Digestive Diseases and Sciences
https://doi.org/10.1007/s10620-019-05663-x

INVITED REVIEW

Going Against the Grains: Gluten-Free Diets in Patients Without Celiac Disease—Worthwhile or Not?

Benjamin A. Lerner[1] · **Peter H. R. Green**[1] · **Benjamin Lebwohl**[1,2]

Abstract
While the gluten-free diet (GFD) is the only known effective therapy for celiac disease, in recent years it has become increasingly popular in the USA and worldwide, with many believing it to be more "healthful" and others claiming that it has beneficial effects for health conditions, many extraintestinal, other than celiac disease. This review examines the evidence for use of the GFD in patients without celiac disease who self-report intestinal and/or extraintestinal symptoms (non-celiac gluten sensitivity), as well as for enhancement of athletic performance and treatment of autism, rheumatoid arthritis, and psychiatric disorders. Overall, the evidence for use of GFDs in conditions other than celiac disease is poor. Though non-celiac gluten sensitivity may ultimately emerge as a biomarker-defined condition, a large proportion of patients with apparent non-celiac gluten sensitivity have, after careful investigation, an alternative diagnosis. In light of this, and coupled with the potential physical and psychological harms associated with the avoidance of gluten, initiating a GFD should not be encouraged for people who have these other conditions or are seeking physical/athletic enhancement.

Keywords Gluten-free diet · Gluten · Non-celiac gluten sensitivity · Rheumatoid arthritis · Autism · Schizophrenia

Introduction

Gluten (from the Latin "glue") is the term for the prolamine storage proteins of the cereal grains wheat, barley, and rye [1]. A gluten-free diet (GFD) is currently the only known effective treatment for celiac disease, an autoimmune disorder that occurs in genetically predisposed individuals who develop an immune reaction to gluten. In the USA, nearly 1% of the population has celiac disease. While the prevalence of celiac disease has remained stable over the past few years [2], interest in GFDs has increased. In 2004, "gluten-free diet" was the most popular diet-related search term for the Google internet search engine in only 1.9% of Nielson designated market areas; by 2014, that figure had risen to 83% [3]. According to a 2018 Gallup poll, 21% of Americans actively attempt to include GF foods in their diets [4], and a 2017 market research survey found the GFD second only to low-carbohydrate diets in popularity, with 11% of Americans having tried the diet within the prior year [5]. The number of Americans without celiac disease who avoid gluten more than tripled between 2009–2010 and 2013–2014, according to data from the National Health and Nutrition Examination Surveys (NHANES) [2].

The reasons for this rise in gluten avoidance are manifold. Thirty percent of people buying GF foods report doing so because they believe that consuming such a diet is healthier [5]. Beyond this general perception of healthfulness, many people claim that GFDs can be used to treat specific diseases. In this review, we assess the evidence for use of GFDs in people who do not have celiac disease. We discuss the entity of non-celiac gluten sensitivity (NCGS), and we examine the effects of GFDs on athletic performance, neuropsychiatric disorders, and rheumatoid arthritis (RA). Finally, we review the potential disadvantages of adhering to a GFD.

Guarantor of the article: Benjamin Lebwohl, MD, MS.

✉ Benjamin Lebwohl
BL114@columbia.edu

[1] Department of Medicine, Celiac Disease Center, Columbia University Medical Center, New York, NY 10032, USA

[2] Department of Epidemiology, Mailman School of Public Health, Columbia University Medical Center, New York, NY 10032, USA

Published online: 17 May 2019

Non-Celiac Gluten Sensitivity

The pathophysiology of celiac disease has been well elucidated. Gluten, rich in glutamine and proline residues, is incompletely digested by gastric, pancreatic, and intestinal brush border peptidases. In affected individuals, the resulting gliadin peptides enter the lamina propria of the small intestine where they are deamidated and bind to human leukocyte antigen (HLA)-DQ2- or HLA-DQ8-positive antigen-presenting cells. The peptides are then presented to gliadin-reactive cluster-of-differentiation (CD)4+ T cells, leading to mucosal inflammation, small intestinal villous atrophy, increased intestinal paracellular permeability, and malabsorption [6]. By contrast, NCGS is a clinical syndrome defined entirely by symptoms that respond to withdrawal of gluten from the diet in the absence of celiac disease or wheat allergy. Common symptoms include irritable bowel-type symptoms of bloating, diarrhea, abdominal pain, and dyspepsia. Extraintestinal manifestations such as fatigue, headache, numbness, and cognitive impairment or "brain fog" are also frequently reported [7]. At present, NCGS has no established biologic basis, with neither specific histologic findings nor serologic markers identified, although a recent study identified serological markers of systemic immune activation and evidence of intestinal epithelial damage in patients with NCGS that were not present in celiac disease or healthy controls [8]. Currently, NCGS is typically a self-diagnosis or a diagnosis made by alternative health practitioners [9]. Estimates of its prevalence vary widely, from 1.7% in the 2013–2014 NHANES to 13% in a population-based questionnaire of 1002 people from the UK [2, 10].

Although NCGS was first described in the late 1970s, it is only within the last decade that researchers have studied the effectiveness of the GFD for this condition using double-blind placebo-controlled trials. The first of these studies, which randomized 34 patients with self-reported gluten-sensitive irritable bowel syndrome (IBS) to consuming GF and non-GF muffins, found higher rates of inadequate symptom control in those exposed to gluten compared with placebo (68 vs. 40%, $p = 0.0001$) [11]. Nevertheless, the same Australian research group later found that the effect of gluten exposure in patients with this phenotype was nullified by the use of a diet low in FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols), raising the possibility that a large proportion of patients with apparent NCGS may actually be sensitive to FODMAPs or other dietary products [12]. On the other hand, researchers at the Mayo Clinic studied a group of diarrhea-predominant IBS patients who had not self-identified as being gluten sensitive and noted reduced bowel frequency while consuming a GFD [13].

Given the difficulty of identifying true NCGS, a panel of experts proposed using the double-blind placebo-controlled crossover gluten challenge as the "gold standard" for diagnosis [14]. Several studies with such design have been performed; some showed higher rates of symptom relapse with gluten challenge [15–17], whereas others actually showed higher rates of symptoms with placebo [18, 19]. A systematic review found that across studies, 40% of subjects had similar or increased symptoms in response to placebo. Accounting for this strong "nocebo" response, only 38 of 231 (16%) of NCGS patients showed gluten-specific symptoms [20]. Taken as a whole, the available data suggest that a large number of patients initially identified as having NCGS are actually not gluten sensitive. Some patients may have symptoms in response to FODMAPs or to other wheat components, such as amylase–trypsin inhibitors. A significant proportion of patients with self-identified NCGS have been diagnosed with other conditions such as lactose and fructose intolerance, small intestinal bacterial overgrowth, and microscopic colitis following medical investigation [9]. Nevertheless, among patients with no known alternative diagnosis, a GFD may be beneficial for some of these patients insofar as it can reduce exposure to other yet-identified dietary triggers. Exclusion of celiac disease prior to introduction of the GFD is, however, imperative.

Athletic Performance

The GFD has become particularly popular among athletes. In a global survey of 910 athletes, 41% reported adhering to a GFD 50–100% of the time [21]. More than half of these athletes believe gluten avoidance improves "exercise performance," and 74% believe it improves "body composition for sport performance." Interestingly, a large minority of athletes not adhering to a GFD hold the same beliefs [21]. Furthermore, some high-profile athletes have publicly attributed their success to avoiding gluten. Novak Djokovic, the top-ranked tennis player with 15 Grand Slam titles, is perhaps its most prominent exemplar, having written a book on the topic, *Serve to Win: The 14-Day Gluten-Free Plan for Physical and Mental Excellence* [22]. To our knowledge, there has only been one published study to date examining the effects of GFD on exercise performance. That study, a double-blind placebo-controlled crossover trial, allocated 13 competitive cyclists to a 7-day gluten-containing diet and GFD separated by a 10-day washout. Gluten and placebo (whey protein) were provided in the form of an indistinguishable food bar. The study found no statistical difference in cycling performance on a 15-min time trial. There were also no differences in gastrointestinal symptoms or inflammatory markers between diets [23]. Future studies could clarify whether remaining on a GFD for a longer period of time yields different outcomes. It is important to consider

that, when not blinded to the intervention, a GFD may improve athletic performance via the placebo effect [24–26].

Rheumatoid Arthritis

RA is a chronic inflammatory joint disease that affects 0.5–1% of most populations [27]. Dietary manipulation is commonly used by patients with RA with the rationale that it theoretically decreases inflammation, increases antioxidant levels, changes lipid profiles, and alters the gut microbiome [28]. Some of the diets most commonly used by patients with RA are vegetarian or vegan, Mediterranean, and GF. The rationale for use of a GFD relates to the mechanistic similarities between celiac disease and RA (both are HLA-associated conditions with immune responses to posttranslationally modified proteins) [29] and also to the presence of higher rates of anti-gliadin antibodies among RA patients [30, 31].

Despite its popularity, the GFD has not been studied on its own in RA patients. An early single-blind randomized controlled trial compared a usual diet with 7–10 days of fasting, followed by 3.5 months of a GF vegan diet, and 9 months of a lacto-vegetarian diet. After 4 weeks, the 27 patients in the intervention group showed significant improvements in the number of tender and swollen joints, pain score, duration of morning stiffness, grip strength, erythrocyte sedimentation rate, and C-reactive protein; only pain score improved significantly in the control group. The differences in outcomes between groups remained present until the end of the 13-month trial, long after gluten was reintroduced, arguing against it being the cause of the improved outcomes [32].

A subsequent study randomized 66 patients with active RA to either a GF vegan diet or a well-balanced non-GF non-vegan diet for 1 year. Forty-one percent of patients in the intervention group fulfilled the American College of Rheumatology ACR20 criteria, defined as at least 20% improvement in the number of tender and swollen joints, as well as at least 20% improvement in three or more of the five remaining core set measures. In contrast, only 4% of patients in the control group met the ACR20 criteria. Despite the substantial clinical improvement, there was no radiographic difference between groups, with both having significant increases in the number of bony erosions over the course of the trial. Significant reductions in IgG anti-gliadin and anti-beta-lactoglobulin levels, however, were noted in the responders to the GF vegan diet, leading the study's authors to hypothesize that the intervention's beneficial effects may have been due to a diminished immune response to exogenous food antigens [33]. While the findings of this study are intriguing, it is not at all clear whether the results are mediated by avoidance of gluten, dairy products, meat, or some other unidentified factor. Additionally, the absence of blinding leaves considerable suspicion that the placebo effect and other factors biased the study. Additional analysis of the study data found that the GF vegan group had decreased low-density lipoproteins (LDL) and oxidized LDL levels, as well as increased levels of atheroprotective antibodies against phosphorylcholine [34], relevant since patients with RA are at increased risk of developing and dying from cardiovascular disease [35]. It seems most likely that the observed changes in lipid profile are the result of veganism, as opposed to the avoidance of gluten, as similar changes have been reported with the consumption of vegetarian diets [36], but not of GFDs [37]. As the GFD in isolation has not been investigated in RA, it is premature to conclude that it is beneficial in this context.

Neuropsychiatric Conditions

Ataxia and Peripheral Neuropathy

It is well established that celiac disease can initially present with a range of neurologic manifestations, most commonly ataxia or peripheral neuropathy, but also epilepsy, encephalopathy, myopathy, and other movement disorders [38–40]. Nevertheless, these neurologic disorders may also be present in patients who have positive serologies for anti-gliadin antibodies in the absence of celiac disease. Indeed, a study of 562 patients with circulating anti-gliadin antibodies and idiopathic neurologic dysfunction found that the majority had no evidence of enteropathy [41]. A study of 53 patients with idiopathic neurologic disorders found that 57% had anti-gliadin antibodies, compared to 5% in the control group, suggesting that a significant percentage of neurologic dysfunction of unknown cause may be related to gluten [42]. Gluten ataxia, defined as ataxia in the presence of circulating anti-gliadin antibodies without an alternative etiology for the ataxia, is the most common neurologic manifestation of both celiac disease and NCGS [41]. A study of 43 patients with gluten ataxia found that use of a GFD for 1 year significantly improved symptoms in both patients with and without enteropathy. Yet, these findings are mitigated by the observations that the study was neither randomized nor blinded and that patients in the intervention group whose anti-gliadin antibodies remained positive were excluded from the analysis [43].

Gluten neuropathy, idiopathic neuropathy in the presence of anti-gliadin antibodies, is the second most common neurologic manifestation of both celiac disease and NCGS [41]. It most commonly initially manifests as a length-dependent sensorimotor peripheral neuropathy, but can also manifest as a sensory ganglionopathy or mononeuritis multiplex. A cross-sectional observational study of 60 patients with gluten neuropathy, the majority of whom did not have celiac disease, found that a strict GFD was associated with an 89% reduction in risk of peripheral neuropathic pain [44].

Similarly, gluten neuropathy patients receiving a GFD for 1 year improved as assessed by increased amplitude of sural sensory nerve action potential when compared to patients consuming a regular diet. Patients in the intervention group also more often reported subjective improvement in their symptoms. These findings remained significant after the 29% of patients with celiac disease were removed from the analysis [45]. These results must be interpreted with caution, though, given that the above study was neither randomized nor blinded.

Cognitive Dysfunction

There is little support for the popular belief in gluten's deleterious effects on cognitive function [46]. Transient cognitive symptoms, informally referred to as "brain fog," are commonly reported in both celiac disease and NCGS, yet remain poorly understood [47]. While researchers have examined this phenomenon in patients with celiac disease, we did not find any studies that deal specifically with cognitive dysfunction in NCGS patients. In a small pilot study, 11 patients with newly diagnosed celiac disease showed improved scores of cognitive tests of verbal fluency and attention after implementation of a GFD. These improvements strongly correlated with duodenal mucosal healing and tissue transglutaminase antibody levels [48]. That study was limited by its small sample size and lack of a control group. Additionally, a large population-based cohort study in Sweden found no increased risk of dementia among celiac disease patients compared to age- and gender-matched controls [49]. Whether the quantity of gluten intake correlates with risk of developing dementia in subjects with and without celiac disease remains to be studied. Further studies are needed to clarify the impact of gluten on cognition in patients with and without celiac disease.

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction, as well as restricted and repetitive patterns of behavior, interests, or activities [50]. ASD is very common, affecting 1 in 59 children in the USA, according to the most recent estimates by the Centers for Disease Control and Prevention [51]. Many parents of children with ASD use complementary and alternative medicine (CAM) therapies, including dietary supplements and restrictive diets. Twenty-eight percent of subjects in the Autism Speaks Autism Treatment Network patient registry reported using some form of CAM; 17% used special diets, approximately half of which were GF [52]. The use of GFDs in ASD stems from the hypothesis that autistic behavior is caused by the passage of inadequately metabolized gluten and casein (the main protein found in milk) through a "leaky gut" into the bloodstream and central nervous system, leading to excessive opioid-like activity and interference with signal transmission [53, 54]. More recent work has suggested a link between ASD and an immune response to gluten. Although ASD is not associated with biopsy-verified celiac disease, it is associated with positive anti-gliadin IgA and IgG serologies [55], with 20% of people with ASD having IgG antibodies to gliadin [56].

There have been several mostly small studies examining the effects of dietary gluten elimination on autistic symptoms. In line with the opioid-excess theory discussed above, the vast majority of these studies examined the gluten-free casein-free (GFCF) diet. The few studies that investigated the GFD without restrictions on casein were small, lacking controls, and showed mixed results. An early trial that placed seven children with ASD on a GFD for 6 months, without a control group, found no connection between gluten and autistic behavior [57]. Another uncontrolled study reported improvement in a number of behavioral measures, but no changes in the urinary peptides that are hypothesized to be the marker of gluten's activity in ASD [58]. More recently, a randomized controlled trial of 80 children with ASD found a significant decrease in gastrointestinal symptoms and a small, but statistically significant improvement in stereotyped behavior and communication among children in the GFD group [59]. However, as with many of the dietary studies in ASD, behavior and symptoms were assessed by parents who were not blinded to the intervention.

Randomized controlled trials of GFCF diets have also yielded mixed results. A small single-blind trial involving 20 children with ASD showed significant improvements in autistic traits, social isolation, and ability to communicate in the GFCF group [60]; a double-blind crossover trial with 15 children, however, revealed no significant difference between groups [61]. Three gluten/casein challenge trials, in which children already on GFCF diets were randomized to receive gluten/casein or placebo foods, showed no significant difference in behavior or gastrointestinal symptoms between groups [62–64]. All studies were relatively small, and there was substantial variation across trials in application of the GFCF diet (some provided education, while others provided the actual food), as well as in assessment of outcomes, with nearly a dozen different rating scales used. In sum, there is currently poor evidence for the use of GF and GFCF diets in ASD, as systematic reviews have also concluded [65–67].

Psychiatric Illness

A possible link between gluten ingestion and the development of psychiatric illness has interested researchers for over half a century [68]. The relationship between gluten and schizophrenia, a brain disorder characterized by

hallucinations, delusions, and disorganized speech and behavior, has been studied the most extensively [50]. Early evidence of a connection was derived from an ecological study conducted during World War II that observed a decrease in first-time hospitalizations for schizophrenia in women that was directly proportional to the reduction in wheat consumption [68]. While this could suggest a contribution of gluten to the development of schizophrenia, it is not hard to produce alternative explanations for why both grain consumption and psychiatric hospitalizations might decrease during wartime. More recently, patients with schizophrenia were found to have higher rates of positive anti-gliadin serologies than the general population, leading some to conclude that schizophrenia may be mediated by an immune response to gluten [69–71].

Several studies have evaluated the effects of a GFD on patients with schizophrenia. The first of these trials randomly assigned 102 male inpatients with schizophrenia to a cereal-free milk-free (CFMF) diet or a high-cereal (HC) diet in a non-blinded manner. After 7 days, 62% of patients in the CFMF arm had significant improvements, compared to 36% of patients in the HC arm [72]; after 90 days, 37% of patients in the CFMF group were discharged from the hospital, compared to 16% in the HC group [73]. In a 14-week double-blind placebo-controlled crossover trial, 14 inpatients with schizophrenia showed improvement in various measures of psychopathology when treated with antipsychotic medications and a CFMF diet. This therapeutic progress paused during a gluten challenge and then resumed when gluten was again removed from the diet [74]. Two gluten challenge trials revealed a heterogeneous response to gluten, with modest effects of gluten on the overall groups that were driven by more pronounced effects on a few individual patients [75, 76]. Yet other studies found no benefit of a GFD in schizophrenia [77–79]. Future studies should exclude patients with celiac disease and may consider anti-gliadin or tissue transglutaminase serologies in their analysis, as was done in two recent pilot studies [80, 81]. The larger of these studies, which followed 16 patients with schizophrenia and elevated anti-gliadin IgG antibodies, found improvement in several measured parameters among those randomized to a GFD during a 5-week observation period [81].

The relationship between gluten and depression has also been much studied, although the vast majority of studies were done in patients with celiac disease [82]. A double-blind crossover study of 22 subjects with self-reported gluten-sensitive IBS, in whom celiac disease was excluded, found that ingestion of gluten was associated with higher depression scores than placebo [83]. A similar result was found in another double-blind crossover trial that involved 61 subjects with NCGS [19]. While these studies suggest that a GFD may be beneficial for patients with depression in the absence of celiac disease, they may not be generalizable since they were both conducted in patients who had self-identified as being gluten-sensitive.

Disadvantages of a Gluten-Free Diet

When considering use of a GFD for conditions other than celiac disease, one must weigh the possibility of benefit against the potential for harm. Several studies have demonstrated that GFDs are often deficient in whole grains and fiber, micronutrients (e.g., vitamin D, vitamin B12, and folate), and minerals (e.g., iron, zinc, magnesium, and calcium) [84–86]. Additionally, GFDs may contain more sugar and saturated fat than their gluten-containing counterparts [86, 87]. Perhaps related to these differences in dietary composition, data from the Nurses' Health Study and Health Professionals Follow-Up Study, comprising over 200,000 people and 4 million person-years of follow-up, demonstrated an inverse relationship between gluten intake and the development of type 2 diabetes among people without celiac disease [88]. While gluten intake itself is not associated with the risk of coronary heart disease, avoidance of dietary gluten may result in decreased intake of whole grains, which carry cardiovascular benefits [89]. The analysis of data collected from NHANES revealed significantly higher urine levels of arsenic and blood levels of mercury, lead, and cadmium in people adhering to GFDs [90], likely as a consequence of GFDs often being rich in fish and rice, both of which can contain high concentrations of these heavy metals. Potential harms of the GFD extend beyond physical effects. Strict adherence to a GFD, as evidenced by mucosal healing in celiac disease patients, is associated with the development of anxiety [91]; "extreme vigilance" in avoiding gluten exposure is also associated with decreased self-rated quality-of-life [92].

Conclusion

GFDs have become increasingly popular in the past decade, with many claims that they offer benefits for people who do not have celiac disease. There is a large group of people who do not have celiac disease but experience symptoms after eating gluten-containing foods. While the entity known as NCGS is still not completely understood, current evidence from placebo-controlled gluten-challenge trials suggests that for a large proportion of these patients gluten itself is not the trigger of these symptoms; rather, they may be reacting to other components of wheat-containing foods, and some may be experiencing a "nocebo" effect. A GFD does not appear to enhance athletic performance, despite high-profile testimonials to the contrary. The effect of GFD on RA cannot be determined from current evidence because, in existing studies, the effect of gluten avoidance is confounded by the

concurrent avoidance of both meat and dairy products. In the absence of celiac disease, patients with gluten ataxia and gluten neuropathy, with elevated antibodies to gliadin, seem to benefit from GFDs, though supportive randomized blinded trials are scarce. Overall evidence for use of GFDs in ASD is poor quality, with mixed results reported from studies with notable biases. A possible positive effect of GFDs in patients with schizophrenia should be explored further, with attention paid to whether patients have celiac disease or other elevated non-celiac gluten-related serologies.

Compliance with ethical standards

Conflict of interest Benjamin Lebwohl serves as a consultant for Takeda and serves on the Advisory Board of Innovate Biopharmaceuticals. Peter HR Green serves on the advisory board of ImmusanT, ImmunogenX, and Innovate Biopharmaceuticals. Benjamin Lerner has no disclosures.

References

1. Lebwohl B, Ludvigsson JF, Green PH. Celiac disease and non-celiac gluten sensitivity. *BMJ*. 2015;351:h4347.
2. Choung RS, Unalp-Arida A, Ruhl CE, Brantner TL, Everhart JE, Murray JA. Less hidden celiac disease but increased gluten avoidance without a diagnosis in the United States: findings from the National Health and Nutrition Examination Surveys from 2009 to 2014. *Mayo Clin Proc*. 2016.
3. Laszkowska M, Shiwani H, Belluz J, et al. Socioeconomic vs health-related factors associated with google searches for gluten-free diet. *Clin Gastroenterol Hepatol*. 2018;16:295–297.
4. Brenan M. Most Americans Try to Eat Locally Grown Foods. https://news.gallup.com/poll/240515/americans-try-eat-locally-grown-foods.aspx. Updated August 7, 2018. Accessed March 2, 2019.
5. The Hartman Group. Health + Wellness 2017 Report. https://www.hartman-group.com/acumenPdfs/gluten-free-9_13_18.pdf. Updated September 13, 2018. Accessed March 2, 2019.
6. Lebwohl B, Sanders DS, Green PHR. Coeliac disease. *Lancet*. 2018;391:70–81.
7. Catassi C, Bai JC, Bonaz B, et al. Non-celiac gluten sensitivity: the new frontier of gluten related disorders. *Nutrients*. 2013;5:3839–3853.
8. Uhde M, Ajamian M, Caio G, et al. Intestinal cell damage and systemic immune activation in individuals reporting sensitivity to wheat in the absence of coeliac disease. *Gut*. 2016;65:1930–1937.
9. Tavakkoli A, Lewis SK, Tennyson CA, Lebwohl B, Green PH. Characteristics of patients who avoid wheat and/or gluten in the absence of Celiac disease. *Dig Dis Sci*. 2014;59:1255–1261.
10. Aziz I, Lewis NR, Hadjivassiliou M, et al. A UK study assessing the population prevalence of self-reported gluten sensitivity and referral characteristics to secondary care. *Eur J Gastroenterol Hepatol*. 2014;26:33–39.
11. Biesiekierski JR, Newnham ED, Irving PM, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol*. 2011;106:508–514. **quiz 15**.
12. Biesiekierski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. *Gastroenterology*. 2013;145:320–328. **e1-3**.
13. Vazquez-Roque MI, Camilleri M, Smyrk T, et al. A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. *Gastroenterology*. 2013;144:903–911. **e3**.
14. Catassi C, Elli L, Bonaz B, et al. Diagnosis of non-celiac gluten sensitivity (NCGS): the Salerno experts' criteria. *Nutrients*. 2015;7:4966–4977.
15. Elli L, Tomba C, Branchi F, et al. Evidence for the presence of non-celiac gluten sensitivity in patients with functional gastrointestinal symptoms: results from a multicenter randomized double-blind placebo-controlled gluten challenge. *Nutrients*. 2016;8:84.
16. Picarelli A, Borghini R, Di Tola M, et al. Intestinal, systemic, and oral gluten-related alterations in patients with nonceliac gluten sensitivity. *J Clin Gastroenterol*. 2016;50:849–858.
17. Shahbazkhani B, Sadeghi A, Malekzadeh R, et al. Non-celiac gluten sensitivity has narrowed the spectrum of irritable bowel syndrome: a double-blind randomized placebo-controlled trial. *Nutrients*. 2015;7:4542–4554.
18. Zanini B, Basche R, Ferraresi A, et al. Randomised clinical study: gluten challenge induces symptom recurrence in only a minority of patients who meet clinical criteria for non-coeliac gluten sensitivity. *Aliment Pharmacol Ther*. 2015;42:968–976.
19. Di Sabatino A, Volta U, Salvatore C, et al. Small amounts of gluten in subjects with suspected nonceliac gluten sensitivity: a randomized, double-blind, placebo-controlled, cross-over trial. *Clin Gastroenterol Hepatol*. 2015;13:1604–1612. **e3**.
20. Molina-Infante J, Carroccio A. Suspected nonceliac gluten sensitivity confirmed in few patients after gluten challenge in double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol*. 2017;15:339–348.
21. Lis DM, Stellingwerff T, Shing CM, Ahuja KD, Fell JW. Exploring the popularity, experiences, and beliefs surrounding gluten-free diets in nonceliac athletes. *Int J Sport Nutr Exerc Metab*. 2015;25:37–45.
22. Djokovic N. *Serve to Win: The 14-Day Gluten-Free Plan for Physical and Mental Excellence*. New York: Zinc Ink; 2013.
23. Lis D, Stellingwerff T, Kitic CM, Ahuja KD, Fell J. No effects of a short-term gluten-free diet on performance in nonceliac athletes. *Med Sci Sports Exerc*. 2015;47:2563–2570.
24. Halson SL, Martin DT. Lying to win-placebos and sport science. *Int J Sports Physiol Perform*. 2013;8:597–599.
25. Lis DM, Fell JW, Ahuja KD, Kitic CM, Stellingwerff T. Commercial hype versus reality: our current scientific understanding of gluten and athletic performance. *Curr Sports Med Rep*. 2016;15:262–268.
26. Beedie C, Foad A, Hurst P. Capitalizing on the placebo component of treatments. *Curr Sports Med Rep*. 2015;14:284–287.
27. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388:2023–2038.
28. Hagen KB, Byfuglien MG, Falzon L, Olsen SU, Smedslund G. Dietary interventions for rheumatoid arthritis. *Cochrane Database Syst Rev*. 2009;1:CD006400.
29. Koning F, Thomas R, Rossjohn J, Toes RE. Coeliac disease and rheumatoid arthritis: similar mechanisms, different antigens. *Nat Rev Rheumatol*. 2015;11:450–461.
30. Paimela L, Kurki P, Leirisalo-Repo M, Piirainen H. Gliadin immune reactivity in patients with rheumatoid arthritis. *Clin Exp Rheumatol*. 1995;13:603–607.
31. O'Farrelly C, Marten D, Melcher D, et al. Association between villous atrophy in rheumatoid arthritis and a rheumatoid factor and gliadin-specific IgG. *Lancet*. 1988;2:819–822.

32. Kjeldsen-Kragh J, Haugen M, Borchgrevink CF, et al. Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. *Lancet*. 1991;338:899–902.
33. Hafstrom I, Ringertz B, Spangberg A, et al. A vegan diet free of gluten improves the signs and symptoms of rheumatoid arthritis: the effects on arthritis correlate with a reduction in antibodies to food antigens. *Rheumatology (Oxford)*. 2001;40:1175–1179.
34. Elkan AC, Sjoberg B, Kolsrud B, Ringertz B, Hafstrom I, Frostegard J. Gluten-free vegan diet induces decreased LDL and oxidized LDL levels and raised atheroprotective natural antibodies against phosphorylcholine in patients with rheumatoid arthritis: a randomized study. *Arthritis Res Ther*. 2008;10:R34.
35. Solomon DH, Karlson EW, Rimm EB, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation*. 2003;107:1303–1307.
36. Wang F, Zheng J, Yang B, Jiang J, Fu Y, Li D. Effects of vegetarian diets on blood lipids: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2015;4:e002408.
37. Brar P, Kwon GY, Holleran S, et al. Change in lipid profile in celiac disease: beneficial effect of gluten-free diet. *Am J Med*. 2006;119:786–790.
38. Leffler DA, Green PH, Fasano A. Extraintestinal manifestations of coeliac disease. *Nat Rev Gastroenterol Hepatol*. 2015;12:561–571.
39. Mearns ES, Taylor A, Thomas Craig KJ, et al. Neurological manifestations of neuropathy and ataxia in celiac disease: a systematic review. *Nutrients*. 2019;11:380.
40. Vinagre-Aragon A, Zis P, Grunewald RA, Hadjivassiliou M. Movement disorders related to gluten sensitivity: a systematic review. *Nutrients.* 2018;10:1034.
41. Hadjivassiliou M, Rao DG, Grinewald RA, et al. Neurological dysfunction in coeliac disease and non-coeliac gluten sensitivity. *Am J Gastroenterol*. 2016;111:561–567.
42. Hadjivassiliou M, Gibson A, Davies-Jones GA, Lobo AJ, Stephenson TJ, Milford-Ward A. Does cryptic gluten sensitivity play a part in neurological illness? *Lancet*. 1996;347:369–371.
43. Hadjivassiliou M, Davies-Jones GA, Sanders DS, Grunewald RA. Dietary treatment of gluten ataxia. *J Neurol Neurosurg Psychiatry*. 2003;74:1221–1224.
44. Zis P, Sarrigiannis PG, Rao DG, Hadjivassiliou M. Gluten neuropathy: prevalence of neuropathic pain and the role of gluten-free diet. *J Neurol*. 2018;265:2231–2236.
45. Hadjivassiliou M, Kandler RH, Chattopadhyay AK, et al. Dietary treatment of gluten neuropathy. *Muscle Nerve*. 2006;34:762–766.
46. Perlmutter D, Loberg K. *Grain Brain: The Surprising Truth About Wheat, Carbs, and Sugar–Your Brain's Silent Killers*. New York: Little, Brown & Company; 2013.
47. Yelland GW. Gluten-induced cognitive impairment ("brain fog") in coeliac disease. *J Gastroenterol Hepatol*. 2017;32:90–93.
48. Lichtwark IT, Newnham ED, Robinson SR, et al. Cognitive impairment in coeliac disease improves on a gluten-free diet and correlates with histological and serological indices of disease severity. *Aliment Pharmacol Ther*. 2014;40:160–170.
49. Lebwohl B, Luchsinger JA, Freedberg DE, Green PH, Ludvigsson JF. Risk of dementia in patients with celiac disease: a population-based cohort study. *J Alzheimers Dis*. 2016;49:179–185.
50. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (5th ed)*. Arlington, VA; 2013.
51. Baio J, Wiggins L, Christensen DL, et al. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 Sites, United States, 2014. *MMWR Surveill Summ*. 2018;67:1–23.
52. Perrin JM, Coury DL, Hyman SL, Cole L, Reynolds AM, Clemons T. Complementary and alternative medicine use in a large pediatric autism sample. *Pediatrics*. 2012;130:S77–S82.
53. Reichelt KL. Gluten-free diet in infantile autism. *Tidsskr Nor Laegeforen*. 1991;111:1286–1287.
54. Whiteley P, Shattock P, Knivsberg AM, et al. Gluten- and casein-free dietary intervention for autism spectrum conditions. *Front Hum Neurosci*. 2012;6:344.
55. Ludvigsson JF, Reichenberg A, Hultman CM, Murray JA. A nationwide study of the association between celiac disease and the risk of autistic spectrum disorders. *JAMA Psychiatry*. 2013;70:1224–1230.
56. Lau NM, Green PH, Taylor AK, et al. Markers of celiac disease and gluten sensitivity in children with autism. *PLoS ONE*. 2013;8:e66155.
57. Sponheim E. Gluten-free diet in infantile autism. A therapeutic trial. *Tidsskr Nor Laegeforen*. 1991;111:704–707.
58. Whiteley P, Rodgers J, Savery D, Shattock P. A gluten-free diet as an intervention for autism and associated spectrum disorders: preliminary findings. *Autism*. 1999;3:45–65.
59. Ghalichi F, Ghaemmaghami J, Malek A, Ostadrahimi A. Effect of gluten free diet on gastrointestinal and behavioral indices for children with autism spectrum disorders: a randomized clinical trial. *World J Pediatr*. 2016;12:436–442.
60. Knivsberg AM, Reichelt KL, Hoien T, Nodland M. A randomised, controlled study of dietary intervention in autistic syndromes. *Nutr Neurosci*. 2002;5:251–261.
61. Elder JH, Shankar M, Shuster J, Theriaque D, Burns S, Sherrill L. The gluten-free, casein-free diet in autism: results of a preliminary double blind clinical trial. *J Autism Dev Disord*. 2006;36:413–420.
62. Hyman SL, Stewart PA, Foley J, et al. The gluten-free/casein-free diet: a double-blind challenge trial in children with autism. *J Autism Dev Disord*. 2016;46:205–220.
63. Navarro F, Pearson DA, Fatheree N, Mansour R, Hashmi SS, Rhoads JM. Are 'leaky gut' and behavior associated with gluten and dairy containing diet in children with autism spectrum disorders? *Nutr Neurosci*. 2015;18:177–185.
64. Pusponegoro HD, Ismael S, Firmansyah A, Sastroasmoro S, Vandenplas Y. Gluten and casein supplementation does not increase symptoms in children with autism spectrum disorder. *Acta Paediatr*. 2015;104:e500–e505.
65. Sathe N, Andrews JC, McPheeters ML, Warren ZE. Nutritional and dietary interventions for autism spectrum disorder: a systematic review. *Pediatrics*. 2017;139:e20170346.
66. Millward C, Ferriter M, Calver S, Connell-Jones G. Gluten- and casein-free diets for autistic spectrum disorder. *Cochrane Database Syst Rev*. 2008;2:CD003498.
67. Piwowarczyk A, Horvath A, Lukasik J, Pisula E, Szajewska H. Gluten- and casein-free diet and autism spectrum disorders in children: a systematic review. *Eur J Nutr*. 2018;57:433–440.
68. Dohan FC. Wheat "consumption" and hospital admissions for schizophrenia during World War II. A preliminary report. *Am J Clin Nutr*. 1966;18:7–10.
69. Cascella NG, Kryszak D, Bhatti B, et al. Prevalence of celiac disease and gluten sensitivity in the United States clinical antipsychotic trials of intervention effectiveness study population. *Schizophr Bull*. 2011;37:94–100.
70. Dickerson F, Stallings C, Origoni A, et al. Markers of gluten sensitivity and celiac disease in recent-onset psychosis and multi-episode schizophrenia. *Biol Psychiatry*. 2010;68:100–104.
71. Samaroo D, Dickerson F, Kasarda DD, et al. Novel immune response to gluten in individuals with schizophrenia. *Schizophr Res*. 2010;118:248–255.
72. Dohan FC, Grasberger JC, Lowell FM, Johnston HT Jr, Arbegast AW. Relapsed schizophrenics: more rapid improvement on a milk- and cereal-free diet. *Br J Psychiatry*. 1969;115:595–596.
73. Dohan FC, Grasberger JC. Relapsed schizophrenics: earlier discharge from the hospital after cereal-free, milk-free diet. *Am J Psychiatry*. 1973;130:685–688.

74. Singh MM, Kay SR. Wheat gluten as a pathogenic factor in schizophrenia. *Science*. 1976;191:401–402.
75. Rice JR, Ham CH, Gore WE. Another look at gluten in schizophrenia. *Am J Psychiatry*. 1978;135:1417–1418.
76. Vlissides DN, Venulet A, Jenner FA. A double-blind gluten-free/gluten-load controlled trial in a secure ward population. *Br J Psychiatry*. 1986;148:447–452.
77. Potkin SG, Weinberger D, Kleinman J, et al. Wheat gluten challenge in schizophrenic patients. *Am J Psychiatry*. 1981;138:1208–1211.
78. Storms LH, Clopton JM, Wright C. Effects of gluten on schizophrenics. *Arch Gen Psychiatry*. 1982;39:323–327.
79. Osborne M, Crayton JW, Javaid J, Davis JM. Lack of effect of a gluten-free diet on neuroleptic blood levels in schizophrenic patients. *Biol Psychiatry*. 1982;17:627–629.
80. Jackson J, Eaton W, Cascella N, et al. A gluten-free diet in people with schizophrenia and anti-tissue transglutaminase or anti-gliadin antibodies. *Schizophr Res*. 2012;140:262–263.
81. Kelly DL, Demyanovich HK, Rodriguez KM, et al. Randomized controlled trial of a gluten-free diet in patients with schizophrenia positive for antigliadin antibodies (AGA IgG): a pilot feasibility study. *J Psychiatry Neurosci*. 2019;44:1–9.
82. Busby E, Bold J, Fellows L, Rostami K. Mood disorders and gluten: it's not all in your mind! A systematic review with meta-analysis. *Nutrients*. 2018;10:1708.
83. Peters SL, Biesiekierski JR, Yelland GW, Muir JG, Gibson PR. Randomised clinical trial: gluten may cause depression in subjects with non-coeliac gluten sensitivity—an exploratory clinical study. *Aliment Pharmacol Ther*. 2014;39:1104–1112.
84. Martin J, Geisel T, Maresch C, Krieger K, Stein J. Inadequate nutrient intake in patients with celiac disease: results from a German dietary survey. *Digestion*. 2013;87:240–246.
85. Vici G, Belli L, Biondi M, Polzonetti V. Gluten free diet and nutrient deficiencies: a review. *Clin Nutr*. 2016;35:1236–1241.
86. Wild D, Robins GG, Burley VJ, Howdle PD. Evidence of high sugar intake, and low fibre and mineral intake, in the gluten-free diet. *Aliment Pharmacol Ther*. 2010;32:573–581.
87. Ohlund K, Olsson C, Hernell O, Ohlund I. Dietary shortcomings in children on a gluten-free diet. *J Hum Nutr Diet*. 2010;23:294–300.
88. Zong G, Lebwohl B, Hu FB, et al. Gluten intake and risk of type 2 diabetes in three large prospective cohort studies of US men and women. *Diabetologia*. 2018;61:2164–2173.
89. Lebwohl B, Cao Y, Zong G, et al. Long term gluten consumption in adults without celiac disease and risk of coronary heart disease: prospective cohort study. *BMJ*. 2017;357:j1892.
90. Raehsler SL, Choung RS, Marietta EV, Murray JA. Accumulation of heavy metals in people on a gluten-free diet. *Clin Gastroenterol Hepatol*. 2018;16:244–251.
91. Ludvigsson JF, Lebwohl B, Chen Q, et al. Anxiety after coeliac disease diagnosis predicts mucosal healing: a population-based study. *Aliment Pharmacol Ther*. 2018;48:1091–1098.
92. Wolf RL, Lebwohl B, Lee AR, et al. Hypervigilance to a gluten-free diet and decreased quality of life in teenagers and adults with celiac disease. *Dig Dis Sci*. 2018;63:1438–1448.