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RECREATIONAL PHYSICAL ACTIVITY AND THE RISK OF CHOLECYSTECTOMY IN WOMEN

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ABSTRACT

Background Physical activity may be an important determinant of the risk of gallstone disease in women, both independently and as a result of its role in maintaining body weight.

Methods We prospectively studied recreational physical activity (such as jogging, running, and bicycling) and sedentary behavior (such as spending hours watching television) in relation to the risk of cholecystectomy, a surrogate for symptomatic cholelithiasis, in a cohort of 60,290 women who were 40 to 65 years of age in 1986 and had no history of gallstone disease. As part of the Nurses' Health Study, the women reported on questionnaires mailed to them every two years both their activity level and whether they had undergone cholecystectomy. During a 10-year follow-up period (1986 to 1996), 3257 cases of cholecystectomy were documented.

Results Recreational physical activity was inversely related to the risk of cholecystectomy. The multivariate relative risk for women in the highest as compared with the lowest quintile of physical activity was 0.69 (95 percent confidence interval, 0.61 to 0.78). In contrast, sedentary behavior was independently related to an increased risk of cholecystectomy. As compared with women who spent less than 6 hours per week sitting while at work or driving, women who spent 41 to 60 hours per week sitting had a multivariate relative risk of 1.42 (95 percent confidence interval, 1.06 to 1.89), and women who spent more than 60 hours per week sitting while at work or driving had a multivariate relative risk of 2.32 (95 percent confidence interval, 1.26 to 4.26). These associations persisted after we controlled for body weight and weight change.

Conclusions In women, recreational physical activity is associated with a decreased risk of cholecystectomy. The association is independent of other risk factors for gallstone disease, such as obesity and recent weight loss. (N Engl J Med 1999;341:777-84.)

GALLSTONES affect 10 to 15 percent of adults in the United States. Symptomatic gallstone disease is less frequent than asymptomatic disease but results in approximately 500,000 cholecystectomies each year. Among digestive diseases requiring hospitalization, gallstones are the most common and most costly; the estimated overall cost of hospitalization for gallstones exceeds $5 billion annually.[1]

In most Western countries, including the United States, an estimated 75 percent of gallstones are of the cholesterol type.[2] Cholesterol gallstones have many causes, but biliary hypersecretion of cholesterol is an important determinant.[3] This condition is profoundly exacerbated by obesity.[4] Obese persons are advised to lose weight to reduce their risk of gallstone disease[5] as well as of other chronic diseases. Rapid weight loss in obese patients is an additional risk factor for gallstones, however.[6]

The potential role of physical activity in preventing the formation of cholesterol gallstones is largely unknown. Physical inactivity is widespread.[7] Regular exercise — in addition to facilitating weight control, alone or in combination with dieting — improves several metabolic abnormalities related to both obesity and cholesterol gallstones, such as hyperinsulinemia, high levels of plasma triglycerides, and low levels of plasma high-density lipoprotein cholesterol.[8] Data supporting a benefit of exercise in preventing gallstone disease in women are limited to three case–control studies[9-11] and two cross-sectional studies.[12,13]

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Two prospective studies have found an inverse association between physical activity and gallstone disease in men.[14,15]

For a period of 10 years, we prospectively studied the total level of recreational physical activity and sedentary behavior in relation to the risk of cholecystectomy in a large cohort of women.

METHODS

Study Population

The Nurses' Health Study was established in 1976 when 121,700 female registered nurses in the United States, between the ages of 30 and 55 years, returned a mailed questionnaire that included items about their medical history and lifestyle. Since then, follow-up questionnaires have been mailed to the cohort every two years to identify newly diagnosed illnesses and to obtain updated information on medical conditions and exposures.

In 1986, the questionnaire was expanded to include a detailed assessment of common leisure-time physical activities. Of the 75,072 women who returned and completed the questionnaire, we excluded 9002 who reported a cholecystectomy or a diagnosis of gallstone disease before 1986, 4299 with cancer (except nonmelanoma skin cancer), and 1481 who completed the food-frequency questionnaire inadequately. The cohort that we studied consisted of the remaining 60,290 women, who were followed until May 31, 1996.

Assessment of Physical Activity

In 1986, 1988, 1992, and 1994, the questionnaire contained a section on mainly nonoccupational physical activities the participants had engaged in throughout the preceding year. The women reported the average time they spent per week in each of the following eight activities: jogging (slower than 10 minutes per mile [6 minutes per kilometer]); running (10 minutes per mile or faster); bicycling (including on stationary machines); lap swimming; tennis; squash or racquetball; calisthenics, aerobics, aerobic dance, or use of a rowing machine; and walking or hiking outdoors. In addition, each woman reported her usual walking pace (the four possible responses ranged from less than 2 miles [3.2 km] per hour to 4 miles [6.4 km] or more per hour) and the number of flights of stairs she climbed daily (the six possible responses ranged from 2 flights or fewer to 15 flights or more). Our calculations did not include household activities or occupational physical activity. Thus, by focusing on recreational physical activity, we are underestimating the total expenditure of energy from all possible activities. We tested the reproducibility and validity of the questionnaire on 149 participants in the Nurses' Health Study II, a similar cohort of younger nurses. The correlation between physical activity reported on the questionnaire and that recorded in four one-week diaries was 0.62.[16]

We multiplied the amount of time spent in each activity per week by its energy-expenditure requirements, expressed as metabolic equivalents (MET),[17] to yield a weekly physical-activity (or MET-hour) score. The MET is the caloric need per kilogram of body weight per hour of activity, divided by the caloric need per kilogram per hour at rest. One MET is defined as the energy expended in sitting quietly, which is equivalent to an oxygen uptake of 3.5 ml per kilogram of body weight per minute for an average adult. To avoid confounding the MET variable by body weight, we did not include body weight in the derivation of energy expenditure associated with physical activity. We calculated a total weekly MET-hour score by summing the weekly expenditures from all activities. We further classified activities as vigorous (6 or more MET) or nonvigorous (less than 6 MET).

In addition, we developed a weekly physical-inactivity score based on the reported average weekly time spent sitting at work or while driving (the 10 possible responses ranged from less than 1/2 hour to 90 or more hours per week). Because this information was first requested in 1990, analyses of inactivity extend from 1990 to 1996. Thus, we excluded from these analyses women who had a cholecystectomy before 1990. Our final assessment of sedentary behavior also included the average weekly time spent watching television (the nine possible responses ranged from 0 to 90 or more hours per week), which was first reported in 1992; thus, in this analysis we began follow-up in 1992 and excluded women who had had a cholecystectomy by 1992.

Identification of Cases of Cholecystectomy

Starting in 1980, we asked each participant whether she had had a cholecystectomy and, if so, the date of surgery. The validity of the self-report was assessed in a random sample of 50 nurses who reported a cholecystectomy in 1982. Of the 43 nurses who responded, all reiterated their earlier report, and surgery was confirmed in all 36 medical records obtained.[18] We focused on cholecystectomy in part because women are probably more likely to report a surgical procedure than untreated gallstones; in fact, in 1986 we ceased collecting information on unremoved gallstones. In addition, in the vast majority of cases, cholecystectomy is used to treat symptomatic cholelithiasis. Only a small percentage of asymptomatic gallstones are diagnosed, typically incidentally, which makes this clinically insignificant condition an unreliable end point. In our cohort, only 12 percent of the women who reported a diagnosis of symptomatic gallstone disease between 1980 and 1986 did not have a cholecystectomy during that period, and 80 percent of the women who had a cholecystectomy between 1980 and 1986 reported a diagnosis of gallstones with accompanying symptoms.

Statistical Analysis

We calculated person-years of follow-up for each participant from the date of return of the 1986 questionnaire to the date of cholecystectomy, diagnosis of cancer, or death or until May 31, 1996. We used relative risk as a measure of association, which we defined as the incidence rate of cholecystectomy among women in various categories of activity divided by the rate in the lowest categories of activity. We used pooled logistic regression with two-year increments to adjust for age; parity; use of oral contraceptives; use of postmenopausal hormones; history of diabetes mellitus; pack-years of smoking; use of cholesterol-lowering drugs; use of thiazide diuretics; use of nonsteroidal antiinflammatory drugs; and intake of energy-adjusted dietary fiber, energy-adjusted carbohydrates, alcohol, and coffee. With short intervals between questionnaires and the low rates of events, this approach yields results similar to those of a Cox regression analysis with time-dependent covariates.[19] For the main analysis, we determined categories of physical activity on the basis of the responses to the 1986 questionnaire. In an additional analysis, we used information on physical activity that had been updated every two years. We conducted stratified analyses to determine whether the influence of physical activity was modified by other risk factors for gallstone disease. All P values are based on two-sided tests.

Because body weight may be in the causal pathway linking the level of physical activity to the risk of gallstone disease, we did not include it in our primary analyses. In additional models, however, we included current body-mass index (defined as the weight in kilograms divided by the square of the height in meters) as a measure of relative weight to assess the effect of physical activity on gallstone disease independent of its effect on body weight. In all models that contained body-mass index, we also included a variable for weight change in the previous two years to account for recent changes in weight.

Finally, we analyzed the effect of measurement error in estimating physical activity.[20] We used data from a random sample of 149 nurses who completed four seven-day diaries on physical activity over a one-year period.[16] This analysis provided an estimate of the association between physical activity and risk of cholecystectomy unattenuated by the effects of measurement error in assessing physical activity.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 60,290 STUDY WOMEN ACCORDING TO QUINTILE OF PHYSICAL ACTIVITY.*

CHARACTERISTIC	QUINTILE OF PHYSICAL ACTIVITY (MET-HR/WK)†				
	0–1.6 (N=12,039)	1.7–4.5 (N=12,075)	4.6–10.5 (N=11,927)	10.6–22.0 (N=12,162)	≥22.1 (N=12,087)
Age (yr)	52.4	52.1	52.2	52.4	52.4
Body-mass index‡	25.9	25.4	25.0	24.6	24.0
Any weight loss in prior 2 yr (%)	27.6	27.0	26.9	28.0	28.4
Routine physical examination between 1986 and 1988 (%)	78	81	81	82	81
Mean parity (no. of births)	2.9	2.9	2.9	2.9	2.8
History of oral-contraceptive use (%)	49	49	49	51	50
Current use of hormone-replacement therapy (%)§	12	14	15	15	16
Current smoker (%)	28	23	20	17	17
History of diabetes (%)	4.0	3.2	3.2	2.8	2.4
Regular use of aspirin (%)	27	27	27	25	25
Regular use of thiazide diuretics (%)	13	12	11	12	11
Mean daily intake					
Total energy (kcal/day)	1771	1767	1784	1783	1800
Carbohydrates (g/day)¶	189	191	193	194	196
Vegetable fat (g/day)¶	25.8	25.5	25.5	25.2	24.6
Vegetable protein (g/day)¶	19.6	19.9	20.3	20.6	20.8
Dietary fiber (g/day)¶‖	17.2	17.9	18.6	19.2	19.8
Alcohol (g/day)	6.0	6.0	6.1	6.5	7.2
Coffee (cups/day)	1.8	1.9	1.9	2.0	2.1

*All values (except age) were standardized to the age distribution of the cohort.

†MET denotes metabolic equivalent. The MET-hours represent the average amount of time per week spent in each of eight activities multiplied by the MET value of each activity. One MET is defined as the energy expended in sitting quietly, which is equivalent to an oxygen uptake of 3.5 ml per kilogram of body weight per minute for an average adult.

‡The body-mass index is the weight in kilograms divided by the square of the height in meters.

§Only postmenopausal women were included.

¶Nutrients were adjusted for total energy intake.

‖The values were derived with the Southgate method, one of various standard procedures for determining the fiber content of foods.[21]

The protocol of the Nurses' Health Study was approved by the institutional review board of Brigham and Women's Hospital in Boston. All study participants were recruited through mailed questionnaires; return of a completed questionnaire was construed as consent.

RESULTS

At base line in 1986, 46 percent of the women reported no vigorous physical activity, and 18 percent reported at least 25 MET-hours per week (equivalent to 30 minutes of moderate exercise five days a week). The more active women tended to be leaner, were less likely to be smokers, and were more likely to use hormone-replacement therapy than the less active women (Table 1). In addition, physically active women consumed more dietary carbohydrates, fiber, alcohol, and coffee on average, although active and inactive women overlapped considerably for these variables.

During 553,381 person-years of follow-up from 1986 to 1996, we identified 3257 women who had undergone cholecystectomy (5 percent of the study group). Physical activity was inversely associated with the risk of cholecystectomy (Table 2). As compared with women in the lowest quintile of physical activity, women in the highest quintile had a multivariate relative risk of 0.69 (95 percent confidence interval, 0.61 to 0.78). When we adjusted for body-mass index and weight change in the previous two-year period, the inverse association was slightly attenuated but remained significant (multivariate relative risk, 0.79). This finding suggests that the apparent protective effect of physical activity on the risk of cholecystectomy can be explained only partly by its effect on body weight.

To test for possible bias induced by a reduction in physical activity among women with preclinical gallstone disease, we repeated our analysis after excluding the first two years and four years of follow-up; the relations were not changed substantially (multivariate relative risk in the highest as compared with the lowest quintile after we excluded the first four years of follow-up, 0.75; 95 percent confidence interval, 0.65 to 0.87). We also examined whether measurement error in assessing physical activity influenced our findings. This analysis required the measurement of

TABLE 2. RELATIVE RISK OF CHOLECYSTECTOMY IN RELATION TO QUINTILE OF PHYSICAL ACTIVITY.*

VARIABLE	QUINTILE OF PHYSICAL ACTIVITY (MET-HR/WK)					P VALUE FOR TREND
	0–1.6	1.7–4.5	4.6–10.5	10.6–22.0	≥22.1	
No. of women who had cholecystectomy	671	785	687	592	522	
Person-yr	95,590	121,651	113,227	112,357	110,556	
Relative risk (95% CI)						
Age-adjusted	1.0	0.92 (0.83–1.01)	0.86 (0.78–0.96)	0.75 (0.67–0.83)	0.67 (0.60–0.75)	<0.001
Multivariate†	1.0	0.92 (0.83–1.02)	0.87 (0.78–0.97)	0.76 (0.67–0.85)	0.69 (0.61–0.78)	<0.001
Multivariate plus BMI and weight change†‡	1.0	0.95 (0.86–1.06)	0.92 (0.83–1.03)	0.83 (0.74–0.93)	0.79 (0.71–0.89)	<0.001

*MET denotes metabolic equivalent, CI confidence interval, and BMI body-mass index (the weight in kilograms divided by the square of the height in meters).

†The multivariate model included the following: age (≤49, 50–54, 55–59, 60–64, or ≥65 years), parity (0, 1, 2 or 3, or ≥4 births), use of oral contraceptives (ever or never), use of hormone-replacement therapy (premenopausal, postmenopausal without hormone-replacement therapy, postmenopausal with previous hormone-replacement therapy, or postmenopausal with current hormone-replacement therapy), history of diabetes mellitus (yes or no), pack-years of smoking (0, 1–9, 10–24, 25–44, 45–64, or ≥65), use of cholesterol-lowering drugs (yes or no), use of thiazide diuretics (yes or no), use of nonsteroidal antiinflammatory drugs (0, 1–6, or ≥7 times per week or dose unknown), intake of energy-adjusted dietary fiber (quintiles), intake of energy-adjusted carbohydrates (quintiles), intake of alcohol (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, or ≥30.0 g per day), and intake of coffee (0, 1, 2 or 3, 4 or 5, or ≥6 cups per day). The adjustment for intake of vegetable protein, vegetable fat, and polyunsaturated fat did not substantially alter the risk estimates for physical activity, so these variables were not included in the multivariate model.

‡We controlled for body-mass index at the beginning of each two-year follow-up interval (10 categories: <20.00, 20.00–22.49, 22.50–24.99, 25.00–27.49, 27.50–29.99, 30.00–32.49, 32.50–34.99, 35.00–37.49, 37.50–39.99, and ≥40) and weight change in the previous two years (weight loss of 10 lb [4.5 kg] or more, weight loss of 5.0–9.9 lb [2.3–4.5 kg], weight change of no more than 4.9 lb [2.2 kg], weight gain of 5.0–9.9 lb, and weight gain of 10 or more lb).

physical activity on a continuous scale.[20] The multivariate relative risk of cholecystectomy that was associated with an increase in physical activity of 25 MET-hours per week was 0.85 (95 percent confidence interval, 0.80 to 0.90), but it was reduced to 0.58 (95 percent confidence interval, 0.43 to 0.77) when we adjusted for errors in measuring physical activity.

We assessed whether the effect of physical activity was modified by established risk factors for gallstone disease (Table 3). We found no significant dose–response relations for women at the extremes of obesity, weight loss, parity, hormone use, or alcohol consumption. However, inverse associations between physical activity and the risk of cholecystectomy were largely similar across less extreme categories of these subgroups, indicating that there was no important change in effect.

To determine whether more extreme physical activity conferred greater benefit, we compared women whose activity level was in the highest 5 percent (50 or more MET-hours per week) with women in the lowest quintile (0 to 1.6 MET-hours per week). The multivariate relative risk was 0.65 (95 percent confidence interval, 0.54 to 0.79), which suggests that there were no large further reductions in risk for more extreme activity levels. The inverse association was somewhat stronger among women with consistently high levels of physical activity over time. Women who consistently fell into the highest quintile in the 1986 and 1988 questionnaires had a multivariate relative risk of 0.57 (95 percent confidence interval, 0.48 to 0.67) from 1988 to 1996, as compared with women who consistently fell into the lowest quintile.

In general, women maintained fairly constant levels of physical activity throughout follow-up. The correlation coefficients for total MET-hours ranged from 0.55 to 0.63 from one questionnaire to the next. However, to address the effect of long-term average physical exercise on the risk of cholecystectomy, we conducted an analysis in which we cumulatively updated the physical-activity level every two years from 1986 to 1994. After the updating, the relation was unchanged (multivariate relative risk for the highest as compared with the lowest quintile, 0.57; 95 percent confidence interval, 0.50 to 0.65).

Physical activity, whether vigorous or not, decreased the risk of cholecystectomy (Table 4). After we entered variables for both vigorous and nonvigorous activity simultaneously in one model and adjusted for multiple confounding factors, there was an 11 percent decrease in the risk of cholecystectomy for each increase in vigorous activity of 10 MET-hours per week (relative risk, 0.89; 95 percent confidence interval, 0.86 to 0.94) and a 9 percent decrease for each increase of 10 MET-hours per week in nonvigorous activity (relative risk, 0.91; 95 percent confidence interval, 0.87 to 0.96).

We also investigated the relation of specific activities to the risk of cholecystectomy. To provide an es-

TABLE 3. RELATIVE RISK OF CHOLECYSTECTOMY IN RELATION TO QUINTILE OF PHYSICAL ACTIVITY, ACCORDING TO SELECTED VARIABLES.*

VARIABLE	NO. OF WOMEN WHO HAD CHOLECYSTECTOMY	QUINTILE OF PHYSICAL ACTIVITY (MET-HR/WK)					P VALUE FOR TREND
		0–1.6	1.7–4.5	4.6–10.5	10.6–22.0	≥22.1	
		relative risk					
Age							
40–49 yr	539	1.0	0.87	0.85	0.79	0.67	0.01
50–59 yr	1437	1.0	1.05	0.94	0.86	0.88	0.04
≥60 yr	1281	1.0	0.88	0.94	0.81	0.75	0.003
Body-mass index†							
≤24	1055	1.0	0.89	0.96	0.74	0.72	<0.001
25–29	1322	1.0	0.96	0.79	0.76	0.76	0.001
≥30	880	1.0	0.96	1.05	1.07	0.93	0.72
Recent weight change‡							
Loss of ≥10.0 lb	363	1.0	0.97	0.96	0.87	0.95	0.72
Loss of 5.0–9.9 lb	311	1.0	0.99	0.81	0.68	0.61	0.005
Stable weight (change, ≤4.9 lb)	1491	1.0	0.96	0.88	0.83	0.76	0.001
Gain of 5.0–9.9 lb	499	1.0	0.95	0.95	0.74	0.71	0.01
Gain of ≥10.0 lb	593	1.0	0.83	0.96	0.86	0.84	0.37
Parity (no. of births)							
0 or 1	2826	1.0	0.93	0.93	0.85	0.78	<0.001
≥2	431	1.0	1.14	0.91	0.73	0.87	0.11
Hormone-replacement therapy							
Premenopausal (nonusers)	982	1.0	0.93	0.93	0.79	0.74	0.003
Never	634	1.0	0.83	1.13	0.79	0.73	0.02
Current	1240	1.0	1.08	0.89	0.91	0.87	0.05
Past	401	1.0	0.87	0.77	0.77	0.81	0.38
Alcohol use							
None	1407	1.0	0.87	0.86	0.84	0.76	0.009
0.1–4.9 g/day	1089	1.0	1.18	1.05	1.00	0.85	0.005
≥5.0 g/day	761	1.0	0.87	0.93	0.66	0.81	0.08

*The multivariate models included the following: age, body-mass index at the beginning of each two-year follow-up interval; weight change in the previous two years; parity; use of oral contraceptives; use of hormone-replacement therapy; history of diabetes mellitus; pack-years of smoking; use of cholesterol-lowering drugs; use of thiazide diuretics; use of nonsteroidal antiinflammatory drugs; and intake of energy-adjusted dietary fiber, energy-adjusted carbohydrates, alcohol, and coffee. In each case, the stratification variable was excluded from the model. Within each stratum, the group with the lowest physical activity served as the reference group. Adjustment for the intake of vegetable protein, vegetable fat, and polyunsaturated fat did not substantially alter the risk estimates for physical activity, so these variables were not included in the multivariate models. MET denotes metabolic equivalent.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡Recent weight change was defined as weight change in the previous two years. To convert pounds to kilograms, divide by 2.2.

timate of the independent effect of each activity, we simultaneously entered all activities in one model and additionally adjusted for multiple risk factors. Significant inverse associations were noted for increasing amounts of time spent jogging or running, playing tennis, doing calisthenics, and walking briskly. For example, the multivariate relative risk associated with an increase in brisk walking of 2.5 hours per week was 0.87 (95 percent confidence interval, 0.81 to 0.94).

We also examined the relation between sedentary behavior and the risk of cholecystectomy (Table 5). After adjustment for multiple confounding factors, including recreational physical activity, we found that as compared with women who spent less than 6 hours per week sitting while at work or driving, women who spent 41 to 60 hours per week sitting had a relative risk of 1.42, and women who spent more than 60 hours per week sitting had a relative risk of 2.32. Increasing amounts of time spent watching television were also positively related to the risk of cholecystectomy. After adjustment for multiple confounding factors, including recreational physical activity, the relative risk associated with an increase of 3 hours per day in time spent watching television was 1.11 (95 percent confidence interval, 1.02 to 1.22). The association with watching television was no longer significant after we controlled for relative body weight and recent weight change.

DISCUSSION

In this prospective study of 60,290 women, increased physical activity was associated with a significant reduction in the risk of cholecystectomy. An average of 2 to 3 hours of recreational exercise per

TABLE 4. RELATIVE RISK OF CHOLECYSTECTOMY IN RELATION TO VIGOROUS AND NONVIGOROUS ACTIVITY.*

VARIABLE	CATEGORY OF PHYSICAL ACTIVITY					P VALUE FOR TREND
	1	2	3	4	5	
Vigorous activity						
MET-hr/wk	0	0.1–1.6	1.7–6.9	7.0–15.9	≥16.0	
No. of women who had cholecystectomy	1,625	440	411	447	334	
Person-yr	250,459	74,271	68,730	86,238	73,683	
Relative risk (95% CI)						
Age-adjusted	1.0	0.93 (0.84–1.04)	0.94 (0.84–1.05)	0.81 (0.73–0.90)	0.71 (0.63–0.80)	<0.001
Multivariate plus nonvigorous activity†‡	1.0	0.89 (0.80–0.99)	0.94 (0.84–1.05)	0.83 (0.74–0.92)	0.75 (0.66–0.85)	<0.001
Multivariate plus nonvigorous activity, BMI, and weight change†‡§	1.0	0.91 (0.81–1.01)	0.97 (0.87–1.09)	0.88 (0.79–0.98)	0.82 (0.73–0.93)	0.001
Nonvigorous activity						
MET-hr/wk	0–0.8	0.9–2.6	2.7–4.4	4.5–10.7	≥10.8	
No. of women who had cholecystectomy	703	731	668	574	581	
Person-yr	108,368	109,170	112,549	113,257	110,037	
Relative risk (95% CI)						
Age-adjusted	1.0	1.04 (0.94–1.16)	0.92 (0.83–1.02)	0.78 (0.70–0.87)	0.80 (0.72–0.89)	<0.001
Multivariate plus vigorous activity†¶	1.0	1.06 (0.95–1.17)	0.95 (0.85–1.06)	0.83 (0.74–0.93)	0.86 (0.77–0.98)	<0.001
Multivariate plus vigorous activity, BMI, and weight change†§¶	1.0	1.09 (0.99–1.22)	0.99 (0.89–1.10)	0.89 (0.79–0.99)	0.95 (0.84–1.06)	0.05

*We defined vigorous activity as activities with 6 or more MET and nonvigorous activity as activities with less than 6 MET. MET denotes metabolic equivalent, CI confidence interval, and BMI body-mass index.

†The multivariate model included the following: age; parity; use of oral contraceptives; use of hormone-replacement therapy; history of diabetes mellitus; pack-years of smoking; use of cholesterol-lowering drugs; use of thiazide diuretics; use of nonsteroidal antiinflammatory drugs; and intake of energy-adjusted dietary fiber, energy-adjusted carbohydrates, alcohol, and coffee. Adjustment for the intake of vegetable protein, vegetable fat, and polyunsaturated fat did not substantially alter the risk estimates for physical activity, so these variables were not included in the multivariate model.

‡We also controlled for nonvigorous activity (five categories).

§We also controlled for body-mass index at the beginning of each two-year follow-up interval and weight change in the previous two years.

¶We also controlled for vigorous activity (five categories).

TABLE 5. RELATIVE RISK OF CHOLECYSTECTOMY IN RELATION TO SITTING WHILE AT WORK OR DRIVING AND TO WATCHING TELEVISION.*

VARIABLE	CATEGORY OF PHYSICAL INACTIVITY (HR/WK)					P VALUE FOR TREND
	0–5	6–20	21–40	41–60	≥61	
Sitting while at work or driving						
No. of women who had cholecystectomy	894	722	236	51	13	
Person-yr	124,936	113,146	32,301	5093	707	
Relative risk (95% CI)						
Age-adjusted	1.00	0.91 (0.82–1.01)	1.07 (0.92–1.24)	1.47 (1.10–1.94)	2.65 (1.53–4.59)	0.008
Multivariate†	1.00	0.92 (0.83–1.02)	1.04 (0.89–1.21)	1.42 (1.06–1.89)	2.32 (1.26–4.26)	0.03
Multivariate plus BMI and weight change†‡	1.00	0.91 (0.82–1.01)	1.01 (0.87–1.18)	1.34 (1.00–1.80)	2.18 (1.19–4.01)	0.08
Watching television						
No. of women who had cholecystectomy	411	324	370	231	39	
Person-yr	59,923	49,649	51,916	27,226	4237	
Relative risk (95% CI)						
Age-adjusted	1.00	0.95 (0.82–1.10)	1.03 (0.90–1.19)	1.21 (1.03–1.43)	1.30 (0.93–1.81)	0.002
Multivariate†	1.00	0.96 (0.82–1.12)	1.02 (0.88–1.19)	1.17 (0.98–1.39)	1.29 (0.91–1.83)	0.02
Multivariate plus BMI and weight change†‡	1.00	0.92 (0.79–1.07)	0.96 (0.82–1.11)	1.05 (0.88–1.25)	1.12 (0.78–1.58)	0.3

*Only data from more recent questionnaires are included, so the number of women studied is smaller. The analysis of sitting while at work or driving was based on the 1990–1996 follow-up period, and the analysis of watching television was based on the 1992–1996 follow-up period. MET denotes metabolic equivalent, CI confidence interval, and BMI body-mass index.

†The multivariate model included the following: total level of recreational physical activity (quintiles); age; parity; use of oral contraceptives; use of hormone-replacement therapy; history of diabetes mellitus; pack-years of smoking; use of cholesterol-lowering drugs; use of thiazide diuretics; use of nonsteroidal antiinflammatory drugs; and intake of energy-adjusted dietary fiber, energy-adjusted carbohydrates, alcohol, and coffee. Adjustment for the intake of vegetable protein, vegetable fat, and polyunsaturated fat did not substantially alter the risk estimates for physical activity, so these variables were not included in the multivariate model.

‡We also controlled for body-mass index at the beginning of each two-year follow-up interval and weight change in the previous two years.

week appeared to reduce the risk by approximately 20 percent. The inverse association was not limited to a particular kind of activity but instead was found for a variety of activities and for a combination of several activities. In contrast, sedentary behavior as assessed by time spent sitting was positively associated with the risk of cholecystectomy. These associations were independent of other known risk factors, including relative body weight and recent weight change, a finding that suggests that physical activity may have an important role beyond its effect on weight control in the prevention of gallstone disease requiring cholecystectomy.

Data on the association between physical activity and the risk of gallstone disease are sparse. Among the few studies that have examined this relation in women, one case–control study found an inverse association with the overall level of physical activity,[9] one case–control study reported an inverse relation with the amount of time spent walking,[10] and one case–control study[11] and two cross-sectional surveys[12,13] found inverse associations with work activity. However, these reports did not address the dose–response relation,[10,11] did not control for potential risk factors other than age,[12,13] and could not rule out the possibility that the level of physical activity was altered as a result of the disease.[12,13]

Two prospective studies, both in men, examined the association between physical activity and the risk of gallstone disease.[14,15] The estimates of the relative risk of cholecystectomy in the present study of women are consistent with the results of both those studies. One study reported a relative risk of 0.60,[14] and the other reported a relative risk of 0.63[15] when men in the highest quantiles of physical activity were compared with those in the lowest.

Our findings are unlikely to be due to biased ascertainment of cholecystectomy cases, given the study sample of nurses and the validity of self-reports of cholecystectomies; moreover, any underascertainment of cases would not bias the observed relative risks.[22] We considered the possibility of measurement error in our assessment of physical activity, weight, diet, and other variables. However, the reporting of physical activity and known confounding variables has been validated extensively in subsamples of the Nurses' Health Study cohort.[16,23-25] Moreover, our prospective study design precluded bias attributable to differential recall of physical activity and other exposures by women who had undergone cholecystectomy and those who had not.

We found no significant dose–response relations between physical activity and the risk of cholecystectomy for women at the extremes of obesity, weight loss, parity, postmenopausal hormone use, or alcohol consumption. One explanation is that our capacity to assess the risk of cholecystectomy within these subgroups was limited by the small numbers of women and the greater probability of misclassification of physical activity in these categories.

There are probably several metabolic pathways by which physical activity may reduce the risk of gallstone disease, and they go beyond the effect of physical activity on weight control. Physical activity improves glucose tolerance[7] even in the absence of weight loss,[26] increases serum high-density lipoprotein cholesterol levels, decreases serum triglyceride levels,[7] reduces exposure to ovarian hormones,[27] and may enhance colonic motility[28] and cholecystokinin release.[29] These factors are all related to the risk of cholesterol gallstone disease.[30,31]

In summary, our data suggest that physical activity reduces the risk of cholecystectomy in women. The apparent protective effect can be achieved not only by vigorous physical activity but also by moderate forms of exercise, such as brisk walking. In addition, physical inactivity may be independently associated with an increased risk of cholecystectomy.

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