GLOBAL PATTERNS OF FRAILTY AND MULTI-MORBIDITY

PURE FRAILTY – PROGNOSTIC IMPORTANCE OF FRAILTY AND MULTI-MORBIDITY IN LOW-, MIDDLE-, AND HIGH-INCOME COUNTRIES

BY KARRIE WONG

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TITLE: PURE Frailty – Prognostic Importance of Frailty and Multi-morbidity in Low-, Middle-, and High- Income Countries

AUTHOR: Karrie Wong, B.Sc. (McMaster University)

SUPERVISOR: Dr. Darryl Leong

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Abstract

Background. Frailty is a syndrome characterized by a decreased resistance to stressors, leading to increased vulnerability to adverse outcomes, including mortality. Multi-morbidity refers to the presence of two or more chronic diseases, and is associated with increased risk of adverse health outcomes. Most of the literature in frailty is based on older people (65+ years) living in high income countries. **Objective**. To compare the predictive ability of three frailty indices for all-cause and one-year mortality among high- (HIC), middle- (MIC), and low- income country (LIC) participants; and to assess the mortality risk associated with multi-morbidity. **Methods**. Using data from the Prospective Urban and Rural Epidemiological (PURE) study, we developed three indices using different definitions of frailty (one phenotypic frailty index; two cumulative deficit indices). All indices were tested for predictive ability for mortality both individually and with multi-morbidity. **Results**. Prevalence of phenotypic frailty was greatest in LIC (8%), intermediate in MIC (7%), and lowest in HIC (4%). Multi-morbidity was most prevalent in HIC (20%), intermediate in MIC (15%), and lowest in LIC (13%). Increased frailty was associated with greater mortality risk using all frailty indices (e.g. HR (95% CI) of 2.63 (2.35-2.95) for the phenotypically frail relative to the robust). At each frailty level, mortality risk was higher within one year of baseline measurement than afterwards, and increased if it was accompanied by concurrent multi-morbidity (e.g. HR of phenotypic frailty increases from 2.27 (1.96-2.62) to 5.08 (4.34-5.95) if accompanied by multi-morbidity). **Conclusion.** All frailty indices predicted mortality. This study is unique in evaluating the prognostic ability of frailty indices in middle-aged adults across HIC, MIC, and LICs.

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Thesis Outline

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LIST OF ABBREVIATIONS

ADR	Activities of daily living
AUC	Area under the curve
CGA	Comprehensive geriatric assessment
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COPD	Chronic obstructive pulmonary disease
COURAGE	Collaborative Research on Ageing in Europe
GDP	Gross domestic product
GFI	Groningen Frailty Index
GNI	Gross national income
HIC	High-income country
HR	Hazard ratio
IQR	Interquartile range
LIC	Low-income countries
LMIC	Low and middle-income countries
MIC	Middle-income countries
MM	Multi-morbidity
PRISMA	Program of Research to Integrate Services for the Maintenance of Autonomy
PURE	Prospective Urban and Rural Epidemiological study
ROC	Receiver Operating Characteristic
RR	Relative risks
SAGE	Study on Global AGEing and Adult Health
SES	Socioeconomic status
SHARE	Survey of Health, Ageing and Retirement in Europe
WHO	World Health Organization

DECLARATION OF ACADEMIC ACHIEVEMENT

The following is a declaration that Karrie Wong has analyzed the data collected in the PURE study and drafted this document. The contributions of Dr. Darryl Leong, Dr. Salim Yusuf, Dr. Parminder Raina, Leanne Dyal, and Wei-Hong Hu are also recognized in the completion of the design, research, analyses, and review of this thesis. Karrie Wong contributed to the study design, and was responsible for data analysis, and the writing of the manuscript. Dr. Darryl Leong contributed to the study design, data analysis, and editing and review of the manuscript. Dr. Salim Yusuf established the PURE study and supervised all aspects of the study. He and Dr. Parminder Raina provided insightful advice, feedback, and contributed to manuscript review. Leanne Dyal and Wei-Hong Hu provided assistance in the data organization and analyses.

CHAPTER 1

INTRODUCTION AND BACKGROUND

1.1. DEFINING FRAILTY

Frailty is a syndrome characterized by a decreased resistance to stressors, leading to increased vulnerability to adverse outcomes, including mortality (Fried, Tangen, & Walston, et al., 2001; Rockwood et al., 1999; Morley et al., 2013). It is typically perceived to exist as a dynamic continuum, ranging anywhere between robust, pre-frail, and frail (Sternberg, Shwartz, Karunananthan, Bergman, & Clarfield, 2011). Frailty has been attributed to an individual's loss of "physiological reserve" (Song, Mitnitski, & Rockwood, 2010), determined by five key factors: genetics, disease, injuries, lifestyle behaviours, and response to the aging process (Bortz, 2002).

1.2. MEASURING FRAILTY & VALIDITY OF PREVIOUS FRAILTY INDICES

There is currently no consensus on either an operational definition of frailty or how it should be clinically assessed (Van Kan, Rolland, Morley, Kritchevsky & Vellas, 2008; Sternberg et al., 2011). For instance, there is debate with regards to whether disabilities should be considered as a component of frailty or a consequence of it (Sternberg et al., 2011). A systematic review of the literature on frailty by Sternberg et al. (2011) found that the physical characteristics most commonly used to evaluate frailty include: physical function, gait speed or mobility, and cognition.

1.2.1. Frailty Phenotype

One of the most commonly used and earliest instruments for measuring frailty is the frailty phenotype (Fried et al., 2001; Cesari, Gambassi, Abellan van Kan, & Vellas, 2014), which characterizes frailty as the presence of three or more of the following five characteristics: unintentional weight loss (≥10 pounds or ≥5% body weight in the past year), weak grip strength (in the lowest fifth of values recorded by those of the similar body-mass index and sex), self-reported exhaustion or poor endurance, slow walking speed (in the lowest fifth of values recorded by those of similar height and sex), and low physical activity (in the lowest fifth of values recorded by those of the same sex). This frailty phenotype was validated in the Cardiovascular Health Study, a U.S study of community-dwelling male and female participants aged 65 and older (N=5,317; Fried et al., 2001). The study assessed the association between frailty and the incidence of a variety of major adverse outcomes over seven years of follow-up, after adjusting for age, gender, income, smoking history, health and disability status, subclinical and clinical diseases, and depressive symptoms (Fried et al., 2001; Table 1). Over seven years, frail individuals (3+/5 components) were significantly more likely to experience worsening activities of daily living (ADL), disability, hospitalization, worsening mobility, and mortality compared to individuals who were not frail (0/5 components) (Table 1). Those with intermediate frailty (1-2/5 components) also had a significantly higher risk of these adverse outcomes compared to those who were robust, but lower than the risk associated with being frail (Table 1).

Table 1. Predictive validity of frailty phenotype for falls, worsening mobility, disability, hospitalization, and death over seven years of follow-up (Fried et al., 2001)

Outcome	Outcome incidence rate (%)			Adjusted Hazard Ratios and 95% Confidence Interval		
	Not Frail (n=2,469)	Intermediate Frailty (n=2,480)	Frail (n=368)	No Frailty (Reference)	Intermediate Frailty (1-2 items/5)	Frail (3+ items/5)
Fall	27	33	41	1	1.12 (1.00-1.26)	1.23 (0.99-1.54)
Worsening Mobility	41	58	71	1	1.41 (1.29-1.54)	1.36 (1.15-1.62)
Worsening ADL Disability	23	41	63	1	1.55 (1.38-1.75)	1.79 (1.47-2.17)
First Hospitalization	79	83	96	1	1.11 (1.03-1.19)	1.27 (1.11-1.46)
Death	12	23	43	1	1.32 (1.13-1.55)	1.63 (1.27-2.08)

Note: ADL = activities of daily living. Hazard ratios adjusted for: age, gender, indicator for minority cohort, income, smoking status, brachial and tibial blood pressure, fasting glucose, albumin, creatinine, carotid stenosis, history of congestive heart failure, cognitive function, major electrocardiogram abnormality, use of diuretics, difficulties with instrumental activities of daily living, self-report health measure, CES-D modified depression measure. Worsening ADL disability was defined as an increase in 1 unit of ADL score.

1.2.2. Cumulative Deficit Frailty Index

Another widely accepted method for measuring frailty is the cumulative deficit frailty index, which calculates frailty as the proportion of deficits assessed that are apparent in a given individual (Mitnitski, Mogilner, & Rockwood, 2001). Since the method of deficit-accumulation was introduced in 2001, various versions of it have been created (Mitnitski et al., 2001). Rockwood, Song, Macknight, et al. (2005) created one of the earliest and widely cited models, consisting of 70 items representing a range of functional, physiological, and social deficits. This index was associated with an increased risk of death

(hazard ratio (HR) 1.26, 95% confidence interval (CI) 1.24-1.29) and institutionalization (HR 1.56 (95% CI 1.48-1.65)) for each of seven increases in level of index score, after adjusting for age, sex, and number of years of education (Rockwood et al., 2005).

There are several limitations with cumulative deficit frailty indices. As with the frailty phenotype, the cumulative deficit approach gives equal weighting to each of its items (Rockwood & Mitnitski, 2007). The idea that all symptoms and diseases should be weighted equally seems counter-intuitive; however, doing so is simple, maximizes generalizability, and has been demonstrated to have strong correlations with prognostic outcomes (Rockwood, Mitnitski, & Song, et al., 2006).

A second important criticism of cumulative deficit indices of frailty is that there is considerable heterogeneity in the number and nature of deficits evaluated in such indices. However, Rockwood et al. (2006) demonstrated that an individual's frailty is better predicted by the proportion of deficits experienced rather than the specific nature of the deficits measured. Over 1000 iterations, Rockwood et al. (2006) randomly sampled 40 deficit variables from the CSHA study and 51 variables from the Gothenburg H-70 cohort study. Each variable was equally weighted and coded as a binary measurement, where "one" indicated the presence of deficit in an individual, and "zero" indicated its absence. Measures of frailty based on the number of deficits accumulated from the randomly sampled variables were separated by quintiles (from most fit to most frail). Using each random sampling of variables, worse frailty was significantly correlated with institutionalization and long-term mortality, indicating that the cumulative deficit

measurement of frailty is robust across different types and total numbers of deficits assessed.

1.2.3. Other Instruments for Measuring Frailty

Some other tools for diagnosing frailty in older people include: tests of gait speed, PRISMA 7 (Program of Research to Integrate Services for the Maintenance of Autonomy) tools, timed up-and-go test, clinical judgment, polypharmacy, Groningen Frailty Indicator (GFI), self-reported health, Study of Osteoporotic Fractures Frailty, Edmonton Frail Scale, and the Canadian Study of Health and Aging Clinical Frailty Scale (Effectiveness Matters, 2015; Kojima, 2015).

Currently, comprehensive geriatric assessment (CGA) is the gold standard instrument for both the diagnosis and treatment of frailty in the elderly population. The CGA involves evaluating the individual's physical, cognitive, and psychosocial characteristics, followed by implementing an appropriate multifaceted therapeutic treatment plan to improve independence (Ward & Reuben, 2013). According to a Cochrane review of twenty-two randomized control trials, compared to general medical care, CGA was associated with lower admission rates to hospital and nursing homes in older people with frailty, and increased likelihood of survival following an emergency hospital admission at up to 12 months of follow-up (Ellis, Whitehead, Robinson, O'Neill, & Langhorne, 2011).

Multicomponent exercise regimes, which include strength, balance and endurance training, also have positive outcomes on older individuals with frailty (Effectiveness

Matters, 2015). Despite the association between frailty and various health outcomes, frailty remains a poorly standardized construct (Theou, Brothers, & Mitnitski, et al., 2013a).

1.2.4. Comparison of the Frailty Phenotype and Cumulative Deficit Index

The frailty phenotype and the cumulative deficit frailty index are among the most commonly used frailty measures, and have been frequently compared to one another (Kulminski, Ukraintseva, Kulminskaya, et al., 2008; Woo, Leung & Morley, 2012; Blodgett, Theou, Kirkland, Andreou, & Rockwood, 2014; Walston & Bandeen-Roche, 2015).

Kulminski et al. (2008) compared the predictive validity of the frailty phenotype (characterized by the presence of ≥3 of: unintentional weight loss, exhaustion, slow walking, low physical activity, and weak grip strength) and a 48-item cumulative deficit frailty index for four-year survival in the Cardiovascular Health Study (the same cohort in which Fried et al. (2001) had originally evaluated the frailty phenotype). The study sample comprised of 4,721 Medicare-eligible participants aged 65 and older, after excluding individuals with a history of stroke (n=196), antidepressant use (n=188), scores below 18 on the Mini-Mental State Examination (n=37), and who refused data release (n=76). Data on the median age or sex distribution of the sample after applying these exclusion criteria were not provided. The frailty phenotype and the cumulative deficit index were compared using two methods. First, both indices were standardized by converting them both into percentages, to enable a direct comparison of one with the other. When both indices were simultaneously included in the same Cox regression model and adjusting for age and sex, the relative risk of four-year death was greater for the cumulative deficit frailty index than

for the frailty phenotype (relative risks (RR) per 1% increase in frailty of 1.035 (95% CI 1.026-1.045) and 1.014 (95% CI 1.009-1.019), respectively). These results led to the conclusion that the cumulative deficit index has greater prognostic importance than the frailty phenotype in predicting frail individuals' risk of death. The study did not directly compare the discriminative ability of the frailty phenotype with that of the cumulative deficit frailty index (using the c-statistic, for instance). The CI do not overlap, however, suggesting that an increase in the number of deficits exhibited is associated with a worse outcome than a proportionate increase in the number of phenotypic frailty characteristics present.

In Kulminski et al.'s (2008) second approach to comparing phenotypic and cumulative deficit frailty models, the cumulative deficit index was categorized into three strata to facilitate direct comparison with the three levels of the frailty phenotype. Participants with three or more positive phenotypic criteria were categorized as frail, whereas the participants with one or two positive criteria were categorized as pre-frail, and those with no positive criteria were categorized as robust. Cumulative deficit indices <0.2 were regarded as robust, 0.2-0.35 as pre-frail, and >0.35 as frail. When each index was tested in a separate univariable model, the pre-frail and frail levels of the phenotypic index resulted in relative risks of mortality of 2.08 (95% CI 1.63-2.66) and 4.81 (95% CI 3.53-6.55), respectively. The relative risks of death for the pre-frail and frail levels of the cumulative deficit index were 1.94 (95% CI 1.45-2.61) and 4.45 (95% CI 3.26-6.08). The univariate analyses suggest that both indices have a monotonic positive relationship with mortality risk, and provide similar levels of prognostic prediction. When both indices were

included in a Cox regression model adjusted for age and sex, the relative risks of the cumulative deficit index's pre-frail and frail groups for four-year survival (1.67 (95% CI = 1.29-2.15) and 3.00 (95% CI = 2.15-4.19), respectively) were comparable to those of the phenotypic frailty index (1.66 (95% CI = 1.23-2.25) and 3.07 (95% CI = 2.20-4.28), respectively). Using these categories, the deficit index identified 939 (19.9%) individuals as frail. Despite having similar relative risks to the deficit index for each level of frailty, the phenotypic frailty definition identified significantly fewer individuals as frail (n=361, 7.6%). Among the 1,073 participants with the lowest four-year survival, the frailty phenotype underestimated the risk of mortality (categorizing them as robust or pre-frail instead of frail) for 720 subjects (67.1% of 1,073 participants), whereas the deficit index only underestimated mortality risk for 134 subjects (12.5% of 1,073 participants). A strength of this study is that it assessed both frailty indices using the same cohort, and directly compared the indices for predictive power for mortality.

1.3. PREVALENCE OF FRAILTY

Estimates of the prevalence of frailty vary depending on how it is measured and in which population (Shamliyan, Talley, Ramakrishnan, & Kane, 2013). Four systematic reviews on the prevalence of frailty have been published within the last five years (Table 2). Two of the reviews assessed frailty prevalence among community-dwelling older adults (65+ years), one assessed nursing home patients (60+ years), and one assessed older adults in developing countries (Table 2). Each review used either the frailty phenotype or a mixture of frailty definitions, as described below. The interpretation of these systematic

reviews is limited by different definitions of frailty among the included studies, as well as by important missing information (e.g. mean age and % females).

Table 2. Summary of systematic review findings on prevalence of frailty and pre-frailty across different populations

Author(s)	Collard, Boter, Schoevers, & Voshaar	Choi, Ahn, Kim, & Won Won[b]	Kojima	Nguyen, Cumming, & Hilmer		
Year of publication	2012	2015	2015	2015		
Target Population	Community-based older adults (65+ yo)	Community-dwelling older adults (65+ yo)	Nursing home patients (60+ yo)	Developing countries		
				Community-dwelling older adults	Geriatric outpatients	Institutionalized older patients
No. of Studies	21	6	9	9	3	2
Total No. of subjects	56,183	40,464	1,373	27,240	561	319
Weighted Mean Age	74.9 (95% CI 74.8-74.9)	--	80.3 (95% CI 80.1-80.5)	Varying age groups; minimum age ranging from 55-65	Varying age groups; minimum age ranging from 60-80	Varying age groups
Female (%)	51.3	Range[c]: 48.8-59.6	59.0	--		
Association with Age	Positive for frailty	--	Positive for frailty	--		
Frailty Definitions	Frailty phenotype[a], SOF, FRAIL scale, Groningen, Tilburg Frailty Indicator, Sherbrooke Postal Questionnaire	Frailty phenotype	Frailty phenotype, EFS, SOF, Groningen, & CSHA-CFS	Most used the frailty phenotype, others used EFS or frailty index	Frailty phenotype	Frailty phenotype
Prevalence of Pre-frailty (%)	41.6	Range: 34.6-50.9	40.2	--		
Prevalence of Frailty (%)	10.7	Range: 4.9-27.3	52.3	Range: 5.4-44%	Range: 27.8-71.3%	Range: 32.3-49.3%

Note: "--" = not reported by the study; EFS = Edmonton Frail Scale; Groningen = Groningen Frailty Indicator; SOF = Study of Osteoporotic Fractures Frailty; CSHA-CFS = Canadian Study of Health and Aging Clinical Frailty Scale.

[a] If a study compared multiple definitions of frailty and provided multiple prevalence rates, the prevalence of the phenotypic frailty index was used.

[b] Authors excluded studies that were not specifically focused on the prevalence of frailty, but on the mechanism, intervention, or management of frailty

[c] Data on gender was not collected in one of the studies included in this systematic review

1.3.1. Prevalence According to Frailty Definition

Collard, Boter, Schoevers, & Voshaar (2012) conducted a systematic literature review to compare the prevalence of frailty and pre-frailty in community-dwelling adults aged 65 and older. In this review, the prevalence of frailty was greater in studies which used a multi-faceted frailty definition compared to a purely physical frailty phenotype. The studies examined were mostly based in North America, Europe, and Australia, with one from Taiwan. Across 20 studies (n=56,183) of the total 21 included, the mean age, weighted according to study sample size, was calculated to be 74.9 years old (95% CI 74.8-74.9) (one study did not provide sufficient information to calculate weighted mean age). Among studies that used a physical definition, such as the phenotypic frailty phenotype, frailty was determined to have a weighted average prevalence of 9.9% (95% CI 9.6-10.2%; 5 studies; n=44,898), and a pre-frailty prevalence of 44.2% (95% CI 44.2-44.7%; 13 studies; n=41,197). In contrast, among studies that used a broader definition of frailty, such as the cumulative deficit index, which includes social and psychological variables, the weighted average prevalence of frailty was 13.6% (95% CI 13.2-14.0%; 8 studies; n=24,072) and 33.5% (95% CI 32.9-34.1%; 4 studies; n=19,996) for pre-frailty. There was a statistically significant difference ($\chi^2 = 217.7$, $df = 1$, $p<0.001$) between the weighted prevalence of frailty as defined by the physical phenotype (9.9%) versus the broad frailty definition (13.6%). However, due to the lack of information on sex distribution from some of the included studies, Collard et al. (2012) did not present sex-standardized estimates of frailty prevalence.

Blodgett et al. (2015) conducted a standardized comparison of a 4-item version of the frailty phenotype with a 46-item cumulative deficit frailty index using a sample of older

adults (mean age 63.4 years ± 10.3; n=4,096; 53.5% women) from the U.S National Health and Nutrition Examination Survey. The frailty phenotype assessed exhaustion, low physical activity, weakness, and low body weight, where 3-4 items indicated frailty, and 1-2 items indicated pre-frailty. The cumulative deficit index included a variety of comorbidities, disabilities, symptoms, and laboratory abnormalities. The prevalence of frailty according to the phenotypic index was 3.6% compared to 34% according to the 46-item cumulative deficit index. This is consistent with the previously mentioned findings that the cumulative deficit measurement identifies a greater proportion of the population as being frail, as compared with the phenotypic frailty approach.

The finding that the cumulative deficit definition reports higher prevalence of frailty than does the phenotypic definition is also supported by Shamliyan et al.'s (2013) systematic review of frailty in the elderly population (pooled estimates of 24% versus 14% by the cumulative deficit definition and the phenotypic definition respectively). This is likely due to the broader and more comprehensive definition of frailty used by the cumulative deficit measure compared to the phenotypic frailty measure.

1.3.2. Determinants of Frailty

1.3.2.1. Age

The prevalence of frailty has been shown to increase with age (Shamliyan et al., 2013). Shamliyan et al. (2013) conducted a systematic review of 24 studies assessing frailty prevalence in community-dwelling adults aged 65 or older, with a predominantly Caucasian sample population. According to studies using the cumulative deficit definition, the prevalence of frailty has been determined to range

from 5-15% for individuals aged 65-70, 8-17% for 70-80 year olds, and 16% or greater for those 80 years and older. Frailty prevalence reported by studies using the phenotypic definition ranges from 3-6%, 5-12%, and 16% or greater, across the same age groups, respectively. However, the heterogeneity of adjustment strategies across the studies synthesized limits the validity of these findings. Thus, the substantial ranges in frailty prevalence may be due to differences between the studies in year of data retrieval (from 1990 to 2010), as well as differences in sample characteristics (e.g. race, socioeconomic background, and country of origin).

Similarly, the previously mentioned systematic review by Collard et al. (2012) found four studies examining phenotypic frailty in community-dwelling older adults (65+ years old) according to age group; two of these studies were conducted in the U.S., while the other two were from Canada and Taiwan. After pooling the four studies' findings (N=8,869), frailty prevalence was found to increase with age ($\chi^2 = 6067$, $df = 1$, $P < 0.001$). As aforementioned, this systematic review is limited by its inability to control for age differences between men and women, likely resulting in overestimation of frailty prevalence attributed to the greater proportion of females in the study sample.

Using data collected in the Statistics Canada's National Population Health Survey, Rockwood et al. (2011) assessed the association between frailty, age, and mortality in men and women aged 15 years and older (N=14,127; mean age = 44.3 years (standard deviation = 18.3 years)). The study characterized frailty using a 42-item cumulative deficit index. Among participants between 15 to 39 years of age,

2.45% were categorized as frail (>18.9 deficits); among the 40 to 69-year-old cohort, 7.96% were frail; among participants 70 years and older, 22.2% were frail. Within each age group, 160-month mortality was higher among those who were frail (e.g. 16% for 40 year olds, and 83% for ages 75 and older) than among the relatively fit (≤ 1 deficit) (2% for 40 year olds, and 42% for ages 75 and older). Overall, the literature suggests that frailty both increases with age, and increases risk of death at each age.

1.3.2.2. Sex

In addition to increasing with age, frailty is also more prevalent among women. Pooled data from 11 community-based studies demonstrated that, at all ages of older adulthood, women were more frail than men, as reflected by higher mean cumulative deficit indices (Figure 1; Mitnitski et al., 2005). Each of the 11 studies calculated cumulative deficit indices using different sets of potential deficits. However, as previously mentioned, the precise variables included in a frailty index are not as important as the proportion of deficits calculated in an individual in assessing frailty (Rockwood et al., 2006). Moreover, in 10 of the 11 studies, approximately 40 deficits were considered (Mitnitski et al., 2005), permitting reasonable comparison between each study sample's respective index values.

Using the phenotypic definition, frailty is up to twice as prevalent among women than men by age group (Fried et al., 2001). The finding that women have greater frailty levels across multiple countries (Canada, U.S. Sweden, Australia), in

spite of different number and nature of deficits considered, and using different definitions of frailty suggests that this is a robust pattern (Mitnitski et al., 2005).

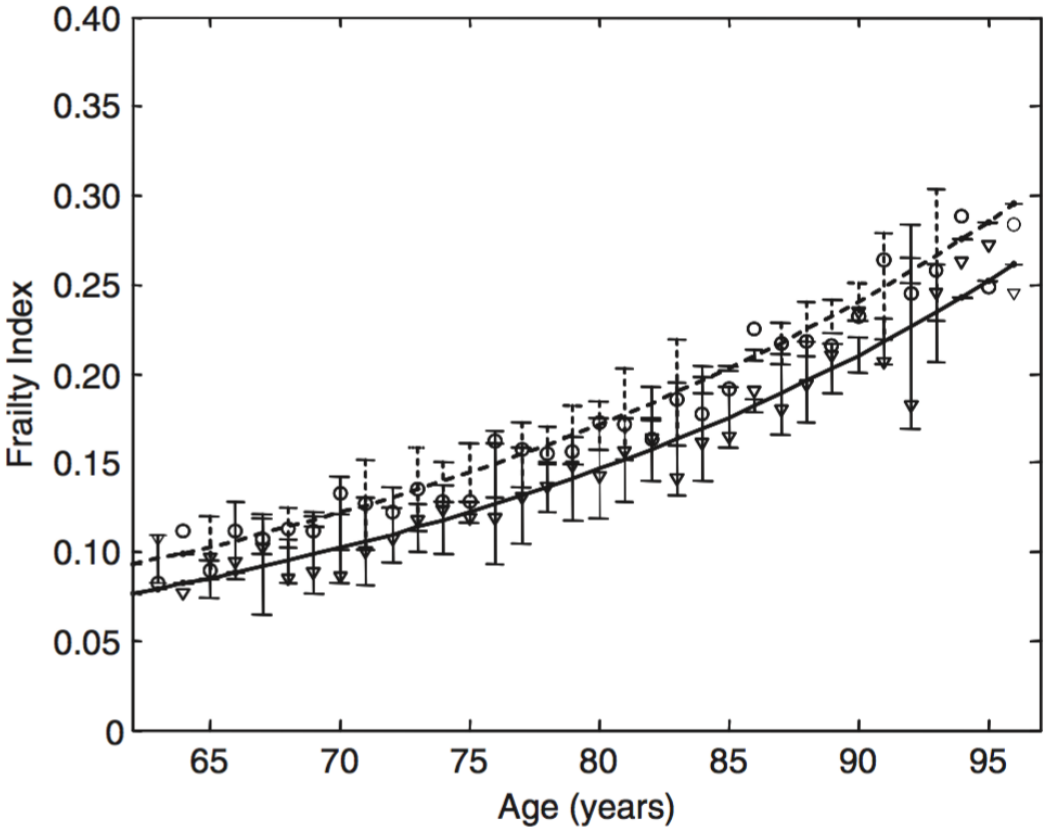


Figure 1. Sex differences in the relationship between mean values of frailty index (± standard error) and age. Women are represented with circles (dashed line), and men are represented with triangles (solid line). Lines are the least squares regressions (Mitnitski et al., 2005).

1.3.2.3. National Socioeconomic Indicators

Eighty percent of the global burden of chronic diseases, including heart disease, stroke, and cancer, occur in low- and middle-income countries (LMICs) (WHO,

2005), so it is likely that a substantial proportion of the global burden of frailty lies in LIMC. There is limited research on the prevalence of frailty in LMIC settings, however (Table 2). A literature search on PubMed using the terms "frailty", "low or middle", "socioeconomic or income" and "country or nation" (using the "AND" Boolean between terms) identified 15 results, among which four were relevant to studying frailty in low or middle income countries (LMICs). A summary of the four studies follows below:

1. Nguyen, Cumming & Hilmer (2015) reviewed 14 articles (9 of community-based individuals and 5 of hospital-based individuals) assessing frailty in various developing countries (Brazil, China, Mexico, Russia, India, and Peru) and found higher frailty rates (Table 2) compared to those reported in developed countries. A limitation of this review is that age distributions among the studies included were not comparable due to differences in reporting. However, except for one study, in which 40% of its participants were 90 years old and older, most the subjects were in their 70s. This age group is comparable to the weighted mean age of the systematic reviews of studies from developed countries, summarized previously in Table 2.
2. A systematic review by Gray, Richardson, & McGuire et al. (2016) assessed the frailty prevalence in LMICs. They identified 36 studies of either community-dwelling individuals or of hospital inpatients (across Medline, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PyschINFO databases) that all assessed frailty using the

frailty phenotype. Among these studies, the median sample size was 569 (interquartile range (IQR) 212 - 1,845), and the countries assessed included: Barbados, Brazil, Chile, Cuba, Colombia, Peru, Mexico, India, and China. In these studies, frailty prevalence estimates ranged from 5.2% (elderly Brazilians who work as caregivers) to 39.2% (urban-dwelling Mexicans aged 70+).

Gray et al. (2016) found twenty community-based LMIC studies that used the cumulative deficit frailty definition. Their median sample size was 3,257 (IQR 2,032-3,847), and the countries included were: China, India, Mexico, Iran, South Africa, and Ghana. Using different frailty index cutoffs, prevalence estimates ranged from 11.6% (people aged 65+ living in China; index cutoff of 0.25), 17.8% (Beijing; ages 55+; cutoff of 0.20), to 27.8% (Mexico; ages 65+; cutoff of 0.20). However, the review could not critically appraise the prevalence of frailty across LMICs due to wide differences in index cutoffs used to define frailty, age cutoffs, data collection methods, and study settings (i.e. community versus hospital). Moreover, only India and Ghana are considered LMICs by the World Bank, whereas Barbados and Chile are considered HIC, and the remaining countries are considered UMIC (World Bank, 2016).

3. One study specifically compared frailty index values among the higher income countries found in the Survey of Health, Ageing and Retirement in Europe (SHARE) database and the lower middle income countries (LMICs)

surveyed in the World Health Organization's SAGE (Study on Global AGEing and Adult Health) (Harttgen, Kowal, Strulik, Chatterji & Vollmer, 2013). The study analyzed levels of frailty in community-dwelling older people (between 50-85 years old), and used variables that were available in both SHARE and SAGE to create two almost identical cumulative deficit frailty indices (39-items and 40-items, respectively) (Table 3). The indices were weighted based on the WHO World Standard population age distribution to facilitate the global comparison. Both SHARE and SAGE used standardized training and survey materials to collect prospective data during face-to-face interviews. SAGE used multistage cluster sampling strategies to maintain nationally representative cohorts (WHO, 2017). SHARE used differing sampling strategies depending on the country, including: single or multi-stage sampling using regional/local population registers, multi-stage sampling using telephone directories, and simple random sampling from national population registers (SHARE, 2016). Harttgen et al. (2013) used data from the second wave of SHARE (from 2006-2007) and the first wave of SAGE (2007-2010) because of their similar timing.

Harttgen et al. (2013) concluded that lower middle income countries (SAGE) had less frailty, as reflected by their lower cumulative deficit frailty indices, compared to higher income countries (SHARE) (Figure 2). However, it is possible that the lower frailty index found in LMICs are explained by ascertainment bias of individual medical

conditions – i.e. LMICs may in general have lower rates of health and deficit diagnoses compared with higher income countries due to differences in health care resources and medical practices (Gray et al., 2016). Moreover, according to the World Bank income categories of 2003 (the time of SAGE's first wave of cohorts), Mexico, Russia and South Africa are classified as UMIC countries. Consequentially, the levels of frailty found in the SAGE countries are not representative of LMICs.

Harttgen et al. (2013) did not report the exact questions used in each of the SHARE and SAGE studies; however, the respective questionnaires are publicly available online. Although the questions used to compare frailty between SHARE and SAGE were similar, slight differences in defining each variable may have biased the results. For example, in reporting the presence of bodily pain or difficulty sleeping, participants in SHARE were asked about the previous six months, whereas participants in SAGE were only asked about the previous thirty days (WHO, 2017; SHARE, 2016). Moreover, 22 of the questions included in Harttgen et al. (2013) were asked in a "yes or no" format in the SHARE study, compared with a five-point scale offered in SAGE. As a result, participants in the SHARE study who reported symptoms may have appeared to be more frail than participants in the SAGE study experiencing similar symptoms, who could rank their symptom as less severe. Thus, Harttgen et al. (2013)'s finding that the HICs in SHARE had greater frailty levels than LICs in SAGE may be partly attributed to this methodologic inconsistency.

Table 3. List of variables assessed in the SHARE and SAGE frailty indices (Harttgen et al., 2013)

	SHARE	SAGE
Topic/Variable	**Response categories and cut-points**	
General Health (1): Self-rated health	**Very Good = 0, Good = 0.25, Moderate = 0.50, Bad = 0.75, Very Bad = 1**	
Medically diagnosed conditions (9)	**1 = yes, 0 = no**	
Arthritis	✓	✓
Asthma	✓	✓
Cataracts	✓	✓
Chronic Obstructive Pulmonary Disease	✓	✓
Depression	✓	✓
Diabetes	✓	✓
Hypertension	✓	✓
	Parkinson's Disease	Angina
Stroke	✓	✓
Medical symptoms (3 (SHARE) or 4 (SAGE)). In the last 30 days how much…*	**None = 0, Mild = 0.25, Moderate = 0.50, Severe = 0.75, Extreme/cannot = 1**	
Bodily aches or pains did you have?	N/A	✓
Of a problem did you have with sleeping?	✓	✓
Difficulty did you have in seeing (person or object) across the road?	✓	✓
Difficulty did you have in seeing an object at arm's length?	✓	✓
Functional activities assessment (13). In the last 30 days how much difficulty did you have with…	**1 = yes, 0 = no**	**None = 0, Mild = 0.25, Moderate=0.50, Severe = 0.75, Extreme/Cannot = 1**
Sitting for long periods of time	✓	✓
Walking 100 meters	✓	✓
Standing up from sitting down	✓	✓
Standing for long periods of time	✓	✓
Climbing one flight of stairs without resting	✓	✓
Stooping, kneeling or crouching	✓	✓
Picking things up with fingers	✓	✓
Extending arms above shoulders	✓	✓
Concentrating for 10 minutes	✓	✓
Walking long distances (1 km)	✓	✓
Carrying things	✓	✓
Getting out of your home	✓	✓
Enjoy what you are doing	✓	✓
Activities of daily living (10). In the last 30 days how much difficulty did you have with…	**1 = yes, 0 = no**	**None = 0, Mild = 0.25, Moderate=0.50, Severe= 0.75, Extreme/Cannot = 1**
Taking care of your household responsibilities	✓	✓
Joining community activities	✓	✓
Bathing/washing	✓	✓
Dressing	✓	✓
Day-to-day work	✓	✓
Moving around inside home	✓	✓
Eating	✓	✓
Getting up from lying down	✓	✓
Getting to and using the toilet	✓	✓
Getting where you want to go	(Using a map outside the house)	(Using private or public transport if needed)

BMI (1): (Weight in kg)/(Height in meters)^2	BMI ≥ 18.5 - < 25 = **0 (Normal)**
	BMI ≥ 25 - < 30 = **0.5 (Overweight)**
	BMI < 18.5 = **1 (Normal)**
	BMI ≥ 30 = **1 (Obese)**
Grip strength (1): Grip (in kg), (Left + right hand)/2	(Male and 0<BMI≤24 and grip ≤ 29)
	Or
	(Male and 24<BMI≤26 and grip ≤ 30)
	Or
	(Male and 26<BMI≤28 and grip ≤ 30)
	Or
	(Male and 28<BMI≤40 and grip ≤ 32)
	Or
	(Female and 0<BMI≤23 and grip ≤ 17)
	Or
	(Female and 23<BMI≤26 and grip ≤ 17.3)
	Or
	(Female and 26<BMI≤29 and grip ≤ 18)
	Or
	(Female and 29<BMI≤40 and grip ≤ 21)
	= 1 (Weak grip)
Timed walk at usual place (1)	(≤ 0.4 m/sec) = **1 (Slow)**
	(> 0.4 m/sec) = **0 (Normal)**

Note: * SHARE used a 6-month time frame for assessing bodily pain and trouble sleeping, and did not specify a time frame for difficulties seeing objects at a distance or at arm's length.

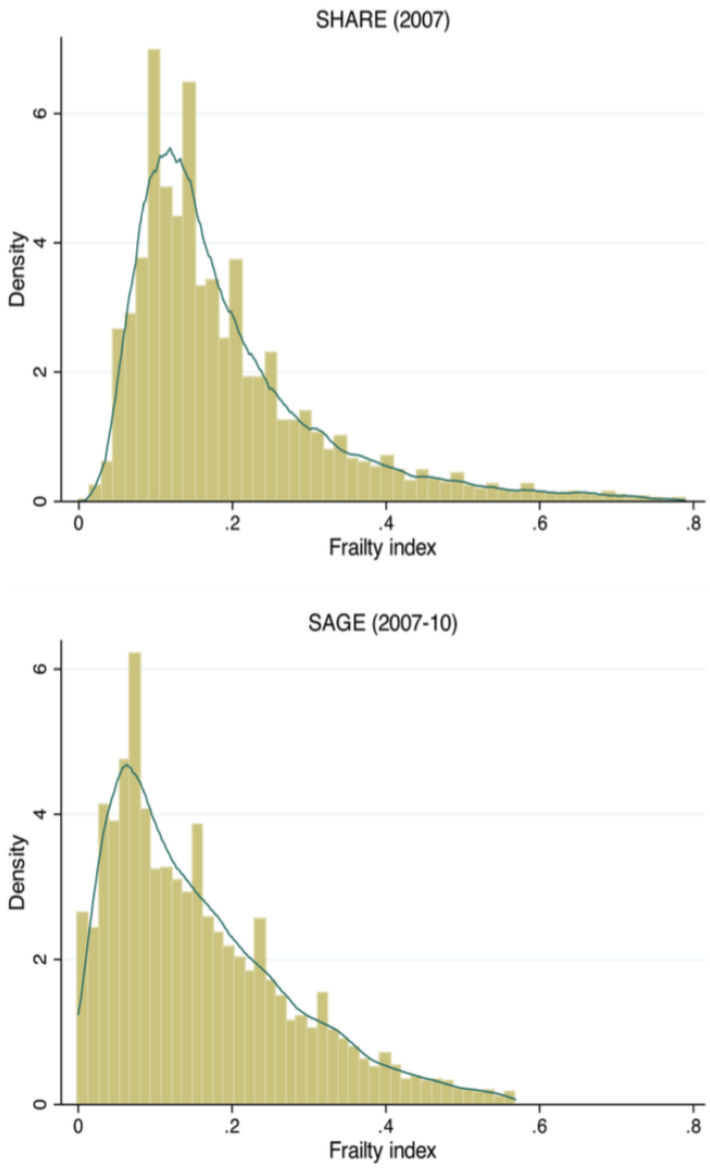


Figure 2. Distribution of frailty index scores by higher income- (SHARE) and lower income- (SAGE) country studies (Harttgen et al., 2013).

Note: SHARE was used in higher income countries (Denmark, Ireland, Netherlands, Germany, Czech Republic, Austria, Italy, Switzerland, Sweden, Greece, France, Belgium, Spain, and Poland) and SAGE was used in lower/middle income countries (China, Mexico, Ghana, South Africa, India, and Russia)

Theou et al. conducted a study that examined frailty patterns within the SHARE cohort (i.e. higher income European countries). The study concluded that the prevalence of frailty was lower in countries with higher GDP (Gross Domestic Product) per capita (Figure 3) (Theou et al., 2013b). Countries were categorized as lower-income if their GDP per capita was between $14,652 - 28,227, and higher-income if their GDP per capita was between $29,222 - $41,137. The study used a 70-item cumulative deficit index consisting of measures of physical health, cognitive ability, behavioural risks, and mental health. The study included non-institutionalized adults aged 50 or older, and had similar age and sex distributions between the lower-income and higher-income countries (median age and standard deviation of 65.0 years ± 0.78 versus 65.0 years ± 0.63, respectively; and 55.0% versus 54.2% women, respectively). The methodology for data retrieval by the SHARE study was previously described on page 17. Countries with higher GDP per capita had lower frailty even after limiting the sample to 50-64 year olds, an age group that is less likely to be affected by varying institutionalization practices between countries. Moreover, 24-month survival of frail individuals was greater in countries with higher GDP per capita, even after adjusting for age and sex (Figure 4). The trend in the data by Theou et al. (2013b) resembled the findings by Harttgen et al. (2013), where among the SHARE countries, the highest mean frailty indices were observed in Italy, Spain, and Poland, and the lowest frailty levels were observed in Denmark, Switzerland, and Ireland.

Theou et al.'s findings may be attributed to the lower health care expenditure in countries with lower GDP per capita. Health care expenditure may have an important

impact on the prevention, diagnosis, and management of diseases. Thus, the greater health care expenditure among higher-income countries may contribute to lower incidence and improved 24-month prognosis of potentially lethal illnesses. However, a limitation of this study is its limited range of country incomes. The countries indicated as "lower-income countries" in the study are all considered high income or upper middle income countries by the World Bank (World Bank, 2016).

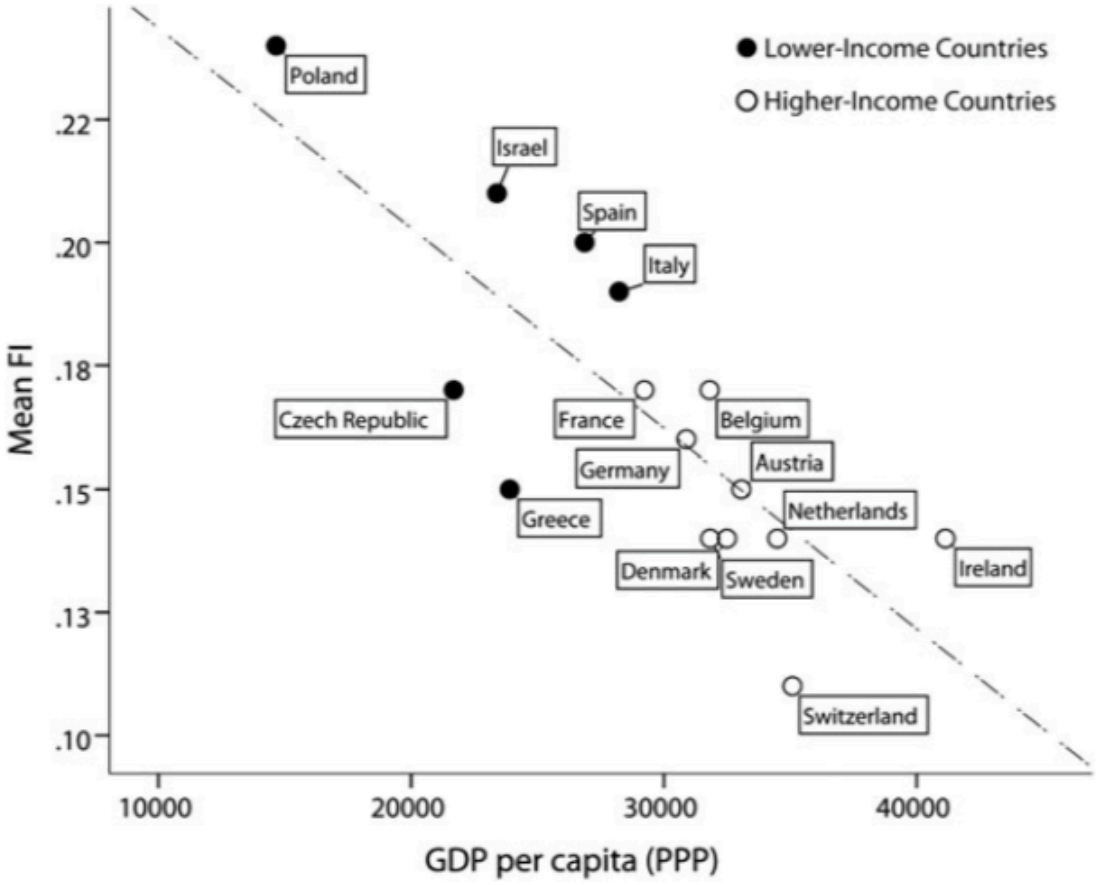


Figure 3. Mean frailty index scores by GDP per capita, within the SHARE cohort (Theou et al., 2013b)

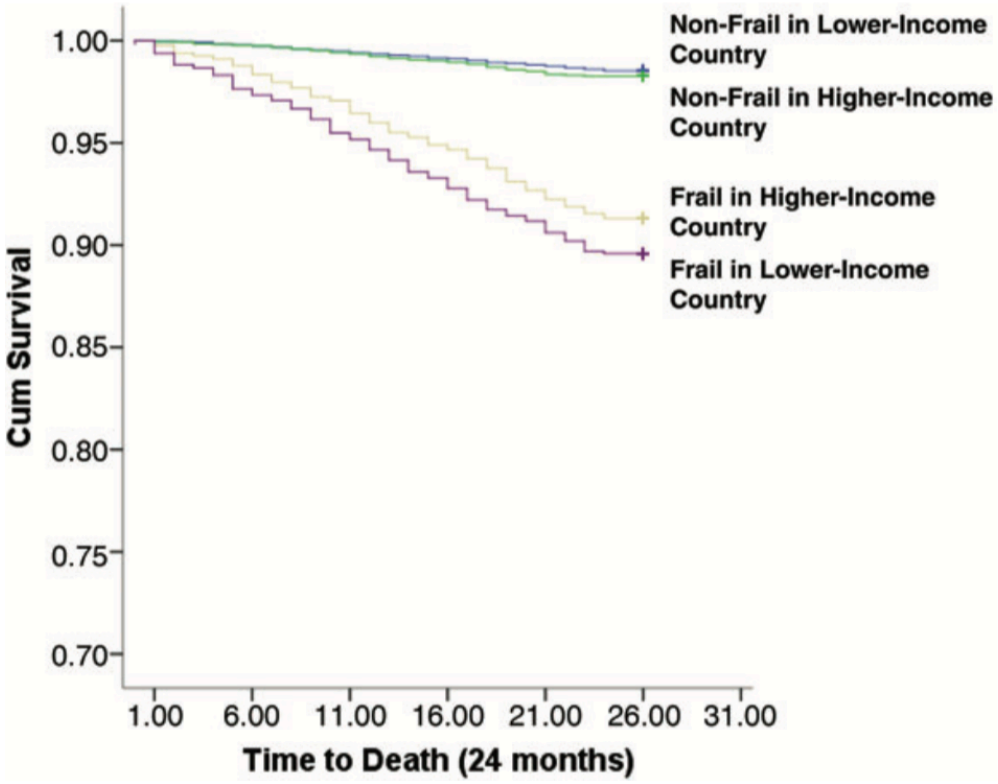


Figure 4. Survival after 24 months by frailty and country income (Theou et al., 2013b)

Together, the findings suggest that frailty level may be greater among HICs (SHARE) than lower-income countries (including the UMICs, LMICs, and LICs as represented in SAGE), but inversely associated with country GDP within HICs. However, the comparison between HICs (SHARE) and lower-income countries (SAGE) by Harttgen et al. (2013) may not be a robust finding due to the previously discussed methodologic differences between the two studies. Further research would be needed to better understand the different factors associated with frailty prevalence across country incomes.

4. The last study identified (Brothers, Theou, & Rockwood, 2014) also used the SHARE database to compare frailty levels among European adults (mean age and standard deviation 64.9 years ± 10.2; 54% females) who were 1) native-born, 2) immigrants born in LMICs, or 3) immigrants born in HICs. Country income classification was based on the 2007 World Bank Development Report. The study used the SHARE survey to develop a 70-item cumulative deficit frailty index. Brothers et al. (2014) found a significant interaction effect for frailty between current region of residence (Northern/Western Europe versus Southern/Eastern Europe) and migrant group (native-born, immigrant born in LMIC, or immigrant born in HIC) (p=0.02). Among those living in Northern/Western Europe, frailty index values were greater in LMIC-born immigrants (adjusted mean index 0.18 (95% CI 0.17-0.19) than both HIC-born immigrants (mean index 0.16 (95% CI 0.16-0.17)) and native-borns (mean index 0.15 (95% CI 0.14-0.15)), after adjusting for age, gender, and education (p<0.001). This finding suggests that frailty in older adulthood is partially influenced by the national socioeconomic and environmental factors from an earlier age. However, although the study adjusted for education, it is possible that the differences in frailty are associated with another socioeconomic factor, such as wealth. Alternatively, the differences in frailty found among Northern/Western Europeans based on their country of birth could be attributed to heredity. In contrast, among those currently living in Southern/Eastern Europe, there was

no significant difference in frailty between migrant groups (p=0.2; Figure 5). This suggests that, in certain cases, the current country of residence may be a more significant determinant of frailty than the country of birth. Thus, the study concluded that frailty among older adults is associated with social and environmental factors over an individual's lifespan.

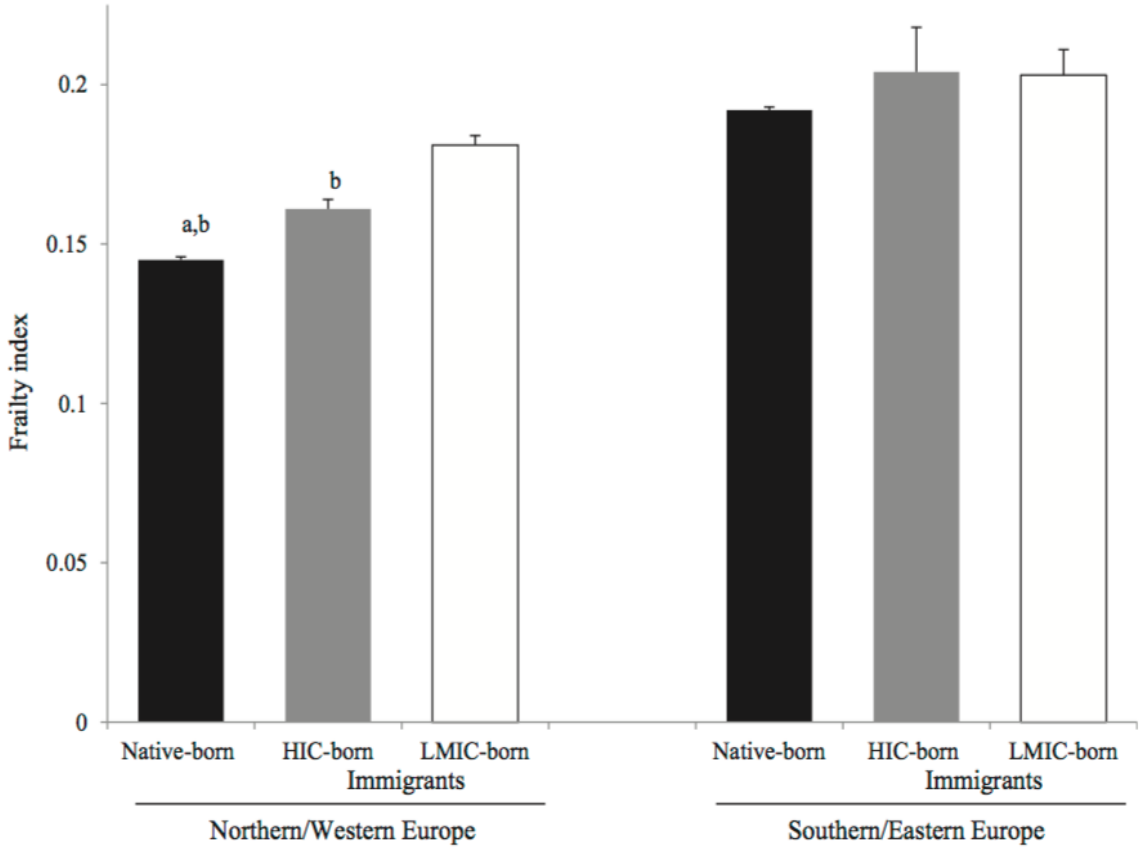


Figure 5. Mean frailty indices ± standard error according to region of residence and migration status. Adjusted for age, gender, and lower education (Brothers et al., 2014)

Among the relatively few studies assessing frailty in LMIC countries, only a small proportion examine low income countries. Even fewer studies use standardized

methods to directly compare frailty between LIC and HICs. Of importance, variations in study designs and definitions of frailty limit the generalizability and cross-comparison of these studies. Although there are mixed findings, the overall patterns suggest that frailty may be associated with living or being born in low income countries.

1.3.2.4. Individual Socioeconomic Status

Frailty has been demonstrated to be inversely associated with individual socioeconomic status in a population of community-dwelling adults (65+ years old) in England (mean age = 74 years old; n=4,818; 55% female) (Lang, Hubbard, Andrew, et al., 2009). Lang et al. (2009) used a 58-item cumulative deficit to assess frailty. In this study, lower individual wealth, as measured by total household assets, was associated with a higher frailty index after adjusting for age, sex, education, degree of urbanization, and duration of residence in their current neighborhood (Table 4). However, since this was a cross-sectional study, the causal relationship between frailty and socioeconomic status could not be inferred.

Table 4. Linear regression analyses of association between individual wealth and cumulative deficit frailty index (Lang et al., 2009)

Wealth Quintiles	Number of deficits (total of 58 items in the Frailty index) (95% Confidence Interval)
Highest	Reference
4th	0.580 (0.116-1.04)
3rd	0.928 (0.406-1.45)
2nd	1.86 (1.22-2.49)
Lowest	3.02 (2.32-3.71)

Note: Model adjusted for age, sex, degree of urbanization, duration of residence in neighbourhood, and age of completion of full-time education.

1.4. SIGNIFICANCE OF STUDYING FRAILTY

1.4.1. Prognostic Importance of Frailty

Frailty is used by general practitioners to aid in assessing risks, predicting outcomes, and evaluating potential interventions (De Lepeleire, Iliffe, Mann, & Degryse, 2009). Even when measured in different ways, frailty is associated with increased mortality, morbidity, functional and cognitive impairment, major adverse cardiac and cerebrovascular events, falls, disability, institutionalization and hospitalization (Sepehri et al., 2014; Theou, Brothers, Mitnitski & Rockwood, 2013).

1.4.2. Reversibility of Frailty

Despite its associated adverse outcomes, frailty is seen to be a treatable condition, with evidence supporting the efficacy of exercise, caloric and protein support, vitamin D, and reduction of polypharmacy (Morley et al., 2013).

Ng, Feng, Nyunt et al. (2015) conducted a randomized controlled trial to compare the efficacy of four different interventions in lowering frailty over 12 months: nutritional supplementation, cognitive training, physical training, combination treatment, and a standard care control. Participants in the nutritional intervention group were given daily standardized doses of carbohydrate, fat, protein, dietary fiber, iron, folate, vitamin B6, vitamin B12, calcium, and vitamin D supplements. The nutritional supplements were designed to increase caloric intake by approximately 20% and provide one third of the recommended daily allowances of vitamins and minerals. The cognitive training intervention consisted of weekly two-hour sessions of activities designed to enhance short-term memory, attention, information-processing, and problem-solving skills. The physical intervention was designed to improve strength and balance, and consisted of 90 minutes of moderate activities twice a week in gradually increasing levels of intensity. In the combination treatment group, individuals participated in all three of the previous interventions. Lastly, participants in the control group were given access to standard care and placebo tablets (which appeared identical to the nutritional supplements). Frailty reduction during follow-up was defined as transitioning to a lower frailty category from baseline (e.g. transition from frail to pre-frail).

The trial recruited a sample of 246 pre-frail and frail community-dwelling residents aged 65 years and older who were living in Singapore and able to walk without personal assistance (mean age and standard deviation 70.0 years ± 4.7; 61% female) (Ng et al., 2015). Participants were identified as pre-frail or frail according to the phenotypic frailty index; individuals with a score of 1 to 2 or 3+ out of 5 components (unintentional weight

loss, weakness, slowness, exhaustion, and low physical activity) were classified as pre-frail and frail, respectively. Significant weight loss was measured as the loss of 10 pounds (4.5 kg) or more within the last six months, or a body mass index of <18.5kg/m^2. Using a 6-meter fast gait speed test, the lowest quintile of values, stratified for height and age, was defined as slowness. Weakness was defined as being in the lowest quintile, by sex and BMI quartile group, for a knee extension test. Exhaustion was denoted as having the lowest quintile of energy score, determined from self-reported answers on the vitality domain of the Medical Outcomes Study SF-12 scale. Low physical activity was denoted as being in the lowest quintile for the average daily time spent on physical activities. Participants were randomly allocated to an intervention or control group using a central, computerized process. Dropout rates were 8% for the nutritional supplementation group, 4% for the physical training group, 6% for the combination intervention, and 8% for the control group (Ng et al., 2015).

At 12 months, frailty score was reduced across all five groups (including the control group) (Table 5; Ng et al., 2015). However, frailty reduction rates were significantly higher among the four intervention groups (ranging from 35.6-47.8% in each intervention cohort) compared to the control group (15.2%) (Table 5). The combination intervention was associated with the highest odds of frailty reduction (Odds ratio, OR 5.00; 95% CI 1.88-13.3) relative to the control group, followed by the physical intervention (OR 4.05; 95% CI 1.50-10.8), nutritional intervention (OR 2.98; 95% CI 1.10-8.07), and cognition intervention (OR 2.89; 95% CI 1.07-7.82) (Table 5). Knee strength improved among participants in the cognition, physical, and combination groups; physical activity increased

significantly among the nutrition and combination group; gait speed improved in the physical intervention group; and energy improved among participants in the combination intervention group (Table 5).

Thus, given the evidence that frailty may be slowed and even reversed by various interventions (De Lepeleire et al., 2009), early assessments of frailty may enable individuals to seek proper care and management.

Table 5. Participant baseline characteristics and effects of 12-month nutritional, physical, cognitive, and combination interventions on frailty reduction compared to control group (Ng et al., 2015).

Results	Interventions				Control (n=50)
	Nutritional (n=49)	Cognitive Training (n=50)	Physical Training (n=48)	Combination (n=49)	
Baseline Characteristics					
Age, mean (SD)	69.7 (4.23)	69.7 (4.31)	79.3 (5.25)	70.4 (4.74)	70.1 (5.02)
Male, n (%)	17 (34.0)	12 (24.0)	21 (43.8)	23 (46.9)	22 (44.0)
Baseline frailty score (mean, SD)	2.1 (0.78)	2.0 (0.91)	2.2 (0.85)	2.1 (0.81)	1.8 (0.80)
Baseline Frailty components, n (%)					
Weight loss	2 (4.10)	2 (4.00)	3 (6.30)	1 (2.00)	3 (6.00)
Slowness	20 (40.8)	13 (26.0)	23 (47.9)	17 (34.7)	15 (30.0)
Weakness	26 (53.1)	28 (56.0)	26 (54.2)	25 (51.0)	20 (40.8)
Exhaustion	7 (14.3)	10 (20.0)	7 (14.6)	8 (16.3)	6 (12.0)
Low physical activity	9 (18.4)	12 (24.0)	11 (22.9)	16 (32.7)	5 (10.0)
Outcomes after 12 months					
Frailty reduction n (% yes)	16 (35.6)	16 (35.6)	19 (41.3)	22 (47.8)	7 (15.2)
Odds ratio of frailty reduction OR (95% CI)	2.98 (1.10-8.07)	2.89 (1.07-7.82)	4.05 (1.50-10.8)	5.00 (1.88-13.3)	1.00 (Reference)
Mean change in frailty score from baseline (95% CI)	-0.63 (-0.92, -0.34)	-0.62 (-0.91, -0.33)	-0.83 (-1.12, -0.54)	-0.92 (-1.21, -0.64)	-0.14 (-0.43, -0.14)
Mean change in frailty components from baseline (95% CI)					
BMI, kg/m^2	0.03 (-0.34-0.40)	-0.22 (-0.59-0.14)	-0.03 (-0.40-0.33)	-0.22 (-0.58-0.15)	0.12 (-0.25-0.48)
Knee strength, kg	1.01 (-0.09-2.12)	1.98 (0.87-3.09)	1.41 (0.31-2.51)	2.35 (1.25-3.44)	-0.24 (-1.34-0.87)
Physical activity	110.1 (71.9-148.2)	10.2 (-43.4-63.8)	36.5 (-1.53-74.5)	40.2 (2.30-78.1)	34.9 (-2.99-72.6)
Slowness (6-meter gait speed test), s	-0.64 (-1.08, -0.20)	-0.16 (-0.59-0.28)	-1.14 (-1.58-0.70)	-0.01 (-0.45-0.43)	-0.41 (-0.84-0.03)
Energy	0.94 (0.34-1.57)	1.01 (0.38-1.64)	0.65 (0.02-1.28)	1.32 (0.70-1.95)	0.30 (-0.33-0.92)

Note: Only pre-frail and frail participants were allocated into the intervention or control groups.

1.4.3. Frailty and Multi-morbidity

The cumulative deficit approach suggests that frailty, along with its associated adverse prognoses, is defined by the accumulation of impairments and diseases. It is also

known that the presence of multiple chronic diseases, known as multi-morbidity, leads to greater risk of mortality and disability than would be expected from individual diseases alone (Verbrugge, Lepkowski, & Imanaka, 1989). Given that both conditions have related outcomes and similar defining features, frailty and multi-morbidity have often been used interchangeably to identify physically vulnerable older adults (Fried, Ferrucci, & Darer, et al. 2004). Indeed, both are significant factors in the health of older adults, and thus increasingly important given the world's aging population (United Nations, 2013). However, frailty and multi-morbidity are separate entities that can each occur in the absence of the other (Fried et al., 2004). Consequentially, in the study of frailty it is important to also discuss the related, yet distinct, concept of multi-morbidity.

1.5. MULTI-MORBIDITY

1.5.1. Introduction

As mentioned, multi-morbidity refers to the co-existence of two or more chronic physical or mental conditions in the same individual (Woo & Leung, 2014; Marengoni et al., 2011). Among Canadian adults diagnosed with multi-morbidity, the most frequently reported chronic diseases from a list of nine include: arthritis (overall population prevalence = 17.6%), mental disorders (11.2%) and asthma (8.1%) (Roberts, Rao, Bennett, Loukine, & Jayaraman, 2015). A systematic literature review by Marengoni et al. (2011) found that the number of publications on multi-morbidity has rapidly increased between the years 1990 and 2010, with 40% of multi-morbidity articles having been published between 2008-2010 (Figure 6).

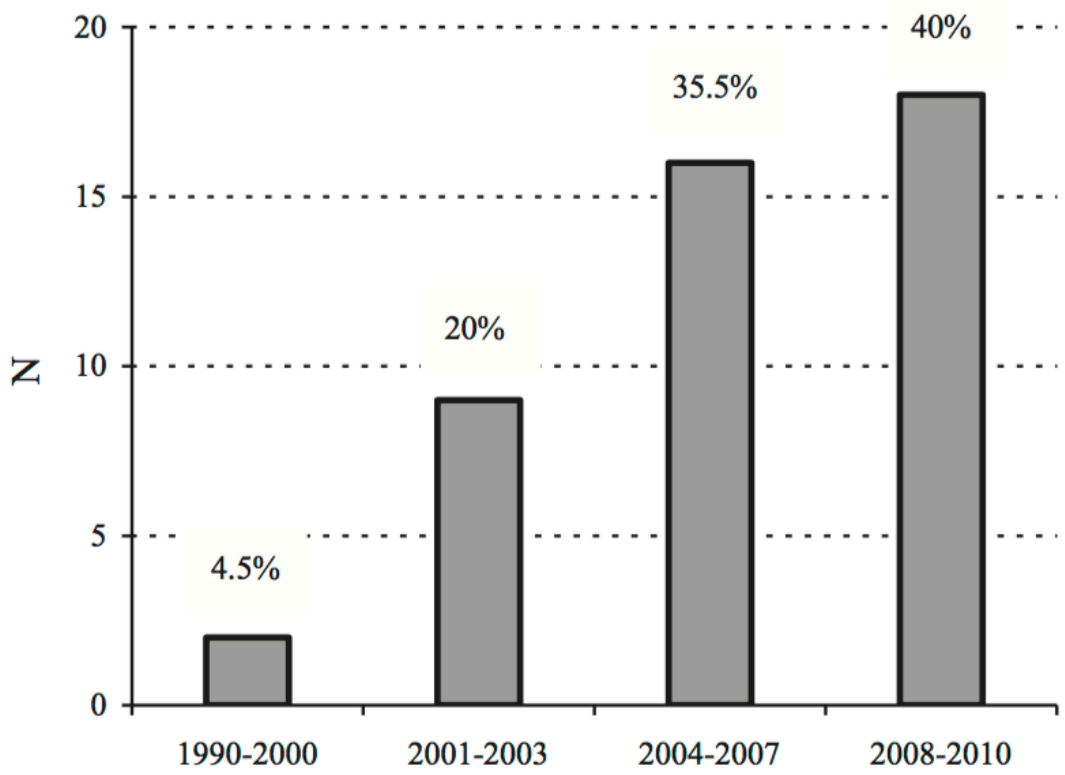


Figure 6. Number and proportion (per 100) of articles on multi-morbidity published between the years 1990 to 2010 (Marengoni et al., 2011).

Despite the growing literature on multi-morbidity, it currently has no gold standard for measurement. The Charlson comorbidity index is a frequently cited instrument for predicting mortality for patients based on both the number and severity of their comorbid diseases (Needham, Scales, Laupacis, & Pronovost, 2005; Charlson, Pompei, Ales, et al. 1987). The Charlson index was developed using one-year mortality rates from 604 patients admitted to a medical centre (Charlson et al., 1987). Based on the adjusted relative risks of each comorbid disease, each condition was assigned a weight of either 1, 2, 3, or 6 (Table 6). Relative risks were adjusted for coexistent comorbid diseases, illness severity, and

reason for admission to the medical centre. Charlson et al. (1987) validated the index's ability to predict mortality attributed to comorbidity in 685 female breast cancer patients. Individuals were categorized into four ranks by their total index value: 0, 1-2, 3-4, and >5. For each increasing index rank, 10-year survival rates were 94%, 78%, 72%, and 51%, respectively. The adjusted relative risk for death with each increasing index rank was 2.0 (95% CI 1.6-2.4). A strength of the Charlson comorbidity index is that it is a relatively simple instrument for estimating risk of death from comorbidity.

Table 6. Weighted Charlson comorbidity index (Charlson et al., 1987)

Assigned weight	Conditions	
1	Myocardial infarction	Connective tissue disease
	Congestive heart failure	Ulcer disease
	Peripheral vascular disease	Mild liver disease
	Cerebrovascular disease	Diabetes
	Chronic pulmonary disease	Dementia
2	Hemiplegia	Leukemia
	Moderate or severe renal disease	Lymphoma
	Diabetes with end organ damage	Any tumour
3	Moderate or severe liver disease	
6	Metastatic solid tumour	
	AIDS	

1.5.2. Prognostic Importance and Prevalence of Multi-morbidity

Similar to frailty, multi-morbidity has been found to increase an individual's risk of several adverse outcomes, including: death, hospitalization, institutionalization, disability, poor quality of life, and health care costs, even after for adjusting for multiple covariates (Charlson et al., 1987; Glynn et al., 2011; Marengoni et al., 2011).

The reported prevalence of multi-morbidity has a broad range, which is generally higher than reported estimates for frailty (Morley et al., 2013); the lowest estimates of multi-morbidity vary from 20-30% of the whole population and 55-98% of the elderly population (60+ year olds) (Marengoni et al., 2011). Moreover, in a study assessing the prevalence and overlaps of multi-morbidity and frailty in community-dwelling adults aged 65 and older, 93% of the sample had multi-morbidity compared to only 13% who were frail (n=2,762) (Fried et al., 2001). The study used the phenotypic definition of frailty, and defined multi-morbidity as the presence of two or more of the following diseases: myocardial infarction, angina, congestive heart failure, claudication, arthritis, chronic obstructive pulmonary disease (COPD), hypertension, diabetes, and cancer (Fried et al., 2001).

1.5.3. Multi-morbidity, Country Income, and Socioeconomic Status

Garin, Koyanagi, & Chatterji, et al., (2016) used data from the Collaborative Research on Ageing in Europe project (COURAGE) and the WHO's SAGE study to explore global multi-morbidity patterns among non-institutionalized older adults (50+ years old). The study included data from a total of 41,909 participants, with a mean age ranging from 65.1 (India) to 66.3 years old (Spain). At the time of entry into the surveys, the COURAGE (studying Spain, Finland, and Poland) and SAGE (China, India, Russia, South Africa, Ghana, and Mexico) surveys represented high-income and low/middle-income countries, respectively, as determined by the World Bank Classification. Multi-morbidity was defined in this study as having two or more of: angina, arthritis, asthma,

cataract, COPD, depression, diabetes, edentulism, hypertension, cognitive impairment, obesity, and stroke. The countries with the greatest proportion of its population exhibiting multi-morbidity were mostly HIC, including Poland (69.39%, n=2,041), Spain (68.73%, n=2,478), and Finland (68.25%, n=1,005). The countries with the smallest proportion of its population experiencing multi-morbidity were China (UMIC; 45.07%, n=6,115) and Ghana (LMIC; 48.30%, n=2,050) (Table 7). The association between higher country income and multi-morbidity may be attributed in part to a survival bias resulting from better medical management and healthcare systems. Better resources for managing chronic diseases, such as asthma and diabetes, may allow affected individuals in HIC to live longer and thus have more opportunity to develop co-morbidities.

Table 7. Prevalence of multi-morbidity across high- and low/middle- income countries among non-institutionalized older adults (50+ years old) arranged in ascending order of country income (Garin et al., 2016)

Characteristics	LMIC	LMIC	UMIC	UMIC	UMIC	UMIC	HIC	HIC	HIC
	Ghana	India	South Africa	China	Mexico	Russia	Poland	Spain	Finland
Mean Age (years) (SD)	64.37 (19.86)	61.48 (13.66)	61.61 (18.42)	62.57 (16.67)	63.04 (18.94)	63.91 (15.44)	64.18 (13.07)	66.26 (14.78)	64.37 (12.26)
Female (n, %)	2,056 (47.55)	3,256 (49.01)	2,201 (55.95)	6,990 (50.25)	1,393 (53.19)	2,432 (61.12)	1,765 (56.50)	1,982 (53.65)	834 (53.97)
Multi-morbidity (n, %)	2,050 (48.30)	3,799 (57.92)	2,376 (63.44)	6,115 (45.07)	1,581 (63.89)	2,779 (71.93)	2,041 (69.39)	2,478 (68.73)	1,005 (68.25)

Garin et al., (2016) also used multivariable logistic regression, adjusting for age, sex, education, wealth, marital status, urbanicity, to examine the association between multi-morbidity and markers of socioeconomic status. After adjustment, having only primary education or less was associated with increased odds of multi-morbidity compared to tertiary education in all countries except for Ghana (OR 0.99 (0.64-1.51). Individual socioeconomic deprivation was associated with multi-morbidity in China, Finland, and Poland, but negatively associated with multi-morbidity in Ghana and South Africa (Table 8). The findings for Ghana and South Africa may be attributed to the consumption of high-calorie foods within wealthier households in Africa, resulting in greater prevalence of obesity and other cardiovascular risk factors (Averett, Stacey & Wang, 2014). Moreover, the multivariable logistic regression may have been over-adjusted, having included both wealth and education. The mixed findings on the association between multi-morbidity and individual wealth suggest that further studies need to be conducted to better understand this relationship.

Table 8. The relationship between wealth (as measured by education and wealth quintile) and multi-morbidity among non-institutionalized older adults (50+ years old) (Garin et al., 2016). The estimates presented are odds ratios (95% confidence intervals) adjusted for age, sex, marital status, urbanicity compared to those with tertiary education and less than the lowest quintile of wealth respectively.

Characteristics Category		Ghana	India	South Africa	China	Mexico	Russia	Poland	Spain	Finland
Female (n, %)		2,056 (47.55)	3,256 (49.01)	2,201 (55.95)	6,990 (50.25)	1,393 (53.19)	2,432 (61.12)	1,765 (56.50)	1,982 (53.65)	834 (53.97)
Education	≥ Tertiary	1	1	1	1	1	1	1	1	1
	Secondary	1.73 (1.14-2.63)	1.82 (1.01-3.25)	1.08 (0.88-1.34)	0.96 (0.31-2.93)	1.46 (1.06-2.02)	1.72 (1.12-2.62)	1.21 (0.79-1.85)	2.06 (1.39-3.06)	1.22 (0.99-1.50)
	≤ Primary	1.97 (1.33-2.91)	1.66 (0.89-3.11)	1.20 (0.95-1.53)	1.41 (0.55-3.61)	2.96 (1.97-4.44)	2.32 (1.69-3.19)	0.99 (0.64-1.51)	2.89 (1.52-5.49)	1.68 (1.09-2.60)
Wealth Quintile	1 (Poorest)	1	1	1	1	1	1	1	1	1
	2	1.07 (0.83-1.39)	1.12 (0.74-1.69)	0.99 (0.86-1.15)	0.66 (0.32-1.37)	1.12 (0.77-1.62)	1.37 (1.01-1.85)	1.31 (1.02-1.69)	1.38 (0.90-2.13)	1.21 (0.79-1.85)
	3	0.98 (0.78-1.23)	1.32 (0.87-2.02)	0.94 (0.81-1.09)	1.12 (0.51-2.47)	0.65 (0.44-0.96)	0.94 (0.68-1.31)	1.39 (1.07-1.80)	1.13 (0.68-1.90)	0.99 (0.66-1.49)
	4	1.01 (0.79-1.29)	1.66 (1.06-2.60)	0.89 (0.75-1.05)	0.79 (0.41-1.50)	0.65 (0.44-0.94)	0.83 (0.63-1.10)	1.47 (1.12-1.93)	1.70 (0.87-3.31)	0.74 (0.49-1.12)
	5 (Wealth-iest)	1.06 (0.84-1.35)	1.89 (1.14-3.13)	0.75 (0.64-0.89)	0.79 (0.35-1.75)	0.67 (0.39-1.15)	0.63 (0.45-0.89)	1.83 (1.36-2.47)	1.20 (0.62-2.35)	0.71 (0.44-1.13)

A United Kingdom study by Mclean, Gunn, Wyke et al. (2014) found that in varying age groups, socioeconomic deprivation was associated with an increased prevalence of seven out of ten most common conditions in multi-morbid individuals: depression, anxiety, drug misuse, dyspepsia, coronary heart disease, pain, and diabetes (Figure 7). Socioeconomic deprivation was associated with depression and anxiety in participants up to the age of 75 years; with drug misuse and pain across all age groups; with dyspepsia amongst participants younger than 65 years of age; with coronary heart disease in those aged 45 or older; and with diabetes amongst participants who were 55 years or older. The study analyzed data from a sample of 1,272,685 adults (obtained from medical

records at Scottish general practice clinics), which was verified to be similar in age, sex, and socioeconomic profile to the general Scottish population (Mclean et al., 2014). Socioeconomic status was determined using the Carstairs index, which evaluates lack of car ownership, low occupational social class, overcrowded households, and male unemployment at the postcode sector level. Multi-morbidity was defined as the presence of two or more of 40 chronic conditions (32 physical, 8 mental). The study examined multi-morbidity prevalence across age groups and deprivation levels (n=103,695 most deprived decile; n=117,708 least deprived decile). Mixed physical and mental multi-morbidity was more prevalent among the most deprived compared to the least deprived group in all age groups under 75 years, by two- to three-fold.

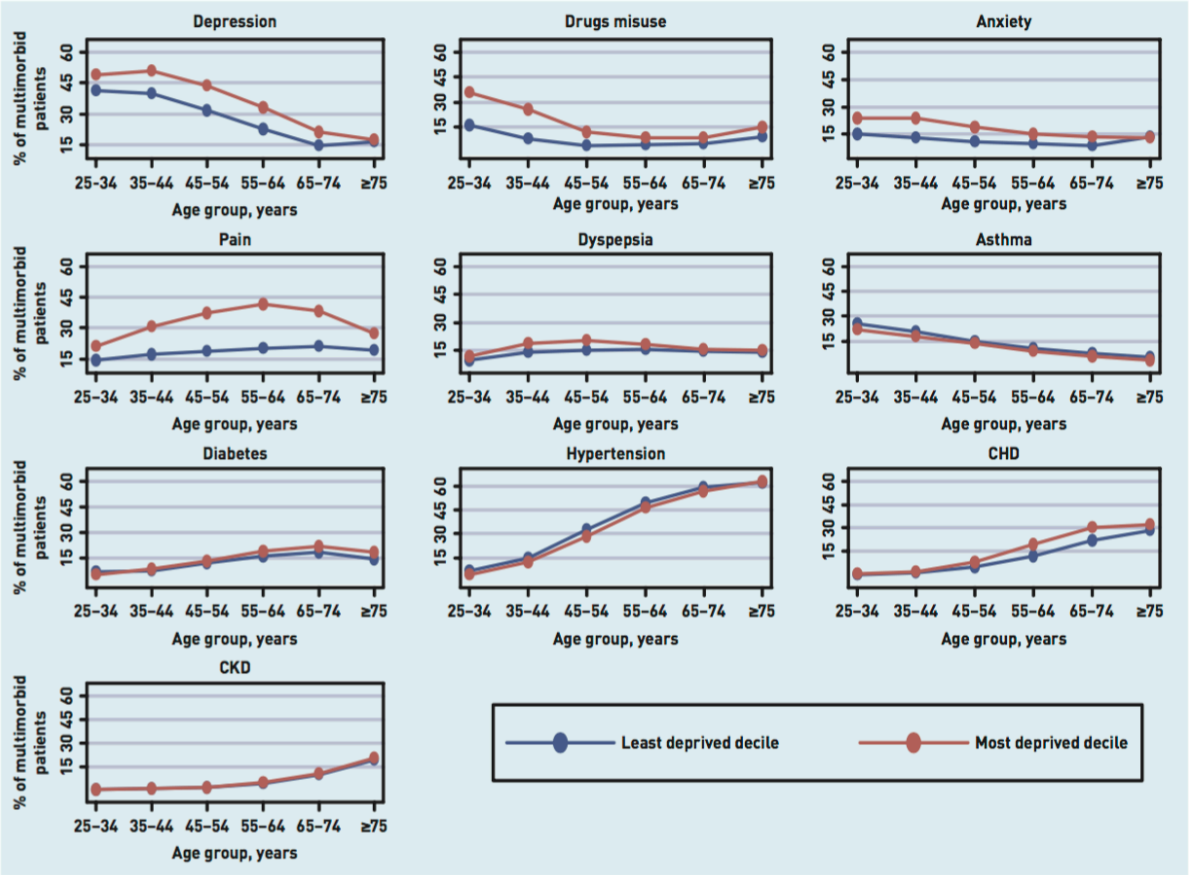


Figure 7. Prevalence of common conditions in multi-morbid patients by age and socioeconomic deprivation (most and least deprived deciles) (Mclean et al., 2014)

Note: CKD = Chronic kidney disease; CHD = Coronary heart disease.

Similarly, a Canadian study using data from the Health Quality Council of Alberta 2010 Patient Experience Survey found an association between lower income and multi-morbidity, independent of age, sex, and family structure (Agborsangaya, Lau, Lahtinen, Cooke, & Johnson, 2012) (Figure 8 & Table 9). This association was most pronounced among individuals between 25 to 44 years of age, compared to older age groups (Table 9).

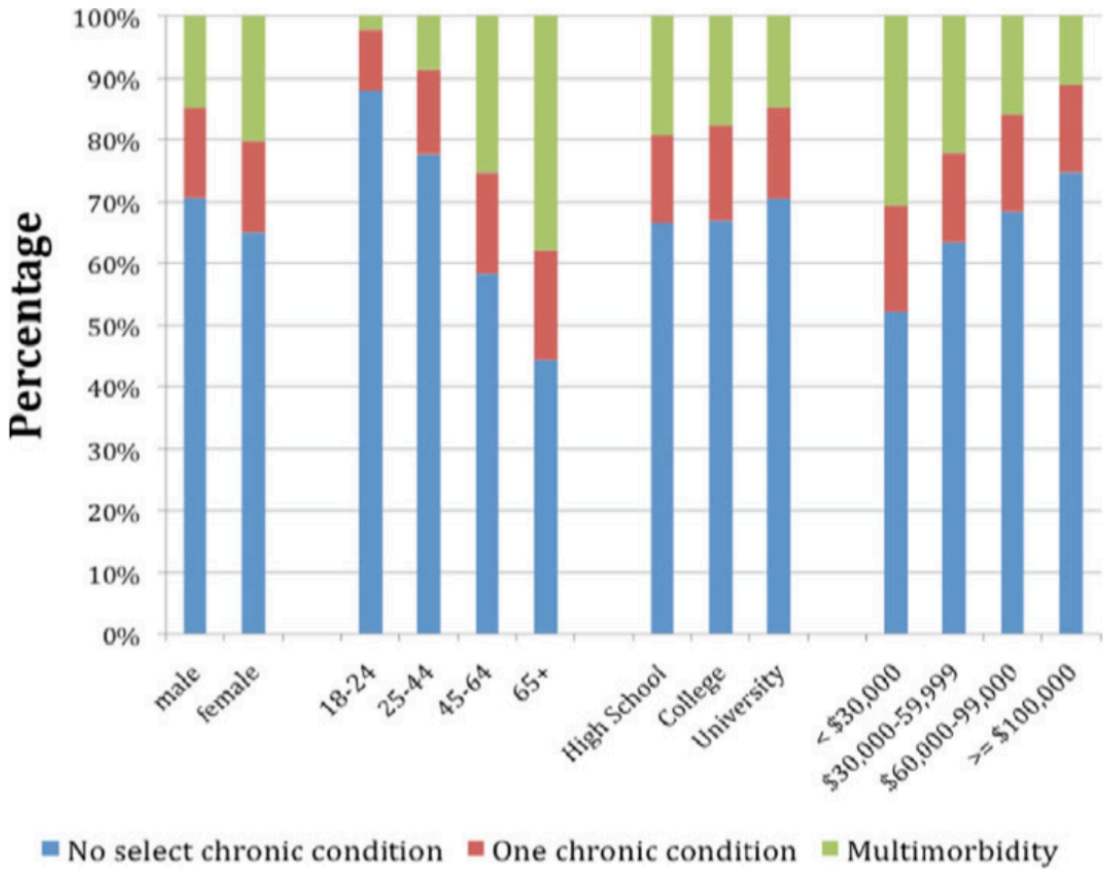


Figure 8. Prevalence of multi-morbidity in adult population by sex, age, education, and household income (Agborsangaya et al., 2012)

Table 9. Association between income and multi-morbidity by age groups (Agborsangaya et al., 2012).

Variables		Ages 25-44	Ages 45-64	Ages 65+
		Multimorbidity Odds Ratio (95% CI)		
Income	**≥ $100,000**	1	1	1
	$60,000-99,999	1.68 (1.01-2.80)	1.38 (1.00-1.97)	2.36 (0.85-6.56)
	$30,000-59,999	1.84 (1.03-3.29)	1.69 (1.17-2.45)	2.50 (0.96-6.48)
	< $30,000	3.72 (2.00-7.01)	2.44 (1.53-3.87)	2.62 (1.00-6.92)

Overall, the literature suggests that multi-morbidity disproportionately affects high-income countries and individuals from lower individual socioeconomic backgrounds.

1.6. PROSPECTIVE URBAN AND RURAL EPIDEMIOLOGICAL (PURE) STUDY

The Prospective Urban and Rural Epidemiological (PURE) study is a prospective, population-based cohort study that recruits subjects aged 35-70 years old in rural and urban settings across seventeen countries. Based on the dates of enrolment, countries were categorized as high, middle and low income countries. The high income countries include: Canada, Sweden, and the United Arab Emirates. The middle income countries include: Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, Poland, South Africa, and Turkey. The low income countries include: Bangladesh, India, Pakistan, and Zimbabwe. PURE collects information on lifestyles, health-related risk factors, the presence of chronic disease, and outcomes (including mortality and cause of death) using standardized methods (Prospective Urban and Rural Epidemiological Study, 2007).

The data are collected using interviewer-based questionnaires at the community, family and individual level. Sampling aimed to achieve a broad, representative sample of adults living in each community. Different sites used varying methods of approaching households. For example, in Canada, invitations to a central clinic were made through mail first, and then by telephone. In rural villages of China and India, community announcements were made through the local community leader, and then by door-to-door visits of each household. At least three attempts of contact were made in all methods of approach. If a household was eligible (at least 1 member was between the ages of 35 and

70 years), then all consent-giving individuals in the household were enrolled. Once recruited, all participants were invited to a study clinic to complete a standardized set of questionnaires and measurements. Information on medically certified death was accessed through central systems of death, where available. Otherwise, event documentation was obtained from household interviews, medical records, death certificates, verbal autopsies, and other sources. Data from the first phase of the study were included in the analyses (153,227 participants with a median follow-up of five years).

CHAPTER 2

OBJECTIVE AND METHODS

2.1. RATIONALE

There has been a recent increase of low- and middle-income country-based (LMIC) studies using frailty screening instruments, including the frailty phenotype and the cumulative deficit frailty index. However, neither of these tools have been validated in LMICs (Gray et al., 2016). These studies tend to feature small sample sizes, are limited to participant data from only one country, or are select samples from nursing homes. Differences in adjustment and frailty definition limit their cross-comparison with frailty studies based in high income countries (Gray et al., 2016). Moreover, evaluations of frailty indices have largely been conducted using elderly participants (65 years and older), despite evidence suggesting that increased frailty, as determined by a higher cumulative deficit index count, is associated with adverse outcomes at all ages of adulthood (Rockwood, Song, & Mitnitski, 2011). Given that frailty can be modified to improve patient outcomes (Effectiveness Matters, 2015), further study of frailty across all ages may be instrumental in diagnosing frailty and beginning treatment as early as possible.

The literature on frailty derived mainly from select HICs may not be fully generalizable to individuals living in LMICs of the world where there may be fewer resources, different lifestyles and behaviours, and a distinct gene pool. As discussed in the previous chapter (e.g. Harttgen et al., 2013), the current literature on the association

between country income and frailty is limited by the methodological inconsistencies between studies examining either HICs or LICs. The advantage of the Prospective Urban and Rural Epidemiological (PURE) study is its diverse and extensive scope of over 150,000 adult participants from seventeen high-income, middle-income, and low-income countries. PURE's standardized methodology in collecting data across country incomes will enable a more robust association between country income and frailty prevalence. Thus, using the PURE study may permit a better understanding of the social determinants of frailty.

2.2. STUDY OBJECTIVE

In this thesis, variables from the Prospective Urban and Rural Epidemiological (PURE) study database were used to develop one phenotypic and two cumulative deficit frailty indices and evaluate their predictive ability for all-cause mortality of individuals living in high income, middle income, and low income countries. Multi-morbidity, a related concept to frailty, was also evaluated for mortality risk.

2.3. HYPOTHESIS

We hypothesize that frailty is associated with an increased mortality risk in countries of all income strata.

2.4. OVERVIEW OF DESIGN

The PURE frailty indices were developed with the goal of achieving both parsimony and excellent discriminatory ability for all-cause mortality. To achieve this,

three models were constructed based on the two main approaches of frailty measurement: the cumulative deficit index and the frailty phenotype. First, a cumulative deficit index was calculated for each individual as $\frac{the\ sum\ of\ deficits}{40\ (i.e. the\ total\ number\ of\ deficits\ measured)}$ (refer to Table 10 for the deficits included). A second modified cumulative deficit index was created that excluded the consideration of baseline chronic diseases as deficits (ten deficits were excluded: asthma, angina/heart attack/coronary heart disease, COPD, diabetes, hepatitis/jaundice, heart failure, high blood pressure, other heart diseases, stroke, and tuberculosis), and was thus calculated as $\frac{the\ sum\ of\ deficits}{30\ (i.e. the\ total\ number\ of\ deficits\ measured)}$ (Table 10). These two versions of the cumulative deficit frailty index were compared to determine the influence of chronic diseases on the predictive validity of frailty for mortality. Lastly, a phenotypic frailty index containing three of the original five components (unintentional weight loss, weakness (grip strength), and low physical activity), was generated. People were divided by quintiles based on their grip strength stratified by sex and country income level. By doing so, participants' grip strength scores were compared with other participants of the same sex and country income. Physical activity was divided by quintiles after stratifying for sex. Two or more of unintentional weight loss, grip strength in the lowest fifth for sex and country income, and physical activity in the lowest fifth for sex, were considered indicative of frailty. Having one of these components was considered as pre-frailty, and no components as robustness.

Table 10. PURE deficit items used in the cumulative deficit indices

#	PURE Deficit Items	Score options
	Current disability; problems…	
1	Using fingers/grasping	0 or 1
2	Walking about	0 or 1
3	Bending/picking up objects	0 or 1
4	Require walking cane	0 or 1
5	Reading/seeing individual rice grains	0 or 1
6	Seeing person across room	0 or 1
7	Speaking/being understood	0 or 1
8	Hearing in conversation	0 or 1
	In the last 6 months…	
9	Chest pain/tightness	0 or 1
10	Breathlessness	0 or 1
11	Cough for 2+ weeks	0 or 1
12	Sputum while coughing	0 or 1
13	Blood in sputum	0 or 1
14	Wheezing/whistling chest	0 or 1
15	Early morning cough with chest tightness	0 or 1
16	Loose stools/diarrhea for 3+ days	0 or 1
17	Vomiting	0 or 1
18	Loss of appetite	0 or 1
19	Painful or bleeding teeth/gums	0 or 1
20	Jaundice	0 or 1
21	Burning while passing urine	0 or 1
22	Swelling of feet	0 or 1
23	Swelling of face	0 or 1
24	Blood in urine	0 or 1
25	Involuntary weight loss of > 3 kg	0 or 1
26	Grip strength	0, .25, 0.50, 0.75, or 1.0
27	Depressed for 2+ weeks in past 12 months?	0 or 1
28	BMI <18.5?	0 or 1
29	Age group by quartile	0, 0.33, 0.67, or 1.0
30	Low physical activity (from PAQ)	0 or 1
Ever been diagnosed with…? *		
31	Diabetes	0 or 1
32	Hypertension/High blood pressure	0 or 1
33	Stroke	0 or 1
34	Angina/heart attack/coronary artery disease	0 or 1
35	Heart failure	0 or 1
36	Other heart disease	0 or 1
37	Hepatitis	0 or 1
38	Chronic Obstructive Pulmonary Disease	0 or 1
39	Asthma	0 or 1
40	Tuberculosis	0 or 1
		40

Note: Grip strength was divided by sex- and country income-specific quintiles, and physical activity was divided by sex-specific quintiles. *Questions 31-40 were only included in the frailty index (including chronic diseases).

2.5. DEVELOPMENT OF PURE FRAILTY INDICES

Data from PURE's Adult Questionnaire and Physical Activity Questionnaire were used to develop the PURE frailty indices. In creating cumulative deficit frailty indices, deficits were selected that make clinical sense, accumulate with increased age, and do not saturate at too early an age (Song et al., 2010; Searle, Mitnitski, Gahbauer et al., 2008). The variables that were included in the PURE cumulative deficit frailty indices were those that can be perceived as physical or psychological deficits, listed in Table 10. Variables which were answered by at least 90% of the participants were included (only "coughing with sputum for three months per year for the last years" was excluded, with 51.2% participants missing data). Similar to Rockwood et al. (2006), each variable was dichotomized, where 1 indicates the presence of deficit and 0 indicates its absence. For continuous covariates, severity levels of the deficit were indicated with additional values. Grip strength was separated by quintiles according to sex and country income, with deficit values of 0.00 (male grip strength range: 0.67-37kg; female range: 0.67-21kg), 0.25 (male range: 25-43kg; female range: 16-26kg), 0.50 (male range: 30-48kg; female range: 19-29kg), 0.75 (male range: 34-53kg; female range: 23-33kg) to 1.00 (male range: 39-90kg; female range: 27-90kg) allocated to each individual. Similarly, age was stratified by quartiles to simply reflect the association between increased age and frailty, with values of 0.00 (median age=38 years), 0.33 (median age=47 years), 0.67 (median age=54 years), and 1.00 (median age=64 years) representing the youngest to the older members of the sample.

2.6. ETHICS

The PURE protocol was approved by the ethics committees of the participating centres. All participants gave informed consent to participating in the study.

2.7. SAMPLE

All participants who had baseline and follow-up data by April 2016, were between the ages of 35-70 years old at recruitment, and whose sex and vital status were recorded at the time of analysis were included. For the phenotypic frailty index, only participants with data available for all three variables (grip strength, weight loss, and physical activity levels) were included in analyses. According to the methodology used by Rockwood et al. (2007), participants missing data on more than two deficits were excluded from the cumulative deficit index (excluding chronic diseases) analyses (maximum of 6.67% missing data) and the cumulative deficit index (including chronic diseases analyses) (maximum of 5.00% missing data), respectively.

2.8. STATISTICAL ANALYSES

The relationship between country income and frailty was evaluated by the odds ratio of frailty in MIC and LIC, as compared with HIC. Poisson regressions were used to compare the number of deficits present among participants from high-, middle-, and low-income countries, using the cumulative deficit indices.

The outcome of interest was time to death. The associations between the PURE frailty indices and all-cause mortality were evaluated by Kaplan-Meier survival curves

stratified by frailty category. Differences in time to death between males and females of the same frailty category were also evaluated using Kaplan-Meier curves. The use of Kaplan-Meier curves is a common way of assessing survival when observations of the study sample are incomplete, or "censored" due to attrition or continued survival past the study's end date (Rich et al., 2010). Log-rank tests for were conducted to evaluate the equality of Kaplan-Meier curves. Cox proportional hazards modeling was used to evaluate the associations between the PURE frailty indices and all-cause mortality, stratified for both frailty level and sex. Receiver operating characteristic (ROC) curves were generated for each frailty index with all-cause as the outcome. ROC curves plot the true positive rate of a diagnostic test or index against the false positive rate, and can be used to compare diagnostic tests. The discriminative ability of the three frailty indices was compared by assessing the area under the ROC curves, where higher AUC values indicate better diagnostic performance. Pearson's chi-squared test was used to test the equality of the areas under the ROC curves.

One-year mortality was subsequently evaluated with Cox proportional hazards modeling to compare the short-term and long-term predictive validity of the frailty indices. Adjusted Cox models for all-cause and one-year mortality were also conducted for covariates in participant characteristics that are likely or known to have a confounding impact on mortality, including: age, sex, country income, education, smoking history, alcohol consumption history, and daily caloric intake.

Cox proportional hazards analysis assumes a constant proportional relationship between different levels of the explanatory variables (the frailty index items) and the

dependent variable (mortality) (Walters, 2009). The appropriateness of the proportional hazards assumption was checked using log-log plots of the Kaplan-Meier survival curves. Log(-log(Survival)) plots, adjusted for other covariates, were also produced. The graphical means of verifying the proportional hazards assumption was chosen, rather than the method of using a statistical goodness-of-fit test, due to the study's large sample size, which would result in a highly significant *p* value given any slight violation of the null hypothesis (Kleinbaum, 2006, p.183). Generating estimated log-log survivor curves is the most popular graphical method of testing the proportional hazards assumption (Kleinbaum, 2006, p.165).

A sensitivity analysis was conducted to determine whether pre-existing baseline chronic diseases confounded the relationship between time to death and frailty, as measured by both the frailty phenotype and cumulative deficit index (excluding chronic diseases). This was done by repeating Cox regression analyses on a subset of the total sample, consisting only of participants without any of the following major pre-existing chronic diseases at baseline: COPD, stroke, diabetes, and coronary heart disease.

Differences between males and females in the mortality risk associated with frailty was evaluated with Kaplan-Meier curves, the stratified log-rank test of equality, and Cox proportional hazards modeling.

Multi-morbidity was assessed using a total of twelve major chronic diseases from the PURE database (diabetes, coronary heart disease, heart failure, other heart disease, stroke, hepatitis/jaundice, hypertension, chronic obstructive pulmonary disease, depression, asthma, AIDS, and cancer). The prevalence of multi-morbidity was evaluated

across the sample stratified by country income and frailty level, separately. The association between multi-morbidity and all-cause mortality was evaluated with Kaplan-Meier curves and Cox proportional hazards modeling, stratified by frailty level.

STATA 14.0 (StataCorp, College Station, TX, USA) was used to compute all statistical analyses and graphs.

CHAPTER 3

RESULTS

3.1. SAMPLE DESCRIPTION

A total of 153,227 subjects were enrolled, and had known vital status information. Ninety-nine individuals with recorded ages of <10 or >100 years were excluded. An additional subject was excluded because their sex was not recorded. The median age of the remaining 153,127 participants included in the study was 50 years old (IQR of 42-58).

Among this sample, the proportions of participants from HIC, MIC, and LIC countries were 10.5% (n=16,057), 67.3% (n=102,998), and 22.2% (n=34,072), respectively. After excluding participants without complete data on grip strength, physical activity, and weight loss history, the sample size for the phenotypic frailty index was 117,660. Among the 35,467 participants who were excluded for missing phenotypic frailty data, 2,400 were from HIC, 12,958 were from MIC, and 20,109 were from LIC.

After excluding participants with missing values for more than two deficits, the sample size for the cumulative deficit analyses excluding and including chronic diseases was 149,576 and 138,173, respectively. A total of 3,551 participants were excluded from the cumulative deficit index (excluding chronic diseases), 123 of whom were from HIC, 1,196 from MIC, and 2,232 from LIC. Among the 14,954 participants excluded from the cumulative deficit index (including chronic diseases), 241 were from HIC, 1,396 were from MIC, and 13,317 were from LIC.

3.2. CHARACTERISTICS OF PRE-FRAIL AND FRAIL PARTICIPANTS

Using the phenotypic frailty definition, the prevalence of frailty (having 2-3 frailty components) among the PURE participant sample was 6.4% and the prevalence of pre-frailty (having 1 frailty component) was 29% (Tables 11a-11b). Frail participants (median age 56 years; IQR 47-64) were older than pre-frail participants (median age 52 years; IQR 44-60), and robust participants (median age 50 years; IQR 42-57). There was no difference in the prevalence of frailty between men (6.35%) and women (6.49%).

Increased phenotypic frailty was associated with lower education, lower daily dietary caloric intake, lower percentage of daily calories from protein (Table 11a). Compared with the robust group, a higher proportion of frail participants had never smoked, and a lower proportion were former smokers (Table 11b). The proportion of participants with baseline chronic diseases increased with frailty for each of the ten diseases assessed (stroke, hypertension, hepatitis/jaundice, heart failure, diabetes, chronic obstructive pulmonary disorder, angina/acute myocardial infarction/coronary artery disease, other heart disease, asthma, and tuberculosis; Table 11a).

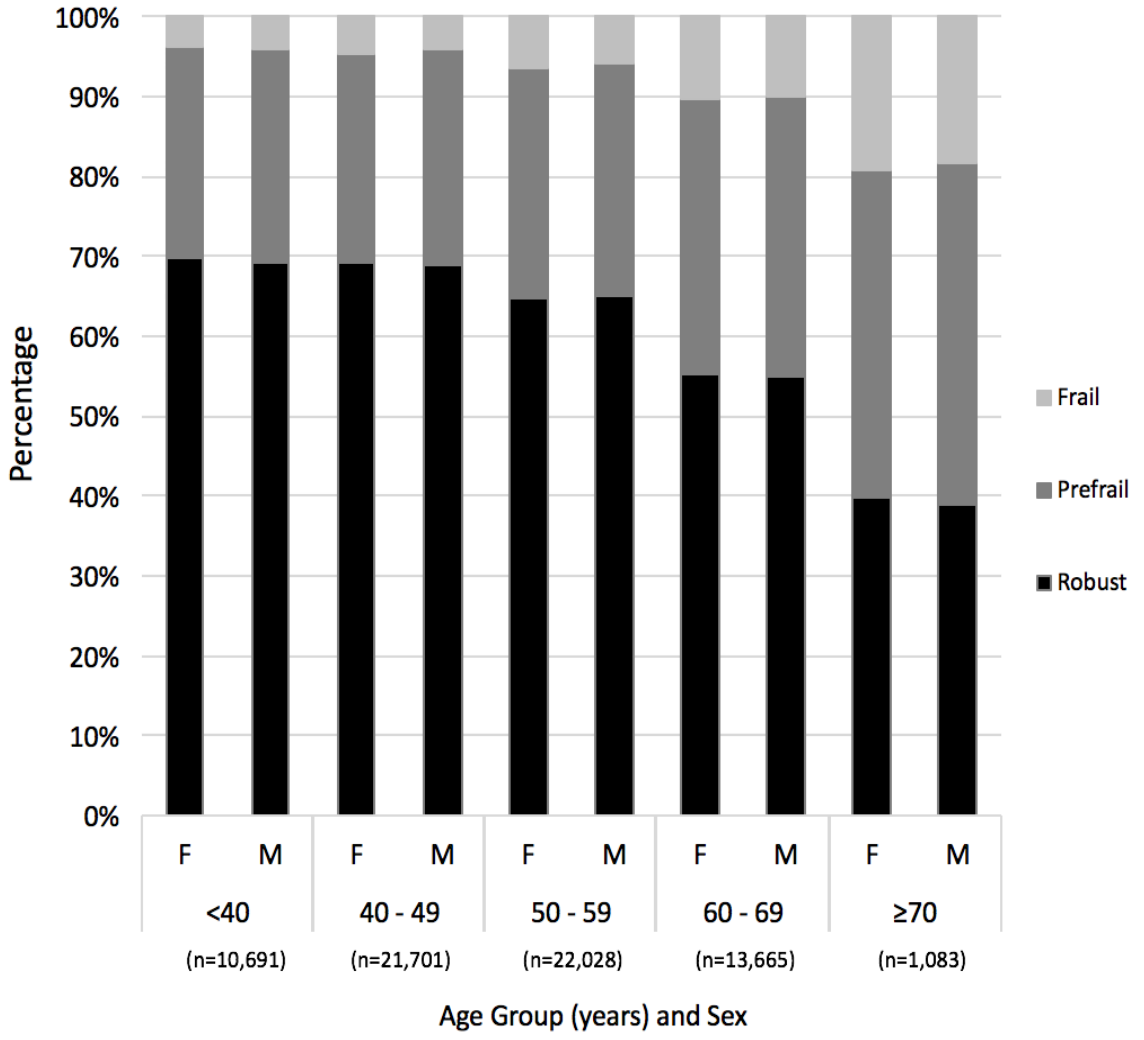


Figure 9. Proportion of sample categorized as robust, pre-frail, and frail using the phenotypic frailty index, by age group and sex (N=117,660)

According to the cumulative deficit index (excluding chronic diseases), the median number of deficits for each increasing quarter were 1.00 (IQR 0.670-1.33), 1.98 (IQR 1.75-2.25), 3.33 (IQR 3.00-4.00), and 6.83 (IQR 5.50-9.00) (Table 12a). As with the phenotypic definition of frailty, increasing levels of frailty by the cumulative deficit index was

associated with older age, lower education, lower daily dietary caloric intake, and lower percentage of calories from protein (Table 12a). In contrast to the phenotypic frailty index, the proportion of females increased with greater frailty quarters; 64% of participants in the highest cumulative deficit frailty quarter were female compared to 54% in the lowest quarter (Table 12b). Increased cumulative deficit frailty was also associated with more former alcohol consumption, fewer individuals who never consumed alcohol, and more former and current smoking (Table 12b). Although chronic diseases were not assessed as deficits in this version of the index, the number of participants with baseline chronic diseases consistently increased with each frailty quarter for every disease assessed (Table 12a).

For the cumulative deficit index (including chronic diseases), the median number of deficits of participants in each increasing frailty quarter were 1.08 (IQR 0.750-1.42), 2.33 (IQR 2.00-2.67), 4.00 (IQR 3.50-4.50), 7.67 (IQR 6.17-10.0) (Table 13a). Similar to the cumulative deficit index (excluding chronic diseases), increasing frailty was associated with increasing proportion of female participants, lower education, lower dietary caloric intake, more former alcohol consumption, fewer individuals who never consumed alcohol, and more former and current smoking (Table 13b). Unlike the cumulative index (excluding chronic diseases), frailty was positively associated with percentage of caloric intake from proteins (Table 13a).

Age-standardized analyses were also computed for all three frailty indices to eliminate any confound of age variability on the association between baseline participant characteristics and frailty. (Tables 11c, 12c, and 13c). After age-standardization, the

difference in prevalence of phenotypic frailty among females and males increased (6.6% of females, and 6% of males) (Table 11c). The associations between increased phenotypic frailty and lower country income, and lower education remained the same. The age-standardized prevalence of former alcohol drinkers who are frail, according to the phenotypic frailty index, was slightly reduced from 8.3% to 7%. Using the cumulative deficit indices, after age-standardization, similar associations were still found between participants' baseline characteristics and frailty (Tables 12c & 13c).

The major differences in participant characteristics among the different frailty indices are summarized in Table 14.

Table 11a. Characteristics of robust, pre-frail and frail participants (as measured by the phenotypic frailty index)

Characteristics	Robust	Pre-frail	Frail
n	75,635	34,460	7,565
Median age, years (IQR)	50 (42-57)	52 (44-60)	56 (47-64)
Dietary caloric intake (kcal) (median and IQR)	2031 (1587-2873)	1934 (1501-2543)	1832 (1376-2456)
% calories from protein (median and IQR)	15.5 (13.4-17.7)	15.2 (13.1-17.5)	15.0 (12.9-17.4)
Baseline chronic diseases, n (%)			
Stroke	910 (1.2%)	734 (2.1%)	489 (6.5%)
Hypertension	15,058 (20%)	8,294 (24%)	2,372 (32%)
Hepatitis/Jaundice	1,960 (2.6%)	904 (2.6%)	415 (5.5%)
Heart Failure	578 (0.77%)	404 (1.2%)	166 (2.3%)
Diabetes	4,442 (5.9%)	3,225 (9.4%)	1,277 (16.9%)
Chronic Obstructive Pulmonary Disease	575 (0.76%)	416 (1.2%)	371 (4.9%)
Angina/Acute myocardial infarction/ Coronary artery disease	2,777 (3.7%)	1,608 (4.7%)	701 (9.3%)
Other Heart disease	1,745 (2.31%)	1,004 (2.92%)	502 (6.64%)
Asthma	2,088 (2.8%)	1,243 (3.6%)	634 (8.4%)
Tuberculosis	467 (0.68%)	346 (1.1%)	336 (4.6%)
Cancer	1,208 (1.6%)	596 (1.7%)	350 (4.6%)

Table 11b. Proportion of participants that was robust, pre-frail and frail stratified by sex, country income, education, alcohol and smoking history

Characteristics	Robust n (row %)	Pre-frail n (row %)	Frail n (row %)
Sex			
Female	44,714 (64.6%)	19,968 (28.9%)	4,486 (6.5%)
Male	30,921 (63.8%)	14,492 (29.9%)	3,079 (6.3%)
Country Income			
HIC (n=13,657)	10,091 (74%)	3,072 (22%)	494 (4%)
MIC (n=90,040)	57,120 (63%)	26,942 (30%)	5,978 (7%)
LIC (n=13,963)	8,424 (60%)	4,446 (32%)	1,093 (8%)
Education			
None/primary/unknown (n=48,033)	27,521 (57.3%)	16,123 (33.6%)	4,389 (9.1%)
Secondary (n=45,031)	30,490 (67.7%)	12,378 (27.5%)	2,163 (4.8%)
Trade/College/University (n=24,417)	17,510 (71.7%)	5,904 (24.2%)	1,003 (4.1%)
Drink alcohol			
Never	48,735 (61.5%)	24,740 (31.2%)	5,805 (7.3%)
Formerly	3,194 (58.8%)	1,790 (32.9%)	450 (8.3%)
Current	23,486 (72.6%)	7,792 (24.1%)	1,071 (3.3%)
Smoking			
Never	50,349 (63.9%)	23,370 (29.6%)	5,094 (6.5%)
Former	9,719 (67.7%)	3,852 (26.8%)	785 (5.5%)
Current	15,129 (64.3%)	7,005 (29.7%)	1,409 (6.0%)

Note: The phenotypic frailty index categorizes participants based on three variables: grip strength, physical activity level, and significant weight loss. The presence of two or three of the variables was considered "frail", the presence of any one variable was considered "pre-frail", and the absence of all three variables was considered "robust". The sample used only includes participants with available information on all three variables.

Table 11c. Age-standardized proportion of participants that was robust, pre-frail and frail stratified by sex, country income, education, alcohol and smoking history

Characteristics	Robust	Pre-frail	Frail
	Age-standardized prevalence*, row % (95% CI)		
Sex			
Female	64.4 (64.0-64.7)	29.0 (28.7-29.4)	6.6 (6.4-6.8)
Male	64 (63.8-64.6)	30 (29.3-30.0)	6 (5.9-6.4)
Country Income			
HIC (n=13,657)	74 (73.5-75.0)	22 (21.1-22.6)	4 (3.2-3.8)
MIC (n=90,040)	63 (63.1-63.7)	30 (29.7-30.3)	7 (6.5-6.8)
LIC (n=13,963)	59 (58.1-59.9)	32 (31.6-33.4)	8 (7.8-8.8)
Education			
None/primary/unknown (n=48,033)	59 (58.6-59.5)	33 (32.2-33.0)	8 (8.1-8.6)
Secondary (n=45,031)	67 (66.3-67.2)	28 (27.6-28.4)	5 (4.9-5.4)
Trade/College/University (n=24,417)	72 (71.1-72.2)	24 (23.7-24.8)	4 (3.9-4.4)
Drink alcohol			
Never	61.4 (61.0-61.7)	31.2 (30.9-31.6)	7.4 (7.2-7.6)
Formerly	61 (69.2-61.9)	32 (30.6-33.2)	7 (6.7-8.1)
Current	72.4 (71.9-72.9)	24.2 (23.7-24.7)	3.4 (3.1-3.5)
Smoking			
Never	63.6 (64.3-63.9)	29.8 (29.4-30.1)	6.6 (6.5-6.8)
Former	70 (68.8-70.4)	25 (24.8-26.3)	5 (4.4-5.1)
Current	64 (63.1-64.3)	30 (29.4-30.6)	6 (5.9-6.5)

*Standardized to the age-distribution of the entire sample used in the phenotypic frailty analysis. Values are reported to two significant figures, except where an additional decimal place is required for each row to add to 100%.

Table 12a. Characteristics of participants in the lowest, second, third, and highest quarters of the cumulative deficit index (excluding chronic diseases)

Characteristic	Lowest Quarter	2nd Quarter	3rd Quarter	Highest Quarter
n	39,224	36,008	37,287	37,057
Median age, years (IQR)	43 (39-50)	52 (45-59)	53 (45-60)	54 (46-61)
Median # of deficits (max = 30) (IQR)	1.00 (0.670-1.33)	1.98 (1.75-2.25)	3.33 (3.00-4.00)	6.83 (5.50-9.00)
Dietary caloric intake (kcal) (median and IQR)	2083 (1627-2666)	2004 (1559-2584)	2008 (1549-2607)	1938 (1479-2563)
% calories from protein (median and IQR)	15.0 (12.8-17.3)	15.2 (12.9-17.5)	15.0 (12.5-17.5)	14.7 (12.2-17.2)
Baseline chronic diseases, n (%)				
Stroke	172 (0.44%)	364 (1.0%)	544 (1.5%)	1,417 (3.8%)
Hypertension	4,496 (11%)	6,885 (19%)	8,538 (23%)	11,776 (32%)
Hepatitis/Jaundice	488 (1.3%)	570 (1.7%)	914 (2.7%)	1,639 (4.9%)
Heart failure	68 (0.18%)	137 (0.41%)	264 (0.78%)	920 (2.8%)
Diabetes	1,631 (4.2%)	2,597 (7.2%)	3,247 (8.7%)	4,536 (12%)
Chronic Obstructive Pulmonary Disease	67 (0.18%)	98 (0.29%)	225 (0.66%)	1,130 (3.4%)
Angina/Acute myocardial infarction/Coronary artery disease	423 (1.1%)	995 (2.8%)	1,536 (4.1%)	2,903 (7.8%
Other heart disease	287 (0.73%)	485 (1.4%)	901 (2.4%)	2,099 (5.7%)
Asthma	438 (1.1%)	581 (1.6%)	1,083 (2.9%)	3,051 (8.2%)
Tuberculosis	125 (0.34%)	152 (0.46%)	282 (0.82%)	916 (2.6%)
Cancer	266 (0.68%)	417 (1.2%)	636 (1.7%)	1,040 (2.8%)

Table 12b. Distribution of participants across the frailty quarters of cumulative deficit index (excluding chronic diseases) by country income, education, alcohol and smoking history

Characteristic	Lowest Quarter n (row%)	2nd Quarter n (row%)	3rd Quarter n (row%)	Highest Quarter n (row%)
Sex				
Female	21,684 (25.03%)	19,687 (22.72%)	21,262 (24.54%)	24,008 (27.71%)
Male	17,540 (27.9%)	16,321 (25.9%)	16,025 (25.5%)	13,049 (20.7%)
Country Income				
HIC (n=15,934)	4,047 (25%)	4,034 (25%)	4,574 (29%)	3,279 (21%)
MIC (n=101,802)	27,348 (27%)	25,888 (25%)	24,396 (24%)	24,170 (24%)
LIC (n=31,840)	7,829 (25%)	6,086 (19%)	8,317 (26%)	9,608 (30%)
Education				
None/primary/unknown	11,008 (17.3%)	13,407 (21.1%)	16,909 (26.6%)	22,215 (35.0%)
Secondary	19,825 (34.9%)	14,837 (26.1%)	12,593 (22.1%)	9,611 (16.9%)
Trade/College/University	8,316 (28.8%)	7,679 (26.6%)	7,706 (26.7%)	5,154 (17.9%)
Drink alcohol				
Never	28,482 (27.3%)	25,767 (24.7%)	25,262 (24.2%)	24,826 (23.8%)
Former	891 (13.4%)	1,221 (18.4%)	1,740 (26.2%)	2,788 (42.0%)
Current	9,737 (25.6%)	8,917 (23.5%)	10,168 (26.8%)	9,143 (24.1%)
Smoking				
Never	28,217 (28.2%)	25,075 (25.0%)	24,583 (24.5%)	22,326 (22.3%)
Former	2,877 (17.0%)	3,682(21.8%)	4,858 (28.7%)	5,486 (32.5%)
Current	7,868 (25.06%)	7,028 (22.38%)	7,617 (24.26%)	8,885 (28.30%)

Percentages are reported to two significant figures, except where additional decimal places are required for each row to add to 100%.

Table 12c. Age-standardized distribution of participants across the frailty quarters of the cumulative deficit index (excluding chronic diseases) by sex, country income, education, alcohol and smoking history

Characteristic	Lowest Quarter	2nd Quarter	3rd Quarter	Highest Quarter
	Age-standardized prevalence, % (95% CI)			
Sex				
Female	24 (24.2-24.7)	23 (22.5-23.1)	25 (24.4-25.0)	28 (27.8-28.4)
Male	29 (28.6-29.2)	26 (25.4-26.1)	25 (24.8-25.4)	20 (20.0-20.6)
Country Income				
HIC (n=15,934)	29 (27.8-29.3)	25 (24.0-25.3)	27 (26.7-28.1)	19 (18.5-19.8)
MIC (n=101,802)	27 (27.3-27.8)	25 (24.9-25.4)	24 (23.5-24.1)	24 (23.3-23.8)
LIC (n=31,840)	22 (21.3-22.3)	19 (19.0-20.0)	27 (26.3-27.4)	32 (31.1-32.3)
Education				
None/primary/unknown	19 (18.9-19.6)	21 (20.5-21.2)	26 (25.8-26.5)	34 (33.4-34.1)
Secondary	32 (31.2-32)	27 (26.6-27.3)	23 (23.0-23.7)	18 (17.8-18.5)
Trade/College/University	28 (27.8-28.8)	27 (26.2-27.2)	27 (26.4-27.4)	18 (17.6-18.5)
Drink alcohol				
Never	27 (26.6-27.1)	25 (24.6-25.2)	24 (24.1-24.6)	24 (23.7-24.2)
Former	16 (15.1-16.9)	19 (17.6-19.6)	26 (24.9-27.1)	39 (38.1-40.5)
Current	26 (25.8-26.7)	23 (22.7-23.6)	27 (26.1-27.0)	24 (23.6-24.4)
Smoking				
Never	27 (27.0-27.5)	25 (25.0-25.6)	25 (24.5-25.1)	23 (22.4-22.9)
Former	22 (20.9-22.4)	21 (20.5-21.8)	28 (26.8-28.3)	29 (28.8-30.3)
Current	25 (24.1-25.0)	22 (22.0-22.9)	24 (23.9-24.8)	29 (28.1-29.1)

*Standardized to the age-distribution of the entire sample used in the cumulative deficit index (excluding chronic diseases)

Table 13a. Characteristics of participants in the lowest, second, third, and highest quarters of the cumulative deficit index (including chronic diseases)

Characteristic	Lowest Quarter	2nd Quarter	3rd Quarter	Highest Quarter
n	35,978	36,288	31,902	34,005
Median age, years (IQR)	44 (39-50)	52 (43-59)	54 (46-60)	55 (47-62)
Median # of deficits (max = 40) (IQR)	1.08 (0.750-1.42)	2.33 (2.00-2.67)	4.00 (3.50-4.50)	7.67 (6.17-10.0)
Dietary caloric intake (kcal) (median and IQR)	2079 (1625-2656)	2022 (1566-2606)	1992 (1537-2581)	1942 (1486-2563)
% calories from protein (median and IQR)	15.1 (13.1-17.4)	15.3 (13.2 17.5)	15.4 (13.2-17.8)	15.5 (13.0-17.7)

Table 13b. Distribution of participants across the frailty quarters of cumulative deficit index (including chronic diseases) by sex, country income, education, alcohol and smoking history

Characteristic	Lowest Quarter n (row%)	2nd Quarter n (row%)	3rd Quarter n (row%)	Highest Quarter n (row%)
Sex				
Female	20,087 (24.9%)	20,097 (24.9%)	18,431 (22.9%)	22,021 (27.3%)
Male	15,891 (27.62%)	16,191 (28.14%)	13,471 (23.41%)	11,984 (20.83%)
Country Income				
HIC (n=15,816)	3,792 (24%)	4,362 (28%)	4,162 (26%)	3,500 (22%)
MIC (n=101,612)	26,754 (26%)	27,246 (27%)	23,021 (23%)	24,581 (24%)
LIC (n=20,755)	5,432 (26.2%)	4,680 (22.5%)	4,719 (22.7%)	5,924 (28.5%)
Education				
None/primary/unknown	9,928 (17.2%)	13,597 (23.5%)	14,381 (24.9%)	19,856 (34.4%)
Secondary	18,533 (35.2%)	14,738 (28.0%)	10,594 (20.1%)	8,822 (16.7%)
Trade/College/University	7,464 (27.1%)	7,887 (28.7%)	6,876 (25.0%)	5,276 (19.2%)
Drink alcohol				
Never	28,364 (26.5%)	28,452 (26.6%)	25,160 (23.5%)	24,986 (23.4%)
Former	831 (12.3%)	1,276 (18.9%)	1,783 (26.5%)	2,849 (42.3%)
Current	9,731 (2.5%)	9,967 (33.9%)	9,737 (33.1%)	8,981 (30.5%)
Smoking, n (col%)				
Never	25,872 (28.03%)	25,140 (27.24%)	20,957 (22.71%)	20,319 (22.02%)
Former	2,477 (15.2%)	3,777 (23.3%)	4,358 (26.8%)	5,631 (34.7%)
Current	7,387 (25.8%)	7,144 (25.0%)	6,357 (22.2%)	7,730 (27.0%)

Note: The cumulative deficit index (including chronic diseases) categorizes participants based on the presence of 40 deficits, including ten baseline chronic diseases (asthma, angina/heart attack/coronary heart disease, chronic obstructive pulmonary disease, diabetes, hepatitis/jaundice, heart failure, high blood pressure, other heart diseases, stroke, and tuberculosis).

Table 13c. Age-standardized distribution of participants across the frailty quarters of the cumulative deficit index (including chronic diseases) by sex, country income, education, alcohol and smoking history

Characteristic	Lowest Quarter	2nd Quarter	3rd Quarter	Highest Quarter
	Age-standardized prevalence, % (95% CI)			
Sex				
Female	24 (24.0-24.6)	25 (24.7-25.3)	23 (22.7-23.3)	28 (27.4-28.0)
Male	29 (28.3-29.0)	28 (27.6-28.4)	23 (22.7-23.4)	20 (20.0-20.6)
Country Income				
HIC (n=15,934)	27 (25.9-27.3)	27 (26.7-28.1)	25 (24.5-25.8)	21 (20.0-21.2)
MIC (n=101,802)	27 (26.3-26.8)	27 (26.5-27.0)	22 (22.3-22.8)	24 (23.9-24.4)
LIC (n=31,840)	23 (22.6-23.7)	23 (21.9-23.2)	24 (23.2-24.5)	30 (29.7-31.1)
Education				
None/primary/unknown	19.4 (19.0-19.7)	23.3 (23.0-23.7)	24.3 (24.0-24.7)	33.0 (32.6-33.4)
Secondary	31.4 (31.1-31.8)	28.7 (28.3-29.1)	21.5 (21.1-21.8)	18.4 (18.0-18.7)
Trade/College/University	27 (26.1-27.0)	29 (28.1-29.2)	25 (24.8-25.8)	19 (19.0-20.0)
Drink alcohol				
Never	27 (26.7-27.2)	27 (26.6-27.2)	22 (22.3-22.9)	24 (23.2-23.8)
Former	14.5 (13.5-15.4)	20.0 (18.9-21.0)	24.4 (23.3-25.5)	41.1 (39.9-42.4)
Current	25.4 (24.9-25.8)	26.0 (25.6-26.5)	24.3 (23.8-24.7)	24.3 (23.9-24.7)
Smoking				
Never	27.2 (26.9-27.5)	27.4 (27.1-27.7)	23.0 (22.8-23.3)	22.4 (22.1-22.7)
Former	20 (19.0-20.4)	24 (22.9-24.4)	25 (24.6-26.0)	31 (30.5-31.9)
Current	25.0 (24.6-25.5)	25.1 (24.6-25.6)	22.4 (21.9-22.9)	27.5 (26.9-28.0)

*Standardized to the age-distribution of the entire sample used in the cumulative deficit index (including chronic diseases). Values are reported to two significant figures, except where an additional decimal place is required for each row to add to 100%.

Table 14. Comparison of participant backgrounds and lifestyle behaviour trends by frailty index

Correlates	Phenotypic Frailty	Cumulative Deficit Frailty (Excluding chronic diseases)	Cumulative Deficit Frailty (Including chronic diseases)
Age	+	+	+
% Female	/	+	+
Education	-	-	-
Dietary caloric intake	-	-	-
% Calories from protein	-	-	+
Drink alcohol	-	+	+
Smoking (Never)	+	-	-
Smoking (Former)	-	+	+
Smoking (Current)	/	+	+
Presence of 1+ baseline chronic disease	+	+	N/A

Note: "+" indicates a positive association between increasing frailty according to the respective index and the correlate being assessed, whereas "-" indicates a negative association, and "/" indicates that there was no clear association. Baseline chronic diseases were by definition calculated as deficits in the cumulative deficit index (including chronic diseases), and were thus not considered in this analysis.

3.3. FRAILTY BY COUNTRY INCOME

Lower country income status was associated with increasing prevalence of phenotypic pre-frailty and frailty (Tables 11b & 11c; Figure 10).

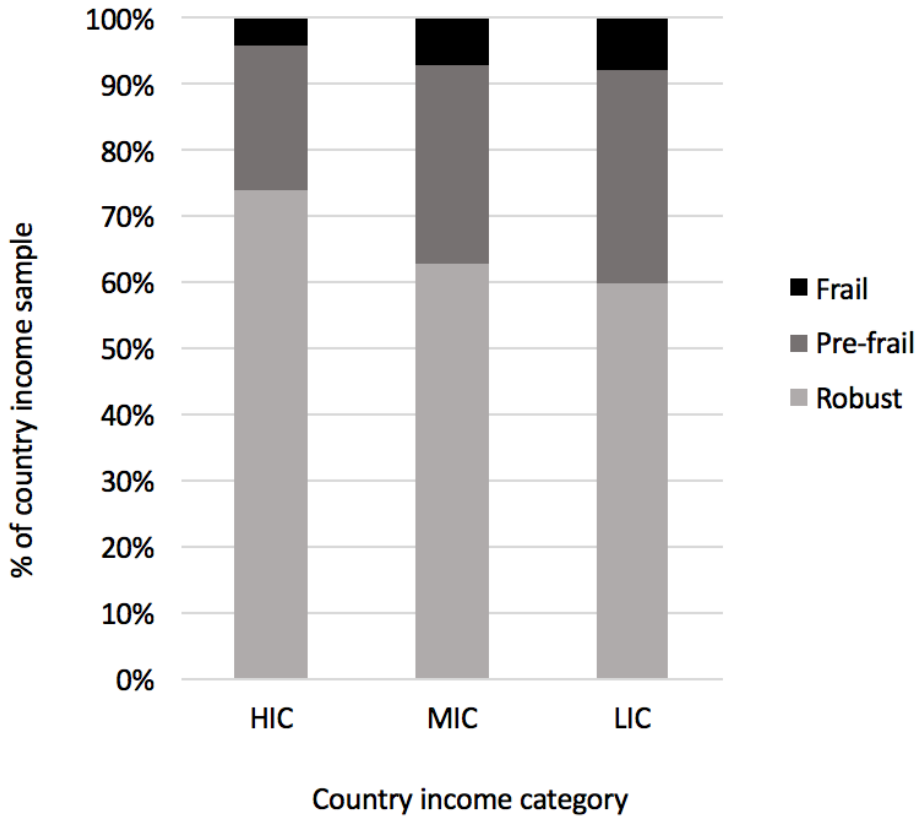


Figure 10. Distribution of phenotypic frailty categories by country income category

According to both cumulative deficit indices (including and excluding chronic diseases), the relative proportions of participants in the highest quarter of frailty was lowest among HIC (22%, n=3,500; and 21%, n=3,279), respectively), intermediate among MIC (24%, n=24,581; and 24%, n=24,170), and highest among LIC (29%, n=5,924; and 30%, n=9,608) (Tables 12 & 13; Figures 11 & 12). Using the cumulative deficit index (excluding chronic diseases), the median number of deficits among HIC, MIC, and LICs participants were 2.5 (IQR 1.5-4.17), 2.5 (IQR 1.5-4.5), and 3.0 (IQR 1.58-5.25), respectively (out of 30 deficits). The median number of deficits for participants assessed by the cumulative

deficit index (including chronic diseases) were 3.0 (IQR 1.75-4.92) for HIC, 2.92 (IQR 1.67-5.08) for MIC, and 3.17 (IQR 1.58-5.67) for LIC (out of 40 deficits). Using Poisson regression, the difference in number of deficits by country income was statistically significant for both cumulative deficit indices ($p < 0.001$).

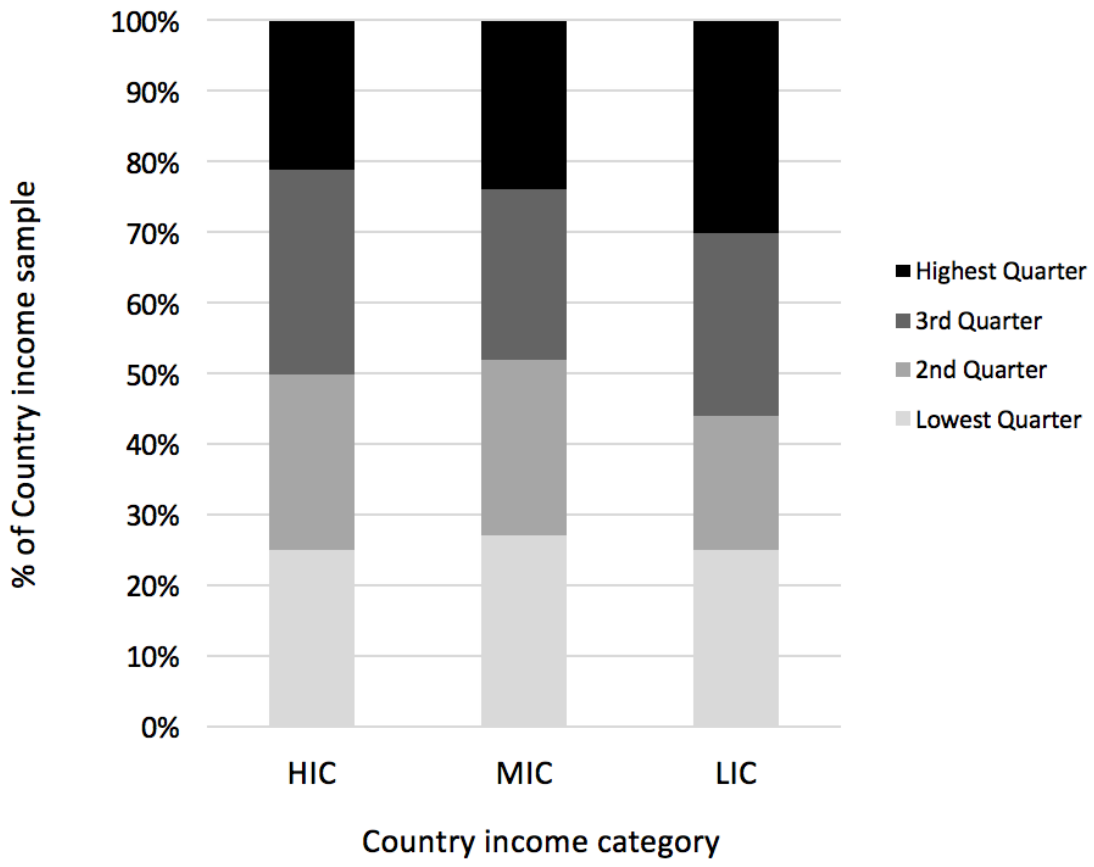


Figure 11. Distribution of participants across the cumulative deficit index frailty quarters (excluding chronic diseases) by country income sample

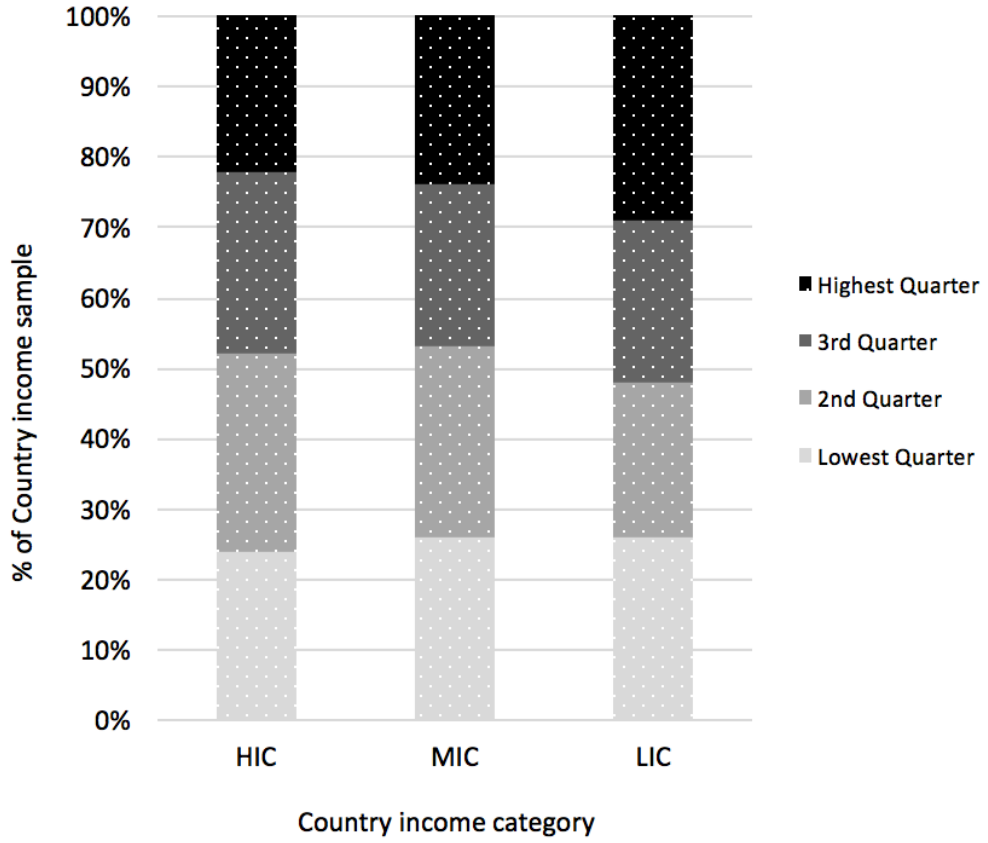


Figure 12. Distribution of participants across the cumulative deficit index frailty quarters (including chronic diseases) by country income sample

The odds of frailty were highest in LIC, followed by MIC and HIC (Table 15). Using the phenotypic definition of frailty, compared with those in HIC, individuals in MIC and LIC had unadjusted odds ratios of being frail of 2.14 and 2.65 respectively (Table 15). Using the cumulative deficit definition (excluding chronic diseases), the unadjusted odds ratios of being in the highest frailty quarter versus the lowest was 1.09 for MIC and 1.51 for LIC, compared to those in HIC (Table 15). The unadjusted odds ratio of being in the

highest frailty quarter, according to the cumulative deficit index (including chronic diseases) was 0.999 for MIC and 1.19 for LIC, compared to HIC participants (Table 15).

Table 15. Frailty Status by Country Income

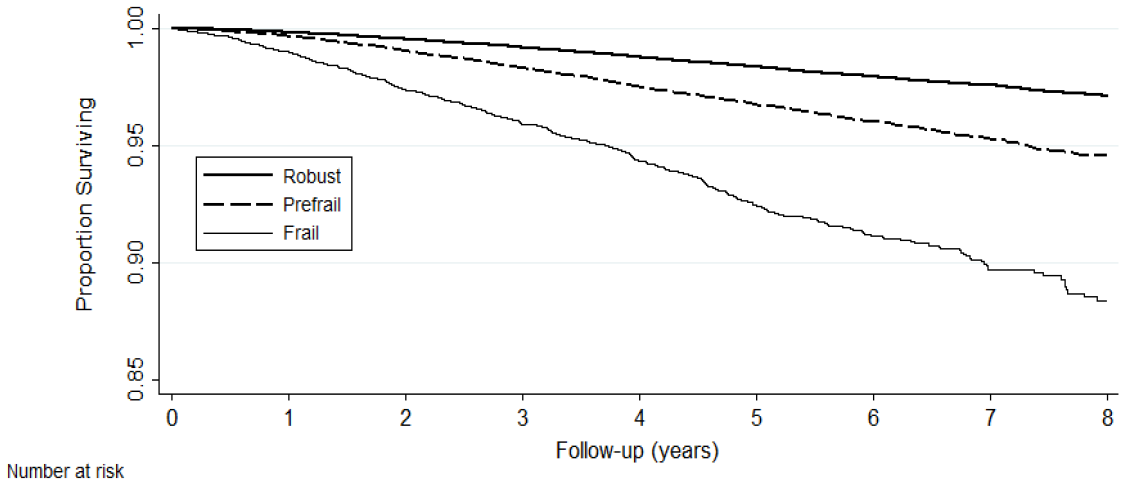
Frailty Status		Participants by Country Income (n, col%)			
Phenotypic frailty		**HIC**	**MIC**	**LIC**	**Total**
	Frail	494 (4%)	5,978 (7%)	1,093 (8%)	7,565 (6.4%)
	Pre-Frail	3,072 (22%)	26,942 (30%)	4,446 (32%)	34,460 (29.3%)
	Robust	10,091 (74%)	57,120 (63%)	8,424 (60%)	75,635 (64.3%)
	Total	**13,657 (100%)**	**90,040 (100%)**	**13,963 (100%)**	**117,660 (100%)**
	Odds (Frail vs robust)	1:20	1:9.6	1:7.7	
	Odds Ratio (Frail vs robust)	**1**	**2.14**	**2.65**	
Cumulative deficit (excluding chronic diseases)		**HIC**	**MIC**	**LIC**	**Total**
	Highest Qtr	3,279 (21%)	24,170 (24%)	9,608 (30%)	37,057 (25%)
	3rd Qtr	4,574 (29%)	24,396 (24%)	8,317 (26%)	37,287 (25%)
	2nd Qtr	4,034 (25%)	25,888 (25%)	6,086 (19%)	36,008 (24%)
	Lowest Qtr	4,047 (25%)	27,348 (27%)	7,829 (25%)	39,224 (26%)
	Total	**15,934 (100%)**	**101,802 (100%)**	**31,840 (100%)**	**149,576 (100%)**
	Odds (Highest Qtr vs lowest)	1:1.23	1:1.13	1:0.82	
	Odds Ratio (Highest Qtr vs lowest)	**1**	**1.09**	**1.51**	
Cumulative deficit (including chronic diseases)		**HIC**	**MIC**	**LIC**	**Total**
	Highest Qtr	3,500 (22%)	24,581(24%)	5,924 (28.5%)	35,978 (26%)
	3rd Qtr	4,162 (26%)	23,021(23%)	4,719 (22.7%)	36,288 (26%)
	2nd Qtr	4,362 (28%)	27,246 (27%)	4,680 (22.6%)	31,902 (23%)
	Lowest Qtr	3,792 (24%)	26,754 (26%)	5,432 (26.2%)	34,005 (25%)
	Total	**15,816 (100%)**	**101,602 (100%)**	**20,755 (100%)**	**138,173 (100%)**
	Odds (Highest Qtr vs lowest)	1:1.08	1:1.09	1:0.93	
	Odds Ratio (Highest Qtr vs lowest)	**1**	**0.999**	**1.19**	

Note: Country income classified according to the World Bank definitions

3.4. ASSOCIATION BETWEEN FRAILTY AND ALL-CAUSE MORTALITY

Among the phenotypic frailty index and cumulative deficit samples (including and excluding chronic diseases), 2,821 of 117,660 (2.4%), 4,581 of 149,576 (3.1%), and 3,758 of 138,173 (2.7%) participants died. The median length of time between baseline and last follow-up for participants was 4.65 years (IQR 3.10-6.46) for the phenotypic frailty analyses, 5.01 years (IQR 3.23-6.95) for the cumulative deficit cohort (excluding chronic diseases), and 4.82 years (IQR 3.14-5.42) for the cumulative deficit cohort (including chronic diseases).

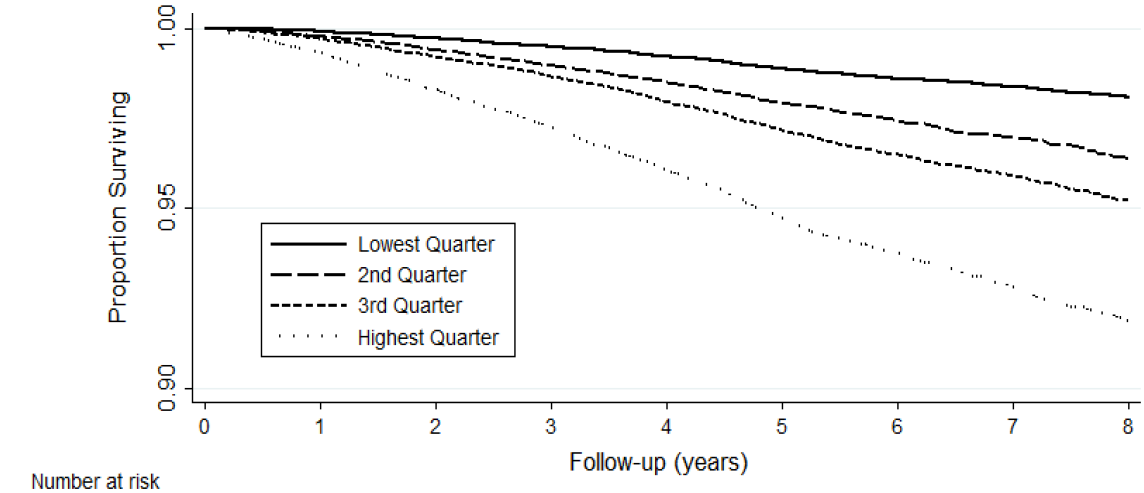
Kaplan-Meier curves comparing survival times among frailty levels of each index are found in Figures 13-15. In all three figures and indices, it is evident that increasing levels of frailty are associated with worse survival rates. Log-rank tests for equality found that the survivor functions of the different frailty levels were significantly different from one another using the phenotypic frailty index (X^2=943, p<0.001), and the cumulative deficit indices (including and excluding chronic diseases) (X^2=1548, p<0.001; and X^2 =1308, p<0.001, respectively).



Number at risk

Robust	75635	74279	71253	59213	44401	35933	26736	16062	8187
Prefrail	34460	33698	31805	26004	19346	14462	10111	5829	2953
Frail	7565	7326	6856	5573	4033	2811	1815	1018	510

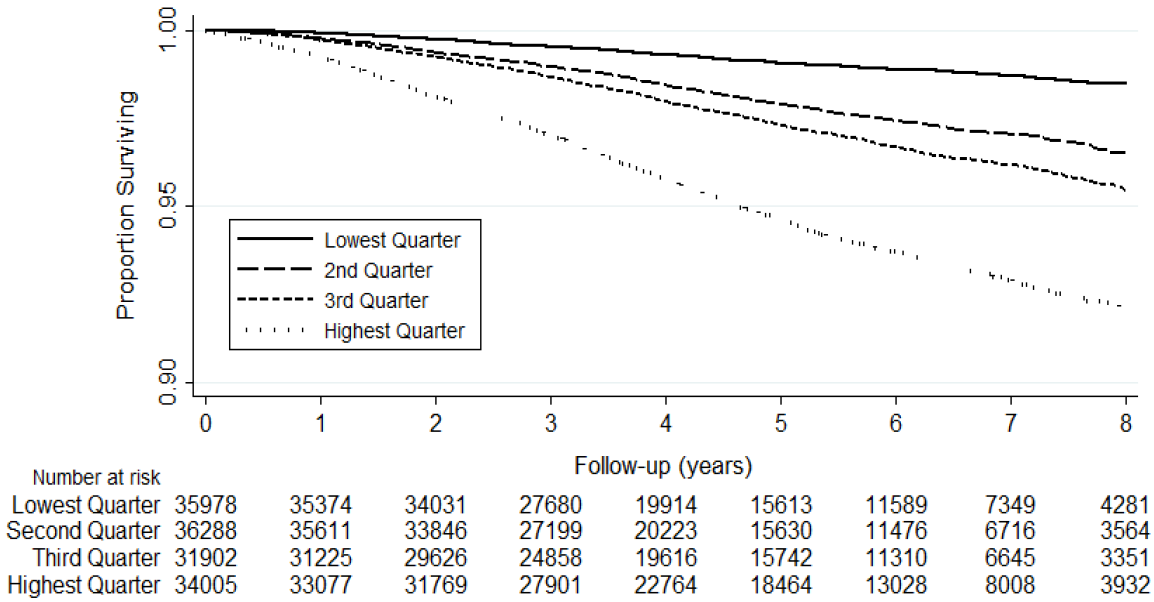
Figure 13. Kaplan-Meier curves for time to death by phenotypic frailty status (N=117,660)



Number at risk

Lowest Quarter	39224	38558	37221	30771	22853	18221	13707	9166	5941
Second Quarter	36008	35322	33609	26953	20254	15898	11928	7404	4573
Third Quarter	37287	36426	34740	29873	24130	19608	14617	9420	5741
Highest Quarter	37057	35981	34640	30857	25847	21313	15715	10611	6352

Figure 14. Kaplan-Meier curves for time to death by cumulative deficit (excluding chronic diseases) frailty quarter (N=149,576)



Number at risk									
Lowest Quarter	35978	35374	34031	27680	19914	15613	11589	7349	4281
Second Quarter	36288	35611	33846	27199	20223	15630	11476	6716	3564
Third Quarter	31902	31225	29626	24858	19616	15742	11310	6645	3351
Highest Quarter	34005	33077	31769	27901	22764	18464	13028	8008	3932

Figure 15. Kaplan-Meier curves for time to death by cumulative deficit (including chronic diseases) frailty quarter (N=138,173)

According to the Cox proportional hazards models, increasing levels of frailty predicted all-cause mortality using all three indices. Adjustment for age, sex, education, country income, smoking history, alcohol consumption history, and dietary caloric intake partly partially attenuated the strength of these associations. According to the phenotypic frailty index, the adjusted hazard ratios of mortality were 1.48 for individuals categorized as pre-frail (95% CI 1.36-1.62) and 2.63 for frail individuals (95% CI 2.35-2.95) compared to those categorized as robust (Table 16). Similarly, being in the highest quarter of frailty on either of the cumulative indices increased participants' risk of mortality by greater than two-fold, compared to the lowest quarter of frailty. All hazard ratios were significant with a p value of <0.001, except for the 2nd quarter of the cumulative deficit index (excluding chronic diseases), which had a p value of 0.02.

Table 16. Cox proportional hazards analysis for all-cause mortality

Frailty Category	Unadjusted		Adjusted*	
	HR (95% CI)	*p*	HR* (95% CI)	*p*
Phenotypic frailty index				
Robust	1	--	1	--
Pre-frail	1.96 (1.80-2.12)	<0.001	1.48 (1.36-1.62)	<0.001
Frail	4.44 (4.00-4.92)	<0.001	2.63 (2.35-2.95)	<0.001
Cumulative deficit index (excluding chronic diseases)				
Lowest Quarter	1	--	1	--
2nd Quarter	1.89 (1.68-2.12)	<0.001	1.15 (1.02-1.30)	0.02
3rd Quarter	2.51 (2.25-2.80)	<0.001	1.35 (1.21-1.52)	<0.001
Highest Quarter	4.53 (4.10-5.01)	<0.001	2.05 (1.84-2.30)	<0.001
Cumulative deficit index (including chronic diseases)				
Lowest Quarter	1	--	1	--
2nd Quarter	2.29 (2.01-2.61)	<0.001	1.42 (1.23-1.64)	<0.001
3rd Quarter	2.94 (2.59-3.35)	<0.001	1.63 (1.42-1.87)	<0.001
Highest Quarter	5.65 (5.02-6.37)	<0.001	2.72 (2.38-3.10)	<0.001

*Adjusted for: age, sex, country income, highest education achieved, smoking history, alcohol consumption history, dietary caloric intake. For phenotypic frailty index, N=117,660 for the unadjusted analyses and N=109,646 for the adjusted analyses. For the cumulative deficit index (excluding chronic diseases), N=149,576 for unadjusted and N=138,021 for the adjusted analyses. For the cumulative deficit index (including chronic diseases), N=138,173 for unadjusted and N=127,169 for the adjusted analyses.

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the three frailty indices' discriminatory ability for all-cause mortality (Figure 16). The cumulative deficit index (including chronic diseases) had the greatest area under the curve (AUC), with a value of 0.68 (95% CI 0.68-0.69), indicating that it had the best discriminatory ability for all-cause mortality. This was closely followed by the cumulative deficit index (excluding chronic diseases), which had an AUC of 0.66 (95% CI 0.63-0.67), and then the phenotypic frailty index, with an AUC of 0.61 (95% CI 0.60-0.62). The chi-

squared test yielded a significance probability of <0.001 ($\chi^2 = 136.02$), indicating there was a statistically significant difference between all three areas.

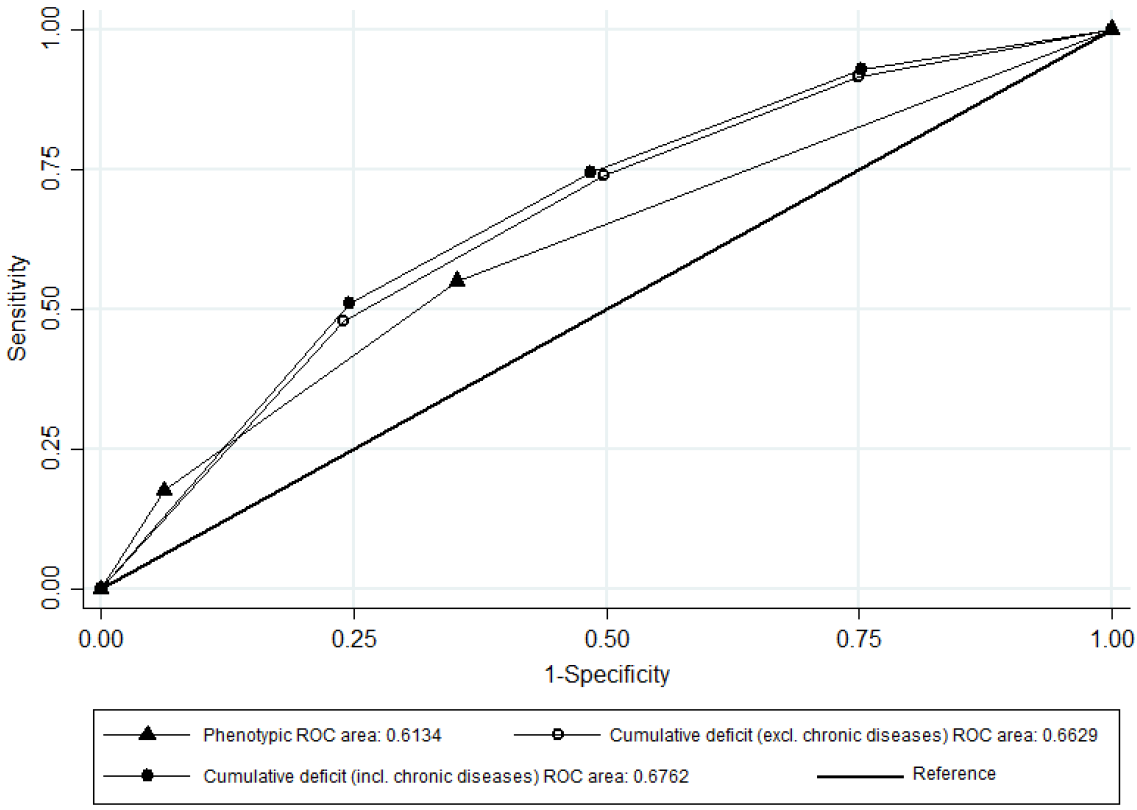


Figure 16. Comparing the receiver operating characteristic (ROC) curves of the phenotypic frailty and cumulative deficit indices

3.4.1. Association of Frailty and All-Cause Mortality by Sex

Despite the association between females and higher levels of cumulative deficit frailty, females demonstrated longer time-to-death than do men, as evident in the Kaplan-Meier survival curves in Figures 17-18. After dividing the participant sample into two groups according to cumulative deficit scores above or below the median, a comparison of

Kaplan-Meier curves demonstrated that females outlive men with comparable frailty scores (Figures 19 & 20). Moreover, there appears to be an interaction between sex and frailty with respect to survival for both cumulative deficit indices; the difference in survival between females and males is greater in the upper two frailty quarters than in the lower two frailty quarters (Figures 19 & 20). Kaplan-Meier curve analysis demonstrated improved survival among women compared to men of the same phenotypic frailty category (Figure 21). Similarly, females have lower mortality risk than do men of the same frailty level (according to all three indices), after adjusting for age and other factors (Tables 17 & 18). Stratified log-rank tests of equality determined that the survival functions of males and females were significantly different across the frailty levels for all three indices (p<0.001).

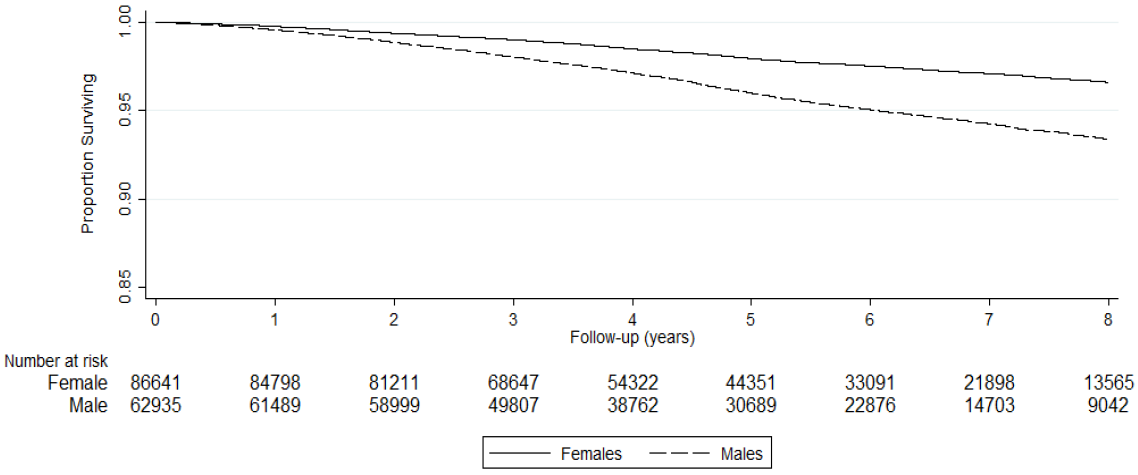


Figure 17. Kaplan-Meier curves for time to death by sex using the cumulative deficit (excluding chronic diseases) frailty sample (N=149,576)

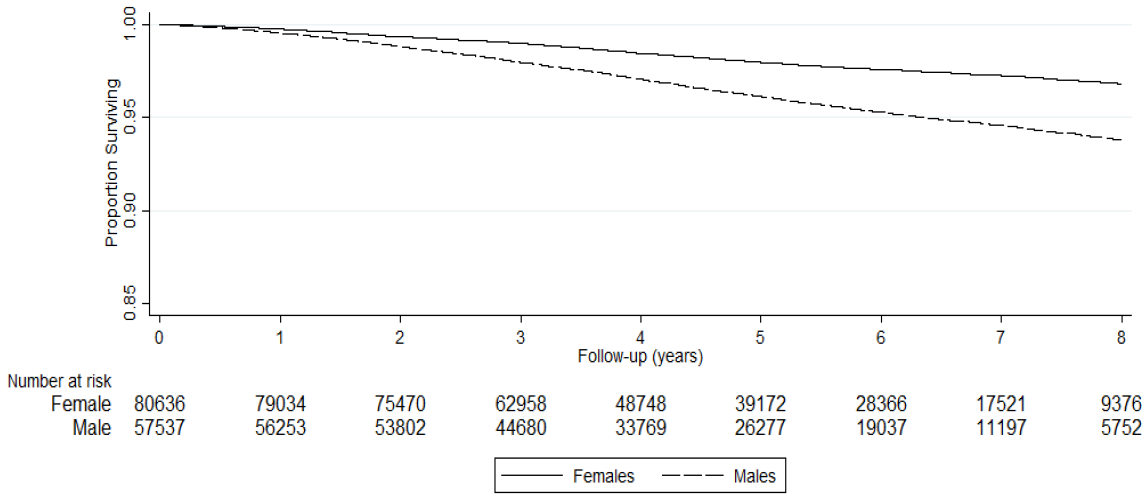


Figure 18. Kaplan-Meier curves for time to death by sex using the cumulative deficit (including chronic diseases) frailty sample (N=138,173)

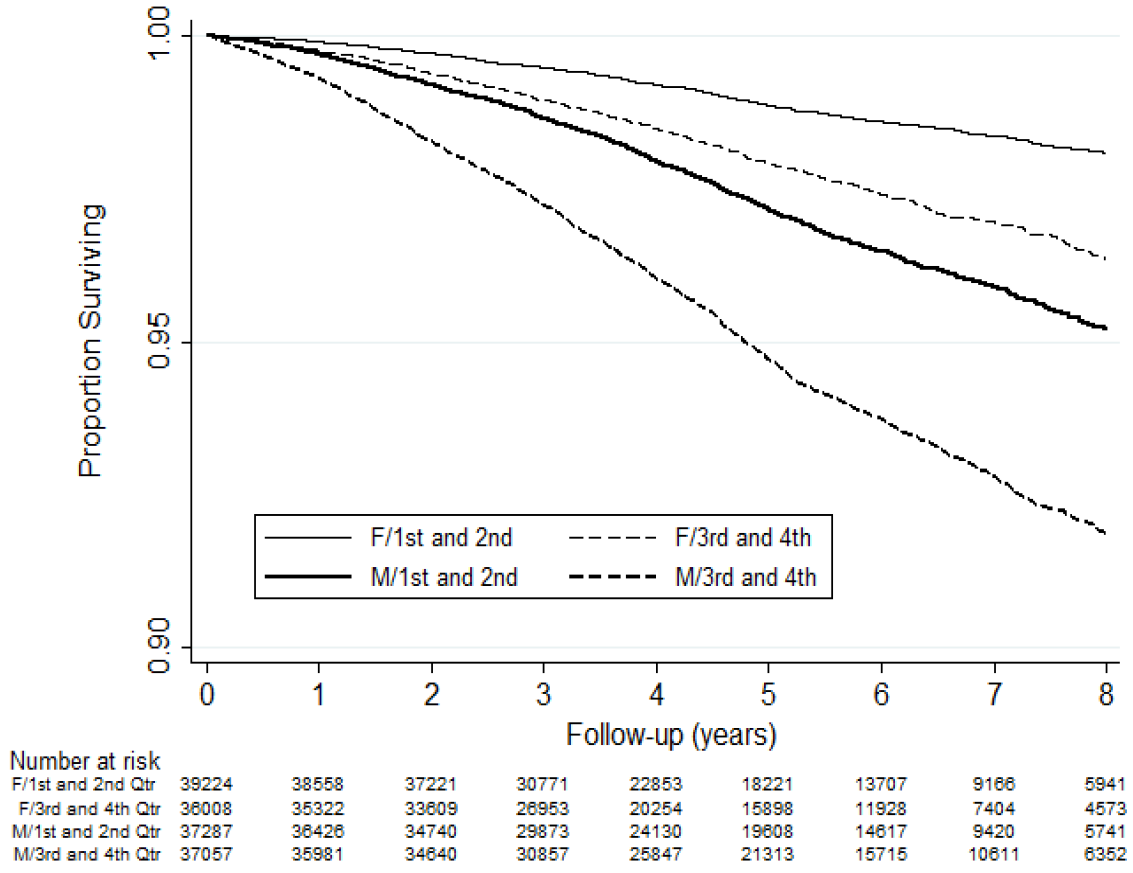


Figure 19. Kaplan-Meier curves for time to death by sex according to the cumulative deficit (excluding chronic diseases) frailty quarter (N=149,576). Note: the analysis grouped the lowest two quarters and the highest two quarters together. F=female, and M=male.

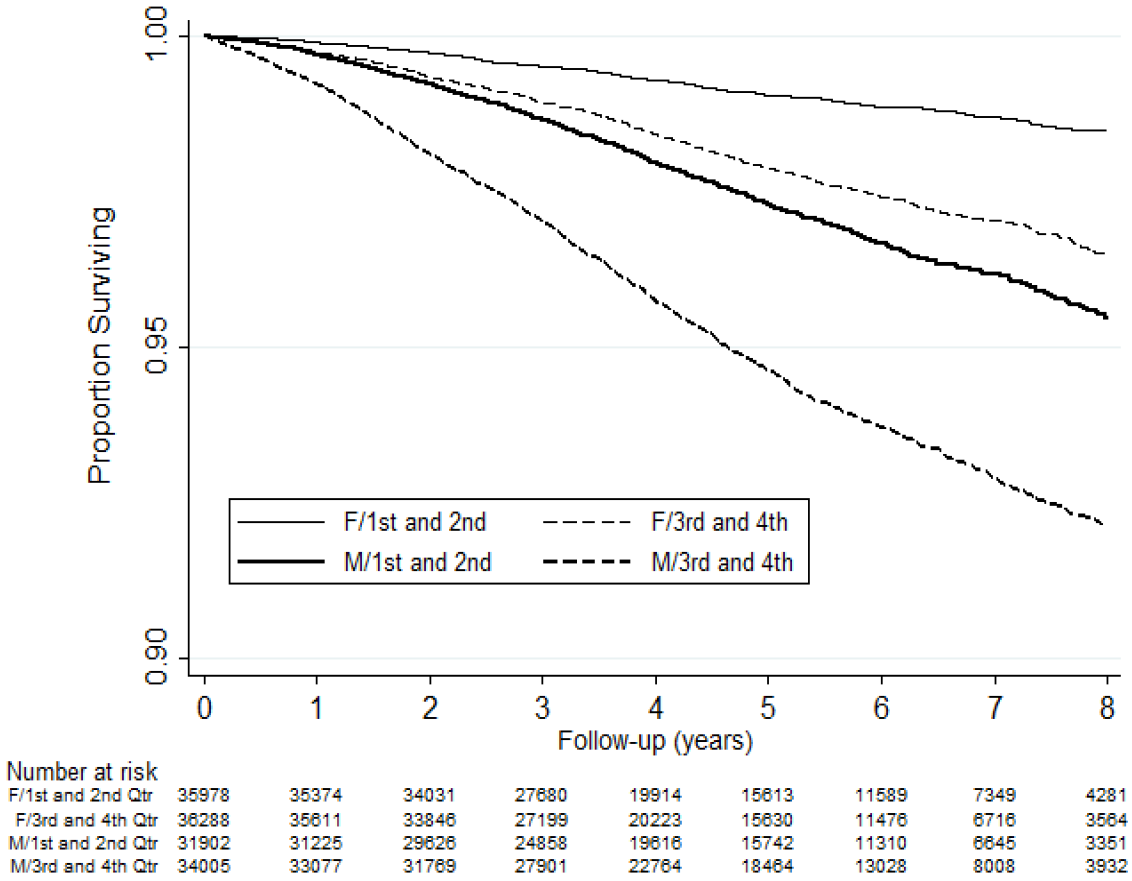


Figure 20. Kaplan-Meier curves for time to death by sex according to the cumulative deficit (including chronic diseases) frailty quarter (N=138,173). Note: the analysis grouped the lowest two quarters and the highest two quarters together. F=female, and M=male.

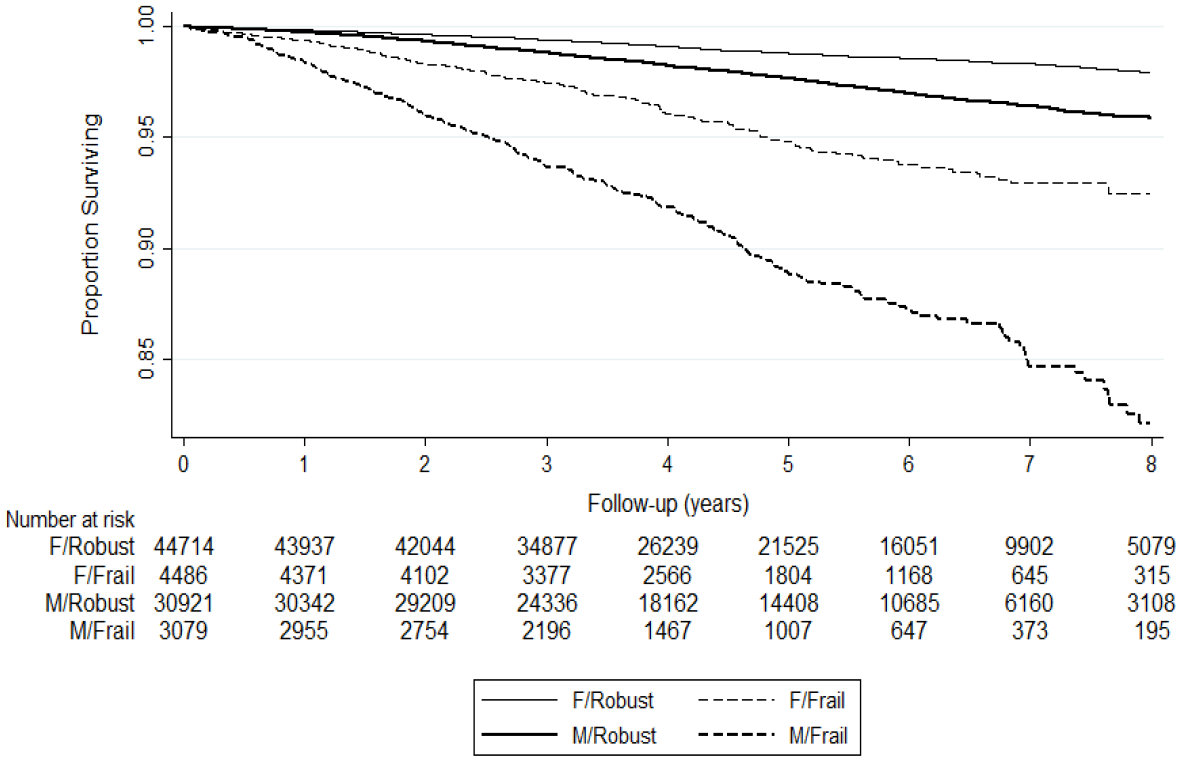


Figure 21. Kaplan-Meier curves for time to death by phenotypic frailty status and sex (N=117,660). F=female, M=male.

Table 17. Adjusted Cox analyses of all-cause mortality by sex and cumulative deficit frailty status.

Frailty Quarter and Sex		HR* (95% CI)	*p*
Cumulative deficit index (excluding chronic diseases)			
1st/ 2nd	**F**	1 (Reference)	--
	M	1.63 (1.44-1.85)	<0.001
3rd/4th	**F**	1.52 (1.36-1.69)	<0.001
	M	2.60 (2.31-2.92)	<0.001
Cumulative deficit index (including chronic diseases)			
1st/ 2nd	**F**	1 (Reference)	--
	M	1.74 (1.51-2.00)	<0.001
3rd/4th	**F**	1.74 (1.54-1.97)	<0.001
	M	2.98 (2.62-3.39)	<0.001

*Adjusted for: age, country income, highest education achieved, smoking history, alcohol consumption history, dietary caloric intake. For the cumulative deficit index (excluding chronic diseases), N=138,021. For the cumulative deficit index (including chronic diseases), N=127,169.

Table 18. Adjusted standard Cox analyses of all-cause mortality by sex and phenotypic frailty status.

Frailty Phenotype and Sex		HR* (95% CI)	*p*
Robust	**F**	1 (Reference)	--
	M	1.72 (1.52-1.95)	<0.001
Pre-frail	**F**	1.55 (1.35-1.76)	<0.001
	M	2.49 (2.19-2.83)	<0.001
Frail	**F**	2.70 (2.28-3.21)	<0.001
	M	4.46 (3.80-5.22)	<0.001

*Adjusted for: age, country income, highest education achieved, smoking history, alcohol consumption history, dietary caloric intake. N=109,464.

3.4.2. TESTS OF PROPORTIONALITY ASSUMPTION

The proportional hazards (PH) assumption of the Cox proportional hazards regressions was tested by plotting the log(-log(Survival)) against follow-up years after baseline, according to the different strata of frailty. This was done because the proportional

hazards assumption is not guaranteed to be met even when the Kaplan-Meier survival function curves do not cross (Kleinbaum, 2006, p.135). A log-log survival curve is generated by taking the natural log of an estimated survival function twice; logs of probabilities always produce negative numbers, and it is impossible to take the log of a negative number. Thus, the mathematical formula for the log-log curve requires taking the negative of the first log to produce a positive value before taking the second log: -ln(-ln(Survival)) (Kleinbaum, 2006, p. 137). The scale for the y-axis of a log-log curve is between $-\infty$ to $+\infty$. Log-log plots adjusted for age, sex, country income, highest education achieved, smoking history, alcohol consumption history, and dietary caloric intake were also produced.

Using algebra, it can be determined that the vertical distance between two log-log curves is equal to the linear sum of differences in the survival estimates of the two curves, and is independent of time (Kleinbaum et al., 2006, p.140). Parallelism of two log-log curves would indicate that there is a constant difference in predictor values between the two curves over time. Thus, the proportionality assumption, which states that the hazard ratios of the predictor's strata are proportional over time, is considered satisfied if the log-log plot produces parallel curves. Kleinbaum et al. (2006; p.172) suggests conservatively accepting the proportional hazards assumption unless there is strong evidence against it. As such, in cases where the parallelism of the log-log survival lines is difficult to discern, it is recommended to consider the proportionality assumption as satisfied. Figures 22-27 demonstrate parallel survival curves, suggesting that the proportional hazards assumption for the phenotypic frailty index and the two cumulative deficit indices is appropriate, with

and without the adjustment of covariates. Moreover, the proportional hazards assumption of the frailty phenotype had been previously deemed reasonable in the study where it was originally validated (Fried et al., 2001).

The parallelism in the nature of the log-log plots (Figures 22-27) does not appear to begin immediately, but rather only after almost a year of follow-up. This suggests that the mortality hazards among the different frailty groups may not be proportional within the first year of follow-up. To explore this, further analysis was done to evaluate the association between frailty and one-year mortality risk (Table 19).

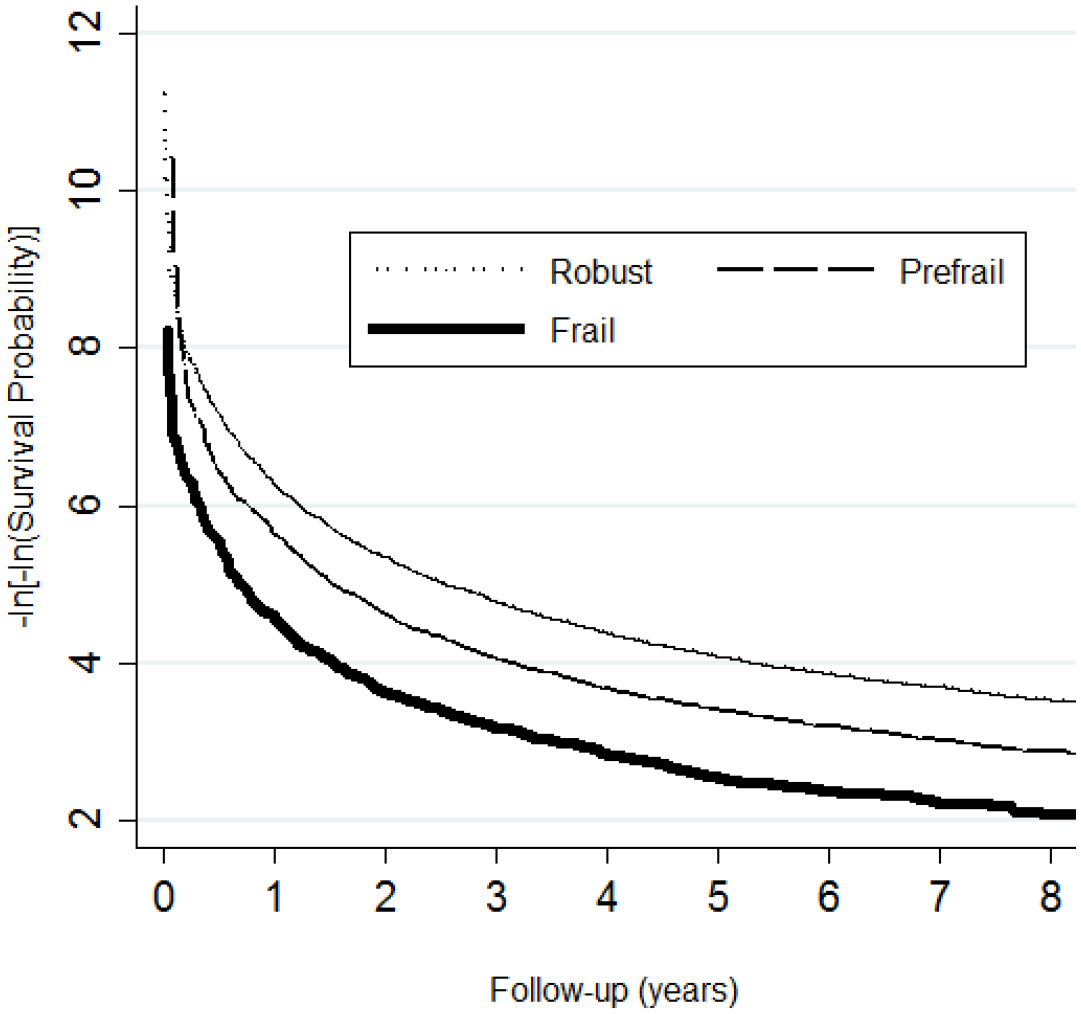


Figure 22. Log-log plots of the Kaplan-Meier survival curves of the phenotypic frailty index (not adjusted) against follow-up years after baseline.

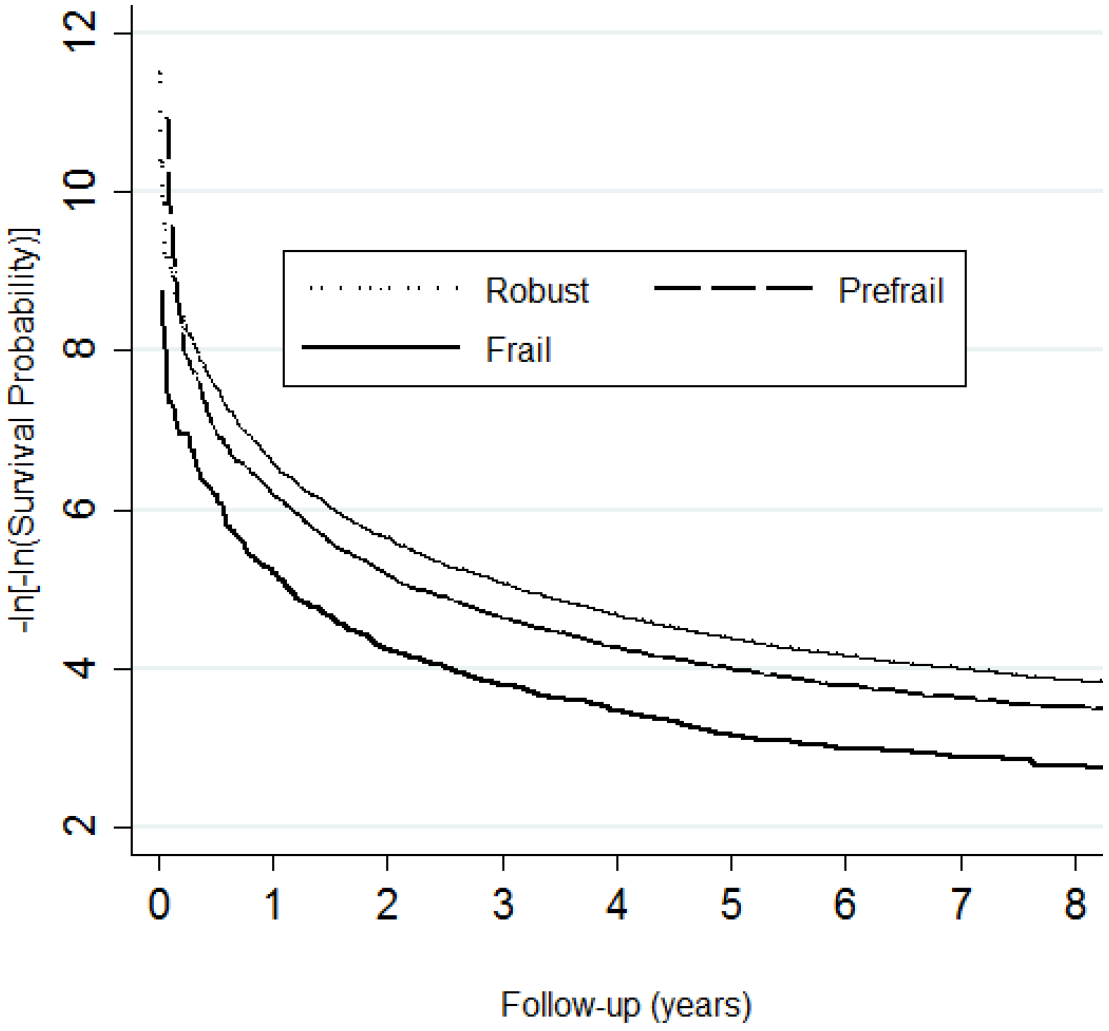


Figure 23. Log-log plots of the Kaplan-Meier survival curves of the phenotypic frailty index (adjusted) against follow-up years after baseline. Adjusted for: age, sex, country income, highest education achieved, smoking history, alcohol consumption history, dietary caloric intake.

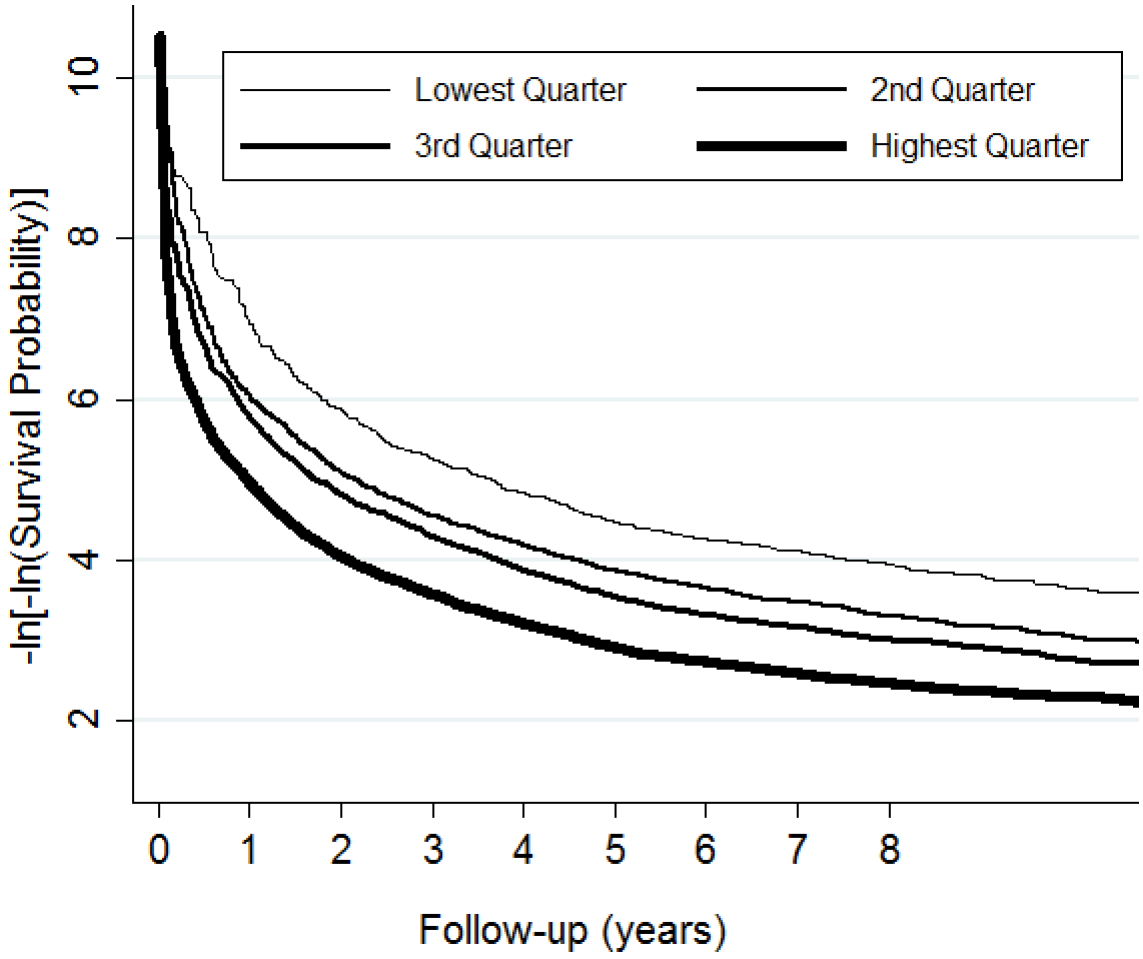


Figure 24. Log-log plots of the Kaplan-Meier survival curves of the cumulative deficit index (excluding chronic diseases) (not adjusted) against follow-up years after baseline

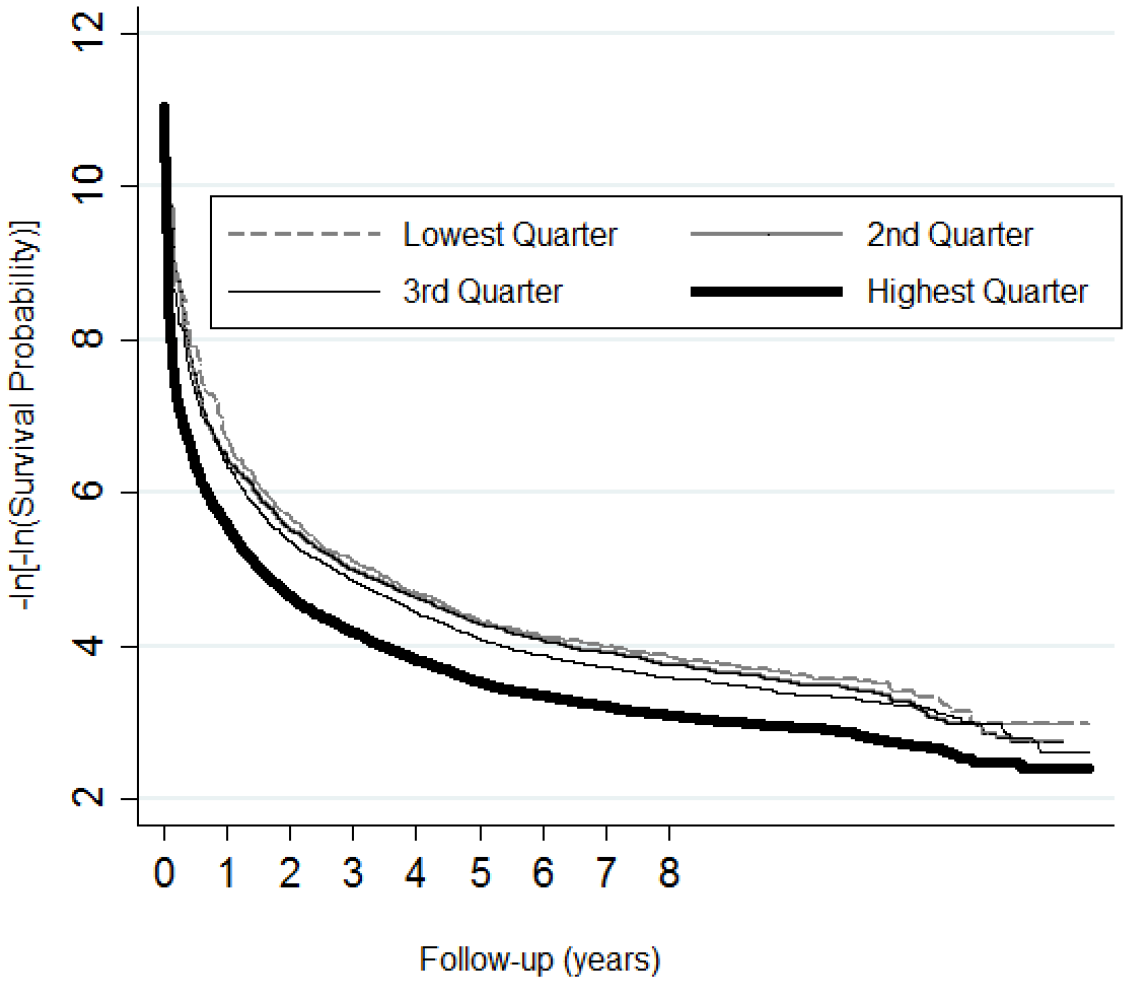


Figure 25. Log-log plots of the Kaplan-Meier survival curves of the cumulative deficit index (excluding chronic diseases) (adjusted) against follow-up years after baseline. Adjusted for: age, sex, country income, highest education achieved, smoking history, alcohol consumption history, dietary caloric intake.

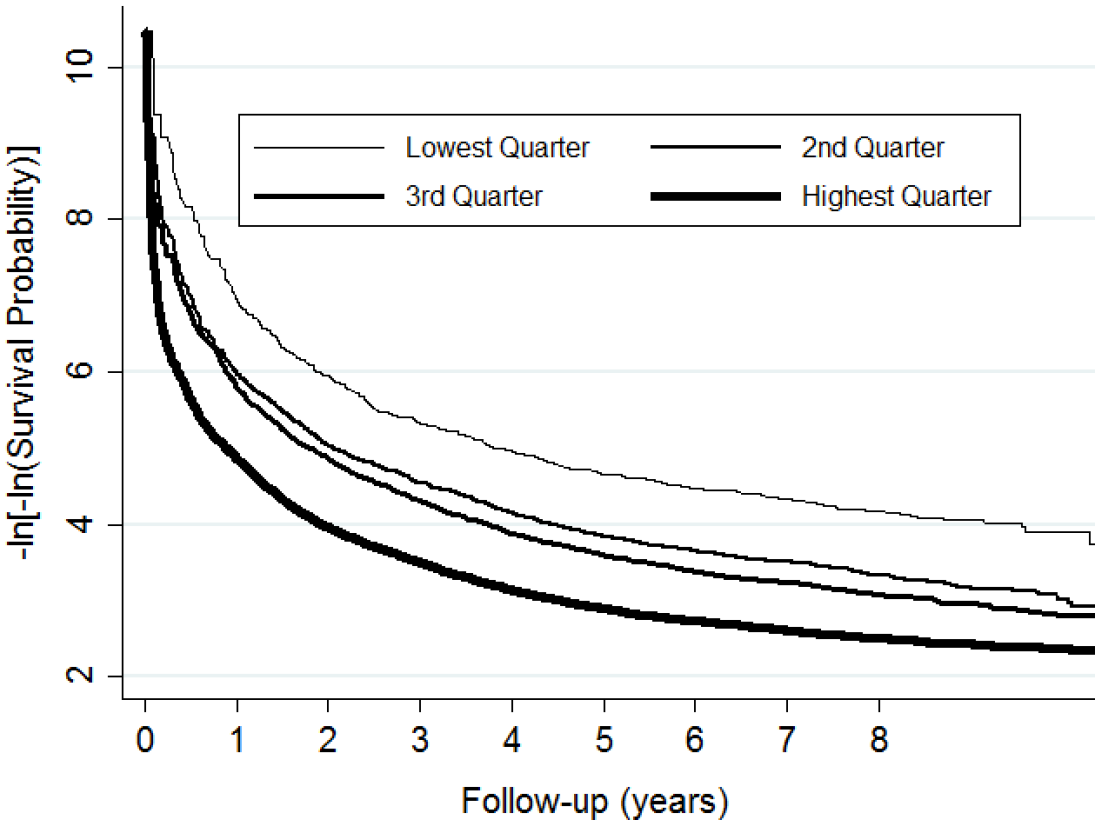


Figure 26. Log-log plots of the Kaplan-Meier survival curves of the cumulative deficit index (including chronic diseases) (not adjusted) against follow-up years after baseline

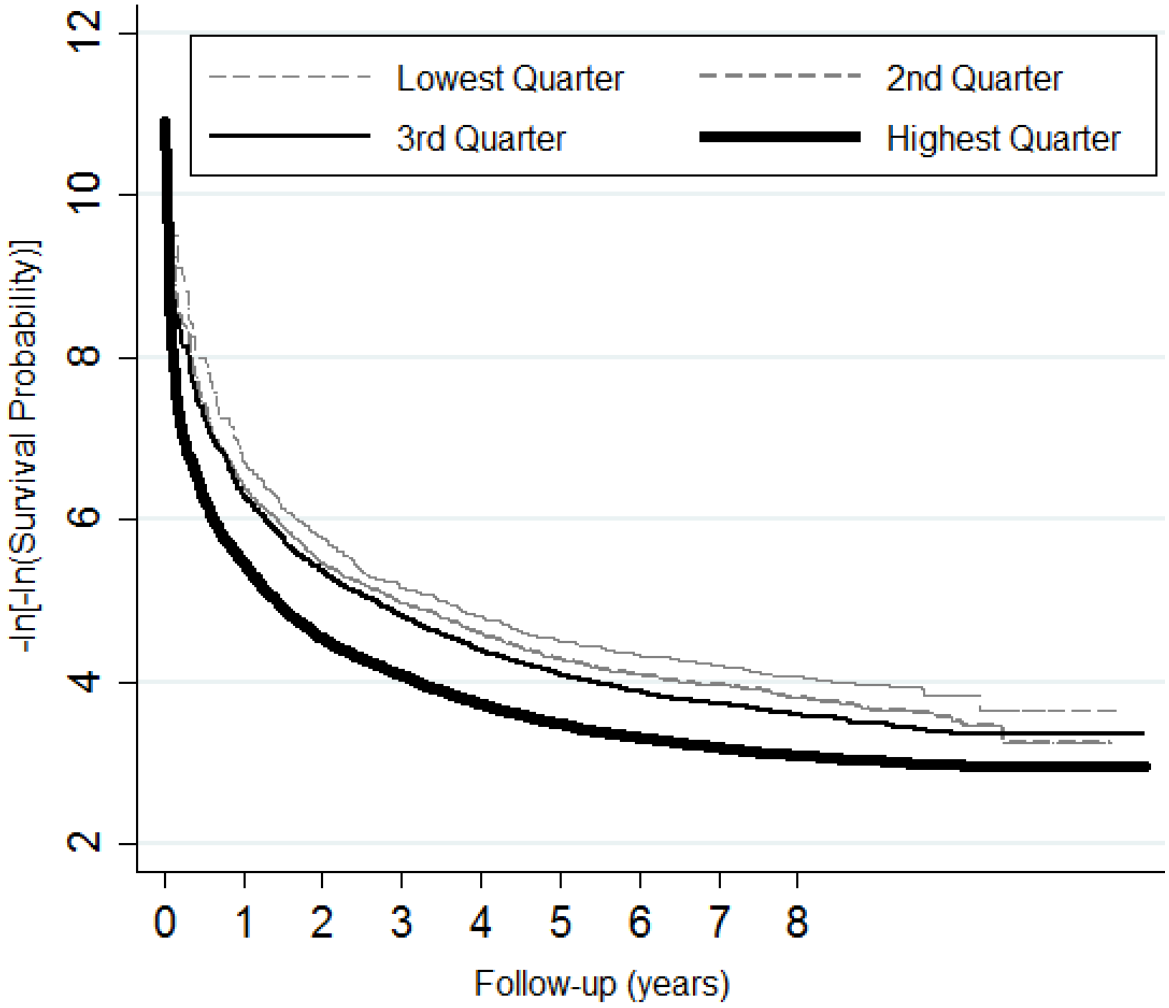


Figure 27. Log-log plots of the Kaplan-Meier survival curves of the cumulative deficit index (including chronic diseases) (adjusted) against follow-up years after baseline. Adjusted for: age, sex, country income, highest education achieved, smoking history, alcohol consumption history, dietary caloric intake.

3.4.3. ASSOCIATION BETWEEN FRAILTY AND ONE-YEAR MORTALITY

The log-log plots of the survival curves demonstrated steep declines in survival within the first year after baseline. To explore this further, adjusted standard Cox analyses were repeated to analyze the association between frailty and one-year mortality.

Among the phenotypic frailty index sample, 313 participants died within one year after baseline. Among the cumulative deficit index samples (excluding and including chronic diseases), 452 participants and 435 participants died within one year, respectively. Across all three indices and at each frailty level, adjusted hazard ratios were greater for one-year mortality than for all-cause mortality (Tables 16 & 19). Among phenotypically pre-frail and frail participants, adjusted hazard ratios and IQR for one-year mortality were 1.51 (1.17-1.95) and 3.17 (2.33-4.32), compared to 1.48 (1.36-1.62) and 2.63 (2.35-2.95) for overall mortality, respectively. According to the cumulative deficit index (excluding chronic diseases), adjusted hazard ratios and IQR for one-year mortality among participants in the second to fourth frailty quarter were 1.50 (1.00-2.23), 1.75 (1.19-2.58), and 3.46 (2.40-5.01). For overall mortality, the respective adjusted hazard ratios and IQR were 1.15 (1.02-1.30), 1.35 (1.21-1.52), and 2.05 (1.84-2.30). Along with the graphical evidence from the log-log plots, this suggests that frailty has an even stronger association to mortality risk within one-year of follow-up than it does in later years.

Table 19. Standard Cox analyses for one-year mortality

Frailty Category	Unadjusted		Adjusted*	
	HR (95% CI)	*p*	HR* (95% CI)	*p*
Phenotypic frailty index				
Robust	1	--	1	--
Pre-frail	1.89 (1.47-2.39)	<0.001	1.51 (1.17-1.95)	<0.001
Frail	5.38 (4.06-7.11)	<0.001	3.17 (2.33-4.32)	<0.001
Cumulative deficit index (excluding chronic diseases)				
Lowest Quarter	1	--	1	--
2nd Quarter	2.38 (1.62-3.50)	<0.001	1.50 (1.00-2.23)	0.05
3rd Quarter	3.23 (2.24-4.65)	<0.001	1.75 (1.19-2.58)	0.005
Highest Quarter	7.23 (5.14-10.16)	<0.001	3.46 (2.40-5.01)	<0.001
Cumulative deficit index (including chronic diseases)				
Lowest Quarter	1	--	1	--
2nd Quarter	2.60 (1.75-3.86)	<0.001	1.79 (1.18-2.71)	0.006
3rd Quarter	3.16 (2.14-4.68)	<0.001	1.86 (1.23-2.84)	0.004
Highest Quarter	8.12 (5.68-11.6)	<0.001	4.14 (2.79-6.13)	<0.001

*Adjusted for: age, sex, country income, highest education achieved, smoking history, alcohol consumption history, dietary caloric intake. For phenotypic frailty index, N=117,660 for the unadjusted analyses and N=109,646 for the adjusted analyses. For the cumulative deficit index (excluding chronic diseases), N=149,576 for unadjusted and N=138,021 for the adjusted analyses. For the cumulative deficit index (including chronic diseases), N=138,173 for unadjusted and N=127,169 for the adjusted analyses.

3.5. MULTI-MORBIDITY

Among the same PURE sample (N=153,127), the prevalence of multi-morbidity (defined as two or more of eleven chronic diseases assessed) was approximately 15% (mean age of 50, IQR 42-58 years) (Table 20). The percentage of the sample with none of the twelve chronic diseases assessed was 56.7%. High income countries had the greatest

proportion of its sample categorized as multi-morbid (20%), followed by middle income countries (15%) and low income countries (13%) (Table 21).

Table 20. Total sample by number of chronic diseases at baseline

No. of Chronic Diseases	n	% of Sample
0	86,881	56.7
1	44,146	28.8
2	15,606	10.2
3	4,571	3.0
4	1,167	0.8
5-7	405	0.3
8-12	351	0.2
Total	**153,127**	**100**

Note: Twelve chronic diseases assessed: diabetes, coronary heart disease, heart failure, other heart disease, stroke, hepatitis/jaundice, hypertension, chronic obstructive pulmonary disease, depression, asthma, AIDS, and cancer.

Table 21. Prevalence of multi-morbidity by country income

Multi-morbidity status	Country Income			Total n (col%)
	High n (col%)	Middle n (col%)	Low n (col%)	
Not multi-morbid (0-1 chronic disease)	12,861 (80%)	87,841 (85%)	29,609 (87%)	130,311 (85%)
Multi-morbid (2+ chronic diseases)	3,196 (20%)	15,157 (15%)	4,463 (13%)	21,816 (15%)
Total	16,057 (100%)	102,998 (100%)	34,072 (100%)	**153,127** (100%)

3.5.1. ASSOCIATION BETWEEN MULTI-MORBIDITY AND FRAILTY

Multi-morbidity was more common among increasing levels of frailty using both the phenotypic frailty and cumulative deficit (excluding chronic diseases) indices (Tables 22-23). Multi-morbidity was more strongly associated with frailty according to the cumulative deficit index (excluding chronic diseases) than the phenotypic frailty index. Among those who were multi-morbid, only 12% were also categorized as phenotypically frail, whereas 54% were phenotypically robust. Using the cumulative deficit index (excluding chronic diseases), the majority (54%) of multi-morbid participants were concurrently categorized in the highest quarter of cumulative deficit frailty, and only 20% of multi-morbid participants were categorized in the lower two frailty quarters.

Table 22. Prevalence of multi-morbidity by phenotypic frailty status (N=117,660)

No. of Chronic Diseases at Baseline		**Phenotypic frailty status n (col%)**			**Total**
		Robust	**Pre-frail**	**Frail**	
Not multi-morbid	**0**	44,883 (59%)	18,360 (53%)	3,208 (42%)	66,451 (56%)
	1	21,317 (28%)	10,166 (29%)	2,334 (31%)	33,817 (29%)
Multi-morbid	**≥2**	9,435 (13%)	5,934 (18%)	2,023 (27%)	17,392 (15%)
Total		75,635 (100%)	34,460 (100%)	7,565 (100%)	117,660 (100%)

Table 23. Prevalence of multi-morbidity by cumulative deficit (excluding chronic diseases) frailty status (N=149,576)

No. of Chronic Diseases at Baseline		Cumulative deficit index (excluding chronic diseases) frailty quarter n (col%)				Total
		Lowest	2nd	3rd	Highest	
Not multi-morbid	0	31,569 (80.5%)	23,145 (64%)	18,584 (50%)	11,123 (30%)	84,421 (56%)
	1	6,356 (16.2%)	9,772 (27%)	13,019 (35%)	14,216 (38%)	43,363 (29%)
Multi-morbid	≥2	1,299 (3.3%)	3,091 (9%)	5,684 (15%)	11,718 (32%)	21,792 (15%)
Total		39,224 (100%)	36,008 (100%)	37,287 (100%)	37,057 (100%)	149,576 (100%)

Percentages are reported to two significant figures, except where an additional decimal place is required for each column to add to 100%.

Kaplan-Meier curves comparing survival times for each combination of frailty and multi-morbidity statuses are displayed in Figures 28-29. Using the phenotypic frailty index, worst survival was associated with being both frail and multi-morbid, followed by being frail-only, multi-morbid-only, and finally neither multi-morbid nor frail (Figure 28). Participants who were both phenotypically frail and multi-morbid had worse unadjusted survival times than would be expected from the survival times of either phenotypic frailty or multi-morbidity separately. Using the cumulative deficit index (excluding chronic diseases), there was significant overlap in the Kaplan-Meier curves between multi-morbid-only participants and frail-only participants, indicating very similar survival outcomes (Figure 29).

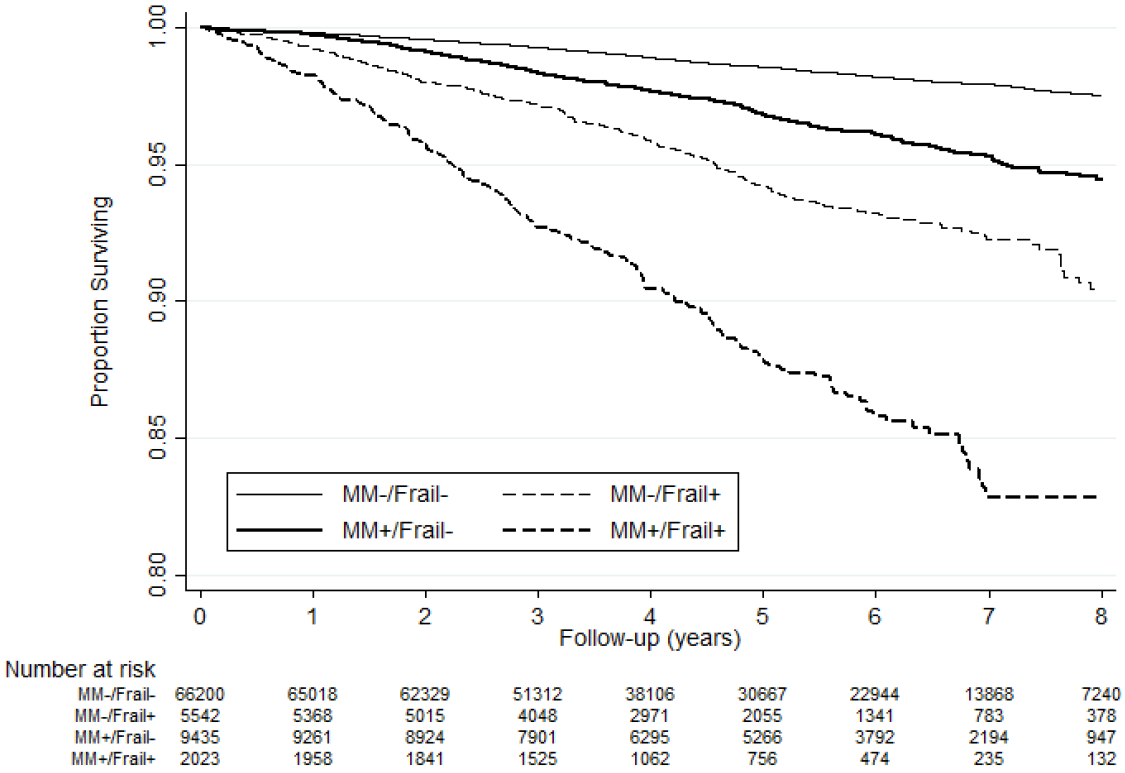


Figure 28. Kaplan-Meier curves for time to death by multi-morbidity and phenotypic frailty status (N=83,200). Note: Frail- = Robust (absence of all three phenotypic frailty variables); Frail+ = Frail (two-three of the phenotypic frailty variables). MM= multi-morbidity (defined as ≥2 chronic diseases)

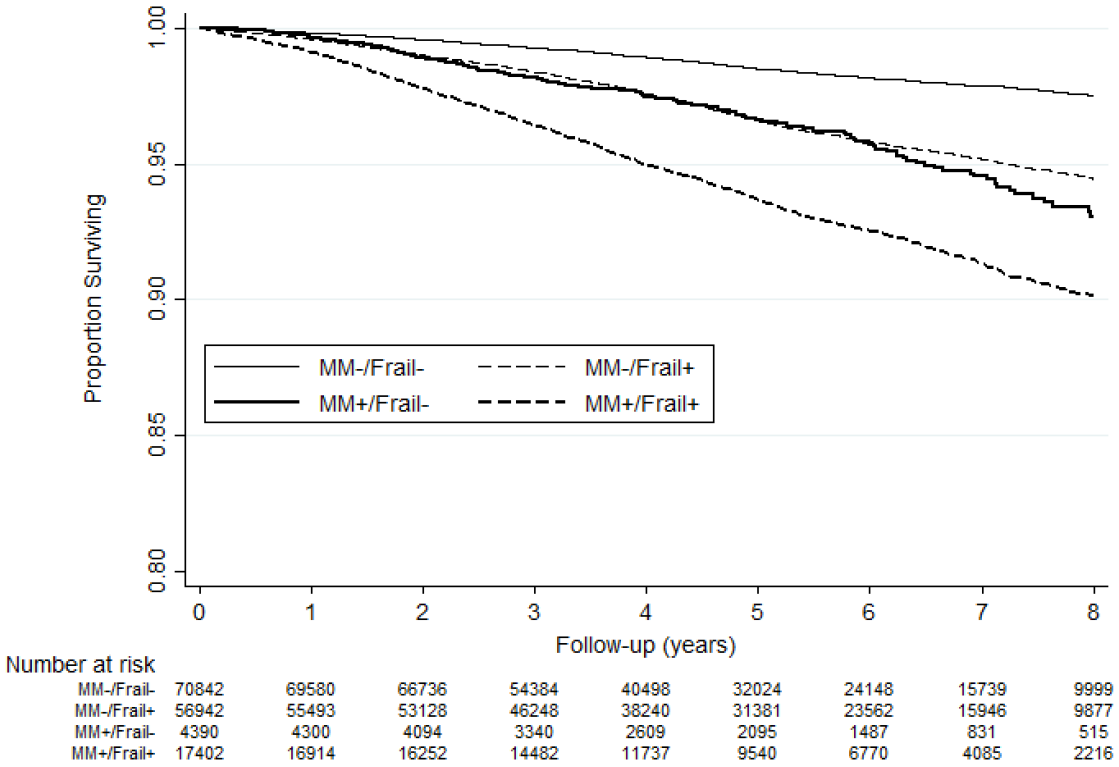


Figure 29. Kaplan-Meier curves for time to death by multi-morbidity and cumulative deficit (excluding chronic diseases) frailty quarter (N=149,576). Note: Frail+ = bottom two quarters of the frailty index; Frail- = top two quarters of the index. MM= multi-morbidity (defined as ≥2 chronic diseases)

Multi-morbidity and frailty, according to both definitions, appear to have independent, additive effects on the risk of mortality. For example, the adjusted hazard ratios (HR) for all-cause mortality for the phenotypically frail category are 2.27 (95% CI 1.96-2.62; $p<0.001$) and 5.08 (95% CI 4.34-5.95; $p<0.001$) for non-multi-morbid and multi-morbid subjects, respectively (Figure 30). Using the cumulative deficit index (excluding chronic diseases), the HRs for individuals in the highest quarter of frailty and in

the non-multi-morbid and multi-morbid categories were 1.80 (95% CI 1.59-2.03; $p<0.001$) and 3.18 (95% CI 2.80-3.62; $p<0.001$), respectively (Figure 31).

According to the phenotypic frailty index, adjusted hazard ratios for mortality were greatest among individuals who were both multi-morbid and frail (5.08 (95% CI 4.34-5.95; $p<.0001$)), followed by multi-morbid and pre-frail (2.81 (95% CI 2.48-3.19; $p<.0001$)) (Figure 30). Individuals who were not multi-morbid but were frail had greater mortality risk (2.27 (95% CI 1.96-2.62; $p<.0001$)) than individuals who were multi-morbid but robust (1.76 (95% CI 1.55-2.01; $p<.0001$)). As expected, individuals who were both robust and not multi-morbid had the lowest mortality risk.

Using the cumulative deficit frailty index (excluding chronic diseases), adjusted mortality risk was greatest among individuals who were multi-morbid and in the highest frailty quarter (3.18 (95% CI 2.80-3.62; $p<.0001$)) compared to individuals who were not multi-morbid and in the lowest frailty quarter (Figure 31). However, among multi-morbid participants, high cumulative deficit frailty was not consistently associated with greater mortality risk after adjustment. On the other hand, multi-morbidity increased mortality risk in individuals at all frailty quarters. Mortality risk for multi-morbid participants in the lowest quarter of frailty was greater than the risk of non-multi-morbid participants in the highest quarter of frailty (HR=219 (95% CI 1.58-3.04; $p<0.001$) versus HR=1.80 (95% CI 1.59-2.03; $p<0.001$)). All values were statistically significant with p values of <0.001, except for non-multi-morbid participants in the second quarter of the cumulative deficit index (excluding chronic diseases), which had a p value of 0.04. Interactions between multi-morbidity and the cumulative deficit index (including chronic diseases) were not

conducted to avoid collinearity in assessing the association between chronic diseases and mortality.

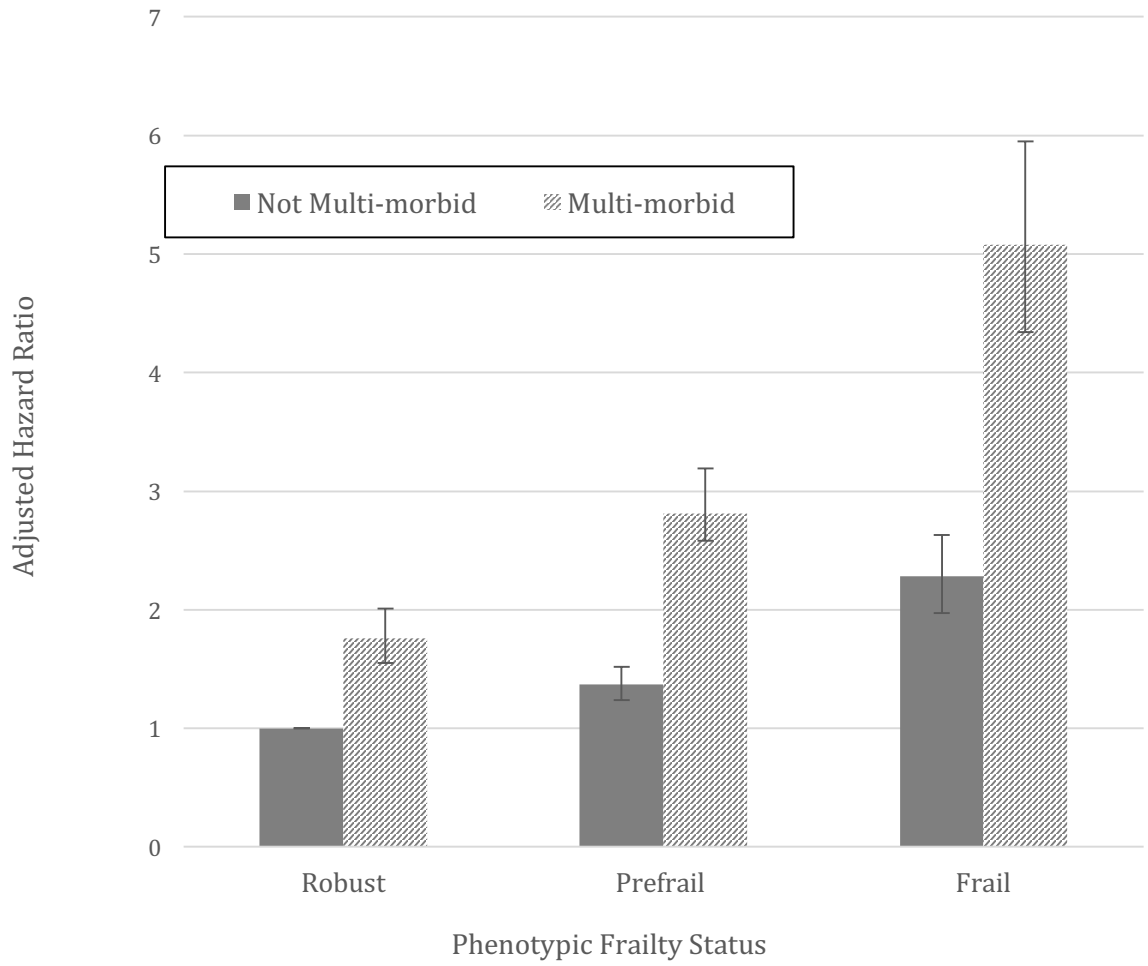


Figure 30. Adjusted hazard ratios for all-cause mortality according to multi-morbidity and phenotypic frailty status.

Note: error bars indicate 95% confidence intervals. Adjusted for: age, sex, country income, highest education achieved, smoking history, alcohol consumption history, dietary caloric intake. The reference category for all comparisons is the non-multi-morbid and robust group. The phenotypic frailty index characterizes participants based on three variables: grip strength, physical activity level, and significant weight loss. The presence of two or three of the variables was considered "frail", the presence of any one variable was considered "pre-frail", and the absence of all three variables was considered "robust".

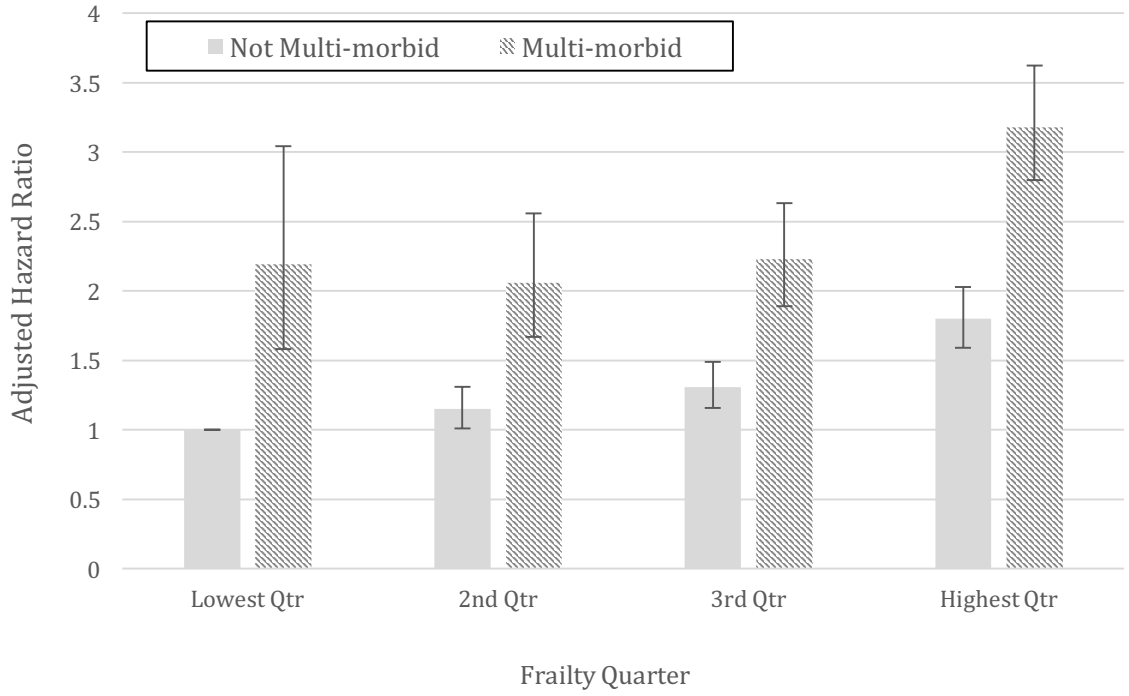


Figure 31. Adjusted hazard ratios for all-cause mortality according to multi-morbidity and cumulative deficit (excluding chronic diseases) frailty quarter.

Note: error bars indicate 95% confidence intervals. Adjusted for: age, sex, country income, highest education achieved, smoking history, alcohol consumption history, dietary caloric intake. The reference category for all comparisons is the non-multi-morbid group with the lowest frailty score by quartile.

CHAPTER 4

DISCUSSION AND CONCLUSION

4.1. KEY FINDINGS

Frailty is associated with increased age, being female (according to the cumulative deficit indices), less education, lower caloric intake, and lower country income. Our analysis also found that frailty was associated with increased all-cause mortality and one-year mortality risk in countries of all income strata, according to all three frailty indices. Multi-morbidity was more common with increased frailty, and in combination with frailty led to additive increases in mortality risk, after adjusting for confounders.

4.1.1. Characteristics of the Frail

a. Age

Our study used a younger sample population (median age of 50 years old (IQR 42-58)) compared to previous frailty literature (both Fried et al., (2001) and Rockwood et al., (2005) limited their sample to participants aged 65 years and older). Still, our results support previous findings that frailty is associated with increased age (Shamliyan et al., 2013; Collard et al., 2012). Moreover, the median age of participants categorized as frail by the phenotypic frailty index was 56 years (IQR of 47-64); for participants in the highest quarter of the cumulative deficit indices, the median ages were 54 (IQR of 46-61) and 55 (IQR of 47-62) (excluding and including chronic diseases, respectively). Importantly, this demonstrates that frailty and its health consequences begin at a lower age than the age

group that is generally examined in frailty studies. Given that frailty exists on a continuum (Sternberg et al., 2011), broadening the scope of frailty research to encompass the full age range which is at risk for frailty could lead to a better understanding of its development and progression.

b. Sex

Frailty was associated with being female according to the cumulative deficit indices, but not according to the phenotypic frailty index, in contrast to the findings of Fried et al. (2001). However, after age-standardization, the difference in prevalence of phenotypic frailty among females and males increased (6.6% of females, and 6% of males). It is possible that the PURE phenotypic frailty index did not categorize more women as frail than men due to the fact that two of its three components (grip strength and physical activity level, but not weight loss) were based on sex-specific reference values. In the original five-item phenotypic frailty index developed by Fried et al. (2001), there was an additional sex-independent frailty component of self-reported exhaustion. The absence of this variable in this study may have led to the unexpected finding that the distributions of men and women were relatively similar across all levels of phenotypic frailty.

On the other hand, the cumulative deficit indices largely did not consider sex-specific reference values, and found an increasing proportion of women among higher frailty quarters. If this finding was a result of women's survival advantage over men – whereby women accumulate more deficits simply due to their longer lifespans –it would be expected that the median age of women in the highest quarter of the cumulative deficit frailty index would be greater than that of men. However, since the median age in the

highest frailty quarter of the cumulative deficit index excluding chronic diseases was actually slightly greater among men than among women (56 years (IQR 48-63 years) versus 53 years (IQR 45-60 years)), whereas the median ages of men and women in the first frailty quarter were almost identical (43 years (IQR 49-50 years) versus 43 years (IQR 38-50 years)), this theoretic confounder is not supported by the findings. The greater prevalence of women in higher quarters of the cumulative deficit indices suggests that women tend to accumulate more deficits than do men. This has been suggested to be caused by women's lower levels of muscle mass, neuroendocrine agents, and protective hormones such as testosterone (Walston & Fried, 1999). Sarcopenia, the age-associated decline in lean muscle mass, is associated with increased risk of falling, and lower thermoregulation abilities, insulin sensitivity, and exercise tolerance, and affects women more than men at all age groups (Walston & Fried, 1999). Moreover, increased levels of testosterone in males may serve to protect muscle maintenance; although its mechanism is not well defined, testosterone replacement therapy has been demonstrated to increase strength (grip and lower extremities), muscle mass, and protein synthesis (Walston & Fried, 1999).

c. Socioeconomic Status Indicators

The trend of increasing frailty with lower education was quite strong across all three indices, supporting previous research that lower education is associated with poorer health outcomes (Albert et al., 1995). The association between education and health may be attributed to its role in determining occupation, income, and lifestyle behaviours (Rowe & Kahn, 1997). Years of education have also been found to correlate with improved maintenance of cognitive function (Albert et al., 1995). Education may also be a surrogate

variable for other factors which may affect health outcomes, including parental socioeconomic status and genetics.

Differences in accessibility to healthcare facilities and participant education may lead to an ascertainment bias, whereby diseases are generally less frequently diagnosed among lower-income populations. If there had been an ascertainment bias in the measurement of chronic diseases in LIC compared to MIC and HIC, the higher prevalence of cumulative deficit frailty in LIC would have been attenuated. However, the finding that frailty increases with lower socioeconomic status, even according to the cumulative deficit index (including chronic diseases), supports the reliability of the PURE data and its standardized methodology.

4.1.2. Frailty and Country Income

Across all three indices, the unadjusted odds of being frail was greatest among low income countries (LIC) compared to middle income countries (MIC) and high income countries (HIC). Similarly, compared to HICs, participants from LICs had higher median numbers of deficits according to both cumulative deficit indices. This contrasts with previous findings by Harttgen et al. (2013), which found higher frailty indices in HICs than in lower-income countries (which included a mix of UMICs, LMICs, and LICs). However, unlike PURE, Harttgen et al. (2013) did not include participants below the age of 50 years, and thus may not have accounted for younger participants in LICs living with frailty who died before reaching 50 years of age.

However, the trend of increasing frailty prevalence with decreasing country income was not entirely consistent across all four frailty quarters of the cumulative deficit indices.

The unadjusted odds ratio of being in the highest frailty quarter versus the lowest was similar between MIC and HIC participants (ORs of 0.999 and 1, respectively) according to the cumulative deficit index (including chronic diseases) (Table 15). Moreover, participants from MICs had similar median number of deficits, if not slightly fewer, compared to HIC participants (e.g. 2.92 (IQR 1.67-5.08) versus 3.0 (IQR 1.75-4.92), respectively, using the cumulative deficit index (including chronic diseases). A survival bias from better health care access may partly contribute to the increased prevalence of multi-morbidity, and thus a greater than expected accumulation of deficits among HIC participants compared to MICs and LICs.

There could be many explanations for why LIC generally have a greater prevalence of frailty than MIC and HIC. Participants living in LIC may be exposed to a greater number of physical, social, and psychological stressors, compared to MIC and HIC participants, increasing their chances of exhibiting a symptom or contracting an illness. One mechanism through which macroeconomic factors can impact health outcomes is varying accessibility to treatment options. Additionally, HIC may offer greater accessibility to treatments and support that could delay or reverse the progression of frailty compared to MIC and LIC. Cuomo & Mackey (2016) found that among LIC and MIC, higher income per capita was associated with a greater number of available essential cancer medications (as determined by the WHO Essential Medicines List) on its national formularies. Countries which rely most on outside financial assistance provide fewer essential cancer medications to their residents (Cuomo & Mackey, 2016). This could result in lower survival rates of cancers and other health issues leading to increased susceptibility to death –and thus frailty– among

LIC compared to MIC and HIC, as found by Theou et al. (2013b). Similarly, access to medications for cardiovascular disease and diabetes is also more limited among LIC and MIC (Wirtz, Kaplan, Kwan, & Laing, 2016; WHO, 2008). Given the integral role of pharmacotherapy (e.g. statins and antiplatelet drugs) in the prevention and management of cardiovascular disease, lack of access to these medicines may be directly related to future frailty.

According to the World Health Organization (WHO), the development of a country is accompanied by a shift in the types of health risks that primarily affect its citizens (WHO, 2009). This epidemiological shift is mediated by various factors, including the improvement of medical resources which reduce the mortality rates of curable conditions like diarrhea; public interventions targeted at reducing the incidence of infectious diseases through providing vaccinations, proper sanitation, and clean water; and the general aging of the population, which manifests as an increase in the prevalence of non-communicable, chronic diseases (WHO, 2009; Kinsella & Phillips, 2005). As a result, LIC tend to be affected by risks such as poverty, malnutrition, dirty water, poor sanitation, and the presence of indoor smoke from solid fuels, which lead to the primary cause of death in LIC being pneumonia, followed by heart disease, diarrhea, HIV/AIDS, and finally stroke (WHO, 2009). The finding that LIC may have greater prevalence of frailty, which has been defined as one's susceptibility to contracting an illness, or experiencing an adverse outcome after contracting an illness, may thus be largely associated with diseases which could easily be prevented or cured with improved public health changes. In contrast, HIC are generally more affected by risks associated with sedentary lifestyles, obesity, and tobacco and alcohol

consumption (WHO, 2009). Consequently, the primary cause of death among HIC is heart disease, followed by stroke, and lung cancer (WHO, 2012). Thus, the clinical picture of frailty may differ between LIC and HIC populations, and require different strategies of prevention and management.

The significance of frailty disproportionately impacting LIC is that according to the WHO regional estimates for 2004, LIC represent approximately 37% of the world's population, whereas MIC represent about 47%, and HIC countries represent about 15% (WHO "Global Health risks", p7, 2009). Moreover, while developed countries currently account for the highest proportions of older people, the number of older citizens is also rapidly increasing in developing countries (Kinsella & Phillips, 2005). By 2030, it is estimated that 71% of the world's older population (ages 65 and above) will be living in less developed countries (Kinsella & Phillips, 2005). Effective management of frailty must then take into consideration the unique challenges and constraints of both developed and developing nations.

4.1.3. Association between Frailty and Mortality

Increased frailty and pre-frailty were both associated with greater risk of all-cause mortality across all indices. The cumulative deficit index (including chronic diseases) was associated with greater mortality risk compared to the cumulative deficit index (excluding chronic diseases) at each corresponding frailty quarter (Table 16). However, even after excluding participants with major chronic diseases (stroke, chronic obstructive pulmonary disease, diabetes, and coronary heart disease/angina/heart attack), increased frailty (according to both phenotypic frailty and the cumulative deficit index (excluding chronic

diseases)) was still associated with greater risk for all-cause mortality. Taken together, the findings indicate that frailty is indeed associated with – but not dependent on –the presence of chronic diseases. To our knowledge, this is the largest scale study to have compared a frailty phenotype with cumulative deficit approaches of measuring frailty in community dwelling populations of individuals who are middle age. Previous studies have focused primarily on the elderly and select HICs.

Frailty was associated with a higher mortality risk within the first year after baseline assessment than it was in the remainder of follow-up (Tables 16 & 22). One likely explanation for this finding is a reverse causation effect, whereby the pre-existing conditions and diseases which characterized individuals with increased frailty also led to earlier disease-associated mortality. However, this may have significant clinical implications on the appropriate management of frail patients within one year of diagnosis and afterwards.

When compared to others within the same half of the cumulative deficit frailty indices, females tend to outlive males and have lower adjusted risk of mortality (Figures 18 & 19; Table 20). This is consistent with the general finding that women have longer lifespans but worse health than do men, particularly at middle and older ages (Hubbard & Rockwood, 2011). These results suggest that sex is a factor that mediates the association between deficit number and adverse health outcomes. Thus, equal-aged men and women with the same number of deficits may have differing vulnerability to mortality and other health risks (Hubbard & Rockwood, 2011; Hazzard, 1994). Similarly, although the ratio of females to males across the phenotypic frailty categories was relatively consistent, the

association between phenotypic frailty status and all-cause mortality risk differed between the sexes; being phenotypically frail worsened survival outcomes more among males than females (Figure 21). These findings, which have been supported by other studies (Puts, Lips, & Deeg, 2005), could be caused by a variety of factors, including differences between sexes in genetics, risk-taking behaviours, and health care utilization (Hubbard & Rockwood, 2011).

Better understanding of the progression of frailty and its association with mortality may lead to improved management and health care planning for frail and pre-frail individuals. Frail individuals have been previously demonstrated to have more gradual, consistent declines in dependent activities of daily living (ADLs) within the last year of life, compared to the large fluctuations in ADL dependencies among organ failure patients, and the steep decline that occurs within the last few months of life among cancer patients (Lunney, Lynn, Foley, Lipson, & Guralnik, 2003). Thus, end-of-life planning for frailty should consider the unique challenges of a steadily reducing reserve capacity and a relatively uncertain terminal period (Lunney et al., 2003).

4.1.4. Comparison of Frailty and Multi-Morbidity

Across the entire sample, prevalence of multi-morbidity was 15% (mean age of 56, IQR 49-63 years), which is over twice the prevalence of phenotypic frailty, 6.4% (mean age of 56, IQR 47-64). Multi-morbid participants were likely to be identified as frail using the cumulative deficit index (excluding chronic diseases) (54% of multi-morbid participants were categorized in the highest quarter) (Table 26). However, only a minority of multi-morbid participants (12%) were concurrently classified as frail according to the

phenotypic frailty definition (having at least two of the three frailty phenotypes) (Table 25). As such, multi-morbidity is more strongly associated with the accumulation of deficits than with the components of phenotypic frailty (low grip strength, low physical activity level, and significant weight loss). This suggests that the phenotypic frailty and cumulative deficit index (excluding chronic diseases) measure two meaningfully different evaluations of frailty. The strong association between multi-morbidity and cumulative deficit frailty classification may be attributed to similar mechanisms resulting in the accumulation of both chronic diseases and other non-chronic physical deficits.

The prevalence of multi-morbidity was positively associated with frailty across both indices, and increased the mortality risk associated with each level of frailty (Tables 25-26; Figures 28-31). After adjustment, having simultaneous multi-morbidity and frailty according to all indices led to additive increases in mortality risk (Figures 30-31). Being multi-morbid but phenotypically robust resulted in lower mortality risk compared to being non-multi-morbid but phenotypically frail (Figure 30-31). This suggests that phenotypic frailty, as defined in this study, has greater ability to predict all-cause mortality than does multi-morbidity. However, this was not the case with the cumulative deficit frailty index (excluding chronic diseases), where mortality risk for non-multi-morbid participants in the highest frailty quarter was lower than the risk for multi-morbid participants in the lowest frailty quarter. Thus, according to the definitions used in this study, all-cause mortality was best predicted by phenotypic frailty, followed by multi-morbidity, and then cumulative deficit frailty (excluding chronic diseases). However, these associations may not be fully

generalizable to studies using different characterizations of phenotypic and cumulative deficit frailty.

4.2. LIMITATIONS

First, the validity of these results may be influenced by the lack of complete data in the cumulative deficit analyses. It is possible that the disproportionately greater percentage of LIC participants, and MIC participants to a lesser extent, with incomplete data is attributed to their greater levels of frailty. If so, our study may have underrepresented the number of LIC and MIC participants in the higher frailty quarters. This may explain the relatively inconsistent association found between country income and frailty prevalence using the cumulative deficit indices. Although PURE takes many measures to avoid missing data (through multiple follow-up attempts and retrieving data from alternative sources), the potential challenge in obtaining complete data in a large community based study across multiple countries and urban and rural settings is daunting and is beyond the scope of this thesis. There could be a meaningful explanation for the disproportionately greater number of participants from LIC missing relevant data, which could affect our frailty analyses. For example, it is possible that having lower educational backgrounds and thus a lack of familiarity with health research led more LIC participants than MIC and HIC participants to choose not to respond to certain PURE questions. However, from the current analysis of the three frailty indices, participants of lower socioeconomic status (less education) tend to be frailer (Tables 11-13). Thus, it is possible that the missing data from LIC participants have in fact attenuated the risk of death associated with frailty.

Participants who were missing over five percent of data from the cumulative deficit indices were excluded (equivalent to two and three deficits from the index excluding chronic diseases and the index including chronic diseases, respectively). It is possible that the absence of data on even one or two deficits affected the validity of each participant's frailty index. For example, a participant who is positive for a certain deficit but failed to give a response to that question may be attributed a score of 5/30=0.17 when their actual frailty index would be 6/30=0.20; their baseline frailty index would be an under-evaluation. Given that the median number of deficits among participants in each increasing frailty quarter of the cumulative deficit index (excluding chronic diseases) is 1.00 (IQR 0.67-1.33), 1.98 (IQR 1.75-2.25), 3.33 (IQR 3.00-4.00), and 6.83 (5.50-9.00), respectively, a difference of one deficit could impact a participant's categorization across the frailty quarters. Standard Cox analyses for all-cause mortality were conducted using participants' "appeared" index values. Thus, it is possible that the missing data in the cumulative deficit analyses exaggerated the association between frailty status and increased mortality risk.

We were able to further investigate the impact of missing data specifically using the deficit of hypertension, which was missing in 443 participants of the cumulative deficit sample. Using PURE's separate, standardized measurement of baseline sitting blood pressure, these individuals were recorded to have a mean systolic blood pressure of 136 (IQR=121-150) and mean diastolic blood pressure of 84 (IQR=75-92). Participants who responded "yes" to being previously diagnosed with hypertension were recorded by PURE at baseline to have mean systolic and diastolic blood pressures of 147 (IQR=131-161) and 89 (IQR=80-97), respectively. In contrast, participants who responded "no" had recorded

mean systolic and diastolic blood pressures of 127 (IQR=114-138) and 80 (IQR=72-87), respectively. Using PURE's standardized measurement of blood pressure, participants who were missing information on hypertension had intermediate blood pressure compared to participants who responded "no" and "yes" to being previously diagnosed with hypertension. Thus, the missing data on hypertension, and possibly other deficits, likely does not have meaningful significance to our analyses.

We also tested the significance of the missing data by performing subsequent cumulative deficit analyses using a sample that was limited to participants with complete data, and still found greater mortality risk among higher levels of frailty. This suggests that the associations between the cumulative deficit indices and mortality were unlikely to be significantly biased by the missing data.

In another sensitivity analyses, participants who were excluded from the phenotypic frailty analyses due to missing information were more likely than those who were included to have low physical activity and significant weight loss, but less likely to have low grip strength (Table 18). The difference in prevalence was greatest for physical activity, where 28.5% of individuals excluded from the analyses had low physical activity, compared to 18.5% of individuals who were included. Thus, the frailty analyses may have underestimated the prevalence of frailty among the PURE sample, as well as the association between phenotypic frailty and adverse outcomes (i.e. all-cause mortality).

Due to the observational design of the study, the mechanism behind the association between frailty and mortality cannot be inferred. For instance, it cannot be determined based on this study's findings how much of a contribution the cardiovascular,

musculoskeletal, immunological systems or other biologic systems have on increasing a person's frailty and resulting risk for mortality. To minimize the chances that greater risk of mortality associated with frailty was attributed to confounding variables, all analyses adjusted for potential confounders, including age, sex, education country income, smoking history, alcohol consumption history, and dietary caloric intake. Adjusting for confounders significantly attenuated the mortality risk associated with increased frailty levels across all three indices (Table 16). This is not an unexpected finding given the physiological impacts of age, sex, smoking, alcohol consumption, and dietary caloric intake. Moreover, the associations between poor health outcomes and both country income (WHO, 2005; Yusuf et al., 2014) and socioeconomic status (including education) (Marmot, 2005; Adler & Ostrove, 1999; Lantz et al., 1998) have been repeatedly demonstrated.

4.3. STRENGTHS OF THE STUDY AND FUTURE DIRECTIONS

This study is unique in evaluating frailty indices on a middle-aged, community-based, large, and diverse sample. An important implication of our findings is that both the phenotypic and cumulative deficit approaches to measuring frailty may be used to assess all-cause mortality risk for adults of all ages across all country incomes. These findings also provide further support for the prognostic utility of regarding frailty as a spectrum ranging from robustness to pre-frailty, and to frailty. Importantly, our findings may be widely generalized across a wide variety of geographic regions, ethnicities, and sociodemographic characteristics.

Frailty is an evolving concept which requires further exploration. In 2013, a frailty consensus conference project agreed that frailty was both multi-dimensional (including the assessment of mobility, gait speed, nutritional status, cognition and mental health) and distinctly separate from disability (Rodríguez-Mañas, Féart, Mann, et al., 2013). However, the group of experts was unable to reach agreement on a single operational definition of frailty, a method of diagnosis, the usefulness of specific biomarkers, nor its relationship with comorbidities (Rodríguez-Mañas et al., 2013). A coordinated effort is needed to work towards developing a consensus on an operational definition frailty, which can be used to assess, prognosticate, and manage the syndrome.

Recommendations for future research also include further evaluation of the phenotypic frailty and cumulative deficit indices for the ability to predict other adverse outcomes, including falls, chronic disease incidence, and hospitalization. The broad age range of the PURE sample may enable more effective tracking of these outcomes, compared to previous studies.

Efforts should be made to facilitate the widespread implementation of frailty assessments into overall patient care. Technological tools such as automated health record systems may be particularly useful for calculating cumulative deficit indices in a streamlined and timely manner. Moreover, further clinical trials should be conducted to test the efficacy of proposed frailty management regimes, such as exercise rehabilitation, and dietary intervention (Morley et al., 2013).

Lastly, using standardized methods of assessing frailty in populations across 17 countries, this study found that frailty levels are generally inversely associated with country

income status and individual socioeconomic status (education). In the future, it would be useful to examine the association between frailty prevalence and country income after adjusting for factors such as diet, alcohol consumption, smoking history, indoor pollution, and other determinants of socioeconomic status, such as household income. Moreover, future studies may include assessing frailty among rural versus urban communities. Further research in these areas may enable a better understanding of the relationship between frailty and socioeconomic status, and lead to an approach for addressing the present health inequalities.

4.4. CLINICAL RELEVANCE

4.4.1. Evaluation of the Phenotypic Frailty and Cumulative Deficit Indices

The frailty phenotype appears to have comparable prognostic power for mortality risk to a cumulative deficit index which includes the consideration of chronic diseases. This finding is of clinical significance since this study used a simplified frailty phenotype, requiring only three variables that are relatively easy to measure: weakness (low grip strength), physical activity level, and significant unintentional weight loss. Further, the phenotypic frailty index could be used to assess risk of developing various diseases in individuals who may not have chronic diseases at baseline.

On the other hand, the strength of the cumulative deficit index (with or excluding chronic diseases) is that it can use any combination of health-related variables available from an individual's medical records to deduce the person's frailty status (Walston & Bandeen-Roche, 2015). Unlike the frailty phenotype, which requires prior assessment of

grip strength, the cumulative deficit method can be easily conducted retrospectively to assess a person's frailty status. Moreover, the cumulative deficit index takes into account the effect of cognitive and psychological deficits, thus taking a more holistic approach to characterizing frailty.

Using the definitions of phenotypic frailty and cumulative deficit frailty as characterized by this thesis, cumulative deficit frailty index (including chronic diseases) was found to have the greatest predictive ability for all-cause mortality (Figure 17). The phenotypic frailty index, which assesses grip strength, physical activity, and unintentional weight loss, was found to have the lowest predictive ability for all-cause mortality. However, this finding may not be fully generalizable to all of the many variations used for defining phenotypic and cumulative deficit frailty across the literature.

4.4.2. Indications for Frailty Assessment and Management

A 2012 consensus group of delegates from six major international and US geriatric medicine and research societies agreed that frailty screening should be implemented in all patients who are 70 years of age or older (Morley et al., 2013). Although the burden of frailty is greater amongst the elderly, frailty across all age groups is associated with increased risk of mortality. Among the PURE cohort, the median age of participants categorized as phenotypically frail was 56 years old (IQR 47-64) (Table 11). The findings from this study suggest that screening for frailty should be recommended for middle age individuals, as early detection of frailty can enable the implementation of lifestyle interventions to reduce frailty and thereby be an additional strategy to improve survival.

Moreover, frail individuals should be recognized prior to considering complicated or invasive treatments (Strandberg, Pitkala, & Tilvis, 2011). Frailty status may be more pertinent than chronological age when assessing the postoperative risks of a given patient (Theou & Rockwood, 2012).

Frailty may also have important implications on the management and reduction of polypharmacy. Using the frailty approach of assessing patient health may help to avoid adverse reactions, drug-drug interactions, and increased costs associated with polypharmacy in treating symptoms and disorders individually (Colley & Lucas, 1993). According to a Canadian public health report in 2014, 76% of seniors living in private households used one of more medications to manage their chronic disease, alleviate pain, and/or improve functional abilities, and 13% used five or more medications over the previous two days (Public Health Agency of Canada, 2014). Moreover, 20% of hospitalizations among people aged 50 years or older are due to improper use of medications (Public Health Agency of Canada, 2014). Being frail may also increase one's sensitivity to polypharmacy, through potential changes in physiological pharmacokinetic parameters, further complicating the issue (Nobili, Garattini, & Mannucci, 2011).

Primary prevention of frailty should start as early as possible, targeting lifestyle behaviours, including physical activity levels, weight control, diet, lower alcohol consumption and smoking, and vaccination (Strandberg, Pitkala, & Tilvis, 2011; Theou & Rockwood, 2012). Secondary prevention, which aims to prevent and improve the prognosis of disability among already frail individuals, may additionally include exercise training to improve measures of mobility and disability, management of chronic diseases, nutrition,

and fall prevention (Strandberg & Pitkala, 2007; Theou & Rockwood, 2012). Given their differing prognostic outcomes for frailty, further studies should also be conducted to determine the most effective frailty management routines for males versus females.

Overall, the frailty framework provides a holistic approach of assessment and treatment of people with complex multi-morbidities.

4.5. FRAILTY AND GLOBAL HEALTH

In addition to being a prognostic tool in the clinical setting, frailty affects society through identifying at-risk populations with extra medical needs and greater levels of dependence (Buckinx, Rolland, & Reginster et al., 2015). This study provides evidence that frailty affects 7% of adults, particularly those in their late forties and older, and is more prevalent in lower socioeconomic status settings and lower income countries. Thus, frailty has important implications on global health research, including setting future directions for a global agenda to support the aging population, and reducing health inequalities associated with socioeconomic status.

The rapid aging of the world's population is driven both by a decline in fertility and improved life-expectancy (WHO, 2011). These events are mediated by many socioeconomic and cultural factors, which affect different regions of the world at different rates. The average number of births per woman declined from three children to two from 1950-1970 in developed countries, but fell from six children to two or three between 1950-2005 in less developed countries (WHO, 2011). As a result, the same change in population age structure may occur in developing nations within a fraction of the time as it does in

more developed nations (WHO, 2011). Thus, there may be a greater urgency for developing countries to adapt more quickly to the needs of an aging population (WHO, 2011). Long-term care policy development may also differ between nations depending on the culture's ideology of whether primary care should primarily be a responsibility of the family unit (the predominant view in the United Kingdom and the United States) or society as a whole (the predominant view in Scandinavia and Japan) (WHO, 2003). Effective policy making should incorporate these considerations in devising an infrastructure that will support the older, frail individual as well as provide education, training, and respite for their caregivers.

Local healthcare systems need to be appropriately adapted to facilitate the assessment and support of frailty in middle-aged and older participants. This may include the use of technology to implement widespread frailty screening which could rapidly assess cumulative deficit frailty based on a list of deficits which could be easily answered by a patient or their primary care physician. Frailty status should be considered in all aspects of health care planning for patients to improve post-operative outcomes, reduce the risk of subsequent falls, minimize the risks of polypharmacy, and improve overall quality of life. Future research focusing on the management of frailty may help to improve prognostic outcomes for pre-frail and frail individuals (De Lepeleire et al., 2009; Ng et al., 2015). Moreover, patients need to be properly educated on health-related issues, including exercise, proper nutrition, and other health promoting behaviours. Accordingly, further health care resources should be allocated to primary and long-term care services, including home care and community health centres, which can provide support and therapeutic rehabilitation to manage and reduce frailty. Such services may be delivered by a team of

health care professionals, including doctors, nurses, social workers, as well as personal care workers, and traditional healers, and provided by nongovernmental organizations, non-for-profit organizations, or the governmental sector (WHO, 2002).

4.6. CONCLUSIONS

In conclusion, frailty significantly affects a significant proportion of the world's population and is associated with greater mortality risk across various frailty indices, age groups, ethnicities, and country income levels. The topic of frailty is particularly significant to the study of global health given that it disproportionately burdens individuals from low income countries and low socioeconomic status. It is recommended that future research be conducted to better understand why low income countries in the PURE study demonstrate the greatest prevalence of frailty across all three indices.

This study determined that both the phenotypic and cumulative deficit indices can be used to assess a person's risk for mortality. The decision on which frailty index method to use may depend on the resources available in that context. Other future steps may include expanding the analyses of the predictive validity of frailty to other adverse event outcomes, such as the incidence of cardiovascular disease, falls, hospitalization, and pneumonia. These analyses may help to better understand and detangle the difference in the clinical significant of frailty as characterized by the phenotypic frailty index compared to the cumulative deficit index.

Improved understanding of the determinants and prognostic power of frailty may dramatically improve health outcomes for adults of all ages living with frailty and pre-

frailty across the world. Given that 1) frailty affects a significant proportion of the world's population, especially older adults, 2) the elderly population is continually growing, 3) frailty is associated with increased mortality risk, and 4) frailty disproportionately impacts lower income countries and individuals from lower socioeconomic status, the study of frailty and its associated adverse outcomes is consequential to both individual and global health.

REFERENCES

Adler, N. E., & Ostrove, J. M. (1999). Socioeconomic status and health: what we know and what we don't. *Annals of the New York Academy of Sciences*, *896*(1), 3-15.

Agborsangaya, C. B., Lau, D., Lahtinen, M., Cooke, T., & Johnson, J. A. (2012). Multimorbidity prevalence and patterns across socioeconomic determinants: A cross-sectional survey. *BMC Public Health, 12*(1), 201.

Albert, M. S., Jones, K., Savage, C. R., Berkman, L., Seeman, T., Blazer, D., & Rowe, J. W. (1995). Predictors of cognitive change in older persons: MacArthur studies of successful aging. *Psychology and Aging*, *10*(4), 578.

Averett, S. L., Stacey, N., & Wang, Y. (2014). Decomposing race and gender differences in underweight and obesity in South Africa. *Economics & Human Biology*, *15*, 23-40.

Blodgett, J., Theou, O., Kirkland, S., Andreou, P., & Rockwood, K. (2015). Frailty in NHANES: Comparing the frailty index and phenotype. *Archives of Gerontology and Geriatrics*, doi:10.1016/j.archger.2015.01.016

Bortz, W. M. (2002). A conceptual framework of frailty a review. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 57*(5), M283-M288.

Brothers, T. D., Theou, O., & Rockwood, K. (2014). Frailty and migration in middle-aged and older Europeans. *Archives of Gerontology and Geriatrics, 58*(1), 63-68.

Buckinx, F., Rolland, Y., Reginster, J. Y., Ricour, C., Petermans, J., & Bruyère, O. (2015). Burden of frailty in the elderly population: perspectives for a public health challenge. *Archives of Public Health*, *73*(1), 1.

Cesari, M., Gambassi, G., Abellan van Kan, G., & Vellas, B. (2014). The frailty phenotype and the frailty index: different instruments for different purposes. *Age and Ageing, 43*, 10-12. doi: 10.1093/ageing/aft160

Charlson M.E., Pompei, P., Ales, K.L., et al. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis*, *40,* 373-83.

Choi, J., Ahn, A., Kim, S., & Won, C. W. (2015). Global prevalence of physical frailty by Fried's criteria in community-dwelling elderly with national population-based surveys. *Journal of the American Medical Directors Association*, *16*(7), 548-550.

Collard, R. M., Boter, H., Schoevers, R. A., & Oude Voshaar, R. C. (2012). Prevalence of Frailty in Community-Dwelling Older Persons: A Systematic Review. *Journal of the American Geriatrics Society, 60*(8), 1487-1492.

Colley, C. A., & Lucas, L. M. (1993). Polypharmacy. *Journal of general internal medicine*, *8*(5), 278-283.

Cuomo, R. E., & Mackey, T. K. (2016). Macroeconomic factors underlying essential cancer medication availability among low-and middle-income countries. *Annals of Global Health*, *82*(3), 328-329.

De Lepeleire, J., Iliffe, S., Mann, E., & Degryse, J. M. (2009). Frailty: an emerging concept for general practice. *British Journal of General Practice, 59*(562), e177-e182.

Effectiveness Matters. (January 2015). Centre for Reviews and Dissemination, University of York. Recognising and managing frailty in primary care.

Ellis, G., Whitehead, M. A., O'Neill, D., Langhorne, P., & Robinson D. (2011). Comprehensive geriatric assessment for older adults admitted to hospital. *The Cochrane Library.*

Fried, L., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., … Tracy, R. (2001). Frailty in older adults: evidence for a phenotype. *Journal of Gerontology: Medical Sciences, 56A*(3), M146-M156.

Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *59*(3), M255-M263.

Garin, N., Koyanagi, A., Chatterji, S., Tyrovolas, S., Olaya, B., Leonardi, M., ... & Haro, J. M. (2016). Global multi-morbidity patterns: A cross-sectional, population-based, multi-country study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *71*(2), 205-214.

Glynn, L. G., Valderas, J. M., Healy, P., Burke, E., Newell, J., Gillespie, P., & Murphy, A. W. (2011). The prevalence of multi-morbidity in primary care and its effect on health care utilization and cost. *Family Practice, 28*(5), 516-523.

Gray, W. K., Richardson, J., McGuire, J., Dewhurst, F., Elder, V., Weeks, J., Walker, R. W. and Dotchin, C. L. (2016), Frailty Screening in Low- and Middle-Income Countries: A Systematic Review. *Journal of the American Geriatrics Society, 64*: 806–823. doi: 10.1111/jgs.14069.

Harttgen, K., Kowal, P., Strulik, H., Chatterji, S., & Vollmer, S. (2013). Patterns of frailty in older adults: Comparing results from higher and lower income countries using the Survey of Health, Ageing and Retirement in Europe (SHARE) and the Study on Global AGEing and Adult Health (SAGE). *PLoS ONE 8*(10): 375847. doi:10.1371/journal.pone.0075847.

Hazzard WR. The sex differential in longevity. In: Hazzard WR, Blass J, Ettinger WH et al., eds. The Principles of Geriatric Medicine and Gerontology, 3th Ed. New York: McGraw-Hill, 1994, pp 37–47.

Hubbard, R. E., & Rockwood, K. (2011). Frailty in older women. *Maturitas*, *69*(3), 203-207.

Kinsella, K. G., & Phillips, D. R. (2005). *Global aging: The challenge of success* (Vol. 60, No. 1, p. 3). Washington: Population Reference Bureau.

Kleinbaum, D. G., & Klein, M. (2006). *Survival analysis: a self-learning text*. Springer Science & Business Media.

Kojima, G. (2015). Frailty as a predictor of future falls among community-dwelling older people: a systematic review and meta-analysis. *Journal of the American Medical Directors Association, 16*(12), 1027-1033.

Kulminski, A. M., Ukraintseva, S. V., Kulminskaya, I. V., Arbeev, K. G., Land, K., & Yashin, A. I. (2008). Cumulative deficits better characterize susceptibility to death in elderly people than phenotypic frailty: lessons from the Cardiovascular Health Study. *Journal of the American Geriatrics Society, 56*(5), 898-903.

Lang, I. A., Hubbard, R. E., Andrew, M. K., Llewellyn, D. J., Melzer, D., & Rockwood, K. (2009). Neighborhood deprivation, individual socioeconomic status, and frailty in older adults. *Journal of the American Geriatrics Society*, *57*(10), 1776-1780.

Lantz, P. M., House, J. S., Lepkowski, J. M., Williams, D. R., Mero, R. P., & Chen, J. (1998). Socioeconomic factors, health behaviors, and mortality: results from a nationally representative prospective study of US adults. *JAMA*, *279*(21), 1703-1708.

Lunney, J. R., Lynn, J., Foley, D. J., Lipson, S., & Guralnik, J. M. (2003). Patterns of functional decline at the end of life. *JAMA*, *289*(18), 2387-2392.

Marengoni, A., Angleman, S., Melis, R., Mangialasche, F., Karp, A., Garmen, A., ... & Fratiglioni, L. (2011). Aging with multi-morbidity: a systematic review of the literature. *Ageing Research Reviews, 10*(4), 430-439.

Marmot, M. (2005). Social determinants of health inequalities. *The Lancet*, *365*(9464), 1099-1104.

McLean, G., Gunn, J., Wyke, S., Guthrie, B., Watt, G. C., Blane, D. N., & Mercer, S. W. (2014). The influence of socioeconomic deprivation on multi-morbidity at different ages: a cross-sectional study. *British Journal of General Practice, 64*(624), e440-e447.

Mitnitski, A. B., Mogilner, A. J., & Rockwood, K. (2001). Accumulation of deficits as a proxy measure of aging. *The Scientific World Journal, 1,* 323-336.

Mitnitski, A., Song, X., Skoog, I., Broe, G. A., Cox, J. L., Grunfeld, E., & Rockwood, K. (2005). Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. *Journal of the American Geriatrics Society, 53(*12), 2184-2189.

Morley, J. E., Vellas, B., van Kan, G. A., Anker, S. D., Bauer, J. M., Bernabei, R., ... & Fried, L.P. (2013). Frailty consensus: a call to action. *Journal of the American Medical Directors Association, 14*(6), 392-397.

Needham, D. M., Scales, D. C., Laupacis, A., & Pronovost, P. J. (2005). A systematic review of the Charlson comorbidity index using Canadian administrative databases: A perspective on risk adjustment in critical care research. *Journal of Critical Care, 20(1),* 12-19. doi:10.1016/j.jcrc.2004.09.007

Ng, T. P., Feng, L., Nyunt, M. S. Z., Feng, L., Niti, M., Tan, B. Y., ... & Yap, K. B. (2015). Nutritional, physical, cognitive, and combination interventions and frailty reversal among older adults: a randomized controlled trial. *The American Journal of Medicine*, *128*(11), 1225-1236.

Nguyen, T., Cumming, R. G., & Hilmer, S. N. (2015). A review of frailty in developing countries. *The journal of nutrition, health & aging, 19*(9), 941-946.

Nobili, A., Garattini, S., & Mannucci, P. M. (2011). Multiple diseases and polypharmacy in the elderly: challenges for the internist of the third millennium. *Journal of Comorbidity*, *1*(1), 28-44.

Prospective Urban and Rural Epidemiological Study. (2007). *PURE Protocol*. Retrieved from http://www2.phri.ca/pure/baseline-docs/Protocol_International_Sep2007.pdf

Public Health Agency of Canada. (2014). The chief public health officer's report on the state of public health in Canada, 2014: Public health in the future.

Puts, M. T., Lips, P., & Deeg, D. J. (2005). Sex differences in the risk of frailty for mortality independent of disability and chronic diseases. *Journal of the American Geriatrics Society*, *53*(1), 40-47.

Rich, J. T., Neely, G., Paniello, R. C., et al. (2010). *Otolaryngol Head Neck Surg, 143*(3), 331336. doi:10.1016/j.otohns.2010.05.007.

Roberts, K. C., Rao, D. P., Bennett, T. L., Loukine, L., & Jayaraman, G. C. (2015). Prevalence and patterns of chronic disease multi-morbidity and associated determinants in Canada. *Health Promotion and Chronic Disease Prevention in Canada, 35*(6), 87-94.

Rockwood, K., & Mitnitski, A. (2007). Frailty in relation to the accumulation of deficits. *Journal of Gerontology: Medical Sciences, 62A*(7), 722-727.

Rockwood, K., Mitnitski, A., Song, X., Steen, B., & Skoog, I. (2006). Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. *JAGS, 54*, 975-979.

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D. B., McDowell, I. & Mitnitski, A. (2005). A global clinical measure of fitness and frailty in elderly people. *CMAJ*, *173*(5), 489-495.

Rockwood, K., Song, X., & Mitnitski, A. (2011). Changes in relative fitness and frailty across the adult lifespan: Evidence from the Canadian National Population Health Survey. *Canadian Medical Association Journal, 183*(8), E487-E494.

Rockwood, K., Stadnyk, K., MacKnight, C., McDowell, I., Hebert, R., & Hogan, D. B. (1999). A brief clinical instrument to classify frailty in elderly people. *Lancet* 353, 205–206.

Rodríguez-Mañas, L., Féart, C., Mann, G., Viña, J., Chatterji, S., Chodzko-Zajko, W., ... & Scuteri, A. (2013). Searching for an operational definition of frailty: a Delphi method based consensus statement. The frailty operative definition-consensus conference project. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *68*(1), 62-67.

Rowe, J. W., & Kahn, R. L. (1997). Successful aging. *TheGgerontologist*, *37*(4), 433-440.

Searle, S. D., Mitnitski, A., Gahbauer, E. A., Gill, T. M., & Rockwood, K. (2008). A standard procedure for creating a frailty index. *BMC Geriatrics, 8*(1), 1.

Sepehri, A., Beggs, T., Hassan, A., Rigatto, C., Shaw-Daigle, C., Tangri, N., & Arora, R. C. (2014). The impact of frailty on outcomes after cardiac surgery: A systematic review. *The Journal of Thoracic and Cardiovascular Surgery, 148*(6), 3110-3117.

Shamliyan, T., Talley, K. M., Ramakrishnan, R., & Kane, R. L. (2013). Association of frailty with survival: A systematic literature review. *Ageing Research Reviews, 12*(2), 719-736.

SHARE (2016). *Survey of health, ageing and retirement in Europe: Wave 2.* Retrieved from: http://www.share-project.org/home0/wave-2.html

Song, X., Mitnitski, A., & Rockwood, K. (2010). Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. *Journal of the American Geriatrics Society, 58*(4), 681-687.

Sternberg, S. A., Schwartz, A. W., Karunananthan, S., Bergman, H., & Mark Clarfield, A. (2011). The identification of frailty: A systematic literature review. *Journal of the American Geriatrics Society, 59*(11), 2129-2138.

Strandberg, T. E., & Pitkälä, K. H. (2007). Frailty in elderly people. *The Lancet*, *360*, 1329-1329.

Strandberg, T. E., Pitkälä, K. H., & Tilvis, R. S. (2011). Frailty in older people. *European Geriatric Medicine*, *2*(6), 344-355.

Theou, O., Brothers, T. D., Mitnitski, A., & Rockwood, K. (2013). Operationalization of frailty using eight commonly used scales and comparison of their ability to predict all-cause mortality. *Journal of the American Geriatrics Society, 61*(9), 1537-1551.

Theou, O., Brothers, T. D., Rockwood, M. R., Haardt, D., Mitnitski, A., & Rockwood, K. (2013). Exploring the relationship between national economic indicators and relative fitness and frailty in middle-aged and older Europeans. *Age and Ageing, 42*(5), 614-619. doi:10.1093/ageing/aft010

Theou, O., & Rockwood, K. (2012). Should frailty status always be considered when treating the elderly patient? *Aging Health*, *8*(3), 261-271.

United Nations, Department of Economic and Social Affairs, Population Division. (2013). World Population Ageing 2013. Retrieved from: http://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf

Van Kan, G. A., Rolland, Y., Bergman, H., Morley, J. E., Kritchevsky, S. B., & Vellas, B. (2008). The IANA Task Force on frailty assessment of older people in clinical practice. *The Journal of Nutrition Health and Aging, 12*(1), 29-37.

Verbrugge, L. M., Lepkowski, J. M., & Imanaka, Y. (1989). Comorbidity and its impact on disability. *The Milbank Quarterly*, 450-484.

Walston, J. D., & Bandeen-Roche, K. (2015). Frailty: a tale of two concepts. *BMC Medicine*, *13*(1), 185.

Walston, J., & Fried, L. P. (1999). Frailty and the older man. *Medical Clinics of North America*, *83*(5), 1173-1194.

Walters, S. J. (2009). What is a Cox model? Second edition. *Hayward Medical Communications*. Retrieved from: http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/Cox_model.pdf

Ward, K., & Reuben, D. (2013). Comprehensive geriatric assessment. *UpToDate*. Retrieved from: http://bmjopen.bmj.com/content/4/12/e006645.short

Wirtz, V. J., Kaplan, W. A., Kwan, G. F., & Laing, R. O. (2016). Access to Medications for Cardiovascular Diseases in Low-and Middle-Income Countries. *Circulation*, *133*(21), 2076-2085.

Woo, J., & Leung, J. (2014). Multi-morbidity, dependency, and frailty singly or in combination have different impact on health outcomes. *Age, 36*(2), 923-931.

Woo, J., Leung, J., & Morley, J. E. (2012). Comparison of frailty indicators based on clinical phenotype and the multiple deficit approach in predicting mortality and physical limitation. *Journal of the American Geriatrics Society*, *60*(8), 1478-1486.

World Bank. (2016). Countries. Retrieved from: http://www.worldbank.org/en/country

World Health Organization. (2011). *Global health and ageing.* Retrieved from: http://www.who.int/ageing/publications/global_health.pdf?ua=1

World Health Organization. (2009). *Global health risks: mortality and burden of disease attributable to selected major risks*.

World Health Organization. (2003). *Key policy issues in long-term care*. Retrieved from: http://www.who.int/chp/knowledge/publications/policy_issues_ltc.pdf

World Health Organization. (2002). *Long-term care in developing countries: Ten case-studies.* Retrieved from: http://www.who.int/chp/knowledge/publications/case_study_intro.pdf?ua=1

World Health Organization. (2005). *Preventing chronic diseases: a vital investment: WHO global report.*

World Health Organization. (2008). *Direct costs and acailability of diabetes medicines in low-income and middle-income countries*. Retrieved from: http://apps.who.int/medicinedocs/en/d/Js18387en/

World Health Organization. (2012). *The top 10 causes of death*. Retrieved from: http://www.who.int/mediacentre/factsheets/fs310/en/index1.html

World Health Organization. (2017). *SAGE waves 0, 1, 2, & 3*. Retrieved from: http://www.who.int/healthinfo/sage/cohorts/en/index2.html

Yusuf, S., Rangarajan, S., Teo, K., Islam, S., Li, W., Liu, L., ... & Yu, L. (2014). Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *New England Journal of Medicine*, *371*(9), 818-827.

APPENDIX A

Sensitivity Analyses

In a sensitivity analysis, we examined whether frailty in the absence of major chronic diseases is still predictive of all-cause mortality. This is contrast to the analyses of the cumulative deficit index (excluding chronic diseases), which did not directly assess the presence of chronic diseases, but still included participants affected by chronic disease.

Participants with diagnosed stroke, chronic obstructive pulmonary disorder, diabetes, or coronary heart disease/angina/heart attack at baseline were excluded from the sample for the purposes of this sensitivity analysis. For the phenotypic frailty analyses, this left 102,627 participants, of whom 1,952 died during follow-up. The sample size for the cumulative deficit index (excluding chronic diseases) analyses was 120,724 of whom 2,664 died during follow-up. Despite some minor overlap in the 95% confidence intervals between the 2nd and 3rd frailty quarters, the adjusted hazard ratios for the sensitivity tests were similar to the main standard Cox analyses, and demonstrated greater mortality risk for individuals in higher levels of frailty (Table 24).

Table 24. Standard Cox analyses for all-cause mortality among participants with no major chronic diseases at baseline

Frailty Category	Unadjusted		Adjusted*	
	HR (95% CI)	*p*	HR* (95% CI)	*p*
Phenotypic frailty index				
Robust	**1**	**--**	**1**	**--**
Pre-frail	1.80 (1.64-1.99)	<0.001	1.38 (1.25-1.53)	<0.001
Frail	3.99 (3.50-4.55)	<0.001	2.27 (1.96-2.62)	<0.001
Cumulative deficit index (excluding chronic diseases)				
Lowest Quarter	**1**	**--**	**1**	**--**
2nd Quarter	1.95 (1.70-2.24)	<0.001	1.20 (1.04-1.40)	0.01
3rd Quarter	2.44 (2.12-2.78)	<0.001	1.38 (1.20-1.59)	<0.001
Highest Quarter	4.17 (3.69-4.72)	<0.001	2.00 (1.74-2.30)	<0.001

*Note; sample excluded participants diagnosed with stroke, COPD, diabetes, coronary heart disease, angina, or heart attack at baseline. Adjusted for: age, sex, country income, highest education achieved, smoking history, alcohol consumption history, dietary caloric intake. For phenotypic frailty index, N=102,627 for adjusted and unadjusted analyses. For the cumulative deficit index, N=120,724 for unadjusted and N=111,434 for adjusted analyses.

The phenotypic frailty analyses were conducted only using participants who had information available on all three of the phenotypic frailty components: significant weight loss, grip strength, and physical activity. Participants missing one of more of the phenotypic frailty components were excluded. Sensitivity analyses were conducted to compare the individual components of the phenotypic frailty index of individuals who were included in the analyses with those of the individuals who were excluded. Individuals who were excluded from the analyses were more likely to have had recent significant weight loss (5.6% of group) and have low physically activity (28.5% of group) compared to participants who met the inclusion criteria for the analyses (4.5% and 18.5% of group, respectively) (Table 25). However, individuals who were excluded from the analyses were less likely to

have low grip strength compared to individuals who were included in the analyses (18.4% of group compared to 19.5%).

Table 25. Sensitivity analysis of the phenotypic frailty components of participants who were included in the study analyses compared to participants who were excluded

Sample group	Presence of baseline phenotypic frailty component		
	Significant weight loss n (% of sample group)	**Low grip strength** n (% of sample group)	**Low physical activity** n (% of sample group)
Included in main analyses (n=117,660)	5,319 (4.5%)	22,922 (19.5%)	21,721 (18.5%)
Excluded from main analyses (n=35,467)	1,222 (5.6%)	4,107 (18.4%)	6,813 (28.5%)

*Note: Among the excluded sample group, 21,670 individuals had data on weight loss, 22,343 individuals had data on grip strength, and 23,955 individuals had data on physical activity. Significant weight loss was determined as the involuntary weight loss of >3kg in last 6 months. Low grip strength was defined as being in the lowest quintile of grip strength by sex and country income. Low physical activity was defined as being in the lowest quintile for daily physical activity by sex.

The main analyses using cumulative deficit indices did not exclude participants who had fewer than three missing variables in order to maximize statistical power and avoid the biased exclusion of study participants. However, a second sensitivity analysis was conducted to test whether frailty would still predict greater hazard ratios for mortality when limiting the sample to participants with available data on all the deficits assessed in the cumulative deficit indices. Subjects with any missing information on any of the respective

cumulative deficit deficits were excluded from the participant sample for these analyses (Table 26):

- Number of subjects who fit the main inclusion criteria and have available data on all 30 deficits of the cumulative deficit index (excluding chronic diseases): **115,117**
  - Among this sample, 2,757 deaths occurred during follow-up
- Number of subjects who fit the main inclusion criteria and have available data on all 40 deficits of the cumulative deficit index (including chronic diseases): **104,834**
  - Among this sample, 2,569 deaths occurred during follow-up

After adjustment for the same covariates, hazard ratios for mortality were still significantly greater at each increasing frailty quarter for both cumulative deficit indices. The only exception was for the second frailty quarter of the cumulative deficit index (excluding chronic diseases), which had a *p* value of 0.06 (Table 27). There was some overlap in the 95% confidence intervals between increasing frailty quarters for both index versions. However, participants in the highest quarter of frailty had significantly higher risks of mortality than participants in the first and second quarter, without overlap in 95% CI. The consistent trend of the hazard risk for mortality increasing with frailty suggests that the findings of the main analyses are not attributed to biases in the missing data.

Table 26. Number of subjects missing data by cumulative deficit index items

Deficit #	Variable Characteristic	Missing Data (n)
	Current disability; problems…	
1	Using fingers/grasping	455
2	Walking about	474
3	Bending/picking up objects	493
4	Require walking cane	538
5	Reading/seeing individual rice grains	523
6	Seeing person across room	531
7	Speaking/being understood	530
8	Hearing in conversation	582
	In the last 6 months…	
9	Chest pain/tightness	515
10	Breathlessness	602
11	Cough for 2+ weeks	584
12	Sputum while coughing	579
13	Blood in sputum	593
14	Wheezing/whistling chest	589
15	Early morning cough with chest tightness	606
16	Loose stools/diarrhea for 3+ days	622
17	Vomiting	676
18	Loss of appetite	748
19	Painful or bleeding teeth/gums	13,657
20	Jaundice	729
21	Burning while passing urine	740
22	Swelling of feet	744
23	Swelling of face	756
24	Blood in urine	795
25	Involuntary weight loss of > 3 kg	13,797
	Ever been diagnosed with…?	
26	Diabetes	383
27	Hypertension/High BP	443
28	Stroke	420
29	Angina/heart attack/coronary artery disease	437
30	Heart failure	14,598
31	Other heart disease	423
32	Hepatitis	13,372
33	COPD	13,586
34	Asthma	533
35	Tuberculosis	10,858
	Miscellaneous	
36	Grip strength	13,124
37	Depressed for 2+ weeks in past 12 months? If yes…	1,346
38	BMI <18.5?	8,665
39	Age Group by Quartile	0
40	Low physical activity (from PAQ)	11,512

Table 27. Cox analysis for all-cause mortality among participants with a complete dataset

Frailty Category	Unadjusted		Adjusted*	
	HR (95% CI)	*p*	HR* (95% CI)	*p*
Cumulative deficit index (excluding chronic diseases)				
Lowest Quarter	**1**	**--**	**1**	**--**
2nd Quarter	2.12 (1.81-2.48)	<0.001	1.17 (1.00-1.38)	0.06
3rd Quarter	2.82 (2.43-3.27)	<0.001	1.39 (1.18-1.52)	<0.001
Highest Quarter	5.17 (4.50-5.95)	<0.001	2.21 (1.90-2.58)	<0.001
Cumulative deficit index (including chronic diseases)				
Lowest Quarter	**1**	**--**	**1**	**--**
2nd Quarter	2.53 (2.13-3.00)	<0.001	1.46 (1.21-1.75)	<0.001
3rd Quarter	3.30 (2.80-3.91)	<0.001	1.64 (1.37-1.96)	<0.001
Highest Quarter	6.38 (5.46-7.47)	<0.001	2.75 (2.31-3.27)	<0.001

*Adjusted for: age, sex, country income, highest education achieved, smoking history, alcohol consumption history, dietary caloric intake. For the cumulative deficit index (including chronic diseases), N=115,117 for the unadjusted analyses, and N=107,321 for the adjusted analyses. For the cumulative deficit index (including chronic diseases), N=104,834 for the unadjusted analyses, and N=97,863 for the adjusted analyses.