Published in final edited form as:

J Pediatr Gastroenterol Nutr. 2012 September ; 55(3): 328–333. doi:10.1097/MPG.0b013e31824d256f.

Pediatric obesity and gallstone disease: results from a cross-sectional study of over 510,000 youth

Corinna Koebnick, PhD¹, Ning Smith, PhD¹, Mary Helen Black, PhD¹, Amy H. Porter, MD², Bradley A. Richie, MD³, Sharon Hudson, PhD¹, Deborah Gililand, DO⁴, Steven J. Jacobsen, PhD¹, and George F Longstreth, MD¹

¹Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA

²Kaiser Permanente Baldwin Park Medical Center, Baldwin Park, CA

³Kaiser Permanente Riverside Medical Center, Riverside, CA

⁴Kaiser Permanente Fontana Medical Center, Fontana, CA

Abstract

Objectives—To investigate the association between childhood and adolescent obesity, the risk of gallstones and the potential effect modification by oral contraceptive use in girls.

Methods—For this population-based cross-sectional study, measured weight and height, oral contraceptive use, and diagnosis of cholelithiasis or choledocholithiasis were extracted from electronic medical records of 510,816 patients aged 10–19 years enrolled in an integrated health plan 2007–2009.

Results—We identified 766 patients with gallstones. The adjusted ORs (95% CI) of gallstones for under/normal weight (=reference), overweight, moderate obesity, and extreme obesity in boys were 1.00, 1.46 (0.94–2.27), 1.83 (1.17–2.85), and 3.10 (1.99–4.83) and in girls 1.00, 2.73 (95% CI 2.18–3.42), 5.75 (4.62–7.17), and 7.71 (6.13–9.71), respectively (*P* for interaction sex × weightclass <0.001). Among girls, oral contraceptive use was associated with higher odds for gallstones (OR 2.00, 95% CI 1.66–2.40). Girls who used oral contraceptives were at higher odds for gallstones than their counterparts in the same weight class who did not use oral contraceptives (*P* for interaction weight class × oral contraceptive use = 0.023).

Conclusions—Due to the shift towards extreme childhood obesity, especially in minority children, pediatricians can expect to face increasing numbers of children and adolescents affected by gallstone disease.

Keywords

obesity; body weight; childhood; gallstones; cholelithiasis; oral contraceptive use

Corresponding author and responsible for reprint requests: Corinna Koebnick, PhD, Department of Research and Evaluation, Kaiser Permanente Southern California, 100 Los Robles, 2nd Floor, Pasadena, CA 91101, Corinna.Koebnick@kp.org, Phone: (626) 564-3693, Fax: (626) 564-3430.

Conflicts of interest and funding sources: Research funding was provided to Dr. Koebnick by the National Institute of Diabetes and Digestive and Kidney Disorders (NIDDK, R21DK085395) and Kaiser Permanente Direct Community Benefit Funds. For the remaining authors none were declared.

Introduction

Cholelithiasis and choledocholithiasis are major health problems in the United States, currently affecting an estimated 20 million adults [1] with total costs of \$6.2 billion in 2004 [2]. Adult gallstone disease is associated with increased all-cause mortality, as well as increased cardiovascular and cancer mortality [3]. Several risk factors for gallstones in adults are well-established, including age, female sex, Hispanic ethnicity, obesity, use of female sex hormones, pregnancy, sedentary lifestyle, and a family history of gallstones [1]. However, scant information is available regarding risk factors for gallstones in the pediatric population.

Although gallstones are a relatively common outcome in obese adults, gallstones in children and adolescents are rare and linked to conditions such as chronic hemolysis [4]. Some clinical reports suggest that hemolytic diseases are no longer the most frequent cause of pediatric gallbladder disease [5, 6]. Concomitant with the epidemic of childhood obesity [7, 8] and the shift towards extreme childhood obesity [7], the prevalence of gallstones in children and adolescents may be increasing due to childhood obesity. Results from small hospital-based studies suggest that obesity may be a risk factor for gallstones in adolescents [9, 10]. Cholecystectomy is also becoming more frequent in this age group [11]. Given the observations that the prevalence of dyslipidemia and diabetes is also increasing in pediatric populations [12, 13], pediatricians may have to be increasingly prepared to recognize and treat conditions in children that traditionally only occurred in adults.

No information is available on the magnitude of the association between overweight, moderate and extreme obesity, and the risk of gallstones in children and adolescents. It is largely unknown whether gallstone risk factors established for adults also apply to pediatric populations. Given the decreasing age of puberty onset in girls [14, 15] and the link between obesity, female sex hormone exposure, and gallstone risk in adults [16], we speculated that girls may be at particularly high risk for gallstones, especially if they are obese and/or take oral contraceptives.

To estimate the magnitude of the association between body mass index (BMI) and the occurrence of gallstones in children, we investigated this association in children with varying degrees of obesity using a multiethnic population-based cohort of children and adolescents in southern California [7].

Methods

Study design and subjects

For this cross-sectional study, we used a subset of patients enrolled in a large population-based cohort study, the Kaiser Permanente Southern California (KPSC) Children's Health Study 2007–2009 (n= 920,034) [17]. Patients enrolled in this study were members of a pre-paid integrated health plan between January 1, 2007 and December 31, 2009. KPSC is the largest health care provider in southern California and provides health care service to over 3.4 million members, about 16% of the total population in the service area. Members received their care in medical offices and hospitals owned by KPSC. Comprehensive electronic health records have been used since enrollment in the KPSC Children's Health Study. We excluded patients who were pregnant (n = 6,856), younger than 10 years of age (n=401,232), and those who had a pre-existing diagnosis of cholelithiasis more than 24 months prior to the study enrollment (n=386), cystic fibrosis (n=318), or hemolytic anemia (n=426), leaving 510,816 patients for the analyses in the present study. The study protocol was reviewed and approved by the Institutional Review Board of KPSC.

Outcome ascertainment

Patients with gallstones in the gallbladder and ducts of the biliary tract (cholelithiasis and choledocholithiasis) were identified by extracting International Classification of Disease, 9th modification (ICD-9) code 574 in electronic health records documenting inpatient and outpatient medical encounters. We identified patients whose gallstone disease was diagnosed within 24 months prior to the study enrollment. According to the study protocol and a priori defined selection criteria, subjects with gallstones over 24 months prior to the study baseline were excluded from the analysis to limit this cross-sectional study to cases with a diagnosis less than 2 years before their first available BMI in the electronic medical record. However, a sensitivity analysis performed a posteriori showed virtually identical results.

To rule out that gallstone suspicion was diagnosed as gallstone disease, we performed a validation study in a random sub-sample of 394 patients with an ICD-9 code 574 indicating gallstone disease. The diagnosis was confirmed or rejected by manual chart review of the electronic medical record using physician notes, radiology reports, and surgical pathology reports from cholelithiasis or choledocholithiasis. The positive predictive value (PPV) of the diagnosis by ICD-9 code was 90.9% and did not differ by weight class.

Body weight and height

Body weight and height were extracted from electronic health records, and body mass index (BMI) was calculated as weight (kilograms) divided by the square of the height (meters). For patients enrolled into the study in years 2007, 2008, and 2009, the median BMI-for-age of all encounters in the year of study enrollment for a patient was used for analysis. Based on a validation study including 15,000 patients with 45,980 medical encounters, the estimated error rate in body weight and height data was <0.4% [18].

Definitions of overweight and obesity in children and adolescents are based on the sex-specific BMI-for-age growth charts developed by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) definitions for overweight and obesity in adults [19–21]. Children were categorized as underweight (BMI-for-age <5th percentile), normal weight (BMI-for-age 5th to <85th percentile), overweight (BMI-for-age 85th to <95th percentile or a BMI 25 to <30 kg/m²), moderately obese (BMI-for age 95th to <1.2 × 95th percentile or a BMI 30 to <35 kg/m²), and extremely obese (BMI-for age 1.2 × 95th percentile or a BMI ≥ 35 kg/m²).

Race/ethnicity and socioeconomic status

We obtained race and ethnicity information from health plan administrative records and birth records. We categorized race/ethnicity as non-Hispanic White, Hispanic, Black, Asian or Pacific Islander, and other, multiple, or unknown race/ethnicity. A validation study compared health plan administrative records and birth certificate records of 325,810 children [22]. The PPV for Hispanic ethnicity was 95.6%. PPV for White, Black, Asian/Pacific Islander, and other race was 89.3%, 86.6%, 73.8%, 51.8% and 1.2%, respectively [22].

When race and ethnicity information was unknown (31.7%), administrative records were supplemented by an imputation algorithm based on surname lists and address information derived from the U.S. Bureau of Census [23–25]. Hispanic ethnicity and Asian race were assigned based on surnames. For Blacks and non-Hispanic Whites, the child's home address was used to link racial/ethnic information from the U.S. Bureau of Census. Race/ethnicity was hierarchically assigned using probability cut-offs of >50% for Asian surname, >50% for Hispanic surname, >75% for Black race from geocoding, and White race >45% from

geocoding if no other assignment could be made before. The specificity and positive predictive values were >98% for all races/ethnicities [7].

As measures of socioeconomic status, neighborhood education was estimated based on the linkage of health plan member's addresses via geocoding with U.S. Census block data.

Oral contraceptive use

Information on oral contraceptive use was extracted from pharmacy records and was defined as any dispensed prescription of oral contraceptives within 24 months prior to the study enrollment.

Statistical analysis

Differences in the distribution of basic demographics across groups defined by weight class were assessed with the chi-square test. For each patient, age was assigned based on their age on July 1st of the year of study enrollment.

Logistic regression models were generated to estimate odds ratios (OR) and their 95% confidence intervals (CI) for gallstones vs. potential risk factors such as sex (male vs. female), race/ethnicity (non-Hispanic White, Hispanic, Black, Asian or Pacific Islander, and Other/Multiple/Unknown race), age group (younger children 10–14 years of age vs. older children 15–19 years of age), weight class (under or normal weight (reference), overweight, moderate obesity, and extreme obesity) and the likelihood of neighborhood education below high school. The categories underweight and normal weight were collapsed due to the small number of cases in the group of underweight children (n=11,456, of which 9 patients had gallstones); the odds ratios for gallstones of underweight and normal weight patients were comparable. The odds ratios for potential gallstone risk factors are presented as crude odds ratios and mutually adjusted for all other risk factors listed: sex, race/ethnicity, age group, weight class, and low education. To examine whether the association between body weight class and gallstones was modified by sex and oral contraceptive use, we conducted both stratified analyses and formal tests of interaction; the statistical significance of the latter were evaluated using likelihood-ratio chi-square. All analyses were conducted using SAS 9.0 (SAS Institute Inc., Cary, NC).

Results

The prevalence of overweight, obesity, and extreme obesity was 19.6%, 13.7%, and 7.7%, respectively. Adolescent patients who were overweight, moderately, or extremely obese were more likely to be older ($P<0.001$), boys ($P<0.001$), and Hispanic or Black, than those who were under/normal weight ($P<0.001$) (Table 1).

We identified 766 patients with gallstones in the gallbladder or biliary ducts. The adjusted OR for gallstones was higher in girls (OR 4.42, 95% CI 3.69–5.29), older children (OR 5.50, 95% CI 4.52–6.69), Hispanics (OR 1.55, 95% CI 1.26–1.91), and individuals living in areas with low neighborhood education (OR 1.23, 95% CI 1.06–1.44, Table 2).

The prevalence of gallstones increased with increasing weight class, but the association was stronger in girls than in boys (p for sex $\times$ weight class interaction <0.001). The adjusted OR for gallstones was 1.00, 1.46, 1.83, and 3.10 (95% CI 1.99–4.83) in under/normal weight (=reference), overweight, moderately obese and extremely obese boys, respectively (Figure 1). In contrast, the OR of gallstones was 1.00, 2.73, 5.75, and 7.71 (95% CI 6.13–9.71) in under/normal weight (=reference), overweight, moderately obese and extremely obese girls, respectively. We did not observe interactions between weight class and race/ethnicity ($P>0.150$).

Oral contraceptive use was associated with higher odds for gallstones (OR 2.00, 95% CI 1.66–2.40). The association between oral contraceptive use and gallstones was modified by weight class (P for interaction weight class $\times$ oral contraceptive use = 0.023). Using girls of under or normal weight that did not use oral contraceptives as the reference group, girls who used oral contraceptives were at higher odds for gallstones than their counterparts in the same weight class (Figure 2). However, the odds for gallstones among extremely obese girls were comparable, regardless of oral contraceptive use.

Discussion

This analysis of a large multiethnic cohort of children and adolescents in southern California showed four key findings. First, excessive body weight was associated with gallstones in youth. Second, Hispanic youth had the highest odds of developing gallstones compared to youth of other races/ethnicities. Third, the association between excessive body weight and gallstones was stronger in girls than in boys. Fourth, oral contraceptive use contributed to gallstone disease in girls.

Obesity is a strong, well-established risk factor for gallstone disease in adults [26–28]. The key factors for cholesterol gallstone formation are the supersaturation of bile with cholesterol and gallbladder dysmotility [28]. Cholesterol supersaturation can be caused by an increased hepatic cholesterol uptake or an increased *de novo* cholesterol synthesis. Obese individuals show increased hydroxyl-3-methylglutaryl (HMG)-CoA reductase activity and, consequently, increased hepatic secretion of biliary cholesterol [29]. With an earlier onset of obesity [7, 8], it can be expected that lithogenic bile will occur earlier in a patient's life, especially with the onset of extreme obesity during childhood. In obese children referred for weight loss, a systematic screening for gallstones revealed that patients with gallstone disease were more severely obese than those without gallstones [9]. However, because this hospital-based study [9] lacked a normal weight control group, it cannot provide estimates of the magnitude of association between obesity and gallstone disease. Using a population-based approach in a small sample of children ($n=307$) [10], the same group of researchers concluded that obesity may be a risk factor for gallstone disease; however, this conclusion was based on only three cases of gallstone disease in the cohort. Thus, while other studies examined a limited number of cases and lacked the power to investigate the effects of being overweight and gallstone risk, results from our large, population-based study found that being overweight during childhood or adolescence is associated with a more than twofold higher odds of gallstone disease, while moderate and extreme obesity are associated with a four- and six-fold higher odds of gallstone disease, respectively.

It is well established that women are at higher risk for gallstones than men [1]. In an obese pediatric population referred for weight loss, female sex has also been suggested to be a risk factor for pediatric gallstone disease [9]. Comparable to studies in women [30], results from our study suggest that adolescent girls already have a more than four times higher odds for gallstone disease than their male counterparts.

Another retrospective study in 31 adolescent girls 14 to 20 years of age found a higher prevalence of obesity in girls with gallstones than in the general population [31]. In our study, the strength of the association between obesity and gallstone disease was also much stronger in girls than in boys. While extremely obese boys have a 3-fold higher odds of gallstone disease, extremely obese girls have almost an 8-fold odds of gallstone disease. Surprisingly, these odds ratios are comparable to estimates from prospective studies in women where women with a BMI >32 kg/m² showed an age-adjusted relative risk of 6.0 (95% CI 4.0–9.0) [32].

Although body weight is an established risk factor in men, the association between body weight and gallstone disease appears to be weaker and less consistent in men than in women [33–36]. While body weight alone may not entirely account for the risk of gallstones in men, a stronger association was observed between abdominal obesity and gallstone disease [26].

In addition to obesity, exogenous estrogen exposure increases the risk of gallstones in women [28, 37]. Results from animal and human studies suggest that estrogen increases the hepatic secretion of biliary cholesterol, which increases the cholesterol saturation of the bile [37]. Although exogenous estrogen exposure from oral contraceptives in girls was of relatively short duration compared to women, we found that oral contraceptive use was associated with a 2-fold higher odds for gallstones after adjustments for race/ethnicity, obesity, and other factors. However, because of the cross-sectional nature of the data and lack of information on duration of estrogen exposure from oral contraceptives in our sample, these results should be interpreted with care.

Studies on oral contraceptive use as a modifier of the association between obesity and gallstones are scant. In women, the association between obesity and cholecystectomy was similar between non-users and users of hormone replacement therapy [27]. Results from our study, however, suggest that the association between body weight and gallstones was stronger in girls using oral contraceptives than in those who did not use oral contraceptives. Compared to normal weight girls who had never used oral contraceptives, moderately obese girls using oral contraceptives showed a 15-fold odds of gallstones compared to about 6-fold odds for moderately obese girls that had not used oral contraceptives.

Racial and ethnic disparities in gallstone disease have been reported in adults [2, 38, 39]. However, such data are lacking in children. Among women, the risk of gallbladder disease is highest among American Indians, followed by Hispanics, non-Hispanic whites, and non-Hispanic blacks. Among men, the prevalence of gallstones was similar between Hispanic and non-Hispanic individuals [38]. In our study, Hispanic youth had 55% higher odds for gallstone disease than their non-Hispanic White counterparts after adjusting for sex, body weight, age, and low neighborhood education. This suggests that racial and ethnic disparities as described in adults also exist in children. Further longitudinal data are needed to investigate factors contributing to the observed racial and ethnic disparities and to implement strategies to reduce and eliminate such disparities.

Race and ethnicity are subject to potential misclassification due to imputation of missing race/ethnicity information in about one third of the study population. However, results did not differ when only children with known race/ethnicity information from administrative records were analyzed. Moreover, prevalence of obesity in children with missing race/ethnicity information were comparable to the over prevalence of obesity suggesting that the racial/ethnic distribution of children with missing race/ethnicity was comparable to those whose race/ethnicity was known [7].

Our study benefited from an extremely large multi-ethnic and diverse pediatric population-base covering almost 16% of the service area in southern California. However, because of the cross sectional design of this study, which does not allow causal conclusions, our findings should be interpreted with care. Both exposure and outcome have been simultaneously assessed, and therefore, no conclusions pertaining to causality can be made. However, several mechanisms have been suggested to explain the association between obesity and gallstone disease, and obesity is an established risk factor for gallstones in adults. It is unlikely that gallstones in turn could have caused obesity or contributed to higher body weight.

The current study is based on a diagnosis of gallstone disease from electronic health records. We cannot rule out a potential underdiagnosis of asymptomatic gallstone disease in patients who have not been examined. The prevalence of asymptomatic gallstone disease is poorly documented in pediatric populations. One study estimated that about 20% of pediatric patients with gallstones are asymptomatic [6] which is markedly lower than in adults where 80% of patients are asymptomatic [1]. Because of the nature of the disease and the symptoms, non-differential misclassification due to underdiagnosis can be assumed across weight classes which would most likely bias our results towards the null.

To address overdiagnosis of gallstone disease because a suspicion of gallstones may have been falsely coded as gallstone disease, we performed a manual chart review of almost 400 youth. The amount of unverified diagnoses of gallstone disease in youths was less than 10%.

Our study can not distinguish between cholesterol and pigment gallstones. To reduce the number of individuals with pigment gallstones, patients with hemolytic anemia were excluded from this study. Pigment gallstones are associated with older age but the underlying cause in adults is often unknown [40]; data on causes of pigment gallstones besides hemolytic anemia in youth are sparse. Because the exclusion was based on a diagnosis of hemolytic anemia, we cannot rule out that some pigment gallstones caused by other or unknown causes were missed.

Exposure to oral contraceptives has been extracted from electronic medical records and does not contain drugs dispensed by other organizations such as the California Family Planning Program. Therefore, we cannot exclude an underestimation of girls who were using oral contraceptives and misclassified as unexposed. However, this misclassification would most likely bias our results towards the null.

The obesity epidemic in children may now put more children at risk of developing gallstone disease. Due to the shift towards extreme childhood obesity, especially in minority children, pediatricians can expect to face an increasing number of children affected by gallstone disease, which has previously been limited to adults. Risk factors identified in adults such as female sex, Hispanic ethnicity, obesity, and oral contraceptive use may also apply to children, which can assist pediatricians to identify pediatric populations at risk. While pediatricians may have to be made aware of the risk for gallstone disease in pediatric populations, information on the prevalence of asymptomatic gallstones is needed to fully understand the risk of extreme pediatric obesity.

Acknowledgments

We thank Theresa Im and Monica L. Levitt for their excellent technical support.

Abbreviations/Acronyms

BMI	body mass index
CI	confidence interval
ICD	International Classification of Disease
KPSC	Kaiser Permanente Southern California
OR	odds ratio
PPV	positive predictive value

References

1. Stinton LM, Myers RP, Shaffer EA. Epidemiology of gallstones. *Gastroenterol Clin North Am*. 2010; 39:157–69. [PubMed: 20478480]
2. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. *Gastroenterology*. 2009; 136:376–86. [PubMed: 19124023]
3. Ruhl CE, Everhart JE. Gallstone disease is associated with increased mortality in the United States. *Gastroenterology*. 2011; 140:508–16. [PubMed: 21075109]
4. Palasciano G, Serio G, Portincasa P, et al. Gallbladder volume in adults, and relationship to age, sex, body mass index, and gallstones: a sonographic population study. *Am J Gastroenterol*. 1992; 87:493–7. [PubMed: 1553937]
5. Miltenburg DM, Schaffer R 3rd, Breslin T, et al. Changing indications for pediatric cholecystectomy. *Pediatrics*. 2000; 105:1250–3. [PubMed: 10835065]
6. Holcomb GW Jr, Holcomb GW 3rd. Cholelithiasis in infants, children, and adolescents. *Pediatr Rev*. 1990; 11:268–74. [PubMed: 2408028]
7. Koebnick C, Smith N, Coleman KJ, et al. Prevalence of extreme obesity in a multiethnic cohort of children and adolescents. *J Pediatr*. 2010; 157:26–31. [PubMed: 20303506]
8. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of high body mass index in US children and adolescents, 2007–2008. *JAMA*. 2010; 303:242–9. [PubMed: 20071470]
9. Kaechele V, Wabitsch M, Thiere D, et al. Prevalence of gallbladder stone disease in obese children and adolescents: influence of the degree of obesity, sex, and pubertal development. *J Pediatr Gastroenterol Nutr*. 2006; 42:66–70. [PubMed: 16385256]
10. Kratzer W, Walcher T, Arnold F, et al. Gallstone prevalence and risk factors for gallstone disease in an urban population of children and adolescents. *Z Gastroenterol*. 2010; 48:683–7. [PubMed: 20517806]
11. Waldhausen JH, Benjamin DR. Cholecystectomy is becoming an increasingly common operation in children. *Am J Surg*. 1999; 177:364–7. [PubMed: 10365870]
12. Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med*. 2004; 350:2362–74. [PubMed: 15175438]
13. Rocchini AP. Childhood obesity and a diabetes epidemic. *N Engl J Med*. 2002; 346:854–5. [PubMed: 11893799]
14. Ahmed ML, Ong KK, Dunger DB. Childhood obesity and the timing of puberty. *Trends Endocrinol Metab*. 2009; 20:237–42. [PubMed: 19541497]
15. Sandhu J, Ben-Shlomo Y, Cole TJ, et al. The impact of childhood body mass index on timing of puberty, adult stature and obesity: a follow-up study based on adolescent anthropometry recorded at Christ's Hospital (1936–1964). *Int J Obes*. 2006; 30:14–22.
16. Thijs C, Knipschild P. Oral contraceptives and the risk of gallbladder disease: a meta-analysis. *Am J Public Health*. 1993; 83:1113–20. [PubMed: 8342719]
17. Koebnick C, Coleman KJ, Black MH, et al. Cohort Profile: The KPSC Children's Health Study, a population-based study of 920 000 children and adolescents in southern California. *Int J Epidemiol*. 2011
18. Smith N, Coleman KJ, Lawrence JM, et al. Body weight and height data in electronic medical records of children. *Int J Pediatr Obes*. 2010; 5:237–42. [PubMed: 19961272]
19. World Health O. Technical Report Series 894: Obesity: Preventing and managing the global epidemic. World Health Organization; Geneva: 2000.
20. Flegal KM, Wei R, Ogden CL, et al. Characterizing extreme values of body mass index for age by using the 2000 Centers for Disease Control and Prevention growth charts. *Am J Clin Nutr*. 2009; 90:1314–20. [PubMed: 19776142]
21. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat*. 2002; 11:1–190.
22. Smith N, Iyer RL, Langer-Gould AM, et al. Health plan administrative records versus birth certificate records: quality of race and ethnicity information in children. *BMC Health Serv Res*. 2010; 10:316. [PubMed: 21092309]

23. Bureau of the Census. Census 2000 surname list. Washington DC: 2009.
<http://www.census.gov/genealogy/www/freqnames2khtml>
24. Fiscella K, Fremont AM. Use of geocoding and surname analysis to estimate race and ethnicity. *Health Serv Res.* 2006; 41:1482–500. [PubMed: 16899020]
25. Word, DL.; Perkins, RC. Technical Working paper No.13. US Bureau of the Census; Washington, DC: 1996. Building a Spanish surname list for the 1990's - A new approach to an old problem.
26. Tsai CJ, Leitzmann MF, Willett WC, et al. Prospective study of abdominal adiposity and gallstone disease in US men. *Am J Clin Nutr.* 2004; 80:38–44. [PubMed: 15213025]
27. Tsai CJ, Leitzmann MF, Willett WC, et al. Central adiposity, regional fat distribution, and the risk of cholecystectomy in women. *Gut.* 2006; 55:708–14. [PubMed: 16478796]
28. Yoo EH, Lee SY. The prevalence and risk factors for gallstone disease. *Clin Chem Lab Med.* 2009; 47:795–807. [PubMed: 19499973]
29. Stahlberg D, Rudling M, Angelin B, et al. Hepatic cholesterol metabolism in human obesity. *Hepatology.* 1997; 25:1447–50. [PubMed: 9185766]
30. Shaffer EA. Gallstone disease: Epidemiology of gallbladder stone disease. *Best Pract Res Clin Gastroenterol.* 2006; 20:981–96. [PubMed: 17127183]
31. Honore LH. Cholesterol cholelithiasis in adolescent females: its connection with obesity, parity, and oral contraceptive use--a retrospective study of 31 cases. *Arch Surg.* 1980; 115:62–4. [PubMed: 7350887]
32. Maclure KM, Hayes KC, Colditz GA, et al. Weight, diet, and the risk of symptomatic gallstones in middle-aged women. *N Engl J Med.* 1989; 321:563–9. [PubMed: 2761600]
33. Attili AF, Capocaccia R, Carulli N, et al. Factors associated with gallstone disease in the MICOL experience. Multicenter Italian Study on Epidemiology of Cholelithiasis. *Hepatology.* 1997; 26:809–18. [PubMed: 9328297]
34. Barbara L, Sama C, Morselli Labate AM, et al. A population study on the prevalence of gallstone disease: the Sirmione Study. *Hepatology.* 1987; 7:913–7. [PubMed: 3653855]
35. Kono S, Kochi S, Ohyama S, et al. Gallstones, serum lipids, and glucose tolerance among male officials of Self-Defense Forces in Japan. *Digestive diseases and sciences.* 1988; 33:839–44. [PubMed: 3259921]
36. Scragg RK, McMichael AJ, Baghurst PA. Diet, alcohol, and relative weight in gall stone disease: a case-control study. *Br Med J.* 1984; 288:1113–9. [PubMed: 6424754]
37. Wang HH, Liu M, Clegg DJ, et al. New insights into the molecular mechanisms underlying effects of estrogen on cholesterol gallstone formation. *Biochim Biophys Acta.* 2009; 1791:1037–47. [PubMed: 19589396]
38. Everhart JE. Gallstones and ethnicity in the Americas. *J Assoc Acad Minor Phys.* 2001; 12:137–43. [PubMed: 11858192]
39. Nguyen GC, Tuskey A, Jagannath SB. Racial disparities in cholecystectomy rates during hospitalizations for acute gallstone pancreatitis: a national survey. *Am J Gastroenterol.* 2008; 103:2301–7. [PubMed: 18844616]
40. Trotman BW. Pigment gallstone disease. *Gastroenterol Clin North Am.* 1991; 20:111–26. [PubMed: 2022417]

Figure 1. Association between body weight and gallstones

Obesity was associated with a higher adjusted OR for gallstones in boys and girls (P for trend < 0.001) with a stronger association in girls compared to boys (P for interaction < 0.001).

Figure 2. Association between body weight and gallstones and the effect modification by oral contraceptive use among girls (n = 258,476)
 The association between weight class and gallstones was modified by oral contraceptive use (p for interaction weight class $\times$ oral contraceptive use = 0.023).

Table 1

Demographic characteristics of the study population according to weight class[/].

	Under/Normal weight (n=301,549)	Over-weight (n=99,987)	Moderately obese (n=70,167)	Extremely obese (n=39,113)	P-value
Male (%)	47.3	48.2	56.0	56.4	<0.001
Age (years)	15.2 ± 2.8	15.2 ± 2.9	14.6 ± 2.8	15.1 ± 2.9	<0.001
Race/Ethnicity (%)					<0.001
Non-Hispanic White	26.8	21.2	16.6	14.4	
Hispanic	44.0	52.2	58.8	59.5	
Black	7.5	7.8	7.4	10.2	
Asian or Pacific Islander	7.2	5.2	4.2	3.1	
Other/Unknown race/ethnicity	14.6	13.6	13.0	12.8	
Neighborhood education (%)					<0.001
Less than high school	25.9	29.3	32.0	34.3	
High school graduate	21.3	21.7	22.0	22.3	
Some college or associate degree	31.2	30.1	29.1	28.4	
Bachelor degree or higher	21.6	18.9	16.9	15.0	

[/] Definition of weight class: underweight was defined BMI-for-age 5th percentile, overweight as BMI-for-age 85th percentile or a BMI 25 kg/m², moderate obesity as 95th percentile or a BMI 30 kg/m², and extreme obesity 1.2 × 95th percentile or a BMI 35 kg/m².

Table 2

Odds ratios (OR) and 95% confidence Intervals (CI) for gallstones according to sex, race, and neighborhood education in a multiethnic cohort of children 10 years and older (n= 510,816)

	Total (n)	Gallstone cases (n)	OR (95%-CI)	
			Crude	Adjusted ¹
Sex				
Boys	252,349	148	1.00 (Reference)	1.00 (Reference)
Girls	258,467	618	4.08 (3.41–4.89)	4.42 (3.69–5.29)
Age group				
10–14 y	248,006	119	1.00 (Reference)	1.00 (Reference)
15–19 y	262,810	647	5.14 (4.23–6.25)	5.50 (4.52–6.69)
Race/Ethnicity				
Non-Hispanic White	119,221	135	1.00 (Reference)	1.00 (Reference)
Hispanic	249,277	528	1.87 (1.55–2.26)	1.55 (1.26–1.91)
Black	39,505	45	1.01 (0.72–1.41)	0.75 (0.54–1.06)
Asian or Pacific Islander	30,972	20	0.57 (0.36–0.91)	0.70 (0.43–1.11)
Other/Unknown race/ethnicity	71,841	38	0.47 (0.33–0.67)	0.41 (0.29–0.60)
Neighborhood education²				
Low	210,055	417	1.71 (1.49–1.97)	1.23 (1.06–1.44)
High	300,761	349	1.00 (Reference)	1.00 (Reference)
Weight class				
Underweight/Normal weight	301,549	215	1.00 (Reference)	1.00 (Reference)
Overweight	99,987	179	2.51 (2.06–3.07)	2.39 (1.96–2.92)
Moderately obese	70,167	199	3.99 (3.29–4.84)	4.56 (3.75–5.55)
Extremely obese	39,113	173	6.23 (5.10–7.61)	6.39 (5.21–7.83)

¹ All odds ratios (OR) are adjusted for age, sex (male vs. female), neighborhood education (low neighborhood education vs. high neighborhood education), race/ethnicity (non-Hispanic White, Hispanic, Black, Asian/Pacific Islander or other), and weight class (under/normal weight, overweight, moderately obese, extremely obese).

² The strata of low and high neighborhood education intakes are defined based on the cut-point representing the mean Census block probability for a neighborhood education below high-school of 28.6% based on the member's most recent address.