Published in final edited form as:
J Am Geriatr Soc. 2013 March ; 61(3): 327–334. doi:10.1111/jgs.12146.

Frailty and Fracture, Disability, and Falls: A Multiple Country Study from the Global Longitudinal Study of Osteoporosis in Women (GLOW)

Sarah E. Tom, PhD, MPH[*], **Jonathan D. Adachi, MD**[†], **Frederick A. Anderson Jr, PhD**[‡], **Steven Boonen, MD, PhD**[§], **Roland D. Chapurlat, MD, PhD**[‖], **Juliet E. Compston, MD**[#], **Cyrus Cooper, MD**[**], **Stephen H. Gehlbach, MD, MPH**[‡], **Susan L. Greenspan, MD**[††], **Frederick H. Hooven, PhD**[‡], **Jeri W. Nieves, PhD**[‡‡], **Johannes Pfeilschifter, MD**[§§], **Christian Roux, MD, PhD**[‖‖], **Stuart Silverman, MD**[##], **Allison Wyman, MS**[‡], and **Andrea Z. LaCroix, PhD**[***]

[*]Group Health Research Institute, Seattle, WA, USA, and Pharmaceutical Health Services Research Department, School of Pharmacy, University of Maryland, Baltimore, MD, USA

[†]St. Joseph's Hospital, McMaster University, Hamilton, ON, Canada

[‡]Center for Outcomes Research, UMASS Medical School, Worcester, MA, USA

[§]Leuven University Center for Metabolic Bone Diseases, Division of Geriatric Medicine, Katholieke Universiteit Leuven, Leuven, Belgium

[‖]Division of Rheumatology, INSERM UMR 1033, Université de Lyon, Hôpital E. Herriot, Hospices Civils de Lyon, Lyon, France

[#]School of Clinical Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK

[**]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK

[††]University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[‡‡]Helen Hayes Hospital and Columbia University, West Haverstraw, NY, USA

[§§]Department of Internal Medicine III, Alfried Krupp Krankenhaus, Essen, Germany

[‖‖]Paris Descartes University, Department of Rheumatology, Paris, France

[##]Department of Rheumatology, Cedars-Sinai/UCLA, Los Angeles, CA, USA

[***]Fred Hutchinson Cancer Research Center, Seattle, WA, USA.

Abstract

Objectives—To test whether women age ≥ 55 years with increasing evidence of a frailty phenotype would have greater risk of fractures, disability, and recurrent falls, compared with women who were not frail, across geographic areas (Australia, Europe, and North America) and age groups.

Address correspondence to Dr Sarah Tom, Group Health Research Institute, Seattle, WA, USA Pharmaceutical Health Services Research Department, School of Pharmacy, Univeristy of Maryland, Baltimore, MD, USA. stom@rx.umaryland.edu Tel: +1 410 706 7841. Fax: +1 410 706 5394.

Sponsor's Role: The sponsor had no involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
The content is solely the responsibility of the authors and does not necessarily represent the official views of the Eunice Kennedy Shriver National Institute of Child Health & Human Development or the National Institutes of Health.

Design—Multinational, longitudinal, observational cohort study.

Setting—The Global Longitudinal Study of Osteoporosis in Women (GLOW).

Participants—Women (n=48,636) age ≥ 55 years enrolled at sites in Australia, Europe, and North America.

Measurements—Components of frailty (slowness/weakness, poor endurance/exhaustion, physical activity, and unintentional weight loss) at baseline and report of fracture, disability, and recurrent falls at 1 year of follow-up were investigated. Women also reported health and demographic characteristics at baseline.

Results—Among those age < 75 years, women from the United States were more likely to be prefrail and frail than women from Australia/Canada, and Europe. The distribution of frailty was similar by region for women age ≥ 75 years. Odds ratios from multivariable models for frailty versus non frailty were 1.23 (95% CI = 1.07–1.42) for fracture, 2.29 (95% CI = 2.09–2.51) for disability, and 1.68 (95% CI = 1.54–1.83) for recurrent falls. The associations for pre-frailty versus non frailty were weaker but still indicated statistically significant increased risk for each outcome. Overall, associations between frailty status and each outcome were similar across age and geographic region.

Conclusion—Increased evidence of a frailty phenotype is associated with increased risk for fracture, disability, and falls among women age ≥ 55 years in 10 countries, with similar patterns across age and geographic region.

Keywords

falls; fracture; frailty; osteoporosis; postmenopausal; women

INTRODUCTION

Frailty is a state of increased vulnerability resulting from decreased reserve, diminished resistance to stressors,[1] and multisystem impairment.[2] Some previous studies have proposed to measure frailty through an index of health deficits,[3-5] while another group of studies has identified similar but not identical scales based on shrinking, weakness, poor endurance, and low activity to describe a frailty phenotype.[1, 6-9] Several frailty phenotype metrics predicted increased risk of future falls,[1, 8, 9] fracture,[6, 8, 10] and disability.[1, 6, 7, 9, 10] Moderate stages of a frailty phenotype, which may be reversible, may be an important prevention target for these health outcomes.[11]

Moderate stages of frailty may relate to risk of future health outcomes. The intermediate stage between no frailty and frailty (pre-frailty) may be associated directly with increased risk for falls, fracture, and disability. In an indirect manner, pre-frailty may increase risk of these outcomes through increasing the risk of becoming frail. However, pre-frailty has been less consistently associated with health outcomes than frailty.[6-8] Some studies showed relationships between pre-frailty and health outcomes that were more moderate in magnitude than those for frailty, [6, 8, 12] but confirmation of these findings is needed.

Whether the associations between frailty with falls, fracture, and disability are stable across different geographic areas and how early in adult life these associations are evident remains unclear. Most examinations of the associations of frailty and subsequent falls, fracture, and disability have taken place in the United States.[7, 10] Additional evaluation of these relationships in countries with different socioeconomic contexts,[13] health care systems,[14] physical environments,[15, 16] and cultures[7] is necessary to validate the utility of a frailty measure in predicting health decline. Previous studies have investigated the consequences of

frailty in older individuals, typically age ≥ 65 years.[1, 6-9] Little is known about the relationship between frailty and health outcomes at oldest ages, or in adults age ≤ 65 years. One study found that associations between frailty and increased risks for falls, death, and fracture were similar among women age ≥ 80 years and women age 69–79 years.[8] To our knowledge, no previous study has examined the consequences of frailty among adults age ≤ 65 years.

Using a measure of frailty that is similar to a previously proposed scale,[6] we examined the associations between baseline frailty and risk of fractures, incident or worsening disability, and recurrent falls during 1 year of follow-up in a large sample of women age ≥ 55 years from Australia, Europe, and North America. We hypothesized that women with increasing evidence of frailty would have greater risk of falls, fracture, and disability, compared with women who were not frail, across geographic areas and age.

METHODS

The Global Longitudinal Study of Osteoporosis in Women (GLOW) is an observational study designed to examine international patterns of risk factors for and health consequences of fragility fractures in women age ≥ 55 years. The study has been described in detail previously.[17] Briefly, 60,393 women age ≥ 55 years from 17 study sites in Australia, Belgium, Canada, France, Germany, Italy, the Netherlands, Spain, the United Kingdom (U.K.), and the United States (U.S.) have participated in GLOW. Physicians were recruited from a list of all available physicians in a study region or through primary care networks. Within each practice, women who were age ≥ 55 years and who had visited the practice within the past 2 years were eligible for study inclusion. Samples were drawn stratified by age such that two thirds of participants were age ≥ 65 years. We excluded women who were unable to complete the survey because of cognitive impairment, language barriers, institutionalization, or ill health. Questionnaires were initially mailed and were available in English, French, German, Spanish, Italian, and Dutch. Telephone interviews were conducted if mailed surveys were not returned or women needed assistance in completing the survey. This analysis uses baseline and the first annual follow-up wave.

Measurement of Frailty

We based our measurement of frailty on the components specified in the Fried model, which accounts for muscle weakness, slow walking speed, exhaustion, low physical activity, and unintentional weight loss.[1] Questions were selected to create a frailty instrument similar to the Women's Health Initiative (WHI) instrument.[6]

Slowness/weakness—The SF-36 physical functioning scale indicated slowness/weakness through asking about limitation with 10 activities, such as climbing one flight of stairs and bathing or dressing. Study participants reported whether they were limited a lot (0 points), limited a little (50 points), or not limited at all (100 points) in each activity. The analysis included only women who responded to ≥ 6 activities.

Poor endurance/exhaustion—The measure of poor endurance/exhaustion came from the following questions from the SF-36 vitality component: "Did you feel full of life?" "Did you have a lot of energy?" "Did you feel worn out?" "Did you feel tired?" Response options were all of the time (0 points), most of the time (25 points), some of the time (50 points), a little of the time (75 points), and none of the time (100 points). We reverse coded responses for the questions about feeling full of life and having a lot of energy. The analysis included respondents who answered ≥ 3 questions.

Physical activity—Women reported the number of days they walked at least 20 minutes in the past 30 days. Only women who answered this question remained in the analysis.

Unintentional weight loss—Women reported whether they unintentionally lost ≥ 10 lb in the past year. Only women who answered this question remained in the analysis.

Classification of frailty—We defined frailty from an aggregate score based on answers to the questions in the four domains above. For slowness/weakness, poor endurance/exhaustion, and physical activity, assignment of points was based on a score in the lowest quarter of the distribution (scores of ≤ 60 and ≤ 50 and ≤ 2 days, respectively). Women in the lowest quarter of slowness/weakness received 2 points, keeping in line with the separate categories for slowness and weakness in the Fried scale.[1, 6] Women in the lowest quarter of poor endurance/exhaustion received 1 point, and women in the lowest quarter for physical activity received 1 point. Women who reported unintentionally losing ≥ 10 lb in the past year received 1 point. The range of aggregate score was 0 to 5. A score of 3, 4, or 5 denoted frailty, and a score of 1 or 2 indicated pre-frailty, an intermediate stage between no frailty and frailty. We considered women with a score of 0 as not frail.

Other Variables

Women reported on sociodemographic and health variables at baseline, including age, race/ethnicity (U.S. only), education (comparable questions available from Canada, France, Italy, Spain, the U.K., and the U.S.), current smoking, alcohol consumption, falls in the past 12 months, depression and anxiety, body mass index (BMI), doctor diagnosis of chronic diseases, the experience of any fractures since age 45 years, and the use of anti-osteoporosis medications, including estrogen. We categorized race/ethnicity as non-Hispanic white, Hispanic white, non-Hispanic nonwhite, and Hispanic nonwhite. The study regions used in analyses were Canada/Australia, Europe, and the U.S. Report of depression and anxiety symptoms was based on the EuroQol EQ-5D.[18,19]

Outcomes

We assessed the outcomes of falls, fracture, and disability. At 1 year of follow-up, women reported number of falls in the past 12 months. We categorized women as recurrent fallers versus nonrecurrent fallers. Women answered questions about limitations with self-care and usual activities (work, school, family). Women who had no limitation at baseline with self-care and usual activities and were somewhat limited or unable to perform in either of these domains at the first year of follow-up were considered to have an incident disability. We considered women who were somewhat limited with self-care or usual activities at baseline and who were unable to perform the task at the 1 year follow-up to have a worsening disability. Because the number of women with worsening disability was small (n = 550), for analyses we combined these women women with incident (n=4850) into one group. We excluded women from the models with disability as the outcome who were unable to perform self-care or usual activities at baseline (n=1018). Women were categorized as having a fracture if they reported that they had fractured any of the following bones in the past 12 months: collar bone or clavicle, upper arm, wrist, spine, rib, hip, pelvis, ankle, upper leg, or lower leg.

A total of 48,636 women provided information on the four variables we used to create the frailty score. At follow-up, 47,780 (98.2%) women reported on fracture, 46,273 (95.1%) women responded to disability questions, and 48,154 (99.0%) women reported on falls.

Statistical Analysis

We describe categorical variables as proportions and test for differences using the chi-square test or the Mantel-Haenszel chi-square test for ordered categories. We describe distributions of continuous variables as medians with 25^{th} and 75^{th} percentiles and test for differences using the Kruskal-Wallis test. For all variables, the distributions of baseline covariates by frailty status were compared. Each outcome was modeled separately using backwards stepwise multivariable logistic regression, beginning with the same set of variables that were statistically significant ($P < .20$) in Table 1. Each model was fit using backwards selection, keeping any variable that was significant at $p < 0.05$; each variable removed during backwards selection was then individually added to the model, and any that were significant at $p < 0.05$ were included in the final model. We first ran age-adjusted and multivariable logistic regression models for each outcome. Then we ran the same models with terms to test for interaction for frailty status by age and frailty status by geographic region. All analyses were conducted in SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

At baseline, 22% of women were frail and 31% were pre-frail. Pre-frail women comprised 31%, 29%, and 33% of the Canada/Australia, Europe and U.S. samples, respectively. The Canada/Australia and U.S. samples had similar proportions of frail women (23% and 24%, respectively), while 19% of women in the Europe sample were frail. Pre-frail women accounted for 32% of women age 55–64 years, 31% of women age 65–74 years and 29% of women age ≥ 75 years. Of women age 55–64 years, 14% were frail, while 20% and 39% of women age 65–74 years and ≥ 75 years were frail, respectively. Women who were frail were older, more likely to live in the U.S., to have fallen ≥2 times in the past 12 months, to have higher levels of depression, and to have a BMI ≥ 30 kg/m^2 than women who were not frail (Table 1). Frail women were less likely to consume alcohol but were more likely to have ever been diagnosed with hypertension, heart disease, osteoarthritis, stroke or to have had a fracture since age 45 years than women who were not frail. In the U.S., frail women were more likely to be non-Hispanic nonwhite. Frail women in Canada, France, Italy, Spain, the U.K., and the U.S. were more likely to have higher secondary education and were less likely to have post-secondary education than women who were not frail. The percentage of women who were pre-frail reporting these characteristics fell between those of women who were frail and women who were not frail.

The distribution of baseline frailty status by geographic region varied according to age (Table 2). Among participants age 55–65 years and 65–74 years, women from Europe, Canada, and Australia were more likely to be nonfrail than U.S. women ($P < .001$). For age ≥ 75 years the distribution of baseline frailty was similar across Canada/Australia, the U.S., and Europe. The percentage of women reporting each outcome by frailty status in each age group was similar across geographic region.

Increasing level of frailty was related to greater risk of falls, fracture, and disability. In an age-adjusted model pre-frail women and frail women had odds of falls that were approximately 50% (OR = 1.57, 95% CI = 1.47–1.68) and 300% (OR = 3.35, 95% CI = 3.13–3.58) greater than those of nonfrail women (Table 3). In a multivariable model compared to nonfrail women, prefrail women had a 23% (OR = 1.23, 95% CI = 1.13–1.32) increase in the odds of falls, while frail women had a 68% increase in odds of falls (OR = 1.68, 95% CI = 1.54–1.83). In an age-adjusted model, pre-frail women and frail women had odds of fracture approximately 40% greater (OR = 1.39, 95% CI = 1.22–1.58) and nearly double (OR = 1.97, 95% CI = 1.73–2.25) the odds of nonfrail women, respectively. In a multivariable model these odds of fracture were attenuated to increases of 23% for pre-frail (OR = 1.23, 95% CI = 1.07–1.42) and 46% for frail (OR = 1.46, 95% CI = 1.26–1.70)

women. In an age-adjusted model, pre-frail women had double (OR = 2.04, 95% CI = 1.90–2.20) and frail women had triple (OR = 3.27, 95% CI = 3.03–3.52) the odds of disability, compared with nonfrail women. In a multivariable model pre-frail women (OR = 1.85, 95% CI = 1.70–2.01) and frail women (OR = 2.29, 95% CI = 2.09–2.51) had approximately double the odds of disability, compared with nonfrail women.

Age modified the relationship between frailty and fracture in multivariable models (*P* value for interaction term between age and frailty status < .01). While pre-frailty among women age 55–64 years was not related to fracture, frail women age 55–64 years had odds of fracture that were 85% (OR = 1.85, 95% CI = 1.43–2.39) greater those of nonfrail women. Among women age 65–74 years, pre-frail and frail women had odds that were 28% (OR = 1.28, 95% CI = 1.02–1.62) and 50% (OR = 1.54, 95% CI = 1.20–1.96) greater than the odds of fracture of nonfrail women, respectively. Among women age ≥ 75 years, pre-frailty was associated with a 31% (OR = 1.31, 95% CI = 1.02–1.68) increase in the odds of fracture, compared with the odds of nonfrailty, while frailty was not related to fracture.

Age also modified the relationship between frailty and disability in multivariable models (*P* value for interaction term between age and frailty status < .01). Compared with nonfrailty in the respective age categories, pre-frailty was associated with an 80–90% increase in odds of disability for women age 55–64 years (OR = 1.90, 95% CI = 1.66–2.18) and age 65–74 years (OR = 1.83, 95% CI = 1.61–2.09). Frailty was associated with almost triple the odds of disability for women age 55–64 years (OR = 2.84, 95% CI = 2.43–3.33) and over double the odds of disability for women age 65–74 years (OR = 2.29, 95% CI = 1.99–2.64), compared with nonfrail women in the respective age groups. For women age ≥ 75 years, odds of disability were 80–95% increased compared with those of nonfrail women for both pre-frail (OR = 1.79, 95% CI = 1.53– 2.09) and frail women (OR = 1.95, 95% CI = 1.68–2.27).

Age did not modify the relationship between frailty and falls. Geographic region did not modify the relationships between frailty and any outcome. Inclusion of education and separately of race/ethnicity did not appreciably alter the results for any outcome for the full sample or any age group.

DISCUSSION

Among women age ≥ 55 years in 10 countries, increasing evidence of a phenotype of frailty was related to increasing risk of fracture, incident or worsening disability, and recurrent falls by 1 year of follow-up. Associations persisted after adjusting for potential confounding variables. Although interactions between frailty status and age group were statistically significant for the outcomes of fracture and disability, the small size of the differences given the large size of the sample were not clinically relevant. Our measure of frailty was similar, but not identical, to previous scales and is based on readily accessible questions. Our results demonstrate relationships between pre-frailty and frailty and health outcomes in geographic areas and age groups that have not been previously examined. Our results suggest that examination of frailty status in younger postmenopausal women may also improve fracture prediction in this group. Nearly one third of fractures in postmenopausal women occur in women age < 65 years,[20] but it is often unclear which women in this age group are at increased risk of fracture.[21-23]

The prevalence of frailty in our study was higher than the prevalence in the WHI study (22.0% vs. 16.3%, respectively), which used a similar frailty scale. [6] Frailty prevalence was higher in GLOW even though women age 50 – 64 years were included in this analysis but excluded from the WHI analysis. This difference could relate to recruiting from physician

practices in GLOW versus from the community in the WHI study. The women in GLOW may have had more health problems that prompted seeking medical care than those in the WHI. Although the prevalence of frailty increased with age, the prevalence of prefrailty was close to 30% for all age groups. The net transfer from the states of not frail and frail to prefrailty may be similar across age, while the net transfer from the states of not frail and prefrail to frail may increase with age.

Our results are consistent with most previous findings. Other studies have shown an association between increasing evidence of frailty and greater risk of fracture,[6, 8, 10, 12] in line with our results. Similarly, our results of a graded relationship between frailty and risk of disability agreed with previous findings.[1, 6, 7, 9, 10, 12] Our findings that frailty and pre-frailty predicted recurrent falls support most previous studies of frailty and falls.[1, 8, 9, 12] However, one study[9] found that frailty and pre-frailty did not predict falls. That study included women who were one third of the most disabled community-dwelling women, who may experience higher overall falls risk than in the present study. Another prior study[8] found that the relationship for increasing evidence of frailty and increased risk of falls was greater for women age ≥ 80 years than for women age 69–80 years. However, age did not meaningfully modify the association between frailty and falls in GLOW.

The GLOW study is unique in the sampling of women over a broad age range from 10 countries. Because this study is one of the first to examine frailty in women in their 50s and early 60s, further examination of frailty in this age group is necessary to validate our results. Inclusion of multiple potential confounding factors further supports the predictive value of frailty, independent of other chronic conditions or health-related behaviors. This analysis had several limitations. The measure of physical activity was based on walking in the past 30 days may not be as sensitive to variation in physical activity as the more detailed instruments used in previous studies.[1, 6] However, a study that used a single question to assess physical activity found similar associations for frailty and disability.[7] The questions included in our frailty scale are simple to assess and may be clinically useful. Although followup is only for 1 year, because of the large sample size we were able to examine associations between baseline frailty status and subsequent health outcomes and whether age and geographic region modified these relationships. While other studies separated disability into subclasses, such as activities of daily living and instrumental activities of daily living, because there were few women in each subclass in GLOW, we could not perform analysis by subclass. Unlike other previous studies,[9, 12, 24] since GLOW did not include an in-person exam, we did not have physical performance measures such as those used in the Cardiovascular Health Study.[1] However, our results are similar to those from datasets with physical performance measures. Our results are also in line with those of studies that used indexes that were similar to the Fried frailty scale but that did not include identical physical performance measures.[6, 7] Self-reports of fracture were not radiographically verified. However, our results support previous findings of a positive association between increased frailty and radiographically verified nonspine fracture and a decreased predictive value of frailty for fracture at oldest ages.[8] The survey did not include some conditions previously shown to be related to frailty, such as diabetes.[25, 26] As our study population consists only of women, results may not be generalizable to men. Women in GLOW were from Western, industrialized nations. Evidence from non-Western and developing nations is needed to verify these relationships in diverse environments. Women with cognitive impairment and living in institutions were excluded from GLOW. Because these women are more likely to be frail, our sample may underestimate the prevalence of frailty and the strength of associations between frailty and health outcomes.

Level of frailty phenotype is related in a graded way to short-term risk for falls, fracture, and disability for women age ≥ 55 years in Australia, Europe, and North America. Frailty is a

generalizable risk factor for important health outcomes in older women around the world, and women of all ages may benefit from intervening on frailty components.

Acknowledgments

We thank the physicians and project coordinators participating in GLOW. Editorial support for the final version of this article, comprising language editing, content checking, formatting and referencing was provided by Sophie Rushton-Smith, PhD. Dr Boonen is senior clinical investigator of the Fund for Scientific Research, Flanders, Belgium (FWO-Vlaanderen) and holder of the Leuven University Chair in Metabolic Bone Diseases.

Financial support for the GLOW study is provided by Warner Chilcott Co, LLC and Sanofi-Aventis to the Center for Outcomes Research, University of Massachusetts Medical School. Dr Boonen is senior clinical investigator of the Fund for Scientific Research, Flanders, Belgium (FWO-Vlaanderen) and holder of the Leuven University Chair in Metabolic Bone Diseases.

Dr. Tom was supported by grant T32AG027677 at the time this paper was designed. Dr. Tom was supported by a research career development award (K12HD052023, PI: Berenson), that is co-funded by the Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD), the Office of Research on Women's Health, and the National Institute of Allergy & Infectious Diseases (NIAID) at the time that this paper was designed, the analysis were conducted, and the first draft was written.

Conflict of Interest

Jonathan D Adachi: Consultant: Amgen, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Nycomed, Pfizer, Procter & Gamble, Roche, sanofi-aventis, Servier, Wyeth and Bristol-Myers Squibb.

Clinical trials for: Amgen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Procter & Gamble, Roche, sanofi-aventis, Wyeth and Bristol-Myers Squibb. Speaker: Amgen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Procter & Gamble, Roche, sanofi-aventis, Wyeth. Clinical trials for Amgen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Procter & Gamble, Roche, sanofi-aventis, Wyeth and Bristol-Myers Squibb.

Frederick A Anderson: Research support: sanofi-aventis, The Medicines Company, Procter & Gamble, and Scios. Consultant for sanofi-aventis, GlaxoSmithKline, and Millennium and Sage. Served on advisory boards for sanofi-aventis and The Medicines Company.

Steven Boonen: No conflicts of interest to disclose.

Roland Chapurlat: Funding: French Ministry of Health, Merck, Servier, Lilly, Procter and Gamble.

Honoraria: Amgen, Servier, Novartis, Lilly, Roche, sanofi-aventis. Consultant/Advisory Board: Amgen, Merck, Servier, Nycomed, Novartis.

Juliet Compston: Paid consultancy work: Servier, Nycomed, Novartis, Amgen, Alliance for Better Bone Health, Gilead, GlaxoSmithKline, Medtronic, Ono Pharmaceuticals, Warner Chilcott. Paid speaking engagements, reimbursement, and travel and accommodation: Servier, Amgen, Nycomed, Merck Sharp & Dohme, Gilead, Warner Chilcott. Research grants from Acuitas and Nycomed.

Cyrus Cooper: has received consulting fees for AMGEN, The Alliance for Better Bone Health (sanofi-aventis and Warner Chilcott), Eli Lily, Merck Sharp and Dohme, Servier, Novartis, and Roche-GSK.

Stephen Gehlbach: Research grant: The Alliance for Better Bone Health (sanofi-aventis and Warner Chilcott).

Susan L Greenspan: Consultant/advisory board: Amgen, Lilly, Merck. Research grants: The Alliance for Better Bone Health (sanofi-aventis and Proctor & Gamble), Lilly.

Frederick H. Hooven: Research grant: The Alliance for Better Bone Health (sanofi-aventis and Warner Chilcott).

Johannes Pfeilschifter: Research grant: AMGEN, Kyphon, Novartis, Roche. Other research support.

Equipment: GE LUNAR. Speakers' bureau: AMGEN, sanofi-aventis, GlaxoSmithKline, Roche, Lilly Deutschland, Orion Pharma, Merck Sharp and Dohme, Merckle, Nycomed, Procter & Gamble. Advisory Board membership: Novartis, Roche, Procter & Gamble, TEVA.

Christian Roux: Honoraria and/or research grants: Alliance, Amgen, Lilly, Merck Sharp and Dohme, Novartis, Nycomed, Roche, GlaxoSmithKline, Servier, Wyeth.

Stuart Silverman: Research grants: Wyeth, Lilly, Novartis, Alliance. Speakers' bureau: Lilly, Novartis, Pfizer, Procter & Gamble. Honoraria: Procter & Gamble. Consultant/ Advisory Board: Lilly, Argen, Wyeth, Merck, Roche, Novartis.

Allison Wyman: Research grant: The Alliance for Better Bone Health (sanofi-aventis and Warner Chilcott).

Andrea Z. LaCroix: Has received funding from The Alliance for Better Bone Health (sanofi-aventis and Warner Chilcott) and is an Advisory Board member for Amgen.

Author Contributions

Sarah E. Tom: Contributed to the design of the statistical analysis and manuscript, drafted the manuscript, revised the manuscript and incorporated revisions of co-authors, and approved the final version.

Jonathan D Adachi: enrolled patients, provided comments on interpretation of data, revised the manuscript, and approved the final version.

Frederick A Anderson: interpreted data, revised the manuscript, and approved the final version.

Steven Boonen: enrolled patients, interpreted data, revised the manuscript, and approved the final version.

Roland Chapurlat: enrolled patients, interpreted of data, revised the manuscript, and approved the final version.

Juliet Compston: interpreted data, revised the manuscript, and approved the final version.

Cyrus Cooper: enrolled patients, interpreted data, revised the manuscript, and approved the final version.

Stephen Gehlbach: interpreted data, revised the manuscript, and approved the final version.

Susan L Greenspan: enrolled patients, interpreted data, revised the manuscript, and approved the final version.

Frederick H. Hooven: interpreted data, revised the manuscript, and approved the final version.

Jeri W. Nieves: enrolled patients, interpreted data, revised the manuscript, and approved the final version.

Johannes Pfeilschifter: enrolled patients, interpreted data, revised the manuscript, and approved the final version.

Christian Roux: enrolled patients, interpreted data, revised the manuscript, and approved the final version.

Stuart Silverman: enrolled patients, interpreted data, revised the manuscript, and approved the final version.

Allison Wyman: performed statistical analysis, contributed to the design of the statistical analysis, interpreted data, revised the manuscript, and approved the final version.

Andrea Z. LaCroix: enrolled patients, contributed to the design of the statistical analysis and manuscript, interpreted data, revised the manuscript, and approved the final version.

REFERENCES

[1]. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56:M146–156. [PubMed: 11253156]

[2]. Rockwood K. Frailty and its definition: A worthy challenge. J Am Geriatr Soc. 2005; 53:1069–1070. [PubMed: 15935037]

[3]. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorld J. 2001; 1:323–336.

[4]. Goggins WB, Woo J, Sham A, et al. Frailty index as a measure of biological age in a Chinese population. J Gerontol A Biol Sci Med Sci. 2005; 60:1046–1051. [PubMed: 16127111]

[5]. Kulminski A, Yashin A, Ukraintseva S, et al. Accumulation of health disorders as a systemic measure of aging: Findings from the NLTCS data. Mech Ageing Dev. 2006; 127:840–848. [PubMed: 16978683]

[6]. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: Emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. J Am Geriatr Soc. 2005; 53:1321–1330. [PubMed: 16078957]

[7]. Avila-Funes JA, Helmer C, Amieva H, et al. Frailty among community-dwelling elderly people in France: The three-city study. J Gerontol A Biol Sci Med Sci. 2008; 63:1089–1096. [PubMed: 18948560]

[8]. Ensrud KE, Ewing SK, Taylor BC, et al. Frailty and risk of falls, fracture, and mortality in older women: The study of osteoporotic fractures. J Gerontol A Biol Sci Med Sci. 2007; 62:744–751. [PubMed: 17634322]

[9]. Bandeen-Roche K, Xue QL, Ferrucci L, et al. Phenotype of frailty: Characterization in the women's health and aging studies. J Gerontol A Biol Sci Med Sci. 2006; 61:262–266. [PubMed: 16567375]

[10]. Forti P, Rietti E, Pisacane N, et al. A comparison of frailty indexes for prediction of adverse health outcomes in an elderly cohort. Arch Gerontol Geriatr. 2012; 54:16–20. doi: 10.1016/j.archger.2011.01.007. Epub 2011 Feb 19. [PubMed: 21339007]

[11]. Lang PO, Michel JP, Zekry D. Frailty syndrome: A transitional state in a dynamic process. Gerontology. 2009; 55:539–549. [PubMed: 19346741]

[12]. Ensrud KE, Ewing SK, Cawthon PM, et al. A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men. J Am Geriatr Soc. 2009; 57:492–498. [PubMed: 19245414]

[13]. Mansyur C, Amick BC, Harrist RB, et al. Social capital, income inequality, and self-rated health in 45 countries. Soc Sci Med. 2008; 66:43–56. [PubMed: 17913321]

[14]. van Doorslaer E, Masseria C, Koolman X, Group OHER. Inequalities in access to medical care by income in developed countries. CMAJ. 2006; 174:177–183. [PubMed: 16415462]

[15]. Saelens BE, Sallis JF, Frank LD. Environmental correlates of walking and cycling: findings from the transportation, urban design, and planning literatures. Ann Behav Med. 2003; 25:80–91. [PubMed: 12704009]

[16]. Pucher J, Dijkstra L. Promoting safe walking and cycling to improve public health: lessons from The Netherlands and Germany. Am J Public Health. 2003; 93:1509–1516. [PubMed: 12948971]

[17]. Hooven FH, Adachi JD, Adami S, et al. The Global Longitudinal Study of Osteoporosis in Women (GLOW): Rationale and study design. Osteoporos Int. 2009; 20:1107–1116. [PubMed: 19468663]

[18]. Brazier JE, Walters SJ, Nicholl JP, Kohler B. Using the SF-36 and Euroqol on an elderly population. Qual Life Res. 1996; 5:195–204. [PubMed: 8998488]

[19]. Brooks R. EuroQol: The current state of play. Health Policy. 1996; 37:53–72. [PubMed: 10158943]

[20]. Siris ES, Brenneman SK, Miller PD, et al. Predictive value of low BMD for 1-year fracture outcomes is similar for postmenopausal women ages 50-64 and 65 and Older: Results from the National Osteoporosis Risk Assessment (NORA). J Bone Miner Res. 2004; 19:1215–1220. [PubMed: 15231007]

[21]. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995; 332:767–773. [PubMed: 7862179]

[22]. Kelsey JL, Browner WS, Seeley DG, et al. Risk factors for fractures of the distal forearm and proximal humerus. The Study of Osteoporotic Fractures Research Group. Am J Epidemiol. 1992; 135:477–489. [PubMed: 1570814]

[23]. Chen YT, Miller PD, Barrett-Connor E, et al. An approach for identifying postmenopausal women age 50-64 years at increased short-term risk for osteoporotic fracture. Osteoporos Int. 2007; 18:1287–1296. [PubMed: 17464525]

[24]. Ensrud KE, Ewing SK, Taylor BC, et al. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. Arch Intern Med. 2008; 168:382–389. [PubMed: 18299493]

[25]. Kalyani RR, Tian J, Xue QL, et al. Hyperglycemia and incidence of frailty and lower extremity mobility limitations in older women. J Am Geriatr Soc. 2011; 60:1701–1707. [PubMed: 22882211]

[26]. Blaum CS, Xue QL, Tian J, et al. Is hyperglycemia associated with frailty status in older women? J Am Geriatr Soc. 2009; 57:840–847. [PubMed: 19484839]

Table 1

Baseline Characteristics by Baseline Frailty Status, All Regions

Characteristic	Nonfrail (n = 22,914)	Pre-frail (n = 15,028)	Frail (n = 10,694)	*P*-Value[a]
Age (years), median (IQR)	66 (60, 72)	67 (60, 74)	72 (65, 79)	<.001
Age group (years)				
55–64	10,399 (45)	6266 (42)	2661 (25)	
65-74	8728 (38)	5421 (36)	3532 (33)	
≥ 75	3787 (17)	3341 (22)	4501 (42)	
Race/ethnicity (U.S. only)				<.001
Non-Hispanic white	9071 (92)	6556 (87)	4501 (83)	
Hispanic white	139 (1.4)	125 (1.7)	77 (1.4)	
Non-Hispanic nonwhite	591 (6.0)	764 (10)	825 (15)	
Hispanic nonwhite	50 (0.5)	67 (0.9)	52 (1.0)	
Study region				<.001
Canada/Australia	2888 (13)	1912 (13)	1440 (13)	
Europe	10086 (44)	5507 (37)	3676 (34)	
USA	9940 (43)	7609 (51)	5578 (52)	
Education (Canada, France, Italy, Spain, U.K., U.S. only)				<.001
Primary or lower secondary/middle school	2998 (18)	2057 (18)	1564 (19)	
Higher secondary	4351 (25)	3606 (31)	3164 (39)	
Post secondary	9733 (57)	6018 (52)	3438 (42)	
Current smoking	1606 (7.0)	1458 (9.7)	1110 (10)	<.001
Falls in the past 12 months				<.001
0	15,572 (68)	9354 (63)	5209 (49)	
1	5058 (22)	3412 (23)	2558 (24)	
≥ 2	2152 (9.5)	2124 (14)	2818 (27)	
EQ-5D depression scale				<.001
Not anxious or depressed	15,771 (69)	7675 (52)	4226 (40)	
Moderately anxious or depressed	6105 (27)	6477 (44)	5511 (52)	
Extremely anxious or depressed	867 (3.8)	734 (4.9)	840 (7.9)	
BMI				<.001
< 18.5	370 (1.7)	260 (1.8)	203 (2.0)	
18.5–24.9	11093 (50)	5511 (38)	2631 (26)	
25–29.9	7524 (34)	5108 (35)	3259 (32)	
≥ 30	3309 (15)	3612 (25)	4120 (40)	
Alcohol consumption (drinks per week)				<.001
0	8626 (38)	7445 (50)	7164 (67)	
< 7	9525 (42)	5253 (35)	2566 (24)	
7–13	3724 (16)	1758 (12)	733 (6.9)	
14–19	869 (3.8)	453 (3.0)	149 (1.4)	
≥ 20	124 (0.5)	79 (0.5)	36 (0.3)	

Characteristic	Nonfrail (n = 22,914)	Pre-frail (n = 15,028)	Frail (n = 10,694)	*P*-Value[a]
Medical history				
Hypertension	9466 (42)	7588 (51)	7058 (67)	< .001
Heart disease	1896 (8.4)	1933 (13)	2941 (28)	< .001
Osteoarthritis	7253 (32)	5831 (40)	6091 (58)	< .001
Rheumatoid arthritis	87 (0.4)	111 (0.8)	187 (1.8)	< .001
Stroke	403 (1.8)	488 (3.3)	934 (8.9)	< .001
Parkinson's disease	45 (0.2)	49 (0.3)	162 (1.5)	< .001
Multiple sclerosis	62 (0.3)	74 (0.5)	162 (1.5)	< .001
Cancer	2873 (13)	2197 (15)	1873 (18)	< .001
Any fracture since age 45 years	4202 (19)	3269 (22)	3475 (33)	< .001
Current use of antiosteoporosis medication	6047 (27)	4048 (28)	2893 (20)	.09

[a]Chi-squared for categorical variables; Mantel-Haenszel chi-square for ordered categories; Kruskal-Wallis for continuous categories.

Values are number (percentage) unless otherwise indicated.

Table 2

Follow-up Recurrent Falls, New/Worsening Disability, and Fracture by Baseline Geographic Region, Age Group, and Frailty Status

Europe	Age group (years)	Nonfrail (%)	Pre-frail (%)	Frail (%)	*P*-Value[a]
All women					
	55–64	4860 (59)	2458 (30)	894 (11)	< .001
	65–74	3822 (54)	2011 (28)	1256 (18)	< .001
	≥ 75	1404 (35)	1038 (26)	1526 (39)	< .001
≥ 2 falls in the past year					
	55–64	333 (6.9)	251 (10)	201 (23)	< .001
	65–74	269 (7.1)	223 (11)	245 (20)	< .001
	≥ 75	123 (8.9)	131 (13)	322 (22)	< .001
New/worsening disability					
	55–64	199 (4.8)	230 (11)	164 (20)	< .001
	65–74	240 (7.3)	240 (7.3)	233 (20)	< .001
	≥ 75	134 (11)	134 (11)	322 (23)	< .001
Fracture in the past year					
	55–64	77 (1.6)	65 (2.7)	37 (4.2)	< .001
	65–74	84 (2.2)	61 (3.1)	60 (4.9)	< .001
	≥ 75	59 (4.3)	47 (4.7)	83 (5.6)	.12
Canada/Australia	Age group (years)	Nonfrail	Pre-frail	Frail	*P*-Value[a]
All women					
	55–64	1414 (54)	843 (32)	362 (14)	< .001
	65–74	998 (48)	638 (30)	457 (22)	< .001
	≥ 75	476 (31)	431 (28)	621 (41)	< .001
≥ 2 falls in past year					
	55–64	110 (7.8)	102 (12)	93 (26)	< .001
	65–74	79 (8.0)	69 (11)	88 (19)	< .001
	≥ 75	33 (7.0)	50 (12)	125 (20)	< .001
New/worsening disability					

Europe	Age group (years)	Nonfrail (%)	Pre-frail (%)	Frail (%)	*P*-Value[a]
	55–64	68 (4.8)	75 (8.9)	48 (13)	< .001
	65–74	75 (7.5)	79 (12)	71 (16)	< .001
	≥ 75	37 (7.8)	66 (15)	141 (23)	< .001
Fracture in the past year					
	55–64	30 (2.2)	20 (2.4)	11 (3.1)	.32
	65–74	15 (1.5)	13 (2.1)	18 (4.0)	.005
	≥ 75	15 (3.2)	17 (4.1)	29 (4.8)	.19
U.S.	Age group (years)	Nonfrail	Pre-frail	Frail	*P*-Value[a]
All women					
	55–64	4125 (49)	2965 (35)	1405 (17)	< .001
	65–74	3908 (46)	2772 (33)	1819 (21)	< .001
	≥ 75	1907 (31)	1872 (31)	2354 (38)	< .001
≥ 2 falls in past year					
	55–64	419 (10)	418 (14)	398 (29)	< .001
	65–74	359 (9.2)	385 (14)	448 (25)	< .001
	≥ 75	185 (9.7)	243 (13)	550 (24)	< .001
New/worsening disability					
	55–64	191 (4.6)	277 (9.3)	259 (18)	< .001
	65–74	225 (5.8)	330 (12)	351 (19)	< .001
	≥ 75	194 (10)	306 (16)	531 (23)	< .001
Fracture in the past year					
	55–64	68 (1.7)	51 (1.8)	75 (5.4)	< .001
	65–74	75 (2.0)	77 (2.8)	62 (3.5)	< .001
	≥ 75	56 (3.0)	96 (5.2)	127 (5.5)	< .001

[a]P value from a Mantel-Haenszel chi-square test

Table 3

Odds Ratios for Falls, Fracture, and Disability by 1-Year Follow-Up by Frailty Status from Age-Adjusted and Multivariable Models

Frailty Status by Outcome		n	Age-adjusted OR (95% CI)	*P*-value	n	Multivariable OR (95% CI)	*P*-value
Falls		48,154		< .001[a]	44,528		< .001[b]
	Pre-frail		1.57 (1.47–1.68)			1.23 (1.13–1.32)	
	Frail		3.35 (3.13–3.58)			1.68 (1.54–1.83)	
Fracture		47,780		< .001[c]	44,072		< .001[d]
	Pre-frail		1.39 (1.22–1.58)			1.23 (1.07–1.42)	
	Frail		1.97 (1.73–2.25)			1.46 (1.26–1.70)	
Disability		46,273		< .001[e]	40,332		< .001[e]
	Pre-frail		2.04 (1.90–2.20)			1.85 (1.70–2.01)	
	Frail		3.27 (3.03–3.52)			2.29 (2.09–2.51)	

[a] C statistic = .63. CI = confidence interval; OR = odds ratio.

[b] C statistic = .63, adjusted for age group, study region, baseline falls, baseline EQ-5D anxiety/depression, medical history of heart disease, medical history of arthritis, medical history of stroke, medical history of multiple sclerosis, medical history of cancer, and baseline fracture.

[c] n = 47,780, c statistic = .59.

[d] C statistic = .68, adjusted for age group, study region, current smoking at baseline, baseline falls, baseline EQ-5D anxiety/depression, baseline use of antiosteoporosis medication, history of arthritis, and baseline fracture.

[e] C statistic = .67.

[f] C statistic = .69, adjusted for age group, study region, current smoking at baseline, baseline falls, baseline EQ-5D anxiety/depression, baseline BMI category, baseline alcohol use, medical history of hypertension, medical history of heart disease, medical history of arthritis, medical history of rheumatoid arthritis, medical history of stroke, and medical history of Parkinson's disease.