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COMPARISON OF TWO MODELS OF FRAILTY FOR THE PREDICTION OF MORTALITY IN BRAZILIAN COMMUNITY-DWELLING OLDER ADULTS: THE FIBRA STUDY

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Abstract: *Background:* Prevalence of frailty is significant in Latin America. However, no previous study evaluated mortality prediction using the two most used frailty models in Brazil. *Objectives:* The aim of the present study was to compare the frailty phenotype and the frailty index with regard to accuracy in the prediction of mortality among community-dwelling older adults. *Methods:* A cohort study was conducted involving 674 older adults. Thirty-five variables (signs, symptoms, chronic diseases and disabilities) were used for the construction of the frailty index (FI). The frailty phenotype index (FPI) was defined based on the criteria proposed in the Cardiovascular Health Study. Periodic verifications were performed in the databank of the Mortality Information System. Cox regression was used to estimate the relative risk (RR) of mortality and Kaplan-Meier survival curves were used in the analysis. *Results:* The prevalence of frailty was greater based using the FI (16.3%) compared to the FPI (5.34%). Older adults classified as frail by the FPI had a greater risk of death (RR: 10.03; 95% CI: 4.43-22.74) that those classified as frail by the FI (RR: 0.87; 95% CI: 0.25-3.00). The lowest survival rate was found in the group of older adults classified as frail based on the FPI and classified as pre-frail and robust based on the FI. *Conclusion:* The FPI demonstrated greater accuracy in predicting the risk of mortality among Brazilian older adults than the FI. The validation of frailty measures is fundamental to the identification of older adults who are more vulnerable to adverse health events.

Key words: Frailty, mortality, prognosis, older adults.

Introduction

Frailty is defined as a clinical syndrome characterized by an increase in vulnerability to adverse health events that stems from the age-associated dysregulation of multiple physiological systems as well as the loss of energy reserves for coping with internal stressors and environmental challenges (1-3). Currently, a consensus is found regarding the concepts of increased vulnerability, heterogeneity of presentation and multidimensionality of biological models and physiopathology related to frailty (3).

Different frailty models are described in the literature, being the most widely accepted and used the frailty phenotype (1) and the frailty index (4-6). In a literature review, Bouillon and colleagues (7) identified 27 possible frailty measures. The frailty phenotype was the most frequently employed (69%), followed by the frailty index (12%) and the Edmonton frail scale (4%), with other measures together accounting for less than 2%. Another authors described similar data for middle-income countries, such as Brazil, Mexico and China (8). Among the 70 studies analyzed, 35 employed the frailty phenotype, 20 the frailty index and 8 used the Edmonton scale for the evaluation of frailty (8).

The model of the frailty index is based on the presupposition that frailty results from the accumulation of deficits throughout one's lifetime under the influence of biological and social variables and such deficits determine the onset and progression of physiological decline in the ageing process (4-6). Based on data from the Canadian Study on Health and Ageing (CSHA), highly prevalent clinical, cognitive, psychological and social variables in older adults have been identified, which may participate in the physiopathogenic events of frailty. A frailty index was created to express the sum of the harm accumulated in each older adult. Associations between this measure and the risk of mortality were identified independently of chronological age. This is an assessment tool based on a mathematical model that does not predict a specific set of clinical markers in old age, but a sum of deficits (diseases and disabilities) observed in different systems at the moment of evaluation (the frailty index) (4-6, 9). Several researchers state that the accumulation of age-associated deficits overshadows the isolated effect of diseases or disorders in relation to adverse health events.

Two American prospective studies – the Cardiovascular Health Study (CHS) (1) and Women´s Health and Aging Study (WHAS) (10) – use a definition of frailty as a clinical syndrome that originates in the decline process related to ageing characterized by a reduction in energy reserves, neuroendocrine dysregulation, immune function decline and a reduction in resistance to stressors, all of which are dependent on gene variations expressed as oxidative stress, mitochondrial loss, shortening of telomeres, DNA damage and cellular ageing. A set of specific signs and symptoms dependent on the joint action of genetic-biological and environmental variables serve as indicators of increased vulnerability to stressors. These

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variables are anorexia, sarcopenia, osteopenia, inactivity, disability and inflammatory diseases, which interlink to have harmful effects on the organism. In the model proposed within the CHS and WHAS, frailty is a clinical syndrome physically defined by the occurrence of three or more specific criteria (unintentional weight loss, fatigue, low grip strength, slowness during gait and a low level of physical activity), which characterizes a phenotype (aka Fried's phenotype).

Frail older adults have poorer survival rates in comparison to non-frail older adults. Indeed the increase in the relative risk of death is 50% based on the frailty phenotype and 15% based on the model of the frailty index (11). This association is more robust in older adults with a greater number of accumulated deficits and those with a greater number of criteria of the frailty phenotype (5, 11, 12). The risk of death is similar between men and women and has a linear relationship with age (11). Using data from the CSHA, Rockwood and colleagues (5) found a moderate correlation between the frailty phenotype and the frailty index (r = 0.65). However, the frailty index demonstrated greater sensitivity in the prediction of institutionalization and death than the frailty phenotype. In a study involving 4,721 community-dwelling older adults, comparing the frailty phenotype and frailty index with regard to the robustness of the respective predictions of mortality, the findings revealed that while the index model underestimated the death of 134 individuals, the phenotypic model underestimated the death of 720 individuals. The lowest survival rate was found in older adults classified as frail in both measures (12).

Brazil is a middle-income country, which has one of the largest percentages of older adults worldwide. There are no Brazilian population-based studies comparing the capacity of different frailty measures to predict mortality in older adults. Thus, the aim of the present study was to compare the frailty phenotype and frailty index with regard to the ability to predict mortality in community-dwelling older adults.

Methods

Study design and ethics

This is a longitudinal derived study from the Fragilidade em Idosos Brasileiros (FIBRA [Frailty in Brazilian Older Adults]) Study, which occurred in the city of Campinas, Southwestern of Brazil, between September 2008 and June 2009 in the context of a multicenter population-based cross-sectional study designed to investigate frailty and its associations with sociodemographic, psychosocial, clinical, cognitive and anthropometric variables as well as functional capacity, physical health and mental health in older adults. In depth details of this study can be found elsewhere (13).

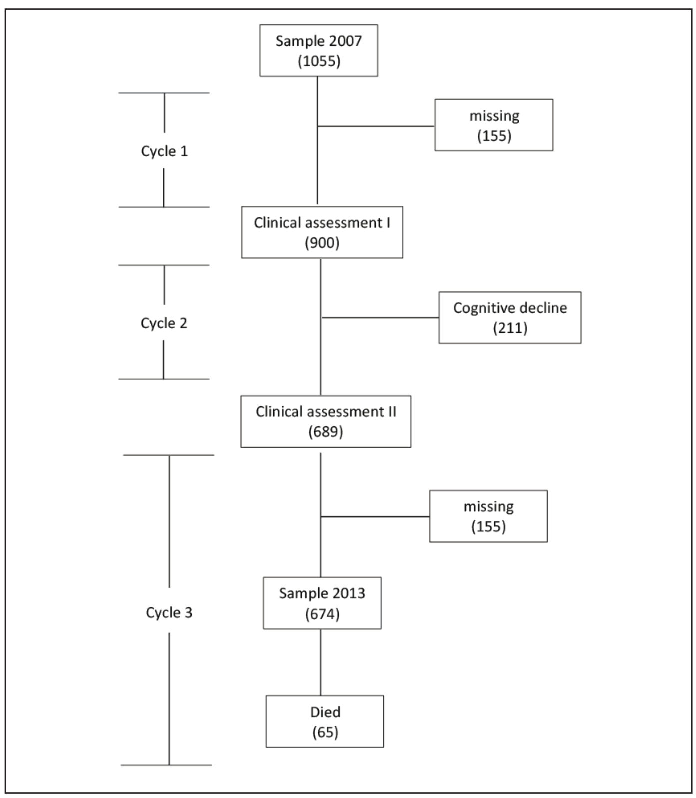
The Mortality Information System for the city of Campinas was searched for death certificated of the years 2009, 2010, 2011, 2012 and 2013, which was accessed at six-month intervals.

The FIBRA Study received approval from the Human Research Ethics Committee of the School of Medical Sciences, State University of Campinas (certificate nº 208/2007) and is registered under a National protocol (C.A.A.E. 39547014.0.1001.5404). The present study was submitted as an addendum to the main project and also received approval (certificate nº 736.943/2010). All participants signed a statement of informed consent during cross-sectional collection data.

Participants and procedures

The participants of the FIBRA Study were randomly selected from individual residences located in 90 urban census sectors in the city of Campinas. Male and female individuals in specific age groups (65 to 69 years, 70 to 74 years, 75 to 79 years and 80 years of older) were recruited proportionally to the population of older adults in each census sector. The eligibility criteria were age 65 years or older and permanent resident in the home and census sector. The following exclusion criteria were used: memory, attention, spatiotemporal orientation or communication problems suggestive of dementia; being bed-ridden; severe consequences stemming from a stroke, with aphasia and/or the loss of strength; advanced stage or unstable Parkinson's disease with severe mobility, speech or affective impairments; severe hearing or visual impairment that hampered communication; and being in a terminal stage; refusal to sign the consent (14).

Figure 1
Flow chart of the FIBRA Cohort



Among the total number of individuals recruited, 1,055 appeared at the data collection sites. Among these individuals, 155 were excluded for not being aged 65 years or older, not residing in the census sectors or deciding not to participate (Figure 1). The 900 older adults selected were evaluated with the use of sociodemographic, anthropometric, clinical and frailty measures (1). In this phase, the scores on a cognitive screening test (15) were used as the inclusion criteria for the second phase of data collection involving self-reports regarding physical health, mental health, functional performance and subjective wellbeing. Six hundred eighty-nine older adults without cognitive deficit suggestive of dementia initiated the present study. Mean age was 72.1 ± 5.3 years and 68.8% of the sample was female.

Measures

The following variables of interest were investigated:

Sex and age: self-reported items: male or female; date of birth; and number of years lived since the date of birth.

Frailty index (FI): This measure does not require the inclusion of a specific number of deficits, but previous studies have used 30 to 70 variables to compose the frailty measure (4-6, 9, 12, 16). According to Searle and colleagues (17), protocols that contain 30 to 40 variables are accurate at predicting adverse health events. To make up part of this index, a variable must be associated with age and negative health outcomes, be present in at least 1% of the population, involve various organic systems, not have more than a 5% rate of missing data and not be saturated (not be present in 80% or more of individuals under 90 years of age) (17). In the present study, 35 variables in different domains were used: body mass index (BMI), waist-to-hip ratio, chronic diseases, signs and symptoms, functional capacity, falls, number of medications, smoking habit, alcohol use, self-perceived health, depressive symptoms and satisfaction with life. Appendix S1 shows the FI deficit variables and cut-off points. With the exception of anthropometric variables, all other variables were based on self-reports. When variables were dichotomous (eg., hypertension – yes or no), the presence of deficit was scored as 1 and the absence was scored as 0. When variables were ordinal, intermediate points were created (eg., self-rated health as very good = 0, good = 0.25, fair = 0.5, poor = 0.75 or very poor = 1.0). Cognitive status was scored based on the quintiles of the cognitive screening test (1st quintile = 1, 2nd quintile = 0.75, 3rd quintile = 0.5, 4th quintile = 0.25 and 5th quintile = 0). The recommendations in the literature were used for the evaluation of the waist-to-hip ratio with regard to cardiovascular risk (18).

For each individual, the FI was calculated from the sum of the scores indicative of frailty divided by 35. For example, considering the 35 possibilities of responses regarding chronic diseases, signs and symptoms, disabilities and metabolic indicators, the FI of an individual who reported having cataracts, hypertension, memory problems and difficulty preparing food would be 0.11 (4/35). In cases for which the individual failed to answer one of the questions that made up part of the protocol, the index was calculated based on the responses given. For the purposes of analysis, the lowest denominator considered was 33 deficits. Based on the criteria proposed by Kulminski and colleagues (12), on a scale of 0 to 1, individuals with an FI ≤ 0.20 were classified as robust, those with an FI between 0.21 and 0.35 were classified as pre-frail and those with an FI > 0.35 were classified as frail.

Frailty phenotype: The indicators and parameters established by Fried and colleagues (1) were used for the frailty phenotype. For the purposes of comparison with the FI, the criteria proposed by Kulminski and colleagues (12) were used. A frailty phenotype index (FPI) was created using the sum of positive criteria divided by the sum of positive and negative criteria for the frailty phenotype. Thus, the frailty phenotype was transformed into an interval measure on a scale of 0 to 1. Individuals with an FPI = 0 were considered robust, those with an FPI between 0.1 and 0.4 were considered pre-frail and those with an FPI > 0.4 were considered frail.

Mortality: Mortality patterns were investigated through semestral verifications of the Mortality Information System for the city of Campinas. For the obtainment of the databank, a probabilistic relationship of records was used with a multistep blocking strategy: first name, last name, year of birth and residential address. Mortality was measured by the proportion of the incidence of deaths among older adults in the city of Campinas and the variable was dichotomized as "yes" or "no".

Statistical analysis

In the Mortality Information System, surviving and non-surviving older adults were identified during each verification of the databank. Either the chi-square test or Fisher's exact test was used for the statistical comparison between the frailty indices (FI x FPI) in the score ranges corresponding to frailty. Bowker's test of symmetry was used to determine the level of agreement between the indices. The Cox regression model was used to investigate the relative risk of mortality among the different levels of frailty. Kaplan-Meier analysis was used for the creation of survival curves. All analyses were performed using the Statistical Analysis System (SAS 9.2), with the level of significance set to 5% ($p \leq 0.05$).

Results

The sample totaled 674 older adults who gave answers to 33 or more of the variables that composed the protocol. Women accounted for 68.7% of the sample; 36.3% were aged 65 to 69 years, 33.3% were aged 70 to 74 years, 19.7% were aged 75 to 79 years and 10.5% were aged 80 years or older. The FI classified 266 individuals as robust, 298 as pre-frail and 110 as frail. The FPI classified 301 individuals as robust, 337 as pre-frail and 36 as frail (Table 1). In the analysis of agreement between the two measures, a greater prevalence of frail individuals was found using the FI (16.3%) than the FPI (5.34%).

Table 1
Results of analysis of agreement between Frailty Phenotype and Frailty Index; FIBRA Study, Campinas, Brazil, 2008 – 2009 (n = 674 older adults)

Categories of Frailty Phenotype Index, n (%)	**Categories of Frailty Index, n (%)**			**Total**
	≤ 0.2	**0.21 – 0.35**	**> 0.35**	
0	146 (21.6)	134 (19.8)	21 (3.12)	301 (44.6)
0.01 – 0.4	117 (17.3)	151 (22.4)	69 (10.24)	337 (50)
> 0.4	3 (0.45)	13 (1.93)	20 (2.97)	36 (5.34)
Total	266 (39.4)	298 (44.2)	110 (16.3)*	674 (100)

*p < 0.001, Bowker's test of symmetry: X2 = 52.9; dF: 3,

Table 2
Relative risk of mortality according to frailty indicators; FIBRA Study, Campinas, Brazil, 2008 – 2009 (n = 674 older adults)

Frailty models	Univariate analysis	Multivariate analysis
Frailty Phenotype Index	Relative risk (95% confidence interval)	
0	--	--
0 – 0.4	1.73 (0.93 – 3.22)	1.91 (1.02 – 3.58)**
> 0.4	6.69 (3.13 – 14.29)*	10.03 (4.43 – 22.74)***
Frailty Index		
0 – 0.2	--	--
0.21 – 0.35	1.10 (0.62 – 1.92)	1.45 (0.44 – 4.79)
> 0.35	0.77 (0.33 – 1.80)	0.36 (0.25 – 3.00)

* p < 0.001; ** p = 0.043; *** p < 0.001

Table 3
Number of survivors and deaths in five years following data collection according to frailty indicators; FIBRA Study, Campinas, Brazil, 2008 – 2009 (n = 674 older adults)

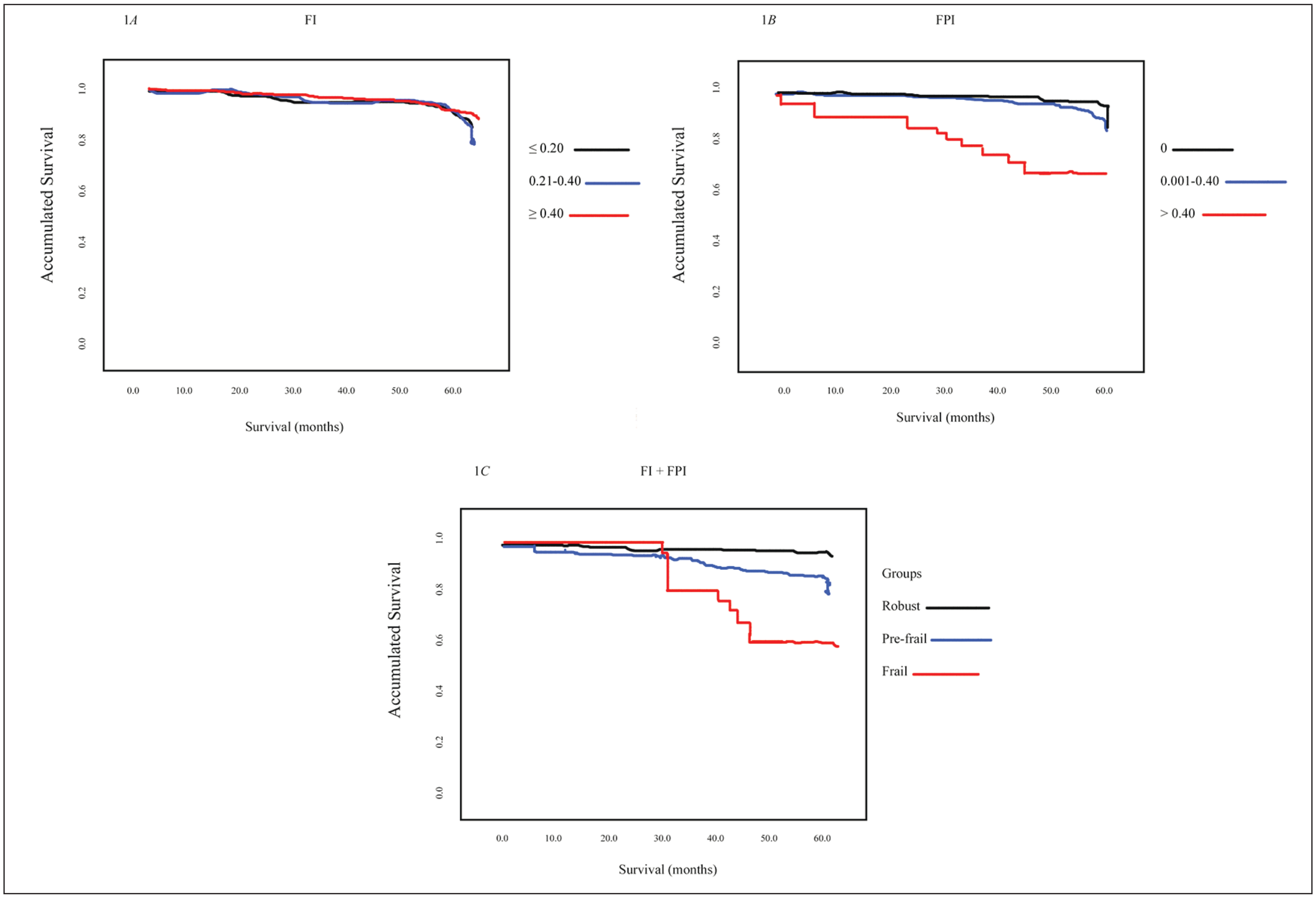
Frailty Phenotype Index			**Frailty Index**	
		0 – 0.2	**0.21 – 0.35**	**> 0.35**
			n (%)	
0	Survivors	140 (95.9)	125 (93.3)	21 (100)
	Deaths	6 (4.1)	9 (6.7)	0
0 – 0.4	Survivors	102 (87.2)	137 (90.7)	69 (100)
	Deaths	15 (12.8)	14 (9.3)	0
> 0.4	Survivors	2 (66.7)	9 (69.3)	13 (65)
	Deaths	1 (33.3)	4 (30.7)	7 (35)*

* Fisher's exact test: p < 0.001.

Fifty-six deaths (8.3%) occurred during follow up. The univariate Cox regression analysis revealed that individuals classified as frail using the FPI had a 6.2-fold greater risk of death than those classified as robust. The risk of death was tenfold greater among older adults classified as frail by the FPI using a multivariate analysis (Table 2). No association was seen between the FI and mortality.

The sample was stratified into nine groups based on the scores obtained on the two frailty measures. As displayed in Table 3, a greater prevalence rate of death was found among the individuals classified as frail both by the FPI (> 0.4) and the FI (> 0.35). In the Kaplan-Meier survival analysis, no

Figure 2
Survival curve for frailty index (2A), frailty phenotype index (2B) and both indices combined (2C)



difference was found among the older adults classified using the FI (Figure 2A), whereas individuals classified as frail by the FPI had a shorter survival rate in comparison to those classified as pre-frail and robust (Figure 2B). In Figure 2C, the sample was grouped based on the scores obtained on both indices. Individuals classified as frail by both the FI and FPI had a shorter survival rate in comparison to those classified as pre-frail and robust.

Discussion

In the present longitudinal study, we aimed to compare the predictive value for mortality of two frailty models, namely the frailty phenotype and a 35-items frailty index, in a population-based sample of older adults from a middle-income country. We found that phenotype model showed a 10-fold relative risk of death. The FI did not show a statistically significant risk. The lowest survival rate was found in the group of older adults classified as frail based on the FPI and classified as pre-frail and robust based on the FI.

The prevalence rates of frailty found in the present study are comparable to those reported in the scientific literature. In the Survey of Health, Ageing and Retirement in Europe (SHARE) (19) involving 10 countries and a sample of 7510 individuals aged 65 years or older, the prevalence of frailty based on the model described by Fried and colleagues (1) ranged from 5.8 to 23%. In a systematic review conducted by Shamlyian and colleagues (11), the prevalence of frailty ranged from 6.9 to 42.7% using the frailty phenotype and from 14.6 to 44.7% using the frailty index. Genetic factors, sociodemographic characteristics, living habits and health conditions can exert an influence on the identification of frail and non-frail older adults in models that use specific biological criteria as well as those that include different domains in the analysis of frailty (8, 11, 15, 19, 20). Measures that include multiple domains, such as the model of accumulated deficits, address the notion of variability in individual components and the classification of frailty in the populations investigated (11, 16, 17, 20).

Frailty is strongly associated with lower survival rates (11). In the survival analysis of the CHS, older adults with three or more components of the frailty phenotype had a lower survival rate than those with two or no components (1). In the study conducted by Kulminski and colleagues (12),12 older adults who answered positively for three or more components of the frailty phenotype had a shorter survival rate than those classified as pre-frail or non-frail. In the comparison of the frailty index and frailty phenotype, the authors found that the former measure was more robust at predicting mortality than the latter. However, the lowest survival rate was found in the subgroup composed of individuals classified as frail by both measures. Rockwood and colleagues report similar findings (5). In the five-year follow-up study, the mean survival rate among older adults classified as robust using the frailty phenotype was 85% for those with a score below 0.25 on the frailty index and 55% for those with higher scores on the frailty index. This reveals the moderate convergence between the frailty phenotype and FI in the detection of unfavorable health events.

The aim of the model of accumulated deficits is to evaluate individual differences in the health conditions of a population independently of chronological age (4, 6). The model is based on the accumulated effect of changes (deficit) associated with the ageing process (17). Comorbidities and disabilities are distinct conditions that compose the frailty index and a clinical evaluation is needed to determine this index (4, 12, 21). The continuous nature of the frailty index can assist in the identification and follow up of older adults who are vulnerable to frailty and adverse health outcomes and favors early intervention in pre-frail stages (21, 22). However, there is a lack of evidence on how variability in health exerts an influence on the occurrence of negative events in old age, as some clinical conditions represent a greater risk of mortality than others (23, 24). For example, older adults who have cardiovascular disease, diabetes and hypertension have lower scores on the frailty index than those with osteoporosis, those with arthritis and those who need assistance using transportation or performing household chores. However, cardiovascular disease, diabetes and hypertension are more lethal than the latter conditions. To date, there is no consensus on the cutoff point as the classificatory criteria for the FI or to characterize frail older adults in difference environmental contexts (5, 9, 12, 16, 25).

Other potential limitations of the FI must be addressed. Drubbel and colleagues performed a systematic review to evaluate the potential of the frailty index as a screening and monitoring tool of frailty in primary care (25). Among the 867 studies evaluated, 20 met the eligibility criteria for inclusion in the review, 19 of which had a longitudinal design and one had a cross-sectional design. The samples ranged from 754 to 36,424 individuals. The analysis of criteria validity demonstrated a moderate power to predict negative health events (mortality, morbidity, hospitalization, number of days of hospitalization, institutionalization, falls, fractures and disabilities with regard to basic activities of daily living). The authors also found a positive correlation between the frailty index and frailty phenotype. When the measures were compared, the frailty index demonstrated 45.9 to 60.7% sensitivity and 83.5 to 90% specificity for adverse health events. The frailty index proved to be a valid screening tool in primary care, but demonstrated only moderate discriminatory power. Its main advantage is the easy application of the measure in primary care based on the availability of a databank on health and functioning or a broad geriatric evaluation (22).

The frailty phenotype has the advantage of characterizing the clinical syndrome of frail older adults and is based on a set of predefined criteria for the evaluation of the presence or absence of signs and symptoms (1, 10). The phenotype measure requires no prior clinical evaluation and can be employed during the first contact with an older adult (1, 15, 21). Thus, the frailty phenotype can be used for the initial stratification of the risk for adverse events based on the profile classification (robust, pre-frail and frail) (1). However, the classification of an older adult as frail using this model does not reveal the underlying causes of risk, which hinders the development of specific intervention protocols (21). The group coordinated by Fried found that there is no perfect overlap among frailty, comorbidities and disabilities (1). In the CHS, 46% of older adults considered frail had comorbidities and 27% had no diseases or disabilities, which suggests that there may be distinct pathways to frailty – one stemming from the presence of diseases and another resulting from the physiological changes associated with the ageing process (1).

The model of the frailty phenotype can be easily applied in the clinical setting due to the fact it is composed of five criteria that have been very well described in the literature (1, 22). However, a factor that may limit the use of this assessment tool regards the collection of objective measures of the phenotype. Thus, this model may not be viable for use, especially in primary care, as it requires the availability of the dynamometer (grip strength) and adequate physical space for the evaluation of gait speed (21, 25).

Limitations of the current study must be stressed. The model adopted by the FIBRA Study for the characterization of frailty was that described by Fried and colleagues (1, 15). For the sake of convenience, the data of the FIBRA Study were collected in a recreational setting located in the community that was well known by the participants and easily accessed. Among the limitations, we can mention the exclusion of bedridden and institutionalized elderly persons, which may have led to the underestimation of the mortality rate. Likewise, the use of the Mini Mental State Examination for the second phase of the data collection process in the FIBRA Study clearly led to the selection of older adults with more preserved cognition. Another element that could have limited the validity of this study was the collection of mortality data. Since the Mortality Information System of the city of Campinas does not register the deaths of its citizens that occur in other cities, it is possible that the mortality rate may have been slightly underestimated. It is possible that the total number of deaths in the period have been insufficient to verify the associations intended for of the variables investigated. It is estimated that 3 to 5% of deaths among older adults could be delayed if frailty were prevented

(11). However, the differences in frailty assessment measures hamper the synthesis of evidence. The characterization of frailty profiles using validated, widely employed assessment tools in the literature is fundamental to the adoption of intervention measures. One promising idea is the combination of both measures in an effort to enhance the precision in the identification of older adults who are more vulnerable to adverse health events. The development of the integration of concepts that unites researchers from different fields could help overcome the shortcomings. A hypothetical future model of frailty in older adults should probably not be as restrictive as the physical phenotype, but also not as broad as the index derived from multiple domains (21, 22, 26, 27).

For the purposes of the present study, the model of the frailty phenotype proved to be more accurate in determining the risk of mortality than the model of the frailty index. This is the first study to compare frailty measures with regard to mortality among Brazilian community-dwelling older adults. Despite its limitations, this study offers methodological contributions regarding the relationship between frailty and adverse health events in the Brazilian population.

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Conflicts of interest: none.

Ethical standards: We have followed international ethical standards and the study was Nationally approved by ethical committee.

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