# 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.

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

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 $\pm$ SD was $64 \pm 7$ 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/m² (underweight) | 967 (1) | 16 (1) | <0.001 |
| 18.5–24.9 kg/m² (normal weight) | 32,910 (41) | 718 (30) | |
| 25–29.9 kg/m² (overweight) | 27,567 (34) | 817 (34) | |
| 30–34.9 kg/m² (moderately obese) | 12,347 (15) | 486 (21) | |
| ≥35 kg/m² (severely obese) | 7118 (9) | 333 (14) | |
| Mean±SD (kg/m²) | 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/m²) | | <0.001 |
| <18.5 kg/m² (underweight) | 0.78 (0.48 to 1.29) | |
| 18.5–24.9 kg/m² (normal weight) | Reference | |
| 25–29.9 kg/m² (overweight) | 1.37 (1.24 to 1.52) | |
| 30–34.9 kg/m² (moderately obese) | 1.84 (1.64 to 2.07) | |
| ≥35 kg/m² (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/m² (underweight) | 0.79 (0.47 to 1.32) | |
| 18.5–24.9 kg/m² (normal weight) | Reference | |
| 25–29.9 kg/m² (overweight) | 1.30 (1.17 to 1.44) | |
| 30–34.9 kg/m² (moderately obese) | 1.62 (1.43 to 1.83) | |
| ≥35 kg/m² (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/m² (underweight) | 0.79 (0.47 to 1.34) | |
| 18.5–24.9 kg/m² (normal weight) | Reference | |
| 25–29.9 kg/m² (overweight) | 1.21 (1.07 to 1.37) | |
| 30–34.9 kg/m² (moderately obese) | 1.36 (1.13 to 1.63) | |
| ≥35 kg/m² (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 $\kappa$) 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 semi-quantitative 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.

Short list of WHI investigators includes the following: Program Office: Jacques Rossouw, Shari Ludlam, Dale Burwen, Joan McGowan, Leslie Ford, and Nancy Geller (National Heart, Lung, and Blood Institute, Bethesda, Maryland).

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## DISCLOSURES

None.

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