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Gastrointestinal Complications of Obesity

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Abstract

Obesity usually is associated with morbidity related to diabetes mellitus and cardiovascular diseases. However, there are many gastrointestinal and hepatic diseases for which obesity is the direct cause (eg, nonalcoholic fatty liver disease) or is a significant risk factor, such as reflux esophagitis and gallstones. When obesity is a risk factor, it may interact with other mechanisms and result in earlier presentation or complicated diseases. There are increased odds ratios or relative risks of several gastrointestinal complications of obesity: gastroesophageal reflux disease, erosive esophagitis, Barrett's esophagus, esophageal adenocarcinoma, erosive gastritis, gastric cancer, diarrhea, colonic diverticular disease, polyps, cancer, liver disease including nonalcoholic fatty liver disease, cirrhosis, hepatocellular carcinoma, gallstones, acute pancreatitis, and pancreatic cancer. Gastroenterologists are uniquely poised to participate in the multidisciplinary management of obesity as physicians caring for people with obesity-related diseases, in addition to their expertise in nutrition and endoscopic interventions.

Keywords

Liver; Pancreas; Gallbladder; Cancer; Fat

Obesity usually is associated with morbidity related to diabetes mellitus and cardiovascular diseases. However, there are many gastrointestinal and hepatic diseases for which obesity is the direct cause (eg, nonalcoholic fatty liver diseases [NAFLDs]) or is a significant risk factor such as in reflux esophagitis and gallstones. When obesity is a risk factor, it may interact with other pathogenetic mechanisms and result in earlier presentation of disease or more complicated disease.

The gastrointestinal tract plays a key role in obesity through its contributions to satiation and satiety, production of gut hormones that influence appetite (such as ghrelin, cholecystokinin, and peptide YY), incretins (eg, glucagon-like peptide-1) that impact postprandial glycemia, absorption of nutrients that ultimately determine the positive energy balance that results in obesity, changes in bile acids and the microbiome, and the metabolic products of microbial digestion of nutrients (short-chain fatty acids) that modify some of the metabolic factors that

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Conflicts of interest

The authors disclose no conflicts.

are associated with obesity. Most of these topics are addressed elsewhere in this issue of *Gastroenterology*. Therefore, this article focuses on the gastrointestinal and hepatobiliary complications of obesity in adults (Figure 1); a separate article addresses the complications of pediatric obesity. Table 1 summarizes the quantified risks (odds ratios [ORs] and relative risks [RRs]) of gastrointestinal complications of obesity in adults.

Esophagus

Many esophageal disorders are associated with obesity.

Esophageal Dysmotility

Obesity increases the prevalence of esophageal motility disorders. For example, esophageal transit time was prolonged significantly in subjects with obesity compared with lean subjects,¹ possibly because of increased gastric and gastroesophageal junction resistance.² The typical abnormalities of esophageal motility are nonspecific abnormalities of esophageal peristalsis and, rarely, lower esophageal sphincter (LES) dysfunction, including isolated hypertensive or hypotensive LES pressures. In a recent population-based study, symptoms of dysphagia were more common in patients with obesity compared with lean controls (OR, 1.22; 95% CI, 1.04–1.43).³ A prospective study of 53 Canadian patients with a mean body mass index (BMI) of 46 kg/m² and documented symptoms (heartburn, 66%; regurgitation, 26%; dysphagia, 43%; and chest pain, 6%) reported that almost 50% had esophageal and LES dysmotility, mainly hypomotility.⁴ However, there was no comparator group of lean controls, and the prevalence of dysmotility was similar in the symptomatic and nonsymptomatic participants.⁴ In another study of 116 obese patients with a mean BMI of 42.9 kg/m², abnormal manometric findings were shown in 41% of patients, but these typically were not associated with symptoms.⁵ Diffuse esophageal spasm and achalasia are rare, and a summary of the literature shows that the prevalence and significance of all these dysmotilities are unclear because studies performed did not include lean controls.^{5,6}

Gastroesophageal Reflux Disease

Excess body weight and, in particular, increased abdominal girth produce higher intra-abdominal pressure and reduces LES pressure. In addition, other factors combine to predispose to gastroesophageal reflux and its complications, including a reduced length of the intra-abdominal portion of the lower esophageal sphincter and peristaltic dysfunction of the esophagus.^{7,8} Obesity also results in increased esophageal acid exposure,^{8,9} and this may be related in part to increased estrogen levels, which are higher in obesity than in lean age- and sex-matched controls and are associated strongly with increased acid exposure and gastroesophageal reflux disease (GERD).^{10–12} These alterations in functions can result in regurgitation, esophagitis, and GERD, which may progress to Barrett's esophagus and esophageal adenocarcinoma.

GERD is a chronic disorder characterized by heartburn and regurgitation that occur when gastric acid or bile reflux from the stomach to the esophagus and induce inflammation of the esophageal mucosa. The prevalence of GERD has increased significantly in the past 20 years in parallel with the increased prevalence of obesity. Several meta-analyses have shown a

positive association between body weight (BMI) and GERD.^{13,14} In addition, central adiposity (apart from BMI) is an independent risk factor of the consequences of GERD, including esophageal inflammation, Barrett's metaplasia, and esophageal adenocarcinoma, and these effects are mediated by reflux-dependent and reflux-independent mechanisms.¹⁵ The association of BMI with GERD is stronger in women with obesity than in men with obesity; this difference has been attributed to increased estrogen levels in women.¹¹ The role of estrogens in the association of central obesity in men and the higher prevalence of GERD is unclear. The association of BMI and GERD also is stronger in Caucasians than in other ethnicities.¹⁶ The strong association between obesity and GERD is reinforced by improvement of GERD symptoms after weight loss,¹⁷ which was confirmed in a well-designed intervention trial focused on weight loss for GERD.¹⁸

Erosive Esophagitis

Erosive esophagitis results from inflammation of the distal esophageal mucosa, which is secondary to GERD. Obesity is one of the known risk factors for developing erosive esophagitis, in addition to male sex, older age, chronic alcohol intake, chronic smoking, and a long history of GERD.¹⁹ Several meta-analyses have shown the association of a higher BMI, increased waist circumference, or increased waist-to-hip ratio with the presence and severity of erosive esophagitis.^{14,15,20} Patients with central adiposity (apple shape) have a 1.87-fold risk of developing erosive esophagitis compared with normal-weight controls, independent of body weight (OR, 1.87; 95% confidence interval [CI], 1.51–2.31).¹⁵ In contrast, obesity with increased hip circumference (pear-shaped) is related inversely to erosive esophagitis and Barrett's esophagus, analogous to its protective role in progression to type 2 diabetes mellitus and cardiovascular disease.²¹

Barrett's Esophagus

Barrett's metaplasia refers to the replacement of the normal squamous epithelium of the distal esophagus by specialized columnar epithelium. Barrett's esophagus is usually a consequence of chronic GERD and predisposes to adenocarcinoma of the esophagus.²² Several studies have shown an association between obesity, abdominal circumference, and metabolic syndrome with Barrett's esophagus.^{23,24} Moreover, BMI and abdominal circumference may be indirect risk factors for Barrett's esophagus through their relationship with GERD.²⁵ However, the association of Barrett's esophagus with abdominal adiposity is even stronger after adjusting for BMI or GERD, suggesting that abdominal adiposity is an independent risk factor.¹⁵ Potential mechanisms are higher levels of leptin, decreased levels of low-molecular-weight adiponectin, and increased cytokines, which mediate chronic inflammation.^{26–28} The relationship of ghrelin and leptin to Barrett's esophagus is complex. Thus, a recent case-control study of patients with a new diagnosis of Barrett's esophagus and 2 control groups (GERD and general population) matched for age, sex, and geographic region found that higher levels of ghrelin were associated with an increased risk of Barrett's esophagus among the general population. In contrast, leptin was associated positively with frequent GERD symptoms, but associated inversely with the risk of Barrett's esophagus among the GERD controls.²⁹

Esophageal Adenocarcinoma

The incidence of esophageal adenocarcinoma is increasing, and this has been attributed to the increased prevalence of Barrett's esophagus, erosive esophagitis, and GERD, all of which are associated with obesity and abdominal adiposity. In patients with Barrett's esophagus, obesity is associated directly with progression to adenocarcinoma, and higher levels of leptin and lower levels of adiponectin have been proposed as markers of progression to adenocarcinoma.³⁰ In a meta-analysis of 2488 cases with esophageal adenocarcinoma, there was a strong association with obesity in both sexes (males: OR, 2.4; 95% CI, 1.9–3.2; females: OR, 2.1; 95% CI, 1.4–3.2).³¹ The risk of esophageal adenocarcinoma also was higher with increased central adiposity (OR, 2.51; 95% CI, 1.56–4.04) when compared with normal body habitus.¹⁵

The molecular mechanisms linking obesity, metabolic syndrome, and esophageal adenocarcinoma have been investigated extensively. These include increased insulin and insulin-like growth factor.^{32,33} There is evidence that insulin-like growth factor-1 and insulin-like growth factor-2 induced increased angiogenesis and cell proliferation, decreased apoptosis, and increased cytokines secondary to obesity-induced chronic inflammation with induction of vascular endothelial growth factor, decreased adiponectin, and increased leptin.²⁸ Leptin stimulates cell proliferation by activating epidermal growth factor receptor; leptin also inhibits apoptosis in esophageal cells.³⁴ Histopathologic studies of esophageal adenocarcinoma from obese patients have shown up-regulated expression of leptin and adiponectin receptors in esophageal tumors.³⁵

Stomach

Gastric physiology and its neurohormonal regulation³⁶ are altered in obesity; however, it is unclear whether gastric function abnormalities are the cause or consequence of obesity. Obesity also is associated with symptoms that may arise in the stomach, such as upper abdominal pain, nausea, vomiting, retching, and gastritis.^{37,38}

Gastric Motor Physiology

Studies have quantified changes in gastric physiological functions using noninvasive approaches. Delgado-Aros et al^{39,40} showed that, across a broad spectrum of BMI, there was an association between higher BMI, higher fasting gastric volume, and decreased satiation shown by a reduced fullness sensation and a higher maximum tolerated volume of Ensure (Abbott Nutrition, Chicago, IL) ingested at a constant rate. These studies showed that an increase in the fasting gastric volume of 50 mL was associated with 114 ± 32 kcal more ingested at maximum satiation. A follow-up Mayo Clinic study⁴¹ of 509 people across the BMI spectrum confirmed that obesity was associated with decreased satiation and, for every 5 kg/m^2 of BMI, there was a 50 kcal higher consumption before sensing fullness. In addition, a higher BMI was associated with a greater fasting gastric volume, and accelerated gastric emptying of solids and liquids (Figure 2).

Erosive Gastritis

Erosive gastritis is an inflammation in the mucosa of the stomach that may be acute or chronic and lead to ulceration and bleeding. Obesity is a risk factor for erosive gastritis and gastric and duodenal ulcers.^{42,43} An association of low adiponectin with erosive gastritis has been reported to be independent of BMI or *Helicobacter pylori* infection.⁴⁴

Gastric Cancer

Obesity is considered a proinflammatory and procarcinogenic state and is recognized as an important, potentially modifiable, risk factor for cancer, including gastric cancer. Different meta-analyses (documented in Table 1) have reported associations of obesity (high BMI) with gastric cancer⁴⁵ and with cancer of the gastric cardia.⁴⁶ It is not clear if the association is related to confounding factors, such as an association of obesity with *H pylori* infection.⁴⁷ Obesity may accelerate *H pylori*-mediated gastric carcinogenesis.⁴⁸ In one report of the relationship between BMI and esophageal-gastric cardia cancer, the meta-analysis of case-control and cohort studies confirmed the strong relationship of overweight and obesity with the cancers, but there was no substantial difference across strata of sex and geographic areas in Italy.⁴⁹ Another meta-analysis supported the hypothesis that longer exposure to estrogen effects of either ovarian or exogenous origin may decrease the risk of gastric cancer.⁵⁰ Thus, the analysis of the effect of sex on obesity as a predisposing factor to gastric cancer is complicated by the possible protective role of estrogens in women and the presence of significant environmental risk factors, predominantly cigarette smoking among men or women.⁵¹

Small Intestine

The small intestine is the site of digestion and absorption of most nutrients. In the past, it was thought that the small intestine played a passive role, simply absorbing the excess calories ingested by obese people. Bile acids play a critically important role in the absorption of fats; the role of bile acids in metabolic regulation⁵² or as potential therapeutic approaches for obesity and metabolic syndrome⁵³ are beyond the scope of this article; however, there is no evidence that bile acid synthesis or enterohepatic circulation is altered by obesity. On the other hand, there is evidence that the small intestine is able to adapt its absorptive functions for the 3 macronutrient classes, as follows: (1) lipid absorption capacity adapts to the fat content of the diet, especially through the coordinated induction of lipid binding proteins, which are involved in the intestinal absorption of long-chain fatty acids as well as their uptake, trafficking, and re-assembly into chylomicrons⁵⁴; (2) energy intake from infusion of intraduodenal whey protein hydrolysate tended to be higher in obese nondiabetic men than in lean controls⁵⁵; and (3) in morbid obesity, glucose absorption in the proximal intestine is accelerated and this is related to increased sodium-glucose linked transporter-1 (SGLT-1) expression. The increased glucose absorption in the proximal gut may predispose to obesity and type 2 diabetes.⁵⁶

Although alterations in the physiology of the small intestine may allow greater absorption capacity,⁵⁴ it is likely that small-bowel absorption adapts to the over-consumption of calories

associated with obesity, leading to more rapid absorption without an increase in energy absorption.

Diarrhea

The prevalence of diarrhea in obese people is higher compared with normal-weight controls.⁵⁷ A population-based survey study of 2660 people showed that the prevalence of diarrhea in obese individuals was 30% compared with 17% in normal-weight controls (OR, 2.7; 95% CI, 1.1–6.8).³⁸ Similar studies have been replicated in Australia and New Zealand.^{58,59} In an epidemiologic study of more than 35,000 persons in France, functional diarrhea was associated with BMI in females (OR, 1.05; 1.03–1.07), but not in males.⁶⁰

Among 1001 Swedes, diarrhea (OR, 2.2; 95% CI, 1.38–3.46), stool urgency (OR, 1.60; 95% CI, 1.04–2.47), and nocturnal urgency (OR, 2.57; 95% CI, 1.33–4.98) were more prevalent in obese people than in lean controls, adjusting for age, sex, and education.⁶¹

The higher prevalence of diarrhea could be attributed to several potential mechanisms associated with obesity: changes in bile acids resulting in bile acid diarrhea,⁶² accelerated colonic transit,⁶³ increased mucosal permeability,^{64,65} or intestinal inflammation as evidenced by increased levels of fecal calprotectin.⁶⁶ These interesting studies require replication. Medications used by obese individuals, such as metformin for type 2 diabetes mellitus or polycystic ovary syndrome, also may cause diarrhea.⁶⁷

Celiac Disease

Celiac disease is an immune response to gluten in genetically susceptible people and it mainly affects the small intestine. The typical presentation includes weight loss, diarrhea, and malabsorption. Paradoxically, the recognition and prevalence of celiac disease in the obese population is increasing. In patients with newly diagnosed celiac disease, the prevalence of obesity varies from 39% to 44%.^{68,69} Obese adult or pediatric patients with celiac disease are more likely to gain more weight on a gluten-free diet.^{68,70,71}

Inflammatory Bowel Diseases

Crohn's disease or ulcerative colitis are autoimmune disorders that mainly target the small bowel and colon, respectively.

Epidemiology—In a case-control study, there was a U-shaped association between BMI and Crohn's disease. Patients who are underweight or overweight were more likely to have Crohn's disease.⁷² These findings were not reproduced in a European cohort, which showed no association between obesity and IBD in adults,⁷³ and a meta-analysis of 24 studies that included 1442 adult patients with IBD disease and 2059 healthy controls showed that obesity was less prevalent in patients with Crohn's disease (OR, –1.88; 95% CI, –2.77 to –1.00) and that there was no difference in ulcerative colitis.⁷⁴ On the other hand, in children, the prevalence of obesity in IBD was similar to that in the general population, but obese children with IBD had more severe disease than normal-weight children.⁷⁵ The latter study also identified that treatment with corticosteroids may be a confounder in the interpretation of the relationship between obesity and IBD because the steroid treatment may have

predisposed to the development of obesity. In addition, ethnic differences, illustrated by the observation that African Americans (OR, 1.64; 95% CI, 1.10–2.48) and those on Medicaid insurance (OR, 1.67; 95% CI, 1.19–2.34), were associated positively with overweight/obese status, and this may provide an explanation for the absence of this association in European cohorts, which likely were more ethnically homogeneous.

Mechanisms of IBD related to obesity—There are similarities in some of the pathophysiological features occurring in metabolic syndrome and IBD, including adipose tissue dysregulation, inadequate immune response, dysbiosis, and inflammation. Thus, in metabolic syndrome and IBD, inflammation affects adipose tissue and disturbs adipokine secretion. Both Crohn's disease and ulcerative colitis are associated with high levels of 2 adipokines (resistin and visfatin) and low levels of a third adipokine (leptin).⁷⁶ Another study showed that active Crohn's disease was associated with significantly lower adiponectin levels compared with the control group.⁷⁷ Given the contradictory data in these 2 studies, the significance of these adipokine levels still is unclear. Inflammatory disease affecting the ileocolonic mucosa also could impact the synthesis or release of incretins, which may have metabolic effects,⁷⁸ and, paradoxically, increased release of glucagon-like peptide-1 has been reported to retard gastric emptying in patients with active inflammatory bowel disease.⁷⁹

Treatment and Outcomes—Obesity is one of the factors associated with increased risk of surgical site infections in patients with IBD.⁸⁰ In a metropolitan US population, patients with obesity and IBD were significantly less likely to receive anti-tumor necrosis factor- α treatment, undergo surgery, or experience hospitalization for their IBD than their nonobese counterparts.⁸¹ These observations require confirmation. Another retrospective study in 1494 patients with IBD addressed the relationship between BMI and dose of medications for IBD, and reported that obesity was associated with a lower dosage (milligrams per kilogram) of purine analogs and biologics.⁸² It is interesting that, although the role of obesity in IBD still is unclear, obesity does influence outcome in IBD management. In a study of 124 patients with IBD naive to biologic therapy, who were started on infliximab, it was observed that higher body weight was associated with an earlier time to loss of response to infliximab, this was independent of the dose in patients with Crohn's disease (adjusted hazard ratio, 3.03; $P < .001$) or ulcerative colitis (adjusted hazard ratio, 9.68; $P = .06$).⁸³ Similar findings were reported for adalimumab in obese patients with Crohn's disease who had a significant loss of response compared with lean controls.⁸⁴

Conversely, in a cohort study of 391 patients who underwent surgery for IBD, obesity did not worsen postoperative complication rates in IBD patients.⁸⁵

Colon and Rectum

Constipation

The association between obesity and constipation is controversial, with a higher prevalence of constipation in obese people in a community-based epidemiologic study in the United States³; this was not reproduced in other large cohort studies.⁵⁹ In children, constipation, but

not constipation-predominant irritable bowel syndrome, is more common in obese individuals.^{86,87}

Diverticular Disease

Obesity is associated with a higher risk of developing diverticulosis,⁸⁸ as well as an increased number of diverticuli⁸⁹ and increased diverticular bleeding and recurrent diverticulitis compared with normal-weight individuals.⁹⁰

Colonic Polyps

There are 3 main types of polyps in the colon: adenomatous, serrated, and hyperplastic polyps. Adenomas and serrated polyps predispose to colon cancer. Several studies have documented an increased prevalence of adenomatous polyps with the highest quartiles of BMI (OR, 2.1; 95% CI, 1.4–2.3) compared with the lowest quartile of BMI.⁹¹ This association was stronger in women (OR, 4.42; 95% CI, 1.53–12.78) than in men (OR, 1.26; 95% CI, 0.52–3.07). Weight gain is another risk factor for adenomas (OR, 2.30; 95% CI, 1.25–4.22).⁹² The association of a higher BMI and colonic adenomatous polyps has been validated in other cohorts and populations.^{93–97} Similarly, obesity is associated with an increased risk of adenoma recurrence,⁹⁸ risk of sessile serrated polyps of the colon (OR, 2.57; 95% CI, 1.75–4.90), and with serrated polyps larger than 1 cm (OR, 3.96; 95% CI, 1.27–12.36).⁹⁹

Colorectal Cancer

Colorectal cancer is the fourth most common cancer in the United States and the second leading cause of cancer deaths. Multiple meta-analyses in more than 70,000 cases of colon cancer show obesity as a risk factor.^{100–103} For every increase in BMI of 5 kg/m², the risk of colon cancer increases by 18%.¹⁰¹ The association of obesity and colorectal cancer is stronger in men (RR, 1.24; 95% CI, 1.20–1.28) than in women (RR, 1.09; 95% CI, 1.04–1.12).¹⁰⁰ The risk of colorectal cancer increases with a higher waist circumference (RR, 1.33; 95% CI, 1.19–1.49 for men; RR, 1.16; 95% CI, 1.09–1.23 for women).¹⁰³ The relationship of obesity, abdominal adiposity, and colon cancer is likely to be multifactorial owing to changes in leptin, adiponectin, the microbiome, secondary bile acids, and insulin resistance, and this relationship has been reviewed extensively elsewhere.¹⁰⁴

Clostridium Difficile Infection

In a retrospective case control study of 6800 hospitalized patients in Israel, 148 cases with *C. difficile* infection were compared with 148 hospitalized controls. A high BMI value (OR, 1.196 per 1-unit increase in kg/m²; 95% CI, 1.12–1.27) was associated significantly with *C. difficile* infection.¹⁰⁵ More studies are needed to verify this relationship.

Anal Canal and Pelvic Floor

Dyssynergic Defecation

Female patients have a higher likelihood of experiencing constipation secondary to pelvic floor disorders (83% in 1 large series of 390 female patients)¹⁰⁶ and, particularly,

constipation associated with descending perineum syndrome,¹⁰⁷ which usually is associated with multiparity and is observed almost exclusively in females. In a representative Swedish cohort of 1001 people in the general population, obesity was associated with incomplete rectal evacuation (OR, 1.64; 95% CI, 1.09–2.47), adjusting for age, sex, and education.⁶¹

Fecal Incontinence

Fecal incontinence, defined as the inability to control bowel movements, producing undesired leakage of stool from the rectum, has been associated with a higher BMI, but the association has been weak or not statistically significant. Studies have reported a range of results from no association to up to 69% of obese subjects having fecal incontinence.^{37,108} Obesity is emerging as a potentially modifiable risk factor in fecal incontinence,¹⁰⁹ and obesity (BMI ≥ 30 kg/m²) was a significant risk factor for increased functional difficulty/dependence as a result of fecal incontinence.¹¹⁰

Liver

The liver is central to nutrient regulation, and frequently is involved in obesity-associated NAFLD. NAFLD has surpassed other chronic liver diseases to become the most prevalent chronic liver disease in the United States and the most frequent cause of increased transaminase levels. It affects approximately 30% of the population; with a worldwide prevalence range of 5%–46%.^{111–113} Population-based studies have shown a positive correlation between body mass index and NAFLD, suggesting shared pathogenic mechanisms. Furthermore, at-risk populations, such as those with diabetes mellitus or co-existent metabolic syndrome, have significantly higher rates of NAFLD, reaching up to 70%.¹¹¹ Obesity is also a risk factor for hepatocellular carcinoma; this risk may occur independently of NAFLD.¹¹⁴

Nonalcoholic Fatty Liver Disease

NAFLD is a heterogeneous disorder, encompassing 2 broad primarily histologic categories, isolated steatosis and nonalcoholic steatohepatitis (NASH) (Figure 3).¹¹¹ Both show macrovesicular steatosis in more than 5% of hepatocytes; however, NASH shows additional histologic characteristics of liver injury including ballooned hepatocytes, inflammatory foci, and fibrosis. NAFLD pathogenesis involves a complex interplay of nutritional overload, metabolic, microbial, and genetic factors. These diverse pathogenetic factors partly explain the heterogeneous nature of the disease. Fat accumulation in the liver results from caloric overload and the ectopic accumulation of triglycerides in the liver (Figure 3), although other lipid species including sphingolipids and phospholipids also accumulate in hepatocytes. Adipose tissue lipolysis supplies the majority of free fatty acids that subsequently are esterified to form hepatic triglycerides; however, de novo lipogenesis and dietary fat also contribute (Figure 3).^{115–117} The abnormal accumulation of lipids contributes to lipotoxicity, broadly defined as the deleterious consequences of accumulated lipids. Target organ damage in this manner leads to insulin resistance, which further exacerbates hepatic steatosis. Radiotracer studies also have shown an increase in hepatic de novo lipogenesis in NAFLD.¹¹⁵ Furthermore, hepatic fatty acid oxidation and very low density lipoprotein

secretion rates are increased.^{117,118} These may represent compensatory mechanisms for the increase in fatty acid influx to the liver.

Patients with NAFLD are at risk for progressive fibrosis and eventual cirrhosis. It is estimated that 20% of NASH patients and less than 5% of patients with isolated steatosis will progress to cirrhosis.¹¹¹ Several studies have sought to identify factors that increase this risk for fibrosis progression. Age, the degree of inflammation, and stage of fibrosis at diagnosis confer fibrosis progression risk.¹¹⁹ In addition, in a meta-analysis, arterial hypertension and a low aspartate aminotransferase:alanine aminotransferase ratio conferred increased risk for fibrosis progression.¹²⁰ Interestingly, it has been calculated that subjects with NASH may progress 1 stage of fibrosis in approximately 7 years; whereas subjects with isolated steatosis may progress 1 stage of fibrosis in approximately 14 years. It is likely that patients diagnosed with isolated steatosis who progressed in fact had low-grade inflammation in the liver, which was insufficient to fulfill NASH diagnostic criteria. Furthermore, a small subset of patients has rapid progression of fibrosis; however, the true estimate of the numbers at risk for rapid progression and the risk factors for rapid progression are incompletely understood. Finally, a substantial proportion (30%–60%) of patients with biopsy-proven NASH can have normal serum transaminase levels, highlighting the need for the development of better disease biomarkers and for a high level of clinical vigilance to detect NAFLD in high-risk populations.

NAFLD confers increased risk of cardiovascular mortality and hepatocellular carcinoma; NASH confers increased risk of liver-related mortality. Therapeutic options for NAFLD target either obesity or hepatic inflammation and fibrosis. The first category includes weight loss through caloric reduction and physical activity and bariatric procedures.^{121–123} In NASH subjects with paired liver biopsies before and after weight loss, histologic improvements in steatosis, hepatocyte ballooning, inflammation, and fibrosis were observed at a weight loss of 5%; although histologic improvement correlated with the degree of weight loss.¹²¹ The greatest fibrosis resolution occurred in those with 10% or greater body weight loss. Interestingly, all patients who lost 10% or greater of body weight showed histologic improvement. Efficacy of bariatric surgery in improving the histologic features of NASH, including reversal of steatosis, diminished hepatocyte apoptosis, and reversing hepatic fibrosis has been shown in several studies.^{124–126} NASH cirrhosis remains the third leading indication for liver transplant and is projected to be the most frequent indication in the near future.¹²⁷

The role of bile acid signaling in improving NASH after bariatric surgery is an area of active investigation. Pioglitazone, vitamin E, and obeticholic acid have shown improvements in liver necroinflammation; however, none has received Food and Drug Administration approval for the treatment of NASH.^{128,129} Several other pharmacologic agents targeting steatosis, inflammation, or fibrosis pathways are in clinical trials for the treatment of NASH; more than 50 open phase 2 and 3 clinical trials currently are registered at www.clinicaltrials.gov. A partial list of these agents is provided in Table 2.

Hepatocellular Carcinoma

Obesity and NAFLD confer increased risk for hepatocellular carcinoma (HCC), the most common primary liver cancer.¹³⁰ A meta-analysis of 11 cohort studies determined that overweight imparted an RR of HCC of 1.17 (95% CI, 1.02–1.34), and obesity an RR of 1.89 (95% CI, 1.51–2.36). In addition, individual studies have shown a greater risk of dying from HCC (RR: 4.5 in men, 1.68 in women) with a BMI of ≥ 35 kg/m².^{114,130} In a more recent nested case–control study, serum markers of inflammation, including C-reactive protein, interleukin 6, C-peptide, and non–high-molecular-weight adiponectin, were associated with a higher incidence rate ratio of HCC, independent of obesity, likely reflecting the procarcinogenic effects of chronic inflammation.¹³¹ In an analysis of the Surveillance, Epidemiology, and End Results registry in the United States from 2004 to 2009, NAFLD was the third most common underlying cause of HCC after chronic hepatitis C and alcoholic liver disease. This study showed a 9% annual increase in NAFLD-related HCC.¹³² Interestingly however, some studies have shown that some NAFLD patients develop HCC in the absence of cirrhosis, whereas other systematic analyses have shown no increased HCC risk in the absence of cirrhosis.^{111,133–135} The discrepancies likely are owing to patients with isolated steatosis, NASH, and NASH cirrhosis being included in cohorts. Although NASH imparts HCC risk, the absolute risk remains lower than viral hepatitis B and C.¹³⁵ Furthermore, co-existent obesity confers poor prognosis, impacting response to therapy as well as decreased disease-free survival and patient survival.^{136,137} NASH confers a significant health care burden; models have predicted annual direct medical costs of \$103 billion.¹³⁸ Given the significant health care costs associated with HCC and the increasing rates of NASH-related HCC, this is a considerable public health problem.¹³⁹

Recently, several experimental studies, using differing dietary models with varying degrees of fidelity to human NASH, have added to our understanding of HCC pathogenesis in NASH.^{140–143} Notably, several of these studies have linked the immune system with cancer risk. The loss of CD4⁺ T lymphocytes is associated with increased HCC, implicating the failure of immune surveillance in 1 dietary model of NASH.¹⁴⁰ However, in another study, T helper 17 lymphocytes, which are a subset of CD4⁺ T lymphocytes, played a pivotal role in insulin resistance, NASH, and HCC.¹⁴² Tumor necrosis factor–driven inflammatory signaling also increased HCC in a mouse model of endoplasmic reticulum stress and fatty liver.¹⁴¹ In human studies, *PNPLA3* rs738409 C>G polymorphism imparted increased risk for HCC in NAFLD, although the magnitude of this risk and mechanism remain to be determined.¹⁴⁴ Thus, experimental studies have linked perturbations of both the adaptive and innate immune systems to increased risk of HCC in NASH. The driver mutations in NASH–HCC remain to be defined.

Gallbladder

Obesity has been well recognized for its strong association with gallstone diseases.^{145,146} Subjects with obesity have a higher incidence of cholelithiasis, cholecystitis, and cholesterosis when compared with lean controls.¹⁴⁷ A meta-analysis showed that the risk for gallbladder disease in men was 1.63 (95% CI, 1.42–1.88) for overweight and 2.51 (95% CI, 2.16–2.91) for obesity; in women, the RR was 1.44 (95% CI, 1.05–1.98) for overweight

and 2.32 (95% CI, 1.17–4.57) for obesity.¹⁴⁸ Abdominal circumference is also a risk factor for gallbladder diseases, independent of BMI.^{149,150} These associations have been attributed to abdominal adiposity, hyperinsulinemia, insulin resistance, hyperleptinemia, hyperlipidemia, and gallbladder dysmotility.^{145,151–153}

Pancreas

Obesity and fat infiltration of the pancreas play a significant role in the endocrine pancreatic dysfunction that leads to the development of type 2 diabetes mellitus (further details are not pertinent for this review).¹⁵⁴ Obesity also has been associated with pancreatitis and pancreatic cancer.

Acute Pancreatitis

Acute pancreatitis is defined as inflammation of the pancreas and can range from mild to fulminant, with mortality up to 20% in severe necrotizing pancreatitis.^{155,156} Obesity is associated with more severe acute pancreatitis. In a meta-analysis, obese subjects had an increased risk of developing severe acute pancreatitis (RR, 2.20; 95% CI, 1.82–2.66), a higher risk of local (RR, 2.68; 95% CI, 2.09–3.43) and systemic complications (RR, 2.14; 95% CI, 1.42–3.21), and a higher risk of in-hospital mortality (RR, 2.59; 95% CI, 1.66–4.03) when compared with lean subjects.¹⁵⁶ These associations have been attributed to low-grade chronic inflammation and low levels of adiponectin.^{157–159}

Pancreatic Cancer

Pancreatic cancer is the ninth most common cancer worldwide.¹⁶⁰ Multiple meta-analyses have reported an association between BMI or abdominal obesity and occurrence of adenocarcinoma of the pancreas. On meta-analysis, there is a 10% increased risk in women and a 13% increased risk in men for every 5 kg/m² higher BMI (95% CI, 1.04–1.22).¹⁶¹ In addition, for every extra 10 cm of waist circumference, there was an 11% increased risk of pancreatic cancer (RR, 1.11; 95% CI, 1.05–1.18).¹⁶¹

Summary

The increased prevalence of gastrointestinal conditions in the general population may be related to the increased prevalence of obesity in Western countries. Thus, it is important to recognize the role of higher BMI and, particularly, increased abdominal adiposity, in the development of gastrointestinal morbidity and, therefore, to measure BMI and waist circumference in patients presenting with gastrointestinal complaints or abnormal liver function.

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Abbreviations used in this paper

BMI	body mass index
CI	confidence interval
GERD	gastroesophageal reflux disease
HCC	hepatocellular carcinoma
LES	lower esophageal sphincter
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
OR	odds ratio
RR	relative risk

References

1. Mercer CD, Rue C, Hanelin L, et al. Effect of obesity on esophageal transit. *Am J Surg.* 1985; 149:177–181. [PubMed: 3966634]
2. Zacchi P, Mearin F, Humbert P, et al. Effect of obesity on gastroesophageal resistance to flow in man. *Dig Dis Sci.* 1991; 36:1473–1480. [PubMed: 1914772]
3. Eslick GD, Talley NJ. Prevalence and relationship between gastrointestinal symptoms among individuals of different body mass index: a population-based study. *Obes Res Clin Pract.* 2016; 10:143–150. [PubMed: 26142872]
4. Côté-Daigneault J, Leclerc P, Joubert J, et al. High prevalence of esophageal dysmotility in asymptomatic obese patients. *Can J Gastroenterol Hepatol.* 2014; 28:311–314. [PubMed: 24945185]
5. Koppman J, Poggi L, Szomstein S, et al. Esophageal motility disorders in the morbidly obese population. *Surg Endosc.* 2007; 21:761–764. [PubMed: 17285388]
6. Jaffin B, Knoepfelmacher P, Greenstein R. High prevalence of asymptomatic esophageal motility disorders among morbidly obese patients. *Obes Surg.* 1999; 9:390–395. [PubMed: 10484299]
7. Lagergren J. Influence of obesity on the risk of esophageal disorders. *Nat Rev Gastroenterol Hepatol.* 2011; 8:340–347. [PubMed: 21643038]
8. Anggiansah R, Sweis R, Anggiansah A, et al. The effects of obesity on oesophageal function, acid exposure and the symptoms of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther.* 2013; 37:555–563. [PubMed: 23305085]
9. Crowell M, Bradley A, Hansel S, et al. Obesity is associated with increased 48-h esophageal acid exposure in patients with symptomatic gastroesophageal reflux. *Am J Gastroenterol.* 2009; 104:553–559. [PubMed: 19223881]
10. Nilsson M, Lundegårdh G, Carling L, et al. Body mass and reflux oesophagitis: an oestrogen-dependent association? *Scand J Gastroenterol.* 2002; 37:626–630. [PubMed: 12126237]
11. Nilsson M, Johnsen R, Ye W, et al. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. *JAMA.* 2003; 290:66–72. [PubMed: 12837713]
12. Nordenstedt H, Zheng Z, Cameron A, et al. Postmenopausal hormone therapy as a risk factor for gastroesophageal reflux symptoms among female twins. *Gastroenterology.* 2008; 134:921–928. [PubMed: 18294635]
13. Corley D, Kubo A. Body mass index and gastroesophageal reflux disease: a systematic review and meta-analysis. *Am J Gastroenterol.* 2006; 101:2619–2628. [PubMed: 16952280]

14. Hampel H, Abraham N, El-Serag H. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann Intern Med.* 2005; 143:199–211. [PubMed: 16061918]
15. Singh S, Sharma A, Murad M, et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2013; 11:1399–1412. [PubMed: 23707461]
16. Corley D, Kubo A, Zhao W. Abdominal obesity, ethnicity and gastro-oesophageal reflux symptoms. *Gut.* 2007; 56:756–762. [PubMed: 17047097]
17. De Groot N, Burgerhart J, Van De Meeberg P, et al. Systematic review: the effects of conservative and surgical treatment for obesity on gastro-oesophageal reflux disease. *Aliment Pharmacol Ther.* 2009; 30:1091–1102. [PubMed: 19758397]
18. Singh M, Lee J, Gupta N, et al. Weight loss can lead to resolution of gastroesophageal reflux disease symptoms: a prospective intervention trial. *Obesity.* 2013; 21:284–290. [PubMed: 23532991]
19. Fass R. Erosive esophagitis and nonerosive reflux disease (NERD): comparison of epidemiologic, physiologic, and therapeutic characteristics. *J Clin Gastroenterol.* 2007; 41:131–137. [PubMed: 17245209]
20. Cai N, Ji GZ, Fan ZN, et al. Association between body mass index and erosive esophagitis: a meta-analysis. *World J Gastroenterol.* 2012; 18:2545–2553. [PubMed: 22654453]
21. Rubenstein JH, Morgenstern H, Chey WD, et al. Protective role of gluteofemoral obesity in erosive oesophagitis and Barrett's oesophagus. *Gut.* 2014; 63:230–235. [PubMed: 23461896]
22. Rustgi AK, El-Serag HB. Esophageal carcinoma. *N Engl J Med.* 2014; 371:2499–2509. [PubMed: 25539106]
23. El-Serag H, Kvapil P, Hacken-Bitar J, et al. Abdominal obesity and the risk of Barrett's esophagus. *Am J Gastroenterol.* 2005; 100:2151–2156. [PubMed: 16181362]
24. Corley D, Kubo A, Levin T, et al. Abdominal obesity and body mass index as risk factors for Barrett's esophagus. *Gastroenterology.* 2007; 133:34. [PubMed: 17631128]
25. Cook M, Greenwood D, Hardie L, et al. A systematic review and meta-analysis of the risk of increasing adiposity on Barrett's esophagus. *Am J Gastroenterol.* 2008; 103:292–300. [PubMed: 17986313]
26. Kendall B, Macdonald G, Hayward N, et al. Leptin and the risk of Barrett's esophagus. *Gut.* 2008; 57:448–454. [PubMed: 18178609]
27. Rubenstein J, Kao J, Madanick R, et al. Association of adiponectin multimers with Barrett's esophagus. *Gut.* 2009; 58:1583–1589. [PubMed: 19570765]
28. Ryan A, Duong M, Healy L, et al. Obesity, metabolic syndrome and esophageal adenocarcinoma: epidemiology, etiology and new targets. *Cancer Epidemiol.* 2011; 35:309–319. [PubMed: 21470937]
29. Thomas SJ, Almers L, Schneider J, et al. Ghrelin and leptin have a complex relationship with risk of Barrett's esophagus. *Dig Dis Sci.* 2016; 61:70–79. [PubMed: 26396004]
30. Duggan C, Onstad L, Hardikar S, et al. Association between markers of obesity and progression from Barrett's esophagus to esophageal adenocarcinoma. *Clin Gastroenterol Hepatol.* 2013; 11:934–943. [PubMed: 23466711]
31. Kubo A, Corley D. Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2006; 15:872–878. [PubMed: 16702363]
32. McElholm A, McKnight A-J, Patterson C, et al. A population-based study of IGF axis polymorphisms and the esophageal inflammation, metaplasia, adenocarcinoma sequence. *Gastroenterology.* 2010; 139:204–212. [PubMed: 20403354]
33. Doyle S, Donohoe C, Finn S, et al. IGF-1 and its receptor in esophageal cancer: association with adenocarcinoma and visceral obesity. *Am J Gastroenterol.* 2012; 107:196–204. [PubMed: 22146489]
34. Ogunwobi O, Beales I. Leptin stimulates the proliferation of human oesophageal adenocarcinoma cells via HBEGF and Tgfbeta mediated transactivation of the epidermal growth factor receptor. *Br J Biomed Sci.* 2008; 65:121–127. [PubMed: 18986098]

35. Howard J, Beddy P, Ennis D, et al. Associations between leptin and adiponectin receptor upregulation, visceral obesity and tumour stage in oesophageal and junctional adenocarcinoma. *Br J Surg.* 2010; 97:1020–1027. [PubMed: 20632267]
36. Camilleri M. Peripheral mechanisms in appetite regulation. *Gastroenterology.* 2015; 148:1219–1233. [PubMed: 25241326]
37. Eslick G. Gastrointestinal symptoms and obesity: a meta-analysis. *Obes Rev.* 2012; 13:469–479. [PubMed: 22188520]
38. Delgado-Aros S, Locke G, Camilleri M, et al. Obesity is associated with increased risk of gastrointestinal symptoms: a population-based study. *Am J Gastroenterol.* 2004; 99:1801–1806. [PubMed: 15330922]
39. Delgado-Aros S, Cremonini F, Castillo J, et al. Independent influences of body mass and gastric volumes on satiation in humans. *Gastroenterology.* 2004; 126:432–440. [PubMed: 14762780]
40. Delgado-Aros S, Camilleri M, Castillo E, et al. Effect of gastric volume or emptying on meal-related symptoms after liquid nutrients in obesity: a pharmacologic study. *Clin Gastroenterol Hepatol.* 2005; 3:997–1006. [PubMed: 16234046]
41. Acosta A, Camilleri M, Shin A, et al. Quantitative gastrointestinal and psychological traits associated with obesity and response to weight-loss therapy. *Gastroenterology.* 2015; 148:537–546. [PubMed: 25486131]
42. Yamamoto S, Watabe K, Takehara T. Is obesity a new risk factor for gastritis? *Digestion.* 2012; 85:108–110. [PubMed: 22269289]
43. Kim H, Yoo T, Park D, et al. Influence of overweight and obesity on upper endoscopic findings. *J Gastroenterol Hepatol.* 2007; 22:477–481. [PubMed: 17376036]
44. Yamamoto S, Watabe K, Tsutsui S, et al. Lower serum level of adiponectin is associated with increased risk of endoscopic erosive gastritis. *Dig Dis Sci.* 2011; 56:2354–2360. [PubMed: 21448696]
45. Yang P, Zhou Y, Chen B, et al. Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies. *Eur J Cancer.* 2009; 45:2867–2873. [PubMed: 19427197]
46. Chen Y, Liu L, Wang X, et al. Body mass index and risk of gastric cancer: a meta-analysis of a population with more than ten million from 24 prospective studies. *Cancer Epidemiol Biomarkers Prev.* 2013; 22:1395–1408. [PubMed: 23697611]
47. Arslan E, Atilgan H, Yava o lu I. The prevalence of *Helicobacter pylori* in obese subjects. *Eur J Intern Med.* 2009; 20:695–697. [PubMed: 19818289]
48. Ericksen R, Rose S, Westphalen C, et al. Obesity accelerates *Helicobacter felis*-induced gastric carcinogenesis by enhancing immature myeloid cell trafficking and TH17 response. *Gut.* 2014; 63:385–394. [PubMed: 23729675]
49. Turati F, Tramacere I, La Vecchia C, et al. A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. *Ann Oncol.* 2013; 24:609–617. [PubMed: 22898040]
50. Camargo MC, Goto Y, Zabaleta J, et al. Sex hormones, hormonal interventions, and gastric cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2012; 21:20–38. [PubMed: 22028402]
51. Cook MB, Kamangar F, Whitman DC, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. *J Natl Cancer Inst.* 2010; 102:1344–1353. [PubMed: 20716718]
52. Vitek L, Haluzík M. The role of bile acids in metabolic regulation. *J Endocrinol.* 2016; 228:R85–R96. [PubMed: 26733603]
53. Fiorucci S, Distrutti E. Bile acid-activated receptors, intestinal microbiota, and the treatment of metabolic disorders. *Trends Mol Med.* 2015; 21:702–714. [PubMed: 26481828]
54. Buttet M, Traynard V, Tran TT, et al. From fatty-acid sensing to chylomicron synthesis: role of intestinal lipid-binding proteins. *Biochimie.* 2014; 96:37–47. [PubMed: 23958439]
55. Hutchison AT, Feinle-Bisset C, Fitzgerald PC, et al. Comparative effects of intra-duodenal whey protein hydrolysate on antropyloroduodenal motility, gut hormones, glycemia, appetite, and energy intake in lean and obese men. *Am J Clin Nutr.* 2015; 102:1323–1331. [PubMed: 26561615]
56. Nguyen NQ, Debrececi TL, Bambrick JE, et al. Accelerated intestinal glucose absorption in morbidly obese humans: relationship to glucose transporters, incretin hormones, and glycemia. *J Clin Endocrinol Metab.* 2015; 100:968–976. [PubMed: 25423571]

57. Moayyedi P. The epidemiology of obesity and gastrointestinal and other diseases: an overview. *Dig Dis Sci.* 2008; 53:2293–2299. [PubMed: 18636328]
58. Talley N, Quan C, Jones M, et al. Association of upper and lower gastrointestinal tract symptoms with body mass index in an Australian cohort. *Neurogastroenterol Motil.* 2004; 16:413–419. [PubMed: 15305996]
59. Talley N, Howell S, Poulton R. Obesity and chronic gastrointestinal tract symptoms in young adults: a birth cohort study. *Am J Gastroenterol.* 2004; 99:1807–1814. [PubMed: 15330923]
60. Le Pluart D, Sabaté JM, Bouchoucha M, et al. Functional gastrointestinal disorders in 35,447 adults and their association with body mass index. *Aliment Pharmacol Ther.* 2015; 41:758–767. [PubMed: 25728697]
61. Aro P, Ronkainen J, Talley NJ, et al. Body mass index and chronic unexplained gastrointestinal symptoms: an adult endoscopic population based study. *Gut.* 2005; 54:1377–1383. [PubMed: 15917313]
62. Sadik R, Abrahamsson H, Ung K-A, et al. Accelerated regional bowel transit and overweight shown in idiopathic bile acid malabsorption. *Am J Gastroenterol.* 2004; 99:711–718. [PubMed: 15089906]
63. Delgado-Aros S, Camilleri M, Garcia M, et al. High body mass alters colonic sensory-motor function and transit in humans. *Am J Physiol Gastrointest Liver Physiol.* 2008; 295:G382–G388. [PubMed: 18617555]
64. Teixeira T, Souza N, Chiarello P, et al. Intestinal permeability parameters in obese patients are correlated with metabolic syndrome risk factors. *Clin Nutr.* 2012; 31:735–740. [PubMed: 22444236]
65. Teixeira T, Collado M, Ferreira CL, et al. Potential mechanisms for the emerging link between obesity and increased intestinal permeability. *Nutr Res.* 2012; 32:637–647. [PubMed: 23084636]
66. Poullis A, Foster R, Shetty A, et al. Bowel inflammation as measured by fecal calprotectin: a link between lifestyle factors and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2004; 13:279–284. [PubMed: 14973103]
67. Bouchoucha M, Uzzan B, Cohen R. Metformin and digestive disorders. *Diab Metab.* 2011; 37:90–96.
68. Dickey W, Kearney N. Overweight in celiac disease: prevalence, clinical characteristics, and effect of a gluten-free diet. *Am J Gastroenterol.* 2006; 101:2356–2359. [PubMed: 17032202]
69. Tucker E, Rostami K, Prabhakaran S, et al. Patients with coeliac disease are increasingly overweight or obese on presentation. *J Gastrointest Liver Dis.* 2012; 21:11–15.
70. Kabbani T, Goldberg A, Kelly C, et al. Body mass index and the risk of obesity in coeliac disease treated with the gluten-free diet. *Aliment Pharmacol Ther.* 2012; 35:723–729. [PubMed: 22316503]
71. Valletta E, Fornaro M, Cipolli M, et al. Celiac disease and obesity: need for nutritional follow-up after diagnosis. *Eur J Clin Nutr.* 2010; 64:1371–1372. [PubMed: 20717130]
72. Mendall M, Gunasekera A, John B, et al. Is obesity a risk factor for Crohn's disease? *Dig Dis Sci.* 2011; 56:837–844. [PubMed: 21221790]
73. Chan S, Luben R, Olsen A, et al. Body mass index and the risk for Crohn's disease and ulcerative colitis: data from a European Prospective Cohort Study (The IBD in EPIC Study). *Am J Gastroenterol.* 2013; 108:575–582. [PubMed: 23318483]
74. Dong J, Chen Y, Tang Y, et al. Body mass index is associated with inflammatory bowel disease: a systematic review and meta-analysis. *PLoS One.* 2015; 10:e0144872. [PubMed: 26658675]
75. Long M, Crandall W, Leibowitz I, et al. Prevalence and epidemiology of overweight and obesity in children with inflammatory bowel disease. *Inflamm Bowel Dis.* 2011; 17:2162–2168. [PubMed: 21910178]
76. Waluga M, Hartleb M, Boryczka G, et al. Serum adipokines in inflammatory bowel disease. *World J Gastroenterol.* 2014; 20:6912–6917. [PubMed: 24944482]
77. Rodrigues VS, Milanski M, Fagundes JJ, et al. Serum levels and mesenteric fat tissue expression of adiponectin and leptin in patients with Crohn's disease. *Clin Exp Immunol.* 2012; 170:358–364. [PubMed: 23121676]

78. Zietek T, Rath E. Inflammation meets metabolic disease: gut feeling mediated by GLP-1. *Front Immunol.* 2016; 7:154. [PubMed: 27148273]
79. Keller J, Binnewies U, Rösch M, et al. Gastric emptying and disease activity in inflammatory bowel disease. *Eur J Clin Invest.* 2015; 45:1234–1242. [PubMed: 26426315]
80. Bhakta A, Tafen M, Glotzer O, et al. Increased incidence of surgical site infection in IBD patients. *Dis Colon Rectum.* 2016; 59:316–322. [PubMed: 26953990]
81. Flores A, Burstein E, CIPHER DJ, et al. Obesity in inflammatory bowel disease: a marker of less severe disease. *Dig Dis Sci.* 2015; 60:2436–2445. [PubMed: 25799938]
82. Seminerio JL, Koutroubakis IE, Ramos-Rivers C, et al. Impact of obesity on the management and clinical course of patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2015; 21:2857–2863. [PubMed: 26241001]
83. Harper JW, Sinanan MN, Zisman TL. Increased body mass index is associated with earlier time to loss of response to infliximab in patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2013; 19:2118–2124. [PubMed: 23863401]
84. Bhalme M, Sharma A, Keld R, et al. Does weight-adjusted anti-tumour necrosis factor treatment favour obese patients with Crohn's disease? *Eur J Gastroenterol Hepatol.* 2013; 25:543–549. [PubMed: 23337170]
85. Guardado J, Carchman E, Danicic AE, et al. Obesity does not impact perioperative or postoperative outcomes in patients with inflammatory bowel disease. *J Gastrointest Surg.* 2016; 20:725–733. [PubMed: 26696530]
86. Teitelbaum J, Sinha P, Micale M, et al. Obesity is related to multiple functional abdominal diseases. *J Pediatr.* 2009; 154:444–446. [PubMed: 19874760]
87. vd Baan-Slootweg O, Liem O, Bekkali N, et al. Constipation and colonic transit times in children with morbid obesity. *J Pediatr Gastroenterol Nutr.* 2011; 52:442–445. [PubMed: 21240026]
88. Kopylov U, Ben-Horin S, Lahat A, et al. Obesity, metabolic syndrome and the risk of development of colonic diverticulosis. *Digestion.* 2012; 86:201–205. [PubMed: 22907510]
89. Peery AF, Keku TO, Martin CF, et al. Distribution and characteristics of colonic diverticula in a United States screening population. *Clin Gastroenterol Hepatol.* 2016; 14:980–985. [PubMed: 26872402]
90. Strate L, Liu Y, Aldoori W, et al. Obesity increases the risks of diverticulitis and diverticular bleeding. *Gastroenterology.* 2009; 136:1215–1220. [PubMed: 19250648]
91. Bird CL, Frankl HD, Lee ER, et al. Obesity, weight gain, large weight changes, and adenomatous polyps of the left colon and rectum. *Am J Epidemiol.* 1998; 147:670–680. [PubMed: 9554606]
92. Sedjo RL, Byers T, Levin TR, et al. Change in body size and the risk of colorectal adenomas. *Cancer Epidemiol Biomarkers Prev.* 2007; 16:526–531. [PubMed: 17372248]
93. Kim Y, Lee S. An association between colonic adenoma and abdominal obesity: a cross-sectional study. *BMC Gastroenterol.* 2009; 9:4. [PubMed: 19144203]
94. Lee GE, Park HS, Yun KE, et al. Association between BMI and metabolic syndrome and adenomatous colonic polyps in Korean men. *Obesity.* 2008; 16:1434–1439. [PubMed: 18388894]
95. Siddiqui A, Pena Sahdala HN, Nazario HE, et al. Obesity is associated with an increased prevalence of advanced adenomatous colon polyps in a male veteran population. *Dig Dis Sci.* 2009; 54:1560–1564. [PubMed: 19399615]
96. Ben Q, An W, Jiang Y, et al. Body mass index increases risk for colorectal adenomas based on meta-analysis. *Gastroenterology.* 2012; 142:762–772. [PubMed: 22245665]
97. Omata F, Deshpande GA, Ohde S, et al. The association between obesity and colorectal adenoma: systematic review and meta-analysis. *Scand J Gastroenterol.* 2013; 48:136–146. [PubMed: 23130996]
98. Laiyemo AO, Doubeni C, Badurdeen DS, et al. Obesity, weight change, and risk of adenoma recurrence: a prospective trial. *Endoscopy.* 2012; 44:813–818. [PubMed: 22926666]
99. Anderson JC, Rangasamy P, Rustagi T, et al. Risk factors for sessile serrated adenomas. *J Clin Gastroenterol.* 2011; 45:694–699. [PubMed: 21325950]

100. Harriss DJ, Atkinson G, George K, et al. Lifestyle factors and colorectal cancer risk (1): systematic review and meta-analysis of associations with body mass index. *Colorectal Dis.* 2009; 11:547–563. [PubMed: 19207714]
101. Ning Y, Wang L, Giovannucci EL. A quantitative analysis of body mass index and colorectal cancer: findings from 56 observational studies. *Obes Rev.* 2010; 11:19–30. [PubMed: 19538439]
102. Moghaddam AA, Woodward M, Huxley R. Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events. *Cancer Epidemiol Biomarkers Prev.* 2007; 16:2533–2547. [PubMed: 18086756]
103. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. *Am J Clin Nutr.* 2007; 86:556–565. [PubMed: 17823417]
104. Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. *Gut.* 2013; 62:933–947. [PubMed: 23481261]
105. Bishara J, Farah R, Mograbi J, et al. Obesity as a risk factor for *Clostridium difficile* infection. *Clin Infect Dis.* 2013; 57:489–493. [PubMed: 23645850]
106. Nullens S, Nelsen T, Camilleri M, et al. Regional colon transit in patients with dys-synergic defaecation or slow transit in patients with constipation. *Gut.* 2012; 61:1132–1139. [PubMed: 22180057]
107. Harewood GC, Coulie B, Camilleri M, et al. Descending perineum syndrome: audit of clinical and laboratory features and outcome of pelvic floor retraining. *Am J Gastroenterol.* 1999; 94:126–130. [PubMed: 9934742]
108. Poylin V, Serrot F, Madoff R, et al. Obesity and bariatric surgery: a systematic review of associations with defecatory dysfunction. *Colorectal Dis.* 2011; 13:E92–E103. [PubMed: 21564470]
109. Bharucha AE, Dunivan G, Goode PS, et al. Epidemiology, pathophysiology, and classification of fecal incontinence: state of the science summary for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) workshop. *Am J Gastroenterol.* 2015; 110:127–136. [PubMed: 25533002]
110. Erekson EA, Ciarleglio MM, Hanissian PD, et al. Functional disability among older women with fecal incontinence. *Am J Obstet Gynecol.* 2015; 212:327, e1–7. [PubMed: 25447956]
111. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. *JAMA.* 2015; 313:2263–2273. [PubMed: 26057287]
112. Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology.* 2011; 140:124–131. [PubMed: 20858492]
113. Loomba R, Sanyal AJ. The global NAFLD epidemic. *Nat Rev Gastroenterol Hepatol.* 2013; 10:686–690. [PubMed: 24042449]
114. Larsson S, Wolk A. Overweight, obesity and risk of liver cancer: a meta-analysis of cohort studies. *Br J Cancer.* 2007; 97:1005–1008. [PubMed: 17700568]
115. Donnelly KL, Smith CI, Schwarzenberg SJ, et al. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. *J Clin Invest.* 2005; 115:1343–1351. [PubMed: 15864352]
116. Lambert JE, Ramos-Roman MA, Browning JD, et al. Increased de novo lipogenesis is a distinct characteristic of individuals with nonalcoholic fatty liver disease. *Gastroenterology.* 2014; 146:726–735. [PubMed: 24316260]
117. Fabbrini E, Mohammed BS, Magkos F, et al. Alterations in adipose tissue and hepatic lipid kinetics in obese men and women with nonalcoholic fatty liver disease. *Gastroenterology.* 2008; 134:424–431. [PubMed: 18242210]
118. Hodson L, McQuaid SE, Humphreys SM, et al. Greater dietary fat oxidation in obese compared with lean men: an adaptive mechanism to prevent liver fat accumulation? *Am J Physiol Endocrinol Metab.* 2010; 299:E584–E592. [PubMed: 20628024]
119. Argo CK, Northup PG, Al-Osaimi AM, et al. Systematic review of risk factors for fibrosis progression in nonalcoholic steatohepatitis. *J Hepatol.* 2009; 51:371–379. [PubMed: 19501928]

120. Singh S, Allen AM, Wang Z, et al. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol*. 2015; 13:643–654. e1–9. quiz e39–40. [PubMed: 24768810]
121. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology*. 2015; 149:367–378. e5. [PubMed: 25865049]
122. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology*. 2012; 55:2005–2023. [PubMed: 22488764]
123. Taitano AA, Markow M, Finan JE, et al. Bariatric surgery improves histological features of nonalcoholic fatty liver disease and liver fibrosis. *J Gastrointest Surg*. 2015; 19:429–437. [PubMed: 25537957]
124. Vargas V, Allende H, Lecube A, et al. Surgically induced weight loss by gastric bypass improves non alcoholic fatty liver disease in morbid obese patients. *World J Hepatol*. 2012; 4:382–388. [PubMed: 23355916]
125. Clark JM, Alkhuraishi AR, Solga SF, et al. Roux-en-Y gastric bypass improves liver histology in patients with non-alcoholic fatty liver disease. *Obes Res*. 2005; 13:1180–1186. [PubMed: 16076987]
126. Schneck AS, Anty R, Patoureaux S, et al. Roux-en Y gastric bypass results in long-term remission of hepatocyte apoptosis and hepatic histological features of non-alcoholic steatohepatitis. *Front Physiol*. 2016; 7:344. [PubMed: 27594839]
127. Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U. S. *Hepatology*. 2014; 59:2188–2195. [PubMed: 24375711]
128. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med*. 2010; 362:1675–1685. [PubMed: 20427778]
129. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet*. 2015; 385:956–965. [PubMed: 25468160]
130. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003; 348:1625–1638. [PubMed: 12711737]
131. Aleksandrova K, Boeing H, Nothlings U, et al. Inflammatory and metabolic biomarkers and risk of liver and biliary tract cancer. *Hepatology*. 2014; 60:858–871. [PubMed: 24443059]
132. Younossi ZM, Otgonsuren M, Henry L, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. *Hepatology*. 2015; 62:1723–1730. [PubMed: 26274335]
133. Margini C, Dufour JF. The story of HCC in NAFLD: from epidemiology, across pathogenesis, to prevention and treatment. *Liver Int*. 2016; 36:317–324. [PubMed: 26601627]
134. White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. *Clin Gastroenterol Hepatol*. 2012; 10:1342–1359. e2. [PubMed: 23041539]
135. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. *J Clin Gastroenterol*. 2013; 47(Suppl):S2–S6. [PubMed: 23632345]
136. Wu SE, Charles HW, Park JS, et al. Obesity conveys poor outcome in patients with hepatocellular carcinoma treated by transarterial chemoembolization. *Diagn Interv Imaging*. 2017; 98:37–42. [PubMed: 27372418]
137. Utsunomiya T, Okamoto M, Kameyama T, et al. Impact of obesity on the surgical outcome following repeat hepatic resection in Japanese patients with recurrent hepatocellular carcinoma. *World J Gastroenterol*. 2008; 14:1553–1558. [PubMed: 18330947]
138. Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. *Hepatology*. 2016; 64:1577–1586. [PubMed: 27543837]

139. Thein HH, Isaranuwachai W, Campitelli MA, et al. Health care costs associated with hepatocellular carcinoma: a population-based study. *Hepatology*. 2013; 58:1375–1384. [PubMed: 23300063]
140. Ma C, Kesarwala AH, Eggert T, et al. NAFLD causes selective CD4(+) T lymphocyte loss and promotes hepatocarcinogenesis. *Nature*. 2016; 531:253–257. [PubMed: 26934227]
141. Nakagawa H, Umemura A, Taniguchi K, et al. ER stress cooperates with hypernutrition to trigger TNF-dependent spontaneous HCC development. *Cancer Cell*. 2014; 26:331–343. [PubMed: 25132496]
142. Gomes AL, Teijeiro A, Buren S, et al. Metabolic inflammation-associated IL-17A causes non-alcoholic steatohepatitis and hepatocellular carcinoma. *Cancer Cell*. 2016; 30:161–175. [PubMed: 27411590]
143. Tessitore A, Ciciarelli G, Del Vecchio F, et al. MicroRNA expression analysis in high fat diet-induced NAFLDNASH-HCC progression: study on C57BL/6J mice. *BMC Cancer*. 2016; 16:3. [PubMed: 26728044]
144. Liu YL, Patman GL, Leathart JB, et al. Carriage of the PNPLA3 rs738409 C >G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. *J Hepatol*. 2014; 61:75–81. [PubMed: 24607626]
145. Tsai C-J. Steatocholecystitis and fatty gallbladder disease. *Dig Dis Sci*. 2009; 54:1857–1863. [PubMed: 19093209]
146. Everhart J. Contributions of obesity and weight loss to gallstone disease. *Ann Intern Med*. 1993; 119:1029–1035. [PubMed: 8214980]
147. Dittrick G, Thompson J, Campos D, et al. Gallbladder pathology in morbid obesity. *Obes Surg*. 2005; 15:238–242. [PubMed: 15802067]
148. Guh D, Zhang W, Bansack N, et al. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health*. 2009; 9:88. [PubMed: 19320986]
149. Tsai C-J, Leitzmann M, Willett W, et al. Prospective study of abdominal adiposity and gallstone disease in US men. *Am J Clin Nutr*. 2004; 80:38–44. [PubMed: 15213025]
150. Tsai CJ, Leitzmann M, Willett W, et al. Central adiposity, regional fat distribution, and the risk of cholecystectomy in women. *Gut*. 2006; 55:708–714. [PubMed: 16478796]
151. Mathus-Vliegen E, Van Ierland-Van Leeuwen M, Terpstra A. Determinants of gallbladder kinetics in obesity. *Dig Dis Sci*. 2004; 49:9–16. [PubMed: 14992428]
152. Nakeeb A, Comuzzie A, Al-Azzawi H, et al. Insulin resistance causes human gallbladder dysmotility. *J Gastrointest Surg*. 2006; 10:940–948. [PubMed: 16843864]
153. Tran K, Goldblatt M, Swartz-Basile D, et al. Diabetes and hyperlipidemia correlate with gallbladder contractility in leptin-related murine obesity. *J Gastrointest Surg*. 2003; 7:857–862. [PubMed: 14592658]
154. Lee J, Kim S, Jun D, et al. Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome. *World J Gastroenterol*. 2009; 15:1869–1875. [PubMed: 19370785]
155. Vege S, Gardner T, Chari S, et al. Low mortality and high morbidity in severe acute pancreatitis without organ failure: a case for revising the Atlanta classification to include “moderately severe acute pancreatitis”. *Am J Gastroenterol*. 2009; 104:710–715. [PubMed: 19262525]
156. Chen S, Xiong G, Wu S. Is obesity an indicator of complications and mortality in acute pancreatitis? An updated meta-analysis. *J Dig Dis*. 2012; 13:244–251. [PubMed: 22500786]
157. John B, Irukulla S, Abulafi A, et al. Systematic review: adipose tissue, obesity and gastrointestinal diseases. *Aliment Pharmacol Ther*. 2006; 23:1511–1523. [PubMed: 16696799]
158. Sharma A, Muddana V, Lamb J, et al. Low serum adiponectin levels are associated with systemic organ failure in acute pancreatitis. *Pancreas*. 2009; 38:907–912. [PubMed: 19696691]
159. Fain J, Madan A, Hiler M, et al. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. *Endocrinology*. 2004; 145:2273–2282. [PubMed: 14726444]
160. Ferlay J, Shin H-R, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010; 127:2893–2917. [PubMed: 21351269]

161. Aune D, Greenwood D, Chan D, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. *Ann Oncol.* 2012; 23:843–852. [PubMed: 21890910]
162. Lauby-Secretan B, Scoccianti C, Loomis D, et al. International Agency for Research on Cancer Handbook Working Group. Body fatness and cancer—viewpoint of the IARC Working Group. *N Engl J Med.* 2016; 375:794–798. [PubMed: 27557308]
163. Kim BC, Shin A, Hong CW, et al. Association of colorectal adenoma with components of metabolic syndrome. *Cancer Causes Control.* 2012; 23:727–735. [PubMed: 22450737]
164. Bellentani S, Marino M. Epidemiology and natural history of non-alcoholic fatty liver disease (NAFLD). *Ann Hepatol.* 2009; 8(Suppl 1):8.
165. Ioannou GN, Weiss NS, Kowdley KV, et al. Is obesity a risk factor for cirrhosis-related death or hospitalization? A population-based cohort study. *Gastroenterology.* 2003; 125:1053–1059. [PubMed: 14517789]

Figure 1.
Gastrointestinal and hepatic morbidity associated with obesity.

Figure 2.

Obesity is associated with higher volume to experience fullness during a nutrient drink test (*upper left*), and faster gastric emptying of solids (*upper right*). *Lower*: noninvasive single-photon emission computerized tomography (SPECT) imaging of the stomach, which is used to measure fasting and postprandial gastric volumes. * $P < .05$; $T_{1/2}$, time to empty 50% of the ingested meal. Reproduced with permission from Acosta et al.⁴¹

Figure 3.

Nonalcoholic fatty liver disease: disease spectrum and sources of triglyceride fatty acids. (A) The spectrum of hepatic manifestations of NAFLD includes isolated steatosis and NASH. Isolated steatosis is characterized by hepatic fat accumulation without any additional pathologic findings or the risk of progression to cirrhosis. NASH is characterized by hepatic inflammation, fibrosis, and risk of progression to cirrhosis. Increased HCC risk is associated with both; although the risk is much greater in NASH. (B) Sources of fatty acids and their respective contribution to hepatic triglycerides are shown. The majority of fatty acids are derived from circulating NEFA, which are derived from adipose tissue lipolysis. Adipose tissue lipolysis is enhanced in insulin resistance. Rates of hepatic de novo lipogenesis are up-regulated in NAFLD. This is the second largest source; newly synthesized fatty acids

account for approximately one fourth of the fatty acids in hepatic triglycerides. The remainder is derived from dietary fats. NEFA, nonesterified fatty acid.

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Table 1

Quantified Risk Ratios of Gastrointestinal Complications of Obesity in Adults

Gastrointestinal disease	Obesity as a risk factor		Reference
	Risk: OR or RR	95% CI	
Esophagus			
GERD	OR, 1.94	1.46–2.57	14
Erosive esophagitis	OR, 1.87	1.51–2.31	15
Barrett's esophagus	OR, 4.0	1.4–11.1	23
Esophageal adenocarcinoma	Men: OR, 2.4	1.9–3.2	31
	Women: OR, 2.1	1.4–3.2	
	RR, 4.8	3.0–7.7	162
Stomach			
Erosive gastritis	OR, 2.23	1.59–3.11	43
Gastric cancer	OR, 1.55	1.31–1.84	45,46
	RR (cardia), 1.8	1.3–2.5	162
Small Intestine			
Diarrhea	OR, 2.7	1.10–6.8	38
Colon and rectum			
Diverticular disease	RR, 1.78	1.08–2.94	90
Polyps	OR, 1.44	1.23–1.70	163
Colorectal cancer	Men: RR, 1.95	1.59–2.39	104
	Women: RR, 1.15	1.06–1.24	
	RR, 1.3	1.3–1.4	162
<i>Clostridium difficile</i> infection	OR, 1.196 per 1 kg/m ² increase in BMI	1.12–1.27	105
Anorectum			
Dyssynergic defecation	OR, 1.64	1.09–2.47	162
Liver			
NAFLD	RR, 4.6	2.5–110	164
Cirrhosis	RR, 4.1	1.4–11.4	165
Hepatocellular carcinoma	RR, 1.89	1.51–2.36	114
	RR, 1.8	1.6–2.1	162
Gallbladder			
Gallstone disease	Men: RR, 2.51	2.16–2.91	148
	Women: RR, 2.32	1.17–4.57	
Gallbladder cancer	RR, 1.3	1.2–1.4	162
Pancreas			
Acute pancreatitis	RR, 2.20	1.82–2.66	156
Pancreatic cancer	Men: RR, 1.10	1.04–1.22	161
	Women: RR, 1.13	1.05–1.18	
	RR, 1.5	1.2–1.8	162

Table 2

Partial List of Drugs in Phase 2 or 3 Clinical Trials for NASH

Drug target	Drug name
Thiazolidinedione	Pioglitazone
Glucagon-like peptide-1 receptor agonists	Liraglutide
PPAR α and δ agonist	Elafibranor
PPAR α and δ agonist	GFT505
Farnesoid X receptor agonist	Obeticholic acid
Farnesoid X receptor agonist	GS-9674
Acetyl-CoA carboxylase inhibitor	GS-0976
Fatty acid synthase inhibitor	3-V Bioscience-2640
Caspase inhibitor	IDN-6556
Immune modulating and antifibrotic	JKB-121
Antioxidant, multiple targets	Vitamin E
Leukotriene-receptor antagonism, inhibition of phosphodiesterases, and inhibition of 5-lipoxygenase	MN-001
CCR2 and CCR5 inhibitor	Cenicriviroc
Anti-LPS antibodies and adjuvants	IMM-124E
Selective aldosterone-receptor antagonist	MT-3995
Liver-directed thyroid hormone receptor- β agonist	MGL-3196
Apical sodium-dependent bile acid transporter	Volixibat