Association between physical health and cardiovascular diseases: Effect modification by chronic conditions

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Abstract

Objectives: This study assessed whether the physical component summary score of the RAND-36 health-related quality-of-life survey was associated with incidence of coronary heart disease, stroke, congestive heart failure, angina, or peripheral arterial disease, and whether baseline chronic conditions modified these associations.

Methods: Analysis was limited to 69,155 postmenopausal women (50–79 years) in the Women's Health Initiative Study who had complete data on the RAND-36, the outcomes, and covariates. Chronic conditions were defined as blood pressure $\geqslant 140/90\,mm$ or self-reported heart disease, diabetes, hypertension, arthritis, asthma, emphysema, cancer, and/or cholesterol-reducing medication use. Outcomes data were ascertained during follow-up (1993–2005) with medical records.

Results: There were 2451 coronary heart disease, 1896 stroke, 1533 congestive heart failure, 1957 angina, and 502 peripheral arterial disease events during follow-up (median 8.2 years). Participants in the lowest physical component summary quintile, compared to the highest, had a significantly higher risk of developing coronary heart disease (hazard ratio (95% confidence interval) 2.0 (1.7, 2.3)), stroke (1.8 (1.5, 2.2)), angina (2.4(2.0, 2.9)), and peripheral arterial disease (3.0 (2.0, 4.4)), irrespective of chronic conditions. Interactions between physical component summary and existing chronic conditions were not significant for any outcome except congestive heart failure (p = 0.005); after adjustment, participants in the lowest physical component summary quintile and with any chronic condition had nearly a twofold higher risk of congestive heart failure (Yes = 4.4 (3.3, 5.8) vs No = 2.4 (1.2, 4.3)).

Conclusion: We found a low physical component summary score was a significant risk factor for individual cardiovascular disease incidence in postmenopausal women.

Introduction

The risk of cardiovascular disease (CVD) increases significantly with menopause. Data indicate as much as three-fourths of all deaths in postmenopausal women can be attributed to CVD along with cerebrovascular diseases. Weight gain, reduction of glucose tolerance, and increase in blood pressure are a few prominent changes out of a multitude of other physiological changes that take place during menopause and are responsible for increased CVD risk.[1] Smoking cessation, uptake of regular physical activity, intake of a heart-healthy diet, weight management, and initiation of hormone replacement therapy are recommended to postmenopausal women as primary prevention measures to decrease the risk of CVD.[2]

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Among postmenopausal women in a subset of the Women's Health Initiative (WHI) Study, we previously reported a significant association between a low baseline physical component summary (PCS) score and incidence of CVD over an average of 9.2 years of follow-up.[3] This finding was consistent with earlier analyses from the EPIC-Norfolk study of community dwelling adults (aged 41–80 years) that showed a strong relationship between a low PCS score and incidence of coronary heart disease (CHD) and stroke, as well as CVD-specific mortality.[4–6] In these studies, the association of low PCS to CVD outcomes was independent of established CVD risk factors (e.g. obesity, cigarette smoking, physical inactivity, and poor dietary habits) that were also correlated with PCS.[7–9]

The PCS (aka physical health) represents the physical domain of the RAND-36 health-related quality-of-life instrument. It consists of four sub-scales, namely, general health perception, physical functioning, bodily pain, and role limitation due to physical health.[10] The PCS score has been found strongly associated with overall and disease-specific mortality.[6,11,12]

The critical issue of whether a low PCS score is a marker of prevalent chronic conditions has been examined in two distinct ways: sensitivity analysis and adjustment.[3,6] In the first approach, CVD events identified in the first 2 years of follow-up were removed prior to modeling. The second models were adjusted for relevant chronic conditions such as diabetes, arthritis, and hypertension. Formal testing of interactions between PCS and existing chronic conditions was not done prior to outcome modeling; hence, residual confounding due to lack of adjustment for the effects of interaction could not be ruled out.

Therefore, the objectives of the current analyses were twofold: to test (1) whether a low PCS or low mental component summary (MCS, aka mental health, the mental domain of RAND-36) score was associated with incidence of individual CVDs among postmenopausal women enrolled in the WHI Observational Study (OS), and (2) whether the presence of chronic conditions at baseline modified the associations of PCS (or MCS) with these outcomes. We assessed the following individual CVD as outcomes: CHD and stroke, angina, congestive heart failure (CHF), and peripheral arterial diseases (PAD).

Methods and measures

Overview of the WHI

The WHI protocol and details on eligibility criteria, data collection, and outcomes identification have been published previously.[13] The WHI OS enrolled 93,676 postmenopausal women (aged 50–79 years) between 1993 and 1998 at 40 clinical centers throughout the United States, with follow-up for the current analyses through 2006. All participants in the WHI study provided written informed consent. All procedures and protocols were approved by the Institutional Review Boards at the National Institute of Health and by all participating institutions. This study relied on WHI OS data and required no additional consent or approval.

Sample

Of the OS cohort (n = 93676), a total of 90,666 were eligible for analysis after excluding 3010 OS participants who were considered physically or cognitively compromised (intestinal removal = 2084; broken hip = 538; multiple sclerosis = 281; Parkinson's disease = 186, and Alzheimer's disease = 62). An additional 21,511 women were further excluded due to missing data for the main exposure variable (RAND-36) and key covariates in the statistical models, resulting in a final analytic study sample of 69,155 women (Supplementary Appendix 1).

Assessments

Quality of life. At study entry, participants completed the RAND-36 survey. All surveys from RAND Health are public documents, available free of charge, so no written copyright permission was required.[14] All questions in the RAND-36 are organized into eight sub-scales (i.e. general health, physical functioning, bodily pain, role limitation due to physical health, mental health, vitality, social functioning, and role limitation due to emotional problems) under two main domains (i.e. physical and MCS scores). The number of questions that constitute a sub-scale varies (e.g. 10 questions for the physical functioning sub-scale and 2 for the pain sub-scale). Each question is scored on a scale from 0 to 100 (0 = lowest and 100 = highest functioning). An aggregate score for questions belonging to any particular sub-scale is compiled as a percentage of the total score. The PCS and MCS summary scores are calculated as the mean average of all of the physically and emotionally relevant questions, respectively.[10,15]

Covariates. At study entry, participants underwent physical measurements (e.g. height, weight, and blood pressure) and completed standardized questionnaires on demography (e.g. age, ethnicity, education, marital, and employment status), lifestyle (e.g. obesity, physical activity, fruit and vegetable consumption, smoking, and alcohol intake), psychosocial status (social support, optimism, hostility, insomnia, and depression), and medical history (self-reported disease condition and/or medication use). Body mass index (BMI) was calculated as kg/m^2. Except for psychosocial variables, other variables have been described previously in detail.[3] Social support was assessed using the 9-item Medical Outcome Study (MOS) Social Support Survey;[16] optimism by the 6-item Life Orientation Test-Revised scale;[17] hostility by the 13-item Cook-Medley Cynicism Scale;[18] and depression by the 8-item Center for Epidemiologic Studies Depression

Scale (CESD).[19] A CESD value $\geqslant 0.06$ was designated as clinical depression.[20] The presence of a chronic condition at baseline was defined as blood pressure $\geqslant 140/90\,mm\,Hg$ or self-reported heart disease, diabetes, hypertension, arthritis, chronic obstructive pulmonary disease (e.g. asthma and emphysema), cancer (except non-melanoma skin cancer), or cholesterol-reducing medication use.

Outcomes. Outcomes were time to incident CHD, stroke, CHF, angina, and PAD. Definitions of these diseases and details regarding their identification, documentation, and validation have been published elsewhere.[21] Briefly, CHD was defined as hospitalized myocardial infarction, definite silent myocardial infarction, or coronary death. Stroke was defined as rapid onset of a persistent neurologic deficit attributed to an obstruction or rupture of the brain arterial system lasting more than 24 h and without evidence of other cause. CHF was defined as symptoms and signs consistent with CHF, plus pulmonary edema by chest X-ray; or dilated ventricle or poor ventricular function by imaging studies; or physician diagnosis of CHF and receiving medical treatment. Angina was defined as symptoms consistent with angina, plus revascularization procedure; or $\geqslant 70\%$ obstruction of any coronary artery; or ST-segment depression $\geqslant 1\,mm$ on stress testing or on resting electrocardiogram (ECG) with pain; or positive scintigraphy or echocardiography stress test; or angina diagnosed by physician and receiving medical treatment for angina. PAD was defined as a disease that is symptomatic and/or requiring intervention and located in the abdominal aorta, iliac arteries, or lower extremities. These outcomes were probed semi-annually by study personnel; any report of outcome was documented using hospital records, which were adjudicated by trained physician investigators. For any given outcome, follow-up was censored at the last clinic visit, end of official follow-up date (2006), or date of death due to any cause, whichever occurred first.

Statistical analyses

Baseline PCS and MCS scores were categorized into quintiles for ease of interpretation. Cumulative survival for each outcome across PCS and MCS quintiles was graphed with Kaplan–Meier plots and compared with log-rank test. Cox proportional hazard regression models were used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) as the measures of association.

Interactions between PCS or MCS quintiles and chronic condition indicator variables were tested for each outcome prior to model building. If the interaction was not significant, variables were introduced sequentially for adjustment: first age at screening, then demographic, lifestyle, psychosocial, self-reported chronic conditions, and finally, MCS (if PCS was the exposure) or PCS (if MCS was the exposure). If the interaction was significant, the same steps were followed, except that the chronic condition indicator variable was used

instead of the individual chronic condition. Variables used for model adjustment were chosen a priori based on the literature review.[3–5] All tests were two-sided and analyses were conducted in SAS version 9.2 (Cary, NC, USA).

Results

The following demographic characteristics were found in our analytic sample: age $=63.3$ years (7.3), BMI $=27.2\,kg/m^2$ (5.8), non-Hispanic white $=85.5\%$, college graduate $=42.2\%$, currently married $=63.7\%$, employed $=37.3\%$ (mean and standard deviation (SD) or frequency). The mean (SD, range) PCS was 48.4 (9.8, 7–73). Over 8.2 years of follow-up, there were 2451 CHD, 1896 stroke, 1533 CHF, 1957 angina, and 502 PAD events.

Participants with a low PCS score had a more adverse health profile than those with a high PCS score. For example, those in the bottom quintile were more likely to be obese and less physically active, consume fewer servings of fruits and vegetables, and more likely to report chronic conditions compared to those in the top quintile (reference) (Supplementary Appendices 2 and 3).

The interaction between PCS quintile and presence of a chronic condition was not significant for CHD (p $=0.34$), stroke (p $=0.71$), angina (p $=0.13$), or PAD (p $=0.78$); it was significant for CHF (p $=0.005$) (data not shown). In the adjusted models, the incidence risk increased monotonically across decreasing PCS quintiles (reference $=$ top quintile). Specifically, the risks were significant for the bottom three quintiles for CHD and all comparison quintiles (bottom four) for stroke, angina, and PAD (Figure 1). For example, women in the bottom PCS quintile had a respective 2.0, 1.8, 2.4, and 3.0 times higher risk of developing CHD, stroke, angina, and PAD compared to women who belonged to the top quintile (Figure 1). The risk of CHF incidence increased with decreasing PCS quintile, and the incidence risk was higher for women with a chronic condition than for women without a chronic condition (Table 1).

There were no significant interactions between MCS quintiles and presence of a chronic condition such as CHD (p $=0.36$), stroke (p $=0.34$), CHF (p $=0.56$), angina (p $=0.37$), or PAD (p $=0.44$) (data not shown). The adjusted models exhibited no definitive pattern of incidence risk for any of these outcomes. The only significant risk was limited to women in the bottom MCS quintile for stroke. Women in this group were 27% more likely to have a stroke than women in the top MCS quintile (reference) (Table 2).

Discussion

A low PCS score was a significant risk factor for incidence of all major types of CVD among postmenopausal women in the WHI OS. Significant associations with incidence of CHD and stroke corroborated similar findings from EPIC-Norfolk cohort study.[4,5] However, significant associations with
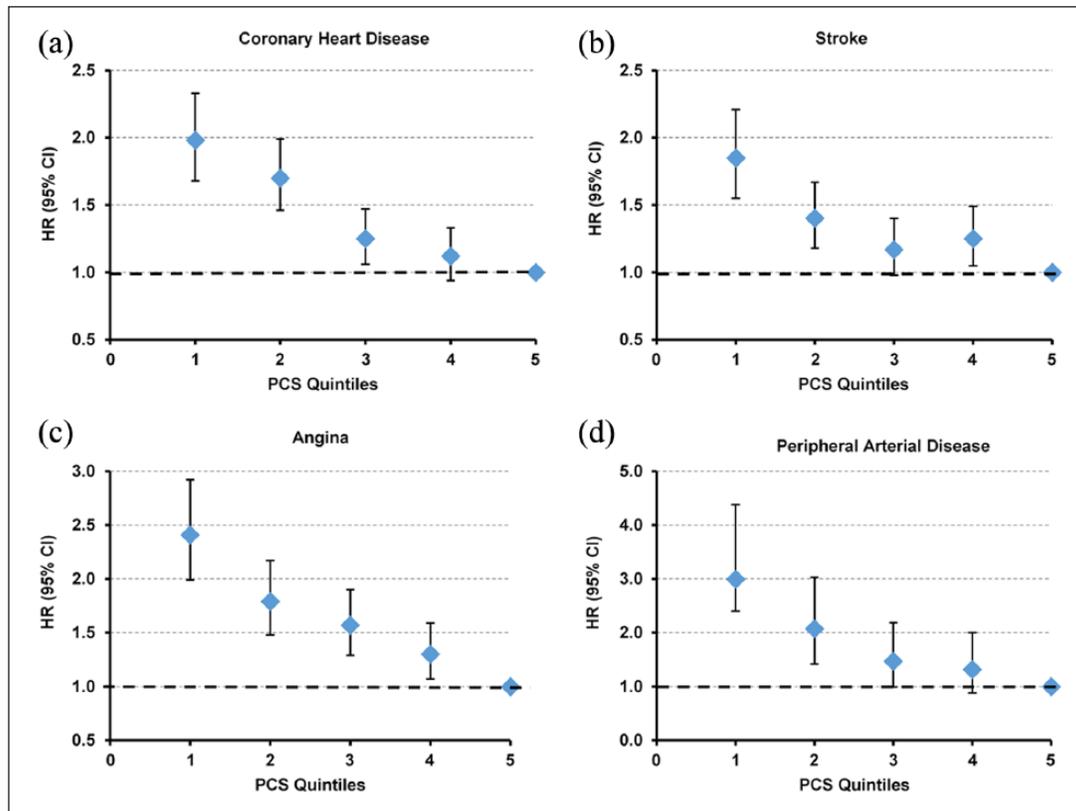
Figure 1. Adjusted associations of physical component summary (PCS) with incidence of major CVD diseases ((a) coronary heart disease; (b) stroke; (c) angina; and (d) peripheral arterial diseases) among women enrolled in the observational cohort of the Women's Health Initiative (WHI) study; n = 69155; median follow-up = 8.5 years; Models were adjusted for age, ethnicity, education, marital status, body mass index, physical activity, fruits and vegetable consumption, smoking pack-years, alcohol intake, self-reported chronic conditions such as heart disease, diabetes, arthritis, cancer (except non-melanoma skin cancer), chronic obstructive pulmonary disease, medication use for elevated cholesterol, systolic and diastolic pressure, and mental component summary.

Table 1. Adjusted associations of physical component summary (PCS) with incidence of congestive heart failure (CHF) among women enrolled in the observational cohort of the Women's Health Initiative (WHI) study; interaction by prevalent chronic condition; n = 69,155; median follow-up = 8.5 years.

PCS	Incidence of congestive heart failure		p value
	Chronic condition = No	Chronic condition = Yes	
	HR (95% CI)	HR (95% CI)	
Q1: 7.0–40.4	2.39 (1.24, 4.34)	4.38 (3.32, 5.79)	0.005
Q2: 40.5–48.9	2.08 (1.21, 3,60)	2.49 (1.88, 3.30)	
Q3: 49.0–53.2	1.51 (0.86, 2.67)	2.08 (1.56, 2.78)	
Q4: 53.3–56.2	1.77 (1.04, 3.02)	1.52 (1.11,2.07)	
Q5: 56.3–73.0	1.00	1.00	

HR: hazard ratio; CI: confidence interval.
Models were adjusted for age, ethnicity, education, marital status, body mass index, physical activity, fruits and vegetable consumption, smoking pack-years, alcohol intake, presence of chronic condition, and mental component summary.

incidence of angina, CHF, and PAD have not been previously reported. With the exception of CHF, the presence of a chronic condition did not modify the associations of a low PCS with CVD outcomes—another finding that has not been reported previously.

The mechanism through which a low PCS score might influence incidence of CVD is unclear, but several have been suggested in previous reports, including the possibility that a low PCS score is a marker of underlying chronic inflammation, stress, or general frailty.[4,22,23]

Table 2. Adjusted associations of mental component summary (MCS) with incidence of major CVD diseases among women enrolled in the observational cohort of the Women's Health Initiative (WHI) study; n = 69155; median follow-up = 8.5 years.

MCS	CHD	Stroke	CHF	Angina	PAD
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95%CI)
Q1: 2.9–47.9	1.03 (0.89, 1.19)	1.27 (1.08, 1.49)	1.00 (0.83, 1.19)	1.16 (0.99, 1.36)	1.11(0.82, 1.52)
Q2: 48.0–53.9	0.99 (0.87, 1.12)	1.05 (0.90, 1.22)	0.97 (0.82, 1.14)	1.08 (0.93, 1.25)	0.86(0.64, 1.16)
Q3: 54.0–57.0	1.01 (0.89, 1.15)	0.98 (0.84, 1.13)	1.07 (0.91, 1.25)	1.06 (0.91, 1.22)	1.18 (0.89, 1.55)
Q4: 57.1–59.3	0.92 (0.81, 1.04)	1.03 (0.90, 1.19)	0.95 (0.80, 1.11)	1.10 (0.95,1.27)	0.97 (0.73, 1.30)
Q5: 59.4–74.3	1.00	1.00	1.00	1.00	1.00

CHD: coronary heart disease; CHF: congestive heart failure; PAD: peripheral arterial diseases; HR: hazard ratio; CI: confidence interval; Q: quintile. Models were adjusted for age, ethnicity, education, marital status, body mass index, physical activity, fruits and vegetable consumption, smoking pack-years, alcohol intake, self-reported chronic conditions such as heart disease, diabetes, arthritis, cancer (except non-melanoma skin cancer), chronic obstructive pulmonary disease, medication use for elevated cholesterol, systolic and diastolic pressure, and physical component summary.

It is also unclear why the presence of a chronic condition modified the association between a low PCS score and CHF incidence. Possible explanations range from a chance finding related to the number of interactions tested (10), to the subjective components of CHF diagnosis (reported symptoms as one of the several criteria used for defining CHF in WHI, and women with a low PCS score had less healthy profiles), to a real effect. Hypertension and chronic obstructive pulmonary diseases are established risk factors for CHF[24,25] and were included in the definition of the chronic medical condition indicator variable.

Similarly, the models were adjusted for common lifestyle and psychosocial variables, yet PCS exerted a strong independent effect beyond its correlation with several of these variables. The effect of PCS could still be explained, at least partly, by subclinical disease conditions; this study and other similar studies have only controlled for a few.[3–5] A comprehensive biochemical and serological comparison between those with a low and high PCS scores might prove helpful in explaining the effect.

The strengths of this study include rigorous and standardized ascertainment of data on outcomes, a large sample, sufficient number of outcome events, and the ability to control via analytic models a large number of covariates. The results generate the hypothesis that self-reported physical functioning may be a proxy for a number of physiological parameters related to aging and inflammation, which should be rigorously examined.

This study may have been limited by restriction to older female participants, self-reported chronic conditions, and 22% of the original cohort being omitted because of incomplete and/or missing data. Another limitation was that only baseline PCS and MCS scores were used in the association with CVD and not the change in the scores over time. The PCS score declines significantly in older women, and home-based physical activity intervention was found to reduce that decline.[26]

In summary, a low PCS was strongly and significantly associated with the incidence of all major types of CVD.

The RAND-36 could be used as a screening tool to identify older women who are at higher risk of developing CVD. As a questionnaire, it should be vetted against other popular CVD screening tools (e.g. Framingham Risk Score[27] or the 2013 ACC/AHA Pooled Cohort Equations[28]) to examine whether it is equally efficient at detecting women who are at high risk for CVD development or if its efficiency increases when it is used in combination with other tools.

Ethical approval

Study procedures and protocols were approved by the Institutional Review Boards at the National Institute of Health and at all 40 participating institutions.

Clinic no.	Institution	Field center	Protocol/ID
12	University of Alabama at Birmingham	Birmingham	F920828009
65	University of Nevada, Reno	Nevada	B04/05-001
56	University of Wisconsin–Madison	Madison	H-2004-0363
67	UT Health Science Center	San Antonio	045-7000-050
64	University of Miami	Miami	20051390
26	University of Medicine and Dentistry of New Jersey	Newark	0120040296
60	Rush-Presbyterian-St. Luke's Medical Center	Chicago Rush	94121901
29	University of Arizona Health Sciences	Tucson/Ph	93-129
22	University California, San Diego	La Jolla	6136
45	University of Hawaiʻi	Honolulu	9760
57	State University of New York at Stony Brook	Stony Brook	20065617
68	University of California, Los Angeles	Los Angeles	04-08-062-04
43	Medical College of Wisconsin	Milwaukee	067-94
61	University of Cincinnati Medical Center	Cincinnati	93-08-24-04 EE
53	Kaiser Foundation Research Institute	Oakland	CN-94RHIAT-02H
16	Northwestern University	Chicago	0499-006
47	Baylor College of Medicine	Houston	H-11609
72	University of Medicine and Dentistry of New Jersey	N Brunswick	0219961844
19	Emory University School of Medicine	Atlanta	022-2004
25	University of Minnesota	Minneapolis	9308M07098
49	Albert Einstein College of Medicine	New York	2004-151
23	Memorial Hospital of Rhode Island	Pawtucket	92-30A

Clinic no.	Institution	Field center	Protocol/ID
48	University of Massachusetts	Worcester	H-11417
24	University of Tennessee	Memphis	4554
30	University of California, Davis	Davis	200210270-14
66	Kaiser Foundation Research Institute	Portland	00000405
15	State University of New York at Buffalo	Buffalo	SPM0290393A
55	Harbor University of California	Torrance	07714-01
62	Wayne State University	Detroit	0409000121
46	University of Florida	Gainesville	376-2004
42	Stanford University	Stanford	95415
44	The George Washington University	GWU	099304
13	Bowman Gray School of Medicine	Winston Salem	BG00-316
51	Medlantic Research Institute	MedStar	1994-037
18	FHCRC	Seattle	3493
63	University of California, Irvine	Irvine	1993-335
58	University of North Carolina at Chapel Hill	Chapel Hill	04-EPID-486
21	The University of Iowa	Iowa City	199309487
28	University of Pittsburgh	Pittsburgh	0404092
50	The Ohio State University	Columbus	1994H0412
14	Brigham and Women's Hospital	Boston	1999P-001544
	FHCRC—Coordinating Center	CCC	3467

Informed consent

Written informed consent was obtained from all subjects before the study.

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