Reply. We thank Drs Siah and Gwee for their interest in our study, in which we reported an exploratory factor analysis of Rome IV symptoms (Clevers et al[1]), which we refer to as the Rome IV exploratory model (R4EM) similar to Siah and Gwee. The Rome IV consensus uses an anatomic basis to subdivide

Table 1. Comparison of the Rome IV, AFGID, and R4EM Symptom Factors in Adults

	Rome IV	AFGID	R4EM
Esophageal	A1. Chest pain A2. Functional heartburn A3. Reflux hypersensitivity	Chest pain and heartburn	Chest pain and heartburn
	A4. Globus A5. Functional dysphagia	Globus, dysphagia, odynophagia	Globus, dysphagia, odynophagia
Gastroduodenal	B1a. Postprandial Distress Syndrome (PDS) B1b. Epigastric Pain Syndrome (EPS) B2a. Gastric belching B2b. Esophageal belching		Upper abdominal symptoms
	B3a. Chronic nausea, vomiting B3b. Cyclic vomiting B3c. Cannabinoid hyperemesis B4. Rumination	Regurgitation, nausea, vomiting	Nausea, vomiting
Bowel	C1. IBS C3. Diarrhea C2. Constipation C4. Bloating, distension	Abdominal pain with diarrhea	IBS Diarrhea Constipation
Pain	D. Abdominal pain		Abdominal pain
Outside Rome IV		Meal-related bowel symptoms Upper abdominal pain with constipation Bloating, fullness, belching, flatulence	

IBS, irritable bowel syndrome.

functional gastrointestinal disorders (Table 1). In their Letter to the Editor,[2] Drs Siah and Gwee made 2 points. First, they stated that R4EM did not quite mirror the Rome IV diagnostic classification. Although we agree that not all disorders defined in Rome IV were captured by the exploratory factor analysis in R4EM, our confirmatory factor analysis showed empirically that agreement with the Rome IV diagnostic classification in R4EM was quite good (Table 1). R4EM thus largely reinforces the Rome IV criteria and their use in research and clinical care.

Second, Siah and Gwee highlight similarities between R4EM and an Asian Rome III factor analysis by Siah et al (Asian Functional Gastrointestinal Disorder [AFGID] Symptom Clusters).[3] We agree that both studies share important similarities. For instance, both identified a globus/dysphagia factor, a heartburn/chest pain factor, and a nausea/vomiting factor (Table 1). The main findings of AFGID were symptom factors characterized by upper abdominal symptoms, associated with bowel function. This type of overlapping conditions is not considered in the Rome consensus and its predominantly anatomic subdivision. The question is how specific this is to the questionnaire used in AFGID and symptom expressions or perceptions in Asia, or whether this is an inherent flaw in the Rome approach.[4]

Drs Siah and Gwee argue that overlap between upper- and lower-tract symptoms also is present in R4EM because loose stools after a meal was part of the diarrhea factor in our analysis. However, this refers to the timing of bowel symptoms in relation to an upper gastrointestinal event (meal intake), rather than location of bowel-associated symptoms in the upper abdomen. The occurrence of bowel symptoms in relation to a meal is not novel and is well established in the literature.[5,6]

The current R4EM analyses found that the lower GI symptoms were not significantly associated with upper GI symptom locations, and vice versa, as shown in Table 1. Hence, taken together, the R4EM adheres most closely to the Rome IV consensus and differs more significantly from the AFGID findings.

However, although factor analysis is a useful tool to validate the Rome questionnaire, this type of analysis is also sensitive to wording and content of questions and various statistical choices, and should be interpreted critically. When comparing the findings of AFGID and R4EM, one needs to take into account that AFGID was conducted in patients presenting to gastroenterology clinics, which may already account for some of the differences. In addition, R4EM used the Rome IV questionnaire, and, hence, confirming categories close to the Rome IV criteria should not come as a surprise. The AFGID questionnaire was based on the Rome III consensus, but adapted and expanded, taking into account Asian languages, culture, and symptom expressions.[3] Because these adaptations were not performed in R4EM, the current analysis cannot deny the relevance of these adaptations.

We are highly appreciative of the contribution of Drs Siah and Gwee, and colleagues in their AFGID report and in the current letter.[2,3] It is also our opinion that the Rome questionnaire, enriched with the questions and concepts as used in AFGID, should be used in a large population of patients (and perhaps the general population) in the West, to determine whether or not the overlapping factors also are found in this part of the world, which would be a major step ahead in

developing a universal symptom analysis and categorization system. Meanwhile, in the West, the Rome IV subdivision seems to have a solid basis for current use in clinical practice and research, while we continue research to increase our knowledge and insights. The Rome Foundation will soon publish the results of a 32-country global epidemiologic study including 8 countries from Asia. Although that study's questionnaire was not enriched with the questions and concepts used in AFGID as discussed earlier, it will provide an excellent opportunity to look further into potential differences between East and West based on the Rome IV diagnostic questionnaire and many potentially associated factors that might explain some of the differences, if found.

EGBERT CLEVERS, PhD
Translational Research Center for Gastrointestinal Disorders
University of Leuven
Leuven, Belgium

Department of Internal Medicine and Clinical Nutrition, Institute of Medicine
Sahlgrenska Academy, University of Gothenburg
Gothenburg, Sweden

WILLIAM E. WHITEHEAD, PhD
OLAFUR S. PALSSON, PhD
Center for Functional Gastrointestinal and Motility Disorders
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

AMI D. SPERBER, MD
Faculty of Health Sciences,
Ben-Gurion University of the Negev
Beer-Sheva, Israel

HANS TÖRNBLOM, MD
Department of Internal Medicine and Clinical Nutrition, Institute of Medicine
Sahlgrenska Academy, University of Gothenburg
Gothenburg, Sweden

LUKAS VAN OUDENHOVE, MD
JAN TACK, MD
Translational Research Center for Gastrointestinal Disorders
University of Leuven
Leuven, Belgium

MAGNUS SIMRÉN, MD
Department of Internal Medicine and Clinical Nutrition, Institute of Medicine
Sahlgrenska Academy, University of Gothenburg
Gothenburg, Sweden

Center for Functional Gastrointestinal and Motility Disorders
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

References

1. Clevers E, et al. Clin Gastroenterol Hepatol 2018;16:1252–1259.e5.
2. Siah KTH, et al. Clin Gastroenterol Hepatol 2018. Epub ahead of print.
3. Siah KTH, et al. Gut 2018;67:1071–1077.
4. Holtmann GJ, et al. Gut 2018;67:1911–1915.
5. Posserud I, et al. United Eur Gastroenterol J 2013;1:358–367.
6. Van Oudenhove L, et al. Gastroenterology 2016;150:866–874.

Conflicts of interest
The authors disclose no conflicts.