Activity, Energy Intake, Obesity, and the Risk of Incident Kidney Stones in Postmenopausal Women: A Report from the Women's Health Initiative

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ABSTRACT

Obesity is a strong risk factor for nephrolithiasis, but the role of physical activity and caloric intake remains poorly understood. We evaluated this relationship in 84,225 women with no history of stones as part of the Women's Health Initiative Observational Study, a longitudinal, prospective cohort of postmenopausal women enrolled from 1993 to 1998 with 8 years' median follow-up. The independent association of physical activity (metabolic equivalents [METs]/wk), calibrated dietary energy intake, and body mass index (BMI) with incident kidney stone development was evaluated after adjustment for nephrolithiasis risk factors. Activity intensity was evaluated in stratified analyses. Compared with the risk in inactive women, the risk of incident stones decreased by 16% in women with the lowest physical activity level (adjusted hazard ratio [aHR], 0.84; 95% confidence interval [95% CI], 0.74 to 0.97). As activity increased, the risk of incident stones continued to decline until plateauing at a decrease of approximately 31% for activity levels ≥10 METs/wk (aHR, 0.69; 95% CI, 0.60 to 0.79). Intensity of activity was not associated with stone formation. As dietary energy intake increased, the risk of incident stones increased by up to 42% (aHR, 1.42; 95% CI, 1.02 to 1.98). However, intake <1800 kcal/d did not protect against stone formation. Higher BMI category was associated with increased risk of incident stones. In summary, physical activity may reduce the risk of incident kidney stones in postmenopausal women independent of caloric intake and BMI, primarily because of the amount of activity rather than exercise intensity. Higher caloric intake further increases the risk of incident stones.

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The prevalence of kidney stones is 8.8%, or 1 in 11 people, in the United States, and during the last 15 years the prevalence has increased by almost 70%.[1] The increased prevalence is especially pronounced among women and may be due to increased rates of obesity, weight gain, and metabolic syndrome.[1–3] Most visits for kidney stones occur in the outpatient setting. From 1992 to 2000, physician office visits primarily for kidney stones increased 43%, representing

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up to 1,825,000 annual visits.[4] This represents a significant burden of disease, and additional efforts are needed to help with prevention.

The increase in the prevalence of kidney stones has paralleled epidemic rates of obesity.[5] In multiple prior studies, obesity has been recognized as a strong and consistent risk factor for kidney stones.[2,6–9] The cause of this increased risk is not well understood. Although obesity and higher body mass index (BMI) are associated with changes in urinary pH and electrolytes, the link with nephrolithiasis probably involves more than an increased solute load due to excess nutrient intake.[6–8,10–12] It has been hypothesized that the proinflammatory state is associated with obesity and that metabolic syndrome may lead to stone formation.[13,14]

Several dietary factors have been linked to an increased risk of kidney stones.[9,15–18] For example, in clinical practice we recommend increased fluid intake, low sodium and low animal-protein intake, and normal calcium intake because these have all been shown to reduce stone recurrence.[19–21] Patients are often interested in dietary modification to prevent stone recurrence.[22]

A person's present-day BMI reflects their historic balance between energy intake and energy expenditure. A restriction in dietary energy intake or increase in energy expenditure might partially offset the risk of stone formation imparted by BMI. The purpose of this study was to evaluate the independent relationship between physical activity, dietary energy intake, and BMI and the risk of incident kidney stone formation.

RESULTS

Of the 84,225 women in our cohort, 2392 reported an incident kidney stone during 610,290 person-years of follow-up. The mean age±SD was 64±7 years, and 84% of women were white (Table 1). In unadjusted analyses, BMI, raw and calibrated dietary energy intake, and physical activity were associated with incident kidney stones (Table 2).

Association between BMI and Nephrolithiasis

In multivariate analyses, higher BMI category was associated with a 1.30-fold (95% confidence interval [95% CI], 1.17 to 1.44) to 1.81-fold (95% CI, 1.57 to 2.10) increased risk of incident kidney stones compared with women with a normal BMI ($P<0.001$) after adjustment for nephrolithiasis risk factors (Table 3).

Independent Association between Physical Activity, Energy Intake, and BMI and Nephrolithiasis

Weekly physical activity, calibrated dietary energy intake, and BMI were each independently associated with incident kidney stones after adjustment for nephrolithiasis risk factors (Table 4). Women in the lowest physical activity category (0.1–4.9 metabolic equivalents [METs]/wk) had a 16% (adjusted hazard ratio [aHR], 0.84; 95% CI, 0.74 to 0.97) decreased risk of incident kidney stones compared with women who reported no physical activity. As weekly physical activity increased there was up to a 31% (aHR, 0.69; 95% CI, 0.58 to 0.83) decreased risk of kidney stone formation ($P<0.001$), with a progressive effect that plateaued above 10 METs/wk. Higher category of dietary energy intake increased the risk of incident kidney stones by up to 42% (aHR, 1.42; 95% CI, 1.02 to 1.98), with higher energy intake being associated with greater risk of kidney stones ($P<0.001$). However, low dietary energy intake (<1800 kcal/d) did not protect against incident kidney stones (aHR, 1.03; 95% CI, 0.74 to 1.43). In this model, higher BMI category remained associated with an increased risk of incident kidney stones ($P=0.01$).

Activity Intensity

In exploratory multivariate adjusted analyses, stone risk did not differ between patients who primarily performed mild, moderate, and strenuous intensity exercise when stratified by total METs per week category. Furthermore, the protective effect of higher total METs per week of physical activity on incident kidney stones was similar for women in all primary exercise categories. No significant interaction was seen between weekly physical activity, calibrated dietary energy intake, or BMI (physical activity×energy intake, $P=0.49$; energy intake×BMI, $P=0.23$; and physical activity×BMI, $P=0.85$). We found moderate correlation between calibrated energy intake and BMI ($r=0.67$) and minimal correlation between physical activity and energy intake ($r=-0.03$) and between physical activity and BMI ($r=-0.24$).

DISCUSSION

To our knowledge, this is the first study to assess the independent effect of weekly physical activity and dietary energy intake on the development of kidney stones. Postmenopausal women who performed greater amounts of physical activity were less likely to develop an incident kidney stone than inactive women, in adjusted analyses. A protective effect was identified even with small amounts of physical activity, and this protective effect increased as physical activity increased up to approximately 10 METs/wk. This threshold represents a moderate amount of weekly activity and is comparable to just over 3 hours of average walking (2–3 miles per hour), 4 hours of light gardening, or 1 hour of moderate jogging (6 miles per hour).[23] This effect appears to be driven primarily by the total amount of activity rather than the intensity of exercise.

Dietary energy intake >2200 kcal/d was associated with an increased risk of incident kidney stones. This risk increased with higher energy intake. However, women with the lowest dietary energy intake did not have a decreased risk of incident kidney stones. This effect appeared to be independent of macronutrient intake typically associated with kidney stone formation, including water, sodium, animal protein, and calcium. Thus, separate from the risk imparted by BMI and diet, a woman

Table 1. Demographic characteristics for postmenopausal women with and without an incident kidney stone in the WHI Observational Study

Characteristic	No Nephrolithiasis, *n* (%) (*n*=81,833 [97.2%])	Incident Nephrolithiasis, *n* (%) (*n*=2392 [2.8%])	*P* Value
Demographics and history			
Age at enrollment			0.003
50–59 yr	26,247 (32)	781 (33)	0.58
60–69 yr	36,298 (44)	1008 (42)	
≥70 yr	19,288 (24)	603 (25)	
Mean±SD (yr)	63.5±7.3	63.6±7.5	
Race/ethnicity			<0.001
White	69,363 (85)	1912 (80)	
Black	5982 (7)	232 (10)	
Hispanic	2746 (3)	120 (5)	
Asian or Pacific Islander	2308 (3)	67 (3)	
Native American	325 (<1)	16 (1)	
Other	893 (1)	34 (1)	
Baseline history of diabetes mellitus	3910 (5)	208 (9)	<0.001
Baseline supplemental calcium use	20,373 (25)	484 (21)	<0.001
Hormone replacement therapy			<0.001
None	31,793 (40)	957 (41)	
Prior	11,802 (15)	414 (18)	
Current	36,530 (46)	950 (41)	
BMI			<0.001
<18.5 kg/m^2 (underweight)	967 (1)	16 (1)	<0.001
18.5–24.9 kg/m^2 (normal weight)	32,910 (41)	718 (30)	
25–29.9 kg/m^2 (overweight)	27,567 (34)	817 (34)	
30–34.9 kg/m^2 (moderately obese)	12,347 (15)	486 (21)	
≥35 kg/m^2 (severely obese)	7118 (9)	333 (14)	
Mean±SD (kg/m^2)	27.1±5.8	28.8±6.5	
Household annual income			<0.001
<$50,000	44,265 (57)	1433 (62)	
≥$50,000	34,057 (43)	866 (38)	
Geographical region			0.03
Northeast	18,810 (23)	557 (23)	
South	20,802 (25)	655 (27)	
Midwest	18,267 (22)	486 (20)	
West	23,954 (29)	694 (29)	
Study participation follow-up (yr)			
Mean±SD	7.2±1.1	7.3±1.0	<0.001
Median (25th–75th percentile)	8 (7–8)	8 (7–8)	<0.001
Physical activity and dietary energy intake			
Any physical activity	70,542 (87)	1927 (82)	<0.001
Physical activity			<0.001
Inactive	10,391 (13)	428 (18)	<0.001
0.1–4.9 METs/wk	15,116 (19)	519 (22)	
5–9.9 METs/wk	13,666 (17)	404 (17)	
10–19.9 METs/wk	21,004 (26)	524 (22)	
20–29.9 METs/wk	10,847 (13)	250 (11)	
≥30 METs/wk	9909 (12)	230 (10)	
Mean±SD (METs/wk)	14.0±14.4	11.8±13.6	
Raw energy intake			<0.001
<1800 kcal/d	59,958 (73)	1683 (70)	<0.001
1800–1999 kcal/d	7294 (9)	197 (8)	
2000–2199 kcal/d	4984(6)	156 (7)	
2200–2499 kcal/d	4511 (6)	139 (6)	

might further increase her risk of incident nephrolithiasis by increasing her total dietary energy intake.

There are several possible explanations for the protective effect of exercise. Physical activity alters the handling of vitamins and minerals important in stone formation. Exercise stimulates thirst, leading to fluid intake in excess of what is lost during exercise, contributing to chronic expansion of total body water.[24] With increased physical activity, urinary sodium excretion decreases 50% because of a combination of increased renal tubular sodium reabsorption and increased sodium loss from sweating.[24,25] Overall, these effects stimulate a 20%–25% increase in circulating blood volume.[24,26–28] This increase in blood volume leads to less sympathetic nervous system stimulation, which is believed to be the primary mechanism by which exercise decreases cardiovascular disease. This decreased sodium excretion, increased fluid intake, and decreased sympathetic tone might all reduce the risk of stone formation. In addition, regular exercise, especially if weight-bearing, may increase or stabilize bone mineral density, and it is possible that this could lead to greater calcium deposition in the bone, rather than calcium excretion in the urine.[29–33] By contrast, individuals who are physically inactive have a contraction of blood volume, which increases the risk of cardiovascular disease by increasing LDL cholesterol levels, whole blood viscosity, and stimulation of the sympathetic nervous system.[34]

Table 1. Continued

Characteristic	No Nephrolithiasis, *n* (%) (*n*=81,833 [97.2%])	Incident Nephrolithiasis, *n* (%) (*n*=2392 [2.8%])	*P* Value
≥2500 kcal/d	5086 (6)	217 (9)	
Mean±SD (kcal/d)	1529±587	1574±679	
Calibrated energy intake			<0.001
<1800 kcal/d	2064 (3)	60 (3)	<0.001
1800–1999 kcal/d	19,288 (15)	491 (22)	
2000–2199 kcal/d	33,822 (44)	869 (39)	
2200–2499 kcal/d	17,774 (23)	651 (29)	
≥2500 kcal/d	3434 (5)	163 (7)	
Mean±SD (kcal/d)	2118±206	2157±235	

Unless otherwise noted, values are the number (percentage) of participants.

Table 2. Univariate odds of incident kidney stone formation in postmenopausal women in the WHI Observational Study

Variable	HR (95% CI)	*P* Value
BMI (kg/m^2)		<0.001
<18.5 kg/m^2 (underweight)	0.78 (0.48 to 1.29)	
18.5–24.9 kg/m^2 (normal weight)	Reference	
25–29.9 kg/m^2 (overweight)	1.37 (1.24 to 1.52)	
30–34.9 kg/m^2 (moderately obese)	1.84 (1.64 to 2.07)	
≥35 kg/m^2 (severely obese)	2.23 (1.96 to 2.54)	
Any physical activity	0.65 (0.59 to 0.72)	<0.001
Physical activity		<0.001
Inactive	Reference	
0.1–4.9 METs/wk	0.83 (0.73 to 0.94)	
5–9.9 METs/wk	0.72 (0.63 to 0.82)	
10–19.9 METs/wk	0.59 (0.52 to 0.67)	
20–29.9 METs/wk	0.54 (0.46 to 0.63)	
≥30 METs/wk	0.55 (0.46 to 0.64)	
Raw energy intake		<0.001
<1800 kcal/d	1.05 (0.91 to 1.22)	
1800–1999 kcal/d	Reference	
2000–2199 kcal/d	1.16 (0.94 to 1.43)	
2200–2499 kcal/d	1.14 (0.92 to 1.41)	
≥2500 kcal/d	1.59 (1.31 to 1.93)	
Calibrated energy intake (kcalories per day)		<0.001
<1800 kcal/d	1.20 (0.91 to 1.58)	
1800–1999 kcal/d	Reference	
2000–2199 kcal/d	0.98 (0.87 to 1.10)	
2200–2499 kcal/d	1.38 (1.23 to 1.55)	
≥2500 kcal/d	1.79 (1.49 to 2.14)	

Physical activity has compellingly been shown to reduce the risk of cardiovascular disease, stroke, hypertension, type 2 diabetes, osteoporosis, obesity, colon and breast cancer, anxiety, and depression.[35–37] Diet and exercise interventions improve BP, reduce insulin resistance, decrease visceral abdominal fat, improve lipoprotein profiles, and decrease the risk of diabetes in a dose-response fashion,[38–42] and all of these health factors are associated with kidney stone formation.

It is also possible that women who engage more physical activity are also implementing other dietary or healthy lifestyle interventions that decrease the risk of stone formation. Regardless, the finding that even mild to moderate weekly physical activity may protect against kidney stone formation is important. For almost everyone, exercise may represent a modifiable risk factor independent of many of the metabolic causes of kidney stones. This is particularly important because metabolic syndrome increases the risk of cardiovascular disease and CKD.[43–45] Exercise may protect against developing metabolic syndrome, and, especially in women, adiposity and physical activity are strong and independent predictors of death.[46]

Elevated BMI is a well established risk factor for developing kidney stones.[2,6–9] As was seen in previous studies, higher BMI category was independently associated with a greater risk of incident kidney stones in the postmenopausal women in this study. The cause of this increased risk is not well understood. BMI is one of many markers of obesity and is associated with a systemic inflammatory state in patients with metabolic syndrome.[13,14,47] Obesity is also a marker of prior energy balance: that is, the balance between energy taken in and energy expended. In this study, the final multivariate model, which included BMI, dietary energy intake, and weekly physical activity, demonstrated that BMI remained an independent predictor of incident kidney stones. Thus, the association between BMI and kidney stones, at least in the postmenopausal women in this study, cannot be explained exclusively by current rates of dietary energy intake or physical activity. This association remained true even after adjustment for known dietary risk factors for kidney stones, such as the intake of water, sodium, animal protein, and dietary calcium. Therefore, the increased risk linked to BMI is not primarily due to differences in the quality of dietary choices or macronutrient intake.

This study has several limitations. The study population is exclusively postmenopausal women, and these findings might vary in men or younger women. Thus, efforts are underway to confirm these findings in a different population. The exclusion of 3400 women with a history of kidney stones slightly reduced our study power but decreased the effect a prior stone event or patient education might have had on behavioral and dietary variables. The incidence of stones in our study is higher than in prior population-based reports. This may be partially due to increased imaging-detecting asymptomatic stones. In addition, although medical record review from Nurse's Health Study I and Health Professionals Follow up Study have

Table 3. Association between BMI category and incident kidney stones in multivariate-adjusted analyses

BMI	aHR[a] (95% CI)	*P* Value
		<0.001
<18.5 kg/m^2 (underweight)	0.79 (0.47 to 1.32)	
18.5–24.9 kg/m^2 (normal weight)	Reference	
25–29.9 kg/m^2 (overweight)	1.30 (1.17 to 1.44)	
30–34.9 kg/m^2 (moderately obese)	1.62 (1.43 to 1.83)	
≥35 kg/m^2 (severely obese)	1.81 (1.57 to 2.10)	

This model does not include physical activity or calibrated dietary energy intake.
[a]Adjusted for age (continuous); race (category); history of diabetes; use of calcium supplement; hormone replacement therapy (category); income (dichotomized); region (category); and quintile intake of water, sodium, animal protein, and dietary calcium.

Table 4. Independent association between weekly physical activity, calibrated energy intake, and BMI and risk of incident kidney stones in multivariate-adjusted analyses

Variable	aHR[a] (95% CI)	*P* Value
Physical activity		<0.001
Inactive	Reference	
0.1–4.9 METs/wk	0.84 (0.74 to 0.97)	
5–9.9 METs/wk	0.78 (0.68 to 0.90)	
10–19.9 METs/wk	0.69 (0.60 to 0.79)	
20–29.9 METs/wk	0.70 (0.59 to 0.83)	
≥30 METs/wk	0.69 (0.58 to 0.83)	
Calibrated energy intake		<0.001
<1800 kcal/d	1.03 (0.74 to 1.43)	
1800–1999 kcal/d	Reference	
2000–2199 kcal/d	1.04 (0.90 to 1.20)	
2200–2499 kcal/d	1.26 (1.03 to 1.55)	
≥2500 kcal/d	1.42 (1.02 to 1.98)	
BMI		0.01
<18.5 kg/m^2 (underweight)	0.79 (0.47 to 1.34)	
18.5–24.9 kg/m^2 (normal weight)	Reference	
25–29.9 kg/m^2 (overweight)	1.21 (1.07 to 1.37)	
30–34.9 kg/m^2 (moderately obese)	1.36 (1.13 to 1.63)	
≥35 kg/m^2 (severely obese)	1.31 (1.02 to 1.68)	

[a]Adjusted for age (continuous); race (category); history of diabetes; use of calcium supplement; hormone replacement therapy (category); income (dichotomized); region (category); and quintile intake of water, sodium, animal protein, and dietary calcium.

demonstrated a 97%–98% accuracy of self-reported stone events, the incident kidney stones in our study were not adjudicated.[17,18] It is reassuring that our prior study[9] identified similar significant dietary and demographic (*e.g.*, age, race, BMI) risk factors and degree of risk compared with the other large epidemiologic studies (the Health Professionals Follow up Study and especially Nurses Health Study I and II).

Self-reported dietary energy intake is often unreliable, and, despite calibration, we may have corrected only some of the biases associated with reporting.[48] Unfortunately, the only variable we were able to calibrate in our study was total dietary energy intake. Water and sodium intake are probably underestimated because the values are calculated on the basis of total beverage and food content of these factors but do not include additional quantities added in preparation or consumed at the table. In a future study we may evaluate the risk from fructose, sucrose, potassium, alcohol, and caffeine in these women, but these have been inconsistently reported as risk factors in the literature and so are not included in our current analyses. BMI, physical activity measurements of METs per week, and the calibration of energy intake are all related to weight, and this may partially attenuate the effect of each of these variables. METs are estimates of activity intensity and duration but do not take into account efficiency of movement or strength; they do not equate to calories burned because they do not account for resting metabolic rate or occupational physical activity. Finally, stone composition and 24-hour urine studies were not performed on these patients, and thus the effects of diet and exercise on urinary parameters are unknown.

In conclusion, mild to moderate amounts of weekly physical activity are associated with a decreased risk of development of kidney stones in postmenopausal women. This effect is driven primarily by the amount of physical activity rather than the intensity of exercise. In addition, higher total dietary energy intake is associated with an increased risk of incident nephrolithiasis, but a low dietary energy intake does not decrease the risk of kidney stones. These effects are independent of the contribution of BMI and other nephrolithiasis risk factors, including dietary intake of water, sodium, animal protein, and calcium. These findings have important clinical implications regarding dietary counseling and reinforcing patient efforts to lose weight and increase physical activity.

CONCISE METHODS

Participants

The prospective Women's Health Initiative (WHI) Observational Study is a longitudinal, multicenter study investigating the health of postmenopausal women.[49–51] A total of 93,676 women, age 50–79 years, enrolled from 1993 to 1998 and were followed for a median of 8 years. Women were identified at 40 clinical centers across the United States from population-based direct mailings to age-eligible women, in conjunction with media awareness programs. Efforts were made to recruit women of racial and ethnic minority groups with a target of 20% of overall enrollment. Participants completed health history questionnaires at enrollment and at 1-year intervals. History and occurrences of incident stones were documented by self-report at enrollment and each follow-up visit. The WHI food-frequency questionnaire was administered to participants at enrollment.[52] Women with a history of kidney stones at enrollment (*n*=3604) were excluded because they may have altered their diets in response to this event. We also excluded 2777 women who never answered the incident kidney stone question and 3,070 women who did not complete the food-frequency questionnaire or reported extreme degrees of energy intake (<600 or >5000 kcal/d).[52] Secondary analyses were performed on the final cohort of 84,225 women.

Measurements

Our primary aim was to evaluate the independent relationship between weekly physical activity, dietary energy intake, and BMI and incident nephrolithiasis. Physical activity was determined by a questionnaire that addressed the frequency, duration, and intensity of participation in different forms of physical activity. Weekly recreational physical activity and walking per kilogram was calculated by multiplying an assigned energy expenditure level for each category of activity by the hours exercised per week to calculate total metabolic equivalents per week (METs per week).[23,53–55] Physical activity was assessed categorically (inactive, 0.1–4.9, 5–9.9, 10–19.9, 20–29.9, ≥30 METs/wk). With use of a random sample of 536 participants, a second measure of all physical activity variables was ascertained approximately 10 weeks after baseline. The test-retest reliability (weighted κ) for the activity variables ranged from 0.53 to 0.72, and the intraclass correlation for total physical activity was 0.77, indicating strong agreement.[49]

Daily dietary energy and nutrient intake was determined by a semiquantitative food-frequency questionnaire targeting intake in the previous 3 months and analyzed using the University of Minnesota Nutrient Data System for Research software (Minneapolis, MN).[52] To correct some of the bias associated with self-reported intake, calibration of dietary energy intake (kilocalories per day) was performed as described elsewhere.[48,56,57] Bootstrapping (500 samples) generated 95% CIs for calibrated energy intake accounting for the sample variation in the calibration coefficient estimates. Calibrated dietary energy intake was analyzed categorically (<1800, 1800–2199, 2200–2499, ≥2500 kcal/d) with 1800–2199 kilocalories per day as the reference category.

Anthropometric variables including body weight were measured using standardized techniques. BMI was analyzed categorically (<18.5, 18.5–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2) as we expected a nonlinear effect of BMI on stone risk. Race/ethnicity was classified by participant and included as a confounder because of the differences in prevalence and incidence of stone formation.[1,58] Age was analyzed as a continuous variable. Baseline history of diabetes mellitus,[59] use of calcium supplements, hormone replacement therapy (none, prior, current), annual family income (<\$50,000 per year and ≥\$50,000 per year), and geographic region (Northeast, South, Midwest, West) were analyzed categorically. Dietary water, salt, animal protein, and calcium were categorized into quintiles.

Statistical Analyses

Baseline characteristics were calculated according to incident nephrolithiasis status. Chi-square analyses were used to compare categorical variables. A *t* test was used to compare continuous variables with normal distribution. Wilcoxon rank-sum test was used to compare continuous variables with non-normal distribution. Cox proportional hazards regression analysis with robust SEMs evaluated the association between BMI category and incident kidney stones with *a priori* adjustment for nephrolithiasis risk factors (age; race/ethnicity; diabetes mellitus; calcium supplementation; hormone replacement therapy; income; geographic region; and daily dietary intake quintiles of water, sodium, animal protein, and calcium). A second model assessed the independent association between weekly physical activity, calibrated dietary energy intake, BMI category, and incident stone formation, adjusting for nephrolithiasis risk factors. A likelihood ratio test was used to evaluate the importance of individual variables in the multivariate models. The potential interactions between calibrated dietary energy intake, weekly physical activity, and BMI were tested by including the product of the variables in a discrete regression model. A correlation matrix evaluated the potential colinearity of these three variables.

Exploratory analyses evaluated the effect of exercise intensity on incident stones accounting for total physical activity. The proportion of total METs per week spent engaged in mild, moderate, and strenuous exercise was determined. The categorization of a particular activity as mild, moderate, or strenuous was predetermined by the WHI. Each participant was then categorized into a primary exercise type (mild, moderate, or strenuous exerciser) on the basis of the greatest contributor to their total METs per week. The association between the participant's primary exercise type and incident kidney stones was evaluated in separate multivariate analyses stratified by total METs per week category adjusting for nephrolithiasis risk factors. This directly tested the significance of exercise intensity in women with similar total expended METs per week. Second, the association between total METs per week category and incident kidney stones was assessed in separate adjusted multivariate analyses stratified by primary exercise type. This evaluated the independent effect of total METs per week of physical activity among women primarily performing a similar intensity of activity.

HRs, aHRs, and 95% CIs were determined. All *P* values were two tailed, and statistical significance was set at $P<0.05$. Analyses were performed using Stata IC, version 10 (Stata Corp., College Station, TX), and SAS software, version 9.1 (SAS Institute, Cary, NC).

This study received institutional review board exemption. For the original WHI Observational Study, the appropriate institutional review board approvals were obtained at all participating institutions and written informed consent was obtained from all participants.

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DISCLOSURES

None.

REFERENCES

1. Scales CD Jr, Smith AC, Hanley JM, Saigal CS; Urologic Diseases in America Project: Prevalence of kidney stones in the United States. *Eur Urol* 62: 160–165, 2012
2. Taylor EN, Stampfer MJ, Curhan GC: Obesity, weight gain, and the risk of kidney stones. *JAMA* 293: 455–462, 2005
3. Taylor EN, Stampfer MJ, Curhan GC: Diabetes mellitus and the risk of nephrolithiasis. *Kidney Int* 68: 1230–1235, 2005
4. Pearle MS, Calhoun EA, Curhan GC; Urologic Diseases of America Project: Urologic diseases in America project: Urolithiasis. *J Urol* 173: 848–857, 2005
5. Lean M, Lara J, Hill JO: ABC of obesity. Strategies for preventing obesity. *BMJ* 333: 959–962, 2006
6. Taylor EN, Curhan GC: Body size and 24-hour urine composition. *Am J Kidney Dis* 48: 905–915, 2006
7. Lee SC, Kim YJ, Kim TH, Yun SJ, Lee NK, Kim WJ: Impact of obesity in patients with urolithiasis and its prognostic usefulness in stone recurrence. *J Urol* 179: 570–574, 2008
8. Hall WD, Pettinger M, Oberman A, Watts NB, Johnson KC, Paskett ED, Limacher MC, Hays J: Risk factors for kidney stones in older women in the southern United States. *Am J Med Sci* 322: 12–18, 2001
9. Sorensen MD, Kahn AJ, Reiner AP, Tseng TY, Shikany JM, Wallace RB, Chi T, Wactawski-Wende J, Jackson RD, O'Sullivan MJ, Sadetsky N, Stoller ML; WHI Working Group: Impact of nutritional factors on incident kidney stone formation: A report from the WHI OS. *J Urol* 187: 1645–1649, 2012
10. Maalouf NM, Sakhaee K, Parks JH, Coe FL, Adams-Huet B, Pak CY: Association of urinary pH with body weight in nephrolithiasis. *Kidney Int* 65: 1422–1425, 2004
11. Powell CR, Stoller ML, Schwartz BF, Kane C, Gentle DL, Bruce JE, Leslie SW: Impact of body weight on urinary electrolytes in urinary stone formers. *Urology* 55: 825–830, 2000
12. Siener R, Glatz S, Nicolay C, Hesse A: The role of overweight and obesity in calcium oxalate stone formation. *Obes Res* 12: 106–113, 2004
13. Rendina D, Mossetti G, De Filippo G, Benvenuto D, Vivona CL, Imbroinise A, Zampa G, Ricchio S, Strazzullo P: Association between metabolic syndrome and nephrolithiasis in an inpatient population in southern Italy: Role of gender, hypertension and abdominal obesity. *Nephrol Dial Transplant* 24: 900–906, 2009
14. West B, Luke A, Durazo-Arvizu RA, Cao G, Shoham D, Kramer H: Metabolic syndrome and self-reported history of kidney stones: The National Health and Nutrition Examination Survey (NHANES III) 1988-1994. *Am J Kidney Dis* 51: 741–747, 2008
15. Curhan GC, Willett WC, Knight EL, Stampfer MJ: Dietary factors and the risk of incident kidney stones in younger women: Nurses' Health Study II. *Arch Intern Med* 164: 885–891, 2004
16. Taylor EN, Stampfer MJ, Curhan GC: Dietary factors and the risk of incident kidney stones in men: New insights after 14 years of follow-up. *J Am Soc Nephrol* 15: 3225–3232, 2004
17. Curhan GC, Willett WC, Rimm EB, Stampfer MJ: A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med* 328: 833–838, 1993
18. Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ: Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. *Ann Intern Med* 126: 497–504, 1997
19. Taylor EN, Fung TT, Curhan GC: DASH-style diet associates with reduced risk for kidney stones. *J Am Soc Nephrol* 20: 2253–2259, 2009
20. Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Giannini A: Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: A 5-year randomized prospective study. *J Urol* 155: 839–843, 1996
21. Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, Novarini A: Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med* 346: 77–84, 2002
22. Consensus conference: Consensus conference. Prevention and treatment of kidney stones. *JAMA* 260: 977–981, 1988
23. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS: 2011 Compendium of Physical Activities: A second update of codes and MET values. *Med Sci Sports Exerc* 43: 1575–1581, 2011
24. Convertino VA: Blood volume: Its adaptation to endurance training. *Med Sci Sports Exerc* 23: 1338–1348, 1991
25. Wade CE: Response, regulation, and actions of vasopressin during exercise: A review. *Med Sci Sports Exerc* 16: 506–511, 1984
26. Kjellberg SR, Rudhe U, Sjostrand T: The correlation of the cardiac volume to the surface area of the body, the blood volume and the physical capacity for work. *Cardiologia* 14: 371–373, 1949
27. Brotherhood J, Brozović B, Pugh LG: Haematological status of middle- and long-distance runners. *Clin Sci Mol Med* 48: 139–145, 1975
28. Dill DB, Braithwaite K, Adams WC, Bernauer EM: Blood volume of middle-distance runners: Effect of 2,300-m altitude and comparison with non-athletes. *Med Sci Sports* 6: 1–7, 1974
29. Nelson ME, Fiatarone MA, Morganti CM, Trice I, Greenberg RA, Evans WJ: Effects of high-intensity strength training on multiple risk factors for osteoporotic fractures. A randomized controlled trial. *JAMA* 272: 1909–1914, 1994
30. Vezzoli G, Soldati L, Arcidiacono T, Terranegra A, Biasion R, Russo CR, Lauretani F, Bandinelli S, Bartali B, Cherubini A, Cusi D, Ferrucci L: Urinary calcium is a determinant of bone mineral density in elderly men participating in the InCHIANTI study. *Kidney Int* 67: 2006–2014, 2005
31. Pocock N, Eisman J, Gwinn T, Sambrook P, Kelly P, Freund J, Yeates M: Muscle strength, physical fitness, and weight but not age predict femoral neck bone mass. *J Bone Miner Res* 4: 441–448, 1989
32. Bevier WC, Wiswell RA, Pyka G, Kozak KC, Newhall KM, Marcus R: Relationship of body composition, muscle strength, and aerobic capacity to bone mineral density in older men and women. *J Bone Miner Res* 4: 421–432, 1989

33. Orwoll ES, Bauer DC, Vogt TM, Fox KM; Study of Osteoporotic Fractures Research Group: Axial bone mass in older women. *Ann Intern Med* 124: 187–196, 1996
34. Stevenson ET, Davy KP, Seals DR: Maximal aerobic capacity and total blood volume in highly trained middle-aged and older female endurance athletes. *J Appl Physiol (1985)* 77: 1691–1696, 1994
35. Reis JP, Loria CM, Sorlie PD, Park Y, Hollenbeck A, Schatzkin A: Lifestyle factors and risk for new-onset diabetes: A population-based cohort study. *Ann Intern Med* 155: 292–299, 2011
36. Johansen KL: Exercise in the end-stage renal disease population. *J Am Soc Nephrol* 18: 1845–1854, 2007
37. Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, Macera CA, Castaneda-Sceppa C; American College of Sports MedicineAmerican Heart Association: Physical activity and public health in older adults: Recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation* 116: 1094–1105, 2007
38. Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, Bales CW, Henes S, Samsa GP, Otvos JD, Kulkarni KR, Slentz CA: Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med* 347: 1483–1492, 2002
39. Lin JS, O'Connor E, Whitlock EP, Beil TL: Behavioral counseling to promote physical activity and a healthful diet to prevent cardiovascular disease in adults: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 153: 736–750, 2010
40. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346: 393–403, 2002
41. Mayer-Davis EJ, D'Agostino R Jr, Karter AJ, Haffner SM, Rewers MJ, Saad M, Bergman RN: Intensity and amount of physical activity in relation to insulin sensitivity: The Insulin Resistance Atherosclerosis Study. *JAMA* 279: 669–674, 1998
42. Johnson JL, Slentz CA, Houmard JA, Samsa GP, Duscha BD, Aiken LB, McCartney JS, Tanner CJ, Kraus WE: Exercise training amount and intensity effects on metabolic syndrome (from Studies of a Targeted Risk Reduction Intervention through Defined Exercise). *Am J Cardiol* 100: 1759–1766, 2007
43. Kurella M, Lo JC, Chertow GM: Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* 16: 2134–2140, 2005
44. Locatelli F, Pozzoni P, Del Vecchio L: Renal manifestations in the metabolic syndrome. *J Am Soc Nephrol* 17[Suppl 2]: S81–S85, 2006
45. Ratto E, Leoncini G, Viazzi F, Vaccaro V, Parodi A, Falqui V, Conti N, Tomolillo C, Deferrari G, Pontremoli R: Metabolic syndrome and cardiovascular risk in primary hypertension. *J Am Soc Nephrol* 17[Suppl 2]: S120–S122, 2006
46. Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE: Adiposity as compared with physical activity in predicting mortality among women. *N Engl J Med* 351: 2694–2703, 2004
47. Sowers JR, Whaley-Connell A, Epstein M: Narrative review: The emerging clinical implications of the role of aldosterone in the metabolic syndrome and resistant hypertension. *Ann Intern Med* 150: 776–783, 2009
48. Lichtman SW, Pisarska K, Berman ER, Pestone M, Dowling H, Offenbacher E, Weisel H, Heshka S, Matthews DE, Heymsfield SB: Discrepancy between self-reported and actual caloric intake and exercise in obese subjects. *N Engl J Med* 327: 1893–1898, 1992
49. Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M: The Women's Health Initiative Observational Study: Baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol* 13[Suppl]: S107–S121, 2003
50. The Women's Health Initiative Study Group: Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials* 19: 61–109, 1998
51. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J; Writing Group for the Women's Health Initiative Investigators: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 288: 321–333, 2002
52. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T: Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol* 9: 178–187, 1999
53. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr, Montoye HJ, Sallis JF, Paffenbarger RS Jr: Compendium of physical activities: Classification of energy costs of human physical activities. *Med Sci Sports Exerc* 25: 71–80, 1993
54. McTiernan A, Kooperberg C, White E, Wilcox S, Coates R, Adams-Campbell LL, Woods N, Ockene J; Women's Health Initiative Cohort Study: Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. *JAMA* 290: 1331–1336, 2003
55. Penson DF, Munro HM, Signorello LB, Blot WJ, Fowke JH; Urologic Diseases in America Project: Obesity, physical activity and lower urinary tract symptoms: Results from the Southern Community Cohort Study. *J Urol* 186: 2316–2322, 2011
56. Neuhouser ML, Tinker L, Shaw PA, Schoeller D, Bingham SA, Horn LV, Beresford SA, Caan B, Thomson C, Satterfield S, Kuller L, Heiss G, Smit E, Sarto G, Ockene J, Stefanick ML, Assaf A, Runswick S, Prentice RL: Use of recovery biomarkers to calibrate nutrient consumption self-reports in the Women's Health Initiative. *Am J Epidemiol* 167: 1247–1259, 2008
57. Prentice RL, Mossavar-Rahmani Y, Huang Y, Van Horn L, Beresford SA, Caan B, Tinker L, Schoeller D, Bingham S, Eaton CB, Thomson C, Johnson KC, Ockene J, Sarto G, Heiss G, Neuhouser ML: Evaluation and comparison of food records, recalls, and frequencies for energy and protein assessment by using recovery biomarkers. *Am J Epidemiol* 174: 591–603, 2011
58. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC: Time trends in reported prevalence of kidney stones in the United States: 1976-1994. *Kidney Int* 63: 1817–1823, 2003
59. Cameron MA, Maalouf NM, Adams-Huet B, Moe OW, Sakhaee K: Urine composition in type 2 diabetes: Predisposition to uric acid nephrolithiasis. *J Am Soc Nephrol* 17: 1422–1428, 2006

See related editorial, "New Insights Regarding the Interrelationship of Obesity, Diet, Physical Activity, and Kidney Stones," on pages 211–212.