Published in final edited form as:

Am J Med. 2013 February ; 126(2): 169.e19–169.e26. doi:10.1016/j.amjmed.2012.06.032.

Cardiovascular and Non-Cardiovascular Disease Associations with Hip Fractures

Yariv Gerber, PhD^{a,c}, L. Joseph Melton III, MD^a, Sheila M. McNallan, MPH^a, Ruoxiang Jiang, BS^a, Susan A. Weston, MS^a, and Véronique L. Roger, MD, MPH^{a,b}

^aDepartment of Health Sciences Research, College of Medicine, Mayo Clinic, Rochester, MN

^bDivision of Cardiovascular Diseases, Department of Internal Medicine, College of Medicine, Mayo Clinic, Rochester, MN

^cDepartment of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Abstract

BACKGROUND—There is growing awareness of an association between cardiovascular disease and fractures, and a temporal increase in fracture risk after myocardial infarction has been identified. To further explore the nature of this relationship, we systematically examined the association of hip fracture with all disease categories and assessed related secular trends.

METHODS—Using resources of the Rochester Epidemiology Project, a population-based incident case-control study was conducted. Disease history was compared between all Olmsted County, Minnesota, residents aged 50 years or older with a first radiographically confirmed hip fracture in 1985–2006 and community control subjects individually matched (1:1) to cases on age, sex, and index year (n=3,808; mean age [SD], 82 [9] years; 76% women).

RESULTS—All cardiovascular and numerous non-cardiovascular disease categories (e.g., infectious diseases, nutritional and metabolic diseases, mental disorders, diseases of the nervous system and sense organs, and diseases of the respiratory system) were associated with fracture risk. However, increasing temporal trends were almost exclusively detected in cardiovascular disease categories. The largest increases in association were observed for ischemic heart disease, other forms of heart disease (including heart failure), hypertension, and diabetes and were more pronounced among elderly women than among other demographic subgroups.

CONCLUSIONS—While the association with hip fracture was not specific to cardiovascular disease, temporal increases were mainly detected in cardio-metabolic diseases, all of which have also been linked previously to frailty. This mechanism and others warrant further investigation.

Keywords

Cardiovascular Disease; Hip Fracture; Epidemiology; Population Studies; Frailty; Surveillance

© 2012 Elsevier Inc. All rights reserved.

Correspondence: Dr. Véronique L. Roger; Mayo Clinic; 200 First Street, SW; Rochester, MN 55905; Phone: 507-538-6916; Fax: 507-284-1516; roger.veronique@mayo.edu.

Conflict of Interest: None

Authorship: All authors had access to the data and participated in the preparation of the manuscript.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

INTRODUCTION

There is growing awareness of a relationship between cardiovascular disease and bone fragility.^{1–4} A strong association with osteoporotic fractures in general, and with hip fracture in particular, has been found for ischemic heart disease,^{5,6} heart failure,^{5,7–10} peripheral artery disease,^{5,11} hypertension,^{7,12} stroke,^{5,7,12} and diabetes.^{13,14} Furthermore, a steady increase in fracture risk after acute myocardial infarction over the past 3 decades has recently been reported, a finding not observed in the general population.¹⁵ This observation has major clinical and public health implications given the growing relative importance of non-cardiovascular comorbid conditions in the genesis of adverse outcomes after myocardial infarction.^{16,17}

While a causal relationship between cardiovascular disease and osteoporotic fractures has been suggested by several authors,^{5,8,12} other mechanisms such as co-occurrence of chronic diseases driven by aging or shared etiologic factors have also been postulated.^{9,18,19} To further elucidate the nature of this relationship, the importance of which is anchored in the enormous burden of both cardiovascular disease and fractures in aging populations,^{20,21} we systematically studied the association of hip fractures with all diseases, including both cardiovascular and non-cardiovascular disease categories, in a large population-based incident case-control study spanning over 20 years, focusing on the strength, consistency over time, and specificity of the relationship.²²

SUBJECTS AND METHODS

Study Setting

Olmsted County, MN, is a fertile ground for epidemiological research because of its relative isolation from other urban centers and because medical care is practically self-contained within the community.²³ Most orthopedic care, for example, is provided by the Mayo Clinic, which has maintained a common medical record with its two affiliated hospitals (St. Marys and Rochester Methodist) for over 100 years.²⁴ Recorded diagnoses and surgical procedures are indexed, including the diagnoses made during outpatient clinic visits, as well as diagnoses recorded for nursing home residents, hospital inpatients, at autopsy, or on death certificates. Medical records of the other providers who serve the local population, most notably the Olmsted Medical Center with its affiliated hospital, are also indexed and retrievable, through the unique medical records linkage system called the Rochester Epidemiology Project.²³

Study Design

Following approval by the appropriate Institutional Review Boards, a case-control study was carried out, comparing disease history between incident hip fracture cases and community-based control subjects. All Olmsted County residents aged 50 years or over with a first documented hip fracture in 1985–2006 (n=1,904) were enrolled, as previously described in detail.²⁴ Briefly, provider-linked inpatient and outpatient medical records were reviewed for any diagnosis attributable to diagnostic rubric 820 in the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* or equivalent codes in earlier classification systems. Radiographic and/or autopsy confirmation was obtained in all cases. Community control subjects, with no history of any osteoporotic fractures (including proximal femur, lumbar/thoracic vertebrae, distal forearm, or humerus fractures),²⁵ were randomly selected from the Olmsted County population and individually matched (1:1) to each case on age (± 1 years), sex, and incidence year. In any 3-year period, nearly all local residents have at least 1 contact with the medical system, and the majority of residents are

attended annually; hence, the Rochester Epidemiology Project provides a virtually complete enumeration of the population from which to sample controls.

Exposure Data

The Rochester Epidemiology Project medical indices were used to obtain information on all diagnoses entered between 1975 and 2006. Disease history, grouped into standard categories,²⁶ was compared between the identified cases and controls. Diagnoses were obtained either from a Mayo extension of the *Hospital Adaptation of the International Classification of Diseases, Eighth Edition (H-ICDA-2)* in 1975–2006 or the *ICD-9-CM* in 1987–2006. In order to help standardize the exposure duration for all participants and to allow a temporal trend analysis, only diagnoses recorded within 10 years prior to the index date were considered. This was required because for the first subjects were enrolled in 1985 while *H-ICDA-2* codes were available starting in 1975. Diagnoses were divided into cardiovascular and non-cardiovascular conditions. Broad cardiovascular disease categories were based on the American Heart Association classification, which consists of coronary heart disease, non-coronary diseases of the heart (including chronic rheumatic fever, pulmonary circulatory diseases, and other forms of heart disease) and noncardiac circulatory diseases (including cerebrovascular diseases, hypertensive diseases, diseases of arteries, arterioles, and capillaries diseases of veins, lymphatic vessels, and lymph nodes, and other and unspecified disorders of the circulatory system).²⁷ For the non-cardiovascular diagnoses, only *H-ICDA-2* codes were available for analysis; in a validation study, the sensitivity of *H-ICDA-2* codes was 80–93% for the broad cardiovascular disease categories. Individual comorbidities were those included in the Charlson index,²⁸ excluding cardiovascular disease entities.

Statistical Analysis

A matched analysis was employed using conditional logistic regression with the matching identification number as a stratification variable.²⁹ Multiple models were constructed to estimate the odds ratio (OR) of hip fracture associated with various disease categories. Temporal trends were formally assessed by including a year-by-disease category interaction term in unconditional logistic regression models. For the latter purpose, year was treated as a continuous variable while adjusting for age and sex. Stratified analysis was used to assess ORs in subgroups or in specific time periods, and the heterogeneity of these estimates was then tested.³⁰ Due to the exploratory nature of this study, no adjustments were made for multiple comparisons.^{31,32} Analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

Data from 1,904 case-control pairs were analyzed. For both groups, the mean age (SD) was 82 (9) years (range, 50–107 years), and 76% were women. Hip fracture cases had a higher prevalence of comorbid conditions than controls (Table 1).

Although an increasing prevalence over time of the broad cardiovascular disease categories occurred in both cases and controls, the magnitude of these trends varied widely. Greater annual increases were noted among cases than controls in coronary heart disease, other diseases of the heart, and noncardiac circulatory diseases (all age- and gender- adjusted *P* for diverging trends <0.05), with a large widening of the gaps around the year 2000 (Fig 1). The ORs of hip fracture in the broad cardiovascular disease categories and their subcategories, overall and during two different time periods (1985–1999 versus 2000–2006 chosen on the basis of visual assessment of the trends) are presented in Table 2. While a positive association with hip fracture risk was observed for all categories and subcategories, a

temporal increase in the association was mostly evident for ischemic heart disease, other forms of heart disease (including heart failure), and hypertensive diseases (mainly essential hypertension). In a stratified analysis by age and sex groups, for each cardiovascular disease category, both the strength of the association (nonsignificant for coronary heart disease) and its increase over time were greater among elderly women than among other segments of the population (Table 3).

The association with hip fracture risk was also examined systematically for all non-cardiovascular categories (Table 4). Numerous categories were associated with fracture risk, including infectious and parasitic diseases, endocrine, nutritional and metabolic diseases, diseases of the blood and blood-forming organs, mental disorders, diseases of the nervous system and sense organs, diseases of the respiratory system, and injury and poisoning. However, no consistent temporal trend was detected in any of these categories. Indeed, none of the individual Charlson index comorbidities evaluated demonstrated a statistically significant trend over time, except for diabetes mellitus which showed an increasing association with hip fracture (odds ratio (OR) 1.03, 95% CI 0.83–1.31 in 1985–1999; OR 1.77, 95% CI 1.33–2.35 in 2000–2006).

DISCUSSION

In this incident case-control study spanning over 20 years, we observed a steady increase in hip fracture risk associated with cardiovascular disease in the Olmsted County population, a phenomenon not detected in non-cardiovascular categories. This alarming trend extends a recent report from our group showing an emerging association between myocardial infarction and osteoporotic fractures over the past 3 decades.¹⁵ Thus, the increasing fracture risk was not specific to myocardial infarction but also included other forms of heart disease, hypertension, and diabetes. Since the controls in our analysis were randomly selected from the same study population and were matched on incidence year, this largely precludes ascertainment bias as a plausible mechanism for the increasing association. Genetic predisposition for cardiovascular disease and hip fractures⁵ cannot explain the upward trend either, leaving changes in cardiac patient profiles as a potential mechanism.

Frailty, a syndrome of physical vulnerability characterized by multisystem dysfunction and lack of physiological reserve, has been linked to cardiovascular disease in several studies,^{33–35} and there is increased awareness of the burden of frailty among cardiovascular disease patients.³⁶ Furthermore, recent studies have detected an upward trend in non-cardiovascular event rates after myocardial infarction, possibly driven by increased comorbidity and frailty.^{15–17} The aging population on one hand,³⁷ and the prolonged survival of cardiovascular patients on the other,^{16,38,39} have presumably led to an increase in the number of cardiac patients with frailty-related impairments.⁴⁰ Frailty in turn is a risk factor for falls and fractures,^{41,42} particularly in the hip.⁴³ Our systematic examination of disease history reported herein revealed that coronary heart disease, other forms of heart disease (including heart failure), hypertension, and diabetes demonstrated the sharpest increase in association to hip fracture over time, which was more pronounced among elderly women. The latter entities also represent the chronic conditions most strongly associated with frailty.^{34,44}

A shared risk factor for frailty-related cardiovascular conditions (e.g., heart failure, hypertension, peripheral artery disease and diabetes) is obesity, which also showed a temporal increase in prevalence in Minnesota over the past decades,⁴⁵ and which doubled among myocardial infarction patients between 1979 and 2006.¹⁵ Contrary to the traditional concept of frailty as a wasting disorder, and despite the fact that weight loss is one of the recognized components of this syndrome, recent studies have identified sarcopenic obesity

(a combination of excess weight and reduced muscle mass or strength) as an emerging cause of frailty in older adults,^{46,47} especially among women.⁴⁸ Unfortunately, we do not have access to data on body mass index in these subjects with which to elucidate this point. Whether “obese frailty” is responsible for the upward trend in the association between cardiovascular disease and hip fracture warrants further investigation.

The current study has some specific limitations related to the use of electronic codes. We relied on *H-ICDA-2* and *ICD-9-CM* diagnostic codes for disease definitions; and, due to the sample size involved, it was not possible to verify the accuracy of the coding by manual chart review. For the non-cardiovascular diagnoses, only *H-ICDA-2* codes were available for analysis. As a result, some degree of exposure misclassification is inevitable⁴⁹. However, because coding approach and data availability were similar regardless of case/control status, we believe this bias to be non-differential. Moreover, some potentially important covariates such as obesity, smoking, and alcohol consumption were not available for analysis. Due to the exploratory nature of this analysis, multiple comparisons were performed, and this needs to be considered while interpreting the results. We did not correct for multiple comparisons since that substantially inflates the likelihood of type II errors, and important associations might thereby be considered nonsignificant.^{31,50} Consequently, we believe that observed patterns which confirm previous findings should be given more weight than isolated results in the context of multiple comparisons.

The current study also has several strengths. We capitalized on the comprehensive data resources of the Rochester Epidemiology Project to systematically evaluate cardiovascular and non-cardiovascular disease associations with hip fractures. We report on a large, population-based inception cohort that included virtually all community residents aged 50 years or older with a first-ever hip fracture.¹³ The controls were randomly selected from an enumeration of the Olmsted County population, and therefore should have been representative of community residents generally. Furthermore, the exposure data, as coded from the detailed inpatient and outpatient medical records, were recorded prior to any knowledge of subsequent development of the outcome under study.

CONCLUSIONS

While the relationship with hip fracture was not specific to cardiovascular disease, secular increases in the association were primarily detected in ischemic heart disease, other forms of heart disease (including heart failure), hypertension and diabetes, all of which have also been linked previously to frailty. Furthermore, both the strength of the association and the observed temporal trends were greater among elderly women than among other segments of the population. Whether changes in cardiac patient profiles, including presence of frailty-related impairments, contribute to these identified trends require further investigation.

Acknowledgments

The authors are indebted to Deborah S. Russell and Mary G. Roberts from the Department of Health Science Research at Mayo Clinic for administrative assistance.

Funding: This was supported by grants from the National Institutes of Health (P01 AG04875 to Dr. Melton; R01 HL59205 and R01 HL72435 to Dr. Roger), and made possible by the Rochester Epidemiology Project (R01 AG034676 from the National Institute on Aging).

References

1. Alagiakrishnan K, Juby A, Hanley D, Tymchak W, Sclater A. Role of vascular factors in osteoporosis. *J Gerontol A Biol Sci Med Sci*. 2003; 58:362–366. [PubMed: 12663699]

2. Anagnostis P, Karagiannis A, Kakafika AI, Tziomalos K, Athyros VG, Mikhailidis DP. Atherosclerosis and osteoporosis: age-dependent degenerative processes or related entities? *Osteoporos Int.* 2009; 20:197–207. [PubMed: 18509713]
3. McFarlane SI, Muniyappa R, Shin JJ, Bahtiyar G, Sowers JR. Osteoporosis and cardiovascular disease: Brittle bones and boned arteries, is there a link? *Endocrine.* 2004; 23:1–10. [PubMed: 15034190]
4. Ezekowitz JA. A new pathway? Failure, fragility and fractures. *Eur Heart J.* 2010; 31:9–11. [PubMed: 19933280]
5. Sennerby U, Melhus H, Gedeberg R, et al. Cardiovascular diseases and risk of hip fracture. *JAMA.* 2009; 302:1666–1673. [PubMed: 19843901]
6. Magnus JH, Broussard DL. Relationship between bone mineral density and myocardial infarction in US adults. *Osteoporos Int.* 2005; 16:2053–2062. [PubMed: 16249840]
7. Sennerby U, Farahmand B, Ahlbom A, Ljunghall S, Michaelsson K. Cardiovascular diseases and future risk of hip fracture in women. *Osteoporos Int.* 2007; 18:1355–1362. [PubMed: 17492247]
8. van Diepen S, Majumdar SR, Bakal JA, McAlister FA, Ezekowitz JA. Heart failure is a risk factor for orthopedic fracture: a population-based analysis of 16,294 patients. *Circulation.* 2008; 118:1946–1952. [PubMed: 18936331]
9. Gerber Y, Melton LJ 3rd, Weston SA, Roger VL. Osteoporotic fractures and heart failure in the community. *Am J Med.* 2011; 124:418–425. [PubMed: 21531231]
10. Carbone L, Buzkova P, Fink HA, et al. Hip fractures and heart failure: findings from the Cardiovascular Health Study. *Eur Heart J.* 2010; 31:77–84. [PubMed: 19892715]
11. Collins TC, Ewing SK, Diem SJ, et al. Peripheral arterial disease is associated with higher rates of hip bone loss and increased fracture risk in older men. *Circulation.* 2009; 119:2305–2312. [PubMed: 19380619]
12. Vestergaard P, Rejnmark L, Mosekilde L. Hypertension is a risk factor for fractures. *Calcif Tissue Int.* 2009; 84:103–111. [PubMed: 19067019]
13. Melton LJ 3rd, Leibson CL, Achenbach SJ, Therneau TM, Khosla S. Fracture risk in type 2 diabetes: update of a population-based study. *J Bone Miner Res.* 2008; 23:1334–1342. [PubMed: 18348689]
14. Janghorbani M, Feskanich D, Willett WC, Hu F. Prospective study of diabetes and risk of hip fracture: the Nurses' Health Study. *Diabetes Care.* 2006; 29:1573–1578. [PubMed: 16801581]
15. Gerber Y, Melton LJ 3rd, Weston SA, Roger VL. Association between myocardial infarction and fractures: an emerging phenomenon. *Circulation.* 2011; 124:297–303. [PubMed: 21709062]
16. Roger VL, Weston SA, Gerber Y, et al. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. *Circulation.* 2010; 121:863–869. [PubMed: 20142444]
17. Kostis WJ, Deng Y, Pantazopoulos JS, Moreyra AE, Kostis JB. Trends in mortality of acute myocardial infarction after discharge from the hospital. *Circ Cardiovasc Qual Outcomes.* 2010; 3:581–589. [PubMed: 20923995]
18. Samelson EJ, Cupples LA, Broe KE, Hannan MT, O'Donnell CJ, Kiel DP. Vascular calcification in middle age and long-term risk of hip fracture: the Framingham Study. *J Bone Miner Res.* 2007; 22:1449–1454. [PubMed: 17542685]
19. Sinnott B, Syed I, Sevrakov A, Barengolts E. Coronary calcification and osteoporosis in men and postmenopausal women are independent processes associated with aging. *Calcif Tissue Int.* 2006; 78:195–202. [PubMed: 16604285]
20. [Accessed September 1, 2011] Facts and statistics about osteoporosis and its impact. <http://www.iofbonehealth.org/facts-and-statistics.html>
21. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart Disease and Stroke Statistics--2011 Update: A Report From the American Heart Association. *Circulation.* 2011; 123:e18–e209. [PubMed: 21160056]
22. Hill AB. The environment and disease: association or causation? *Proc R Soc Med.* 1965; 58:295–300. [PubMed: 14283879]
23. Melton LJ 3rd. History of the Rochester Epidemiology Project. *Mayo Clin Proc.* 1996; 71:266–274. [PubMed: 8594285]

24. Melton LJ 3rd, Kearns AE, Atkinson EJ, et al. Secular trends in hip fracture incidence and recurrence. *Osteoporos Int.* 2009; 20:687–694. [PubMed: 18797813]
25. Dawson-Hughes B, Tosteson AN, Melton LJ 3rd, et al. Implications of absolute fracture risk assessment for osteoporosis practice guidelines in the USA. *Osteoporos Int.* 2008; 19:449–458. [PubMed: 18292975]
26. [Accessed September 20, 2011] <http://icd9cm.Chrisendres.Com/>
27. Gerber Y, Jacobsen SJ, Frye RL, Weston SA, Killian JM, Roger VL. Secular trends in deaths from cardiovascular diseases: a 25-year community study. *Circulation.* 2006; 113:2285–2292. [PubMed: 16682616]
28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987; 40:373–383. [PubMed: 3558716]
29. Hosmer, DW.; Lemeshow, S. *Applied Logistic Regression.* New York: John Wiley & Sons, Inc; 1989.
30. Abramson JH. WINPEPI (PEPI-for-Windows): computer programs for epidemiologists. *Epidemiol Perspect Innov.* 2004; 1:6. [PubMed: 15606913]
31. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology.* 1990; 1:43–46. [PubMed: 2081237]
32. Thomas DC, Siemiatycki J, Dewar R, Robins J, Goldberg M, Armstrong BG. The problem of multiple inference in studies designed to generate hypotheses. *Am J Epidemiol.* 1985; 122:1080–1095. [PubMed: 4061442]
33. Chen JS, Hogan C, Lyubomirsky G, Sambrook PN. Women with cardiovascular disease have increased risk of osteoporotic fracture. *Calcif Tissue Int.* 2011; 88:9–15. [PubMed: 21046091]
34. Newman AB, Gottdiener JS, McBurnie MA, et al. Associations of subclinical cardiovascular disease with frailty. *J Gerontol A Biol Sci Med Sci.* 2001; 56:M158–166. [PubMed: 11253157]
35. Singh M, Rihal CS, Lennon RJ, Spertus JA, Nair KS, Roger VL. Influence of Frailty and Health Status on Outcomes in Patients With Coronary Disease Undergoing Percutaneous Revascularization. *Circ Cardiovasc Qual Outcomes.* 2011 In press.
36. Singh M, Alexander K, Roger VL, et al. Frailty and its potential relevance to cardiovascular care. *Mayo Clin Proc.* 2008; 83:1146–1153. [PubMed: 18828975]
37. Majeed A, Aylin P. The ageing population of the United Kingdom and cardiovascular disease. *BMJ.* 2005; 331:1362. [PubMed: 16339247]
38. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med.* 2010; 362:2155–2165. [PubMed: 20558366]
39. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA.* 2004; 292:344–350. [PubMed: 15265849]
40. Michel JP, Newton JL, Kirkwood TB. Medical challenges of improving the quality of a longer life. *JAMA.* 2008; 299:688–690. [PubMed: 18270358]
41. 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]
42. Tinetti ME, Inouye SK, Gill TM, Doucette JT. Shared risk factors for falls, incontinence, and functional dependence. Unifying the approach to geriatric syndromes. *JAMA.* 1995; 273:1348–1353. [PubMed: 7715059]
43. Parkkari J, Kannus P, Palvanen M, et al. Majority of hip fractures occur as a result of a fall and impact on the greater trochanter of the femur: a prospective controlled hip fracture study with 206 consecutive patients. *Calcif Tissue Int.* 1999; 65:183–187. [PubMed: 10441647]
44. Lee PG, Cigolle C, Blaum C. The co-occurrence of chronic diseases and geriatric syndromes: the health and retirement study. *J Am Geriatr Soc.* 2009; 57:511–516. [PubMed: 19187416]
45. Centers for disease control and prevention (cdc). Behavioral risk factor surveillance system survey data. Atlanta, georgia: U.S. Department of health and human services, centers for disease control and prevention; 2011.

46. Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V. Sarcopenic obesity: a new category of obesity in the elderly. *Nutr Metab Cardiovasc Dis.* 2008; 18:388–395. [PubMed: 18395429]
47. Jarosz PA, Bellar A. Sarcopenic obesity: an emerging cause of frailty in older adults. *Geriatr Nurs.* 2009; 30:64–70. [PubMed: 19226689]
48. Blaum CS, Xue QL, Michelon E, Semba RD, Fried LP. The association between obesity and the frailty syndrome in older women: the Women's Health and Aging Studies. *J Am Geriatr Soc.* 2005; 53:927–934. [PubMed: 15935013]
49. StSauver, J.; Buntrock, J.; Rademacher, D., et al. Technical Report No 3. Department of Health Sciences Research, Mayo Clinic; Rochester, MN: 2010. Comparison of Mayo Clinic Coding Systems.
50. Williams SM, Haines JL. Correcting away the hidden heritability. *Ann Hum Genet.* 2011; 75:348–350. [PubMed: 21488852]

Figure 1.

Temporal trends in prevalence of coronary heart disease (CHD), non-CHD other diseases of the heart, and non-cardiac circulatory diseases among Olmsted County, Minnesota, residents with a first hip fracture in 1985–2006 vs community control subjects. The *P* values for differential temporal trend are adjusted for age and sex. A moving 4-year average is used for the trendlines.

Table 1

Pertinent clinical characteristics among hip fracture cases compared with controls

<i>Characteristic</i>	<i>Hip Fracture Status</i>	
	Cases	Controls
n	1,904	1,904
Age, years, mean (SD)	82.2 (9.5)	82.1 (9.4)
Female, n (%)	1,444 (76)	1,444 (76)
Selected Comorbidities, n (%)		
Myocardial infarction	366 (19)	261 (14) *
Heart failure	533 (28)	336 (18) *
Peripheral vascular disease	275 (14)	201 (11) *
Cerebrovascular disease	628 (33)	405 (21) *
Dementia	563 (30)	211 (11) *
Chronic pulmonary disease	303 (16)	175 (9) *
Ulcer	466 (24)	316 (17) *
Diabetes	306 (16)	253 (13) **
Cancer	424 (22)	309 (16) *

* P value < 0.01** P value = 0.02

Table 2

Prevalence (%) along with odds ratios (OR) and 95% confidence intervals (95% CI) of hip fracture associated with cardiovascular disease (CVD) categories and subcategories *

CVD Categories and Subcategories	Prevalence		Overall		1985–1999		2000–2006		<i>P</i> _{Heterogeneity of ORs} [†]
	Cases	Controls	OR	95% CI	OR	95% CI	OR	95% CI	
Coronary heart disease (CHD)									
Ischemic heart disease	39%	29%	1.65	1.43–1.91	1.44	1.20–1.72	2.09	1.64–2.67	0.02
	39%	29%	1.65	1.43–1.91	1.44	1.20–1.72	2.09	1.64–2.67	0.02
Non-CHD disease of the heart									
Chronic rheumatic fever	65%	46%	2.19	1.91–2.52	1.91	1.62–2.25	2.99	2.30–3.87	<0.01
	20%	14%	1.54	1.29–1.83	1.41	1.12–1.76	1.75	1.33–2.30	0.23
Pulmonary circulatory diseases	8%	3%	2.53	1.85–3.45	2.45	1.50–4.03	2.57	1.73–3.85	0.89
Other forms of heart disease	62%	44%	2.15	1.87–2.47	1.88	1.59–2.21	2.91	2.25–3.76	0.01
Noncardiac circulatory diseases									
Cerebrovascular diseases	84%	71%	2.13	1.81–2.50	1.75	1.46–2.11	4.03	2.78–5.83	<0.01
	33%	20%	2.02	1.73–2.35	2.02	1.67–2.45	2.01	1.56–2.60	0.98
Hypertensive diseases	66%	56%	1.55	1.35–1.77	1.27	1.09–1.49	2.70	2.04–3.58	<0.01
Diseases of arteries, arterioles, and capillaries	31%	23%	1.53	1.32–1.77	1.50	1.25–1.79	1.60	1.26–2.04	0.67
Diseases of veins, lymphatic vessels, and lymph nodes	38%	25%	1.87	1.62–2.15	1.74	1.45–2.09	2.06	1.65–2.58	0.25
Other and unspecified disorders of the circulatory system	21%	12%	1.98	1.65–2.38	2.04	1.60–2.61	1.91	1.45–2.51	0.73

* only subcategories with prevalence ≥ 5% are shown; CVD categories are defined according to American Heart Association classification.

[†] refers to differences between the two time periods.

Table 3

Prevalence (%) along with odds ratios (OR) and 95% confidence intervals (95% CI) of hip fracture associated with cardiovascular diseases (CVD) categories in mutually exclusive age and sex groups^{*}

CVD Categories	Prevalence		Overall		1985–1999		2000–2006		<i>P</i> _{Heterogeneity of ORs[‡]}
	Cases	Controls	OR	95% CI	OR	95% CI	OR	95% CI	
Coronary heart disease (CHD)									
Male 80 years	60%	51%	1.55	1.04–2.31	1.43	0.82–2.50	1.68	0.96–2.97	0.69
Female 80 years	40%	27%	1.77	1.46–2.15	1.48	1.17–1.86	2.57	1.81–3.64	0.01
Male <80 years	39%	32%	1.44	0.93–2.23	1.08	0.62–1.89	2.30	1.10–4.83	0.11
Female <80 years	25%	19%	1.47	1.05–2.07	1.55	1.00–2.40	1.36	0.79–2.36	0.72
<i>P</i> for heterogeneity of ORs [‡]				0.70		0.76		0.23	
<u>Non-CHD disease of the heart</u>									
Male 80 years	76%	65%	1.69	1.12–2.56	1.46	0.89–2.41	2.30	1.10–4.83	0.32
Female 80 years	71%	47%	2.62	2.17–3.17	2.17	1.74–2.71	4.18	2.86–6.11	<0.01
Male <80 years	53%	42%	1.61	1.04–2.48	1.32	0.76–2.29	2.18	1.07–4.45	0.28
Female <80 years	49%	36%	1.75	1.32–2.32	1.74	1.24–2.43	1.77	1.05–2.99	0.96
<i>P</i> for heterogeneity of ORs [‡]				0.03		0.22		0.05	
<u>Noncardiac circulatory diseases</u>									
Male 80 years	91%	84%	1.80	1.04–3.11	1.56	0.83–2.93	2.75	0.88–8.64	0.39
Female 80 years	87%	67%	3.22	2.55–4.07	2.46	1.89–3.19	8.25	4.53–15.02	<0.01
Male <80 years	73%	71%	1.07	0.65–1.74	1.16	0.63–2.14	0.92	0.40–2.08	0.68
Female <80 years	76%	73%	1.24	0.90–1.71	1.12	0.70–1.58	2.29	0.94–5.57	0.15
<i>P</i> for heterogeneity of ORs [‡]				<0.01		<0.01		0.03	

^{*} based on 512 (13%) men 80 years, 2,033 (53%) women 80 years, 408 (11%) men <80 years, and 855 (23%) women <80 years.

[‡] refers to differences between the two time periods.

[‡] refers to differences between the demographic subgroups.

Table 4

Prevalence (%) along with odds ratios (OR) and 95% confidence intervals (95% CI) of hip fracture associated with non-cardiovascular disease (CVD) categories*

Non-CVD Categories	Prevalence		Overall		1985–1999		2000–2006		$P_{\text{Heterogeneity of ORs}}^{\dagger}$
	Cases	Controls	OR	95% CI	OR	95% CI	OR	95% CI	
<u>Infectious and parasitic diseases</u>									
Intestinal infectious diseases	11%	7%	1.77	1.39–2.25	1.58	1.17–2.12	2.19	1.44–3.32	0.21
Other bacterial diseases	9%	4%	2.15	1.61–2.89	2.07	1.44–2.98	2.32	1.41–3.82	0.72
Other viral diseases	11%	8%	1.38	1.09–1.73	1.10	0.83–1.45	2.27	1.48–3.48	0.01
Mycoses	21%	14%	1.66	1.37–2.00	1.43	1.11–1.84	1.96	1.48–2.59	0.10
<u>Neoplasms</u>									
Secondary malignant neoplasms	7%	4%	1.76	1.29–2.40	1.48	1.01–2.17	2.44	1.41–4.23	0.14
<u>Endocrine, nutritional and metabolic diseases, and immunity disorders</u>									
Disorders of thyroid gland	22%	16%	1.36	1.14–1.62	1.46	1.16–1.84	1.23	0.93–1.61	0.35
Diseases of other endocrine glands	21%	18%	1.19	1.01–1.41	0.99	0.80–1.24	1.55	1.19–2.02	0.01
Avitaminoses, malabsorption, and other nutritional deficiencies	9%	3%	2.96	2.14–4.09	3.46	2.20–5.45	2.48	1.56–3.95	0.32
Other metabolic diseases	37%	43%	0.76	0.66–0.87	0.74	0.62–0.88	0.79	0.62–1.01	0.67
<u>Diseases of the blood and blood-forming organs</u>									
Diseases of the blood and blood-forming organs	39%	19%	2.74	2.32–3.24	2.40	1.93–2.98	3.29	2.53–4.29	0.07
<u>Mental disorders</u>									
Psychoses associated with organic brain syndromes	16%	5%	3.44	2.64–4.48	3.21	2.35–4.38	4.05	2.45–6.70	0.44
Nonpsychotic organic brain syndromes	30%	11%	4.06	3.30–5.01	3.64	2.85–4.66	5.24	3.52–7.80	0.13
Psychoses not attributed to physical conditions	9%	4%	2.40	1.79–3.23	2.40	1.66–3.47	2.41	1.47–3.96	0.99
Neurosis	37%	21%	2.24	1.91–2.62	1.89	1.55–2.29	3.11	2.34–4.13	0.01
Personality disorders and certain other nonpsychotic mental disorders	9%	4%	2.43	1.80–3.27	2.23	1.56–3.20	2.89	1.69–4.94	0.43
Special symptoms	29%	13%	2.83	2.35–3.41	2.35	1.86–2.96	3.82	2.79–5.23	0.02
Transient situational disturbances	9%	7%	1.53	1.19–1.97	1.32	0.94–1.84	1.87	1.26–2.77	0.19
<u>Diseases of the nervous system and sense organs</u>									
Other disorders of the CNS	28%	15%	2.29	1.92–2.73	2.62	2.09–3.28	1.84	1.39–2.44	0.06
Inflammatory diseases of eye	20%	17%	1.23	1.04–1.47	1.26	1.02–1.56	1.19	0.88–1.59	0.76
Other diseases and conditions of the eye	71%	65%	1.27	1.10–1.47	1.34	1.12–1.59	1.14	0.89–1.47	0.30

Non-CVD Categories	Prevalence		Overall		1985–1999		2000–2006		$P_{\text{Heterogeneity of ORs}}^{\dagger}$
	Cases	Controls	OR	95% CI	OR	95% CI	OR	95% CI	
<u>Diseases of the respiratory system</u>									
Acute upper respiratory infections	30%	25%	1.29	1.11–1.50	1.21	1.00–1.46	1.43	1.12–1.84	0.29
Pneumonia	27%	13%	2.38	1.98–2.85	2.31	1.84–2.90	2.49	1.85–3.35	0.69
Bronchitis, emphysema, asthma and related conditions	37%	29%	1.45	1.26–1.67	1.40	1.18–1.67	1.55	1.21–1.99	0.51
Other diseases of respiratory system	26%	14%	2.29	1.91–2.75	2.07	1.65–2.60	2.73	2.00–3.72	0.16
<u>Diseases of the digestive system</u>									
Diseases of oral cavity, salivary glands, and jaws	27%	23%	1.22	1.05–1.42	1.16	0.96–1.41	1.33	1.03–1.71	0.40
Diseases of esophagus, stomach, and duodenum	34%	26%	1.40	1.21–1.62	1.35	1.12–1.62	1.50	1.18–1.90	0.49
Hernia of abdominal cavity	28%	23%	1.31	1.12–1.53	1.29	1.07–1.55	1.35	1.02–1.80	0.79
Other diseases of intestines and peritoneum	46%	34%	1.60	1.39–1.84	1.43	1.20–1.70	1.97	1.54–2.51	0.04
Diseases of the liver, gallbladder, and pancreas	12%	11%	1.15	0.93–1.41	1.00	0.77–1.30	1.47	1.03–2.10	0.09
<u>Diseases of the genitourinary system</u>									
Nephritis and nephrosis	15%	9%	1.72	1.39–2.15	1.66	1.21–2.26	1.79	1.32–2.44	0.74
Other diseases of urinary system	47%	32%	1.86	1.62–2.14	1.67	1.41–1.99	2.28	1.79–2.91	0.04
Diseases of male genital organs	12%	13%	1.02	0.77–1.36	0.75	0.52–1.09	1.60	1.01–2.53	0.01
Diseases of the breast male and female	10%	10%	0.94	0.75–1.17	1.17	0.88–1.55	0.61	0.41–0.91	0.01
<u>Diseases of the skin and subcutaneous tissue</u>									
Infections of skin and subcutaneous tissue	21%	15%	1.52	1.27–1.82	1.35	1.08–1.70	1.83	1.36–2.45	0.11
Other inflammatory conditions of skin and subcutaneous tissue	33%	28%	1.19	1.03–1.38	1.22	1.02–1.46	1.14	0.89–1.46	0.66
Other diseases of skin and subcutaneous tissue	55%	48%	1.28	1.12–1.47	1.18	1.00–1.38	1.56	1.22–2.01	0.07
<u>Diseases of the musculoskeletal system and connective tissue</u>									
Osteomyelitis and other diseases of bone and joint	44%	31%	1.76	1.52–2.04	1.82	1.52–2.19	1.66	1.30–2.12	0.56
Other diseases of musculoskeletal system	41%	36%	1.23	1.07–1.41	1.23	1.03–1.45	1.23	0.97–1.55	1.00
<u>Congenital anomalies</u>									
Congenital anomalies	9%	7%	1.35	1.05–1.73	1.30	0.94–1.81	1.42	0.96–2.10	0.74
<u>Symptoms, signs, and ill-defined conditions</u>									
Symptoms, signs, and ill-defined conditions	93%	86%	2.35	1.85–2.98	2.24	1.73–2.90	3.08	1.61–5.91	0.37
<u>Injury and poisoning</u>									
Fracture of skull, spine, and trunk	25%	6%	4.68	3.70–5.92	4.76	3.56–6.37	4.52	3.02–6.75	0.84

Non-CVD Categories	Prevalence		Overall		1985–1999		2000–2006		$P_{\text{Heterogeneity of ORs}}^{\ddagger}$
	Cases	Controls	OR	95% CI	OR	95% CI	OR	95% CI	
Fracture of upper limb	22%	4%	8.16	5.97–11.16	7.72	5.34–11.16	9.33	5.15–16.93	0.60
Other musculoskeletal injuries	24%	17%	1.56	1.32–1.84	1.51	1.23–1.85	1.66	1.25–2.19	0.59
Laceration and open wound of head, neck, and trunk	14%	9%	1.44	1.16–1.80	1.43	1.08–1.90	1.46	1.03–2.08	0.93
Superficial injury	12%	8%	1.68	1.33–2.12	1.33	0.99–1.78	2.53	1.68–3.81	0.01
Unspecified injury	13%	8%	1.71	1.36–2.15	1.59	1.18–2.14	1.89	1.33–2.70	0.46
Contusion	28%	15%	2.20	1.85–2.63	2.08	1.68–2.58	2.46	1.82–3.33	0.38
Adverse effects of medical agents	31%	20%	1.78	1.51–2.08	1.79	1.46–2.18	1.76	1.35–2.29	0.92
Toxic effects of substances chiefly nonmedical	10%	7%	1.55	1.22–1.98	1.61	1.19–2.19	1.45	0.96–2.19	0.69

* only categories with prevalence 5% are shown.

[†] refers to differences between the two time periods.