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Combined Impact of Geriatric Syndromes and Cardiometabolic Diseases on Measures of Functional Impairment

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Background. Examine the independent and joint effects of geriatric syndromes (GS) and cardiometabolic diseases (CMDs) on functional impairment.

Methods. Cross-sectional analysis of baseline data from the Women's Health Initiative, including 62,829 women aged 65 years or older. GS (urinary incontinence, falls, and depression measured by the shortened Center for Epidemiological Studies-Depression scale/Diagnostic Interview Schedule screening instrument) and CMD (coronary artery disease, coronary heart failure, and diabetes) were self-reported. Physical and social functioning and general health subscales of the Short Form-36 dichotomized at the median for the study sample were used to assess functional impairment. Additive interaction between burden of GS and CMD was assessed using logistic regression models.

Results. Forty-three percent of women had at least one GS; 14.1% had at least one CMD; and 6.9% had at least one of each. Compared with women with no GS or CMD, women with one or more GS but no CMD were as likely to have physical functioning impairments (odds ratio [OR] = 1.79; 95% confidence interval [CI] = 1.73, 1.86) as those with CMD alone (OR = 1.97; CI = 1.84, 2.10). The association with social functioning was stronger for GS alone (OR = 2.10; CI = 2.02, 2.18) compared with CMD (OR = 1.60; CI = 1.50, 1.71). The association with general health was stronger for CMD alone (OR = 2.15; CI = 2.01, 2.29) compared with GS (OR = 1.68; CI = 1.62, 1.74). Significant interactions between GS and CMD were observed for all functional measures with 20%–30% of observed ORs attributable to additive interaction.

Conclusion. GSs alone are associated with functional impairment in older women; the association is stronger in the presence of even one CMD.

Key Words: Geriatric syndromes—Cardiometabolic disease—Physical functioning.

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GERIATRIC syndromes (GS) are a loosely defined group of conditions that are highly prevalent in the elderly population but often are not considered discrete diseases; these include falls, urinary incontinence (UI), and depression among others (1). These conditions are typically multifactorial, share risk factors, and are closely linked with functional decline and frailty (1). Cardiometabolic diseases (CMDs) are also highly prevalent in older populations, and their cooccurrence with GS is common (2–8).

Due to the relatively high prevalence of both GS and CMDs, cooccurrence of the two can be expected on purely statistical grounds. However, GS and CMDs share risk factors and may be risk factors for one another, suggesting a biologic association (8–12). In addition, medications prescribed for cardiometabolic disorders may increase risk for GS (7). Geriatric disorders and chronic diseases have been shown to independently affect quality-of-life and physical functioning measures (6,13–18). Multiple CMDs or multiple GS have a cumulative effect on functioning and disability measures (16,19). Poor functioning and disability are known to increase hospitalizations, nursing home placement, incident dementia, and death (20–22). Despite the known high

cooccurrence of GS and CMDs, little is known about the combined impact of these conditions on functioning.

We examine the cooccurrence of several GS with CMDs in women aged 65 years and older who participated in the baseline assessments of the Women's Health Initiative (WHI). In addition, we assessed the presence of interactions between GS and CMDs on physical and social functioning and on general health ratings.

Methods

This was a cross-sectional analysis using the baseline data of women aged 65 years and older who participated in the WHI.

Study Population

The WHI enrolled 161,808 postmenopausal women into one or more study components (hormone therapy trial, dietary modification trial, calcium and vitamin D trial, or an observational study). Details of the study have been published elsewhere (23). Women were recruited at 40 clinical centers across the United States from 1993 to 1998 through community-based methods (24). Exclusion criteria were minimal and included conditions with predicted survival of less than 3 years or those that would interfere with compliance, such as substance abuse (23). All women provided informed consent prior to participation.

Women were included in these analyses if they were aged 65 years and older (n = 71,039). Women were excluded from analyses if they had missing data on any CMDs, GS, or the Short Form-36 (SF-36) subscales. This resulted in exclusion of 8,210 (11.6%) women for a final study population of 62,829. There were no age differences between those with missing data and those without. However, those excluded due to missing data were more likely to be African American or Hispanic, widowed, have an income below $50,000, smoke currently, and not have completed high school.

Assessment of Cardiometabolic and GS

Inclusion of CMDs and GS was based on the following criteria: (a) known associations between specific diseases and syndromes (7–12), (b) CMDs rather than conditions that are risk factors for these diseases, (c) a focus on coronary rather than on peripheral cardiovascular events, and (d) availability of data in the WHI. As a result, we focused on the following CMDs (coronary artery disease, coronary heart failure [CHF], and diabetes) and GS (urinary incontinence [UI], falls, and depression) assessed at screening or baseline. Coronary artery disease was defined as a self-report of ever having had a myocardial infarction or angina. All women were asked at screening if they had ever been told that they had diabetes or high blood sugar while not pregnant. Women reported a doctor ever telling them that they had heart failure (CHF).

UI was defined as reporting any urine leakage at least once per week in the past year (25). Women were asked how many times they had fallen and landed on the floor or ground in the past year. Fallers in this study were defined as having had at least two falls in the past year. Depression was measured by the shortened Center for Epidemiological Studies-Depression scale/Diagnostic Interview Schedule screening instrument with a cutoff of 0.06 used to identify those meeting criteria for high depressive symptoms (26).

Assessment of Functioning

The SF-36 was administered to all women at baseline (27). The SF-36 has been shown to have high validity and reliability in older adults (28). A nine-item subscale was used to assess physical functioning. Social functioning was measured by a two-item subscale, and general health was determined through the five-item subscale. Scores for all scales ranged from 0 to 100, with 100 indicating better function or health (27).

Assessment of Covariates

Demographic variables were recorded at either the screening or the baseline visit. Age was reported to the nearest year. Ethnicity was self-identified as non-Hispanic White (Caucasian), Black or African American, Hispanic/Latino, Asian or Pacific Islander, American Indian or Alaskan native, or other. Current marital status was reported as never married, divorced or separated, widowed, presently married, or marriage-like relationship; these last two categories were combined for all analyses. Highest educational achievement was recorded in 11 different categories that were combined to form the following 5 categories: less than high school, high school diploma, technical school or some college, college degree, and postgraduate degree. Family income was recorded as less than $10,000, $10,000–$19,999, $20,000–$34,999, $35,000–$49,999, $50,000–$74,999, $75,000–$99,999, $100,000–$149,999, and $150,000 or more. The first four categories were combined to include all those with income less than $50,000, and the last two categories were combined to include those making more than $100,000. Because study enrollment was not mutually exclusive, four variables were used to indicate enrollment or nonenrollment in each: hormone therapy trial, dietary modification trial, calcium and vitamin D trial, or the observational study.

Statistical Analysis

Descriptive analyses were used to determine the prevalence and cooccurrence of cardiometabolic and GS. Due to skewed distributions, all function measures were dichotomized at the median. Logistic regression was used to assess odds ratios (OR) and 95% confidence intervals (CI) between conditions and low physical functioning, social

functioning, and general health after adjustment for demographic characteristics. It has been demonstrated using the sufficient cause model that interaction on the additive, rather than on the multiplicative, scale represents presence of true biological interaction (26). Biologic interaction was assessed here by calculating the interaction contrast or relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and associated 95% CI (29,30). The RERI is calculated by the formula: RERI = $OR_{11} - OR_{10} - OR_{01} + 1$, where the subscripts represent presence (1) or absence (0) of the two exposures (CMDs and GS) (30). RERI represents the portion of the observed OR that is due to interaction when both exposures are present. The attributable proportion due to interaction (AP) is calculated by the formula AP = $RERI/OR_{11}$ and represents the percentage of the observed OR that is due to interaction (30). A value different than 0 for each of these measures indicates biologic interaction. All analyses were performed in SAS 9.1.3 and Microsoft Excel 2007.

Results

These analyses included 62,829 women between the ages of 65 and 81 years (mean = 70.1, *SD* = 3.7). The majority of the women were Caucasian (*n* = 54,788, 87.5%); African Americans made up 6.3% (*n* = 3,935) of the study sample, Hispanics 2.2% (*n* = 1,365), Asians 2.6% (*n* = 1,644), American Indian or Alaskan Native 0.3% (*n* = 211), and 1.1% were classified as other (*n* = 708). More than half of the women were married or cohabitating (*n* = 35,085, 56.1%). This was a generally well-educated population with only 5.8% (*n* = 3,606) not having completed high school and 26.1% (*n* = 16319) had some postcollege education. The majority of women reported current incomes below $50,000 (*n* = 42,390, 73.0%). Women in the observational study (*n* = 39,489, 62.9%) were not enrolled in any of the experimental arms. Participants could be enrolled in one or more experimental arms of the study: 10,438 (16.6%) in the hormone therapy, 15,442 (24.6%) in the diet modification, and 11,901 (18.9%) in the calcium and vitamin D trial. Of these, 11,403 (18.1%) were enrolled in two trials and 1,519 (2.4%) were enrolled in all three trials.

UI was the most common of all the conditions with a prevalence of 31.2% in this population (Table 1). The GS were overall more common than the CMDs; 14.1% of women had at least one CMD, and 43% had at least one geriatric syndrome. CHF had the highest cooccurrence with the other CMDs and with GS (Table 1). Among GS, UI was the least likely to cooccur with other GS, and depression was the most likely to cooccur with CMDs (Table 1).

The median score for the SF-36 subscales was 85 for physical functioning, 100 (no limitations) for social functioning, and 75 for general health. Although a majority of participants had no limitations on social functioning, 32.8% scored below 100 on this measure. Multivariable analyses show that all conditions were independently associated with reduced physical and social functioning and general health after adjustment for age, race, marital status, education, income, study enrollment, and all other conditions (data not shown).

Presence of multiple GS alone and multiple CMDs alone affected physical functioning about equally, whereas GS had a greater contribution to social functioning and CMDs to general health in adjusted models (Table 2, Figure 1). A significant biologic interaction between GS and CMDs was observed for all three functional measures. The combined OR for physical functioning was 3.93 (CI = 3.66, 4.23) of which 1.17 (CI = 0.88,1.47) was due to interaction (Table 2, Figure 1). For social functioning, the combined OR was 3.36 (CI = 3.15, 3.59) with 0.66 (CI = 0.43, 0.89) attributable to interaction. The combined OR for general health was 3.74 (CI = 3.49, 4.01) with 0.91 (CI = 0.64, 1.19) due to interaction. The strongest interaction was observed for physical functioning; 30% (CI = 24%, 36%) of the combined OR was attributable to the interaction effect. The contribution from interaction was only slightly less for social functioning (20%; CI = 14%, 26%) and general health (24%; CI = 18%, 31%; Table 2).

Our estimates of interaction effects may be affected by the higher prevalence of UI compared with all other conditions. We conducted the same analyses classifying GS as either 0–1 or 2–3 with CMDs remaining as 0 or 1+. The results obtained from these analyses were not qualitatively different from those presented here, although the interaction effects were stronger for all outcome variables (data not shown).

Discussion

In these relatively healthy women of age 65 years and older, occurrence of multiple GS and/or multiple CMDs was not uncommon. About one third of the study sample (34.4%) had a single geriatric syndrome with 8.2% having two or more, 12.4% had one of the CMDs, and 1.6% had two or more CMDs. Both GS and CMDs were found to independently contribute to functional impairment as measured by the SF-36 subscales for physical function, social function, and general health. In addition, an additive interaction was observed when GS and CMDs were both present compared with the expected effect from the presence of geriatric or cardiometabolic conditions alone. Between 20% and 30% of the risk for functional impairments was attributable to interaction when both types of conditions were present.

Lee and colleagues (3) assessed cooccurrence of CMDs and GS in a large population-based sample of men and women aged 65 years and older. Although CMDs were more prevalent and GS less so in their mixed sex sample than in our women-only study, the patterns of cooccurrence were similar. The research on directionality of the association

Table 1. Burden of CMDs and Geriatric Syndromes (GS) Among Women Aged ≥65 years

	Prevalence	0 CMD	1 CMD	2+ CMD	0 GS	1 GS	2+ GS
		n = 54,066	*n* = 7,765	*n* = 998	*n* = 36,060	*n* = 21,628	*n* = 5,141
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
CMD							
CAD	7.5 (7.3, 7.7)	—	81.5 (80.4, 82.6)	18.5 (17.4, 19.6)	51.8 (50.4, 53.2)	37.5 (36.1, 38.9)	10.7 (9.9, 11.6)
CHF	1.4 (1.3, 1.5)	—	64.4 (61.2, 67.5)	35.6 (32.5, 38.8)	44.6 (41.3, 47.8)	40.6 (37.3, 43.8)	14.8 (12.5, 17.2)
Diabetes	6.8 (6.6, 7.0)	—	79.5 (78.3, 80.7)	20.5 (19.3, 21.8)	48.0 (46.5, 49.5)	39.2 (37.7, 40.6)	12.8 (11.8, 13.9)
GS							
Falls	11.8 (11.6, 12.1)	83.4 (82.6, 84.3)	14.1 (13.3, 14.9)	2.5 (2.2, 2.9)	—	52.7 (51.6, 53.9)	47.3 (46.1, 48.4)
UI	31.2 (30.9, 31.6)	83.4 (82.9, 83.9)	14.5 (14.0, 15.0)	2.1 (1.9, 2.3)	—	76.3 (75.7, 76.9)	23.7 (23.2, 24.3)
Depression	8.5 (8.3, 8.7)	81.3 (80.2, 82.3)	16.1 (15.1, 17.1)	2.6 (2.3, 3.1)	—	51.5 (50.1, 52.8)	48.5 (47.2, 49.9)

Note: CAD = coronary artery disease; CHF = coronary heart failure; CI = confidence interval; UI = urinary incontinence.

between CMDs and GS is sparse. However, in a meta-analysis, diabetes was shown to be a risk factor for incidence of several GS, including dementia, mobility decline, disability, falls, and UI but not depression (5). Depression has been shown to increase risk for both incident cardiovascular disease and cardiovascular mortality (11). Additionally, it has been suggested that the high rates of cooccurring GS with CHF could at least in part be due to side effects of prescribed medications for CHF (7).

A number of articles have shown that CMDs and GS have an impact on physical functioning, disability, and other quality-of-life measures (6,13–19), but few studies have assessed whether these conditions have an independent association in the presence of the other type of conditions, and none have looked at interactions between them. Cigolle and colleagues (16) demonstrated an independent association of GS with activity of daily living limitations after adjustment for various chronic conditions. They also showed that the ORs for GS were as large as those for the chronic conditions, similar to our findings for physical and social limitations. It has been previously shown that cooccurrence of multiple chronic diseases can have synergistic effects on disability measures (31); we show here that the same can be true for cooccurrence of chronic diseases with GS.

Table 2. Interaction of Multiple GS and CMD on Impairments in Physical Functioning, Social Functioning, and General Health Measures From the Short Form-36

#GS/#CMD	Physical Function		Social Function		General Health	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
0/0	Ref		Ref		Ref	
0/1+	1.97	1.84, 2.10	1.60	1.50, 1.71	2.15	2.01, 2.29
1+/0	1.79	1.73, 1.86	2.10	2.02, 2.18	1.68	1.62, 1.74
1+/1+	3.93	3.66, 4.23	3.36	3.15, 3.59	3.74	3.49, 4.01
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
RERI	1.17	0.88, 1.47	0.66	0.43, 0.89	0.91	0.64, 1.19
AP	0.30	0.24, 0.36	0.20	0.14, 0.26	0.24	0.18, 0.31

Notes: AP = attributable proportion due to interaction; CI = confidence interval; CMD = cardiometabolic diseases (coronary artery disease, coronary heart failure, and diabetes); GS = geriatric syndromes (falls, urinary incontinence, and depression); OR = odds ratio; RERI = relative excess risk due to interaction.

[a]Adjusted for age, race, marital status, education, income, and study enrollment.

Loss of function is likely a multisystem phenomenon involving the neuromuscular, endocrine, immune, and cardiovascular systems (1). Impairments could result directly from the presence of a given condition as with UI leading to psychological distress and shame that directly affects social functioning (32). In contrast, impairments may result from common risk factors or pathways related to chronic disease and GS (31). For example, frailty, which leads to physical impairments, has been associated with inflammatory markers (33) that are also associated with CMDs (34). The concept of biological interactions between individual GS on disability and mortality is not new (1), but interactions between geriatric syndrome burden with burden of chronic conditions have not previously been assessed. Whether these interactions are due to an underlying biological mechanism, such as inflammation, or to an accumulation of deficits due to presence of conditions affecting different biological systems is unclear.

The WHI data set provided a large population of older women with data on several CMDs and GS as well as demographic information. In addition, the SF-36 provided a well-validated and reliable source of data on functional ability. However, the WHI was a combination of observational study and clinical trial and likely represents a healthier population of older women than the general population. Self-report of baseline conditions also may underestimate prevalence of the CMD and GS. We were also limited in that data on cognitive function, known to be associated both with other GS (35,36) and with CMDs (8,37), were available in only a subset of participants and were therefore not considered here. In addition, the cross-sectional nature of this data does not allow for the assessment of temporal trends. The conditions considered here may have led to functional decline, or the declines in function may have contributed to the onset, severity, or reporting of the geriatric and cardiometabolic conditions.

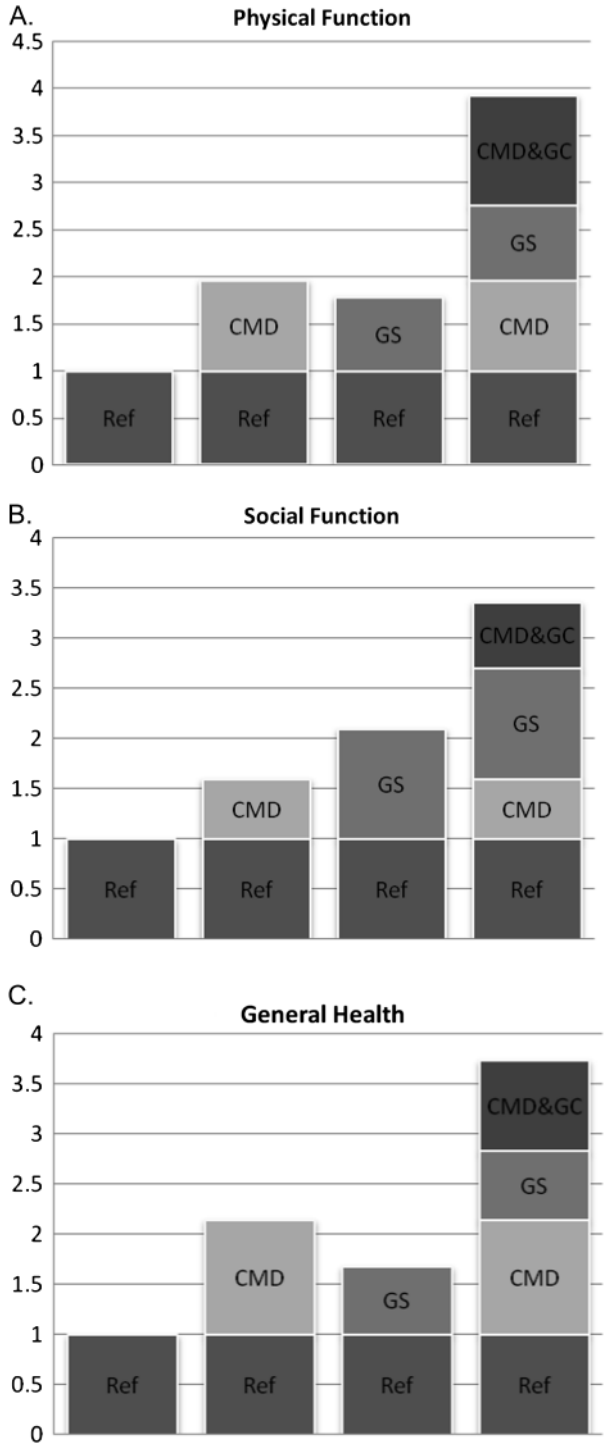

Figure 1. Proportion of odds ratios attributable to cardiometabolic diseases (CMDs), geriatric syndromes (GS), and the interaction of the two (CMD and GS) for impairments to physical functioning (A), social functioning (B), and general health (C) measures from the Short Form-36.

GS are known to significantly affect functional abilities in older women. In this cross-sectional analysis of women aged 65 years or older who participated in the WHI, we observed an association between GS and self-reported functional ability. In addition, our data show that this association is greater in the presence of CMDs. An additive synergistic interaction was observed between the presence of GS and CMDs on functional measures. Future clinical research should focus on interventions to enhance function among women with GS, in particular among women with comorbid CMDs. Common pathways between GS and CMDs may represent an opportunity to improve clinical and functional outcomes in this population of women.

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References

1. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. *J Am Geriatr Soc.* 2007;55:780–791.
2. Flood KL, Rohlfing A, Le CV, Carr DB, Rich MW. Geriatric syndromes in elderly patients admitted to an inpatient cardiology ward. *J Hosp Med*. 2007;2:394–400.
3. 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.
4. Gure TR, Kabeto MU, Blaum CS, Langa KM. Degree of disability and patterns of caregiving among older Americans with congestive heart failure. *J Gen Intern Med*. 2008;23:70–76.
5. Lu FP, Lin KP, Kuo HK. Diabetes and the risk of multi-system aging phenotypes: a systematic review and meta-analysis. *PLoS One*. 2009; 4:e4144.
6. Vischer UM, Bauduceau B, Bourdel-Marchasson I, et al. A call to incorporate the prevention and treatment of geriatric disorders in the management of diabetes in the elderly. *Diabetes Metab*. 2009;35: 168–177.
7. Imazio M, Cotroneo A, Gaschino G, et al. Management of heart failure in elderly people. *Int J Clin Pract*. 2008;62:270–280.
8. Araki A, Ito H. Diabetes mellitus and geriatric syndromes. *Geriatr Gerontol Int*. 2009;9:105–114.
9. Hall SA, Cinar A, Link CL, et al. Do urological symptoms cluster among women? Results from the Boston Area Community Health Survey. *BJU Int*. 2008;101:1257–1266.
10. Mast BT, Miles T, Penninx BW, et al. Vascular disease and future risk of depressive symptomatology in older adults: findings from the Health, Aging and Body Composition Study. *Biol Psychiatry.* 2008; 64:320–326.
11. Wassertheil-Smoller S, Shumaker S, Ockene J, et al. Depression and cardiovascular sequelae in postmenopausal women. The Women's Health Initiative (WHI). *Arch Intern Med*. 2004;164:289–298.
12. Shaw FE, Kenny RA. The overlap between syncope and falls in the elderly. *Postgrad Med J*. 1997;73:635–639.
13. Sinclair AJ, Conroy SP, Bayer AJ. Impact of diabetes on physical function in older people. *Diabetes Care*. 2008;31:233–235.
14. Ryerson B, Tierney EF, Thompson TJ, et al. Excess physical limitations among adults with diabetes in the U.S. population, 1997–1999. *Diabetes Care*. 2003;26:206–210.
15. Kiebzak GM, Pierson LM, Campbell M, Cook JW. Use of the SF36 general health status survey to document health-related quality of life in patients with coronary artery disease: effect of disease and response to coronary artery bypass graft surgery. *Heart Lung*. 2002;31:207–213.

16. Cigolle CT, Langa KM, Kabeto MU, Tian Z, Blaum CS. Geriatric conditions and disability: the Health and Retirement Study. *Ann Intern Med*. 2007;147:156–164.
17. Bluestein D, Rutledge CM. Perceived health and geriatric risk stratification: observations from family practice. *Can Fam Physician*. 2006;52:626–627.
18. Coll-Planas L, Denkinger MD, Nikolaus T. Relationship of urinary incontinence and late-life disability: implications for clinical work and research in geriatrics. *Z Gerontol Geriatr*. 2008;41:283–290.
19. Stone MA, Khunti K, Squire I, Paul S. Impact of comorbid diabetes on quality of life and perception of angina pain in people with angina registered with general practitioners in the UK. *Qual Life Res*. 2008; 17:887–894.
20. Miller DK, Wolinsky FD, Andresen EM, Malmstrom TK, Miller JP. Adverse outcomes and correlates of change in the Short Physical Performance Battery over 36 months in the African American health project. *J Gerontol A Biol Sci Med Sci*. 2008;63(5):487–494.
21. Taaffe DR, Irie F, Masaki KH, et al. Physical activity, physical function, and incident dementia in elderly men: the Honolulu-Asia Aging Study. *J Gerontol A Biol Sci Med Sci*. 2008;63(5):529–535.
22. Keeler E, Guralnik JM, Tian H, Wallace RB, Reuben DB. The impact of functional status on life expectancy in older persons. *J Gerontol A Biol Sci Med Sci*. 2010;65(7):727–733.
23. Prentice RR, J, Furberg C, Johnson S, et al. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. *Control Clin Trials*. 1998;19:61–109.
24. Hays J, Hunt JR, Hubbell FA, et al. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol*. 2003;13:S18–S77.
25. Brown JS, Vittinghoff E, Wyman JF, et al. Urinary incontinence: does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group. *J Am Geriatr Soc*. 2000;48:721–725.
26. Tuunainen A, Langer RD, Klauber MR, Kripke DF. Short version of the CES-D (Burnam screen) for depression in reference to the structured psychiatric interview. *Psychiatry Res*. 2001;103: 261–270.
27. Brunner RL, Cochrane B, Jackson RD, et al. Calcium, vitamin D supplementation, and physical function in the Women's Health Initiative. *J Am Diet Assoc*. 2008;108:1472–1479.
28. Bohannon RW, DePasquale L. Physical functioning scale of the Short Form (SF) 36: internal consistency and validity with older adults. *J Geriatr Phys Ther*. 2010;33:16–18.
29. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*, (3rd ed.). Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
30. Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. *Eur J Epidemiol*. 2005;20:575–579.
31. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci*. 2010;59(3):255–263.
32. Margalith I, Gillon G, Gordon D. Urinary incontinence in women under 65: quality of life, stress related to incontinence and patterns of seeking health care. *Qual Life Res*. 2004;13:1381–1390.
33. Reiner AP, Aragaki AK, Gray SL, et al. Inflammation and thrombosis biomarkers and incident frailty in postmenopausal women. *Am J Med*. 2009;122:947–954.
34. Hansson GK. Inflammatory mechanisms in atherosclerosis. *J Thromb Haemost*. 2009;7(suppl 1):328–331.
35. Verghese J, Mahoney J, Ambrose AF, Wang C, Holtzer R. Effect of cognitive remediation on gait in sedentary seniors. *J Gerontol A Biol Sci Med Sci*. 2010;65(12):1338–1343.
36. Crocco EA, Castro K, Loewenstein DA. How late-life depression affects cognition: neural mechanisms. *Curr Psychiatry Rep*. 2010;12(1): 34–38.
37. Roberts RO, Knopman DS, Geda YE, Cha RH, Roger VL, Petersen RC. Coronary heart disease is associated with non-amnestic mild cognitive impairment. *Neurobiol Aging*. 2010;31(11):1894–1902.