Table 1

Characteristics of respondents who reported stiff or painful joints 'never' or 'rarely' at Time 1

Variable	Mid-age women (n = 5,650)			Older women (n = 5,207)		
	Respondents included n = 4,780)	Respondents excluded[a] (n = 870)	P value[b]	Respondents included (n = 3,970)	Respondents excluded[a] (n = 1,237)	P value[b]
Age (years, mean ± standard deviation)	52.53 ± 1.49	52.57 ± 1.52	0.366	75.39 ± 1.51	75.60 ± 1.51	<0.001
Education (%)			<0.001			<0.001
Less than high school	13.5	18.7		26.8	34.7	
Some high school	47.8	50.9		52.7	47.7	
Completed high school	20.5	17.4		11.6	9.2	
Trade certificate/university degree	17.4	12.0		4.7	2.3	
Missing	0.9	1.0		4.3	6.1	
Area of residence (%)			<0.001			<0.001
Urban	38.1	43.3		40.2	39.8	
Large town	13.5	11.4		11.6	14.1	
Small town/remote area	47.1	42.4		46.6	42.6	
Missing	1.3	2.9		1.6	3.6	
Country of birth (%)			0.001			0.003
Australia	74.6	70.9		74.7	71.9	
Other English-speaking	14.0	12.9		12.4	11.2	
Non-English speaking	7.9	12.1		6.8	9.3	
Missing	3.5	4.1		6.0	7.7	
Depression (%)			0.023			<0.001
No	91.6	89.2		94.3	87.6	
Yes	8.4	10.8		3.4	7.6	
Number of chronic diseases (%)			0.037			<0.001

Table 1 *(Continued)*

Characteristics of respondents who reported stiff or painful joints 'never' or 'rarely' at Time 1

0	55.8	52.6		32.0	42.5
1	31.0	30.5		37.0	20.3
2	9.7	11.8		20.0	18.0
3	2.7	3.7		7.6	10.5
4 or more	0.8	1.4		3.3	8.7
Smoking status (%)			<0.001			0.006
Never	55.4	54.8		61.0	58.5
Former	32.2	26.1		27.6	26.8
Current	12.2	18.3		4.9	7.4
Missing	0.2	0.8		6.4	7.4
Body mass index (%)			<0.001			<0.001
<20 kg/m²	5.1	5.9		3.4	4.4
≥ 20 and <25 kg/m²	41.9	38.6		48.4	46.1
≥ 25 and <30 kg/m²	28.0	26.3		26.5	23.8
≥ 30 kg/m²	17.4	16.8		9.7	9.1
Missing	7.5	12.4		12.0	16.6
Physical activity (%)			<0.001			<0.001
None (<40 MET.min/week)	14.9	22.2		24.4	40.1
Very low (40 to <300 MET.min/week)	18.4	19.5		14.0	14.2
Low (300 to <600 MET.min/week)	18.0	15.6		22.7	14.0
Moderate (600 to <1,200 MET.min/week)	22.5	19.6		15.8	12.2
High (1,200+ MET.min/week)	26.2	23.1		23.1	19.6

MET, metabolic equivalent value. [a]Women were excluded if they did not provide data on physical activity at Time 1 or did not provide data on symptoms of stiff or painful joint at Time 2. The 243 mid-age women and 987 older women who were missing physical activity data are not included in the percentage of excluded respondents in each physical activity category. [b]P value is for the difference between women included and those excluded from the analysis.

Descriptive characteristics of samples

The mid-age women were aged 48–55 years at T1. Most reported not completing 12 years of high school, reported living in a small rural town or remote area, reported being born in Australia, reported having one or no chronic diseases, reported not having a diagnosis of depression, and reported never having been a smoker. Almost one-half were overweight or obese (45.4%), and almost one-half (48.7%) met the national Australian physical activity guidelines by accruing 600 or more MET minutes of physical activity per week [34], which is equivalent to 150 minutes or more per week of moderate-intensity physical activity. Slightly more than one-third (36.4%) reported very low to low levels of physical activity (40–600 MET.min/week), which equates to 10–149 minutes per week of moderate-intensity physical activity. The remaining 14.9% were sedentary (<40 MET.min/week): they did not report even 10 minutes of moderate-intensity physical activity per week. At T2, 41.4% of the women reported 'never' having stiff or painful joints, 17.9% reported them 'rarely,' 30.8% reported them 'sometimes,' and 9.9% reported them 'often.'

The older women were aged 72–79 years at T1. As for the mid-age women, most reported not completing 12 years of high school, reported living in a small rural town or remote area, reported being born in Australia, reported not having a diagnosis of depression, reported having one or no chronic diseases, and reported never having been a smoker. Fewer older women (36.2%) than mid-age women were overweight or obese, and fewer were physically active. Less than one-half of the older women met the national physical activity guidelines (38.9%), and a similar percentage (38.7%) reported very low to low levels of physical activity. One-quarter (24.4%) of the older women were sedentary. At T2, 45.9% reported stiff or painful joints 'never', 12.2% reported them 'rarely,' 30.0% reported them 'sometimes,' and 11.8% reported them 'often.'

Mid-age women

In univariate analysis, the odds of reporting stiff or painful joints 'sometimes or often' at T2 were significantly lower for mid-age women in the 'low' ($P = 0.011$), 'moderate' ($P = 0.043$), and 'high' ($P = 0.003$) physical activity categories at T1 than for those who were sedentary (see Table 2). The odds of reporting stiff or painful joints 'often' were significantly lower only for respondents in the 'moderate' physical activity category ($P = 0.032$). After adjusting for all variables that were significantly associated with stiff or painful joints in the univariate analyses, associations between physical activity and self-reported stiff or painful joints in the mid-age women were attenuated and no longer statistically significant ($P > 0.05$; see Table 2).

Older women

In univariate analysis, older women in the 'moderate' ($P = 0.033$) and 'high' ($P = 0.040$) physical activity categories at T1 had significantly lower odds of reporting stiff or painful joints 'sometimes or often' at T2 than those in the 'none' category.

Significantly lower odds of reporting stiff or painful joints 'often' were found for those in the 'low' ($P = 0.001$), 'moderate' ($P < 0.001$) and 'high' ($P < 0.001$) physical activity categories (see Table 3).

As was the case for the mid-age women, the association between physical activity and self-reported stiff or painful joints 'sometimes or often' was no longer statistically significant ($P = 0.252$) in the multivariable analysis in the older cohort. The odds for reporting stiff or painful joints 'often,' however, remained significantly lower for older women in the 'low' ($P = 0.024$), 'moderate' ($P < 0.001$) and 'high' ($P = 0.001$) physical activity categories than for those in the 'none' category (see Table 3).

Discussion

Our aim was to explore the association between physical activity and the incidence of stiff or painful joints in cohorts of mid-age women and older women. Our main findings were that physical activity did not increase or decrease the odds of self-reported stiff or painful joints 'often' among the mid-age women; however, 'low,' 'moderate,' and 'high' levels of physical activity among the older women were associated with decreased odds of developing stiff or painful joints 'often' over 3 years, even after adjusting for confounding variables. This last finding indicates that, among older women who do not have or rarely have stiff or painful joints, participation in at least 75 minutes per week of moderate-intensity physical activity may be protective against complaints of 'often' having arthritis symptoms within the next 3 years. The results also suggest that engaging in at least 150 minutes of moderate-intensity physical activity per week, in accordance with the recommendations of the American College of Sports Medicine and the US Centers for Disease Control and Prevention [35], may be even more protective. These findings consequently indicate that public health and clinical advice for older women not currently experiencing stiff or painful joints should routinely include counseling on ways to be physically active to reduce their risk of developing stiff or painful joints.

Different findings between the two ALSWH cohorts with respect to the relationship between physical activity and stiff or painful joints 'often' were unexpected. One explanation is that occupational physical activity was not included in our assessment of physical activity and that many women in the mid-age cohort of the ALSWH were in paid work [36], whereas the older women were not. Failure to account for occupational physical activity may have resulted in greater misclassification of physical activity levels among the mid-age women than among the older women, which might explain the difference in findings between the two cohorts. Researchers who have used a crude measure of work-related physical activity have not, however, found a prospective association between occupational physical activity and arthritis in women

Table 2

Association between risk factors and having stiff or painful joints among mid-age women (*n* = 4,780)

	Stiff or painful joints 'sometimes or often'		Stiff or painful joints 'often'	
Variable at Time 1	Unadjusted odds ratio (95% confidence interval)	Adjusted[a] odds ratio (95% confidence interval)	Unadjusted odds ratio (95% confidence interval)	Adjusted[a] odds ratio (95% confidence interval)
Education				
Less than high school	1.00	1.00	1.00	1.00
Some high school	0.77 (0.65–0.92)	0.83 (0.69–0.99)	0.55 (0.43–0.71)	0.58 (0.45–0.75)
Completed high school	0.73 (0.60–0.90)	0.80 (0.65–0.99)	0.50 (0.37–0.68)	0.55 (0.40–0.76)
Trade certificate/ university degree	0.64 (0.52–0.78)	0.70 (0.56–0.87)	0.49 (0.35–0.67)	0.55 (0.39–0.77)
Missing	0.97 (0.51–1.82)	0.92 (0.48–1.75)	1.51 (0.70–3.26)	1.30 (0.58–2.93)
Area of residence				
Urban	1.0	1.0	1.0	1.0
Large town	0.87 (0.73–1.05)	0.87 (0.72–1.05)	0.8 (0.58–1.11)	0.77 (0.55–1.07)
Small town/remote area	1.11 (0.98–1.26)	1.09 (0.96–1.24)	1.14 (0.93–1.39)	1.08 (0.88–1.34)
Missing	0.83 (0.49–1.40)	0.83 (0.49–1.42)	0.3 (0.75–1.28)	0.32 (0.76–1.33)
Country of birth				
Australia	1.00	1.00	1.00	1.00
Other English-speaking	1.07 (0.91–1.27)	1.12 (0.95–1.33)	0.70 (0.51–0.95)	0.70 (0.51–0.97)
Non-English speaking	0.97 (0.78–1.21)	1.02 (0.82–1.28)	0.96 (0.67–1.36)	0.99 (0.69–1.43)
Missing	1.35 (0.99–1.84)	1.36 (0.99–1.88)	1.64 (1.06–2.53)	1.61 (1.02–2.53)
Depression				
No	1.00	1.00	1.00	1.00
Yes	1.56 (1.29–1.94)	1.44 (1.17–1.78)	2.10 (1.60–2.77)	1.76 (1.32–2.35)
Number of chronic diseases				
0	1.00	1.00	1.00	1.00

Table 2 *(Continued)*

Association between risk factors and having stiff or painful joints among mid-age women (*n* = 4,780)

1	1.41 (1.24–1.61)	1.35 (1.18–1.54)	1.78 (1.43–2.20)	1.62 (1.30–2.02)
2	1.54 (1.26–1.89)	1.37 (1.11–1.67)	2.67 (2.01–3.54)	2.17 (1.61–2.91)
3	1.93 (1.35–2.75)	1.67 (1.17–2.40)	2.53 (1.55–4.14)	1.96 (1.18–3.25)
4 or more	1.47 (0.77–2.82)	1.10 (0.56–2.14)	3.04 (1.32–7.01)	1.89 (0.79–4.49)
Smoking status				
Never	1.00	1.00	1.00	1.00
Former	1.00 (0.88–1.14)	0.99 (0.87–1.12)	1.23 (1.00–1.54)	1.21 (0.97–1.50)
Current	1.14 (0.95–1.36)	1.08 (0.90–1.30)	1.44 (1.09–1.91)	1.35 (1.01–1.81)
Missing	2.23 (0.63–7.91)	2.11 (0.59–7.60)	2.56 (0.54–12.10)	2.70 (0.55–13.2)
Body mass index				
<20 kg/m^2	1.03 (0.79–1.36)	1.03 (0.78–1.36)	1.22 (0.76–1.95)	1.25 (0.78–2.01)
≥ 20 and <25 kg/m^2	1.00	1.00	1.00	1.00
≥ 25 and <30 kg/m^2	1.10 (0.96–1.27)	1.06 (0.92–1.23)	1.46 (1.15–1.86)	1.36 (1.06–1.74)
≥ 30 kg/m^2	1.63 (1.38–1.92)	1.46 (1.23–1.73)	2.22 (1.73–2.86)	1.83 (1.41–2.38)
Missing	1.32 (1.05–1.66)	1.29 (1.02–1.62)	1.43 (0.98–2.08)	1.35 (0.92–2.00)
Physical activity				
None (<40 MET.min/week)	1.00	1.00	1.00	1.00
Very low (40 to <300 MET.min/week)	0.86 (0.71–1.05)	0.93 (0.76–1.14)	0.92 (0.67–1.26)	1.08 (0.78–1.49)
Low (300 to <600 MET.min/week)	0.77 (0.63–0.94)	0.88 (0.71–1.08)	0.87 (0.63–1.19)	1.15 (0.82–1.60)
Moderate (600 to <1,200 MET.min/week)	0.82 (0.68–0.99)	0.94 (0.77–1.14)	0.71 (0.52–0.97)	0.91 (0.66–1.27)
High (1,200+ MET.min/week)	0.75 (0.62–0.90)	0.88 (0.72–1.06)	0.78 (0.58–1.05)	1.06 (0.78–1.45)

[a]Adjusted for all other variables in the table.

Table 3

Association between risk factors and having stiff or painful joints among older women (_n_ = 3,970)

Variable at Time 1	Stiff or painful joints 'sometimes or often' at Time 2		Stiff or painful joints 'often' at Time 2	
	Unadjusted odds ratio (95% confidence interval)	Adjusted[a] odds ratio (95% confidence interval)	Unadjusted odds ratio (95% confidence interval)	Adjusted[a] odds ratio (95% confidence interval)
Education				
Less than high school	1.00	1.00	1.00	1.00
Some high school	0.89 (0.76–1.04)	0.90 (0.76–1.05)	0.86 (0.68–1.09)	0.90 (0.71–1.16)
Completed high school	0.92 (0.74–1.13)	0.97 (0.78–1.20)	1.06 (0.77–1.44)	1.17 (0.85–1.62)
Trade certificate/ university degree	1.01 (0.83–1.23)	1.06 (0.86–1.30)	0.80 (0.59–1.10)	0.93 (0.67–1.28)
Missing	0.89 (0.64–1.24)	0.91 (0.64–1.29)	1.25 (0.79–1.97)	1.37 (0.84–2.22)
Area of residence				
Urban	1.00	1.00	1.00	1.00
Large town	0.94 (0.76–1.16)	0.91 (0.73–1.13)	0.94 (0.67–1.31)	0.88 (0.62–1.24)
Small town/remote area	1.04 (0.91–1.19)	1.02 (0.89–1.18)	1.20 (0.98–1.48)	1.15 (0.93–1.42)
Missing	0.72 (0.42–1.22)	0.75 (0.43–1.29)	0.41 (0.13–1.32)	0.41 (0.12–1.33)
Country of birth				
Australia	1.00	1.00	1.00	1.00
Other English-speaking	0.95 (0.78–1.15)	0.93 (0.76–1.14)	0.87 (0.64–1.18)	0.90 (0.65–1.23)
Non-English speaking	1.00 (0.78–1.29)	0.92 (0.71–1.20)	1.02 (0.70–1.49)	0.90 (0.60–1.34)
Missing	0.94 (0.72–1.23)	0.94 (0.70–1.27)	1.02 (0.68–1.52)	0.91 (0.58–1.42)
Depression				
No	1.00	1.00	1.00	1.00
Yes	1.48 (1.04–2.09)	1.29 (0.90–1.84)	2.15 (1.41–3.29)	1.75 (1.13–2.72)
Number of chronic diseases				
0	1.00	1.00	1.00	1.00

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Table 3 *(Continued)*

Association between risk factors and having stiff or painful joints among older women (*n* = 3,970)

1	1.26 (1.08–1.48)	1.23 (1.05–1.44)	1.42 (1.09–1.85)	1.37 (1.05–1.79)
2	1.90 (1.59–2.28)	1.83 (1.52–2.19)	2.09 (1.57–2.77)	1.93 (1.44–2.57)
3	2.43 (1.89–3.14)	2.33 (1.80–3.02)	2.83 (1.99–4.03)	2.53 (1.77–3.63)
4 or more	3.06 (2.12–4.43)	2.93 (2.02–4.26)	5.02 (3.28–7.69)	4.24 (2.74–6.57)
Smoking status				
Never	1.00	1.00	1.00	1.00
Former	1.07 (0.93–1.24)	1.08 (0.93–1.25)	1.22 (0.99–1.52)	1.27 (1.01–1.59)
Current	1.05 (0.78–1.40)	1.10 (0.81–1.49)	1.17 (0.76–1.82)	1.17 (0.75–1.84)
Missing	1.01 (0.77–1.31)	1.04 (0.78–1.37)	1.06 (0.71–1.59)	1.07 (0.70–1.64)
Body mass index				
<20 kg/m^2	1.04 (0.72–1.48)	0.97 (0.67–1.39)	0.98 (0.54–1.77)	0.86 (0.47–1.58)
≥ 20 and <25 kg/m^2	1.00	1.00	1.00	1.00
≥ 25 and <30 kg/m^2	1.46 (1.26–1.70)	1.39 (1.19–1.63)	1.46 (1.15–1.84)	1.33 (1.04–1.68)
≥ 30 kg/m^2	1.42 (1.14–1.77)	1.26 (1.00–1.58)	1.68 (1.23–2.31)	1.32 (0.95–1.84)
Missing	1.13 (0.92–1.39)	1.07 (0.87–1.32)	1.52 (1.13–2.05)	1.36 (1.00–1.85)
Physical activity				
None (<40 MET.min/week)	1.00	1.00	1.00	1.00
Very low (40 to <300 MET.min/week)	0.98 (0.80–1.22)	1.04 (0.84–1.29)	0.87 (0.65–1.17)	0.94 (0.70–1.27)
Low (300 to <600 MET.min/week)	1.00 (0.83–1.20)	1.11 (0.92–1.34)	0.63 (0.48–0.82)	0.72 (0.55–0.96)
Moderate (600 to $<1,200$ MET.min/week)	0.80 (0.65–0.98)	0.89 (0.72–1.10)	0.48 (0.34–0.67)	0.54 (0.39–0.76)
High (1,200+ MET.min/week)	0.83 (0.69–0.99)	0.94 (0.78–1.14)	0.51 (0.38–0.68)	0.61 (0.46–0.82)

[a]Adjusted for all other variables in the table.

[9]. More precise measures of occupational physical activity are required to further explore these associations.

We did not observe a statistically significant association between physical activity and self-reported stiff or painful joints 'sometimes or often' in either cohort. This finding may reflect a wider variability in interpretation of the phrase 'sometimes' than 'often,' with some respondents exaggerating the frequency of their symptoms by selecting 'sometimes' when symptoms occurred 'rarely,' resulting in a weakened ability to detect an association.

The present study was the first to assess the prospective association between physical activity and symptoms of arthritis in two different age cohorts of women. Our observation of no statistically significant associations in three of the four multivariable analyses supports the results of prospective studies that have assessed the long-term associations between physical activity and arthritis in other large cohorts of women [5,7]. In a 25-year cohort study that included 4,073 women 20–87 years of age, Cooper Clinic (US) researchers [7] reported no statistically significant association between walking or jogging and self-reported physician-diagnosed hip and knee osteoarthritis for women after controlling for BMI, alcohol, smoking status, and caffeine consumption. In the 20-year Alameda County Cohort Study (US) [5], no statistically significant association between leisure-time physical activity and self-reported arthritis was seen among the 1,148 women who participated (mean age = 43 years for all participants) after controlling for age, race, BMI, and the presence of five or more depressive symptoms. Assessment of the risk factors for radiographic knee osteoarthritis among 715 mid-age women (aged 54 ± 6 years) in the Chingford Study Cohort (UK) [9] revealed that walking, occupational physical activity, and sport were not statistically significantly associated with incident osteophytes over 4 years after adjusting for age, social class, BMI, and smoking status among other factors – only walking was associated with decreased odds of joint space narrowing (OR = 0.38, 95% CI = 0.15–0.93) over that same time period after adjusting for the same variables.

Our finding that physical activity is protective against complaints of stiff or painful joints 'often' in older women does not support the results from these other studies [5,7-9]. Only the Framingham Study [8], however, focused specifically on older women. In that study, the researchers found an *increased* risk of radiographic knee osteoarthritis over 10 years (but not after 20 or 40 years) among the 69 older women (mean age = 71 $\pm$ 5 years for the sample of men and women) in the highest quartile of physical activity in a model adjusted for age, BMI, cigarette smoking, and other covariates (OR = 3.1, 95% CI = 1.1–8.6). In contrast, our results showed a clear dose-response relationship between physical activity and incident stiff or painful joint 'often' over 3 years in women aged 72–79 years at T1.

Interpretation of our results in the context of the findings from other studies should be made with caution because each study of the risk factors for arthritis has used a different measure of physical activity. In our study, a generic physical activity score reflected participation in walking as well as moderate-intensity and vigorous-intensity leisure-time activities during the past week, whereas other studies have used 24-hour recall [8], have focused on specific physical activities, such as walking [7,9], or have used their own physical activity index to evaluate habitual leisure-time physical activity [5]. Moreover, the outcomes of each study differed. While our study examined arthritis symptoms, other studies assessed self-reported arthritis [5], self-reported osteoarthritis [7], or radiographic osteoarthritis [8,9]. It should also be noted that different studies used follow-up periods ranging from 4 to 40 years [5,7-9]. Although our follow-up period of 3 years was short, it was appropriate for assessing the development of symptoms of arthritis rather than arthritis itself, which can take much longer to develop.

Our study does not provide insight into the mechanisms by which physical activity may impact development of arthritis symptoms in older women; however, the constellation of significant factors (physical activity, BMI, and smoking) supports the suggestion that there is a metabolic basis to the development of arthritis [9]. Alternatively, the links between physical activity and arthritis symptoms might be explained by exercise-related endorphin release, by protection against fibromyalgia, by increased resistance to musculoskeletal injury, by differences in pain threshold for people who exercise regularly, or by other psychological mechanisms [37].

Unique to the present study, risk factors for arthritis symptoms were examined separately in mid-age women and in older women, which allowed us to detect age-related differences in the association between physical activity and stiff or painful joints. Other strengths of this study were that it included a large population-based sample of women and used a prospective design. Women in each cohort who reported stiff or painful joints 'sometimes' or 'often' at T1 were excluded to reduce the possibility of reverse causation (that is, women became inactive because they had stiff or painful joints). Other strengths were that we used a validated and reliable measure of physical activity [25-27] and that we provided evidence of the predictive validity for our stiff and painful joints measure against self-reported physician-diagnosed arthritis and physical functioning.

A major limitation of this study was that all the data were self-reported. We did not have radiological or clinical measures, so we chose to focus on symptoms rather than on clinically diagnosed arthritis. This provided the opportunity to include women who may not have yet sought medical care or not yet been diagnosed with the problem. While it could be argued that the question about symptoms lacks specificity and sensi-

tivity when compared with more objective measures, other researchers have shown that reporting these symptoms is associated with decreased ability to conduct functional tasks and with disability [38]. Previous studies have also shown that people underreported confirmed diagnoses when asked to report physician-diagnosed osteoarthritis, indicating that the burden of arthritis in the population has been underestimated [7,39].

Another limitation is the potential effect of participation bias on the results. Although the ALSWH included a fairly representative national sample of mid-age women and older women at the first data collection point [21], as with all prospective studies, there is continual attrition over time, with a tendency for more healthy women to remain in the cohort [40]. This 'healthy' participation bias was further exaggerated here by our inclusion of only women who did *not* report having stiff or painful joints 'sometimes' or 'often' at T1. While this was done to reduce the possibility of reverse causation (as described above), the original participation bias, together with the selection bias of women without joint pain or stiffness and exclusion of women with missing physical activity data, meant that our samples were more physically active than the general population of mid-age women and older women. The findings cannot, therefore, be generalized to all women in these age groups.

We were unable to examine factors associated with specific sites of the joint symptoms (for example, knee versus wrist), or about the year when the stiff or painful joint symptoms first developed, precluding the use of survival analysis or other procedures that require the exact duration of follow-up to be known. Finally, because few women in the ALSWH cohorts reported levels of physical activity that would be typically associated with 'athletic' training, we were unable to confirm findings from previous studies indicating that competitive sport and associated injuries might be involved in the development of osteoarthritis [8,10].

Conclusion
The prevalence of arthritis in Australia is rapidly approaching that of cardiovascular disease [2]. As the cost to the Australian healthcare system of managing arthritis and its symptoms is likely to be greater than for other prominent health problems such as diabetes and asthma [2], the identification of physical inactivity as a potentially modifiable risk factor of incident stiff or painful joints among older women is important. Indeed, if preventive intervention strategies, such as increasing physical activity participation by even small amounts, could delay the onset and development of symptoms of arthritis, there could be considerable cost savings to the healthcare system and to older women themselves, not to mention reductions in pain and suffering caused by this often debilitating health problem.

Competing interests
The authors declare that they have no completing interests.

Authors' contributions
KCH and YDM participated in the study conception and design, statistical analyses, interpretation of the data, and drafting of the manuscript. WJB participated in the study conception, study design, data acquisition, interpretation of the data, and drafting of the manuscript. All authors have read and approved the final manuscript.

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論文名	Relationship between physical activity and stiff or painful joints in mid-aged women and older women: a 3-year prospective study
著 者	Heesch KC, Miller YD, Brown WJ
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PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/17394630

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	52.53±1.49歳、	███████			（　　　）				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	なし	なし	なし	介護予防	（　　　）	（　　　）
	維持・改善	なし	なし	なし	なし	（　　　）	（　　　）

図 表

Table 2 (Continued)

Association between risk factors and having stiff or painful joints among mid-age women (n = 4,780)

Table 3 (Continued)

Association between risk factors and having stiff or painful joints among older women (n = 3,970)

*Adjusted for all other variables in the table.

図表掲載箇所	P8of13, Table2, P10of13, Table3

概 要（800字まで）

本研究は、オーストラリアのThe Australian Longitudinal Study on Women's Health(ALSWH)に参加した中年女性4,780名と高齢女性3,970名を対象に3年間の追跡調査を行い、身体活動量と関節痛発症リスクの関連を検討したものである。ベースライン測定時に、身体活動量について、過去1週間のうち、通勤や余暇時間の速歩、中強度余暇身体活動、高強度余暇身体活動に費やした時間と頻度を尋ね、それらの合計により総身体活動量を得た。身体活動量は、None(40メッツ分/週未満)、Very low(40-300メッツ分/週)、Low(300-600メッツ分/週)、Moderate(600-1200メッツ分/週)、High(1200メッツ分/週以上)の5群に分類した。また、ベースライン時、3年後測定時に過去1年間に関節のこわばりや痛みを感じた経験を尋ね、ときどき、しばしばの2群に分類した。高齢女性において、関節痛発症がときどきと答えた集団では身体活動との関連はみられなかったが、関節痛発症がしばしばと答えた集団では、身体活動量がLow、Moderate、Highの集団で関節痛発症リスクがそれぞれ0.72(95%信頼区間:0.55-0.96)、0.54(0.39-0.76)、0.61(0.46-0.82)と有意に減少した。中年女性においては、いずれも差はみられなかった。

結 論（200字まで）

高齢女性において、身体活動量と関節痛発症リスクに量反応的な関連が明らかとなった。

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使用された研究である。高齢女性において、少ない身体活動量と高い関節痛発症リスクに量反応的な関連が明らかにした点に意義がある。ロコモに対する身体活動の予防効果について今後の研究が期待される。

担当者　久保絵里子・村上晴香・宮地元彦

ORIGINAL PAPER

Physical activity and breast cancer risk among pre- and postmenopausal women in the U.S. Radiologic Technologists cohort

Regan A. Howard · Michael F. Leitzmann · Martha S. Linet · D. Michal Freedman

Abstract To clarify aspects of the association between physical activity and breast cancer, such as activity intensity required, and possible effect modification by factors such as menopausal hormone therapy (MHT) use. We prospectively examined physical activity in relation to breast cancer risk among 45,631 women participating in the U.S. Radiologic Technologists cohort. Participants provided information at baseline regarding hours spent per week engaging in strenuous activity, walking/hiking for exercise, and walking at home or work. We estimated multivariable relative risks (RR) and 95% confidence intervals (CI) of breast cancer using Cox regression. We identified 864 incident-invasive breast cancers. Greatest risk reduction was observed among women who reported walking/hiking for exercise 10 or more hours per week (RR, 0.57; 95% CI, 0.34–0.95) compared with those reporting no walking/hiking. The association between walking/hiking for exercise and breast cancer was modified by MHT use (p for interaction = 0.039). Postmenopausal women who never used MHT had reduced risks of breast cancer associated with physical activity whereas no relation was observed among ever users of MHT. Our study suggests moderate intensity physical activity, such as walking, may protect against breast cancer. Further, the relation between physical activity and breast cancer may be modified by MHT use.

Keywords Breast cancer · Physical activity · Cohort studies · Hormones

Introduction

Breast cancer is the most commonly diagnosed cancer among women in the United States [1]. Physical activity represents one of the few established risk factors for breast cancer that can be modified through behavior changes. Numerous observational studies have reported a reduced risk of breast cancer in relation to increasing levels of physical activity [2–6], with evidence of this association classified as "convincing" in 2002 by IARC [7]. Several biological mechanisms have been proposed to explain the relationship between physical activity and breast cancer risk, including a decrease in endogenous hormone levels, reduction of insulin and insulin-like growth factors, favorable modification of menstrual characteristics, and enhanced immune function [8–11].

Several aspects of the association between physical activity and breast cancer risk remain uncertain including the type of activity, timing in life of activity, dose of activity required (including duration, frequency, and intensity), and whether risks differ among certain population subgroups. The current investigation will primarily focus on the intensity level of physical activity and the association between physical activity and breast cancer according to menopausal status and menopausal hormone therapy use. Inconsistencies exist regarding the intensity of physical activity required for risk reduction, and it is important to investigate whether moderate intensity

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physical activity can also reduce risk. Some studies observe risk reduction with strenuous or moderate forms of physical activity [5, 12, 13] and others suggest that strenuous activity is required for risk reduction [14, 15]. A recent review reported that although moderate intensity activity has been associated with reduced risk of breast cancer, the reductions are even stronger with vigorous intensity activity [16]. In addition, results of epidemiologic studies also suggest that the association between physical activity and breast cancer may differ by menopausal status. The majority of studies report a reduced risk of breast cancer related to increased physical activity among postmeno-pausal women, but the evidence for this association among premenopausal women is much less consistent [6, 16–19]. Further, a few studies have evaluated the modifying effects of menopausal hormone therapy among postmenopausal women [4, 5, 13, 19–23].

In this study, we examine the association between physical activity of varying intensities and breast cancer risk in the U.S. Radiologic Technologists (USRT) cohort, with special emphasis on potential effect modification of the physical activity and breast cancer relation by meno-pausal hormone therapy among postmenopausal women.

Materials and methods

The U.S. Radiologic Technologists cohort

The USRT cohort is a collaborative effort between the U.S. National Cancer Institute, the University of Minnesota, and the American Registry of Radiologic Technologists (ARRT). The study is composed of a cohort of radiologic technologists residing in the United States and who were certified by the ARRT for at least 2 years between 1926 and 1982. Detailed information on the study population and methods has been published previously [24, 25].

In brief, an initial questionnaire was mailed in 1983–1989 that collected detailed information on employment history, demographic and lifestyle factors, and reproduc-tive and medical history. The current study, however, uses as its baseline the second self-administered questionnaire (1994–1998), which ascertained incident cancers and col-lected information on demographic, reproductive, and other potential risk factors, including physical activity. Of the 94,495 known living female technologists who were mailed the second questionnaire, 69,998 responded (74%). A third questionnaire distributed in 2004–2005 collected additional information on cancer risk factors and updated health outcomes. Out of the 69,998 female responders to the second questionnaire, 52,563 women responded to the third questionnaire (75%).

Study population

We included 51,473 women who responded to the second questionnaire, were cancer-free (except for non-melanoma skin cancer) at completion of the second questionnaire and who responded to the third questionnaire or died during the intervening period. We excluded 5,842 women with missing data on any of the three physical activity questions ($n = 5,759$) or unrealistic data on physical activity (defined as women who reported spending 80 or more hours a week participating in a combination of strenuous activity and walking/hiking for exercise) ($n = 83$), resulting in an analytic cohort consisting of 45,631 women. The 5,842 excluded women did not differ appreciably from women in the analytic cohort on most covariates; however, excluded women tended to be older at baseline and were more likely to be smokers.

Cohort maintenance

Annual follow-up is conducted through re-certification with the ARRT. For individuals who fail to renew certification, vital status is determined through linkage to mortality and national address change databases, including the Social Security Death Index and National Death Index Plus. The Institutional Review Boards of the National Cancer Institute and the University of Minnesota approved this study.

Assessment of physical activity

Participants provided information at baseline (1994–1998) regarding the number of hours spent per week during the previous year engaging in each of the following activities as written on the questionnaire: exercising strenuously (e.g., aerobics, jogging, swimming), walking or hiking for exercise and walking at home or at work. Response options for each question included: 'none', '<1 h', '1–3 h', '4–9 h', '10–19 h', '20–39 h', or 'over 40 h'. A midpoint value was assigned for the number of hours per week spent engaging in physical activity (the 'over 40 h' category was assigned a value of 41) and multiplied by the estimated metabolic equivalent task (MET) value specific to that intensity level. MET values for strenuous exercise, walking for exercise, and walking at home or work were assigned MET values of 7, 4, and 3, respectively [26]. We created a total physical activity score by summing the MET-hours per week for all the three physical activity variables. The MET-hours per week were divided into quintiles for the analyses, based on their distribution in the total popula-tion. Studies assessing the reliability and validity of self-reported physical activity have concluded that question-naires, in general, are a reasonably useful method of

estimating physical activity in large epidemiologic studies [27, 28].
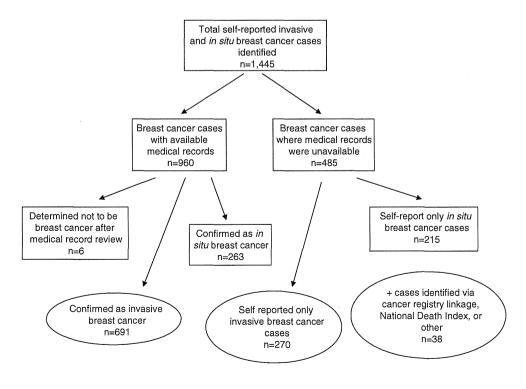
Breast cancer validation

A total of 1,445 self-reported breast cancers were identified between the second and third surveys (Fig. 1). Participants were asked to say whether they had been diagnosed with invasive or in situ breast cancer. The case definition was limited to invasive breast cancer, and in situ breast cancers were excluded. Pathology reports or medical records were obtained for 960 (66.4%) patients reporting breast cancer (invasive or in situ); of which 954 breast cancer cases were confirmed, resulting in a 99% confirmation rate. We excluded the six incorrectly reported "breast cancers". The 954 validated breast cancers included 263 in situ breast cancer cases, which we excluded, leaving 691 confirmed invasive breast cancers. Since such a large percentage of self-reported breast cancer cases were confirmed among women for whom medical records could be obtained, we included 270 self-reported invasive breast cancer cases for whom medical records were unavailable and excluded 215 self-reported in situ breast cancers. We also included 38 breast cancer cases identified via cancer registry linkage ($n = 26$), linkage with the National Death Index with breast cancer as the underlying cause of death ($n = 8$), and incidental reports (originally reported as non-breast cancers but later found to be invasive breast cancer through validation) ($n = 4$). Of the 999 total invasive breast cancer cases available ($n = 691 + 270 + 38$), 864 breast cancer

cases remained from 45,631 women for analysis after exclusions due to missing physical activity data. Cases identified using death certificates had a diagnosis date imputed by subtracting the average breast cancer survival time (based on data from the Surveillance, Epidemiology, and End Results Program) from the date of death.

Statistical analysis

To assess the association between physical activity and breast cancer, we used multivariable Cox proportional hazards regression to estimate relative risks (RRs) and corresponding confidence intervals (CIs), with age as the underlying time scale. Analyses were stratified at baseline for 5-year birth cohorts to control for secular trends. Person-time began at the completion of the second questionnaire and ended at the date of first reported cancer diagnosis (except non-melanoma skin cancers), death, or response to the third questionnaire, whichever occurred first.

In the analysis, we assessed risk using three models, one adjusting for age only, one adjusting for age and potential confounders (described below), and an additional model that was mutually adjusted for the three categories of physical activity. For strenuous activity and walking for exercise, we selected as the reference group women who reported never engaging in physical activity. To evaluate the relations with time spent walking at home or work, <1 h/week served as the referent group. Women who reported never walking at home or work were not used as

Fig. 1 Diagram showing case validation and inclusion steps

the referent group because their inactivity may have been due to underlying disease potentially related to breast cancer. A similar approach has been used previously to account for this effect [22, 29].

Analyses that adjusted for confounding included the following factors, which are commonly included in breast cancer analyses: age at menarche (<11, 11–14, 15+, unknown), number of live births (none, 1–3, 4+, unknown), age at first live birth (<20, 20–<25, 25–<30, 30–<35, 35+ and nulliparous, unknown), age at menopause (pre-menopausal, <35, 35–<40, 40–<45, 45–<50, 50–<55, 55+), family history of breast cancer (no, yes, unknown), personal history of breast disease (no, yes, unknown), use of oral contraceptives (never, ever, unknown), race (white, black, Asian, other/unknown), menopausal hormone therapy use (MHT) (never/pre-menopausal, ever, unknown), smoking (never, quit and ≤20 cigarettes/day, quit and >20 cigarettes/day, current smoker and ≤20 cigarettes/day, current smoker and >20 cigarettes/day, unknown), alcohol (<1 drink/week, 1–6 drinks/week, 7–12 drinks/week, 13+ drinks/week, unknown), and body mass index (BMI) (<25 kg/m², 25–<30 kg/m², 30+ kg/m², unknown). Missing values for menopausal status and/or age at menopause were imputed for 7.3% of participants using mean values for women of similar age. Other covariates (height, years spent working, marital status, and vitamin use) were evaluated for potential confounding but were not included in the models because they did not appreciably affect the risk estimates and have generally not been shown to confound an association with physical activity in previous studies.

Trend tests for each physical activity variable were calculated by assigning the median value to each exposure category and treating each as a single continuous variable in the model. Effect modification was tested using the resulting p-value of a cross-product interaction term between the physical activity variable and the covariate of interest together with the main effects in the appropriate model. The coefficient of the interaction term was evaluated using a Wald test. All tests of statistical significance were two sided and $p < 0.05$ was considered statistically significant. The statistical analyses were conducted using the PHREG procedure of the Statistical Analysis System (SAS) software package (version 8.2, SAS Institute, Inc., Cary, NC).

Results

During a mean length of follow-up of 8.9 years (total person-years: 404,457), we identified 864 incident cases of breast cancer. Age-adjusted study population characteristics stratified by total physical activity score (in quintiles)

are listed in Table 1. The mean age of study participants at baseline was 47.2 years. More active women were slightly younger at first birth, had lower parity, consumed more alcohol, and had a lower BMI than their inactive counterparts. Unexpectedly, more active women were more likely to be current smokers. Modest differences were observed across physical activity quintiles for other variables.
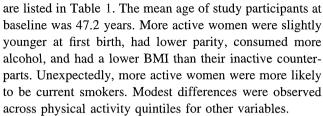
Table 2 shows age- and multivariable-adjusted risk estimates for associations of four indices of physical activity with breast cancer incidence. Risk estimates were similar after multivariable adjustment for several risk factors, including BMI. Risk reduction was greatest among women who reported walking/hiking for exercise 10 or more hours per week (RR, 0.57; 95% CI, 0.34–0.95) compared to women who never walk/hike for exercise, although the trend was not significant ($p = 0.321$). Breast cancer risk was slightly reduced among women reporting 40 or more hours per week of walking at home or at work (RR, 0.88; 95% CI, 0.67–1.16), compared to women walking less than 1 h per week. After mutually adjusting for the three categories of physical activity evaluated in the questionnaire, observed risk estimates for all the three exercise variables were slightly attenuated. Further, the association between walking/hiking for exercise and breast cancer was similarly attenuated among women who reported that they never engaged in strenuous physical activity (data not shown). Total physical activity (based on MET-score) was not statistically significantly associated with breast cancer risk ($p = 0.174$); however, risk was suggestively decreased among women in the highest two quintiles (RR, 0.87; 95% CI, 0.70–1.08 and RR, 0.91; 95% CI, 0.74–1.13, respectively).

We examined the relation of physical activity to risk of breast cancer according to menopausal status and menopausal hormone therapy use (Table 3). In pre-menopausal women, decreased risk of breast cancer was greatest among women walking/hiking for exercise for 10 or more hour per week (RR, 0.37; 95% CI, 0.16–0.84), although the trend was not statistically significant. The relationship at ≥10 h/week remained even after adjustment for participation in other types of physical activity. Slightly reduced breast cancer risks were also observed for pre-menopausal women engaging in strenuous exercise and time spent walking at home/work, but risks for strenuous activity were attenuated after adjusting for other types of physical activity. No statistically significant effect modification was observed for any of the physical activity variables and menopausal status (data not shown).

Postmenopausal women who never used MHT experienced reduced risks of breast cancer with each of the three types of physical activity. Associations approaching statistical significance were observed for increasing levels of strenuous activity (RR comparing extreme categories, 0.57;

Table 1 Age-adjusted baseline characteristics according to total physical activity: U.S. Radiologic Technologists Study[a]

Characteristic	Quintiles of total physical activity score (MET hr/wk)				
	Q1 (0.0–9.5)	Q2 (11.5–23.0)	Q3 (23.5–45.5)	Q4 (46.0–96.5)	Q5 (≥97.0)
Number of participants	9,154	9,058	9,509	9,000	8,910
Mean age (years)	48.9	47.0	47.0	46.6	46.1
Mean body mass index (kg/m^2)	26.6	25.5	25.1	24.8	24.8
Race (%)					
White	96.4	97.1	97.5	97.6	96.8
Black	2.8	2.2	1.8	1.9	2.6
Asian	0.8	0.7	0.7	0.5	0.6
Family history of breast cancer (%)[b]	9.6	9.9	10.1	9.8	9.4
Personal history of breast disease (%)	33.0	34.9	34.8	34.5	34.7
Currently married (%)	76.8	76.8	77.6	77.0	73.9
Age at menarche (%), years					
<11	7.0	7.2	6.4	6.7	7.6
11–14	85.3	85.2	85.4	85.6	83.6
15+	7.7	7.6	8.2	7.7	8.8
Age at first birth (%), years					
<20	2.9	3.3	2.9	3.5	3.6
20–24	36.8	37.9	38.1	38.9	39.5
25–29	39.0	38.4	40.1	39.4	39.3
30+	21.4	20.5	18.8	18.2	17.6
Parity (%)					
0	19.4	19.8	19.1	19.3	20.3
1–3	72.4	72.4	72.8	72.4	72.1
4+	8.2	7.8	8.1	8.3	7.6
Age at menopause (%), years					
Premenopausal	58.4	59.6	58.9	59.2	58.0
<40	13.1	12.3	12.4	12.6	13.8
40–44	9.1	8.7	9.0	8.8	9.4
45–49	9.3	9.3	9.2	9.4	9.5
50–54	8.5	8.7	8.7	8.6	8.1
55+	1.6	1.4	1.7	1.4	1.2
Current smoker (%)	13.2	12.3	10.3	11.5	15.4
Alcohol consumption, drinks/week (%)					
<1	67.7	61.3	58.7	57.0	58.6
1–6	24.0	29.4	31.4	32.4	30.8
7–12	4.2	5.2	5.7	5.9	6.0
13+	4.1	4.1	4.2	4.8	4.6
Menopausal hormone therapy, current use (%)	22.0	22.8	24.0	23.5	24.4
Oral contraceptive use, ever (%)	73.2	76.3	76.3	75.8	77.0

[a] Cohort restricted to respondents of the baseline questionnaire who were cancer free (except nonmelanoma skin cancer) at time of response. Values calculated from participants with nonmissing data for each variable and standardized to the age distribution of the study population

[b] Any first-degree relative with breast cancer

95% CI, 0.23–1.42, $p = 0.070$) and walking/hiking for exercise (RR comparing extreme categories, 0.39; 95% CI, 0.09–1.62, $p = 0.078$). There was, however, no clear association between physical activity and breast cancer risk among postmenopausal MHT users. We observed a slight decrease in breast cancer risk among women who reported engaging in no walking at home/work compared with the reference group. A significant interaction was observed between MHT use and walking/hiking for exercise among postmenopausal women ($p = 0.039$), although the interaction was not significant for strenuous activity ($p = 0.150$).

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Table 2 Risk of breast cancer according to various measures of physical activity

Exercise variable	Cases	Person-years	Age-adjusted HR	Multivariate[a] HR	Multivariate[a] HR + other activity variables
Strenuous exercise (hours/week)					
Never	469	200,372	1.0	1.0	1.0
<1	169	90,368	0.94 (0.78–1.12)	0.93 (0.78–1.11)	0.93 (0.77–1.11)
1–3	161	75,989	1.06 (0.88–1.27)	1.03 (0.86–1.24)	1.02 (0.85–1.23)
4–9	55	31,415	0.86 (0.65–1.14)	0.83 (0.62–1.10)	0.82 (0.61–1.09)
10+	10	6,312	0.76 (0.41–1.43)	0.76 (0.40–1.42)	0.90 (0.47–1.71)
p_{trend}			0.298	0.196	0.320
Walking/hiking for exercise (hours/week)					
Never	187	82,030	1.0	1.0	1.0
<1	223	110,068	0.96 (0.79–1.17)	0.97 (0.80–1.18)	1.01 (0.82–1.24)
1–3	295	139,260	1.01 (0.84–1.21)	1.02 (0.84–1.22)	1.06 (0.87–1.29)
4–9	143	60,083	1.08 (0.87–1.34)	1.10 (0.88–1.37)	1.16 (0.92–1.46)
10+	16	13,016	0.56 (0.33–0.92)	0.57 (0.34–0.95)	0.63 (0.37–1.07)
p_{trend}			0.264	0.321	0.662
Walking at home or work (hours/week)					
Never	57	20,851	1.20 (0.88–1.63)	1.21 (0.88–1.65)	1.21 (0.88–1.67)
<1	131	58,598	1.0	1.0	1.0
1–3	233	105,771	1.00 (0.81–1.24)	1.01 (0.81–1.25)	1.00 (0.80–1.24)
4–9	177	83,370	0.98 (0.78–1.23)	0.99 (0.79–1.24)	0.97 (0.77–1.23)
10–19	82	41,678	0.92 (0.70–1.21)	0.92 (0.70–1.21)	0.92 (0.69–1.22)
20–39	101	48,537	0.98 (0.76–1.28)	1.00 (0.77–1.29)	0.99 (0.76–1.29)
40+	83	45,652	0.87 (0.66–1.14)	0.88 (0.67–1.16)	0.90 (0.68–1.20)
p_{trend}			0.330	0.401	0.623
Total MET-score					
Q1 (0.0–9.5)	188	79,694	1.0	1.0	
Q2 (11.5–23.0)	181	80,264	1.04 (0.85–1.27)	1.02 (0.83–1.26)	
Q3 (23.5–45.5)	190	84,697	1.03 (0.84–1.26)	1.02 (0.83–1.25)	
Q4 (46.0–96.5)	152	80,381	0.88 (0.71–1.09)	0.87 (0.70–1.08)	
Q5 (≥97.0)	153	79,420	0.92 (0.74–1.14)	0.91 (0.74–1.13)	
p_{trend}			0.170	0.174	

[a] Adjusted for entry age, body mass index, age at menarche, parity, age at first birth, age at menopause, family history of breast cancer, personal history of breast disease, OC use, menopausal hormone therapy, race, smoking, and alcohol consumption

The association between physical activity and breast cancer risk was not modified by age, body mass index, race, age at menarche, parity, family history of breast cancer, personal history of breast disease, oral contraceptive use, smoking, or alcohol consumption. In addition, to investigate the effect of undiagnosed cancer on physical activity levels, we excluded the first year of follow-up. We found reported associations between physical activity and breast cancer remained largely unchanged.

Discussion

Results from this large prospective cohort of radiologic technologists support a modest inverse relationship between physical activity and breast cancer risk. The strongest associations were observed for walking for exercise among premenopausal women and postmenopausal women who never used MHT, although dose–response relationships were not observed. This is one of few studies to evaluate physical activity and breast cancer risk among postmenopausal women according to MHT use. Further, these data provide additional support that even forms of physical activity of moderate intensity may confer protection against breast cancer.

Our finding of a decrease in breast cancer risk with physical activity is consistent with most previous research [6, 7]. However, the intensity of physical activity required to decrease breast cancer risk is an important public health issue, on which results from previous studies are largely

Table 3 Risk of breast cancer according to physical activity, menopausal status, and menopausal hormone therapy use

Exercise variable	Premenopausal				
	Cases	Person-years	Age-adjusted HR	Multivariable[b] HR	Multivariable[b] HR + other activity variables
Strenuous exercise (hours/week)					
Never	213	107,051	1.0	1.0	1.0
<1 h	92	60,047	0.84 (0.66–1.08)	0.84 (0.65–1.07)	0.87 (0.67–1.12)
1–3	95	50,550	1.05 (0.82–1.34)	0.99 (0.78–1.27)	1.00 (0.78–1.29)
4–9	34	20,867	0.90 (0.63–1.29)	0.83 (0.57–1.20)	0.84 (0.58–1.21)
10+	6	4,073	0.80 (0.36–1.81)	0.79 (0.35–1.78)	1.04 (0.45–2.40)
p_{trend}			0.663	0.429	0.698
Walking/hiking for exercise (hours/week)					
Never	97	45,517	1.0	1.0	1.0
<1 h	114	68,851	0.80 (0.61–1.04)	0.80 (0.61–1.05)	0.87 (0.66–1.16)
1–3	154	86,071	0.87 (0.67–1.12)	0.86 (0.66–1.11)	0.94 (0.72–1.24)
4–9	69	34,702	0.94 (0.69–1.28)	0.92 (0.68–1.26)	1.02 (0.74–1.42)
10+	6	7,445	0.38 (0.17–0.86)	0.37 (0.16–0.84)	0.41 (0.18–0.98)
p_{trend}			0.170	0.130	0.330
Walking at home or work (hours/week)					
Never	34	11,993	1.49 (0.99–2.25)	1.46 (0.96–2.21)	1.39 (0.91–2.13)
<1 h	66	34,429	1.0	1.0	1.0
1–3	113	63,179	0.94 (0.69–1.27)	0.92 (0.68–1.25)	0.91 (0.67–1.24)
4–9	88	50,373	0.91 (0.66–1.25)	0.90 (0.65–1.24)	0.88 (0.64–1.22)
10–19	42	25,331	0.87 (0.59–1.28)	0.86 (0.58–1.26)	0.86 (0.58–1.27)
20–39	54	29,702	0.95 (0.66–1.36)	0.95 (0.66–1.36)	0.95 (0.66–1.37)
40+	43	27,580	0.81 (0.55–1.19)	0.79 (0.54–1.16)	0.82 (0.56–1.22)
p_{trend}			0.419	0.434	0.689
Total MET-score					
Q1 (0.0–9.5)	82	43,528	1.0	1.0	
Q2 (11.5–23.0)	101	49,084	1.15 (0.86–1.53)	1.12 (0.83–1.50)	
Q3 (23.5–45.5)	96	51,249	1.04 (0.77–1.39)	1.00 (0.74–1.35)	
Q4 (46.0–96.5)	80	49,673	0.89 (0.65–1.21)	0.85 (0.63–1.16)	
Q5 (≥97.0)	81	49,052	0.91 (0.67–1.24)	0.88 (0.65–1.20)	
p_{trend}			0.174	0.123	

Table 3 continued

Exercise variable	Postmenopausal[a]										p interaction among postmenopausal women	p interaction among all three groups
	Ever used MHT					Never used MHT						
	Cases	Person-years	Age-adjusted HR	Multivariate[b] HR	Multivariable[b] HR + other activity variables	Cases	Person-years	Age-adjusted HR	Multivariate[b] HR	Multivariable[b] HR + other activity variables		
Strenuous exercise (hours/week)												
Never	162	58,061	1.0	1.0	1.0	94	34,652	1.0	1.0	1.0		
<1 h	55	19,027	1.22 (0.89–1.66)	1.20 (0.88–1.63)	1.13 (0.83–1.55)	22	11,069	0.79 (0.49–1.27)	0.81 (0.51–1.30)	0.81 (0.50–1.32)		
1–3	48	16,744	1.16 (0.84–1.60)	1.17 (0.84–1.62)	1.10 (0.79–1.52)	18	8,507	0.84 (0.51–1.40)	0.86 (0.51–1.44)	0.87 (0.52–1.47)	0.150	0.951
4–9	16	6,930	0.90 (0.54–1.50)	0.89 (0.53–1.50)	0.85 (0.51–1.44)	5	3,558	0.54 (0.22–1.34)	0.57 (0.23–1.42)	0.61 (0.24–1.53)		
10+	4	1,373	1.16 (0.43–3.14)	1.12 (0.41–3.03)	1.19 (0.43–3.34)	0	829	–	–	–		
p_{trend}			0.982	0.929	0.870			0.051	0.070	0.111		
Walking/hiking for exercise (hours/week)												
Never	50	21,722	1.0	1.0	1.0	40	14,511	1.0	1.0	1.0		
<1 h	70	26,332	1.24 (0.86–1.79)	1.29 (0.90–1.87)	1.20 (0.82–1.74)	39	14,620	1.04 (0.66–1.62)	1.05 (0.67–1.64)	1.18 (0.73–1.90)		
1–3	100	34,174	1.39 (0.99–1.95)	1.47 (1.04–2.08)	1.31 (0.92–1.88)	41	18,668	0.83 (0.53–1.29)	0.86 (0.55–1.35)	1.03 (0.64–1.65)	0.039	0.063
4–9	57	16,436	1.58 (1.08–2.31)	1.71 (1.16–2.52)	1.56 (1.04–2.33)	17	8,792	0.70 (0.39–1.23)	0.73 (0.41–1.31)	0.89 (0.49–1.62)		
10+	8	3,471	1.05 (0.50–2.22)	1.15 (0.54–2.43)	1.05 (0.48–2.31)	2	2,022	0.36 (0.09–1.48)	0.39 (0.09–1.62)	0.55 (0.13–2.33)		
p_{trend}			0.298	0.187	0.293			0.048	0.078	0.268		
Walking at home or work (hours/week)												
Never	9	5,627	0.64 (0.31–1.32)	0.62 (0.30–1.30)	0.67 (0.32–1.42)	14	3,152	1.38 (0.73–2.62)	1.48 (0.77–2.83)	1.54 (0.78–3.03)		
<1 h	36	14,824	1.0	1.0	1.0	29	9,138	1.0	1.0	1.0		
1–3	89	27,287	1.38 (0.94–2.03)	1.42 (0.97–2.10)	1.37 (0.92–2.03)	31	15,018	0.64 (0.39–1.07)	0.65 (0.39–1.09)	0.68 (0.41–1.15)		
4–9	65	20,797	1.37 (0.91–2.05)	1.41 (0.93–2.12)	1.34 (0.89–2.03)	24	12,011	0.65 (0.38–1.13)	0.71 (0.41–1.22)	0.74 (0.42–1.29)	0.511	0.861
10–19	30	10,348	1.28 (0.79–2.08)	1.31 (0.81–2.13)	1.24 (0.76–2.03)	10	5,863	0.56 (0.27–1.15)	0.58 (0.28–1.19)	0.63 (0.30–1.31)		
20–39	31	12,085	1.18 (0.73–1.91)	1.24 (0.76–2.00)	1.17 (0.71–1.90)	16	6,646	0.84 (0.46–1.56)	0.88 (0.47–1.64)	0.94 (0.50–1.77)		
40+	25	11,165	1.08 (0.64–1.80)	1.13 (0.68–1.89)	1.10 (0.65–1.87)	15	6,786	0.76 (0.40–1.42)	0.76 (0.40–1.43)	0.84 (0.44–1.61)		
p_{trend}			0.501	0.600	0.544			0.879	0.913	0.667		
Total MET-score												
Q1 (0.0–9.5)	59	22,267	1.0	1.0		47	13,597	1.0	1.0			
Q2 (11.5–23.0)	56	19,861	1.13 (0.78–1.63)	1.15 (0.80–1.66)		24	11,096	0.65 (0.40–1.07)	0.66 (0.40–1.08)			
Q3 (23.5–45.5)	68	21,192	1.28 (0.91–1.82)	1.33 (0.93–1.89)		26	12,087	0.64 (0.40–1.04)	0.66 (0.40–1.07)		0.441	0.414
Q4 (46.0–96.5)	54	19,543	1.15 (0.79–1.67)	1.19 (0.82–1.74)		18	10,970	0.50 (0.29–0.87)	0.52 (0.30–0.91)			
Q5 (≥97.0)	48	19,270	1.10 (0.75–1.62)	1.15 (0.78–1.70)		24	10,865	0.71 (0.43–1.17)	0.71 (0.43–1.17)			
p_{trend}			0.895	0.727				0.253	0.273			

[a] Postmenopausal women with "unknown MHT status ($n = 143$) were excluded from the ever used/never used stratified analysis

[b] Adjusted for entry age, body mass index, age at menarche, parity, age at first birth, family history of breast cancer, personal history of breast disease, OC use, race, smoking, and alcohol consumption. Model conducted among postmenopausal women were additionally adjusted for age at menopause

inconclusive. Among studies that differentiate between exercise intensity, most report stronger breast cancer risk reduction associated with strenuous physical activity [14, 15, 30, 31]. However, several studies have also observed risk reductions with moderate forms of physical activity [5, 12, 13, 19, 21, 32–34]. With regard to strenuous activity, results of the present study are similar to those reported by Dorn et al. [14] where breast cancer risk reduction was modest in the highest level of activity and no evidence of a dose–response relationship was observed.

Few studies [5, 14, 35] have specifically evaluated the effects of walking on breast cancer risk. In the current study, women reporting the highest levels of walking/hiking for exercise (10 or more hours per week) experienced the greatest reduction in breast cancer risk, even after accounting for strenuous activity. Modest risk reduction was also observed for women reporting the highest levels of walking at home or work. These findings are promising and suggest that women may not necessarily have to engage in the most strenuous activities to reduce their breast cancer risk. Discrepancies across study results may be attributed to difficulty in accurately recalling moderate levels of intensity as opposed to more strenuous forms of exercise as has been described previously [36, 37].

Findings from our study of pre-menopausal women add to the data suggesting that increased physical activity may decrease risk of breast cancer in this population. Results from previous studies of premenopausal women have been largely inconsistent [6]. Some studies have observed a decreased risk of breast cancer among premenopausal women [3, 32, 38, 39], whereas others have not [18, 30, 35, 40–43]. Results from the Nurses' Health Study I observed an approximately 20% risk reduction associated with the highest category of physical activity in both pre- and postmenopausal women [12]. However, the Nurses' Health Study II, which was conducted in a cohort of pre-menopausal women only, found no overall association between physical activity and risk of breast cancer [35].

Studies among postmenopausal women have consistently observed an inverse relationship between physical activity and breast cancer risk [3, 5, 6, 22, 29, 41]. A recent review [6] classified the evidence as strong for this association, with risk reductions in postmenopausal women ranging from 20 to 80%. In our study, MHT use among postmenopausal women modified the relationship between physical activity and risk of breast cancer. We found that among postmenopausal women who never used MHT, both moderate and strenuous physical activity reduced the risk of breast cancer. No reduction in risk with physical activity was observed for women who reported ever using MHT at baseline.

Evidence is accumulating that MHT use may modify the association between physical activity and breast cancer

risk. A study by Patel et al. [22] observed a stronger association between recreational physical activity and breast cancer among women who were not currently using MHT, similar to the results of our investigation. In a more recent study, both Hispanic and non-Hispanic white women who were postmenopausal and not recently exposed to hormones experienced the most consistent reduction in breast cancer risk [44]. Based on this pattern, it has been suggested that physical activity may affect breast cancer risk in postmenopausal women through hormonal pathways.

Several biologic mechanisms have been proposed to explain the association between physical activity and breast cancer risk. One likely explanation is that physical activity may reduce risk by diminishing adipose tissue. In postmenopausal women, adiposity increases the production of estrogen, which is the main source of circulating estrogen in women not taking MHT [18, 45]. Moderate levels of physical activity on hormone levels in women already at lower levels of baseline circulating estrogen may be sufficient to reduce breast cancer risk whereas more intense activity may be required in women with higher baseline levels of estrogen [22]. Other biological mechanisms proposed to explain the protective effect of physical avtivity include changes in insulin-related factors, regulation of the immune system, and hormonal and cellular metabolism pathways [16].

We found a slight decrease in breast cancer risk among postmenopausal ever-users of MHT who engaged in no walking at home/work compared to the reference group. A similar observation among all postmenopausal women was noted in a previous study [22]. As suggested in that report, this pattern may be due to the presence of conditions such as osteoporosis in "never walkers". Osteoporosis is associated with lower levels of circulating estrogens and consequently lower breast cancer risk; women with osteoporosis are also less likely to engage in physical activity. In the subgroup of postmenopausal women who reported never walking at home/work, women who ever took MHT were more likely to report osteoporosis than those reporting some walking. However, results did not change appreciably after excluding women who reported osteoporosis at baseline.

Strengths of this study include its prospective design, large cohort size and number of incident breast cancers, and extensive information on potential confounders and effect modifiers. Potential limitations of this study result from the use of self-reported physical activity measures. Because physical activity was not a primary study aim in the USRT study, only limited indicators of physical activity were included in the questionnaire for analysis, incomplete dietary information was available, and physical activity measures in our questionnaire were not specifically