In 1978, the term nonceliac gluten sensitivity (NCGS) was coined in a case report describing the resolution of persistent gastrointestinal symptoms in a patient (in which celiac disease had been excluded) with the adoption of a gluten-free diet. Currently, NCGS has been defined as a clinical entity induced by the ingestion of gluten leading to intestinal and/or extraintestinal symptoms that resolve once the gluten-containing foodstuff is eliminated from the diet and when celiac disease and wheat allergy have been ruled out. The main gluten-containing cereals are wheat, barley, and rye. Whereas the adaptive immune system is involved in celiac disease, NCGS was shown to be mediated by an innate immune response to gluten-containing food. Nevertheless, it remains highly controversial whether the symptoms of NCGS are effectively due to consumption of gluten proteins. The current study of Skodje et al found no evidence for induction of symptoms by consumption of gluten in participants with self-reported NCGS and rather attributed symptoms to the fructans present in wheat. These data confirm the results of a previous study that failed to demonstrate specific or dose-dependent effects of gluten in a placebo-controlled cross-over rechallenge study in NCGS patients on a low FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet. Similarly, other studies identified only 5% and 14%, respectively, of the participants as responders to gluten in double-blind placebo controlled trials, suggesting that factors other than gluten are implicated in NCGS. Therefore, some authors suggested that the term nonceliac wheat sensitivity is more appropriate than nonceliac gluten sensitivity. However, because the effects are not limited to wheat but also apply for barley and rye, this nomenclature is confusing and debatable.

In addition to gluten, other components of wheat, rye and barley have been identified as potential culprits for the induction of symptoms, including FODMAPs and α-amylase-trypsin inhibitors (ATIs; Figure 1). In this issue of Gastroenterology, Skodje et al carefully investigated the contribution of gluten and FODMAPs in the induction of symptoms. The participants (n = 59) in this randomized, placebo-controlled, cross-over study were all on a gluten-free diet and consumed daily 1 muesli bar containing either 5.7 g gluten (but not fructans) or 2.1 g fructans (but no gluten) or placebo (neither gluten nor fructans). Each intervention period lasted 7 days and washout periods were at least 7 days. Gastrointestinal symptoms as well as quality of life, anxiety and depression, and fatigue were recorded before and after each intervention period using validated questionnaires. After correction for multiple testing, gastrointestinal symptoms were borderline significantly higher after intervention with fructans compared with gluten (P = .049). The authors concluded that fructans are more likely to induce the NCGS symptoms than gluten, despite the very small differences between the 3 interventions.

Fructans are nondigestible but fermentable carbohydrates that belong to the class of FODMAPs. In contrast to inulin-type fructans, the fructans in cereal grains are branched and contain fructosyl units with both β(2-1) and β(2-6) linkages. The average degree of polymerization amounts to 4 for wheat flour and barley, whereas oat and rye kernels contain higher degree of polymerization fructans. Among the cereal grains, fructan concentrations are highest in rye (3.6%-6.6% of dry matter). Concentrations in wheat vary between 0.7% and 2.9%, whereas barley contains only trace amounts of fructans. The daily intake of fructans in a Western diet has been estimated between 1 and 10 g, depending on geographic and demographic parameters. Fructans are considerably degraded during some types of cereal processing such as bread baking because of the yeast enzyme yeast invertase. FODMAPs trigger gastrointestinal symptoms in subjects who are hypersensitive to luminal distention owing to osmotic effects, attracting water to the intestinal lumen, and bacterial fermentation, resulting in (excessive) gas production. As such, the immune system is not involved in symptom generation, and the symptoms should be classified as food intolerance rather than food sensitivity. Although intolerance to fructans and other FODMAPs may contribute to NCGS, they may only explain gastrointestinal symptoms and not the extraintestinal symptoms observed in NCGS patients, such as neurologic dysfunction, psychological disturbances, fibromyalgia, and skin rash. Therefore, it is unlikely that they are the sole cause of NCGS.

ATIs are plant-based proteins that make up not more than 4% of the wheat proteins. They protect the plant against pests and parasites by inhibiting their digestive enzymes. Breeding of wheat varieties that are high yielding and highly pest resistant has led to increasing concentrations in wheat vary between 0.7% and 2.9%, whereas barley contains only trace amounts of fructans. The daily intake of fructans in a Western diet has been estimated between 1 and 10 g, depending on geographic and demographic parameters. Fructans are considerably degraded during some types of cereal processing such as bread baking because of the yeast enzyme yeast invertase. FODMAPs trigger gastrointestinal symptoms in subjects who are hypersensitive to luminal distention owing to osmotic effects, attracting water to the intestinal lumen, and bacterial fermentation, resulting in (excessive) gas production. As such, the immune system is not involved in symptom generation, and the symptoms should be classified as food intolerance rather than food sensitivity. Although intolerance to fructans and other FODMAPs may contribute to NCGS, they may only explain gastrointestinal symptoms and not the extraintestinal symptoms observed in NCGS patients, such as neurologic dysfunction, psychological disturbances, fibromyalgia, and skin rash. Therefore, it is unlikely that they are the sole cause of NCGS.

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dendritic cells to mesenteric lymph nodes and contact with already primed T cells might also worsen inflammation at extraintestinal sites. This mechanism might explain the exacerbation of inflammation upon ingestion of ATI-containing grains in patients with preexisting diseases, whereas the majority of healthy adults will not develop symptoms. At present, studies directly comparing modern wheat with high ATI content with ancient cultivars like Einkorn and Emmer that contain low levels of ATIs in NCGS are lacking. To better support the role of ATIs as triggers of NCGS, additional human trials are required using such varieties or ATI-free diets.

To improve the clinical management of patients with NCGS, the causative factor(s) needs to be identified and studies, like that of Skodje et al., 4 that carefully disentangle the contribution of the different suspected components in cereal grains are highly warranted. They might stimulate the food industry to develop adapted food products eliminating the need for gluten-free diets for NCGS patients. Adoption of a gluten-free diet might reduce the consumption of cereal fiber or whole grains, affecting cardiovascular risk, 20 and should therefore not be encouraged in subjects without celiac disease.

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References
Colonoscopy Risks: What Is Known and What Are the Next Steps?

Colonoscopy is an essential, commonly used tool in gastroenterology, with a primary role in colorectal cancer prevention as well as the diagnosis and management of lower gastrointestinal symptoms. However, colonoscopy is associated with potentially serious complications, and the risk of adverse events has been a topic of extensive study. In this issue of *Gastroenterology*, Wang et al. provide important new data regarding the risks of both diagnostic and screening/surveillance colonoscopy.

The gastrointestinal risks of colonoscopy are well-understood, with an increased risk of perforation or lower gastrointestinal bleeding. The recent US Preventive Services Task Force technical review estimated risks of perforation of 4 per 10,000 (95% confidence interval, 2-5) and major hemorrhage of 8 per 10,000 (95% confidence interval, 5-14) with screening colonoscopy. However, the risks of colonoscopy-related nongastrointestinal complications, such as cardiovascular or cerebrovascular events, are less well-understood. Prior studies used varied methodologies and populations, and did not always include comparison groups not undergoing colonoscopy. An increased risk of cardiovascular events after colonoscopy was suggested in a prior study using Medicare data, but the risk of cardiovascular events and stroke was similar to the underlying population not undergoing colonoscopy in a German study.

Wang et al. used pooled data from the California State Ambulatory Surgery and Services, Emergency Department, and Inpatient Databases to identify patients undergoing outpatient colonoscopy as well as comparison cohorts undergoing procedures with a presumed low risk of systemic complications. Joint aspiration, joint injection, and lithotripsy were chosen as low-risk comparator procedures with minimal systemic risk, arthroscopy/carpal tunnel release as minor procedures with anesthesia, and cataract surgery as a minimally invasive procedure with anesthesia. Screening/surveillance and diagnostic colonoscopies were examined separately, and multiple potential risk factors for both gastrointestinal and nongastrointestinal complications were evaluated. The overall risk of any serious complication within 30 days after screening/surveillance colonoscopy was low; however, complications were significantly higher than after joint injection/aspiration/lithotripsy, but were lower than after cataract surgery. The risk of serious nongastrointestinal complications, such as pulmonary, cardiovascular, or cerebrovascular events, showed a similar pattern with respect to the comparison procedures. In contrast, after diagnostic colonoscopies, the risks of all serious complications and nongastrointestinal complications were similar to joint injection/aspiration/