accompanied by higher atherogenic lipid profiles, which may increase the risk of stroke.³³⁶ The lack of effect modification by fat mass

in the association between frailty and IHD suggests a different mode of mechanism in this relationship.

8.4.5 Strengths and limitations

CKB has several notable strengths, including its large and diverse study population, length of follow-up, and availability of repeat assessments. CKB's large size permitted detailed investigation of a range of outcomes and effect modification by several variables of interest, which have been previously understudied. In addition, CKB's efforts regarding active follow-up of participants have resulted in extremely low rates of lost-to-follow-up, meaning that bias from the healthy survivor effect is unlikely. Similarly, the low missingness of variables suggests the risk of systematic bias due to missing data is less likely. The adjudication of outcomes (first incident cases of stroke and IHD) in CKB also means that outcomes are measured with high validity and the risk of misclassification bias is low. Finally, the availability of repeat assessments in CKB allowed for the correction of regression dilution bias, accounting for the within-person variability in the FI that was shown in **Chapters 3 and 6**.

Nevertheless, analyses were constrained by several limitations. First, the FI includes self-reported measures that may be unreliable and led to misclassification of the exposure. For instance, lifestyle variables, such as alcohol consumption, smoking, and physical activity levels, which were self-reported may have resulted in under- or over-estimation of the exposure. Physical activity may have been over-estimated, while drinking and smoking habits under-estimated due to social desirability bias, which may have resulted in some measurement error in FI and contributed to the within-person variability in the FI (**Chapters 3 and 6**). However, the interview-administered questionnaire to ascertain alcohol and smoking consumption in CKB was very detailed. For instance, smoking information included the frequency, type and amount of smoking, the degree of inhalation, age at which smoking was started or stopped, and the reason for cessation. Thus, former smokers who had quit due to illness were reclassified as current smokers in the present study. Additionally, smoking exposure was validated by exhaled carbon monoxide (CO) levels, which showed higher levels

of exhaled CO among current smokers, in those with increasing level of the daily amount smoked, and in those with lower age at which smoking was started than other groups.^{38,337,338} There was also a graded increase in the risk of cancer³³⁸ and mortality³⁸ according to these different smoking variables, which demonstrates that while self-reported the validity of smoking exposure in CKB is high.

Second, the inclusion of CVD RFs in the FI is a major issue when analysing the association between frailty and CVD as it introduces circularity in the relationship. Since the FI is a flexible measure without a fixed set of deficits, it is common practice to exclude relevant deficits from the FI. However, the exclusion of deficits is usually done conservatively. For instance, to study the association between frailty and CVD, previous studies have excluded select CVD RFs while still including adiposity traits like BMI and WHR. However, BMI and WHR are also strongly associated with CVD, so the issue of circularity remains. The present study made more stringent exclusions, excluding all cardiovascular and adiposity deficits, and found nearly 2-fold differences in risk estimates compared with the original FI. However, whether the differences in risk can be solely attributed to the exclusion of these specific deficits is uncertain given that FIs of different item lengths were shown to have different measurement properties. For instance, Nguyen *et al.* (2021) showed that the number of deficits included in the FI can strongly influence their reliability, which presents challenges when comparing the performance of different FIs.³¹⁰ This means that the reduction in the strength of associations between frailty and outcomes following modifications may be explained partly by the reduction in item length of the FI rather than the exclusion of specific deficits.

Third, the FI used in the present thesis included fewer deficits (21-28) than recommended (30-40+).⁷² A major limitation of this is the failure to capture a wide range of deficits and the multidimensional nature of frailty, which may have led to underestimation of true associations between frailty and outcomes. Also, including fewer deficits and excluding specific domains in the FI introduces sampling bias – e.g. the exclusion of cardiovascular deficits may fail to capture individuals with severe frailty, which can limit the generalisability of findings.

Fourth, the effect of multimorbidity on the associations between frailty and outcomes was not accounted for in the present thesis. The overlap in the definition of the FI and multimorbidity means that it is difficult to investigate and disentangle their individual effects.³³⁹ The considerable co-existence of frailty and multimorbidity in older people (72% of frail individuals had multimorbidity and 16% of multimorbid were frail)¹¹ means the omission of multimorbidity as a covariate is a notable limitation of this thesis. Previous studies have shown that frailty and multimorbidity may have synergistic effects, i.e. their combined effect is greater than the sum of their individual effects, on adverse outcomes³⁴⁰ and life expectancy.³⁴¹ This means that considering both frailty and multimorbidity may lead to better prediction of outcomes.³⁴² The degree to which the associations between frailty and adverse outcomes remain after accounting for multimorbidity is uncertain.²³⁰

Lastly, the association between frailty and the outcomes studied in this chapter may be biased by reverse causation. Rather than higher levels of frailty predicting a greater risk of CVD or mortality, the reverse association may be more responsible whereby poor underlying health in those who develop CVD or are closer to death result in higher frailty. The present chapter used prospective data (13 years of follow-up) and individuals without a history of IHD and stroke/TIA at baseline to mitigate the effect of this reverse causation bias. The presence of reverse causation bias was particularly evident between frailty and mortality outcomes, with almost 20% attenuation from the shortest (1 year) to longest (13 years) follow-up period, compared to frailty and incident stroke and IHD that had corresponding attenuations of 5%-7%. While the sensitivity analyses mitigated the effects of reverse causation bias, it is important to acknowledge that observational analyses are unable to fully exclude reverse causation bias as frailty and CVD have a long latency period. Even longer periods of follow-up or alternative methodological approaches may be needed to completely account for this bias.

8.5 Conclusions

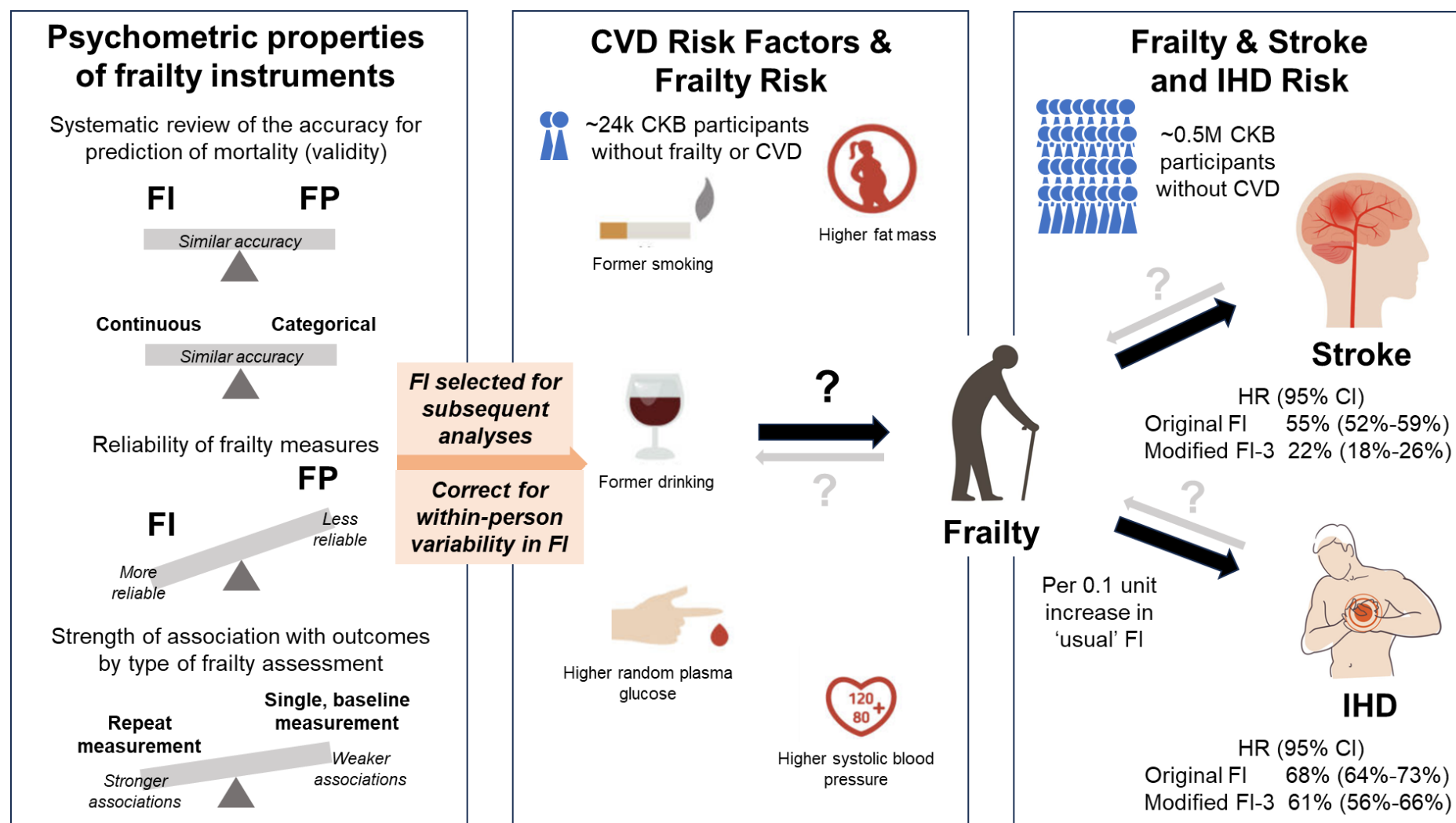
The present chapter presents novel evidence on the prospective associations between frailty and CVD outcomes and all-cause mortality in ~0.5M Chinese adults without prior CVD. A higher level of frailty was associated with higher risks of stroke and IHD, including the different subtypes and event types (fatal or overall), in Chinese middle-aged to older adults. Associations were also corrected for regression dilution bias given the wide within-person variability of FI measurements detected in previous chapters, thus the present chapter reports more reliable estimates of frailty-CVD relationship than previous studies. Associations were linear even at ranges of frailty normally considered non-frail, thus any amount of frailty conferred risk for adverse cardiovascular outcomes across all ages. Importantly, these associations were less susceptible from the issue of circularity – that frailty is associated with CVD due to the composition of the FI (i.e. inclusion of CVD RFs) rather than frailty itself. Each successive exclusion of deficits (cardiovascular and adiposity traits) resulted in the attenuation of associations, suggesting that previous reports of the association between frailty and CVD may have been overestimated. However, even after these exclusions, significant and positive, linear associations remained, highlighting the potential importance of frailty in the development of CVD.

9 Discussion

9.1 Summary of main findings

Figure 9.1 summarises the main findings of the thesis. The thesis first compared **the measurement properties of the main frailty instruments, the frailty phenotype (FP) and frailty index (FI)**. A systematic review of the accuracy of the FP and FI to predict all-cause mortality found suboptimal and comparable performance but continuous instruments were a better predictor of mortality. The reliability of frailty measurements over time was also generally low with wide within-person variability among Irish older adults, but the FI was a more reliable instrument than FP. Thus, the remaining analyses of the thesis assessed frailty using the FI. **The prospective associations between CVD RFs and risk of frailty** were examined in CKB. Among ~24,000 Chinese adults aged 30-79 years without prevalent CVD or frailty, none of the CVD RFs studied had a strong association with frailty risk after adjustment for potential confounders and circularity. While positive associations between SBP, RPG, and fat mass with incident frailty were detected according to the original FI definition, these associations attenuated significantly or changed in shape when relevant deficits were removed from the FI suggesting circularity in the associations between CVD RFs and FI. Lastly, **the prospective associations between usual levels of frailty and risk of stroke and IHD** were investigated in CKB. Among ~0.5M CKB participants without prior CVD, higher levels of usual frailty were associated with significantly higher risk of stroke and IHD, which attenuated after exclusion of cardiovascular and/or adiposity deficits but remained statistically significant. However, the observational analyses involving both frailty and CVD are likely to be constrained by potential for reverse causation bias despite attempts to control for it. Thus, the relevance of CVD RFs for risk of frailty and of frailty for CVD remain uncertain.

Figure 9.1 Main findings of the thesis



9.2 Consistency with previous literature

The main findings of the thesis have been compared with the existing literature in detail in previous chapters and will be summarised here. **Figure 9.2** summarises the findings of the prospective associations between modifiable CVD RFs and risk of frailty from the literature and the thesis. The findings of the thesis were generally consistent with those in previous studies, but substantial uncertainties persist about the shape and strength of these associations.

Figure 9.2 Key findings of the prospective associations between CVD RFs and frailty risk in the literature review and thesis

	Literature review		Thesis	
Adiposity	WC/WHR BMI	$\oplus^*$ U-shape	Fat mass Original FI mFI-3	$\oplus$ $\ominus$
Hypertension/SBP	Hypertension	$\oplus^*$	SBP Original FI mFI-1/3	$\oplus$ $\otimes$
Diabetes/RPG	Diabetes	$\oplus^*$	RPG Original FI mFI-1/3	$\oplus$ $\otimes$
Smoking	Current	$\oplus$	Ex-regular ≥ 25 cig/d	$\oplus$ $\oplus$
Alcohol consumption	U-shape / $\ominus$		Ex-regular Weekly	$\oplus$ $\ominus$
Lean body mass	J-shape / $\ominus$		Null association	$\otimes$

*Reported associations attenuated in studies with longer follow-up.
Symbols: + positive association; - inverse association; x null association

The positive associations between fat mass and frailty risk found in the present thesis are consistent with previous studies reporting positive associations between central obesity (WC or WHR) and frailty. The thesis additionally showed that the exclusion of cardiovascular and adiposity deficits from the FI resulted in the attenuation of strong positive associations into a weaker inverse one that was more consistent with the U-shaped associations between general obesity (BMI) and frailty reported in the literature. Thus, the apparent positive association may be explained by circularity in the relationship and U-shaped associations may better explain the relationship between adiposity and frailty risk. However, since reverse causation cannot be completely excluded in observational analyses, the U-shaped associations where those with low adiposity have increased risk of frailty may be partly explained weight loss associated with advanced frailty.

The positive associations between SBP and RPG and frailty risk found in the present thesis were also consistent with those found in the literature for hypertension and diabetes, but similar uncertainties about the associations persist. The attenuation of associations with the exclusion of cardiovascular deficits again suggests circularity in the relationships. Additionally, the attenuations in the associations in existing studies with prolonged duration of follow-up suggest potential for several biases, including regression dilution bias, attrition of study participants, and reverse causation bias. Regarding the latter bias, higher blood pressure and glucose levels may be a consequence of underlying frailty rather than a predictor. For instance, the ACT study¹⁹⁷ compared associations by the timing of glucose measurements and reported that more recent measures were associated with a higher risk of frailty, consistent with reverse causation bias.

An inverse association between alcohol consumption (weekly drinking) and risk of frailty in CKB was similar to the findings of the literature review. While a true inverse association between alcohol consumption and frailty may be possible, it may also be explained by residual confounding and misclassification bias in the exposure. Another potential explanation is reverse causation bias whereby pre-existing illnesses influence drinking patterns – those with

underlying frailty may be less likely to consume alcohol. Accordingly, the greatest risk of frailty was among ex-regular drinkers in the prospective analysis of CKB whilst any amount of drinking (occasional, monthly, and weekly consumption) cross-sectionally was associated with reduced frailty risk. Similarly, existing studies with a shorter follow-up period found a negative association between alcohol consumption and frailty risk (non-drinkers had much higher risk of frailty), but those with very long follow-up, such as the Nurses' Healthy Study¹⁷⁴ and Helsinki Businessmen Study,¹⁸⁸ reported positive associations.

The thesis found positive associations between current and former smoking with frailty risk, whilst the literature review found both positive and negative associations between current smoking and frailty risk. Given the reliable recording of smoking status in CKB, the inverse association between smoking and frailty found in the literature may be due to misclassification of smoking status. For instance, smokers who quit due to underlying illness were likely to be classed as former or non-smokers, which may have underestimated the association between current smoking and frailty risk. Another explanation is reverse causation bias – the negative association between smoking and frailty risk may be explained by people with underlying illness who quit smoking before the onset of frailty.

Finally, the literature identified one study between lean body mass and frailty risk, reporting an inverse, J-shaped association. However, the present thesis found no prospective association between lean body mass and frailty risk, suggesting that sarcopenia or muscle wasting, which is common in people with frailty, may be a symptom of frailty rather than its cause.

Overall, the findings of the thesis and literature suggest that the true magnitude of the association between CVD RFs and frailty is masked by residual confounding, circularity in the relationship, and reverse causation bias, thus none could be identified as modifiable RFs of frailty. While reverse causation bias appears to be the most likely explanation for the reported associations, few studies including the present thesis could sufficiently explore the effects of reverse causation.

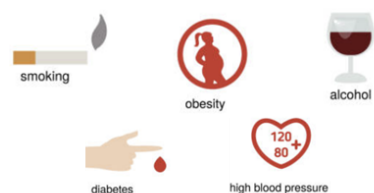
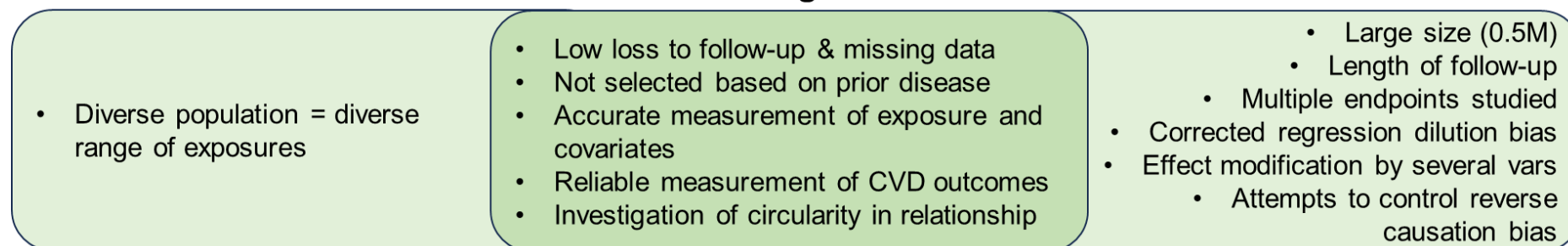
The positive associations between frailty and incident stroke and IHD found in the present thesis are also consistent with those found in the literature review. However, the differences in the study participants, frailty model, and definition of CVD outcomes limit direct comparison of the magnitude of associations. The associations reported in the present thesis accounted for regression dilution bias resulting from variability in the frailty measurement and presented a range of possible associations by accounting for various degrees of circularity present in the exposure-outcome relations, thus are believed to be more accurate estimations of CVD risk from frailty. However, the risk of reverse causation bias still exist – frailty may be a consequence of the severe stages of CVD associated with unintentional weight loss, inability to walk independently, and heavy reliance on basic activities of daily living – which may distort any true associations of frailty with CVD.

9.3 Strengths and limitations

The main strengths and limitations of the thesis and the CKB study, which are illustrated in **Figure 9.3**, have been described in detail in previous chapters and are summarised here.

Figure 9.3 Summary of the strengths and limitations of the thesis

Strengths



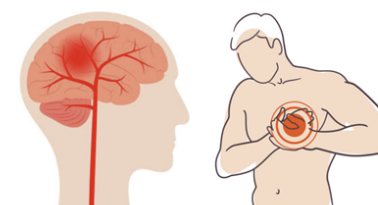
CVD Risk Factors

Analysis 1

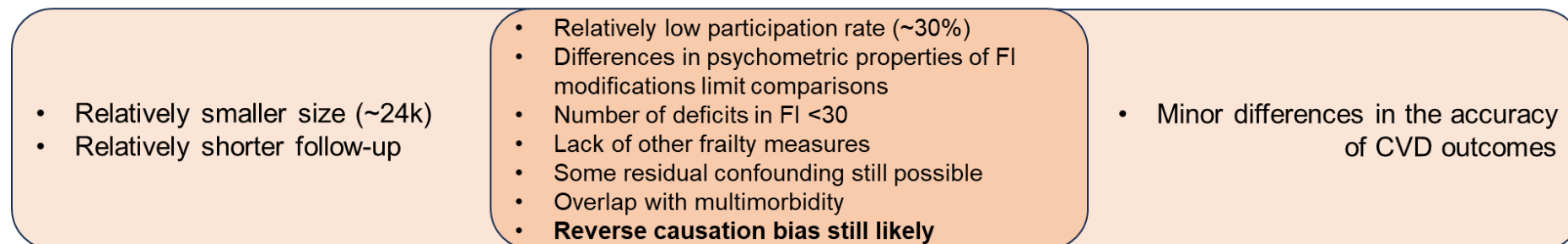


Frailty

Analysis 2



Stroke & IHD



Weaknesses

The present thesis had several strengths. The large size, very low loss of follow-up (<1%), and length of follow-up (13 years) of the CKB study resulted in a large number of CVD events, enabling reliable estimates, assessment of previously understudied subgroups, and sensitivity analyses to control for reverse causality. The CKB resurveys also enabled repeat measurements of frailty and estimation of within-person variability in frailty and associated regression dilution bias. Correcting this bias meant more reliable estimation of the strength of associations between frailty and CVD. The diversity of the data recorded in CKB enabled the assessment of the FI and comprehensive adjustment for confounders. The diverse range of exposures allowed investigation of the shape of several CVD RF-frailty relationships. Furthermore, CKB's quality procedures minimised missing data and reduced the likelihood of systematic error, measurement error, and misclassification bias in the data. Similarly, outcomes had high accuracy and were obtained from multiple, established reporting systems reducing the risk of under-reporting. The thesis investigated the presence of reverse causation bias and circularity in the relationship between frailty and CVD (RFs), presenting a range of possible strengths and shape of associations. Lastly, a detailed comparison of the measurement properties of the major frailty instruments allowed evidence-based selection of the optimum instruments to assess frailty.

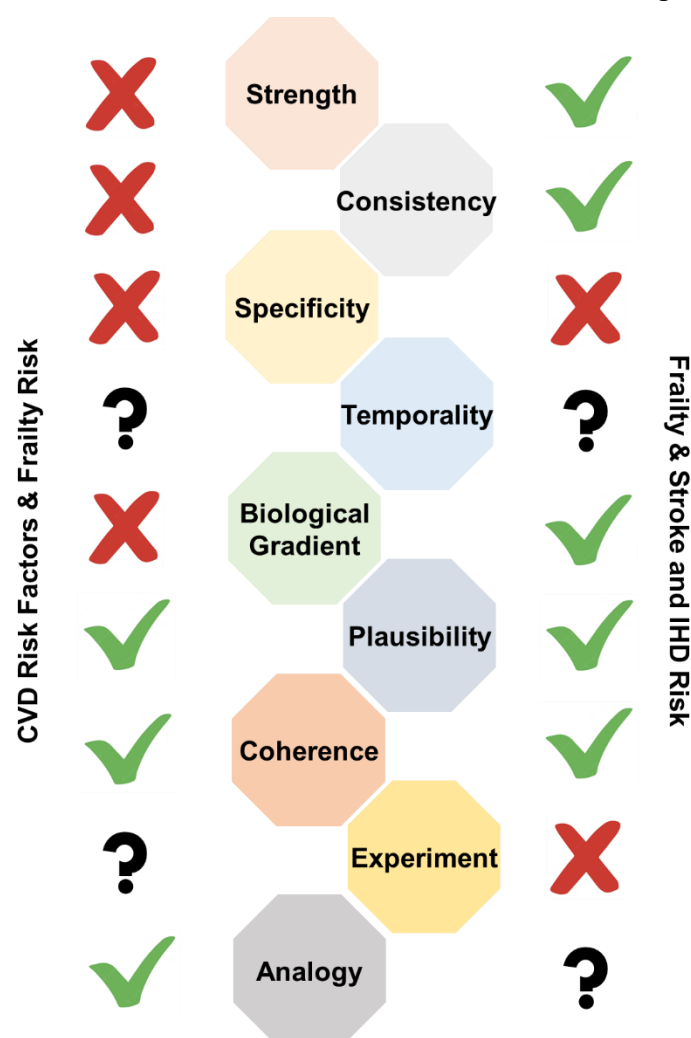
The thesis, however, also had several limitations. The overall participation rate in CKB was low, which may have resulted in the selection of "healthy volunteers" with lower mortality rates than non-volunteers leading to an underestimation of the risk.³⁴³ Additionally, those who were not able to participate due to severe diseases or physical mobility may have been frailer; thus, the under-representation of participants with frailty may have resulted in underpowered and underestimated associations. Also, the relationship between CVD RFs and incident frailty (**Chapter 7**) was studied in ~5% of CKB, which likely underpowered analyses. The thesis compared different modifications of the FI with exposures or outcomes, but their comparability is uncertain due to differences in their psychometric properties. Another key limitation is that the FI used in the present thesis included fewer items than recommended (21-28 versus 30-

40+ items).⁷² Thus, whether the FI adequately represents the frailty index and its multidimensional nature is uncertain and limits comparability with other studies. Also, some residual confounding even after comprehensive adjustment of confounders may slightly alter the strength of associations. Another weakness is the overlap in concept with multimorbidity, which was not accounted for in the present thesis. However, the main limitation of the thesis is its observational study design. While extensive attempts to control for reverse causality were made, the observational design of the study and the long subclinical period of frailty and CVD means that the reverse causation bias likely persist. Thus, whether the observed associations are causal or correlation cannot be distinguished, which limit the impact of the thesis findings.

9.4 Appraisal of findings with respect to causality

Bradford Hill outlined 9 criteria to assess the causal nature of observational exposure-outcome associations: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy.³⁴⁴ The causal relevance of the relationships studied in the thesis were appraised using these criteria, which are summarised in **Figure 9.4**.

Figure 9.4 Application of the Bradford Hill criteria to thesis findings



The thesis found **strong positive associations** between frailty and stroke and IHD that persisted even after rigorous attempts to control for confounding, circularity, and reverse causality. The log-linear shape of the associations suggests strong dose-response relationships (**biological gradient**), which were largely **consistent** across the 10 diverse CKB regions and with previous large prospective studies. While the prospective design of the study and the exclusion of participants with prevalent CVD should ensure that frailty precedes CVD (**temporality**), reverse causation is likely to persist in observational studies where diseases have long subclinical phases. The aetiology of frailty remain elusive, but these relations are likely to involve age-related biological processes like inflammation that contributes to the atherosclerotic process (**plausibility**) and existing evidence using animal models of frailty support poorer cardiovascular function in frailty (**coherence**).³⁴⁵ The effect of frailty reduction

on CVD risk has not been studied (**experiments**) given the lack of clear modifiable targets of frailty. While other age-related symptoms have reported similar associations (**analogy**) – e.g. lower grip strength was associated with greater risk of all-cause and CVD mortality,³⁴⁶ none are likely to be a perfect analogy to frailty.

The thesis found **weak associations** between CVD RFs and incident frailty after controlling for confounding, circularity, and reverse causation (exclusion of prevalent frailty and CVD). Also, evidence of a monotonic dose-response relationship was not observed (except between fat mass and incident frailty using the original FI and mFI-1) (**biological gradient**), although complex, non-linear dose-response relationships may exist.³⁴⁷ The **temporality** criteria is unlikely to be fulfilled due to the same reasons outlined above and evidence was **inconsistent** in the literature. CVD RFs are also likely to contribute to frailty through ageing processes like inflammation (**plausibility**) and other CVD RFs, e.g. fatty acids,³⁴⁸ have been reported to have a causal relationship with frailty (**analogy**). Several RCTs and frailty interventions conducted in primary care settings have shown that frailty interventions like physical exercise programs and nutritional supplementation improves the level of frailty (**experiment**),^{349,350} but findings have been conflicting and the quality of evidence was considered to be low. Lastly, the **specificity** criterion is less relevant in observational epidemiological studies involving diseases with a multifactorial origin like frailty and CVD. In light of these criteria, the thesis does not support a causal relationship between frailty and stroke or IHD or CVD RFs and frailty.

The above Bradford Hill criteria serve as useful criteria to assess support for causality, but causation can rarely be proven or disproven in observational analyses. Recent advancements in genetic epidemiology and integration of -omics data should increase the ability to study causal relationships, and their potential to advance the findings of the thesis will be discussed next.

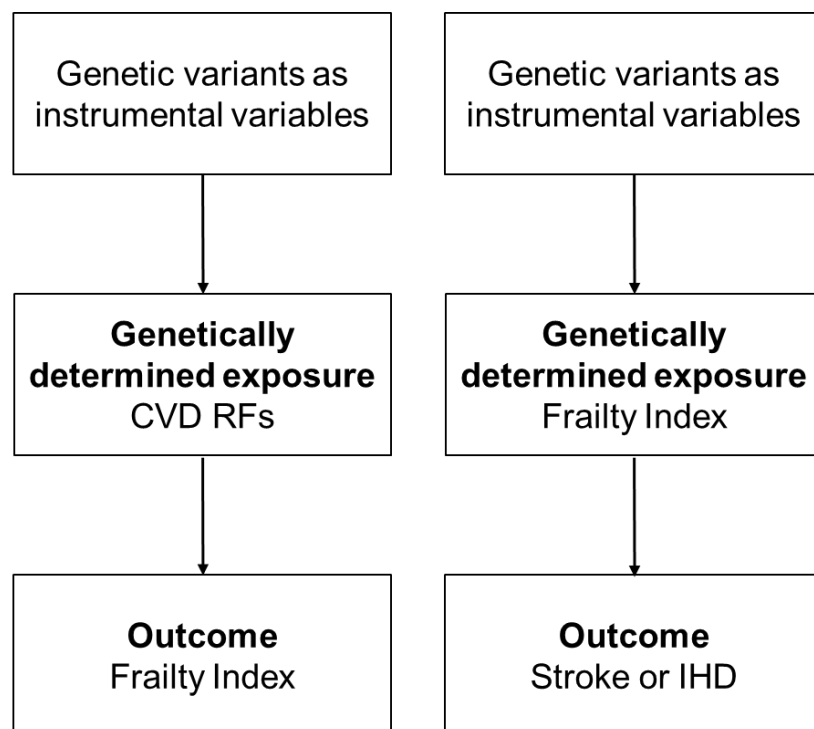
9.5 Future research

The present thesis investigated the correlates and consequences of frailty in Chinese middle- and older aged adults. The discussion so far, however, has outlined significant potential for reverse causation bias in the observational associations involving frailty and CVD, limiting causal inference and our ability to understand the aetiology of frailty. Future studies should address the limitations of the present thesis and employ recent advances in epidemiology.

Reverse causality could be further investigated using Mendelian randomisation (MR) analyses. MR is a technique that allows causal inference of an exposure and outcome relationship through the use of genetic variants as instrumental variables (IV) using observational data.³⁵¹

A schematic representation of a possible future MR study is illustrated in **Figure 9.5**.

Figure 9.5 Schematic view of Mendelian randomisation study design

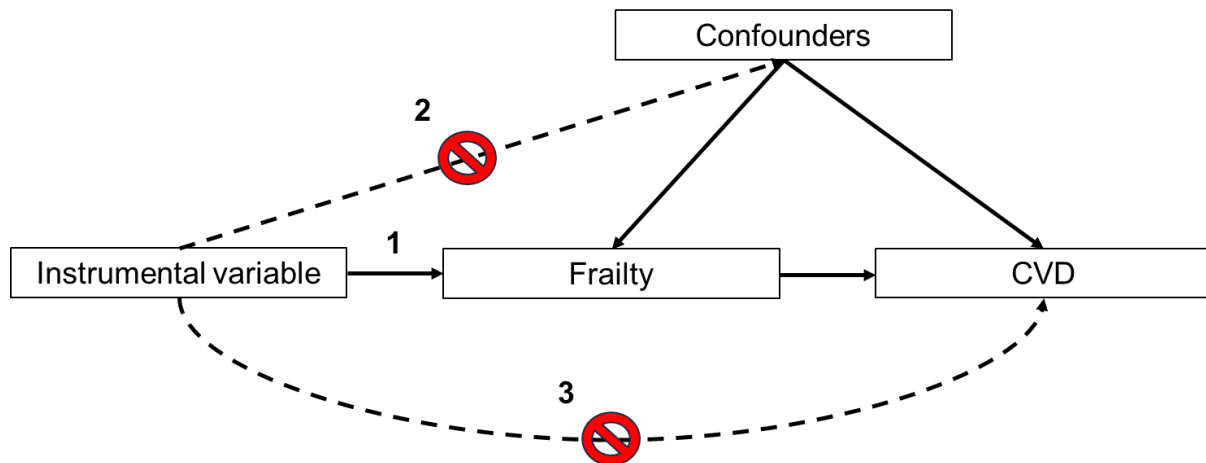


Instrumental variables are variables associated with an exposure but not the outcome (other than the causal pathway through the exposure).³⁵² Genetic variants significantly associated with exposures are identified from previous GWAS studies.

In MR, randomisation of participants occur at conception via random assortment of genes in the population.³⁵³ Therefore, participants can be divided into controls or treatment groups like

RCTs (the gold standard for testing medical interventions) by whether genetic variants representing the exposure is present or absent, respectively, with all other factors being equal. This design limits unmeasured confounding as the random assortment of genes at conception ensures random distribution of confounding factors and reverse causation as one's genotype cannot be altered by disease progression. Thus, causal inference is possible. Genotyping is available in ~100k CKB participants and this unique data has already been leveraged.^{79,354–356} Other recent studies have also used MR to investigate the associations of interest in this thesis. They supported a causal relationship between several CVD RFs and frailty, smoking^{357–360} and cholesterol,^{361,362} but not alcohol consumption,^{358,359} homocysteine,³⁶³ and triglycerides.³⁶⁴ Consistent with the observational analyses of the thesis, recent MR studies supported a causal effect of frailty on stroke^{365–367} and CAD.³⁶⁶ Thus, the existing MR evidence suggests causal associations between frailty and CVD and its risk factors, which is further supported by the bidirectional MR analyses of frailty and CVD.³⁶⁶ However, these studies have used participants of European ancestry, so replication of analyses in Asian populations is needed since frequency of genetic variants and frailty and CVD aetiology may vary by ethnicity. Findings of such future studies will help to establish the directionality of associations, which will also help to streamline efforts to develop diagnostic and therapeutic targets of frailty. For instance, interventions to modify frailty can be focussed on shared, modifiable RFs like smoking, which will have the added benefit of being cost-effective by reducing CVD. However, the validity of these MR findings rest on several assumptions, which are shown in **Figure 9.6**.

Figure 9.6 Graphical representation of Mendelian randomisation assumptions



The assumptions of instrumental variables (IV):³⁵³

1. The IV is associated with the exposure.
2. The IV is not associated with the outcome via a confounding pathway.
3. The IV does not directly affect the outcome (only indirectly via the exposure).

Whether IVs for frailty and CVD RFs satisfy these assumptions is uncertain. Given the hypothesised, shared biological mechanisms of frailty and CVD that involve multiple physiological systems, it can be expected that IVs for frailty and CVD RFs may violate several MR assumptions. In fact, the genetics of frailty have been shown to involve traits related to CVD like BMI, WHR, physical activity, and smoking initiation.³⁶⁸ Therefore, its genetic variants may be associated with confounders of the frailty-CVD association (assumption 2) and influence the CVD outcome independently of the exposure (assumption 3) (**Figure 9.6**). Thus, future MR studies of frailty should carefully consider the plausibility of these assumptions. While violations these assumptions cannot be conclusively ruled out, there are certain statistical tests to judge the suitability of IVs, e.g. testing whether the IVs are associated with a covariate (assumption 2), tests to detect pleiotropy (IV is associated with other phenotypes) (assumption 3), and comparing the effect of exposure and outcome for individual genetic variants or conducting leave-one-out analyses.³⁵³

To better understand the biology of frailty and the underlying mechanisms through which frailty influences disease (e.g. CVD), future studies can also utilise other unique features of blood-based studies, such as large-scale -omics profiling. In addition to the genetic data, CKB

includes metabolomic (~1000 metabolites) and proteomic (~10,000 proteins) data for a subset of the participants.³⁶⁹ Recent CKB studies found observational and genetic associations between BMI and circulating proteins, including IL-6 and IL-8,^{370,371} which support the hypothesis that the underlying mechanism of the CVD RF and frailty relationship may involve inflammaging. If fat mass indeed causes frailty, similar mechanisms may be involved. The integration of genetic data provides further useful insight into the causal relevance of such associations, which should help identify novel targets for drug development for frailty. The data may also be useful to explore patterns of multimorbidity in frailty to understand how the biology and genetics of frailty differ from those of multimorbidity. Another potential use of -omics data is the development of biomarker-based frailty measures. Since biomarkers are closer to the pathophysiology of frailty than conventional phenotypes (e.g. grip strength), omics-based frailty or ageing measures may serve as superior diagnostic tools than phenotype-based measures. For example, a biomarker-based age developed in the UK Biobank was found to have greater ability than chronological age to predict mortality even among seemingly healthy populations.⁵⁸ Also, recent biomarker- and test-based frailty indices found that such measures were able to detect higher and broader ranges of frailty levels compared to conventional, self-reported FIs, suggesting that frailty may be detected in younger, healthier individuals with greater potential for earlier intervention.^{319,372} These biomarkers of age and frailty also showed different patterns by sex, which highlight another potential to investigate the biological reasons for the sex-differences seen in frailty.

9.6 Public health implications

China is experiencing a dramatic change in population structure as a result of rapidly decreasing fertility and increasing life expectancy. This population ageing is occurring faster than almost any other country in the world and China is expected to see the fastest rate of doubling in the proportion of older people,^{373,374} meaning that the anticipated public health burden arising from frailty will increase substantially. In addition, the present thesis demonstrated that elevated levels of frailty were associated with higher risk of incident stroke

(and its subtypes) and IHD (including MI and MCE), and CVD and all-cause mortality even after rigorous adjustment for circularity, regression dilution bias, and reverse causality. This implies that with the projected increases in the prevalence of frailty due to population ageing, the future health burden due to CVD incidence and mortality will be substantial. Thus, development of policies to delay and treat frailty is urgently required.

Over the last decades, major advances have been made in frailty research with respect to defining frailty in older people, understanding population-level patterns of frailty, and identification of its risk factors and adverse outcomes. Longitudinal analyses and intervention studies of frailty have also shown that frailty fluctuates and is potentially modifiable.^{375–377}

Despite this, clear strategies to reduce severity of frailty have not been identified and there is large uncertainty about population-level approaches to manage or prevent frailty. The present thesis sought to identify modifiable RFs of frailty, but the associations were underpowered and inconclusive, which mirrored the weak and conflicting evidence found in the literature review of the prospective associations between CVD RFs and frailty.

This lack of clear evidence on the modifiable risk factors of frailty is reflected in the limited clarity in current national policies aimed at managing frailty. For example, in the UK the NHS's Long Term Plan³⁷⁸ states that individuals identified as moderately frail according to the electronic frailty index⁵⁹ will be offered targeted support for their health needs including CVD and frailty. What this targeted support will exactly include is unclear, but examples stated were multidisciplinary care to maintain independence and prevent falls via exercise programs and strength training. In the literature, several different types of frailty interventions have been proposed and investigated, namely lifestyle modifications like dietary modifications and physical exercise and clinical interventions like hormone supplements and health education.^{349,350} However, these interventions reported mixed outcomes and generally low quality of evidence for improvement in frailty,^{349,350} thus the effectiveness of existing policies is uncertain. Future studies using MR coupled with -omics data should lead to the identification of modifiable or druggable targets of frailty, which can streamline efforts to develop effective

frailty interventions. For example, recent proteomic profiling of frailty identified proteins in pathways related to inflammation, blood coagulation, cell growth,³⁷⁹ lipid metabolism, and musculoskeletal development and function.³⁸⁰ Putative causal proteins may be investigated further using MR studies by studying the effects of genetically predicted protein levels on frailty and their side effects on other diseases.³⁸¹ Identified drug targets should then undergo a process of target validation via which their safety and ‘druggability’ are assessed prior to testing in animal models or clinical trials.³⁸²

Regardless of what the precise frailty intervention will entail, the findings of the present thesis also suggest that management of frailty would benefit from the inclusion of a wider range of populations than typically targeted, such as individuals who are younger and less frail. The present thesis found positive, log-linear associations between frailty and CVD outcomes, which were generally strong regardless of the subtype or type of event. This suggests that management of frailty in individuals who are not currently considered frail, but may be younger or in a less frail state, may prove to be effective in reducing the adverse effects of frailty at the population level.

9.7 Conclusion

Despite the increasing prevalence of frailty in Chinese older people, there is limited understanding of the correlates and consequences of frailty in this population. The analyses of this thesis, based on 24,000 to 0.5 million middle-aged and older adults from diverse regions in China, have shown positive log-linear associations between frailty and the incidence of stroke and IHD, including their subtypes. These risks were independent of other CVD RFs and potential circularity in the associations by the inclusion of cardiovascular components in the frailty instrument. Findings of this thesis suggest that management of frailty in the general population, not just targeted to those already severely frail, may be effective to reduce the adverse effects of frailty on CVD incidence. However, the thesis found no clear association between the major CVD RFs and frailty after accounting for the circularity in the relationship,

meaning that future studies are is needed to identify modifiable risk factors of frailty. In particular, MR studies will be able to confirm whether observational associations are casual.

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Table S2.1 Search strategy and results for Ovid Medline

Searches	Results
1 epidemiologic studies/	8530
2 follow-up studies/ or longitudinal studies/ or prospective studies/ or feasibility studies/ or multicenter studies as topic/ or twin studies as topic/ or epidemiological monitoring.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1319134
3 (cohort adj (study or studies or analys*)).ti,ab.	233200
4 ((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.	259582
5 ((longitudinal or prospective) and (study or studies or review or analys* or cohort*)).ti,ab.	739201
6 or/1-5	1938363
7 exp case control studies/ or exp control groups/	1137451
8 cross-sectional studies/ or prevalence/ or ((cross-sectional or prevalence or transversal) adj3 (study or studies)).ti,ab.	687687
9 ((case* and control*) or (case* and comparison*) or control group*).ti,ab.	1045791
10 or/7-9	2574173
11 6 not 10	1403654
12 ("Rockwood K" or "Mitnitski A").au. or (Rockwood or Mitnitski or "frailty index" or FI or "accumulated deficit*" or "cumulative deficit*" or "deficit accumulation").ti,ab.	12181
13 (frailty or "frail elderly").ti,ab. or Frailty/ or Frail Elderly/	23836
14 11 and 12 and 13	525
15 (frailty or non-frail* or nonfrail or prefrail* or pre-frail* or frail*).ti,ab. or Frail Elderly/	28093
16 (Fried or CHS or phenotyp* or syndrome* or "cardiovascular health study").ti,ab. or Phenotype/ or "Fried L".au.	1646774
17 (physical* adj3 frail*).ti,ab.	1552
18 (frail* adj3 criteri*).ti,ab.	616
19 (frail* adj3 defin*).ti,ab.	1190
20 or/16-19	1648520
21 11 and 15 and 20	1296
22 14 and 21	202
23 exp mortality/ or exp fatal outcome/ or exp survival/ or exp survival analysis/ or exp prognosis/ or exp cause of death/ or (mortality or death* or died or dead or survival or prognosis or fatal*).ti,ab.	3867502
24 22 and 23	118
25 limit 24 to (english language and yr="2000 -Current")	118
26 (case reports or comment or editorial or letter or "review").pt.	6452479
27 25 not 26	111

Table S2.2 Data extraction forms

Author (year)		Country (Name of Study)		Size (male %)		Mean age (SD)		Follow-up (years)						
Author (year)	Size	Statistic reported	Results (estimate and confidence interval)	Adjustments in model	Result rating	Study quality (SIGN checklist)		Comments (if any, e.g. why results cannot be rated)						
FI continuous														
FI categorical														
FP continuous														
FP categorical														

Table S2.3 SIGN Methodology Checklist 3: Cohort studies

Methodology Checklist 3: Cohort studies

SIGN

Study identification (Include author, title, year of publication, journal title, pages

Guideline topic:

Key Question No: Reviewer:

Before completing this checklist, consider:

Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.

Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

SECTION 1: INTERNAL VALIDITY

In a well conducted cohort study:

Does this study do it?

1.1 The study addresses an appropriate and clearly focused question.

Yes ☐ No ☐
Can't say ☐**SELECTION OF SUBJECTS**

1.2 The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.

Yes ☐ No ☐
Can't say ☐ Does not apply ☐

1.3 The study indicates how many of the people asked to take part did so, in each of the groups being studied.

Yes ☐ No ☐
Does not apply ☐

1.4 The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.

Yes ☐ No ☐
Can't say ☐ Does not apply ☐

1.5 What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.

1.6 Comparison is made between full participants and those lost to follow up, by exposure status.

Yes ☐ No ☐
Can't say ☐ Does not apply ☐**ASSESSMENT**

1.7 The outcomes are clearly defined.

Yes ☐ No ☐
Can't say ☐

1.8 The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.

Yes ☐ No ☐
Can't say ☐ Does not apply ☐

1.9 Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.

Yes ☐ No ☐
Can't say ☐

1.10 The method of assessment of exposure is reliable.

Yes ☐ No ☐
Can't say ☐

1.11 Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.

Yes ☐ No ☐
Can't say ☐ Does not apply ☐

1.12 Exposure level or prognostic factor is assessed more than once.

Yes ☐ No ☐
Can't say ☐ Does not apply ☐**CONFOUNDING**

1.13 The main potential confounders are identified and taken into account in the design and analysis.

Yes ☐ No ☐
Can't say ☐**STATISTICAL ANALYSIS**

1.14 Have confidence intervals been provided?

Yes ☐ No ☐**SECTION 2: OVERALL ASSESSMENT OF THE STUDY**

2.1 How well was the study done to minimise the risk of bias or confounding?

High quality (++) ☐
Acceptable (+) ☐
Unacceptable – reject 0

2.2 Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?

Yes ☐ No ☐
Can't say ☐

2.3 Are the results of this study directly applicable to the patient group targeted in this guideline?

Yes ☐ No ☐

2.4 Notes. Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.

Table S2.4 PRISMA 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.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5,6
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.	Protocol was not published
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.	6
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.	5,6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix Table 2
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).	6
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.	7, Appendix Table 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.	5
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.	6, 8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
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.	8
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).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
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.	9, 24
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.	9, 22

Section/topic	#	Checklist item	Reported on page #
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).	22
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.	25
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	9, 10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12, 13, 26
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).	13-15
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).	15, 16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
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.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009).³⁸³

Table S2.5 Rationale for SIGN checklist statement (Refer to Supplementary Table 2.3 SIGN Methodology Checklist 3: Cohort studies, page 259).

	Chao (2018)	Romero-Ortuno and Soraghan (2014)	Ding (2017)	Woo (2012)	Li (2015)	Zucchelli (2019)	Op Het Veld (2019)	Widagdo (2015)	Gonzalez-Harmand (2017)	Thompson (2019)
SECTION 1: INTERNAL VALIDITY										
1.1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
SELECTION OF SUBJECTS										
1.2	All 'Can't say' – different frailty groups may not be comparable in all other respects.									
1.3	No	Yes	No	No	No	No	No	No	No	No
1.4	All 'No' – there is no likelihood that eligible subjects might have the outcome (mortality) at enrolment.									
1.5	No %	23-34.3%	No %	No %	No %	No %	No %	No %e	No %	No %
1.6	No	No	No	No	No	No	No	No	No	Yes
ASSESSMENT										
1.7	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.8	Does not apply to statement 'The assessment of outcome is made blind to exposure status' because the outcome (mortality) is completely objective.									
1.9	As above									
1.10	All 'Can't say' because the reliability of exposure (frailty measurements) is uncertain									
1.11	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.12	No	No	No	No	No	No	No	No	No	Yes
CONFOUNDING										
1.13	Yes	Yes	No	No	Yes	No	No	No	Yes	Yes
STATISTICAL ANALYSIS										
1.14	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes
SECTION 2: OVERALL ASSESSMENT OF THE STUDY										
Notes	Overall response rate by wave reported elsewhere; Lost to f-u mitigated by active f-u; Missing values were imputed	Response rates reported elsewhere; Flow chart of participants reported by frailty group; Compares baseline characteristic of participants by outcome.	Response rate by study wave reported elsewhere; Response rate is high; Missing values were imputed	Compared patient characteristics of those f-u and lost to f-u	Baseline characteristics by frailty group & overall response rate reported; Outcome self-reported but adjudication attempted; Missing values imputed	Baseline response rate & attrition rate by age group reported elsewhere	Baseline response rate reported elsewhere; Missing values were imputed	Baseline response rate reported elsewhere; Sensitivity analysis carried out using participants with complete data	Death data was systematically collected with a standardised interview	Compares frailty status at baseline and follow-up status by frailty categories.
#	4	7	3	4	6	5	2	3	5	7
yes										
2.1	+	++	0	+	++	+	0	0	+	++

Rating given ++ if mostly 'yes' (6-7); + if some 'yes' (4-5); and 0 if few 'yes' (2-3).

Table S2.6 Rationale given by the authors for continuous and categorical labels

Author (year)	Continuous and/or categorical	Rationale
Chao (2018)	Continuous and categorical	p9 - "The predictive power of three frailty indices in continuous scales or dichotomous status regarding mortality..."
Li (2015)	Continuous and categorical	p1 - "(1) investigated the relationship with adverse health outcomes by increasing per one-fifth (i.e., 20%) of the FI and PF; (2) trichotomized the FI based on the overlap in the density distribution of the FI by the three groups (robust, pre-frail and frail) which were defined by the FP"
Widagdo (2015)	Continuous and categorical	In 'Statistical analysis' – "This analysis used a dichotomised frailty status (frail and non-frail); for those measures that had a pre-frail group, this was combined into non-frail... The AUC values for the full model (i.e. multilevel or continuous scale) of the frailty measures were also assessed."
Thompson (2019)	Continuous and categorical	In Methods – "Three iterations of the FP were used: a Continuous FP; ... and a 3-Category FP... Three iterations of the FI were used: a Continuous FI; ... and a 3-Category FI"
Romero-Ortuno and Soraghan (2014)	Continuous	p14 – Figures showing the ROC curve suggest continuous scores were used
Ding (2017)	Continuous	p4 - "1 unit of increase in..."
Zucchelli (2019)	Continuous	p3 - "The AUC was obtained using non-parametric ROC analysis, including the different indicators as continuous variables"
Kusumastuti (2017)	Categorical	p3 - "health indicators were dichotomized into..., FI score of <0.2 and >0.3, Frailty Phenotype score of 0 and >1"
Woo (2012)	Categorical	p7 - Figures showing the ROC curve suggest categorical scores were used

Table S2.7 Details of the FP

Author (year)	Exhaustion (poor endurance and energy)	Physical activity	Weight loss/shrinking	Weakness	Gait speed/slowness	Cutoff
Fried (2001) ORIGINAL	Self-rated exhaustion 2 items from the CES-D Scale [35]: "I feel that everything I do is an effort" and "I cannot get going"	Low physical activity Low energy expenditure (male < 383 kcal/week, female < 270 kcal/week)	Unintentional weight loss ≥ 4.5 kg or $\geq 5\%$ within one year (self-report)	Low grip strength In the lowest 20% at baseline (adjusted for sex and BMI)	Walking time/15 ft (4.5 m) Slowest 20% at baseline (adjusted for sex and height)	Frail, ≥ 3 variables present; Pre-frail, 1–2 variables present; Non-frail, no variables present.
Li (2015)	Feel that everything was an effort or could not get going for ≥ 3 days in the last week The Medical Outcomes Study 36-item Short Form Survey (SF-36) vitality component's four questions on whether they felt worn out, felt full of life, felt tired, or had a lot of energy. For responses to feeling worn out and feeling tired, the scores were 100 points for none of the time, 75 points for a little of the time, 25 points for most of the time, and 0 point for all of the time. The scores were reversely coded for responses to having a lot of energy and feeling full of life. The <u>lowest quartile</u> of poor endurance and exhaustion obtained 1 point.	Lowest 25% in the number of days that in the past 30 days they had walked at least 20 minutes.	Unintentional loss of >10 lb in the past year	The Medical Outcomes Study 36-item Short Form Survey (SF-36) physical functioning component to assess the limitations in 10 activities such as running, bathing, bending, and walking. In each of the activities, participants received 0 point if they reported they were limited a lot, and 50 points if they were limited a little, and 100 points if they were not limited at all respectively. The <u>lowest quarter</u> of slowness and weakness received 2 points	Frail, ≥ 3 variables present; Pre-frail, 1–2 variables present; Non-frail, no variables present.	
Widagdo (2015)	Self-rated exhaustion (CES-D scale) Feel that everything was an effort or could not get going for ≥ 3 days in the last week	Walking for exercise or recreation in the past 2 weeks	BMI < 20 kg/m ²	Grip strength in the lowest 20% at baseline (adjusted for sex and BMI)	Slowest 20% at baseline (adjusted for sex and height) using TUG test (8ft/2.4m)	Frail, ≥ 3 variables present; Pre-frail, 1–2 variables present; Non-frail, no variables present.
Ding (2017)	Binary variable based on a positive reply to either or both of 2 items in CES-D scale on whether the respondent "felt everything they did during the past week was an effort" and "could not get going much of the time in the past week"	Lowest 4 categories of physical activity (sedentary)	Weight loss of >5 kg from waves 0 to 2(on average 4 years)	Dominant hand grip strength in kg which is multiplied by 1.5 for women (1.5 represents the relative difference in gender-specific and population-dependent	The average gait speed (m/s) of 2 attempts at walking distance of 2.4m multiplied by -1	n/s

Author (year)	Exhaustion (poor endurance and energy)	Physical activity	Weight loss/shrinking	Weakness	Gait speed/slowness	Cutoff
Zucchelli (2019)	Participants were asked if they experienced fatigue in the last three months. (Positive answer)	Participants were asked “do you regularly engage in light exercise (e.g. walking along roads or in parks, walking in the woods, short bicycle rides, light aerobics, golf)?” and “do you regularly engage in moderate to intense exercise, now or previously (e.g. jogging, long power walks, heavy-duty gardening, long bicycle rides, high-intensity aerobics, long distance ice skating, swimming, ball sports (not golf) or other similar activity)?” (“less than 2-3 times/month” for both questions)	Participants were asked “did you suffer from any weight loss in the last 3 months?”. (Reporting of loss of at least 1 kilogram)	values for grip strength). After that the values are reversed through multiplying by -1. Grip strength in the lowest 20th percentile, adjusted for sex and body-mass-index. Participants were asked to employ maximum force while squeezing the handle of an electronic dynamometer (Grippit®), one time for each hand. The best value was recorded.	Slowest 20th percentile, adjusted for sex and height. Participants were asked to walk at usual speed over a 6-meter straight path. If the subjects reported slow walking speed or if, because of space issues, the full-length track was not available, a 2.4-meter was used. Walking speed was registered as m/s. A value of 0 was accounted if the subject was unable to walk.	Frail, ≥3 variables present; Pre-frail, 1–2 variables present; Non-frail, no variables present.
Woo (2012)	Self-reported no energy	Lowest 25% for Physical Activity Scale for the Elderly (PASE) score	BMI < 18.5 kg/m ²	Grip strength in the lowest 25%, measured using a dynamometer (JAMAR hand dynamometer 5030JI; Sammons Preston, Bolingbrook, IL). The average of two readings on the right and left side was used.	Slowest 25% using TUG test (6m)	Frail, ≥3 variables present; Pre-frail, 1–2 variables present; Non-frail, no variables present.

Author (year)	Exhaustion (poor endurance and energy)	Physical activity	Weight loss/shrinking	Weakness	Gait speed/slowness	Cutoff
Chao (2018)	Yes to either of two CES-D items: (i) Felt that everything I did was an effort in last week. (ii) Could not get going in last week.	Lowest 20% (sex-specific) in frequency of three intensities of activity	BMI <18.5 kg/m ²	Grip strength in the lowest 20% (adjusted for sex and BMI)	Time to walk eight feet, converted to time to walk 15 feet categorized by height and sex	Dichotomised as Frail (≥3) or not.
Romero-Ortuno and Soraghan (2014)	"In the last month, have you had too little energy to do things you wanted to do? (yes/no)."	"How often do you engage in activities that require a low or moderate level of energy such as gardening, cleaning the car, or going for a walk?." ("one to three times a month" or "hardly ever or never")	"What has your appetite been like" ("diminuation in desire for food") or "So have you been eating more or less than usual?" ("less")	Highest of four consecutive dynamometer measurements of handgrip strength (two from each hand), applying gender and body mass index cutoffs set by Fried and associates	"Because of a health problem, do you have difficulty [expected to last more than 3 months] walking 100 meters" or "... climbing one flight of stairs without resting"	Frail, ≥3 variables present; Pre-frail, 1–2 variables present; Non-frail, no variables present.
Thompson (2019)	Original method	Australian Bureau of Statistics National Health Survey (<100 METs per week)	Weight Loss: > 10% weight loss over four years (clinic measurement)	Original method	Self-report 'a lot' to health limits walking 100m (36-Item Short Form Health Survey Q11)	Frail, ≥3 variables present; Pre-frail, 1–2 variables present; Non-frail, no variables present.

Table S2.8 Details of the FI

Author (year)	Item no.	Included items			Cutoff
Li (2015)	34	1. Taking/taken five or more medications 2. Has chronic bronchitis or emphysema 3. Has osteoarthritis or degenerative joint disease 4. Has rheumatoid arthritis 5. Suffers from stroke 6. Has ulcerative colitis or Crohn's disease 7. Has celiac disease 8. Has Parkinson's disease 9. Has multiple sclerosis 10. Has cancer	11. Has diabetes (type-1) 12. Has hypertension 13. Has heart disease 14. Has high cholesterol 15. Self rating of health 16. Limitations in vigorous activities 17. Limitations in moderate activities 18. Limitations in lifting or carrying in groceries 19. Limitations in climbing one flight of stairs 20. Limitations bending, kneeling or stooping 21. Limitations walking one hundred yards 22. Limitations in bathing or dressing yourself 23. Needs arms to help stand up from a chair	24. Number of days to walk at least 20 minutes in the past 30 days 25. Self rating of mobility 26. Self rating of self-care 27. Self rating of usual activities 28. Feels full of life 29. Has a lot of energy 30. Feels worn out 31. Feels tired 32. Self rating of pain/discomfort 33. Unintentional weight loss of 10 pounds 34. Times of visiting a healthcare provider to get medical care in the past year	Frail (>0.35), Pre-frail (0.20–0.35), Non-frail (<0.20)
Widagdo (2015)	39	1. Live alone 2. Self-rated health (Poor = 1; Fair = 0.75; Good = 0.5; Very good = 0.25; Excellent = 0) 3. Arthritis 4. Asthma 5. History of heart attack 6. Hypertension 7. Migraine 8. Parkinson's disease 9. History of stroke 10. Thyroid disease 11. Ear, nose or throat problem 12. Mental disorder 13. Genito-urinary problem	14. Diabetes 15. Cancer 16. Chest pain 17. Constipation 18. Dental problem 19. Sleep problem (Rarely/never = 0; Sometimes = 0.5; Often/almost always = 1) 20. Spinal problem 21. Hearing difficulty 22. Eye trouble 23. Skin problem 24. Problem with hands shaking (No difficulty at all or a little difficulty = 0; Some/a lot of difficulty = 1) 25. Stooping/crouching/kneeling problem (No difficulty at all or a little difficulty = 0; Some/a lot of difficulty or just unable to do = 1)	26. Difficulty with bathing 27. Difficulty with personal grooming 28. Difficulty with dressing 29. Difficulty with eating 30. Difficulty with toileting 31. Difficulty with going out 32. Difficulty with moving around 33. Difficulty with laundry/linen 34. Difficulty with housework 35. Difficulty with preparing meals 36. Difficulty with using telephone 37. Difficulty with managing money 38. Difficulty with using public transport 39. Difficulty with shopping	Frail (>0.25)
Ding (2017) ¹	30(29?)	1. Chronic illness: Hypertension 2. Chronic illness: Myocardial Infarction 3. Chronic illness: Congestive heart failure 4. Chronic illness: Diabetes Mellitus 5. Chronic illness: Stroke 6. Chronic illness: Arthritis 7. Chronic illness: Cancer	11. Psychological condition: Feeling effortful (CESD) 12. Psychological condition: Feeling happy (CESD): reverse 13. Psychological condition: Feeling lonely (CESD) 14. Psychological condition: Could not get going (CESD) 15. Poor self-rated health 16. Mobility: walking 100 yards	20. BADL: dressing 21. BADL: walking 22. BADL: bathing 23. BADL: eating 24. BADL: toileting 25. IADL: shopping 26. IADL: taking medication 27. IADL: doing housework	Frail (>0.25), Pre-frail (0.08 - 0.25), Non-frail (<0.08)

Author (year)	Item no.	Included items			Cutoff
		8. Chronic illness: Obesity 9. Psychological condition: Dementia 10. Psychological condition: Feeling depressed (CESD)	17. Mobility: getting up from chair 18. Mobility: climbing stairs 19. Mobility: lifting weights	28. IADL: managing finances 29. Weak grip strength	
Zucchelli (2019)	45	1. Hypertension 2. Thyroid disorders 3. Anaemia 4. Atrial Fibrillation 5. Blindness and other visual impairments 6. Cerebrovascular diseases 7. Chronic kidney disease 8. Chronic Obstructive Pulmonary Disease, emphysema and chronic bronchitis 9. Deafness and other hearing impairments 10. Dementia 11. Depression and other mood disorders 12. Diabetes 13. Heart failure 14. Inflammatory bowel diseases 15. Ischemic heart disease	16. Osteoporosis 17. Parkinson disease and parkinsonisms 18. Peripheral arterial diseases 19. Peripheral neuropathies 20. Sleep disorders 21. Solid neoplasm 22. Inability to autonomously take and prepare medications 23. Inability to autonomously shop 24. Inability to autonomously cook and prepare meals 25. Inability to autonomously do house chores 26. Inability to autonomously do the laundry 27. Inability to autonomously manage finances 28. Inability to autonomously use the telephone 29. Inability to autonomously use means of transportation 30. Minimental State Examination score 1 if < 18, 0.5 if 18 ≤ score < 23, 0.25 if ≤24 score < 27, 0 if ≥ 27	31. Inability to autonomously bath 32. Inability to autonomously dress 33. Inability to autonomously use the toilet 34. Incontinence 35. Inability to autonomously move in and out from bed or chair 36. Inability to autonomously feed him-/herself 37. Usage of stick during walking 38. Reporting dyspnoea 39. Evidence of swollen legs at physical examination 40. Reporting anxiety symptoms 41. Self-reporting appetite loss 42. Self-reporting sense of worthlessness 43. Reporting pain 44. Feeling older than actual age 45. Self-reporting low quality of life	Frail (>0.25), Pre-frail (0.08 - 0.25), Non-frail (<0.08)
Woo (2012)	47	Self-reported health, history of falls in the past 12 months, history of osteoporotic fractures, presence of back pain limiting activities, clumsiness in walking, clumsiness using hands, number of prescription medications, and any difficulty performing activities of daily living (walking 2–3 blocks outside on level ground, climbing 10 steps without resting, preparing own meals, doing heavy housework such as scrubbing floors or washing windows, and doing own shopping for groceries or clothes). The presence or absence of disease was based on participant report of diagnosis by their doctor. Depressive symptoms were assessed using the Geriatric Depression Scale (GDS), ²¹ which has been validated in elderly Chinese adults, with a score of 8 or greater representing depressive symptoms. Cognitive impairment was assessed using the Cognitive Screening Instrument for Dementia (CSID) with a cutoff of 28.4. Physical activity level was assessed the Physical Activity Scale for the Elderly (PASE).			Cutoff points used 0.05, 0.1, 0.15, 0.2, 0.25
Height, weight, time and number of steps taken to walk 6 m, grip strength, blood pressure, and ankle brachial index (ABI) were measured on the same day that the questionnaire was administered. Step length was calculated by dividing 6 m by the total number of steps taken. Body weight was measured with participants wearing a light gown using the Physician Balance Beam Scale (Healthometer, Alsip, IL). Height was measured using the Holtain Harpenden stadiometer (Holtain Ltd, Crosswell, UK). BMI was calculated by dividing weight in kg by the square of height in meters. Grip strength was measured using a dynamometer (JAMAR hand dynamometer 5030JI; Sammons Preston, Bolingbrook, IL). The average of two readings on the right and left side was used. Blood pressure was measured twice in the supine position using a mercury sphygmomanometer and the average used. Duplicate measures of supine blood pressure in the right arm and both ankles were					

Author (year)	Item no.	Included items			Cutoff
		taken using a standard mercury sphygmoma- nometer and an 8-MHz Doppler probe (Pocket Doppler Model 841-A; Parks Medical Electronics, Inc., Aloha, OR). ABI was calculated for each leg by dividing the pos- terior tibial systolic pressure in each lower extremity by the upper extremity pressure. The current standard for diagnosing peripheral vascular disease is defined as an ABI less than 0.90. An ABI of less than 0.90 is 95% sensitive and 99% specific for angiographically diagnosed peripheral arterial disease. The lower ABI of the 2 was used to determine the extent of ischaemic disease.			
Chao (2018) ²	24	1. Problems getting dressed 2. Problems with bathing 3. Urinary incontinence 4. Toileting problems 5. Impaired mobility 6. Falls 7. Feeling sad, blue, depressed 8. Tiredness all the time	9. Depression (clinical impression) 10. Changes in general mental functioning 11. Memory changes 12. Sleep changes 13. History relevant to cognitive impairment or loss 14. Arterial hypertension 15. Seizures, generalized 16. Headache	17. Cerebrovascular problems 18. History of diabetes mellitus 19. Musculoskeletal problems 20. Congestive heart failure 21. Lung problems or respiratory problems 22. Malignant disease 23. Other medical history 24. Proxy memory rating	Frail (>0.2)
Romero-Ortuno and Soraghan (2014)	70	1. Self-Rated Health 2. Hospitalization in Past Year 3. Heart attack 4. Stroke or CVD 5. High blood cholesterol 6. Diabetes mellitus or high blood sugar 7. Chronic lung disease 8. Asthma 9. Long-term illness 10. Arthritis 11. Osteoporosis 12. Cancer 13. High blood pressure 14. Stomach or duodenal ulcer 15. Parkinson disease 16. Cataracts 17. Heart trouble or angina 18. Hip or femoral fracture 19. Falling down 20. Sleeping problems 21. Dizziness 22. Swollen legs 23. Stomach or intestine problems	24. Incontinence 25. Persistent cough 26. Require dentures 27. Difficulty biting on hard foods 28. Problems with eyesight 29. Hearing problems 30. Pain in any joint 31. Breathlessness 32. Climbing several flights of stairs 33. Stooping/kneeling/crouching 34. Sitting for about 2 hours 35. Reaching or extending arms 36. Pulling/pushing large objects 37. Lifting/carrying weights >5 kg 38. Walking 100 m 39. Picking up a small coin from table 40. Dressing 41. Walking across a room 42. Getting up from a chair 43. Bathing or showering 44. Eating 45. Getting in or out of bed 46. Preparing a hot meal	47. Using the toilet 48. Using a map to get around 49. Making telephone calls 50. Taking medications 51. Shopping for groceries 52. Managing money 53. Vigorous activities 54. Moderate activities 55. Doing work around house/garden 56. Limitations with activities 57. Orientation 58. Mathematical performance 59. Delayed recall test 60. Verbal fluency score 61. Suicidality 62. Trouble sleeping 63. Depression 64. Interest 65. Appetite 66. Fatigue 67. Pessimism 68. Concentration 69. Lack of enjoyment 70. Fear of falling down	n/s
Thompson (2019)	34	1. Angina 2. Heart attack 3. Osteoporosis 4. Osteoarthritis	13. Weak grip strength 14. Falls 15. Hospital emergency admission 16. Low activity level (<100 METs per week)	25. Health limits walking 100m 26. Felt lonely 27. Felt that could not get going	Frail (>0.21),

Author (year)	Item no.	Included items	Cutoff
		5. Rheumatoid and any other arthritis 6. Stroke or TIA 7. Diabetes 8. Any mental health problem 9. Systolic blood pressure 10. Diastolic blood pressure 11. 10% weight loss over 4 years 12. FEV1/FVC post ratio	17. Healthy as anybody I know 18. Health is excellent 19. Self-reported health 20. Health limits lifting or carrying groceries 21. Health limits climbing several flights of stairs 22. Health limits climbing one flight of stairs 23. Health limits bending, kneeling or stooping 24. Health limits walking more than 1km 28. Difficulty keeping mind on what you were doing 29. Felt everything was an effort 30. Physical & emotional problems interfered with social activities 31. Felt full of life 32. Felt calm and peaceful 33. Felt worn out 34. Felt tired
			Pre-frail (0.10 - 0.21), Non-frail (<0.10)

¹Rationale for no. of items <30: Manuscript says 30 items, but the FI list suggests 29 items. (List obtained from a previous publication by Ding *et al.* (2017)³⁸⁴ using the same dataset)

²Rationale for no. of items <30: The authors could only not retrieve the same variables to approximate the 70-items from the original study they tried to recreate.

Table S2.9 Domains included in the FI

Author (year)	Item no.	Energy	Physical activity	Weight loss/BMI	Strength ^a	Gait ^b	Cognition	Mood	ADL	Self-rated health	Hearing and vision	Incontinence	Medication	Sleep	Hospitalisation	Comorbidities	Symptoms	Social support	Falls
Chao (2018)	24	X					X	X	X			X		X		X	X		X
Romero-Ortuno and Soraghan (2014)	70	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Ding (2017)	30 (29?)	X			X	X	X	X	X	X			X			X			
Woo (2012)	47		X	X	X	X	X	X	X	X			X			X	X		X
Li (2015)	34	X	X	X	X	X		X	X	X			X		X	X	X		
Zucchelli (2019)	45					X	X	X	X	X	X	X	X	X		X	X		
Widagdo (2015)	39				X	X	X		X	X	X	X		X		X	X		
Thompson (2019)	34	X	X	X	X	X	X	X	X	X					X	X	X		X

^aItems like grip strength and difficulty lifting weights over 10 lbs.

^bItems like gait speed, can you walk 100m, difficulty with moving around, and usage of a walking stick.

List of domains adapted from Theou *et al.* (2014).³⁸⁵

Figure S3.1 Data collected in the Computer Assisted P Interview (CAPI) and Self-C Questionnaire (SCQ) in TILDA at each wave

Table 3. Data collected in the CAPI and SCQ at each wave

Demographic data	Physical health
Education ¹⁻⁴	Self-rated health ¹⁻⁴
Languages (SCQ) ²	Limiting long-standing illness/disability ¹⁻⁴
Childhood and siblings ¹⁻⁴	Sensory function ¹⁻⁴
Migration history ¹⁻⁴	Cardiovascular disease ¹⁻⁴
Marital status and marriage history ¹⁻⁴	Non-cardiovascular chronic illness ¹⁻⁴
	Falls/fear of falling/steadiness ¹⁻⁴
Social circumstances	Fractures ¹⁻⁴
Transfers to (and from) children ¹⁻⁴	Chronic pain ¹⁻⁴
Transfers to (and from) parents ¹⁻⁴	Incontinence ¹⁻⁴
Transfers to (and from) others ¹⁻⁴	Medical screening ¹⁻⁴
(Instrumental) activities of daily living ¹⁻⁴	Oral health ¹⁻⁴
Helpers ¹⁻⁴	Medications ¹⁻⁴
Social networks ¹⁻⁴	Health care use ¹⁻⁴
Volunteering and caring ¹⁻⁴	
Participation in social activities (SCQ) ¹⁻⁴	Mental and psychological health
Religion ¹⁻⁴	Self-reported mental health ¹⁻⁴
Relationship quality (SCQ) ¹⁻⁴	Depression ¹⁻⁴
Sexual activity (SCQ) ^{2,4}	Life satisfaction ¹⁻⁴
	Anxiety ¹ (SCQ) ²⁻⁴
Employment and lifelong learning	Worry (SCQ) ¹⁻⁴
Employment situation ¹⁻⁴	Loneliness (SCQ) ¹⁻⁴
Job history ¹⁻⁴	Perceived stress (SCQ) ^{1,3,4}
Lifelong learning ¹	Stressful life events (SCQ) ^{1,2}
	Coping Inventory for stressful situations (SCQ) ³
Retirement and expectations	Quality of life (SCQ) ¹⁻⁴
Planning for retirement ¹⁻⁴	Resilience ^{3,4}
Expectations ¹⁻⁴	Ageing perceptions (SCQ) ^{1,3}
Fear of crime ^{3,4}	Personality (SCQ) ²
Advanced Care Planning ⁴	Falls efficacy (SCQ) ^{2,3}
	Post-traumatic stress disorder (SCQ) ⁴
Income and assets	Purpose in life (SCQ) ⁴
Sources of income ¹⁻⁴	
House ownership ¹⁻⁴	Cognitive health
Other assets ¹⁻⁴	Self-rated memory ¹⁻⁴
	Mini-Mental State Examination (MMSE) ²⁻⁴
Literacy	Word-list learning (recall) ¹⁻⁴
Financial literacy ³	Verbal fluency ¹⁻⁴
Health literacy ⁴	Prospective memory ¹⁻⁴
Behavioural health	Other
Smoking ¹⁻⁴	Heating and accommodation (SCQ) ²⁻⁴
Physical activity ¹⁻⁴	Neighbourhood ^{2,4}
Sleep ¹⁻⁴	Address history ³
Alcohol (SCQ) ^{1-4, a}	Transport and driving ¹
Dietary intake (SCQ) ^{3,4}	

¹⁻⁴Indicate the wave in which data were collected (i.e. Wave 1, Wave 2, Wave 3, Wave 4). Data collected in CAPI unless otherwise stated.

^aAlcohol questions are included in the CAPI for proxy interviews but in the SCQ for self-interviews.

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Figure S3.2 Tests included in the TILDA health assessment of each wave

Table 5. Tests included in the TILDA health assessment at each health wave

Neuropsychological function	Gait and mobility
Mini-Mental State Examination (MMSE) ^{1,a}	Timed up-and-go (TUG) ^{1,3,d}
Montreal Cognitive Assessment (MOCA) ^{1,3}	Repeated chair stands ³
Sustained Attention to Response Task (SART) ^{1,3}	GAITRite assessment
Picture memory test ¹	– normal pace ^{1,3,c}
National Adult Reading Test (NART) ³	– dual task (manual) ^{1,c}
Visual reasoning ¹	– dual task (cognitive) ^{1,3,c}
Choice reaction time ^{1,3}	– maximum pace ^{3,c}
Colour trails test ^{1,3}	
Centre for Epidemiological Studies Depression (CES-D) 8-item scale ^{1,3,b}	Bone health
State trait anxiety inventory ³	Heel bone ultrasound ^{1,3,c}
	Anthropometric/other
Cardiovascular function	Grip strength ^{1,3,d}
Blood pressure (Omron) ^{1,3}	Height ^{1,3}
Pulse wave velocity ^{1,3,c}	Weight ^{1,3}
Heart rate variability ^{1,3,c}	Waist and hip circumference ^{1,3}
Phasic blood pressure ^{1,3,c}	Blood samples ^{1,3,c}
Near-infrared spectroscopy (NIRS) ^{3,c}	Hair sample ^{3,f}
	Physical activity question ^{3,c}
Sensory function	Oral health ^{3,c,g}
Visual acuity ^{1,3,c}	Accelerometry ^{3,g}
Contrast sensitivity ^{1,3,c}	MRI ^{3,c,g}
Macular pigment optical density ^{1,c}	
Retinal photograph ^{1,3,c}	
Sound-induced flash illusion (SHAMS) ^{3,c}	

^{1,3}Indicate the wave in which data were collected (i.e. Wave 1, Wave 3).

^aMMSE was included in Waves 2, 3 and 4 CAPI.

^bCESD-20 was included in Waves 1 and 2 CAPI; CESD-8 was included in Waves 3 and 4 CAPI.

^cIncluded in the health centre assessment only.

^dTUG and grip strength were included in Waves 2 and 4 CAPI.

^eBlood sample analytes: lipid profile, folate, Vitamin B12, Vitamin D, Vitamin E, C-reactive protein, interleukin-18, creatinine, cystatin C, haemoglobin A1c, lutein, zeaxanthin, lycopene, alpha-carotene, beta-carotene, DNA (seven single nucleotide polymorphisms associated with age-related macular degeneration).

^fHair sample hormone assays: cortisol, cortisone, testosterone, beta-estradiol, progesterone, melatonin.

^gIncluded for a sub-study only, due to resource availability (i.e. limited accelerometers, availability of dentist, limited MRI funding).

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Table S3.1 Baseline characteristics of participants followed-up versus participants lost to follow-up

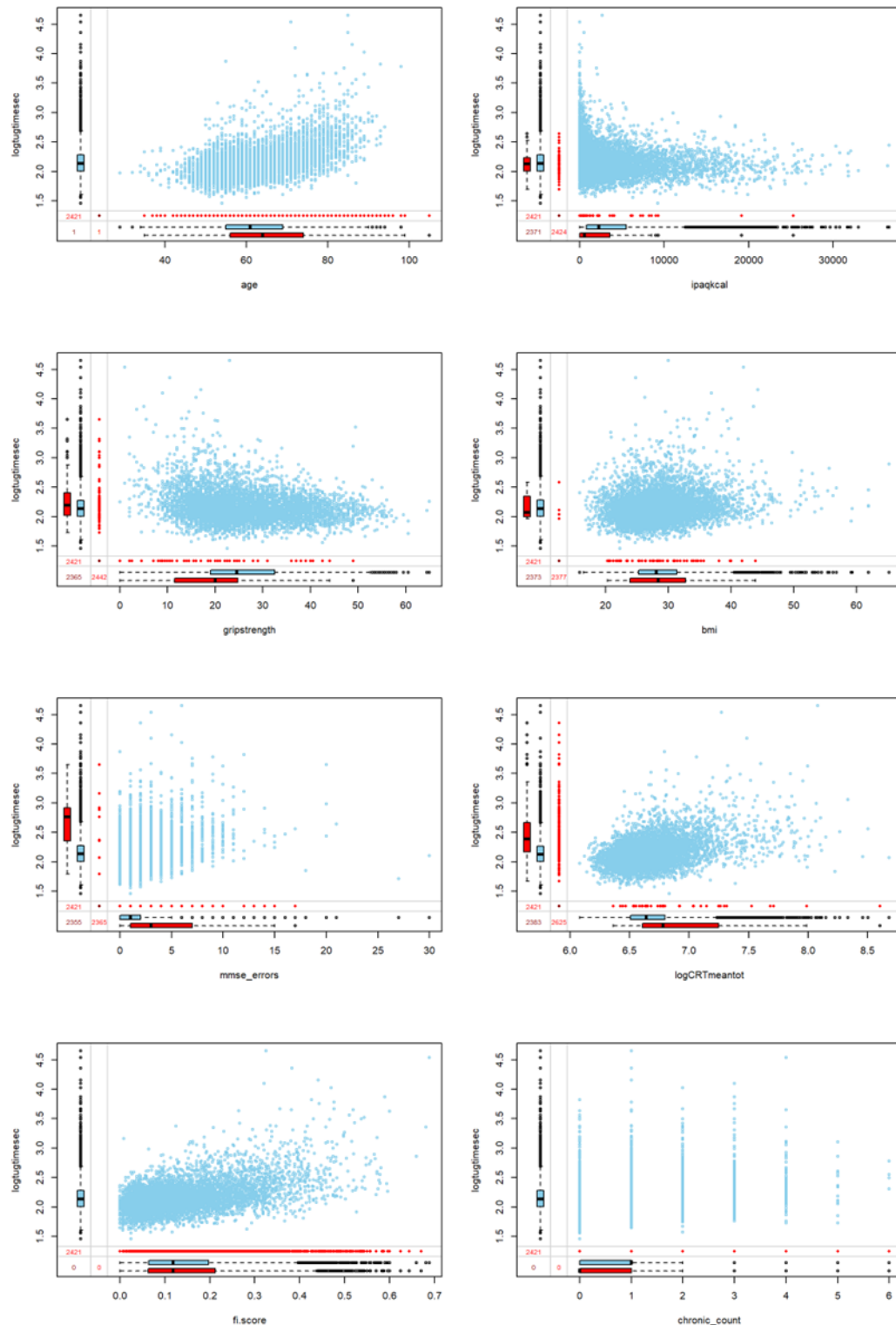
Mean (SD) or N (%), unless specified	Followed-up	Lost to follow-up	p-value*
Total	7493 (88.1%)	1011 (11.9%)	
Age	62.8 (9.9)	63.6 (10.7)	0.02
Sex (Female)	4054 (55.6 %)	579 (57.3 %)	0.35
Education level			<0.001
Primary	2469 (33.9 %)	403 (39.9 %)	
Secondary	2983 (40.9 %)	380 (37.6 %)	
Tertiary	1617 (22.2 %)	179 (17.7 %)	
Married	5170 (71 %)	709 (70.1 %)	0.61
Residential area	3501 (48.1 %)	498 (49.3 %)	0.69
Rural			
Another city	2056 (28.2 %)	272 (26.9 %)	
Dublin	1728 (23.7 %)	241 (23.8 %)	
Lives alone	1510 (20.7 %)	221 (21.9 %)	0.43
Occupation type			<0.001
Manual	1931 (26.5 %)	328 (32.4 %)	
Non-manual	5354 (73.5 %)	683 (67.6 %)	
BMI	28.7 (5.1)	28.7 (5)	0.96
Current smoker	1264 (17.4 %)	238 (23.5 %)	<0.001
Drinking above the weekly limit†	402 (5.5 %)	42 (4.2 %)	<0.001
Depressed	674 (9.3 %)	111 (11 %)	0.01
Chronic diseases (≥2)	1295 (17.8 %)	159 (15.7 %)	0.12
Cardiovascular diseases (≥3)	848 (11.6 %)	109 (10.8 %)	0.45
MMSE errors, median (IQR)	1 (0-2)	2 (0-4)	<0.001
Accident and emergency (ever)	1077 (14.8 %)	142 (14 %)	0.57
Overnight hospitalisation (ever)	905 (12.4 %)	122 (12.1 %)	0.79
Attended health assessment centre	4927 (67.6 %)	290 (28.7 %)	<0.001
FI score, median (IQR)	0.12 (0.06-0.2)	0.12 (0.06-0.19)	0.57
FP count, median (IQR)	0 (0-1)	1 (0-2)	0.02
Grip strength (kg)	26.1 (9.9)	26.1 (10.1)	0.94
TUG time (s)	9 (3.6)	9.5 (3.3)	0.02
IPAQ (kcal), median (IQR)	2347 (830.9-5600.4)	2096 (692.4-5074.3)	0.03

*p-values refer to the Chi-square/Fisher's exact tests for categorical variables or the t-test or Wilcoxon test for continuous variables.

†The weekly limit on standard drinks (1/2 pint of beer or a glass of wine) according to the government guidelines (>21 for men; >14 for women).

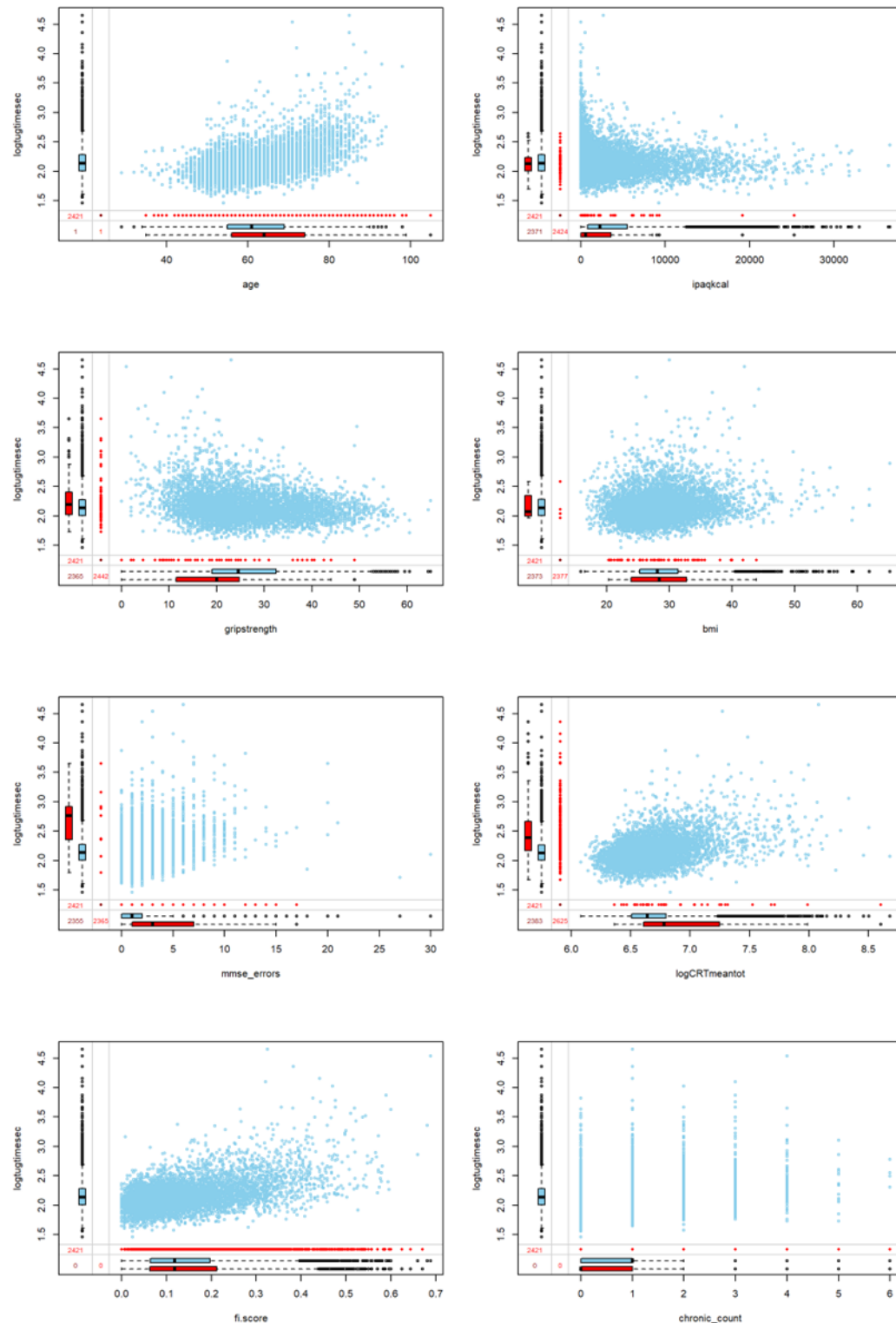
Abbreviations: BMI=body mass index; FI=frailty index; FP=frailty phenotype; IPAQ=International Physical Activity Questionnaire; MMSE=Mini-Mental State Examination; TUG=Timed-Up-and-Go.

Figure S3.3 Margin plots between grip strength and other participant characteristics at Wave 1 to assess MAR assumption



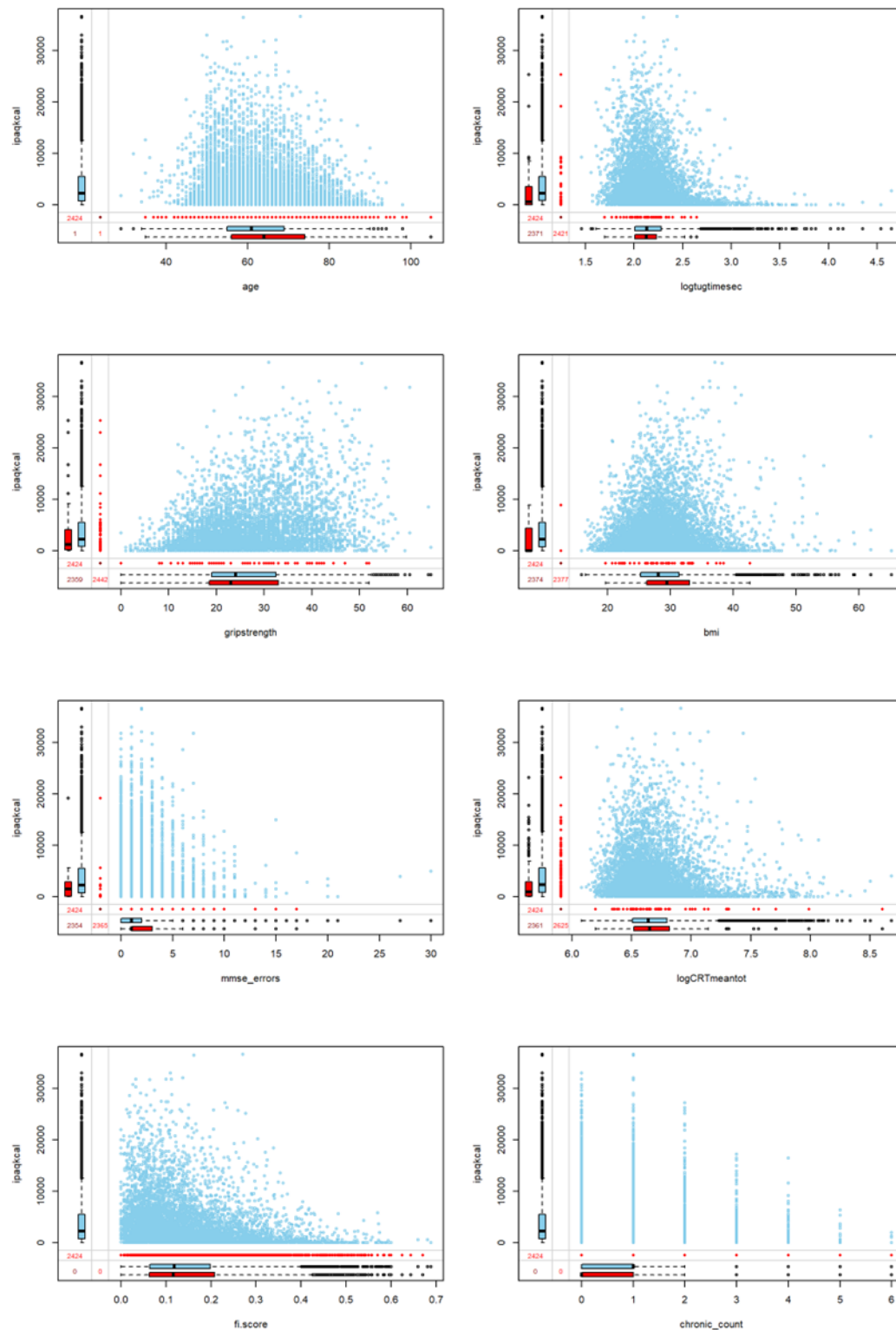
Non-missing values (in blue) and missing values (in red) are displayed. The distributions of the values in the y-axis are displayed in the left box plots (near the y-axis) by whether the x-axis variable is observed (left blue box) or unobserved (left red box), and vice versa. Participant characteristics assessed were: age, physical activity (ipaqkcal), grip strength (gripstrength), BMI (bmi), the number of errors in Mini-Mental State Examination (mmse_errors), creatinine (logCRTmeantot), FI score (fi.score), and the number of comorbidities (chronic_count).

Figure S3.4 Margin plots between Timed-Up-and-Go (TUG) time and other participant characteristics at Wave 1 to assess MAR assumption



Non-missing values (in blue) and missing values (in red) are displayed. The distributions of the values in the y-axis are displayed in the left box plots (near the y-axis) by whether the x-axis variable is observed (left blue box) or unobserved (left red box), and vice versa. Participant characteristics assessed were: age, physical activity (ipaqkcal), grip strength (gripstrength), BMI (bmi), the number of errors in Mini-Mental State Examination (mmse_errors), creatinine (logCRTmeantot), FI score (fi.score), and the number of comorbidities (chronic_count).

Figure S3.5 Margin plots between physical activity and other participant characteristics at Wave 1 to assess MAR assumption



Non-missing values (in blue) and missing values (in red) are displayed. The distributions of the values in the y-axis are displayed in the left box plots (near the y-axis) by whether the x-axis variable is observed (left blue box) or unobserved (left red box), and vice versa. Participant characteristics assessed were: age, TUG time (logtugtimesec), grip strength (gripstrength), BMI (bmi), the number of errors in Mini-Mental State Examination (mmse_errors), creatinine (logCRTmeantot), FI score (fi.score) and the number of comorbidities (chronic_count).

Table S4.1 Search terms used in the literature to identify prospective studies reporting the association between CVD RFs and frailty

Search criteria	Search terms for Medline (1946-) or Embase (1974-)
Study design	follow-up studies/ OR longitudinal studies/ OR prospective studies/ OR cohort studies/ OR ((cohort OR follow up OR case cohort or nested case control) adj (study OR studies OR analys*)).ti,ab. OR ((longitudinal OR prospective) AND (study OR studies OR review OR analys* OR cohort*)).ti,ab.
Frailty	(frail OR frailty).ti,ab. OR Frailty/ OR Frail Elderly/
Adiposity	(adiposity or anthropometry or "waist hip ratio" or waist or WHR or "body fat distribution" or "body composition" or "waist circumference" or "hip circumference" or "body mass index" or BMI or "body mass" or "body weight" or impedance or "body fat" or "fat mass" or obesity or "central obesity" or "central adiposity" or "central fat distribution" or "abdominal fat" or "abdominal obesity" or "abdominally obese" or obese or overweight).ti,ab.
Lean body mass	("lean mass" OR "lean body mass" OR "body composition" OR "muscle mass" OR "sarcopenia" OR "skeletal muscle" OR "bio-impedance" OR "bioimpedance").ti,ab.
Alcohol	(alcohol or "drinking alcohol" or "excessive drinking" or "hazardous drinking" or "problem drinking" or "problematic drinking" or "alcohol consumption" or "alcohol intake" or "heavy drinking" or "alcohol abuse").ti,ab.
Smoking	(smoking OR tobacco OR cigarette).ti,ab.
Diabetes	(diabetes or glucose or "blood sugar" or hyperglycemia).ti,ab.
Hypertension	("blood pressure" OR hypertens*).ti,ab.

Table S4.2 Search terms used in the literature review to identify prospective studies reporting the association between frailty and stroke and ischaemic heart disease

		Search terms for MEDLINE (Ovid)	Search terms for Embase
Study design	1	follow-up studies/ OR longitudinal studies/ OR prospective studies/ OR cohort studies/ OR ((cohort OR follow up OR case cohort or nested case control) adj (study OR studies OR analys*)).ti,ab. OR ((longitudinal OR prospective) AND (study OR studies OR review OR analys* OR cohort*)).ti,ab.	follow-up studies/ OR longitudinal studies/ OR prospective studies/ OR cohort studies/ OR ((cohort OR follow up OR case cohort or nested case control) adj (study OR studies OR analys*)).ti,ab. OR ((longitudinal OR prospective) AND (study OR studies OR review OR analys* OR cohort*)).ti,ab.
Frailty	2	(frail OR frailty).ti,ab. OR Frailty/ OR Frail Elderly/	(frail OR frailty).ti,ab. OR frailty/ OR frail elderly/
Ischaemic heart disease	3	("isch?emic heart disease" or "myocardial infarction" or "myocardial isch?emia" or "heart infarction" or "acute coronary syndrome" or "coronary heart disease" or "coronary artery disease" or "heart muscle isch?emia").ti,ab. or Myocardial infarction/ or Myocardial Ischemia/ or Coronary Disease/ or Acute Coronary Syndrome/ or Coronary Artery Disease/	("isch?emic heart disease" or "myocardial infarction" or "myocardial isch?emia" or "heart infarction" or "acute coronary syndrome" or "coronary heart disease" or "coronary disease" or "coronary artery disease" or "heart muscle isch?emia").ti,ab. OR heart infarction/ OR heart muscle ischemia/ OR acute coronary syndrome/ OR coronary artery disease/
Stroke	4	(stroke* OR cerebrovascular OR cva OR cvas).ti,ab. OR ((brain OR vascular OR lacunar OR venous OR cerebral OR intracerebral OR isch?emic) adj2 (accident* OR infarct* OR event* OR attack* OR h?emorrhage)).ti,ab. OR Stroke/ OR Hemorrhagic Stroke/ OR Ischemic Stroke/ OR Cerebrovascular Disorders/	(stroke* OR cerebrovascular OR cva OR cvas).ti,ab. OR ((brain OR vascular OR lacunar OR venous OR cerebral OR intracerebral OR isch?emic) adj2 (accident* OR infarct* OR event* OR attack* OR h?emorrhage)).ti,ab. OR cerebrovascular accident/ OR cerebrovascular disease/ OR brain hemorrhage/ OR ischemic stroke/ OR brain ischemia/
Cardiovascular disease	5	"cardiovascular disease".ti,ab. or Cardiovascular Diseases/	"cardiovascular disease".ti,ab. or cardiovascular diseases/
Search	6	1 AND 2 AND (3 OR 4 OR 5)	
Limitations	8	Limit 6 to English language & Publication year 2001-Current	Limit 6 to English language & Publication year 2001-Current

Figure S5.1 Section of the CKB baseline questionnaire on personal and family medical history

Section 7: Personal & family medical history

7.1 How is your current general health status?

7.1.1 Self-rated health status?

☐ Excellent

☐ Good

☐ Fair

☐ Poor

7.1.2. Compared to someone of your own age?

☐ Better

☐ About the same

☐ Worse

☐ Don't know

7.2 If you were walking on level ground with other healthy people of the same age, would you usually:

7.2.1 Become short of breath? ☐ Yes ☐ No ☐ Disabled

7.2.2 Slow down due to chest discomfort? ☐ Yes ☐ No ☐ Disabled

7.3 During the past 12 months, have you usually had the following symptoms?

7.3.1 Cough frequently?

☐ No

☐ Yes, for <3 months

☐ Yes, for ≥3months

7.3.2 Cough up sputum after getting up in the morning?

☐ No

☐ Yes, for <3 months

☐ Yes, for ≥3 months

7.4 Has a doctor EVER told you that you had had the following disease?

	Diagnosed disease?		Age at first diagnosis	Still on treatment?		
	Yes	No		Yes	No	
Diabetes	☐	☐		☐	☐	For CHD, stroke, and hypertension what is the current medication: 1. Aspirin 2. ACE-I 3. Beta-blocker 4. Statins 5. Diuretics 6. Ca ⁺⁺ antagonist & for diabetes, the above list plus 7. Chlorpropamide or metformin 8. Insulin
CHD	☐	☐		☐	☐	
Stroke or TIA	☐	☐		☐	☐	
Hypertension	☐	☐		☐	☐	
Rheumatic heart dis.	☐	☐		☐	☐	
TB	☐	☐		☐	☐	
Emphysema/bronchitis	☐	☐		☐	☐	
Asthma	☐	☐		☐	☐	
Cirrhosis/chronic hepatitis	☐	☐		☐	☐	
Peptic ulcer	☐	☐		☐	☐	
Gallstone/gallbladder dis.	☐	☐		☐	☐	
Kidney disease	☐	☐		☐	☐	
Fracture	☐	☐		☐	☐	
Rheumatoid arthritis	☐	☐		☐	☐	
Psychiatric disorders	☐	☐		☐	☐	
Neurasthenia	☐	☐		☐	☐	
Head injury	☐	☐		☐	☐	
Cancer*	☐	☐		☐	☐	

***If yes, please indicate the site of cancer** ☐ (If more than one, choose the one that occurred first)

0. Lung 1. Esophagus 2. Stomach 3. Liver 4. Intestine 5. Breast 6. Prostate 7. Cervix 8. Other

CKB Baseline questionnaire (page 10) obtained from the CKB website (<https://www.ckbiobank.org/study-resources/survey-data>).

Table S5.1 Example of metabolic equivalent of task (MET) values for specific activities from the updated 2011 Adult Compendium of Activities

Codes	METs	Major heading	Specific activities
1003	14	bicycling	bicycling, mountain, uphill, vigorous
1004	16	bicycling	bicycling, mountain, competitive, racing
1008	8.5	bicycling	bicycling, BMX
1009	8.5	bicycling	bicycling, mountain, general
1010	4	bicycling	bicycling, <10 mph, leisure, to work or for pleasure (Taylor Code 115)
1011	6.8	bicycling	bicycling, to/from work, self selected pace
1013	5.8	bicycling	bicycling, on dirt or farm road, moderate pace
1015	7.5	bicycling	bicycling, general
1018	3.5	bicycling	bicycling, leisure, 5.5 mph
01019	5.8	bicycling	bicycling, leisure, 9.4 mph
1020	6.8	bicycling	bicycling, 10-11.9 mph, leisure, slow, light effort
1030	8	bicycling	bicycling, 12-13.9 mph, leisure, moderate effort
1040	10	bicycling	bicycling, 14-15.9 mph, racing or leisure, fast, vigorous effort
1050	12	bicycling	bicycling, 16-19 mph, racing/not drafting or > 19 mph drafting, very fast, racing general
1060	15.8	bicycling	bicycling, > 20 mph, racing, not drafting
1065	8.5	bicycling	bicycling, 12 mph, seated, hands on brake hoods or bar drops, 80 rpm
1066	9.0	bicycling	bicycling, 12 mph, standing, hands on brake hoods, 60 rpm
1070	5	bicycling	unicycling
02001	2.3	conditioning exercise	activity promoting video game (e.g. Wii Fit), light effort (e.g. balance, yoga)
02003	3.8	conditioning exercise	activity promoting video game (e.g. Wii Fit), moderate effort (e.g. aerobic, resistance)
02005	7.2	conditioning exercise	activity promoting video/arcade game (e.g. Exergaming, Dance Dance Revolution), vigorous effort
2008	5.0	conditioning exercise	army type obstacle course exercise, boot camp training program
2010	7	conditioning exercise	bicycling, stationary, general
2011	3.5	conditioning exercise	bicycling, stationary, 30-50 watts, very light to light effort
2012	6.8	conditioning exercise	bicycling, stationary, 90-100 watts, moderate to vigorous effort
2013	8.8	conditioning exercise	bicycling, stationary, 101-160 watts, vigorous effort
2014	11	conditioning exercise	bicycling, stationary, 161-200 watts, vigorous effort
2015	14	conditioning exercise	bicycling, stationary, 201-270 watts, very vigorous effort
2017	4.8	conditioning exercise	bicycling, stationary, 51-89 watts, light-to-moderate effort
2019	8.5	conditioning exercise	bicycling, stationary, RPM/Spin bike class

List of METs from: <https://sites.google.com/site/compendiumofphysicalactivities/home>

Table S6.1 Coding of individual frailty deficits in the CKB questionnaire and using ICD-10 codes

	Definition of frailty deficit according to variables in the CKB questionnaire	Coding of variables	Equivalent ICD-10 description	ICD-10 codes
1	Self-reported diagnosis of hypertension by a doctor, self-reported use of antihypertension drugs, systolic blood pressure measured to be ≥ 140 mm Hg, or diastolic blood pressure measured to be ≥ 90 mm Hg	Yes=1.00; no=0.00	Hypertension	I10
2	Self-reported diagnosis of heart disease by a doctor	Yes=1.00; no=0.00	Heart disease	I05 - I09, I11, I13, I20 - I28, I30 - I52
3	Self-reported diagnosis of stroke or transient ischaemic attack by a doctor	Yes=1.00; no=0.00	Stroke or TIA	I60 - I64, I69.0 - I69.4, G45 - G46
4	Self-reported diagnosis of emphysema or chronic bronchitis by a doctor	Yes=1.00; no=0.00	Emphysema or bronchitis	J41 - J44
5	Self-reported diagnosis of tuberculosis by a doctor	Yes=1.00; no=0.00	Tuberculosis	A15 - A19, J65, K23.0, K67.3, M01.1, M49.0, M90.0, N33.0, N74.0 - N74.1, O98.0, P37.0
6	Self-reported diagnosis of asthma by a doctor	Yes=1.00; no=0.00	Asthma	J45 - J46
7	Self-reported diagnosis of peptic ulcer by a doctor	Yes=1.00; no=0.00	Peptic ulcer	K25 - K28
8	Self-reported diagnosis of gallstone disease, with or without cholecystitis, by a doctor	Yes=1.00; no=0.00	Cholelithiasis/ cholecystitis	K80 - K81
9	Self-reported diagnosis of rheumatoid arthritis by a doctor	Yes=1.00; no=0.00	Rheumatoid arthritis	M05 - M06, M08, M45
10	Self-reported diagnosis of fracture by a doctor	Yes=1.00; no=0.00	Fracture	S72.0 - S72.2, S72.7, S72.9; S12.0 - S12.7, S12.9; S22.0 - S22.1; S32.0 - S32.8; S32.2; S42.2 - S42.4, S42.7; S52.0 - S52.9
11	Self-reported diagnosis of neurasthenia by a doctor	Yes=1.00; no=0.00	Neurasthenia	F48.0
12	Self-reported diagnosis of diabetes, fasting blood glucose measured to be ≥ 7.0 mmol/L, or random blood glucose measured to be ≥ 11.1 mmol/L	Yes=1.00; no=0.00	Diabetes	E10 - E14
13	Self-reported diagnosis of cancer by a doctor	Yes=1.00; no=0.00	Cancer	C00 - C97
14	Self-reported diagnosis of chronic kidney disease by a doctor	Yes=1.00; no=0.00	Chronic kidney disease	E10.2, E11.2, E12.2, E13.2, E14.2, I12, I13, N03, N07, N11, N18
15	If you were walking on level ground with other healthy people of the same age, would you usually become short of breath or slow down because of chest discomfort?	Yes=1.00; no=0.00	Shortness of breath	R06.0
16	During the past month, did you have any of the following for ≥ 3 days per week: (1) taking >30 min to fall asleep after going to bed or waking up in the middle of the night; (2) waking up early and not being able to go back to sleep; or (3) having difficulty staying alert while at work, eating, or meeting people during the daytime?	Yes=1.00; no=0.00	Sleep problem	F51, G47
17	How often do you have bowel movements each week?	<3 times per week=1.00; other=0.00	Abnormal frequency of bowel movement	R19.4

	Definition of frailty deficit according to variables in the CKB questionnaire	Coding of variables	Equivalent ICD-10 description	ICD-10 codes
18	During the past 12 months, did you have pain or discomfort in your body lasting ≥ 3 months that interfered with your life?	Yes=1.00; no=0.00	Pain, not elsewhere classified	R52
19	During the past 12 months, have you developed a frequent cough?	Yes, for ≥ 3 months=1.00; yes, for < 3 months=0.50; no=0.00	Cough	R05
20	Do you brush your teeth rarely or never, or have false teeth?	Yes=1.00; no=0.00	Dental problem	K00 - K08
21	Physical activity in the past 12 months, including the usual type and duration of activities in occupational, commuting, domestic, and leisure time-related domains	Lowest quintile stratified by sex=1.00; other=0.00	Low level of physical activity	Z72.3
22	During the past 12 months, have you lost weight (≥ 2.5 kg) despite not trying to intentionally lose weight?	Yes=1.00; no=0.00	Unintentional weight loss	R63.4
23	During the past 12 months, did you feel much sadder, or more depressed, than usual for ≥ 2 weeks?	Yes=1.00; no=0.00	Feel sad or depressed	R45.2, R45.3
24	How is your current general health status?	Poor=1.00; fair=0.50; good=0.25; excellent=0.00	Self-reported health status	n/a
25	Body-mass index (kg/m^2)*	< 18.5 or $\geq 28.0 = 1.00$; ≥ 24.0 and $< 28.0 = 0.50$; ≥ 18.5 and $< 24.0 = 0.00$ ≥ 0.95 for men or ≥ 0.90 for women=1.00; ≥ 0.90 and < 0.95 for men or ≥ 0.85 and < 0.90 for women=0.50; < 0.90 for men or < 0.85 for women=0.00	Body-mass index (kg/m^2)*	n/a
26	Waist circumference (cm) to hip circumference ratio	< 0.90 for men or < 0.85 for women=0.00 ≤ 60 or $> 100 = 1.00$; ≥ 60 and $\leq 100 = 0.00$	Waist circumference (cm) to hip circumference ratio	n/a
27	Measured heart rate, beats per min	≤ 60 or $> 100 = 1.00$; ≥ 60 and $\leq 100 = 0.00$	Abnormal heart rate	R00
28	The ratio of forced expiratory volume in 1 s to the forced vital capacity measured to be < 0.7	Yes=1.00; no=0.00	Lung function	n/a

Table S6.2 Odds ratios (95% CI) of associations between demographic factors and frailty measures at baseline

	Original FI OR (95% CI)	Modified FI-1 OR (95% CI)	Modified FI-2 OR (95% CI)	Modified FI-3 OR (95% CI)
Highest education				
No formal school	1.00 (0.96-1.04)	1.00 (0.96-1.04)	1.00 (0.94-1.06)	1.00 (0.95-1.05)
Primary School	0.89 (0.87-0.92)	0.87 (0.85-0.89)	0.86 (0.82-0.90)	0.85 (0.81-0.88)
Middle School	0.88 (0.84-0.93)	0.86 (0.82-0.90)	0.93 (0.86-0.99)	0.86 (0.81-0.92)
High School	0.78 (0.72-0.84)	0.80 (0.75-0.85)	0.84 (0.75-0.94)	0.85 (0.78-0.93)
Technical school/college	0.86 (0.74-1.00)	0.88 (0.77-1.01)	1.13 (0.92-1.38)	1.09 (0.92-1.29)
University	0.63 (0.52-0.77)	0.70 (0.59-0.84)	0.82 (0.63-1.06)	0.87 (0.70-1.08)
Household income (yuan)				
<2,500	1.00 (0.94-1.06)	1.00 (0.95-1.06)	1.00 (0.92-1.09)	1.00 (0.93-1.08)
2,500-4,999	0.88 (0.84-0.93)	0.87 (0.83-0.91)	0.81 (0.75-0.87)	0.82 (0.77-0.88)
5,000-9,999	0.75 (0.72-0.79)	0.74 (0.71-0.77)	0.74 (0.70-0.78)	0.70 (0.67-0.74)
10,000-19,999	0.66 (0.63-0.68)	0.61 (0.59-0.63)	0.62 (0.58-0.65)	0.55 (0.52-0.57)
20,000-34,999	0.59 (0.56-0.62)	0.53 (0.51-0.56)	0.55 (0.51-0.59)	0.50 (0.47-0.53)
≥35,000	0.56 (0.53-0.60)	0.49 (0.46-0.52)	0.48 (0.44-0.52)	0.42 (0.38-0.45)
Marital status				
Married	1.00 (0.98-1.02)	1.00 (0.98-1.02)	1.00 (0.98-1.03)	1.00 (0.98-1.03)
Widowed, separated or divorced	1.09 (1.04-1.14)	1.12 (1.07-1.17)	1.13 (1.06-1.20)	1.15 (1.09-1.22)
Never married	1.58 (1.30-1.92)	1.57 (1.33-1.86)	1.61 (1.24-2.08)	1.59 (1.29-1.97)
Alcohol consumption (men only)				
Never regular	1.00 (0.94-1.07)	1.00 (0.94-1.06)	1.00 (0.92-1.08)	1.00 (0.93-1.07)
Ex-regular	1.58 (1.44-1.75)	1.50 (1.37-1.64)	1.49 (1.32-1.69)	1.45 (1.30-1.61)
Occasional	0.55 (0.52-0.59)	0.58 (0.55-0.61)	0.50 (0.45-0.55)	0.53 (0.49-0.58)
Monthly	0.56 (0.47-0.66)	0.54 (0.47-0.62)	0.43 (0.33-0.56)	0.45 (0.37-0.56)
Reduced intake	1.25 (1.13-1.39)	1.17 (1.06-1.28)	1.10 (0.95-1.27)	1.05 (0.93-1.19)
Weekly	0.59 (0.55-0.63)	0.56 (0.53-0.60)	0.52 (0.47-0.57)	0.52 (0.48-0.57)
Smoking status (men only)				
Never	1.00 (0.91-1.10)	1.00 (0.92-1.09)	1.00 (0.88-1.13)	1.00 (0.90-1.11)
Occasional	1.07 (0.96-1.19)	1.04 (0.94-1.14)	1.05 (0.91-1.22)	1.06 (0.94-1.20)
Ex regular	2.28 (2.14-2.44)	2.29 (2.15-2.43)	2.45 (2.25-2.66)	2.39 (2.22-2.57)
Smoker	1.09 (1.05-1.14)	1.14 (1.10-1.19)	1.10 (1.04-1.17)	1.12 (1.06-1.18)

Logistic regression models were adjusted for age, sex, region, education level, income level, marital status, alcohol consumption, and smoking status (where appropriate).

FI definitions: Original FI = 28-item FI; Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits); Modified FI-2 = 25-item FI (original FI excluding adiposity deficits); Modified FI-3 = 21-item FI (original FI excluding cardiovascular and adiposity deficits)

Table S6.3 Associations between baseline frailty measures and adverse outcomes

	Hospitalisation		Low grip strength		All-cause mortality	
	Cases / non-cases	OR (95% CI)	Cases / non-cases	OR (95% CI)	Cases / non-cases	HR (95% CI)
Original FI						
Non-frail	1660 / 12833	1.00 (0.95-1.06)	1025 / 13399	1.00 (0.93-1.07)	15136 / 275819	1.00 (0.98-1.02)
Pre-frail	1811 / 8094	1.42 (1.36-1.48)	1517 / 8286	1.22 (1.16-1.28)	28584 / 176458	1.64 (1.62-1.66)
Frail	199 / 443	2.25 (1.95-2.59)	189 / 434	1.80 (1.56-2.08)	5738 / 10989	3.19 (3.10-3.29)
Per 1 SD	3670 / 21370	1.29 (1.24-1.33)	2731 / 22119	1.19 (1.15-1.24)	49458 / 463266	1.41 (1.40-1.42)
Modified FI-1						
Non-frail	1670 / 12506	1.00 (0.95-1.06)	1053 / 13046	1.00 (0.94-1.07)	16942 / 269658	1.00 (0.98-1.02)
Pre-frail	1804 / 8378	1.35 (1.29-1.41)	1504 / 8581	1.24 (1.18-1.30)	27463 / 182176	1.46 (1.44-1.48)
Frail	196 / 486	2.10 (1.82-2.42)	174 / 492	1.65 (1.42-1.92)	5053 / 11432	2.64 (2.56-2.73)
Per 1 SD	3670 / 21370	1.23 (1.19-1.27)	2731 / 22119	1.16 (1.12-1.20)	49458 / 463266	1.30 (1.29-1.32)
Modified FI-2						
Non-frail	2477 / 16964	1.00 (0.95-1.05)	1639 / 17701	1.00 (0.95-1.06)	24144 / 366483	1.00 (0.98-1.02)
Pre-frail	1082 / 4177	1.43 (1.35-1.52)	987 / 4194	1.26 (1.18-1.33)	21862 / 91527	1.79 (1.76-1.81)
Frail	111 / 229	2.16 (1.79-2.61)	105 / 224	1.71 (1.41-2.07)	3452 / 5256	3.09 (2.98-3.20)
Per 1 SD	3670 / 21370	1.25 (1.21-1.30)	2731 / 22119	1.17 (1.12-1.21)	49458 / 463266	1.39 (1.38-1.40)
Modified FI-3						
Non-frail	2472 / 16285	1.00 (0.95-1.05)	1635 / 17016	1.00 (0.95-1.06)	25941 / 354276	1.00 (0.99-1.02)
Pre-frail	1094 / 4835	1.28 (1.21-1.36)	1008 / 4844	1.21 (1.14-1.28)	20450 / 103354	1.45 (1.43-1.47)
Frail	104 / 250	1.93 (1.59-2.35)	88 / 259	1.35 (1.09-1.66)	3067 / 5636	2.54 (2.45-2.65)
Per 1 SD	3670 / 21370	1.18 (1.15-1.22)	2731 / 22119	1.13 (1.09-1.17)	49458 / 463266	1.27 (1.26-1.28)

Logistic regression models were adjusted for age, sex, region, education level, income level, marital status, alcohol consumption, and smoking status; Cox regression models were stratified by age-at-risk, sex, and region and adjusted for education level, income level, marital status, alcohol consumption, and smoking status.

FI definitions: Original FI = 28-item FI; Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits); Modified FI-2 = 25-item FI (original FI excluding adiposity deficits); Modified FI-3 = 21-item FI (original FI excluding cardiovascular and adiposity deficits)

Figure S6.1 Prevalence of individual frailty deficits

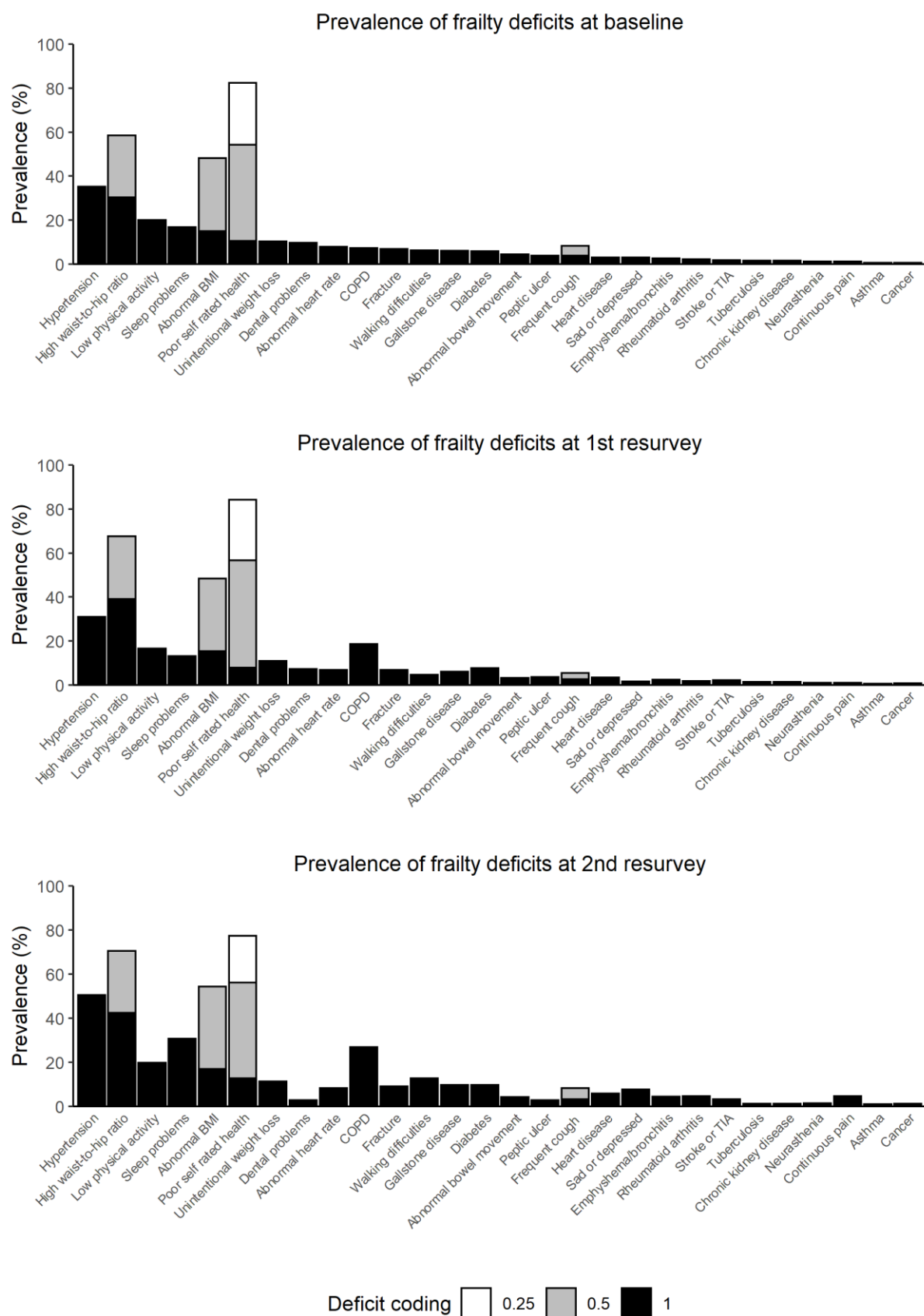


Figure S6.2 Prevalence of individual frailty deficits at baseline by age group

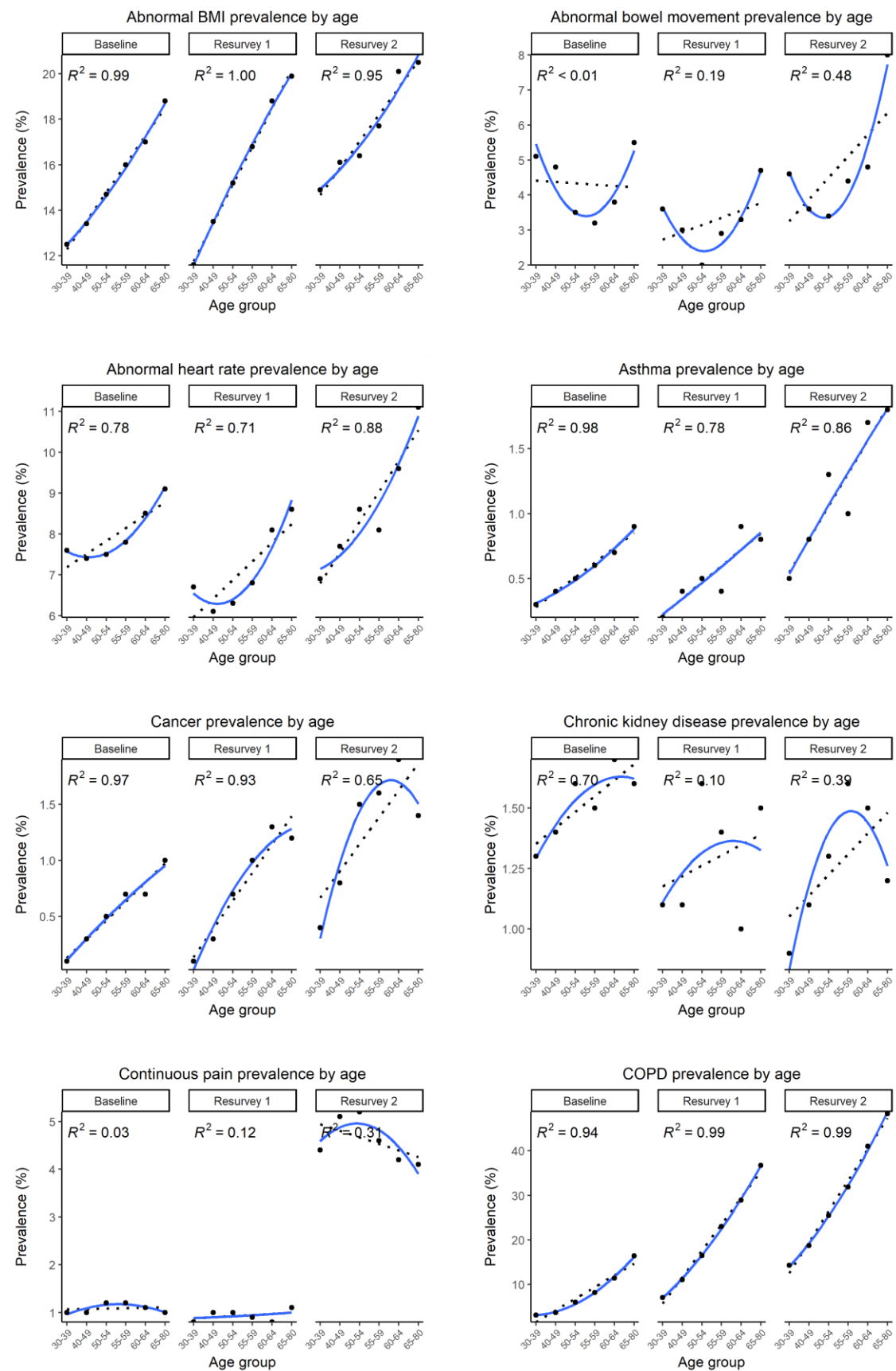


Figure S6.2 continued

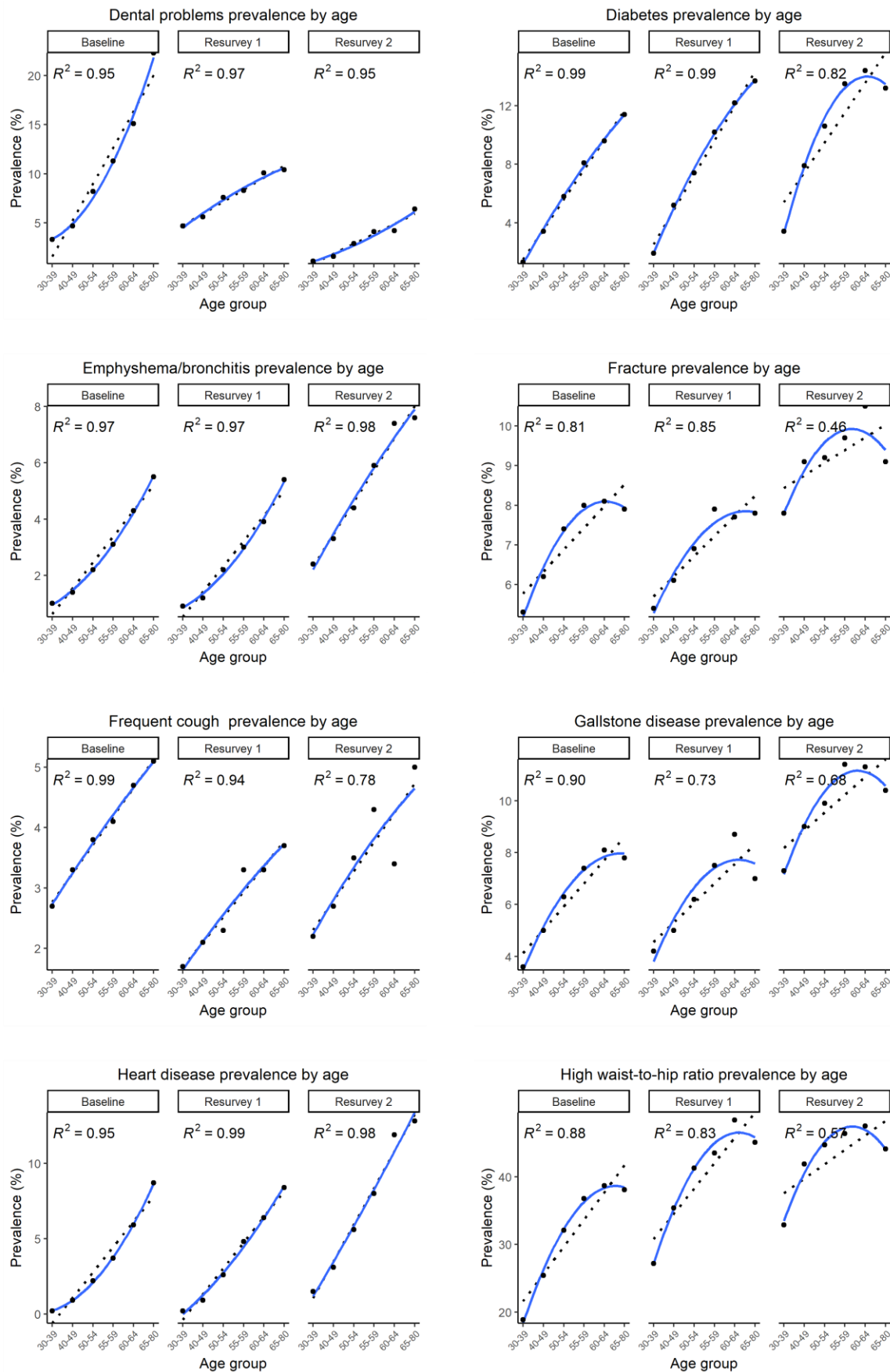


Figure S6.2 continued

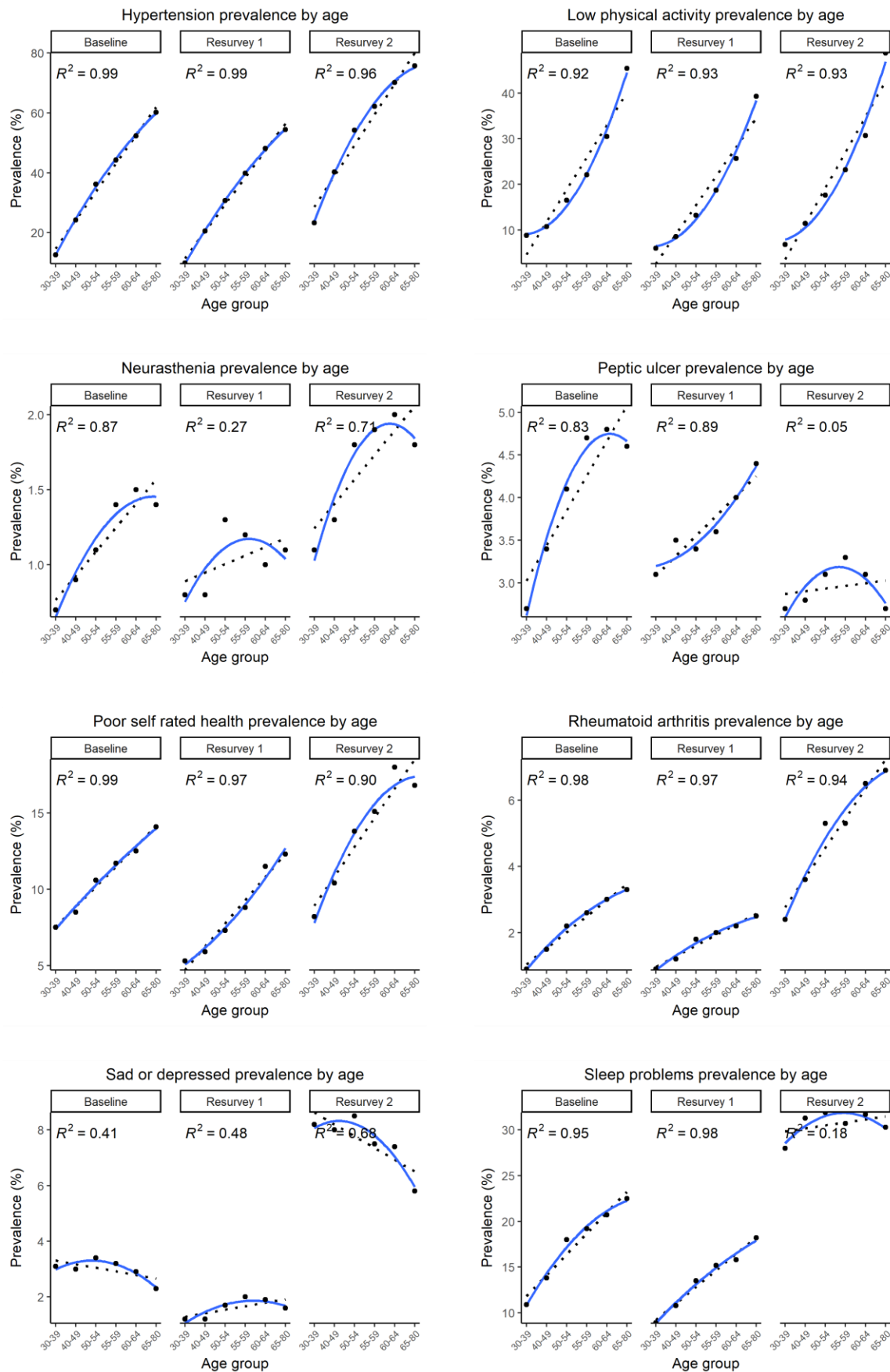


Figure S6.2 continued

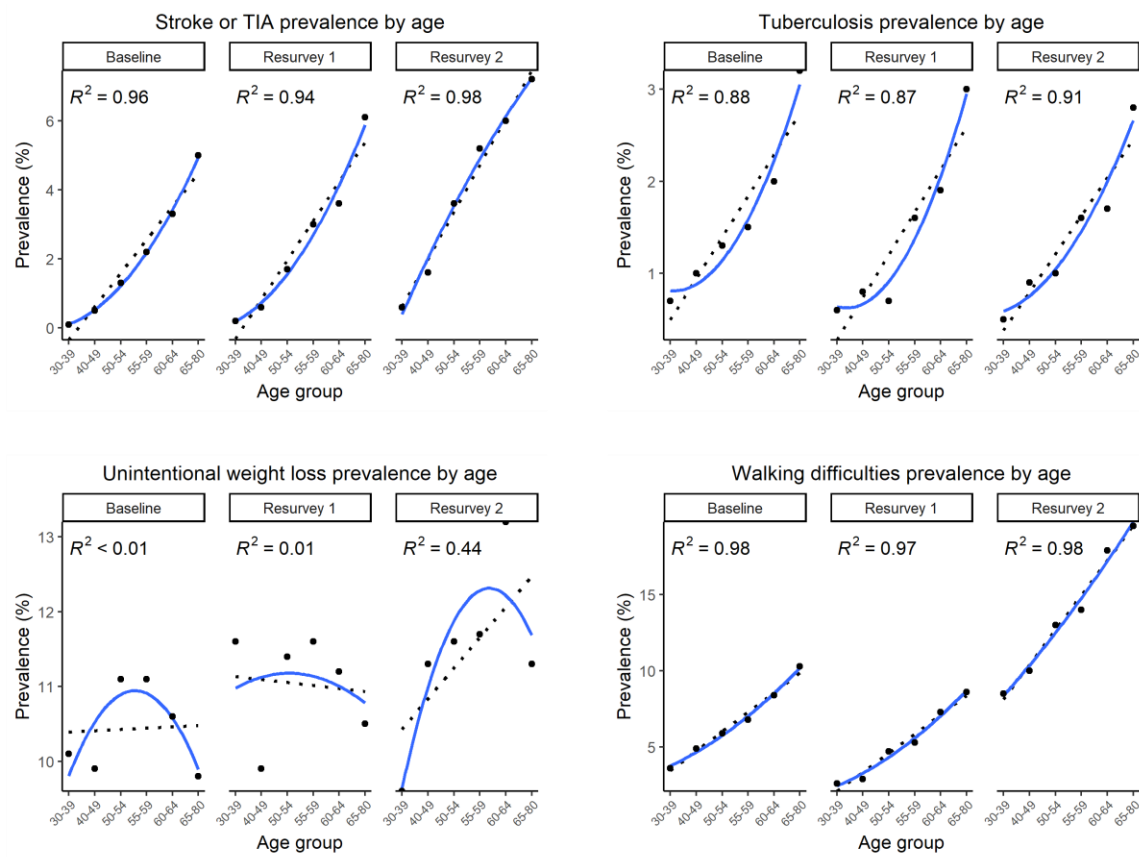


Figure S6.3 Prevalence of individual frailty deficits at baseline by sex

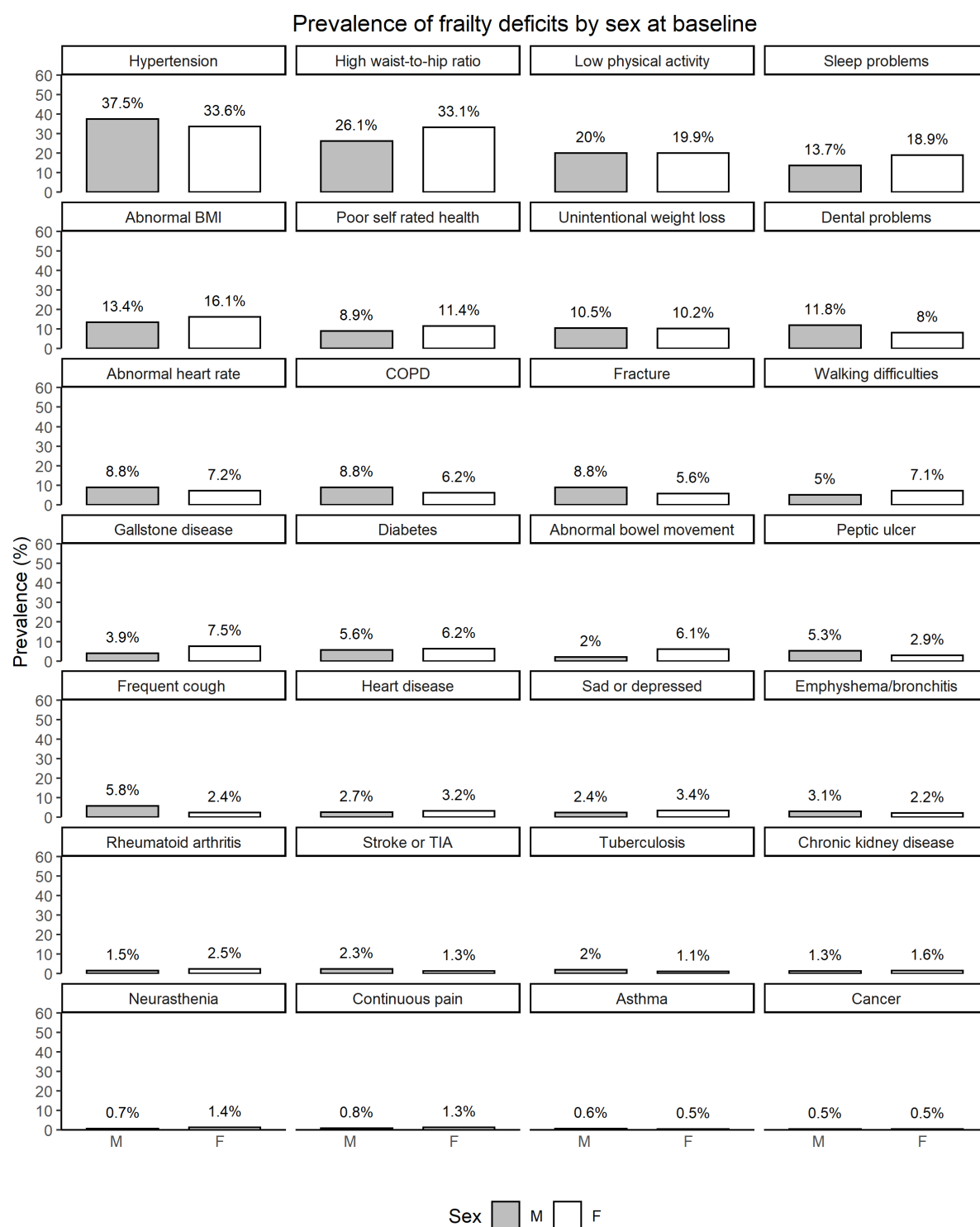


Figure S6.4 Prevalence of individual frailty deficits at baseline by region

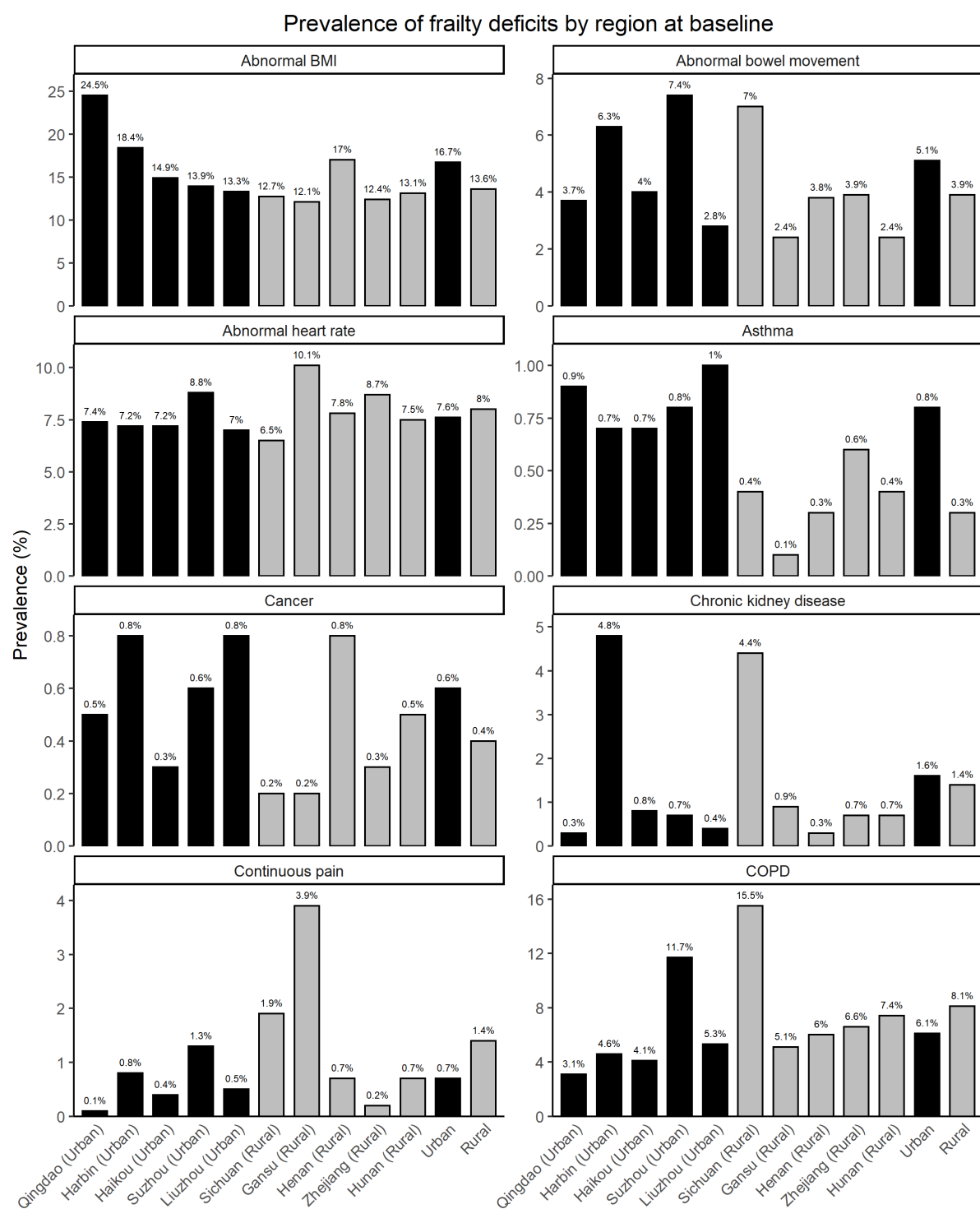


Figure S6.4 continued

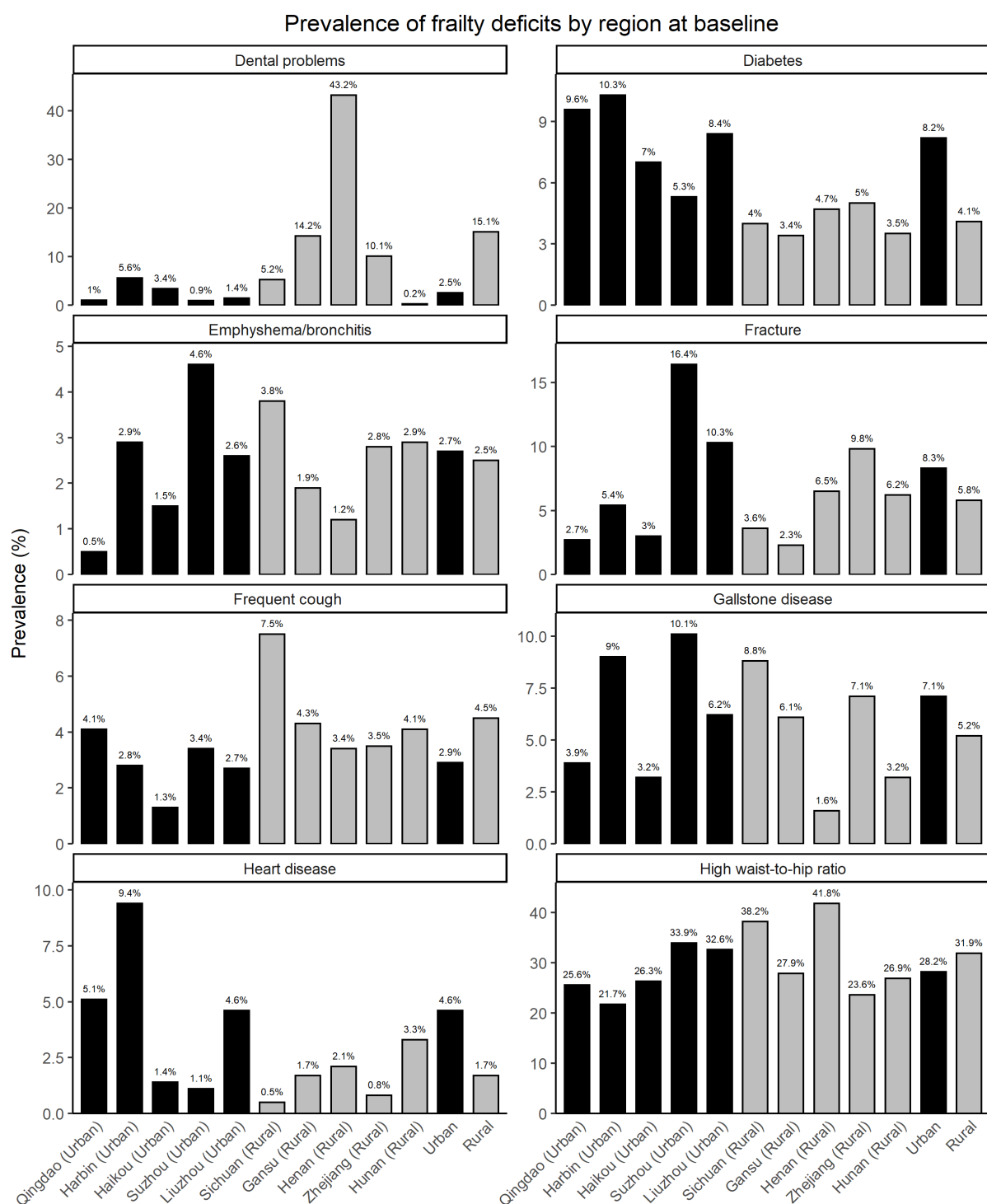


Figure S6.4 continued

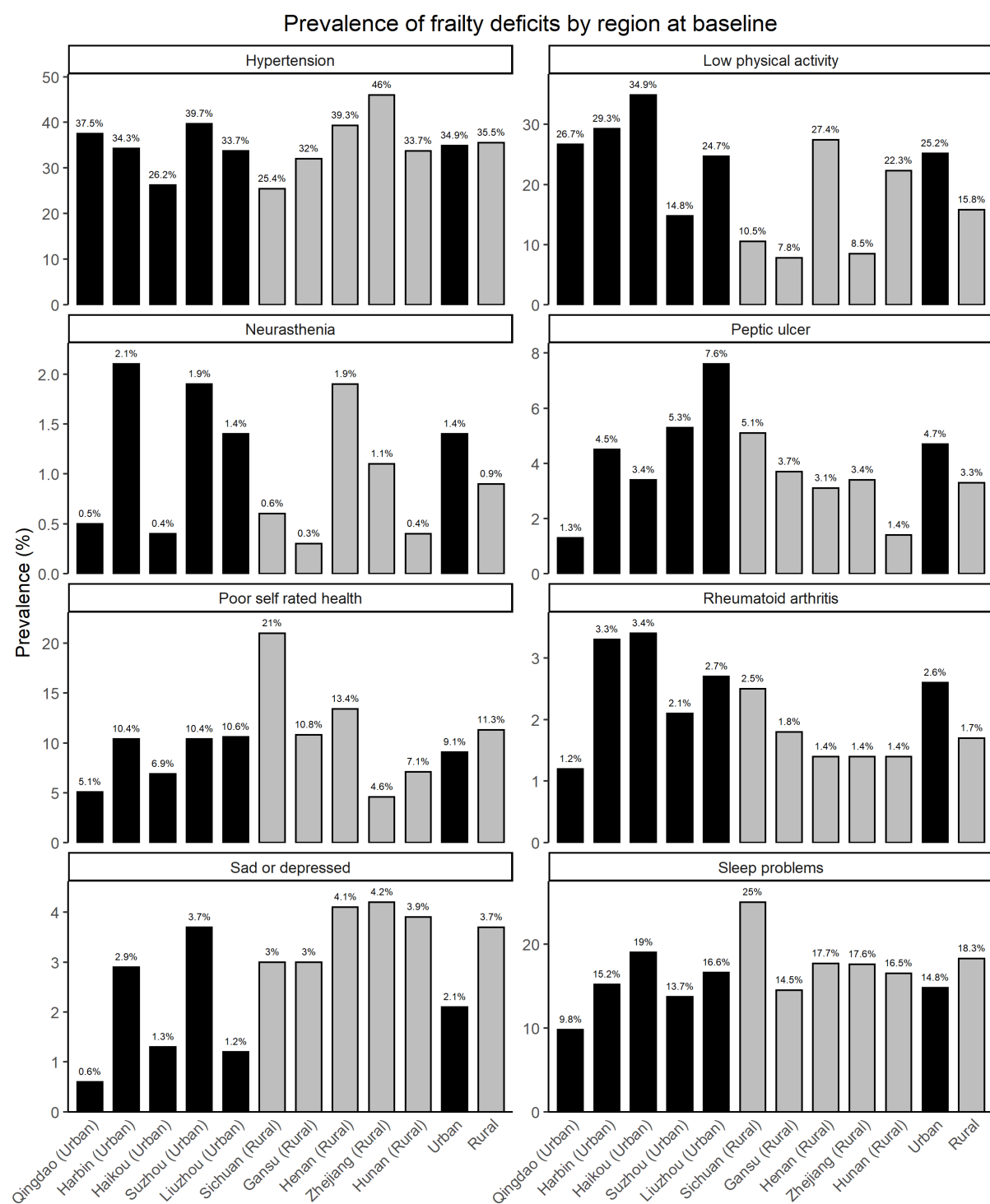


Figure S6.4 continued

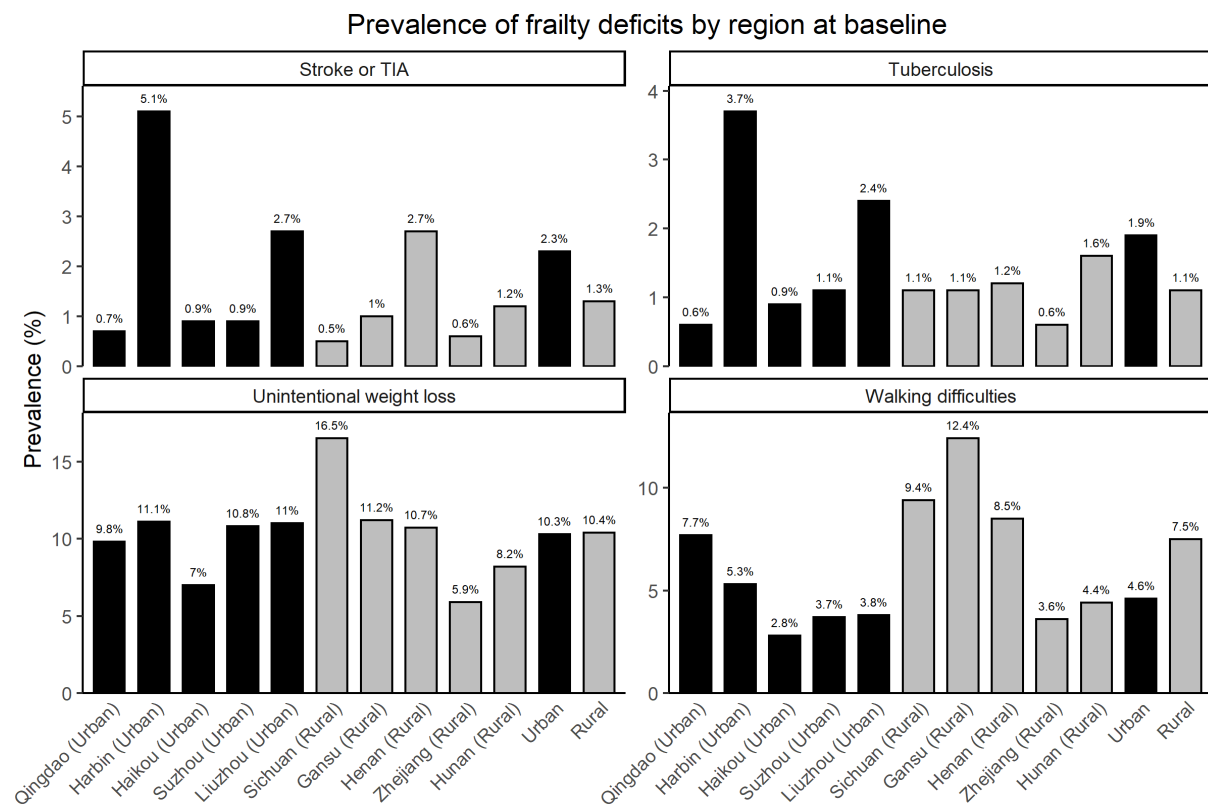
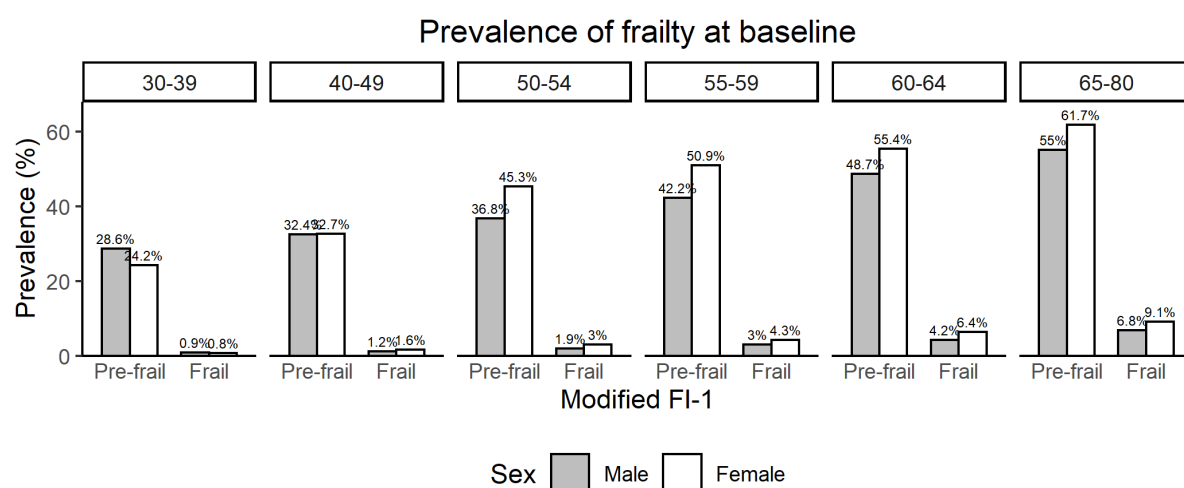
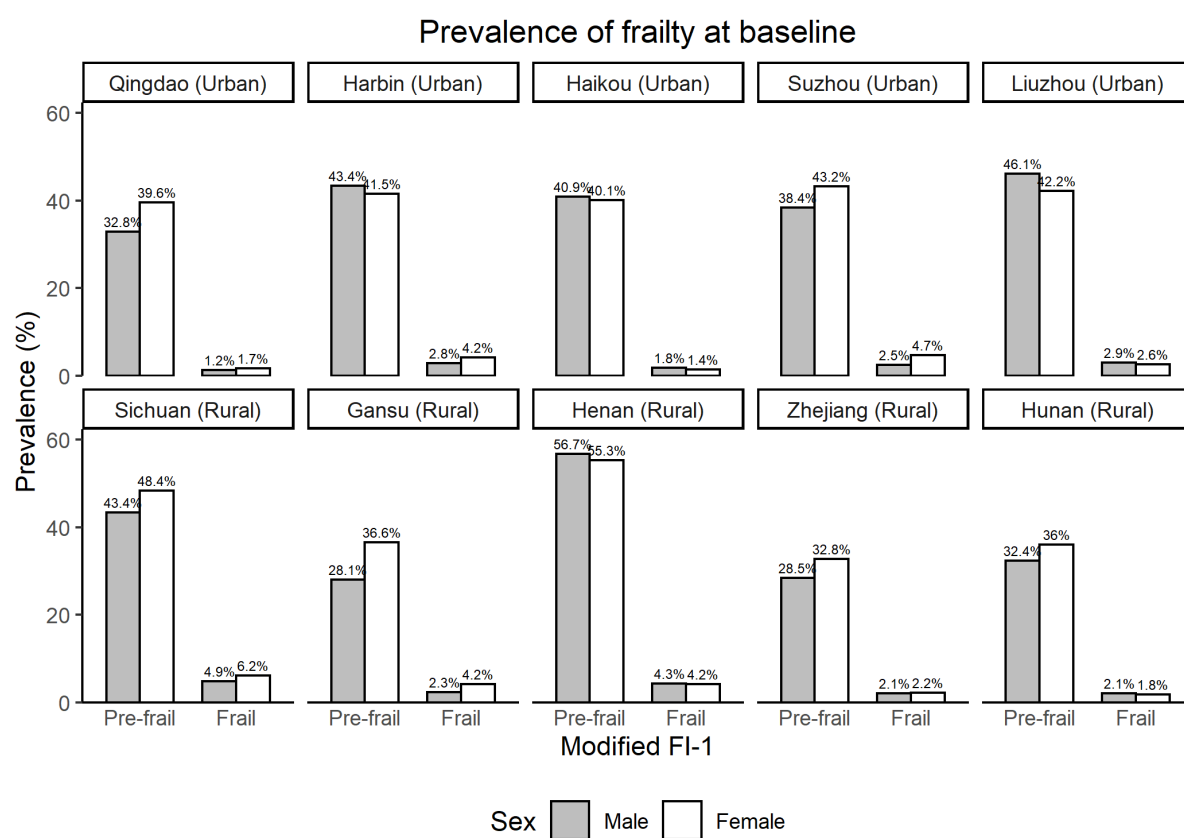


Figure S6.5 Prevalence of frailty (mFI-1) at baseline by age group and sex



FI definition: Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits)

Figure S6.6 Prevalence of frailty (mFI-1) at baseline by region and sex



FI definition: Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits)

Figure S6.7 Prevalence of individual frailty deficits (based on ICD-10 codes)

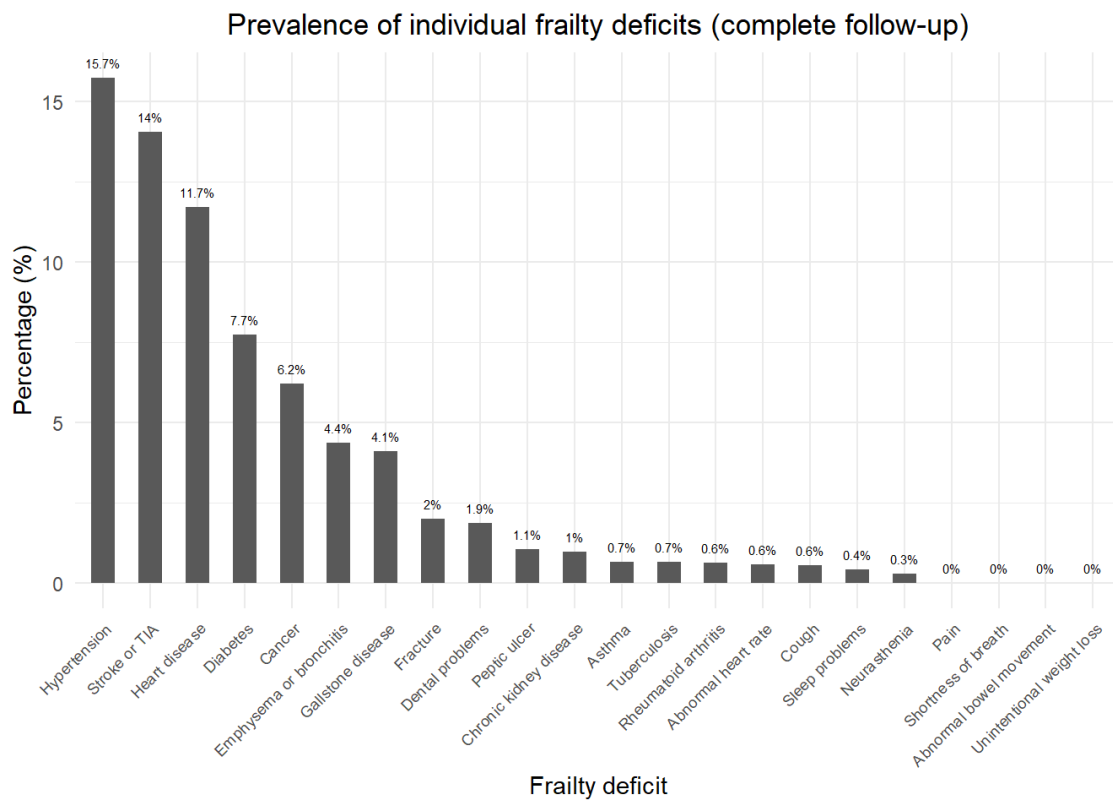


Figure S6.8 Number of unique deficits (based on ICD-10 codes) by year of study entry

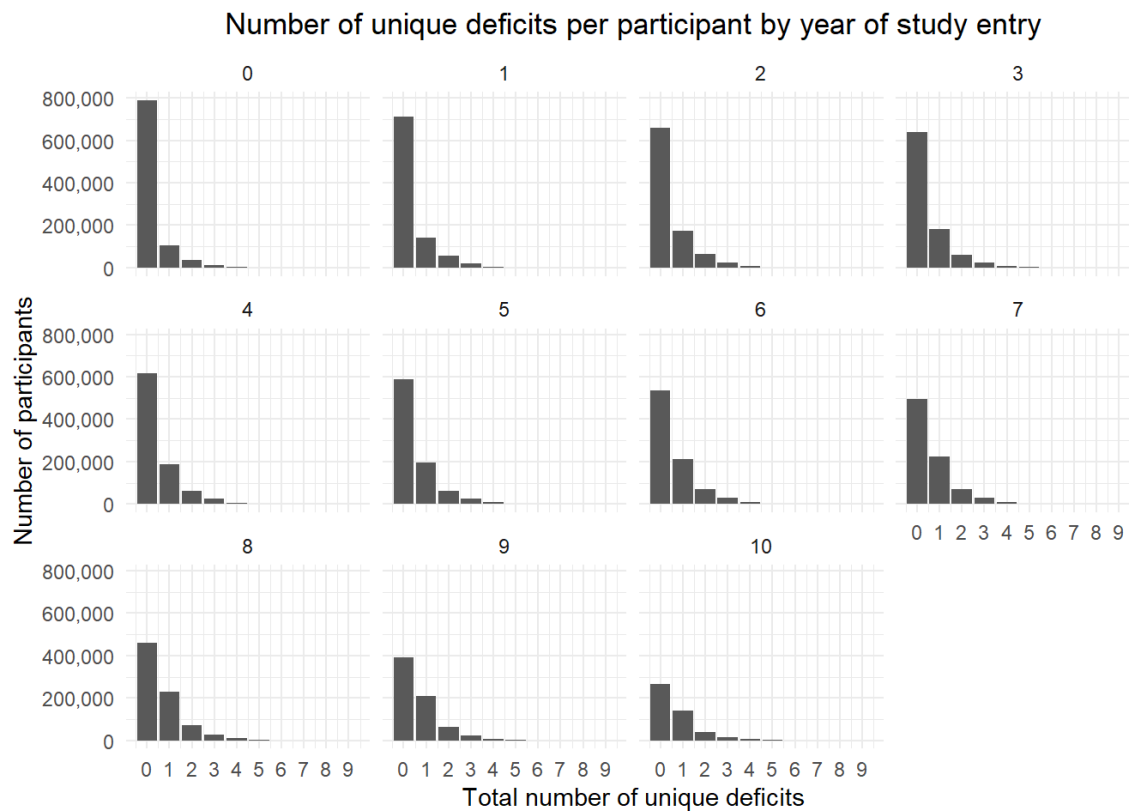


Table S7.1 Odds ratios (95% CI) of cross-sectional associations between CVD RFs and frailty at baseline in 489,448 participants

	Original FI OR (95% CI)	Modified FI-1 OR (95% CI)	Modified FI-2 OR (95% CI)	Modified FI-3 OR (95% CI)
Alcohol consumption (men only)				
Never regular	1.00 (0.93-1.07)	1.00 (0.94-1.06)	1.00 (0.92-1.09)	1.00 (0.93-1.08)
Ex-regular	1.56 (1.40-1.74)	1.55 (1.40-1.71)	1.53 (1.34-1.75)	1.59 (1.41-1.78)
Occasional	0.56 (0.52-0.60)	0.57 (0.54-0.61)	0.51 (0.46-0.56)	0.54 (0.50-0.58)
Monthly	0.56 (0.47-0.66)	0.53 (0.46-0.61)	0.44 (0.34-0.58)	0.46 (0.37-0.57)
Reduced- intake	1.18 (1.05-1.31)	1.15 (1.04-1.27)	1.14 (0.98-1.32)	1.17 (1.02-1.33)
Weekly	0.55 (0.51-0.59)	0.54 (0.51-0.58)	0.52 (0.47-0.57)	0.55 (0.51-0.60)
Never regular	1.00 (0.93-1.07)	1.00 (0.94-1.06)	1.00 (0.92-1.09)	1.00 (0.93-1.08)
Smoking status (men only)				
Never smoker	1.00 (0.91-1.10)	1.00 (0.92-1.09)	1.00 (0.88-1.14)	1.00 (0.90-1.11)
Occasional	1.11 (1.00-1.24)	1.06 (0.96-1.17)	1.09 (0.93-1.26)	1.08 (0.95-1.22)
Ex regular	2.31 (2.15-2.48)	2.33 (2.18-2.49)	2.50 (2.28-2.74)	2.50 (2.30-2.71)
<20 cig/d	1.12 (1.05-1.20)	1.10 (1.03-1.16)	1.05 (0.96-1.14)	1.01 (0.94-1.09)
20-25 cig/d	1.15 (1.06-1.25)	1.17 (1.09-1.25)	1.08 (0.96-1.21)	1.08 (0.99-1.19)
≥25 cig/d	1.32 (1.20-1.46)	1.35 (1.24-1.47)	1.23 (1.07-1.42)	1.16 (1.03-1.30)
Systolic blood pressure (mmHg)				
<120	1.00 (0.95-1.05)	1.00 (0.96-1.04)	1.00 (0.93-1.07)	1.00 (0.95-1.05)
120-139	1.01 (0.97-1.04)	0.87 (0.85-0.90)	0.96 (0.91-1.01)	0.85 (0.82-0.88)
≥140	1.92 (1.86-1.98)	0.84 (0.82-0.87)	1.86 (1.78-1.94)	0.76 (0.73-0.80)
Random plasma glucose (mmol/L)				
<5.8	1.00 (0.97-1.03)	1.00 (0.97-1.03)	1.00 (0.96-1.04)	1.00 (0.97-1.04)
5.8-7.7	1.12 (1.08-1.15)	1.04 (1.01-1.07)	0.98 (0.93-1.03)	0.92 (0.89-0.96)
7.8-11	1.89 (1.78-2.00)	1.33 (1.25-1.41)	1.49 (1.37-1.63)	1.01 (0.93-1.11)
≥11	4.11 (3.91-4.32)	1.98 (1.87-2.10)	3.17 (2.95-3.41)	1.52 (1.40-1.64)
Fat mass (kg) quintile (mean of quintile group)				
1 (8.6)	1.00 (0.95-1.06)	1.00 (0.96-1.05)	1.00 (0.94-1.07)	1.00 (0.95-1.06)
2 (12.8)	0.62 (0.59-0.66)	0.60 (0.57-0.63)	0.75 (0.70-0.80)	0.72 (0.68-0.76)
3 (16.1)	0.80 (0.76-0.85)	0.74 (0.71-0.78)	0.74 (0.69-0.80)	0.68 (0.64-0.72)
4 (19.9)	1.16 (1.11-1.21)	1.06 (1.02-1.11)	0.83 (0.78-0.89)	0.74 (0.69-0.79)
5 (27.4)	2.10 (2.01-2.18)	1.80 (1.73-1.87)	1.03 (0.96-1.10)	0.88 (0.83-0.94)
Lean body mass (kg) quintile (mean of quintile group)				
1 (33.6)	1.00 (0.95-1.05)	1.00 (0.96-1.05)	1.00 (0.93-1.08)	1.00 (0.94-1.07)
2 (37.7)	0.77 (0.73-0.81)	0.76 (0.73-0.79)	0.75 (0.70-0.81)	0.73 (0.69-0.78)
3 (41.3)	0.77 (0.74-0.80)	0.72 (0.69-0.74)	0.69 (0.65-0.74)	0.66 (0.62-0.69)
4 (46.3)	0.63 (0.59-0.67)	0.55 (0.52-0.58)	0.55 (0.50-0.59)	0.49 (0.46-0.53)
5 (54.5)	0.68 (0.63-0.74)	0.54 (0.51-0.58)	0.46 (0.41-0.51)	0.41 (0.37-0.45)

Logistic regression models were adjusted for age, sex, region, marital status, income level, education level, alcohol consumption, smoking status, systolic blood pressure (mmHg), random plasma glucose (mmol/L), fat mass, and lean body mass, where appropriate.

Abbreviations: FI=frailty index. FI definitions: Original FI = 28-item FI; Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits); Modified FI-2 = 25-item FI (original FI excluding adiposity deficits); Modified FI-3 = 21-item FI (original FI excluding cardiovascular and adiposity deficits)

Figure S7.1 Odds ratios (95% CI) of cross-sectional associations between CVD RFs and frailty (mFI-1) at baseline in 489,448 participants by the 10 CKB study regions

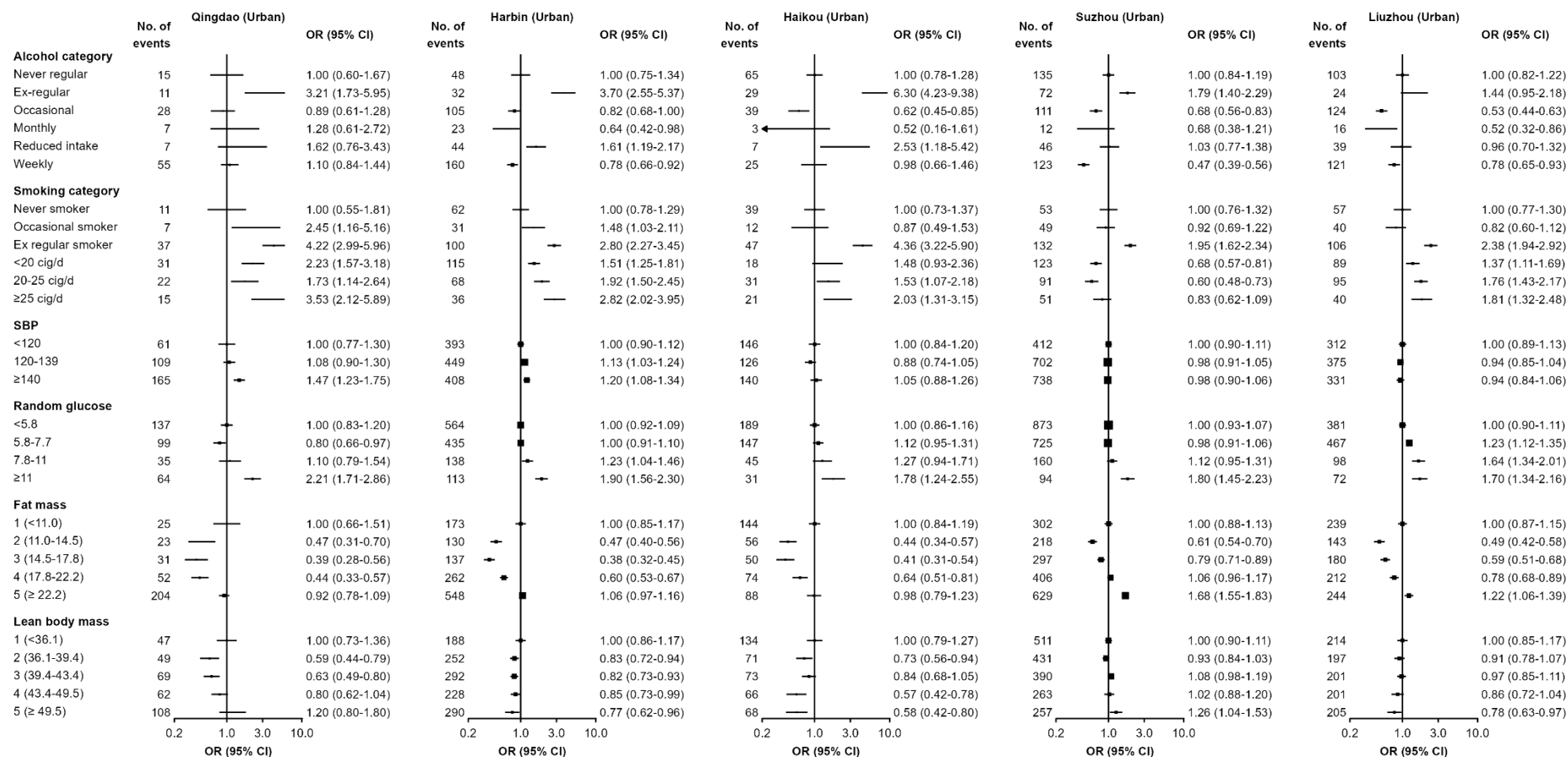


Figure S7.1 continued

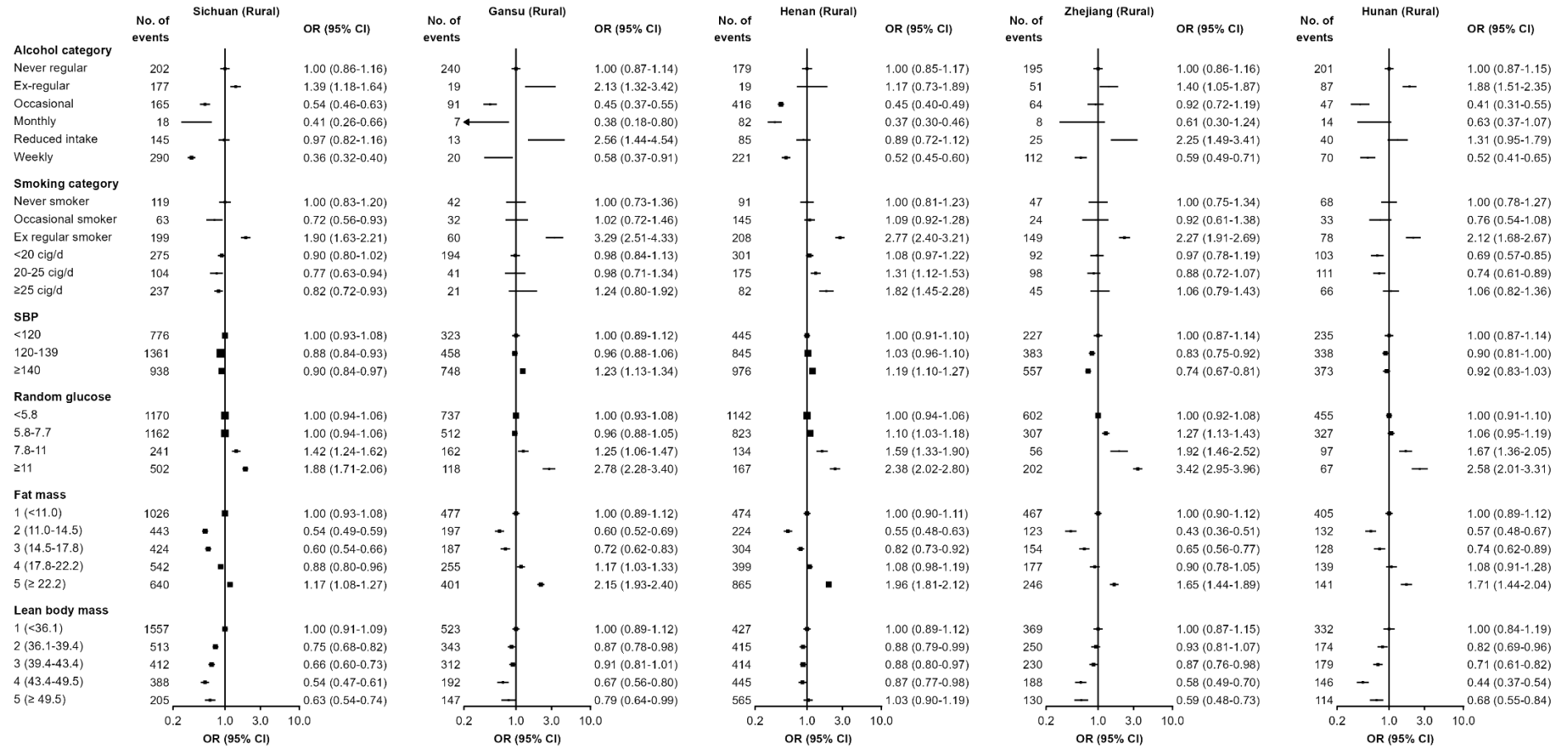


Figure S7.2 Odds ratios (95% CI) of cross-sectional associations between CVD RFs and frailty (mFI-2) at baseline in 489,448 participants by the 10 CKB study regions

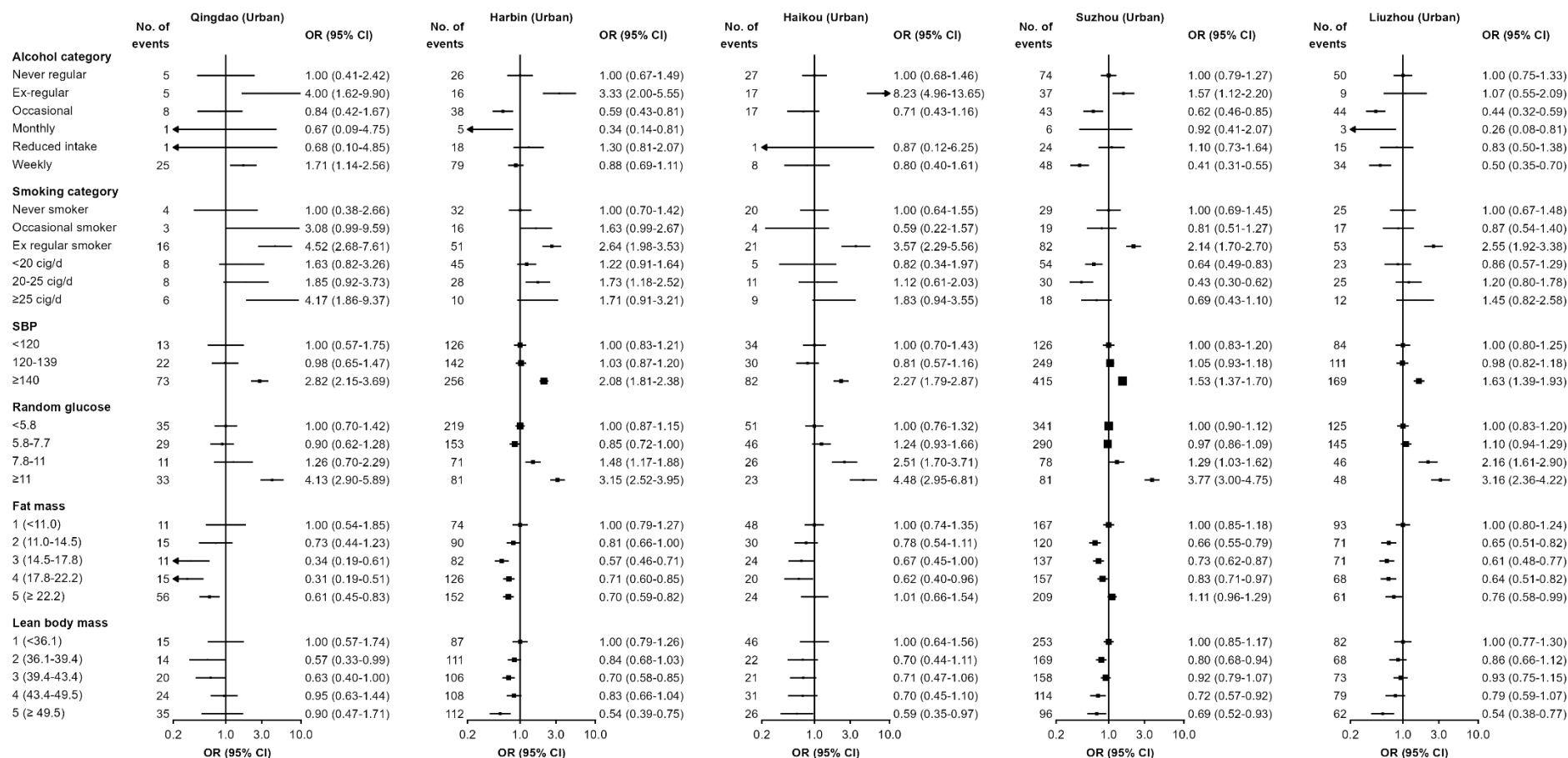


Figure S7.2 continued

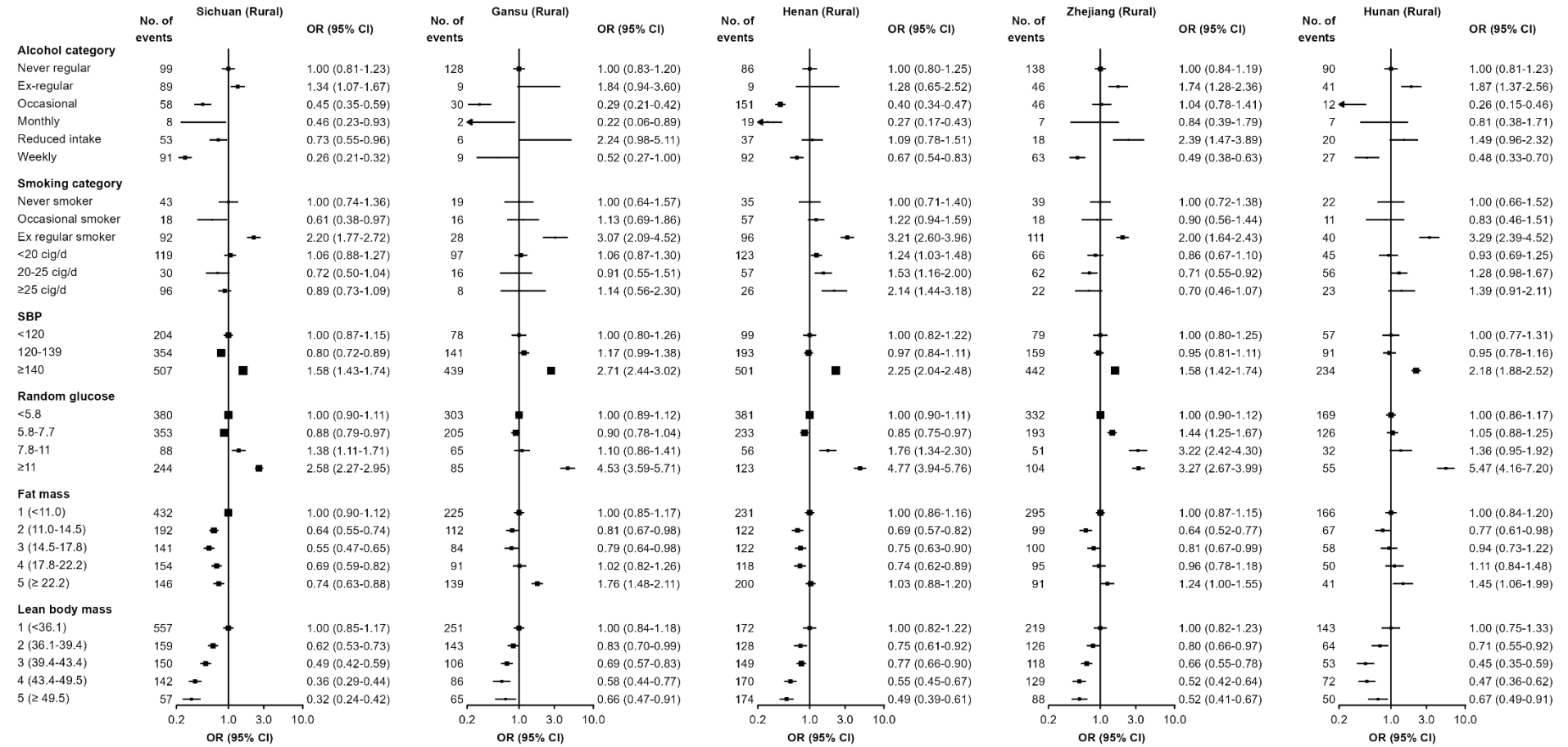


Figure S7.3 Odds ratios (95% CI) of cross-sectional associations between CVD RFs and frailty (mFI-3) at baseline in 489,448 participants by the 10 CKB study regions

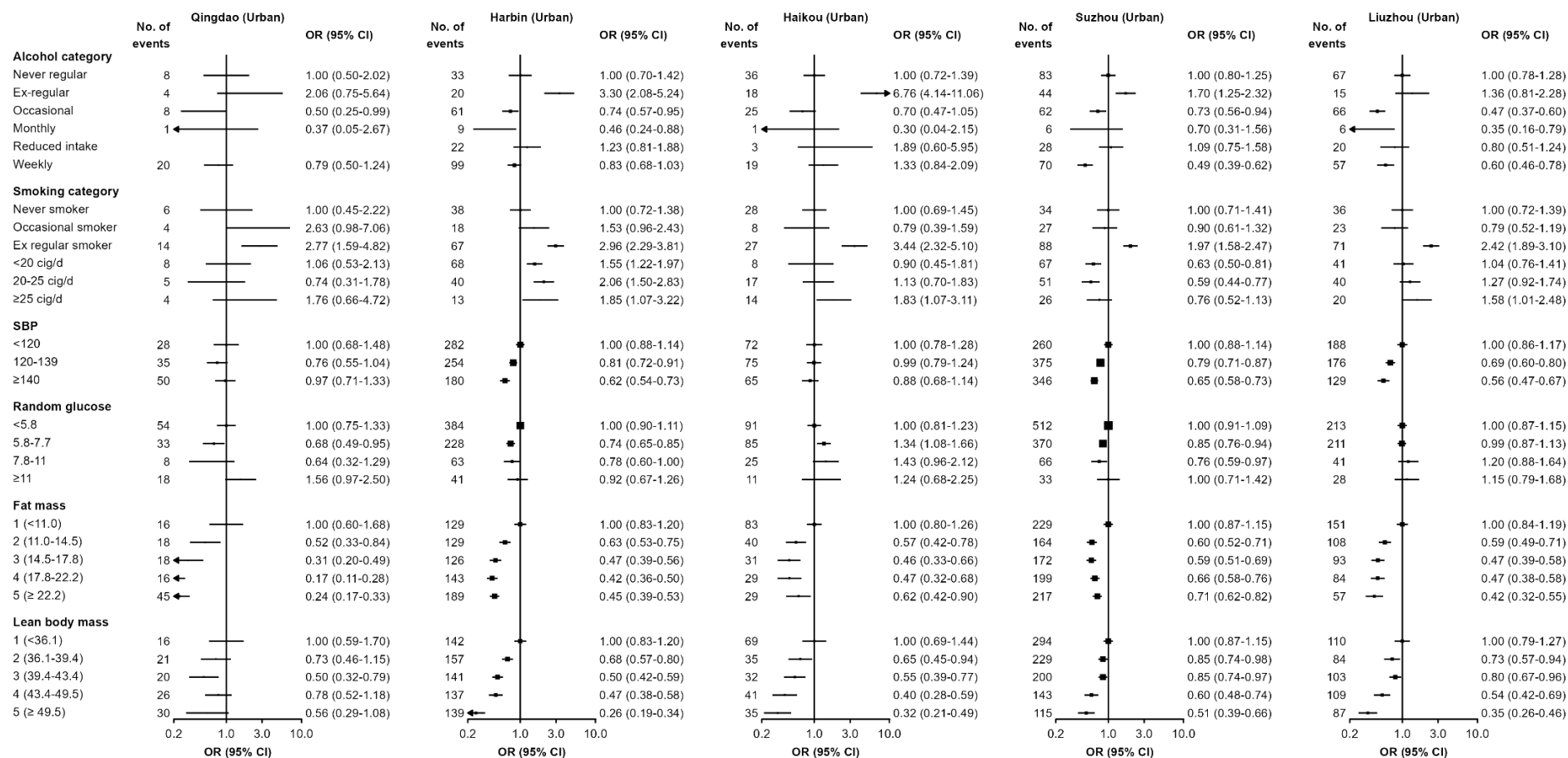


Figure S7.3 continued

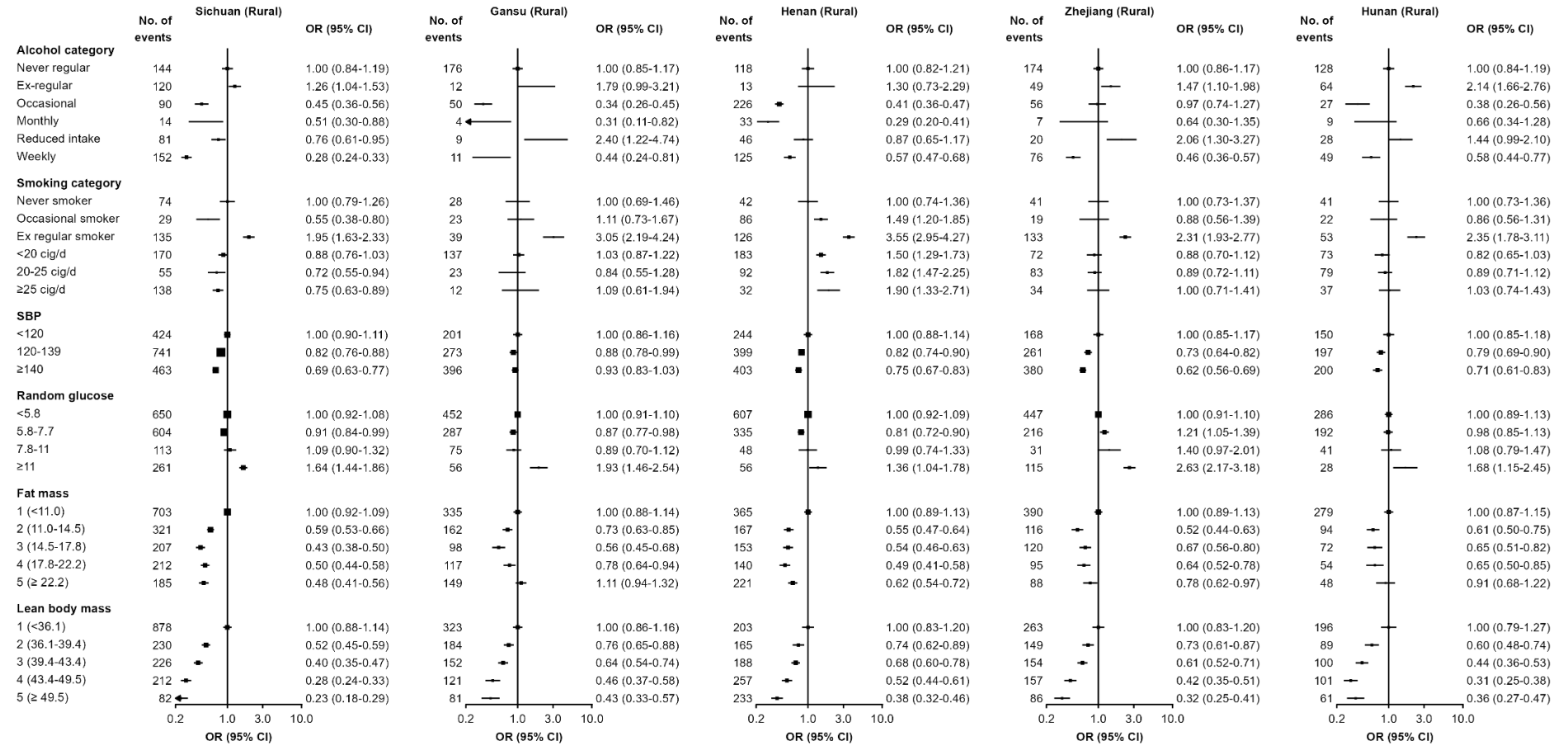


Figure S7.4 Odds ratios (95% CI) of prospective associations between CVD RFs and incident frailty (mFI-1) 2nd resurvey in ~24,000 participants by the 10 CKB study regions

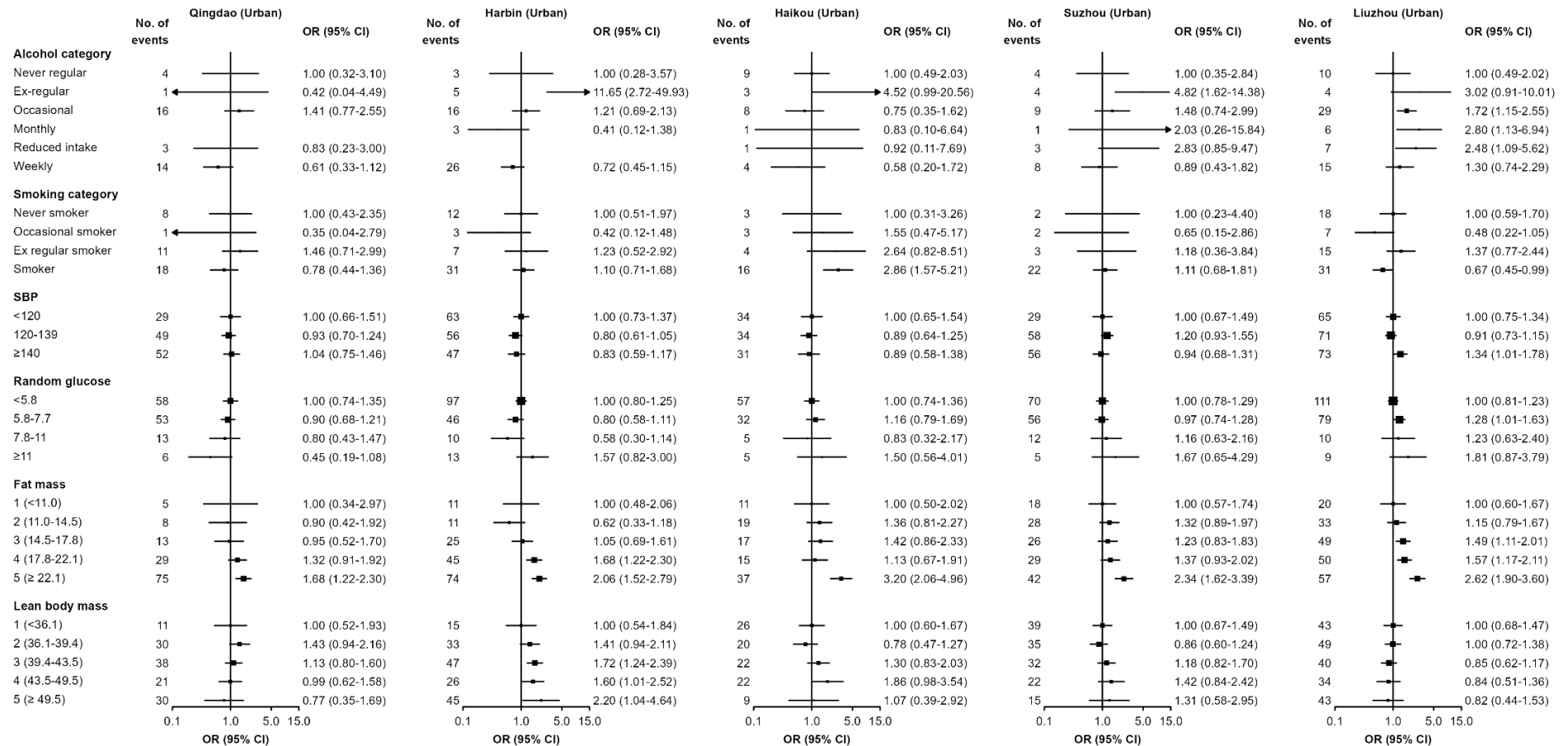


Figure S7.4 continued

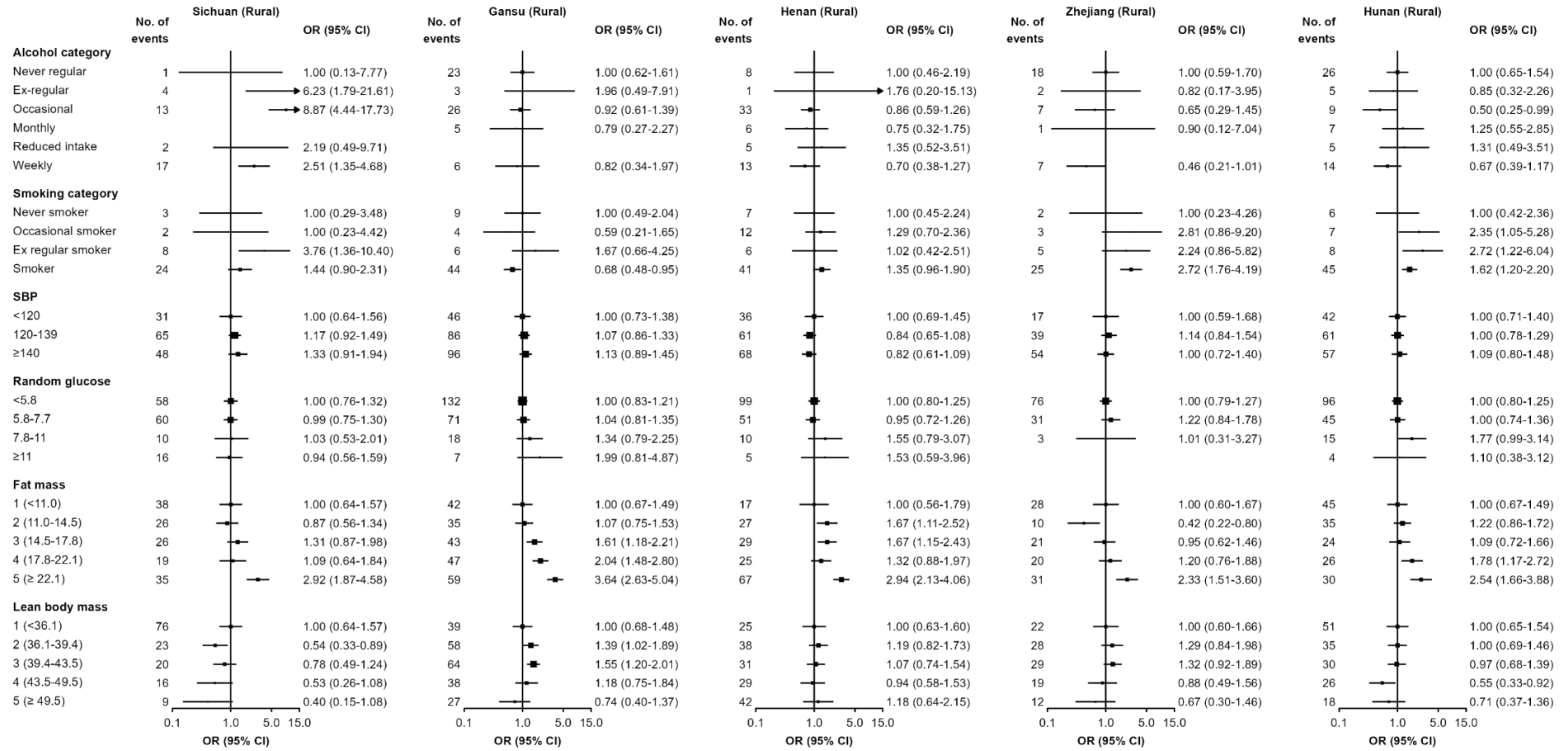


Figure S7.5 Odds ratios (95% CI) of prospective associations between CVD RFs and incident frailty (mFI-2) 2nd resurvey in ~24,000 participants by the 10 CKB study regions

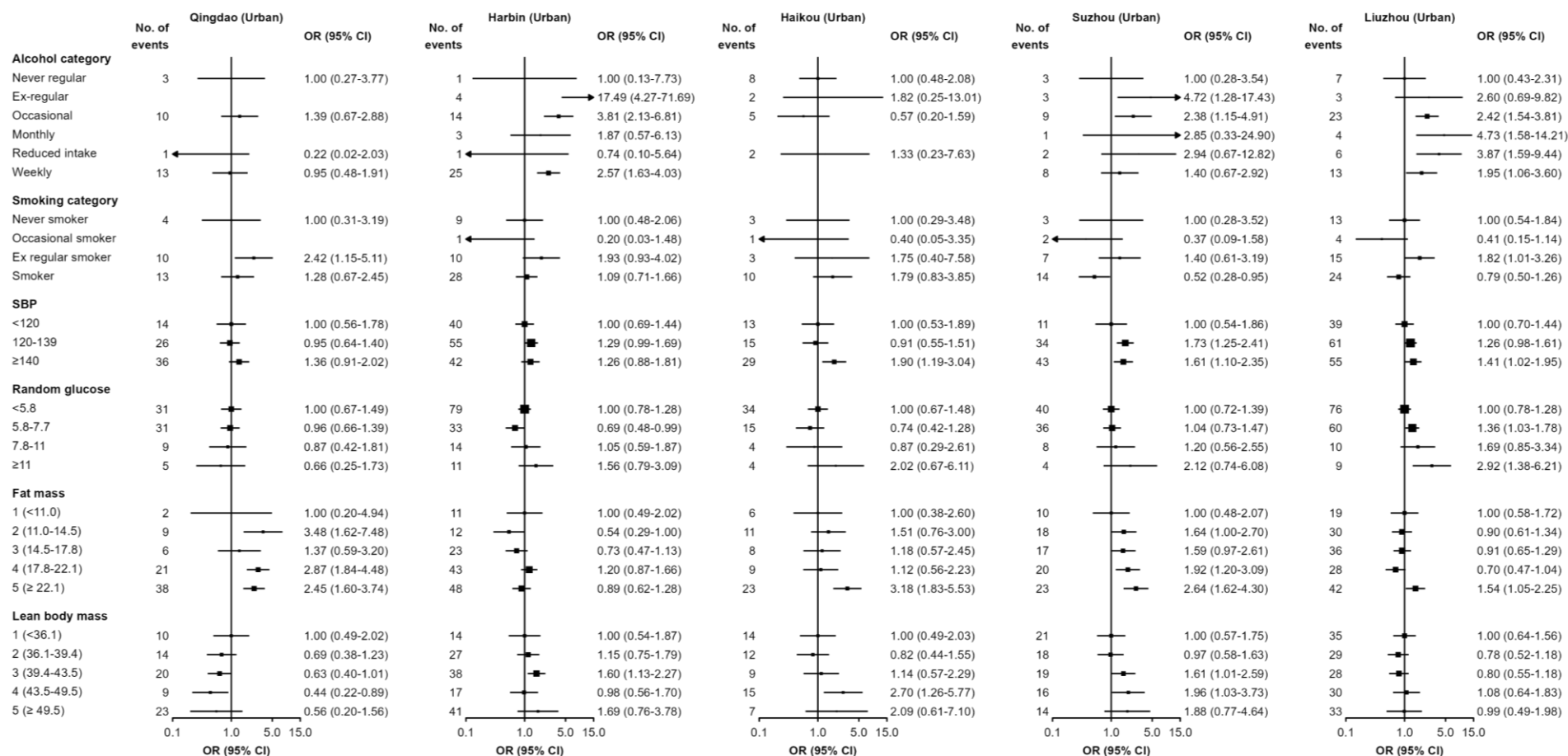


Figure S7.5 continued

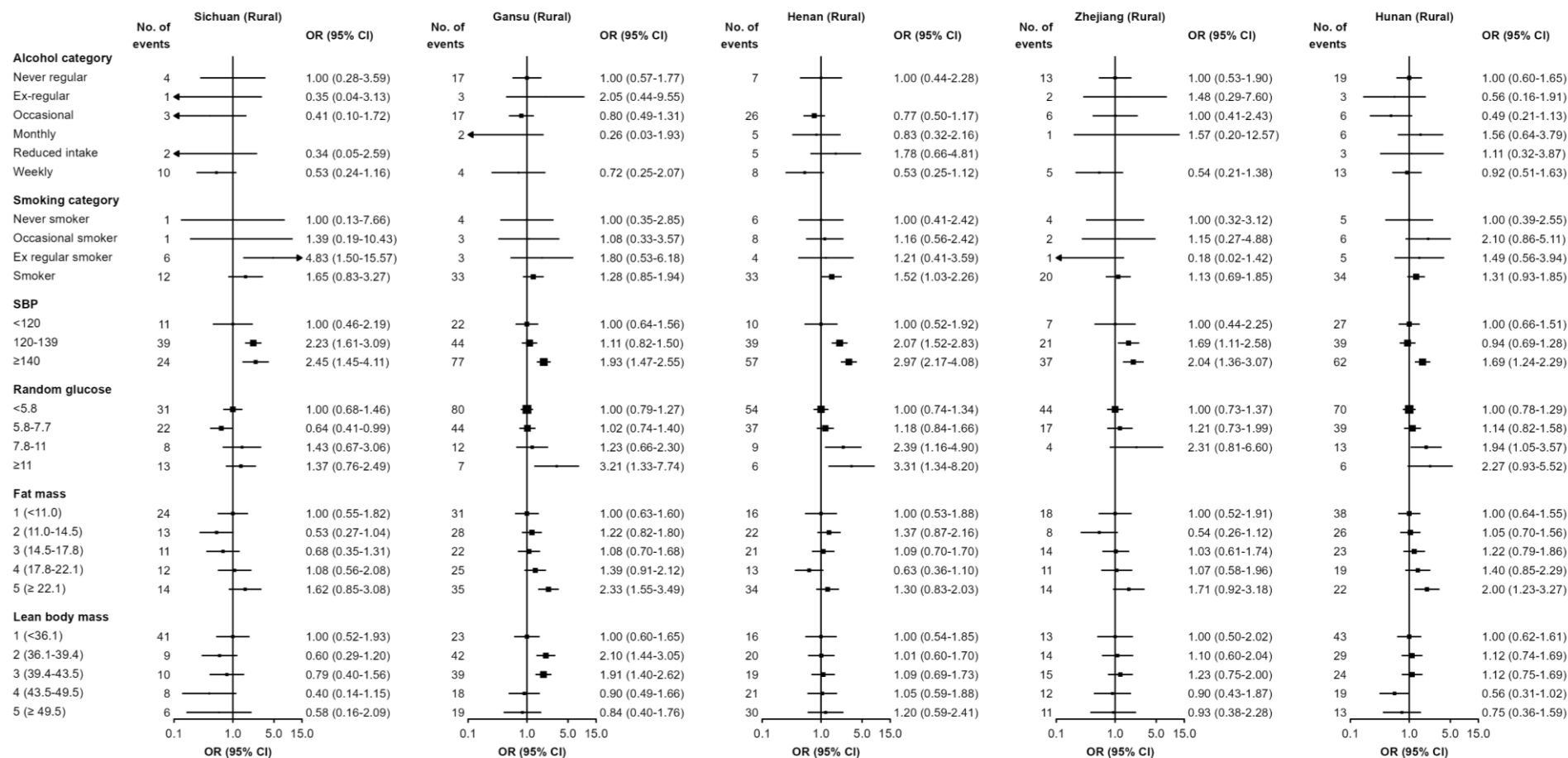


Figure S7.6 Odds ratios (95% CI) of prospective associations between CVD RFs and incident frailty (mFI-3) 2nd resurvey in ~24,000 participants by the 10 CKB study regions

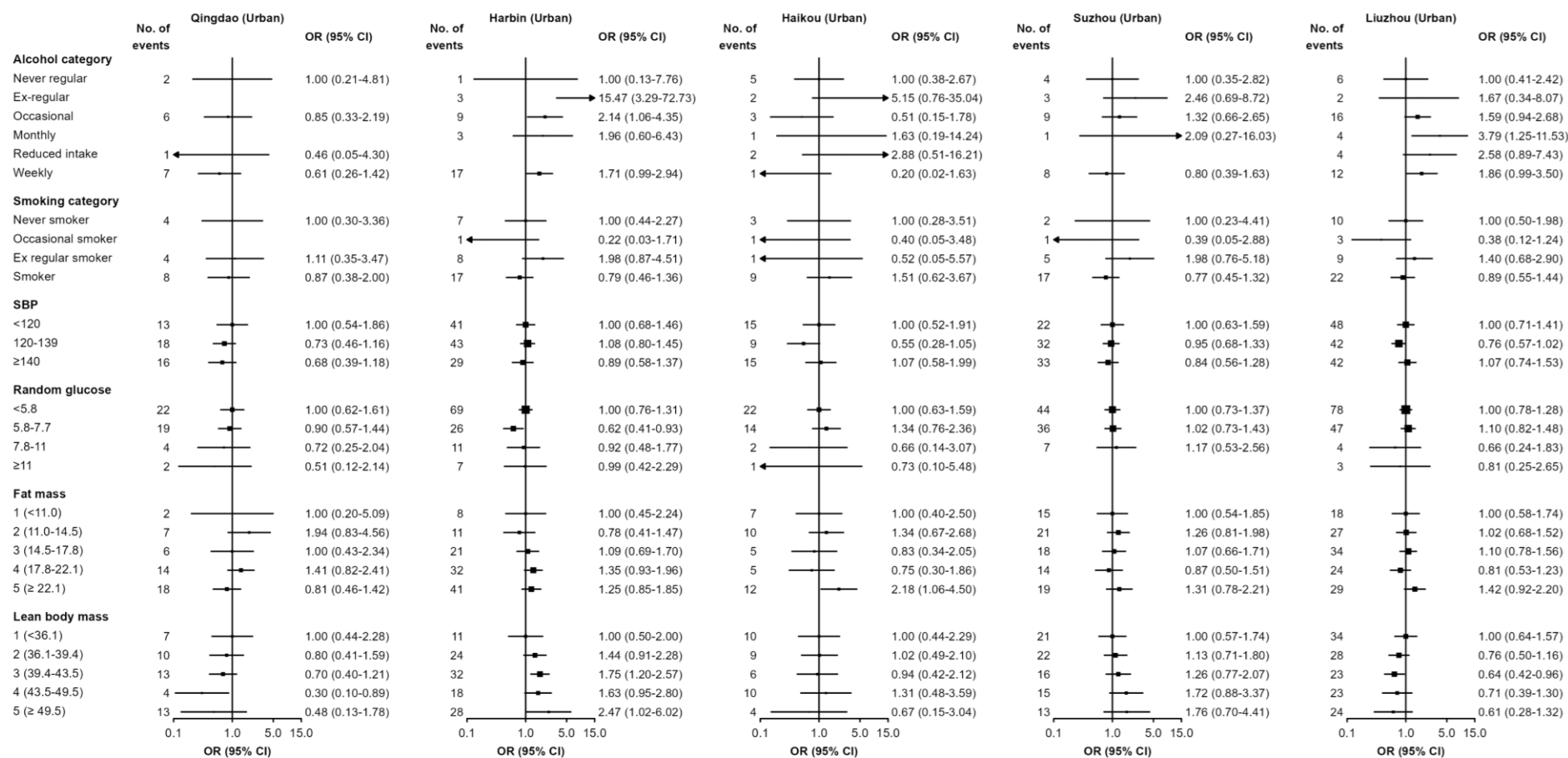


Figure S7.6 continued

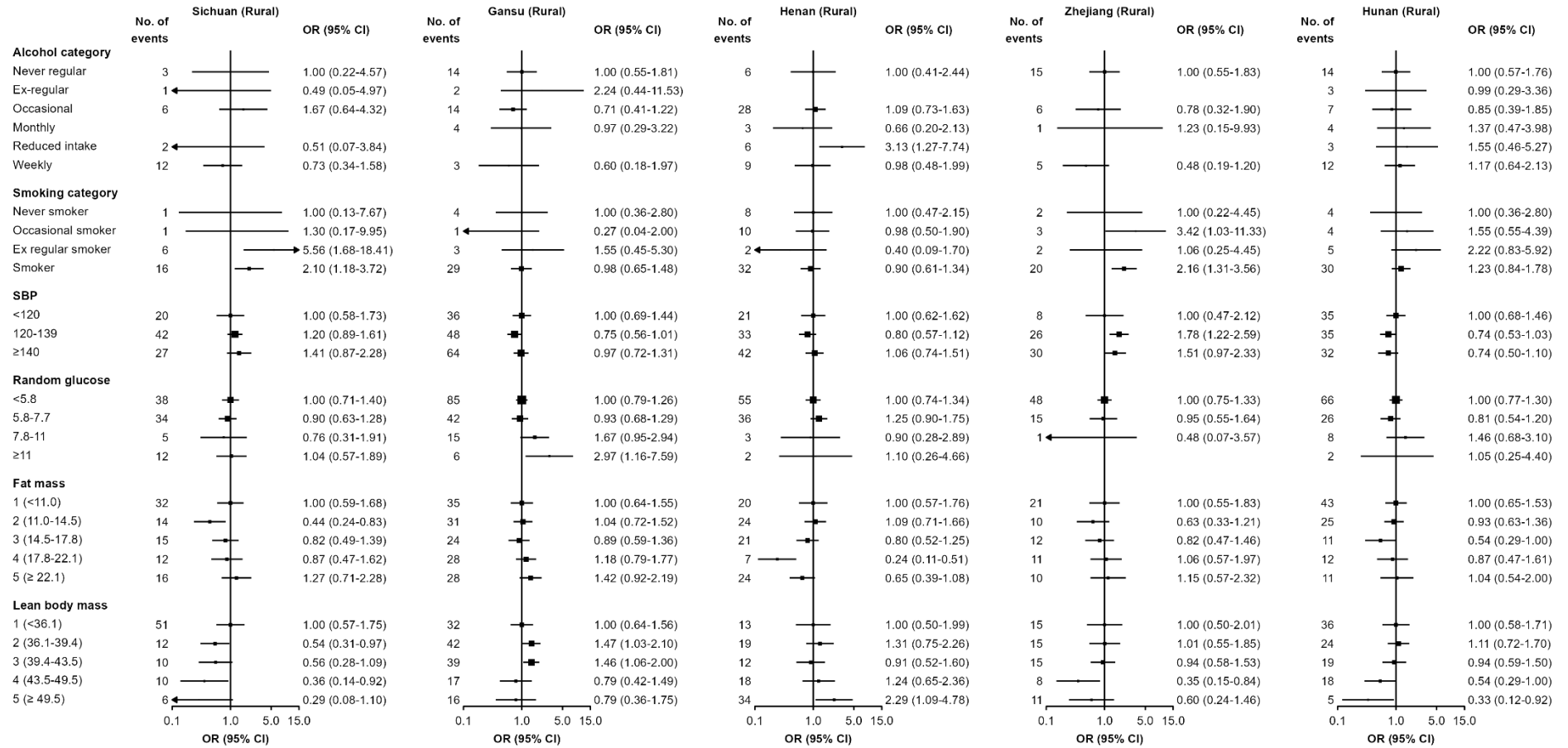
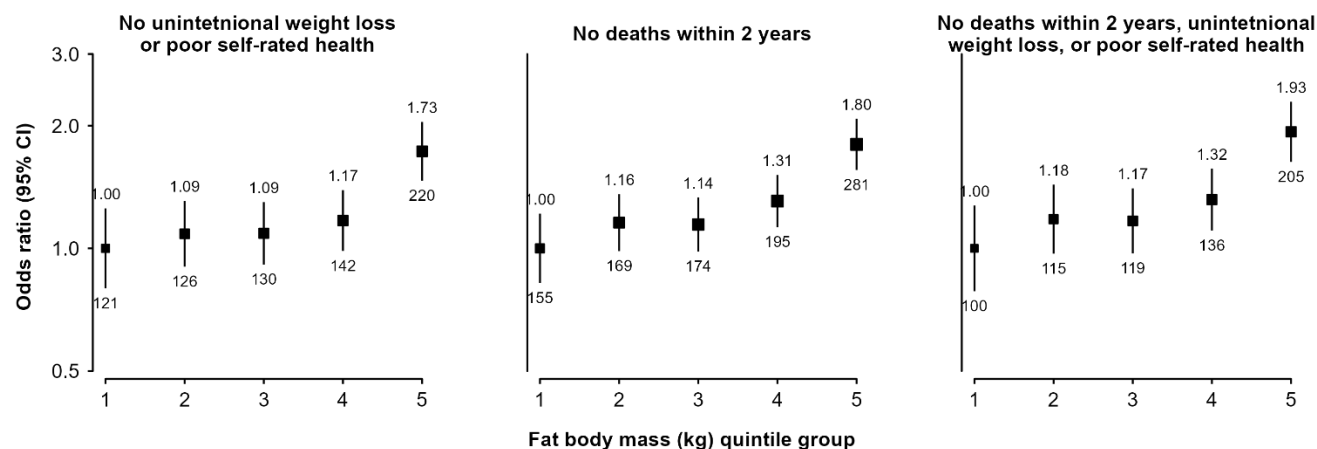
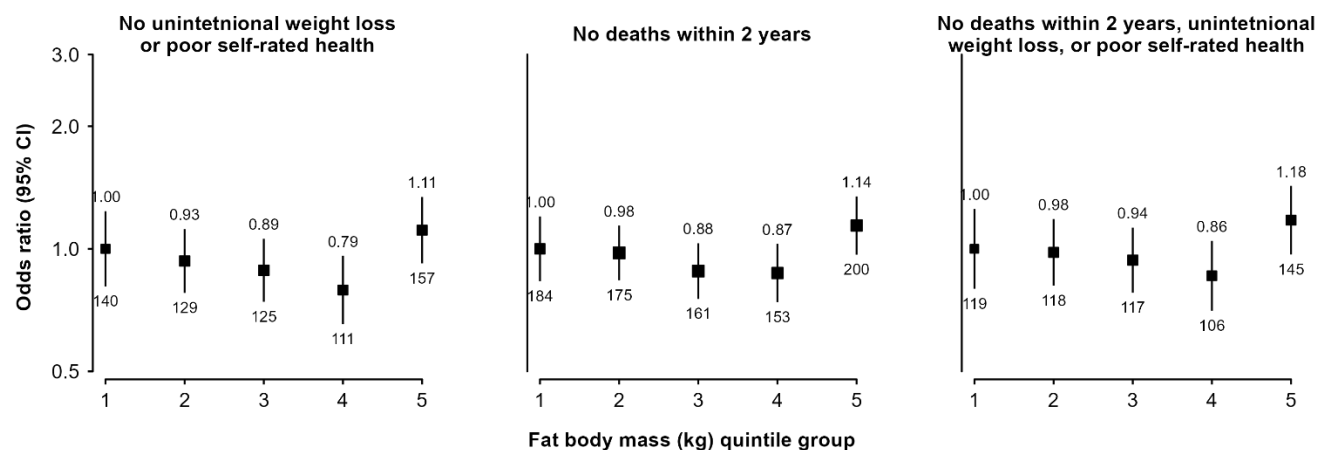


Figure S7.7 Associations between baseline fat mass (quintile) and incident frailty at 2nd resurvey in participants by participant exclusions on unintentional weight loss and self-reported health status at baseline and mortality after follow-up

A

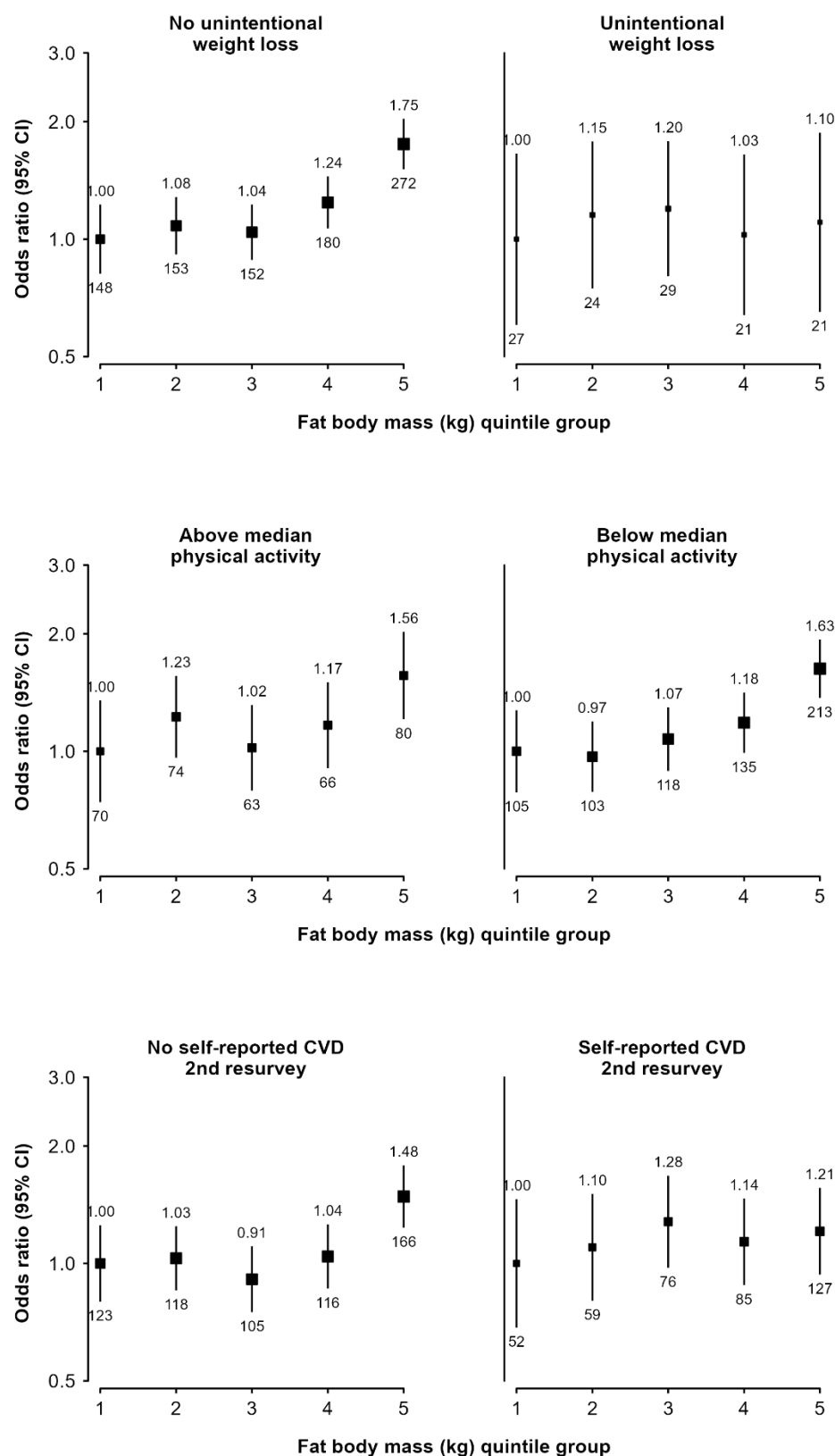


B



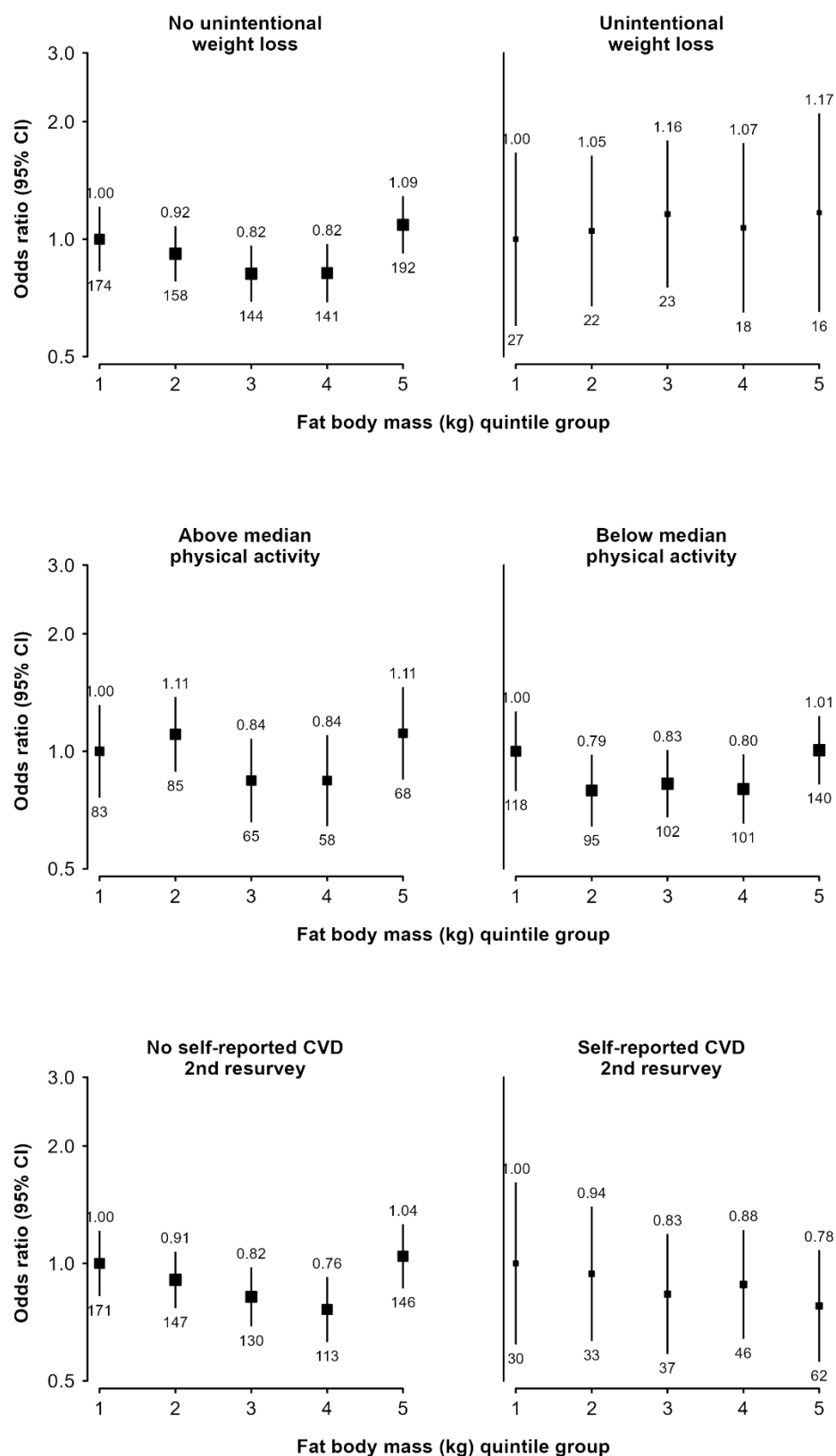
Panel: A= Modified FI-2 (25-item FI excluding adiposity deficits); B=Modified FI-3 (21-item FI excluding cardiovascular and adiposity deficits); Logistic regression models were adjusted for age, sex, region, income level, education level, alcohol consumption, smoking status, systolic blood pressure, random plasma glucose, and lean body mass; Fat body mass quintile groups refer to: <11.0, 11.0-14.5, 14.5-17.8, 17.8-22.1, ≥22.1kg

Figure S7.8 Association between baseline fat mass (quintile) and incident frailty (mFI-2) by unintentional weight loss and physical activity at baseline and self-reported CVD at the 2nd resurvey



Logistic regression models were adjusted for age, sex, region, income level, education level, alcohol consumption, smoking status, systolic blood pressure, random plasma glucose, and lean body mass; Fat body mass quintile groups refer to: <11.0, 11.0-14.5, 14.5-17.8, 17.8-22.1, ≥22.1kg

Figure S7.9 Association between baseline fat mass (quintile) and incident frailty (mFI-3) by unintentional weight loss and physical activity at baseline and self-reported CVD at the 2nd resurvey



Logistic regression models were adjusted for age, sex, region, income level, education level, alcohol consumption, smoking status, systolic blood pressure, random plasma glucose, and lean body mass; Fat body mass quintile groups refer to: <11.0, 11.0-14.5, 14.5-17.8, 17.8-22.1, ≥22.1kg

Table S8.1 Adjusted hazard ratios (95% CI) for the associations between baseline and usual FI and incident stroke, IS, and HS

	Original FI			Modified FI-1			Modified FI-3		
	No. events	Baseline FI HR (95% CI)	Usual FI HR (95% CI)	No. events	Baseline FI HR (95% CI)	Usual FI HR (95% CI)	No. events	Baseline FI HR (95% CI)	Usual FI HR (95% CI)
Stroke (fatal)									
Non-frail	2588	1.00 (0.95-1.05)	-	3133	1.00 (0.96-1.05)	-	4770	1.00 (0.96-1.04)	-
Pre-frail	5409	1.67 (1.63-1.70)	-	4858	1.25 (1.21-1.28)	-	3511	1.17 (1.14-1.21)	-
Frail	671	1.95 (1.79-2.13)	-	677	1.40 (1.28-1.52)	-	387	1.30 (1.16-1.45)	-
Per 1 SD	8668	1.26 (1.23-1.29)	1.46 (1.41-1.52)	8668	1.12 (1.09-1.14)	1.29 (1.23-1.35)	8668	1.09 (1.07-1.11)	1.21 (1.15-1.27)
Per 0.1 unit		1.46 (1.41-1.52)	1.86 (1.76-1.98)		1.19 (1.15-1.23)	1.49 (1.38-1.61)		1.15 (1.11-1.19)	1.37 (1.27-1.47)
Stroke (incident)									
Non-frail	20712	1.00 (0.98-1.02)	-	22798	1.00 (0.98-1.02)	-	35045	1.00 (0.99-1.01)	-
Pre-frail	30939	1.39 (1.38-1.40)	-	28810	1.17 (1.16-1.18)	-	17811	1.09 (1.08-1.11)	-
Frail	2542	1.45 (1.39-1.51)	-	2585	1.18 (1.13-1.23)	-	1337	1.08 (1.02-1.15)	-
Per 1 SD	54193	1.18 (1.17-1.19)	1.31 (1.29-1.33)	54193	1.08 (1.07-1.09)	1.19 (1.17-1.22)	54193	1.06 (1.05-1.06)	1.13 (1.11-1.15)
Per 0.1 unit		1.31 (1.29-1.33)	1.55 (1.52-1.59)		1.13 (1.11-1.15)	1.32 (1.28-1.37)		1.09 (1.08-1.11)	1.22 (1.18-1.26)
Ischaemic stroke (fatal)									
Non-frail	822	1.00 (0.91-1.10)	-	1023	1.00 (0.92-1.08)	-	1592	1.00 (0.94-1.07)	-
Pre-frail	2004	1.67 (1.61-1.73)	-	1812	1.25 (1.19-1.31)	-	1353	1.20 (1.14-1.27)	-
Frail	252	1.87 (1.60-2.17)	-	243	1.33 (1.14-1.55)	-	133	1.23 (1.01-1.49)	-
Per 1 SD	3078	1.25 (1.20-1.30)	1.44 (1.35-1.53)	3078	1.11 (1.07-1.16)	1.28 (1.18-1.39)	3078	1.08 (1.04-1.12)	1.19 (1.09-1.29)
Per 0.1 unit		1.44 (1.35-1.53)	1.81 (1.63-2.02)		1.19 (1.12-1.26)	1.48 (1.29-1.69)		1.13 (1.07-1.20)	1.33 (1.16-1.51)
Ischaemic stroke (incident)									
Non-frail	17601	1.00 (0.98-1.02)	-	19290	1.00 (0.98-1.02)	-	29945	1.00 (0.99-1.01)	-
Pre-frail	26366	1.35 (1.34-1.37)	-	24662	1.16 (1.15-1.17)	-	15047	1.08 (1.07-1.10)	-
Frail	2076	1.37 (1.31-1.44)	-	2091	1.13 (1.08-1.19)	-	1051	1.02 (0.96-1.09)	-
Per 1 SD	46043	1.16 (1.15-1.17)	1.28 (1.25-1.30)	46043	1.07 (1.06-1.08)	1.17 (1.15-1.20)	46043	1.05 (1.04-1.06)	1.11 (1.09-1.13)
Per 0.1 unit		1.28 (1.25-1.30)	1.49 (1.45-1.53)		1.12 (1.10-1.13)	1.28 (1.24-1.33)		1.08 (1.06-1.09)	1.19 (1.14-1.23)
Haemorrhagic stroke (fatal)									
Non-frail	1764	1.00 (0.94-1.06)	-	2108	1.00 (0.95-1.06)	-	3172	1.00 (0.95-1.05)	-
Pre-frail	3376	1.66 (1.62-1.71)	-	3025	1.24 (1.20-1.28)	-	2137	1.15 (1.10-1.20)	-
Frail	419	1.98 (1.78-2.21)	-	426	1.39 (1.25-1.55)	-	250	1.32 (1.15-1.51)	-
Per 1 SD	5559	1.27 (1.23-1.30)	1.48 (1.41-1.54)	5559	1.12 (1.09-1.15)	1.28 (1.21-1.36)	5559	1.08 (1.06-1.11)	1.20 (1.14-1.27)
Per 0.1 unit		1.48 (1.41-1.54)	1.89 (1.76-2.04)		1.19 (1.14-1.24)	1.49 (1.35-1.63)		1.14 (1.10-1.19)	1.35 (1.23-1.49)
Haemorrhagic stroke (incident)									
Non-frail	3743	1.00 (0.96-1.04)	-	4428	1.00 (0.96-1.04)	-	6557	1.00 (0.97-1.03)	-
Pre-frail	6159	1.59 (1.56-1.63)	-	5462	1.18 (1.15-1.21)	-	3606	1.10 (1.06-1.13)	-
Frail	623	1.82 (1.67-1.99)	-	635	1.30 (1.19-1.41)	-	362	1.25 (1.12-1.40)	-
Per 1 SD	10525	1.26 (1.23-1.29)	1.46 (1.41-1.51)	10525	1.10 (1.08-1.12)	1.24 (1.18-1.30)	10525	1.07 (1.05-1.09)	1.16 (1.11-1.21)

	Original FI			Modified FI-1			Modified FI-3		
	No. events	Baseline FI HR (95% CI)	Usual FI HR (95% CI)	No. events	Baseline FI HR (95% CI)	Usual FI HR (95% CI)	No. events	Baseline FI HR (95% CI)	Usual FI HR (95% CI)
Per 0.1 unit		1.46 (1.41-1.51)	1.86 (1.76-1.96)		1.16 (1.12-1.20)	1.40 (1.31-1.51)		1.12 (1.08-1.15)	1.28 (1.19-1.37)

Abbreviations: FI=frailty index

FI definitions: Original FI = 28-item FI; Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits); Modified FI-2 = 25-item FI (original FI excluding adiposity deficits); Modified FI-3 = 21-item FI (original FI excluding cardiovascular and adiposity deficits)

Table S8.2 Adjusted hazard ratios (95% CI) for the associations between baseline and usual FI and incident IHD, MI and MCE

	Original FI			Modified FI-1			Modified FI-3		
	No. events	Baseline FI HR (95% CI)	Usual FI HR (95% CI)	No. events	Baseline FI HR (95% CI)	Usual FI HR (95% CI)	No. events	Baseline FI HR (95% CI)	Usual FI HR (95% CI)
IHD (fatal)									
Non-frail	2001	1.00 (0.94-1.06)	-	2302	1.00 (0.95-1.05)	-	3772	1.00 (0.96-1.04)	-
Pre-frail	4500	1.69 (1.65-1.73)	-	4190	1.44 (1.40-1.48)	-	3008	1.29 (1.25-1.34)	-
Frail	652	2.54 (2.32-2.78)	-	661	2.10 (1.93-2.30)	-	373	1.72 (1.53-1.93)	-
Per 1 SD	7153	1.35 (1.31-1.38)	1.63 (1.56-1.69)	7153	1.23 (1.20-1.26)	1.60 (1.52-1.69)	7153	1.17 (1.15-1.20)	1.44 (1.37-1.51)
Per 0.1 unit		1.63 (1.56-1.69)	2.22 (2.07-2.37)		1.39 (1.34-1.44)	2.11 (1.94-2.29)		1.30 (1.25-1.35)	1.81 (1.67-1.97)
IHD (incident)									
Non-frail	19508	1.00 (0.98-1.02)	-	20552	1.00 (0.98-1.02)	-	31836	1.00 (0.99-1.01)	-
Pre-frail	27856	1.38 (1.37-1.39)	-	26629	1.28 (1.26-1.29)	-	16626	1.23 (1.21-1.25)	-
Frail	2573	1.71 (1.64-1.78)	-	2756	1.59 (1.52-1.65)	-	1475	1.49 (1.41-1.57)	-
Per 1 SD	49937	1.21 (1.20-1.23)	1.37 (1.35-1.40)	49937	1.16 (1.15-1.17)	1.40 (1.37-1.43)	49937	1.14 (1.13-1.15)	1.34 (1.31-1.36)
Per 0.1 unit		1.37 (1.35-1.40)	1.68 (1.64-1.73)		1.27 (1.25-1.29)	1.71 (1.65-1.77)		1.23 (1.22-1.25)	1.61 (1.56-1.66)
MI (fatal)									
Non-frail	1151	1.00 (0.93-1.08)	-	1306	1.00 (0.93-1.07)	-	2101	1.00 (0.94-1.06)	-
Pre-frail	2450	1.65 (1.60-1.70)	-	2288	1.39 (1.34-1.45)	-	1655	1.23 (1.17-1.29)	-
Frail	350	2.35 (2.08-2.66)	-	357	1.93 (1.72-2.18)	-	195	1.55 (1.32-1.81)	-
Per 1 SD	3951	1.31 (1.26-1.35)	1.55 (1.47-1.64)	3951	1.20 (1.16-1.24)	1.51 (1.40-1.62)	3951	1.14 (1.11-1.18)	1.35 (1.26-1.45)
Per 0.1 unit		1.55 (1.47-1.64)	2.05 (1.87-2.24)		1.33 (1.27-1.40)	1.91 (1.71-2.15)		1.24 (1.18-1.31)	1.64 (1.46-1.83)
MI (incident)									
Non-frail	2557	1.00 (0.95-1.05)	-	2881	1.00 (0.95-1.05)	-	4622	1.00 (0.96-1.04)	-
Pre-frail	4661	1.52 (1.49-1.55)	-	4352	1.29 (1.26-1.33)	-	2857	1.18 (1.14-1.22)	-
Frail	531	1.95 (1.77-2.15)	-	516	1.58 (1.43-1.74)	-	270	1.33 (1.17-1.52)	-
Per 1 SD	7749	1.25 (1.22-1.28)	1.44 (1.38-1.50)	7749	1.15 (1.13-1.18)	1.39 (1.31-1.46)	7749	1.11 (1.08-1.13)	1.26 (1.19-1.32)
Per 0.1 unit		1.44 (1.38-1.50)	1.81 (1.70-1.94)		1.26 (1.21-1.30)	1.68 (1.54-1.82)		1.18 (1.14-1.22)	1.45 (1.34-1.58)
MCE (incident)									
Non-frail	3223	1.00 (0.95-1.05)	-	3664	1.00 (0.96-1.04)	-	5913	1.00 (0.97-1.03)	-
Pre-frail	6204	1.57 (1.54-1.60)	-	5787	1.33 (1.29-1.36)	-	3876	1.22 (1.18-1.26)	-
Frail	766	2.19 (2.02-2.38)	-	742	1.75 (1.62-1.90)	-	404	1.50 (1.35-1.68)	-
Per 1 SD	10193	1.29 (1.26-1.32)	1.51 (1.46-1.57)	10193	1.18 (1.16-1.21)	1.47 (1.40-1.54)	10193	1.13 (1.11-1.15)	1.33 (1.27-1.39)
Per 0.1 unit		1.51 (1.46-1.57)	1.97 (1.86-2.09)		1.31 (1.27-1.35)	1.84 (1.71-1.98)		1.23 (1.19-1.27)	1.59 (1.48-1.71)

Abbreviations: FI=frailty index; IHD=ischemic heart disease; MCE=major coronary event; MI=myocardial infarction

FI definitions: Original FI = 28-item FI; Modified FI-1 = 24-item FI (original FI excluding cardiovascular deficits); Modified FI-2 = 25-item FI (original FI excluding adiposity deficits); Modified FI-3 = 21-item FI (original FI excluding cardiovascular and adiposity deficits)

Figure S8.1 Adjusted hazard ratios (95% CI) for the association between usual mFI-1 and incident stroke in subgroups

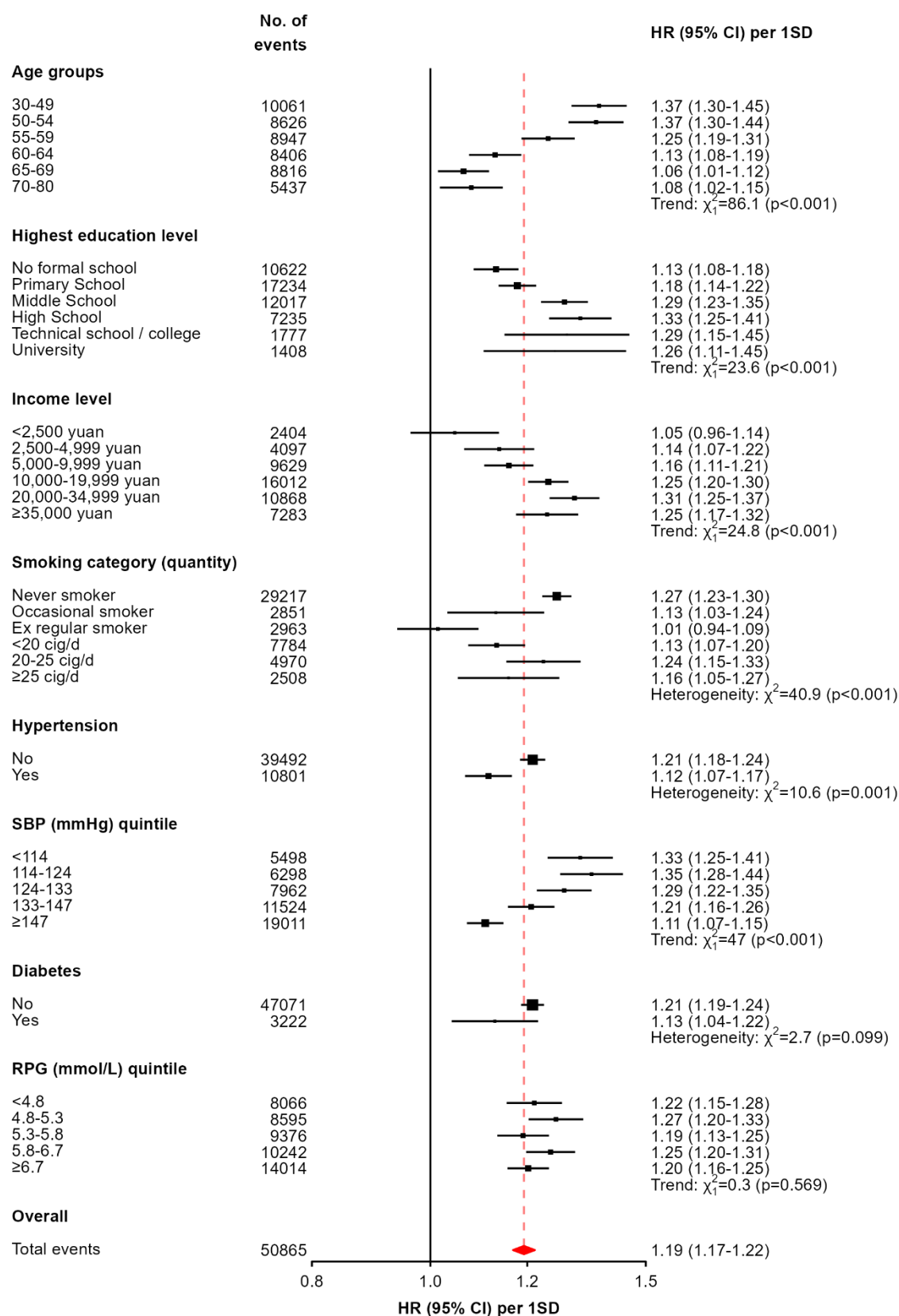


Figure S8.2 Adjusted hazard ratios (95% CI) for the association between usual mFI-3 and incident stroke in subgroups

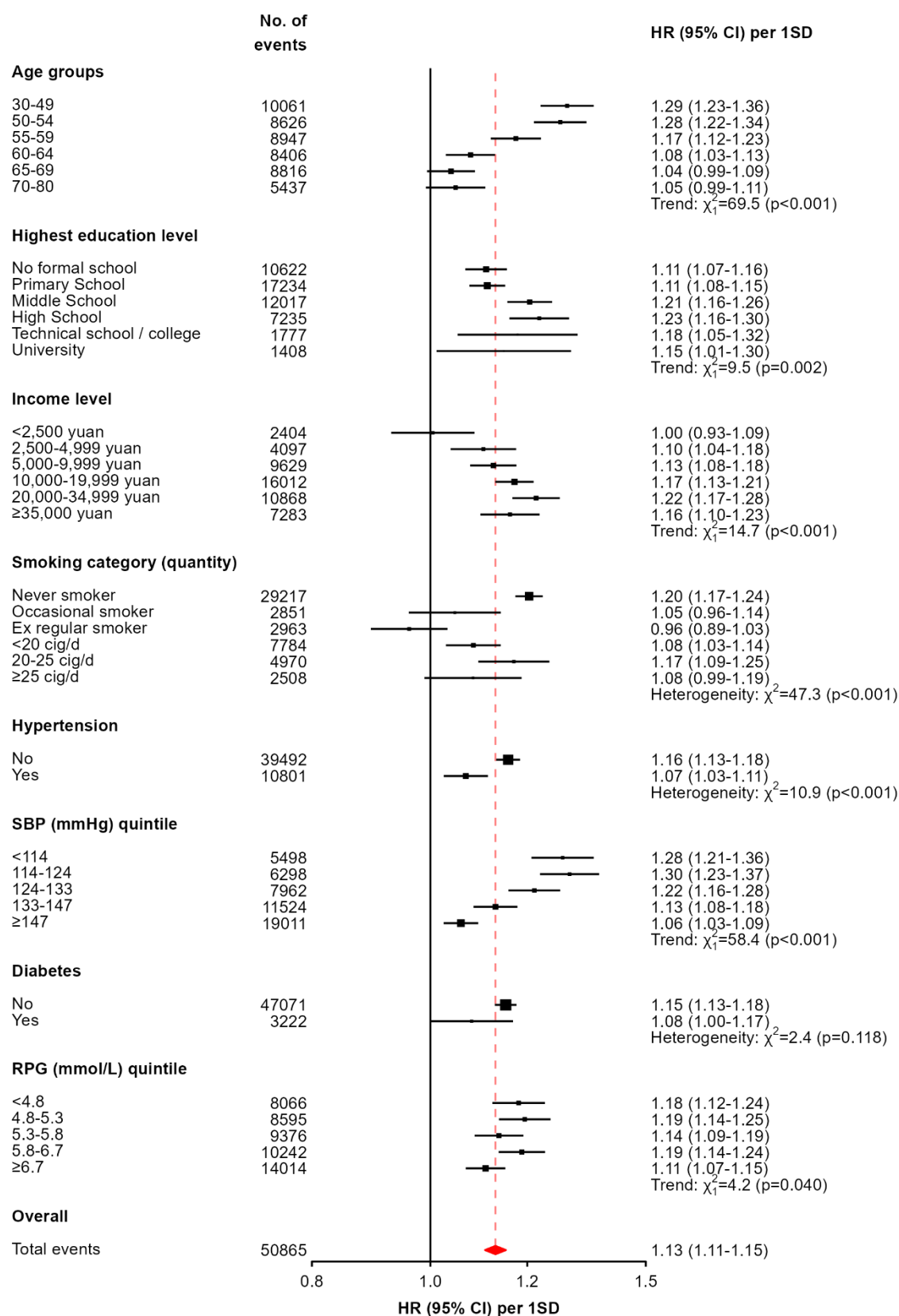


Figure S8.3 Adjusted hazard ratios (95% CI) for the association between usual mFI-1 and incident IHD in subgroups

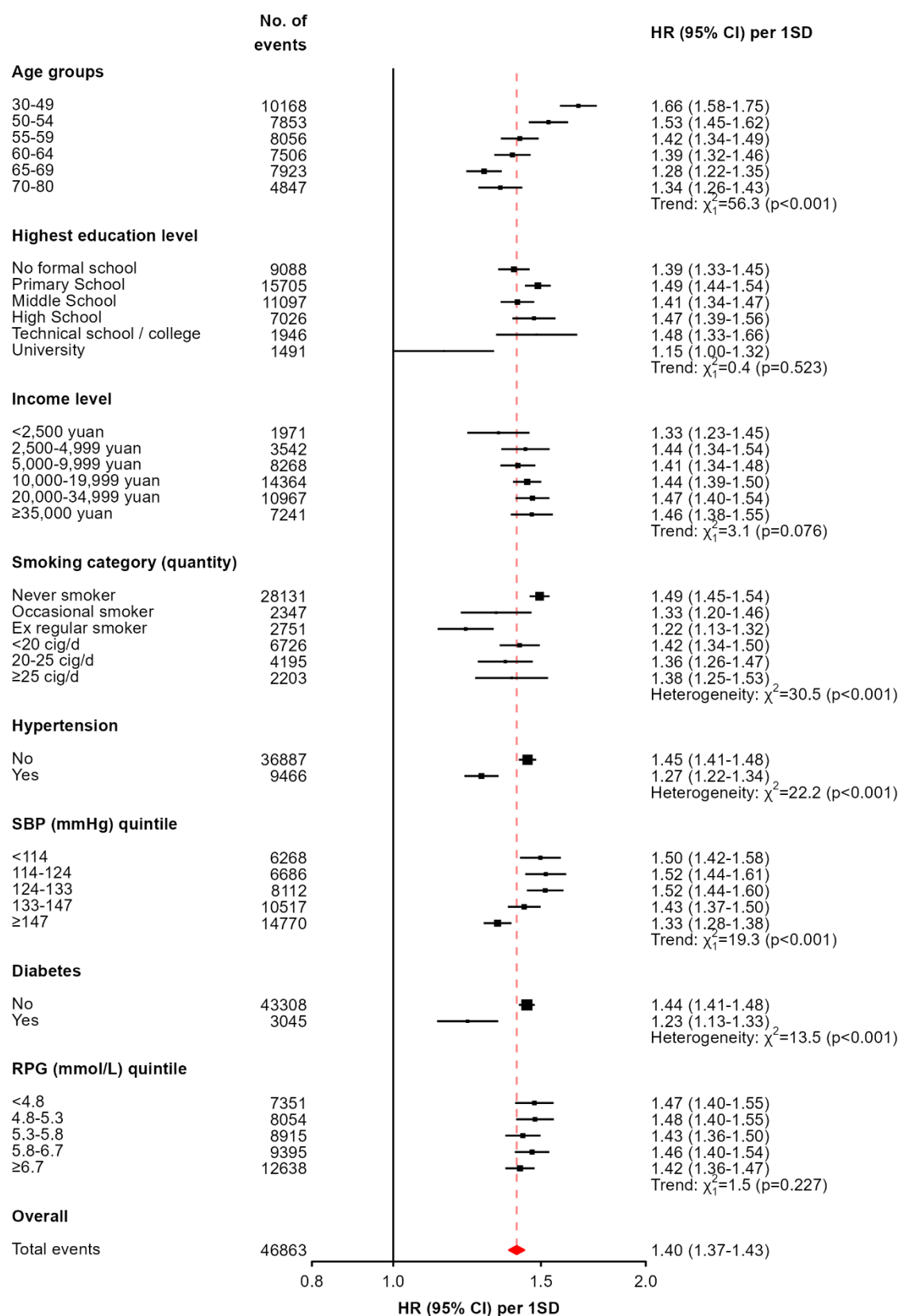


Figure S8.4 Adjusted hazard ratios (95% CI) for the association between usual mFI-3 and incident IHD in subgroups

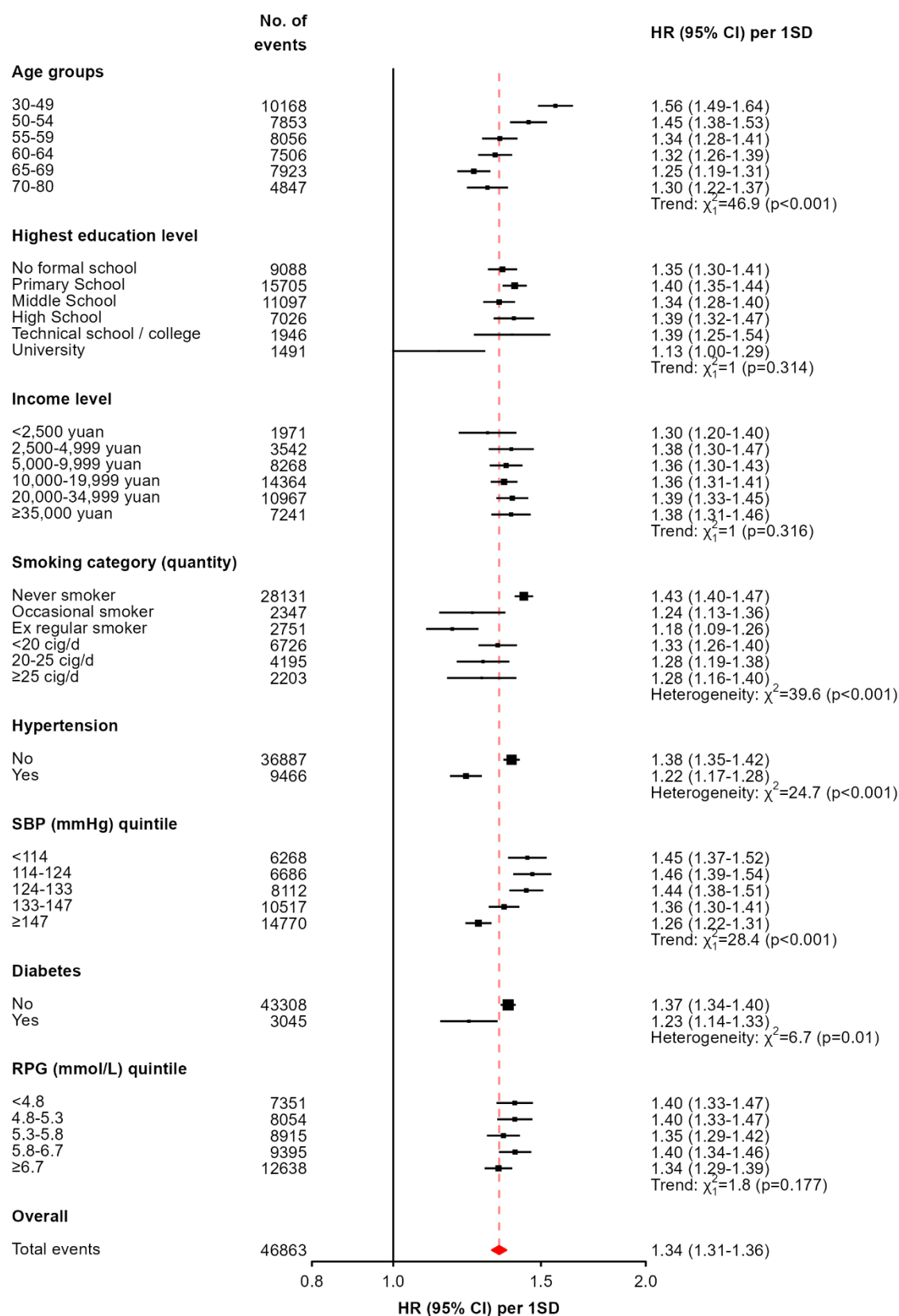


Figure S8.5 Adjusted hazard ratios (95% CI) for the association between usual mFI-1 and CVD mortality in subgroups

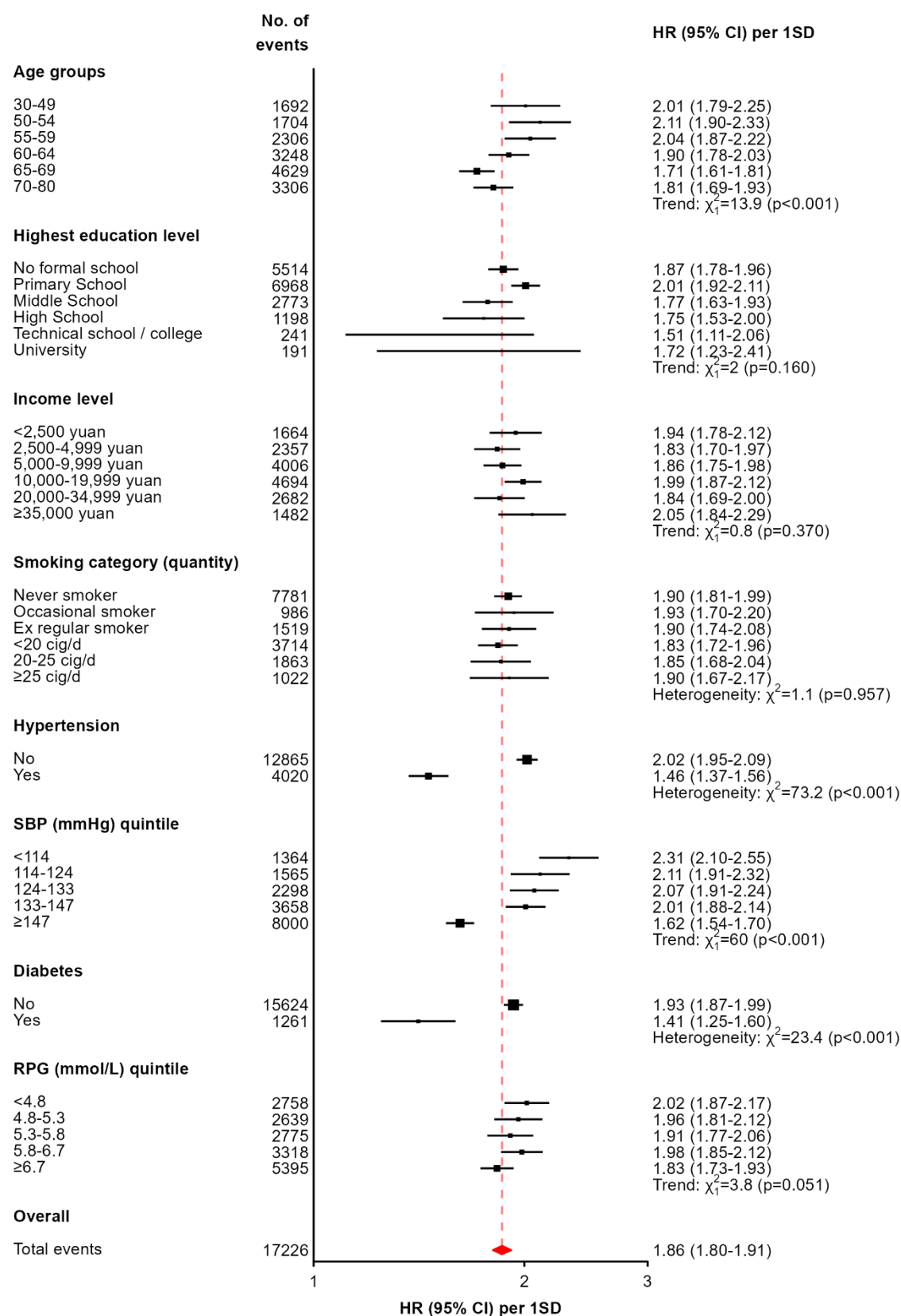


Figure S8.6 Adjusted hazard ratios (95% CI) for the association between usual mFI-3 and CVD mortality in subgroups

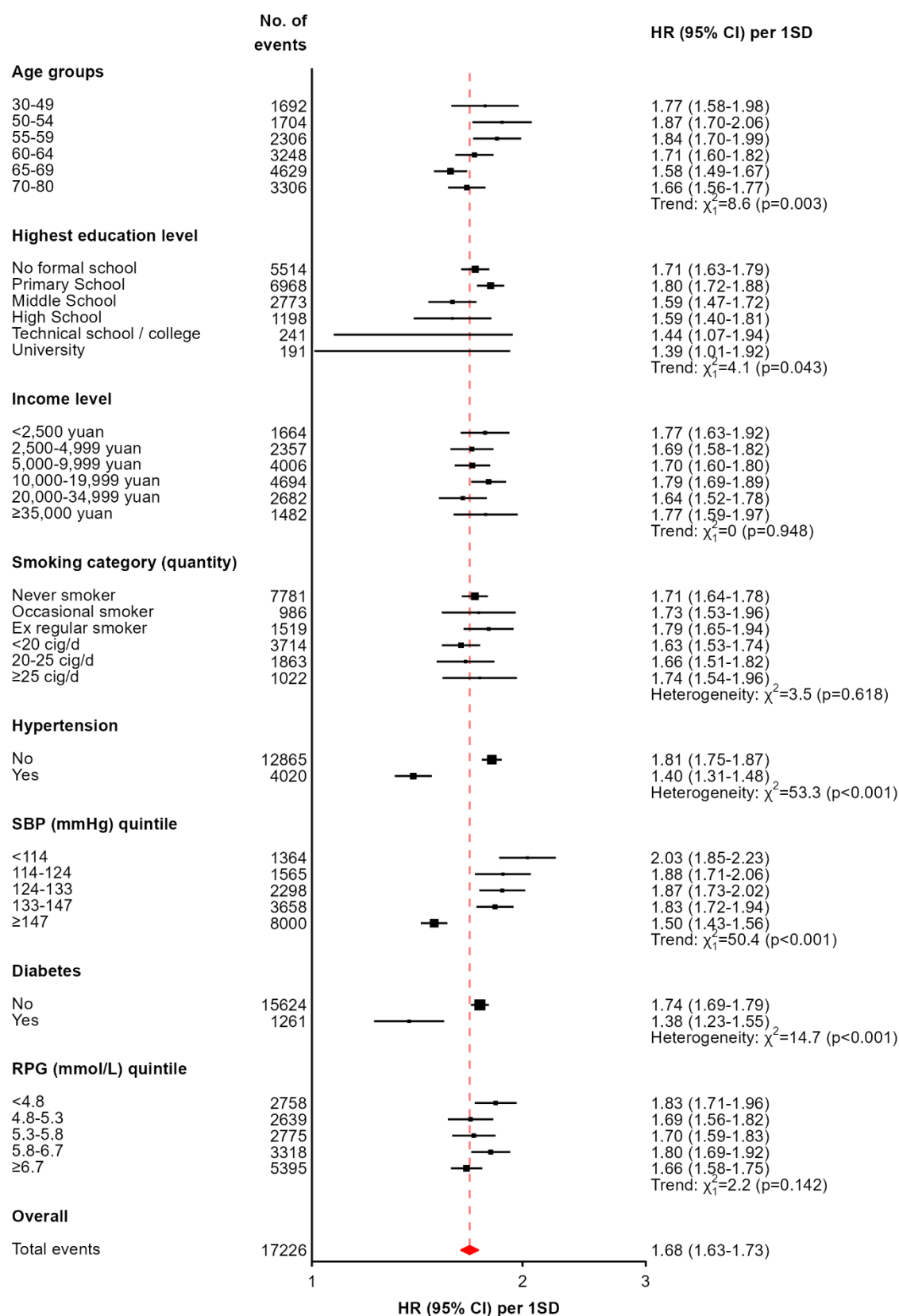


Figure S8.7 Adjusted hazard ratios (95% CI) for the association between usual mFI-1 and all-cause mortality in subgroups

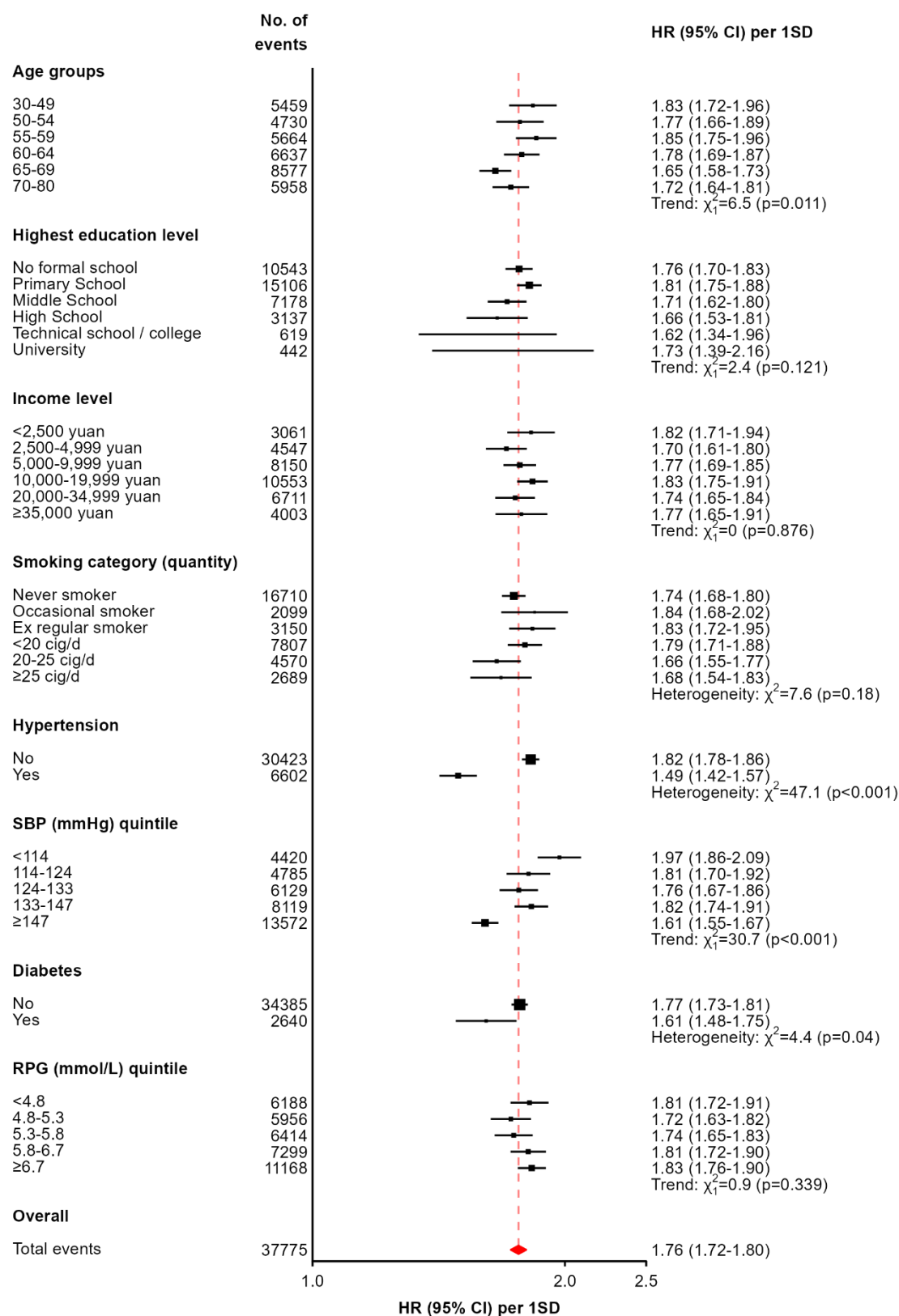


Figure S8.8 Adjusted hazard ratios (95% CI) for the association between usual mFI-3 and all-cause mortality in subgroups

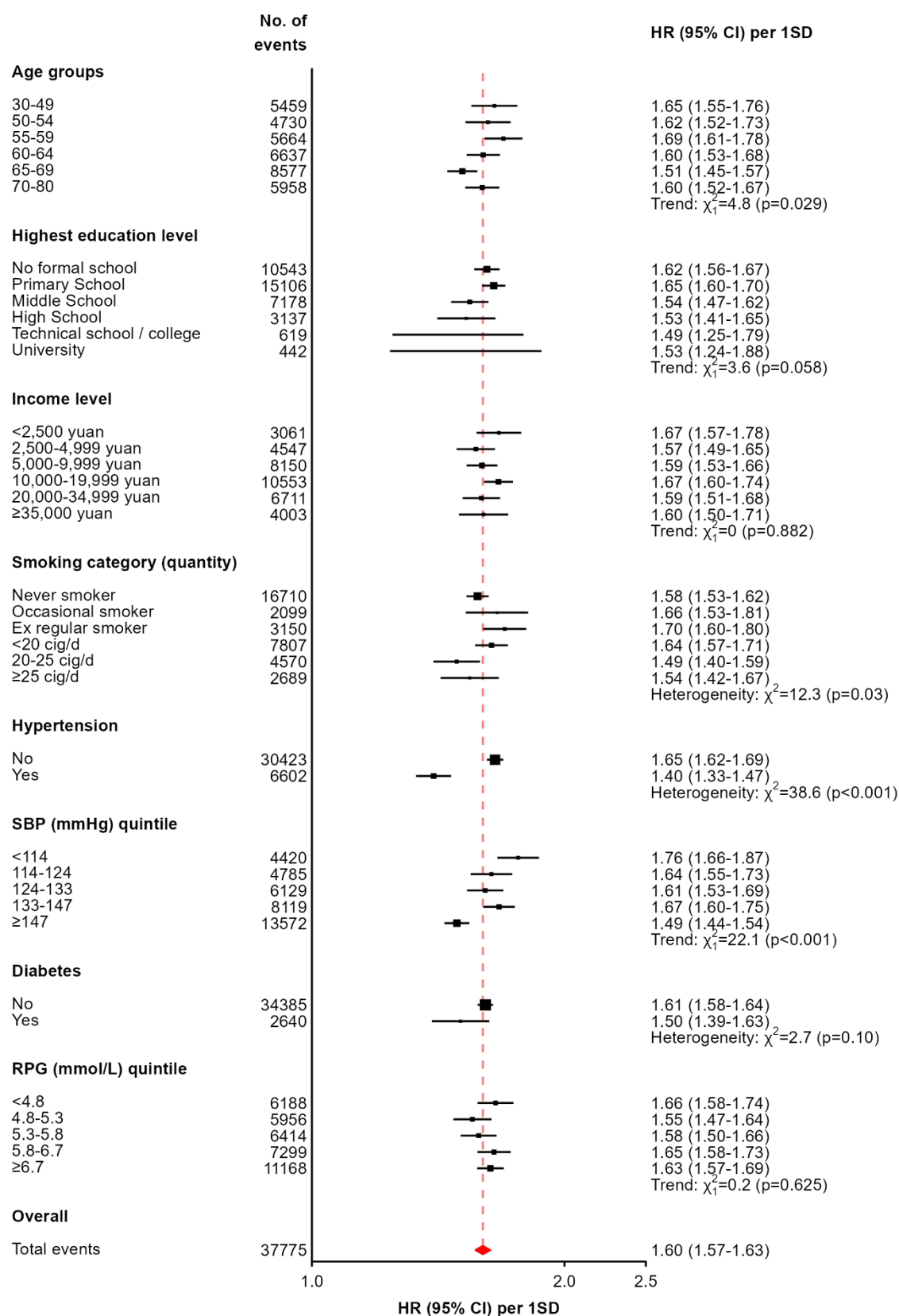


Figure S8.9 Adjusted hazard ratios (95% CI) for the association between usual mFI-1 and incident stroke by study site

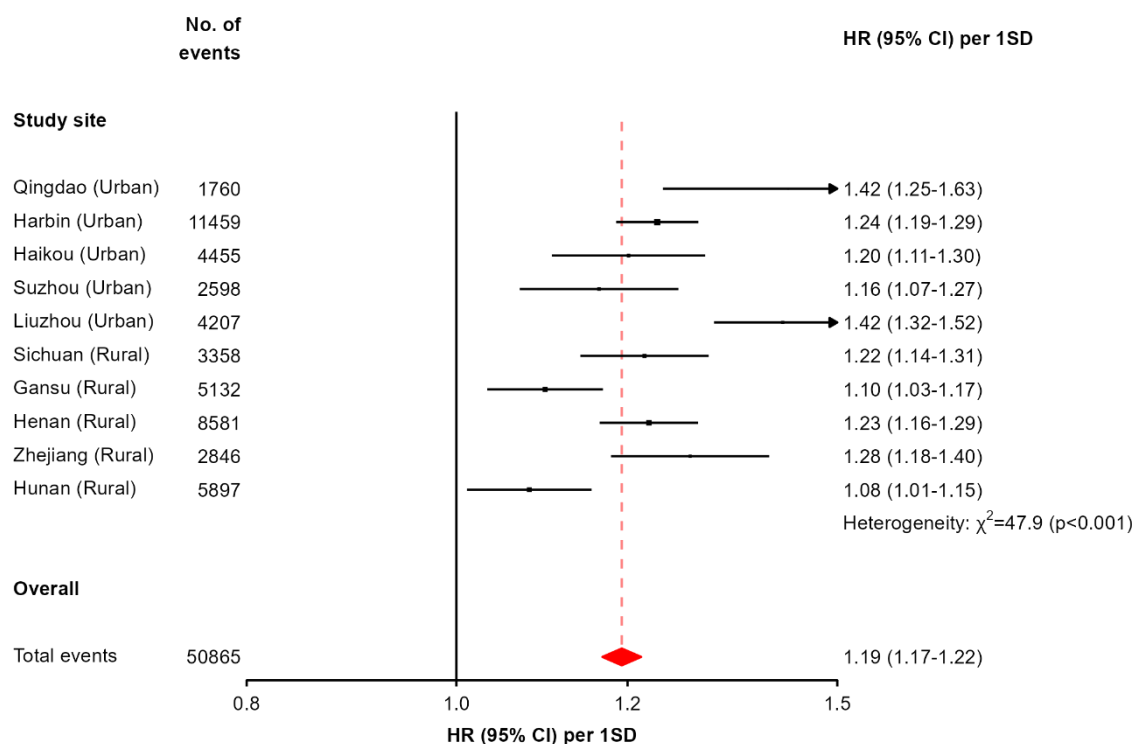


Figure S8.10 Adjusted hazard ratios (95% CI) for the association between usual mFI-3 and incident stroke by study site

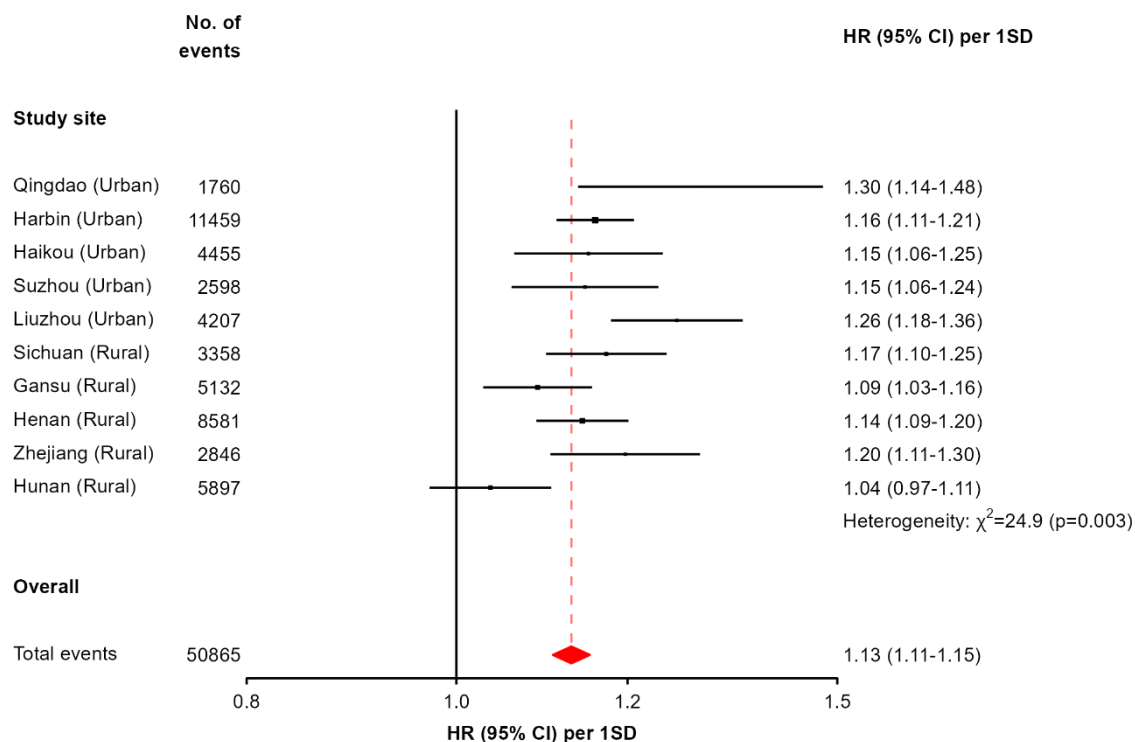


Figure S8.11 Adjusted hazard ratios (95% CI) for the association between usual mFI-1 and incident IHD by study site

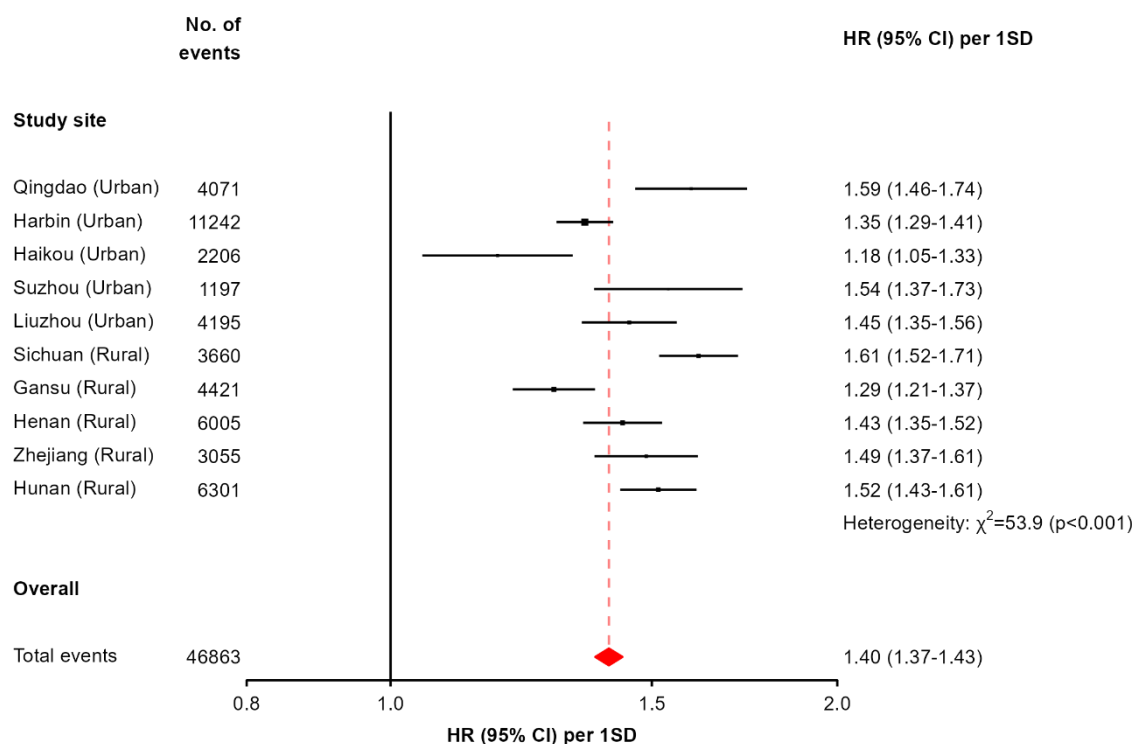


Figure S8.12 Adjusted hazard ratios (95% CI) for the association between usual mFI-3 and incident IHD by study site

