atrophy are not clear. This may relate to variable compliance but no data regarding dietary compliance were collected. In selecting symptomatic patients, this may have also selected a more severe phenotype although the correlation between gastrointestinal symptoms and clinical phenotype is debatable.[7] This is further reinforced by the present study where some symptoms were inversely associated with villus atrophy. The second point is the question of refractory coeliac disease (RCD). Based on current definitions, up to two-thirds of the recruited participants would be defined as having refractory coeliac disease – a condition reported to be uncommon.[8] This might be interpreted as cause for alarm, but a more pragmatic interpretation would be that the existing definitions of RCD need to be interpreted with caution.

The authors have provided important insights into associations with villus atrophy which might allow clinicians to target specific groups for more intensive endoscopic follow-up. The study also highlights shortcomings of current definitions of refractory coeliac disease which can increase patient anxiety. Ideally, similar large scale studies should be prospective in design, collect thorough data on dietary adherence, and assess both long-term disease outcomes and markers of refractory coeliac disease such as T-cell receptor clonality.

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Editorial: risk factors for persistent villus atrophy in coeliac disease – is it time to reconsider definitions for refractory coeliac disease? Authors' reply

S. Mahadev* , J. A. Murray†, P. H. R. Green*, D. A. Adelman‡ & B. Lebwohl*

*Celiac Disease Center, Columbia University College of Physicians and Surgeons, New York, NY, USA.
†Division of Gastroenterology and Hepatology, The Mayo Clinic, Rochester, MN, USA.
‡Division of Allergy/Immunology, Department of Medicine, University of California, San Francisco, CA, USA.
E-mail: dadelman57@gmail.com

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Sirs, We appreciate the invited comments from Braude and Newnham,[1] who raise the question of whether a sizeable proportion of participants in the present study might meet the criteria for refractory coeliac disease (RCD).[2] The current established definition of RCD requires the presence of malabsorptive symptoms despite strict adherence to a gluten-free diet for 6–12 months, following exclusion of other causes of nonresponsive coeliac disease.[3]

Although all subjects had persistent symptoms, and 38% had persistent villus atrophy, most would probably not meet the criteria to support a diagnosis of RCD. First, a broad variety of symptoms were reported among participants that were not suggestive of malabsorption, which is required for RCD. Second, the diagnosis of RCD requires systematic exclusion of alternative aetiologies, including persistent gluten exposure, bacterial overgrowth, irritable bowel syndrome, and other food intolerances. Study subjects were recruited from a variety of settings and it is not known whether they were under the care of a coeliac specialist or dietitian to guide this workup. Most importantly – as Braude and Newnham note – RCD requires confirmation of a strict gluten-free diet, and dietitian assessment was not performed in this trial. Our previous studies demonstrated that the

majority of coeliac disease patients are not followed regularly by a dietitian, nor undergo follow-up care according to guidelines.[4, 5] The fact that 40% of patients with persistent villus atrophy in the cohort had positive coeliac disease serologies is suggestive of ongoing inadvertent gluten exposure. Indeed, the aim of this trial was to test a gluten endopeptidase/endoprotease medication which, taken with meals, would treat symptoms and histological damage induced by inadvertent gluten ingestion.[6] In the underlying trial, restoration of villus architecture was seen over the course of the study in the majority of patients, including those with the most severe histological injury, making RCD an unlikely explanation.

While aspects of our study limit our ability to infer the causes of the persistent villus atrophy and nonresponsive coeliac disease seen, we believe the population reflects a 'real-world' experience of patients who fail to respond despite attempts at adherence to the gluten-free diet.

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