Does the incidence of frailty differ between men and women over time?

Abstract

Background/Objective: The mechanisms, risk factors and influence of sex on the incidence of frailty components are not fully understood. The aim of this study was to analyse sex differences in factors associated with the increase in the number of frailty components.

Methods: A 12-year follow-up analysis was conducted with 1,747 participants aged ≥ 60 of the ELSA Study with no frailty at baseline. Generalised linear mixed models were used to analyse the increase in the number of frailty components stratified by sex, considering socioeconomic, behavioural, clinical and biochemical characteristics as exposure variables.

Results: The increase in the number of frailty components in both sexes was associated with an advanced age (70 to 79 years and 80 years or older), low educational level, sedentary lifestyle, elevated depressive symptoms, joint disease, high C-reactive protein levels, perception of poor vision and uncontrolled diabetes ($p < 0.05$). Osteoporosis, low weight, heart disease, living with one or more people and perception of poor hearing were associated with an increase in the number of frailty components in men. High fibrinogen concentration, controlled diabetes, stroke and perception of fair vision were associated with the outcome in women ($p < 0.05$). Obese women and men and overweight women had a lower increase in the number of frailty components compared to those in the ideal weight range.

Conclusions: Socioeconomic factors, musculoskeletal disorders, heart disease and low weight seem to sustain the frailty process in men, whereas cardiovascular and neuroendocrine disorders seem to sustain the frailty process in women.

Keywords: Frailty, Ageing, Musculoskeletal system, Chronic disease, ELSA study

Abbreviations: English Longitudinal Study of Ageing (ELSA), C-reactive protein (CRP); body mass index (BMI); Center for Epidemiological Studies - Depression (CES-D); Physical Activity and

Sedentary Behaviour Assessment Questionnaire (PASBAQ); Health Survey for England (HSE); glycated haemoglobin (HbA1c); blood pressure (BP); High-density lipoprotein (HDL); Low-density lipoprotein (LDL); GLMMs, generalized linear mixed models.

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1. Introduction

Frailty is a clinical syndrome characterised by the reduction in the homeostatic reserve and resistance to stressors and is the result of the accumulative decline of multiple physiological systems, which increases the risk of negative outcomes later in life (Fried et al., 2001; Morley et al., 2013). The regulation and dysregulation of physiological systems and the probability of living a longer or shorter time with the syndrome has been associated with socioeconomic, behavioural, clinical and biochemical factors (Feng et al., 2017; Fried et al., 2001; Gale et al., 2013), which may differ between men and women (Alexandre et al., 2018).

Although the associations between comorbidities and frailty do not prove causality, there are socioeconomic, biological, biochemical, behavioral and sociocultural issues to which men and women are exposed differently throughout life and which can culminate in different processes of biological vulnerability (E. H. Gordon & Hubbard, 2020; E. Gordon & Hubbard, 2018). Differences in body composition, fat deposition, and their impact on musculoskeletal, neuroendocrine, metabolic and cardiovascular diseases can converge to different profiles of comorbidities capable of influencing the higher risk of frailty differently between genders (Afilalo et al., 2014; Gao et al., 2019; Kautzky-Willer et al., 2016; Soh & Won, 2021; Yuan et al., 2021).

To date, it is known that women have a higher prevalence and earlier onset of syndrome (Cohen et al., 2018). However, after they develop frailty they live longer with the syndrome than men (E. Gordon & Hubbard, 2018). The explanation for such phenomena is complex and relates to gender differences such as the expression of psychological identity and distinct cultural attributes, social roles and access to resources throughout life (E. H. Gordon & Hubbard, 2020). Such differences result in, for example,

to a higher exposure in men to occupational hazards, unhealthy dietary choices and higher alcohol and tobacco consumption which are the main risk factors to highly fatal non-communicable chronic diseases and, consequently, a shorter life expectancy in men (Crimmins et al., 2011).

The male-female health-survival paradox is not fully understood and influenced by genetic, hormonal, and immunological factors. Genetically, the presence of two X chromosomes, longer telomers and a slower shortening process are potential explanations for the longer survival in women (Eskes & Haanen, 2007; Haapanen et al., 2018). The positive effects of oestrogen on the vascular and lipid profile in women before the menopause seemed to contribute to a later and smaller impact of atherosclerosis. However, their deprivation after the menopause could also influence specific diseases in women (Eskes & Haanen, 2007). Furthermore, testosterone is likely to inhibit the innate and adaptative immune responses resulting in a weaker immune system in men which in turn make them more vulnerable to infections and, ultimately, death (Gubbels Bupp, 2015).

As a result, men are more likely to develop fatal diseases such as cerebral vascular accidents, myocardial infarction, and cancer (Avendano & Mackenbach, 2008; Crimmins et al., 2011). On the other hand, women seemed to present a higher inflammatory activity than men and abdominal obesity, that accumulates more in pre-menopausal women, are likely to contribute to this difference (Hubbard et al., 2010). In addition, women have higher prevalence of conditions that cause functional incapacity such as obesity, sarcopenia, osteoarthritis, cataract and depression (Avendano & Mackenbach, 2008; Crimmins et al., 2011). Therefore, the male-female health-survival paradox seems to play a role in the dysregulation of the homeostatic process and development of frailty components and is referred as the "sex-frailty paradox".

Few studies have investigated this topic focusing on the frailty components. For example, in a cross-sectional study involving 1,413 individuals aged 60 or older, Alexandre et al. (Alexandre et al., 2014)

found that age, schooling, a sedentary lifestyle and depressive symptoms were similarly associated with more than one component of frailty in both sexes. However, a longitudinal analysis of these individuals during four years follow-up (Alexandre et al., 2018) revealed differences in the factors that sustain the specific physiopathology of each component. Physiological dysregulation in men was associated with a greater consumption of alcohol and tobacco, diabetes, and cognitive decline, whereas joint disease, obesity and physical inactivity were associated factors in women.

The present study, therefore, aims to investigate whether sex differences exist in factors associated with the increase in the number of frailty components over time.

2. Methods

2.1.Study population

The data came from the English Longitudinal Study of Ageing (ELSA), which is a longitudinal panel study involving English individuals aged 50 years or older initiated in 2002 (Steptoe et al., 2013). All participants provided informed consent and the ELSA study was approved by the Multicentre Research Ethics Committee (MREC/01/2/91).

2.2.Frailty assessment

Frailty was analysed using the phenotype proposed by Fried et al. (Fried et al., 2001) and subsequently adapted (de Oliveira et al., 2021; Liljas, Carvalho, Papachristou, De Oliveira, et al., 2017). Unintentional weight loss was defined as the loss of 5% of body weight in the interval between interviews or by a body mass index (BMI) < 18.5 kg/m² at baseline. Exhaustion was defined as agreement with one of the following statements taken from the Center for Epidemiological Studies -

Depression (CES-D) (Radloff, 1977) scale: "I felt that everything I did was an effort in the last week " or "I could not get 'going' in the last week". Weakness was considered the lowest quintile in grip strength stratified by sex in each BMI quartile. Slowness was considered the slowest quintile for walking based on the best time between two walking trials (2.4 meters) stratified by mean height and sex. Low physical activity level was determined using three questions taken from the Physical Activity and Sedentary Behaviour Assessment Questionnaire (PASBAQ) used in the Health Survey for England (HSE). For such, the participant reported the frequency (once per week, more than once per week, one to three times per month and rarely or never) of the practice of vigorous, moderate, or light exercises. Those who reported never performing exercises of moderate intensity were considered to have a low physical activity level (de Oliveira et al., 2021).

Our initial sample comprised of 2,324 ELSA participants aged 60 or older with no frailty component at baseline (2004), when anthropometric data and physical performance were collected for the first time. However, 577 were excluded due to a lack of information on the exposure variables, resulting in an analytical sample of 1,747 individuals (854 men and 893 women). The participants were reassessed after four, eight and twelve years. The incidence of the increase in frailty components was analysed and ranged from 0 to 5.

2.3.Variables of interest

Variables associated with frailty and its components were included (Alexandre et al., 2014, 2018; de Oliveira et al., 2021; Feng et al., 2017). Socioeconomic characteristics were age (60 to 69; 70 to 79; 80 years or older), marital status (with/without a conjugal life), living alone or with other people, skin colour (white or non-white), household wealth (categorised in quintiles) and schooling (0 to 11, 12 to 13 or >13 years).

Behavioural characteristics (de Oliveira et al., 2021) were weekly frequency of alcohol intake, smoking and physical activity level, which was categorised in two groups according to reports of intensity and frequency: active lifestyle (practice of light, moderate or vigorous physical activity at least once per week) or sedentary lifestyle (no weekly physical activity).

Clinical conditions were recorded based on self-reports of a medical diagnosis of stroke, heart disease, cancer, lung disease, joint disease, osteoporosis, falls in the previous year. Information on the medical diagnosis of dementia was provided by participants' carers. Diabetes was confirmed by the use of medications and glycated haemoglobin (HbA1c) level (Nebuloni et al., 2020) and participants were classified into three groups: non-diabetic, controlled diabetic (self-reported diabetes and/or use of medications and HbA1c < 7.0%) and uncontrolled diabetic (self-reported diabetes and/or use of medication and HbA1c ≥ 7.0%). Hypertension was confirmed by the use of medications as well as systolic and diastolic blood pressure (BP) and the sample was classified in three groups: non-hypertensive, controlled hypertensive (self-reported hypertension and/or use of medications and BP < 140/90 mmHg) and uncontrolled hypertensive (self-reported hypertension and/or use of medications and BP ≥ 140/90 mmHg).

Perceptions of hearing (Ferrite et al., 2011; Liljas, Carvalho, Papachristou, Oliveira, et al., 2017) and vision (Liljas, Carvalho, Papachristou, De Oliveira, et al., 2017; Zimdars et al., 2012) were assessed through the following questions: 1) How would you rate your hearing and 2) How would you rate your vision? (Excellent, very good, good, fair or poor). Self-reported hearing and vision answers were then categorised into good (excellent, very good and good), fair or poor. Depressive symptoms were defined using the CES-D (Radloff, 1977) and the risk of depression was considered when the score was ≥ 4 points. BMI was classified as low weight (< 18.5 kg/m²), ideal range (≥ 18.5 kg/m^2 and < 25 kg/m^2), overweight (≥ 25 kg/m^2 and < 30 kg/m^2) and obesity (≥ 30 kg/m²) (Organization, 2000). Memory was evaluated using the word list test, on which the participants heard a list of ten words,

which they were immediately asked to recall. After approximately two minutes, the participants were asked to recall as many of the same ten words as possible. The score was the sum correctly recalled words (one point per word) in the two attempts, with the total ranging from 0 to 20 points (de Oliveira et al., 2021; Huppert FA, Gardener E, McWilliams B, 2006).

Biomarkers were collected during the health examination after all participants fasted for five hours (except water). Further information can be found elsewhere (NatCen Social Research, 2018). The following biomarkers were included (de Oliveira et al., 2021): triglycerides (high: ≥ 150 mg/dl), total cholesterol (high: ≥ 200 mg/dl), HDL (low: < 40 mg/dl for men and < 50 mg/dl for women), LDL (high: ≥ 100 mg/dl), fibrinogen (high: > 3.8 g/l), anaemia (haemoglobin < 12 mg/dL for women and < 13 mg/dL for men) and CRP (high: > 3 mg/l).

2.4.Statistical analyses

The sample characteristics were expressed as means, standard deviation and proportions. Differences among the individuals at baseline per sex were tested using the chi-square test and Student's t-test. A p-value < 0.05 was considered indicative of statistical significance.

Generalised linear mixed models (GLMMs) using the XTMIXED procedure in Stata 15® SE (Stata Corp, College Station, TX, USA) were done to estimate trajectories of the increase in frailty components by sex. This is the best modelling method when using unbalanced data with repeated measures and enables the analysis of changes in a time-dependent variable as well as time-dependent changes in the magnitude of the association between variables of interest (Liang & Zeger, 1986; Zeger & Liang, 1986).

Univariate analyses were performed to select variables associated with the increase in frailty components and to incorporate them into the final model stratified by sex. Variables with a p-value ≤ 0.20 were selected for the multiple models (Greenland, 2008).

No differences in the intercept occurred in the trajectories of the increase in frailty components because individuals with any component at baseline were excluded. Therefore, the models present the slope, which indicates the trajectory of the increase in frailty components by sex as a function of the variables of interest and interactions with time and whether time *per se* is the determinant of the increase in components. The results for the trajectories were compared using the β coefficients and their respective 95% confidence intervals.

3. Results

Out of 1,747 individuals evaluated at baseline, 72.3%, 53.2% and 34.1% were reassessed at four, eight and 12-year follow-ups, respectively. The mean age was 68 years. The baseline characteristics are displayed in Table 1.

The passage of time *per se* was a determinant of the increase in frailty components in women, but not in men. Age (70 to 79 years and 80 years or older), low schooling, sedentary lifestyle, elevated depressive symptoms, joint disease, high CRP, perception of poor vision and uncontrolled diabetes were associated with the increase in frailty components in both sexes ($p < 0.05$) (Tables 2 and 3).

Osteoporosis, low weight, heart disease, living with one or more people and perception of poor hearing were associated with the increase in the number of frailty components exclusively in men ($p < 0.05$) (Table 2 and Fig. 1). High fibrinogen concentration, controlled diabetes, stroke, and perception of fair vision were associated with the outcome in exclusively in women ($p < 0.05$). Obese women and men

and overweight women had a lower increase in the number of frailty components compared to those in the ideal weight range ($p < 0.05$) (Table 3 and Fig. 2).

4. Discussion

Our main findings showed that despite some common factors in women and men being associated to increases in frailty components, there were important sex differences that should be considered during clinical assessment. Old age (Alexandre et al., 2014, 2018; Fried et al., 2001), low schooling (Alexandre et al., 2014; Feng et al., 2017; Fried et al., 2001) and a sedentary lifestyle (Kehler & Theou, 2019) are known factors associated with frailty (Feng et al., 2017; Fried et al., 2001) and the components of frailty in cross-sectional (Alexandre et al., 2014) and longitudinal (Alexandre et al., 2018) studies both in men and women. The ageing process is accompanied by progressive homeostatic dysregulation and the accumulation of deficits in multiple physiological systems, culminating in the loss of adaptive physiological capacity to tolerate stressors, which exerts a direct influence on the frailty process in both sexes (Angioni et al., 2020).

Low schooling impacts negatively on work opportunities and access to health and can lead to unhealthy behaviours, predisposing individuals to chronic diseases that contribute to frailty (Etman et al., 2015). A sedentary lifestyle predisposes individuals to a proinflammatory state, altering the metabolism of lipids and glucose, increasing muscle catabolism, changing the quality of musculoskeletal tissue due to the infiltration of fat and favouring a decline in both strength and gait speed (Kehler & Theou, 2019).

Depressive symptoms were also associated with the increase in frailty components, which confirms the results from previous studies (Alexandre et al., 2014; Feng et al., 2017). The exhaustion component is based on the CES-D, which is also used for the assessment of depressive symptoms, indicating

possible collinearity. Both clinical conditions are capable of reducing energy availability, which can affect multiple physiological systems and favour a reduction in physical functioning (Abbiss & Laursen, 2005).

The frailty process can also be exacerbated by chronic diseases (Ahrenfeldt et al., 2019; Angioni et al., 2020). Joint disease increased the risk for the increase in frailty components in both sexes. Together with changes in bone mass, reductions in muscle strength and mass limit mobility, favoring the development of frailty (Bindawas et al., 2018).

Elevated C-reactive protein serum levels were associated to increases in frailty components in women and men (Feng et al., 2017). Comorbidities could result in an accumulation of low grade inflammatory processes in women (Gale et al., 2013), while in men, increases in C-reactive protein serum levels seem to be linked to diseases' severity (Wysham et al., 2020). Chronic inflammation could be considered the main pathogenic factor of the syndrome (Chen et al., 2014) and is present in most of the chronic diseases in this study, influencing frailty via the pro-inflammatory cytokines' cascade found in the musculoskeletal, cardiovascular, endocrine and haematological systems (Chen et al., 2014).

Despite the similarities in the risk factors for the increase in the number of frailty components over time, differences in body composition and fat deposition location between genders throughout life and in old age can directly trigger the appearance of frailty components or, indirectly, mediating metabolic changes that culminate in the emergence of diseases that increase the risk of frailty (Ahrenfeldt et al., 2019; Kautzky-Willer et al., 2016; Soh & Won, 2021). For example, while underweight in men is often associated with sarcopenia and increased risk of frailty, overweight in women and obesity in both sexes decreased this risk. However, although the increase in BMI is, in principle, a protective factor for frailty, it is important to assess where this fat is, how it was accumulated throughout life, and what is its long-term metabolic impact (Soh & Won, 2021; Yuan et al., 2021). Men tend to accumulate

abdominal fat early and, consequently, have a worse metabolic profile (Fávaro-Moreira et al., 2016). This condition has been associated with greater low-grade chronic inflammation that leads to greater reduction in muscle mass, reduced neuromuscular strength and walking speed, two important components of frailty (Fávaro-Moreira et al., 2016). Women, on the other hand, tend to present, before menopause, a more subcutaneous and less inflammatory deposit of fat (Sun et al., 2019). However, with menopause, the distribution of fat becomes more abdominal, which worsens their metabolic picture (Soh & Won, 2021). However, this scenario has a distinct impact between genders on the occurrence of comorbidities such as diabetes, heart disease and stroke, which can increase the risk of frailty (Gao et al., 2019; Kautzky-Willer et al., 2016).

With regards to diabetes, an important risk factor in the frailty process, it is known that obesity is a preponderant component for the development of the disease (Kautzky-Willer et al., 2016; Soh & Won, 2021). However, while overweight and obesity are more prevalent in younger men, obesity is more prevalent in women after 45 years of age (Kautzky-Willer et al., 2016). One of the factors that explains this increase in female obesity at older ages is the loss of estrogenic protection, which results in a change in body composition with greater accumulation of abdominal fat (Soh & Won, 2021). This circumstance leads to a worse female metabolic profile, mediated by increased adiposity and greater insulin resistance (Kautzky-Willer et al., 2016). This whole condition may be the explanation for the fact that controlled diabetes was a risk factor for frailty in women while uncontrolled diabetes was a risk factor for frailty in both sexes.

Regarding cardiovascular disease, the incidence of heart disease is higher in younger men, which is reflected in the increased risk of frailty, as seen in our results. On the other hand, women have a higher risk of stroke than men, as well as the occurrence of their first stroke event is later and with greater functional repercussions (Afilalo et al., 2014; Gao et al., 2019; Pandey et al., 2019). Furthermore, recent studies have shown that among women, fibrinogen levels differ between cortical and lacunar

areas, which could point to differences in the underlying mechanisms of stroke (Donkel et al., 2019). Therefore, sex differences in the haemostatic system could contribute to both an increased risk and a worse outcome after stroke in women than in men (Girijala et al., 2017) with a higher risk of frailty.

All these conditions explain the distinct associations between genders found in the present study. However, it is worth mentioning that there may be a synergy between sex differences in body composition with metabolic implications and in diseases such as diabetes, heart disease and stroke, with different impacts on the frailty process in men and women (Gao et al., 2019; Kautzky-Willer et al., 2016; Soh & Won, 2021) who need be further explored in future research.

Another important gender difference found in the present study was the fact that osteoporosis is exclusively associated with the frailty process in men (Alswat, 2017). Although men have more resistant bones and reach peak bone mass later than women, this male advantage does not seem to be sustained during the aging process, since cortical bone loss is more pronounced in men than in women (Loures et al., 2017). However, given that bones and muscles are interconnected tissues, when altered, they may contribute to osteosarcopenia and influence the appearance of weakness and slowness components more markedly in men than in women (Kirk et al., 2020). Furthermore, despite the prevalence of osteoporosis and the incidence of fractures, as a result of this disease, being higher in women, men have more risk factors for osteoporosis, such as smoking and weight loss, as well as having more functional complications after the fracture, favoring the frailty process (Alswat, 2017; Li et al., 2019).

Living with one or more people, could contribute to men being less socially active i.e. less social participation and more vulnerable to become physically dependent to perform their basic activities of the daily living and more likely to develop frailty. On the other hand, women have a higher level of

social participation, wider social networks and tend to seek more socioemotional support (Alexandre et al., 2018; E. H. Gordon & Hubbard, 2020).

The perception of poor hearing was associated with the increase in frailty components in men. The prevalence of hearing loss is greater in men compared to women (30% and 20%, respectively) due to a greater exposure to noise and ototoxic substances in occupational tasks (Huang & Tang, 2010). This aspect can predispose individuals to greater social isolation, favouring depression and physical activity, which can contribute to the emergence of frailty (Liljas, Carvalho, Papachristou, Oliveira, et al., 2017).

Poor vision in both sexes and fair vision in women were also associated with increases in frailty components. Microvascular diseases and neurodegeneration can lead to sensory loss, contributing to the emergence of frailty through the reduction in gait speed, social isolation and depression (Liljas, Carvalho, Papachristou, De Oliveira, et al., 2017; Tan et al., 2020). Compared to men, women are more sensitive to physical changes of the body, report health problems more often, have greater access to health care and receive earlier diagnoses (E. H. Gordon & Hubbard, 2020).

However, gender differences seem to come from socioeconomic, biological, biochemical, behavioral and sociocultural processes to which men and women are distinctly exposed throughout life and which can converge to the existence of comorbidities contributing exponentially, but in a different way, to the frailty process (E. H. Gordon & Hubbard, 2020; E. Gordon & Hubbard, 2018). Therefore, these results could be used to advise interventional health programs between the sexes. In men, the prevention of cardiovascular diseases and osteoporosis could be done through education on smoking cessation, reduction of alcohol consumption, dietary counselling and implementation of physical activity, regular medical check-ups of hearing, stimulation of autonomic social activities and adequate diet for

underweight individuals. In women, the early and continuous monitoring of cardiovascular and metabolic diseases and visual can potentially prevent, postpone or the onset of frailty in later life.

The present study has some strengths. We have used standard tools for the identification of frailty. The study was conducted with a representative sample and had a long follow-up period. The generalised linear mixed models enabled coping with the dynamic nature of frailty according to the multiple exposure variables associated with the increase in the components over time and stratified by sex. Lastly, this is the first study to perform a longitudinal analysis of the trajectories of the increase in frailty components in individuals with no component at baseline, pointing out similarities and differences between the sexes.

Among the limitations of this study, we used a slighted modified version of frailty (Fried et al., 2001) due to the limitation of the data. The analysis of physical activity levels was restricted to the frequency and intensity of exercise, with no information on calorie intake. However, the data were obtained through interviews and physical examinations comparable to the original study (Fried et al., 2001). In ELSA, data on male and female hormones were not collected. Changes in testosterone and estrogen serum concentrations of may increase the risk of morbidity and frailty in both sexes (E. H. Gordon & Hubbard, 2020; E. Gordon & Hubbard, 2018). Lastly, losses to follow-up could be considered a source of bias but are inevitable in longitudinal studies.

5. Conclusion

In conclusion, despite similarities in the trajectory of the increase in the components of frailty between the sexes, socioeconomic characteristics, changes in the musculoskeletal system, heart disease and low weight seem to sustain the frailty process in men, whereas cardiovascular and neuroendocrine disorders seem to sustain the frailty process in women.

Acknowledgments The authors are grateful to all collaborators and participants of the English Longitudinal Study of Ageing.

Funding support This work was supported by the Brazilian fostering agency Coordination for the Advancement of Higher Education Personnel – CAPES [Financing Code 001 and grant number 88882.332837/2019-01 to D.C.O]. The National Council of Scientific and Technological Development – CNPq [grants numbers: 303981/2017-2, 303577/2020-7], Sao Paulo Research Assistance Foundation – FAPESP [grant number: 18/13917-3] and Institution Internalization Program (CAPES-PRINT) [grant number 88887.570076/2020-00] to T.S.A. ELSA is funded by the National Institute on Aging (R01AG017644), and by UK Government Departments coordinated by the National Institute for Health and Care Research (NIHR). This work was supported by the Economic and Social Research Council [grant number ES/T008822/1]. The funders had no involvement in the manuscript.

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CAPTION FOR TABLES AND ILLUSTRATIONS

Figure. 1 Trajectory of increase in frailty components in men in 12-year follow-up. ELSA, England, 2004/2005 – 2016/2017. Predictions adjusted for age, vision perception, depression, osteoporosis, body mass index (BMI), heart disease, schooling, diabetes, joint disease, C-reactive protein, physical activity, living arrangements and hearing perception

Figure. 2 Trajectory of increase in frailty components in women in 12-year follow-up. ELSA, England, 2004/2005 – 2016/2017. Predictions adjusted for age, depression, schooling, body mass index (BMI), vision perception, diabetes, C-reactive protein, fibrinogen, physical activity, joint disease and stroke

Table 1. Socioeconomic, behavioural, biochemical and clinical characteristics of individuals with no frailty components at baseline in ELSA Study (2004-05)

Table 2. Generalized linear mixed model estimates of increase in frailty components in men according to trend of associated factors in 12-year follow-up. ELSA (2004/2005 – 2016/2017)

Table 3. Generalized linear mixed model estimates of increase in frailty components in women according to trend of associated factors in 12-year follow-up. ELSA (2004/2005 – 2016/2017)

Table 1 Socioeconomic, behavioural, biochemical and clinical characteristics of individuals with no frailty components at baseline in ELSA Study (2004-05)

	No frailty components		
	Total (n = 1,747)	**Men** (n = 854) 48.9%	**Women** (n = 893) 51.1%
Socioeconomic variables			
Age, years (SD)	68.2 ± 6.2	68.3 ± 6.1	68.1 ± 6.3
Age, %			
60 ─ 69 years	62.8	62.1	63.6
70 ─ 79 years	31.9	33.1	30.7
80 years or more	5.3	4.8	5.7
With conjugal life (yes), %	72.6	81.7*	63.9*
Living with one or more people (yes), %	93.2	93.9	92.5
Non-white skin colour (yes), %	1.1	0.9	1.2
Household wealth (quintiles), %			
Highest quintile	29.4	30.2	28.6
2nd quintile	25.6	26.6	24.8
3rd quintile	20.9	22.1	19.7
4th quintile	14.8	13.6	15.9
Lowest quintile	8.3	6.9	9.7
Not declared	1.0	0.6	1.3
Schooling, %			
> 13 years	30.5	37.2*	24.0*
12–13 years	24.3	24.4	24.2
0–11 years	45.2	38.4*	51.8*
Behavioural variables			
Alcohol intake, %			
≤ 1 day per week	13.3	8.1*	18.4*
2-6 days per week	44.3	41.3	47.1
Daily	37.1	44.3*	30.1*
Not declared	5.3	6.3	4.4
Smoking, %			
Non-smoker	41.7	30.8*	52.2*
Ex- smoker	50.1	59.7*	40.9*
Smoke	8.2	9.5	6.9
Clinical conditions			
Stroke (yes), %	2.4	3.2	1.7
Heart disease (yes), %	19.2	21.5*	17.0*
Cancer (yes), %	7.5	6.4	8.5
Lung disease (yes), %	14.5	14.2	14.8
Joint disease (yes), %	29.6	24.1*	34.9*
Osteoporosis (yes), %	5.4	1.4*	9.2*
Falls (yes), %	24.1	17.7*	30.2*
Dementia (yes), %	0.3	0.3	0.2
Systemic arterial hypertension, %			
Not hypertensive	60.2	61.0	59.5
Controlled hypertensive	18.2	18.2	18.2

Uncontrolled hypertensive	21.6	20.8	22.3
Diabetes, %			
Non-diabetic	93.8	92.6	94.9
Controlled diabetic	4.1	5.1	3.2
Uncontrolled diabetic	2.1	2.3	1.9
Perception of hearing, %			
Good	81.8	76.0*	87.2*
Fair	14.9	19.6*	10.5*
Poor	3.3	4.4	2.3
Perception of vision, %			
Good	93.1	93.5	92.7
Fair	5.8	5.6	5.9
Poor	1.1	0.9	1.4
Depressive symptoms, %			
No	97.9	98.6	97.2
Yes	1.7	1.1	2.4
Not declared	0.4	0.3	0.4
BMI (kg/m²), %			
Normal weight (≥ 18.5 and < 25)	29.3	24.6*	33.8*
Overweight (≥ 25 and < 30)	46.6	53.0*	40.5*
Obesity (≥ 30)	24.1	22.4	25.7
Mean recall score, points (SD)	10.3±3.1	9.9±3.0*	10.7±3.2*
Biochemical characteristics			
Triglycerides (≥150 mg/dL), %	38.0	41.2	34.9
Total cholesterol (≥200 mg/dL), %	74.4	65.7*	82.6*
HDL *(*<40 mg/dL M;<50 mg/dL W*)*, %	12.0	12.6	11.3
LDL (≥100 mg/dL), %	85.6	81.5*	89.5*
Fibrinogen (>3.7 g/l), %	21.1	19.1	23.0
Anaemia (<13 g/dL M; <12g/dl W), %	3.1	3.6	2.7
C-reactive protein (>3 mg/l), %	0.9	1.0	0.7

Data expressed as mean, standard deviation and proportion. All participants with a sedentary lifestyle at baseline were excluded. Thus, the physical activity variable at baseline corresponds only to individuals with an active lifestyle. Abbreviations: CES-D: Center for Epidemiological Studies-Depression Scale; SD: standard deviation; BMI: body mass index; HDL – high-density lipoprotein; LDL – low-density lipoprotein. * Chi-square with gender difference ($p < 0.05$)

.

Table 2 Generalized linear mixed model estimates of increase in frailty components in men according to trend of associated factors in 12-year follow-up. ELSA (2004/2005 – 2016/2017)

Increase in frailty components	**Men**
	n = 854
Associated factors	Estimated parameters (95% CI)
Time, years	0.015 (-0.018 ─ 0.048)
Slope (follow-up)	
Age	
Time x 60 to 69 years	Reference
Time x 70 to 79 years	0.071 (0.048 ─ 0.095)*
Time x 80 years or more	0.136 (0.079 ─ 0.192)*
Perception of vision	
Time x Good	Reference
Time x Fair	0.014 (-0.006 ─ 0.033)
Time x Poor	0.069 (0.031 ─ 0.106)*
Depression	
Time x No	Reference
Time x Yes	0.052 (0.023 ─ 0.080)*
Osteoporosis	
Time x No	Reference
Time x Yes	0.065 (0.034 ─ 0.097)*
BMI	
Time x Normal weight	Reference
Time x Undernourished	0.151 (0.087 ─ 0.216)*
Time x Overweight	-0.010 (-0.025 ─ 0.005)
Time x Obesity	-0.048 (-0.069 ─ -0.028)*
Heart disease	
Time x No	Reference
Time x Yes	0.020 (0.004 ─ 0.036)**
Schooling	
Time x > 13 years	Reference
Time x 12–13 years	0.010 (-0.015 ─ 0.034)
Time x 0–11 years	0.044 (0.022 ─ 0.066)*
Diabetes	
Time x Non-diabetic	Reference
Time x Controlled diabetic	0.022 (-0.007 ─ 0.051)
Time x Uncontrolled diabetic	0.054 (0.021 ─ 0.086)**
Joint disease	
Time x No	Reference
Time x Yes	0.027 (0.012 ─ 0.042)**
C-reactive protein	
Time x ≤ 3 mg/l	Reference
Time x > 3 mg/l	0.016 (0.004 ─ 0.028)**
Physical activity	
Time x Active lifestyle	Reference
Time x Sedentary lifestyle	0.150 (0.122 ─ 0.179)*
Living arrangements	
Time x Live alone	Reference
Time x Live one or more people	0.040 (0.017 ─ 0.063)**
Perception of hearing	
Time x Good	Reference
Time x Fair	-0.006 (-0.019 ─ 0.006)
Time x Poor	0.024 (0.002 ─ 0.045)**

All participants had no frailty components at baseline. Model for men adjusted by age, perception of vision, depression, osteoporosis, BMI (kg/m²), heart disease, schooling, diabetes, joint disease, C-reactive protein, physical activity, living arrangements and perception of hearing. CI: confidence interval. *p < 0.05. **p < 0.01

Table 3 Generalized linear mixed model estimates of increase in frailty components in women according to trend of associated factors in 12-year follow-up. ELSA (2004/2005 – 2016/2017)

Increase in frailty components	**Women**
	n = 893
Associated factors	Estimated parameters (95% CI)
Time, years	0.062 (0.041 ─ 0.083)*
Slope (follow-up)	
Age	
Time x 60 to 69 years	Reference
Time x 70 to 79 years	0.075 (0.053 ─ 0.097)*****
Time x 80 years or more	0.253 (0.204 ─ 0.301)*****
Depression	
Time x No	Reference
Time x Yes	0.076 (0.057 ─ 0.096)*****
Schooling	
Time x > 13 years	Reference
Time x 12–13 years	-0.004 (-0.027 ─ 0.020)
Time x 0–11 years	0.024 (0.002 ─ 0.045)******
BMI	
Time x Normal weight	Reference
Time x Undernourished	0.065 (-0.024 ─ 0.153)
Time x Overweight	-0.017 (-0.032 ─ -0.003)******
Time x Obesity	-0.040 (-0.060 ─ -0.020)*****
Perception of vision	
Time x Good	Reference
Time x Fair	0.020 (0.004 ─ 0.037)******
Time x Poor	0.045 (0.009 ─ 0.081)**
Diabetes	
Time x Non-diabetic	Reference
Time x Controlled diabetic	0.046 (0.018 ─ 0.073)******
Time x Uncontrolled diabetic	0.043 (0.004 ─ 0.082)******
C-reactive protein	
Time x ≤ 3 mg/l	Reference
Time x > 3 mg/l	0.019 (0.005 ─ 0.032)******
Fibrinogen	
Time x ≥ 3.7 g/l	Reference
Time x > 3.7 g/l	0.018 (0.005 ─ 0.032)******
Physical activity	
Time x Active lifestyle	Reference
Time x Sedentary lifestyle	0.134 (0.098 ─ 0.170)*****
Joint disease	
Time x No	Reference
Time x Yes	0.026 (0.012 ─ 0.039)*****
Stroke	
Time x No	Reference
Time x Yes	0.053 (0.015 ─ 0.090)******

All participants had no frailty components at baseline. Model for women adjusted by age, depression, schooling, BMI (kg/m²), perception of vision, diabetes, C-reactive protein, fibrinogen, physical activity, joint disease and stroke. CI: confidence interval. *p < 0.05. **p < 0.01