States, the reported retail cost of fluticasone at 500 μg per day (half the dose used in this study) is $194 per month.[10]

The investigators report a hazard ratio for exacerbations of 1.05 among patients who stopped taking glucocorticoids, as compared with those who continued the glucocorticoid regimen. The upper bound of the confidence interval was within the prespecified range of noninferiority for glucocorticoid withdrawal. Similar results were seen in a variety of subgroup analyses and support the hypothesis that the withdrawal of glucocorticoids in patients receiving therapy with LABAs and LAMAs does not result in an increased risk of exacerbation. Patients in the glucocorticoid-withdrawal group had small reductions in the FEV_1 and in measures of health-related quality of life, although the clinical importance of these changes is not clear. As the authors state, the trial leaves some questions unanswered. Is it necessary to taper the glucocorticoid dose or could one-step withdrawal provide the same results? Is a period of 6 weeks of maximal therapy required before glucocorticoid withdrawal?

The results of this trial, taken together with the findings of other studies, suggest that the rationale for continuing glucocorticoid therapy in patients who are also taking long-acting bronchodilators should be based on symptomatic improvement attributable to the glucocorticoid rather on the prevention of exacerbations. They also show that a trial of glucocorticoid withdrawal will not increase the risk of exacerbation, even in patients with severe COPD. The findings may prompt clinicians to consider other preventive interventions, such as daily azithromycin, in patients who continue to have frequent exacerbations while receiving long-acting bronchodilators.[11]

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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The Missing Environmental Factor in Celiac Disease

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"How can I protect my child from the development of celiac disease?" Parents and parents-to-be frequently ask this question when a family member has this condition. Until now, many clinicians have recommended the administration of small amounts of gluten during the "window of opportunity" — at 4 to 6 months of age — preferably while maintaining breast-feeding. This advice was based on experience from the Swedish celiac disease epidemic, in which a large increase in the prevalence of the disease among infants was attributed to earlier introduction of gluten,[1] as well as on U.S. data indicating that the introduction of gluten at 4 to 6 months may reduce the risk of celiac disease autoimmunity.[2]

In this issue of the *Journal*, two articles examine the risk of celiac disease among children who were randomly assigned to the introduction of gluten at 4 to 6 months of age (in the Prevent Coeliac Disease [PreventCD] clinical trial reported by Vriezinga et al.[3]) or at 6 months or 12 months of age (in the Risk of Celiac Disease and Age at Gluten Introduction [CELIPREV] clinical trial reported by Lionetti et al.[4]). Although these studies ultimately have the same aim — to define whether early or late introduction of gluten could reduce the risk of celiac disease — they differ on important points and yield slightly different information. However, their main findings do agree. First, the timing of introduction of gluten in high-risk children does not appear to influence the development of celiac disease in childhood. Second, there is no evidence that the duration of breast-feeding or the maintenance of breast-feeding when gluten is introduced influences the risk of celiac disease later in life. Finally, the only identified risk factor for celiac disease later in life is the HLA genotype.

Although the lack of an association between the timing of introduction of gluten, the duration of breast-feeding, and clinically diagnosed celiac disease later in life has been reported previously,[5] the current studies show that this association is also lacking in screening-detected celiac disease and celiac disease autoimmunity. We believe the studies in this issue of the *Journal* will change the conceptual landscape of celiac disease. From now on, it will be hard for anyone to continue to recommend the introduction of gluten specifically at the age of 4 to 6 months, since Vriezinga et al. did not find that exposure to gluten at this age decreased the risk of celiac disease, and Lionetti et al. in fact found a delay in the development of celiac disease in children who were first exposed to gluten at the age of 12 months. The researchers also did not find any evidence that breast-feeding, the duration of breast-feeding, or the introduction of gluten during breast-feeding influenced later development of celiac disease. Although we recognize the overall importance of breast-feeding for child health, breast-feeding does not appear to protect against celiac disease in children. Establishing the HLA-DQ2 and HLA-DQ8 status of an infant who is at risk for celiac disease may be important, however, since this status determines whether a risk of celiac disease exists.[6]

What is the reason for the striking increase in the incidence of celiac disease over recent decades in Finland, the United States, and the United Kingdom? The presence of the necessary HLA risk variants (in >25% of persons in the Western world, as reported by Vriezinga et al.) has not changed, nor has the gluten content of wheat flour[7] that is consumed by 99% of people who eat wheat. Other environmental factors must be contributing to the fact that celiac disease develops in only 1% of the global population and that this percentage has increased by a factor of 4 or 5 over a period of 50 years.[8] Although relative risks have tended to be small, the other factors implicated in the pathogenesis of celiac disease include elective cesarean section, perinatal and childhood infections, and the use of antibiotics and proton-pump inhibitors.[9] Some of these factors implicate changes in the microbiome.

Another factor that has so far received little attention is "vital wheat gluten." This form of gluten processed from wheat flour is increasingly used in the preparation of baked goods and processed foods. It was investigated in the PreventCD study, and although that study showed negative results, the role of vital gluten needs to be explored further. Of note, the amount of gluten administered to the children in the study was very low (about 2 to 3% of the amount of gluten in a slice of bread).

Finally, both of the current studies looked at celiac disease confirmed by means of antibody levels and small-bowel biopsy. In the past few years, "non-celiac gluten sensitivity"[10] has become increasingly recognized, and researchers are just beginning to define this entity. It is important to acknowledge that research on risk factors in celiac disease cannot be extrapolated to persons with non-celiac gluten sensitivity.

Although these two trials increase our knowledge of celiac disease and are likely to alter the treatment of children who are at increased risk, they are the beginning rather than the end of research in this field.

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