



## Original Contribution

### Physical Activity and Albuminuria

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Higher urinary albumin excretion predicts future cardiovascular disease, hypertension, and chronic kidney disease. Physical activity improves endothelial function so activity may reduce albuminuria. Among diabetics, physical activity decreases albuminuria. In nondiabetics, prior studies have shown no association. The authors explored the cross-sectional association between physical activity and albuminuria in 3,587 nondiabetic women in 2 US cohorts, the Nurses' Health Study I in 2000 and the Nurses' Health Study II in 1997. Physical activity was expressed as metabolic equivalents per week. The outcome was the top albumin/creatinine ratio (ACR) decile. Multivariate logistic regression was used. Secondary analyses explored the ACR association with strenuous activity and walking. The mean age was 58.6 years. Compared with women in the lowest physical activity quintile, those in the highest quintile had a multivariate-adjusted odds ratio for the top ACR decile of 0.65 (95% confidence interval (CI): 0.46, 0.93). The multivariate-adjusted odds ratio for the top ACR decile for those with greater than 210 minutes per week of strenuous activity compared with no strenuous activity was 0.61 (95% CI: 0.37, 0.99), and for those in the highest quintile of walking compared with the lowest quintile, it was 0.69 (95% CI: 0.47, 1.02). Greater physical activity is associated with a lower ACR in nondiabetic women.

albuminuria; exercise; kidney diseases; proteinuria; walking

Abbreviations: ACR, albumin/creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; MET, metabolic equivalent; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; NSAID, nonsteroidal antiinflammatory drug.

Albuminuria is a known predictor of cardiovascular disease and chronic kidney disease (1). The albumin/creatinine ratio (ACR) is a valid estimate of daily albumin excretion (2). ACR values as low as 5 mg of albumin/g of creatinine when measuring ACR, or 6 mg/day of albumin excretion, have been shown to predict cardiovascular disease, incident hypertension, and all-cause mortality (1, 3, 4). Lifestyle factors that are associated with albuminuria even at these low levels could have important health implications.

Greater physical activity may be associated with less albuminuria. Physical activity has protective effects on the vascular endothelium in patients with cardiac diseases (5–7). Endothelial dysfunction in the renal vasculature is associated with albuminuria. If there are similar effects of physical activity on the renal vasculature as there are on the cardiac vasculature, physical activity could protect against

albuminuria (8). In diabetic populations, physical activity is associated with lower albumin excretion, and it has led to regression of albuminuria in 5 of 6 subjects with baseline microalbuminuria in an interventional study (9, 10). However, in nondiabetics, the 2 studies that have addressed this question have not found an association (11, 12).

The relation between physical activity and albuminuria is complicated by the phenomenon of postexercise proteinuria. Transient proteinuria, including albuminuria, is common after intense exercise, and the prevalence ranges from 18% to 100%, depending on the type and intensity of the exercise (13, 14). The mechanism may be related to increased acid or free radical production (14, 15).

Because the overall association between physical activity and albuminuria may be clinically meaningful in nondiabetic populations, we examined this association in 3,587

participants in 2 US cohorts, the Nurses' Health Study (NHS) I in 2000 and the NHS II in 1997.

## MATERIALS AND METHODS

### Study participants

NHS I began in 1976, when 121,700 female nurses aged 30–55 years completed a detailed questionnaire pertaining to health-related information such as illnesses, medications, and lifestyle. NHS II started in 1989, when 116,430 female nurses aged 25–42 years completed a similar questionnaire. Since the start of the studies, these women have completed questionnaires to update health-related information every 2 years and detailed dietary questionnaires every 4 years.

The NHS participants in this analysis were part of a study of analgesic use and renal function, since we have urinary albumin and creatinine measured for this cohort (16). This substudy was approved by the Brigham and Women's Hospital Institutional Review Board, and the use of this cohort for the current study was also approved by this review board. This subcohort included women who provided an initial blood sample in 1989 for NHS I ( $n = 32,826$ ) or a blood and urine sample in 1997 for NHS II ( $n = 29,616$ ) and returned a supplementary questionnaire about analgesic use in 1999 for NHS I ( $n = 3,876$ ) and 1998 for NHS II ( $n = 4,024$ ). We wanted to mail a supplementary questionnaire to a subset of these women who were likely to have a high lifetime intake of analgesics and women who were likely to have low intake. Therefore, we oversampled women who had reported a high frequency of analgesic use ( $\geq 15$  days per month) on biennial questionnaires and also women who reported no analgesic use on biennial questionnaires. NHS I participants included in this study also submitted blood and urine samples in 2000 ( $n = 3,123$ ). This was the first urine sample for this cohort. Because of financial constraints, 2,712 women from NHS I and 1,643 women from NHS II were selected for these analyses, with oversampling of those with the highest levels of lifetime analgesic consumption but including women of all levels of lifetime intake including low levels. Women with a history of cardiovascular disease or a history of cancer (except for nonmelanoma skin cancer) in 1989 for NHS I and 1997 for NHS II were excluded from the initial blood collection. However, women who developed cardiovascular disease or cancer after these dates were not excluded.

For the current study, we excluded 187 diabetics as well as 30 women with missing physical activity information. Diabetes was defined by self-report. Fifteen women with ACR values of greater than 355 mg/g of creatinine (the threshold for "macroalbuminuria" in women) (17) were also excluded, because it is likely that the mechanisms for small amounts of urinary albumin may be different from those for larger amounts of urinary albumin (18). Additionally, 34 women were excluded because of missing information regarding body mass index, serum creatinine, or ACR. We excluded 501 women whose urine samples were not first morning samples. First morning samples have been shown to be more accurate reflections of daily albumin excretion than spot samples (19), and we also wanted to avoid post-

exercise proteinuria (14). After exclusions, 3,587 women remained in the study, 2,317 from NHS I and 1,270 from NHS II. There were 163 women with missing information regarding walking who were excluded from the walking analysis.

### Assessment of physical activity

Physical activity information was obtained from the questionnaire in the year of the urine collection, which was in 2000 for NHS I and 1997 for NHS II. Participants were asked to report the average time each week spent on different forms of physical activity. Specifically, participants were asked about walking for exercise or to work, running, jogging, bicycling, tennis, squash, racquetball, lap swimming, "other aerobic exercise," low-intensity exercise, "other vigorous activities," weight training, and resistance exercise. Metabolic equivalent (MET) values were assigned on the basis of a standard classification (20) and are expressed as METs/week. A MET value is a ratio of the metabolic rate of an activity compared with the resting metabolic rate. For example, running is 12 METs and is presumed to require 12 times the energy required at rest. Physical activity was divided into quintiles for analysis, with the lowest quintile as the referent group. The validity and reproducibility of the physical activity questionnaire have been demonstrated in NHS II. The correlation coefficient between past-week activity recalls and the physical activity questionnaire was 0.79, and the test-retest correlation between 2 years was 0.59 (21). Secondary analyses examined the association between strenuous activity (defined as running, jogging, swimming laps, bicycling, tennis, squash, racquetball, and aerobics) and albuminuria, as well as the association between walking and albuminuria, because walking was the primary means of activity for many of our study participants.

### Assessment of covariates

Smoking status, body mass index, and multivitamin use were obtained from the 2000 questionnaire for NHS I and the 1997 questionnaire for NHS II. Information on current aspirin, acetaminophen, and nonsteroidal antiinflammatory drug (NSAID) use was also obtained from these questionnaires. Total lifetime analgesic use was obtained from the supplementary analgesic questionnaire. Alcohol and protein intake information was obtained from dietary questionnaires in 1998 and 2002 in NHS I and 1995 and 1999 in NHS II, the closest dietary surveys to the urine collections. These values were then averaged. The serum creatinine in blood samples from 2000 in NHS I and 1997 in NHS II was measured by using a modified Jaffe method (coefficient of variation, 10%); the estimated glomerular filtration rate (eGFR) was calculated by using the 4-variable Modification of Diet in Renal Disease formula for eGFR:  $186 \times [\text{creatinine}]^{-1.154} \times \text{age}^{-0.203} \times 0.742 (\times 1.21 \text{ if black})$  (22). History of hypertension, history of high cholesterol, and family history of hypertension were derived from questionnaires up to the year of the blood and urine collections. Participants taking anti-hypertensive medications were also classified as hypertensive. Blood pressure measurements were obtained from

self-report on the 1998 questionnaire for NHS I and the 1999 questionnaire for NHS II, the closest available dates. Self-reported diabetes and hypertension have been validated by medical record review in these cohorts and have been found to correlate with expected results (23, 24). Because our study participants were 96% Caucasian, race was not explored as a covariate.

### Assessment of the albumin/creatinine ratio

The ACR was calculated from the urinary albumin and creatinine measurements and expressed as milligrams of albumin per gram of creatinine (mg/g). Urinary albumin was measured by immunoassay (coefficient of variation, 8%). Urinary creatinine was measured by the modified Jaffe method (coefficient of variation, 2%).

### Statistical analysis

The ACR distribution was not normal and, because of the large number of values at or near zero, log transformation did not normalize the distribution. Therefore, ACR was analyzed as a dichotomous variable instead of as a continuous variable. In diabetics, studies of physical activity and albuminuria have looked at an outcome of "microalbuminuria" (9, 10, 25). However, our study included only nondiabetics, who have a much lower range of ACR values. On the basis of the cohort-specific ACR distributions as well as newer studies showing clinical significance of "normal" ACR levels (1, 3), we defined "cases" as the top decile (top 10%) of ACR values. We have previously shown that this outcome of top decile of ACR in our populations is correlated with the exposure of postmenopausal hormone use (26). The minimum value in the top decile was 9.0 mg/g in NHS I and 6.0 mg/g in NHS II. In secondary analyses, we also examined a cutoff of the cohort-specific top quartile (4.7 mg/g for NHS I and 3.6 mg/g for NHS II), because this had been used in prior studies (1, 3). We conducted additional analyses using cutoffs of 5 mg/g and 25 mg/g, the latter of which is the traditional definition for female-specific microalbuminuria (17).

Multivariate logistic regression was used to determine the odds ratio and 95% confidence interval of being a case by category of physical activity in the combined NHS I and NHS II cohorts. We decided a priori to include age, eGFR, body mass index, history of hypertension, and smoking status in the multivariate model. The following covariates were then examined as additional potential confounders: history of hypercholesterolemia, daily aspirin use, multivitamin use, alcohol intake, protein intake, family history of hypertension, and total lifetime use of aspirin, acetaminophen, or NSAIDs. In NHS I, we also considered postmenopausal hormone use and angiotensin-converting enzyme inhibitor or calcium channel blocker use. We did not have information on specific antihypertensives in NHS II, nor did we have enough postmenopausal women to explore postmenopausal hormone use. If inclusion of a covariate changed the odds ratio for physical activity by 10% or more, the covariate was included in the final model. We tested for an interaction between history of hypertension and body

mass index  $\geq 25$  kg/m<sup>2</sup> with physical activity in relation to albuminuria. We performed secondary analyses excluding women who reported that health problems limited moderate physical activity, as these health problems may also predispose them to an increased ACR. We also performed secondary analyses including those women with a urine sample that was not a known first morning urine sample. Some of these women may have exercised prior to giving a sample, and we were attempting to explore the impact of postexercise proteinuria.

All analyses were performed with SAS, version 9, statistical software (SAS Institute, Inc., Cary, North Carolina). All reported *P* values are 2 sided.

## RESULTS

### Characteristics of the cohort

Demographic, laboratory, and other health-related data are presented by quintile of physical activity in Table 1. There was no substantial difference in age among the groups. Those in the higher quintiles of physical activity had a lower prevalence of hypertension and high cholesterol, and they had lower blood pressures and body mass indexes. There were fewer current smokers in the highest quintile but more past smokers.

Unadjusted medians and interquartile ranges for urinary albumin, creatinine, and ACR are also displayed in Table 1. Urinary creatinine concentrations did not differ by level of physical activity. For the top decile of ACR, the median urinary albumin level was 11.3 mg/dL, and the median urinary creatinine level was 71.2 mg/dL. For those not in the top ACR decile, the median urinary albumin level was 1.8 mg/dL, and the median urinary creatinine level was 78.1 mg/dL.

### Primary analysis

After adjustment for age, women in the highest quintile of physical activity had a significantly lower odds of being in the top ACR decile (odds ratio = 0.65, 95% confidence interval (CI): 0.46, 0.91) (Table 2). Additional adjustment for body mass index, eGFR, hypertension, and smoking status did not substantially change the results. Further adjustment for all other potential confounders did not impact the results. The association did not vary by body mass index ( $P_{\text{interaction}} = 0.15$ ) or history of hypertension ( $P_{\text{interaction}} = 0.48$ ).

Effect estimates were similar with ACR quartiles, an ACR cutoff of  $\geq 5$  mg/g, and an ACR cutoff of  $\geq 25$  mg/g.

After excluding women who reported that health problems limit moderate physical activity, we found the effect estimates to be similar but not statistically significant. For example, the odds ratio for the highest quintile of physical activity compared with the lowest quintile was 0.74 (95% CI: 0.50, 1.09).

After including women whose urine was not a known first morning sample, we found that the results in NHS I were similar to those for the restricted cohort. However, for NHS II, the effect estimates were different. For example, compared with the first quintile, quintiles 2–5 had odds ratios of 0.93, 0.98, 1.11, and 0.72, respectively.

**Table 1.** Age-adjusted Characteristics of the Study Population by Quintile of Physical Activity in the Nurses' Health Study I, United States, 2000, and the Nurses' Health Study II, United States, 1997<sup>a</sup>

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
No.	728	702	730	707	720
Metabolic equivalents/week, median (range)	1.4 (0.2–3.4)	6.6 (3.5–9.2)	12.7 (9.3–17.1)	22.6 (17.2–30.7)	46.2 (30.9–223.3)
Age, years	59.3 (12.6)	57.7 (12.8)	58.5 (12.7)	58.4 (12.5)	59.2 (12.4)
Body mass index, kg/m <sup>2</sup>	28.2 (6.3)	26.8 (5.6)	26.1 (5.0)	25.2 (4.6)	24.9 (4.6)
Hypertension, %	47	42	38	35	34
Systolic blood pressure, <sup>b</sup> mm Hg	129.7 (14.9)	127.9 (13.4)	125.9 (13.9)	125.0 (13.8)	123.8 (14.3)
Diastolic blood pressure, <sup>b</sup> mm Hg	79.0 (8.4)	78.0 (7.9)	76.9 (8.2)	76.7 (8.5)	75.4 (8.8)
Hypercholesterolemia, %	49	51	47	40	42
eGFR, mL/minute/1.73 m <sup>2</sup>	83.4 (19.8)	85.1 (18.8)	83.0 (17.9)	83.0 (17.5)	82.2 (16.8)
Serum creatinine, mg/dL	0.80 (0.17)	0.78 (0.15)	0.79 (0.15)	0.79 (0.14)	0.80 (0.15)
Daily aspirin, %	32	31	33	28	31
Current smoking, %	9	7	7	6	5
Past smoking, %	37	37	38	40	46
Alcohol, g/day <sup>c</sup>	0.9 (0.0–5.0)	1.1 (0.0–5.6)	1.5 (0.0–7.6)	2.0 (0.0–7.2)	2.2 (0.0–8.3)
Daily multivitamin, %	61	63	62	60	59
Urinary albumin, mg/dL <sup>c</sup>	2.1 (1.2–4.0)	2.1 (1.2–3.7)	2.0 (1.2–3.6)	2.0 (1.2–3.7)	1.9 (1.1–3.2)
Urinary creatinine, mg/dL <sup>c</sup>	80 (54–120)	83 (53–128)	79 (52–120)	76 (49–121)	71 (49–114)
Urinary ACR, mg of albumin/g of creatinine <sup>c</sup>	2.7 (1.6–4.8)	2.7 (1.7–4.2)	2.6 (1.8–4.3)	2.7 (1.7–4.4)	2.6 (1.7–4.0)

Abbreviations: ACR, albumin/creatinine ratio; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation.

<sup>a</sup> Values are means (SD) except where noted.

<sup>b</sup> Values from 1998 because not recorded on 2000 survey.

<sup>c</sup> Values are medians (IQR); not age adjusted.

### Strenuous activity analysis

More than 210 minutes per week of strenuous activity were associated with a lower odds of being in the top ACR decile (multivariate odds ratio = 0.61, 95% CI: 0.37, 0.99;  $P_{\text{trend}} = 0.009$ ) when compared with no strenuous activity (Table 3).

### Walking time analysis

As 34% of the total METs expended in this population were from walking, we analyzed walking separately (Table 4). When compared with those in the lowest quintile, women

in the second through fifth quintiles of minutes of walking per week had a lower odds of being in the top ACR decile.

## DISCUSSION

Overall, physical activity was inversely and independently associated with albuminuria. This association held for both walking and strenuous activity.

### Clinical implications

Albuminuria at levels as low as 5 mg/g of creatinine is predictive of incident hypertension, major cardiovascular

**Table 2.** Age- and Multivariate-adjusted Odds Ratio of Being in the Top Decile of the Albumin/Creatinine Ratio by Quintile of Physical Activity in the Nurses' Health Study I, United States, 2000, and the Nurses' Health Study II, United States, 1997

	Quintiles of Physical Activity, METs/week									
	Quintile 1 (n = 728)		Quintile 2 (n = 702)		Quintile 3 (n = 730)		Quintile 4 (n = 707)		Quintile 5 (n = 720)	
Median	1.4		6.6		12.7		22.6		46.2	
Cases, no.	95		65		69		69		61	
	Odds Ratio (Referent)	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	
Age adjusted	1.0	0.73	0.52, 1.04	0.79	0.57, 1.11	0.86	0.62, 1.19	0.65	0.46, 0.91	
Multivariate adjusted <sup>a</sup>	1.0	0.71	0.51, 1.00	0.75	0.53, 1.04	0.77	0.55, 1.09	0.65	0.46, 0.93	

Abbreviation: MET, metabolic equivalent.

<sup>a</sup> Adjusted for age, estimated glomerular filtration rate, body mass index, hypertension, and smoking.

**Table 3.** Age- and Multivariate-adjusted Odds Ratio of Being in the Top Decile of the Albumin/Creatinine Ratio by Category of Strenuous Activity in the Nurses' Health Study I, United States, 2000, and the Nurses' Health Study II, United States, 1997

	Categories of Strenuous Activity, minutes/week									
	None (n = 1,618)	>0-60 (n = 616)		>60-120 (n = 423)		>120-210 (n = 370)		>210 (n = 287)		
Cases, no.	187	616		38		28		20		
	Odds Ratio (Referent)	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	
Age adjusted	1.0	0.84	0.61, 1.14	0.78	0.54, 1.12	0.64	0.42, 0.97	0.59	0.37, 0.96	
Multivariate adjusted <sup>a</sup>	1.0	0.84	0.62, 1.15	0.77	0.53, 1.11	0.66	0.44, 1.01	0.61	0.37, 0.99	

<sup>a</sup> Adjusted for age, estimated glomerular filtration rate, body mass index, hypertension, smoking, and walking.

events, and all-cause mortality, even in patients without a baseline history of cardiovascular disease (1, 3, 4). It is unlikely that albuminuria directly causes the vascular disease. Instead, although the pathophysiology is not completely elucidated, it seems that albuminuria is an early marker of generalized endothelial dysfunction and permeability (1, 27, 28). If this is the case, any intervention that prevents albuminuria may also confer protection on the endothelium and prevent progression from early endothelial dysfunction to clinical manifestations of cardiovascular disease.

Although the mean age of our population was 58.6 years, modifying risk factors for future development of hypertension is still paramount. The Systolic Hypertension in the Elderly Program known as the "SHEP Trial" demonstrated that, in individuals over the age of 60 years, treatment of systolic hypertension reduced both stroke and major cardiovascular events, and baseline hypertension was predictive of a more rapid decline in renal function (29, 30). The Hypertension in the Very Elderly Trial known as the "HYVET Trial" then demonstrated that even individuals with a mean age of 83.6 years had a benefit from antihypertensive treatment in preventing stroke, heart failure, and overall mortality (31). Therefore, prevention of albuminuria in this age group could be important in preventing the development of hypertension and subsequent major cardiovascular events.

### Comparison with prior studies

There are only 2 published studies exploring the relation between physical activity and albuminuria in the general population, and although the analytical approaches were different from ours, both of these studies found no association. Finkelstein et al. (11) studied 13,753 participants in the Third National Health and Nutrition Examination Survey (NHANES) aged 18 years or older. After multivariate adjustment, physical activity was not significantly associated with ACR. Stratified analyses for sex, age, and race did not alter this. There are some important differences between that study and ours that could account for these disparate results. The median ACR in NHANES was 14.7 mg/g in participants without metabolic syndrome, whereas in our population it was 2.9 mg/g. The NHANES population was 42% Caucasian, 27% African American, and 27% Mexican American, whereas ours was 96% Caucasian. African Americans and Mexican Americans are known to have a higher prevalence of microalbuminuria, which may account for the contrasting results (32). In addition, the NHANES used linear regression without log transformation. The likely clustering of ACR values at zero or the right skew of the data may have decreased power to detect an association. As it was not mentioned whether these were first-morning urine samples, there may have been some effect of postexercise proteinuria, biasing the results toward the null.

**Table 4.** Age- and Multivariate-adjusted Odds Ratio of Being in the Top Decile of the Albumin/Creatinine Ratio by Quintile of Walking in the Nurses' Health Study I, United States, 2000, and the Nurses' Health Study II, United States, 1997

	Quintiles of Walking, minutes/week									
	Quintile 1 (n = 535)	Quintile 2 (n = 802)		Quintile 3 (n = 783)		Quintile 4 (n = 670)		Quintile 5 (n = 634)		
Median, minutes/week	0	40		90		150		270		
Cases, no.	78	77		77		51		61		
	Odds Ratio (Referent)	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	
Age adjusted	1.0	0.64	0.45, 0.89	0.66	0.47, 0.92	0.49	0.34, 0.71	0.63	0.44, 0.90	
Multivariate adjusted <sup>a</sup>	1.0	0.64	0.45, 0.91	0.72	0.50, 1.02	0.57	0.38, 0.85	0.69	0.47, 1.02	

<sup>a</sup> Adjusted for age, estimated glomerular filtration rate, body mass index, hypertension, smoking, and strenuous activity.

Another study of 5,670 participants aged 40–78 years from a New Zealand workforce study also found no association between leisure-time physical activity and albuminuria in first-morning urine samples (12). The multivariate-adjusted odds ratio for slight albuminuria (29–299 mg/L in men and 30–299 mg/L in women) was 1.11 (95% CI: 0.85, 1.46) for moderate activity and 0.82 (95% CI: 0.55, 1.22) for vigorous activity when compared with no regular activity. There were several differences compared with our study that could account for these results. The definition they used for vigorous activity corresponded to 60 minutes/week of strenuous activity in our study. Our highest category was >210 minutes/week. In addition, they used albumin concentrations instead of ACR values. Failing to account for creatinine excretion or urinary concentration may increase misclassification, biasing results toward the null.

There are published studies of diabetics showing similar results to our study of nondiabetics. In the Finnish Diabetic Nephropathy Study, a cross-sectional analysis included 1,945 type 1 diabetics who gave three 24-hour urine specimens. Participants with microalbuminuria were more likely to participate only in low-intensity physical activity than those with normoalbuminuria ( $P \leq 0.05$ ) (33). An interventional study looked at urinary albumin excretion in a cohort of 30 type 2 diabetics at baseline and after a 6-month exercise program. Microalbuminuria was found in 6 participants at baseline. After 3 months, only 3 patients had microalbuminuria. After 6 months, only 1 patient still had microalbuminuria. Although there was no mention of whether any of the other 24 study subjects developed microalbuminuria, this study suggests that aerobic exercise may cause regression of albuminuria in diabetics (10).

**Potential mechanisms.** The mechanism for the benefit of physical activity on albuminuria is unknown but may be due to effects on the vascular endothelium, possibly mediated by nitric oxide. Damage to the renal vascular endothelium is associated with increased urinary albumin excretion (8). Nitric oxide is a vasorelaxant, and nitric oxide synthase inhibition in rats causes albuminuria (34). In patients with coronary artery disease, exercise training improves endothelium-dependent vasodilation in coronary vessels (6). In patients with congestive heart failure, physical exercise improves both endothelial nitric oxide formation and endothelium-dependent vasodilation of skeletal muscle vasculature (5). Physical activity could have similar effects on the renal vascular endothelium, decreasing albuminuria.

### Effect of postexercise proteinuria

Because physical activity can induce a transient increase in urinary albumin excretion, the association between regular physical activity and albuminuria can be difficult to study (13). We tried to minimize this effect by excluding women who did not have confirmed first-morning urine. This exclusion appeared to be important in NHS II, as the association was blunted when non-first morning urine samples were included.

### Limitations

Limitations of our study deserve mention. Our study was cross-sectional, so we could not determine temporality;

however, it is unlikely that small differences in urinary albumin excretion, all within the “normal” range, would impact a person’s behavior regarding physical activity. Despite multivariate adjustment for multiple potential confounders, there remains a possibility of residual confounding. Misclassification bias is possible because we had only 1 urine measurement; within-person variation in urinary albumin is as high as 14% over 2 days (35). However, this would bias results toward the null. Our study population was a subset of the main NHS cohorts, with oversampling from women with frequent analgesic use. Although NSAIDs have been shown to influence albuminuria, they usually cause larger amounts of albuminuria than we see here (36). In addition, a recent study by Agodoa et al. (37) found that there was no association between analgesic use and albuminuria. However, we carefully adjusted for analgesic use with no impact on results. Our study may not be generalizable to populations other than nondiabetic, Caucasian women.

### Conclusion

In conclusion, higher levels of physical activity are associated with lower urinary albumin excretion in nondiabetic women. Physical activity may be beneficial in reducing albuminuria.

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