Frailty in a Global Population: Should Geographic Region Influence Frailty Definitions?

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A Thesis Submitted to the McMaster University School of Graduate Studies

in Partial Fulfilment of the Requirements for the Degree

Master of Science

TITLE:	Frailty in a Global Population: Should Geographic Region Influence Frailty Definitions?
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NUMBER OF PAGES:	ix, 73

Abstract

Introduction:

The frailty phenotype is a commonly used tool to study frailty. Two characteristics evaluated as part of the frailty phenotype are “low” grip strength and “low” physical activity, defined by the lowest quintile thresholds for age and sex. In studies of frailty in different geographic regions of the world, it is not established whether these thresholds should be applied universally or whether region-specific thresholds of grip strength and physical activity should be applied. This study aims to determine which way of defining frailty is more appropriate.

Methods:

Using data from the Prospective Urban Rural Epidemiology study, two variations of the frailty phenotype were defined: *universal frailty* in which thresholds for low grip strength and physical activity were taken to be the lowest quintile of the entire study population and *region-specific frailty*, in which these thresholds were calculated separately for each region. Frailty prevalence was calculated for each definition and Cox proportional hazards modelling was used to determine which definitions predicted mortality. Likelihood ratio tests statistics, area under the receiver operating characteristics curve, and the net reclassification improvement index were also calculated.

Results:

Overall frailty prevalence was 5.6% using *universal definitions of frailty* and 5.8% for *region-specific definitions of frailty*. Across regions, *universal frailty* prevalence ranged from 2.4% (North America/Europe) to 20.1% (Africa), while *region-specific frailty* ranged from 4.1% (Russia and Central Asia) to 8.8% (Middle East). The hazards ratios for all-cause mortality were 2.66 (95% CI: 2.47-2.86) and 2.09 (95% CI: 1.94-2.26) for *universal frailty* and *region-specific frailty* respectively (adjusted for age, sex, education, smoking status and alcohol consumption); statistical tests indicated that *universal frailty* better fit survival data and predicted mortality slightly better.

Conclusions:

Frailty prevalence varies greatly across regions depending on how the thresholds for low physical activity and grip strength are calculated. Using region-specific thresholds does not help improve the predictive value of frailty when measuring frailty in heterogenous populations using the frailty phenotype.

Acknowledgments

I owe immense gratitude to my thesis supervisor Dr. Darryl Leong, without whose mentorship, advice, and encouragement I could not have completed my Master's degree. Not only am I grateful for the invaluable guidance Dr. Leong provided throughout my Master's, but I am also grateful for his patience when I had to take a break from thesis work due to the birth of my baby boy. I would also like to thank my committee members, Dr. Salim Yusuf for providing me with the opportunity to use the PURE dataset to answer my thesis questions and Dr. Shrikant Bangdiwala for ensuring that my thesis was well-written, and that the methodology was statistically rigorous. I would also like to extend thanks to Dr. Alex Papaioannou for whom I feel very fortunate to have as my external examiner.

I am eternally grateful to my parents for always pushing me to excel academically and to my brothers, Majid and Malik, for always inspiring me. Maryem, your humour and memes, albeit sometimes a distraction, carried me through the most stressful days of graduate school. To my husband Abubakar, thank you for your enduring belief in me, especially when I lost belief in myself, and for letting me pick your brain whenever I felt like I hit a roadblock. To my dearest Mustafa, my biggest blessing, I hope this work inspires you to always have a thirst for knowledge and pursue a course of lifelong learning. Finally, completing this Master's during the COVID-19 pandemic, while pregnant and constantly relocating, was very challenging and I thank God for testing me with this challenge and allowing me to grow because of it.

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List of all Abbreviations and Symbols

AUC	Area Under the Curve
BADL	Basic Activities of Daily Living
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
GDP	Gross Domestic Product
HR	Hazard Ratio
IADL	Instrumental Activities of Daily Living
IPAQ	International Physical Activity Questionnaire
LMICs	Low- and Middle-Income Countries
LRT	Likelihood Ratio Test
NHANES	National Health and Nutrition Examination Survey
NRI	Net Reclassification Improvement
OR	Odds Ratio
PURE	Prospective Urban and Rural Epidemiology
ROC	Receiver Operating Characteristics
SHARE	Survey of Health, Aging and Retirement in Europe

Declaration of Academic Achievement

The following is a declaration that Maheen Farooqi performed the data analysis and drafted this thesis, using data collected in the PURE study. 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 reviewed the final document. Dr. Bangdiwala ensured the methodological rigour of the analyses used and reviewed the document. He and Dr. Yusuf provided insightful advice and feedback. Dr. Alex Papaioannou provided feedback as the external examiner.

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Chapter 1: Introduction

1.1 Thesis Overview

This section summarizes the content of each of the five chapters included in this thesis.

Chapter 1 summarizes the background and rationale for the objectives of the study and provides a description of the data source.

Chapter 2 provides detail on the concept and definitions of frailty, its prognostic importance, as well as its prevalence in low- and middle-income countries and in middle-aged populations.

Chapter 3 describes the study design and statistical methods used to achieve the research objectives. This includes a description of what variables are used to construct the modified frailty phenotype definitions, how frailty prevalence is measured, details on the data source, how the association between frailty and mortality is determined and how the predictive and discriminative ability of the two frailty classifications are compared.

Chapter 4 describes the results, including the sample description, frailty prevalence and comparison across regions using the two frailty classifications and their association with mortality.

Chapter 5 provides the discussion and conclusion of the thesis, in which the results are interpreted, study limitations are noted and directions for future study are explored.

1.2 Background and Rationale

Frailty is a clinical syndrome characterized by reduced physiological reserve and increased vulnerability to stressors.[1–3] It is associated with poor clinical outcomes, including falls, hospitalizations, and mortality.[1,2,4] Frailty is closely associated with age.[5,6] Depending on the operational definition of frailty used, it affects 22-34% of individuals aged 65-85 years and 43-47% of those aged >85 years.[1–3] The World Health Organization estimates that by 2050, one in five people will be 60 years or older, totalling 2 billion people worldwide.[7] Consequently, the global burden of frailty will also rise. Despite increasing recognition that frailty is a public health priority, especially in the context of global aging, the prevalence of frailty in low- and middle-income countries (LMICs) is unclear.[8–12]

It is important to study the prevalence and determinants of frailty in LMICs because the rate of population aging is higher in these regions compared to high-income countries.[9,13] In addition to age, disease and disability are important determinants of frailty, and 80% of the global burden of chronic diseases occurs in low-income and middle-income countries.[14] However, most frailty research has been restricted to high-income countries and research on the prevalence and determinants of frailty in LMICs remains limited.[9–13,15] While there has been an increase in the study of frailty in LMICs in the last ten years, most of these studies have small sample sizes and provide insufficient data to allow for comparisons of frailty prevalence across regions.[9] Moreover, due to several competing definitions of frailty and the lack of a standard operational measure for frailty, the methods used to gather data on the prevalence of frailty in LMICs are heterogenous, leading to wide differences in the reported prevalence of frailty in these regions.[8–12] For example, the most recent meta-analysis on the global prevalence of frailty in community-dwelling adults, which assessed frailty across 62 different countries, in 1,731,107 individuals aged 50 years and older, found that the prevalence of frailty ranged from 5.7% to 38% in South Africa alone, depending on the

frailty instrument used.[8] Furthermore, the majority of studies on frailty in LMICs are done on populations from middle-income or lower-middle income countries, particularly, Brazil, China, India and Latin America.[8] While this is promising, more research needs to be done on frailty in low-income countries.

Common operational definitions of frailty rely on metrics such as poor grip strength and low physical activity, to classify individuals as frail or not frail.[1,15] In these definitions of frailty, certain cut-offs or thresholds are used to classify individuals as having poor grip strength or low physical activity, based on their age, sex and body mass index (BMI). However, the thresholds for these measures have only been validated in high-income, predominantly Caucasian populations. Although, these frailty definitions have been extrapolated in the study of populations across the world, it is not known whether these thresholds are appropriate or optimal for use in non-Caucasian populations from LMICs.[12,15–17] A 2016 meta-analysis compared normative data for grip strength values across seven different United Nations regions, and found that developed countries had similar grip strength cut points for consensus definitions of sarcopenia (loss of muscle mass associated with aging) and frailty, but highlighted the need for different cut points in developing regions.[15,18] This provides some evidence that there may be region-based differences in grip strength that influence frailty prevalence in these populations, particularly when comparing developed and developing regions.

Thus, to further our understanding of the epidemiology of frailty in LMICs, there is a need for a standardized methodology in collecting frailty data across geographically heterogeneous populations. This will enable a more robust comparison of frailty across the different regions and help determine if current frailty measurement tools need to be modified to better capture frailty in diverse populations.

The Prospective Urban Rural Epidemiology (PURE) study is a large prospective cohort of adults aged 35-70 years from countries of all income strata.[19,20] It provides an excellent data source for the study of frailty in LMICs as well as high-income countries. Recruitment for the PURE study began in 2002 and as of January 2021, there were 202,497 participants enrolled in PURE across twenty-eight different countries. Countries are classified as low-, lower-middle, upper-middle and high-income, based on their Gross Domestic Product (GDP) per capita using the World Bank classifications on the dates the countries were enrolled. In PURE, data are collected on a wide variety of modifiable lifestyle factors (e.g.: diet and physical activity), non-modifiable determinants (e.g.: country income), health measures (e.g.: diseases, multi-morbidity), and anthropometric measurements (e.g.: grip strength). This allows for the study of frailty using multiple different operational definitions. The PURE dataset also contains extensive longitudinal data, thereby enabling evaluation of the associations between the aforementioned variables and outcomes such as mortality.

In this thesis, a modified version of the operational definition of frailty formulated by Fried et al., known as the frailty phenotype, will be used to measure frailty in the PURE dataset. According to Fried's frailty phenotype, an individual is frail if they exhibit **three** or more of the following five characteristics (and individuals with **one** or **two** of these characteristics are classified as pre-frail)[1]:

1. Unintentional weight-loss (≥10 pounds in the past year)
2. Self-reported exhaustion
3. Slow walking speed (below the 20th percentile for people with the same height and sex)
4. Low physical activity levels (below the 20th percentile for people of the same sex)
5. Weak grip strength (grip strength in the lowest 20th percentile, adjusted for sex and body mass index (BMI)).

The PURE study provides data on weight-loss, physical activity levels and grip strength, which can all be used to create a 3-variable modified frailty phenotype definition. In the modified version, individuals with **two** or **three** of the above characteristics (#1, #4, #5) are considered frail, and individuals with **one** of these characteristics are classified as pre-frail.

1.3 Study Objectives and Hypothesis

The objectives of this thesis are to determine 1) the prevalence of frailty and pre-frailty in adults from countries at varying levels of income and ethnicity and 2) to determine if applying region-specific grip strength and physical activity cut offs for lowest quintile improves the ability of frailty in predicting all-cause mortality, when measuring frailty in geographically and ethnically heterogeneous populations. In order to meet these objectives, I will first measure the proportion of individuals classified as frail in the PURE cohort using the modified frailty phenotype definition. This frailty classification will be called *universal frailty.* To meet the second objective, a second frailty classification, called *region-specific frailty,* will also be formed. The difference between *universal frailty* and *region-specific frailty* is that for *universal frailty* the lowest quintiles for low physical activity levels and poor grip strength values are not adjusted for region, whereas for *region-specific frailty*, the lowest quintiles for low physical activity levels and poor grip strength values are calculated separately for each region. Thus, I will determine if region is a relevant factor, such as sex or BMI, when classifying individuals as having poor grip strength and low physical activity. The two frailty classifications will then be compared to test which has better discriminative ability for predicting all-cause mortality.

I hypothesize that a region-based frailty classification will be better at predicting all-cause mortality than a frailty definition in which universal cut-offs for grip strength and physical activity are applied. Several studies suggest that normative grip strength values differ based

on ethnicity and across socioeconomically heterogeneous populations.[15,16,21,22] Furthermore, a review done in 2020 on the global epidemiology of frailty reported variations in frailty prevalence between ethnic minority migrants in developed countries compared to their domestic counterparts, reporting that ethnic migrants tended to be more frail and were more likely to be frail when younger.[12] Although geographic region or country of origin are not synonymous with ethnicity, they are a useful proxy for ethnicity. Thus, it is reasonable to hypothesize that a region-based frailty classification may be better at capturing the prevalence of frailty in heterogeneous populations compared to a frailty classification in which region is not taken into account.

Chapter 2: Background on Frailty

2.1 Operational Definitions of Frailty

2.1.1 Frailty Phenotype

There is no consensus operational definition of frailty, despite increasing recognition of its importance in the context of a globally aging population. Several operational definitions exist. Most notable of these are 1. Fried's phenotype definition[1] and 2. The cumulative deficit index.[2] According to Fried's frailty phenotype, an individual is frail if they exhibit **three** or more of the following five characteristics shown in Table 1. Individuals with **one** or **two** of these characteristics are classified as pre-frail. This operational definition of frailty was first validated in the 2001 Cardiovascular Health Study on a population of community dwelling male and female adults aged 65 years and older in the United States.[1]

Table 1: Summary of the five frailty criteria used in the original frailty phenotype definition

Characteristic	**Cardiovascular Health Study Measure**
Shrinking/ Unintentional weight loss	>10 lbs lost unintentionally in prior year
Weakness	Grip strength (Kgs): lowest 20%, stratified by sex & body mass index (BMI)
Low physical activity	Physical activity (Kcals/week): lowest 20% males: <383 Kcals/week females: <270 Kcals/week
Poor endurance	"Exhaustion" (self-reported)
Slow gait speed	Walking time/15 feet: slowest 20% (by gender, height)

This frailty phenotype has since been repeatedly validated as a predictor of falls, decline in activities of daily living (ADL), worsening mobility, hospitalization, and death in many other populations.[4,13] The frailty phenotype definition allows frailty to be efficiently assessed

through a short clinical assessment. Most studies of frailty in LMICs have used an adaptation of Fried's phenotypic definition of frailty.[8]

2.1.1.1 Implications of Stratifying Grip Strength and Physical Activity by Region

Grip strength and physical activity are key measures that make up the frailty phenotype definition. There is increasing recognition of the importance of grip strength as a risk stratification tool for mortality and cardiovascular disease, as well as its use in the identification of sarcopenia and frailty.[17,23,24] A large number of studies have been published describing the normative values of hand grip strength for different geographic regions and populations.[22,25,26] These studies typically divide data by age and sex sub-groups with the aim of providing age- and sex-specific reference ranges for grip strength. Comparing findings from these studies immediately reveals that there are important differences between reference ranges for handgrip strength across regions. For example, previous research from the PURE study on reference ranges for grip strength values has demonstrated that median grip strength can vary from 51 kg (interquartile range (IQR): 44-58 kg) in men aged less than 40 years from Europe/North America to 36 kg (IQR: 26-44 kg) kg in men from of the same age range from Southeast Asia.[22] Thus, the need arises to examine if region should be taken into account when forming the thresholds for poor grip strength to be implemented in the frailty phenotype. Under the original definition, low grip strength is defined as participants who fall under the lowest quintile for grip strength, stratified by sex and BMI.[1] However, given the heterogeneity in grip strength values across different geographic regions, even among people with the same sex and BMI, it may be necessary to stratify grip strength by region as well, in order to accurately identify frail individuals.[27] Otherwise, when measuring frailty in a geographically diverse population, individuals from regions in which grip strength tends to be higher will exhibit disproportionately lower levels of frailty and individuals from regions where grip strength tends to be lower will exhibit higher levels of frailty, if the same grip

strength cut-offs are applied regardless of region. The same case can be made for physical activity levels. Ignoring regions when creating the quintiles for low grip strength and physical activity may therefore lead to biased estimates of frailty prevalence.[16]

To my knowledge, only one study has explored the effect of implementing ethnicity-stratified grip strength and physical activity thresholds when measuring frailty. This study drew data from a sample of community dwelling Mexican Americans (n=394) and European Americans (n=355) between the ages of 65 and 80 years who participated in the baseline examination of the San Antonio Longitudinal Study of Aging.[16] Investigators compared the prevalence of frailty using an 'ethnic-specific criteria' with the prevalence of frailty using 'conventional criteria'. For the conventional definition of the frailty phenotype, the authors used all five of Fried's frailty criteria, and standardized grip strength by sex and BMI, physical activity by sex and walking speed by height and sex across the pooled sample. For the ethnic-specific frailty criteria, first, individuals were identified as either Mexican American or European American, and then the frailty criteria were applied to each ethnicity separately. Thus, the lowest quintile thresholds for physical activity, grip strength and walking speed differed between the measures of frailty. Under the conventional criteria, the prevalence of frailty in Mexican Americans and European Americans was 11.3% and 7.0% respectively. Under the ethnic-specific criteria, the prevalence of frailty for both Mexican Americans and European Americans was 9.9%. The authors concluded that applying universal thresholds for the various criteria used in the frailty phenotype definition can lead to a disproportionately high number of ethnic minorities being classified as frail. Given that there are known differences in height and BMI across ethnic groups, standardizing frailty criteria to only these physical characteristics may create misleading ethnic disparities in frailty.[16,27] In turn, this can lead clinicians to incorrectly classify non-Caucasian patients as being more likely to be frail and modify treatment plans accordingly, even when these patients are not truly frail and might

benefit from aggressive interventions. However, this study did not perform a longitudinal analysis to determine whether stratifying individual frailty criteria by ethnicity changes the predictive ability of the frailty phenotype.

2.1.1.2 Heterogeneity in grip strength measurement

Despite the increasing number of studies related to grip strength measurement being published in recent years, studies differ on how grip strength is measured, even when measuring grip strength for the same purpose, i.e. to classify an individual as frail using the frailty phenotype.[17] Most studies that have utilized Fried's operationalization of frailty have deviated in some way from the original method in which grip strength was first used to classify someone as weak according to the frailty criteria.[17] In the original Cardiovascular Health Study, grip strength was measured three times on the dominant hand using a hand held dynamometer and the average of the three readings was used.[1] Common modifications to this include using readings from the right hand only and using the highest out of three readings to determine the grip strength value.[17] A 2017 systematic review aimed to analyse the different protocols used to measure grip strength in the context of frailty and sarcopenia assessment.[17] The authors assessed whether the protocols identified addressed the following seven questions, all of which assess factors that can influence grip strength values obtained during measurement: 1. Which dynamometer was used for measuring grip strength? 2. Which hand was used? 3. What was the individual's posture? 4. What was the arm position? 5. Which handle position was used? 6. How long did the measurement take? 7. How long were the intervals between the measurements? The review included 72 articles, 33 of which measured frailty, 37 which measured sarcopenia and two that measured both sarcopenia and frailty. The authors found that most articles provided limited information on the protocols used to measure grip strength. Only five studies specified if the dynamometer used was calibrated, 33 studies measured grip strength in the dominant hand only, four studies obtained measurement

in the non-dominant hand and 25 studies measured grip strength in both hands. There was also considerable heterogeneity around the posture the subject took when using the dynamometer as well as heterogeneity or missing information on whether encouragement was provided while the measurement was taken. The authors of this review concluded that there is high heterogeneity in the measurement of grip strength values, which precludes comparisons between studies on either frailty or sarcopenia, thereby reinforcing the need for more standardized procedures in the assessment of these conditions as well as in studies that present normative data.

2.1.2 Other Definitions of Frailty

A second common operational definition of frailty is the cumulative deficit index, which measures frailty as a proportion of deficits exhibited by an individual out of the total number of health deficits assessed.[2] For example, if a study measures 40 deficits and an individual presents 10 of these, the frailty index score would be 0.25. Typically, the cut-off point to be considered frail is 0.25.[2] The most widely cited model is Rockwood's 70-item index, which comprises a range of functional, physiological, psychological and social deficits.[2] This frailty index has been associated with an increased risk of death (hazard ratio (HR): 1.039, 95% CI: 1.033-1.044) per 0.01 increase in frailty index score (i.e.: for a 10% change it is almost a 40% increase in risk) and has been validated in multiple diverse cohorts.[28] Since the frailty index aims to measure deficit accumulation, it can be created using any combination of symptoms, signs, deficits or diseases, provided the deficits meet all of the following five criteria:

1. Associated with health status

2. Prevalence increases with age.

3. Not saturate too early (i.e.: not be found in all individuals early on, such as presbyopia, which is nearly universal by age 55)

4. Associated with adverse outcomes.

5. Cover several body systems.

Subsequent studies by Rockwood and others have demonstrated that the cumulative deficit index retains predictive validity even after reducing the number of deficits to 30 variables.[3]

Some other common frailty measures include the Edmonton Frail Scale and the Comprehensive Geriatric Assessment (CGA).[29,30] These measures have been less commonly used than the frailty phenotype or the frailty index in the study of frailty in LMICs. Briefly, the Edmonton Frail Scale assesses the following nine domains, using a combination of self-reported questions, physical tests and cognitive tests: cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance. This tool was designed to allow healthcare providers who do not have specialised geriatrics training to identify frail patients more efficiently in in-patient and out-patient settings.[29] Finally, the CGA is a multidisciplinary process in which the medical, psychosocial and functional abilities of an older adult are evaluated by a team of health professionals with the aim of developing goals of care for an individual patient. Meta-analyses have found that based on the exact model of CGA used, this assessment and associated treatment planning can improve survival and reduce hospitalizations.[30,31]

2.1.3 Comparison of the Frailty Phenotype and the Frailty Index

The frailty phenotype and the frailty index are the two most common tools used to measure frailty. They have often been compared to one another and both tools demonstrate that frailty is associated with adverse health outcomes.[28,32,33] One 2015 study, performed by Theou and colleagues, on a cross-sectional sample of 4,096 adults aged 50 years or older, compared the two frailty measures using data from the National Health and Nutrition Examination Survey (NHANES).[34] This study found that both frailty measures demonstrate a right-skewed

distribution, both exhibited an exponential increase of frailty with age, both measures reported higher levels of frailty in women, and strong associations with poor self-reported health (odds ratio (OR) for frailty phenotype: 39.8, 95% CI: 24.02-66.03; OR for frailty index: 38.38, 95% CI: 26.11-56.4)) and healthcare utilization (OR for frailty phenotype: 6.54, 95% CI: 4.3-9.65; OR for frailty index: 15.27, 95% CI: 10.6-22.0).

However, there are some key differences between these two frailty measures which suggest that they should not be used as substitutes for one another. First, even though the study described above by Blodgett and colleagues applied the two frailty classifications in the same sample, the prevalence of frailty varied drastically based on the classification used. According to the frailty phenotype, the prevalence of frailty was 3.6%, and according to the frailty index, it was 34%.[34] Furthermore, some studies have found that the frailty index is associated with adverse health outcomes among people who are classified as non-frail by the frailty phenotype. In the study described above, a sub-analysis in individuals classified as frail using the frailty index, but non-frail using the frailty phenotype, found that frailty was still associated with poor self-reported health (OR: 23.44, 95% CI: 14.76-37.23) and healthcare utilization (OR: 12.05, 95% CI: 8.00-18.51).[34] Similarly, Theou et al reported in 2013 that, when comparing the areas under the curve (AUC) for the frailty phenotype and the frailty index at predicting 5-year mortality, the AUC for the frailty index is higher (0.75 in men and 0.73 in women) compared to the AUC for the frailty phenotype (0.71 in men and 0.70 in women).[32] This suggests that the frailty index may be a bit more sensitive at detecting individuals who are at the lower end of the frailty continuum, before they reach an absolute frail state. Thus, the frailty index identifies more individuals who have adverse outcomes as frail compared to the frailty phenotype.

Most criticism of the frailty index is regarding the complexity of collecting data on the large number of deficits (a minimum of 30 items) to generate the index.[35] This can be especially

difficult in areas where resources such as electronic medical records are lacking. Another related consideration is that people from LMICs may be more likely to be living with undiagnosed diseases, due to less stringent screening and diagnostic procedures, and their frailty index scores may be lower than they should be. Cesari et al. note the simplicity of the frailty phenotype in comparison to the frailty index, suggesting it is a good measure of frailty for risk stratification of the different frailty levels, and note that it can be applied to an individual at a first clinic visit, as it does not require a preliminary clinical evaluation.[35] They also suggest that using the frailty phenotype may be better for younger populations for early detection of frailty, because this frailty classification does not rely on deficit accumulation or disability. Furthermore, it is important to note that while both frailty classifications have strong agreement, they are conceptually different, with the frailty phenotype supporting the hypothesis that frailty can cause disability in individuals even in the absence of any diagnosed clinical disease. Therefore, it may be more appropriate to use in a population of younger, non-disabled subjects.[35] Finally, measuring grip strength is an efficient, non-invasive and inexpensive means for assessing the frailty risk of a patient, which may explain the popularity of the frailty phenotype in the study of frailty in LMICs.[17]

2.2 Prevalence of Frailty in LMICS and High-income Countries

Given the considerable heterogeneity around how frailty is defined and operationalized, and the heterogeneity of the populations it is measured in (in terms of age, country-income level, whether subjects are community dwelling or nursing home residents, etc.), providing a single prevalence estimate for frailty can be difficult.[36,37] The most recent systematic review and meta-analysis of the prevalence of frailty was done in 2021, and included data from 242 studies across 62 countries, with a pooled sample of 1,755,497 participants.[8] Studies were included if participants were community- dwelling adults aged 50 years and older. The

pooled frailty prevalence according to the frailty phenotype was 12%, compared to 24% for the frailty index. The pre-frailty prevalence was 46% and 49% for the frailty phenotype and frailty index respectively.

Even when frailty is measured using a single definition, it is often modified from the original definition. A 2015 systematic review by Theou and colleagues found that out of 264 articles assessed, 223 articles applied at least one modification to the Fried's frailty phenotype criteria, and that these modifications can impact the classification and predictive ability of the frailty definition.[36] These authors applied various frailty phenotype definitions to the Survey of Health, Aging and Retirement (SHARE) database (a representative sample of community dwelling adults aged over 50 years from twelve high-income European countries, n=3,115) and found the frailty phenotype prevalence to range from 12.7% to 28.2% depending on the modification performed.

In 2012, Collard et al published the first systematic review on the prevalence of frailty, estimating it to be 10.7% using the frailty phenotype definition.[5] This review consisted of 21 studies done in high-income, Western countries. The sample size was 56,183 and the mean age of participants was 75 years. A more recent review (2020) on the global prevalence of frailty also reported the same frailty phenotype prevalence in high-income countries, 10%, and reported that LMICs tend to have higher rates of frailty prevalence, ranging from 20% in Latin America and the Caribbean to 65% in Thailand.[12] The authors suggest that this is due to the exponential growth in ageing populations in these regions. In the last six years, there has been a dramatic increase in the number of studies aimed at identifying the prevalence of frailty in LMICs.[9–13,37] A recent (2018) meta-analysis identified 56 studies (sample size range 54-12,373) that examined the prevalence of frailty in community-dwelling adults from LMICs.[9] The mean age of participants ranged from 68.2±5.8 years to 77.2± 6.4 years. The most common frailty assessment method used was the frailty phenotype. The pooled frailty

and pre-frailty prevalence for studies using the frailty phenotype were 12.7% (95% CI: 10.9%-14.5%) and 33.8% (95% CI: 27.6%-40.4%) respectively. The frailty index was used in 4 studies, in which the prevalence of frailty was 15.6% (95% CI: 5.8%-35%). Out of the 56 studies included in the review, only one examined frailty prevalence in a low-income country, whereas the rest of the countries studied were middle-income countries. Despite analysing frailty in heterogeneous populations, these reviews did not discuss using region-specific thresholds for the frailty criteria.

2.3 Frailty in middle-aged adults

Most frailty research has been conducted in populations aged 65 years and older.[34,38–40] As frailty increases with age, it may already be well-established in many participants in these cohorts.[38] It is important to study frailty in middle-aged adults because frailty may be amenable to modification or reversal in its early stages.[38] Since frailty can predict future disability, identifying and reducing frailty in middle-aged adults can have important prognostic implications, and identify ways to optimize care as individuals age.[13,28,38,41] Estimates of the prevalence of frailty among middle-aged adults are scant, and the ability of frailty to predict mortality has not been well demonstrated in younger cohorts.[39,40]

One study that has examined the prevalence of frailty in younger cohorts was done using Canadian Health Measures Study data.[40] This study compared the prevalence of frailty using the frailty phenotype (n=7,353) versus the frailty index (n=10,995) in the same cohort of 18-79 year olds. The study consisted of three data collection cycles, two of which included data on the frailty phenotype domains and one that did not. The frailty index was calculated for all three cycles. The rates of frailty by age group using the frailty phenotype and the frailty index respectively were: 5.3% vs. 1.8% in the 18–34 age group, 5.7% vs. 4.3% in the 35–49 age group, 6.9% vs. 11.6% in the 50–64 age group, and 7.8% vs. 20.2% in the 65+ age group.

Of note, there appeared to be a systematic differential bias in the reported frailty rates as the phenotype prevalence is lower than the frailty index at younger ages and the reverse at older ages. Although this study reported the prevalence of frailty among those younger than 65 years, it did not explore the association between frailty and adverse health outcomes in this age group.

A recent (2018) prospective analysis by Hanlon and colleagues of over 400,000 participants from the UK Biobank (a large community cohort of over half a million people aged 37–73 years) examined the association between frailty and mortality.[38] Using the frailty phenotype definition, they found that 3% of participants were frail and 38% were pre-frail. Both frailty and pre-frailty were associated with higher 7-year mortality for all age strata in men and women (except in women aged 37–45 years), with hazard ratios ranging from 1.36 (95% CI: 1.04-1.79) to 2.70 (95% CI: 1.58-4.64), after adjusting for age, sex, BMI, smoking status, alcohol use and multi-morbidity count. Similar prevalence rates were found in 18,227 randomly selected community dwelling individuals who were enrolled in the Survey of Health, Aging and Retirement in Europe (SHARE). In this study of middle-aged and older adults in Europe, 4.1% were frail (95% CI 3.4–4.7) and 37.4% (95% CI 35.8–39.1) were pre-frail.[42]

Despite a recent increase in published studies on frailty in LMICs, there is a paucity of literature on frailty and pre-frailty in middle-aged adults in these regions. Whether similar patterns of frailty in middle-aged adults exist across LMICs has not yet been explored in depth. The few studies of frailty in people younger than 65 years have lower age limits, ranging from 50 to 65 years of age, have small sample sizes, and are restricted to middle-income or high-income countries.[38,39]

2.4 Frailty and Country Income

On an individual level, income has been inversely associated with frailty, using both the frailty phenotype definition and the frailty index.[43,44] However, on a population level, the relationship between national socioeconomic indicators and frailty is less clear. A study in 2013 by Harttgen and colleagues compared frailty levels between higher income countries from the SHARE study, and lower income countries from the World Health Organization's Study on Global AGEing and Adult Health (SAGE).[45] This study was done on community dwelling adults between the ages of 50 and 85. Since it involved comparison of two different databases, only variables common to both SHARE and SAGE were used to create almost identical cumulative deficit frailty indices. This study concluded that lower income countries had lower frailty index scores compared to high income countries. However, LMICs may have lower rates of diagnosed diseases compared to high income countries because of differences in healthcare resources such as advanced diagnostic technology. Thus, ascertainment bias of individual medical conditions could explain the lower frailty prevalence found in LMICs. Estimating the prevalence of frailty in LMICs using the phenotypic definition can reduce this bias.

Another study using the SHARE database by Theou et al., (2013) evaluated the relationship of frailty with national income and healthcare spending across higher income European countries.[46] 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. A total of 36,306 community dwelling adults aged >50 years from 15 countries were included in the sample. Age and sex distributions were similar between the lower income and higher income countries (mean 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). Theou et al., constructed a 70-item cumulative deficit index, and frailty was found to be lower in countries with a higher

GDP per capita compared to lower income countries. The contradictory findings from Hartgen et al.'s and Theou et al.'s studies indicate that further study is needed to understand the patterns of frailty prevalence in low-, middle- and high-income countries. Currently, most studies of frailty include participants from a single country. Comparing the prevalence of frailty using a standardized method across low-, middle- and high-income countries will enable more reliable comparisons of frailty rates in these different settings.

2.5 Prognostic Importance of Frailty

Knowledge about an individual's frailty status can help inform clinical decisions around risk assessment, outcome prediction, and treatment selection.[47] Several studies have established the importance of frailty in predicting adverse health outcomes. Frailty, defined using any of the instruments previously discussed, is associated with disability, functional and cognitive impairment, emergency department visits, hospitalization, post-operative complications, institutionalization, and mortality.[1,3,13,37,47–49] The prognostic significance of frailty remains after adjusting for factors such as age, sex, education and race.

The prognostic value of frailty has been established in high-income populations as well as in LMICs. A study on 11,015 community-dwelling men and women across eleven countries of the European Union demonstrated the association between the frailty phenotype with functional disability and morbidity.[4] The mean age of participants was 70 years for men and 71 years for women, and 13% of the population was frail(using the frailty phenotype definition). Disabilities assessed included mobility disability, defined as self-reported difficulty in any one of eight upper and lower extremity mobility tasks, as well as disability in instrumental activities of daily living (IADL) (e.g. cooking, grocery shopping, or taking medications), and disability in basic activities of daily living (BADL) (e.g. bathing, toileting and eating). Participants were followed up for two years and those who were frail were more

likely to develop mobility disability (OR: 3.07; 95% CI: 1.02-9.36), or report worsened mobility disability (OR: 2.94; 95% CI: 2.19- 3.93), and were more likely to develop IADL disability (OR: 5.52; 95% CI: 3.76-8.10) or BADL disability (OR: 5.13; 95% CI: 3.53-7.44). They were also more likely to report worsening IADL disability (OR: 4.43; 95% CI: 3.19-6.15) and BADL disability (OR: 4.53; 95% CI: 3.14-6.54). The association between frailty and morbidity was also assessed in this study. Worsening morbidity was defined as an increase in the number of chronic conditions observed among individuals at 2 years follow-up, and was associated with frailty (OR: 1.77; 95% CI: 1.35-2.32). Age, sex, income, and baseline disability and morbidity were adjusted for in this study.[4]

The prognostic value of frailty has also been explored in a few LMICs. One such population-based cohort study was performed on 13,924 older adults from Cuba, Dominican Republic, Venezuela, Mexico, Peru, India, and China.[13] In this study, investigators used the frailty phenotype, and the outcomes studied were mortality and the onset of dependence, which was identified through a series of open ended questions to key informants such as, 'Who shares the home? What kind of help does the participant need inside and outside of the home? Who, in the family, is available to care?' The study found that being frail vs. non-frail according to the frailty phenotype, predicted the onset of dependence (HR: 1.28, 95% CI: 1.10-1.48) and mortality (HR: 1.18, 95% CI: 1.06-1.33), after adjusting for age, sex, education, chronic diseases and disability. In addition to being studied in community dwelling adults, the prognostic importance of frailty has been well-documented in patients who are critically ill, as well as in those with heart failure, acute coronary syndrome and cancer.[50–52]

The independent prognostic effect of Fried's five frailty criteria have also been explored.[20,24,53] A prospective cohort study by Rothman and colleagues of 754 non-disabled, community-dwelling adults aged >70 years, examined the association between slow gait speed, low physical activity, weight loss, exhaustion, and weakness, with the occurrence of

chronic disability, long-term nursing home stays, injurious falls, and death.[53] The follow-up period was 8 years. In this study, slow gait speed, low physical activity, and weight loss were independently predictive of chronic disability, long-term nursing home stays, and death. The hazard ratios ranged from 1.7 (95% CI: 1.2-2.4) for slow gait speed predicting death, to 3.9 (95% CI: 2.2-6.7) for slow gait speed predicting nursing home stay.[53] In a larger study by Leong and colleagues on the PURE cohort, the prognostic value of grip strength alone was examined.[20] The sample size was 139,691, and median follow-up time was 4 years. This study found that grip strength was inversely associated with all-cause mortality, with a hazard ratio of 1.16 (95% CI: 1.13-1.20) per 5 kg reduction in grip strength. Moreover, this study found that grip strength was a stronger predictor for all-cause mortality than systolic blood pressure. Thus, both individual frailty phenotype criteria and their aggregate are powerful predictors of death and disability.

2.6 Regression from Frailty States

Despite the substantial evidence that frail and pre-frail individuals are at an increased risk for various adverse outcomes, frailty is known to be a reversible phenomenon, particularly among younger populations.[39,54] One recent meta-analysis, published in 2020, estimated the 'natural rate of frailty regression' (defined as an improvement in frailty status) from frail and pre-frail states among community-dwelling older adults aged at least 60 years.[54] Data from twenty-five studies, including twenty-six different countries and over 50,000 individuals, were used. The pooled prevalence of frailty and pre-frailty was 12.8% and 50.5%, respectively. The median follow-up period was three years, and the authors found that up to 35.2% of surviving frail individuals regressed naturally to either a pre-frail or robust state from frailty. The pooled regression rates among people with pre-frailty and frailty were 80.4 (95% CI: 61.7-104.6) and 135.3 (95% CI: 98.1-186.5) per 1,000 person-years, respectively.

This meta-analysis included twenty studies that used the frailty phenotype definition, three that used the frailty index, one study that used both the frailty index and the frailty phenotype ,and one that used the Vulnerable Elders Survey-13 screening tool. It comprised countries of varying levels of income, across North America, Europe, South America, Asia, and Australia. The authors reported that rates of regression of frailty status varied based on factors such as gender (females were more likely to regress to improved frailty states), frailty assessment methods, and duration of follow-up.[54] A similar systematic review was carried out by Kojima and colleagues in 2019.[55] This review was restricted to studies that used the frailty phenotype definition, and included studies that examined the natural regression from frailty states in longitudinal samples. The median follow-up time was 3.9 years, and sixteen studies with data from 42,775 participants were included. In their pooled analysis, the authors found that 13.7% of individuals had an improved frailty status after follow-up, 29.1% worsened, and 56.5% maintained their frailty status. Evidence from these reviews shows that frailty states may be dynamic, and reversal of an individual's frailty status is possible. Alternatively, these findings suggest that current frailty instruments are subject to measurement error, thereby explaining the shifts in frailty status at different time points. This can also be explained by regression to the mean and not necessarily a true reversal of frailty states. However, there is still potential benefit of early detection of frailty and pre-frailty.

Chapter 3: Methods

3.1 Rationale

Given the gaps and inconsistencies in the literature pertaining to the prevalence of frailty in geographically and ethnically diverse populations, as well as the lack of data on the prevalence of frailty in middle-aged adults from LMICs, there is need for a standardized methodology in collecting frailty data on a large and diverse sample to improve our understanding of the epidemiology of frailty in different regions. Moreover, the inclusion of region as a factor that is adjusted for when developing the frailty phenotype has yet to be thoroughly evaluated and can have large implications on how the frailty phenotype is measured and used when applied to individuals from varying backgrounds. The PURE study provides an extensive dataset that makes it possible to perform such research.

3.2 Objectives

1. To calculate the prevalence of frailty, using adaptations of the frailty phenotype in middle-aged and older adults from countries at varying levels of income and in different ethnic groups.
2. To determine if applying region-specific grip strength and physical activity cut offs for lowest quintile improves the ability of frailty to predict all-cause mortality

3.3 Hypothesis

I hypothesize that a region-based frailty classification will be better at predicting all-cause mortality than a frailty definition in which universal cut-offs for grip strength and physical activity are applied.

3.4 Overview of the PURE Study Design

The Prospective Urban and Rural Epidemiological (PURE) study is a large multinational prospective study that was designed to yield insights into the relationship between a wide variety of primordial and primary risk factors, and cardiovascular as well as non-cardiovascular events.[56] As of January 2021, there are 27 countries enrolled in PURE (See Appendix I), which comprise 800 urban and rural communities and 202,497 unique subjects. Details on the study design, data collection and recruitment strategy have been previously published.[19,20,56] To summarize, communities from participating countries were identified using pre-specified criteria, and eligible households and individuals within these households were recruited. Recruitment strategy differed based on country income level. For example, in high-income countries, mail and telephone follow-ups were common means of recruitment and follow-up. In low-income countries and/or rural communities, contact was first established with local authorities (e.g.: community leaders), followed by in-person door-to-door household visits. All individuals within these households between 35 and 70 years providing written informed consent, were enrolled. Trained study personnel used standardized data collection procedures to gather data at the community, household and individual levels. Baseline data encompassed self-reported demographics, cardiovascular risk factors, other chronic diseases, various symptoms (including unintentional weight loss), education levels, employment status, physical activity levels (using the International Physical Activity Questionnaire (IPAQ)), tobacco and alcohol use, diet, anthropometrics, muscle strength as measured using a handgrip dynamometer, and blood pressure.

3.5 Ethics

The PURE study was approved by the relevant research ethics committees in the participating countries. All participants provided written informed consent.

3.6 Study Sample

All individuals aged 35-70 years for whom baseline data on sex, age, BMI as well as variables for the three frailty domains needed to create the frailty phenotype classifications (grip strength, weight loss and physical activity), were included in the analysis. A total of 137,499 out of 202,497 were included in the final frailty calculations. Data available by January 11, 2021, was used.

3.7 Data Collection

3.7.1 Development of Frailty Classifications

Data from the baseline PURE Adult Questionnaire and International Physical Activity Questionnaire were used to develop two frailty classifications, namely *universal frailty* and *region-specific frailty*. Table 2 describes how the frailty criteria developed by Fried et al. were measured in the PURE study and illustrates how the two frailty criteria used in this thesis differ. The key difference between *universal frailty* and *region-specific frailty* is that in *region-specific frailty*, grip strength is adjusted for region in addition to sex, and BMI and physical activity is adjusted for region in addition to sex.

Table 2: Frailty criteria and method of measurement

Characteristic	**CHS Measure**	**PURE Universal Measure**	**PURE Region-specific Measure**
Unintentional weight loss	Baseline: >10 lbs lost unintentionally in prior year	Involuntary weight loss of > 3kg in the last six months	Involuntary weight loss of > 3kg in the last six months
Weakness	Grip strength: lowest 20% (stratified by sex & body mass index (BMI)	Grip strength: lowest 20% (stratified by sex, body mass index)	Grip strength: lowest 20% (stratified by sex, body mass index, and **region**)
Low physical	Kcals/week: lowest 20%	MET-minutes/week:	MET-minutes/week: lowest

activity	males: <383 Kcals/week females: <270 Kcals/week	lowest 20% (stratified by sex)	20% (stratified by sex, and **region**)
Poor endurance; Exhaustion	"Exhaustion" (self-report)	Not measured	Not measured
Slow gait speed	Walking time/15 feet: slowest 20% (by gender, height)	Not measured	Not measured

3.7.2 Weight Loss

Unintentional weight loss was assessed using the PURE Adult Questionnaire through participant's response to the self-report question: 'Have you experienced involuntary weight loss of more than 3 kg in the last six months?' Responses to the questions were treated as a binary variable and given a score of 0 for 'no' or 1 for 'yes'.

3.7.3 Physical Activity

Physical activity levels were assessed using the International Physical Activity Questionnaire (IPAQ). The IPAQ is a self-report questionnaire which has long been accepted as a reasonable measure for the monitoring of population levels of physical activity for those between the ages of 18 and 65 years, in diverse settings.[57] Data from the IPAQ were collected as MET-minutes per week (MET-minutes/week). This is a slight modification to how Fried et al., originally measured physical activity, where they used kilocalories expended per week, measured through the Minnesota Leisure Time activity questionnaire.[5] For *universal frailty*, the IPAQ MET-minutes/week were stratified by sex and divided into quintiles. Individuals whose MET-minutes/week values fell below the lowest quintile cut-off (i.e.: the lowest 20%) for their sex, were given a score of 1, and everyone else was scored a 0. For *region-specific frailty*, the same approach was used; however, region was also included as a variable that was

stratified for before creating the quintiles. The specific MET-minutes/week cut-offs used for each stratum are provided in Appendix II for the two frailty classifications.

3.7.4 Grip Strength

Grip strength (in kilograms (kg)) was measured by study personnel using a Jamar dynamometer according to a standardized protocol. Grip strength was measured three times on each hand. In this study, the average of three readings from the dominant hand was used. In cases where grip strength values were missing for one hand but available for the other hand, missing values (n=38,411) were imputed using the regression coefficient and constant from the linear regression of the non-dominant hand with dominant hand grip strength. For *universal frailty*, grip strength was stratified by sex, and BMI (underweight: <18.5 kg/m2, normal: ≥18.5 & <25 kg/m^2, overweight: ≥25 kg/m^2 & <30 kg/m^2 and obese: ≥30 kg/m^2), and divided into quintiles. Individuals who fell below the lowest quintile (i.e.: the lowest 20%) for their sex and BMI, were given a score of 1 and all other individuals were scored a 0. The same approach was used for the *region-specific frailty* classification, with the only difference being that individuals were stratified by region as well as sex and BMI when forming the thresholds for the lowest quintile. The grip strength cut-off values for each stratum for both frailty classifications are available in Appendix II.

Once all eligible individuals (n=137,499) were given scores of 0 or 1 for each of weight loss, physical activity and grip strength, their scores were summed, so that each individual had a frailty score ranging from 0-3. Using this score, they were classified as either frail, pre-frail or non-frail: individuals with a frailty score of 0 were non-frail, those with a frailty score of 1 were pre-frail and those with a frailty score of 2 or 3 were frail. Separate scores were calculated for both *region-specific frailty* and *universal frailty*.

3.7.5 Outcome Event Ascertainment

Where available, information on medically certified death was obtained. In other cases, death documentation was obtained from household interviews, medical records, verbal autopsies, and other sources.[20]

3.8 Statistical Analysis

3.8.1 Frailty Prevalence

To address the first objective, the prevalence of frailty and pre-frailty was measured as the proportion of individuals classified as frail or pre-frail as a percentage of the entire sample. This was done for both *universal frailty* and *region-specific frailty*. To further explore these results, the proportion of frail and pre-frail individuals in each of the eight regions separately (South Asia, China, Southeast Asia, Russia and Central Asia, Africa, North America/Europe, Middle East and South America) was also calculated. The prevalence of frailty was also calculated for each country income category (high, upper-middle, lower-middle and low) across the different age strata (35-40 years, 41-50 years, 51-60 years, 61-70 years) using the two frailty classifications. Frailty prevalence rates were age- and sex- standardized when comparing frailty prevalence across regions, and sex-standardised when comparing frailty prevalence across the different age groups.

3.8.2 Cox Proportional Hazards Modelling

To assess the association between the two frailty classifications with death, Cox proportional hazard modelling was used to calculate hazard ratios of time to all-cause mortality, stratified by frailty level and adjusted for the following covariates: age, sex, education, smoking status and alcohol consumption. The hazard ratios for the two frailty classifications were compared. Kaplan-Meier survival curves stratified by frailty category were generated for the two

different classifications of frailty. Stratified log-rank tests were done to test for differences in survival between the two frailty classifications using the standard chi-squared formula: $\chi^2 = \sum \frac{(observed-expected)^2}{expected}$.

The appropriateness of the proportional hazards assumption was checked by visual inspection of the log-log survival against log time plots.

3.8.3 Comparison of Discriminative Ability of the Two Frailty Classifications

To compare the two frailty classifications, three methods were used: the log likelihood tests for the Cox survival analyses were compared, as was the area under the receiver operating characteristics (ROC) for a binary survival outcome, and the net reclassification improvement index was calculated. First, the log likelihood ratio test was performed to determine which frailty definition fits the longitudinal data better. To test this, three survival analysis were run: (1) with only the five covariates (age, sex, education, smoking status, alcohol consumption) (2) with covariates and *universal frailty* (3) with covariates and *region-specific frailty*. Then two likelihood ratio test statistics (a chi-squared test with 2 degrees of freedom) were calculated, first for model (2) vs. model (1) and second for model (3) vs model (1). The model with the larger likelihood ratio test was determined to fit the data better.

Second, receiver operating characteristic (ROC) curves were generated for the two frailty classifications with all-cause mortality as the binary outcome variable (death or no death at any time during follow-up). The discriminative ability of the two frailty classifications was compared by assessing the area under the curves (AUCs), with higher values indicating better prognostic ability. A chi-squared test was done to determine if the two AUCs were statistically different. Second, a net reclassification improvement index was calculated to determine what proportion of individuals were correctly re-classified into a frailty risk group

when switching from *universal frailty* to *region-specific frailty*. I used the model proposed by Pencina et al., which allows the comparison of a new classification model with a reference model based on the following calculation[58]:

$$\frac{\#\,\textbf{cases, risk}\uparrow - \#\,\textbf{cases, risk}\downarrow}{\#\,\textbf{of cases}} - \frac{\#\,\textbf{noncases, risk}\uparrow - \#\textbf{noncases, risk}\downarrow}{\#\,\textbf{of noncases}}$$

In the equation above, 'up arrow' refers to the new classification placing a subject into a higher risk group (e.g: from non-frail to pre-frail or frail) and the 'down arrow' refers to the new classification placing a subject into a lower risk category (e.g: frail/pre-frail to non-frail). Cases refer to deaths based on the all-cause mortality variable. Frail and pre-frail individuals were considered to be high-risk, and non-frail individuals were considered low risk. In this paper, *region-specific frailty* was considered the new classification model and *universal frailty* was considered the standard reference. The NRI index is expressed as a percentage of individuals correctly re-classified into a risk group by the new classification system (see calculation and Table 3 below):

$$\mathbf{NRI} = \frac{\mathbf{D} - \mathbf{C}}{\mathbf{A} + \mathbf{B} + \mathbf{C} + \mathbf{D}} - \frac{\mathbf{D}' - \mathbf{C}'}{\mathbf{A}' + \mathbf{B}' + \mathbf{C}' + \mathbf{D}'}$$

Table 3: Outline of method used to calculate Net Reclassification Improvement index

<table>
<tr><td colspan="5">Death at any time in follow up</td></tr>
<tr><td colspan="2"></td><td colspan="3">Region-specific frailty</td></tr>
<tr><td colspan="2"></td><td>Non-frail</td><td>Pre-frail</td><td>Frail</td></tr>
<tr><td rowspan="3">Universal frailty</td><td>Non-frail</td><td>B</td><td colspan="2">D</td></tr>
<tr><td>Pre-frail</td><td rowspan="2">C</td><td colspan="2" rowspan="2">A</td></tr>
<tr><td>Frail</td></tr>
<tr><td colspan="5">No death at any time in follow up</td></tr>
<tr><td colspan="2"></td><td colspan="3">Region-specific frailty</td></tr>
<tr><td colspan="2"></td><td>Non-frail</td><td>Pre-frail</td><td>Frail</td></tr>
<tr><td rowspan="3">Universal frailty</td><td>Non-frail</td><td>B’</td><td colspan="2">D’</td></tr>
<tr><td>Pre-frail</td><td rowspan="2">C’</td><td colspan="2" rowspan="2">A’</td></tr>
<tr><td>Frail</td></tr>
</table>

3.8.4 Sensitivity Analysis

Two sensitivity analyses were performed. First, a sensitivity analysis was performed to determine whether variations in frailty prevalence across regions are confounded by individuals who have pre-existing baseline chronic diseases. This was done by measuring the proportion of frail individuals in a subset of the whole sample after excluding participants

with the following baseline chronic conditions: angina/heart attack/coronary artery disease/stroke, hypertension, hepatitis/jaundice, heart failure, diabetes, chronic obstructive pulmonary disease (COPD), asthma, tuberculosis and cancer. The overall and region-specific frailty and pre-frailty prevalence in this subset was reported. As with the main analysis, the hazard ratios for time to all-cause mortality were compared for the two frailty classifications in this subset. The second sensitivity analysis was done by repeating the main analysis in older adults (those aged 60 years and above) only, similar to the original population of Fried et al. The prevalence of frailty and pre-frailty in this age-group overall and by region was reported, as were the hazard ratios for the two frailty classifications and all-cause mortality.

All statistical analyses were computed using STATA 14.0 (StataCorp, College Station, TX, USA).

Chapter 4: Results

4.1 Sample Description

A total 202,497 subjects were enrolled in PURE as of January 11, 2021; of those, 137,499 participants were included in the analysis. Subjects were excluded if they had data missing on one or more of the following variables: weight loss (n=38,994), physical activity (n=14,662) , grip strength (n=40,049), or sex (n=386) (because a frailty score could not be calculated for them). Subjects were also excluded if they reported an age less than 35 years or greater than 70 years (n=3,133). Most excluded subjects were from LICs (excluding subjects based on the above criteria dropped the proportion of subjects from LICs from 21% to 12%) Other demographic variables we considered such as sex did not change meaningfully. The median age of the final sample was 51 years (25^{th}-75^{th} percentile: 43-59 years) and 60.1% (n=82,644) of the sample were female. The proportions of participants from high-income countries, upper-middle income countries, lower-middle income countries and low-income countries were 11.4% (n=15,672), 28.2% (n=38,783), 48.4% (n=66,502), and 12.0% (n=16,542), respectively. The regions which contributed the highest number of participants to the sample were China, South America, and then North America/Europe, representing 33.2%, 17.7%, and 13.5% of the sample, respectively. Within every region, the proportion of women was higher than the proportion of men, particularly for Southeast Asia, Russia and Central Asia, and Africa, where women made up about three-quarters of the sample. The median age by region ranged from 47 years (Middle East and South Asia) to 54 years (Russia and Central Asia). The distribution of the sample by region, along with proportions of men and women from each region, is shown in Figure 1. The distribution of age by region, including median age and interquartile range (25^{th} to 75^{th} percentile) for each region, is shown in Figure 2.

Figure 1: Distribution of sample by region with proportions of male and female participants for each region

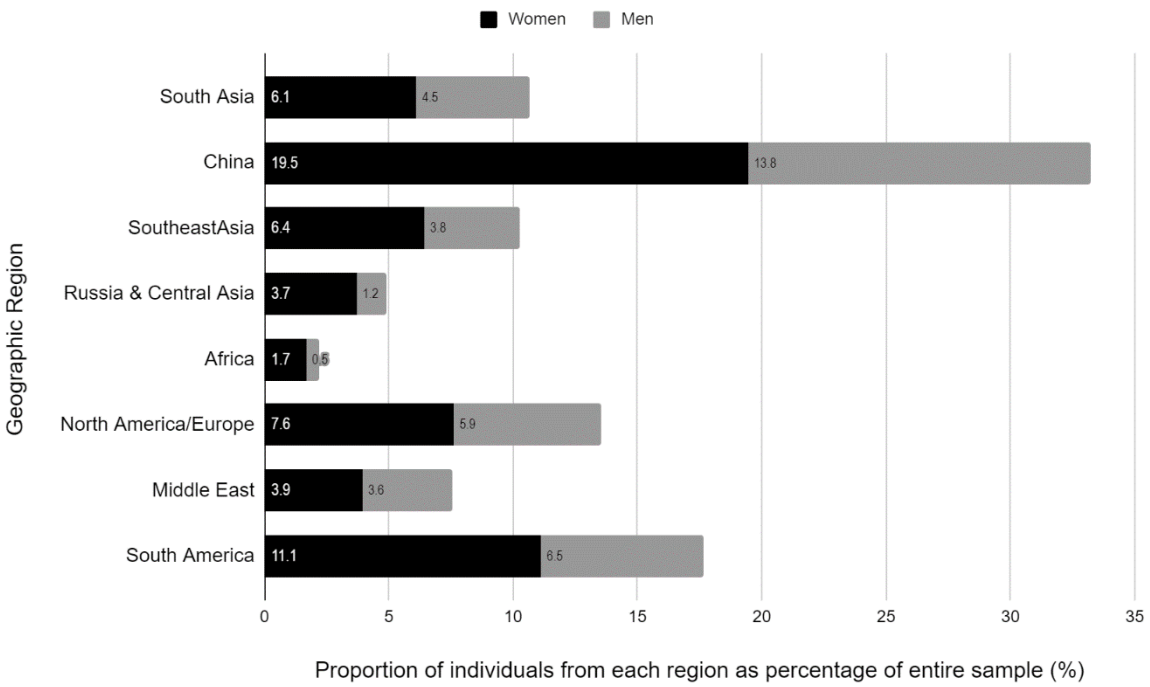
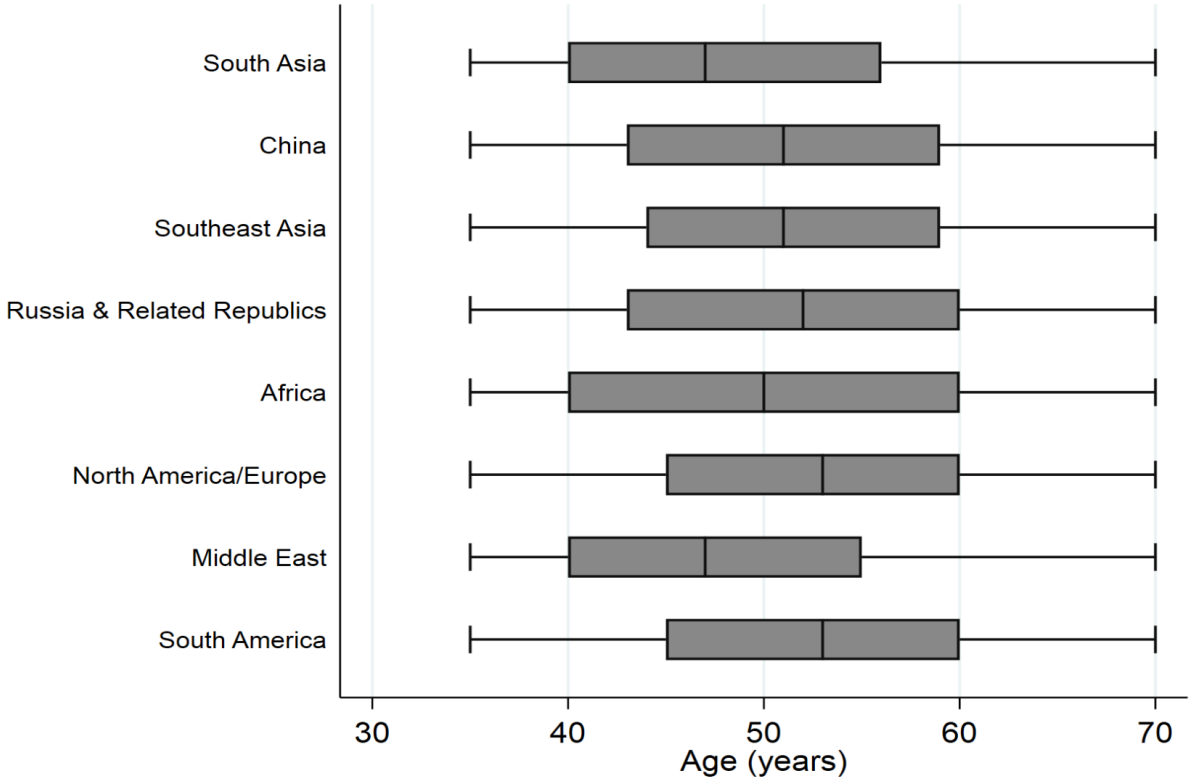


Figure 2: Distribution of ages by region in the PURE sample. The inclusion criteria for age was individuals between 35 to 70 years.



Note: In the box-and-whisker plots above, the 25th to 75th percentile for age range is shown by the horizontal grey rectangles, and the central black line within them illustrates the median age of each region.

4.2 Prevalence and Characteristics of the Frail and Pre-Frail

Using the *universal frailty* classification, in which a single, region-agnostic threshold for poor grip strength and low physical activity levels was implemented, the prevalence of frailty and pre-frailty were 5.6% and 28.1%, respectively. Using the *region-specific frailty* classification, whereby grip strength and physical activity thresholds were stratified by region, the prevalence of frailty and pre-frailty were similar (5.8% and 29.3%, respectively) to the prevalence using the universal frailty classification.. The numbers of people classified as frail, pre-frail, and non-frail according to both frailty classifications are listed in Table 4.

Table 4: Frailty and pre-frailty prevalence using the two definitions (n=137,499). In parenthesis we show the percentage in each class according to the two definitions.

		Universal Frailty			
		Non-frail	**Pre-frail**	**Frail**	**Total**
Region-specific Frailty	**Non-frail**	83,151	5,801	368	**89,320 (65.0)**
	Pre-frail	7,618	30,971	1,673	**40,262 (29.3)**
	Frail	334	1,906	5,677	**7,917 (5.8)**
	Total	**91,103 (66.3)**	**38,678 (28.1)**	**7,718 (5.6)**	**137,499 (100)**

4.2.1 Comparison of baseline characteristics by frailty status

According to the *universal frailty* classification (whereby poor grip strength is stratified by sex and BMI; and low physical activity is stratified by sex; and **neither are stratified by region**), the median ages for frail, pre-frail and non-frail participants were 56 (IQR: 47-64), 52 (IQR 43-60), and 50 (IQR 42-58) years, respectively. According to *region-specific frailty*

(in which poor grip strength is stratified by sex and BMI, and low physical activity is stratified by sex, and **both are stratified by region**), the median ages for frail, pre-frail and non-frail participants were: 56 years (IQR: 48-64), 53 years (IQR: 44-60), and 50 years (IQR: 42-57), respectively. For *universal frailty*, the proportion of frail individuals did not differ significantly based on sex: 5.6% of women and men were frail. Using *region-specific frailty*, the rates of frailty in women (5.7%) and men (5.9%) were also similar. Table 5 compares the baseline characteristics of participants based on the two frailty classifications.

I also summarize in Table 5 the prevalence of frailty based on education level, smoking status, and alcohol consumption, finding that the trends are generally similar for the two frailty classifications. For example, using either *universal frailty* or *region-specific frailty*, I found that the proportion of individuals who were frail decreased with increasing levels of education. More precisely, the proportion of individuals classified as frail for those with no education or primary education only (8.2% for both *universal frailty* and *region-specific frailty*) was approximately double the proportion of people classified as frail with a trade or college/university education (3.4% for *universal frailty* and 4.1% for *region-specific frailty*). For both frailty classifications, the proportion of people classified as frail was higher among those who reported never consuming alcohol (6.6% for *universal frailty* and 6.4% for *region-specific frailty*) compared to those who reported consuming alcohol less than once a day (2.8% for *universal frailty* and 3.7% for *region-specific frailty*) or more than once a day (3.1% for *universal frailty* and 4.0% for *region-specific frailty*).

Since frailty has been associated with many chronic diseases, I also assessed the prevalence of frailty in individuals with the following chronic diseases during their baseline assessment: angina/heart attack/coronary artery disease/stroke, hypertension, hepatitis/jaundice, heart failure, diabetes, chronic obstructive pulmonary disease (COPD), asthma, tuberculosis, and

cancer. Frailty was especially common among people with COPD (15% using *universal frailty* and 18% using *region-specific frailty*) and tuberculosis (13% using *universal frailty* and 14% using *region-specific frailty*). Table 6 summarizes the proportions of frail individuals for each chronic disease.

Table 5: Baseline characteristics of participants by frailty classification method. Data are median (25th-75th percentile) and count (row %)

	Universal frailty			*Region-specific frailty*			**Total**
Characteristic	**Non-frail**	**Pre-frail**	**Frail**	**Non-frail**	**Pre-frail**	**Frail**	
Median age	50 (42-58)	52 (43-60)	56 (47-64)	50 (42-57)	53 (44-60)	56 (48-64)	-
Sex							
Female n (%)	54,967 (66.5)	23,029 (27.9)	4,648 (5.6)	53, 318 (65.0)	24,086 (29.4)	4,640 (5.7)	82,644
Male n (%)	36,136 (65.9)	15,649 (28.5)	3,070 (5.6)	35,316 (64.4)	16,301 (29.7)	3,238 (5.9)	54,855
Smoking status							
Never n (%)	61,308 (65.3)	27,147 (28.9)	5,420 (5.8)	60,755 (64.7)	27,800 (29.6)	5,320 (5.7)	93,875
Former n (%)	11,487 (70.9)	3,950 (24.4)	766 (4.7)	10,843 (66.9)	4,457 (27.5)	903 (5.6)	16,203
Current n (%)	17,844 (67.6)	7,287 (27.6)	1,283 (4.9)	17,262 (65.4)	7,723 (29.2)	1,429 (5.4)	26,414
Alcohol use							
Never n (%)	56,872 (62.4)	28,267 (31.0)	6, 057 (6.6)	56,945 (62.4)	28,392 (31.1)	5,859 (6.4)	91,196
Less than once/day n (%)	21,573 (75.5)	6,211 (21.7)	800 (2.8)	20,448 (71.5)	7,074 (24.8)	1,062 (3.7)	28,584
More than once/day n (%)	9,857 (74.6)	2,948 (22.3)	407 (3.1)	9,156 (69.3)	3,531 (9.1)	525 (4.0)	13,212
Education							
None/Primary/Unknown n (%)	31,194 (58.8)	17,522 (33.0)	4,360 (8.2)	31,002 (58.4)	17,713 (33.4)	4,361 (8.2)	53,076
Secondary/Higher Secondary n (%)	35,853 (69.2)	13, 724 (26.5)	2,256 (4.4)	35,287 (68.1)	14,334 (27.7)	2,212 (4.3)	51,833
Trade or College/University n (%)	23,938 (73.9)	7,378 (22.8)	1,093 (3.4)	22,921 (70.7)	8,155 (25.2)	1,333 (4.1)	32,409

Table 6: Proportion of individuals classified as frail, pre-frail and not-frail for the different chronic diseases studied. Data are count (row %).

	Universal frailty			***Region-specific frailty***		
Chronic diseases n (%)	**Non-frail (N=91,103)**	**Pre-frail (N=38,678)**	**Frail (N=7,718)**	**Non-frail (N=89,320)**	**Pre-frail (N=40,262**	**Frail (N=7,917)**
Angina/Heart Attack/CAD/Stroke	4,599 (39)	2,574 (22)	916 (8)	4,271 (37)	2,778 (24)	1,040 (9)
Hypertension	19,213 (41)	9,683 (21)	2,492 (5)	18,880 (41)	9,978 (21)	2,530 (5)
Hepatitis/Jaundice	2,517 (57)	1,017 (23)	405 (9)	2,408 (55)	1,084 (25)	447 (10)
Heart Failure	1,013 (30)	602 (18)	225 (7)	932 (28)	669 (20)	239 (7)
Diabetes	5,592 (34)	4,074 (25)	1,488 (9)	5,761 (35)	3,955 (24)	1,438 (9)
Chronic Obstructive Pulmonary Disease	881 (37)	584 (25)	355 (15)	806 (34)	583 (25)	431 (18)
Asthma	2,668 (36)	1,555 (21)	646 (9)	2,646 (36)	1,524 (21)	699 (10)
Tuberculosis	846 (35)	570 (23)	325 (13)	919 (38)	489 (20)	333 (14)
Cancer	1,476 (42)	644 (18)	311 (9)	1,341 (38)	708 (20)	382 (11)

CAD: coronary artery disease

4.3 Frailty by Region

To understand the effect of stratifying thresholds by region, sex- and age-standardized frailty prevalence rates were calculated for each of the following eight regions: South Asia, China, Southeast Asia, Russia, Africa, North America/Europe, Middle East, South America (the relative income levels of each region are available in Appendix I). The prevalence of frailty by geographic region varied considerably based on the classification for frailty used. According to *universal frailty*, the prevalence of frailty was highest in Africa, where it was 20.1%, and lowest in North America/Europe at 2.4%. Similarly, pre-frailty prevalence was highest in Africa at 55.0% and lowest in North America/Europe at 17.4%. The sex- and age-standardized non-frailty, pre-frailty and frailty prevalence rates by geographic region are presented in Table 7.

Using the *region-specific* classification, frailty and pre-frailty prevalence were more evenly distributed across the different regions. With the *region-specific* thresholds, frailty was highest in the Middle East, at 8.8%, and lowest, at 4.1%, in Russia and Central Asia. The pre-frailty prevalence ranges from 33.9% in Africa to 24.7% in Russia and Central Asia. Thus, relative to *universal frailty*, I observed a qualitative change in the order of regions ranked by frailty prevalence, and a decrease in the magnitude of the difference between the highest frailty prevalence and lowest frailty prevalence. This indicates that applying region-based thresholds for poor grip strength and low physical activity, eliminated some but not all of the inter-region variability in frailty and pre-frailty prevalence. Table 7 summarizes these results.

Table 7: Age- and sex-standardized frailty prevalence across the eight PURE regions

Universal frailty								
	South Asia	**China**	**Southeast Asia**	**Russia & Central Asia**	**Africa**	**North America/Europe**	**Middle East**	**South America**
Non-frail n (%)	7,177 (49.4)	32,800 (72.3)	7,308 (52.1)	4,992 (74.3)	744 (24.9)	14,810 (80.3)	5,786 (56.0)	16,327 (67.7)
Pre-frail n (%)	5,768 (39.7)	11,070 (24.4)	5,302 (37.8)	1,512 (22.5)	1,644 (55.0)	3,209 (17.4)	3,534 (34.2)	6,584 (27.3)
Frail n (%)	1,584 (10.9)	1,361 (3.0)	1,417 (10.1)	215 (3.2)	601 (20.1)	443 (2.4)	1,013 (9.8)	1,206 (5.0)
Total	14,529	45,367	14,027	6,719	2,989	18,443	10,332	24,116
Region-specific frailty								
	South Asia	**China**	**Southeast Asia**	**Russia & Central Asia**	**Africa**	**North America/Europe**	**Middle East**	**South America**
Non-frail n (%)	8,705 (59.9)	29,126 (64.2)	9,256 (66.0)	4,784 (71.2)	1,841 (61.6)	12,091 (65.6)	6,394 (61.9)	16,227 (67.3)
Pre-frail n (%)	4,678 (32.2)	13,928 (30.7)	4,026 (28.7)	1,660 (24.7)	1,013 (33.9)	5,146 (27.9)	3,027 (29.3)	6,656 (27.6)
Frail n (%)	1,133 (7.8)	2,314 (5.1)	757 (5.4)	275 (4.1)	135 (4.5)	1,199 (6.5)	909 (8.8)	1,230 (5.1)
Total	14,529	45,367	14,027	6,719	2,989	18,443	10,332	24,116

The results above show that based on the frailty classification method used, the number of people classified as frail or pre-frail varies drastically for each region. For example, according to *region-specific frailty*, only 135 subjects (4.5%) from Africa are frail, whereas according to *universal frailty*, 601 (20.1%) are frail. Figure 3 and Figure 4 depict this variation. Geographic regions that predominantly comprise low-income or lower-middle income countries such as Africa and South Asia show a reduction in the proportion of people classified as frail when applying the *region-specific* definition. Conversely, those regions that are predominantly composed of populations from upper-middle income or high-income countries such as China or North America/Europe, had an increase in the proportion of people classified as frail after applying the *region-specific classification* compared to the *universal classification*.

Figure 3: *Universal frailty* and *region-specific frailty* by region

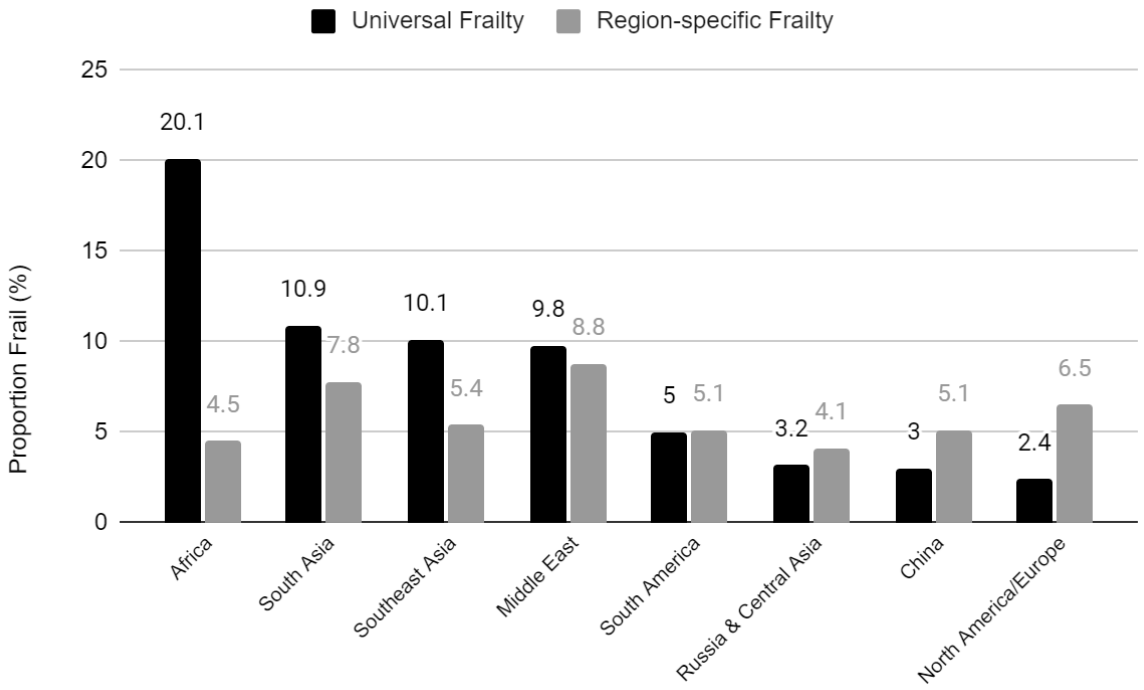
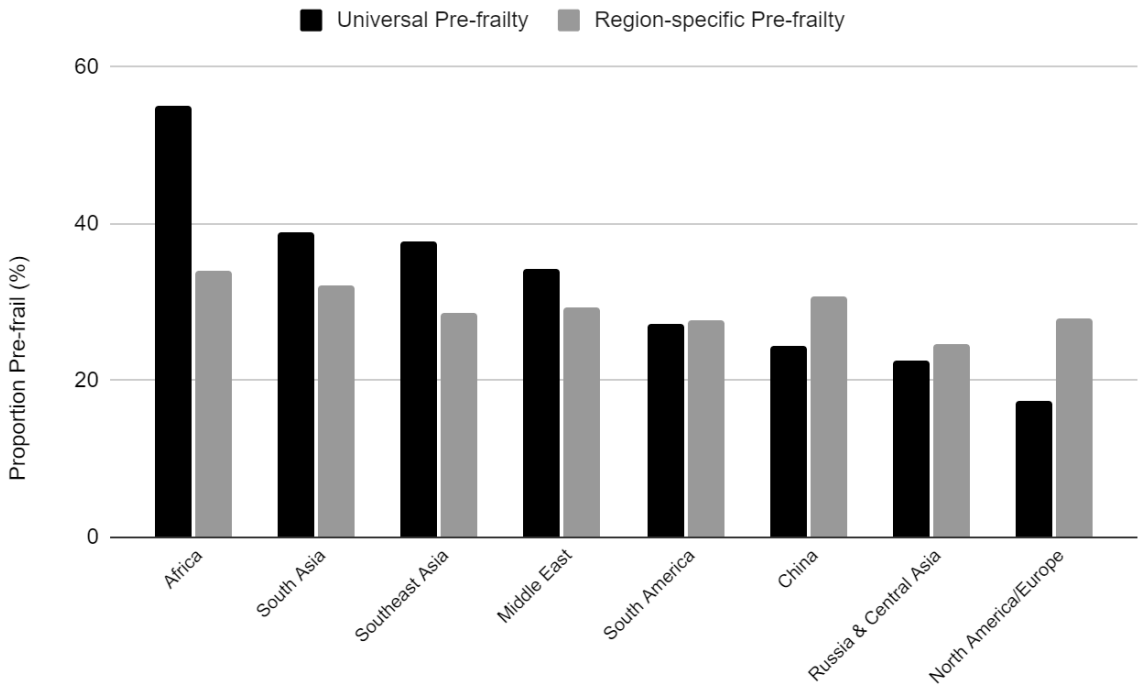


Figure 4: *Universal pre-frailty* and *region-specific pre-frailty* by region



4.4 Frailty and Country Income

To understand the effect of country income on frailty, the prevalence of frailty, according to each definition, was calculated separately for low-income, lower-middle income, upper-middle income and high-income countries. The countries comprising each country's income category are shown in Appendix II. As seen with frailty prevalence and region (section 4.3), when using *region-specific frailty*, the proportions of frail and pre-frail individuals across the four country income categories were more closely distributed compared to when *universal frailty* was used. More precisely, according to the *universal frailty* classification, low-income countries had the greatest proportion of frail people, at 10.6% (n=1,608), followed by upper-middle income countries at 7.4% (2,939), then high-income countries at 4.3% (n=671).

Lower-middle income countries had the lowest frailty prevalence of 3.7% (n=2,404). Using *region-specific frailty*, the prevalence of frailty differed much less across country income categories. The highest prevalence of frailty was in low-income countries at 6.8% (n=1,009), followed by high-income countries at 6.4% (n=1,022), then upper-middle income countries at 6.3% (2,492), then lower-middle income countries at 5.0% (n=3,318). Table 8 describes the different frailty and pre-frailty prevalence for each country income category. Figure 5 and Figure 6 illustrate how the prevalence of frailty and pre-frailty change based on the classification method used. Since there was some variation in age and sex across the country income categories (e.g. the median age was 47 in low-income countries and 52 for high-income countries), the prevalence rates below were age- and sex-standardized.

Table 8: Age- and sex-standardized frailty prevalence and country income

			Universal frailty			***Region-specific frailty***			
Country income	**Median age (IQR) (years)**	**Proportion of females (%)**	**Non-frail**	**Pre-frail**	**Frail**	**Non-frail**	**Pre-frail**	**Frail**	**Total**
High	52 (44-60)	53.3	11,676 (74.1)	3,301 (21.2)	671 (4.3)	10,153 (64.9)	4,473 (28.7)	1,022 (6.4)	15,648
Upper Middle	52 (44-60)	62.1	24,098 (63.1)	11,343 (29.5)	2,939 (7.4)	24,669 (64.6)	11,219 (29.0)	2,492 (6.3)	38,380
Lower Middle	51 (43-58)	59.5	46,471 (70.3)	17,149 (26.0)	2,404 (3.7)	43,449 (65.8)	19,257 (29.2)	3,318 (5.0)	66,024
Low	47 (40-57)	56.8	8,286 (47.8)	6,576 (41.5)	1,608 (10.6)	10,467 (61.6)	4,994 (31.6)	1,009 (6.8)	16,470

Note: *Region-specific frailty* leads to a frailty classification in which the proportions of frail, pre-frail and non-frail people are more evenly distributed across country income compared to *universal frailty*.

Figure 5: *Universal frailty* and *region-specific frailty* across country income

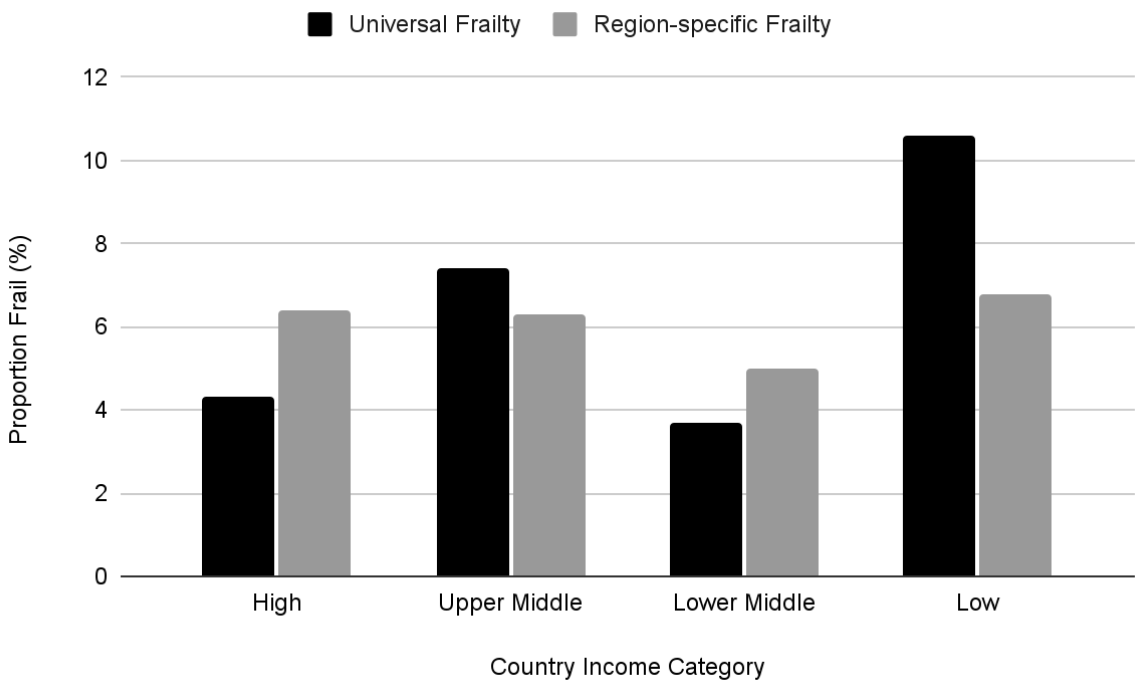
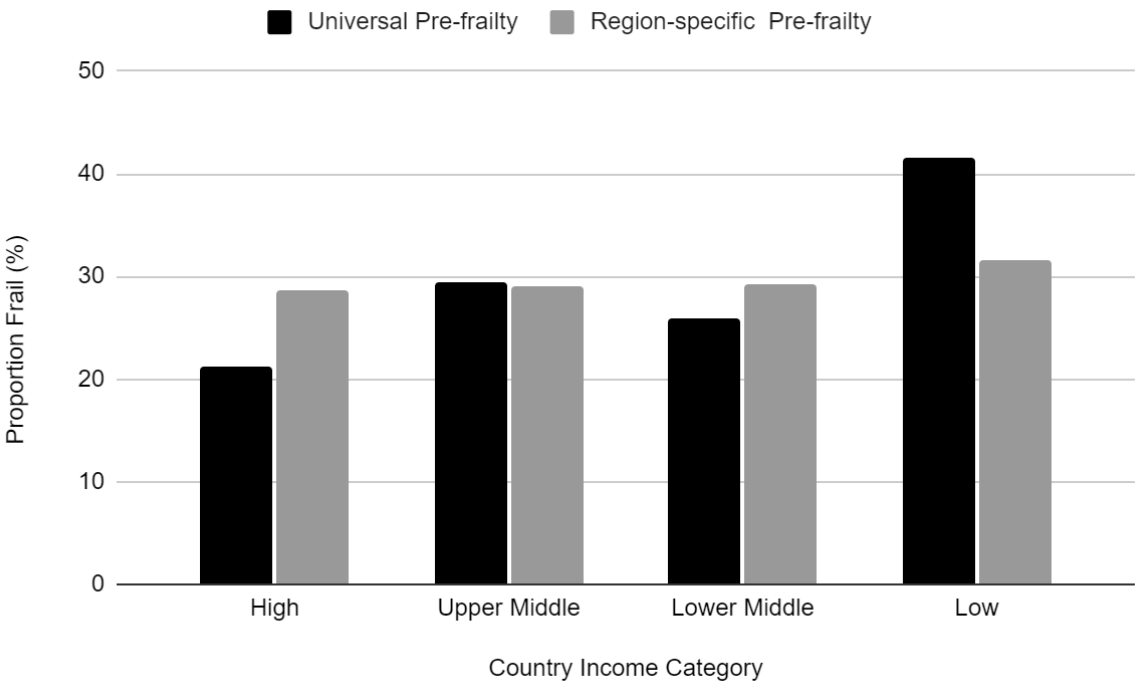


Figure 6: *Universal pre-frailty* and *region-specific pre-frailty* across country income



4.5 Frailty in Different Age Strata Among Middle-aged Adults

This section details the prevalence of frailty in middle-aged adults, as there is limited previous literature on frailty and pre-frailty in younger populations, particularly in LMICs. I divided the study population into four age groups: 35-40 years, 41-50 years, 51-60 years, and 61-70 years. The prevalence of frailty and pre-frailty by age group for *universal frailty* and for *region-specific frailty* are shown in Table 9. I generally find that, as expected, frailty prevalence increases with increasing age, without meaningful differences between the two definitions.

Table 9: Frailty prevalence in middle-aged adults in PURE

Frailty Classification	**Age Group**			
	35-40	**41-50**	**51-60**	**61-70**
***Universal frailty* (n)**	935	1,693	2,417	2,577
%	**3.8**	**4**	**5.71**	**9.48**
***Region-specific frailty* (n)**	880	1,716	2,487	2,758
%	**3.57**	**4.05**	**5.87**	**10.14**

To further explore the results above, I analyzed frailty prevalence by age groups and by country income levels. Within each age group, I found that, as before, *region-specific frailty* yielded frailty prevalence rates that were closer across the four country income levels, ranging from a minimum frailty prevalence of 3.1% for subjects from lower-middle income aged 35-40 to a maximum prevalence of 11.9% for subjects from low-income countries aged 61-70. With *universal frailty*, the frailty prevalence rates varied more widely across country income level, ranging from 2.1% to 17.7% for the same two subgroups. Table 10 summarizes the frailty prevalence for the different age groups based on country income.

Table 10: Sex-standardized frailty prevalence in middle-aged adults in LMICs

Country Income Level	*Universal frailty* n (%)				*Region-specific frailty* n (%)			
	35-40	**41-50**	**51-60**	**61-70**	**35-40**	**41-50**	**51-60**	**61-70**
High-income	117 (5.4)	175 (3.6)	184 (3.7)	195 (5.4)	135 (6.2)	242 (5.0)	301 (6.0)	344 (9.54)
Upper-Middle	263 (4.4)	644 (5.3)	989 (8.0)	1,043 (12.5)	215 (3.6)	529 (4.4)	803 (6.5)	945 (11.4)
Lower-Middle	246 (2.1)	474 (2.3)	810 (3.8)	874 (6.9)	361 (3.1)	686 (3.3)	1,116 (5.3)	1155 (9.1)
Low-income	309 (6.3)	400 (7.9)	434 (11.4)	465 (17.7)	169 (3.4)	259 (5.1)	267 (7.0)	314 (11.9)

4.6 Frailty and Mortality

To understand which definition of frailty is a more useful prognostic indicator, I carried out longitudinal analyses to determine the association of frailty with all-cause mortality. This section outlines the results of three different ways I compared *universal frailty* and *region-specific frailty*: Cox proportional hazards modelling, area under the ROC curve for the discrimination of death, and the net reclassification improvement index.

4.6.1 Survival Analysis

The association between both *universal frailty* and *region-specific frailty* with all-cause mortality was first calculated using Cox proportional hazards modelling, using follow-up data from subsequent visits. Follow-up data were available for 125,253 participants (91% of the participants). The mean length of time between baseline and last follow-up for participants was 8.9 (±3.1) years. A total of 7,339 out of 125,253 (5.9%) participants died.

Results from the Cox proportional hazards modelling demonstrate that increasing levels of frailty were associated with all-cause mortality for ***both*** frailty classifications. The unadjusted hazard ratios for individuals classified as pre-frail and frail using the *universal frailty* classification were 1.94 (95% CI: 1.84-2.04) and 4.26 (95% CI: 3.97-4.57), respectively.

Under the *region-specific frailty* classification, the unadjusted hazard ratios for pre-frail and frail individuals were 1.75 (95% CI: 1.67-1.84) and 3.48 (95% CI: 2.24-3.73), respectively. After adjustment for age, sex, education, smoking status, and alcohol use, increasing frailty levels continued to be predictive of all-cause mortality. The adjusted hazard ratios for pre-frail and frail individuals under the *universal frailty* classification were 1.56 (95% CI: 1.48-1.65) and 2.66 (95% CI: 2.47-2.86), respectively. After adjustment for the same covariates, the hazard ratios for individuals classified as pre-frail and frail using the *region-specific* classification were 1.34 (95% CI: 1.28-1.41) and 2.09 (95% CI: 1.94-2.26), respectively. A description of the results from the Cox proportional hazards model is provided in Table 11. The likelihood ratio test (LRT) statistic was calculated to determine which definition of frailty is a better predictor of mortality. Compared to the baseline model of only covariates, the *region-specific* model had an LRT χ^2 value of 382.3 and the *universal frailty* model had a value of 703.1. These results suggest that *region-specific frailty* is less predictive of mortality than *universal frailty*.

Table 11: Cox proportional hazards analysis for all-cause mortality

	Unadjusted HR (95% CI)	**Log likelihood**	**Adjusted HR* (95% CI)**	**Log likelihood**
Universal frailty				
Non-frail	**1**	**-82762.317**	**1**	**-77124.21**
Pre-frail	**1.94 (1.84-2.04)**		**1.56 (1.48-1.65)**	
Frail	**4.26 (3.97-4.57)**		**2.66 (2.47-2.86)**	
Region specific frailty				
Non-frail	**1**	**-82978.099**	**1**	**-77284.611**
Pre-frail	**1.75 (1.67-1.84)**		**1.34 (1.28-1.41)**	
Frail	**3.48 (2.24-3.73)**		**2.09 (1.94-2.26)**	

n=125,253 for unadjusted analysis, n=120,658 after adjustment for covariates. Covariates adjusted for are age, sex, education, smoking status and alcohol consumption.

The survival curves in Figure 7 and Figure 8 below demonstrate that higher levels of frailty are associated with worse survival rates for both frailty classifications. The log-rank test to assess if there is a significant difference for survival between the frailty levels at any given time point found that the survivor functions were significantly different from each other using both the *universal frailty* classification (χ^2=2107.7, p<0.001) and the *region-specific* classification (χ^2= 1471.3, p<0.001). The χ^2 value is higher for *universal frailty*, which is in line with the hazard ratio being higher for *universal frailty*, suggesting that it is a better predictor of all-cause mortality than *region-specific frailty*.

Figure 7: Kaplan-Meier curves for time to death by frailty status using *universal frailty*

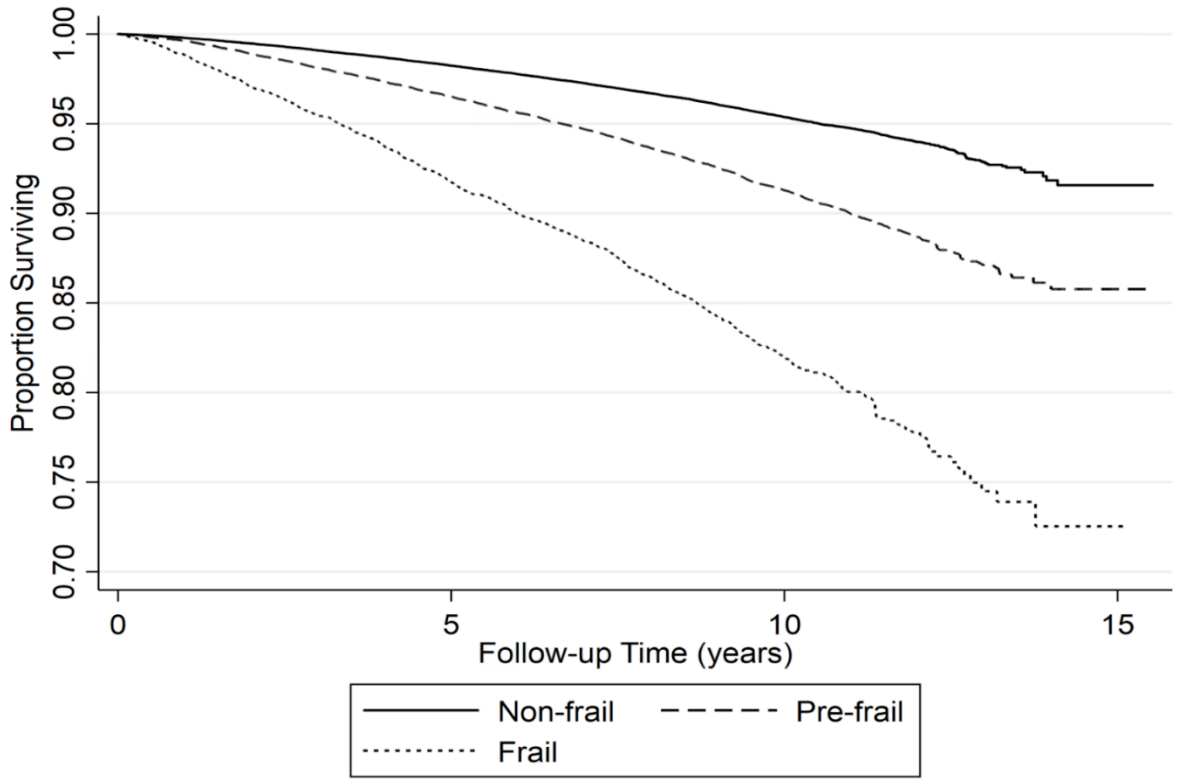
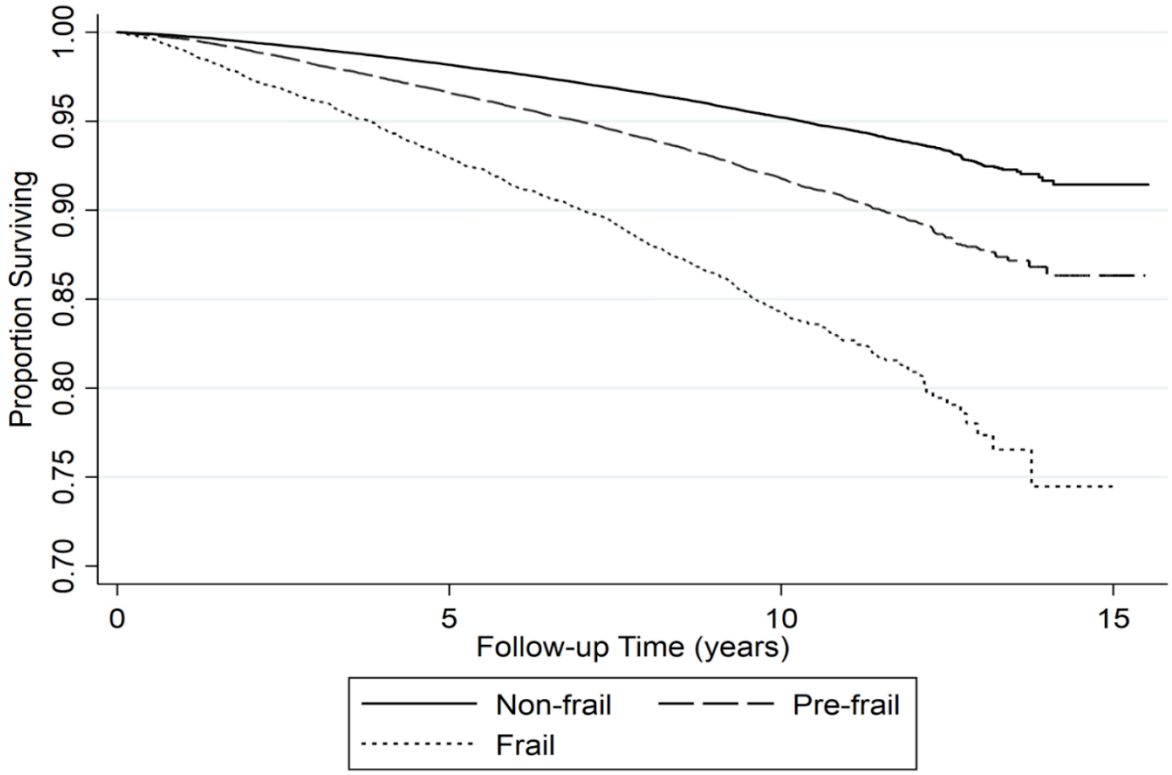


Figure 8: Kaplan-Meier curves for time to death by frailty status using *region-specific frailty*



4.6.2 Test of Proportional Hazards Assumptions

The proportional hazards assumption, which states that there is a proportional relationship between the predictor variables and the hazard ratio over time, was tested graphically using the log-log survival vs log time plots. Figure 9 and Figure 10 depict the log-log plots for *universal frailty* and *region-specific frailty*, respectively. Three mainly parallel lines indicate a constant difference in predictor values between the two curves over time, and suggest that the proportional hazards assumption is met in general; however less well in cases with smaller follow-up time. As seen in Figure 9 and Figure 10, the plots are basically parallel, although the parallelism between the pre-frail and non-frail groups appears some period after the baseline visit. This suggests that the hazard ratios between these two groups may not be

proportional immediately but does become proportional within a few months after the first visit, once the 'early failures' are no longer contributing information.

Figure 9: Log-log plot for *universal frailty*

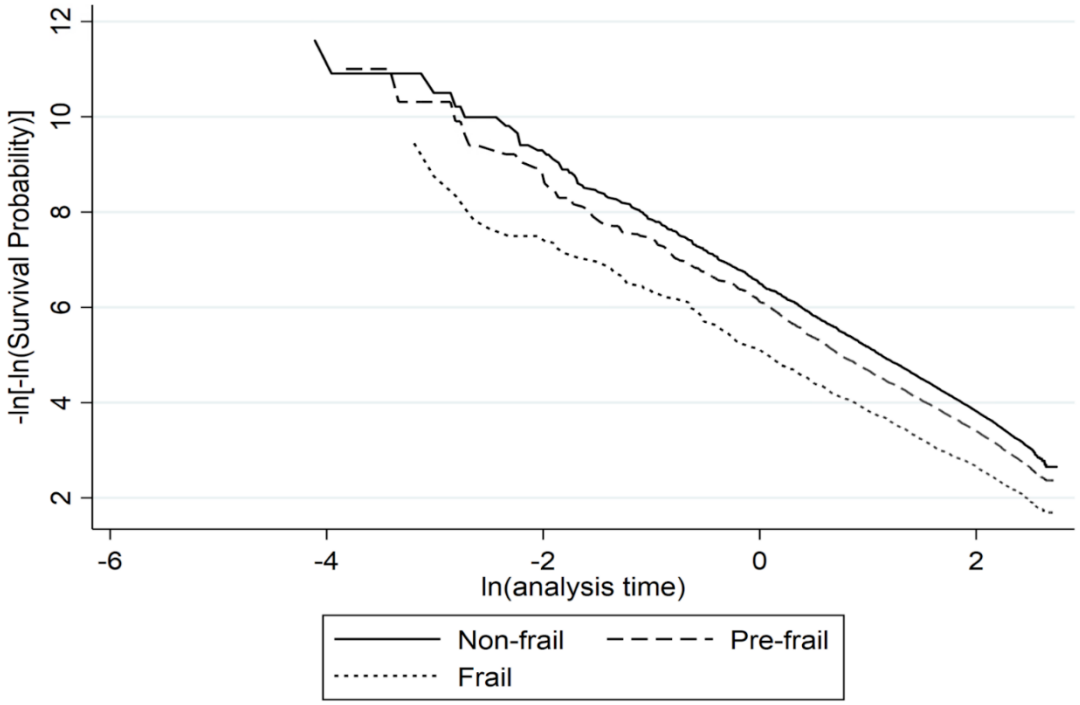
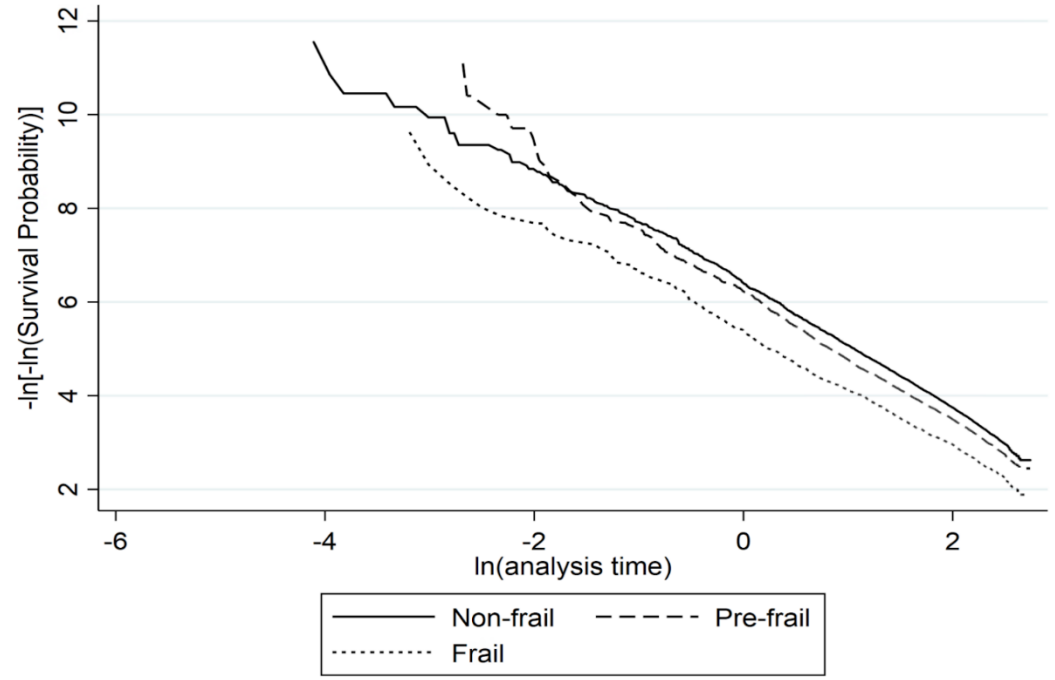


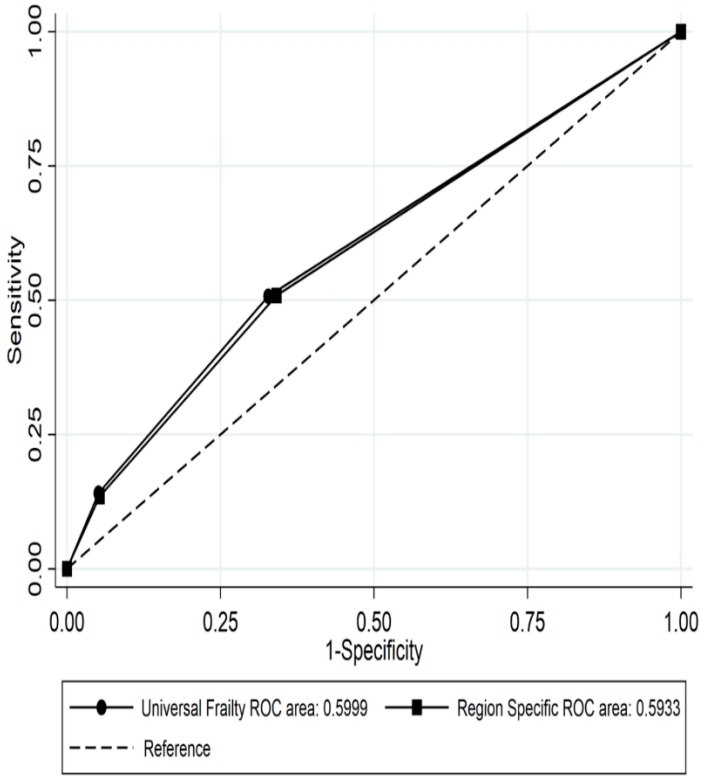
Figure 10: Log-log plot for *region-specific frailty*



4.6.3 Area under the ROC Curve

To further compare the discriminative ability of the two frailty classifications, the area under the curve was calculated for the receiver operating characteristics (ROC) curves for each frailty classification, based on a classifier to predict all-cause mortality using survival data from subsequent visits. *Universal frailty* had a very slightly higher area under the curve (AUC) value of 0.5999 (95% CI: 0.594-0.606) compared to 0.5933 (95% CI: 0.587-5.99) for *region-specific frailty*. This, in line with the previous results, indicates that *universal frailty* has a slightly better discriminative ability for all-cause mortality compared to *region-specific frailty*. Despite the small magnitude of the difference in AUC values, the chi-square test comparing the two AUCs found that they are statistically different ($\chi 2$=11.4, p=0.0007). The two ROC curves are shown in Figure 11.

Figure 11: Receiver Operating Characteristics Curve for *Universal frailty* and *Region-specific frailty*



4.6.4 Net Reclassification Improvement Index

To further compare the two models, a net reclassification improvement index (NRI) was calculated based on the model suggested by Pencina et al.[58] The NRI allows for the comparison of a new classification model with a reference model. The NRI can be interpreted as the net change in the proportion of subjects assigned a more appropriate risk category under the new model.

Table 12a and Table 12b show the risk tables used to calculate the NRI.

Table 12a: Classification of subjects who died as non-frail or pre-frail/frail, according to both frailty definitions, used for the calculation of the net reclassification improvement index.

Region-specific frailty	***Universal frailty***		
	Non-frail	**Pre-frail/Frail**	**Total**
Non-frail	3,205	398	3,603
Pre-frail/Frail	409	3,327	3,736
Total	3,614	3,725	7,339

Table 12b: Classification of subjects who did not die as non-frail or pre-frail/frail, according to both frailty definitions, used for the calculation of the net reclassification improvement index.

Region-specific frailty	***Universal frailty***		
	Non-frail	**Pre-frail/Frail**	**Total**
Non-frail	79,946	5,771	85,717

Pre-frail/Frail	7,543	36,900	44,443
Total	87,489	42,671	130,160

NRI calculation: (409-398)/7,339 - (7,543-5,771)/130,160 = -0.012

Using the data from tables 12a and 12b and the formula for the NRI, the NRI calculated was -0.012 or -1.2%. This value suggests that there are a number of participants (n=1,761) who are better classified into a risk group when *universal frailty* is applied, compared to when *region-specific frailty* is applied. Thus, the NRI also suggests that *universal frailty* is a better measure of frailty when assessing the value of frailty in predicting death in heterogeneous populations.

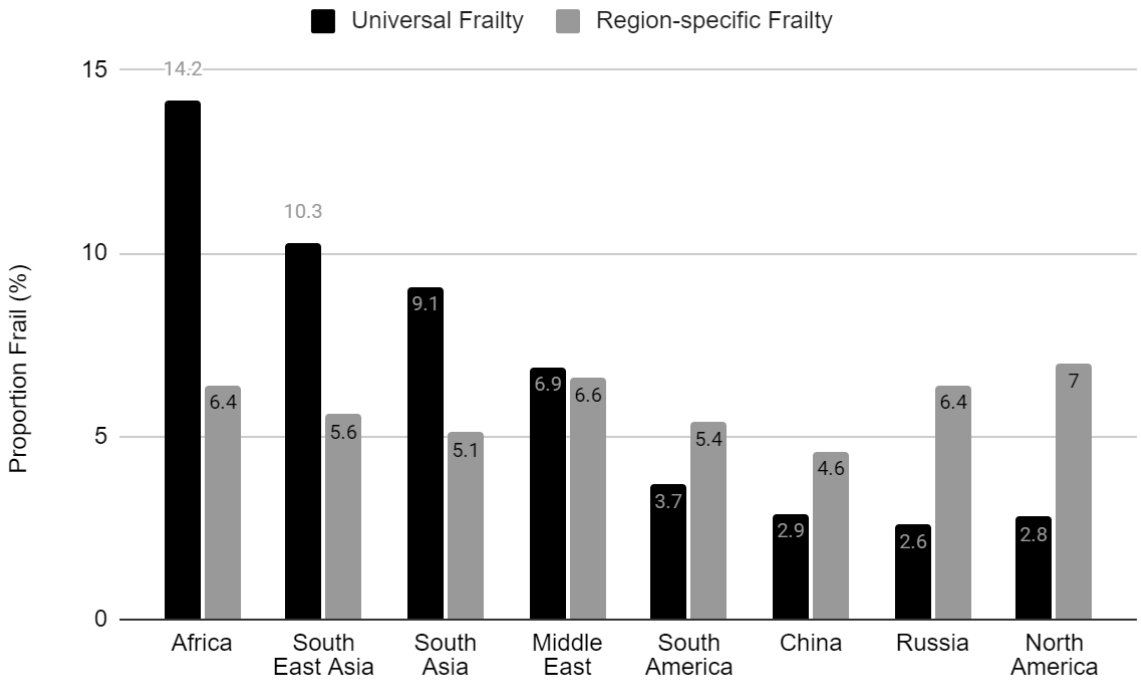
4.7 Sensitivity Analysis

4.7.1 Sensitivity Analysis in Healthy Subset of Population

To test whether the patterns noted regarding frailty prevalence and the longitudinal analysis are robust, two sensitivity analyses were performed. First, the proportion of people classified as frail by region was re-calculated only in the healthy subset of the population. In this sensitivity analysis cohort, the overall frailty prevalence was again similar between the two frailty classifications. For *universal frailty,* the prevalence of frailty and pre-frailty was 5.4% (n=4,317) and 39.9% (32,191), respectively. For *region-specific frailty,* the prevalence of frailty and pre-frailty was 5.4% (4,357) and 40.5% (n=32,581), respectively. However, there was considerable variation in frailty prevalence across regions. The pattern seen earlier persisted; namely, that the regions comprising low-income and lower-middle income countries showed a decrease in frailty prevalence when switching from the *universal frailty* to

region-specific frailty, and regions comprising upper-middle income and high-income countries showed an increase in frailty prevalence. Figure 12 demonstrates these trends. All frailty prevalence were age- and sex- standardized.

Figure 12: Frailty prevalence across regions after removing individuals with baseline chronic diseases from the cohort



Cox proportional hazard modelling was performed to determine the association between the two frailty classifications with all-cause mortality in this sensitivity analysis cohort. Just as the results from the larger sample demonstrated that *universal frailty* predicts a higher risk of death at any given point during follow-up compared to *region-specific frailty* as determined by the hazard ratios, these results also held in the sensitivity analysis cohort. The hazard ratios, after adjusting for age, sex, education, smoking status and alcohol use were 1.98 (95% CI: 1.84-2.13) and 2.26 (95% CI: 1.99-2.57) for *universal pre-frailty* and *universal frailty*, respectively. The hazard ratios for *region-specific pre-frailty* and *frailty*, after adjusting for the same covariates, were 1.70 (95% CI: 1.58-1.84) and 1.82 (95% CI: 1.59-2.06),

respectively. Thus, I found again that using *universal frailty* resulted in higher hazard ratios than *region-specific frailty*. These results are summarized in Table 13. (The same analyses in individuals with chronic diseases are presented in appendix III).

Table 13: Cox proportional hazards analysis for all-cause mortality among adults without baseline chronic conditions.

	Unadjusted HR (95% CI)	**Adjusted HR* (95% CI)**
Universal frailty		
Not-frail	1	1
Pre-frail	2.51 (2.34-2.70)	1.98 (1.84-2.13)
Frail	3.68 (3.26-4.16)	2.26 (1.99-2.57)
Region specific frailty		
Not-frail	1	1
Pre-frail	2.30 (2.14-2.47)	1.70 (1.58-1.84)
Frail	3.08 (2.71-3.48)	1.82 (1.59-2.06)

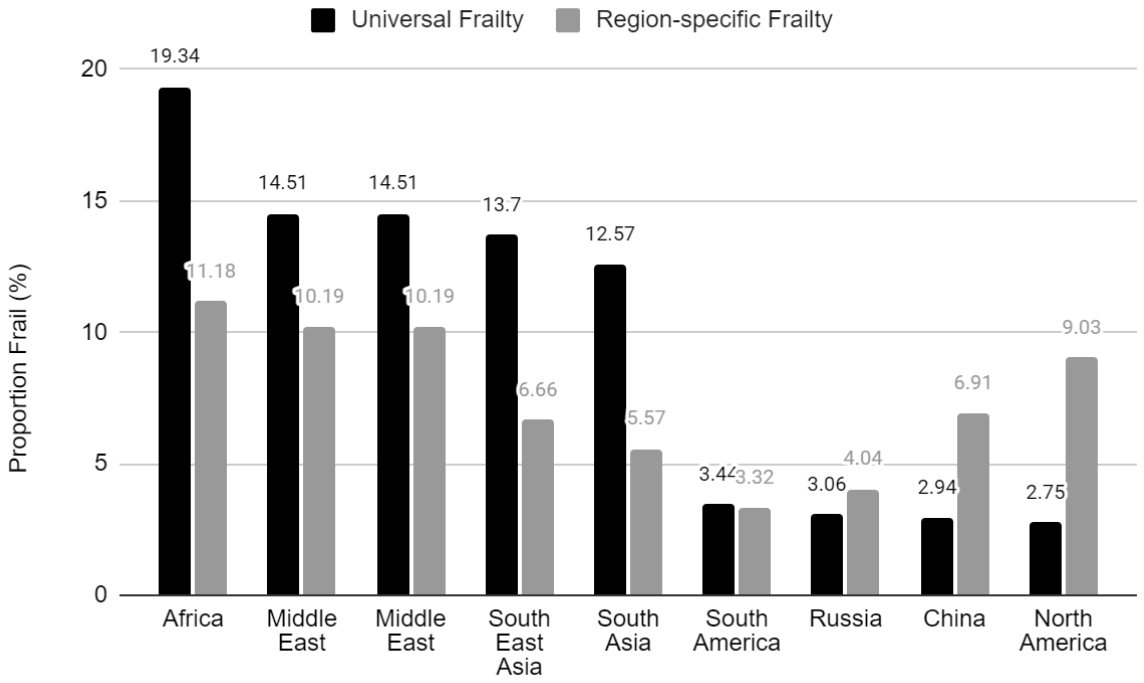
n=73,215 for unadjusted analysis and n=70,216 for adjusted analysis. Covariates adjusted for are age, sex, education, smoking status and alcohol consumption.

4.7.2 Sensitivity Analysis in older adults

A second sensitivity analysis was performed in adults aged 65 years and over. This was performed due to the fact that frailty is often studied in older populations, including Fried et al.'s original work, which validated phenotypic frailty in individuals aged 65 years and above. In this population, the overall pre-frailty and frailty prevalence using the *universal frailty* classification was 26.6% and 6.1%, respectively. Using the *region-specific frailty* classification, the overall pre-frailty and frailty prevalence was 28.9% and 7.1%. Once again,

considerable inter-region variations in frailty prevalence were observed. This variation is depicted in Figure 13.

Figure 13: Frailty Prevalence among older adults (aged 65 and over) across the eight regions



I also assessed the association of the two frailty classifications with all-cause mortality in the older adult cohort, by performing Cox proportional hazards modelling. The pattern of results previously observed in the healthy subset of the sample as well as in the overall sample were also observed in this cohort. *Universal frailty* predicted a stronger association between worsening frailty status and all-cause mortality (HR: 3.04, 95% CI: 2.59-3.58) compared to *region specific frailty* (HR: 2.37, 95% CI: 2.01-2.80). *Universal pre-frailty* also predicted a stronger association with all-cause mortality (HR: 1.77, 95% CI: 1.59-1.98) compared to *region specific frailty* (HR: 1.54, 95% CI: 1.37-1.72). Overall, these two sensitivity analyses lend confidence to the results that the *universal frailty* is a stronger predictor of mortality, as compared to *region-specific frailty*. These results are summarized in Table 14.

Table 14: Cox proportional hazards analysis for all-cause mortality in older adults

	Unadjusted HR (95% CI)	**Adjusted HR* (95% CI)**
Universal frailty		
Not-frail	1.00	1.00
Pre-frail	1.93 (1.74-2.14)	1.77 (1.59-1.98)
Frail	3.49 (3.00-4.07)	3.04 (2.59-3.58)
Region-specific frailty		
Not-frail	1.00	1.00
Pre-frail	1.66 (1.49-1.86)	1.54 (1.37-1.72)
Frail	2.72 (2.32-3.20)	2.37 (2.01-2.80)

Covariates adjusted for are age, sex, education, smoking status and alcohol consumption.

Chapter 5: Discussion and Conclusions

5.1 Key Findings

In my thesis, I have evaluated the effects of applying different measures of frailty on its estimated prevalence and prognostic value. Specifically, I formulated and evaluated two definitions of frailty in this work: a *universal frailty* definition in which single thresholds for grip strength and physical activity are applied; and a *region-specific frailty* definition, in which the thresholds for grip strength and physical activity that indicate frailty vary according to participants' geographic region. The overall prevalence of frailty in PURE did not differ meaningfully based on the definition, with 5.6% of the study population classified as frail using the *universal frailty* definition and 5.8% using the *region-specific frailty* definition. However, the frailty prevalence rates across regions varied widely based on the frailty definition used. With *universal frailty*, frailty prevalence ranged from 20.2% in Africa to 2.4% in North America/Europe. With *region-specific frailty*, frailty prevalence ranged from 8.8% in the Middle East to 4.1% in Russia and Central Asia. Our work is the first to study frailty prevalence rates in middle-aged adults from LMICs. According to both definitions, frailty prevalence was generally highest in low-income countries across age groups, though the differences were more pronounced for *universal frailty*. In LMICs, frailty was found to significantly increase with increasing age. This trend was generally seen in HICs as well, but to a lesser degree. Based on several analyses, *universal frailty* was found to be a stronger predictor of all-cause mortality compared to *region-specific frailty*, and this was true even when the association between the two frailty definitions with all-cause mortality was studied in a healthy subset of the population, as well as when it was only studied in older adults.

5.2 Correlates of Universal Frailty and Region-Specific Frailty

The median age of frail participants was higher than of pre-frail and non-frail participants, using both *universal frailty* and *region-specific frailty*. This finding is supported by previous research, which establishes that frailty increases with age.[1,3,38] For both measures of frailty, frailty was higher in people with lower education levels and did not vary meaningfully based on smoking status. Frailty

was more common in those who reported to have never consumed alcohol. This finding, although surprising, was also observed in the UK Biobank study, where alcohol use was inversely associated with frailty status.[38] The authors of the UK Biobank study suggested this may be because of abstainer bias (i.e. those with poorer health were advised not to drink alcohol). An alternative explanation is that alcohol may be a marker of socioeconomic status whereby individuals with lower income cannot afford alcohol and also tend to be more frail, which would explain the inverse association observed. Using *universal frailty*, the frailty prevalence in men and women did not differ, and using *region-specific frailty*, the difference in frailty prevalence for men and women was not large (5.9% for men vs 5.7% for women). This contrasts with previous research in which frailty is typically more common in women.[1,4,38] A possible explanation for this is that two of the three frailty criteria examined in PURE, namely grip strength and physical activity levels, were measured using sex-specific thresholds, and two sex-independent criteria from the frailty phenotype definition, namely, self-reported exhaustion and gait speed, were not included in the PURE frailty analysis. Finally, frailty, using either classification, was most common in individuals with COPD, tuberculosis, and asthma.

5.3 Effect of Applying Region-Specific Thresholds

In this thesis, I evaluated the effect of applying region-specific thresholds to two important criteria of the frailty phenotype, namely, poor grip strength and low physical activity levels, on the prevalence and prognostic ability of frailty. The motivation for this lies in the fact that threshold values for poor grip strength and low physical activity were originally established and validated by Fried et al. on data from the Cardiovascular Health Study, which took place in the United States and consisted of a population that was approximately 89% Caucasian and 11% African American.[1] Thus, the cut-off values for the frailty criteria were derived from a high-income, predominantly Caucasian population. The frailty phenotype was subsequently validated in other studies such as the Survey of Health, Aging and Retirement in Europe and the UK Biobank.[4,38] Both studies applied the same grip strength cut-offs used in the Cardiovascular Health Study, rather than recalculating them for their given population. This choice may be justified given the comparable populations across the three studies.

However, frailty is increasingly being studied in populations of diverse ethnicities and country income levels, and the frailty phenotype cut-offs commonly used in previous frailty research have not been extensively validated in these diverse populations.[9–11,13]

A recent systematic review and meta-analysis on the prevalence of frailty in community dwelling adults in LMICs, revealed that there is no consensus in how grip strength and physical activity are measured when assessing frailty in these regions.[9] Some studies use cut-offs created by Fried et al., others develop their own cut offs based on Fried's method, and yet others modify how weakness is measured entirely (e.g. using self-reported weakness, rather than handgrip strength). Given this variation, it is important to understand which method of calculating cut-off values leads to the most useful definition of frailty, as measured by the frailty definition's ability to predict adverse outcomes like mortality. Furthermore, studies in the literature have established that ethnic-specific variations exist in body composition.[16,59] For example, known differences in BMI and waist circumference for different ethnicities have led to the proposal for ethnic specific cut-points for obesity.[60] Similarly, ethnic variations in muscle mass exist, and this merits investigation into whether we should use different cut-offs for grip strength when measuring physical frailty in heterogeneous populations.[22] This work utilizes PURE's diverse study population to address this question.

Our findings indicate that frailty prevalence rates differ dramatically depending on whether thresholds for poor grip strength and low physical activity levels are adjusted for region or not (e.g. frailty prevalence in Africa increases from 4.5% to 20.2% when I adjust for region). Similar findings have been observed by Espinoza et al., who suggested ethnicity should not be ignored when measuring phenotypic frailty, as this may over-represent frailty in some populations, and under-represent it in others.[16] This is also consistent with prior studies that show that grip strength and skeletal muscle mass vary considerably across ethnicities and regions.[22] To further explore the importance of accounting for ethnicity/geographic region differences in computing frailty, I performed a survival analysis comparing *region-specific frailty* and *universal frailty*. Longitudinal analyses revealed that both definitions of frailty are comparable in their predictive ability for all-cause mortality, with *universal frailty* offering a higher hazard ratio (HR: 2.66; 95% CI: 2.47-2.86 for *universal frailty* vs

HR: 2.09; 95% CI: 1.94-2.26 for *region-specific frailty*). I compared the two frailty classifications in several ways, including the AUC for the ROC curve predicting survival (Figure 11) and the Net Reclassification Improvement Index, and these metrics also confirmed that while there is not a large difference in the model fit between the two frailty classifications, *universal frailty* is the slightly better frailty classification. This provides evidence against my initial hypothesis, which was that using region-specific thresholds for the frailty criteria would create a frailty classification that better predicted mortality compared to universal frailty.

One explanation for the higher proportion of deaths predicted by *universal frailty* may be because the *universal frailty* definition classifies a larger proportion of people from LMICs as frail and it is deaths in these LMICs that are driving the higher hazard ratios observed using *universal frailty*. There are multiple explanations for why low-income and lower-middle income countries have higher mortality. These include higher rates of infectious diseases such as HIV or malaria in these regions, lower access to treatments and medications, lower income per capita (which is associated with poor health outcomes), as well as the increase in the older adult population and rising rates of non-communicable diseases in these regions. It remains to be investigated whether the higher hazards predicted by *universal frailty* are due to factors related to frailty in LMICs or whether they are due to confounding by factors like those listed previously. Our findings nevertheless challenge the notion of separate thresholds for each region (e.g.: as has been proposed for obesity-related thresholds), as I produce better models when I define thresholds for grip strength and physical activity using the universal thresholds.

5.4 Limitations and Strengths

One limitation of this study is that it applies an adapted version of the frailty phenotype definition proposed by Fried et al. Because the PURE study currently does not measure gait speed and self-reported exhaustion at baseline, I used only three of the five criteria originally used to create the frailty phenotype classification. This may partially affect the validity of the results, as the proportion of people who are classified as frail or pre-frail may be subject to change upon the inclusion of the

two missing criteria: gait speed and self-reported exhaustion. Nevertheless, the prevalence of frailty reported in this paper is generally similar to what has been previously published. Furthermore, despite the missing factors, this study establishes there is a significant relationship between the frailty phenotype and mortality.

A second limitation is the observational nature of this study, which precludes drawing causal associations between frailty risk status (i.e. being frail or pre-frail) and outcomes such as mortality. However, I can rely on the large size and scope of the PURE study, as well as the methodological rigor applied to ensure standardized assessments across all study sites globally, to be confident in the associations observed between the different factors studied, particularly frailty and mortality.

Finally, another limitation to consider is the potential intra-regional variation in population makeup that this thesis did not account for. This refers to the fact that out of the eight regions studied, some of the regions comprise of countries and ethnicities that differ more dramatically than in other regions. For example, two countries in the North America/Europe group are Canada and Poland. From an ethnic and socioeconomic perspective, these populations may be more comparable than two countries within the Africa region such as South Africa and Tanzania. This may generate concerns regarding the appropriateness of applying the same grip strength and physical activity cut-offs to members of a single region, when in fact the countries that comprise them are heterogeneous. However, in order to ensure that each group was adequately powered, and to limit noise which can result from smaller samples, I deemed it useful to aggregate countries by geographic region. Furthermore, as some countries also have considerable intra-country variation in population characteristics, the decision to aggregate populations to create generalizable results needs to be made at some level of the population.

This study has several strengths. The first is the novelty of the question explored. Frailty is an increasingly popular area of study all over the world, but to my knowledge, there is limited research on how to properly define frailty for individuals across different geographic regions, particularly outside of high-income Western countries. I consider for the first time, how the frailty phenotype should be defined for a global population, and how different definitions are associated with mortality.

Secondly, the large size and scope of the PURE study and its standardized methods are important strengths, as is its longitudinal nature. As the PURE study has been previously found to share baseline characteristics from independent national data, this provides confidence about the generalizability of this study's findings.[19] Thirdly, I have provided a comprehensive list of grip strength and physical activity cut-off values for frailty based on eight regions, four BMI levels and sex (See Appendix II). This comprehensive list can be used by other researchers who are studying the frailty phenotype in any of the 27 countries studied in this analysis. Fourthly, this study reports the prevalence of frailty by both geographic region and country income, thereby allowing comparisons with numerous other studies. In addition, this is one of the largest studies to have explored frailty prevalence in middle-aged adults, and to my knowledge, is the only study to explore the frailty prevalence in this age-group in LMICs. Finally, this study demonstrates that there is a strong association between frailty and mortality in heterogeneous populations, which is even true in two sensitivity analyses on different subpopulations of interest.

5.5 Conclusions

Our study demonstrates that the thresholds for grip strength and physical activity used to compute frailty have an important effect on which individuals are considered frail. Thresholds that are calculated for each region separately produce more similar prevalence rates of frailty and pre-frailty across different regions, as compared to universal thresholds, but they do *not* improve the ability of frailty to predict all-cause mortality; rather, they very slightly decrease it. Our results suggest that a single set of thresholds could be applied for heterogeneous populations.

Our methodology can be extended in several ways. For example, we can do a time-dependent analysis to assess the prognostic value of each definition of frailty over time (e.g.: with time-dependent ROCs). We can also consider other variables by which frailty criteria thresholds are stratified, such as BMI, sex, and age. In the original definition of phenotypic frailty, grip strength and physical activity thresholds are calculated for these strata separately. We can analyse whether this stratification produces better predictive models for all-cause mortality, or whether it is more appropriate to create shared thresholds for different groups. For a global population, the choice of which factors to stratify

by needs to be further studied as well, e.g.: country income vs. region. I hope that this work is the first of many that study how to properly define frailty for a heterogeneous, global population.

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Appendix I: Details of countries included in analysis

Table 1: Details of each countries comprising each region

Region	Country	n	Country Income Level
South Asia	Bangladesh	2,578	Low
	India	9,874	Low
	Pakistan	2,105	Low
China	China	45,725	Lower-middle
Southeast Asia	Malaysia	9,566	Upper-middle
	Philippines	4,717	Lower-middle
Russia and Central Asia	Russia	2,798	Upper-middle
	Kazakhstan	2,091	Upper-middle
	Kyrgyzstan	1,881	Lower-middle
Africa	South Africa	1,061	Upper-middle
	Tanzania	1,302	Low
	Zimbabwe	683	Low
North America/Europe	Canada	8,941	High
	Sweden	3,779	High
	Poland	1,855	Upper-middle
	Turkey	3,972	Upper-middle
Middle East	Iran	5,920	Lower-middle
	United Arab Emirates	911	High
	Palestine	1,489	Lower-middle
	Saudi Arabia	2,041	High
South America	Brazil	5,232	Upper-middle
	Colombia	6,770	Lower-middle
	Chile	3,091	Upper-middle
	Uruguay	1,902	Upper-middle
	Argentina	7,215	Upper-middle

Appendix II: Cut off values for grip strength and physical activity

Table 1: Physical activity cut-offs for lowest 20th percentile (*universal frailty*)

Physical Activity Cut-off (met-mins/week)	
Men	**Women**
<524 n=75,760	<693 n=111,710

Table 2: Grip strength cut-offs for lowest 20th percentile (*universal frailty*)

Grip Strength Cut-off (Kgs)			
Men			
Underweight	**Normal**	**Overweight**	**Obese**
<23 n=4,195	<29 n=28,298	<32 n=23,693	<33 n=9,477
Women			
Underweight	**Normal**	**Overweight**	**Obese**
<15 n=4998	<19 n=38,646	<19 n=31,511	<19 n=20,410

Table 3: Physical activity cut-offs for lowest 20th percentile (*region-specific frailty*)

Physical Activity Cut-off (met-mins/week)		
Region	**Men**	**Women**
South Asia	<490 n=13,604	<579 n=16,890
China	<630 n=19,557	<864 n=27,491
Southeast Asia	<66 n=7,660	<420 n=11,644
Russia and Central Asia	<480 n=2,305	<840 n=6,111
Africa	<590 n=1,201	<636 n=3,320
North America/Europe	<1,080 n=12,572	<1,170 n=19,304
Middle East	<240 n=5,307	<300 n=5,804
South America	<396 n=13,554	<462 n=21,146

Table 4: Grip strength cut-offs for lowest 20th percentile (*region-specific frailty*)

Grip Strength Cut-off (Kgs)								
	Men				Women			
Region	**Underweight**	**Normal**	**Overweight**	**Obese**	**Underweight**	**Normal**	**Overweight**	**Obese**
South Asia	<23 n=2,807	<25 n=7,045	<27 n=2,951	<24 n=612	<15 n=3,163	<16 n=7,604	<17 n=4,354	<17 n=1,838
China	<28 n=545	<32 n=10,707	<34 n=7,012	<34 n=1,164	<17 n=727	<21 n=14,993	<21 n=9,442	<21 n=2,090
Southeast Asia	<23 n=270	<26 n=2,577	<28 n=2,150	<28 n=840	<15 n=457	<16 n=3,874	<17 n=3,262	<17 n=1,822
Russia and Central Asia	<22 n=18	<30 n=469	<32 n=758	<33 n=555	<19 n=61	<20 n=1,547	<20 n=1,846	<20 n=2,004
Africa	<22 n=357	<19 n=949	<16 n=201	<15 n=109	<12 n=256	<11 n=1,313	<10 n=1,046	<10 n=1,417
North America/Europe	<27 n=26	<37 n=2,238	<38 n=4,265	<37 n=2,347	<21 n=108	<23 n=3,898	<22 n=3,638	<21 n=3,541
Middle East	<32 n=82	<33 n=1,527	<34 n=2,134	<33 n=1,319	<17 n=55	<19 n=989	<20 n=2,094	<20 n=2,275
South America	<29 n=90	<31 n=2,786	<33 n=4222	<33 n=2,531	<19 n=171	<20 n=4,428	<19 n=5,829	<20 n=5,423

Appendix III: Supplementary data to the sensitivity analysis

Results for individuals with any baseline chronic disease (including angina, CAD, stroke, hypertension, hepatitis, heart failure, diabetes, COPD, asthma, tuberculosis and cancer)

	Unadjusted HR (95% CI)	**Adjusted HR* (95% CI)**
Universal frailty		
Not-frail	1	1
Pre-frail	2.00 (1.87-2.14)	1.84 (1.72-1.98)
Frail	3.69 (3.33-4.09)	2.94 (2.65-3.28)
Region specific frailty		
Not-frail	1	1
Pre-frail	1.85 (1.73-1.98)	1.67 (1.56-1.80)
Frail	3.22 (2.91-3.58)	2.52 (2.26-2.81)

N=38,465. Covariates adjusted for are age, sex, education, smoking status and alcohol consumption.