

Weight Cycling and Risk of Gallstone Disease in Men

Chung-Jyi Tsai, MD, ScD; Michael F. Leitzmann, MD, DrPH;
Walter C. Willett, MD, DrPH; Edward L. Giovannucci, MD, ScD

Background: The long-term effect of repeated intentional weight loss and weight regain on the risk of gallstone disease in men is not clear.

Methods: Participants in the Health Professionals Follow-up Study provided information on intentional weight loss during the previous 4 years in 1992. Weight cyclers were men who had intentional weight loss and weight regain. Men free of gallstone disease at baseline were followed from 1992 to 2002. On biennial questionnaires the participants reported newly diagnosed gallstone disease.

Results: During 264 760 person-years of follow-up we ascertained 1222 cases of symptomatic gallstones. We examined the effect of weight cycling on the risk of gallstone disease. The multivariate relative risk of weight cyclers, compared with weight maintainers, after adjusting

for potential confounding variables, including body mass index, was 1.11 (95% confidence interval [CI], 0.94-1.31) in light cyclers, 1.18 (95% CI, 0.97-1.43) in moderate cyclers, and 1.42 (95% CI, 1.11-1.81) in severe cyclers. We further examined the effect of number of cycling episodes. Among weight cyclers, the relative risk associated with having more than 1 weight cycle, compared with weight maintainers, was 1.10 (95% CI, 0.88-1.37) in light cyclers, 1.28 (95% CI, 1.03-1.59) in moderate cyclers, and 1.51 (95% CI, 1.13-2.02) in severe cyclers.

Conclusions: Our findings suggest that weight cycling, independent of body mass index, may increase the risk of gallstone disease in men. Larger weight fluctuation and more weight cycles are associated with greater risk.

Arch Intern Med. 2006;166:2369-2374

Author Affiliations: Division of Digestive Diseases and Nutrition, University of Kentucky Medical Center, Lexington (Dr Tsai); Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass (Drs Tsai, Willett, and Giovannucci); Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston (Drs Willett and Giovannucci); and Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Md (Dr Leitzmann).

GALLSTONE DISEASE IS COMMON among adults in Western countries, and it is a major source of abdominal morbidity.¹

Obesity is a potent risk factor for cholesterol gallstone disease, although it tends to be found less consistently in men than in women.² Rapid weight loss for treatment of morbid obesity is also associated with gallstone formation.³ Obesity has become a serious public health problem in the United States over the past 2 to 3 decades. Approximately 34% of adults in the United States are overweight, and 30.5% are obese according to the third National Health and Nutrition Examination Survey.⁴ The adverse health effects of overweight and obesity are well recognized, and it is recommended that those who are overweight or obese with obesity-related risk factors should lose weight by a combination of increased physical activity and dieting.⁵ Although approximately 30% of adult US men are trying to lose weight,⁶ intentional weight loss is rarely sustained and is often associated with unintentional weight regain, leading to weight

cycling.⁷⁻⁹ The long-term health consequences of repeated intentional weight loss and the mechanisms of weight recovery are still not well understood. Studies have suggested that large weight fluctuations at some point earlier in life represent an independent risk factor for chronic diseases, including metabolic syndrome.¹⁰⁻¹³

Intentional weight loss is an independent predictor of subsequent weight gain among men¹⁴; however, the effect of repeated intentional weight loss and weight regain on risk for gallstones in men is unclear. In a large cohort of US male health professionals, we examined the relationship of weight cycling to the risk for gallstones. Furthermore, we examined whether more weight cycles would increase the risk of gallstone disease.

METHODS

STUDY POPULATION

The Health Professionals Follow-up Study is a prospective investigation of 51 529 US male health care professionals aged 40 to 75 years in 1986 who returned a mailed questionnaire

regarding anthropometric measures, diet, medications, and medical history. It was estimated that 96% of the participants were white. Follow-up questionnaires were sent every 2 years to update information on exposures and to ascertain the occurrence of newly diagnosed illnesses, including gallstone disease. Diet was assessed every 4 years. Baseline height, age, and body weight were ascertained on the 1986 questionnaire, and participants were asked to report their weight on each subsequent questionnaire. In 1992, participants were asked to provide information on intentional weight loss during the previous 4 years. The questions on weight loss were specifically designed to address the long-term health consequences of intentional weight loss. We excluded men who reported a cholecystectomy or a diagnosis of gallstone disease in 1992. We also excluded men who had a diagnosis of cancer, men who had a daily energy intake outside the range of 800 to 4200 Kcal per day, men who reported 70 or more blank food items on the questionnaires, and men who did not complete the questions on intentional weight loss. The average response rate for biennial questionnaires was greater than 94% in each 2-year follow-up cycle.¹⁵

ASSESSMENT OF WEIGHT CYCLING

Participants were asked to provide information on intentional weight loss in 1992. The questions included the number of intentional weight loss episodes of varying magnitude. Participants were asked, "Within the last 4 years, how many times did you lose each of the following amounts of weight on purpose (excluding illness)?" Weight loss categories were 5 to 9 lb (2.3-4.1 kg), 10 to 19 lb (4.5-8.6 kg), 20 to 49 lb (9.0-22.1 kg), and more than 50 lb (>22.5 kg). The number of intentional weight loss episodes and the amount of weight lost during each episode were assessed for the 4 years during 1988 to 1992. In addition to this information, we used the self-reported weights in the biennial questionnaires to determine net trends in weight change. The validity of self-reported weight was assessed in a random sample of 123 participants in the greater Boston, Mass, area.¹⁶ The Pearson correlation between self-reported weight and measured weight by technicians was 0.97. We defined weight pattern categories by combining the data on intentional weight loss with the net weight trend for the period 1988 to 1992. Weight maintainers (n=7443) were men who had no intentional weight loss and whose net weight remained stable at ± 5 lb (± 2.25 kg). Weight cyclers (n=17 286) were men who had intentional weight loss and weight regain. Weight cyclers were further divided into 3 categories: light cyclers (n=10 027) (maximum intentional weight loss per episode, 5-9 lb [2.3-4.1 kg]), moderate cyclers (n=5185) (maximum intentional weight loss per episode, 10-19 lb [4.5-8.6 kg]), and severe cyclers (n=2074; maximum intentional weight loss per episode, 20 lb [9.0 kg] or more). A total of 24 729 men, including weight cyclers and weight maintainers, were followed from 1992 to 2002.

ASSESSMENT OF DIET

Dietary information was derived from a 131-item semiquantitative food frequency questionnaire (SFFQ).¹⁷ Participants were asked to indicate the frequency, on average, of consuming a typical serving of selected foods during the previous year. Nutrient scores were computed by multiplying the frequency of consumption of each unit of food from the SFFQ by the nutrient content of the specified portion according to food composition tables from the US Department of Agriculture.¹⁸ A full description of the SFFQ and the procedures used for calculating nutrient intake, as well as data on reproducibility and validity in this cohort, were reported previously.¹⁹

ASCERTAINMENT OF END POINTS

The primary end point was incident symptomatic gallstones. On the 1986 questionnaire and on each follow-up questionnaire, participants were asked whether they had undergone a cholecystectomy or had been diagnosed as having gallstones by a physician. Participants were also asked whether the gallstone diagnosis had been confirmed by radiographic procedures or surgery and whether their gallstones were symptomatic. To verify the self-reports of clinical gallbladder disease, including surgical cholecystectomy and diagnosed but unremoved gallstones, a random sample of 441 medical records of participants who reported a cholecystectomy or gallstones were reviewed, and the diagnosis was confirmed in nearly all (99%) of these. Moreover, we confirmed all but 1 of the self-reported diagnostic procedures and all self-reported symptoms by medical record review.

STATISTICAL ANALYSIS

For each participant, follow-up time accrued from the month of return of the 1992 questionnaire and ended at the month of cholecystectomy, diagnosis of symptomatic gallstones, death, or the end of the study period (January 31, 2002), whichever occurred first. Men with asymptomatic gallstones or those whose gallstone diagnosis was not based on radiologic findings were excluded from subsequent follow-up.

By using weight maintainers as the reference category, models were used to analyze the effect of weight cycling from 1988 to 1992 and the risk of gallstone disease from 1992 to 2002. The incidence rates were calculated by dividing the number of events by person-years of follow-up in each category. Relative risks (RRs) were calculated as the incidence rate of gallstone disease among men in different categories of exposure compared with the incidence rate among men in the reference category, with adjustment for age. To account for the possibility that the impact of weight cycling might differ with height and body weight, we additionally controlled for body mass index (BMI, calculated by dividing weight in kilogram by the square of height in meters) in the analysis. We controlled for BMI as continuous and categorical (5 categories) variables to ensure that our results for weight cycling were robust. In this way, we were able to estimate the RR for gallstone disease resulting from weight cycling while controlling for weight at the beginning of each follow-up period. The RRs were calculated by using the Cox proportional hazards model. Tests of linear trend across increasing categories were conducted by assigning the median value of exposure for each category and treating these as a single continuous variable. In the multivariate analyses, in addition to adjusting for BMI, we simultaneously included intake of total energy and potential confounding covariates including biennially updated age (1-year category); physical activity (quintiles); pack-years of smoking (6 categories); history of diabetes mellitus (yes or no); intakes of the following: alcohol (5 categories); dietary fiber (quintiles); carbohydrates (quintiles); intake of vegetable protein (quintiles); saturated, *trans*, polyunsaturated, and monounsaturated fats (quintiles); caffeine (quintiles); and use of thiazide diuretics (yes or no) or nonsteroidal anti-inflammatory drugs (yes or no). Tests for interaction were performed using likelihood ratio tests by comparing 2 nested models, 1 with the main effects only and the other with both the main effects and interaction terms. All RRs are presented with 95% confidence intervals (CIs), and all reported *P* values are 2-sided. We considered *P* values smaller than .05 to be statistically significant. All analyses were performed with SAS statistical software (release 8.2; SAS Institute, Cary, NC).

Table 1. Baseline Characteristics and Weight Cycling* From 1988 to 1992 Among US Men in the HPFS

Characteristic	Weight Maintainer	Light Cycler	Moderate Cycler	Severe Cycler
Participants, No.	7443	10 027	5185	2074
Age, mean, y	55.1	55.1	55.0	55.1
BMI, mean	23.9	25.4	26.9	28.8
METs/wk†	21.4	20.9	19.4	17.2
Pack-years of smoking	10.3	11.1	14.3	17.1
Regular use of thiazide diuretics, %	6.5	8.3	10.2	12.8
Regular use of NSAIDs %	31.1	35.8	37.2	37.5
Mean daily intake†				
Total energy, kcal/d	2046	1964	1952	1931
Carbohydrates	240	235	230	226
Alcohol	11.1	11.6	11.5	10.7
Caffeine, mg/d	217	241	262	280
Saturated fat	23.9	24.2	24.9	25.6
Polyunsaturated fat	13.1	13.3	13.4	13.5
Monounsaturated fat	26.8	27.1	27.7	28.2
Trans fat	2.8	2.8	2.8	2.9
Dietary fiber	21.1	21.1	21.0	20.9

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent task (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); NSAIDs, nonsteroidal anti-inflammatory drugs (including aspirin).

*Weight maintainers were men who had no intentional weight loss and whose net weight remained stable at ± 5 lbs (2.3 kg). Weight cyclers were men who had intentional weight loss and weight regain. Weight cyclers were further divided into 3 categories: light cyclers (maximum intentional weight loss per episode of 5 to 9 lbs [2.3-4.1 kg]), moderate cyclers (maximum intentional weight loss per episode of 10 to 19 lbs [4.5-8.6 kg]), and severe cyclers (maximum intentional weight loss per episode of 20 lbs [9.0 kg] or more).

†Nutrients were energy adjusted; values are given in grams per day except where noted.

Table 2. Age-Adjusted and Multivariate Analyses of Weight Cycling From 1988 to 1992 and Subsequent Risk for Gallstone Disease (GD) From 1992 to 2002 Among US Men in the HPFS

Variable	Type of Cycler				P Value for Trend
	Weight Maintainer	Light Cycler	Moderate Cycler	Severe Cycler	
Cases of GD, No. (person-years)	258 (61 495)	392 (84 890)	214 (44 263)	111 (17 374)	
Model No., RR (95% CI)					
1. Age-adjusted	1.00	1.21 (1.03-1.41)	1.35 (1.13-1.63)	1.82 (1.45-2.29)	<.001
2. Multivariate*	1.00	1.21 (1.03-1.42)	1.38 (1.15-1.67)	1.76 (1.40-2.23)	<.001
3. Multivariate†	1.00	1.11 (0.94-1.31)	1.18 (0.97-1.43)	1.42 (1.11-1.81)	.002

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; RR, relative risk.

*Multivariate model included the following: age, physical activity, thiazide diuretics, nonsteroid anti-inflammatory drugs, history of diabetes mellitus, pack-years of smoking, alcohol intake, caffeine intake, dietary fiber, carbohydrate intake, vegetable protein intake, intakes of saturated, *trans*, polyunsaturated, and monounsaturated fats, and total energy intake.

†Model 2 additionally adjusted for body mass index.

RESULTS

Among the weight cyclers who had repeated intentional weight loss and subsequent weight gain in the 4-year exposure period from 1988 to 1992, 58% were light cyclers, 30% were moderate cyclers, and 12% were severe cyclers. At baseline, severe cyclers, compared with light cyclers, tended to be heavier, sedentary, and heavier smokers and to consume more saturated and monounsaturated fats and caffeine but less alcohol (**Table 1**).

During 264 760 person-years of follow-up from 1992 to 2002, we ascertained 1222 cases of symptomatic gallstones, of which patients had undergone cholecystectomy. By using weight maintainers as the reference category, we examined the effect of weight cycling from 1988

to 1992 on the risk of gallstone disease from 1992 to 2002. In the multivariate analysis after controlling for known or suspected risk factors for gallstones, all the weight cyclers were significantly associated with an increased risk: the RRs were 1.21 (95% CI, 1.03-1.42) in light cyclers, 1.38 (95% CI, 1.15-1.67) in moderate cyclers, and 1.76 (95% CI, 1.40-2.23) in severe cyclers (*P* value for trend, <.001) (model 2 in **Table 2**). After additional adjustment for BMI as a categorical variable, the estimates of the effect of weight cycling became more conservative; however, the statistical significance of the RR for severe cyclers persisted (model 3 in **Table 2**). After entering BMI as a continuous variable in the multivariate model, the RRs among cyclers were little changed: the multivariate RRs were 1.12 (95% CI, 0.95-1.32) in light cyclers, 1.19

Table 3. Age-Adjusted and Multivariate Analyses of Cycling Frequency From 1988 to 1992 and Subsequent Risk for GD From 1992 to 2002 Among US Men in the HPFS

Type of Cycler	Model, RR (95% CI)		
	1, Age-Adjusted	2, Multivariate*	3, Multivariate†
Weight maintainer	1.00	1.00	1.00
Light cycler			
1 Cycle	1.21 (1.02-1.43)	1.21 (1.02-1.44)	1.11 (0.93-1.33)
≥2 Cycles	1.20 (0.97-1.49)	1.21 (0.97-1.50)	1.10 (0.88-1.37)
Moderate cycler			
1 Cycle	1.17 (0.89-1.55)	1.14 (0.86-1.51)	0.99 (0.74-1.32)
≥2 Cycles	1.44 (1.17-1.77)	1.52 (1.23-1.87)	1.28 (1.03-1.59)
Severe cycler			
1 Cycle	1.60 (1.15-2.23)	1.56 (1.11-2.18)	1.30 (0.92-1.83)
≥2 Cycles	1.98 (1.50-2.60)	1.93 (1.46-2.54)	1.51 (1.13-2.02)

Abbreviations: GD, gallstone disease; HPFS, Health Professionals Follow-up Study.

*Model 2: Multivariate model included the following: age; physical activity; thiazide diuretics; nonsteroid anti-inflammatory drugs; history of diabetes mellitus; pack-years of smoking; and intakes of the following: alcohol; caffeine; dietary fiber; carbohydrate; vegetable protein; saturated, *trans*, polyunsaturated, and monounsaturated fats; and total energy.

†Model 3: Model 2 additionally adjusted for body mass index.

(95% CI, 0.98-1.44) in moderate cyclers, and 1.40 (95% CI, 1.10-1.79) in severe cyclers (*P* value for trend, .002)

To examine whether the association between weight cycling and risk of gallstone disease was modified by risk factors for gallstones, we repeated the multivariate analyses within subgroups of potential confounding variables. The positive associations between weight cycling and risk of gallstone disease persisted, and there was no change in effect (test of interaction, *P* > .05). Particularly, we stratified BMIs into 3 groups (BMI < 25, BMI of 25-30, and BMI > 30) and found no effect modification (test of interaction, *P* = .54).

We further examined number of cycling episodes from 1988 to 1992 and the risk of gallstone disease from 1992 to 2002. In the multivariate model that included the same covariates as those in model 2 in Table 2, compared with weight maintainers, numbers of cycles increased the risk in moderate and severe cyclers but not in light cyclers. The multivariate RRs for gallstone disease associated with having more than 1 weight cycle were 1.52 (95% CI, 1.23-1.87) in moderate cyclers and 1.93 (95% CI, 1.46-2.54) in severe cyclers (model 2 in Table 3). In the multivariate model that included the same covariates as those in model 3 in Table 2, the RRs of increased number of cycles among moderate and severe cyclers were slightly attenuated but remained significant (model 3 in Table 3). After entering BMI as a continuous variable in the multivariate model, the RRs were little changed: the multivariate RRs for gallstone disease associated with having more than 1 weight cycle were 1.29 (95% CI, 1.04-1.60) in moderate cyclers and 1.50 (95% CI, 1.12-2.00) in severe cyclers.

COMMENT

In this large prospective study among men, we found that weight cycling with periods of intentional weight loss and

weight regain was common between 1988 and 1992, whereas maintenance of stable weight was relatively uncommon. In the subsequent 10-year follow-up period, the risk of symptomatic gallstone disease increased by approximately 40% in men who had 1 or more weight loss and gain cycles of more than 20 lb (9.1 kg). More weight cycles also increased risk: 2 or more weight cycles increased the risk by approximately 30% in men who had weight loss and gain cycles of 10 to 19 lb (4.5-8.6 kg) and by approximately 50% in men who had weight loss and gain cycles of more than 20 lb (9.1 kg). This effect was independent of BMI and other known or suspected risk factors for gallstones.

Many factors have been associated with the risk of cholesterol gallstones,²⁰ but supersaturation of bile with cholesterol, which is closely related to total body fat, is an important determinant. The potential mechanisms contributing to the association between weight cycling and gallstone formation observed in our study are likely to be multiple. In a follow-up study of men who lost about 15% of their body weight during exposure to modest energy restriction sustained over 2 years during confinement,²¹ it was found that 6 months after exit from confinement, the weight regained was almost exclusively accounted for by an increase in body fat. Studies have shown that large swings of body weight, especially the phase of weight recovery, are particularly sensitive to the accumulation of body fat and to the development of metabolic abnormalities, including insulin resistance,^{11,12} and thereby may facilitate gallstone formation.^{22,23} In animals, weight cycling was demonstrated to be associated with significant fluctuation of lipogenic enzymes, serum triglycerides, glucose, and insulin.²⁴ In addition, 2 weight cycles could remodel the whole-body fatty acid composition in animals and markedly lowered the ratio of polyunsaturated to saturated fatty acids in tissues, which potentially may increase the risk for gallstones.²⁵⁻²⁷ Serum leptin and insulin levels were demonstrated to be significantly greater for weight cyclers than for weight maintainers.²⁸ In addition, large weight fluctuation is a risk factor for the development of metabolic syndrome later in life.^{11,12} All of these may increase the risk of gallstone formation.^{22,29,30}

Our findings were consistent with a report on the relation of weight cycling to cholecystectomy in women.³¹ Although the association between total obesity and cholesterol gallstones has been less consistent and more difficult to demonstrate in men than women,² rapid weight loss was more consistently found to increase risk for gallstones in both sexes^{3,32-35} because of increased bile cholesterol supersaturation, decreased gallbladder contractility, and enhanced cholesterol crystal nucleation. In short-term studies, the prevalence of new gallstones reached 10% to 12% after 8 to 16 weeks of a low-calorie diet and more than 30% within 12 to 18 months after gastric bypass surgery.³ After weight stabilization at a lower level, bile cholesterol supersaturation could return to reference range and could allow spontaneous dissolution of gallstones.

In the assessment of weight fluctuations during the 4-year period, some misclassification of weight cycler sta-

tus might exist. Although participants were asked to exclude weight loss related to ill health, there might be variability in how the participants interpreted the questions, and some of the weight reported as lost intentionally was lost unintentionally. However, it is unlikely that men repeatedly lost large amounts of weight unintentionally. A limitation of the study is that the effect of weight cycling during the 4-year period might not represent entirely the effect of weight cycling in earlier life.

The prospective design of our study avoids the potential for differential recall of exposures between gallstone cases and noncases because all data were collected before the diagnosis of gallstone disease. If recall error is not associated with weight loss intent or the study end point, and is thus nondifferential, then it would have no effect or would bias the effect toward the null and weaken any true relationship. Previous studies have shown that self-reports of intentional weight loss and weight change are reliable.^{36,37} Our study had serial measurements of weight from which the 4-year weight change was calculated and had information on the number of times weight was lost intentionally. The large size of our study sample allowed us to assess the impact of weight change within these groups. Consistently high follow-up rates of the participants also reduce the possibility that our results could be biased by men lost to follow-up.

Because the participants in this cohort are relatively homogeneous with regard to race and socioeconomic status, and our results focused on clinically relevant gallstone disease in men, including surgical cholecystectomy or diagnostically confirmed but unremoved symptomatic gallstones, the results may not be generalizable to the entire population with gallstones.

Although we assessed and adjusted for a number of potential confounders, we cannot exclude the possibility of residual confounding as in any observational studies. It is possible that the positive association was due to some unmeasured variable, such as socioeconomic status. However, because the population we studied is relatively homogeneous with respect to education and occupation, confounding by socioeconomic status was minimized. Residual confounding probably could not entirely explain the observed relationship.³⁸

In this large study it was not possible to perform diagnostic screening procedures for the presence of gallstones. Because most gallstones are silent in men, it is likely that there was considerable underascertainment of gallstones. It was not likely that the presence of silent gallstones at baseline was associated with the reporting of weight patterns. As RR estimation in follow-up cohort studies would not be biased by uniform underascertainment,³⁹ our results were not likely biased owing to silent gallstones.

In conclusion, our findings suggest that weight cycling, independent of BMI, may increase the risk of gallstone disease among men. Larger weight fluctuation and more weight cycles are associated with greater risk.

Accepted for Publication: August 19, 2006.

Correspondence: Chung-Jyi Tsai, MD, ScD, Division of Digestive Diseases and Nutrition, University of Ken-

tucky Medical Center, 800 Rose St, Lexington, KY 40536-0298 (hpcjt@channing.harvard.edu).

Author Contributions: *Study concept and design:* Tsai, Leitzmann, Willett and Giovannucci. *Acquisition of data:* Willett and Giovannucci. *Analysis and interpretation of data:* Tsai, Leitzmann, Willett and Giovannucci. *Drafting of the manuscript:* Tsai, Leitzmann, Willett and Giovannucci. *Critical revision of the manuscript for important intellectual content:* Tsai, Leitzmann, Willett and Giovannucci. *Statistical analysis:* Tsai, Leitzmann, Willett and Giovannucci. *Obtained funding:* Willett and Giovannucci. *Administrative, technical, and material support:* Willett and Giovannucci. *Study supervision:* Willett and Giovannucci.

Financial Disclosure: None reported.

Funding/Support: This study was supported by research grants from the National Institutes of Health (CA55075 and DK46200) and from the Centers for Disease Control and Prevention.

Acknowledgment: We thank the participants of the Health Professionals Follow-up Study for their continued cooperation and participation and the research staff in the study for their expert help.

REFERENCES

1. Kang JY, Ellis C, Majeed A, et al. Gallstones: an increasing problem: a study of hospital admissions in England between 1989/1990 and 1999/2000. *Aliment Pharmacol Ther.* 2003;17:561-569.
2. Erlinger S. Gallstones in obesity and weight loss. *Eur J Gastroenterol Hepatol.* 2000;12:1347-1352.
3. Weinsier RL, Wilson LJ, Lee J. Medically safe rate of weight loss for the treatment of obesity: a guideline based on risk of gallstone formation. *Am J Med.* 1995;98:115-117.
4. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA.* 2002;288:1723-1727.
5. National Institutes of Health. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report.* Washington, DC: US Dept of Health and Human Services; 1998. NIH publication 98-4083.
6. Serdula MK, Mokdad AH, Williamson DF, et al. Prevalence of attempting weight loss and strategies for controlling weight. *JAMA.* 1999;282:1353-1358.
7. Curioni CC, Lourenco PM. Long-term weight loss after diet and exercise: a systematic review. *Int J Obes (Lond).* 2005;29:1168-1174.
8. Elfhag K, Rossner S. Who succeeds in maintaining weight loss? a conceptual review of factors associated with weight loss maintenance and weight regain. *Obes Rev.* 2005;6:67-85.
9. Blackburn GL, Wilson GT, Kanders BS, et al. Weight cycling: the experience of human dieters. *Am J Clin Nutr.* 1989;49(5) (suppl):1105-1109.
10. Hamm P, Shekelle RB, Stamler J. Large fluctuations in body weight during young adulthood and twenty-five-year risk of coronary death in men. *Am J Epidemiol.* 1989;129:312-318.
11. Dulloo AG, Jacquet J, Montani JP. Pathways from weight fluctuations to metabolic diseases: focus on maladaptive thermogenesis during catch-up fat. *Int J Obes Relat Metab Disord.* 2002;26(suppl 2):S46-S57.
12. Cettour-Rose P, Samec S, Russell AP, et al. Redistribution of glucose from skeletal muscle to adipose tissue during catch-up fat: a link between catch-up growth and later metabolic syndrome. *Diabetes.* 2005;54:751-756.
13. Crescenzo R, Samec S, Antic V, et al. A role for suppressed thermogenesis favoring catch-up fat in the pathophysiology of catch-up growth. *Diabetes.* 2003;52:1090-1097.
14. Coakley EH, Rimm EB, Colditz G, et al. Predictors of weight change in men: results from the Health Professionals Follow-up Study. *Int J Obes Relat Metab Disord.* 1998;22:89-96.
15. Rimm EB, Stampfer MJ, Colditz GA, et al. Effectiveness of various mailing strategies among non-respondents in a prospective cohort study. *Am J Epidemiol.* 1990;131:1068-1071.
16. Rimm EB, Stampfer MJ, Colditz GA, et al. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology.* 1990;1:466-473.

17. Rimm EB, Giovannucci EL, Stampfer MJ, et al. Reproducibility and validity of an expanded self-administered semi-quantitative food frequency questionnaire among male health professionals. *Am J Epidemiol.* 1992;135:1114-1126.
18. US Department of Agriculture. *Composition of Foods: Raw, Processed, and Prepared, 1963-1992.* Washington, DC: Dept of Agriculture, US Government Printing Office; 1993. Agricultural Handbook Series, No. 8.
19. Willett WC. *Nutritional Epidemiology.* 2nd ed. New York, NY: Oxford University Press; 1998.
20. Cohen DE. Pathogenesis of gallstones. In: Zakim D, Boyer TD, eds. *Hepatology: A Textbook of Liver Disease.* 4th ed. Philadelphia, Pa: WB Saunders; 2002:1713-1743.
21. Weyer C, Walford RL, Harper IT, et al. Energy metabolism after 2 y of energy restriction: the biosphere 2 experiment. *Am J Clin Nutr.* 2000;72:946-953.
22. Misciagna G, Guerra V, Di Leo A, et al. Insulin and gallstones: a population case control study in southern Italy. *Gut.* 2000;47:144-147.
23. Dubrac S, Parquet M, Blouquit Y, et al. Insulin injections enhance cholesterol gallstone incidence by changing the biliary cholesterol saturation index and apo A-I concentration in hamsters fed a lithogenic diet. *J Hepatol.* 2001;35:550-557.
24. Sea MM, Fong WP, Huang Y, et al. Weight cycling-induced alteration in fatty acid metabolism. *Am J Physiol Regul Integr Comp Physiol.* 2000;279:R1145-R1155.
25. Ayyad N, Cohen BI, Ohshima A, et al. Prevention of cholesterol cholelithiasis by dietary unsaturated fats in hormone-treated female hamsters. *Lipids.* 1996;31:721-727.
26. Jonnalagadda SS, Trautwein EA, Hayes KC. Dietary fats rich in saturated fatty acids (12:0, 14:0, and 16:0) enhance gallstone formation relative to monounsaturated fat (18:1) in cholesterol-fed hamsters. *Lipids.* 1995;30:415-424.
27. Tsai CJ, Leitzmann MF, Willett WC, et al. The effect of long-term intake of cis unsaturated fats on the risk for gallstone disease in men: a prospective cohort study. *Ann Intern Med.* 2004;141:514-522.
28. Ball GD, Gingras JR, Fimrite A, et al. Weight relapsers, maintainers, and controls: metabolic and behavioural differences. *Can J Appl Physiol.* 1999;24:548-558.
29. Mendez-Sanchez N, Chavez-Tapia NC, Motola-Kuba D, et al. Metabolic syndrome as a risk factor for gallstone disease. *World J Gastroenterol.* 2005;11:1653-1657.
30. Grundy SM. Cholesterol gallstones: a fellow traveler with metabolic syndrome? *Am J Clin Nutr.* 2004;80:1-2.
31. Syngal S, Coakley EH, Willett WC, et al. Long-term weight patterns and risk for cholecystectomy in women. *Ann Intern Med.* 1999;130:471-477.
32. 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;319:1567-1572.
33. Liddle RA, Goldstein RB, Saxton J. Gallstone formation during weight-reduction dieting. *Arch Intern Med.* 1989;149:1750-1753.
34. Kamrath RO, Plummer LJ, Sadur CN, et al. Cholelithiasis in patients treated with a very-low-calorie diet. *Am J Clin Nutr.* 1992;56(1) (suppl):255S-257S.
35. Iglezias Brandao de Oliveira C, Adami Chaim E, da Silva BB. Impact of rapid weight reduction on risk of cholelithiasis after bariatric surgery. *Obes Surg.* 2003;13:625-628.
36. Wannamethee SG, Shaper AG, Whincup PH, et al. Characteristics of older men who lose weight intentionally or unintentionally. *Am J Epidemiol.* 2000;151:667-675.
37. French SA, Jeffery RW, Folsom AR, et al. Relation of weight variability and intentionality of weight loss to disease history and health-related variables in a population-based sample of women aged 55-69 years. *Am J Epidemiol.* 1995;142:1306-1314.
38. Flanders WD, Khoury MJ. Indirect assessment of confounding: graphic description and limits on effect of adjusting for covariates. *Epidemiology.* 1990;1:239-246.
39. Rothman KJ, Greenland S. *Modern Epidemiology.* Philadelphia, Pa: Lippincott Williams & Wilkins; 1998.