Risk of symptomatic gallstones in women with severe obesity[1–3]

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ABSTRACT Although obesity is a well-recognized risk factor for gallstones, the excess risks associated with higher levels of obesity and recent weight change are poorly quantified. We evaluated these issues in the Nurses' Health Study. Among 90 302 women aged 34–59 y at baseline followed from 1980 to 1988, 2122 cases of newly diagnosed symptomatic gallstones occurred during 607 104 person-years of follow-up. From 1980 to 1986, 488 cases of newly diagnosed unremoved gallstones were documented. We observed a striking monotonic increase in gallstone disease risk with obesity; women with a body mass index (BMI) > 45 kg/m^2 had a sevenfold excess risk compared with those whose BMI was < 24 kg/m^2. Women with a BMI > 30 kg/m^2 had a yearly gallstone incidence of > 1% and those with a BMI ≥ 45 kg/m^2 had a rate of ≈2%/y. Recent weight loss was associated with a modestly increased risk after adjustment for BMI before weight loss. Current smoking was an independent risk factor; women smoking ≥ 35 cigarettes/d had a relative risk of 1.5 (95% CI 1.2–1.9). *Am J Clin Nutr* 1992;55: 652–8.

KEY WORDS Cholecystectomy, gallstones, obesity, women, cigarette smoking, weight loss

Introduction

Obesity is a well-established risk factor for gallstones (1–7). The magnitude of the increased risk and the rates of occurrence of symptomatic gallstones, however, have not been well quantified, particularly among the most obese, who are at highest risk. Women who embark on rapid weight-loss programs using very-low-calorie diets are apparently at increased risk for lithogenesis (8, 9). However, because such women are generally obese, the excess risk due to the extreme diet is difficult to quantify because rates of symptomatic gallstones among the very obese have not been published. In an earlier report from the Nurses' Health Study based on 4 y of follow-up, we found that compared with women with a body mass index (BMI measured in kg/m^2) < 20, those women with a BMI of ≥ 32 had a relative risk of symptomatic gallstones of 6.0 [95% confidence interval (CI) 4.0–9.0] and that ≈70% of the gallstones in those women were attributable to obesity (1). In this report we extend the follow-up to 8 y and examine both the rates of occurrence and the relative risks by level of obesity, paying particular attention to the highest levels of overweight.

Data on the effect of weight loss on gallstone disease in a general population are also sparse. Hence, we also assess the impact of weight change in a 2-y interval on risk of clinically symptomatic gallstones in the subsequent 2-y interval. Previous work suggested an association between smoking and gallstones (4). We also address this issue in our large prospective cohort of women.

Subjects and methods

The Nurses' Health Study cohort

The Nurses' Health Study began in 1976 when 121 700 female registered nurses living in 11 large US states completed a mailed questionnaire that included items about their medical history and risk factors for coronary disease and cancer (10) including height, weight, current and past smoking habits, and use of postmenopausal hormones. Height and weight were used to compute BMI, defined as weight in kilograms divided by height in meters to the second power, as an index of adiposity. Every 2 y, follow-up questionnaires were mailed to update the information on potential risk factors and to identify newly diagnosed cases of various illnesses. In 1980 a semiquantitative food frequency questionnaire was added (11).

Identification of symptomatic gallstones

Starting with the 1982 follow-up questionnaire, we asked the participating nurses to report whether they had had a cholecystectomy or had been given a diagnosis of gallstones without removal. We also inquired whether symptoms were present and, for the cases without cholecystectomy, whether the diagnosis was confirmed by x ray or ultrasound. In the 1988 questionnaire the question about untreated gallstones was omitted but the item concerning cholecystectomy was retained.

We assessed the validity of the self-report of cholecystectomy and unremoved gallstones in two random samples of 50 nurses each who reported these conditions. Of 43 who responded for

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cholecystectomy all reiterated the initial report, and this was confirmed in all cases for which we could obtain records (n = 36 records reviewed). For unremoved gallstones the original diagnosis was reiterated by all 35 respondents and confirmed in 15 of the 16 medical records we could obtain (1).

Population for analysis

The population was limited to women who returned the follow-up questionnaires in 1982 or in subsequent follow-up cycles and who provided information on height and current weight. Because we were interested in newly diagnosed illness, we excluded women with cholecystectomy or a diagnosis of gallstones before the return of the 1980 questionnaire. In our earlier reports (1, 12) the main focus was on dietary determinants of gallbladder disease. To avoid the possibility that symptomatic but undiagnosed gallstones might influence the report of diet, we excluded from those earlier analyses all women who reported on the supplementary questionnaire that they had experienced symptoms of gallstones before return of the 1980 questionnaire even if the diagnosis was made after the return of that questionnaire. In the present analysis the focus is on incidence rates and relative risks by categories of overweight; hence, we only excluded women whose diagnosis of gallstones preceded the return of the 1980 questionnaire. The earlier exclusions were justified in a dietary study to avoid bias because symptoms attributed to gallstones by the subject (whether correctly or not) may have led her to alter her diet. However, in the present analysis such an exclusion would result in gross underestimation of incidence rates, especially because the report of symptoms due to gallstones is notoriously inaccurate (13). Also, such an exclusion would be unnecessary because the presence of prediagnostic symptoms of gallbladder disease would be unlikely to influence body weight. Even if it did, such a change would be taken into consideration in the analysis because weight is updated every 2 y on the follow-up questionnaires. We excluded women who reported the diagnosis of gallstones without symptoms, which usually occurred as an incidental finding during an examination or surgery for another indication. Such women were excluded from subsequent follow-up and were not counted as cases in this analysis.

We validated the self-report of weight in a sample of Boston-area participants by comparing their self-reported weights with technician-measured values taken 6–12 mo after the questionnaire was completed. The correlation between the self-report and measured values was $r = 0.97$ (14). The mean self-reported weight was 1.5 kg lower than the measured weight, compatible with the difference between a casual weight with light clothing and a morning postvoid nude weight.

In 1980, 90 302 women entered the analysis for the 1980–1982 interval. During the 8 y of follow-up from the return of the 1980 questionnaire until June 1, 1988, we accrued 607 104 person-years of follow-up. The follow-up for newly diagnosed symptomatic but unremoved gallstones extended from the return of the 1980 questionnaire until June 1, 1986, for a total of 474 768 person-years of follow-up.

Our procedures are approved by the ethics committees of Brigham and Women's Hospital and Harvard Medical School, and the Harvard School of Public Health, and are in accord with the Helsinki Declaration.

Data analysis

The primary analysis is based on incidence rates using person-months of follow-up as the denominator. For each participant, person-months were allocated according to the 1980 exposure variables and updated according to subsequent follow-up-questionnaire information. For women who were diagnosed with gallstones, person-months were assigned according to the status reported on the most recently completed questionnaire but follow-up was terminated with the diagnosis of gallstones. If no questionnaire was returned for a follow-up cycle or if weight was not reported, that follow-up time was assigned to the missing category and was not included in the analysis. Thus, we only considered in the analysis the follow-up with up-to-date reports of body weight.

We also assessed the change in risk associated with weight change during the preceding 2-y interval. Because these analyses required report of weight both at the beginning of a given interval as well as on the previous questionnaire, there were fewer person-years of follow-up. Missing values resulted in exclusion of 4.8% of person-years from the analysis of cholecystectomy (1980–1988) and 3.6% from the analysis of diagnosed but unremoved gallstones (1980–1986).

We used the relative risk as the measure of association, defined as the incidence rate of gallstones or cholecystectomy among women in various categories of BMI (estimated as the number of events divided by person-years of follow-up in that BMI category) divided by the corresponding rate among women in the reference category of < 24 kg/m^2. This category was chosen as the comparison group because in our previous analysis we found that the relative risk for gallstones was essentially not associated with BMI < 24 kg/m^2. A BMI of 24 kg/m^2 in a woman of average height (165 cm) corresponds to a weight of 65.4 kg. Age-specific (or BMI-specific) rates using 5-y categories were individually calculated and used to compute age-adjusted (or BMI-adjusted) relative risks with 95% CIs (15). To adjust for multiple risk factors simultaneously, proportional-hazards models (16) were used. All P values are two-tailed. The incidence rates were age standardized by the direct method to the age distribution of the entire cohort.

Results

During 607 104 person-years of follow-up from 1980 to 1988 we identified 2122 cases of cholecystectomy. The follow-up for newly diagnosed symptomatic but unremoved gallstones extended from the return of the 1980 questionnaire until June 1, 1986, for a total of 474 768 person-years of follow-up during which we ascertained 488 cases.

We observed a strong linear association between BMI and the incidence rate of symptomatic gallstones (combining cholecystectomy and unremoved stones) (**Fig 1**). **Table 1** shows the number of cases and age-standardized rates and the age-adjusted relative risks with 95% CI for cholecystectomy and for unremoved symptomatic gallstones. The incidence rate of cholecystectomy ranged eightfold from 202/100 000 person-years in the reference category of BMI of 24 kg/m^2 to 1622/100 000 person-years in the 45+ kg/m^2 category. (BMI of 45 kg/m^2 for a 165 cm woman corresponds to a weight of 122.5 kg.) The incidence rates of unremoved symptomatic gallstones are lower but rise in a similar manner with increasing BMI. Because of the smaller number of cases the rates are statistically less stable than those for cholecystectomy. For both end points we observed only minor differences between the crude and age-standardized rates, reflecting the weak relation between age and risk of gallstones in

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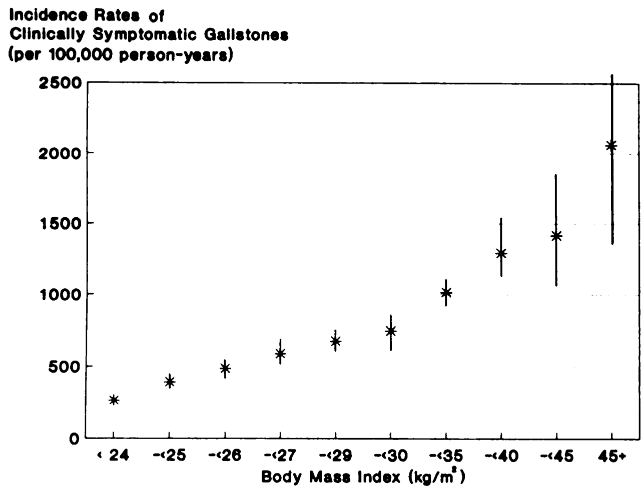

FIG 1. Incidence rates of cholecystectomy or newly diagnosed symptomatic unremoved gallstones combined by categories of body mass index (BMI) in the Nurses' Health Study. The vertical lines represent the 95% confidence intervals around the estimated rates, assuming a Poisson distribution. The upper bound for the highest BMI category is 3016 per 100,000 person-years.

this cohort (1). Thus, the effect of obesity was far more important than that of age.

Incidence rates for the combined endpoint of unremoved symptomatic gallstones plus cholecystectomy are shown in Table 1. Women with a BMI ≥ 30 kg/m^2 had an annual rate of > 1%, and women in the highest category of 45+ kg/m^2 had an incidence rate that exceeded 2%/y.

Table 2 shows the incidence of cholecystectomy and symptomatic unremoved gallstones according to weight change in the previous 2 y. The highest rates were found in the extreme categories of weight change. However, the age-standardized rates are confounded by the strong association between obesity and weight loss; slender women are unlikely to lose > 10 kg in a 2-y interval (17). Moreover, in a previous analysis of predictors of weight change we found that the best predictor of 2-y future weight gain was weight loss in the previous 2-y interval. Obese women are also more likely to have substantial weight gain than women of average relative weight. Hence, the extremes of both weight loss and gain are enriched with obese women. This confounding is quite apparent when differences in the age-standardized rates are compared with the age- and BMI-adjusted relative risks, which estimate the association with weight change apart from the obesity effect. For example the rate for cholecystectomy in the 10+ kg weight-gain group was 734.7/100 000 person-years compared with 298.1 for those with stable weight. This 2.5-fold-higher rate is reduced to a nonsignificant 4% increase in risk after adjusting for BMI. After that adjustment we observed moderate but significantly increased risks of both categories of gallstones with loss of ≥ 4 kg in the previous 2 y. Women with a weight loss of ≥ 10 kg had a BMI-adjusted relative risk of cholecystectomy of 1.99 (95% CI 1.55–2.56) compared with women with a weight change of < 4 kg and 1.97 (95% CI 1.57–2.47) for the combined endpoint of cholecystectomy plus unremoved symptomatic gallstones.

The analyses of weight change in **Tables 2** and **3** compare rates of clinically symptomatic gallstones according to weight change in the previous 2 y adjusting for current attained weight. However, part of the increase in risk among those who lost weight may be due to their excess weight 2 y before. To assess that issue, we compared incidence rates for women of similar weight 2 y before who had maintained their weights or lost ≥ 10 kg in the subsequent 2 y. The relative risk of cholecystectomy in the 2-y interval after a ≥ 10-kg weight loss, adjusting for BMI before the weight loss, was 1.17 (0.82–1.67) (**Table 4**). The apparent lack of increase in risk in the 85-kg women who did not lose weight (compared with the 65-kg category) is most likely a chance finding attributable to small numbers.

It is of interest to assess the extent to which the elevated rates of symptomatic gallstones among the obese women may be at-

TABLE 1
Age-standardized* incidence rates per 100,000 person-years, and relative risks and 95% confidence intervals for cholecystectomy† and symptomatic unremoved gallstones‡ in the Nurses' Health Study

	Cholecystectomy			Symptomatic gallstones, not removed			Cholecystectomy plus symptomatic gallstones	
BMI	Cases	Incidence rate	Relative risk (95% CI)	Cases	Incidence rate	Relative risk (95% CI)	Incidence rate	Relative risk (95% CI)
<24	642	202	1.0 (referent)	181	75	1.0 (referent)	277	1.0 (referent)
24–<25	196	318	1.57 (1.34–1.84)	32	71	0.94 (0.64–1.36)	389	1.43 (1.24–1.66)
25–<26	181	370	1.82 (1.55–2.14)	41	112	1.48 (1.05–2.07)	482	1.74 (1.51–2.02)
26–<27	148	461	2.25 (1.89–2.67)	29	122	1.62 (1.10–2.38)	582	2.11 (1.80–2.47)
27–<29	266	540	2.56 (2.23–2.94)	54	145	1.92 (1.43–2.59)	685	2.53 (2.23–2.86)
29–<30	121	590	2.87 (2.38–3.46)	22	140	1.95 (1.26–3.01)	729	2.67 (2.25–3.17)
30–<35	384	814	3.98 (3.54–4.47)	69	198	2.64 (2.03–3.45)	1012	3.69 (3.32–4.11)
35–<40	127	928	4.58 (3.86–5.45)	39	360	5.24 (3.85–7.13)	1287	4.72 (4.06–5.49)
40–<45	36	912	4.46 (3.29–6.06)	16	591	7.56 (4.90–11.67)	1504	5.11 (3.97–6.56)
45+	21	1622	7.56 (5.23–10.92)	5	469	6.64 (3.08–14.31)	2091	7.36 (5.28–10.26)

* Age-standardized to the distribution of the cohort, 1980–1988.
† Findings from 1980–1988.
‡ Follow-up from 1980–1986.

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TABLE 2
Weight change in previous 2 y* and risk of cholecystectomy† and symptomatic unremoved gallstones‡

	Cholecystectomy			Symptomatic gallstones, not removed			Cholecystectomy or unremoved gallstones	
Weight change	Cases	Rate per 100 000 person-years§	BMI-adjusted relative risk (95% CI)‖	Cases	Rate per 100 000 person-years§	BMI-adjusted relative risk (95% CI)‖	Rate per 100 000 person-years§	BMI-adjusted relative risk (95% CI)‖
10+ kg loss	63	839.4	1.99 (1.55–2.56)	14	259.7	1.87 (1.10–3.19)	1099.1	1.97 (1.57–2.47)
4.0–9.9 kg loss	194	505.7	1.38 (1.19–1.61)	58	197.8	1.75 (1.33–2.32)	703.5	1.45 (1.27–1.66)
≤3.9 kg gain or loss	1313	298.1	1.0 (referent)	311	92.7	1.0 (referent)	392.6	1.0 (referent)
3.9–9.9 kg gain	365	466.7	0.94 (0.83–1.06)	74	126.1	0.87 (0.66–1.13)	577.2	0.92 (0.83–1.03)
10+ kg gain	76	734.7	1.04 (0.80–1.35)	22	269.6	1.12 (0.69–1.81)	1004.3	1.06 (0.84–1.33)

* Women with missing data are excluded.
† Follow-up from 1980–1988.
‡ Follow-up from 1980–1986.
§ Age-standardized to the distribution of the cohort, 1980–1988.
‖ Adjusted for BMI at the beginning of each follow-up interval for the categories listed in Table 1 using stratified analyses.

tributable to other gallstone risk factors that might be associated with adiposity. Thus, for example, it is well established that heavier women tend to drink less alcohol than leaner women (18). Because alcohol intake is associated with decreased risk of gallstones (1), part of the effect of obesity may reflect decreased alcohol intake. Conversely, heavier women tend to use postmenopausal hormones less frequently than leaner women (19). Estrogen use increases the risk of gallstones (20), so this potential confounding factor may bias the rates in the opposite direction. Also, these factors may confound the association between weight loss and gallstones. Table 3 shows the relative risks for cholecystectomy in the different categories of BMI and recent weight change after simultaneous adjustment for known or suspected gallstone risk factors: age, parity, postmenopausal hormone use, alcohol intake, polyunsaturated fatty acid intake (12), total energy, and smoking (1), using proportional hazards models. These adjusted relative risks for BMI are generally similar to those observed in Table 1, suggesting that only a small portion of the dramatic rise in risk with increasing adiposity can be attributed to confounding factors. Similarly, the elevated relative risks associated with weight loss were largely unchanged in the multivariate analyses that adjusted for current attained weight.

TABLE 3
Multivariate-adjusted* relative risks for cholecystectomy, symptomatic unremoved gallstones, and both endpoints together by BMI and weight change in the past 2 y, adjusting simultaneously for various risk factors for gallstones†

	Cholecystectomy	Gallstones, unremoved	Cholecystectomy or unremoved gallstones
BMI			
<24	1.0 (referent)	1.0 (referent)	1.0 (referent)
24–<25	1.48 (1.24–1.77)	1.01 (0.70–1.46)	1.36 (1.16–1.60)
25–<26	1.61 (1.33–1.93)	1.54 (1.10–2.15)	1.60 (1.36–1.88)
26–<27	2.00 (1.63–2.46)	1.66 (1.12–2.45)	1.92 (1.60–2.30)
27–<29	2.38 (2.03–2.79)	1.96 (1.44–2.65)	2.32 (2.02–2.66)
29–<30	2.82 (2.27–3.51)	1.96 (1.25–3.05)	2.63 (2.16–3.19)
30–<35	3.77 (3.26–4.37)	2.62 (1.96–3.49)	3.52 (3.11–3.98)
35–<40	4.35 (3.48–5.44)	4.98 (3.46–7.17)	4.64 (3.86–5.57)
40–<45	4.60 (3.15–6.72)	6.93 (4.07–11.81)	5.42 (4.01–7.34)
45+	7.08 (4.22–11.86)	5.91 (2.37–14.75)	6.99 (4.48–10.90)
Weight change			
10+ kg loss	1.91 (1.43–2.54)	2.03 (1.18–3.47)	1.94 (1.50–2.50)
4.0–9.9 kg loss	1.32 (1.11–1.56)	1.91 (1.44–2.53)	1.44 (1.25–1.67)
≤3.9 kg gain or loss	1.0 (referent)	1.0 (referent)	1.0 (referent)
4.0–9.9 kg gain	0.90 (0.78–1.03)	0.93 (0.71–1.21)	0.90 (0.80–1.02)
10+ kg gain	0.95 (0.72–1.26)	1.24 (0.78–1.98)	1.01 (0.80–1.28)

* Simultaneously adjusted for BMI, weight change, age (5-y categories), alcohol intake (five categories), postmenopausal hormone use (current, past, never), smoking (never, past, and current at four amounts of cigarettes per day), parity (six categories), energy intake (five categories), polyunsaturated fatty acid intake (five categories).
† 95% CI in parentheses.

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TABLE 4
The risk of cholecystectomy in relation to a 10-kg weight loss in the prevous 2 y, adjusting for BMI before the weight loss*

	Weight 2 y ago					
	65 kg		75 kg		85 kg	
Current weight (kg)	55	65	65	75	75	85
Weight loss (kg)	10+	±4	10+	±4	10+	±4
Cases	20	190	10	40	6	10
Person-years	2319	22 137	1048	5341	389	1412
Risk next year (%)	0.862	0.858	0.954	0.749	1.544	0.708
Relative risk for 10 kg weight loss† (96% CI)	1.00 (0.63–1.59)		1.27 (0.64–2.55)		2.18 (0.79–5.99)	

* Projected for a woman 140 cm in height.

† Overall relative risk for 10 kg weight loss = 1.17 (0.82–1.67), by using the Mantel-Haenszel method.

In this cohort we observed a higher risk of gallstones for current smokers (**Table 5**), particularly for heavy smokers. For women smoking ≥ 35 cigarettes per day, the relative risk for symptomatic gallstones (cholecystectomy and unremoved) compared with that for women who had never smoked was 1.51 (95% CI 1.20–1.89) after adjustment for BMI, weight change, and other risk factors.

Discussion

In this large prospective cohort study we confirmed the importance of obesity as a risk factor for gallstone disease and, because of the size of the study, we could estimate rates for clinically diagnosed gallstones and cholecystectomy at various BMIs. Rates of gallstone disease for obese people are known to be high but have not previously been quantified in a large, well-defined population. The incidence rates increased monotonically with increasing obesity, ≈1%/y for women with a BMI of 30–35 kg/m^2 and exceeding 2%/y for women with a BMI of ≥ 45 kg/m^2. Substantial weight loss during the preceding 2 y was also a significant risk factor for gallstones, independent of current BMI, with a relative risk of 1.94 (95% CI 1.50–2.50) for a loss of > 10 kg. Comparing the risk among women with that weight loss to those of the same original weight, the impact was much less with a nonsignificant relative risk of 1.17 (0.82–1.67). We also confirmed an independent association between cigarette smoking and gallstone disease, as others have observed (4, 21, 22).

It was not possible in this study to screen participants with ultrasound or other techniques for the presence of gallstones. Hence, we focused on cholecystectomy and diagnostically confirmed but unremoved symptomatic gallstones. We recognize that there was substantial underascertainment of gallstones because a large proportion of prevalent stones are completely asymptomatic (6, 13, 23). For example, Jorgensen (13) observed that two-thirds or more of gallstones were asymptomatic and that it is difficult to distinguish symptomatic from asymptomatic stones. Moreover, it is likely that in many of the cases diagnosed during the follow-up interval, gallstones were present but asymptomatic at baseline. We have not attempted to estimate the incidence of gallstone formation but rather the incidence of newly symptomatic gallstone disease, an entity of direct clinical and public health importance.

The findings are based entirely on self-report of weight and the occurrence of gallstone disease on the biennial questionnaires. The self-report of weight in this cohort is quite accurate when compared with measured weights in a sample of the participants (r = 0.97) (14). By comparing the questionnaire reports with medical records in a sample of participants we also found that these registered nurses had a very high level of accuracy in reporting cholecystectomy and diagnostically confirmed but unremoved gallstones (1). Similar accuracy of reporting was demonstrated for several other diagnoses (24). Although we do not know the composition of the stones, we may estimate that 85–90% were cholesterol stones (25, 26).

Our results are consistent with the limited data from previous studies. The Rome Group (7) and Barbara et al (6) both found that BMI is a significant predictor of gallstone prevalence among women in a screened population but provided no prevalence rates by level of obesity. In a small screening study of 249 obese and 60 nonobese women the prevalence of gallstones was 31% among the obese vs 10% among the controls (23). Jorgensen (21) screened 1680 Danish women and provided gallstone prevalence rates specific for categories of BMI. Women with a BMI of ≥ 30 kg/m^2 had a prevalence of 30% (41 of 135) as compared with 6% (13 of 231) among women with a BMI < 20 kg/m^2. Although these numbers cannot be compared directly with incidence rates for symptomatic gallstones, a prevalence of 30% could result, for example, from a net incidence rate of silent gallstone formation of 2%/y followed by an average duration of gallstones of ≈17 y. Using cross-sectional data from a large cohort of weight-conscious women, Bernstein et al (27) estimated incidence rates of diagnosed gallstones by using life-table methods. They found that women in the highest obesity category (mean BMI ≈38.3) had an estimated incidence 2–6.25-fold higher depending on age than the reference category (mean BMI ≈23.0). These results are similar to our findings.

Data from cohort studies are also sparse. In the Framingham Study (28) the risk of clinically diagnosed gallstones was 77% higher than average for women with weight (adjusted for height) ≥ 20% higher than the cohort median (49 cases), but for those in the 10–19% excess-weight category (15 cases) the risk was

TABLE 5
Multivariate-adjusted* relative risks for cholecystectomy, symptomatic unremoved gallstones, and both endpoints together by cigarette smoking

	Cholecystectomy	Unremoved, symptomatic gallstones	Both endpoints
Never	1.0 (referent)	1.0 (referent)	1.0 (referent)
Past	1.06 (0.94–1.18)	1.09 (0.89–1.33)	1.06 (0.96–1.17)
Current			
1–14 cigarettes/d	1.13 (0.94–1.36)	1.06 (0.74–1.50)	1.10 (0.93–1.29)
15–24 cigarettes/d	1.21 (1.04–1.42)	0.93 (0.68–1.29)	1.03 (0.90–1.19)
25–34 cigarettes/d	1.36 (1.11–1.67)	1.21 (0.81–1.31)	1.31 (1.09–1.58)
35+ cigarettes/d	1.59 (1.24–2.05)	1.30 (0.78–2.16)	1.51 (1.20–1.89)

* Simultaneously adjusted for BMI, weight change, age (5-y categories), alcohol intake (five categories), postmenopausal hormone use (current, past, never), smoking (never, past, and current at four amounts of cigarettes per day), parity (six categories), energy intake (five categories), polyunsaturated fatty acid intake (five categories).

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36% lower than average. In a large cohort study of women attending a family-planning clinic in Oxford, UK, 227 young women had a cholcystectomy during nearly 155 000 person-years of follow-up (22). The crude rates in that population were lower than we observed (perhaps reflecting in part differences in surgical practice) and increased steadily from 96/100 000 (25 cases) for < 20 kg/m^2 to 626 for 30 kg/m^2 (22 cases). However, the relative risks were similar to what we observed, particularly given the modest number of cases in the Oxford study, which yielded fairly unstable rates. They found, as we did, that the risk did not materially increase until a BMI of 24 kg/m^2 was exceeded, and in their study a relative risk of 6.5 was observed for BMI of ≥ 30 kg/m^2.

The link between obesity and gallstones is explained by the increased saturation of bile with cholesterol in obese people (29–31). The saturation appears to be increased still further during rapid weight loss (29, 31), suggesting that weight loss could induce gallstone formation (32). Jorgensen (21) addressed this issue in his population screening survey and found that slimming treatments were associated with an increased prevalence of gallstones in both sexes; moreover, the number of slimming treatments was also associated with gallstone prevalence. However, such treatments were associated with obesity and in multivariate analyses adjusting for BMI, the association with slimming treatments was attenuated and in women (but not men), no longer statistically significant. His findings are quite compatible with the moderate association we observed for substantial previous weight loss.

The incidence of clinical gallstone formation during very rapid weight loss has been estimated in several recent small studies that used 2092–2176-kJ/d (500–520-kcal/d) diets. Among 51 patients initially free from gallstones according to ultrasound, Liddle et al (8) found that after 8 wk of dieting (mean weight loss, 16.5 kg), 13 had developed gallstones and 3 of those had symptoms severe enough to require cholecystectomy. In a 16-wk trial of ursodeoxycholic acid in rapid weight loss (22.6 kg mean loss), 7 of 33 patients on placebo or aspirin developed new gallstones, and 2 of them were symptomatic (33). Yang et al (9) found that in a 16-wk rapid-weight-loss program, 15 of 154 subjects free from gallstones at baseline who completed the program developed gallstones diagnosed by ultrasound on screening. No details were reported on the proportion that were symptomatic but the risk was higher for men, for those with more weight loss, and for those who were more obese at baseline. If one assumes the same ratio of symptomatic to asymptomatic stones in the Yang et al study as observed by Liddle (8) and Broomfield (33) et al, then putting the three studies together yields a cumulative incidence of 9 per 238 subjects, or 3.8% (95% CI 2.0–7.0%) over a 2–4-mo weight-loss program. This should be considered a maximum estimate because these subjects were all under intense surveillance and any symptoms would be likely to be attributed to the stones.

We have no data from the Nurses' Health Study on the incidence of gallstones with rapid weight loss and do not know if any of the participants were enrolled in such programs. Our data suggest that a history of substantial weight loss over a 2-y period is a risk factor for clinically symptomatic gallstones independent of the effect of current obesity. The analysis that assesses the impact of weight loss adjusting for previous rather than attained weight (Table 5) suggests that much of the apparent effect of weight loss may be attributable to the excess weight present before the loss. Also, part of the risk associated with weight loss may be attributable to the tendency of women who lost weight in a given 2-y interval to gain weight in the subsequent 2-y interval (17). The impact of obesity on risk is far stronger than that of weight loss in our cohort. Although women on a very-low-calorie diet appear to be at increased risk for gallstones, much of the excess risk is probably attributable to the underlying obesity. If sustained weight reduction eventually decreases the risk to the level of the attained weight, as one might expect, the net long-term impact of weight loss could be a reduction in the incidence of gallstones despite a transient increase in short-term risk. ■

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References

1. Maclure MK, Hayes KC, Colditz GA, Stampfer MJ, Speizer FE, Willett WC. Weight, diet, and the risk of symptomatic gallstones in middle-aged women. N Engl J Med 1989;321:563–9.
2. Kern F Jr. Epidemiology and natural history of gallstones. Semin Liver Dis 1983;3:87–96.
3. Scragg RK, McMichael AJ, Baghurst PA. Diet, alcohol, and relative weight in gallstone disease: a case-control study. Br Med J 1984;288: 1113–9.
4. Diehl AK, Hakkner SM, Hazuda HP, Stern MP. Coronary risk factors and clinical gallbladder disease: an approach to the prevention of gallstones? Am J Public Health 1987;77:841–5.
5. Wysowski DK, Goldberg EL, Comstock GW, Diamond EL. A study of a possible association between breast cancer and gallbladder disease. Am J Epidemiol 1986;123:532–43.
6. Barbara L, Sama C, Morselli-Labate AM, et al. A population study of the prevalence of gallstone disease: the Simione study. Hepatology 1987;7:913–7.
7. The Rome Group for Epidemiology and Prevention of Cholelithiasis (GREPCO). The epidemiology of gallstone disease in Rome, Italy. Part II. Factors associated with the disease. Hepatology 1988;8:907–13.
8. Liddle RA, Goldstein RB, Saxton J. Gallstone formation during weight reduction dieting. Arch Intern Med 1989;149:1750–3.
9. Yang HY, Petersen GM, Marks JW, Roth MP, Schoenfield LJ. Risk factors for gallstone formation during rapid weight loss. Gastroenterology 1990;98(suppl 5):A266(abstr).
10. Colditz GA. The Nurses' Health Study: findings during 10 years of follow-up of a cohort of US women. Curr Probl Obstet Gynecol Fertil 1990;13:129–74.
11. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
12. Maclure KM, Hayes KC, Colditz GA, Stampfer MJ, Willett WC. Dietary predictors of symptom-associated gallstones in middle-aged women. Am J Clin Nutr 1990;52:916–22.
13. Jorgensen T. Abdominal symptoms and gallstone disease: an epidemiologic investigation. Hepatology 1989;9:856–60.
14. Rimm EB, Stampfer MJ, Colditz GA, Litin L, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990;1:466–73.
15. Rothman KJ, Boice JD Jr. Epidemiologic analysis with a programmable calculator. Washington, DC: Public Health Service, 1979. [NIH publication 79–1649].
16. Cox DR. Regression models and life-tables. J R Stat Soc [B] 1972;34: 187–220.

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17. Colditz GA, Willett WC, Stampfer MJ, London SL, Segal MR, Speizer FE. Patterns of weight change and their relation to diet in a cohort of healthy women. Am J Clin Nutr 1990;51:1100–5.
18. Colditz GA, Giovannucci E, Rimm EB, et al. Alcohol intake in relation to diet and obesity among men and women. Am J Clin Nutr 1991;54:49–55.
19. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. Prev Med 1990;20:47–63.
20. A Report from the Boston Collaborative Drug Surveillance Program, Boston University Medical Center. Surgically confirmed gallbladder disease, venous thromboembolism, and breast tumors in relation to postmenopausal estrogen therapy. N Engl J Med 1974;290:15–9.
21. Jorgensen T. Gallstones in a Danish population. Relation to weight, physical activity, smoking, coffee consumption, and diabetes mellitus. Gut 1989;30:528–34.
22. Layde PM, Vessey MP, Yeates D. Risk factors for gall-bladder disease: a cohort study of young women attending family planning clinics. J Epidemiol Community Health 1982;36:274–8.
23. Tucker LE, Tangedahl TN, Newmark SR. Prevalence of gallstones in obese Caucasian American women. Int J Obes 1982;6:247–51.
24. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study in women. Am J Epidemiol 1986;123:894–900.
25. Trotman BW, Soloway RD. Pigment vs cholesterol cholelithiasis: clinical and epidemiological aspects. Am J Dig Dis 1975;20:735–40.
26. Soloway RD, Trotman BW, Ostrow JD. Pigment gallstones. Gastroenterology 1977;72:167–82.
27. Bernstein RA, Giefer EE, Vieira JJ, Wener LH, Rimm AA. Gallbladder disease. II. Utilization of the like table method in obtaining clinically useful information; a study of 62,739 weight-conscious women. J Chronic Dis 1977;30:529–41.
28. Friedman GD, Kannel WB, Dawber TR. The epidemiology of gallbladder disease: observations in the Framingham Study. J Chronic Dis 1966;19:273–92.
29. Bennion LJ, Grundy SM. Effects of obesity and caloric intake on biliary lipid metabolism in man. J Clin Invest 1975;56:996–1011.
30. Freeman JB, Meyer PD, Printen KJ, Mason EE, DenBesten L. Analysis of gallbladder bile in morbid obesity. Am J Surg 1975;129: 163–6.
31. Mok HYI, Von Bergmann K, Crouse JR, Grundy SM. Biliary lipid metabolism in obesity. Effects of bile acid feeding before and during weight reduction. Gastroenterology 1979;76:556–67.
32. Amaral JF, Thompson WR. Gallbladder disease in the morbidly obese. Am J Surg 1985;149:551–7.
33. Broomfield PH, Chopra R, Sheinbaum RC, et al. Effects of ursodeoxycholic acid and aspirin on the formation of lithogenic bile and gallstones during loss of weight. N Engl J Med 1988;319:1567–72.

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