Buik belang

Gut4u Manifesto

Using the gut microbiome for health benefits within the ‘Buikbelang’ initiative!

Foreword

This is the manifesto Buikbelang. Buikbelang is an initiative of the Dutch Digestive Foundation (MLDS), the University Medical Center Groningen (UMCG) and Wageningen University & Research (WUR). Various experts, including microbiologists, gastro-enterologists and brain researchers, have contributed. Buikbelang aims to get to know the functioning of the microbiome better. On the one hand to prevent disorders and diseases from arising in and from your intestines. And on the other hand to better treat diseases and reduce symptoms. To achieve these ambitions, we are launching a national research program in which important questions surrounding the microbiome are investigated in order to take a first step towards possible applications for clinical practice and which may ultimately benefit society as a whole.

What affects our health? I've been looking for the answer to that question all my career. We already have insight into factors that influence illness and health. But to what extent does the complex interaction between our DNA, our environment and the composition of our gut microbiome influence disease and health? We will investigate this with Buikbelang in the coming years. And like to think in solutions. Solutions that in the end affect research, society and individual citizens.

This manifesto is intended to inform and enthuse current and potential partners. We hope that the content invites you to get involved with Buikbelang. To make an impact together with us and many stakeholders!

Help us to give the gut microbiome the attention it deserves through Buikbelang. Together we can bring the beautiful sentences from this manifesto into reality, and actually ensure health gain for everyone.

Cisca Wijmenga, rector magnificus of the University of Groningen and member of the steering committee of Buikbelang.

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Contents

Summary

Buikbelang is a movement that aims to achieve health gain through awareness, research and implementation of applications. The gut is an important source of health but can also be the origin of disease. We want to understand more about the gut microbiome and how to influence it with the aim of making health impact: improving disease treatments, alleviating symptoms and preventing disorders that start in the gut, which contains the gut microbiome.

The need

One in four people in the Netherlands has gone to their general practitioner with gastrointestinal problems or symptoms. That is a huge number. About 2 million Dutch people have been diagnosed with a gastrointestinal disease such as inflammatory bowel disease (IBD; which includes Crohn's disease and Colitis Ulcerosa), irritable bowel syndrome (IBS), coeliac disease or gastrointestinal cancers. We also know that people in a low socioeconomic position live unhealthier lives and on average live shorter lives. Buikbelang will therefore work together with this target group to achieve impact.

Biomedical research has shown that there is a relation between the gut microbiome and these gastrointestinal disorders. For example, it was recently discovered that excessive growth of a specific bacterium contributes to IBS symptoms [1]. A relation has also been found between a gut microbiome imbalance and IBD, cancer and coeliac disease. Furthermore, conditions as diverse as migraines and ADHD, as well as diseases such as Parkinson's, Multiple Scleroses (MS), diabetes and depression, may have their origin in the gut. A possible relation with the gut microbiome has been demonstrated, via the gut-brain axis.

Four ambitions

To achieve health gains through the gut microbiome, the following four ambitions have been established:

Ambition 1
Augment knowledge

Improve our understanding of how the gut microbiome relates to diseases and distinguish causes and effects better (causality). This will enable us to discover how the gut microbiome can be used to promote health. To achieve this ambition, intensified research collaboration is being facilitated at the national and international level between disciplines, ongoing initiatives/centres (including universities and research institutes) and research funding agencies

Ambition 2
Develop applications

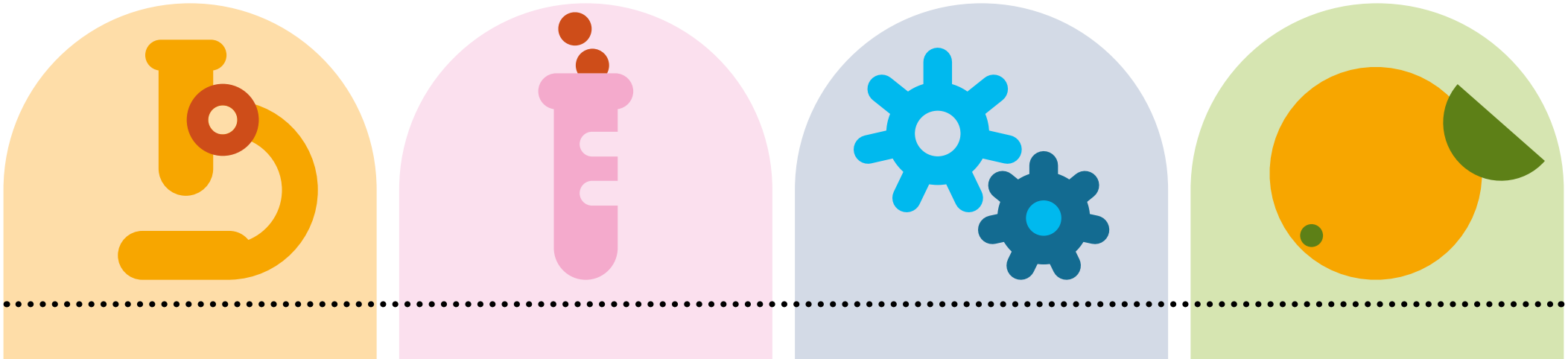
Improve disease treatment or prevention through gut microbiome monitoring, diagnostics and/or modification. To promote health, we need to translate insights from scientific research into actual applications through, for example, nutrition or targeted treatment. To this end, collaboration between researchers and various stakeholders (including policymakers, healthcare, patient associations, industry and research funding agencies) is encouraged. This focuses on developing clinical applications for people who are ill and on lifestyle interventions for the healthy population.

Ambition 3
Clinical application

Healthcare professionals and patients understand how adaptation of the gut microbiome can be used for health enhancement. As a result, they can start putting these insights and applications into practice. This ambition thus promotes the implementation of clinical applications among various stakeholders (including physicians, dieticians and pharmacists) who use these applications to improve the treatment of patients.

Ambition 4
Awareness and behavioural change

Everyone needs to know that the gut microbiome has an impact on health and on the courses of action they can take in this regard. This enables people to take good care of their gut microbiome, so they are more likely to stay healthy for a longer time. Together with various stakeholders (including educational institutions, child healthcare centres ('consultatiebureaus'), paramedical healthcare professionals such as dieticians, and health funds and insurers), this ambition thus raises awareness among the Dutch public. This is done through education and the use of apps, for example, that enable the Dutch population to follow lifestyle recommendations to maintain or improve gut microbiome health.



Four ambitions

These four ambitions lead to prevention, monitoring and treatment of all possible disorders that originate - entirely or partly - in the gastrointestinal tract.

Impact of Buikbelang in 2027

Each ambition has various impact goals that can take a long time to achieve. For example, the study of causal relations requires following large cohorts of healthy or diseased people over a long period of time. Raising awareness and changing behaviour among a large public is also a process that requires long-term commitment. But, even in the shorter term - in the next five years - we want to achieve impact goals for all four ambitions:

1. By understanding more about the gut microbiome through collaboration and a research programme, more will be known about which environmental and lifestyle factors (including diet) increase the risk for specific diseases.

2. Clinical applications are being developed that include targeted treatments for people with diseases such as Parkinson's and IBD. In addition, lifestyle interventions are being developed for the healthy population.

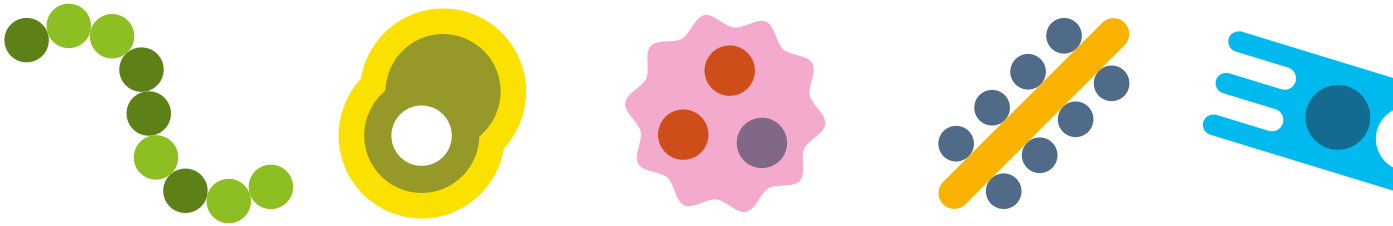
3. Recently developed or existing applications are put into practice through incentivisation and agenda-setting among healthcare professionals. In the medium term, this leads to applications based on the gut microbiome such as diagnostics and targeted prevention of specific diseases.

4. People acquire a positive association with gut micro-organisms and are aware of lifestyle recommendations to keep the gut microbiome healthy. The aforementioned impact goals also contribute to this.

Support Buikbelang

Buikbelang wants to make a significant contribution to the health of the Netherlands by working together to turn untapped health opportunities of the gut microbiome into health impact. We are stronger due to the support of all stakeholders: microbiome researchers, universities, research institutes, research initiatives, patient organisations, individual patients and their relatives, civil society organisations, government agencies, healthcare professionals, health insurers, health funding agencies, industry and experts active in the fields of health, gastrointestinal medicine, nutrition and dietary interventions.

The Microbiome



The gut - and especially the gut microbiome, i.e. the organisms living in the gut - are a source of both health and disease.

The human gastrointestinal tract has a huge surface area, as much as 250-400m^2 [2], which provides a habitat for large numbers of micro-organisms. The body has several protective mechanisms to ensure that potentially harmful micro-organisms do not pose a threat to humans, such as stomach acid and the intestinal mucosa [2, 3]. In addition, there are also 'good' micro-organisms, mostly bacteria, which we actually want to colonise the large intestine due to their beneficial effects in the gut. In this chapter, we take a closer look at these bacteria and why they are so important for our development and health.

What is the gut microbiome?

Our gastrointestinal tract, and particularly our large intestine, contains the microbiome: a complex composition of bacteria, viruses, fungi and other organisms. Through co-evolution, these organisms have formed a mutually beneficial relation with the host - in this case, humans [2, 4]. With over 10^{14} microbial organisms, the ratio of human cells to microbial cells in our bodies is about 1:1 [5].
The gut microbiome is crucial for our health; it is connected to the important systems in the human body [6, 7]. The microbiome is essential in digesting food, especially for converting fibre and producing certain vitamins [8, 9]. In addition, it may have an effect on physiological aspects such as intestinal integrity, defence against pathogens, or regulation of the immune system [2, 10]. The gut microbiome also plays a role in metabolic processes, and thus may influence the development of metabolic diseases such as obesity [11, 12]. Perhaps even more surprising, the gut microbiome affects our brain through the 'gut-brain axis' and may be related to, for example, stress and neuro-psychiatric disorders such as Parkinson's disease [13]. Because the microbiome plays such a major role in various important processes in the body, it is crucial that the composition of the microbiome is balanced.

Development of the gut microbiome

Micro-organisms begin to colonise the gut from birth. Within the first year, microbial diversity increases and the composition of the gut microbiome composition begins to resemble that of an adult [14]. From the age of 2.5 years children have developed a personal gut microbiome [15]. The first years of life are therefore incredibly important for the development of the gut microbiome [6]. The composition of the microbiome can be influenced by environmental factors such as antibiotic treatment, gestational age, smoking during pregnancy, mode of birth and especially diet [6, 16]. The gut microbiome can become unbalanced due to environmental factors, which can alter its composition and function. When it is out of balance, it is even possible for disease to develop, such as asthma and allergies [16].
In the adult years, the gut microbiome is reasonably stable, although it remains sensitive to (temporary) changes caused by environmental factors [17]. The gut microbiome in the elderly (≥65 years) can be distinguished from the adult phase due to its changing composition and decreasing diversity [2]. Environmental factors can also play a role in this. For example, a significant relation has been found between the mode of living, such as long-term residential care or community housing, and the diversity of the gut microbiome [18].

The gut microbiome and disease

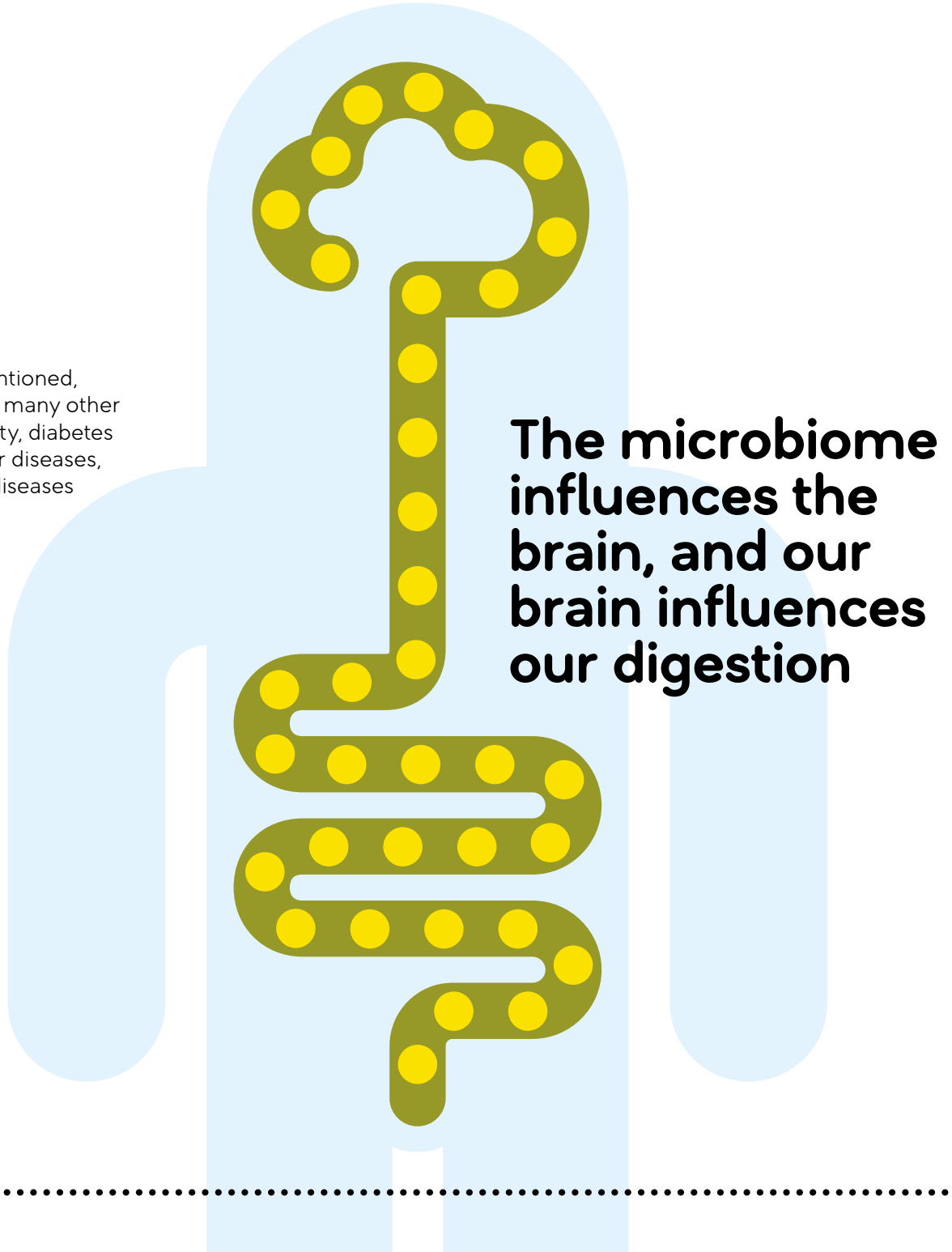
The gut microbiome plays a central role in the health of the human body, and research has shown an association between the gut microbiome and gastrointestinal diseases.

Gastrointestinal disease

The gut microbiome may play a role in the development or symptoms of several, common gastrointestinal diseases (Table 1). An out-of-balance gut microbiome is one of the main gut-related factors associated with diseases such as IBD, IBS, various types of cancer and coeliac disease. For example, excessive growth of a specific bacterium has recently been shown to contribute to IBS symptoms [1]. Unfortunately, no causal links have yet been found: it is unclear whether disruption of a balanced gut microbiome is the cause of disease or vice versa. In addition, a link has been found for IBD and IBS with the gut-brain axis [19, 20].

Gut-brain axis

Research has increasingly pointed to a relation between the gut and brain, called the gut-brain axis, and the development of certain diseases. The gut-brain axis involves a two-way communication between the gut and the brain, which occurs involuntarily through various processes. Direct signals are carried by the autonomic nervous system (the vagus nerve), which connects the brain to the enteric nervous system of the gut. However, signals via the immune system, hormones or substances produced by the micro-organisms in the gut are also exchanged, thus enabling the brain and gut to communicate with each other [13]. In addition, a disrupted gut-brain axis may play a role in stress, depression, neuro-psychiatric disorders such as migraine, Alzheimer's or Parkinson's disease or developmental diseases such as autism and ADHD. Given that these are common conditions (Table 1), it is important to continue studying the relationship with the gut-brain axis, with a focus on clinically applicable outcomes. Table 1 is not complete. In addition to the diseases mentioned, there are also indications of many other relations, such as with obesity, diabetes mellitus , MS, cardiovascular diseases, allergies and autoimmune diseases such as rheumatism.



The microbiome influences the brain, and our brain influences our digestion

GI-tract and brain-related disorders linked to the gut microbiome

Table 1
The prevalence of disorders in the Netherlands related to the gut microbiome, the common gastrointestinal symptoms associated with these diseases and the phase of life where it is relatively most common [21-28].

GI disorders
GI disorders with link to the brain
Brain disorders with link to the gut

Disease	Cancer	Coeliac disease	IBD (Crohn's disease and ulcerative colitis)	IBS	Stress	Migraine	Depression	ADHD	Autism	Parkinson's	Alzheimer's
Figures for the Netherlands	- Oesophageal cancer (2,530/y) - Stomach cancer (1,680/y) - Bowel cancer (13,145/y) - Pancreatic cancer (2,895/y) - Liver cancer (1,070/y)	170,000 patients	167,200 patients are known to general practitioners in the Netherlands	226,900 patients are known to general practitioners in the Netherlands, with an estimated total of 1,870,000 patients	2,200,000 Dutch people feel psychologically unhealthy	276,400 patients are known to general practitioners	1,000,000 people	260,000 patients are known to general practitioners	31,000 children (4-12 years old) 170,000 adults	52,000 patients	1,100,000 patients
Common gastro-intestinal symptoms	Abdominal pain, diarrhoea, fatigue, blood in stools, decreased appetite and unintentional weight loss	Bloating, chronic diarrhoea, constipation, gas, lactose intolerance due to damage to the small intestine, loose, fatty, bulky and bad-smelling stools, nausea or vomiting and abdominal pain	Abdominal pain and cramps, fever, diarrhoea, fatigue, blood in stools, decreased appetite and unintentional weight loss	Abdominal pain and cramps, diarrhoea, constipation, flatulence and bloating	Diarrhoea, constipation and abdominal pain	Nausea	Diarrhoea, constipation and abdominal pain	Constipation and faecal incontinence	Diarrhoea, constipation and abdominal pain	Severe constipation, excessive bacterial growth and abdominal pain (bloating)	Constipation, faecal incontinence
Life phase	All ages, but frequency increases with age	All ages	Often detected between 15 and 30 years old, but can occur at all ages	Often detected during early childhood, but can occur at all ages, but usually during early childhood	Often detected among young people up to 30 years old	Most common between the ages of 40 and 54 and are much more common in women	Most common between the ages of 40 and 50, but risk among young adults increased during the coro-na pandemic	Often detected between 10 and 19 years old	All ages, but especially in children	Often detected between 50 and 70 years old	Often detected among elderly people over 65 years old

Ambition 1
Augment knowledge

Knowledge and research agenda

A lot of fundamental research on the gut microbiome is taking place; the Netherlands is one of the world's leaders in this field. Unfortunately, important aspects are missing that prevent this knowledge from being used in practice. To achieve health benefits, we need to understand the various mechanisms by which the onset and progression of disease can be recognised and influenced in the gut microbiome. Consider, for example, the gut-brain axis and how the composition and function of the gut microbiome can be influenced in a targeted way through specific interventions. Various disease states correlate with digestion and the composition and functioning of the gut microbiome, but it is not always clear whether these are causal relations.

We also jointly develop a long-term vision and a knowledge and research agenda containing the essential questions to be answered. With these questions, clear action plans will be formulated. The agenda will be developed jointly with gut microbiome researchers in the Netherlands, based on a substantive scope that was given shape by the founders and current core partners (MLDS, WUR and UMCG). These action plans include the role of the small intestine in intestinal disorders, personalised diet-microbiome interactions for health within different target groups, including people with a low socioeconomic position, and a citizen science study on the gut microbiome, fibre and fermented foods.

Research collaboration

By strengthening research collaboration within the Netherlands, we accelerate the effective attainment of insights that we can use for health promotion and clinical applications. To achieve this, the connections between research funding agencies, scientific health research and gut microbiome initiatives/centres will be facilitated. Standardisation of sampling, analysis methods and efficient and structured data sharing are central with the aim of improved health monitoring, diagnostics and early detection using the gut microbiome.

What we want to achieve in the next five years

- By 2024, the first funded multidisciplinary research proposal will have been launched, emerging from the Buikbelang research programme;
- An infrastructure will be available to research institutes and researchers, within which they can more easily collaborate across university and institutional boundaries and interact with more stakeholders (e.g. organisations, businesses and patients) outside of academia. Based on the collaboration within this infrastructure, we can attain and communicate the necessary insights so we can start to make more impact;
- In collaboration with funding agencies, far-reaching plans will be in place for a national research programme on the gut microbiome and health. This programme will have a clear governance structure and scientific autonomy. Various researchers will propose projects for this research programme, such as causal links between the microbiome and disease states, gut-brain axis research, standardisation and data sharing, and multidisciplinary monitoring studies;
- We will know more about which environmental or lifestyle factors (including nutrition) increase or decrease risk in relation to the cause of disease (prevention-oriented).

Ambition 2
Develop applications

Applications

For patients or high-risk groups, a few (limited) applications are already available in the area of gut microbiome testing and monitoring, such as a gut microbiome self-test; these aim to provide insight into gut microbiome composition and diversity. Some commercial parties are linking applications, such as a gut microbiome self-test, to disease or health. This is done, for example, through personal lifestyle advice, but the scientific evidence for this is still very limited. Sufficient understanding of causal links between gut microbiome and disease states or health is still lacking.

The Buikbelang initiative aims to accelerate implementation of the application of both existing and new knowledge and insights, thus enabling gut microbiome monitoring, diagnostics and/or adaptation to be used to treat diseases. To achieve this, research on various ways to change the composition and/or functioning of the gut microbiome should be continued in order to exert effects on disease states or disease onset. The focus here is on conditions that originate entirely or partly in the gut: primarily gastrointestinal disorders, but also disorders associated with the gut-brain axis like Parkinson's and depression. Buikbelang focuses on the following applications with implementation options:

> Clinical treatment options: gut microbiome intervention strategies for high-risk groups and patients
> Clinical lifestyle interventions: options to improve quality of life for people with chronic conditions
> Lifestyle interventions for the healthy population, with specific attention for people with a low socioeconomic position (apps, dietary advice, courses of action) to achieve a longer healthy lifespan and improve quality of life

Collaboration between stakeholders

By collaborating with many different stakeholders, we aim to encourage and facilitate the development of more scientifically sound applications through the Buikbelang initiative. These include an app that displays the status (composition) of the gut microbiome in an understandable and reliable way and links it to other health parameters that existing health apps already use.

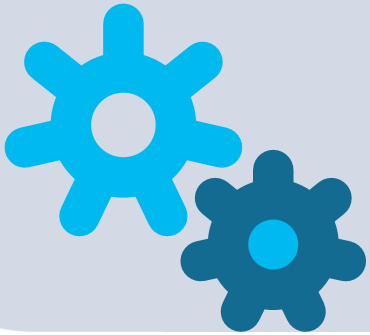
To create real impact in society, many relevant stakeholders will have to be involved who will take ownership in terms of developing applications. This will certainly involve healthcare professionals, paramedical healthcare professionals, individual patients and patient associations, researchers and health funds, but also health insurers, research funding agencies, policymakers, industry, and universities and research institutes (technical and otherwise).

What we want to achieve in the next five years

Multiple stakeholders will have been brought together and will be working on applications. A joint strategy will have been laid out and the first results will be visible. Examples include:

> Clinical applications: more effective treatment for Parkinson's, where the composition of the gut microbiome plays a role in the effectiveness of drugs for treating this disease. These insights are communicated in a targeted way and used in treatment. In addition, findings from longitudinal research, for example monitoring the gut microbiome in IBD patients, can be used for targeted applications such as using microbial targets as predictors of disease progression;
> Lifestyle interventions, raising awareness and behavioural change: more tools are available to provide personalised advice. These tools are being developed for the healthy population and patients. However, this will not be possible for all diseases, especially not within five years. IBD disease is a starting point whereby personalised dietary changes can influence the gut microbiome and thus physical well-being.

Ambition 3
Clinical application



Broad dissemination of applications in healthcare

A number of clinical gut-microbiome-related treatment options are known that can improve patients' quality of life, such as the use of pre-biotics and pro-biotics, faecal transplants, or dietary counselling to accompany certain medications. In addition, the gut microbiome can influence the effectiveness of medication, as in the case of the drug Levodopa in Parkinson's disease [29]. These treatment options and knowledge are not yet widely applied or disseminated in Dutch healthcare. Therefore, in addition to developing applications, Buikbelang also focuses on broad dissemination within the healthcare system of gut-microbiome-related clinical treatment options and lifestyle interventions. In this way, patients' quality of life can be improved in a relatively short period of time.

Collaboration in applying clinical innovation

To put gut-microbiome-related applications on the agenda and disseminate them within the healthcare sector, we will collaborate with health insurers, patient associations, centres of expertise and professional associations of healthcare professionals (including doctors and dieticians) and other organisations. The collaboration aims to raise awareness of gut-microbiome-related clinical applications and courses of action among healthcare professionals and patients, especially in the low socioeconomic status groups. A secondary aim of raising awareness about clinical applications is to attract entrepreneurs who will actually further develop, produce and market such applications. Buikbelang acts as a networking partner to link entrepreneurs, industry and healthcare.

What we want to achieve in the next five years

> Buikbelang will enjoy a national reputation among healthcare professionals as a healthcare knowledge resource on clinical applications related to the gut microbiome.
> Patients' quality of life will have been improved for specific diseases by having access to gut-microbiome-related clinical treatment options that enhance the effectiveness of their medication. This can be used as an appealing example to continue raising awareness among healthcare professionals.
> In the medium term, diagnosis and targeted prevention of specific diseases using the gut microbiome will be applied.

Ambition 4
Awareness and behavioural change

The current situation in the Dutch population

Besides promoting clinical applications for people who are ill, it is also important to promote applications emerging from scientific research for the benefit of the whole population. This will enable people to care effectively for their gut microbiome. Indeed, current knowledge among our population regarding the gut microbiome and health and disease is low (Figure 1).

Working together for public awareness and behavioural change

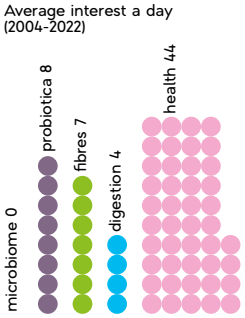
To enhance public awareness, other stakeholders (e.g. healthcare sector, local and national government agencies, educational institutions, paramedical healthcare professionals such as dieticians, and health funds and insurers) also recognise the importance of caring effectively for the gut microbiome. They can influence the physical and social environment so that it contributes to a healthy gut microbiome. This involves aspects such as hygiene (in schools, the outdoor environment for adults or hygiene guidelines used by midwives) and lifestyle (nutrition education in relation to gut health, advice at child healthcare centres ('consultatiebureaus') or lifestyle advice in gastrointestinal care). Buikbelang will therefore implement an awareness campaign targeting these stakeholders, with clear action perspectives that can be put into practice. Collaboration with behavioural and social scientists is essential to develop an effective awareness campaign with realistic action perspectives.

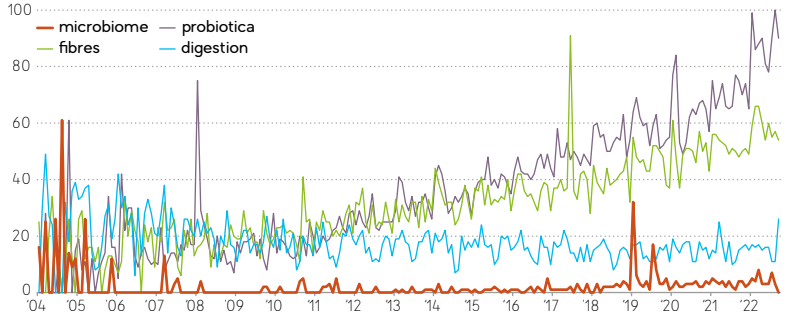
Besides raising awareness, we are taking the first steps towards behavioural change in the Dutch population:

> Buikbelang is a partner in providing more reliable advice and communications (especially on food, possibly also other lifestyle advice). Buikbelang can advise on 'what is truly healthy food for the gut microbiome', not only as an adult, but also during pregnancy and early life. This advice can be included in various phases of education. Child healthcare centres for newborns are another route for influencing families in a more targeted way and having an impact on eating behaviour - as are dieticians. Insurers could also play a role by placing more emphasis on healthy lifestyle and diet in insured care. Special attention is also paid with regards to communication to people in a low socioeconomic position.

> Buikbelang provides substantive input to the Alliantie Voeding voor de Gezonde Generatie (Nutrition Alliance for the Healthy Generation) that they can use in their lobbying and actions to promote a healthier eating environment.

Figure 1
Google trend analysis of specific search terms and their popularity in the Netherlands relative to each other at the relevant time point. A value of 0 means that there was not enough data for this search term for that time point. For clarity, health (green bar) has been removed from the line graph [30].





What we want to achieve in the next five years

> That through awareness-raising strategies and modifications in the food environment attention will be paid to a healthy gut microbiome.

> Everyone will have a mainly positive association with the gut microbiome and health.

> Everyone will be aware of 'general lifestyle recommendations' to keep their gut microbiome healthy: especially eating fibre, more diverse foods, more fermented foods and fewer empty calories (energy-rich foods without essential nutrients). In addition, ensuring sufficient exercise, reduced stress and enough fresh air are important.

Supporters of Buikbelang

(as of February 2023)

"We've been talking about the importance of a healthy gut for the overall health since 1935. We look forward to bringing the importance of the gut to the attention of the Netherlands together with other organisations and that is why we think this initiative is so important"

Martine van der Velde, Yakult

Hersenstichting / ParkinsonNL / Diabetes Fonds / Nederlandse Coeliakie Vereniging / One Planet Research Center / Nationaal MS fonds / Crohn en Colitis NL / Stichting Darmgezondheid / Alzheimercentrum Amsterdam / Vereniging Arts en Leefstijl / Keep Food Simple / TNO / Yakult / Voedingscentrum / Alliantie Voeding voor de Gezonde Generatie

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"Through a personal approach, including the explanation of gut microbiome results right after the dietary intervention study, awareness is raised that changes in food intake have a direct effect."

Prof. dr. Remco Kort, ARTIS Micropia & VU Amsterdam about the Citizen Science study

This is the list of supporters on 24-02-2023. This list is supplemented weekly with new partners. Go to this page for the latest version

"The Buikbelang initiative looks beyond borders by stimulating multidisciplinary collaboration. With this initiative we want to help as many patients and consumers as possible. I wholeheartedly support that."

Dr. Edwin Abeln, TNO

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