How regional versus global thresholds for physical activity and grip strength influence physical frailty prevalence and mortality estimates in PURE: a prospective multinational cohort study of community-dwelling adults

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ABSTRACT

Objectives Handgrip strength and physical activity are commonly used to evaluate physical frailty; however, their distribution varies worldwide. The thresholds that identify frail individuals have been established in high-income countries but not in low-income and middle-income countries. We created two adaptations of physical frailty to study how global versus regional thresholds for handgrip strength and physical activity affect frailty prevalence and its association with mortality in a multinational population.

Design, setting and participants Our sample included 137499 adults aged 35–70 years (median age: 61 years, 60% women) from Population Urban Rural Epidemiology Studies community-dwelling prospective cohort across 25 countries, covering the following geographical regions: China, South Asia, Southeast Asia, Africa, Russia and Central Asia, North America/Europe, Middle East and South America.

Primary and secondary outcome measures We measured and compared frailty prevalence and time to all-cause mortality for two adaptations of frailty.

Results Overall frailty prevalence was 5.6% using global frailty and 5.8% using regional frailty. Global frailty prevalence ranged from 2.4% (North America/Europe) to 20.1% (Africa), while regional frailty ranged from 4.1% (Russia/Central Asia) to 8.8% (Middle East). The HRs for all-cause mortality (median follow-up of 9 years) were 2.42 (95% CI: 2.25 to 2.60) and 1.91 (95% CI: 1.77 to 2.06) using global frailty and regional frailty, respectively, (adjusted for age, sex, education, smoking status, alcohol consumption and morbidity count). Receiver operating characteristic curves for all-cause mortality were generated for both frailty adaptations. Global frailty yielded an area under the curve of 0.600 (95% CI: 0.594 to 0.606), compared with 0.5933 (95% CI: 0.587 to 5.99) for regional frailty (p=0.0007).

Conclusions Global frailty leads to higher regional variations in estimated frailty prevalence and stronger associations with mortality, as compared with regional frailty. However, both frailty adaptations in isolation are limited in their ability to discriminate between those who will die during 9 years’ follow-up from those who do not.

INTRODUCTION

Frailty is increasingly recognised as a public health priority.1,2 However, most research to understand the prevalence and prognostic importance of frailty is conducted in high-income and upper middle-income countries. There is a relative paucity of data on the prevalence, patterns and prognostic importance of frailty in heterogeneous populations including low-income and lower-middle-income countries (LMIC).3–7

Physical frailty is a measure of frailty that focuses on the measurement of physical characteristics such as muscle strength and physical activity. In the seminal paper by Fried et al physical frailty was defined by the presence of ≥3 of: unintentional weight-loss, self-reported exhaustion, slow walking speed, low physical activity levels and weak handgrip, where slow
gait speed, low physical activity and weak handgrip were identified if below the 20th percentile using data from community-dwelling adults in the USA. This model of frailty has been applied to international cohorts, however unlike frailty studies done on high-income cohorts, this frailty model has not been extensively validated in its ability to predict adverse outcomes in diverse populations. Furthermore, normative values for measures of muscle strength and physical activity vary according to geographical region, and 20th percentile thresholds in LMICs are likely to differ from the 20th percentile of Fried’s cohort which was a North America cohort. It is not known whether thresholds of muscle strength and physical activity that have been implemented in populations from high-income countries to study frailty should be extrapolated to heterogeneous study populations including participants from LMIC; or whether it is more informative to implement thresholds that are specific to each geographical region. Furthermore, the association of frailty with adverse outcomes suggests the need to determine which frailty thresholds are more strongly associated with mortality. Therefore, in this paper, we aim to evaluate the differences in the prevalence and prognostic importance of physical frailty when measured using criteria specific to geographical regions, as compared with globally applied criteria. Using data from the Population Urban Rural Epidemiology Study (PURE), we developed two adaptations of physical frailty based on the PURE study population: global frailty and regional frailty and compared their prevalence and mortality estimates.

METHODS
Study design and participants
Data from the PURE study were used. The PURE study, which began recruiting from 2002 was designed to yield insights into the relationship between various primordial and primary risk factors, and cardiovascular and non-cardiovascular events. There are 25 countries participating in PURE, across eight geographical regions, (South Asia, China, Southeast Asia, Russia and Central Asia, Africa, North America/Europe, Middle East and South America) including countries from all income levels. Details on the study design, recruitment strategy and data collection have been previously published. To summarise, communities from participating countries were identified using prespecified criteria. Eligible households and individuals within these households between 35 and 70 years providing written informed consent, were enrolled. Study personnel used standardised procedures to gather data at the community household and individual levels. Baseline data include self-reported demographics, cardiovascular risk factors, chronic diseases, various symptoms (eg, unintentional weight loss), physical activity levels and muscle strength. Individuals aged 35–70 years for whom baseline data on sex, age, body mass index (BMI), as well as variables for the PURE frailty criteria, were included in the analysis. The following baseline demographic variables were used in this study: age, sex, education levels, smoking status, alcohol consumption and morbidity count (ie, multimorbidity) for the following chronic diseases: cardiovascular disease, hypertension, heart failure, diabetes, chronic obstructive pulmonary disease, asthma and cancer.

Development of frailty classifications
Of the five frailty phenotype criteria, (handgrip strength, weight loss, physical activity, gait speed and self-reported exhaustion), three criteria were collected at baseline in PURE and were used to develop the PURE frailty adaptations: handgrip strength, weight loss and physical activity. Unintentional weight loss was assessed by participants’ response to the question: ‘Have you experienced involuntary weight loss of more than 3 kg in the last 6 months?’ Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ), with activity levels estimated in metabolic equivalent of task (MET)-minutes/week according to an established algorithm. Handgrip strength (in kilograms) was measured by study personnel using a Jamar dynamometer according to a standardised protocol. Handgrip strength was measured three times on each hand and the maximum value for each hand was used to obtain the mean of the non-dominant and dominant hand. In cases where values were available for one hand but missing for the other hand (n=38 411) we imputed values for the missing hand using the coefficient and constant from the linear regression of non-dominant and dominant hand handgrip strength. This method of calculating handgrip strength has been applied in previous PURE analyses and was implemented in this study for consistency.

Of note, the assessment of the frailty criteria is similar but not identical to that used by Fried et al in that we used the IPAQ to quantify physical activity levels, while Fried et al used the Minnesota Leisure Time Activity Questionnaire. In addition, the PURE baseline data set is limited in that it does not measure self-reported exhaustion and grip strength at baseline, which were both used in Fried’s original frailty phenotype definition. However, previous work shows that there are several hundred physical frailty adaptations of Fried’s original model and that despite their modifications they continue to be predictive of adverse outcomes in older adults, thus lending confidence to our PURE frailty classifications.

We created two versions of PURE frailty, adapting previous work that operationalised frailty using the assessments available in the PURE study. Global frailty was defined as the presence of two or three of: unintentional weight-loss, weakness and low physical activity levels, where weakness was considered a handgrip strength below the lowest cohort-wide quintile for BMI and sex; and low physical activity was considered an activity level below the lowest cohort-wide quintile for each sex. Regional frailty was also defined as the presence of two or three of: unintentional weight-loss, weakness and low physical activity levels, but in contrast to global frailty, weakness was...
considered a handgrip strength below the lowest region-specific quintile for BMI and sex; and low physical activity was considered activity levels below the lowest region-specific quintile for sex. Pre-frailty was considered the presence of only one of: unintentional weight-loss, weakness and low physical activity levels. This three-item PURE frailty scale was not evaluated for content validity.

**Outcomes**
The primary endpoint was all-cause mortality. 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. We included all outcome data available by January 2019.

**Statistical analysis**
We estimated the age-standardised and sex-standardised prevalence of frailty using both global frailty and regional frailty separately, for the entire cohort and for each geographical region. Kaplan-Meier survival curves stratified by frailty category were generated for the two different classifications of frailty. The prognostic impact of frailty using each of the frailty definitions was assessed using Cox proportional hazard models of the time to death. This analysis was done for the entire cohort, and within each region separately. We also quantified the heterogeneity in frailty prevalence across regions between the two frailty adaptations using the $\chi^2$ statistic, treating the frailty prevalence in each region as a separate observation. HRs, stratified by frailty level, were calculated and adjusted for the following covariates: age, sex, education, smoking status, alcohol consumption and morbidity count. These covariates have been previously shown to be predictive of mortality in similar cohorts from LMICs as well as in high-income, North American cohorts.

To determine which of the two PURE frailty classifications was more strongly associated with mortality, the likelihood ratio test statistics for the survival models using global frailty vs regional frailty were computed, compared with a baseline covariates-only model. In addition, receiver operating characteristic (ROC) curves for all-cause mortality were generated for the two frailty classifications. The discriminant ability of the two PURE frailty classifications was compared by assessing the area under the curves (AUCs), with higher values indicating better discrimination. A $\chi^2$ test was done to determine if the two AUCs were statistically different. Finally, to further compare the two models, the Net Reclassification improvement Index (NRI) was calculated based on the model suggested by Pencina et al. The NRI allows for the comparison of a new classification model (regional frailty) with a reference model (global frailty). The NRI can be interpreted as the net change in the proportion of subjects assigned a more appropriate risk category under the new model. Statistical analyses were computed using Stata V.15.0 (StataCorp, College Station, Texas, USA).

To test whether the patterns noted regarding PURE frailty prevalence and the longitudinal analysis are robust, two sensitivity analyses were performed. In the first sensitivity analysis, the proportion of people classified as frail by region was recalculated only in the healthy subset of the population. A second sensitivity analysis was performed in adults aged 65 years and over. The results of these sensitivity analysis can be found in online supplemental file 1.

**RESULTS**

**Prevalence and characteristics of the frail and pre-frail**
A total of 137,499 participants were included in the analysis, after removing subjects with missing data. 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), handgrip strength (n=10,049) or sex (n=386) (because a frailty score could not be calculated for them). Sample sizes for each region were: China: n=45,367, South America: n=24,116, North America/Europe: n=18,443, South Asia: n=14,529, Southeast Asia: n=14,027, Middle East: n=10,332, Russia and Central Asia: n=6,719, Africa: n=2,989 (see online supplemental table 1). Most excluded subjects were from low-income countries (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 after excluding participants with missing data. The median age of participants at enrolment was 51 years (25th–75th percentile: 43–59 years) and 60.1% (n=82,644) of the sample were women. The proportions of participants from high-income countries, upper-middle income countries, LMICs and LICs were 11.4% (n=15,672), 28.2% (n=38,783), 48.4% (n=66,502) and 12.0% (n=16,542), respectively.

Using global frailty, in which single, region-agnostic thresholds for poor handgrip strength and low physical activity levels were implemented, the age-standardised and sex-standardised prevalence of frailty and pre-frailty were 5.6% and 28.1%, respectively. Using the regional frailty classification, whereby handgrip strength and physical activity thresholds were stratified by region, the age-standardised and sex-standardised prevalence of frailty and pre-frailty were similar: 5.8% and 29.3%, respectively. For both definitions, frailty was associated with older age and there was no meaningful difference in frailty rates among men and women. The trends of frailty with education levels, smoking status, alcohol consumption and morbidity count were generally similar for the two frailty classifications. The baseline characteristics of participants by frailty status are shown in table 1.
Table 1  Baseline characteristics of participants by frailty classification method (row % are provided)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Global frailty</th>
<th>Regional frailty</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-frail (91 103 [66.3])</td>
<td>Pre-frail (38 678 [28.1])</td>
<td>Frail (7 718 [5.6])</td>
</tr>
<tr>
<td>Median age</td>
<td>50 (IQR 42–58)</td>
<td>52 (IQR 43–60)</td>
<td>56 (IQR 47–64)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female n (%)</td>
<td>54 967 (66.5)</td>
<td>23 029 (27.9)</td>
<td>4648 (5.6)</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>36 136 (65.9)</td>
<td>15 649 (28.5)</td>
<td>3070 (5.6)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never n (%)</td>
<td>61 308 (65.3)</td>
<td>27 147 (28.9)</td>
<td>5420 (5.8)</td>
</tr>
<tr>
<td>Former n (%)</td>
<td>11 487 (70.9)</td>
<td>39 500 (24.4)</td>
<td>766 (4.7)</td>
</tr>
<tr>
<td>Current n (%)</td>
<td>17 844 (67.6)</td>
<td>7 287 (27.6)</td>
<td>1 283 (4.9)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never n (%)</td>
<td>56 872 (62.4)</td>
<td>28 267 (31.0)</td>
<td>6 057 (6.6)</td>
</tr>
<tr>
<td>Less than once/day n (%)</td>
<td>21 573 (75.5)</td>
<td>6 211 (21.7)</td>
<td>800 (4.7)</td>
</tr>
<tr>
<td>More than once/day n (%)</td>
<td>9 857 (74.6)</td>
<td>2 948 (22.3)</td>
<td>407 (3.1)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/primary/unknown n (%)</td>
<td>31 194 (58.8)</td>
<td>17 522 (33.0)</td>
<td>4 360 (8.2)</td>
</tr>
<tr>
<td>Secondary/higher secondary n (%)</td>
<td>35 853 (69.2)</td>
<td>13 724 (26.5)</td>
<td>2 256 (4.4)</td>
</tr>
<tr>
<td>Trade or college/university n (%)</td>
<td>23 938 (73.9)</td>
<td>7 378 (22.8)</td>
<td>1 093 (3.4)</td>
</tr>
<tr>
<td>Multimorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No long-term conditions n (%)</td>
<td>62 116 (68.8)</td>
<td>24 242 (26.8)</td>
<td>3 975 (4.4)</td>
</tr>
<tr>
<td>One long-term condition n (%)</td>
<td>21 254 (64.4)</td>
<td>9 622 (29.2)</td>
<td>2 106 (6.4)</td>
</tr>
<tr>
<td>Two long-term conditions n (%)</td>
<td>6 088 (57.4)</td>
<td>3 538 (33.3)</td>
<td>990 (9.3)</td>
</tr>
<tr>
<td>More than two long-term conditions (%)</td>
<td>1 645 (46.1)</td>
<td>1 276 (35.8)</td>
<td>647 (18.1)</td>
</tr>
</tbody>
</table>
Prevalence of frailty by region

The prevalence of frailty by geographical region varied considerably based on the classification for PURE frailty used. According to global frailty, the prevalence of frailty was highest in Africa, where it was 20.1%, and lowest in North America/Europe at 2.4% (see figure 1A). Pre-frailty rates also differed across regions (see figure 1B). Using regional frailty, rates of frailty and pre-frailty were more homogeneous across the different regions. With the regional 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. The sex-standardised and age-standardised non-frailty, pre-frailty and frailty prevalence rates by geographical region are presented in online supplemental table 1.

![Figure 1](http://bmjopen.bmj.com/)
To quantify the variability of frailty across regions we computed the χ² value treating each region’s frailty prevalence as a separate observation for the two definitions. We found that the χ² value of global frailty was 2420.7 (df=7, p<0.001) while the χ² value for regional frailty was 296.1 (df=7, p<0.001). This demonstrates that regional frailty attenuates the variability of frailty prevalence across regions. The same overall trend was observed for pre-frailty where the χ² value decreased from 4018.8 (df=7, p<0.001) to 247.1 (df=7, p<0.001).

Global and regional frailty and mortality

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 7339 (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, and this graded association persisted after adjustment for age, sex, education, smoking status, alcohol use and morbidity count. These results are shown in table 2.

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global frailty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-frail</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pre-frail</td>
<td>1.94 (1.84 to 2.04)</td>
<td>1.51 (1.43 to 1.59)</td>
</tr>
<tr>
<td>Frail</td>
<td>4.26 (3.97 to 4.57)</td>
<td>2.42 (2.25 to 2.60)</td>
</tr>
<tr>
<td>Regional frailty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-frail</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pre-frail</td>
<td>1.75 (1.67 to 1.84)</td>
<td>1.31 (1.24 to 1.37)</td>
</tr>
<tr>
<td>Frail</td>
<td>3.48 (2.24 to 3.73)</td>
<td>1.91 (1.77 to 2.06)</td>
</tr>
</tbody>
</table>

n=125,253 for unadjusted analysis, n=120,658 after adjustment for covariates.

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

When compared with a baseline covariates-only model, the regional frailty Cox model had a likelihood ratio statistic of 295.5 (p<0.001) and the global frailty model had a likelihood ratio statistic of 577.3 (p<0.001). These results suggest that global frailty produced better models for the survival data compared with regional frailty. Both frailty adaptations had low discriminatory power. The AUC value for global frailty was 0.600 (95% CI: 0.594 to 0.606), which was similar to 0.593 (95% CI: 0.587 to 0.599) for the AUC value of regional frailty. The χ² test comparing the two AUCs found that they were statistically different (χ² = 11.4, p=0.0007), likely due to the large sample sizes. Finally, the NRI calculated was −0.012 (95% CI: −0.005 to 0.019). This value means that net (n=1761) participants are better classified into a risk group when global frailty is applied, compared with when regional frailty is applied.

Finally, we performed two sensitivity analyses to explore the robustness of our findings. Repeating the longitudinal analyses in two subsets of the population demonstrated that the overall frailty prevalence patterns across regions persisted and that global frailty yielded higher HRs associated with all-cause mortality for both frailty classifications.
for all-cause mortality compared with regional frailty (see online supplemental file 1).

**DISCUSSION**

In this study, we formulated two definitions of PURE frailty: one in which separate thresholds for physical activity and handgrip strength were defined for each region, and a second where a single set of thresholds was defined for the global study population. Our major findings from this analysis are that (1) estimates of regional frailty prevalence vary substantially depending on whether regional or global thresholds are implemented to define physical markers of frailty, with regional thresholds attenuating the differences observed between regions; and (2) the higher HRs for global frailty suggest that it is associated with mortality more strongly than regional frailty, however in isolation both global frailty and regional frailty had low discriminatory ability for all-cause mortality.

The two definitions of frailty agreed in many respects. The median age of frail participants was higher than that of pre-frail and non-frail participants, using both global frailty and regional frailty. This finding is supported by previous research, which establishes that frailty increases with age. The finding that frailty, according to both definitions, was more common in those who reported to have never consumed alcohol, although unexpected, was also observed in previous literature such as the UK Biobank study, where alcohol use was inversely associated with frailty status. The authors of that study suggested this may be because of abstainer bias (ie, those with poorer health were advised not to drink alcohol). Furthermore, in the PURE study, participants from LICS have the highest rates of never drinking alcohol and never smoking. They also have the highest rates of frailty; this provides another plausible explanation of why we observe higher associations between never smoking or drinking and frailty. The frailty prevalence did not differ significantly between men and women with either frailty definition. This contrasts with previous research in which frailty is typically more common in women. A possible explanation for this is that two of the three frailty criteria we used, namely handgrip strength and physical activity levels, were measured using sex-specific thresholds. In contrast, in Fried’s original frailty index, three of the five criteria did not adjust for sex so the original definition may be more sensitive to frailty characteristics that differ between men and women.

Despite these similarities, we found that regional frailty prevalence rates differ dramatically depending on whether thresholds are adjusted for region or not (see figure 1A,B). Our findings indicate that applying region-based thresholds for poor handgrip strength and low physical activity, eliminated much of the inter-region variability in frailty and pre-frailty prevalence. The most marked variation was observed in Africa, where frailty prevalence rates varied nearly fivefold depending on which thresholds of handgrip strength and physical activity were implemented, with single, global thresholds leading to an increase in frailty prevalence estimates in Africa and other LICS. Similar findings to our study were observed by Espinoza and colleagues, who compared frailty prevalence in individuals who were Mexican American and European American. They found that when applying ethnic-specific thresholds to the frailty criteria, the frailty prevalence was 10% for both Mexican Americans and European Americans. However, when applying ethnic-independent thresholds, the frailty prevalence was 11% for Mexican Americans and 7% for European Americans. Our findings, like those of Espinoza and colleagues, demonstrate that the choice of thresholds can have a marked effect on estimated frailty rates, which can have important implications for the interpretation of epidemiological data. In Fried et al’s original work, the two main ethnic groups studied were Caucasian who comprised 85% of the sample and African American, comprising 15% of the sample. Fried and colleagues observed that frailty was associated with the African American race, suggesting that frailty is more prevalent among certain ethnic groups. Our work extends on this notion, and tests whether the thresholds for the frailty criteria should be tailored to an individual’s ethnicity or geographical region.

Choosing a single set of thresholds offers some advantages in terms of parsimony: it is less cumbersome to use a single set of thresholds than to use different thresholds for each geographical region. To determine whether using global thresholds compromises the prognostic value of frailty, we conducted analyses to measure the association of both definitions of frailty with all-cause mortality. We determined that PURE frailty according to single, global thresholds for physical activity and handgrip strength actually led to a slightly better proportional hazards model fit and a higher HR (see table 2) as compared with using region-specific thresholds. This suggests that when constructing a single frailty variable to measure frailty in geographically heterogeneous populations, it may be preferable to use global thresholds, especially as such an approach is more parsimonious. However, our analyses suggest that in some regions, regional frailty may be more strongly associated with mortality than global frailty. Therefore, for analyses limited to a specific geographical region, region-specific thresholds should be considered. While more research in diverse regions is needed to confirm these findings and identify optimal thresholds for each region, ours represents the largest study to apply standardised methodologies for evaluating frailty in populations from highly heterogeneous countries and geographical regions.

Both frailty adaptations offered limited ability to discriminate between those who died from those who did not die during a median of 9 years’ follow-up. Global frailty had an AUC of 0.600 versus 0.593 for regional frailty. These values are consistent with previous studies that have examined the frailty phenotype’s ability to discriminate all-cause mortality, in which ROC AUCs have ranged
from 0.57 to 0.79.\textsuperscript{27} That our ROC AUCs are on the lower end of this range may be explained by the fact that our study population is far more heterogeneous than previous studies (in ethnic origin and age), as well as our adaptation of frailty using only three of the five criteria from the original frailty phenotype. Furthermore, while both frailty adaptations had low discriminatory value for mortality, this is consistent with other risk factors that are considered clinically important as change in ROC AUCs are known to have fairly low sensitivity for prognostically relevant risk factors.\textsuperscript{28,29}

Finally, we note that the calculation of NRIs demonstrate that a small number of participants are better classified into a mortality risk group when \textit{global frailty} is applied, compared with when \textit{regional frailty} is applied. One explanation for the higher proportion of deaths predicted correctly by \textit{global frailty} may be that the \textit{global frailty} definition leads to a larger proportion of people from LMICs (where mortality rates are higher) being classified as frail. However, we are not certain whether this relationship is driven by frailty itself or by confounding factors that are more frequent in LMIC and that lead to an increased mortality risk.

\subsection*{Strengths and limitations}

To our knowledge, ours is the first longitudinal study to examine the effect of adjusting for region when defining the criteria for physical frailty. The sample size was large and included geographical regions across much of the inhabited world. Our findings are limited in that only three of the five criteria originally used to create the frailty phenotype classification were measured in the PURE study and some of the assessments (eg, for physical activity levels) are slightly different than those originally used by Fried et al.\textsuperscript{1} While the modifications used may make it difficult to compare our findings directly to other studies, such adaptations to the frailty phenotype operationalisation are not uncommon in the literature, and the prevalence of frailty and the characteristics of the frail reported in this paper are generally similar to what has been previously published for similar regions and age-groups.\textsuperscript{7,17,23,30} Furthermore, despite the missing factors, this study establishes there is a significant relationship between PURE frailty and mortality. We hope that future studies will explore the implementation of regional versus cohort-wide quintiles in physical frailty studies that include all five of the original frailty phenotype domains.

Another potential limitation of our study is the choice to aggregate by geographical region, despite potential variation in population makeup in each region. This intraregional variation may generate concerns regarding the appropriateness of applying the same handgrip strength and physical activity cut-offs to members of a single region when, in fact, the countries that comprise them are heterogeneous. However, the decision to aggregate populations at some geographical level is unavoidable to ensure that each group is adequately powered and to limit noise that results from smaller samples. Even then, sample sizes from certain regions were relatively small (eg, 2989 samples from Africa), so further research is needed to validate our findings in these regions. Finally, it should be noted that frailty is associated with several adverse outcomes including falls, fractures and hospitalisations.\textsuperscript{8,9,31} While our work focuses on mortality alone, future studies can apply our methodology to examine how adjusting for region can effect the association between the frailty phenotype and other outcomes.

\section*{Conclusions}

Our study demonstrates that the thresholds for handgrip 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 with global thresholds, but do not improve the ability of frailty to predict all-cause mortality. Our results suggest that it may be appropriate to apply a single set of thresholds for poor handgrip strength and low physical activity when measuring physical frailty in heterogeneous populations and points to the need for future work to examine this relationship using all five of the frailty domains.

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\section*{Contributors}

DL: conceived the initial research question, contributed to the design of the research, supported data analysis, ensured methodological rigour, co-wrote the first through final draft and supervised the overall project and acts as guarantor for the overall content of the paper. MF: conceived the initial research question, performed data analysis, co-wrote the draft manuscripts and the final draft. AP: provided guidance and insight on the research question and methods and contributed to the final draft. SB: contributed to the statistical analysis plan, ensured methodological rigour and reviewed the draft and final manuscripts. SJ: oversaw data collection and managed the PURE study database and reviewed the final manuscript.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Data availability statement The data analysed in this study are not publicly available because we have not obtained participants’ consent to share their data. Data will be shared as per the PHRI Data Sharing Policy, which requires approval of the proposed use of the data by a review committee.

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