From bugs to buttermilk
Feenstra, Ettje

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Summary

The research described in this thesis is aimed at the characterization of gut health. The definition for gut health is indistinct and impeded by the multiple domains that it encompasses. The base definition for gut health used in this work includes the five major criteria proposed by Bischoff (2011, BMC Medicine): effective digestion and absorption of food, absence of gastrointestinal (GI) illness, normal and stable microbiota, an effective immune status, and a general state of wellbeing (“quality of life” (QoL)). The results from this thesis focus on expanding our knowledge on aspects of gut microbiota composition, food intake, and biomarkers, as well as quality of life and the associations of these aspects and parameters to gut health.

Chapter 1 describes the LifeLines DEEP (LLD) cohort (n=1539) that was used for measuring gut health. LLD is a subgroup taken from the general population cohort LifeLines. Detailed methods of information and biosample collection are described as well as the study population’s basic characteristics. Moreover, we defined a standardized procedure for collecting stool (feces). We found that 34.8% (n=409) of the LLD participants reported gastrointestinal complaints associated with functional GI disorders (FGIDs), including 21% (n=249) participants who fulfilled the Rome III criteria for irritable bowel syndrome (IBS).

The next four chapters (chapters 2-5) focus on different aspects of the gut microbiome and its association to gut health. In chapter 2 we explore the concurrent development of the fields of genetics and microbiome analysis and their rapid technical advances in the past 20 years. This chapter also discusses the role of gut microbiota in immune homeostasis and autoimmunity. Chapters 3 and 4 give insights into the biological and environmental factors that are associated with microbiota composition. Chapter 3 describes the association between gut microbiota composition and stool consistency in 1126 LLD participants. We observed significant associations of stool consistency with 67 intestinal bacteria, for example, more loose stools were positively associated with *Faecalibacterium prausnitzii* and negatively associated with members of the *Clostridia* class. These results show that stool consistency is one of the factors that interact with the gut bacteria, and this highlights the need for careful registration of these factors in microbiota-related research. Chapter 4 reports the largest metagenomic profiling study so far of the association between microbiota composition and 207 environmental and intrinsic factors in 1135 LLD individuals. We describe 126 associations with dietary factors (n=60), diseases (n=12), medication (n=19), smoking (n=4) and host characteristics (n=31), together explaining 18.7% of the variation in gut microbiota composition. We thus identified important factors that play a role in shaping the gut microbiota, and discovered the role of chromogranin A as a marker for gut health. In chapter 5 the changes in microbiota composition occurring before, during and after a four-week, gluten-free diet intervention are described. We found that gut microbiota are stable over a period of three months, and that inter-individual differences are larger than the differences that could be introduced by changes in diet. Moreover, we saw that a change in dietary gluten content induced changes in gut microbial pathway activities.
This thesis further describes the associations between food intake and GI complaints (chapters 6 and 6.1). In **Chapter 6** we compare habitual dietary intake in 194 IBS patients to that of 186 healthy controls from the Maastricht IBS cohort (MIBS). Habitual dietary intake, the extent to which the diet adhered to the Dutch nutritional guidelines ("nutritional adequacy") and the association between GI symptoms and food intake were assessed. We observed differences in dietary intake between IBS cases and controls, for example, IBS-patients had a lower intake of fiber, fructose and pasta. We also found a lower score for nutritional adequacy in IBS patients versus controls and observed associations between specific food products and GI symptoms.

**Chapter 6.1** describes the cross-sectional analysis of habitual dietary intake in participants with (n=381) and without (n=717) GI symptoms from the LLD cohort and compares it to the results of food intake in clinically diagnosed IBS patients from MIBS (chapter 6). We observed differences between participants with and without gastrointestinal complaints, for example, in the higher intake of meat and lower intake of dairy products in persons with GI complaints, but also found large differences between subgroups of FGID patients. From this work it became evident that attention should be paid to the nutritional adequacy of the diet in persons with GI symptoms and that IBS-patients may benefit from individual nutritional guidance. A person’s beliefs about foods that trigger their GI symptoms and their perceived food intolerances are also important aspects that need to be taken into account in studies looking at gut health.

The association between overall wellbeing and gut health was studied in **Chapter 7**, in which we compared the quality of life in patients with a range of gastrointestinal symptoms to controls, using the LLD and MIBS cohorts. We found a clear link between the severity of GI symptoms and gut health, as we observed the lowest quality of life in clinically diagnosed patients, who on average had more severe GI symptoms, followed by population patients with often milder GI symptoms. The highest quality of life scores were reported by healthy controls. In **Chapter 7.1** we explored the association between quality of life and genetics, and found suggestive associations with 60 SNPs linked to mental health and 53 SNPs linked to physical health. These associations need to be replicated in future research.

In **Chapter 8** we aimed to develop a panel of biomarkers to discriminate between IBS patients and healthy controls. From 43 biomarker candidates, we selected and measured the 15 with the highest potential based on our literature search and expert discussions. Using statistical analysis we identified a panel of eight biomarkers (i.e. IL-1β, IL-6, IL-12, TNFα, chromogranin A, human β-defensin 2, calprotectin, caproate) that best discriminated between IBS patients and controls, with 88.1% sensitivity and 86.5% specificity, in a clinical cohort (MIBS). Moreover, the biomarker panel was found to correlate moderately with the severity of GI symptoms.

Finally, **Chapter 9** presents reflections on the main findings of this thesis and places them in a broader perspective. Some recommendations for future research are also made.