Obesity, Weight Gain, and the Risk of Kidney Stones

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Context Larger body size may result in increased urinary excretion of calcium, oxalate, and uric acid, thereby increasing the risk for calcium-containing kidney stones. It is unclear if obesity increases the risk of stone formation, and it is not known if weight gain influences risk.

Objective To determine if weight, weight gain, body mass index (BMI), and waist circumference are associated with kidney stone formation.

Design, Setting, and Participants A prospective study of 3 large cohorts: the Health Professionals Follow-up Study (N=45 988 men; age range at baseline, 40-75 years), the Nurses' Health Study I (N=93 758 older women; age range at baseline, 34-59 years), and the Nurses' Health Study II (N=101 877 younger women; age range at baseline, 27-44 years).

Main Outcome Measures Incidence of symptomatic kidney stones.

Results We documented 4827 incident kidney stones over a combined 46 years of follow-up. After adjusting for age, dietary factors, fluid intake, and thiazide use, the relative risk (RR) for stone formation in men weighing more than 220 lb (100.0 kg) vs men less than 150 lb (68.2 kg) was 1.44 (95% confidence interval [CI], 1.11-1.86; $P=.002$ for trend). In older and younger women, RRs for these weight categories were 1.89 (95% CI, 1.52-2.36; $P<.001$ for trend) and 1.92 (95% CI, 1.59-2.31; $P<.001$ for trend), respectively. The RR in men who gained more than 35 lb (15.9 kg) since age 21 years vs men whose weight did not change was 1.39 (95% CI, 1.14-1.70; $P=.001$ for trend). Corresponding RRs for the same categories of weight gain since age 18 years in older and younger women were 1.70 (95% CI, 1.40-2.05; $P<.001$ for trend) and 1.82 (95% CI, 1.50-2.21; $P<.001$ for trend). Body mass index was associated with the risk of kidney stone formation: the RR for men with a BMI of 30 or greater vs those with a BMI of 21 to 22.9 was 1.33 (95% CI, 1.08-1.63; $P<.001$ for trend). Corresponding RRs for the same categories of BMI in older and younger women were 1.90 (95% CI, 1.61-2.25; $P<.001$ for trend) and 2.09 (95% CI, 1.77-2.48; $P<.001$ for trend). Waist circumference was also positively associated with risk in men ($P=.002$ for trend) and in older and younger women ($P<.001$ for trend for both).

Conclusions Obesity and weight gain increase the risk of kidney stone formation. The magnitude of the increased risk may be greater in women than in men.

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Kidney stones are a major cause of morbidity. The lifetime prevalence of symptomatic nephrolithiasis is approximately 10% in men and 5% in women,[1-3] and more than $2 billion is spent on treatment each year.[4,5] About 80% of kidney stones contain calcium, and the majority of calcium stones consist primarily of calcium oxalate.[6,7] The identification of common, modifiable risk factors for kidney stones may result in new approaches to treatment and prevention.

Obesity is associated with insulin resistance and compensatory hyperinsulinemia, metabolic derangements that may lead to the formation of calcium-containing kidney stones. A recent metabolic trial demonstrated that insulin resistance was associated with defects in renal ammonium production,[8] and an examination of more than 4500 patients with a history of kidney stones showed that urinary pH was inversely related to body weight.[9] A defect in renal acid excretion could lead to hypocitraturia, an important risk factor for calcium nephrolithiasis.[6,10] Hyperinsulinemia may contribute to the development of calcium stones by increasing the urinary excretion of calcium.[11-13]

Larger body size may also result in increased urinary excretion of uric acid and oxalate, risk factors for calcium oxalate kidney stones.[14-16] In one study of nearly 6000 individuals with nephrolithiasis, men weighing more than 120 kg excreted 37% more uric acid than men who weighed less than 100 kg.[17] Similar results were seen in women.[17] Urinary oxalate excretion increases with increasing lean body mass, presumably reflecting changes in endogenous oxalate synthesis.[18]

Although larger body size may increase the urinary supersaturation of calcium salts, prospective data on the relation between body size and the risk of kidney stone formation are limited. We have previously reported on the association between higher body mass index (BMI) and an increased risk of incident nephrolithiasis in the Nurses' Health Study (NHS) I, a large cohort of older women.[19] However, we did not ob-

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serve this association in the Health Professionals Follow-up Study (HPFS), a cohort of men.[19] To date, no prospective study has evaluated the relation between body size and the risk of kidney stone formation in younger women, and no study has determined if weight gain influences risk. In addition, it is unknown if measures of central adiposity, such as waist circumference, are associated with risk.

To determine if weight, weight gain, BMI, and waist circumference are associated with incident kidney stone formation, we conducted a prospective study of 3 cohorts: the HPFS and the NHS I and II. Eight years of additional follow-up in the HPFS resulted in a near doubling of the number of incident kidney stones, providing a marked increase in statistical power to reevaluate the relation between BMI and stone formation in men. The inclusion of the NHS II in our analyses represents the first study of the relation between body size and kidney stone formation in younger women.

METHODS

Study Population

HPFS. In 1986, 51 529 male dentists, optometrists, osteopathic physicians, pharmacists, podiatrists, and veterinarians between the ages of 40 and 75 years completed and returned an initial questionnaire that provided detailed information on diet, medical history, and medications. This cohort, like those of the NHS I and NHS II, was followed by biennial mailed questionnaires that included inquiries about the incidence of newly diagnosed diseases such as kidney stones.

NHS I. In 1976, 121 700 female registered nurses between the ages of 30 and 55 years enrolled in the NHS I by completing and returning an initial questionnaire. Since we first asked NHS I participants about kidney stones in 1992, the current analysis was limited to women who answered questionnaires in 1992 or later. For this study we started follow-up in 1980, since before that date we lacked information on diet.

NHS II. In 1989, 116 671 female registered nurses between the ages of 25 and 42 years enrolled in the NHS II by completing and returning an initial questionnaire. Dietary information was first collected from this cohort in 1991.

Assessment of Body Size

For each cohort, information on weight and height was obtained on the baseline questionnaire. The baseline questionnaire also asked about weight in early adulthood (age 21 years in men and 18 years in women). Self-reported weight was updated every 2 years. Body mass index was calculated as the weight in kilograms divided by the square of height in meters. Self-reported weight has been validated in the HPFS and NHS I.[20] Self-reported weights from 123 men and 140 women in the 2 cohorts were highly correlated with values obtained by technicians who visited the participants at home ($r=0.97$ for men and women).[20]

Waist and hip circumference were reported in the HPFS in 1987 and 1996, in the NHS I in 1986 and 1996, and in the NHS II in 1993. For waist circumference, participants were instructed to measure their waist circumference at the level of the navel, and for hip circumference they were instructed to measure the largest circumference around the hips (including the buttocks). If a tape measure was not available, the questionnaire instructed participants to leave the question blank. The questionnaire also instructed the participants to perform the measurements while standing and to avoid measuring over bulky clothing. Participants reported their waist and hip circumference to the nearest quarter inch (0.64 cm). The self-reported measures of waist and hip circumference have also been validated: the correlation coefficients between self-reported waist and hip circumferences and measurements obtained by technicians sent to the homes of participants were 0.95 and 0.88, respectively, for men and 0.89 and 0.84, respectively, for women.[20]

Assessment of Diet

The semiquantitative food frequency questionnaire (first mailed to the HPFS in 1986, to the NHS I in 1980, and to the NHS II in 1991) asked about the annual average use of more than 130 foods and beverages. In addition, respondents provided information on the use of nutritional supplements, taken either alone or in multivitamin form. Subsequently, a version of this food frequency questionnaire has been mailed to study participants every 4 years. The reproducibility and validity of the food frequency questionnaires in the HPFS and NHS I have been documented.[21,22]

Nutrient intake was computed from the reported frequency of consumption of each specified unit of food and from United States Department of Agriculture data on the content of the relevant nutrient in specified portions. Nutrient values were adjusted for total caloric intake to determine the nutrient composition of the diet independent of the total amount of food eaten.[23,24]

The intake of supplements (such as vitamin C and calcium) in multivitamins or isolated form was determined by the brand, type, and frequency of reported use.

Assessment of Nondietary Covariates

Information on age was obtained on the baseline questionnaire. In the HPFS and NHS II, thiazide diuretic use was updated every 2 years. In the NHS I, thiazide use was determined in 1980, 1982, and then every 6 years until 1994, when biennial updates started. In the HPFS and NHS II, a family history of kidney stones was ascertained in 1994 and 1997, respectively. Information on hypertension and diabetes mellitus was obtained at baseline and then every 2 years. The validity of these self-reported diseases has been documented.[25-27]

Assessment of Kidney Stones

The primary outcome was an incident kidney stone accompanied by pain or hematuria. The participants reported on the interval diagnosis of kidney stones every 2 years. Any study participant who reported a new kidney stone was sent an additional questionnaire to determine the date of occurrence and the symptoms produced by the stone. We confirmed the validity of the self-reported stones in the HPFS by obtaining medical records from a random sample of 60 men in the cohort; chart review confirmed 97% of the cases.[28] A similar study in the NHS I examined medical records from a random sample of 90 women who reported a kidney stone. The records confirmed the diagnosis for all but 1 participant (98%).[29]

Statistical Analysis

The study design was prospective; information on body size was collected before the diagnosis of the kidney stone. For the HPFS, person-months of follow-up were counted from the date of the return of the 1986 questionnaire to the date of a kidney stone or death or to January 31, 2002 (whichever came first). For the NHS I, person-months of follow-up were counted from the date of the return of the 1980 questionnaire to the date of a kidney stone or death or to May 31, 2000. For the NHS II, person-months of follow-up were counted from the date of the return of the 1991 questionnaire to the date of a kidney stone or death or to May 31, 2001.

Weight was updated every 2 years. We allocated person-months of follow-up according to exposure status at the start of each follow-up period. If a participant did not provide a weight for a time period, the weight from the previous time period was used. However, if weight data were missing for more than 2 consecutive time periods, no value was imputed. Instead, the participant was assigned to the missing category for that time period. Of the 4827 incident kidney stones in the study, 33 occurred in participants missing data on weight. Missing values for height, waist circumference, and hip circumference were assigned to missing categories.

Categories of body size were chosen to examine relative extremes while preserving adequate person-time in each category. Body mass index categories were selected to include World Health Organization cutoffs for overweight (BMI ≥25) and obese (BMI ≥30). Unlike men, few women (especially in the NHS II) had a waist circumference greater than 43 in (109.2 cm); therefore, different categories of waist circumference were used for men and women (though the range from highest to lowest category of waist circumference was identical).

Dietary exposures were updated every 4 years. If complete information on diet was missing at the start of a time period, the participant was excluded for that time period.

We determined the relative risk (RR) of kidney stone formation for each category of body size compared with the referent category using Cox proportional hazards regression. The Mantel extension test was used to evaluate linear trends across categories of body size.

We adjusted our analyses for age (continuous), the use of thiazide diuretics (yes or no), alcohol intake (7 categories), supplemental calcium use (4 categories), and dietary intake of fluid, animal protein, calcium, magnesium, phosphorous, phytate, potassium, sodium, sucrose, vitamin B_6, vitamin C, and vitamin D (quintile groups). To account for the fact that a given weight gain in a heavier individual represents a smaller fractional increase than the same weight gain in a lighter individual, we adjusted our weight change analyses for baseline weight. We calculated 95% confidence intervals (CIs) for all RRs. All P values are 2-tailed; $P<.05$ was used to determine statistical significance.

All data were analyzed using SAS version 8.2 (SAS Institute Inc, Cary, NC). The study was approved by the human research committees at the Harvard School of Public Health and Brigham and Women's Hospital, Boston, Mass; completion of the self-administered questionnaire was considered to imply informed consent.

RESULTS

After excluding participants with a history of kidney stones at baseline, we studied a total of 45 988 men (HPFS), 93 758 older women (NHS I), and 101 877 younger women (NHS II).

Over a combined 2 808 334 person-years of follow-up, we documented 4827 new symptomatic kidney stones: 1609 in the HPFS, 1687 in the NHS I, and 1531 in the NHS II. The unadjusted incidence of stones was 301 per 100 000 person-years in the HPFS, 117 per 100 000 person-years in the NHS I, and 183 per 100 000 person-years in the NHS II.

Weight

Greater weight was associated with an increased risk of incident kidney stone formation in men (HPFS) and in older and younger women (NHS I and NHS II) (TABLE 1). The multivariable RR in men weighing more than 220 lb (100.0 kg) compared with men weighing less than 150 lb (68.2 kg) was 1.44 (95% CI, 1.11-1.86; $P=.002$ for trend). In older and younger women for the same weight comparisons, the multivariable RRs were 1.89 (95% CI, 1.52-2.36; $P<.001$ for trend) and 1.92 (95% CI, 1.59-2.31; $P<.001$ for trend), respectively. Since women weighed less on average than men, we also determined the risk of stone formation in women who weighed less than 130 lb (59.1 kg). No appreciable difference in risk was observed in younger or older women who weighed between 130 and 149 lb (59.1-67.7 kg) compared with those who weighed less than 130 lb.

Weight Change

Weight gain since early adulthood (age 21 years in men and age 18 years in women) was associated with an increased risk of incident kidney stone formation in both men and women (TABLE 2). The multivariable RR in men who gained more than 35 lb (15.9 kg) since early adulthood compared with those whose weight did not change was 1.39 (95% CI, 1.14-1.70; $P=.001$ for trend). The corresponding multivariable RRs for older and younger women were 1.70 (95% CI, 1.40-2.05; $P<.001$ for trend) and 1.82 (95% CI, 1.50-2.21; $P<.001$ for trend), respectively.

Table 1. Weight and the Relative Risk of Symptomatic Kidney Stones in Men (HPFS) and Older and Younger Women (NHS I and NHS II)*

	Weight, lb (kg)					
	<150 (68.2)	150-169 (68.2-76.8)	170-189 (77.3-85.9)	190-220 (86.4-100.0)	>220 (100.0)	*P* Value for Trend
HPFS						
Category median, lb (kg)	142 (64.5)	160 (72.7)	178 (80.9)	200 (90.9)	235 (106.8)	
Cases of new stones	108	379	543	418	132	
Person-years	46 332	137 820	167 603	130 239	37 681	
Age-adjusted RR (95% CI)	1.00	1.11 (0.90-1.37)	1.26 (1.03-1.56)	1.23 (0.99-1.52)	1.32 (1.02-1.70)	.02
Fully adjusted RR (95% CI)†	1.00	1.15 (0.93-1.43)	1.34 (1.09-1.66)	1.33 (1.07-1.65)	1.44 (1.11-1.86)	.002
NHS I						
Category median, lb (kg)	132 (60.0)	158 (71.8)	177 (80.5)	200 (90.9)	240 (109.1)	
Cases of new stones	750	401	240	198	96	
Person-years	772 856	320 732	175 003	118 065	46 382	
Age-adjusted RR (95% CI)	1.00	1.27 (1.12-1.43)	1.37 (1.18-1.58)	1.65 (1.41-1.93)	1.99 (1.61-2.46)	<.001
Fully adjusted RR (95% CI)†	1.00	1.29 (1.14-1.46)	1.37 (1.18-1.59)	1.61 (1.37-1.89)	1.89 (1.52-2.36)	<.001
NHS II						
Category median, lb (kg)	130 (59.1)	156 (70.9)	177 (80.5)	200 (90.9)	245 (111.4)	
Cases of new stones	712	290	194	193	140	
Person-years	466 077	157 863	88 842	74 364	46 872	
Age-adjusted RR (95% CI)	1.00	1.22 (1.06-1.40)	1.46 (1.25-1.71)	1.75 (1.49-2.05)	2.02 (1.68-2.42)	<.001
Fully adjusted RR (95% CI)†	1.00	1.26 (1.10-1.45)	1.49 (1.27-1.75)	1.73 (1.47-2.04)	1.92 (1.59-2.31)	<.001

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; RR, relative risk.
*For illustrative purposes, category medians for weight were derived from responses to the 1990 (HPFS), 1992 (NHS I), and 1991 (NHS II) questionnaires. However, the period-specific category values were used for the complete analyses.
†The fully adjusted model includes age, use of thiazide diuretics (yes or no), alcohol use (7 categories), calcium supplement use (4 categories), and dietary intake of fluid, animal protein, calcium, magnesium, potassium, sodium, and vitamin C (all in quintiles).

Table 2. Weight Change and the Relative Risk of Symptomatic Kidney Stones in Men (HPFS) and Older and Younger Women (NHS I and NHS II)*

	Weight Change, lb (kg)					
	<–5 (–2.3)	–5 to +4 (–2.3 to +1.8)	+5 to +19 (+2.3 to +8.6)	+20 to +35 (+9.1 to +15.9)	>+35 (+15.9)	*P* Value for Trend
HPFS						
Category median, lb (kg)	–13 (–5.9)	0	+11 (+5.0)	+25 (+11.4)	+45 (+20.5)	
Cases of new stones	96	146	498	398	345	
Person-years	39 832	59 282	159 203	125 009	102 337	
Age-adjusted RR (95% CI)	1.03 (0.79-1.33)	1.00	1.26 (1.05-1.52)	1.32 (1.09-1.60)	1.45 (1.19-1.76)	<.001
Fully adjusted RR (95% CI)†	1.05 (0.81-1.36)	1.00	1.24 (1.03-1.49)	1.27 (1.04-1.53)	1.39 (1.14-1.70)	.001
NHS I						
Category median, lb (kg)	–14 (–6.4)	0	+12 (+5.5)	+26 (+11.8)	+50 (+22.7)	
Cases of new stones	85	132	324	367	672	
Person-years	105 953	151 132	362 574	324 929	413 853	
Age-adjusted RR (95% CI)	0.94 (0.72-1.24)	1.00	1.02 (0.83-1.25)	1.27 (1.04-1.55)	1.80 (1.49-2.17)	<.001
Fully adjusted RR (95% CI)†	0.93 (0.71-1.23)	1.00	1.00 (0.82-1.22)	1.23 (1.01-1.50)	1.70 (1.40-2.05)	<.001
NHS II						
Category median, lb (kg)	–12 (–5.5)	0	+10 (+4.5)	+25 (+11.4)	+50 (+22.7)	
Cases of new stones	81	134	353	324	620	
Person-years	52 658	96 155	246 143	186 784	245 635	
Age-adjusted RR (95% CI)	1.11 (0.84-1.47)	1.00	1.05 (0.86-1.28)	1.30 (1.06-1.59)	1.92 (1.59-2.32)	<.001
Fully adjusted RR (95% CI)†	1.13 (0.86-1.50)	1.00	1.03 (0.84-1.26)	1.27 (1.03-1.55)	1.82 (1.50-2.21)	<.001

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; RR, relative risk.
*For illustrative purposes, category medians for weight gain were derived from responses to the 1990 (HPFS), 1992 (NHS I), and 1991 (NHS II) questionnaires. However, the period-specific category values were used for the complete analyses. Relative risks are for the risk for stone formation compared with the group that had a median weight gain of zero pounds.
†The fully adjusted model includes age, baseline weight at age 21 years (HPFS) or 18 years (NHS I and NHS II), use of thiazide diuretics (yes or no), alcohol use (7 categories), calcium supplement use (4 categories), and dietary intake of fluid, animal protein, calcium, magnesium, potassium, sodium, and vitamin C (all in quintiles).

Weight loss was not associated with a reduced risk of kidney stone formation. However, only 7% of the total person-time in the study was contributed by participants who lost weight since early adulthood.

Body Mass Index

Body mass index was positively associated with the risk of kidney stone formation in both men and women (TABLE 3). The multivariable RR in men with a BMI of 30 or greater compared with men with a BMI of 21 to 22.9 was 1.33 (95% CI, 1.08-1.63; $P<.001$ for trend). In older and younger women the corresponding multivariable RRs were 1.90 (95% CI, 1.61-2.25; $P<.001$ for trend) and 2.09 (95% CI, 1.77-2.48; $P<.001$ for trend), respectively.

The multivariable RRs in older and younger women with a BMI of 35 or greater compared with women with a BMI between 21 and 23 were 2.27 (95% CI, 1.85-2.81) and 2.28 (95% CI, 1.87-2.79), respectively. There was inadequate person-time to evaluate the RR of men with a BMI of 35 or greater (only 1.5% of the total person-time in men was contributed by such individuals).

For men in the referent category of BMI (21-22.9), the annual incidence of kidney stones was 278 per 100 000 men. The population-attributable risk of developing an incident kidney stone associated with a BMI of 23 or greater was 31 per 100 000 men annually. For older and younger women in the referent category of BMI, the annual incidence of kidney stones was 84 per 100 000 women and 131 per 100 000 women, respectively. The population-attributable risk of developing an incident kidney stone associated with a BMI of 23 or greater was 28 per 100 000 older women annually and 47 per 100 000 younger women annually.

Waist Circumference

Waist circumference was positively associated with the risk of incident kidney stone formation in both men and women (TABLE 4 and TABLE 5), even after adjusting for height. On average, men had a larger waist circumference than women. The multivariable RR for men with a waist circumference greater than 43 in (109.2 cm) compared with men with a waist circumference less than 34 in (86.4 cm) was 1.48 (95% CI, 1.13-1.93; $P=.002$ for trend). The multivariable RRs for older and younger women with a waist circumference greater than 40 in (101.6 cm) compared with women with a waist circumference less than 31 in (78.7 cm) were 1.71 (95% CI, 1.40-2.10; $P<.001$ for trend) and 1.94 (95% CI, 1.49-2.52; $P<.001$ for trend), respectively.

Hip circumference and the ratio of waist circumference to hip circumference were also associated with an increase in risk, but the magnitudes of the RRs were smaller than that seen with waist circumference alone.

Further adjustment for family history of kidney stones, diabetes, and hypertension did not materially change the results for any measure of body size.

COMMENT

Our results confirm that body size is independently associated with the development of incident kidney stones. Because lean body mass is positively correlated with percent body fat[30] and may play an important role in stone formation,[18] it is possible that greater lean body mass is at least partly responsible for the observed association between higher BMI and increased risk. However, the strong association between

Table 3. Body Mass Index and the Relative Risk of Symptomatic Kidney Stones in Men (HPFS) and Older and Younger Women (NHS I and NHS II)*

	BMI†						*P* Value for Trend
	<21	21-22.9	23-24.9	25-27.4	27.5-29.9	≥30	
HPFS							
Cases of new stones	40	200	362	537	255	186	
Person-years	20 193	71 863	138 174	163 510	74 629	51 061	
Age-adjusted RR (95% CI)	0.76 (0.54-1.07)	1.00	0.93 (0.78-1.10)	1.16 (0.98-1.36)	1.19 (0.99-1.44)	1.27 (1.04-1.55)	<.001
Fully adjusted RR (95% CI)‡	0.73 (0.52-1.03)	1.00	0.94 (0.79-1.12)	1.20 (1.02-1.41)	1.24 (1.03-1.50)	1.33 (1.08-1.63)	<.001
NHS I							
Cases of new stones	204	237	308	313	225	398	
Person-years	208 445	280 998	289 472	274 997	147 997	229 644	
Age-adjusted RR (95% CI)	1.19 (0.98-1.43)	1.00	1.26 (1.06-1.49)	1.34 (1.13-1.58)	1.77 (1.47-2.12)	1.98 (1.68-2.34)	<.001
Fully adjusted RR (95% CI)‡	1.15 (0.95-1.38)	1.00	1.26 (1.07-1.50)	1.34 (1.13-1.59)	1.75 (1.45-2.10)	1.90 (1.61-2.25)	<.001
NHS II							
Cases of new stones	253	222	232	234	146	403	
Person-years	159 992	169 482	144 984	125 419	68 208	145 244	
Age-adjusted RR (95% CI)	1.18 (0.98-1.41)	1.00	1.23 (1.02-1.48)	1.44 (1.20-1.74)	1.66 (1.35-2.05)	2.18 (1.85-2.57)	<.001
Fully adjusted RR (95% CI)‡	1.13 (0.94-1.36)	1.00	1.24 (1.04-1.50)	1.47 (1.22-1.77)	1.68 (1.36-2.07)	2.09 (1.77-2.48)	<.001

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; RR, relative risk.
*For illustrative purposes, category medians for BMI were derived from responses to the 1990 (HPFS), 1992 (NHS I), and 1991 (NHS II) questionnaires. However, the period-specific category values were used for the complete analyses. Relative risks are for the risk for stone formation compared with the group that had a BMI of 21-22.9.
†Calculated as weight in kilograms divided by the square of height in meters.
‡See Table 1 footnote for description of fully adjusted model used here.

weight gain since early adulthood and the risk of incident stone formation suggests that adiposity plays a central role in the relation between body size and nephrolithiasis. Although lean body mass does increase somewhat as the average individual gains weight, the majority of weight gain since early adulthood is due to increases in fat rather than muscle.[31] Furthermore, 2 distinct measures of obesity—body mass index and waist circumference adjusted for height—were associated with an increased risk of kidney stone formation.

In a prior analysis, we did not detect a statistically significant association between BMI and the risk of incident kidney stones in men.[19] However, the current study of the male cohort encompasses 8 years of additional follow-up and nearly twice the number of incident kidney stones.[19] Thus, the present study has a marked increase in statistical power.

The mechanism whereby obesity increases the risk of incident stone formation is uncertain. However, hyperinsulinemia is associated with obesity and has a significant effect on urine composition. More than 30 years ago, seminal work demonstrated that the ingestion of carbohydrates transiently increased the urinary excretion of calcium,[32] probably by decreasing the renal reabsorption of filtered calcium.[33] Subsequent animal experiments showed that this "carbohydrate-induced calciuria" could be inhibited by pharmacologically blocking the pancreatic secretion of insulin.[34] Experiments in humans undergoing euglycemic hyperinsulinemic clamp demonstrate that insulin, by an as-yet unknown mechanism, increases the kidney's fractional excretion of calcium.[11-13] Clamp studies have also suggested that insulin increases the intestinal absorption of calcium.[35] Insulin-mediated postprandial increases in levels of urinary calcium, coupled with postprandial increases in levels of urinary oxalate, could create a urinary environment highly conducive to the formation of calcium-containing stones.

Insulin resistance, also associated with obesity, can also alter the composition of the urine. Insulin resistance may manifest in the kidney as a defect in ammonium production and the ability to excrete acid.[36] Recent data in humans, also using hyperinsulinemic euglycemic clamp, have confirmed that insulin resistance is associated with

Table 4. Waist Circumference and the Relative Risk of Symptomatic Kidney Stones in Men (HPFS)*

	Waist Circumference, in (cm)					
	<34 (86.4)	34-36 (86.4-91.4)	37-39 (94.0-99.1)	40-43 (101.6-109.2)	>43 (109.2)	*P* Value for Trend
Category median, in (cm)	33.0 (83.9)	35.5 (90.2)	38.0 (96.5)	41.0 (104.1)	45.0 (114.3)	
Cases of new stones	123	387	366	232	106	
Person-years	47 536	130 720	120 335	76 537	34 356	
Age-adjusted RR (95% CI)	1.00	1.21 (0.99-1.49)	1.32 (1.08-1.63)	1.36 (1.09-1.69)	1.38 (1.06-1.80)	.007
Fully adjusted RR (95% CI)†	1.00	1.23 (1.00-1.51)	1.37 (1.11-1.69)	1.42 (1.13-1.78)	1.48 (1.13-1.93)	.002

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; RR, relative risk.
*For illustrative purposes, category medians for waist circumference were derived from responses to the 1996 questionnaire. However, the period-specific values were used for the complete analyses.
†The fully adjusted model includes age, height (in quintiles), use of thiazide diuretics (yes or no), alcohol use (7 categories), calcium supplement use (4 categories), and dietary intake of fluid, animal protein, calcium, magnesium, potassium, sodium, and vitamin C (all in quintiles).

Table 5. Waist Circumference and the Relative Risk of Symptomatic Kidney Stones in Older and Younger Women (NHS I and NHS II)*

	Waist Circumference, in (cm)					
	<31 (78.7)	31-33 (78.7-83.8)	34-36 (86.4-91.4)	37-40 (94.0-101.6)	>40 (101.6)	*P* Value for Trend
NHS I						
Category median, in (cm)	28.5 (72.4)	32.0 (81.3)	35.0 (88.9)	38.0 (96.5)	43.0 (109.2)	
Cases of new stones	349	235	217	164	143	
Person-years	389 075	213 295	166 447	118 773	86 769	
Age-adjusted RR (95% CI)	1.00	1.23 (1.04-1.46)	1.45 (1.22-1.73)	1.52 (1.26-1.84)	1.78 (1.45-2.17)	<.001
Fully adjusted RR (95% CI)†	1.00	1.24 (1.05-1.47)	1.44 (1.21-1.72)	1.49 (1.23-1.80)	1.71 (1.40-2.10)	<.001
NHS II						
Category median, in (cm)	28.0 (71.1)	32.0 (81.3)	35.0 (88.9)	38.0 (96.5)	44.0 (111.8)	
Cases of new stones	397	118	85	83	68	
Person-years	246 954	75 904	44 027	30 139	20 959	
Age-adjusted RR (95% CI)	1.00	0.98 (0.80-1.21)	1.22 (0.98-1.56)	1.77 (1.39-2.24)	2.08 (1.61-2.69)	<.001
Fully adjusted RR (95% CI)†	1.00	0.98 (0.80-1.21)	1.21 (0.96-1.54)	1.71 (1.34-2.17)	1.94 (1.49-2.52)	<.001

Abbreviations: CI, confidence interval; NHS, Nurses' Health Study; RR, relative risk.
*For illustrative purposes, category medians for waist circumference were derived from responses to the 1996 (NHS I) and 1993 (NHS II) questionnaire. However, the period-specific category values were used for the complete analyses.
†See Table 4 for description of fully adjusted model used here.

lower urinary pH and that urinary ammonium excretion in normal individuals increases during hyperinsulinemia.[8] Indeed, studies of 3 large groups of individuals with nephrolithiasis have demonstrated that higher weight is associated with lower urinary pH.[9,17] Although a lower urinary pH is generally associated with uric acid stones, an impaired ability to excrete acid could result in hypocitraturia, an important risk factor for calcium stones.

Urinary uric acid is a risk factor for calcium oxalate stones and is also positively associated with obesity. Higher serum uric acid levels in obese individuals may result from increased uric acid production, decreased renal excretion, or both.[37] Although no dietary information was available (high levels of purine intake can increase the production of uric acid), data from nearly 6000 individuals with a history of kidney stones suggests that urinary uric acid excretion is higher in heavier patients.[17] Men who weighed more than 120 kg had a urinary concentration of uric acid 13% greater than that for men who weighed less than 100 kg.[17] Similar changes were observed in women. A smaller study of about 500 individuals with nephrolithiasis showed a positive association between BMI and the urinary excretion of uric acid. In this study, men with a BMI of 30 or greater excreted 19% more urinary uric acid per day than men with a BMI less than 25 (similar results were seen in women).[38]

Although BMI increased risk in all 3 cohorts, the magnitude of this effect appeared greater in women. However, women generally have a higher percent body fat than men.[39] Therefore, a woman with a given BMI will, on average, have more adipose tissue than a man with the same BMI. In this way, the difference we observed in the relation between BMI and risk by sex could have more to do with estimation of adiposity than with any fundamental difference in physiology.

Higher lean body mass may account for the greater incidence of kidney stone formation in men compared with women. Previously, we analyzed the 24-hour urine composition in a subset of men and women from these cohorts.[40] Although the daily urine volume was similar in men and women, the absolute amount of most excreted solutes, including calcium, was higher in men.[40] Therefore, the concentration of lithogenic factors in the urine was greater in men than women. Some authorities have postulated that estrogen reduces the urinary excretion of calcium and therefore may lower the risk of calcium-containing kidney stones.[41] However, our group has found no independent association between menopause or postmenopausal hormone use and the risk of kidney stone formation.[42]

The limitations of our study deserve mention. The measures of body size used in our study were self-reported. However, validation studies demonstrated the accuracy of these reports. In addition, any misclassification is likely to be random with respect to case status and therefore would bias the study results toward the null. Because relatively few participants lost weight over time, our study also lacked statistical power to determine if weight loss reduced the risk of kidney stone formation. Furthermore, the generalizability of our results may be limited. Only a small proportion of our study population is nonwhite, and we do not have data on stone formation in men younger than 40 years. However, no data suggest that the effect of body size on urine composition varies by age or race. Finally, we currently lack 24-hour urine collections and analyses of stone composition from most of the participants in our study. Thus, we were unable to determine if larger body size increases the risk of certain stone types but not others. We also cannot ascertain if differences in urine composition are responsible for the effect of sex on the association between body size and the risk of nephrolithiasis.

In conclusion, our results show that obesity and weight gain are associated with an increased risk of symptomatic nephrolithiasis. The positive association between body size and the risk of kidney stone formation could not be explained by differences in the intake of dietary factors that affect risk. The magnitude of the increased risk may be higher in women. Future studies should explore the effect of obesity and sex on urine composition, and weight loss should be explored as a potential treatment to prevent kidney stone formation. For now, clinicians have an additional reason to encourage weight control in their patients.

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Study concept and design: Taylor, Curhan.
Acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis: Taylor, Stampfer, Curhan.
Drafting of the manuscript: Taylor.
Obtained funding; administrative, technical, or material support; study supervision: Stampfer, Curhan.

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REFERENCES

1. 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*. 2003;63:1817-1823.
2. Johnson CM, Wilson DM, O'Fallon WM, Malek RS, Kurland LT. Renal stone epidemiology: a 25-year study in Rochester, Minnesota. *Kidney Int*. 1979;16:624-631.
3. Hiatt RA, Dales LG, Friedman GD, Hunkeler EM. Frequency of urolithiasis in a prepaid medical care program. *Am J Epidemiol*. 1982;115:255-265.
4. Pearle M, Calhoun E, Curhan GC; National Institute of Diabetes and Digestive and Kidney Diseases. Urolithiasis. In: Litwin MS, Saigal CS, eds. *Urologic Diseases in America.* Washington, DC: US Dept of Health and Human Services; 2004:34.
5. Lingeman JE, Saywell RM Jr, Woods JR, Newman DM. Cost analysis of extracorporeal shock wave lithotripsy relative to other surgical and nonsurgical treatment alternatives for urolithiasis. *Med Care*. 1986;24:1151-1160.
6. Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. *N Engl J Med*. 1992;327:1141-1152.
7. Levy FL, Adams-Huet B, Pak CY. Ambulatory evaluation of nephrolithiasis: an update of a 1980 protocol. *Am J Med*. 1995;98:50-59.
8. Abate N, Chandalia M, Cabo-Chan AV Jr, Moe OW, Sakhaee K. The metabolic syndrome and uric acid neph-

rolithiasis: novel features of renal manifestation of insulin resistance. *Kidney Int*. 2004;65:386-392.
9. Maalouf NM, Sakhaee K, Parks JH, Coe FL, Adams-Huet B, Pak CY. Association of urinary pH with body weight in nephrolithiasis. *Kidney Int*. 2004;65:1422-1425.
10. Hamm LL. Renal handling of citrate. *Kidney Int*. 1990;38:728-735.
11. Kerstetter J, Caballero B, O'Brien K, Wurtman R, Allen L. Mineral homeostasis in obesity: effects of euglycemic hyperinsulinemia. *Metabolism*. 1991;40:707-713.
12. Shimamoto K, Higashiura K, Nakagawa M, et al. Effects of hyperinsulinemia under the euglycemic condition on calcium and phosphate metabolism in non-obese normotensive subjects. *Tohoku J Exp Med*. 1995;177:271-278.
13. Nowicki M, Kokot F, Surdacki A. The influence of hyperinsulinaemia on calcium-phosphate metabolism in renal failure. *Nephrol Dial Transplant*. 1998;13:2566-2571.
14. Coe FL, Kavalach AG. Hypercalciuria and hyperuricosuria in patients with calcium nephrolithiasis. *N Engl J Med*. 1974;291:1344-1350.
15. Pak CY, Arnold LH. Heterogeneous nucleation of calcium oxalate by seeds of monosodium urate. *Proc Soc Exp Biol Med*. 1975;149:930-932.
16. Coe FL, Strauss AL, Tembe V, Le Dun S. Uric acid saturation in calcium nephrolithiasis. *Kidney Int*. 1980;17:662-668.
17. Powell CR, Stoller ML, Schwartz BF, et al. Impact of body weight on urinary electrolytes in urinary stone formers. *Urology*. 2000;55:825-830.
18. Lemann J Jr, Pleuss JA, Worcester EM, Hornick L, Schrab D, Hoffmann RG. Urinary oxalate excretion increases with body size and decreases with increasing dietary calcium intake among healthy adults. *Kidney Int*. 1996;49:200-208.
19. Curhan GC, Willett WC, Rimm EB, Speizer FE, Stampfer MJ. Body size and risk of kidney stones. *J Am Soc Nephrol*. 1998;9:1645-1652.
20. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology*. 1990;1:466-473.
21. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol*. 1992;135:1114-1126, 1127-1136.
22. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122:51-65.
23. Willett WC. *Nutritional Epidemiology*. New York, NY: Oxford University Press; 1990.
24. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol*. 1986;124:17-27.
25. Colditz G, Marin P, Stampfer M, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol*. 1986;123:894-900.
26. Manson JE, Rimm EB, Stampfer MJ, et al. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet*. 1991;338:774-778.
27. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB. Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Arch Intern Med*. 2001;161:1542-1548.
28. 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*. 1993;328:833-838.
29. 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*. 1997;126:497-504.
30. Willett WC. *Nutritional Epidemiology*. 2nd ed. New York, NY: Oxford University Press; 1998.
31. Elia M. Obesity in the elderly. *Obes Res*. 2001;9(suppl 4):244S-248S.
32. Lemann J Jr, Piering WF, Lennon EJ. Possible role of carbohydrate-induced calciuria in calcium oxalate kidney-stone formation. *N Engl J Med*. 1969;280:232-237.
33. Lemann J Jr, Lennon EJ, Piering WR, Prien EL Jr, Ricanati ES. Evidence that glucose ingestion inhibits net renal tubular reabsorption of calcium and magnesium in man. *J Lab Clin Med*. 1970;75:578-585.
34. Wood RJ, Allen LH. Evidence for insulin involvement in arginine- and glucose-induced hypercalciuria in the rat. *J Nutr*. 1983;113:1561-1567.
35. Rumenapf G, Schmidtler J, Schwille PO. Intestinal calcium absorption during hyperinsulinemic euglycemic glucose clamp in healthy humans. *Calcif Tissue Int*. 1990;46:73-79.
36. Krivosikova Z, Spustova V, Dzurik R. Participation of P-dependent and P-independent glutaminases in rat kidney ammoniagenesis and their modulation by metabolic acidosis, hippurate and insulin. *Physiol Res*. 1998;47:177-183.
37. Yamashita S, Matsuzawa Y, Tokunaga K, Fujioka S, Tarui S. Studies on the impaired metabolism of uric acid in obese subjects: marked reduction of renal urate excretion and its improvement by a low-calorie diet. *Int J Obes*. 1986;10:255-264.
38. Siener R, Glatz S, Nicolay C, Hesse A. The role of overweight and obesity in calcium oxalate stone formation. *Obes Res*. 2004;12:106-113.
39. Blaak E. Gender differences in fat metabolism. *Curr Opin Clin Nutr Metab Care*. 2001;4:499-502.
40. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. *Kidney Int*. 2001;59:2290-2298.
41. Heller HJ, Sakhaee K, Moe OW, Pak CY. Etiological role of estrogen status in renal stone formation. *J Urol*. 2002;168:1923-1927.
42. Mattix Kramer HJ, Grodstein F, Stampfer MJ, Curhan GC. Menopause and postmenopausal hormone use and risk of incident kidney stones. *J Am Soc Nephrol*. 2003;14:1272-1277.

> The greater part of our happiness or misery depends on our dispositions and not our circumstances.
> —Martha Washington (1731-1802)

