Diplomarbeit

The influence of a multispecies probiotic on the health-related quality of life in patients undergoing long term proton pump inhibitor therapy

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Markus Steinwender

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unter der Anleitung von

Assoz.Prof. Priv.-Doz. Dr.med.univ. Vanessa Stadlbauer-Köllner

und

Mag.rer.nat. Angela Horvath, PhD

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AFFIDAVIT

I hereby declare that the present diploma thesis and the work reported herein was originated and composed entirely by myself and without any assistance from third parties. Furthermore, I confirm that no other sources than those indicated in the text have been used in the preparation of this diploma thesis. Finally, I declare that I have no conflict of interests.

Graz, 24.06.2020 *Markus Steinwender eh*

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Zusammenfassung

Der Einfluss eines multispecies Probiotikums auf die gesundheitsbezogene Lebensqualität von PatientInnen unter Langzeit PPI Therapie

Hintergrund

Protonen Pumpen Hemmer (PPIs) sind weltweit häufig eingenommene Medikamente. Aber auch sie zeigen Nebenwirkungen, wie zum Beispiel Veränderungen im Darm-Mikrobiom. Solche wurden mit intra- und extra-intestinalen Erkrankungen in Verbindung gebracht, worunter in weiterer Folge die Lebensqualität leidet. Diese Studie zielt darauf ab herauszufinden, ob die Einnahme von Probiotika zur Verbesserung der Lebensqualität in Langzeit PPI therapierten Menschen führt.

Material und Methoden

Im Rahmen einer unverblindeten, unkontrollierten Pilotstudie wurden im Zeitraum von 2017 bis 2018 56 PatientInnen, die seit mindestens 6 Monaten mit PPIs therapiert wurden, an der Medizinischen Universität Graz rekrutiert. Die Teilnehmenden wurden für 3 Monate mit einem Probiotikum therapiert. Die Messung der Lebensqualität wurde mittels SF36 und GIQLI Fragebogen vor der Intervention, danach und nach 3 Monaten Follow-up durchgeführt.

Ergebnisse

Die Daten von 39 (20 männlich, 19 weiblich) TeilnehmerInnen wurden ausgewertet. Im GIQLI verbesserten sich einige Konzepte der Lebensqualität im Zuge der Probiotika Einnahme signifikant (Median; Q_1; Q_2, [Punkte], vorher vs. nachher): Symptome (53.5; 48; 60.5 vs. 60; 52.5; 65.5; p=0.006), Emotionen (14.5; 11.8; 17 vs. 16; 12.3; 19; p=0.018) und der Gesamtscore (99; 88.3; 114.5 vs. 108; 100; 121; p=0.003). Während der Probiotikatherapie kam es zu keinem statistisch signifikanten Abfall eines der erhobenen Scores. Während der Follow-up Periode kam es zur Abnahme einiger SF36-Konzepte: Körperliche Funktionsfähigkeit (80; 50.3; 93.9 vs. 62.5; 47.5; 90; p=0.032; vor Intervention vs. nach Follow-up), Soziale

Rollenfunktion (100; 75; 100 vs. 75; 53.1; 100; p=0.015; nach Intervention vs. Follow-up); sowie GIQLI-Konzepte: soziale Items (13; 9.5; 16 vs. 11; 8; 14; p=0.012; nach Intervention vs. Follow-up) und gestört durch medizinische Behandlung (4; 3; 4 vs. 3; 2; 4; p=0.009; nach Intervention vs. Follow-up).

Schlussfolgerung

Probiotika könnten als nützliche Ergänzung zu einer länger dauernden PPI Therapie zur Verbesserung der Lebensqualität angesehen werden, nachdem es zu einer Reduktion von gastrointestinalen Symptomen und zu einer besseren Gemütslage kommt. Um klarere Aussagen zu erhalten sind jedoch weitere Untersuchungen von Nöten.

Schlüsselwörter: Leberzirrhose, gesundheitsbezogene Lebensqualität, intestinales Mikrobiom, metabolische Symbiose

Abstract

Background

Proton pump inhibitors (PPIs) are frequently prescribed worldwide. Like any other drug, they come with side effects, one of them is alteration of the human gut microbiome. Changes in the microbiome have been associated with intra- and extra-intestinal diseases, severely influencing quality of life (QoL). This study aims to test if probiotics can positively influence the QoL in patients undergoing long term PPI therapy.

Material and Methods

In a single centre, open label, uncontrolled interventional pilot study between 2017 and 2018, 56 patients (under PPI therapy for at least 6 months) were enrolled at the Medical University of Graz to take probiotics for 3 months. QoL was assessed using SF36 and GIQLI questionnaire before intervention, after intervention and after 3 months of follow-up.

Results

39 (20 male 19 female) patients were suitable for analysis. In GIQLI, probiotics led to better Symptoms scores (53.5; 48; 60.5 vs. 60; 52.5; 65.5, p=0.006), Emotions scores (14.5; 11.8; 17 vs. 16; 12.3; 19, p=0.018) and Overall scores (99; 88.3; 114.5 vs. 108; 100; 121, p=0.003) (Median; Q_1; Q_2, [points], before vs. after). During intervention no HRQoL concept decreased significantly. During follow-up period, decreases in QoL were observed in SF36: physical functioning (80; 50.3; 93.9 vs. 62.5; 47.5; 90; p=0.032; before intervention vs. follow-up), social role functioning (100; 75; 100 vs. 75; 53.1; 100, p=0.015; after intervention vs. follow-up); as well as in GIQLI: Social Items (13; 9.5; 16 vs. 11; 8; 14, p=0.012; after Intervention vs. follow-up) and Medical Treatment (4; 3; 4 vs. 3; 2; 4, p=0.009; after intervention vs. follow-up).

Conclusion

Probiotics might represent an appropriate supplement which is capable to increase the QoL in patients undergoing long term PPI therapy by decreasing bowel

symptoms and improving emotional wellbeing. To get more conclusive information further investigation is needed.

Keywords: Liver cirrhosis; health related quality of life; intestinal microbiome, metabolic symbiosis

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Abbreviations

BCFAs ..... Branched Chain Fatty Acids
CAM ..... Complementary and Alternative Medicine
cfu/g ..... colony forming unit per gram
DASS ..... Depression Anxiety and Stress Scale
EbM ..... Evidence based Medicine
EFSA ..... European Food Safety Authority
FDA ..... U.S. Food and Drug Administration
GHQ ..... General Health Questionnaire
GIQLI ..... Gastrointestinal Quality of Life Index
HRQoL ..... Health related Quality of Life
IBS ..... Irritable Bowel Syndrome
LPS ..... Lipopolysaccharides
NSAIDs ..... non-steroidal anti-inflammatory drugs
PPIs ..... Proton Pump Inhibitors
p^i value ..... p-value with Bonferroni correction
QoL ..... Quality of Life
RCT ..... Randomised Controlled Trial
SCFAs ..... Short Chain Fatty Acids
SIBO ..... Small Intestinal Bacterial Overgrowth
SF-36 ..... Short Form 36 questionnaire
TKIs ..... Tyrosine Kinase Inhibitors
TLRs ..... Toll Like Receptors
TMAO ..... Trimethylamine N-oxide
WHO ..... World Health Organisation

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1 Introduction

1.1 The human microbiome

One of the recently raised issues in modern research is the human microbiome and its impact on human health. Within the last 20 years, the number of publications regarding the gut microbiome has notably increased and the knowledge on this topic is growing (1). As awareness of this symbiosis is advancing the gut microbiome is even referred to as “a virtual organ within an organ” or “the forgotten organ” (2, 3). For a long time, the human foetus has been considered sterile as long as the amniotic sac is intact. But in recent studies using modern technologies, the sterile amnion theory is challenged by new evidence, which was summarized by Perez-Muñoz et al., suggesting that microbes are part of foetal development (4). In young humans, lactobacilli, which come from the mother´s physiologic vaginal microflora as well as from breast milk, occupy a pioneer role in colonizing the gastrointestinal tract (5, 6). From that point on, the symbiosis between our body cells and other living microorganisms starts to be crucial for many body functions including nutrient exchange and maturation of the host immune system (7). The number of bacteria harboured by the skin, mouth, vagina, respiratory and mainly the gastrointestinal tract were considered to outnumber the individuals cell count by the factor of up to 10, although recent calculations suggest that the cell-bacteria ratio might be 1:1, considering a 70 kg individual to consist of around $3*10^{13}$ body cells and harbouring $3.8*10^{13}$ bacterial cells (8) which is still a notable amount. All human body surfaces, primarily the gut, harbour viruses, eukaryotic, prokaryotic cells and fungi which are collectively referred as microbiota. The genome of the microbiota is aggregately referred as microbiome and contains huge amounts of information which is not encoded in human cells. Consecutively, these inhabitants, predominantly Firmicutes and Bacteroidetes (7, 9) can provide irreplaceable functions for the hosting organism (10). Physiologic metabolic functions of microbes in healthy individuals include the synthesis of vitamins and amino acids, biotransformation of bile and metabolism of carbohydrates (11). Figure 1 gives an overview of the human microbiome and its contribution to host´s health and disease (12). Some of the key physiologic connections will be exemplarily explained.

Figure 1: The gut microbiome and its connection to health and disease, adapted from (12)

The microbiome contributes to health by preventing growth of pathogens. Usually, microbiota fulfil a vital task in the network of first line defence in the gut besides human functions like IgA secretion, gastric acid secretion, and digestive enzymes as other crucial factors. One major role of the beneficial microbiota is preventing pathogens from adherence and colonialization, due to competition for nutrients and attachment sites in the gastrointestinal tract (13). Furthermore, direct interaction with both, innate and adaptive immune system takes place. Commensal bacteria interact

for example with toll like receptors (TLRs) and support the maturation of the immune response (9).

Today, the key question of what makes a healthy microbiome is currently under examination. The settlement of microbes on the human body surfaces differs between each person, which makes answering this question even harder. Nevertheless, once the bacterial colonisation substantially gets out of balance patients start being frail in health. In other words, if there is a dysbiosis in the gut, diseases start emerging and heavily impact an individual´s health condition.

IBD is an exemplary condition where a context to microbiotic dysbiosis as well as host genetics, environmental factors and perturbed immune response has been shown. It is not clear, whether dysbiosis leads to IBD or vice versa, however future directions point to a treatment which includes an alteration of the gut colonization (14). Also extra intestinal diseases have been associated with microbiotic dysbiosis in the gut. Recently reviewed data shows that a healthy gastrointestinal microbiome is able to prevent allergies (15). Correlations between gut dysbiosis and elevated IgE serum levels were found in children who were suffering from allergic airway diseases and asthma, compared to healthy individuals (16). Similarly, links between the pathogenesis of rheumatoid arthritis and altered intestinal microbiome were found (17). Liver diseases including liver cirrhosis have been associated with reduced Bacteroidetes and Firmicutes counts (18). Also the stage of liver injury closely correlates with the severity of dysbiosis (19). The gut-brain-axis describes the connections between the gut microbiome and the central nervous system and illustrates how the intestinal mucosal barrier and systematic inflammation (20) can contribute to extraintestinal diseases and behavioural disorders, such as depression (21, 22), Alzheimer´s disease (23), schizophrenia (24), multiple sclerosis (25) and may even path the way to brain cancer (26).

As alteration of the gut microbiome correlates with systemic inflammation, the question rises if bringing the commensal composition back to a more healthy state can help patients. One way of favourably altering the commensal composition is the use of probiotics. The term “probiotic” is derived from Latin and Greek and literally means “for life” (27). Probiotics are defined as “live microorganisms, which, when consumed in adequate amounts, confer a health benefit on the host.” (28). Even early humans unknowingly derived benefits from effects of bacteria (29). In the 19th century it was noticed that fermented milk products apparently have a positive health

effect, but the clear mechanisms were not found then (30). A universal comprehension of mechanisms of action of probiotics remains missing until today. However, the theory of supporting the natural barrier function in the mucosa of the gut is well established because different ways of how this interference works have been shown. One of the key pathways of microbial intervention is positive influence on the functioning of the immune system, both innate and adaptive (31). By now we know that probiotics have positive impacts on human health and favourable physiological functions, including alteration of perturbed intestinal microbial communities, competitive exclusion of pathogens, interference with the metabolism of toxins and carcinogens and production of SCFAs (Short Chain Fatty Acids) and BCFAs (Branched Chain Fatty Acids) and an influential role in behaviour via the gut-brain-axis (32). Quality of Life (QoL) is also positively influenced by probiotics in certain diseases. Probiotics can improve gastrointestinal symptoms and QoL in patients after gastric bypass surgery (33) and in constipated female university students a probiotic supplement had positive impacts on QoL (34). Other gastrointestinal diseases where probiotics led to improved QoL include ulcerative colitis (35), IBS with diarrhoea (36) and colorectal cancer (37). Not only gastrointestinal diseases are positively influenced by probiotics, also patients suffering from extraintestinal diseases including seasonal allergies (38), cystic fibrosis – where children benefited from a reduced number of pulmonary exacerbations – (39), chronic kidney disease (40) and upper respiratory tract infections (41) experienced enhanced body region specific and/or overall QoL after being treated with probiotics.

Additionally, concerns about safety or harmful side effects have not been shown and can be neglected in not immunosuppressed patients so far (42). Nonetheless, neither the FDA (U.S. Food and Drug Administration) nor the EFSA (European Food Safety Authority) have accepted any probiotic strain as a drug. Currently, they are mostly sold as dietary supplements (32), a fact which undermines their potential in health and disease.

Besides from probiotics there are well known other factors which impact the gut colonialization positively or negatively, including infant feeding, dietary intake geography and of course medication (12, 43). What surely adversely affects the diversity and taxonomic richness of the microbiota is antibiotic (Latin “anti” = against, Greek “bios” = life) treatment. This therapy is intended to destroy pathogenic

bacteria but also impairs the physiologic microbiome (44). Especially in children, where the ordinary microbiome is under construction, antibiotic treatment can have a long term negative impact on health. Not only is there a correlation between antibiotic intake and risk of obesity, diabetes, IBD or allergies, but recent experiments indicate also a causality in these connections, due to perturbed gastrointestinal microbiotic composition (45).

Other drugs have also shown antimicrobial side effects. In their review, Maier et al. analysed 1,000 different drugs, of which 24% percent inhibited at least one out of 40 analysed human gut bacterial strains in vitro (46). Another review which was published in 2017 and included 20 papers in their analysis, shows that non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), opioids, statins, metformin and antipsychotics also have an impact on the gut microbiome (47). The microbiome of patients taking in NSAIDs differs from humans who do not take them in. Furthermore, adding laxatives and antidepressants leads to changes in the microbiome. Moreover, individuals taking in a combination of NSAIDs and PPIs showed differences in their gut colonialization (48). Also PPIs alone were associated with changes in the gastrointestinal microbiome (49) and are further addressed in the next section.

1.2 Proton Pump Inhibitors

The stomach is the first reservoir of the gastrointestinal tract inside the peritoneal cavity. One crucial function of the hollow organ is to produce gastric acid. Hydrochloric acid dissolves the nutritional components, can destroy pathogenic bacteria and provides a milieu in which vitamin B12 is released and can be bound to the intrinsic factor, to be later absorbed in the small intestine (50, 51).

The concentration of H_3O^+ ions in the stomach can reach 10^{-1}mmol/L (52), which could easily severely damage the organ´s wall. The stomach has evolved features to protect its wall from being digested, including several mucosal layers and the ability of the apical membrane of the gastric epithelial cell to resist acid (53). A disbalance towards the aggressive factors may lead to acid related diseases such as peptic ulcer disease, where the integrity of the mucosal layer is disrupted (54).

The first line therapy of acid related disorders is the prescription of Proton Pump Inhibitors (PPIs) which are benzimidazole prodrugs. By blocking the hydrogen-potassium ATPase – which is crucial to produce gastric acid – of the gastric parietal cells, less acid is produced, leading to a rise to a less harmful pH-level. Less hydronium ions means less chemical aggression for the mucosa, which makes it easier to heal in case of gastric ulcer for example (55).

Twenty-five years after the introduction of PPIs, no other drug succeeded them in effectiveness of treating acid related disorders. Lots of indications for PPI use have been tested over the last decades, of which many have been proven to be irrational including asthma and non-specific cough (56). Furthermore, inappropriate usage of PPIs is a problem which still remains today (57). Widespread prescription by general practitioners and gastroenterologists (58) led to investigations, which have shown overuse of PPIs in both, hospital settings and in the community (59). At the moment, there are just few indications remaining, which are treatment of:

- Peptic ulcer disease
- Gastroesophageal reflux disease
- Zollinger-Ellison syndrome
- NSAID-associated ulcers
- Eradication of Helicobacter pylori (55, 57)

In terms of effectiveness, PPIs have shown to be the right choice for the mentioned indications. Coupled with low rates of short term adverse effects the advantages of PPIs may outweigh their disadvantages (60). However, concerns about long term side effects and possible negative impacts on the physical integrity are growing (61). Long term adverse effects of PPIs include lower vitamin B12 (62) and iron serum levels (63, 64), potentially leading to anaemia (65, 66), a higher risk of bone fractures in elderly people (58, 67), a higher prevalence of acute kidney injury (68), as well as an increased overall risk of developing chronic renal disease (69). Nardelli et al. carried out a review and found, that in patients suffering from chronic liver diseases, such as liver cirrhosis, PPI usage correlates with complications, including poorer survival rates as well as higher rates of hepatic decompensation, hepatocellular carcinoma, infectious complications and hepatic encephalopathy. Without making any suggestions about the causality of PPIs on these complications respectively, they recommend a thoroughly considered prescription of these drugs (70). PPIs are also known to influence the metabolism and the pharmacology of certain drugs.

Patients with coronary artery disease undergoing treatment with clopidogrel for example are at higher risks of adverse events under PPI therapy (71). In cancer patients the concomitant use of PPIs and tyrosine kinase inhibitors (TKIs) is associated with a higher risk of mortality, compared to those who get TKIs without PPIs (72).

If gastric acid – which is a strong bactericide – is taken away, it is inevitable that the gastrointestinal microbiome changes. Several recent reviews summarize effects of PPIs on the microbiome. All of them agree that PPIs may shift the commensal composition towards a less healthy state (49, 73-77). PPIs lead to small intestinal bacterial overgrowth (SIBO) (78). SIBO means that more than 10^5 bacteria per ml are detected when culturing upper gut aspirates. This condition leads to gastrointestinal symptoms (79), including weight loss, malabsorption, diarrhoea, bloating (73) and abdominal pain (74). Long term PPI use is also associated with a higher risk in gastrointestinal bacterial infection, caused by *Clostridium difficile* (80) as well as *Salmonella* and *Campylobacter* (77). Also Spontaneous Bacterial Peritonitis appears more often in PPI users (81). Just few studies exist, addressing a link between viral infections and PPI use. Yet it is assumed, that acid suppressing drugs come with a higher risk in viral infections, as for example community acquired respiratory infections appear more frequently in patients undergoing PPI therapy (75). What is more, PPIs are not only targeting the gastric hydrogen-potassium ATPase but also directly inhibiting bacterial P-type ATPase, which leads to a bacteriostatic effect (49). Likewise, pantoprazole inhibited the growth of *Lactobacillus* species in vitro (82). Long term use of PPIs leads to dysbiosis in all parts of the gastrointestinal tract (73). An increased risk of developing inflammatory and infectious diseases is associated with that fact (76). Extensive impacts of gut dysbiosis on human health and the influential role of probiotics have been described in section 1.

Long term therapy with PPIs appears to impact health because of a variety of adverse effects. Hence negative impacts on Quality of Life (QoL) as a result of PPI caused perturbations of the microbial composition are mentioned in the literature (74). QoL is a concept which addresses health status and impacts on daily routine. It is therefore suitable as an outcome parameter where several aspects of human functioning are taken into account.

1.3 Quality of life

“Salus aegroti suprema lex” – The well-being of the patient is the most important law. Not only is this the main principle of the Medical University of Graz, which has even been embedded in the seal of the institution, but also a general ethical principal, how doctors should pursue their work. But what is the well-being of a patient, and how can it be defined?

The biopsychosocial model has become a central health concept, which not only focuses on the physical parts and functions of the body, but also on psychological and social components of health as well as their interference with each other. Rather than suggesting that health purely comes with the absence of disease, this concept also includes two other edges of a triangle (physical, psychological and social components), of which each angle is equally important to maintain (83). Another holistic comprehension of health is given by the WHO (World Health Organisation) definition as "state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity." (84) With this in mind, it becomes obvious, that therapy outcomes can no longer be sufficiently evaluated by just observing changes of laboratory parameters.

Nowadays, treatments in modern western medicine are based on evidence. Evidence based medicine (EbM) has brought huge progress in fighting diseases, providing a longer lifespan and increasing public health. But just relying on guidelines might not be adequate enough to satisfy individual´s needs and this is where the edges of evidence based medicine lie (85). Many patients who prefer CAM (complementary and alternative medicine) over western medicine rely on soft facts as well as subjective impressions rather than hard clinical data which is of course easier to measure and to compare. To give an illustration, recent scientific papers have thoroughly analysed the reasons for patients to choose CAM over EbM. Reasons for choosing particular therapies include “relieve of symptoms”, “relieve of pain”, “increase of energy” and “improvement in general health”. Many patients “value the emphasis on treating the whole person” and appreciate that “CAM considers the interrelatedness of body mind and spirit” (86). It might seem unorthodox to talk about CAM in a scientific paper, but there is a necessity to get awareness of people´s preferences to choose therapies. As the WHO defines health in a holistic manner, it becomes clear that soft facts and subjective experiencing –

such as well-being and QoL – are essential outcome parameters not only in a patients point of view, but should also be considered in modern evidence based research. Coupled with this literary evidence, the daily routine of health care workers to ask patients how they are and how they feel indicates that having a look at QoL as a primary outcome parameter as it is used in this work seems reasonable.

In order to create valid and comparable results, a definition of QoL which is universally agreed on has to be found, which unfortunately has not been the case yet (87). Sometimes even living standard and QoL are mentioned all in one breath (see German “Handbook of Society (88)), making it even hard to distinguish between a socio-economic term from an idea which includes feelings of a person, respectively. Different professions, for example philosophy, sociology, economy philosophy and medicine are describing QoL differently (89). Health care workers and questionnaires used in the field of medicine preferably talk about health-related quality of life (HRQoL), which describes the health aspects of QoL. Although these terms are used interchangeably (87) the definition of HRQoL in this work is “how well a person functions in their life and his or her perceived wellbeing in physical, mental, and social domains of health” (87, 90). This definition is related to the WHO definition of health and the main content of the questionnaires.

To evaluate QoL in general and HRQoL in specific, it is necessary to find suitable tools. As quality of life is a subjective sensation, mostly influenced by personal feelings it is reasonable to avoid unstructured interviews and use questionnaires to ask standardised and predefined personal questions instead. Requirements of quality of life questionnaires include ease of use, time needed to fill in the answers and of course validation (91-94).

The Short Form 36 questionnaire (SF-36) was first published in the early 1990ies. Since then the validated short form health survey originally available in English language was translated into at least 16 other languages, including Indo-European ones (e.g. Dutch, German and French) and Japanese (95). Consequently, the SF-36 survey has become a popular tool to assess HRQoL all over the world.

The Gastrointestinal Quality of Life Index (GIQLI) is a questionnaire created by a group around a German surgeon at the beginning of the 1990s. The main idea was to create a tool which gives an objective evaluation of subjective well-being. As by that time there was no specially designed survey for patients suffering from gastrointestinal diseases available, this was a whole new approach (93).

Although there is little agreement on clearly defining the terms QoL, HRQoL and well-being they become more important as interests in measurement of health care outcomes emerged apart from just observing death rates (87). Nowadays lots of studies can be found measuring therapy effectiveness using one of these or other questionnaires (96).

1.4 Hypothesis and aims

Dysbiosis caused by PPIs negatively impacts host health (73) and QoL (74). Probiotics on the other hand lead to improved QoL in patients suffering from various disease. Therefore, we hypothesised that the intake of probiotics increases quality of life in patients undergoing chronic PPI therapy. The aim of this study was to examine the impact of probiotic intake on quality of life during PPI therapy.

2 Material and Methods

2.1 Study

2.1.1 Study design and recruitment

Patients were recruited at the Medical University of Graz at the Department of Gastroenterology and Hepatology as part of the interventional study “Probiotic modulation of intestinal microbiota in long-term intake of proton pump inhibitors: Pilot study on the influence on intestinal inflammation and digestion.” The study was performed according to the principles of Good Clinical Practice as well as the Declaration of Helsinki. An approval of the Research Ethics Board of the Medical University of Graz was given prior to the inclusion of the first patient (Registration number: 29-552 ex 16/17). Patients were appointed to visit the outpatients clinic between September 2017 and June 2018. The study was conducted as open label uncontrolled interventional study. The results have been published in 2020 in the following original paper: “The effects of a multispecies synbiotic on microbiome-related side effects of long-term proton pump inhibitor use: A pilot study” (97).

2.1.2 Inclusion and exclusion criteria

Inclusion criteria

- Age >18
- Informed Consent
- PPI intake for at least 6 months

Exclusion criteria

- Active infections at time of inclusion
- Antibiotic therapy within the last 14 days (includes prophylactic use)
- Inflammatory bowel diseases
- Consumption of pre/synbiotics other than the product provided during the trial

- Concomitant diseases or other circumstances that suggest that the patients are not eligible for participation in the study

2.1.3 Study product

The study product that patients were asked to take in was a probiotic blend consisting of 4g of yellowish powder made of corn starch, maltodextrin, fructo-oligosaccharide P6, inulin P2, vegetable protein and 12 bacterial strains, which are as follows:

- *Bacillus coagulans W183*
- *Bacillus subtilus W201*
- *Bifidobacterium bifidum W23*
- *Bifidobacterium lactis W52*
- *Bifidobacterium lactis W51*
- *Lactobacillus acidophilus W37*
- *Lactobacillus acidophilus W22*
- *Lactobacillus casei W56*
- *Lactobacillus salivarius W24*
- *Lactococcus lactis W19*
- *Propionibacterium freudenreichii W200*
- *Lactobacillus rhamnosus W71*

The concentration is an estimated 2 x 10^9 cfu/g
The study product contains 20 kilocalories per sachet. The powder had to be dissolved in 125 ml of water for 10 minutes and consumed immediately after stirring.

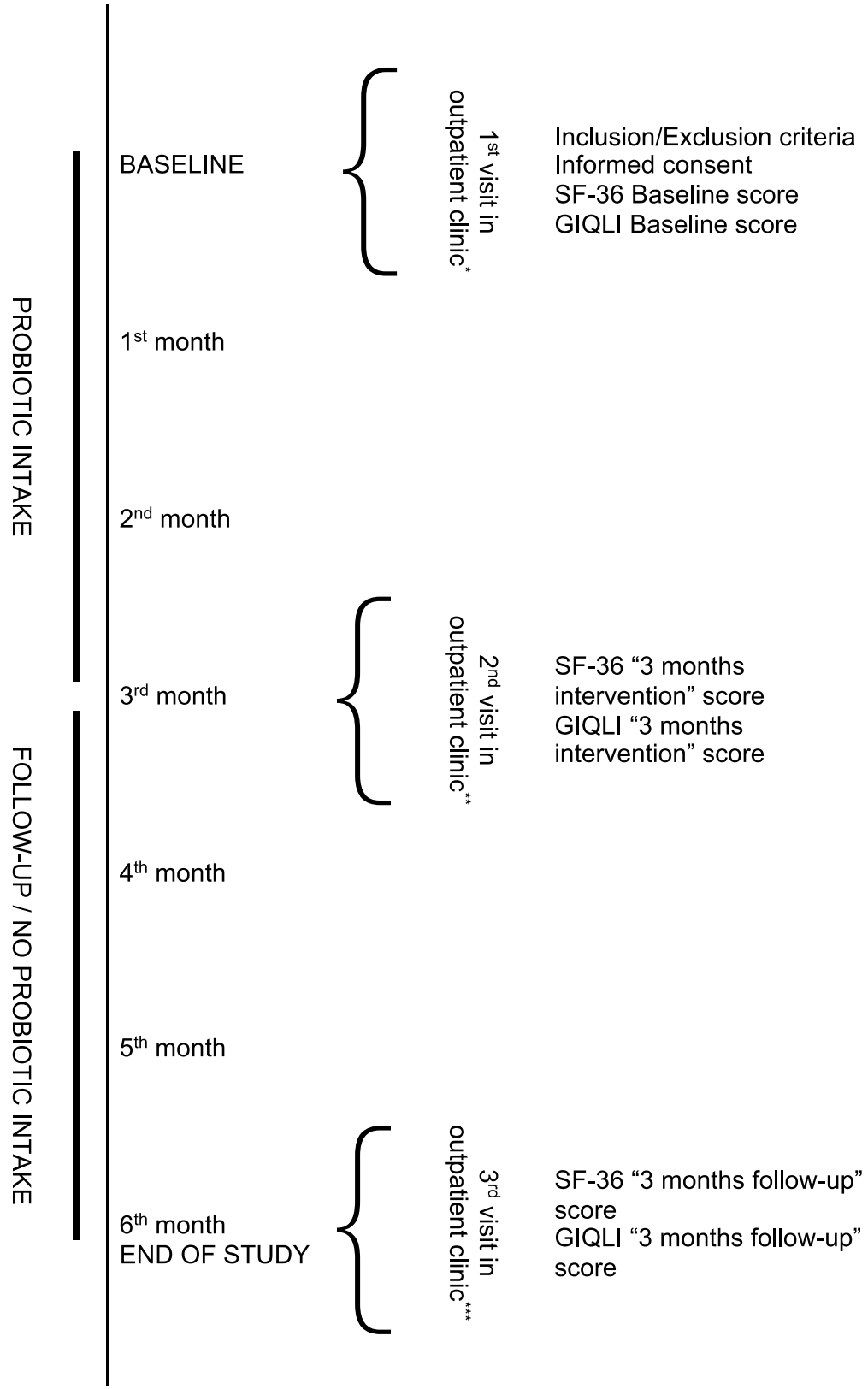
2.1.4 Implementation of the study

Patients who fulfilled inclusion criteria were given two questionnaires, “Gastrointestinal Quality of life Index” (GIQLI) and “Short Form 36” (SF-36), to monitor their quality of life and to record possible influences of the probiotic. The patients were seen three times during a period of six months, where they filled in the forms during their study visit (see figure 2).

Firstly, the questionnaires were filled in at their first visit (baseline), as soon as the patients agreed on participating in this study and had given written informed consent.
Secondly, patients were instructed to take in a daily dose of a multispecies probiotic for the next three months until their next visit. At which point, both questionnaires had to be filled in again (3 months intervention).
Thirdly, patients were observed for another 3 months without any probiotic intake.
Finally, patients got an appointment after this period (3 months follow-up) and the questionnaires were filled in a third time.
At their first visit additional information was collected, including date of birth, anthropometric data like body weight and height, presence of liver cirrhosis, comorbidities, medications and physical examination.

2.1.5 Endpoints

The primary endpoint was defined as the change of quality of life between baseline and directly after intervention.
Secondary endpoints included comparisons of baseline scores with follow-up scores as well as after intervention with follow-up scores.



*… also 1st day of probiotic therapy
**… 1st±1 day after ceasing probiotic therapy
***… 3 months after ceasing probiotic therapy

Figure 2: Study design

2.2 SF-36 Questionnaire

The SF-36 differentiates between two main conceptual areas of health: physical health and mental health. These pillars are represented by 8 concepts which can be assessed by 36 questions:

Physical functioning contains 10 questions, which is more than any other in this questionnaire. It assesses the impact of the health status on basic physical activities, like walking, climbing stairs, carrying groceries or managing personal hygiene (bathing, dressing) for example.

Physical role functioning is about limitations, reduced amount of time and difficulty to perform work or other daily activities.

Bodily pain measures the intensity of pain and its influence on daily tasks, in- and outside the house.

General health addresses the personal perception of health at the moment, including the current health status, expectations for the future and the resilience to diseases.

Vitality includes the distinction of energy level and fatigue and captures differences in subjective well-being (feeling full of energy vs. tired and exhausted).

Social functioning, as an extension of mental and physical health, evaluates the disease´s impacts on daily social activities.

Emotional role functioning scale represents the impact of emotions on work and other daily activities.

Mental health contains the general mental subjective well-being, including anxiety, depression, loss of behavioural and emotional control as well as psychological well-being.

At large these questions are asked referring to the last 4 weeks. Before analysing and interpreting the SF-36 scale, answers have to be digitalised and missing values have to be adjusted. Missing values are defined as unanswered questions or questions where patients have given two or more answers. These values are substituted by the mean score of correctly given answers within each concept if more than 50% of them are valid. Items where less than 50% of the questions are missing are excluded from data analysis. Ten items have to be recalibrated before

adding them to their corresponding concept. This method is necessary to get standardised results which are better suitable for comparison and interpretation. After recalibration, sum scores were transformed into a scale from 0 to 100 points, where higher scores represent better quality of life. (91, 98)

2.3 GIQLI Questionnaire

The GIQLI contains 36 questions representing 4 different dimensions of quality of life as well as one solitary aspect and a comprehensive score:

Symptoms score includes gastrointestinal symptoms like pain in the abdomen, bloating, epigastric fullness or bowel frequency.

Emotions score gives an overview of patients´ evaluation of coping with stress, sadness about the disease, anxiety, satisfaction and frustration.

Physical Functions score addresses fatigue, bodily strength, fitness and physical discomfort.

Social Functions score includes daily activities, leisure activities, relationship to other persons and sexual life. None of these questions is specified more closely.

Troubled by medical treatment is one question asking whether patients are troubled by medical treatment.

Overall score is a sum score of all mentioned items. All areas are summarised within this score and provide a general overview on the patients quality of life related to his or her gastrointestinal health.

This survey generally asks about the patients perceptions during the last 2 weeks. Each of the 36 questions has five answers to choose from. The response categories can later be transformed into numerical values, ranging from 0 (worst possible answer) to 4 (best possible answer). A sum score of one dimension is created by adding the transformed numerical values of each question belonging to the concept. The highest possible score of the particular concept depends on the items contained in this concept. Consequently, each of the described points has another high score. For symptoms score, there is a maximum of 76 points, for emotions score it is 20 points, for physical items 28, for social functions 16, for troubled by medical treatment the high score is 4, as this question is surveyed solitarily. Counting

everything together, a highest possible overall score of 144 points is achievable. 0 points is the worst possible result for each concept.
Higher scores mean better quality of life, or better aspects of quality of life, dependent on what is observed. In other words, a higher symptoms score means, that patients suffer less, for example.
Before analysis, missing values had to be addressed and removed. If more than 50% of the questions within one score had been filled in properly, the missing values were replaced with the mean of the available values. (92, 93)

2.4 Data Analysis

Each patient was administered a unique study code which was used instead of identifying information as name, date of birth, patient identifier from the hospital etc. A list linking the study code to the person is kept confidential by authorized study personnel. The original questionnaires as well as study protocols, informed consent and case report forms are stored safely in a locked office at the ZMF. Data analysis was carried out by using the anonymised data sheets.
The results of both questionnaires were analysed in a similar way. The Kolmogorov-Smirnov-Test was applied to assess whether the sum scores were normally distributed or not. Findings showed that this situation was not given. Consecutively, non-parametric tests were used to further analysis.
Independent samples Mann-Whitney U test was applied to find differences between study subpopulations at baseline. Further analysis, which means comparison of the different points of measurement, was formally carried out as multiple Wilcoxon signed rank test. Applying statistical tests on the same sheet more than once leads to an increased type I error, as there is a higher possibility to mistakenly find statistical significance. Thus, the p value had to be corrected. Bonferroni correction was utilized, meaning the concerned p-values were multiplied by the number of statistical tests carried out on the same data record which is in this case 3 times. (99) Corrected p-values are recognizable as “p^i-value”.
Data was sorted and stored with Microsoft Office Excel. Also sum scores were computed with this software. For statistical analysis IBM SPSS Statistics 25.0 was

used. The graphics in the Results section of this work were created with GraphPad version 6.02 and RStudio.

For literature research and finding references data banks such as “PubMed” and “UpToDate” as well as the library of the Medical University of Graz were consulted.

3 Results

3.1 Descriptive Statistics

3.1.1 Study population

Fifty-six patients fulfilled the inclusion criteria. Seven of them did not fill in any questionnaire. From further 10 individuals only one questionnaire at baseline was available. Therefor 17 patients had to be excluded from analysis. Of the study population thirty-nine individuals (20 men and 19 women) completed and turned in at least two questionnaires (two questionnaires in 9 cases– either “Baseline” and “3 Months Intervention” or “Baseline” and “3 Months Follow-up” or “3 Months Intervention” and “3 Months Follow-up”, all 3 questionnaires in 30 cases). Thus, they were suitable for analysis (see figure 3).

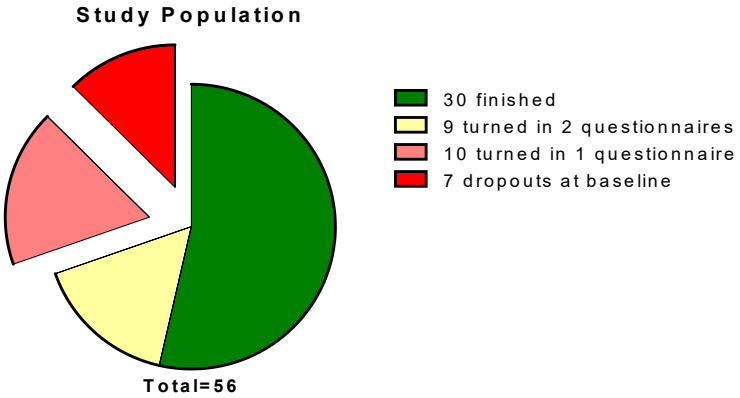


Figure 3: Study population

Of these 39 patients, 20 (51%) were male and 19 (49%) were female (see figure 4). The mean duration of PPI intake was 76 months (~6.3 years). The minimum duration was 6 months, as required in the inclusion criteria, and the longest duration of PPI intake was 21 years.

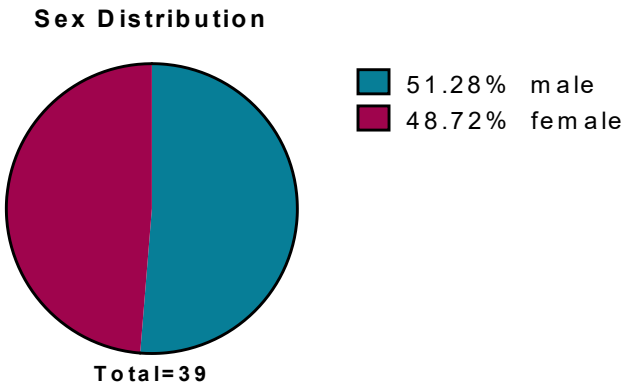


Figure 4: Sex distribution

Fourteen patients (36%) were included in the liver cirrhosis group, whereas the other 25 individuals (64%) were included in the non-cirrhosis group (see figure 5). In these groups women were more frequently represented among the non-cirrhotic patients.

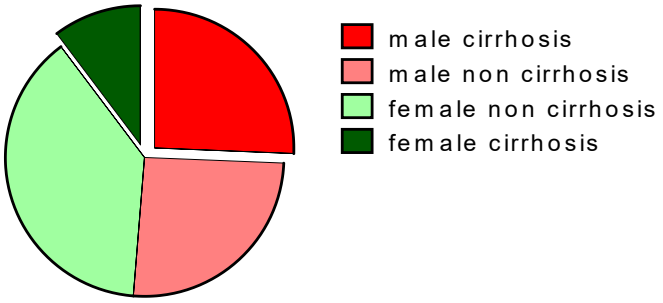


Figure 5: Cirrhotic and non-cirrhotic participants

Of the patients in the cirrhosis group 10 were male and 4 were female. In non-cirrhosis group, there were 10 male and 15 female individuals (see table 1). Although the proportion of female patients in the non-cirrhosis group (60%) was more than four times higher than in the cirrhosis group (14%), there was no statistically significant association between presence of cirrhosis and patient´s gender (Fisher´s exact test: p=0.096).

Table 1: Gender and presence of cirrhosis

		PRESENCE OF CIRRHOSIS	
		non-cirrhosis	*cirrhosis*
GENDER	*male*	10	10
	female	15	4

The mean age of the participating patients was 63 years, ranging from 36 years to 83 years. Most patients had an age of 51 to 70 years (22 patients), five patients were younger than 51 years and 12 patients were older than 70 years (see figure 6).

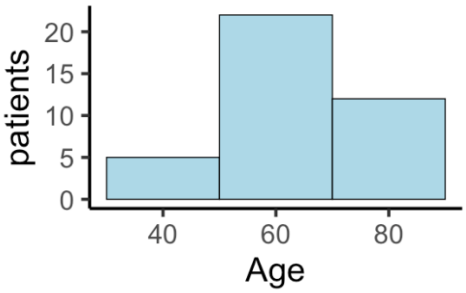


Figure 6: Age distribution

3.2 Explorative Statistics

3.2.1 SF-36 - Baseline analysis

To begin with, the impact of presence of cirrhosis and gender were investigated. Baseline scores of the cirrhosis group were compared with those of the non-cirrhosis group and showed that presence of cirrhosis had no statistically significant impact on the different dimensions of QoL (see figure 7).
Baseline scores did not differ between male and female participants (see figure 8). All mean values and distributions are group wise listed in table 2, as well as each p-value.

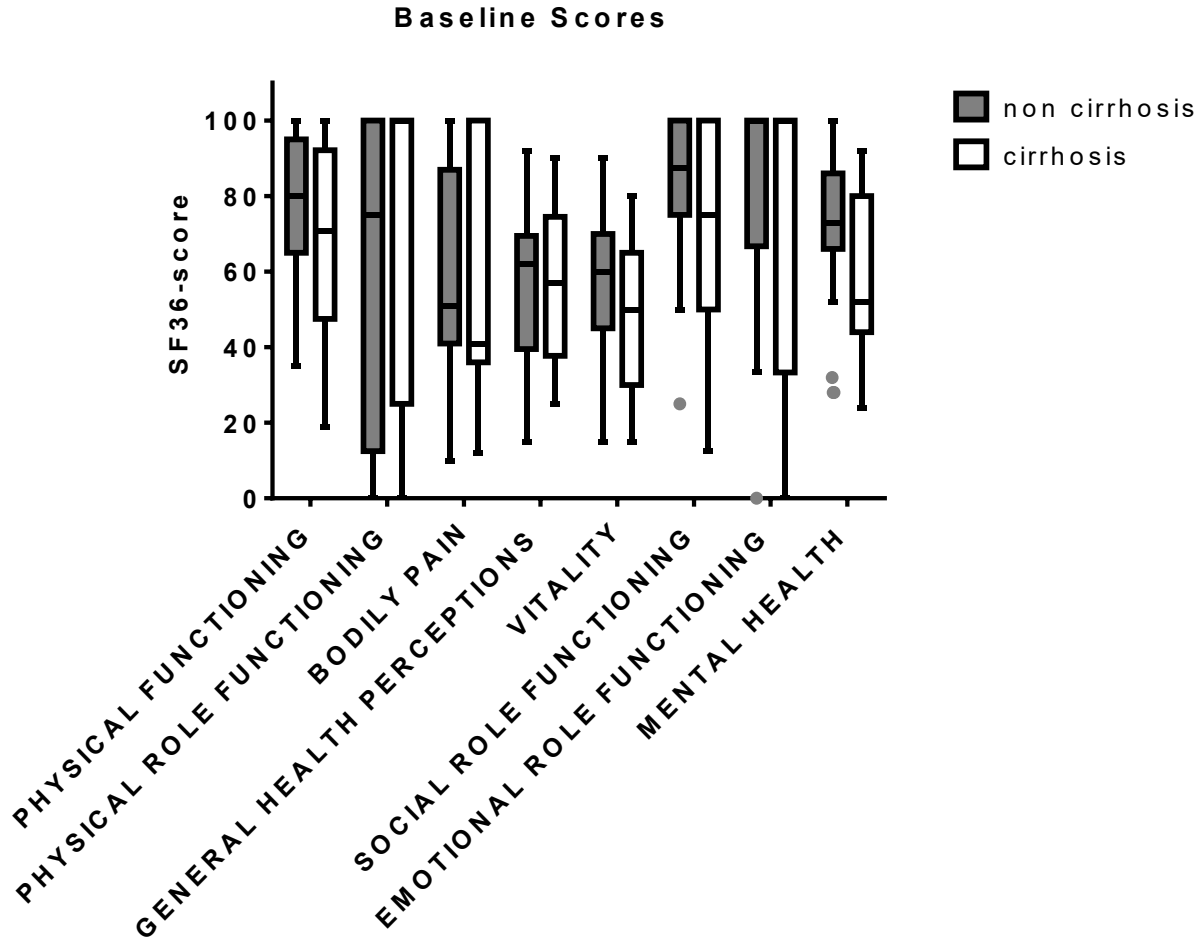


Figure 7: SF-36 baseline scores; cirrhotic vs. non cirrhotic

Table 2: SF-36 baseline scores, comparison of subgroups

		Baseline M (Q_1; Q_3)	**Baseline** M (Q_1; Q_3)	**p-value**
gender				
		male	female	
	Physical Functioning	83.9 (55.4; 95)	80 (50; 92.9)	0.641
	Physical Role Functioning	87.5 (37.5; 100)	75 (18.8; 100)	0.913
	Bodily Pain	42 (41; 100)	51 (41; 100)	0.954
	General Health Perceptions	57 (37; 78.3)	62 (42; 67)	0.916
	Vitality	50 (42.5; 61.3)	62.5 (33.8; 70)	0.214
	Social Role Functioning	75 (50; 100)	87.5 (75; 100)	0.435
	Emotional Role Functioning	100 (83.3; 100)	100 (58.3; 100	0.563
	Mental Health	70 (51; 80)	80 (65; 89)	0.265
presence of cirrhosis				
		cirrhotic	non-cirrhotic	
	Physical Functioning	70.8 (47.5; 92.1)	80 (65; 95)	0.378
	Physical Role Functioning	100 (25; 100)	75 (12.5; 100)	0.435
	Bodily Pain	41 (36; 100)	51 (41; 87)	0.927
	General Health Perceptions	57 (37.8; 74.5)	62 (39.5; 69.5)	0.860
	Vitality	50 (30; 65)	60 (45; 70)	0.324
	Social Role Functioning	75 (50; 100)	87.5 (75.5; 100)	0.411
	Emotional Role Functioning	100 (33.3; 100)	100 (66.7; 100)	0.973
	Mental Health	52 (44; 80)	73 (66; 86)	0.207

independent samples Mann-Whitney U test; significance $p \geq 0.05$
M = Median; Q1=first quartile, Q3=third quartile
SF-36 = Short Form 36 questionnaire

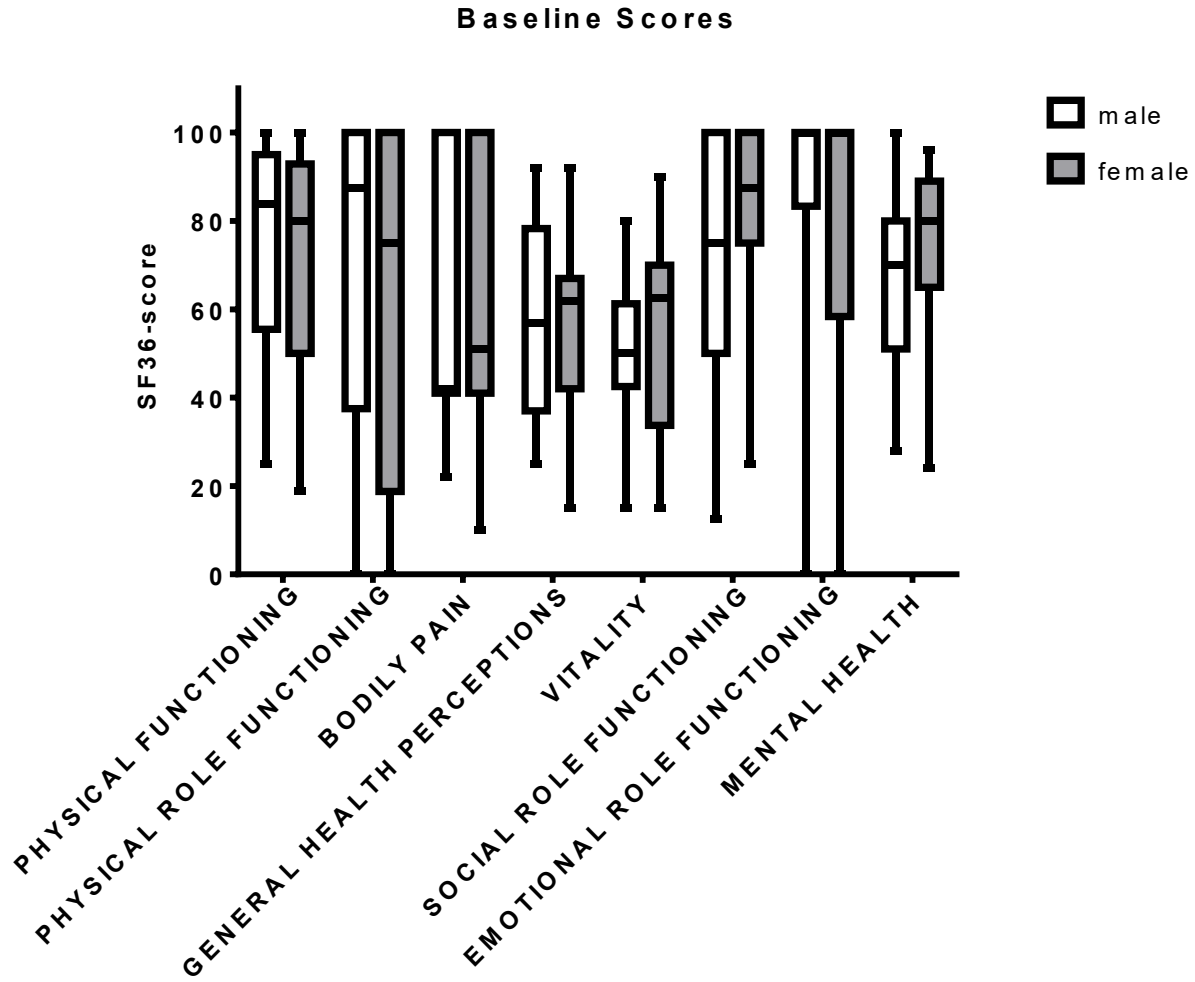


Figure 8: SF-36 Baseline scores; male vs. female

3.2.2 Effect of probiotic intervention in SF-36

HRQoL was assessed at three different time points using SF36 and GIQLI questionnaire: At baseline, after three months of intervention and three months after ceasing intervention (see figure 2). As described above baseline score did not differ between men and women or cirrhotic and non-cirrhotic patients. Further analysis was carried out on the whole study population without subgroups.

3.2.2.1 PHYSICAL FUNCTIONING

In Physical Functioning score no changes after three months of intervention compared to baseline can be observed (80 (55.3; 93.9) vs. 75 (56.7; 90), p^i=0.999) as well as after ceasing the intervention and three months follow up (75 (56.7; 90) vs. 62.5 (47.5; 90), p^i=0.141). Physical functioning score significantly dropped from baseline to three months follow up (80 (55.3; 93.9) vs. 62.5 (47.5; 90), p^i=0.032), with a decrease of 17.5 points of the median value (see figure 9).
P-values are adjusted with Bonferroni correction and therefore recognizable as p^i.

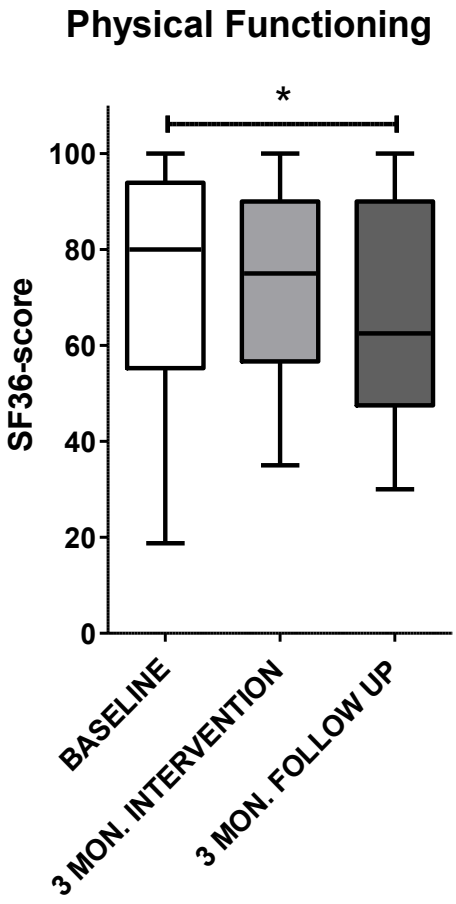


Figure 9: Comparison of "Physical Functioning"

3.2.2.2 PHYSICAL ROLE FUNCTIONING

Baseline score and 3 months intervention score of Physical Role Functioning did not differ significantly (75 (25; 100) vs. (62.5 (25; 100), p^i=0.513). No statistically significant change was observed, neither between 3 months after intervention and 3 months follow up (62.5 (25; 100) vs. 50 (0; 100), p^i=0.999) nor between baseline and 3 months follow up (75 (25; 100) vs. 50 (0; 100), p^i =0.372). (see figure 10)
P-values are adjusted with Bonferroni correction and therefore recognizable as p^i.

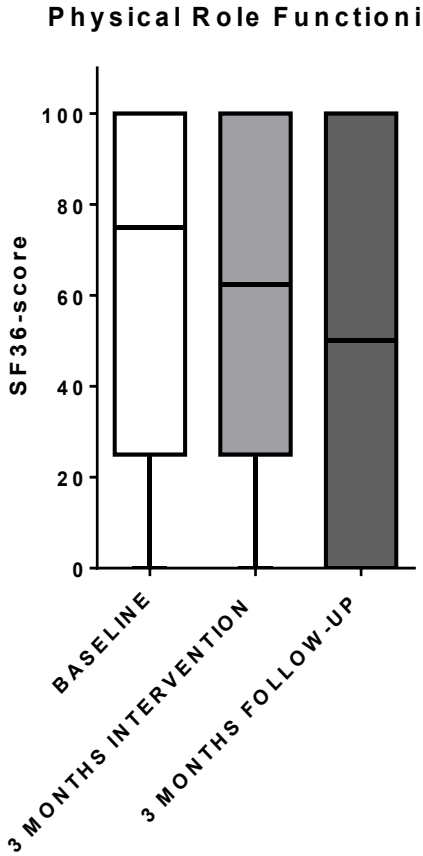


Figure 10: Comparison of “Physical Role Functioning”

3.2.2.3 BODILY PAIN

Bodily Pain did not change significantly during the period of observation (see figure 11). Between baseline and 3 months of intervention (51 (41; 100) vs. 68 (41; 100), p^i=0.228), 3 months of intervention and 3 months follow up (68 (41; 100) vs. 46.5 (34.3; 74), p^i=0.282) as well as baseline and 3 months follow up (51 (41; 100) vs. 46.5 (34.3; 74), p^i=0.999) no statistically significant differences were found.
P-values are adjusted with Bonferroni correction and therefore recognizable as p^i.

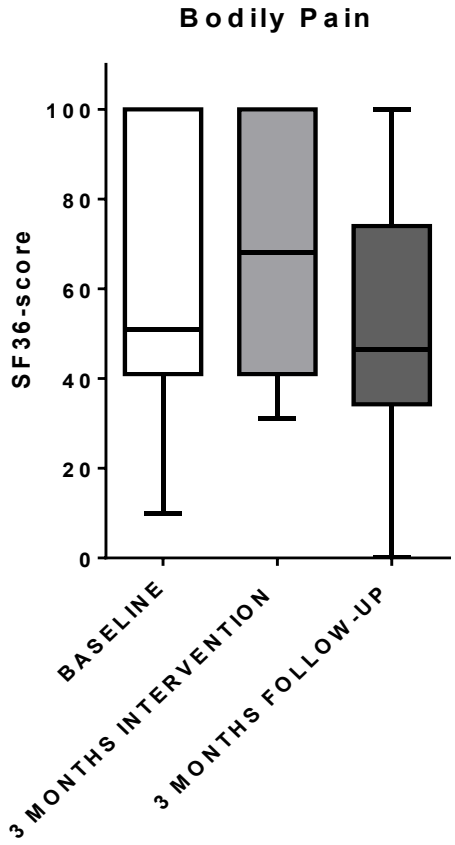


Figure 11: Comparison of “Bodily Pain”

3.2.2.4 GENERAL HEALTH PERCEPTIONS

General Health Perceptions score showed no statistically significant changes over the period of intervention as well as after ceasing the intervention. Between baseline and 3 months of intervention (62 (38.5; 69.5) vs. 57 (42.5; 72), p^i=0.999), 3 months of intervention and 3 months follow up (57 (42.5; 72) vs. 52 (35.5; 70.8), p^i=0.504) as well as baseline and 3 months follow up (62 (38.5; 69.5) vs. 52 (35.5; 70.8), p^i=0.999) none of the differences were statistically significant. (see figure 12)
P-values are adjusted with Bonferroni correction and therefore recognizable as p^i.

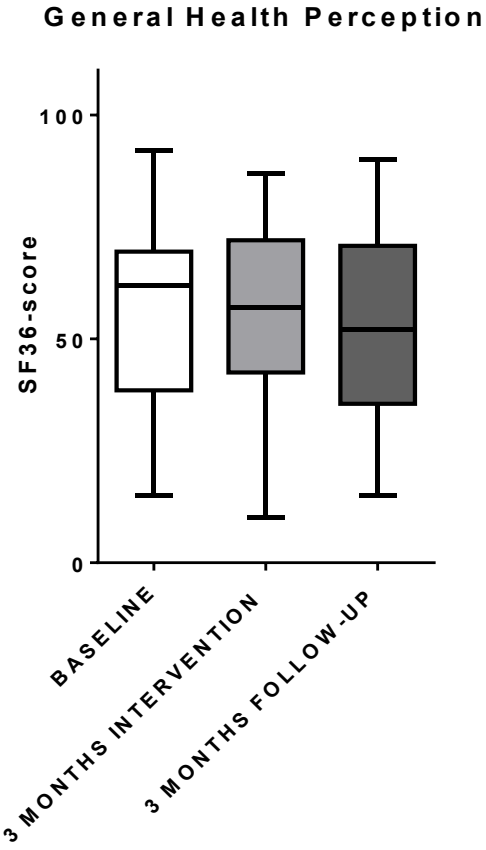


Figure 12: Comparison of "General Health Perceptions"

3.2.2.5 VITALITY

Vitality score showed no significant changes. Comparing baseline with 3 months intervention score (57.5 (37.5; 70) vs. 55 (47.5; 67.5), p^i=0.999), as well as 3 months intervention and 3 months follow-up score (55 (47.5; 67.5) vs. 45 (35; 67.5), p^i=0.438) and baseline and 3 months follow-up score (57.5 (37.5; 70) vs. 45 (35; 67.5), p^i=0.999) no statistically significant changes in the course of time were found (see figure 13).

P-values are adjusted with Bonferroni correction and therefore recognizable as p^i.

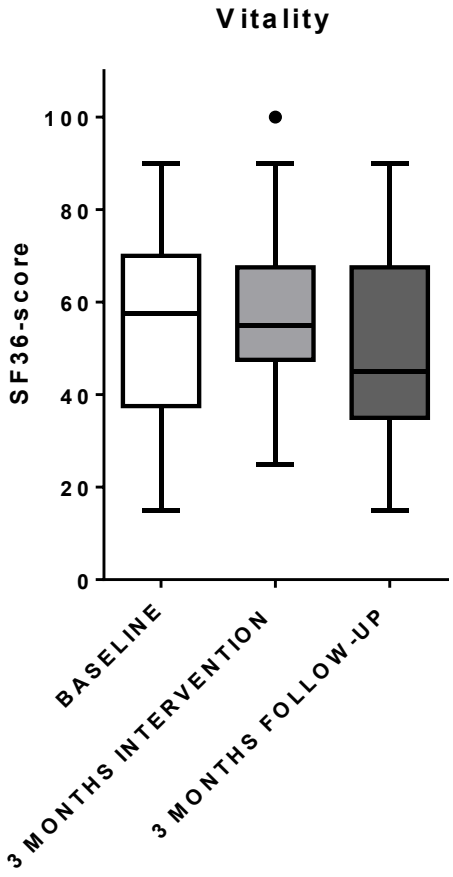


Figure 13: Comparison of "Vitality"

3.2.2.6 SOCIAL ROLE FUNCTIONING

Social Role Functioning revealed no statistically significant change of HRQoL due to probiotic intake (baseline vs 3 months intervention (87.5 (71.9; 100) vs. 100 (75; 100), p^i=0.303)). Yet, 21 of 36 patients experienced maximal Social Role Functioning after intervention, as assessed with SF-36. However, after ceasing the intervention Social Role Functioning dropped significantly (3 months intervention vs. 3 months follow-up (100 (75; 100) vs. 75 (53.1; 100), p^i=0.015), with only 9 of 32 patients reaching the highest score of 100 points. Social Role Functioning stayed the same during probiotic intake and got worse after the therapy was ended. The worst median and first quartile were reached at the end of the study (baseline vs. follow-up (87.5 (71.9; 100) vs. 75 (53.1; 100), p^i=0.858) (see figure 14).
P-values are adjusted with Bonferroni correction and therefore recognizable as p^i.

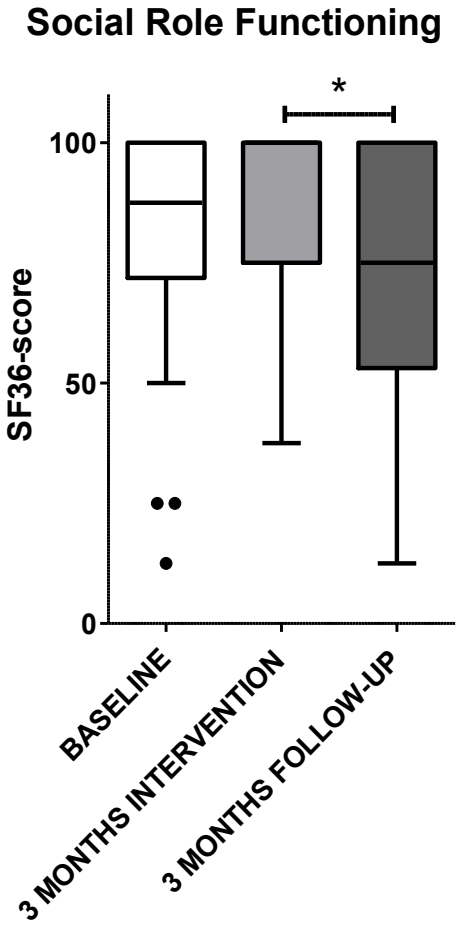


Figure 14: Comparison of "Social Role Functioning"

3.2.2.7 EMOTIONAL ROLE FUNCTIONING

Throughout the whole trial Emotional Role Functioning stays fairly high. The distribution of values with median value as well as first and third quartile stay the same during the whole observation (100 (66.7; 100)). The testing of each time point with each other suggests no changes at all (p^i=0.999), no significant changes were found (see figure 15).

P-values are adjusted with Bonferroni correction and therefore recognizable as p^i.

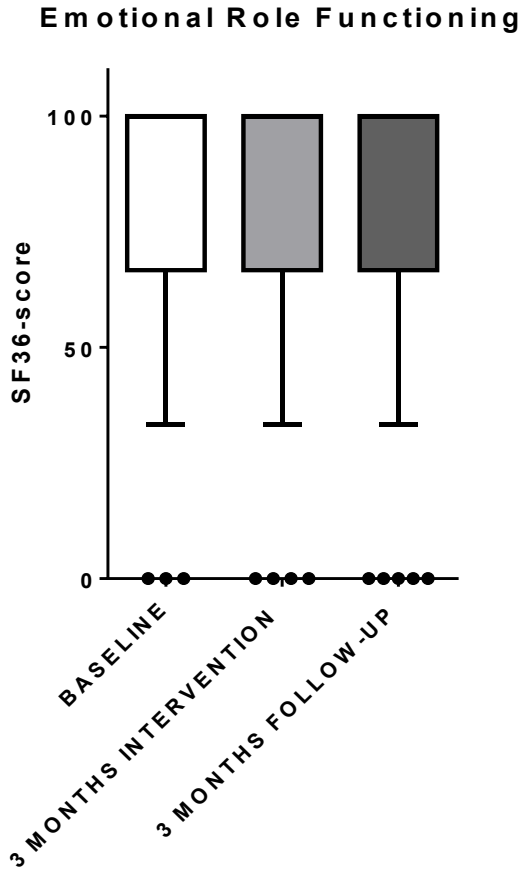


Figure 15: Comparison of “Emotional Role Functioning”

3.2.2.8 MENTAL HEALTH

Mental Health did not change significantly after probiotics intake (baseline vs. after intervention: 72.5 (52; 84) vs. 76 (70; 84), p^i=0.921). The same was observed for the two other comparisons which were carried out (after intervention vs. follow-up 76 (70; 84) vs. 72 (56; 80), p^i=0.999), baseline vs. follow-up: 72.5 (52; 84) vs. 72 (56; 80), p^i=0.999). (see figure 16)

P-values are adjusted with Bonferroni correction and therefore recognizable as p^i.

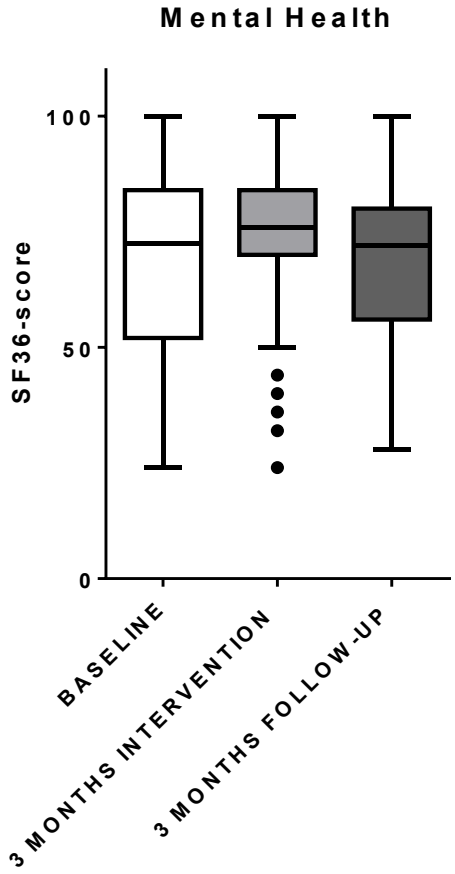


Figure 16: Comparison of "Mental Health"

3.2.3 Summary of SF-36 scores

After comparing baseline and 3 months after intervention score with each other of the eight SF36 HRQoL concepts, no statistically significant differences could be found. Consequently, probiotics had no impact on Quality of Life measured by SF-36 score. The median value of three concepts insignificantly improved after intervention (Bodily Pain, Social Role Functioning and Mental Health), remained unchanged in Emotional Role Functioning and decreased in four concepts (Physical Functioning, Physical Role Functioning, General Health Perceptions, Vitality).

Yet, two statistically significant results were found during follow up period. Firstly, Physical Functioning scores decreased in the whole cohort after 3 months of follow-up compared to baseline, whereas no significant changes were observed during probiotic therapy. Secondly, Social Role Functioning showed a significant decrease within the 3 months follow-up period.

An overview of all scores, median values as well as first and third quartiles can be seen in table 6.

3.2.4 GIQLI – Baseline Analysis

Baseline scores of the GIQLI were compared between male/female and cirrhosis/non cirrhosis patient groups, which is shown in table 3.

Patients who were suffering from liver cirrhosis showed significantly lower baseline scores of Social Items compared to non-cirrhotic patients (baseline cirrhosis vs. non-cirrhosis: 9 (7; 13) vs. 13 (11; 16), p=0.01, independent samples Mann-Whitney U test) (see figure 18). Half of the patients in the cirrhosis group managed to score 9 points and more, whereas on the other hand, patients who were not diagnosed with this disease scored more than 13 points in 50% of the cases. At least a quarter of non-cirrhotic patients did not have any limitations in social life and reached the highest possible score of 16 points. Thus, other measurement points of Social Items were also investigated thoroughly, if there were any differences between the mentioned groups (see section 3.2.5.4). Other items did not show significant differences between cirrhotic and non-cirrhotic patients at baseline. Other minor differences between cirrhotic and non-cirrhotic patients at baseline were statistically insignificant.

No statistically significant differences could be found after comparing each item and the overall score of male and female group at baseline (see figure 17).

Table 3: GIQLI baseline scores, comparison of subgroups

		Baseline M (Q_1; Q_3)	**Baseline** M (Q_1; Q_3)	**p-value**
gender				
		male	female	
	Symptoms	54 (50; 59)	53 (48; 63)	0.863
	Emotions	14 (10; 16)	15 (13; 17)	0.488
	Physical Items	16 (12; 19)	16 (13; 20)	0.931
	Social Items	11 (9; 14)	12 (11;15)	0.47
	Medical Treatment	4 (2; 4)	4 (3;4)	0.863
	Overall Score	96 (90; 116)	102 (83; 114)	0.751
presence of cirrhosis				
		cirrhotic	non-cirrhotic	
	Symptoms	55 (52; 66.5)	52 (46; 59)	0.91
	Emotions	12 (9.5; 16.5)	15 (12.5; 17.5)	0.272
	Physical Items	16 (9; 19)	16 (13; 22.5)	0.259
	Social Items	9 (7; 13)	13 (11; 16)	**0.01**
	Medical Treatment	4 (2; 4)	4 (3; 4)	0.738
	Overall Score	96 (85; 117)	102 (86.5; 112.5)	0.808

independent samples Mann-Whitney U test; significance p≥0.05
M = Median; Q1=first quartile, Q3=third quartile
GIQLI = Gastrointestinal Quality of Life Index

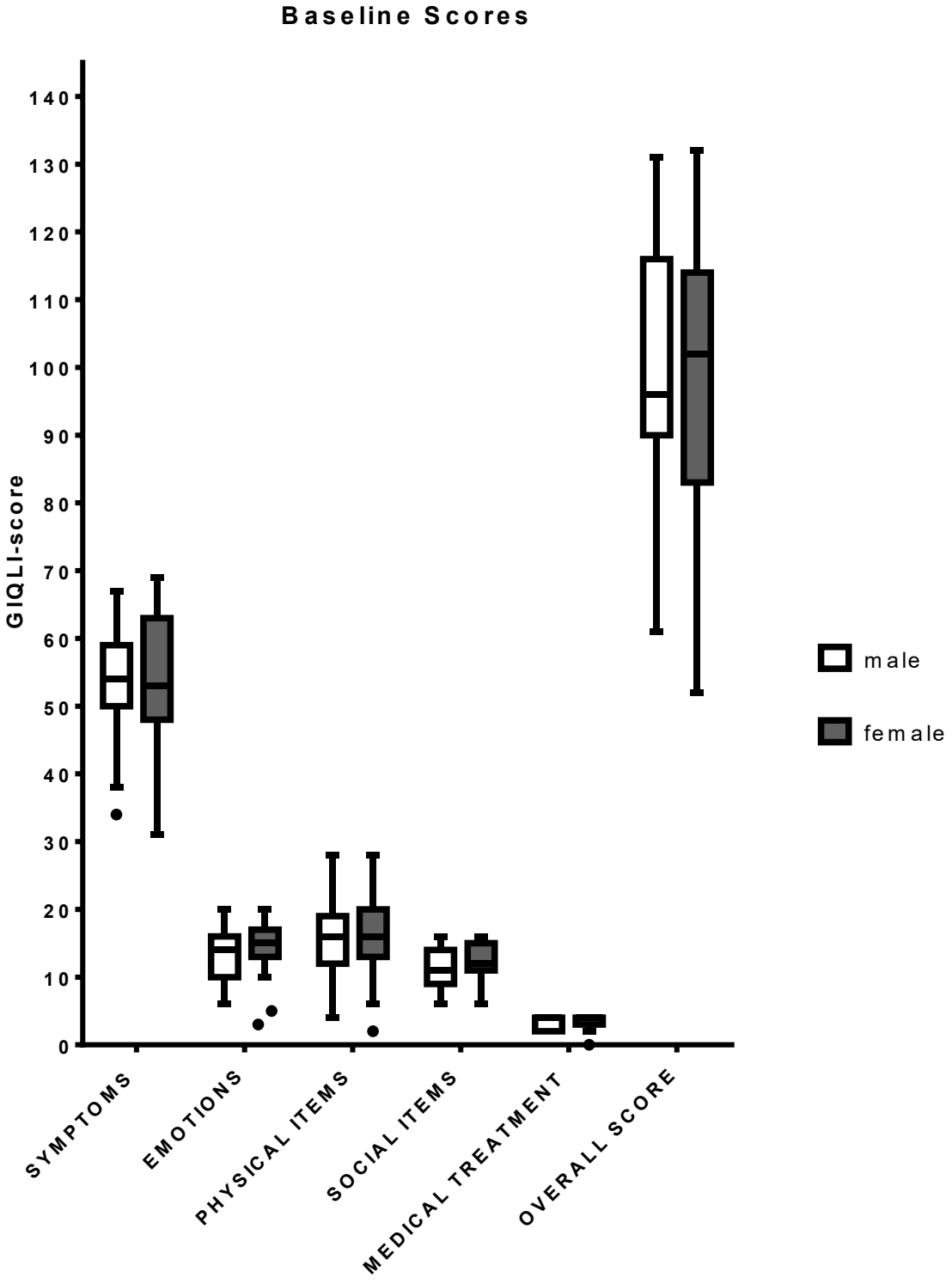


Figure 17: GIQLI Baseline scores; male vs. female

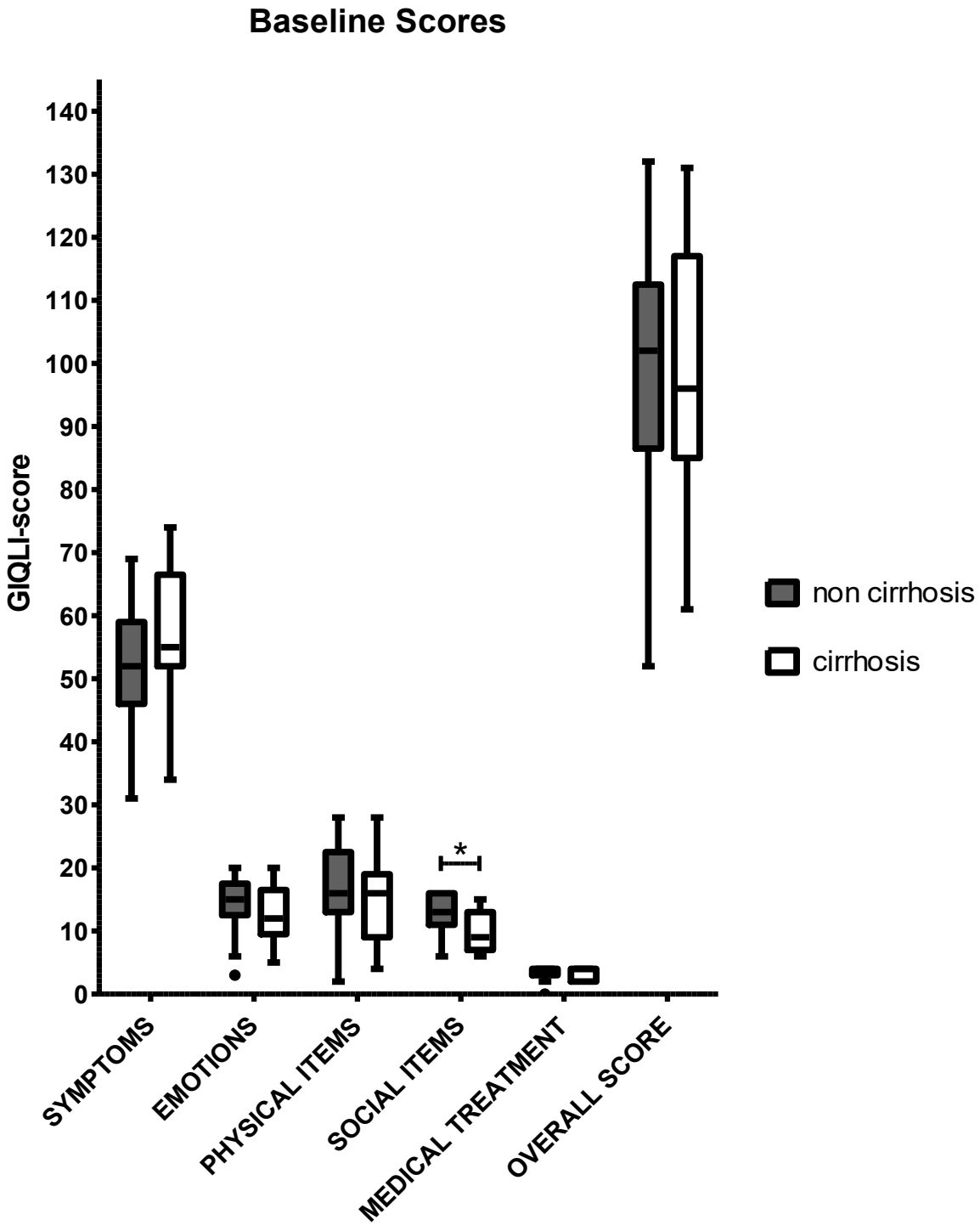


Figure 18: GIQLI baseline scores; cirrhotic vs. non cirrhotic

3.2.5 Effect of probiotic intervention in GIQLI

3.2.5.1 SYMPTOMS

After 3 months of probiotic intake patients had significantly less symptoms than at baseline. The score increased from a median 53.5 (48; 60.5) at baseline to 57 (51; 61) points after intervention (p^i=0.006). This means that patients had for instance less pain in the abdomen, less diarrhoea, less meteorism and less constipation. During the 3 months follow up period a slight, statistically not significant decrease of symptoms score can be observed (60 (52.5; 65.5) vs. 57 (51; 61), p^i=0.999). Comparing baseline score and follow-up, it appears that gastrointestinal symptoms were as frequent at the beginning of the study as in the end (53.5 (48; 60.5) vs. 57 (51; 61) p^i=0.084). The highest possible score of 76 points was not achieved, meaning no patient claimed being free of symptoms at any observed time. (see figure 19)

P-values are adjusted with Bonferroni correction and therefore recognizable as p^i.

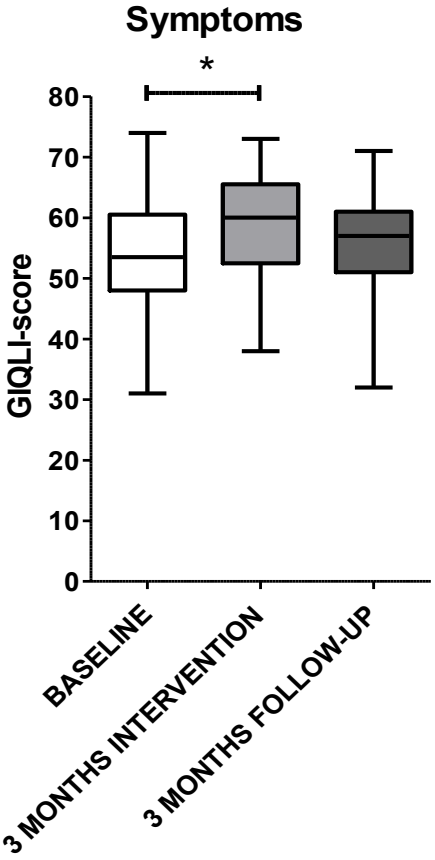


Figure 19: Comparison of "Symptoms"

3.2.5.2 EMOTIONS

The emotions of the patients significantly improved after probiotic intervention. (baseline vs. after intervention: 14.5 (11.8; 17) vs. 16 (12.3; 19), p^i=0.018). At every measurement point some patients did not feel any negative emotions and therefore reached a top score of 20 points. After stopping the intervention Emotions score dropped again, yet statistically not significant (16 (12.3; 19) vs. 14 (11.5; 18), p^i=0.249) (see figure 20).

P-values are adjusted with Bonferroni correction and therefore recognizable as p^i.

After intervention, Emotions scores of cirrhotic patients were significantly lower than of non-cirrhotic patients. (cirrhosis vs. non cirrhosis: 14 (11.5; 16) vs. 18 (14; 19); p=0.043; independent samples Mann Whitney U test).

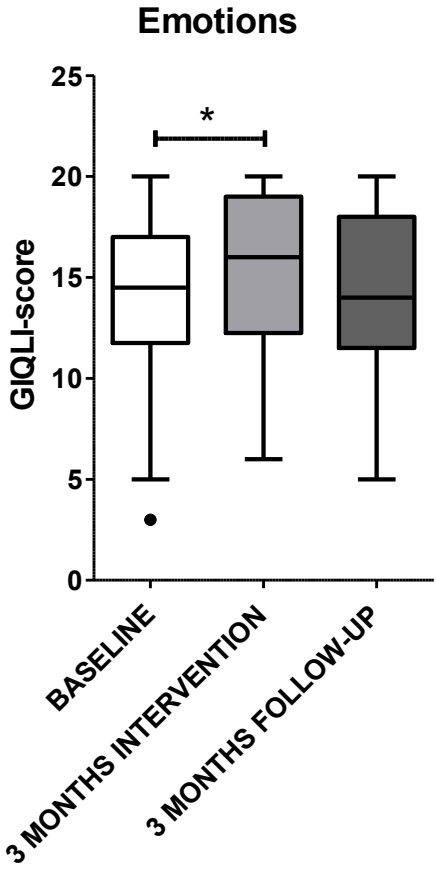


Figure 20: Comparison of "Emotions"

3.2.5.3 PHYSICAL ITEMS

No statistically significant changes in Physical Items score could be detected over the three time points. Higher distribution parameters after intervention are statistically insignificant (baseline vs. after intervention: 16 (12.8; 19.3) vs. 18 (15; 22), p^i=0.372). After follow-up the distribution of values returns to almost the same as at baseline (after intervention vs. follow-up: 18 (15; 22) vs. 16 (12; 19), p^i=0.288; baseline vs. follow-up: (16 (12.8; 19.3) vs. 16 (12; 19), p^i=0.999) (see figure 21). P-values are adjusted with Bonferroni correction and therefore recognizable as p^i.

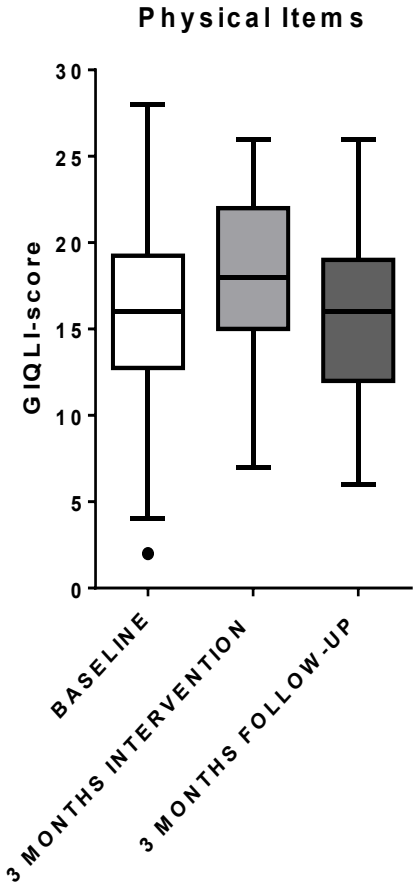


Figure 21: Comparison of "Physical Items"

3.2.5.4 SOCIAL ITEMS

Social Items score of cirrhotic patients were significantly lower at baseline, than of those patients who were not diagnosed with the disease (baseline cirrhosis vs. non-cirrhosis: 9 (7; 13) vs. 13 (11; 16), p=0.01, independent samples Mann-Whitney U test). Consecutively, a closer look was also taken on the other measurement points and cirrhotic as well as non-cirrhotic patients separately. Moreover the groups were investigated jointly (like all the other items).

To begin with, Social Items scores did not change significantly after intervention (12 (9; 15) vs. 13 (9.5; 16), p^i=0.279). A significant decrease of Social Items scores took place in the whole cohort after ceasing the intervention. The comparison between 3 months intervention and 3 months follow-up score reveals that patients felt socially most uncomfortable at the end of the study (13 (9.5; 16) vs. 11 (8; 14), p^i=0.012) (see figure 22). The difference between baseline and 3 months follow-up scores did not reach statistical significance (12 (9; 15) vs. 11 (8; 14), p^i=0.115) (see table 6).

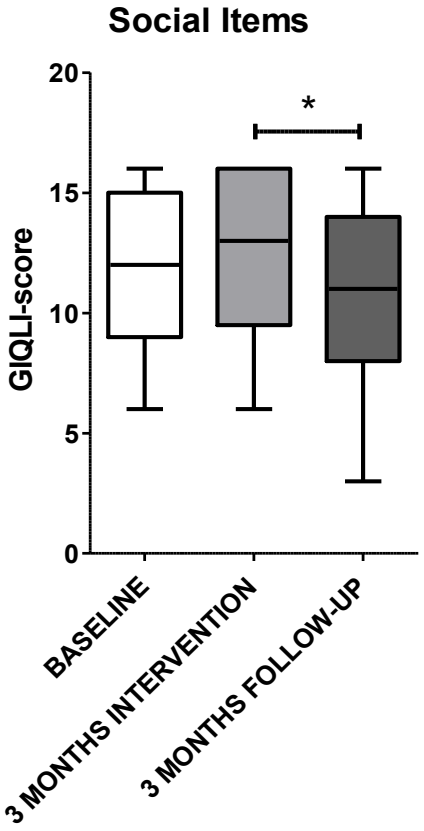


Figure 22: Comparison of "Social Items", all groups included

When splitting the cohort into cirrhotic and non-cirrhotic patients, it was shown that non-cirrhotic patients significantly decreased their Social Items during the follow-up period (non-cirrhotic group after intervention vs. follow-up: 15 (10; 16) vs. 12.5 (9; 14.8), p^i=0.021). Directly after 3 months of probiotics intake no significant changes were observed in non-cirrhotic patients (non-cirrhotic group baseline vs. after intervention: 13 (11; 16) vs. 15 (10; 16), p^i=0.999). The difference between non-cirrhotic baseline and follow-up scores did not reach statistical significance (13 (11; 16) vs. 12.5 (9; 14.8), p^i=0.153).

In cirrhotic patients, insignificant changes during intervention (cirrhotic group baseline vs. after intervention: 9 (7; 14) vs. 12 (8.8; 13.3), p^i=0.498) as well as during follow-up (cirrhotic group after intervention vs. follow-up: 12 (8.8; 13.3) vs. 8 (8; 11.5), p^i=0.69) were observed (see figure 23). The group was small with 15 participants. Finally, there was no difference between cirrhotic group baseline and follow-up scores (9 (7;13) vs. 8 (8; 11.5), p^i=0.999).

P-values are adjusted with Bonferroni correction and therefore recognizable as p^i.

Social Items scores of cirrhotic patients were lower throughout the whole trial than those on non-cirrhotic participants. After 3 months of intervention, this inequality is statistically significant (after intervention cirrhosis vs. non-cirrhosis: 12 (8.8; 13.3) vs. 15 (10; 16); p=0.017, independent samples Mann-Whitney U test). After 3 months of follow-up the social well-being of cirrhotic patients remained lower than that of the other group, yet statistically not significant (follow-up cirrhosis vs. non-cirrhosis: 8 (8; 11.5) vs. 12.5 (9; 14.8), p=0.086, independent samples Mann-Whitney U test) (see figure 23).

Table 4 lists the scores of each group separately and the corrected p values (recognizable as p^i-value) within the groups, comparing the measurement points among each other.

Table 4: GIQLI Social Items, comparison by presence of cirrhosis

SOCIAL ITEMS				
	Baseline	**After Intervention**	**Follow-up**	**p^i-values**
	M (Q_1; Q_3)	M (Q_1; Q_3)	M (Q_1; Q_3)	
cirrhosis (n=14)				
	9 (7; 13)	12 (8.8; 13.3)	8 (8; 11.5)	$^1p^i$=0.498 $^2p^i$=0.69 $^3p^i$=0.999
non-cirrhosis (n=25)				
	13 (11; 16)	15 (10; 16)	12.5 (9; 14.8)	$^1p^i$=0.999 **$^2p^i$=0.021** $^3p^i$=0.153

related samples Wilcoxon signed rank test, p-values corrected with Bonferroni correction, significance level p≥0.05
$^1p^i$… corrected p-value, comparison between baseline and after intervention
$^2p^i$… corrected p-value, comparison between after intervention and follow-up
$^3p^i$… corrected p-value, comparison between baseline and follow-up

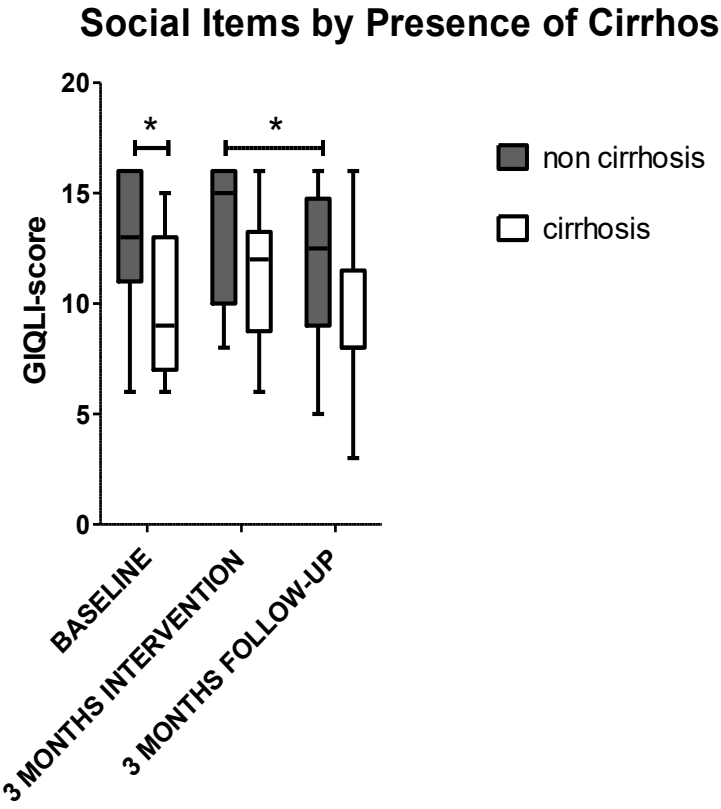


Figure 23: Comparison of "Social Items"; cirrhotic vs non-cirrhotic

3.2.5.5 TROUBLED BY MEDICAL TREATMENT

This item contains one question, asking “During the past 2 weeks, how much have you been troubled by the medical treatment of your illness?”

During probiotic intake patients did not show increased bothering by medical treatment than at baseline. More than 50% of the participants stated, that they were “not at all” troubled by medical treatment. This also applies for cirrhotic patients. After ceasing the probiotic therapy, patients responded to be troubled more by medical treatment than before, with some documenting that they were troubled by medical treatment all the time during the last four weeks. The decrease in this score after finishing the therapy was statistically significant (4; 3; 4; vs. 3; 2; 4; p^i=0.009) No statistical significant changes between baseline score and 3 months follow-up score were found (see figure 24).

P-values are adjusted with Bonferroni correction and therefore recognizable as p^i.

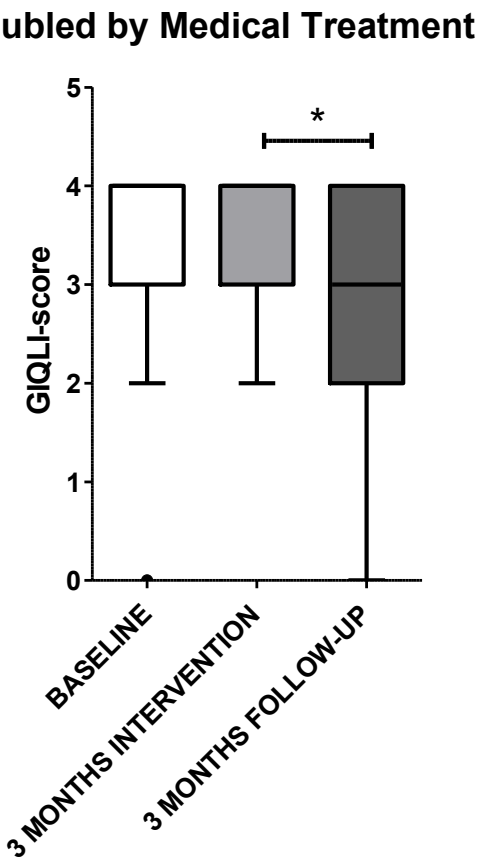


Figure 24: Comparison of "Troubled by Medical Treatment"

3.2.5.6 OVERALL SCORE

In the whole cohort, a statistically significant rise in overall GIQLI score was found. After 3 months of Probiotics treatment patients had a better gastrointestinal quality of life (99 (88.3; 114.5) vs. 108 (100; 121) p^i=0.003) (see table 6). After ceasing therapy, there was a slight, though statistically not significant decrease (after intervention vs. follow-up: 108 (100; 121) vs. 102 (89; 111.5), p^i=0.195). Overall score at the first evaluation was basically the same as overall score at the end of the study. To that end, the frequency of bowel symptoms was similarly high at baseline as after follow-up (99 (83.3; 114.5) vs. 102 (89; 111.5), p^i=0.486) (see figure 25).

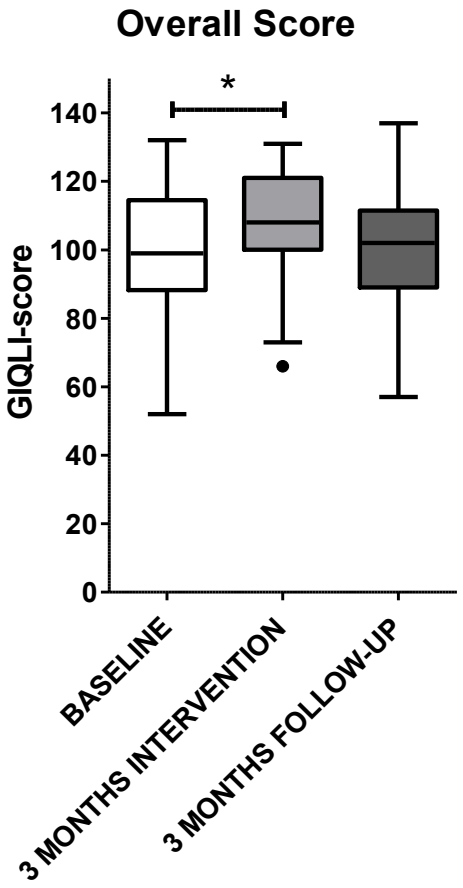


Figure 25: Comparison of "Overall Score"

As the overall score sums up all items of the GIQLI, the results are more conclusive concerning HRQoL than each separate dimension. Cirrhotic and non-cirrhotic patients were analysed separately. Firstly, the non-cirrhosis group was investigated more thoroughly.

The overall score of non-cirrhotic patients significantly increased after probiotic therapy (non-cirrhosis baseline vs. after intervention: 102 (86.5; 112.5) vs. 111 (101; 123), p^i=0.012). Changes of non-cirrhotic patients' GIQLI Overall Score during follow-up were statistically insignificant (non-cirrhosis after intervention vs. follow-up: 111 (101; 123) vs. 102 (88.5; 116.5); p^i=0.123) (see figure 26). Baseline median value and follow-up median value are almost the same in non-cirrhotic patients, indicating that baseline values were reached again after follow-up (non-cirrhosis baseline vs. follow-up: 102 (86.5; 112.5) vs. 102.5 (88.5; 116.5), p^i=0.999).

Most probably because of small sample size no statistically significant change of overall gastrointestinal quality of life was found in cirrhotic patients, neither after intervention (cirrhosis baseline vs. after intervention: 96 (85; 117) vs. 104 (97.5; 111), p^i=0.252), nor during the follow-up period (cirrhosis after intervention vs. follow-up: 104 (97.5; 111) vs. 96 (83.5; 109.5), p^i=0.348). Overall scores at the beginning and at the end of the study reach almost the same values (cirrhosis baseline vs. follow-up: 96 (85; 117) vs. 96 (83.5; 109.5), p^i=0.348).

P-values are adjusted with Bonferroni correction and therefore recognizable as p^i.

Differences between cirrhotic and non-cirrhotic patients were statistically insignificant at any observed measurement point (baseline cirrhosis vs. non-cirrhosis: 96 (85; 117) vs. 102 (86.5; 112.5) p=0.808; after intervention cirrhosis vs. non-cirrhosis: 104 (97.5; 111) vs. 111 (101; 123), p=0.097; follow-up cirrhosis vs. non-cirrhosis: 96 (83.5; 109.5) vs. 102.5 (88.5; 116.5), p=0.624, Mann-Whitney U test).

Table 5 lists the scores of each group separately and the corrected p values (recognizable as p^i-value) within the groups, comparing the measurement points among each other.

Table 5: GIQLI Overall Score, comparison by presence of cirrhosis

OVERALL SCORE				
	Baseline	**After Intervention**	**Follow-up**	**p^i-values**
	M (Q_1; Q_3)	M (Q_1; Q_3)	M (Q_1; Q_3)	
cirrhosis (n=14)				
	96 (85; 117)	104 (97.5; 111)	96 (83.5; 109.5)	$^1p^i$=0.252 $^2p^i$=0.999 $^3p^i$=0.348
non-cirrhosis (n=25)				
	102 (86.5; 112.5)	111 (101; 123)	102.5 (88.5; 116.5)	**$^1p^i$=0.012** $^2p^i$=0.123 $^3p^i$=0.999

related samples Wilcoxon signed rank test, p^i-value = adjusted with Bonferroni correction, significance level p≥0.05
$^1p^i$… corrected p-value, comparison between baseline and after intervention
$^2p^i$… corrected p-value, comparison between after intervention and follow-up
$^3p^i$… corrected p-value, comparison between baseline and follow-up

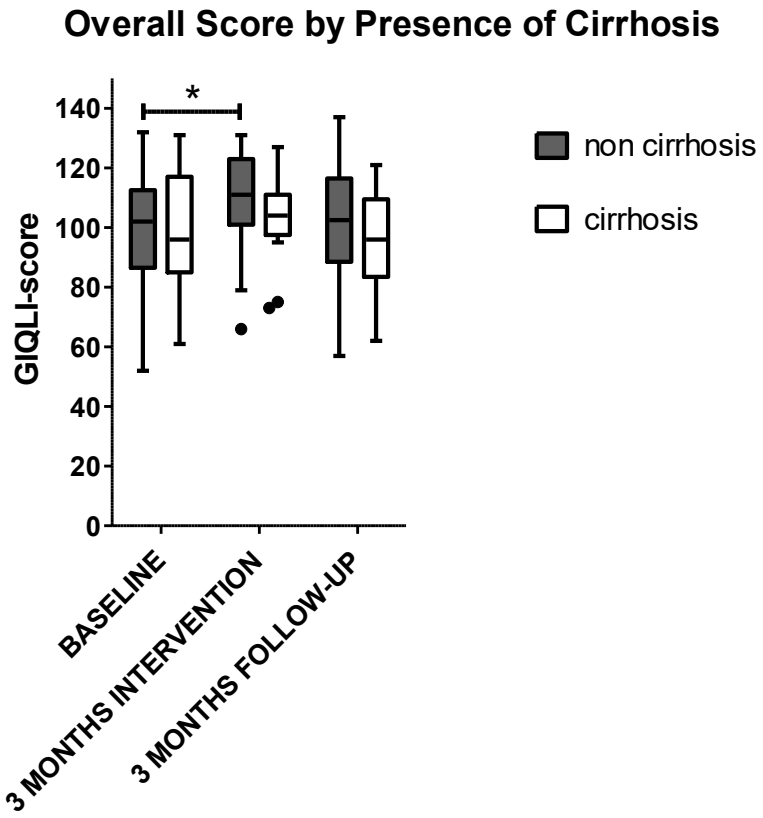


Figure 26: Comparison of "Overall Score"; cirrhotic vs. non-cirrhotic

3.2.6 Summary of GIQLI scores

The majority of the GIQLI concepts changed significantly in the course of the study. Also, differences between cirrhotic and non-cirrhotic patients were observed. These are the statistically significant findings:

The whole cohort improved their HRQoL in three GIQLI concepts during intervention: Symptoms, Emotions and Overall Score. This means, that patients reported less bowel symptoms as well as better emotions in association with probiotic therapy. Adding Symptoms and Emotions scores as well as all the other items (which rose insignificantly after intervention), a higher Overall score was achieved. On the other hand, patients felt significantly worse in certain areas after ceasing the probiotic therapy, such as in Social Items and they felt like they were troubled more severely by medical treatment.

A closer look on the influence of cirrhosis on the reported HRQoL was just taken at baseline and on certain concepts, such as Overall Score (because it summarizes the information of all the other concepts) and Social Items (because there was a significant difference at baseline). Cirrhotic patients´ Social Items scores were significantly lower than those of non-cirrhotic patients at baseline and after 3 months of probiotic therapy. Although lower at all measurement points, Overall Scores of cirrhotic patients were not significantly different from non-cirrhotic patient´s scores throughout the whole study.

Table 6: SF-36 and GIQLI Scores at different measurement points

		Baseline M (Q_1; Q_3)	After Intervention M (Q_1; Q_3)	Follow-up M (Q_1; Q_3)	p^i-values
SF-36					
	Physical Functioning	80 (55.3; 93.9)	75 (56.7; 90)	62.5 (47.5; 90)	$^1p^i$=0.999 $^2p^i$=0.141 $^3p^i$=**0.032**
	Physical Role Functioning	75 (25; 100)	62.5 (25; 100)	50 (0; 100)	$^1p^i$=0.513 $^2p^i$=0.999 $^3p^i$=0.372
	Bodily Pain	51 (41; 100)	68 (41; 100)	46.5 (34.3; 74)	$^1p^i$=0.228 $^2p^i$=0.282 $^3p^i$=0.999
	General Health Perceptions	62 (38.5; 69.5)	57 (42.5; 72)	52 (35.5; 70.8)	$^1p^i$=0.999 $^2p^i$=0.504 $^3p^i$=0.999
	Vitality	57.5 (37.5; 70)	55 (47.5; 67.5)	45 (35; 67.5)	$^1p^i$=0.999 $^2p^i$=0.438 $^3p^i$=0.999
	Social Role Functioning	87.5 (71.9; 100)	100 (75; 100)	75 (53.1; 100)	$^1p^i$=0.303 $^2p^i$=**0.015** $^3p^i$=0.858
	Emotional Role Functioning	100 (66.7; 100)	100 (66.7; 100)	100 (66.7; 100)	$^1p^i$=0.999 $^2p^i$=0.999 $^3p^i$=0.999
	Mental Health	72.5 (52; 84)	76 (70; 84)	72 (56; 80)	$^1p^i$=0.921 $^2p^i$=0.999 $^3p^i$=0.999
GIQLI					
	Symptoms	53.5 (48; 60.5)	60 (52.5; 65.5)	57 (51; 61)	$^1p^i$=**0.006** $^2p^i$=0.999 $^3p^i$=0.084
	Emotions	14.5 (11.8; 17)	16 (12.3; 19)	14 (11.5; 18)	$^1p^i$=**0.018** $^2p^i$=0.249 $^3p^i$=0.999
	Physical Items	16 (12.8; 19.3)	18 (15; 22)	16 (12; 19)	$^1p^i$=0.372 $^2p^i$=0.288 $^3p^i$=0.999
	Social Items	12 (9; 15)	13 (9.5; 16)	11 (8; 14)	$^1p^i$=0.279 $^2p^i$=**0.012** $^3p^i$=0.115
	Medical Treatment	4 (3; 4)	4 (3; 4)	3 (2; 4)	$^1p^i$=0.222 $^2p^i$=**0.009** $^3p^i$=0.819
	Overall Score	99 (88.3; 114.5)	108 (100; 121)	102 (89; 111.5)	$^1p^i$=**0.003** $^2p^i$=0.195 $^3p^i$=0.486

related samples Wilcoxon signed rank rest; significance level $p \geq 0.05$; p^i value = adjusted with Bonferroni correction; SF-36 = Short Form 36 questionnaire, GIQLI = Gastrointestinal Quality of Life Index; M = Median; Q_1=first quartile, Q_3=third quartile

$^1p^i$ … comparison between baseline and after intervention

$^2p^i$ … comparison between after intervention and follow-up

$^3p^i$ … comparison between baseline and follow-up

4 Discussion

In this study, the question if probiotic intake can ameliorate the HRQoL in patients under long term PPIs therapy was addressed. Therefore, the QoL was assessed with two different questionnaires (SF-36 and GIQLI) at three different time points. After the first assessment at baseline the therapy started. QoL was re-evaluated after 3 months of therapy. Another evaluation was carried out after 3 months of follow up. The most relevant findings during the study include a rise in three out of five GIQLI items after intervention (Symptoms, Emotions, Overall score). Other items also showed a rise, yet not statistically significant (e.g. SF36 Bodily Pain, Social Role Functioning and Mental Health score as well as GIQLI Physical Items and Social Items score). Notably, no significant worsening of quality of life concepts´ median values was detected in any of the questionnaires, suggesting that side effects of probiotics at least in the last four weeks of intervention are neglectable in the observed patients. On the other hand, significantly decreased physical functioning scores after follow up compared to baseline were observed in SF-36 as well as decreased social role functioning, social items and medical treatment after follow up compared to the score after intervention respectively. This indicates that probiotics have the potential to improve gastrointestinal HRQoL by relieving gastrointestinal symptoms as well as improving emotions in patients undergoing long term PPI therapy.

It was already shown that probiotics have the potential to relieve abdominal problems (100). In our study patients had less gastrointestinal symptoms according to GIQLI after probiotic intake. Equivalently Lorenzo-Zúñiga et al. found that in patients with irritable bowel syndrome (IBS) and diarrhoea the quality of life improved significantly due to probiotic intake (36), a finding which correlates well with two other systematic reviews, which found reduced symptoms in IBS patients treated with probiotics (101, 102). Similar observations were made with probiotic treatment in other diseases, including ulcerative colitis, where Van der Waal et al. found that 57% of patients reacted positively to probiotic consumption, while no patient reported any negative impact (103). Furthermore, it was recently shown that in patients with reflux esophagitis who were treated with esomeprazole, the administration of a probiotic containing B. subtilis and E. faecium had a beneficial effect in terms of frequency of diarrhoea and time to relapse. Additionally, less SIBO

was observed in the probiotic group (104). On the other hand, a publication from the year 2008 reveals, that the administration of probiotic yoghurt increased the occurrence of adverse events (metallic taste, diarrhoea, abdominal pain, abdominal distension and gastric acid regurgitation) in patients with helicobacter pylori gastritis undergoing triple therapy (41.1% in triple plus yoghurt group vs. 26.3 in triple only group). They suspect a response bias, because patients ate yoghurt for another two weeks after finishing triple therapy, which only had lasted seven days. Yet a lower eradication rate from 78.7% in patients who just received triple therapy compared to 87.5% in patients who additionally received yoghurt was detected in per protocol analysis. Some mechanisms they consider are lactic acid (which inhibits *H. pylori* urease), bacteriocins, inhibition of the attachment of *H. pylori* to gastric cell lines as well as immunologic response improvement and gastric barrier effects. All of these effects are attributed to lactic acid bacteria like *Lactobacillus*, *Bifidobacterium* and *Enterococcus faecium* (105). Another study included 128 children suffering from gastrointestinal reflux disease and therefore undergoing PPI treatment for 12 weeks. Patients were split into two groups, of which one group was additionally treated with a single strain probiotic containing *Lactobacillus reuteri*, the other group got placebo. In the probiotics group only 6.2% of the children had SIBO, compared with 56.2% in placebo group (106). Yet the duration of probiotic intake in the cited study differs from that in this study, these findings underline the effects of PPIs on the gastrointestinal microbiome as well as benefits of probiotics on these circumstances.

Symptoms scores are not the only concepts of HRQoL. If gastrointestinal HRQoL – in this study represented by GIQLI Overall Score – is ameliorated, it is likely that more than one concept improved throughout the trial, like Emotions score for example. In the context of the gut brain axis probiotics may have the potential to exert substantial positive effects on the overall human health and quality of life. While a study at the medical university of Graz has shown negative correlations between microbial diversity in the gut in both duration of bipolar disorder and depressive symptoms (107), researchers have also already discovered that probiotics reduce the risk of depression (108).

In 2015, Iranian scientists conducted a trial to test the impact of probiotics on the mental health of petrochemical workers. The participants were randomly divided into three different subgroups: the first group received probiotic yoghurt and a placebo

capsule, the second conventional yoghurt and a probiotic capsule and the third group conventional yoghurt and a placebo capsule each day for a period of 6 weeks. Mental health was assessed using general health questionnaire (GHQ) and depression anxiety and stress scale (DASS). Both, GHQ and DASS improved after probiotic therapy including probiotic yoghurt and probiotic capsule. (109) These findings support the results in our study, where GIQLI Emotions score was significantly better after probiotic consumption.

In 2015 Steenberg et al. showed that negative thoughts associated with sad mood were reduced with the help of probiotics. The probiotic mixture contained *Bifidobacterium bifidum W23*, *Bifidobacterium lactis W52*, *Lactobacillus acidophilus W37*, *Lactobacillus casei W56*, *Lactobacillus salivarius W24* and *Lactococcus lactis W19* (110). All of these strains were also in our study product, inconclusively indicating that this mixture has positive effects.

A re-assessment of HRQoL after a three month washout phase was intended to serve as control parameter as no second group was included in this trial. A shorter period than three months might have been too short to detect a change, as a trial in children with autism shows, where a washout period of three weeks was chosen and no changes in gastrointestinal symptoms and QoL were identifiable (111). Another trial aiming to reduce oral *Streptococcus mutans* in children´s oral microbiome by using probiotics first led to a reduction in *S. mutans* and detected a rise again after six months of follow up (112). It is hard to determine when the effective period of probiotics is ending after ceasing the intervention. Nevertheless, the three months washout period in our trial led to decreased scores in all items, of which three were statistically significant, including SF36 Social Role Functioning as well as GIQLI Social Items and Troubled by Medical Treatment score.

Poor HRQoL correlates well with low scores in physical, emotional and social scores. This was shown in a cross sectional study, which was conducted in Karachi, Pakistan using the GIQLI. Low overall scores were associated with low scores in all the mentioned domains (113). In our study, GIQLI revealed an increase in several different items after intervention. Significant increases in Symptoms and Emotions scores after probiotic intervention as well as not significant increases in physical items and Social Items contributed to a considerable rise in Overall Score. Moreover, Social Items score and Medical Treatment score significantly dropped during follow-up period, which contrasts well the observations made during therapy.

The significant drop of GIQLI Social Items score also corresponds well with the significantly lower SF-36 Social Role Functioning score.

GIQLI and SF-36 are well evaluated tools to assess HRQoL. Hon-Yi Shi et al. used both questionnaires to determine, whether these surveys are appropriate to detect minimal clinically important differences after cholecystectomy. They found that both tools were able to detect differences after the intervention. Yet they also observed that both questionnaires showed so called floor and ceiling effects, meaning that many patients reach the minimum or maximum score, respectively. (114) These effects impose an obstacle in the assessment of the results, as negative changes cannot be detected if the score is at minimum at the beginning (floor effect) alike positive changes if the score is high at baseline (ceiling effect). In our study, SF36 Emotional Role Functioning showed a ceiling effect. In this case the questionnaire shows a limited responsiveness (=sensitivity to change), which is the ability to detect important changes in health status in the course of time, even if they are small. Responsiveness is especially important for individual patients, as statistically significant changes in experiments with high case numbers do not necessarily have to be of importance for a single person, still they are essential for clinical decision making (115). Further investigation using other and more personalised evaluation tools have the potential to provide definitive answers when it comes to determining individual probiotic therapy effect.

As this trial was conducted as a pilot study, which was designed to find out whether probiotic intake can help to ameliorate HRQoL of patients under long term PPI therapy, no placebo control group was included. This fact imposes the biggest disadvantage in the protocol. Repeating this study as double blinded randomised controlled trial (RCT) could lead to more accurate results in terms of validity, although the suitability of RCTs for nutritional research and especially for the evaluation of the effectiveness of probiotics is also challenged. D. Zeilstra et al. argue, that patients enrolled in probiotic study should be screened for confounders before equally being assigned to intervention or placebo group. Also they challenge the implementation of crossover designs in probiotic research as even long washout effects cannot prevent potential carryover effects (116). Each microbiome and their interactions with humans are individual. Therefore, new approaches in probiotic research could help tailor individual solutions for patients.

Nevertheless, strong recommendations can only be drawn from RCTs or systematic reviews and they are therefore essential in all fields of medical research (117). In their perspective paper Suez et al. see large-scale randomized and blinded clinical trials as a mainstay of modern research in probiotics. They clearly advocate for taking individual differences into account by objectively assessing endpoints to detect confounders (118).

Further addressing confounders, the influence of liver cirrhosis on HRQoL and therapy effectiveness was addressed. Therefore, we carried out a baseline analysis, comparing SF36 and GIQLI scores depending on liver cirrhosis. Compared to age and gender matched controls, cirrhotic patients show significantly worse HRQoL, as assessed with SF36 (119). In our study, most items of both SF36 and GIQLI indicate that cirrhotic patients have worse HRQoL then the other patients, yet statistically significance was just reached in GIQLI Social Items. The missing significance in our study might be due to small sample size, as just fourteen cirrhotic patients were included in analysis. That is the reason, why a deeper analysis in most of the Items at other time points was not further pursued. Also, no gender differences in SF-36 and GIQLI baseline scores were found. The influence of gender on therapy efficacy was not further addressed in the course of the study as most female patients were non-cirrhotic and hence a certain gender bias was assumed.

Another drawback of this study design is, that it remains elusive whether the observed positive changes are just imputable to probiotic intake, as other changes in lifestyle during intervention were not observed. Furthermore, response shift bias and recall bias may occur, which are major limitations in the field of monitoring changes in HRQoL especially when using subjective wellbeing measurements. Recall bias typically occurs in retrospective evaluation, response shift however may occur in prospective studies. Both limit the validity and reliability of the assessment of changes in HRQoL assessed with subjective wellbeing measurements (120). Recalibration, reconceptualization and reprioritization are the three different types of response shift (121). In other words, response shifts can be caused by a change in concepts, inner values or internal standards of people in the course of time. These alterations in personal perceptions may lead to incomparable results in HRQoL research. The comparison of HRQoL as it is assessed at different time points is based on the assumption that personal concepts, individual beliefs and measurement scales remain stable over the course of time (122). Given this context,

the insignificantly better scores of cirrhotic patients in SF-36 Physical Functioning score and GIQLI Symptoms score in our study might not be completely arbitrary but an indicator of a difference in inner concepts. On the other side, this assumption is inconclusive, as patients in the non-cirrhosis group were not healthy but mostly suffering from less severe disease.

The problem of response shift bias is also present when using standardised questionnaires, such as the SF-36. Tools which can detect response shifts have already been applied to enhance the interpretation of HRQoL changes in other studies (123). Finally, HRQoL measurements still are not seen as tightly regulated outcome parameters as these tools are very subjective. Nevertheless, other subjective concepts besides from HRQoL like satisfaction with therapy and perceived effectiveness were found to be important parameters in a patient´s point of view (86). This fact underlines the importance of subjective experiencing. Combining “hard” clinical measurements like laboratory parameters or microbiome analysis with HRQoL surveys can widen horizons in interpreting the clinical significance of study outcomes.

Further limitations include the uncertainty of which combination of strains, which duration and which amount of administered probiotics show the highest beneficial outcome. This question was addressed by Y. Zhang et al. They conducted a meta-analysis of 21 RCTs where IBS patients received a daily dose of probiotics or were administered to a control group. The outcome they looked at, was overall symptoms on the one hand and HRQoL on the other hand. Generally, they concluded, that probiotic therapy is beneficial for IBS patients in terms of overall symptoms reduction as well as improvement of HRQoL. Furthermore, number of strains, therapy duration and amount of bacteria in the product were more closely examined. Speaking of the 9 included trials which used HRQoL as an outcome parameter, the single strain probiotic therapy showed a higher impact on HRQoL, yet only one study using a single strain probiotic was included. In two studies, less then 10^{10}cfu/d were given and compared to those where a higher amount of bacteria were administered, those who received the smaller dose had higher increases in HRQoL. The third parameter, therapy duration, indicates that a therapy duration of less than 8 weeks (4 studies) appears to be more effective. No evidence of publication bias was found there (124). Another review including five studies also addressed the efficacy of probiotics containing Bifidobacterium infantis in IBS. Yuan F. et al. came to contrary results

than Y. Zhang et al. as far as the number of strains is concerned. Primary outcomes were abdominal symptoms including pain, bloating, distension and bowel habit. Composite probiotics containing B. infantis showed positive impacts. Yet, no significant improvement was found in patients receiving single probiotic B. infantis (125). As these findings are contradictory no clear conclusion can be drawn from these two reviews as far as number of strains is concerned, which makes further research in this field necessary.

Some of the cited studies are financially supported or conducted by pharma companies. A question which frequently rises when interventional studies are financed by (pharma-) industries is whether the results are less trustworthy. In 2019 a systematized review comparing industry funded studies with non-funded studies carried out, that industry funding of studies in which probiotics were used as a treatment of acute diarrhoea had no impact on the outcome (126).

In conclusion, supplementary probiotic treatment in patients undergoing long term PPI therapy might be useful to ameliorate gastrointestinal HRQoL. To get a more complete understanding further investigations are needed to determine optimal therapy duration, dosage and composition of strains. RCTs should therefore be used as golden standard, yet approaches addressing individual outcomes may help tailor patient specific therapies.

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Fragebogen zur gastrointestinalen Lebensqualität nach Eypasch 1993

1. Wie häufig in den letzten zwei Monaten hatten Sie Schmerzen im Bauch?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

2. Wie oft in den letzten zwei Monaten hat Sie Völlegefühl im Oberbauch gestört?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

3. Wie oft in den letzten zwei Monaten fühlten Sie sich belästigt durch Blähungen oder das Gefühl, zu viel Luft im Bauch zu haben?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

4. Wie oft in den letzten zwei Monaten fühlten Sie sich durch Windabgang gestört?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

5. Wie oft in den letzten zwei Monaten fühlten Sie sich durch Rülpsen oder Aufstoßen belästigt?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

6. Wie oft in den letzten zwei Monaten hatten Sie auffallende Magen- oder Darmgeräusche?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

7. Wie oft in den letzten zwei Monaten fühlten Sie sich durch heftigen Stuhlgang gestört?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

8. Wie oft in den letzten zwei Monaten hatten Sie Spaß und Freude am Essen?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(4)	(3)	(2)	(1)	(0)

9. Wie oft haben Sie bedingt durch Ihre Erkrankung auf Speisen, die Sie gerne essen, verzichten müssen?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

10. Wie sind Sie während der letzten zwei Monate mit dem alltäglichen Stress fertig geworden?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(4)	(3)	(2)	(1)	(0)

11. Wie oft in den letzten zwei Monaten waren Sie traurig darüber, dass Sie krank sind?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

12. Wie häufig in den letzten zwei Monaten waren Sie nervös oder ängstlich wegen Ihrer Erkrankung?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

13. Wie häufig in den letzten zwei Monaten waren Sie mit Ihrem Leben allgemein unzufrieden?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

14. Wie häufig in den letzten zwei Monaten waren Sie frustriert über Ihre Erkrankung?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

15. Wie häufig in den letzten zwei Monaten haben Sie sich müde oder abgespannt gefühlt?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

16. Wie häufig in den letzten zwei Monaten haben Sie sich unwohl gefühlt?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

17. Wie oft während der letzten Woche (eine Woche) sind sie nachts aufgewacht?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

18. In welchem Maße hat Ihre Erkrankung zu störenden Veränderungen Ihres Aussehens geführt?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

19. Wie sehr hat sich bedingt durch Ihre Erkrankung, Ihr allgemeiner Kräftezustand verschlechtert?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

20. Wie sehr haben sie, bedingt durch Ihre Erkrankung, Ihre Ausdauer verloren?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

21. Wie sehr haben Sie durch Ihre Erkrankung Ihre Fitness verloren?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

22. Haben Sie Ihre normalen Aktivitäten z.B. Beruf, Schule, Haushalt während der letzten zwei Monate fortführen können?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(4)	(3)	(2)	(1)	(0)

23. Haben Sie während der zwei letzten Monate Ihre normalen Freizeitaktivitäten (Sport, Hobby usw.) fortführen können?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(4)	(3)	(2)	(1)	(0)

24. Haben Sie während der zwei letzten Monate durch die medizinische Behandlung sehr beeinträchtigt gefühlt?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

25. In welchem Ausmaß hat sich das Verhältnis zu Ihnen nahstehenden Personen durch Ihre Erkrankung verändert?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

26. In welchem Ausmaß ist Ihr Sexualleben durch Ihre Erkrankung verändert?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

27. Haben Sie sich in den letzten zwei Monaten durch Hochlaufen von Flüssigkeiten oder Nahrung in den Mund beeinträchtigt gefühlt?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

28. Wie oft in den letzten zwei Monaten haben Sie sich durch Ihre langsame Essgeschwindigkeit beeinträchtigt gefühlt?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

29. Wie oft in den letzten zwei Monaten haben Sie sich durch Beschwerden beim Schlucken Ihrer Nahrung beeinträchtigt gefühlt?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

30. Wie oft in den letzten zwei Monaten wurden Sie durch dringenden Stuhlgang belästigt?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

31. Wie oft in den letzten zwei Monaten hat Durchfall Sie belästigt?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

32. Wie oft in den letzten zwei Monaten hat Verstopfung Sie belästigt?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

33. Wie oft in den letzten zwei Monaten haben Sie sich durch Übelkeit beeinträchtigt gefühlt?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

34. Wie oft in den letzten zwei Monaten hat Blut im Stuhlgang Sie beunruhigt?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

35. Wie oft in den letzten zwei Monaten fühlten Sie durch Sodbrennen gestört?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

36. Wie oft in den letzten zwei Monaten fühlten Sie sich durch ungewollten Stuhlgang gestört?

Die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

(1) SF36 - Fragebogen zum Gesundheitszustand

Name:		Unters.-Datum:	
Vorname:		ID-Nr.:	
Geb.-Datum:		Tel.-Nr.:	

In diesem Fragebogen geht es um Ihre Beurteilung Ihres Gesundheitszustandes. Der Bogen ermöglicht es, im Zeitverlauf nachzuvollziehen, wie Sie sich fühlen und wie Sie im Alltag zurechtkommen.

Bitte beantworten Sie jede der folgenden Fragen, indem Sie bei den Antwortmöglichkeiten die Zahl ankreuzen, die am besten auf Sie zutrifft.

1. Wie würden Sie Ihren Gesundheitszustand im allgemeinen beschreiben? (Bitte kreuzen Sie nur eine Zahl an)

Ausgezeichnet	1
Sehr gut	2
Gut	3
Weniger gut	4
Schlecht	5

2. Im Vergleich zum vergangenen Jahr, wie würden Sie Ihren derzeitigen Gesundheitszustand beschreiben? (Bitte kreuzen Sie nur eine Zahl an)

Derzeit viel besser als vor einem Jahr	1
Derzeit etwas besser als vor einem Jahr	2
Etwa so wie vor einem Jahr	3
Derzeit etwas schlechter als vor einem Jahr	4
Derzeit viel schlechter als vor einem Jahr	5

3. Im folgendem sind einige Tätigkeiten beschrieben, die Sie vielleicht an einem normalen Tag ausüben. Sind Sie durch Ihren derzeitigen Gesundheitszustand bei diesen Tätigkeiten eingeschränkt? Wenn ja, wie stark? (Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

Tätigkeit	Ja, stark eingeschränkt	Ja, etwas eingeschränkt	Nein, überhaupt nicht eingeschränkt
a. anstrengende Tätigkeiten, z.B. schnell laufen, schwere Gegenstände heben, anstrengenden Sport treiben	1	2	3
b. mittelschwere Tätigkeiten, z.B. einen Tisch verschieben, staubsaugen, kegeln, Golf spielen	1	2	3
c. Einkaufstaschen heben oder tragen	1	2	3
d. mehrere Treppenabsätze steigen	1	2	3
e. einen Treppenabsatz steigen	1	2	3
f. sich beugen, knien, bücken	1	2	3
g. mehr als 1 Kilometer zu Fuß gehen	1	2	3
h. mehrere Straßenkreuzungen weit zu Fuß gehen	1	2	3
i. eine Straßenkreuzung weit zu Fuß gehen	1	2	3
j. sich baden oder anziehen	1	2	3

4. Hatten Sie in den vergangen 4 Wochen aufgrund Ihrer körperlichen Gesundheit irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause? (Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

Schwierigkeiten	Ja	Nein
a. Ich konnte nicht so lange wie üblich tätig sein	1	2
b. Ich habe weniger geschafft, als ich wollte	1	2
c. Ich konnte nur bestimmte Dinge tun	1	2
d. Ich hatte Schwierigkeiten bei der Ausführung (z.B. ich mußte mich besonders anstrengen)	1	2

5. Hatten Sie in den vergangenen 4 Wochen aufgrund seelischer Probleme irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause (z.B. weil Sie sich niedergeschlagen oder ängstlich fühlen)? (Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

Schwierigkeiten	Ja	Nein
a. Ich konnte nicht so lange wie üblich tätig sein	1	2
b. Ich habe weniger geschafft, als ich wollte	1	2
c. Ich konnte nicht so sorgfältig wie üblich arbeiten	1	2

6. Wie sehr haben Ihre körperliche Gesundheit oder seelischen Probleme in den vergangenen 4 Wochen Ihre normalen Kontakte zu Familienangehörigen, Freunden, Nachbarn oder zum Bekanntenkreis beeinträchtigt? (Bitte kreuzen Sie nur eine Zahl an)

Überhaupt nicht	1
Etwas	2
Mäßig	3
Ziemlich	4
Sehr	5

7. Wie stark waren Ihre Schmerzen in den vergangenen 4 Wochen? (Bitte kreuzen Sie nur eine Zahl an)

Ich hatte keine Schmerzen	1
Sehr leicht	2
Leicht	3
Mäßig	4
Stark	5
Sehr stark	6

8. Inwieweit haben die Schmerzen Sie in den vergangenen 4 Wochen bei der Ausübung Ihrer Alltagstätigkeit zu Hause und im Beruf behindert? (Bitte kreuzen Sie nur eine Zahl an)

Überhaupt nicht	1
Etwas	2
Mäßig	3
Ziemlich	4
Sehr	5

9. In diesen Fragen geht es darum, wie Sie sich fühlen und wie es Ihnen in den vergangenen 4 Wochen gegangen ist. (Bitte kreuzen Sie in jeder Zeile die Zahl an, die Ihrem Befinden am ehesten entspricht).

Wie oft waren Sie in den vergangenen 4 Wochen ...

Befinden	Immer	Meistens	Ziemlich oft	Manchmal	Selten	Nie
a. ... voller Schwung?	1	2	3	4	5	6
b. ... sehr nervös?	1	2	3	4	5	6
c. ... so niedergeschlagen, daß Sie nichts aufheitern konnte?	1	2	3	4	5	6
d. ... ruhig und gelassen?	1	2	3	4	5	6
e. ... voller Energie?	1	2	3	4	5	6
f. ... entmutigt und traurig?	1	2	3	4	5	6
g. ... erschöpft?	1	2	3	4	5	6
h. ... glücklich?	1	2	3	4	5	6
i. ... müde?	1	2	3	4	5	6

10. Wie häufig haben Ihre körperliche Gesundheit oder seelischen Probleme in den vergangenen 4 Wochen Ihre Kontakte zu anderen Menschen (Besuche bei Freunden, Verwandte usw.) beeinträchtigt? (Bitte kreuzen Sie nur eine Zahl an)

Immer	1
Meistens	2
Manchmal	3
Selten	4
Nie	5

11. Inwieweit trifft jede der folgenden Aussagen auf Sie zu? (Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

Aussagen	Trifft ganz zu	Trifft weitgehend zu	Weiß nicht	Trifft weitgehend nicht zu	Trifft überhaupt nicht zu
a. Ich scheine etwas leichter als andere krank zu werden	1	2	3	4	5
b. Ich bin genauso gesund wie alle anderen, die ich kenne	1	2	3	4	5
c. Ich erwarte, daß meine Gesundheit nachläßt	1	2	3	4	5
d. Ich erfreue mich ausgezeichneter Gesundheit	1	2	3	4	5