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Original Research

Sex Differences in Frailty Incidence in Greek Community-Dwelling Older People: The HELIAD Study

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Abstract

BACKGROUND: Previous frailty studies found higher prevalence of frailty in female than in male participants. This was mainly attributed to the fact that compared to men, women show increased longevity. Recent studies have reported that the observed difference between sexes applies irrespectively of the age of older people.

OBJECTIVES: To provide data on sex differences in incident frailty by applying both phenotypic and multi-domain frailty measures in the same population of Greek community-dwelling older people.

DESIGN: Longitudinal study.

SETTING: Data were drawn from the Hellenic longitudinal Investigation of Aging and Diet (HELIAD), a population-based, multidisciplinary study designed to estimate the prevalence and incidence of dementia in the Greek population.

PARTICIPANTS: 1104 participants aged 65 year and above were included in this longitudinal study. This incidence cohort was re-evaluated after a mean follow-up period of 3.04±0.90 years.

MEASUREMENTS: Frailty was operationalized using 5 different definitions in the same population: the Fried Frailty Phenotype (FFP) definition, the FRAIL Scale, the Frailty Index (FI), the Tilburg Frailty Indicator (TFI) and the Groningen Frailty Index (GFI). Frailty incidence was calculated a) for the whole sample, b) separately for men and women and c) after both age and sex stratification.

RESULTS: Age and sex stratification revealed that irrespective of age and frailty measurement, women showed higher incidence rates of frailty than men. Specifically, frailty seems to be a condition concerning women >65 years old, but when it comes to men, it is more frequent in those aged more than 75 years old. Finally, in relation to overall frailty incidence and comparing our results to previous studies, we detected a lower frailty incidence in the Greek population.

CONCLUSIONS: Differences between the two sexes indicate that when exploring the factors that are related to frailty, studies should provide data disaggregated for men and women.

Key words: Sex differences, frailty, incidence, phenotypic and multi-domain measures.

Introduction

Frailty is a highly prevalent geriatric condition that reflects a state of increased vulnerability and reduced function (1). In frailty, even minor stressors may trigger severe and long-term deterioration of people's health and thus frail individuals are more likely to experience adverse health events, including hospitalization and mortality (1). A common finding of previous frailty studies is the higher prevalence of frailty in female than in male participants (2, 3). In the past, this was mainly attributed to the fact that compared to men, women show increased longevity. However, recent studies have reported that the observed difference between sexes applies irrespectively of the age of older people, i.e. females tend to be frailer than age-matched male peers are (4-9).

Although some studies have focused on the sex differences observed in frailty, most of them have measured frailty either with the Fried Frailty Phenotype [(FFP) the most widely used frailty tool that focuses on physical deficits of older people), or with the Frailty Index [(FI) a tool that takes into account a more integral view of the individual's functioning] (1, 10). Other frailty measurements, including the Tilburg Frailty Indicator, the Groningen Frailty Index and the FRAIL Scale, remain quite unexplored in terms of potential sex differences. Another shortcoming of the current literature lies to the fact that most studies examining sex differences in frailty have used a cross-sectional design, while the existing longitudinal cohort studies have focused on mortality rates of frail people and not on frailty incidence. The few existing studies on incident frailty do not provide sex specific data of incidence rates (11-13).

Thus, the aim of the present study was to expand previous evidence and add to the efforts made to acquire a more reliable epidemiological picture of the sex-frailty differences by applying different frailty tools in the same population. Specifically, we intended to estimate incident frailty of Greek community-dwelling older people, and also provide data disaggregated by both age and sex.

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Methods

Participants

Participants were drawn from the Hellenic Longitudinal Investigation of Aging and Diet (HELIAD) described in detail elsewhere (14). Briefly, HELIAD is a population-based, multidisciplinary study designed to estimate the prevalence and incidence of Mild Cognitive Impairment, Alzheimer's disease, other types of dementia, as well as other neuropsychiatric conditions of aging in the Greek population. Participants were at least 65 years old and were randomly selected from the records of two Greek municipalities, including urban and rural areas of Greece. They were all informed about the purpose of the study and gave their informed consent prior to study participation. The participants are reevaluated at intervals of approximately 3 years, repeating the baseline procedures (described below) at each follow-up. The baseline assessment took place from 2009 to 2015 and the first 3-year follow-up visit was completed on 2019. The participants included in the present analyses were chosen from the entire study population and according to the inclusion criteria, they were non-frail at their first evaluation and had completed a second evaluation.

Procedures

Participants were interviewed in person by neurologists, neuropsychologists and other health professionals, and provided information regarding their demographics, medical problems (including neurologic conditions, psychiatric and behavioral symptoms), current medication, hospitalizations, surgeries, family medical history, lifestyle activities and nutrition. Additionally, an extensive structured physical examination, evaluating neurologic signs and symptoms, was conducted for each participant.

Moreover, a complete neuropsychological assessment to evaluate cognitive function was performed by trained neuropsychologists and included all major cognitive domains: Orientation (15), Non-verbal and Verbal Memory (16, 17), Language (18, 19), Visuo-perceptual Ability (20-22), Attention and Information Processing Speed (23), Executive Functioning (16) and a gross estimate of intellectual level (24).

Regular diagnostic consensus meetings were conducted between neurologists and neuropsychologists involved in the study in order to decide on the diagnosis of each participant after thorough examination of their record.

Frailty Assessment

In HELIAD study, frailty was assessed using five different tools, belonging to both phenotypic and multidomain approach of frailty, as described in detail elsewhere (25-27). The phenotypic approach focuses on the physical aspects of frailty, while the multidomain approach takes into consideration a combination of both physical, psychological and socioeconomic factors. Briefly:

The Fried Frailty Phenotype (FFP) (1)

As, proposed by Fried and colleagues in the Cardiovascular Health Study, the phenotypic approach of frailty includes 5 criteria (slow walking speed, loss of weight, poor endurance, low physical activity and weakness (1)). In the current study, operationalization of FFP criteria was performed as follows; (1) participants showing the shrinking/weight loss criterion were considered those with a Body Mass Index (BMI) <18.5kg/m^2; (2) Physical activity was estimated based on three questions regarding the frequency of participants' involvement in common physical activities (walking, participating in other physical activities, such as swimming, sports or gym and gardening) (14). A very rare involvement in these activities (less than once a month) was indicative of frailty; (3) Slow walking speed was defined as the lowest 20% of our study population for the 4 meters walking speed test (adjusted for sex and height); (4) Poor endurance/exhaustion was evaluated as a negative response to the question taken from the Geriatric Depression Scale "Do you feel full of energy?"(28); (5) Weakness was defined as grip strength in the lowest 20% adjusted for sex and BMI. Grip strength of the dominant hand was measured with an electronic dynamometer (model MG-4800, UK) and the mean strength of three trials was used in the current analysis. Participants who met 3 or more of these criteria were considered frail, those with 1 or 2 criteria presented as pre-frail, and those who met none criterion as non-frail.

Compared to our previous cross-sectional studies on frailty, in the current study we operationalized low physical criterion differently because in the follow-up assessment, we lacked data on the Athens Physical Activity Questionnaire (APAQ, (29)) which calculates participants' daily energy expenditure for physical activities and was used in the baseline as an assessment of physical activity criterion. However, as the current work focused on incidence rates of frailty, we considered it necessary to measure frailty with the same way and, thus, we excluded data from the APAQ for both the baseline and the follow-up assessment.

The FRAIL scale

This scale contains information both from the phenotypic and from the multi-domain definition of frailty. Overall, it includes 5 components: fatigue, resistance, ambulation, illness and loss of weight. A score range from 3-5 represents frail, from 1-2 pre-fail and 0 represents robust health status (30).

The Frailty Index (FI)

The operationalization of the Frailty Index in the HELIAD study is based on 61 age-related deficits, including diseases, syndromes, functionality in activities of daily living, cognitive decline, mood disorders and performance on physical activities. The frailty index of each participant was calculated. According to this index, a score of 0.25 was used as the cut-off point for frailty, with higher scores indicating the presence of more "deficits" and, thus, a greater degree of frailty (31).

Table 1. Frailty incidence rate for men and women per frailty measurement

	MEN			WOMEN		
	Number of new cases	Incidence Proportion (%)	Incidence Rate (per 1000 person years)	Number of new cases	Incidence Proportion (%)	Incidence Rate (per 1000 person years)
FFP	11	2.5	8.37	37	6	19.60
FRAIL	16	1.8	11.92	38	2.9	18.98
TFI	47	13.5	43.67	96	19.9	64.28
FI	58	14.9	49.21	109	20.4	49.20
GFI	92	23.7	78.19	136	27.4	89.20

Note. FFP = Fried Frailty Phenotype; FRAIL = Frail Scale; TFI = Tilburg Frailty Indicator; FI = Frail Index; GFI = Groningen Frailty Indicator.

The Tilburg Frailty Indicator (TFI)

The Tilburg definition measures human functioning by assessing 15 different components including physical, psychological and social aspects of older people's everyday functions. The psychological part consists of questions about anxiety, mood disorders and memory problems. The physical part is assessed by asking questions concerning weight loss, balance, walking, vision, fatigue, hand strength and hearing. The social part is evaluated by asking questions about missing people, receiving enough support and living alone. In the current study, 12 out of 15 criteria were used. Participants who met ≥5 criteria of the Tilburg definition were considered frail (32).

The Groningen Frailty Indicator (GFI)

The Groningen definition includes 15 self-report questions concerning the physical, cognitive, psychological and social domain of older people's life. Specifically, individuals were asked about their functioning in instrumental and daily living activities, reported vision and hearing impairment, loss of weight, number of medications consumed, memory impairment or memory complaints, feelings of depression or anxiety, feelings of emptiness and loneliness and rated their physical fitness. A score ≥4 is indicative of frailty (33).

Statistical Analyses

All statistical analyses were performed using SPSS 24 (SPSS, Chicago, Illinois). Incidence proportions were calculated as the number of new frailty cases reported by each frailty instrument divided by the number of population at risk. Frailty incidence was calculated a) for the total sample, b) separately for men and women and c) after both age and sex stratification. Age categorization was performed as follows: a) participants 65 to 69, b) 70 to 74, c) 75 to 79, d) 80 to 84 and e) ≥85 years old.

Results

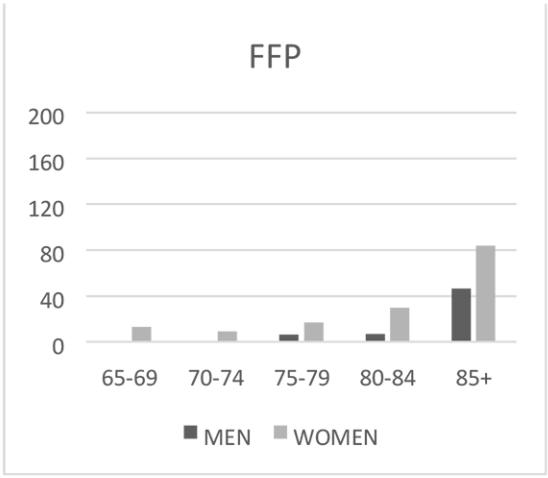
Out of 1984 individuals who initially participated in HELIAD, the follow-up cohort consisted of 1104 participants and the mean follow-up time was 3.05±0.85 years (median: 3 years). Excluding participants who died, those included in our analyses did not differ in a statistically significant manner with respect to age, sex, and education compared to participants without follow-up information.

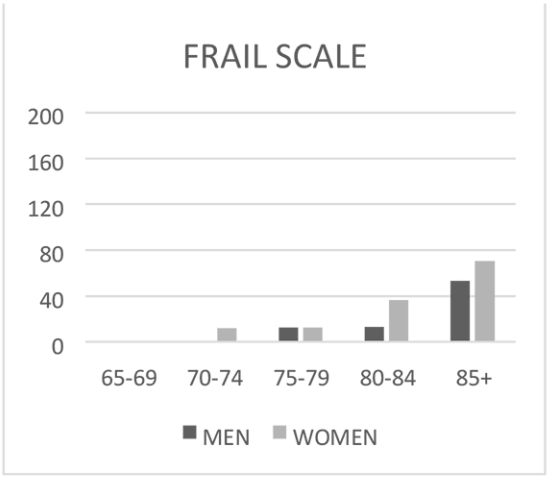
Regarding frailty, 55, 6, 181, 306 and 217 individuals were frail at baseline based on FFP definition, FRAIL Scale, FI, TFI and GFI respectively. Participants with frailty at baseline (depending on the frailty definition) were selectively excluded from the analyses, in order to measure the occurrence of new frailty cases. Moreover, participants with missing data on baseline frailty status were also excluded from the analyses. The number of participants with missing data on frailty were 1, 2, 4 and 3 when frailty was measured with FFP, FRAIL Scale, TFI and GFI respectively. In the case of FI, we noticed no missing data.

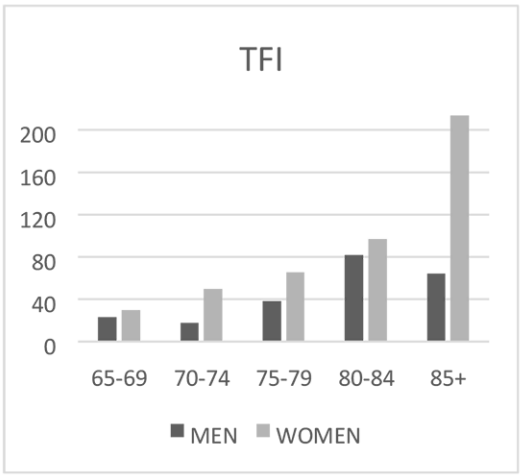
The incidence proportions of frailty differed depending on the definition used. The lowest proportion was detected when frailty was measured with the FRAIL Scale (2.5%, or 16.1 new cases of frailty per 1000 person-years) and the highest when GFI was used (25.8%, 88.7 new cases of frailty per 1000 person-years). Operationalization of frailty with FFP, TFI, FI and definition revealed a 3-years crude incidence proportion of 4.6%, 17.2%, and 18.1% (15, 55.7 and 59.3 new cases of frailty per 1000 person-years respectively).

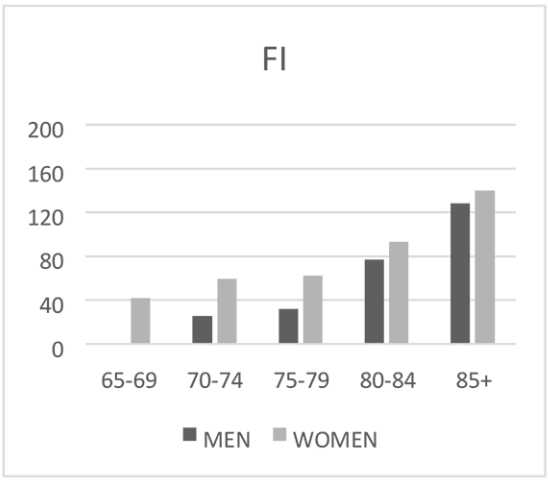
After dividing our sample based on sex, we observed that, irrespective of the definition used, compared to men, women showed higher frailty incidence rate (Table 1). Additional, age and sex stratification revealed that women, irrespective of age and frailty measurement, had higher incidence rates of frailty than men. A remarkable finding was that that in the youngest age groups, there were few cases of frail men. Specifically, among male participants aged 65-69 years, there were only 33.2 new cases of frailty per 1000 person-years, as measured only with the TFI. When other tools were used to assess frailty, there was no new frailty case among male participants aged 65-69. This was further noticed in frailty tools that belong to the phenotypic approach of frailty (FFP and FRAIL Scale): even in the group of men participants aged 70-74 years, there was no case of frailty. In general, we observed that in the group of the youngest-old male participants, the new frailty cases (as measured with the FFP, FRAIL Scale and FI) were few and tended to increase greatly in the age groups of 80-84 and 85+ years. On the contrary, irrespective of the frailty definition used, new frailty cases were present in all age groups of women participants (Figure 1).

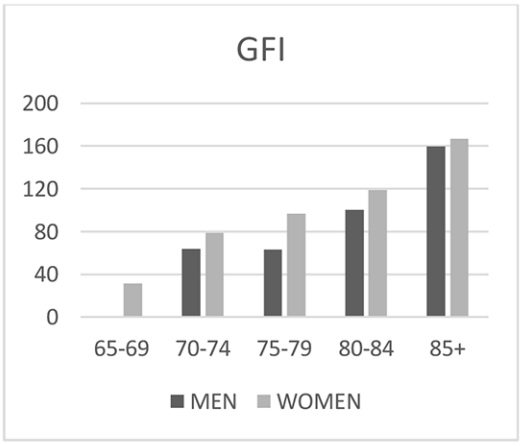
Figure 1. Incidence rates per sex and age group for: (a) Fried Frailty Phenotype (FFP), (b) FRAIL Scale, (c) Tilburg Frailty Indicator (TFI), (d) Frailty Index (FI) and (e) Groningen Frailty Index GFI)











Discussion

The present study aimed to investigate the frailty incidence and explore frailty sex differences in a population of Greek community-dwelling older people. The extensive dataset of the HELIAD study enabled the use of five different definitions (of the phenotypic and the multi-domain approach) and the respective tools for the assessment of frailty. Our results

indicated that male-female differences of frailty incidence are observed across the age groups. Frailty seems to be a condition concerning women >65 years old, and when it comes to men, it is more frequent in those aged more than 70 or even 75 years old.

Our results confirm the findings of the existing literature, according to which at all ages, women have higher frailty than men (3, 9, 34). In the current literature this sex frailty differences have been reported for FFP and FI tools. Regarding FFP, SHARE study reported that, compared to other European countries, in Southern Europe (Spain, Portugal, Italy and Greece) there is the largest sex difference in frailty (34). Specifically, the sample of SHARE study consisted of community-dwelling participants above the age of 50 and sex differences in frailty were significant between men and women of more than 60 years old, a population quite similar to that included in our study. The authors explained this finding by the fact that in Southern Europe, women experience a greater number of disabling but nonfatal comorbidities, whereas men experience more life-threatening conditions (more heart attacks, strokes, lung diseases etc.). Regarding FI, a meta-analysis of five large studies of community-dwelling older adults showed that in every age group, women had higher FI than men (3).

In the current study, we expanded previous findings by providing data for frailty tools that had not been explored so far: although frailty incidence rates per sex and age group varied in magnitude between scales, the male-female difference in rates exists in all scales. Still, it seems that frailty tools that measure mainly the phenotypic approach of frailty (FFP and FRAIL Scale) show a bigger difference between male and female scores (even in younger ages, as there were no case of frailty in male participants before the age of 75 years-old). Taking into account the criteria included in the phenotypic approach of frailty, one could suggest that women show an earlier decline of their physical health.

The mechanisms underlying the observed sex-differences are unknown; many biological and socio-behavioral factors could possibly attribute to this phenomenon (5). A possible explanation of the fact that women show higher frailty scores than men in any given age after 65 years old could be that frail men may die younger and studies end up measuring men who are less frail and in a better health condition than women. Moreover, studies have shown a higher prevalence of non-lethal diseases in women than in men, implying that even if women accumulate more deficits, and thus they become frailer, they are more resistant to mortality (9). Thus, an important factor contributing to frailty is not the number of the deficits accumulated but the nature of these deficits.

Nevertheless, the pattern of sex differences in frailty is consistent between studies and this may suggest that there is an innate sex difference in the process of deficit accumulation (3). Hormones and genetics may play a role. It is well established that the presence of two X-chromosomes with longer telomeres and estrogens could give a survival advantage in female but do not protect them from deficit accumulation (35). Sex differences in inflammation and immune cell changes could also partially explain the frailty differences observed between the two sexes (36). Other social, behavioral and cultural factors should not be ignored. Sex differences in psychological factors, such as mood disorders and stress or in social and behavioral factors, such as socio-economic, educational level and nutrition would play a major role in understanding this paradox and strengthen the multidimensional side of frailty. Finally, one could hypothesize that part of the difference in rates may be related to the fact that frailty tools measure aspects in which men have a biological advantage and thus, even when using sex-specific criteria, these tools biased towards women. Although this is not the aim of the current study and cannot be answered by the analyses performed, it remains a theoretical question regarding frailty definitions.

In relation to overall frailty incidence and comparing our results to previous studies exploring frailty incidence in community dwelling older people, we detected a lower frailty incidence in the Greek population. Specifically, according to a recent meta-analysis the incidence rate of frailty was 40.0 cases per 1000 person-years when the FFP was used to measure frailty and 71.3 cases per 1000 person-years when other criteria of frailty (mainly the FI) were adopted (37). In comparison to that, we observed lower frailty rates: 15 cases per 1000 person-years for the FFP tool and 59.33 cases per 1000 person-years for the FI. Lower frailty rates could be explained by the fact that participants in this cohort more frequently engage in habits that are close to the Mediterranean way of living, such as plant-based diet, sleep patterns, socialization, social support and physical activity (27, 38).

There are some limitations in the present analysis that need to be taken into consideration. A limitation common to longitudinal studies is the loss of participants to follow up, which may lead to a relatively healthy or younger sample. However, participants who completed the follow-up evaluation did not differ from those who did not in terms of age, sex and educational level. Moreover, the average follow-up time was approximately 3 years, and it is uncertain how incidence would change over the longer-term. In the HELIAD study many data regarding frailty criteria are self-reported and thus their reliability is subject to recall bias. However, in the case that a participant had significant cognitive problems or was diagnosed with dementia, the information was collected from a proxy.

A major strength of our study is the use of five different frailty measurements in the same population. Moreover, the study's sample was large and representative as it was derived both from urban and rural areas, enabling the generalization of our findings at least in the Greek population.

Conclusions

Taken together, the current study provides data regarding sex differences in frailty incidence by applying both phenotypic and multi-domain frailty instruments by age groups. Overall, we found that the youngest-old women had higher frailty incidence rates than the youngest-old men. Understanding the pathophysiology of frailty in two sexes may lead to more effective strategies of frailty prevention. Under this view, the current results suggest that studies investigating the factors

that prevent or contribute to frailty, should also explore sex differences and provide data disaggregated for men and women.

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Conflicts of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical standard: The HELIAD study has been approved by the National and Kapodistrian University of Athens Ethics Committee (256/10-05-2021). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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