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Physical activity, sedentary behavior, and endometrial cancer risk in the NIH-AARP Diet and Health Study

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Consistent with a strong hormonal etiology, endometrial cancer is thought to be influenced by both obesity and physical activity. Although obesity has been consistently related to risk, associations with physical activity have been inconclusive. We examined relationships of activity patterns with endometrial cancer incidence in the NIH-AARP Diet and Health Study cohort, which included 109,621 women, ages 50–71, without cancer history, who in 1995–1996 completed a mailed baseline questionnaire capturing daily routine and vigorous (defined as any period of ≥20 min of activity at work or home causing increases in breathing, heart rate, or sweating) physical activity. A second questionnaire, completed by 70,351 women, in 1996–1997 collected additional physical activity information. State cancer registry linkage identified 1,052 primary incident endometrial cancers from baseline through December 31, 2003. In multivariate proportional hazards models, vigorous activity was inversely associated with endometrial cancer in a dose-response manner (*p* for trend = 0.02) (relative risk (RR) for ≥5 times/week *vs.* never/rarely = 0.77, 95% confidence interval (CI): 0.63–0.95); this association was more pronounced among overweight and obese women (body mass index ≥25; RR = 0.61, 95% CI: 0.47–0.79) than among lean women (body mass index <25; RR = 0.76, 95% CI: 0.52–1.10; *p* for interaction = 0.12). Although we observed no associations with light/moderate, daily routine or occupational physical activities, risk did increase with number of hours of daily sitting (*p* for trend = 0.02). Associations with vigorous activities, which may interact with body mass index, suggest directions for future research to clarify underlying biologic mechanisms, including those relating to hormonal alterations.

Key words: endometrial neoplasms/epidemiology; exercise/physiology; recreation/physiology; health behavior; prospective studies

Endometrial cancer is the most common gynecologic malignancy and the fourth most common cancer among women in the US,[1] and excess weight is estimated to account for over half of endometrial cancers.[2] Whereas body mass index (BMI) is an established risk factor,[3] evidence for an independent role of physical activity in reducing endometrial cancer risk is inconclusive.[4] Clarifying the relationship between physical activity, a potentially modifiable risk factor, and endometrial cancer could have important etiologic and public health implications.

To date, 10 cohort studies[5–14] and twelve case–control studies[15–26] have examined the association between physical activity and endometrial cancer. Of these, only 2 cohort studies[6,14] have examined whether sedentary behaviors are associated with endometrial cancer and results were suggestive of an elevated risk with longer durations of TV watching or sitting. Two recent systematic reviews concluded that results suggest an inverse association between physical activity and endometrial cancer but are limited by inconsistent dose-response relationships and may depend on activity type and intensity.[27,28] In addition, because BMI is associated with both physical activity and endometrial cancer, special attention to BMI as a confounding factor is required.[27] Additional evidence from prospective cohort studies is needed before specific types and time periods of physical activity might be recommended as a strategy to reduce risk.[27,28] We therefore investigated physical activity and endometrial cancer risk within the large prospective NIH-AARP Diet and Health Study cohort. We considered various types of physical activity during different time periods, evaluated sedentary behaviors, and paid particular attention to potential confounding by BMI.

Material and methods

Study population

The NIH-AARP Diet and Health Study design and methodology have been described in detail.[29] The study was initiated in 1995–1996 when a questionnaire was mailed to 3.5 million members of the AARP (formerly known as the American Association of Retired Persons), ages 50–71 years, who resided in 1 of 8 US states (CA, FL, PA, NJ, NC, LA, GA, and MI). This baseline questionnaire captured diet history, demographic characteristics, current weight and height, smoking status, physical activity, medical and reproductive history, menopausal status, menopausal hormone therapy (HT), and personal and familial history of cancer. A total of 617,119 (17.6%) questionnaires were returned, of which 567,169 were satisfactorily completed; of these, 179 duplicate questionnaires were excluded. In 1996–1997, a second questionnaire was sent to the baseline questionnaire respondents to collect additional information on physical activity, menopausal HT use, medical history, and history of cancer. A total of 337,074 men and women completed this questionnaire.

After excluding individuals who died (n = 261) or moved out of the cancer registry ascertainment area (n = 321) before their baseline questionnaire was received and scanned, proxy respondents to the baseline questionnaire (n = 15,760), 6 individuals who withdrew from the study, and 325,174 men, the baseline study population included 225,468 potentially eligible women. The study was approved by the Special Studies Institutional Review Board of the U.S. National Cancer Institute.

Assessment of physical activity

The baseline questionnaire captured several measures of physical activity. Participants were asked to select a response that best described their current daily routine activity, excluding exercise or

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sports: sit without walking very much; sit but walk fair amount; stand or walk a lot without carrying or lifting things; lift or carry light loads or climb stairs/hills often; or do heavy work or carry heavy loads. Participants were asked to indicate their frequency of vigorous physical activity during a typical month in the past 12 months: never, rarely, 1–3 times per month, 1–2 times per week, 3–4 times per week, or ≥5 times per week. Vigorous activity was defined as physical activity at work or home including exercise, sports, and carrying heavy loads that lasted ≥20 minutes and caused increases in breathing, heart rate, or sweating. Using the same response categories, participants were also asked to recall their frequency of participation in physical activities or sports during a typical month around the ages of 15–18 years old. We collapsed the never and rarely response categories for analysis.

The second questionnaire asked about several domains of physical activity: occupational, recreational and household, and physical inactivity. History of occupational physical activity was assessed by asking participants if they ever had a job requiring physically demanding work. Those responding affirmatively were asked to report the number of (none, 1–2, 3–5 or ≥6 jobs) and total number of years spent (none or <1 year, 1–2, 3–5, 6–9, or ≥10 years) in these jobs. The second questionnaire also assessed whether participants ever had a job in which they walked or biked to work for most days of the week and if so, the total number of years they did so (none, <1 year, 1–2, 3–5, 6–9, or ≥10 years). We combined none and <1 year response categories for analysis.

Participants were instructed not to include occupational physical activity when reporting how often they participated in "light" and "moderate and vigorous" recreational and household activities. They could choose from the following options: never, rarely, weekly but <1 hr per week, 1–3 hr per week, 4–7 hr per week, and >7 hr per week. Participants were asked to read lists of examples of "light" and "moderate and vigorous" recreational and household activities and to select the option that best described how often they participated during various ages and time periods: 15–18, 19–29 and 35–39 years old, and in the past 10 years. The never and rarely response categories were collapsed for analysis. Because these physical activity questions captured frequency and dose, we calculated hours exercised per week and metabolic equivalent (MET) hours per week using the Compendium of Physical Activities as a guide.[30] First, midpoint values were used for each category of reported frequency/dose of participation in weekly activity: never/rarely was assigned a value of 0 hr; <1 hr per week was assigned a value of 0.5 hr; 1–3 hr per week was assigned a value of 2 hr; 4–7 hr per week was assigned a value of 5.5 hr; and >7 hr per week was assigned a value of 8 hr. MET values were then assigned to each level of activity: light activities, 3.0 MET; and moderate/vigorous activities, 7.0 MET. These MET values were multiplied by the values of activity hours per week and summed across the activity levels to determine MET-hours per week for each of the various ages and time periods.

Information on physical inactivity was based on 2 questions. Participants were asked about time spent watching TV or videos during a typical 24-hr period over the past 12 months. Time spent watching TV or videos was categorized as none, <1, 1–2, 3–4, 5–6, 7–8 and ≥9 hr. In a separate question, participants were also asked to indicate the number of hours spent sitting during a typical 24-hr period over the past 12 months: <3, 3–4, 5–6, 7–8 and ≥9 hr. Both measures of inactivity were collapsed as <3, 3–4, 5–6 and ≥7 hr per day.

Cohort follow-up

Cohort members were followed annually for address changes and vital status. Address changes were identified by matching the cohort database to the US Postal Service's National Change of Address database. Vital status was updated through linkage to the US Social Security Administration Death Master File, identifying cohort members who are presumed deceased. Results were verified through a follow-up search of the National Death Index Plus, a central computerized index of death record information compiled annually from state vital statistics offices for research purposes.

Ascertainment of endometrial cancer

Incident endometrial cancers were initially identified through probabilistic linkage to 8 state cancer registries using first and last name, address, sex, date of birth, and Social Security Number. The cancer registry ascertainment area was recently expanded to include 3 additional states (TX, AZ, and NV) to capture cancer occurring among participants who moved to those states during follow-up. Histology was defined using International Classification of Diseases for Oncology codes, 3rd edition.[31] A previous validation study in this cohort estimated that registry linkage validly identified approximately 90% of all incident cancers.[32]

Analytic sample

In our analysis of baseline physical activity data, we excluded 23,911 women who reported a personal cancer history other than non-melanoma skin cancer, 82,132 who reported a prior hysterectomy, and 2,934 women with unknown hysterectomy status. We also excluded women who reported at baseline that their menstrual periods stopped because of surgery (n = 1,829) or because of radiation or chemotherapy (n = 117), 76 who developed non-epithelial endometrial cancer during follow-up, 8 with no follow-up, 421 (including 4 cases) who were missing baseline information on both daily routine and vigorous activity, and women with missing (n = 3,530, including 31 cases) or extreme (defined as > 2 interquartile ranges from the mean; n = 889, including 33 cases) values for baseline BMI (weight in kilograms divided by the square of height in meters). Thus, 109,621 women were included in the baseline physical activity analysis. From baseline through December 31, 2003, 1,052 women developed endometrial cancer, the majority of which were adenocarcinomas (n = 978).

To use the physical activity and inactivity data collected in the second questionnaire, we created an analytic subsample restricted to women who responded to the second questionnaire. Of the 109,621 women included in the baseline analysis, 72,046 women (including 701 endometrial cancer cases) responded to the second questionnaire. We further excluded women who died or moved out of the cancer registry ascertainment area before their second questionnaire was received and scanned (n = 338), proxy respondents to the second questionnaire (n = 565, including 7 prevalent endometrial cancer cases), women with a personal history of cancer at the time of the second questionnaire (n = 633, including 44 prevalent endometrial cancer cases), those missing recreational/household activity and physical inactivity information on the second questionnaire (n = 82 non-cases), women with extreme values for BMI (n = 16 non-cases with BMI > 2 interquartile ranges from the mean BMI of those responding to the second questionnaire), women with unknown history of HT use at the time of the second questionnaire (n = 58 non-cases), and 3 women with no follow-up, resulting in an analytic subsample of 70,351 women completing both study questionnaires. Of these, 650 women developed endometrial cancer from the time of the second questionnaire through December 31, 2003; adenocarcinoma accounted for 95% of these cancers.

Statistical analysis

Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals (CI) for endometrial cancer associated with physical activity; age was the time scale[33] and ties were handled by complete enumeration.[34] Follow-up began at the age at which the baseline questionnaire (for the main analyses) or the second questionnaire (for the analytic subsample) was received and scanned and continued through the earliest of the following dates: participant diagnosed with endometrial cancer, moved out of her registry catchment area, died from any cause, or December 31, 2003. To test the proportional hazards assumption, we generated time-dependent covariates by including interactions of physical activity measures with the natural log of age (the time metric); probability values for all time-dependent covariates were >0.05, consistent with proportional hazards.

For the main analyses, we examined the combined effect of baseline vigorous activity and baseline daily routine activity in relation to endometrial cancer by creating a single six-level variable based on the cross-tabulation of vigorous activity (never/rarely, 1 time per month to 2 times per week, or ≥3 times per week) and daily routine activity (sit much of day with some walking *vs.* do more than sit most of day). Multivariate models were used to control for age at entry, race/ethnicity, smoking status, parity, ever use of oral contraceptives, menopausal status (premenopausal, natural menopause at <45, 45–49, 50–54 or ≥55 years of age, or unknown age at menopause), and ever use of HT. Because BMI is positively associated with endometrial cancer risk and inversely associated with physical activity, separate multivariate models additionally adjusted for BMI.

In the multivariate models restricted to the analytic subsample of women who completed both questionnaires, we replaced ever use of HT with HT formulation (never used, estrogen only use, estrogen-progestin only use, HT use of other/unknown formulation). In analyses of frequency of light physical activity during a specific time period, we adjusted for frequency of moderate/vigorous physical activity during that same time period, and vice versa. We used a likelihood ratio test, comparing models with and without the interaction terms, to separately examine effect modification by HT formulation and BMI.

Tests for linear trends across the physical activity exposure categories were calculated by treating these categorical variables as ordinal variables. In subsequent models, we adjusted individually for calendar time and several additional factors, including education, age at menarche, self-reported diabetes, self-rated health quality, and alcohol intake; results were essentially the same and are not shown here. In addition, we assessed the internal consistency between physical activity items reported within and between questionnaires by examining pairwise Spearman's rank correlations.

Probability values of <0.05 were considered statistically significant. All tests of statistical significance were two-tailed. Analyses were performed using SAS software release 9.1.3 (SAS Institute, Cary, NC).

Results

Among the 109,621 mostly white, postmenopausal women in this report, current daily routine physical activity (excluding exercise or sports) was most frequently described as standing or walking a lot without carrying or lifting things (38.8%), followed by sitting during much of the day but walking a fair amount (33.6%). Including exercise and sports, 21.8% of women reported never or rarely engaging in vigorous activity in the past 12 months, whereas 14.4, 21.3 and 42.5% reported engaging in vigorous activity 1–3 times per month, 1–2 times per week, and ≥3 times per week, respectively. More than half (55.7%) of the women reported participating in physical activities or sports ≥3 times per week between the ages of 15–18 years old.

At baseline, women with the most active current daily routine or most frequent participation in vigorous activity in the past 12 months were leaner than their less-active counterparts (Tables I and II). Compared with the least active women, women with the most active current daily routine were less likely to be white, to have attended post-secondary education, and to have ever used exogenous hormones, and were more likely to be current smokers. In contrast, women who frequently participated in vigorous activity were more likely to have attended post-secondary education and to have ever used hormone therapy, and were less likely to be current smokers as compared with those who never/rarely engaged in vigorous activity.

The 109,621 women accrued 766,170.7 person-years during an average follow-up of 3.80 years for cases (range: 1 day–8.03 years) and 7.02 years for non-cases (range: 1 day–8.18 years). The mean (SD) ages for entry and exit were 62.6 (5.2) and 66.4 (5.5) years for cases and 61.6 (5.5) and 68.6 (5.6) years for non-cases, respectively. The standardized incidence ratio for endometrial cancer in the full cohort compared with the US National Cancer Institute's Surveillance, Epidemiology and End Results rate (ages 50–79 years) was 0.92 (95% CI: 0.87–0.97), indicating that the rate in our cohort was slightly lower than that of the US population. As previously described in this cohort,[35,36] endometrial cancer risk was positively associated with BMI, later age at natural menopause, and use of menopausal HT; reduced endometrial cancer risk was associated with non-white race/ethnicity, smoking, later age at menarche, parity, and oral contraceptive use.

We examined the risk of endometrial cancer according to self-reported physical activity at baseline (Table III). The risk of endometrial cancer decreased with increasing categories of daily routine activity, excluding exercise or sports (*p* for trend <0.0001), though this was no longer statistically significant in multivariate analysis further adjusted for BMI (*p* for trend = 0.07). Increasing frequency of vigorous activity, including exercise and sports, was associated with reduced endometrial cancer risk in a dose-response manner before and after adjustment for BMI (*p* for trend = 0.02), such that the relative risk (RR) of endometrial cancer for vigorous activity ≥5 times per week compared with never or rarely engaging in vigorous activity was 0.77 (95% CI: 0.63–0.95). Frequency of participation in physical activities or sports during a typical month between the ages of 15–18 years old was not related to endometrial cancer in age-adjusted or multivariate analyses. Compared with women who reported both never/rarely engaging in vigorous activity and sitting for much of the day, women who participated in vigorous activity ≥3 times a week over the past 12 months were at a significant 25% reduced relative risk of endometrial cancer irrespective of their current daily routine activity level (data not shown).

The majority of women who responded to the second questionnaire never had a physically demanding job lasting more than a year (85.1%) and never had a job in which they walked or biked to work most days of the week for a period longer than 1 year (87.2%) (Table IV). We found no statistically significant associations between any of the measures of prior occupational physical activity and endometrial cancer. In addition, we detected no statistically significant relationships between endometrial cancer and MET-hours per week of recreational and household activities during ages 15–18, 19–29 or 35–39 years, or during the past 10 years after adjustment for BMI (data not shown). Although time spent watching TV/videos was not associated with endometrial cancer after adjustment for BMI, we observed a positive association between endometrial cancer risk and number of hours spent sitting during a typical 24-hour period in the past 12 months both before and after adjustment for BMI (RRs for 3–4, 5–6 and ≥7 *vs.* <3 hours/day = 1.07, 1.31 and 1.26, respectively; *p* for trend = 0.02) (Table V). To assess whether the association with hours spent sitting was influenced by physical activity, we additionally adjusted for frequency of baseline vigorous activity and observed a slight attenuation in the risk estimates (RRs for sitting 3–4, 5–6 and ≥7 *vs.* <3 hours/day = 1.07, 95% CI: 0.84–1.36; 1.29, 95% CI: 1.02–1.63; and 1.23, 95% CI: 0.96–1.57, respectively; *p* for trend = 0.04).

There was no evidence for effect modification of the association between current daily routine activity, vigorous activity, and hours spent sitting during the past 12 months and endometrial cancer by HT formulation (data not shown). In addition, there was no evidence for effect modification of the association between current daily routine activity and hours spent sitting and endometrial cancer by BMI; however, the association with frequency of baseline vigorous activity was more pronounced among overweight and obese women than in lean women (BMI <25), although the interaction was not statistically significant (p for interaction for BMI <25 *vs.* ≥25 = 0.12) (Table VI).

TABLE I – SELECT CHARACTERISTICS OF WOMEN ACCORDING TO DAILY ROUTINE PHYSICAL ACTIVITY LEVEL AT BASELINE, NIH-AARP DIET AND HEALTH STUDY

Characteristic	Current daily routine activity at work or home									
	Sitting (n = 9,293)		Sitting and walking (n = 36,032)		Walking and standing (n = 41,606)		Climbing stairs or carrying heavy loads (n = 18,600)		Heavy work or carrying heavy loads (n = 1,737)	
	n	%[1]	n	%	n	%	n	%	n	%
Age at baseline questionnaire (years)										
<55	2,317	24.9	6,860	19.0	5,535	13.3	2,319	12.5	317	18.2
55–59	2,675	28.8	9,459	26.3	8,879	21.3	3,784	20.3	488	28.1
60–64	2,286	24.6	9,459	26.3	11,628	27.9	5,250	28.2	467	26.9
65–69	1,844	19.8	9,274	25.7	14,035	33.7	6,494	34.9	424	24.4
70+	171	1.8	980	2.7	1,529	3.7	753	4.0	41	2.4
Body mass index at baseline (kg/m^2)										
<25	3,122	33.6	15,289	42.4	21,056	50.6	9,861	53.0	829	47.7
25–29	2,717	29.2	11,474	31.8	13,350	32.1	5,834	31.4	604	34.8
30+	3,454	37.2	9,269	25.7	7,200	17.3	2,905	15.6	304	17.5
Race/ethnicity										
Caucasian/non-Hispanic white	8,515	91.6	32,838	91.1	37,761	90.8	17,239	92.7	1,540	88.7
Other/unknown	778	8.4	3,194	8.9	3,845	9.2	1,361	7.3	197	11.3
Education										
<High school/high school grad	2,501	27.4	9,894	28.1	12,598	31.1	5,701	31.4	703	42.6
Post-high school+	6,614	72.6	25,293	71.9	27,928	68.9	12,472	68.6	948	57.4
Smoking										
Never	3,544	39.2	15,231	43.4	18,696	46.2	8,675	48.0	722	43.4
Former	4,063	45.0	14,382	41.0	16,214	40.1	6,666	36.8	573	34.5
Current	1,425	15.8	5,475	15.6	5,569	13.8	2,750	15.2	368	22.1
Age at menarche (years)										
<13	4,727	51.0	17,603	49.0	19,155	46.2	8,634	46.5	771	44.6
13–14	3,790	40.9	15,164	42.2	18,244	44.0	8,017	43.2	724	41.9
15+	749	8.1	3,166	8.8	4,101	9.9	1,897	10.2	234	13.5
Parity										
Nulliparous	1,702	18.6	6,538	18.4	6,521	15.9	2,863	15.5	282	16.5
One	1,192	13.0	4,132	11.6	4,277	10.4	1,831	9.9	190	11.1
Two	2,479	27.0	9,746	27.4	11,097	27.0	4,624	25.1	394	23.1
Three or more	3,802	41.4	15,152	42.6	19,215	46.7	9,104	49.4	842	49.3
Ever used oral contraceptives										
No	4,858	52.5	19,846	55.4	25,372	61.4	11,549	62.5	1,072	62.1
Yes	4,388	47.5	15,968	44.6	15,977	38.6	6,943	37.5	655	37.9
Ever used HT at baseline										
No	5,446	58.6	21,027	58.4	24,569	59.1	11,431	61.5	1,179	67.9
Yes	3,847	41.4	15,005	41.6	17,037	40.9	7,169	38.5	558	32.1
Age at menopause (years)										
Premenopausal	960	10.3	2,764	7.7	2,171	5.2	891	4.8	99	5.7
<45	952	10.2	3,698	10.3	4,399	10.6	1,993	10.7	216	12.4
45–49	2,305	24.8	9,011	25.0	10,705	25.7	4,741	25.5	450	25.9
50–54	3,983	42.9	15,794	43.8	18,585	44.7	8,329	44.8	756	43.5
55+	756	8.1	3,426	9.5	4,268	10.3	1,994	10.7	145	8.3
Postmenopausal, age unknown	337	3.6	1,339	3.7	1,478	3.6	652	3.5	71	4.1
Frequency of vigorous physical activity during typical month in past 12 months[2]										
Never/Rarely	3,854	41.7	8,944	25.0	7,886	19.1	2,322	12.6	152	8.9
1–3 times/month	1,585	17.2	6,087	17.0	5,514	13.4	2,156	11.7	98	5.7
1–2 times/week	1,673	18.1	7,848	21.9	8,940	21.7	4,030	21.8	228	13.3
3–4 times/week	1,380	14.9	8,238	23.0	11,303	27.4	5,783	31.3	477	27.9
5+ times/week	745	8.1	4,693	13.1	7,644	18.5	4,161	22.6	757	44.2

[1]Missing values were excluded from percentage calculations.–[2]Defined as physical activity that lasted at least 20 mins and caused increases in breathing, heart rate, or sweating.
HT, hormone therapy.

In general, the correlations between activity responses asked on the 2 questionnaires were statistically significant and offered some suggestion of internal consistency (data not shown). For instance, hours spent sitting per day was positively correlated with hours spent watching TV/videos per day (r = 0.21) and inversely associated with baseline activity (r = –0.46 for current daily routine activity at work or home and r= –0.15 for frequency of vigorous activity).

Discussion

In this large prospective study, increased frequency of vigorous physical activity, but not activity of lower intensity, was associated with a 23% reduced RR of endometrial cancer. The association with vigorous activity appeared to be stronger among overweight and obese women (BMI ≥25). We did not observe an association with risk for current daily routine or occupational physical activities. Number of hours spent sitting per day, but not watching TV, was related to an increased risk of endometrial cancer, and the association was statistically independent of BMI in this model.

Our findings for vigorous activity are remarkably consistent with a recently reported pooled estimate of the association between endometrial cancer and physical activity from cohort studies published through 2006, also showing a 23% decreased risk of endometrial cancer for the most active compared with the least active women (OR = 0.77, 95% CI: 0.70–0.85).[27] Few studies have reported relative risk estimates specifically for vigorous

TABLE II – SELECT CHARACTERISTICS OF WOMEN ACCORDING TO FREQUENCY OF VIGOROUS PHYSICAL ACTIVITY LEVEL AT BASELINE, NIH-AARP DIET AND HEALTH STUDY

Characteristic	Frequency of vigorous physical activity during typical month in past 12 months[1]									
	Never/rarely (n = 23,685)		1–3 times/month (n = 15,724)		1–2 times/week (n = 23,195)		3–4 times/week (n = 27,785)		5+ times/week (n = 18,462)	
	n	%[2]	n	%	n	%	n	%	n	%
Age at baseline questionnaire (years)										
<55	3,363	14.2	3,093	19.7	4,088	17.6	4,265	15.4	2,706	14.7
55–59	5,249	22.2	4,134	26.3	5,656	24.4	6,299	22.7	4,247	23.0
60–64	6,529	27.6	4,175	26.6	6,243	26.9	7,652	27.5	4,931	26.7
65–69	7,681	32.4	3,920	24.9	6,496	28.0	8,650	31.1	5,913	32.0
70+	863	3.6	402	2.6	712	3.1	919	3.3	665	3.6
Body mass index at baseline (kg/m^2)										
<25	8,677	36.6	6,277	39.9	10,397	44.8	14,560	52.4	10,916	59.1
25–29	7,311	30.9	5,195	33.0	7,854	33.9	8,816	31.7	5,322	28.8
30+	7,697	32.5	4,252	27.0	4,944	21.3	4,409	15.9	2,224	12.0
Race/ethnicity										
Caucasian/non-hispanic white	21,244	89.7	14,380	91.5	21,305	91.9	25,301	91.1	16,958	91.9
Other/unknown	2,441	10.3	1,344	8.5	1,890	8.1	2,484	8.9	1,504	8.1
Education										
<High school/high school grad	9,347	40.5	4,592	29.9	6,323	27.9	7,164	26.5	4,701	26.2
Post-high school+	13,727	59.5	10,773	70.1	16,304	72.1	19,904	73.5	13,274	73.8
Smoking										
Never	9,669	42.0	6,600	43.0	10,345	45.8	12,579	46.6	8,376	46.8
Former	8,535	37.1	5,887	38.4	8,804	38.9	11,437	42.4	7,802	43.6
Current	4,823	20.9	2,853	18.6	3,460	15.3	2,962	11.0	1,727	9.6
Age at menarche (years)										
<13	11,582	49.1	7,606	48.5	10,979	47.5	12,861	46.4	8,611	46.8
13–14	9,804	41.5	6,644	42.3	9,997	43.2	12,165	43.9	7,942	43.1
15+	2,212	9.4	1,443	9.2	2,162	9.3	2,676	9.7	1,859	10.1
Parity										
Nulliparous	4,056	17.3	2,735	17.6	3,861	16.8	4,394	16.0	3,129	17.2
One	2,663	11.4	1,823	11.8	2,562	11.2	2,841	10.3	1,914	10.5
Two	5,846	25.0	3,983	25.7	6,171	26.9	7,619	27.7	5,038	27.6
Three or more	10,826	46.3	6,965	44.9	10,347	45.1	12,613	45.9	8,148	44.7
Ever used oral contraceptives										
No	14,755	62.7	8,859	56.6	13,255	57.5	15,886	57.5	11,004	60.0
Yes	8,773	37.3	6,781	43.4	9,816	42.5	11,723	42.5	7,351	40.0
Ever used HT at baseline										
No	16,019	67.6	9,239	58.8	13,607	58.7	15,331	55.2	10,572	57.3
Yes	7,666	32.4	6,485	41.2	9,588	41.3	12,454	44.8	7,890	42.7
Age at menopause (years)										
Premenopausal	1,263	5.3	1,179	7.5	1,643	7.1	1,790	6.4	1,074	5.8
<45	2,965	12.5	1,622	10.3	2,371	10.2	2,638	9.5	1,854	10.0
45–49	6,393	27.0	4,036	25.7	5,757	24.8	6,810	24.5	4,617	25.0
50–54	10,049	42.4	6,923	44.0	10,307	44.4	12,560	45.2	8,267	44.8
55+	2,199	9.3	1,412	9.0	2,351	10.1	2,928	10.5	1,897	10.3
Postmenopausal, age unknown	816	3.4	552	3.5	766	3.3	1,059	3.8	753	4.1
Current daily routine activity at work or home										
Sit during day without much walking	3,854	16.6	1,585	10.3	1,673	7.4	1,380	5.1	745	4.1
Sit much of day but walk fair amount	8,944	38.6	6,087	39.4	7,848	34.5	8,238	30.3	4,693	26.1
Stand/walk a lot during day without carrying/lifting things	7,886	34.1	5,514	35.7	8,940	39.4	11,303	41.6	7,644	42.5
Lift/carry light loads or climb stairs/hills often	2,322	10.0	2,156	14.0	4,030	17.7	5,783	21.3	4,161	23.1
Heavy work or carry heavy loads	152	0.7	98	0.6	228	1.0	477	1.8	757	4.2

[1]Defined as physical activity that lasted at least 20 mins and caused increases in breathing, heart rate, or sweating.–[2]Missing values were excluded from percentage calculations.
HT, hormone therapy.

activity: our results are similar to those from 2 case–control studies suggesting reduced risk associated with vigorous activity,[20,23] but are in contrast with those from 2 cohort studies observing no association.[5,7] Whereas several previous case–control[20,21] and cohort[5,11,12] studies have demonstrated risk reductions for light and moderate physical activities, we did not observe associations between frequency of light or moderate/vigorous recreational and household activities and endometrial cancer risk during recent years or earlier time periods. We observed no effect modification by HT, and our findings are generally consistent with previous investigations as reviewed in Refs. [7,27] and [28]. In the present study, we observed a stronger protective effect associated with vigorous activity among overweight and obese women, although the interaction was not statistically significant. Although most cohort and case–control studies have not observed any effect modification by BMI as reviewed in Refs. 27,28, our findings are in contrast with 1 case–control study[22] that observed a stronger effect in women with a lower BMI and are consistent with other cohort[8,14] and case–control studies[19,26] that found stronger associations with physical activity among women with a high BMI.

Associations with non-vigorous activity were less clear. Occupational physical activity has been associated with a reduced risk of endometrial cancer in three[8,9,13] of six[6–10,13] prior cohort studies, which were conducted in Europe and China. We did not observe an association with history of occupational activity; however, we were limited by lack of information on intensity and dose of these activities, as well as by small numbers of women reporting physically demanding jobs, suggesting that occupational activity is unlikely to be an important population-level source of physical activity among similar groups of AARP-eligible women. Our

TABLE III – MULTIVARIATE ADJUSTED RR AND 95% CI FOR THE ASSOCIATION BETWEEN BASELINE PHYSICAL ACTIVITY AND ENDOMETRIAL CANCER INCIDENCE, NIH-AARP DIET AND HEALTH STUDY

Physical activity	No. cancers	Person–years	RR[1]	95% CI	*p* for trend	RR[2]	95% CI	*p* for trend	RR[3]	95% CI	*p* for trend
Current daily routine activity at work or home											
Sit without much walking	104	63,656.5	1.00		<.0001	1.00		<.0001	1.00		0.07
Sit but walk fair amount	389	250,987.7	0.90	(0.73–1.12)		0.89	(0.72–1.11)		1.09	(0.87–1.35)	
Stand/walk a lot without carrying/lifting things	370	292,047.1	0.70	(0.56–0.87)		0.68	(0.55–0.85)		0.97	(0.77–1.21)	
Lift/carry light loads or climb stairs/hills often	150	130,859.8	0.63	(0.49–0.81)		0.62	(0.48–0.79)		0.89	(0.69–1.16)	
Heavy work or carry heavy loads	12	12,284.4	0.57	(0.31–1.03)		0.59	(0.32–1.06)		0.81	(0.45–1.48)	
Vigorous physical activity during typical month in past 12 months											
Never/Rarely	292	162,322.2	1.00		<.0001	1.00		<.0001	1.00		0.02
1–3 times/month	149	110,490.4	0.78	(0.64–0.95)		0.77	(0.63–0.93)		0.84	(0.69–1.02)	
1–2 times/week	221	162,617.4	0.77	(0.65–0.92)		0.74	(0.62–0.89)		0.88	(0.73–1.04)	
3–4 times/week	244	195,345.4	0.70	(0.59–0.83)		0.66	(0.56–0.79)		0.85	(0.72–1.02)	
5+ times/week	139	130,077.2	0.60	(0.49–0.73)		0.56	(0.46–0.68)		0.77	(0.63–0.95)	
Frequency of participation in physical activities or sports during typical month between ages 15–18 years old											
Never/Rarely	169	129,904.3	1.00		0.22	1.00		0.16	1.00		0.22
1–3 times/month	81	71,174.2	0.89	(0.68–1.16)		0.90	(0.69–1.18)		0.91	(0.70–1.19)	
1–2 times/week	197	137,879.0	1.10	(0.90–1.35)		1.10	(0.90–1.35)		1.13	(0.92–1.39)	
3–4 times/week	258	184,622.4	1.06	(0.88–1.29)		1.09	(0.89–1.32)		1.10	(0.91–1.34)	
5+ times/week	340	237,840.6	1.09	(0.90–1.31)		1.10	(0.92–1.32)		1.09	(0.91–1.31)	

[1]Relative risks adjusted for age (continuous).–[2]Relative risks adjusted for age (continuous), race (white vs. other/unknown), smoking status (never, former, current or unknown), parity (nulliparous, one, two, ≥three births or unknown), ever use of oral contraceptives (no, yes, unknown), age at menopause (premenopausal, natural menopause at <45, 45–49, 50–54, or ≥55 years of age, or unknown age at menopause) and ever use of hormone therapy (no, yes).–[3]Relative risks additionally adjusted for body mass index (continuous).

Not shown are unknown current daily routine activity (27 cancers and 16,335 person–years), vigorous activity (7 cancers and 5,318 person–years) and activity between the ages of 15–18 years (7 cancers and 4,750 person–years).

CI, confidence interval; RR, relative risk.

TABLE IV – MULTIVARIATE ADJUSTED RR AND 95% CI FOR THE ASSOCIATION BETWEEN HISTORY OF OCCUPATIONAL PHYSICAL ACTIVITY AND ENDOMETRIAL CANCER INCIDENCE AMONG WOMEN WHO COMPLETED THE SECOND QUESTIONNAIRE, NIH-AARP DIET AND HEALTH STUDY

Occupational physical activity	No. cancers	Person–years	RR[1]	95% CI	*p* for trend	RR[2]	95% CI	*p* for trend	RR[3]	95% CI	*p* for trend
Number of physically demanding jobs											
None	525	370,721.1	1.00		0.78	1.00		0.48	1.00		0.95
1–2	90	63,460.0	1.03	(0.82–1.29)		1.07	(0.85–1.33)		0.99	(0.79–1.23)	
3–5	18	13,188.5	1.01	(0.63–1.62)		1.09	(0.68–1.74)		0.98	(0.61–1.57)	
6+	10	6,898.9	1.07	(0.57–2.00)		1.14	(0.61–2.13)		1.03	(0.55–1.93)	
Number of years with physically demanding jobs											
None or less than 1 year	548	387,002.0	1.00		0.59	1.00		0.36	1.00		0.90
1–2	8	9,532.9	0.62	(0.31–1.25)		0.66	(0.33–1.32)		0.60	(0.30–1.20)	
3–5	24	12,877.6	1.38	(0.92–2.08)		1.47	(0.97–2.21)		1.34	(0.89–2.02)	
6–9	9	10,146.5	0.66	(0.34–1.28)		0.69	(0.36–1.33)		0.63	(0.33–1.23)	
10+	54	34,800.6	1.12	(0.84–1.48)		1.17	(0.88–1.54)		1.06	(0.80–1.40)	
Number of years walked or biked to work most days											
None or less than 1 year	560	395,140.9	1.00		0.89	1.00		0.62	1.00		0.68
1–2	31	17,599.2	1.26	(0.88–1.80)		1.27	(0.88–1.82)		1.23	(0.86–1.76)	
3–5	25	19,280.8	0.91	(0.61–1.36)		0.88	(0.59–1.32)		0.88	(0.59–1.31)	
6–9	18	8,009.2	1.55	(0.97–2.48)		1.50	(0.94–2.40)		1.54	(0.96–2.46)	
10+	13	12,625.6	0.70	(0.40–1.21)		0.65	(0.37–s1.12)		0.66	(0.38–1.15)	

[1]Relative risks adjusted for age (continuous).–[2]Relative risks adjusted for age (continuous), race (white vs. other/unknown), smoking status (never, former, current or unknown), parity (nulliparous, one, two, ≥three births or unknown), ever use of oral contraceptives (no, yes, unknown), age at menopause (premenopausal, natural menopause at <45, 45–49, 50–54, or ≥55 years of age, or unknown age at menopause), and hormone therapy formulation (never used, ET use, EPT use or unknown HT use).–[3]Relative risks additionally adjusted for body mass index (continuous).

Not shown are unknown number of physically demanding jobs (7 cancers and 3,084 person–years), number of years with a physically demanding job (7 cancers and 2,993 person–years), and number of years walked or biked to work (3 cancers and 4,697 person–years).

CI, confidence interval; RR, relative risk.

TABLE V – MULTIVARIATE ADJUSTED RR AND 95% CI FOR THE ASSOCIATION BETWEEN SEDENTARY BEHAVIORS AND ENDOMETRIAL CANCER INCIDENCE AMONG WOMEN WHO COMPLETED THE SECOND QUESTIONNAIRE, NIH-AARP DIET AND HEALTH STUDY

Sedentary behavior	No. cancers	Person–years	RR[1]	95% CI	*p* for trend	RR[2]	95% CI	*p* for trend	RR[3]	95% CI	*p* for trend
Hours spent watching TV/videos during typical 24 hour period in past 12 months											
<3	198	167,821.7	1.00		0.002	1.00		0.0003	1.00		0.26
3–4	286	192,076.6	1.20	(1.00–1.44)		1.24	(1.03–1.49)		1.11	(0.92–1.33)	
5–6	117	70,739.4	1.30	(1.03–1.64)		1.36	(1.08–1.72)		1.08	(0.86–1.37)	
7+	48	24,935.6	1.53	(1.12–2.10)		1.66	(1.20–2.28)		1.21	(0.87–1.67)	
Hours spent sitting during typical 24 hour period in past 12 months											
<3	111	98,017.6	1.00		<.0001	1.00		<.0001	1.00		0.02
3–4	171	130,998.9	1.14	(0.90–1.45)		1.15	(0.90–1.46)		1.07	(0.85–1.37)	
5–6	203	123,374.0	1.48	(1.17–1.86)		1.48	(1.18–1.87)		1.31	(1.04–1.65)	
7+	164	102,884.6	1.54	(1.21–1.96)		1.56	(1.22–1.99)		1.26	(0.99–1.62)	

[1]Relative risks adjusted for age (continuous).–[2]Relative risks adjusted for age (continuous), race (white vs. other/unknown), smoking status (never, former, current or unknown), parity (nulliparous, one, two, ≥three births or unknown), ever use of oral contraceptives (no, yes, unknown), age at menopause (premenopausal, natural menopause at <45, 45–49, 50–54 or ≥55 years of age, or unknown age at menopause), and hormone therapy formulation (never used, ET use, EPT use or unknown HT use).–[3]Relative risks additionally adjusted for body mass index (continuous).

Not shown are unknown hours spent watching TV/videos (1 cancer and 1,779 person–years) and hours spent sitting (1 cancer and 2,077 person–years).

CI, confidence interval; RR, relative risk.

results showing a positive dose-response relation between increased duration of sitting, but not watching TV, and endometrial cancer risk after additional adjustment for BMI are not directly comparable with the findings from the Swedish Mammography and Cancer Prevention Study II Cohorts, which both measured inactivity with a combined question for TV and sitting; one study found elevated risk among those watching TV/sitting ≥5 hr per day,[6] whereas the other did not observe a statistically significant association for hours per day of TV/sitting after adjustment for BMI.[14]

There are several plausible biologic mechanisms for the observed associations between vigorous activity, inactivity and endometrial cancer. Endometrial carcinogenesis is thought to be caused, in part, by estrogens that are insufficiently counterbalanced by progesterone.[3,37] Physical activity may reduce endometrial cancer risk directly by decreasing levels of biologically available estrogens, as evidenced by studies reporting lower serum estrogen levels among more active women.[38,39] Physical activity may also indirectly influence endometrial cancer risk through

TABLE VI – MULTIVARIATE ADJUSTED RR AND 95% CI FOR THE ASSOCIATION BETWEEN BASELINE VIGOROUS PHYSICAL ACTIVITY AND ENDOMETRIAL CANCER BY BMI, NIH-AARP DIET AND HEALTH STUDY

Vigorous physical activity during typical month in past 12 months	No. cancers	Person–years	RR[1]	95% CI	*p* for trend	RR[2]	95% CI	*p* for trend	*p* for interaction
BMI <25									
Never/Rarely	53	59,559.7	1.00		0.92	1.00		0.21	0.12
1–3 times/month	37	44,116.1	0.98	(0.65–1.50)		0.89	(0.59–1.36)		
1–2 times/week	70	73,250.7	1.10	(0.77–1.58)		0.97	(0.68–1.38)		
3–4 times/week	102	102,612.0	1.13	(0.81–1.58)		0.93	(0.67–1.31)		
5+ times/week	62	77,168.1	0.91	(0.63–1.32)		0.76	(0.52–1.10)		
BMI 25+									
Never/Rarely	239	102,762.5	1.00		<.0001	1.00		<.0001	
1–3 times/month	112	66,374.3	0.76	(0.61–0.95)		0.76	(0.61–0.95)		
1–2 times/week	151	89,366.7	0.74	(0.61–0.91)		0.73	(0.60–0.90)		
3–4 times/week	142	92,733.5	0.66	(0.53–0.81)		0.66	(0.53–0.81)		
5+ times/week	77	52,909.1	0.62	(0.48–0.80)		0.61	(0.47–0.79)		

[1]Relative risks adjusted for age (continuous).–[2]Relative risks adjusted for age (continuous), race (white vs. other/unknown), smoking status (never, former, current or unknown), parity (nulliparous, one, two, ≥three births or unknown), ever use of oral contraceptives (no, yes, unknown), age at menopause (premenopausal, natural menopause at <45, 45–49, 50–54, or ≥55 years of age, or unknown age at menopause), and ever use of hormone therapy (no, yes).

Not shown are unknown vigorous activity among women with BMI <25 (1 cancer and 2,362 person–years) and unknown vigorous activity among women with BMI 25+ (6 cancers and 2,956 person–years).

BMI, body mass index; CI, confidence interval; RR, relative risk.

lower body weight,[40] because peripheral conversion of androgens to estrogens by aromatase occurs in the adipose tissue.[41] Hence, the reduction in bioavailable estrogens associated with increased physical activity may in part explain the stronger associations we observed for vigorous activity among overweight and obese women, who have increased peripheral estrogen synthesis. Although physical activity and BMI are strongly linked, we observed significant dose-response relationships for vigorous activity and inactivity after adjustment for BMI and other potential confounding factors, suggesting that vigorous activity and inactivity independently affect endometrial cancer risk apart from their association with BMI. However, measurement error or residual confounding by BMI could also explain the apparent independence of these correlated factors. Finally, physical activity may influence growth factors and changes in immune function,[4] both of which are thought to be related to endometrial cancer risk.[2,42]

Although we assessed numerous potential confounding factors, it is possible that the observed associations may be explained by unmeasured lifestyle factors, such as socioeconomic status, which was shown to confound the association between occupational activity and endometrial cancer in a previous study.[15] Inclusion of education in multivariate analyses, however, did not materially change results for any of the activity measures. Additional limitations may have affected our findings. Physical activity was self-reported, introducing the possibility of exposure misclassification which would most likely attenuate any true association between physical activity and endometrial cancer if all misclassification were non-differential. Nevertheless, we detected a significant inverse association for frequent vigorous activity of ≥20 min in duration. Previous studies have demonstrated better recall for vigorous activities than activities of lower intensity,[43,44] which could have contributed to the observed reduced risk with vigorous activity as opposed to null associations for light and moderate/vigorous recreational and household activities in our study. Our physical activity questions were not validated, but the measure of vigorous activity was structured according to the American College of Sports Medicine's physical activity guidelines, which recommend ≥20 min of continuous vigorous exercise 3 times per week as a means of improving cardiorespiratory fitness.[45] In addition, most of the pairwise correlations between reported physical activity questionnaire items were weak to modest, indicating both good internal consistency for activity types as well as an ability for the questions to measure different aspects of physical activity without being redundant.

In summary, this study provides evidence for a protective effect of vigorous activity and a deleterious role of inactivity with respect to endometrial cancer risk. Our findings are in support of the accumulating body of evidence from epidemiologic studies, which suggest that physical activity is important in the etiology of endometrial cancer. It will be important to clarify underlying mechanisms, including those relating to hormonal alterations.

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対象の内訳

	ヒト	動物	地 域	欧米	研究の種類	縦断研究
対象	一般健常者	空白		(　　)		コホート研究
性別	女性	(　　)		(　　)		(　　)
年齢	50-71歳			(　　)		前向き研究
対象数	10000以上			(　　)		(　　)

調査の方法	質問紙	(　　)				
アウトカム　予 防	なし	なし	ガン予防	なし	(　　)	(　　)
アウトカム　維持・改善	なし	なし	なし	なし	(　　)	(　　)

図 表

TABLE III – MULTIVARIATE ADJUSTED RR AND 95% CI FOR THE ASSOCIATION BETWEEN BASELINE PHYSICAL ACTIVITY AND ENDOMETRIAL CANCER INCIDENCE, NIH-AARP DIET AND HEALTH STUDY

Physical activity	No. cases	Person-years	RR[1]	95% CI	p for trend	RR[2]	95% CI	p for trend	RR[3]	95% CI	p trend
Current daily routine activity at work or home											
Sit without much walking	106	63,656.5	1.00		<.0001	1.00		<.0001	1.00		0.07
Sit but walk fair amount	380	250,987.7	0.90	(0.73–1.12)		0.89	(0.72–1.11)		1.09	(0.87–1.35)	
Stand/walk a lot without carrying/lifting things	376	292,047.1	0.70	(0.56–0.87)		0.68	(0.55–0.85)		0.97	(0.77–1.21)	
Lift/carry light loads or climb stairs/hills often	150	130,459.8	0.63	(0.49–0.81)		0.62	(0.48–0.79)		0.89	(0.69–1.16)	
Heavy work or carry heavy loads	12	12,284.4	0.57	(0.31–1.03)		0.59	(0.33–1.06)		0.81	(0.45–1.48)	
Vigorous physical activity during typical month in past 12 months											
Never/Rarely	202	162,322.2	1.00		<.0001	1.00		<.0001	1.00		0.02
1–3 times/month	149	116,280.6	0.78	(0.64–0.95)		0.77	(0.63–0.95)		0.84	(0.69–1.02)	
1–2 times/week	221	162,617.4	0.77	(0.63–0.92)		0.74	(0.62–0.89)		0.88	(0.73–1.04)	
3–4 times/week	244	195,365.4	0.70	(0.59–0.83)		0.66	(0.56–0.79)		0.85	(0.72–1.02)	
5+ times/week	179	150,077.2	0.60	(0.49–0.73)		0.56	(0.46–0.68)		0.77	(0.63–0.95)	
Frequency of participation in physical activities or sports during typical month between ages 15–18 years old											
Never/Rarely	160	129,904.3	1.00		0.22	1.00		0.16	1.00		0.22
1–3 times/month	81	71,174.2	0.89	(0.68–1.16)		0.90	(0.69–1.18)		0.91	(0.70–1.19)	
1–2 times/week	197	137,879.0	1.10	(0.90–1.35)		1.10	(0.90–1.35)		1.13	(0.92–1.39)	
3–4 times/week	238	184,023.4	1.06	(0.88–1.29)		1.09	(0.89–1.32)		1.10	(0.91–1.34)	
5+ times/week	340	237,940.6	1.09	(0.90–1.31)		1.10	(0.93–1.32)		1.09	(0.91–1.31)	

CI, confidence interval; RR, relative risk.

TABLE V – MULTIVARIATE ADJUSTED RR AND 95% CI FOR THE ASSOCIATION BETWEEN SEDENTARY BEHAVIORS AND ENDOMETRIAL CANCER INCIDENCE AMONG WOMEN WHO COMPLETED THE SECOND QUESTIONNAIRE, NIH-AARP DIET AND HEALTH STUDY

Sedentary behavior	No. cases	Person-years	RR[1]	95% CI	p for trend	RR[2]	95% CI	p for trend	RR[3]	95% CI	p for trend
Hours spent watching TV/videos during typical 24 hour period in past 12 months											
<3	108	167,321.7	1.00		0.002	1.00		0.0003	1.00		0.26
3–4	286	192,076.6	1.20	(1.00–1.44)		1.24	(1.03–1.49)		1.11	(0.92–1.33)	
5–6	117	70,739.4	1.30	(1.03–1.64)		1.36	(1.08–1.72)		1.08	(0.86–1.37)	
7+	48	24,935.6	1.53	(1.12–2.10)		1.66	(1.20–2.28)		1.21	(0.87–1.67)	
Hours spent sitting during typical 24 hour period in past 12 months											
<3	111	98,017.6	1.00		<.0001	1.00		<.0001	1.00		0.02
3–4	171	130,998.9	1.14	(0.90–1.45)		1.15	(0.90–1.46)		1.07	(0.83–1.37)	
5–6	203	123,234.0	1.48	(1.17–1.86)		1.48	(1.18–1.87)		1.31	(1.04–1.65)	
7+	164	102,864.6	1.54	(1.21–1.96)		1.56	(1.23–1.99)		1.35	(0.99–1.82)	

CI, confidence interval; RR, relative risk.

図表掲載箇所	P2144, Table3, P2145, Table5
概 要（800字まで）	本研究は、アメリカのThe NIH-AARP Diet and Health Studyに参加した閉経後の女性109,621名を対象に約8年間追跡調査し、身体活動や不活動と子宮内膜がん発症との関連を検討したものである。質問紙により、1)余暇身体活動を除く日常活動、2)高強度身体活動、3)職業活動や徒歩・自転車による通勤、4)余暇身体活動や家事活動、5)不活動についてそれぞれの頻度を尋ねた。過去1年間の典型的な月における高強度身体活動について、ほとんどない、1-3回/月、1-2回/週、3-4回/週、5回/週以上の5群に分類した。また、過去1年間の典型的な日における不活動について、テレビ視聴時間および座位時間が3時間未満、3-4時間、5-6時間、7時間以上の4群に分類した。高強度身体活動をほとんど行わない集団と比較すると、量反応的に子宮内膜がん発症リスクが減少し(Ptrend=0.02)、週当たり5回以上行う集団ではがん発症リスクが0.77(95%信頼区間:0.63-0.95)と有意に減少した。テレビ視聴時間と子宮内膜がん発症リスクとの関連については有意な差はみられなかったものの、座位時間とがん発症リスクについては、1日当たり3時間未満の集団と比較すると、量反応的にリスクが上昇し(Ptrend=0.02)、1日当たり5-6時間の集団で1.31(1.04-1.65)と有意にリスクの上昇がみられた。その他の因子について
結 論（200字まで）	閉経後の女性コホートにおける身体活動と子宮内膜がんの関連について、高強度身体活動の頻度が高い集団で発症リスクが抑えられ、特に肥満女性(BMI>25)における強力な保護効果が明らかとなった。また、肥満度とは独立して座位時間の延長ががん発症リスクを上昇させることが明らかとなった。
エキスパートによるコメント（200字まで）	身体活動基準の策定に用いられた研究の1つである。子宮内膜がんの発症と身体活動、不活動との関係を大規模な集団で検討した非常に重要な論文であり、高強度の身体活動の増大と座位時間の短縮の重要性を示唆している。座位時間は職業等によって大きく影響され、それは個人の意思に関わらないため、個人で改善可能な高強度の身体活動との相互作用についても今後検討されることが望まれる。

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Physical Activity and Risk of Cardiovascular Disease Events: Inflammatory and Metabolic Mechanisms

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ABSTRACT

HAMER, M., and E. STAMATAKIS. Physical Activity and Risk of Cardiovascular Disease Events: Inflammatory and Metabolic Mechanisms. *Med. Sci. Sports Exerc.*, Vol. 41, No. 6, pp. 1206–1211, 2009. **Purpose**: The biological mechanisms through which physical activity lowers the risk of cardiovascular disease (CVD) are incompletely understood. We examined the extent to which inflammatory/hemostatic factors (C-reactive protein and fibrinogen), metabolic factors (adiposity, total cholesterol, and HDL cholesterol), and hypertension mediate the association between physical activity and risk of CVD events. **Methods**: Data were collected from a nationally representative sample of 7881 men and women that were linked to a patient-based database of CVD hospital admissions and deaths up to September 2006. **Results**: A total of 226 incident CVD events (64 fatal) occurred over an average follow-up of 7.2 yr. The risk of CVD decreased in relation to physical activity groups according to current recommendations (at least 30 min of moderate activity five times per week or vigorous activity three times per week). The lowest risks for CVD were seen in participants meeting the recommendations through undertaking vigorous activity (hazard ratio = 0.47, 95% CI = 0.22–0.99), although being physically active below the guidelines also conferred protection (hazard ratio = 0.57, 0.42–0.77). Biological risk factors collectively explained between 39.4% and 22.6% of the cardioprotective effects of moderate and vigorous physical activity, respectively. Inflammation and hypertension tended to explain the largest proportion of variance. **Conclusions**: Participation in any physical activity, irrespective of meeting current guidelines, was associated with a lower risk of CVD. The inverse association between physical activity and CVD risk is partly mediated by biological risk factors. **Key Words:** CARDIOVASCULAR DISEASE, INFLAMMATION, ADIPOSITY, HYPERTENSION, EXERCISE, EPIDEMIOLOGY

Regular physical activity is widely accepted as playing a crucial role in cardiovascular disease (CVD) prevention (6,7,14,15,20,21). Current physical activity recommendations for the general population advocate the accumulation of at least 30 min of moderate physical activity on 5 $d \cdot wk^{-1}$ or vigorous activity three times per week (9), which is specifically associated with approximately a 30% reduction in risk of CVD death (13). The biological mechanisms through which physical activity lowers the risk of CVD are, however, incompletely understood. Exercise training studies demonstrate modest but consistent improvements in various risk factors such as blood pressure (4), HDL cholesterol (12), C-reactive protein (CRP), and other inflammatory markers (8,11). Recent evidence from the Women's Health prospective study showed that inflammatory and hemostatic risk factors and blood pressure made the largest contribution to the inverse association between physical activity and CVD events (17). To extend these findings, we examined the extent to which biological factors mediate the association between physical activity recommendations and CVD risk in a sample of men and women from the Scottish Health Survey (SHS).

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METHODS

Participants. The Scottish Health Survey (SHS) is a periodic survey (typically every 3–5 yr) that draws a nationally representative sample of the general population living in households. The sample was drawn using multistage stratified probability sampling with postcode sectors selected at the first stage and household addresses selected at the second stage. Different samples were drawn for each survey. The present analyses combined data from the 1998 and the 2003 SHS. Participants gave full informed consent to participate in the study, and ethical approval was obtained from the London Research Ethics Council.

Baseline assessment. Survey interviewers visited eligible households and collected data on demographics and health behaviors (physical activity, smoking, etc.). On a separate visit, nurses collected information on medical history (including medications) and took anthropometry variables (height, weight, and waist circumference) and blood samples from consenting adults. The overall response rate ranged between 60% and 76% for the different survey year, with approximately 40% of all eligible participants seeing a nurse. Detailed information on the survey method can be found elsewhere (22).

Exposure and outcome variables. Physical activity questions inquired about participation in the 4 wk before the interview. Frequency, duration, and intensity of participation were assessed across three domains of activity: leisure time sports (e.g., cycling, swimming, running, aerobics, dancing, and ball sports such as football and tennis), walking for any purpose, and domestic physical activity (e.g., heavy housework, home improvement activities, manual and gardening work). The coding of exercise intensity was based on the compendium of physical activities (1) (light, < 3 METs; moderate, 3–6 METs; vigorous, > 6 METs). The criterion validity of the SHS questionnaire is supported by the results of a recent study on 106 British adults from the general population (45 men), where the output of accelerometers (worn for two nonconsecutive weeks over a month period) was compared against the questionnaire output. The questionnaire appeared to be a valid measure of time spent in moderate to vigorous physical activity. Pearson correlation coefficients were 0.47 in men ($P = 0.03$) and 0.43 in women ($P = 0.02$), which is comparable in magnitude to other validation studies (5). In terms of test–retest reliability, the coefficients of time spent in moderate to vigorous physical activity were 0.89 for men ($P < 0.001$) 0.76 for women ($P < 0.001$).

The main outcome was first occurring fatal or nonfatal cardiovascular events (including myocardial infarction, coronary artery bypass, percutaneous coronary angioplasty, cerebrovascular events, and heart failure). This information was obtained from a patient-based database of CVD hospital admissions and deaths (Information Services Division, Scotland) that was linked to the surveys. The Information Services Division database has demonstrated 94% accuracy and 99% completeness when samples of computerized CVD records from the Scottish national database were compared with the original patient case notes. Classification of the underlying cause of death was based on information collected from the death certificate together with any additional information provided subsequently by the certifying doctor. Mortality from cardiovascular causes was coded according to *International Classification of Diseases, Ninth Revision* (*ICD-9*) (390–459) and *ICD-10* (I01–I99). Data on CVD hospital admissions were available between 1980 and September 2006, which allowed us to exclude participants with existing CVD at baseline.

Biological risk markers. Peripheral blood was collected in citrate and serum tubes and spun at room temperature. All blood samples were frozen at −70°C until assay. The analysis of CRP levels from serum was performed using the N Latex high-sensitivity CRP mono immunoassay on the Behring Nephelometer II analyzer. The limit of detection was 0.17 $mg{\cdot}L^{-1}$, and the coefficient of variation (CV) was less than 6% for this assay. Fibrinogen levels were determined using the Organon Teknika MDA 180 analyzer, using a modification of the Clauss thrombin clotting method, with a CV of less than 10%. Total and HDL cholesterol were measured using the DAX cholesterol oxidase assay method on an Olympus 640 analyzer. All analyses were carried out in the same laboratory according to Standard Operating Procedures by State Registered Medical Laboratory Scientific Officers. Existing hypertension was confirmed from self-reported doctor's diagnosis (an elevated blood pressure reading, >140/90 mm Hg, on three separate occasions). Obesity was defined as body mass index (BMI) ≥30 $kg{\cdot}m^{-2}$ and central obesity as waist >102 cm in men and >88 cm in women.

Statistical analysis. Cox proportional hazards models were used with months as the time scale to estimate the risk of cardiovascular events by physical activity exposure. For participants who survived, the data were censored to September 2006. Physical activity was categorized according to existing recommendations (9). Groups consisted of participants who were sedentary (referent), participants who were active but not meeting guidelines, participants who met the guidelines through participating in moderate to vigorous activity (e.g., at least 30 min of moderate activity five times or more per week or 3 d of moderate activity and 1 d of vigorous activity) and those that met guidelines through predominantly participating in vigorous activity (i.e., at least 30 min vigorous activity three times or more per week). The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure, although no appreciable violations were noted. Test for linear trend was obtained by entering the categorical variables as continuous parameters in the models. In the basic multivariate model, we adjusted for potential confounders, including age, gender, socioeconomic group (SEG) using the Registrar General Classification (I/II professional/intermediate, III skilled nonmanual/skilled manual, IV/V part-skilled/unskilled), and smoking (never, ex-smoker, current smoker). To test the extent to which biological risk factors mediated the association between physical activity and cardiovascular events, we grouped together CVD risk factors considered to be potential mediators on an *a priori* basis. This included an inflammatory/hemostatic factor (CRP and fibrinogen), a metabolic factor (adiposity measures, total cholesterol, and HDL cholesterol), and a blood pressure factor (diagnosed hypertension). We separately added these risk factors, one set at a

BASIC SCIENCES

TABLE 1. Descriptive characteristics of participants at baseline by physical activity exposure.

Variable	Sedentary, n = 1508	Active/below Guideline, n = 3510	Meeting Guideline,[a] n = 2027	Meeting Guideline,[b] n = 837
Total h·wk^{-1} MVPA	0	0.8*	3.3*†	3.4*†
% total time as VPA	NA	21.5	8.7	56.2
% total time as MPA				
Heavy domestic work	NA	59.3	37.2	22.8
Other	NA	19.2	54.1	21.0
Age, yr	54.8 ± 16.4	46.0 ± 15.2‡	43.2 ± 13.8‡	38.1 ± 14.1‡
Men, %	45.8	39.7*	49.0†	60.5‡
SEG, % grade I/II	24.6	35.4*	32.8‡	37.3*
Current smokers, %	35.1	30.9*	33.5	22.6‡
BMI, kg·m^{-2}	27.7 ± 5.6	26.8 ± 4.8*	26.1 ± 4.4*†	26.0 ± 4.1*†
Waist circumference, cm	91.8 ± 14.4	87.8 ± 13.3*	86.8 ± 12.5*†	86.3 ± 11.9*†
Total cholesterol, mmol·L^{-1}	5.71 ± 1.16	5.59 ± 1.17*	5.52 ± 1.25*	5.25 ± 1.07‡
HDL cholesterol, mmol·L^{-1}	1.45 ± 0.43	1.48 ± 0.41	1.50 ± 0.42*	1.48 ± 0.38
CRP, mg·L^{-1}	5.20 ± 8.50	3.30 ± 6.56*	2.54 ± 5.17*†	2.14 ± 4.36*†
Fibrinogen, g·L^{-1}	3.11 ± 0.81	2.86 ± 0.73*	2.72 ± 0.65*†	2.64 ± 0.64*†
% hypertension	25.8	13.9*	11.5*	8.9*†
% on CV medications[c]	19.5	6.9*	3.9*†	3.6*†

Values are presented as group mean ± SD.
[a] Participants that meet recommendation through moderate to vigorous activity.
[b] Participants that meet recommendation through predominantly vigorous activity.
[c] Includes beta blockers, diuretics, ACE inhibitors, calcium blockers, lipid lowering medications.
* Significant difference compared with sedentary reference group ($P < 0.05$).
† Significant difference compared with active/below guidelines group ($P < 0.05$).
‡ Different from all other groups ($P < 0.05$).
MVPA, moderate to vigorous physical activity.

time, into the basic model. Finally, we performed a fully adjusted analysis that included all CVD risk factors simultaneously. The proportion of CVD risk reduction explained by each set of CVD risk factors was computed as follows: $(HR_{basic\ model} - HR_{adjusted}) / HR_{basic\ model} - 1) \times 100$ (17). All blood variables were included as categorical variables—cholesterol, HDL cholesterol, and fibrinogen as tertiles—and CRP were categorized according to previously defined cut points (19), representing low (<1 mg·L^{-1}), medium (1 to <3 mg·L^{-1}), and high-risk (≥3 mg·L^{-1}) groups. Analyses were also run entering risk markers as continuous values, although this did not appreciably alter the results. We used analysis of variance with Scheffe *post hoc* tests and chi-square tests to examine univariable relationships of the confounders with the exposure and the outcome variables. In preliminary analysis, we fitted a gender by physical activity term into the models, although there was no evidence of any interaction. We therefore present all results for men and women combined. All analyses were performed using the Statistical Package for the Social Sciences for Windows (version 14; SPSS Inc, Chicago, IL), and all tests of statistical significance were based on two-sided probability.

RESULTS

Complete data were available in 8037 participants, although participants with existing CVD were removed from the analyses (n = 156), leaving a final sample size of 7881 (45.9% men, aged 46.4 ± 15.6 yr). There were a total of 226 incident CVD events (64 fatal) over an average of 7.2 yr of follow-up. Coronary heart disease accounted for 61% of nonfatal events and 66% of fatal CVD events. Thirty-six percent of participants met the physical activity guidelines and 19% reported no physical activity at all. Sedentary

TABLE 2. The extent to which biological risk factors explain the association between recommended physical activity levels and cardiovascular events.

Model		Sedentary	Active/below Guideline	Meeting Guideline[a]	Meeting Guideline[b]	P for Trend
	Events/N	99/1508	76/3510	43/2027	8/837	
	Event rate	6.6%	2.2%	2.1%	1.0%	
Model 1						
HR (95% CI)		1.00	0.57 (0.42–0.77)	0.67 (0.46–0.98)	0.47 (0.22–0.99)	0.002
Model 2						
HR (95% CI)		1.00	0.60 (0.44–0.82)	0.73 (0.50–1.07)	0.53 (0.25–1.11)	0.011
% explained			7.0	18.2	13.2	
Model 3						
HR (95% CI)		1.00	0.58 (0.43–0.79)	0.72 (0.49–1.05)	0.52 (0.25–1.09)	0.005
% explained			2.3	15.2	9.4	
Model 4						
HR (95% CI)		1.00	0.62 (0.45–0.84)	0.74 (0.51–1.09)	0.52 (0.25–1.08)	0.015
% explained			11.6	21.2	9.4	
Fully adjusted						
HR (95% CI)		1.00	0.64 (0.47–0.87)	0.80 (0.54–1.17)	0.59 (0.28–1.23)	0.034
Total % explained			16.3	39.4	22.6	

Model 1 adjusted for age, gender, social economic group, and smoking.
Model 2 adjusted for age, gender, social economic group, smoking + CRP, and fibrinogen.
Model 3 adjusted for age, gender, social economic group, smoking + obesity, central obesity, cholesterol, and HDL cholesterol.
Model 4 adjusted for age, gender, social economic group, and smoking + doctor-diagnosed hypertension.

participants were older, were more likely to be of lower social status and be smokers, and have higher levels of biological risk factors than the other groups (Table 1). Participants who met physical activity guidelines also had lower risk factors compared with the active/below guidelines group, with the exception of hypertension and total cholesterol, where only the vigorously active differed (see Table 1). All physically active groups demonstrated a lower relative risk of cardiovascular events during follow-up after basic adjustments for age, gender, SEG, and smoking (Table 2), but the vigorously active demonstrated the greatest risk reduction with an event rate of 1%. Medication use was slightly higher in the active/below guidelines group compared with those meeting the guidelines, although additional adjustment for medications did not appreciably modify the risk of CVD events in this group (hazard ratio [HR] = 0.61, 95% CI = 0.45–0.83). When we examined the extent to which biological risk factors mediated the association between physical activity and CVD events, each factor appeared to explain a modest amount that differed according to the physical activity category (see Table 2). For example, in the vigorous activity group, all biological risk factors collectively explained 22.6% of the association in the fully adjusted model (inflammatory/hemostatic factors explained 13.2%, metabolic factors 9.4%, hypertension 9.4%) compared with the active but below guidelines group where these factors only explained a total of 16.3% (inflammatory/hemostatic factors explained 7.0%, metabolic factors 2.3%, hypertension 11.6%).

Several of the biological risk markers were independently associated with CVD events, which included HDL cholesterol >1.5 mmol·L^{-1} (HR = 0.66, 95% CI = 0.47–0.94, P = 0.022), CRP ≥3 mg·L^{-1} (HR = 1.73, 95% CI = 1.11–2.70, P = 0.016), and hypertension (HR = 2.04, 95% CI = 1.55–2.71, P < 0.001). In Table 3, we present further analyses where participants were stratified according to physical activity (none vs any) and presence of risk factors (CRP ≥3 mg·L^{-1}, hypertension, HDL <1.5 mmol·L^{-1}, and obesity). The results show that any physical activity was associated with lower CVD risk despite the presence of several risk factors, including inflammation, low HDL, obesity, and smoking. In contrast, participants that were physically active but diagnosed with hypertension did not have a lower risk of CVD compared with sedentary hypertensives, which suggests that physical activity that reduces hypertension is critical for cardiovascular prevention. Overall, physically active participants with no risk factors demonstrated the lowest CVD risk.

There were a total of 254 deaths during follow-up, and there was a relationship between risk of all-cause mortality and physical activity levels in models adjusted for age, gender, SEG, and smoking, active but not meeting guidelines (HR = 0.55, 95% CI = 0.41–0.71), and meeting guidelines through moderate (HR = 0.36, 95% CI = 0.23–0.56) or vigorous activity (HR = 0.29, 95% CI = 0.11–0.80). The inclusion of all biological risk factors in the models mediated these associations by approximately 6%.

DISCUSSION

The main aim of the present study was to quantify the extent to which biological risk factors mediate the association between physical activity recommendations and CVD events, which has not been widely examined. Our data suggest that the biological factors explained between 39% and 22% of the cardioprotective effects of moderate and vigorous physical activity, respectively. The total amount of variance explained is lower than that in a previous study of US women where biological risk factors explained 59% of the activity related reduction in CVD, with inflammation/hemostatic biomarkers making the largest contribution to lowered risk, followed by blood pressure, lipids, and BMI (17). We demonstrated a similar trend showing that inflammatory biomarkers and hypertension made the largest contribution to lowered risk. However, we did not measure as

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TABLE 3. Stratified analyses according to physical activity and presence of risk factors in relation to incident cardiovascular events.

	Sedentary		Physically Active[a]	
Risk factor	+Risk Factor	No Risk Factor	+Risk Factor	No Risk Factor
Inflammation (CRP ≥3 mg·L^{-1})				
Model 1 HR (95% CI)	1.00	0.55 (0.37–0.81)*	0.49 (0.33–0.72)*	0.34 (0.24–0.48)*
Model 2 HR (95% CI)	1.00	0.65 (0.43–0.97)*	0.53 (0.36–0.78)*	0.42 (0.29–0.61)*
Physician-diagnosed hypertension				
Model 1 HR (95% CI)	1.00	0.66 (0.45–0.98)*	0.79 (0.52–1.22)	0.29 (0.20–0.43)*
Model 2 HR (95% CI)	1.00	0.76 (0.49–1.19)	0.83 (0.54–1.29)	0.36 (0.23–0.57)*
HDL cholesterol (<1.5 mmol·L^{-1})				
Model 1 HR (95% CI)	1.00	0.46 (0.30–0.70)*	0.46 (0.33–0.64)*	0.31 (0.21–0.46)*
Model 2 HR (95% CI)	1.00	0.48 (0.31–0.74)*	0.51 (0.37–0.71)*	0.37 (0.25–0.55)*
Obesity (BMI ≥30 kg·m^{-2})				
Model 1 HR (95% CI)	1.00	0.84 (0.55–1.29)	0.55 (0.33–0.92)*	0.43 (0.28–0.65)*
Model 2 HR (95% CI)	1.00	1.20 (0.78–1.84)	0.64 (0.38–1.08)	0.68 (0.44–1.05)
Current cigarette smoker				
Model 1 HR (95% CI)	1.00	0.33 (0.22–0.48)*	0.42 (0.28–0.64)*	0.23 (0.16–0.32)*
Model 2 HR (95% CI)	1.00	0.33 (0.22–0.49)*	0.47 (0.31–0.71)*	0.26 (0.19–0.38)*

Model 1 adjusted for age and gender.
Model 2 adjusted for age, gender, medication use, and mutually for the other risk factors.
[a] Physical activity was defined as at least 30 min·wk^{-1} of any type of activity.
* Significantly different from referent category (P < 0.05).

many biomarkers that might be a reason for the considerably lower amount of variance explained in the present study. In a large cohort of UK participants, adjustment for traditional CVD risk factors (blood pressure, diabetes, BMI, and lipids) and CRP only slightly (less than 10%) attenuated the association between physical activity and risk of coronary artery disease (2). Thus, unmeasured mediators such as endothelial function (10), insulin sensitivity (16), and mental health (3) may also play a role.

There is surprisingly little epidemiological evidence for the cardioprotective effects of physical activity in relation to current recommendations. In a large prospective study of over 200,000 participants, those meeting the physical activity recommendations had the lowest risk of CVD, although those that met the recommendations through vigorous activity demonstrated slightly lower risks (32%) compared with those meeting recommendations through moderate activity (27%) (13). Our findings are consistent with these results and additionally show that participants meeting recommendations through vigorous activity had lower biological risk markers, for example, 59% lower levels of CRP than the sedentary. Being active below the recommendations also appeared to confer benefit for protection against CVD and was actually associated with a similar event rate compared with participants meeting guidelines through moderate activity (2.2% vs 2.1% for active/below guidelines and active at moderate level, respectively). This finding might be possibly explained by residual confounding from unmeasured variables. Participants meeting guidelines through moderate activity consisted of a slightly higher proportion of cigarette smokers, although smoking did not appear to appreciably diminish the protective effects of physical activity (see Table 3), which appears to be at odds with recently published data (18). However, the contribution of biological risk factors to the activity related reduction in CVD was greater for those participating in moderate to vigorous activity. Interestingly, exercise intensity has not been associated with any of the favorable training effects on HDL cholesterol and blood pressure (4,12), although insufficient studies have been performed in relation to inflammatory/hemostatic factors. It is possible that a threshold effect may exist for some risk factors or that there is an intensity versus volume trade-off.

Several limitations of the present study warrant consideration. We have only assessed physical activity once at baseline; thus, we cannot exclude the possibility that changes in activity over time could have influenced our results. Physical activity, hypertension status, and medication use were assessed by self-report; thus, it is possible that more precise assessment of these factors may have affected the results. Given that lower levels of physical activity could reflect subclinical disease, we cannot discount reverse causality. We did, however, attempt to control for this potential bias by removing participants with existing clinical CVD events at baseline. In additional analyses, we also removed participants reporting angina symptoms (n = 150), although this did not appreciably alter the results (data not shown). We were unable to assess all of the potential biological mediators of physical activity, and these may have accounted for additional unexplained variance. However, the availability of clinically confirmed CVD events, extensive clinical biomarkers, and use of a nationally representative sample from Scotland are significant strengths of this study.

In summary, we have observed that the inverse association between physical activity and CVD risk is partly mediated by biological risk factors including inflammatory/hemostatic factors (CRP and fibrinogen), metabolic factors (adiposity, total cholesterol, and HDL cholesterol), and hypertension.

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対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		( )		コホート研究
	性別	男女混合	( )		( )		( )
	年齢	46.4(±15.6)歳	[redacted]		( )		前向き研究
	対象数	5000～10000			( )		( )
調査の方法	質問紙	( )					
アウトカム	予 防	心疾患予防	なし	なし	なし	死亡	( )
	維持・改善	なし	なし	なし	なし	( )	( )

図 表

TABLE 2. The extent to which biological risk factors explain the association between recommended physical activity levels and cardiovascular events.

Model		Sedentary	Active/below Guideline	Meeting Guideline[a]	Meeting Guideline[b]	P for Trend
	Events/N	99/1508	76/3510	43/2027	8/837	
	Event rate	6.6%	2.2%	2.1%	1.0%	
Model 1						
HR (95% CI)		1.00	0.57 (0.42–0.77)	0.67 (0.46–0.98)	0.47 (0.22–0.99)	0.002
Model 2						
HR (95% CI)		1.00	0.60 (0.44–0.82)	0.73 (0.50–1.07)	0.53 (0.25–1.11)	0.011
% explained			7.0	18.2	13.2	
Model 3						
HR (95% CI)		1.00	0.58 (0.43–0.79)	0.72 (0.49–1.05)	0.52 (0.25–1.09)	0.005
% explained			2.3	15.2	9.4	
Model 4						
HR (95% CI)		1.00	0.62 (0.45–0.84)	0.74 (0.51–1.09)	0.52 (0.25–1.08)	0.015
% explained			11.6	21.2	9.4	
Fully adjusted						
HR (95% CI)		1.00	0.64 (0.47–0.87)	0.80 (0.54–1.17)	0.59 (0.28–1.23)	0.034
Total % explained			16.3	39.4	22.6	

Model 1 adjusted for age, gender, social economic group, and smoking.
Model 2 adjusted for age, gender, social economic group, smoking + CRP, and fibrinogen.
Model 3 adjusted for age, gender, social economic group, smoking + obesity, central obesity, cholesterol, and HDL cholesterol.
Model 4 adjusted for age, gender, social economic group, and smoking + doctor-diagnosed hypertension.

図表掲載箇所	P.1208, Table2
概 要 (800字まで)	本研究は、The Scottish Health Survey (SHS)に参加した男女7,881名を対象に平均7.2年間の追跡調査を行い、身体活動量と心血管疾患発症リスクとの関連を検討したものである。質問紙を用い、過去1ヶ月間における身体活動の頻度、期間、強度を3つの領域について聞き取った。1)余暇時間活動(サイクリング、水泳、ランニング、エアロビクス、球技など)、2)目的に応じた歩行、3)家事などの生活活動(家の修繕作業、手作業やガーデニングなど)。この質問紙を基に、座位中心で不活動、ガイドラインの推奨量に達していないが活動的、ガイドライン推奨量に達しており中強度活動中心、ガイドライン推奨量に達しており高強度活動中心の4群に分類した。座位中心で不活動な集団と比較すると、それぞれの集団の心血管疾患発症リスクは、0.64(95%信頼区間:0.470.87)、0.80(0.54-1.17)、0.59(0.28-1.23)と量反応的に減少した。また、生化学的なリスクファクター(炎症マーカーや血圧、代謝因子など)は、中強度活動中心の身体活動を行うことと高強度活動中心の身体活動による心保護作用のそれぞれ39%、22%を説明していた。また、総死亡リスクに関しては、座位中心の集団と比較するとそれぞれ、0.55(0.41-0.71)、0.36(0.23-0.56)、0.29(0.11-0.80)と全ての群で有意にリスクが減少した。
結 論 (200字まで)	ガイドラインの推奨量に達していなくても、活動的であるとこで心血管疾患発症リスクを軽減させることが明らかとなった。
エキスパートによるコメント (200字まで)	身体活動基準の策定に用いられた研究の1つである。身体活動量と心血管疾患発症リスクや総死亡との関係を検討した論文で、身体活動量の増加と心血管疾患の発症、総死亡との間に量反応関係を認めている。またそのメカニズムとして、炎症マーカーや血圧、代謝因子が関与していることを示唆しており、身体活動と疾患発症や死亡との関連を考えるうえで重要な知見を与えている。

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Research article

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Relationship between physical activity and stiff or painful joints in mid-aged women and older women: a 3-year prospective study

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Abstract

This prospective study examined the association between physical activity and the incidence of self-reported stiff or painful joints (SPJ) among mid-age women and older women over a 3-year period. Data were collected from cohorts of mid-age (48–55 years at Time 1; $n = 4,780$) and older women (72–79 years at Time 1; $n = 3,970$) who completed mailed surveys 3 years apart for the Australian Longitudinal Study on Women's Health. Physical activity was measured with the Active Australia questions and categorized based on metabolic equivalent value minutes per week: none (<40 MET.min/week); very low (40 to <300 MET.min/week); low (300 to <600 MET.min/week); moderate (600 to <1,200 MET.min/week); and high (1,200+ MET.min/week). Cohort-specific logistic regression models were used to examine the association between physical activity at Time 1 and SPJ 'sometimes or often' and separately 'often' at Time 2. Respondents reporting SPJ 'sometimes or often' at Time 1 were excluded from analysis. In univariate models, the odds of reporting SPJ 'sometimes or often' were lower for mid-age respondents reporting low (odds ratio (OR) = 0.77, 95% confidence interval (CI) = 0.63–0.94), moderate (OR = 0.82, 95% CI = 0.68–0.99), and high (OR = 0.75, 95% CI = 0.62–0.90) physical activity levels and for older respondents who were moderately (OR = 0.80, 95% CI = 0.65–0.98) or highly active (OR = 0.83, 95% CI = 0.69–0.99) than for those who were sedentary. After adjustment for confounders, these associations were no longer statistically significant. The odds of reporting SPJ 'often' were lower for mid-age respondents who were moderately active (OR = 0.71, 95% CI = 0.52–0.97) than for sedentary respondents in univariate but not adjusted models. Older women in the low (OR = 0.72, 95% CI = 0.55–0.96), moderate (OR = 0.54, 95% CI = 0.39–0.76), and high (OR = 0.61, 95% CI = 0.46–0.82) physical activity categories had lower odds of reporting SPJ 'often' at Time 2 than their sedentary counterparts, even after adjustment for confounders. These results are the first to show a dose–response relationship between physical activity and arthritis symptoms in older women. They suggest that advice for older women not currently experiencing SPJ should routinely include counseling on the importance of physical activity for preventing the onset of these symptoms.

Introduction

Arthritis is a musculoskeletal condition of the joints. In Australia, it is a leading cause of pain and disability [1], affecting 3.4 million adults or 17% of the population [2]. Estimates are that by 2020 arthritis will affect 4.6 million Australians, or 20% of the adult population [2]. The current prevalence in Australia is slightly less than that in the United States, where 21% of the population has arthritis [3], making it the most prevalent chronic condition for mid-age and older people in the United States [4]. As in the United States, more Australian women than men have arthritis [2,4,5], and the incidence and prevalence of arthritis increase with age [4-6]. As the proportion of older people in both countries continues to rise, more individuals, particularly women, will be at risk of developing arthritis, and the burden of this disease will continue to increase. Identifying modifiable risk factors for the effects of arthritis is crucial to the prevention of its associated disability, especially in mid-age women and in older women.

Physical activity has been identified as a potentially modifiable risk factor in prospective population-based studies assessing risk factors for arthritis among women [5,7-9]. The results from

ALSWH = Australian Longitudinal Study on Women's Health; BMI = body mass index; CI = confidence interval; OR = odds ratio; MET = metabolic equivalent value; SPJ = stiff or painful joints.

these studies, however, are equivocal. One study [9] found walking to be protective against radiographic evidence of arthritis in women (defined as joint space narrowing), whereas others [5,7] found no association between leisure-time physical activity and risk of self-reported arthritis in women. In contrast, being in the highest quartile of total daily physical activity in the Framingham cohort study [8] *increased* the risk of incident radiographic arthritis in women in the short term (8 years), although not over a longer time period (20–40 years). Results of studies assessing risk factors for arthritis in male and female athletes indicate increased risk among competitive elite athletes in some sports, such as soccer, football, and rugby [10-13]. Together, the findings of these studies suggest that high levels of some competitive athletic sports increase the risk of arthritis but that moderate to vigorous leisure-time physical activities in nonathletes may have no association or reduce risk of the disease. Few studies have examined the association between physical activity and risk of arthritis in nonathletes, however, so this association is unclear.

The Australian Longitudinal Study on Women's Health (ALSWH) provides an opportunity to evaluate the prospective association between physical activity and increased risk of arthritis symptoms in two large cohorts of women. This prospective cohort study includes questions about walking and about moderate-intensity and vigorous-intensity physical activities. It also asks about physician diagnosis of arthritis and about women's experiences of a range of symptoms, including 'stiff or painful joints.' As there are more than 100 types of arthritis, all characterized by pain, stiffness, and disability [14], the self-report of these symptoms allows for the identification of women who have early and mild symptoms of arthritis, but have not yet been diagnosed with the disease. This is important because women with symptoms of arthritis do not always seek a professional diagnosis: estimates from the US National Health Interview Survey suggest that 16% of adults reporting arthritis have never seen a physician about this condition [15]. Indeed, many arthritis sufferers treat their symptoms with nonprescription medications or rely on alternative therapies [16-19]. There is also evidence to suggest that arthritis symptoms predict disability more strongly than radiological changes, which may not always be apparent in the early stages of the disease [20]. In exploring risk factors that contribute to the development of arthritis, the assessment of arthritis symptoms, therefore, may provide a more relevant and accurate indicator of the onset of the disease.

The aim of this study was to explore the association between physical activity and incidence of self-reported 'stiff or painful joints' in the mid-age and older cohorts of the ALSWH. Understanding the role of this potentially modifiable risk factor could be important in the development of strategies for the prevention of the disabling symptoms associated with arthritis in women.

Materials and methods

The ALSWH sample

The ALSWH is an ongoing study of the health and well-being of Australian women. As reported elsewhere [21], in 1996 random samples of women aged 18–23 years ('young'), 45–50 years ('mid-age'), and 70–75 years ('older') were drawn from the national Medicare health insurance database, which includes all Australian residents as well as immigrants and refugees. Women from rural and remote areas were intentionally over-represented. Data from the 2001 (Time 1 (T1)) and 2004 (Time 2 (T2)) surveys of the mid-age cohort and from the 1999 (T1) and 2002 (T2) surveys of the older cohort were used in the analyses reported here. The study was approved by the University of Newcastle Ethics Committee. Informed consent was received from all respondents. More details about the study can be found online [22].

Assessment of stiff or painful joints

Respondents were asked whether they had experienced 'stiff or painful joints' in the past 12 months. Response options of 'never,' 'rarely,' 'sometimes,' or 'often' were dichotomized into 'sometimes or often,' or 'never or rarely' and also into 'often' or 'not often' (never, rarely, sometimes) to examine the sensitivity of the categorization chosen for determining the women at risk for incident joint pain. It was hypothesized that the women experiencing stiff or painful joints 'often' were those most likely to be suffering early symptoms of arthritis, and therefore physical activity would be more strongly associated with the onset of experiencing symptoms 'often' than 'sometimes or often.'

Because the validity of this item had not been examined, its predictive validity was assessed by exploring its ability to predict self-reported physician-diagnosed arthritis and physical functioning. Arthritis was assessed at T2 by asking 'In the last 3 years, have you been diagnosed with or treated for arthritis (including osteoarthritis, rheumatoid arthritis)?' [23]. Respondents who reported at T1 that they had been diagnosed with or treated for arthritis by a physician were excluded. In univariate logistic regression models, the odds of reporting arthritis at T2 were significantly increased among the mid-age women who reported stiff or painful joints 'sometimes or often' at T1 (odds ratio (OR) = 2.48, 95% confidence interval (CI) = 2.16–2.83, $P < 0.001$) and, similarly, among those who reported these symptoms 'often' (OR = 2.56, 95% CI = 2.13–3.09, $P < 0.001$). In the older women, reporting stiff or painful joints 'sometimes or often' also increased the odds of reporting arthritis (OR = 3.94, 95% CI = 3.38–4.58, $P < 0.001$), and reporting these symptoms 'often' increased the odds even more (OR = 5.28, 95% CI = 4.23–6.61, $P < 0.001$).

Physical function was measured with the Physical Function subscale of the Medical Outcomes Study Short Form [24]. A lower score on the subscale represents lower physical functioning. In univariate linear regression models, reporting stiff or painful joints 'sometimes or often' at T1 was associated with significantly lower physical function scores at T2 in both the mid-age women (B = -7.78, 95% CI = -8.58 to -6.99, P < 0.001) and older women (B = -14.15, 95% CI = -15.92 to -12.38, P < 0.001). Reporting the symptoms 'often' was associated with even lower physical function scores in the mid-age women (B = -14.37, 95% CI = -15.69 to -13.04, P < 0.001) and older women (B = -23.57, 95% CI = -26.42 to -20.73, P < 0.001).

Assessment of physical activity

Survey items to assess physical activity were based on those developed for the Active Australia survey in 1997, a validated and reliable measure [25-27]. The frequency and time duration (in at least 10-min sessions) in the previous week spent walking briskly (for travel or leisure), in moderate-intensity leisure-time physical activities, and in vigorous leisure-time physical activities were reported. A physical activity score was calculated as the sum of the products of total time in each of the three categories of activity and the metabolic equivalent value (MET) assigned to each category [28,29]: (walking minutes × 3.0 METs) + (moderate physical activity minutes × 4.0 METs) + (vigorous physical activity minutes × 7.5 METs), in accordance with the Compendium of Physical Activities [30]. Physical activity was then categorized based on total MET minutes per week: none (<40 MET.min/week); very low (40 to <300 MET.min/week); low (300 to <600 MET.min/week); moderate (600 to <1,200 MET.min/week); and high (1,200+ MET.min/week).

Assessment of potential confounding factors

A list of variables considered potential confounders in the relationship between physical activity and stiff or painful joints was derived from previous studies [31] (see Table 1). Area of residence categories were derived from postcodes. To measure the number of chronic diseases, respondents were asked whether they had been told by a doctor in the previous 3 years that they had any of the diseases listed. The list of diseases was adapted from the Australian 1989–1990 National Health Survey [23]. Diagnosis of depression was determined by a single item modified from the Australian 1989–1990 National Health Survey [23]: 'In the last 3 years, have you been told by a doctor that you have depression?' ('yes' or 'no').

Height without shoes and weight without clothes or shoes were reported, and the body mass index (BMI) was calculated as weight divided by height squared. The BMI was then categorized as underweight (BMI <20 kg/m^2), healthy weight (BMI ≥20 and <25 kg/m^2), overweight (BMI ≥25 and <30 kg/m^2), or obese (BMI ≥ 30 kg/m^2) in accordance with the Australian National Health and Medical Research Council classification system [32]. The World Health Organization classification of a BMI less than 18.5 kg/m^2 as 'underweight' [33] was not used because few in the samples had a BMI meeting this criterion at the first ALSWH survey.

Data analysis

The initial analysis samples were mid-age women and older women who did not report having stiff or painful joints 'sometimes' or 'often' at T1. From this group, respondents were excluded if they had missing physical activity data at T1 or had missing stiff or painful joint data at T2. Differences between women included in our analysis and those excluded were examined using Pearson's chi-square tests for categorical variables and an independent *t* test for the one continuous variable (age). Univariate associations between each potential confounding variable at T1 and the two outcomes (having stiff or painful joints 'sometimes or often;' having these symptoms 'often') at T2 were computed separately for each cohort. Variables having a statistically significant association with at least one outcome in at least one cohort (P < 0.05) were included in multivariable logistic regression models computed to evaluate the association between physical activity and stiff or painful joints in each cohort, after adjusting for the other factors. For each confounding variable for which some respondents' data were missing, a missing category was included in all analyses to maintain as large a sample as possible, and the missing category was compared with the reference category in the same way the other categories were compared with the reference category. Interactions between physical activity and each potential confounding variable were examined, but none were significant. No interaction terms were therefore included in the final models. Odds ratios and 95% confidence intervals were computed for all models.

Results

Samples

In total, 5,650 (52.2%) mid-age women and 5,207 (54.9%) older women reported having stiff or painful joints 'never' or 'rarely' at T1. Of these, 475 mid-age women and 843 older women were excluded because they did not participate in the T2 survey. Another 208 mid-age women and 199 older women were excluded because they had missing values for physical activity at T1. After the additional exclusion of women who did not report whether they had painful or stiff joints at T2 (187 mid-age women and 195 older women excluded), data from 4,780 mid-age women and 3,970 older women were included in these analyses.

Meaningful and statistically significant differences were seen between those who were included and those who were excluded from the analysis (see Table 1). In both cohorts, women who were excluded from the analysis were less physically active and had lower levels of education (P < 0.001). These women were also were more likely to live in a large town, to have been born in a non-English-speaking country, to have four or more chronic diseases, and to be smokers than women who were included (P < 0.05). Older women who were excluded were also more likely to have depression (P < 0.001).