Maturitas 168 (2023) 1–6

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Original article

Frailty and the risk of infection-related hospitalizations in older age: Differences by sex

Caterina Trevisan [a,b,c], Marianna Noale [d,*], Claudio Barbiellini Amidei [e], Eliana Ferroni [e], Cristina Basso [e], Ugo Fedeli [e], Giovannella Baggio [f], Stefania Maggi [d], Giuseppe Sergi [a]

[a] Geriatric Unit, Department of Medicine, University of Padova, via Giustiniani 2, 35128 Padova, Italy
[b] Department of Medical Science, University of Ferrara, via Aldo Moro 2, 44124 Ferrara, Italy
[c] Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, 17177 Stockholm, Sweden
[d] Neuroscience Institute, National Research Council, via Giustiniani 2, 35128 Padova, Italy
[e] Epidemiological Department (SER), Azienda Zero, via Avanzo 35, 35132 Padova, Italy
[f] Italian Center for the Studies on Gender Health and Medicine, via Giustiniani 2, 35128 Padova, Italy

ARTICLE INFO

Keywords:
Frailty
Infectious diseases
Hospitalization
Sex differences

ABSTRACT

Objectives: To investigate the extent to which frailty is associated with infection-related hospitalizations in older men and women, and to explore whether, among women, previous exposure to endogenous estrogens in terms of age at menopause and number of pregnancies modify such a relationship.
Study design: The sample comprised 2784 participants in the Progetto Veneto Anziani aged ≥65 years. At baseline and after 4.4 years, frailty was identified according to the presence of three or more of the following: weakness, exhaustion, weight loss, low physical activity, and low walking speed. A passive follow-up on infection-related hospitalizations and mortality was performed for 10 years of observation through linkage with regional registers.
Main outcome measures: The association between frailty and infection-related hospitalizations was assessed through mixed-effects Cox regressions.
Results: Frailty was significantly associated with a 78 % higher risk of infection-related hospitalization, with stronger results in men (hazard ratio = 2.32, 95 % confidence interval 1.63–3.30) than in women (hazard ratio = 1.54, 95 % confidence interval 1.18–2.02). Focusing on women, we found a possible modifying effect for the number of pregnancies but not menopausal age. Women who had experienced one or no pregnancy demonstrated a higher hazard of infection-related hospitalization as a function of frailty (hazard ratio = 3.00, 95 % confidence interval 1.58–5.71) than women who had experienced two or more pregnancies (hazard ratio = 1.68, 95 % confidence interval 1.18–2.39).
Conclusion: Frailty in older age increases the risk of infection-related hospitalizations, especially in men. The "immunologic advantage" of the female sex in younger age seems to persist also after menopause as a function of the number of pregnancies a woman has experienced.

1. Introduction

Over the last 20 years, frailty, a geriatric syndrome with reduced resilience to adverse events and stressors, has become one of the central aspects assessed in geriatric clinical practice and research [1–3]. Several adverse outcomes have been associated with this condition, including the development of chronic diseases, functional and cognitive decline, worsening quality of life, and mortality [1,4–6]. However, some aspects remain poorly explored, such as the relationship between frailty and the risk of infectious diseases [7,8].

In this regard, frailty may make individuals more vulnerable to infections by exacerbating the changes in the immune system and establishing a status of mild chronic inflammation, called *inflammaging* [9–11]. These mechanisms represent the physio-pathological basis of frailty and can also predispose individuals to infectious diseases. Concerning the changes in the immune system, the term *immunosenescence*

* Corresponding author at: National Research Council - Neuroscience Institute, Aging Branch, Via Giustiniani 2, 35128 Padova (PD), Italy.
E-mail addresses: caterina.trevisan.5@studenti.unipd.it (C. Trevisan), marianna.noale@in.cnr.it (M. Noale), eliana.ferroni@azero.veneto.it (E. Ferroni), cristina.basso@azero.veneto.it (C. Basso), ugo.fedeli@azero.veneto.it (U. Fedeli), giovannella.baggio@unipd.it (G. Baggio), stefania.maggi@in.cnr.it (S. Maggi), giuseppe.sergi@unipd.it (G. Sergi).

https://doi.org/10.1016/j.maturitas.2022.10.009
Received 29 June 2022; Received in revised form 20 October 2022; Accepted 26 October 2022
Available online 4 November 2022

refers to the quantitative and qualitative age-related decline in innate and acquired immunity [12]. Such changes, however, may vary between men and women according to the sex-specific differences that characterize immunity from the pre-birth period to adult age and are influenced by genetic and hormonal factors [12,13].

In particular, estrogens could stimulate the immune system, especially cellular and humoral responses, promoting antibody production [13] and making women more likely to present autoimmune diseases and have stronger vaccine responses than men [12]. On the contrary, androgens may inhibit natural killer cells, CD8+ T-lymphocytes, and cytokines and antibody production [13]. Overall, these sex-specific aspects might determine an immunologic advantage of women compared with men in young and adult age. However, this picture may change with aging due to the steep reduction in women' estrogen levels at menopause and the gradual decline in androgen concentrations in men [12–14]. To the best of our knowledge, evidence about possible sex-specific differences in the predisposition to infections in older age is scarce. Moreover, it is unclear whether greater estrogen exposure at a younger age may determine a kind of "immunologic reserve", which can preserve the advantage of women compared with men.

This study hypothesized that frailty could increase the risk of experiencing infection-related hospitalization in older people with some sex differences. In particular, we expected that women, especially those more exposed to estrogens at their younger age, may keep an immunological advantage counteracting the frailty-induced vulnerability to infectious diseases.

Therefore, we aimed to investigate the association between frailty and the risk of infection-related hospitalizations in older men and women and to explore if, among the female population, previous exposure to endogenous estrogens in terms of menopause age and number of pregnancies can modulate such a relationship.

2. Methods

2.1. Study population

This work uses data from the Progetto Veneto Anziani (Pro.V.A.), a prospective study that involved individuals aged ≥65 years who lived in Padova e Rovigo provinces in northern Italy. Participants were randomly enrolled through a multistep method stratified by age and sex (details can be found elsewhere [15]). The response rate was 77 % and 64 % for male and female participants, respectively, obtaining a final sample of 3099 individuals (1245 M, 1854 F). Participants' baseline assessments were performed from 1995 to 1997 by trained nurses and physicians. Active follow-ups were performed after a mean of 4.4 and 7 years from baseline. Passive follow-up on hospitalizations and mortality was performed until 2018 through linkage with regional registers.

The study protocol was approved by the Ethics committees from the University of Padova, the Local Health Units no.15 and 18 of the Veneto Region, and the province of Padova center. All participants signed informed consent. The study complies with the principles of the Declaration of Helsinki.

For the present study, we excluded 314 individuals who did not present complete information on frailty at baseline and one participant for whom linkage to regional registers was not possible. The final analytical sample consisted, therefore, of 2784 older adults.

2.2. Data collection

Assessments of the study participants were performed through physical examinations and tests, radiologic and biochemical analyses, evaluation of medical records, and administration of validated scales. In this work, in particular, we considered the following data: sociodemographic information (age, sex, living arrangements [living with somebody vs living alone vs living in a nursing home]), educational level (categorized as < vs ≥5 years), monthly income (categorized as ≤ vs >1000 euros, according with the minimum pension value in Italy at the time of the baseline assessment), smoking habits (classified as never, former, and current smoking), alcohol consumption (defined as no/occasional, light to moderate with <7 units of alcohol [UA]/week for women and <14 UA/week for men, and heavy with ≥7 UA/week for women and ≥14 UA/week for men), and the self-reported information on having received the flu vaccine in the last year. The research team assessed anthropometric measures, including body weight and height, and computed the body mass index (BMI) from the ratio between weight and height squared. The number of pregnancies (categorized as < vs ≥2, based on the lowest tertile value) and menopause age were also collected for the female participants.

Concerning health status, the presence of the following diseases was ascertained by skilled physicians: arterial hypertension, orthostatic hypotension, ischemic heart diseases, atrial fibrillation, heart failure, peripheral artery diseases, stroke, anaemia, osteoporosis, osteoarthrosis (at the hand, knee, or hip), congenital intellectual deficits, Parkinson's disease and parkinsonism, chronic obstructive pulmonary disease (COPD), diabetes mellitus, chronic kidney disease, cancer (including breast and uterus malignancy), vision deficits, hearing deficits, asthma, dyslipidemia, discopathy, urinary incontinence, and faecal incontinence. From the sum of the conditions mentioned above, we obtained the total number of chronic diseases for each participant as an indicator of multimorbidity.

Cognitive status was assessed through the Mini-Mental State Examination (MMSE), a validated tool to evaluate cognitive performance in older people. The MMSE total score ranges from 0 to 30 with increasing cognitive performance, and the cutoff of 24 is used to detect the presence of cognitive impairment [16]. Functional status was measured through the Activities of Daily Living (ADL) scale, including assessment of self-sufficiency in bathing, dressing, transferring, toileting, continence, and feeding [17].

2.2.1. Definition of exposures

Frailty at baseline and the 4.4-year follow-up was defined according to the criteria proposed by Fried et al. [1], as the presence of at least three items among weakness, exhaustion, weight loss, low physical activity, and low walking speed.

Weakness was defined based on the participants' handgrip, using our population's lowest sex- and BMI-specific 20th percentile of handgrip as a cutoff [1]. The measurement of the handgrip was performed using a dynamometer, with two trials per hand. When constructing the frailty variable, those who had missing data on handgrip were considered weak if they reported being unable to eat autonomously based on the specific ADL item, assuming that grip strength is a fundamental requisite for feeding ability [18].

Exhaustion was defined based on the 30-item Geriatric Depression Scale (GDS) [19]. In particular, a participant was considered exhausted if he/she declared not feeling full of energy and he/she scored ≥11 points at the GDS.

Weight loss was defined based on self-reported information on a loss of ≥5 kg in the last year.

Low physical activity was defined after computing the estimated energy expenditure for daily activities (collected through a structured questionnaire) and using the lowest sex-specific 20th percentile as a cutoff [1].

Low walking speed was defined considering walking time at the usual pace over a 4-m distance, using the lowest sex- and height-specific 20th percentile as a cutoff [1]. Those who had missing data on walking speed were considered to have a low walking speed whether they were declared unable to move around autonomously (walking aids were admitted).

2.2.2. Definition of outcome

Infection-related hospitalizations until 2008 were obtained through linkage from regional registers, considering the ICD-9 codes reported at

discharge as primary or secondary diagnosis (for the list of ICD-9 codes, please see Supplementary Table 1, [20,21]).

For this study, we considered infection-related hospitalizations over the first 10 years of observations, distinguishing two time windows:

- from baseline to the first follow-up assessment (median duration of 4.4 years), and.
- from the first follow-up assessment to the end of observation (median duration of 5.8 years).

Deaths during the observation periods were derived from regional registers.

2.3. Statistical analysis

The baseline characteristics of the study participants for the total sample and by sex are described as mean (standard deviation) and count (frequency) for quantitative and qualitative variables, respectively. The comparison of such characteristics between men and women (and, among women, between those who had 0–1 vs 2+ pregnancies) was performed through Student *t*-test and the Fisher or Chi-squared test.

Mixed-effects Cox regressions were performed to evaluate the association between frailty and the risk of infection-related hospitalizations over the two time periods considered (from baseline to the first follow-up and from the first follow-up to 2008). The model intercept was set as random to take into account the presence of multiple observations per participant. In this analysis, we considered time to the first infection-related hospitalization or, for those who did not experience any event, time to death or the end of observation, as appropriate. Analyses were run first adjusted only for age and sex (Model 1) and, second, also for other potential confounders in the association (living arrangements, education, monthly income, smoking habits, alcohol consumption, flu vaccine in the past year, number of chronic diseases, and Mini-Mental State Examination; Model 2). As a sensitivity analysis, we performed the same models considering separately respiratory, gastrointestinal, genitourinary, and other site infections as outcomes. Moreover, a further sensitivity analysis was run after adjusting the model for the ADL score in order to consider the possible confounding related to functional status.

The modifying effect of sex, menopausal age, and the number of pregnancies in that association was investigated by including the multiplicative interaction terms in the adjusted models and performing appropriate stratified analyses.

All analyses were performed through R version 4.0.5, and a *p*-value <0.05 was set as statistically significant.

3. Results

The characteristics of the sample as a whole and by sex (1135 M, 1649 F) are reported in Supplementary Table 2, and those comparing frail and non-frail men and women are shown in Table 1. The sample had a mean age of 75.9 (SD: 7.7) years, with no substantial differences by sex, and a low educational level, with around half having attended ≥5 years of schooling, especially men and frail individuals. Most participants lived in the community, and only 2.2 % were institutionalized. Men and women significantly differed on the frequency of risk behaviours, the former being more likely to smoke or have smoked and consume alcoholic beverages. Concerning health status, the total sample had, on average, almost five chronic conditions, a pretty high level of self-sufficiency in basic ADL, and an MMSE score of 23.4. Worse results on these aspects were observed in frail participants. Considering sex differences, women presented a higher prevalence of diabetes, chronic kidney disease, and osteoarticular conditions, while men were more likely to suffer from COPD and cardiovascular diseases.

Regarding frailty, 226 participants (8.1 %) were frail at baseline, while considering the 1924 individuals who underwent the 4.4-year assessment, frailty was present in 348 (12.5 %). No significant differences in frailty prevalence between men and women were observed in both evaluations.

During the 10-year follow-up, 1355 (48.7 %) individuals died. During the first time window, the number of individuals experiencing at least one infection-related hospitalization was 278 (10 %), while in the second time window, it was 477 (24.8 %). The most common infections

Table 1
Baseline characteristics of the male and female participants by frailty status.

	Men			Women		
	Non-frail	Frail	p-Value	Non-frail	Frail	p-Value
n	1055	80		1503	146	
Age (years)	75.68 (7.65)	83.22 (6.67)	<0.001	75.12 (7.40)	81.00 (6.91)	<0.001
≥2 pregnancies	–	–	–	910 (75.8)	75 (84.3)	0.093
Menopausal age (years)	–	–	–	48.84 (5.69)	48.05 (5.74)	0.125
Education ≥5 years	347 (32.9)	41 (51.2)	0.001	869 (57.8)	107 (73.3)	<0.001
Living arrangements			0.071			0.078
Living with somebody	953 (90.3)	68 (85.0)		1126 (74.9)	107 (73.3)	
Living alone	86 (8.2)	8 (10.0)		337 (22.4)	30 (20.5)	
Living in nursing home	14 (1.3)	4 (5.0)		35 (2.3)	7 (4.8)	
Smoking habits			0.001			0.274
Never	230 (21.8)	31 (38.8)		1296 (86.2)	134 (91.8)	
Former	649 (61.5)	46 (57.5)		138 (9.2)	9 (6.2)	
Current	175 (16.6)	3 (3.8)		65 (4.3)	3 (2.1)	
Alcohol consumption			<0.001			0.609
No or occasional	494 (46.8)	60 (75.0)		1260 (83.8)	127 (87.0)	
Light to moderate	253 (24.0)	13 (16.2)		217 (14.4)	17 (11.6)	
Heavy	308 (29.2)	7 (8.8)		26 (1.7)	2 (1.4)	
COPD	163 (15.5)	21 (26.2)	0.018	73 (4.9)	10 (6.8)	0.394
Diabetes mellitus	85 (8.1)	9 (11.2)	0.43	156 (10.4)	22 (15.1)	0.109
Cancer	89 (8.4)	9 (11.2)	0.511	103 (6.9)	13 (8.9)	0.45
Gynecological cancer						0.57
Breast cancer	–	–	–	28 (1.9)	4 (2.7)	
Uterus	–	–	–	6 (0.4)	0 (0.0)	
Chronic kidney disease	217 (20.7)	25 (31.6)	0.032	526 (35.1)	77 (52.7)	<0.001
Cardiovascular diseases	304 (28.9)	31 (38.8)	0.082	257 (17.1)	63 (43.2)	<0.001
Osteoarticular diseases	443 (42.2)	52 (65.0)	<0.001	1053 (70.2)	130 (89.0)	<0.001
Neurologic diseases	120 (11.4)	26 (32.9)	<0.001	167 (11.1)	39 (26.7)	<0.001
N. chronic diseases	4.43 (2.37)	6.92 (2.69)	<0.001	4.95 (2.25)	7.45 (2.40)	<0.001
Mini-Mental State Examination	24.28 (5.63)	20.24 (5.77)	<0.001	23.34 (5.93)	19.72 (5.98)	<0.001
Activities of Daily Living	5.35 (1.30)	3.81 (1.79)	<0.001	4.96 (1.39)	3.49 (1.81)	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease. Individuals with missing values in: education (n = 1), smoking habits (*n* = 5), living arrangements (n = 9), Activities of Daily Living (*n* = 7). *P*-values refer to the comparison between frail and non-frail individuals, among men and women.

were those affecting the respiratory tract, followed by the genitourinary and gastrointestinal ones (Supplementary Table 3).

As shown in Table 2, frailty was significantly associated with a 77 % higher risk of infection-related hospitalization compared with no frailty. After testing the interaction between sex and frailty ($p_{interaction} = 0.12$), analyses were stratified by sex. We found that the hazard of infection-related hospitalization linked to frailty was more marked among men (HR = 2.32, 95%CI: 1.63–3.30) than women (HR = 1.55, 95%CI: 1.18–2.03), even when adjusted for potential confounders. Results were also confirmed when considering only respiratory, genitourinary, and other infections, while no significant associations were observed for the gastrointestinal ones (Supplementary Table 4). No substantial differences emerged when adjusting also for functional status (Supplementary Table 5).

Of the 1289 female participants with information on the number of pregnancies, 985 (76.4 %) had ≥2 pregnancies. The latter were more likely to report menopause at an older age, have a worse educational level, be never smokers, cohabit, and have a lower frequency of cancer (Supplementary Table 5). No differences in other sociodemographic and medical characteristics were observed. Among the 1512 women who had available data on the age at menopause, the mean age at menopause was 48.8 (SD: 5.7) years. Menopausal age did not modify the association between frailty and hospital admissions due to infectious diseases ($p_{interaction} = 0.81$, data not shown). Instead, the number of pregnancies seemed to modify that association ($p_{interaction} = 0.11$), with those who had experienced <2 pregnancies demonstrating a higher hazard of infection-related hospitalization as a function of frailty (HR = 3.00, 95% CI:1.58–5.71), compared with women who had ≥2 pregnancies (HR = 1.68, 95%CI: 1.18–2.39) (Table 3).

4. Discussion

This study demonstrates that the impact of frailty on the risk of ward admissions due to infectious diseases in older age presents some relevant sex differences, with men showing a higher frailty-induced vulnerability to infections than women. Such differences seem to be modulated by hormonal exposure at a younger age. In particular, women with more pregnancies showed the weakest impact of frailty on the risk of infection-related hospitalizations.

Infectious diseases are frequent acute conditions in older age and, in this population, are linked to high morbidity and mortality. Approximately >15 % of hospitalizations in individuals aged 65 years or older are due to infectious diseases, mainly affecting the urinary and respiratory tracts [22]. In line with previous reports, we found that the frequency of infection-related hospitalizations increased from the first to the second time windows considered, in parallel with the aging of our cohort. Indeed, in the first period, around one out of ten individuals experienced at least one hospitalization for infectious diseases, while, in the second period, the frequency increased almost up to one out of four participants [23,24].

Frailty is a condition that increases the vulnerability of external stressors and may worsen the course and prognosis of acute and chronic diseases [6,25–27]. In the field of infectious diseases, previous studies have demonstrated the impact of frailty on the recovery of acute infections [28] and its association with infection-related hospitalizations in specific populations [7]. The mechanisms through which frailty could make individuals more vulnerable to infectious diseases include the reduction of innate immunity efficiency and the number and functions of B and T lymphocytes [8,12]. Our study found that the detrimental effect of frailty on the risk of infections was greater among older men. Although the male population has shown a higher incidence and mortality due to infectious diseases in young and adult age, in older people, such sex difference seems to attenuate, mainly due to hormonal changes [12]. Our results support the hypothesis of an “immunologic reserve” that can preserve the advantage of women not only against the risk of infections in advanced age but also frailty-related immunosenescence.

To explore the mechanisms underlying this effect, we tested whether the exposure to endogenous estrogens, in terms of the number of pregnancies and menopausal age, could interact with frailty in influencing the risk of infection-related hospitalizations. We found that the detrimental impact of frailty on immune function seemed to be counteracted by a higher number of pregnancies rather than late-onset menopause. Several studies investigated the intriguing relationship between reproductive effort and longevity in the latter decades, uncovering a negative link in many species [29,30]. However, evidence on humans is still scarce and contrasting. Some researchers considered the association between the number of children and telomeres length. Although women who had fewer children had shorter telomere length in one work [31], in other studies, parity was associated with signs of accelerated cellular aging [32,33]. Evidence is even more limited concerning the effect of reproductive effort on the immune system. On the one hand, a study on women in the preindustrial period suggested a possible detrimental influence of twinning (but not the total number of pregnancies) on immunosenescence, finding a higher risk of dying of tuberculosis in twin mothers [29]. On the other hand, the works of Barrat and colleagues in animal models uncovered that multiparity might counteract the involution of the immune system, allowing maintaining the balance between naïve and memory T lymphocytes [34] and marrow lymphopoiesis and myelopoiesis B [35]. These effects would help preserve a high reserve of B lymphocytes in older age [35] and delay the development of immunosenescence [36]. In line with these findings, a recent study focusing on the short- and long-term impact of motherhood on hippocampal neurogenesis, microglia and systemic cytokines' levels observed a persistent reduction of IL-4 in primiparous but not in nulliparous rats and an age-related increase in IFN-γ and IL-10 levels and IL-5 decrease only among the nulliparous ones [37]. These findings support our results and align with previous reports showing that the number of pregnancies influenced the onset and development not only of gynecologic diseases (e.g., breast cancer [38]) but also chronic conditions typical of older age and linked to inflammation, such as Alzheimer's disease [39]. Despite the existent data on the effects of estrogens and progesterone in modulating immune system compositions and function [13,14], further studies are still needed to explore how these changes can determine sex differences in the occurrence and severity of infectious diseases,

Table 2
Association between frailty and the risk of infection-related hospitalizations in the total sample and by sex.

	All ($n = 2784$)			Men ($n = 1135$)			Women ($n = 1649$)		
	N. events, person-years	Model 1	Model 2	N. events, person-years	Model 1	Model 2	N. events, person-years	Model 1	Model 2
No frailty	611, 19,788.3	[ref]	[ref]	249, 7441.8	[ref]	[ref]	362, 12,346.5	[ref]	[ref]
Frailty	144, 1856.1	1.95 (1.59–2.40) $p < 0.001$	1.77 (1.43–2.20) $p < 0.001$	55, 552.2	2.33 (1.65–3.29) $p < 0.001$	2.32 (1.63–3.30) $p < 0.001$	89, 1303.8	1.79 (1.38–2.31) $p < 0.001$	1.55 (1.18–2.03) $p = 0.001$

Model 1 is adjusted for age and sex (as appropriate). Model 2 is adjusted also for living arrangements, education, monthly income, smoking habits, alcohol consumption, flu vaccine in the past year, number of chronic diseases, and the Mini-mental state examination.

Table 3
Association between frailty and the risk of infection-related hospitalizations in the female participants by number of pregnancies.

	N. pregnancies < 2 (n = 304)			N. pregnancies ≥ 2 (n = 985)		
	N. events, person-years	Model 1	Model 2	N. events, person-years	Model 1	Model 2
No frailty	72, 2692.9	[ref]	[ref]	227, 8443.8	[ref]	[ref]
Frailty	16, 203.9	2.58 (1.41–4.72) p = 0.002	2.87 (1.50–5.49) p = 0.002	62, 924.9	1.94 (1.41–2.66) p < 0.001	1.66 (1.17–2.36) p = 0.005

Model 1 is adjusted for age. Model 2 is adjusted also for living arrangements, education, monthly income, smoking habits, alcohol consumption, flu vaccine in the past year, number of chronic diseases, Mini-Mental State Examination, and age at menopause.

especially in the presence of increasing-vulnerability conditions like frailty.

In addition, the effect of social network on the relationship between the number of pregnancies and the risk of infectious diseases in advanced age should be further evaluated. Indeed, having more social interactions could pose the individual at a higher risk of contact with possible sources of transmissible diseases [40]. At the same time, greater social connections (as a consequence of a larger family unit) have been linked to favourable health outcomes and reduced chronic inflammation [41] and may ensure adherence to behavioural preventive actions to reduce the risk of contracting infections [42].

Our findings need to be interpreted in light of some limitations. These include, first, the presence of missing data on the number of pregnancies in 21.8 % of the sample and the relatively small number of female participants with none or one pregnancy, which could have affected the statistical power of our stratified analyses. A second limitation lies in the lack of data on the menarche age that would have allowed us to more precisely estimate the length of the fertile period and explore the modifying effect of endogenous estrogens in the association between frailty and infectious diseases. Third, we did not have information on hormone replacement therapy, which has been shown to have a possible protective role in some infections [14]. However, we may argue that the prevalence of women under estrogen treatment would have been negligible since it was around 12 % in similar study populations [43]. On the other hand, the large sample size and long follow-up are strengths of the study, and the exploratory analysis on the possible modifying effect of multiparity supports the novelty and relevance of our work.

In conclusion, frailty in older age may increase the risk of ward admissions due to infectious diseases, with a more marked effect in men than in women. The “immunologic advantage” of the female sex in younger age seems to persist also after menopause and could be influenced by the number of pregnancies a woman has experienced. This advantage might counteract the greater vulnerability to infections induced by the presence of frailty syndrome. Overall, this study supports the need to adopt sex- and gender-specific approaches in the clinical and epidemiological fields to improve the delivery of personalized medical services.

Contributors

Caterina Trevisan contributed to conception and design of the study, acquisition of data, statistical analysis, interpretation of data, drafting the article and revision of the article.

Marianna Noale contributed to acquisition of data, interpretation of data, and critical revision of the article.

Claudio Barbiellini Amidei contributed to interpretation of data and critical revision of the article.

Eliana Ferroni contributed to interpretation of data and critical revision of the article.

Cristina Basso contributed to interpretation of data and critical revision of the article.

Ugo Fedeli contributed to interpretation of data and critical revision of the article.

Giovannella Baggio contributed to interpretation of data and critical revision of the article.

Stefania Maggi contributed to critical revision of the article.

Giuseppe Sergi contributed to critical revision of the article.

All authors saw and approved the final version and no other person made a substantial contribution to the paper.

Funding

The data collection phase of the PRO.V.A. study was supported by the Fondazione Cassa di Risparmio di Padova e Rovigo; the University of Padova; Veneto Region's Local Health and Social Care Services No. 15 and No. 18 (Azienda Unità Locale Socio Sanitaria 15 and 18); and a grant from the Veneto Regional Authority (Ricerca Sanitaria Finalizzata n.156/03). The data analysis phase was financed by a grant from the “Ricerca Sanitaria Finalizzata Bando 2017, Regione Veneto” (RSF-2017-00000533, deliberazione n. 490 17.04.2018).

Ethical approval

The study protocol was approved by the Ethics committees from the University of Padova, the Local Health Units No. 15 and No. 18 of the Veneto Region, and the province of Padova center. All participants signed informed consent. The study complies with the principles of the Declaration of Helsinki.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Declaration of competing interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.maturitas.2022.10.009.

References

[1] L.P. Fried, C.M. Tangen, J. Walston, A.B. Newman, C. Hirsch, J. Gottdiener, T. Seeman, R. Tracy, W.J. Kop, G. Burke, M.A. McBurnie, Frailty in older adults: evidence for a phenotype, J. Gerontol. A Biol. Sci. Med. Sci. 56 (2001) M146–M156. http://www.ncbi.nlm.nih.gov/pubmed/11253156.

[2] K. Rockwood, A. Mitnitski, Frailty in relation to the accumulation of deficits, J. Gerontol. A Biol. Sci. Med. Sci. 62 (2007) 722–727. http://www.ncbi.nlm.nih.gov/pubmed/17634318.

[3] J.E. Morley, B. Vellas, G. Abellan van Kan, S.D. Anker, J.M. Bauer, R. Bernabei, M. Cesari, W.C. Chumlea, W. Doehner, J. Evans, L.P. Fried, J.M. Guralnik, P. R. Katz, T.K. Malmstrom, R.J. McCarter, L.M. Gutierrez Robledo, K. Rockwood, S. von Haehling, M.F. Vandewoude, J. Walston, Frailty consensus: a call to action, J. Am. Med. Dir. Assoc. 14 (2013) 392–397, https://doi.org/10.1016/j.jamda.2013.03.022.

[4] S. von Haehling, S.D. Anker, W. Doehner, J.E. Morley, B. Vellas, Frailty and heart disease, Int. J. Cardiol. 168 (2013) 1745–1747, https://doi.org/10.1016/j.ijcard.2013.07.068.

[5] R. Rizzoli, J.-Y. Reginster, J.-F. Arnal, I. Bautmans, C. Beaudart, H. Bischoff-Ferrari, E. Biver, S. Boonen, M.-L. Brandi, A. Chines, C. Cooper, S. Epstein, R.A. Fielding, B. Goodpaster, J.A. Kanis, J.-M. Kaufman, A. Laslop, V. Malafarina, L.R. Mañas, B. H. Mitlak, R.O. Oreffo, J. Petermans, K. Reid, Y. Rolland, A.A. Sayer, Y. Tsouderos, M. Visser, O. Bruyère, Quality of life in sarcopenia and frailty, Calcif. Tissue Int. 93 (2013) 101–120, https://doi.org/10.1007/s00223-013-9758-y.

[6] K.E. Ensrud, S.K. Ewing, B.C. Taylor, H.A. Fink, K.L. Stone, J.A. Cauley, J.K. Tracy, M.C. Hochberg, N. Rodondi, P.M. Cawthon, Study of osteoporotic fractures research group, frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures, J. Gerontol. A Biol. Sci. Med. Sci. 62 (2007) 744–751. http://www.ncbi.nlm.nih.gov/pubmed/17634322.

[7] D.A. Piggott, A.D. Muzaale, R. Varadhan, S.H. Mehta, R.P. Westergaard, T. T. Brown, K.V. Patel, J.D. Walston, S.X. Leng, G.D. Kirk, Frailty and cause-specific hospitalization among persons aging with HIV infection and injection drugUse, J. Gerontol. A Biol. Sci. Med. Sci. 72 (2016) glw142, https://doi.org/10.1093/gerona/glw142.

[8] D.L. Vetrano, F. Triolo, S. Maggi, R. Malley, T.A. Jackson, A. Poscia, R. Bernabei, L. Ferrucci, L. Fratiglioni, Fostering healthy aging: the interdependency of infections, immunity and frailty, Ageing Res. Rev. 69 (2021), https://doi.org/10.1016/J.ARR.2021.101351.

[9] C. Franceschi, J. Campisi, Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases, J. Gerontol. Ser. A Biol. Med. Sci. 69 (2014) S4–S9, https://doi.org/10.1093/gerona/glu057.

[10] H. Li, B. Manwani, S.X. Leng, Frailty, inflammation, and immunity, Aging Dis. 2 (2011) 466–473. http://www.ncbi.nlm.nih.gov/pubmed/22396895.

[11] S.X. Leng, Q.L. Xue, J. Tian, J.D. Walston, L.P. Fried, Inflammation and frailty in older women, J. Am. Geriatr. Soc. 55 (2007) 864–871, https://doi.org/10.1111/j.1532-5415.2007.01186.x.

[12] C. Giefing-Kröll, P. Berger, G. Lepperdinger, B. Grubeck-Loebenstein, How sex and age affect immune responses, susceptibility to infections, and response to vaccination, Aging Cell 14 (2015) 309–321, https://doi.org/10.1111/acel.12326.

[13] S.L. Klein, K.L. Flanagan, Sex differences in immune responses, Nat. Rev. Immunol. 16 (2016) 626–638, https://doi.org/10.1038/nri.2016.90.

[14] M. Sund, O. Fonseca-Rodríguez, A. Josefsson, K. Welen, A.M. Fors Connolly, Association between pharmaceutical modulation of oestrogen in postmenopausal women in Sweden and death due to COVID-19: a cohort study, BMJ Open 12 (2022), https://doi.org/10.1136/BMJOPEN-2021-053032.

[15] M.-C. Corti, J.M. Guralnik, L. Sartori, G. Baggio, E. Manzato, P. Pezzotti, G. Barbato, S. Zambon, L. Ferrucci, S. Minervini, E. Musacchio, G. Crepaldi, The effect of cardiovascular and osteoarticular diseases on disability in older italian men and women: rationale, design, and sample characteristics of the progetto Veneto anziani (PRO.V.A.) study, J. Am. Geriatr. Soc. 50 (2002) 1535–1540, https://doi.org/10.1046/j.1532-5415.2002.50409.x.

[16] P.F. Malloy, J.L. Cummings, C.E. Coffey, J. Duffy, M. Fink, E.C. Lauterbach, M. Lovell, D. Royall, S. Salloway, Cognitive screening instruments in neuropsychiatry: a report of the committee on research of the american neuropsychiatric association, J. Neuropsychiatry Clin. Neurosci. 9 (1997) 189–197, https://doi.org/10.1176/jnp.9.2.189.

[17] S. Katz, T.D. Downs, H.R. Cash, R.C. Grotz, Progress in development of the index of ADL, Gerontologist 10 (1970) 20–30, https://doi.org/10.1093/geront/10.1_part_1.20.

[18] C. Trevisan, G. Grande, D. Vetrano, S. Maggi, G. Sergi, A. Welmer, D. Rizzuto, Gender differences in the relationship between marital status and the development of frailty: a swedish longitudinal population-based study, J. Women's Health (Larchmt) 29 (2020) 927–936, https://doi.org/10.1089/JWH.2019.8095.

[19] J.A. Yesavage, T.L. Brink, T.L. Rose, O. Lum, V. Huang, M. Adey, V.O. Leirer, Development and validation of a geriatric depression screening scale: a preliminary report, J. Psychiatr. Res. 17 (1982) 37–49, https://doi.org/10.1016/0022-3956(82)90033-4.

[20] M. Drozd, E. Garland, A.M.N. Walker, T.A. Slater, A. Koshy, S. Straw, J. Gierula, M. Paton, J. Lowry, R. Sapsford, K.K. Witte, M.T. Kearney, R.M. Cubbon, Infection-related hospitalization in heart failure with reduced ejection fraction: a prospective observational cohort study, Circ. Heart Fail. (2020), https://doi.org/10.1161/CIRCHEARTFAILURE.119.006746.

[21] W.S. Yang, Y.C. Chang, M.L. Hsieh, J.L. Wang, L.C. Wu, C.H. Chang, Stratified risks of infection-related hospitalization in patients with chronic kidney disease - a prospective cohort study, Sci. Rep. 10 (2020) 4475, https://doi.org/10.1038/S41598-020-61144-6.

[22] R. Wittenberg, L. Sharpin, B. McCormick, J. Hurst, Understanding Emergency Hospital Admission of Older People, 2014.

[23] C. Czaja, L. Miller, N. Alden, H. Wald, C. Cummings, M. Rolfes, E. Anderson, N. Bennett, L. Billing, S. Chai, S. Eckel, R. Mansmann, M. McMahon, M. Monroe, A. Muse, I. Risk, W. Schaffner, A. Thomas, K. Yousey-Hindes, S. Garg, R. Herlihy, Age-related differences in hospitalization rates, clinical presentation, and outcomes among older adults hospitalized with influenza-U.S. Influenza Hospitalization Surveillance Network (FluSurv-NET), Open Forum Infect. Dis. 6 (2019), https://doi.org/10.1093/OFID/OFZ225.

[24] J. Redondo-Sánchez, I. Del Cura-González, L. Díez-Izquierdo, R. Rodríguez-Barrientos, F. Rodríguez-Cabrera, E. Polentinos-Castro, M. López-Miguel, L. Marina-Ono, L. Llamosas-Falcón, A. Gil-de Miguel, Trends in urinary tract infection hospitalization in older adults in Spain from 2000–2015, PLoS One 16 (2021), e0257546, https://doi.org/10.1371/JOURNAL.PONE.0257546.

[25] P.R.G. Forti, E. Rietti, N. Pisacane, V. Olivelli, B. Maltoni, A comparison of frailty indexes for prediction of adverse health outcomes in an elderly cohort, Arch. Gerontol. Geriatr. 54 (2012) 16–20, https://doi.org/10.1016/j.archger.2011.01.007.

[26] T. Gilbert, J. Neuburger, J. Kraindler, E. Keeble, P. Smith, C. Ariti, S. Arora, A. Street, S. Parker, H.C. Roberts, M. Bardsley, S. Conroy, Development and validation of a hospital frailty risk score focusing on older people in acute care settings using electronic hospital records: an observational study, Lancet 391 (2018) 1775–1782, https://doi.org/10.1016/S0140-6736(18)30668-8.

[27] M.D. Rothman, L. Leo-Summers, T.M. Gill, Prognostic significance of potential frailty criteria, J. Am. Geriatr. Soc. 56 (2008) 2211–2216, https://doi.org/10.1111/j.1532-5415.2008.02008.x.

[28] C. Park, W. Kim, H. Rhim, E. Lee, J. Kim, K. Cho, D. Kim, Frailty and hospitalization-associated disability after pneumonia: a prospective cohort study, BMC Geriatr. 21 (2021), https://doi.org/10.1186/S12877-021-02049-5.

[29] S. Helle, V. Lummaa, J. Jokela, Accelerated immunosenescence in preindustrial twin mothers, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 12391–12396, https://doi.org/10.1073/PNAS.0402215101.

[30] É. Le Bourg, Does reproduction decrease longevity in human beings? Ageing Res. Rev. 6 (2007) 141–149, https://doi.org/10.1016/J.ARR.2007.04.002.

[31] C.K. Barha, C.W. Hanna, K.G. Salvante, S.L. Wilson, W.P. Robinson, R.M. Altman, P.A. Nepomnaschy, Number of children and telomere length in women: a prospective, longitudinal evaluation, PLoS One 11 (2016), 146424, https://doi.org/10.1371/JOURNAL.PONE.0146424.

[32] A.Z. Pollack, K. Rivers, K.A. Ahrens, Parity associated with telomere length among US reproductive age women, Hum. Reprod. 33 (2018) 736–744, https://doi.org/10.1093/HUMREP/DEY024.

[33] C.P. Ryan, M.G. Hayes, N.R. Lee, T.W. McDade, M.J. Jones, M.S. Kobor, C. W. Kuzawa, D.T.A. Eisenberg, Reproduction predicts shorter telomeres and epigenetic age acceleration among young adult women, Sci. Rep. 8 (2018), https://doi.org/10.1038/S41598-018-29486-4.

[34] F. Barrat, B.M. Lesourd, A. Louise, H.J. Boulouis, S. Vincent-Naulleau, D. Thibault, M. Sanaa, T. Neway, C. Pilet, Surface antigen expression in spleen cells of C57Bl/6 mice during ageing: influence of sex and parity, Clin. Exp. Immunol. 107 (1997) 593, https://doi.org/10.1046/J.1365-2249.1997.3021199.X.

[35] F.S. Barrat, B.M. Lesourd, A.S. Louise, H.J. Boulouis, D.J. Thibault, T. Neway, C. A. Pilet, Pregnancies modulate B lymphopoiesis and myelopoiesis during murine ageing, Immunology 98 (1999) 604, https://doi.org/10.1046/J.1365-2567.1999.00918.X.

[36] F. Barrat, B. Lesourd, H.J. Boulouis, D. Thibault, S. Vincent-Naulleau, B. Gjata, A. Louise, T. Neway, C. Pilet, Sex and parity modulate cytokine production during murine ageing, Clin. Exp. Immunol. 109 (1997) 562–568, https://doi.org/10.1046/J.1365-2249.1997.4851387.X.

[37] R.S. Eid, J.A. Chaiton, S.E. Lieblich, T.S. Bodnar, J. Weinberg, L.A.M. Galea, Early and late effects of maternal experience on hippocampal neurogenesis, microglia, and the circulating cytokine milieu, Neurobiol. Aging 78 (2019) 1–17, https://doi.org/10.1016/J.NEUROBIOLAGING.2019.01.021.

[38] S. Nandi, R. Guzman, G. Thordarson, L. Rajkumar, Pregnancy levels of estrogen prevents breast cancer, Breast Cancer Res. 5 (2003) 19, https://doi.org/10.1186/BCR678.

[39] M. Colucci, S. Cammarata, A. Assini, R. Croce, F. Clerici, C. Novello, L. Mazzella, N. Dagnino, C. Mariani, P. Tanganelli, The number of pregnancies is a risk factor for Alzheimer's disease, Eur. J. Neurol. 13 (2006) 1374–1377, https://doi.org/10.1111/J.1468-1331.2006.01520.X.

[40] J. Mossong, N. Hens, M. Jit, P. Beutels, K. Auranen, R. Mikolajczyk, M. Massari, S. Salmaso, G.S. Tomba, J. Wallinga, J. Heijne, M. Sadkowska-Todys, M. Rosinska, W.J. Edmunds, Social contacts and mixing patterns relevant to the spread of infectious diseases, PLoS Med. 5 (2008), e74, https://doi.org/10.1371/JOURNAL.PMED.0050074.

[41] B.N. Uchino, R. Trettevik, R.G. Kent de Grey, S. Cronan, J. Hogan, B.R.W. Baucom, Social support, social integration, and inflammatory cytokines: a meta-analysis, Health Psychol. 37 (2018) 462–471, https://doi.org/10.1037/HEA0000594.

[42] L.C.J. Steijvers, S. Brinkhues, C.J.P.A. Hoebe, T.G. Van Tilburg, V. Claessen, N. Bouwmeester-Vincken, F. Hamers, P. Vranken, N.H.T.M. Dukers-Muijrers, Social networks and infectious diseases prevention behavior: a cross-sectional study in people aged 40 years and older, PLoS One 16 (2021), https://doi.org/10.1371/JOURNAL.PONE.0251862.

[43] M. Baldereschi, A. Di Carlo, V. Lepore, L. Bracco, S. Maggi, F. Grigoletto, G. Scarlato, L. Amaducci, Estrogen-replacement therapy and Alzheimer's disease in the italian longitudinal study on aging, Neurology 50 (1998) 996–1002, https://doi.org/10.1212/WNL.50.4.996.