

Health-related and socio-demographic factors associated with frailty in the elderly: a systematic literature review

Fatores sociodemográficos e de saúde associados à fragilidade em idosos: uma revisão sistemática de literatura

Factores sociodemográficos y de salud asociados con la fragilidad en ancianos: una revisión sistemática de la literatura

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Abstract

Frailty is a syndrome that leads to practical harm in the lives of elders, since it is related to increased risk of dependency, falls, hospitalization, institutionalization, and death. The objective of this systematic review was to identify the socio-demographic, psycho-behavioral, health-related, nutritional, and lifestyle factors associated with frailty in the elderly. A total of 4,183 studies published from 2001 to 2013 were detected in the databases, and 182 complete articles were selected. After a comprehensive reading and application of selection criteria, 35 eligible articles remained for analysis. The main factors associated with frailty were: age, female gender, black race/color, schooling, income, cardiovascular diseases, number of comorbidities/diseases, functional incapacity, poor self-rated health, depressive symptoms, cognitive function, body mass index, smoking, and alcohol use. Knowledge of the complexity of determinants of frailty can assist the formulation of measures for prevention and early intervention, thereby contributing to better quality of life for the elderly.

Frail Elderly; Quality of Life; Risk Factors

Resumo

A fragilidade é uma síndrome que gera prejuízos práticos à vida do idoso, pois está relacionada à maior risco de dependência, quedas, hospitalização, institucionalização e morte. O objetivo desta revisão sistemática foi identificar os fatores socio-demográficos, psicocomportamentais, de condições de saúde, estado nutricional e estilo de vida associados à fragilidade em idosos. Quatro mil cento e oitenta e três trabalhos publicados entre 2001 e 2013 foram detectados nas bases bibliográficas e selecionados 182 artigos completos. Após a leitura integral e aplicação dos critérios de seleção, restaram 35 artigos elegíveis para análise. Os principais fatores associados foram: idade, sexo feminino, raça/cor da pele preta, escolaridade, renda, doenças cardiovasculares, número de comorbidades/doenças, incapacidade funcional, autoavaliação de saúde ruim, sintomas depressivos, função cognitiva, índice de massa corporal, tabagismo e uso de álcool. O conhecimento da complexidade dos determinantes da fragilidade auxilia na formulação de ações de prevenção e intervenção precoce, garantindo maior qualidade de vida.

Idoso Fragilizado; Qualidade de Vida; Fatores de Risco

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Introduction

Frailty in the elderly is defined as a clinical syndrome characterized by a decrease in energy reserve, strength, and performance, resulting in a cumulative decline in multiple physiological systems, leading to a state of greater vulnerability^{1,2}. This condition causes practical harm to the life of elders and their families, both clinically and psychosocially, since it is associated with greater risk of adverse consequences such as dependency, falls, hospitalization, institutionalization, and death^{1,2,3,4,5}. Prevalence in Americans is 6.3%², and in Brazilians it varies from 10 to 25% in persons above 65 years and 46% above 85 years⁴.

The syndrome should not be confused with functional dependency or comorbidity. Frailty refers to the fact that a person needs help or requires assistance to perform an activity, or fails to perform it. Individuals are classified as dependent when they need help from someone else or are unable to perform a task^{3,6}. Meanwhile, comorbidity is a general concept that encompasses the presence of several diagnosed illnesses³.

Studies have focused on understanding the causes and pathophysiology of frailty, defining and improving criteria to identify elderly at risk and analyzing factors that influence development of the syndrome. There are different definitions for the identification of frailty. The most widely used is that of Fried et al.², who define frail elderly as those with three or more of the following indicators: unintentional weight loss, low level of physical activity, reduced grip strength, reduced gait speed, and self-reported fatigue. Another criterion that has been discussed in the scientific literature is that of Rockwood et al.⁷, which adds cognitive and emotional aspects to the diagnostic indicators. There are still other criteria, with no consensus in the academic community on the best approach to diagnosis; however, in a recently published report¹, experts agreed that health professionals should choose a well-validated model among the existing ones.

Since the factors related to the syndrome are not fully known, it is extremely important to understand it in order for targeted measures to be planned and implemented. Many of these health problems can be prevented at the primary care level, as long as healthcare professionals are alert to the determinant factors for the syndrome and aware of the importance of early detection. Studies have shown that various physiological, socio-demographic, psychological, and nutritional factors may be involved in the origin of frailty, in addition to related comorbidities^{5,8,9}.

The current systematic review aims to identify socio-demographic, psycho-behavioral, health-related, nutritional, and lifestyle factors associated with frailty in the elderly.

Methods

Databases and search strategy

Articles published from 2001 to 2013 were selected from the following databases: MEDLINE via PubMed, Scopus, LILACS, and ISI Web of Knowledge. The descriptors and MeSH terms consulted in the search engines were: “age factors” OR “risk factors” OR “socioeconomic factors” OR “demographic factors” OR “clinical factors”, “biological factors” OR “behavior factors” OR “elderly nutrition” OR “nutrition”, “health status” OR “epidemiological factors” OR “elder nutritional physiological phenomena” in the field all words in the literature bases, in combination using the Boolean connector *AND* with “aging” OR “aged” OR “elderly” OR “senescence”, in the field all words and associated by the Boolean connector *AND* with “frail elderly” OR “frailty” OR “fragility” OR “elderly frail” OR “frail older adults” in the field Title and/or *abstract + key words*. Articles in English, Spanish, and Portuguese were selected.

Selection criteria

The review used the following selection criteria: original scientific articles published in Brazilian or international periodicals; publication from 2001 to March 2013; study population 60 years or older; observational study design (cross-sectional, cohort, or case-control); individual selection by probabilistic sample or article showing the sampling design; and identification of factors associated with frailty in the elderly as the principal or secondary objective.

Importantly, there are different diagnostic criteria for frailty, with no consensus in the literature as to the most adequate markers for its identification. However a widely used and well-accepted criterion in the scientific community is that of Fried et al.², published in 2001. Based on a study of Americans participating in the *Cardiovascular Health Study*, the group proposed that the syndrome’s pathophysiology can be identified by a phenotype, using five measurable components:

- Self-reported unintentional weight loss of 4.5kg or 5% of body weight in the previous year;
- Self-reported fatigue assessed by the following: “I felt tired all the time” and “I could not get

going”, from the depression scale of the Center for Epidemiological Studies (CES-D) ¹⁰;

- Decreased grip strength, measured with a dynamometer in the dominant hand, stratified by gender and body mass index (BMI) quartiles;
- Low level of physical activity measured as weekly energy expenditure in kcal, with information obtained from the reduced version of the *Minnesota Leisure Time Activity Questionnaire* ¹¹, stratified by gender;
- Decreased gait speed in seconds, calculated by recording the time to walk 4.6m at a comfortable pace, stratified by gender and mean height.

The presence of three or more components defines a frail elder. The presence of one to two identifies those at high risk of developing the syndrome (pre-frail). We only selected articles that reported using this criterion to identify frailty, so the article search began in 2001, the year this definition was published.

Data extraction

Article selection and data extraction were performed independently by three reviewers, using

a standardized instrument containing: country and study site; sampling number; type of sample; study design; characteristics of sample member; study variables; criterion used to identify frailty; statistical technique; principal results; and limitations.

Assessment of risk of bias

Assessment of the articles included in the analysis used verification of the risk of bias, as suggested by the Cochrane Collaboration ¹². To orient the assessment of this risk, an adapted version of the *Newcastle-Ottawa Scale* ¹³ was used (Table 1). The original *Newcastle-Ottawa Scale* was developed to assess the quality of observational studies and contains eight items that analyze three dimensions: selection, comparability, and outcome (in the case of cohort studies) or exposure (case-control). For each item there is a series of options in which the one that best reflects quality is marked with a star; the more the stars, the higher the study's quality ¹⁴. In the current study, questions were adjusted to investigate exposure and outcome (frailty according to the definition

Table 1

Adaptation of the *Newcastle-Ottawa Scale* ¹³ to assess quality of studies using the definition of frailty according to Fried et al. ² as the outcome variable.

Exposure	
Independent variables	a) Secure recording + primary measurements * (<i>low risk of bias</i>) b) Structured interview + primary measurements, without knowledge of outcome * (<i>low risk of bias</i>) c) Interview with knowledge of outcome (<i>high risk of bias</i>) d) Non-secure sources and self-assessment (<i>high risk of bias</i>) e) Does not describe clearly (<i>uncertain risk of bias</i>)
Outcome	
Is the assessment of frailty adequate?	a) Yes, according to Fried et al. ² * (<i>low risk of bias</i>) b) Yes, with some changes (2 or 1 components) (<i>uncertain risk of bias</i>) c) Yes, with many changes (3 or more components) (<i>high risk of bias</i>) d) Does not describe clearly (<i>uncertain risk of bias</i>)
Representativeness of sample	a) Representative of local population * (<i>low risk of bias</i>) b) Possibility of selection bias (<i>high risk of bias</i>) c) Does not describe clearly (<i>uncertain risk of bias</i>)
Selection of participants	a) Community * (<i>low risk of bias</i>) b) Hospital or part of hospital sample (<i>high risk of bias</i>) c) Does not describe clearly (<i>uncertain risk of bias</i>)
Definition of the control group or cohort (only for longitudinal studies)	a) Without previous history of the syndrome * (<i>low risk of bias</i>) b) Does not describe clearly (<i>uncertain risk of bias</i>)

* Represents an item for classification of low risk of bias.

by Fried et al. 2), and risk of bias was divided into low risk of bias, uncertain risk of bias, and high risk of bias, according to the item being assessed. Each star represents an item for classification of low risk of bias.

Results

The literature search identified 4,183 publications. Of these, we eliminated 629 duplicates that came from two or more databases, and after reading the titles and abstracts, 3,372 were ruled out because frailty was an independent variable, the study was designed as an intervention, review, or validation of a diagnostic criterion, or the

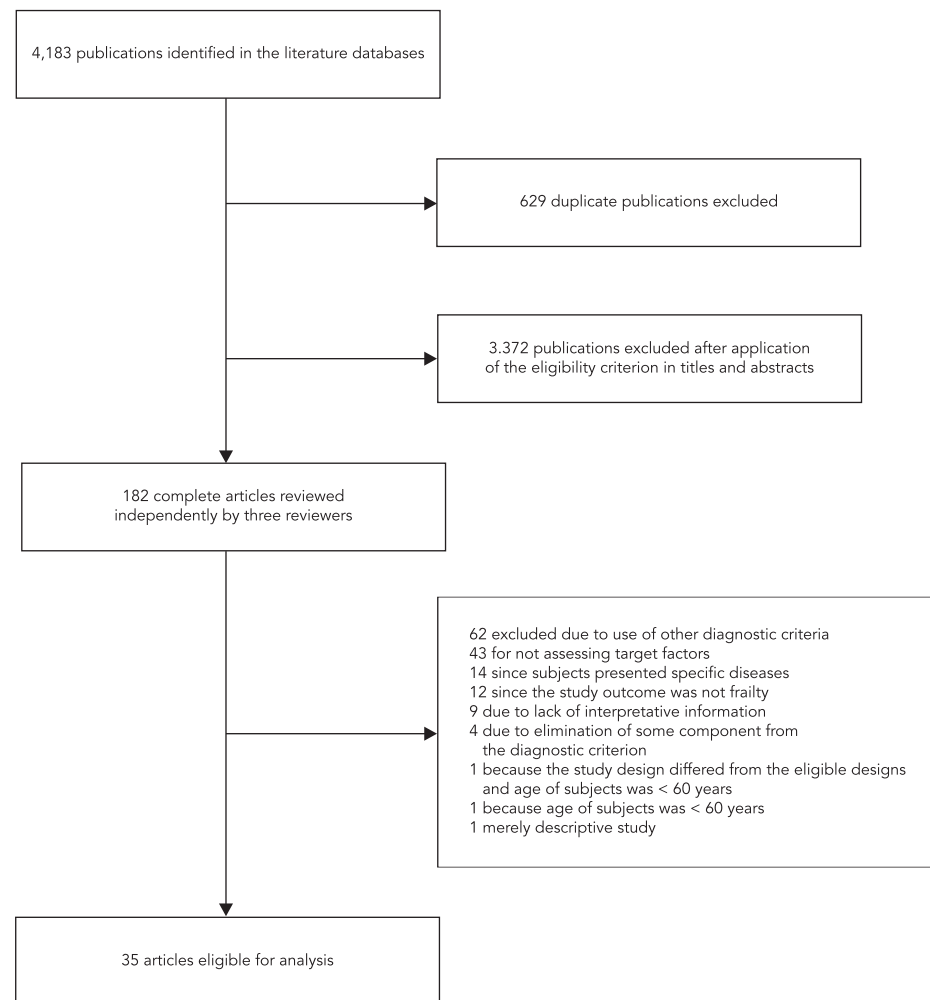
publication was a book or journal commentary or editorial. A total of 182 complete articles were selected for analysis. After reading them and applying the selection criteria, 35 eligible articles were left. Figure 1 shows the study selection flow.

Overall study characteristics

In the 35 studies, the data collection period ranged from 1989 to 2011. The year with the most publications was 2012 (n = 10). Most studies were on North American participants (n = 12), followed by Europeans (n = 11), Latin Americans (n = 9), and Asians (n = 3). The number of subjects varied from 77 to 40,657, and most studies had samples greater than 600 individuals. Age of

Figure 1

Flow chart for selection of articles for analysis.



the elderly was greater than 65 years, except for three studies, in which it was greater than 60. The results analyzed in this article are mainly from cross-sectional studies (n = 27).

Table 2 shows details on the main characteristics of the 35 studies, with the design, independent variables, statistical technique, principal results, and limitations listed by authors.

The most widely studied independent variables were demographic (n = 33), diseases and health conditions (n = 30), socioeconomic (n = 30), psycho-behavioral (n = 23), and nutritional (n = 17), and the least studied were lifestyle variables (n = 11). The majority of the studies used logistic regression models (n = 24). All the results presented here were statistically significant.

Demographic and socioeconomic factors and frailty

Of the 35 studies, demographic factors were assessed by 33 and socioeconomic factors by 30. The most frequently assessed demographic variable was age (n = 31) and the most common socioeconomic value was schooling or educational level (n = 27). In general, age, black race/color, and female gender showed a positive association with frailty, while there was an inverse association between frailty and schooling and income.

Diseases, health conditions, and frailty

The principal diseases assessed by the studies were cardiovascular diseases (CVD) (n = 17), diabetes mellitus (n = 17), systemic arterial hypertension (SAH) (n = 14), pulmonary diseases (n = 10), arthritis (n = 11), cancer (n = 8), and stroke (n = 7). Fourteen studies also included comorbidities/diseases as an independent variable. Frailty showed a positive association especially with CVD and number of comorbidities/diseases. As predicted, no disease showed an inverse association with frailty or was considered to have a protective effect.

Sixteen studies investigated functional status, measured mainly by activities of daily living (ADL) and instrumental activities of daily living (IADL), and diagnosis of functional incapacity showed a positive association with frailty in nine.

Eight studies analyzed self-rated health and found a positive association between poor self-rated health and frailty.

Psycho-behavioral factors and frailty

Depressive symptoms were assessed in 17 studies, and cognitive function was tested in 15. The instrument most widely used to assess cognitive

function was the *Mini Mental State Examination* (MMSE)¹⁵, and the elderly that tested highest were considered to have the best cognitive function. An inverse association was found between cognitive function and frailty, while depressive symptoms showed a positive association with the syndrome.

Nutritional status, lifestyle and frailty

The most widely assessed nutritional variable was BMI (n = 13). Lifestyle factors were the least analyzed in the selected articles and included smoking (n = 10), alcohol consumption (n = 6), and physical activity (n = 2). A positive association was found between smoking and frailty in two studies, and an inverse association was observed between alcohol and frailty in three studies. Most of the studies found a positive association between frailty and BMI, and two studies showed that underweight elderly according to BMI had a positive association with frailty.

Limitations listed by the authors of the articles analyzed in the final sample

The limitations most frequently cited by the authors of the selected articles were: cross-sectional design (not allowing causal inferences); adaptations of scales suggested by Fried et al.²; and self-reporting of data.

Assessment of risk of bias

Table 3 summarizes the assessment of risk of bias in the studies, and Figure 2 shows the graph for each question in the adapted *Newcastle-Ottawa Scale*¹³.

In relation to analysis of the risk of bias, 34 studies collected information on the independent variables using a structured interview, anthropometric measurements, and clinical tests (low risk of bias), and only one failed to clearly describe the method (uncertain risk of bias).

As for participant selection, all were local community-dwelling, non-institutionalized elders (low risk of bias).

More than half of the studies (n = 19) showed changes in three or more of the components in the criterion adopted by Fried et al.² (high risk of bias).

Only one article mentioned that the sample was representative of the local population (low risk of bias).

Only one of the longitudinal studies (n = 7) specified that the sample did not present the syndrome at the beginning of the cohort (low risk of bias).

Table 2

Factors associated with frailty in the elderly according to observational studies.

Article (year)	Study design	Independent variables	Statistical technique	Variables used in adjustment of final model	Principal results		Methodological limitations according to the authors
					Positive association with frailty	Inverse association with frailty	
Fried et al. ² (2001)	Longitudinal	Demographic: age, gender, race Socioeconomic: schooling, income, living alone Diseases and health conditions: number of diseases, comorbidities (CVD, COPD, SAH, diabetes mellitus, arthritis, cancer) Psycho-behavioral: cognitive function, depressive symptoms Other: ADL, IADL, self-rated health, functional incapacity	Cochran-Mantel-Haenszel test	Age	Female gender, black race, poor self-rated health, living alone, number of diseases (2 or more), CVD, lung diseases, arthritis and diabetes, functional incapacity and depressive symptoms	Income, schooling and cognitive function	Measures used in operationalization of the frailty criterion were limited to those used during the data collection for other study purposes; weight at the beginning of study was self-reported
Newman et al. ²⁷ (2001)	Longitudinal	Demographic: age, gender, race Socioeconomic: schooling, income Diseases and health conditions: CVD Psycho-behavioral: cognitive function, depressive symptoms Other: ADL, IADL, self-rated health, functional incapacity	Bivariate analysis and multinomial logistic regression	Age, gender and race	Female gender, black race, CVD	Income, schooling and cognitive function	Use of self-reported measures; few details on fatigue and energy expenditure (Kcal); cross-sectional study, does not allow causal inferences

(continues)

Table 2 (continued)

Article (year)	Study design	Independent variables	Statistical technique	Variables used in adjustment of final model	Principal results		Methodological limitations according to the authors
					Positive association with frailty	Inverse association with frailty	
Blaum et al. ³³ (2005)	Cross-sectional	Demographic: age, gender, race Socioeconomic: schooling Diseases and health conditions: CVD, COPD, osteoarthritis Nutritional status: BMI Other: functional status (ADL and IADL)	Multinomial logistic regression	All variables listed	Pre-frailty and frailty: overweight/obesity	-	-
Woods et al. ²⁹ (2005)	Longitudinal	Demographic: age, race Socioeconomic: schooling, income, living alone Diseases and health conditions: comorbidity (CVD, SAH, diabetes mellitus, fractures, COPD, arthritis, stroke) Lifestyle: smoking, alcohol use Nutritional status: BMI Psycho-behavioral: depressive symptoms Other: functional status (ADL)	Bivariate analysis and multivariate logistic regression	All	Age, black and Hispanic race, underweight and overweight/obesity (BMI), comorbidities, depressive symptoms, history of fall, functional incapacity, poor self-rated health, smoking	Income, schooling, living alone, alcohol use	Lack of information on physical activity and unintentional weight loss; study limited to sample of women, not possible to make inferences for men; low cognitive function may be confounder
Hirsch et al. ²⁵ (2006)	Cross-sectional	Demographic: age, gender, race Socioeconomic: schooling, income Diseases and health conditions: CVD, SAH, COPD, diabetes mellitus and arthritis Psycho-behavioral: cognitive function Nutritional status: BMI	Multinomial logistic regression	Gender and obesity	Non-obese blacks	-	Cross-sectional study, does not allow causal inferences; possible selection bias in subject recruitment; introduction of bias by excluding individuals with missing data

(continues)

Table 2 (continued)

Article (year)	Study design	Independent variables	Statistical technique	Variables used in adjustment of final model	Principal results		Methodological limitations according to the authors
					Positive association with frailty	Inverse association with frailty	
Michelon et al. ¹⁷ (2006)	Cross-sectional	Demographic: age, race, marital status Socioeconomic: schooling, income Lifestyle: smoking, alcohol use Nutritional status: BMI, self-reported weight loss and low appetite Other: functional incapacity, self-rated health	Bivariate analysis	-	Age, black race, widowhood, smoking, self-reported weight loss, low appetite, use of dentures, problems with swallowing, poor self-rated health, BMI, functional incapacity	Income, schooling, alcohol use	Cross-sectional study, does not allow causal inferences; non-inclusion of dietary analyses
Semba et al. ³⁴ (2006)	Longitudinal	Demographic: age, race, marital status Socioeconomic: schooling, income Lifestyle: smoking, alcohol use Nutritional status: BMI, self-reported weight loss and low appetite Other: functional incapacity, self-rated health	Bivariate analysis	-	Age, CVD, low appetite	BMI, schooling	-
Ávila-Funes et al. ¹⁶ (2008)	Longitudinal	Demographic: age, gender, race, marital status Socioeconomic: schooling, income, living alone Diseases and health conditions: CVD, COPD, diabetes mellitus, SAH, cancer and arthrosis Lifestyle: smoking, alcohol use Psycho-behavioral: cognitive function and depressive symptoms Nutritional status: food intake Other: functional incapacity, self-rated health	Bivariate analysis	-	Age, female gender, chronic diseases, functional incapacity, depressive symptoms, poor self-rated health	Schooling, income, cognitive function, alcohol use and smoking	Adaptation of scale from Fried et al. ² for weight loss and grip strength

(continues)

Table 2 (continued)

Article (year)	Study design	Independent variables	Statistical technique	Variables used in adjustment of final model	Principal results		Methodological limitations according to the authors
					Positive association with frailty	Inverse association with frailty	
Alvarado et al. ³⁹ (2008)	Cross-sectional	Demographic: age, gender, marital status Socioeconomic: schooling, socioeconomic status Diseases and health conditions: comorbidities, childhood and adulthood diseases Lifestyle: physical activity Other: social history	Logistic regression	Social history, comorbidity, gender, childhood diseases, schooling, occupation, marital status, socioeconomic status	Female gender	Living conditions in childhood	Adaptation of scale from Fried et al. ² for weight and gait speed; absence of mortality study; recall bias for information on poverty in childhood
Chaves et al. ³⁵ (2008)	Cross-sectional	Demographic: age, race Diseases and health conditions: CVD, diabetes mellitus Psycho-behavioral: cognitive function, depressive symptoms Other: self-rated health	Multivariate logistic regression	-	Age, depressive symptoms, CHF	-	Cross-sectional study, does not allow causal inferences
Endeshaw et al. ⁴⁰ (2009)	Cross-sectional	Demographic: age, race Diseases and health conditions: SAH, diabetes mellitus, CVD, stroke Psycho-behavioral: cognitive function Nutritional status: BMI Other: functional status (ADL)	Multivariate logistic regression	-	In men: age, black race, CVD, stroke In women: age, obesity	-	Cross-sectional study, does not allow causal inferences

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Table 2 (continued)

Article (year)	Study design	Independent variables	Statistical technique	Variables used in adjustment of final model	Principal results		Methodological limitations according to the authors
					Positive association with frailty	Inverse association with frailty	
Masel et al. ²⁶ (2009)	Cross-sectional	Demographic: age, gender, marital status Socioeconomic: schooling, difficulty paying expenses Diseases and health conditions: CVD, stroke, arthrosis, SAH, diabetes mellitus, fractures, number of comorbidities Nutritional status: BMI Other: quality of life	Bivariate analysis	-	Age, chronic diseases, arthritis, underweight (BMI), low quality of life	Married, schooling, overweight (BMI)	Cross-sectional study, does not allow causal inferences; ethnic homogeneity; some variables self-reported
Ottenbacher et al. ⁴¹ (2009)	Longitudinal	Demographic: age, gender, marital status Socioeconomic: financial status, schooling Diseases and health conditions: CVD, stroke, arthritis, cancer, diabetes mellitus Lifestyle: smoking Nutritional status: weight, height Psycho-behavioral: cognitive function and depressive symptoms Other: functional status (ADL, IADL)	Multiple linear regression	All, in 3 models	Age, history of smoking, diabetes mellitus, arthritis, BMI, depression, number of comorbidities	Cognitive function	Conditions and comorbidities self-reported; original sample excludes individuals that did not complete the performance tests required to calculate frailty construct. Persons that remained in the study represented the healthier members of the original sample
Szanton et al. ³⁶ (2009)	Cross-sectional	Demographic: age, race Socioeconomic: schooling Diseases and health conditions: number of chronic diseases Nutritional status: BMI Lifestyle: smoking	Bivariate analysis	-	Age, BMI	Schooling	Cross-sectional study, does not allow causal inferences

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Table 2 (continued)

Article (year)	Study design	Independent variables	Statistical technique	Variables used in adjustment of final model	Principal results		Methodological limitations according to the authors
					Positive association with frailty	Inverse association with frailty	
Wu et al. ⁴² (2009)	Cross-sectional	Demographic: age Diseases and health conditions: SAH, diabetes mellitus, CHF, osteoarthritis Psycho-behavioral: depression Nutritional status: BMI, waist/hips ratio Lifestyle: smoking	Bivariate analysis and logistic regression	-	Age, depression, waist/hips ratio (> 95cm)	-	Cross-sectional study, does not allow causal inferences; sample considered small
Alcalá et al. ¹⁸ (2010)	Cross-sectional	Demographic: age, gender, marital status Socioeconomic: schooling Diseases and health conditions: chronic diseases Other: functional status (ADL, IADL)	Logistic regression	Age, schooling, comorbidities, functional incapacity	Age (> 85 years), comorbidities, functional incapacity	Schooling	Advanced age of participants (> 71 years), different socioeconomic characteristics and lack of homogeneity in measurement of frailty criteria may have influenced the observed differences
Chang et al. ³⁷ (2010)	Cross-sectional	Demographic: age, race Socioeconomic: schooling Diseases and health conditions: CKD, lung disease, CVD, diabetes mellitus, anemia, arthritis, peripheral artery disease, total number of inflammatory diseases Psycho-behavioral: depressive symptoms	Multivariate logistic regression	Age, race, schooling	All diseases, depressive symptoms	-	Cross-sectional study, does not allow causal inferences; study limited to sample of women, cannot make inferences for men; sample with higher percentage of black women than the general population; imprecise estimate of CKD due to the diagnostic method used

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Table 2 (continued)

Article (year)	Study design	Independent variables	Statistical technique	Variables used in adjustment of final model	Principal results		Methodological limitations according to the authors
					Positive association with frailty	Inverse association with frailty	
Chen et al. 28 (2010)	Cross-sectional	Demographic: age, gender, marital status Socioeconomic: schooling Diseases and health conditions: CVD, gout, diabetes mellitus, kidney disease, COPD, osteoarthritis, osteoporosis, arthritis, osteoporosis, ulcer, cancer, SAH, cataract, liver and gall bladder disease, number of comorbidities, geriatric syndromes Psycho-behavioral: depressive symptoms Other: functional incapacity	Bivariate analysis	-	Age, female gender, absence of spouse, functional incapacity, comorbidity for chronic diseases, depression, geriatric syndromes	Schooling	-
Hubbard et al. 43 (2010)	Cross-sectional	Nutritional status: BMI, WC	Logistic regression	Age, gender, schooling, wealth/assets, smoking	WC \geq 88cm in women and \geq 102cm in men	-	Adaptation of scale from Fried et al. 2 on criterion for weight loss
Syddaal et al. 44 (2010)	Longitudinal	Demographic: age, gender Socioeconomic: socioeconomic status, schooling, number of cars, own home Lifestyle: physical activity, smoking, alcohol use	Multivariate logistic regression	Age, comorbidity, lifestyle, socioeconomic status, car	In men: number of cars, age	In men: schooling, own home In women: without own home	Cross-sectional study, does not allow causal inferences; did not assess other socioeconomic variables like income; analysis of information bias: age and behaviors such as smoking and social factors such home ownership suffer neighborhood influence

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Table 2 (continued)

Article (year)	Study design	Independent variables	Statistical technique	Variables used in adjustment of final model	Principal results		Methodological limitations according to the authors
					Positive association with frailty	Inverse association with frailty	
Szanton et al. ³⁸ (2010)	Cross-sectional	Demographic: age, race Socioeconomics: schooling, income, number of home, poverty Diseases and health conditions: number of chronic diseases Lifestyle: smoking	Multinomial logistic regression	Race, schooling, smoking, state of insecurity, number of chronic diseases	Black race	Schooling, income	Cross-sectional study, does not allow causal inferences; only considered white and black races
Drey et al. ⁴⁵ (2011)	Cross-sectional	Demographic: age, gender Socioeconomic: schooling Psycho-behavioral: cognitive function, depressive symptoms Other: quality of life	Bivariate analysis	-	Number of diseases, depressive symptoms	Cognitive function, quality of life	-
Giménez et al. ⁴⁶ (2011)	Cross-sectional	Demographic: age, gender Socioeconomic: marital status, schooling, income, living alone Nutritional status: not malnourished / malnourished (MNA) Diseases and health conditions: comorbidity Psycho-behavioral: depressive symptoms Other: functional status (ADL, IADL)	Bivariate analysis	-	Female gender, comorbidity, depressive symptoms, functional dependency, malnutrition	-	Cross-sectional study, does not allow causal inferences

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Table 2 (continued)

Article (year)	Study design	Independent variables	Statistical technique	Variables used in adjustment of final model	Principal results		Methodological limitations according to the authors
					Positive association with frailty	Inverse association with frailty	
Garcia-Garcia et al. 47 (2011)	Cross-sectional	Demographic: age, gender Socioeconomic: conjugal status, mean years of schooling, educational level Diseases and health conditions: comorbidities (SAH, diabetes mellitus, CVD, COPD, peptic ulcer, fractures, osteoporosis, arthritis, dementia, Parkinson, cancer, osteoporosis, osteoarthritis, kidney, thyroid, and liver diseases, high cholesterol, stroke) Psycho-behavioral: cognitive function, depressive symptoms Other: functional status (ADL, IADL)	Bivariate analysis	-	Age, CVD, Parkinson, stroke, dementia, COPD, hip fracture, depressive symptoms, functional dependency, cognitive impairment	-	-
Hoeck et al. 48 (2011)	Cross-sectional	Demographic: age, gender Socioeconomic: socioeconomic status, schooling, income familiar, housing situation Diseases and health conditions: comorbidities Other: year of interview	Bivariate analysis and multivariate logistic regression	Age, gender, comorbidity	Comorbidities, Wallonia (Belgium), rented housing	More recent interview year, schooling, family income	-

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Table 2 (continued)

Article (year)	Study design	Independent variables	Statistical technique	Variables used in adjustment of final model	Principal results		Methodological limitations according to the authors
					Positive association with frailty	Inverse association with frailty	
Danon-Hersch et al. ⁴⁹ (2012)	Cross-sectional	Demographic: year of birth, gender Diseases and health conditions: number of chronic diseases (CVD, stroke, diabetes mellitus, SAH, cancer, chronic respiratory disease, arthritis), self-reported disease Other: functional status (ADL, IADL)	Bivariate analysis and multivariate logistic regression	Gender, components of frailty	Number of chronic diseases, diseases self-reported (except hypercholesterolemia)	Functional capacity, year of birth	Since the analysis was from a cohort, losses of information may have occurred; differences in operationalization of the components in criterion from Fried et al. ²
Lakey et al. ⁵⁰ (2012)	Longitudinal	Psycho-behavioral: depressive symptoms	Multinomial logistic regression	Age, income, schooling, race, living alone, BMI, self-rated health, ADL, smoking, alcohol consumption, hormone replacement therapy, SAH, diabetes mellitus, CVD, COPD, hip fracture, falls, arthritis, cancer, stroke, number of comorbidities	Depressive symptoms	-	Lack of information on indication for antidepressants, dosage, and treatment adherence

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Table 2 (continued)

Article (year)	Study design	Independent variables	Statistical technique	Variables used in adjustment of final model	Principal results		Methodological limitations according to the authors
					Positive association with frailty	Inverse association with frailty	
Bastos-Barbosa et al. ⁵¹ (2012)	Cross-sectional	Demographic: age, gender, race Socioeconomic: schooling, income, conjugal status, work Diseases and health conditions: blood pressure, number of diseases, comorbidities (SAH, dyslipidemia, osteoporosis, osteoarthritis, diabetes mellitus, hypothyroidism) Psycho-behavioral: cognitive function Nutritional status: BMI, waist circumference	Fixed-effects linear models and ANOVA	Age, gender	Systolic and diastolic pressure, waist circumference	-	Selection of frail and non-frail participants according to specific criteria, which does not allow extrapolating to other elderly; small sample: results cannot be extrapolated to populations with very different living conditions
Jürschik et al. ⁵² (2012)	Cross-sectional	Demographic: age, gender, race Socioeconomic: schooling, income, conjugal status, work, living alone Diseases and health conditions: number of comorbidities Psycho-behavioral: cognitive function, depressive symptoms, quality of life, social relations Lifestyle: smoking, alcohol consumption Nutritional status: nutritional risk (MNA), BMI, waist circumference Other: functional status (ADL, IADL), self-rated health	Bivariate analysis and logistic regression	-	Age, female gender, conjugal status widowed or single, smoking, alcohol consumption, number of comorbidities, functional incapacity, depressive symptoms, cognitive decline, risk of malnutrition, visual impairment, poor self-rated health	Social interaction, quality of life	Modification of criterion for unintentional weight loss; cross-sectional study, does not allow causal inferences

(continues)

Table 2 (continued)

Article (year)	Study design	Independent variables	Statistical technique	Variables used in adjustment of final model	Principal results		Methodological limitations according to the authors
					Positive association with frailty	Inverse association with frailty	
Chang et al. ⁵³ (2012)	Cross-sectional	Demographic: age, gender Socioeconomic: Living alone Diseases and health conditions: blood pressure, number of comorbidities, diseases (SAH, diabetes mellitus, CVD, arthritis, peptic ulcer) Psycho-behavioral: cognitive function, depressive symptoms, health-related quality of life, social relations	Bivariate analysis and multivariate regression analysis	Age, number of comorbidities, living alone, falls in previous year, arthritis, peptic ulcer, depression	Age, number of comorbidities, living alone, arthritis, peptic ulcer, depression	Components of health-related quality of life scale, like physical and mental	Cross-sectional study, does not allow causal inferences; study population predominantly urban, which does not allow extrapolating the findings to the rural population; small sample of frail elderly; lack of specific cutoff points for components of the diagnostic criterion for frailty in the study population; low response rate due to exclusion of many comorbidities
Sousa et al. ⁵⁴ (2012)	Cross-sectional	Demographic: age, gender, race Socioeconomic: conjugal status, family arrangement, household situation, schooling, monthly income, occupation Diseases and health conditions: comorbidities, chronic diseases (SAH, diabetes mellitus, CVD, malignant tumors, arthritis or rheumatism, lung diseases, stroke, osteoporosis) Psycho-behavioral: cognitive function, depressive symptoms Other: falls, functional status (ADL, IADL), self-rated health	Bivariate analysis and binary logistic regression	Socio-demographic factors, functional status, chronic diseases, self-rated health	Advanced age osteoporosis, stroke, depression, falls, presence of comorbidities, functional dependency, poor self-rated health	-	Cross-sectional study, does not allow causal inferences

(continues)

Table 2 (continued)

Article (year)	Study design	Independent variables	Statistical technique	Variables used in adjustment of final model	Principal results		Methodological limitations according to the authors
					Positive association with frailty	Inverse association with frailty	
Neri et al. ⁵⁵ (2012)	Cross-sectional	Demographic: age, gender Socioeconomic: family income, family arrangement Diseases and health conditions: number of chronic diseases (SAH, diabetes mellitus, CVD, cancer, arthritis or rheumatism, ischemia, stroke, depression, osteoporosis) Psycho-behavioral: cognitive function, depressive symptoms Other: perception of social support, social isolation	Bivariate analysis and univariate and multivariate logistic regression	-	No factors significantly associated with frailty were found	-	Cross-sectional study, does not allow causal inferences; difficulty in controlling each variable's effect; limitations in design and sample size; unequal number of men and women in sample; lack of information on care
Schnittger et al. ⁵⁶ (2012)	Cross-sectional	Demographic: age, gender Socioeconomic: educational level, living alone Diseases and health conditions: age-adjusted comorbidity index Psycho-behavioral: cognitive function, psychological status Nutritional status: nutritional risk (MNA), BMI Other: functional status (ADL, IADL)	Bivariate analysis and Kaiser-Meyer-Olkin test	-	Psychological distress (mood, stress, neuroticism, and emotional loneliness)	-	Cross-sectional study, does not allow causal inferences; dimensions of psychological distress measured are specific to the study population, and cannot be generalized to other population

(continues)

Table 2 (continued)

Article (year)	Study design	Independent variables	Statistical technique	Variables used in adjustment of final model	Principal results		Methodological limitations according to the authors
					Positive association with frailty	Inverse association with frailty	
Casale-Martínez et al. 57 (2012)	Cross-sectional	Socioeconomic: educational level, parents' educational level, conjugal status, household assets and situation, socioeconomic status, employment benefits, occupational history, friends and family members living in the same neighborhood, financial support Diseases and health conditions: childhood history Psycho-behavioral: ability to make important decisions Other: religion, volunteer work, abuse	Multinomial logistic regression	-	Not having companion, not making important decisions, poor economic status, abuse	Employment benefits	-
Macuco et al. 58 (2012)	Cross-sectional	Demographic: age, gender Socioeconomic: years of schooling, monthly family income Psycho-behavioral: cognitive function, loneliness, adverse life events Other: functional status (IADL)	Bivariate analysis and univariate and multivariate linear regression	-	Age	Cognitive function, years of schooling, monthly family income	Rigid exclusion criteria; high number of younger elderly in the sample; cross-sectional study, no follow-up of cohort

ADL: activities of daily living; BMI: body mass index ; CHF: congestive heart failure; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; IADL: instrumental activities of daily living; MNA: mini nutritional assessment; SAH: systemic arterial hypertension; WC: waist circumference.

Note: the variables and results presented here are those related to this study's objective.

Table 3

Assessment of risk of bias according to adaptation of *Newcastle-Ottawa Scale* ¹³.

Article (year)	Independent variables obtained	Is the assessment of frailty adequate?	Representativeness of sample	Participant selection	Definition of control group or cohort *
Fried et al. ² (2001)	B	B	I	B	I
Newman et al. ²⁷ (2001)	B	B	I	B	I
Blaum et al. ³³ (2005)	B	A	I	B	-
Woods et al. ²⁹ (2005)	B	A	I	B	I
Hirsch et al. ²⁵ (2006)	B	B	I	B	-
Michelon et al. ¹⁷ (2006)	B	I	I	B	-
Semba et al. ³⁴ (2006)	B	I	I	B	I
Ávila-Funes et al. ¹⁶ (2008)	B	A	I	B	I
Alvarado et al. ³⁹ (2008)	B	A	I	B	-
Chaves et al. ³⁵ (2008)	B	A	A	B	-
Endeshaw et al. ⁴⁰ (2009)	B	B	I	B	-
Masel et al. ²⁶ (2009)	B	I	I	B	-
Ottenbacher et al. ⁴¹ (2009)	B	I	I	B	I
Szanton et al. ³⁶ (2009)	B	A	I	B	-
Wu et al. ⁴² (2009)	B	A	I	B	-
Alcalá et al. ¹⁸ (2010)	B	A	B	B	-
Chang et al. ³⁷ (2010)	B	A	I	B	-
Chen et al. ²⁸ (2010)	I	A	I	B	-
Hubbard et al. ⁴³ (2010)	I	A	B	B	-
Syddaal et al. ⁴⁴ (2010)	B	A	I	B	I
Szanton et al. ³⁸ (2010)	B	A	A	B	-
Drey et al. ⁴⁵ (2011)	B	B	I	B	-
Giménez et al. ⁴⁶ (2011)	B	A	I	B	-
García-García et al. ⁴⁷ (2011)	B	I	B	A	-
Hoeck et al. ⁴⁸ (2011)	I	A	B	B	-
Danon-Hersch et al. ⁴⁹ (2012)	B	A	B	B	-
Lakey et al. ⁵⁰ (2012)	B	A	I	B	B
Bastos-Barbosa et al. ⁵¹ (2012)	B	B	I	B	-
Jürschik et al. ⁵² (2012)	B	A	I	B	-
Chang et al. ⁵³ (2012)	B	A	I	B	-
Sousa et al. ⁵⁴ (2012)	B	B	I	B	-
Neri et al. ⁵⁵ (2012)	B	B	I	B	-
Schnittger et al. ⁵⁶ (2012)	B	I	I	B	-
Casale-Martínez et al. ⁵⁷ (2012)	I	I	I	B	-
Macuco et al. ⁵⁸ (2012)	B	B	I	B	-

Classification of items: B – low risk of bias; I – uncertain risk of bias; A – high risk of bias.

* Only for longitudinal studies.

Discussion

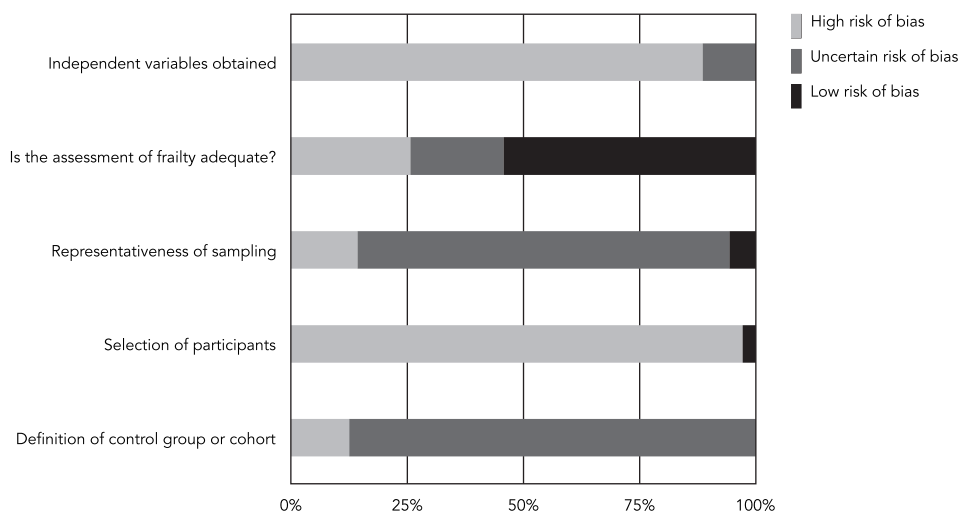
The principal socio-demographic, psycho-behavioral, health-related, nutritional, and lifestyle factors positively associated with frailty were: age, female gender, black race/color, cardiovascular diseases, number of comorbidities/diseases, functional incapacity, poor self-rated health, depressive symptoms, BMI, and smok-

ing. Inversely associated factors were schooling, income, cognitive function, and alcohol use.

Although the selected studies had different designs, sample sizes, and locations, they showed homogeneity in the relations between the demographic and socioeconomic variables and frailty. A longitudinal study of 5,317 North Americans over 65 years of age showed that prevalence of frailty was higher in the oldest old, women,

Figure 2

Graph on risk of bias in selected studies.



blacks, and low-income individuals². This association was also found in a longitudinal study of French elderly¹⁶ and in cross-sectional studies of both American and Spanish elderly^{17,18}. At more advanced ages there is an increase in pre-frail and frail elderly, suggesting that frailty is a progressive condition; the phenomenon occurs more significantly after 80 years of age. One hypothesis for this relationship between increasing age and frailty lies in the cellular oxidative stress that accumulates over the years, modulated by exogenous and endogenous agents that influence the production of reactive oxygen species, leading to DNA damage. Such damage induces alterations at the cellular and systemic levels, with deregulations in the processes of inflammation, apoptosis, necrosis, and proliferation that result in various adverse conditions that increase over the years, such as loss of muscle mass (sarcopenia), diabetes, cancer, and frailty^{19,20,21}.

The higher prevalence of frailty in women can be explained by the greater physiological muscle mass loss in females during aging, in addition to their being more prone to the development of sarcopenia, an intrinsic risk for developing the frailty syndrome⁵. Other hypotheses included women's greater longevity and the fact that they show a higher prevalence of chronic illnesses than men²².

Race is a strong conditioning factor for health status, since blacks are at a disadvantage

in relation to whites. Studies have shown that black race/color is an important indicator of low socioeconomic status and is associated with deficient health and high mortality risk^{23,24}, contributing indirectly and directly to development of the syndrome. Furthermore, some authors believe that race is a marker for genetic polymorphisms that have an influence on the emergence of frailty²⁵.

Income and schooling do not act directly in the pathophysiology of frailty, but interfere in the individual's lifestyle and quality of life and thus in factors that vary with socioeconomic status, including gender and age, which can influence the frailty process²⁵.

As for diseases associated with frailty, CVD and the presence of two or more comorbidities are relevant for the occurrence of this syndrome in the elderly. In a cross-sectional study of 1,008 elderly Mexicans, self-reported chronic diseases such as CVD, hypertension, diabetes mellitus, and arthritis were associated with frailty²⁶. A cross-sectional and longitudinal study in North Americans, but with diagnosis by clinical examination, showed an equivalent association^{2,27}. Some researchers contend that CVD and some comorbidities are related to atherosclerosis, a chronic inflammatory state that can result in systemic catabolism and other pathophysiological changes, which can contribute to the clinical manifestations of frailty^{2,27}.

A direct association was also observed between functional incapacity and frailty. Recent cross-sectional studies in both Chinese and Spanish subjects showed that a major portion of the frail elderly show functional incapacity^{18,28}. A longitudinal study in a robust sample of 5,317 elderly also showed this relationship². The authors contend that frailty can be a precursor of functional incapacity. However, one cannot overlook the possibility of reverse causality between functional capacity and frailty.

In the area of psycho-behavioral variables, decreased cognitive function and the presence of depressive symptoms have been related to frailty. Studies with different samples, (American, Mexican, and French elderly) showed increased prevalence of frailty in elders submitted to different questionnaires with scales for depression or cognitive function and that presented depressive symptoms or cognitive impairment according to the tests^{2,16,18}. Elderly with cognitive impairment probably experience greater difficulty in eating, exercising, and walking, which can lead to weight loss and decreased motor function and favor the syndrome's onset and progression. As for depressive symptoms, the literature shows that the relationship to frailty is biologically plausible, since depressed persons normally present weight loss, limited activity, and isolation, thus predisposing to progressive loss of muscle mass and strength, conditions that accelerate the establishment of the syndrome⁵.

As for nutritional and lifestyle variables, underweight elderly according to BMI and those with a higher proportion of overweight according to BMI showed a higher prevalence of frailty. In a study of elderly Mexicans, Masel et al.²⁶ found that underweight was related to frailty. However, although Woods et al.²⁹ found the same association, they showed that frailty could also be associated with overweight and obesity. The association between frailty and underweight may be related to the common loss of muscle mass in individuals with unintentional weight loss³⁰. Meanwhile, the relationship between frailty and overweight and obesity may be due to the fact that excess weight can be associated with activation of inflammatory processes, which trigger systemic alterations, which in turn can influence the onset of frailty⁵. Still other authors speculate that weight extremes in the elderly are related to loss of muscle mass in arms and legs, and that the phenomenon of "sarcopenic obesity", referring to weight gain concurrent with loss of muscle mass, leads to difficulty in mobility, reduced strength, and thus physical inactivity, one of the elements in the frailty cycle^{31,32}.

As for studies that showed an inverse association between alcohol consumption and frailty^{16,17,29} and a positive association between smoking and the syndrome^{17,29}, the authors do not discuss the possible explanations for such findings. Woods et al.²⁹ merely mention that when stratifying the variable in doses per week, elders with moderate alcohol consumption had 13 to 31% lower odds of presenting frailty syndrome, even after adjusting for chronic diseases that have been associated with moderate alcohol use. Caution has been suggested when analyzing such associations, especially those related to alcohol consumption, since not all the studies conducted regression analyses or adjusted for potential confounders when cross-analyzing such variables.

Since 9 of the 35 studies (26%) only included women, a comparison was made between factors associated with frailty in both genders and in studies only with females, showing that there was no difference between the associated factors, suggesting that the elder's gender does not have a decisive weight in the establishment of the syndrome.

Importantly, the studies varied in both their design and the methods used to measure the independent variables. Most adopted a cross-sectional design, which does not allow establishing a cause-and-effect relationship between the independent variables and the outcome. In addition, 18 studies performed bivariate analyses, and a total of 16 did not adjust for potential confounders. However, in general such limitations appear not to have influenced the associations, considering the consistency between results.

As for assessment of risk of bias, a question that called considerable attention was the adequacy of the diagnostic assessment of frailty. As mentioned, the choice of the criterion adopted by Fried et al.² (among various existing criteria) to assess frailty in this review was due to the lack of a consensus or gold standard for identifying the syndrome and to the fact that Fried's definition is widely used in other Brazilian and international scientific studies. The current review did not aim to critically discuss the instruments for evaluating frailty proposed by the literature, so the analysis of bias in the assessment of frailty merely aimed to verify the extent to which the studies analyzed in the sample deviated from the original proposal by Fried et al.².

Focusing on this point, we found that only 36% of the studies assessed frailty comprehensively as Fried et al.² proposed, and that 74% performed some modification of the five components. Changes in proposed criteria can lead to erroneous conclusions when comparing the

results to those of other studies. Meanwhile, the instruments proposed to assess some component, as for example the questionnaire proposed by Fried et al.² to estimate low level of physical activity, may contain items that do not agree with the study's local reality, which would probably lead the authors to adapt the questionnaire to obtain a more adequate and true response. Furthermore, other authors adopted other criteria and validated such changes in relation to the proposal by Fried et al.², while still others did not conduct a validation process or failed to report it. Thus, common sense is recommended when analyzing articles for comparison with data from other authors.

In addition, some studies drawing on the same cohort^{17,33,34,35,36,37,38} used different descriptions of the instruments used to measure the component of the criterion used by Fried et al.², which raises doubts in their analysis.

This review presents some limitations. First, by limiting the languages of the publications to English, Portuguese, or Spanish and the databases for the article search, some relevant study may have been left out. The second relates to the limiting the diagnostic criterion for frailty according to Fried et al.². The scientific literature provides different instruments with various markers, which are being tested in international studies. Thus, some outstanding studies may have been lost. Another limitation relates to restricting the presentation of results to those with statistical significance. This decision was due to the fact that one cannot reach conclusions on associations that are not statistically significant, and due to the number and scope of the target variables.

Final remarks

The worldwide increase in prevalence of frailty among the elderly raises challenges for all countries. Knowledge of the factors associated with the syndrome and the complexity of its determinants helps formulate measures for prevention and early intervention, thus fostering aging with better quality of life and greater dignity. Although the studies and their comparison present limitations, this review highlights a series of socio-demographic, psycho-behavioral, health-related, and nutritional factors that assist the identification of more vulnerable groups and that are amenable to intervention.

Importantly, although demographic determinants showed a relationship to frailty in the elderly, some determinants are not subject to changes and interventions. For example, it is impossible to alter age or gender, but they should be considered anyway, since various health conditions increase with age and occur differently between men and women.

Thus, planning of individual and collective health measures for the elderly should consider the factors identified here as related to the frailty syndrome, such as: age, black race/color, female gender, CVD, number of comorbidities/diseases, functional incapacity, poor self-rated health, depressive symptoms, BMI, smoking, schooling, income, cognitive function, and alcohol consumption (the latter with caution). It is also important to investigate other factors not explored in this review, besides conducting meta-analyses aimed at a critical assessment of the evidence and a discussion of the possible heterogeneity of results, in addition to an analysis of the strength of available evidence on the association found between a given variable and frailty in order to better understand how the way of living can interfere in the way of aging and favor the establishment of this syndrome.

Resumen

La fragilidad es un síndrome que causa daño en la vida práctica de ancianos, ya que está relacionada con un mayor riesgo de dependencia, caídas, hospitalización, institucionalización y muerte. El objetivo de esta revisión sistemática fue identificar factores sociodemográficos, psicoconductuales, de condiciones de salud, nutrición y estilo de vida asociados a fragilidad en ancianos. Se detectaron 4.183 estudios publicados entre 2001 y 2013 en las bases bibliográficas y se seleccionaron 182 artículos completos. Después de la lectura y aplicación de los criterios de selección, quedaron 35 artículos elegibles para análisis. Los principales factores asociados fueron edad, sexo femenino, raza negra, educación, ingresos, enfermedad cardiovascular, número de comorbilidades/enfermedad, incapacidad funcional, auto-percepción de mala salud, síntomas depresivos, función cognitiva, índice de masa corporal, tabaquismo y consumo de alcohol. El conocimiento de la complejidad de los determinantes de fragilidad ayuda en la formulación de medidas preventivas e intervención temprana, asegurando mejor calidad de vida.

Anciano Frágil; Calidad de Vida; Factores de Riesgo

Contributors

A. C. Mello participated in all stages of the article's elaboration. E. M. Engstrom and L. C. Alves contributed to the literature review, article selection, and data extraction, besides participating in writing and critically revising the article.

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