Eating for science

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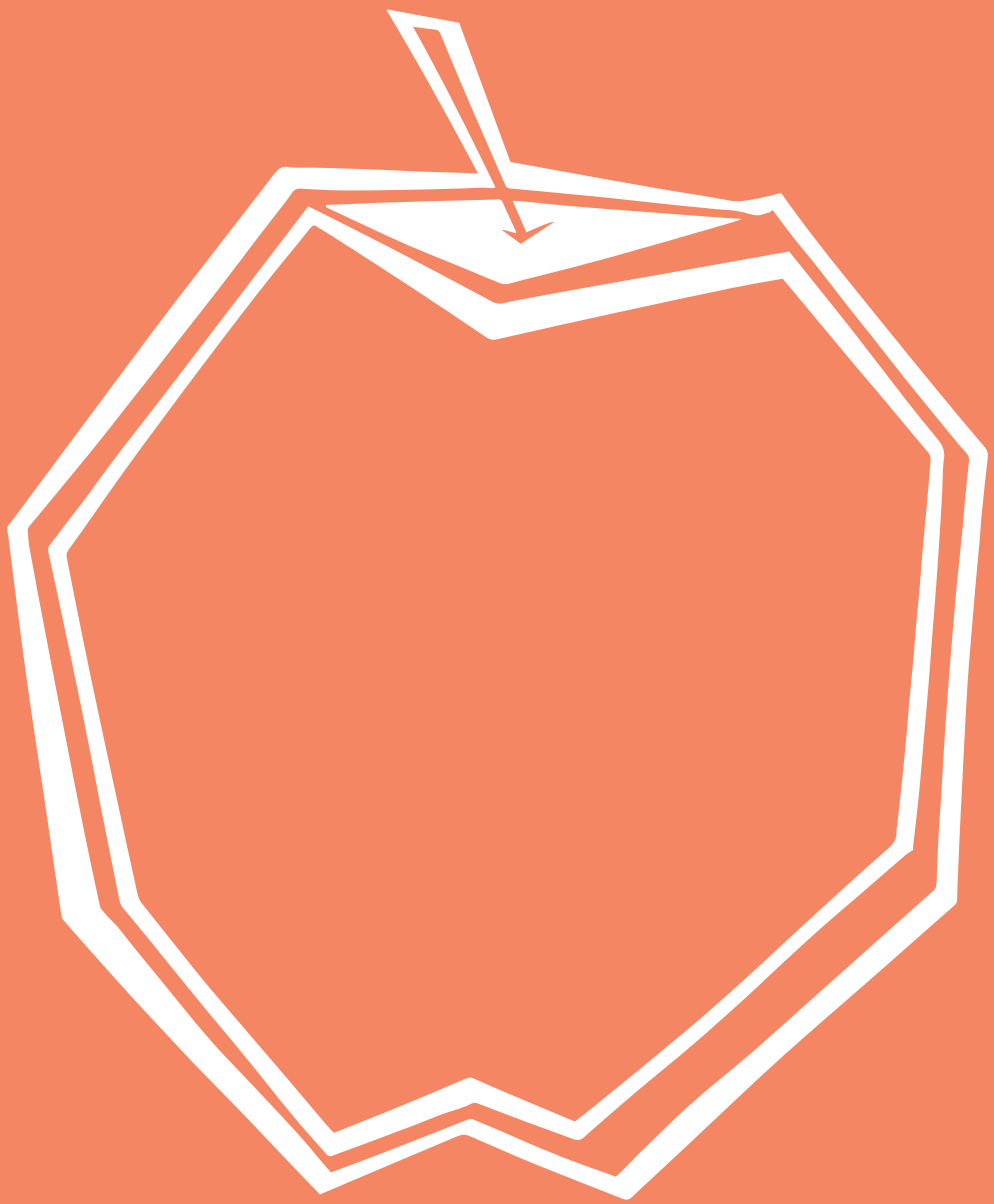

Chapter 1

General introduction

Health Challenge

Although life expectancy is increasing, human health in Europe is deteriorating with a rise in prevalence of diseases such as cancer, cardiovascular disease (CVD), type 2 diabetes (T2D), pulmonary disease and depression.[1] These diseases are known as non-communicable diseases (NCD's), because they cannot be transferred from one person to another like a bacterial or viral infection. In the Netherlands, people get their first NCD when they are around 45 years old.[2] Since these conditions are chronic and the average life expectancy is 81 years, on average every person needs medical attention for these NCD's almost half their life.[2] The disability-adjusted life years (DALY's) is a measure of societal cost of disease, by expressing the number of years lost due to disability or premature mortality. In high income countries 85% of DALY's are due to NCD's, and in the Netherlands 9 of the top 10 causes for DALY's are NCD's (**Figure 1**).[1] Recently the urgency for societal health improvements became all the more clear with the outbreak of the coronavirus in 2019 (SARS-CoV-2) that turned into the COVID-19 pandemic in 2020. Individuals with obesity[3–5], CVD[6], T2D[7] or pulmonary disease had more severe disease progression and higher mortality rates than individuals who were in good health before contracting the virus.[8–14] This caused a great burden on health care systems worldwide, with hospitals having to reduce non-urgent medical care, or even (close to) failing care for patients needing urgent medical attention, thereby creating an enormous medical and economic debt for societies.

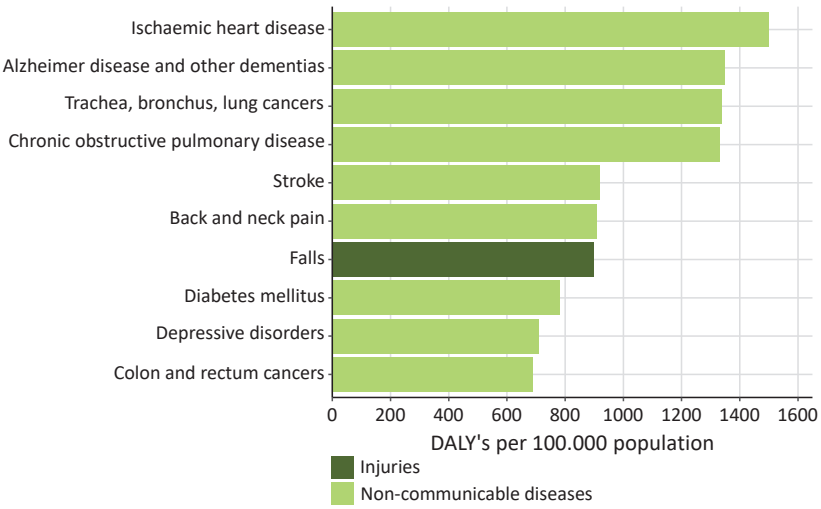

Figure 1. Top 10 causes of DALY's in the Netherlands in 2019. Figure adapted from World Health Organisation.[1]

An integral part of many NCD's is the metabolic syndrome (MetS), which is a combination of several cardiometabolic derangements frequently associated with weight gain, including abdominal obesity, unfavourable blood lipid profile, high blood pressure, and insulin resistance.[15] According to International Diabetes Federation[15], an individual is diagnosed with MetS when central obesity is present (assessed by waist circumference >94 cm for European men and >80 cm European women; circumference may vary with different ethnicities) as well as at least 2 of the following factors: elevated triglyceride level (>150 mg/dL or >1.7 mmol/L); reduced HDL cholesterol level (men: <40mg/dL or <1.03mmol/L; women:

<50mg/dL or <1.29 mmol/L); increased blood pressure (systolic blood pressure >130mmHg or diastolic blood pressure >85 mmHg), increased fasting plasma glucose level (>100 mg/dL or >5.6 mmol/L), or medical treatment for any of the previously mentioned factors.[15] Detection of MetS and correcting the underlying etiology as early as possible could alleviate the prevalence of NCD's and work towards a healthier society, also in light of the recent COVID-19 pandemic.

The evolution of lifestyle

To reduce or prevent the etiology of MetS and consequently NCD's, it is useful to understand the ultimate processes that regulate energy balance from an evolutionary point of view. The species Homo Sapiens evolved between 240.000 and 200.000 years ago.[16] They were hunter-gatherers and estimated to eat a diet consisting of around 35% animal foods and 65% plant foods.[17–19] They used different strategies to acquire food, e.g. big-game and small-prey hunting, forest animal produce (like bee-keeping) and fishing.[16] Hunter-gatherers experienced periods of famine in between periods of surplus. To this day few hunter-gatherer populations remain (e.g. the Hadza in Tanzania, the Inuit in Canada, !Kung in Botswana, and Ache in Paraguay), of which the lifestyle and health characteristics have been investigated. These studies indeed comment on the large health disparities of traditional hunter-gatherers and individuals living in industrialized societies.[20–22]

The hunter-gatherer lifestyle started to change with the advent of agriculture about 10.000 years ago.[16,23,24] Farming and domestication of animals improved the predictability of food availability, reducing the threat of famine. This agricultural revolution led to a change in diet, increasing carbohydrate and dairy intake, allowing higher success of pregnancies and weaning of infants and reducing overall infant mortality in farmers compared to hunter-gatherers.[16,25] The amount of plant products eaten was increased, while the amount of (wild) animals eaten was reduced.[26] Not only the amount, but also the food content changed. Compared to free-living animals, meat of domesticated animals contains more fat (resp. 30% versus 3.9% fat)[17,27,28], at the expense of protein[17,29,30], and thus contains more calories.

After the agricultural revolution, the industrial revolution took place around two centuries ago. Besides dramatically upscaling the agricultural yields, it also tremendously increased availability of new types of energy dense and palatable foods including refined cereals, refined sugars, refined vegetable oils, and foods with added sugar and salt.[31] In the past couple of decades our main dietary intake has shifted from mainly non-processed foods to mainly (ultra-)processed foods[32–36], according to the classification made by Monteiro et al.[36] This classification is based on how processed a food product is; 1) unprocessed or minimally processed foods, these are for instance edible parts of plants or animals (e.g. seeds, fruit, muscle, eggs, milk), 2) processed culinary ingredients (e.g. oils, butter, sugar, salt), 3) processed foods, made by adding group 2 foods to group 1 foods, (e.g. canned vegetables or fish, cheeses, freshly made breads), and 4) ultra-processed foods, which are made mostly from substances derived from foods or additives, with little or no intact group 1 foods (e.g. pre-prepared frozen meals, soft drinks, packaged snacks).[36]

Not only our diet changed due to the industrial (lifestyle) revolution, the level of physical activity changed with it. To get an idea of the amount of physical activity

exerted during the hunter-gatherer era, abovementioned hunter-gatherer groups were examined and found to have total energy expenditure (EE, corrected for body weight) almost twice as high as that of Western humans (200 Kj/(kg/day) vs 133 Kj/(kg/day)).[37,38] EE consists mostly of resting metabolic rate (RMR), energy needed for the body to function, and physical activity. The RMR of Western humans is slightly lower compared to hunter-gatherers, probably due to the higher fat and lower lean mass[39], but especially the amount of physical activity is nowhere near as high as in the hunter-gatherer groups (**Figure 2**).[37]

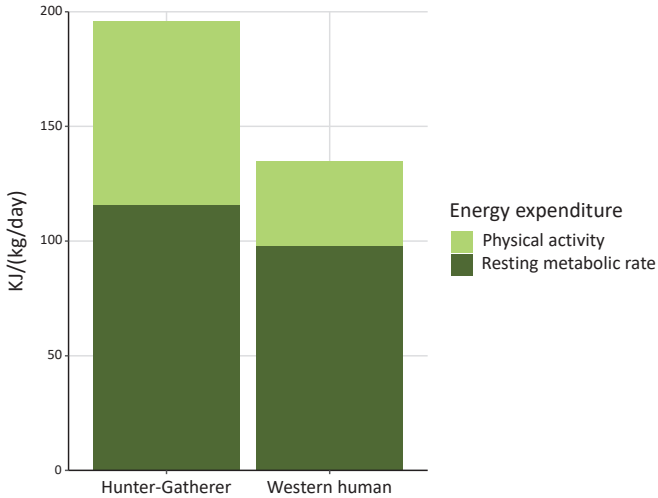

Figure 2. Estimated energy expenditure in hunter-gatherers and Western humans.[37,38]

Besides the factors directly related to energy balance, also psychological challenges imposed by the environment have changed considerably in the transition from the hunter-gatherers towards those living in the industrial age. In the hunter-gatherer era, humans probably experienced stress associated with immediate threats (e.g., the approach of - and attack by a dangerous animal or a rival) more often than humans in today's society do. In the case one would be lucky enough to survive such an event (i.e., due to the appropriate expression of the so called fight-flight response), recovery would take place, involving for instance activation of the immune system, healing of injuries, energetic recovery, etc.[40–43] However, fight – flight responses most frequently do not offer solutions for our current stress problems. For example, work-related stress (including working at times when they would normally be asleep), being lonely or bullied, feeling worthless and insignificant relative to (apparently more successful) peers are often chronic sources of psychosocial stress, from which it is very difficult to escape. Our body perceives abovementioned psychosocial stress probably the same way as prehistoric threats.[44] This means that it causes the release of stress hormones that activate the cardiovascular system and the release of stored energy substrates to fuel a potential fight - flight response that almost never happens anymore. Mood enhancement to endure the often inescapable psychosocial stressors could be achieved by consuming highly palatable, ultra-processed foods.[45–49] These comfort foods, however, only temporarily alleviate the emotional component of stressors, but probably aggravate the physiological and cardiovascular/ metabolic consequences of them[49–51], leading to long-term activation of the immune system, increasing the risk for inflammatory related diseases like NCD's.[44]

On an evolutionary scale abovementioned changes happened quickly (**Figure 3**), while our genetic make-up is still highly comparable to that of our ancestors, who were adapted to a completely different environment and lifestyle compared to the one we are living in today. Current hunter-gatherer groups are lean when they follow their traditional lifestyle and diet, whereas they have a tendency to develop abdominal obesity when exposed to high, refined carbohydrate intake.[52–58] This is similar to what is happening in the industrialized society due to the prolonged exposure to refined high calorie diets.

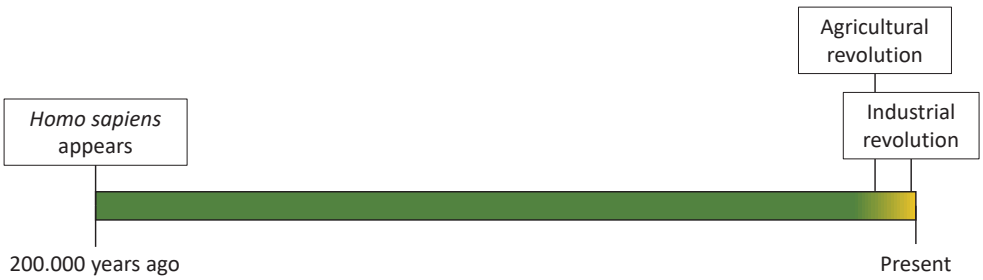

Figure 3. Timeline of genetic and lifestyle changes.

Although our genetic make-up may be similar to that of our ancestors, the influence of the environment on gene expression by altering readability of the gene without changing the DNA sequence (i.e., epigenetics) could be another factor in the relation between health and lifestyle. The fact that the environment can influence health by epigenetics was observed when studying the consequences of foetal development during the six-month Dutch famine in World War II. This was a period of undernutrition for several cities in the west of the Netherlands, with daily rations dropping down to between 400-800 calories between December 1944 and April 1945.[59] Pregnant women were entitled to extra food but at the height of the famine this was no longer available. This led to maternal malnutrition during different periods of gestation which were shown to be related to health later in life, depending on which organs were developing at that time. At 50 years of age, those who were exposed to famine during their foetal stage had reduced glucose tolerance[60], increased risk for T2D[61,62], a more atherogenic lipid profile with higher risk for CVD[63], higher BMI[64,65], and increased prevalence of obstructive airway disease.[66] This indicates that foetal undernutrition can affect the structure and physiology of the developing organs.[60] In addition, the transition from nutritional deprivation in (early) gestation, preparing a foetus for a life of scarcity, to nutritional adequacy may be the cause for disease due to metabolic conflicts.[60] The opposite may also be happening, with a period of surplus during gestation influencing health of the offspring. Maternal obesity and/or a high-fat diet may predispose the foetus to a higher prevalence of T2D, CVD, and obesity.[67,68]

In summary, during the lifestyle change from hunting and gathering to farming to the Western lifestyle present today, some genes could have evolved accordingly but our current genetic make-up largely resembles that of hunter-gatherers. Besides genetic make-up, lifestyle may also influence our health through epigenetics. Together these mechanisms may have contributed to a mismatch between our (epi)genetic make-up and the environment we live in today resulting in several cardiometabolic or mental derangements.

Lifestyle of the Dutch

As illustrated above NCD's became highly prevalent worldwide as lifestyle evolved from hunter-gatherer to industrialized citizen. However, regional differences may exist due to differences in the habitual diet and physical activity varying between countries or cultural structures. In the Netherlands, the Health Council recommends a diet called the "Wheel of Five". It resembles the Mediterranean diet and focusses on intakes in five food groups. It recommends the intake of (1) high amounts of vegetables and fruit, (2) mainly wholegrain bread, cereal products and potatoes, (3) dairy, nuts, fish, legumes, meat and eggs, with focus on more plant-based and less animal products, low-fat dairy, and unsalted nuts, (4) soft and liquid fats and oils for food preparation, and (5) enough liquids, focused on water, tea and black coffee. A food diary application ("Eetmeter") is available for the Dutch population for measuring dietary intake, including how well individuals adhere to the national guidelines. In the Dutch national Food Consumption Survey (2012-2016)[69], 13% of the investigated Dutch population (n=4313) followed a special diet (e.g. energy restricted, diabetes, diet because of allergy, fat-restricted), and 3% did not consume any meat. Non-alcoholic beverages, cereal products (especially bread), dairy and fats and oils were food groups that were consumed daily, whereas fish and legumes were consumed once a week or less. The extent to which the Dutch dietary guidelines were followed ranged from 0-50% across product groups. The guidelines that were followed most closely were those for fish, alcohol, and wholegrain products and those followed least closely were vegetables, fruit, unsalted nuts, legumes, sugary drinks and salt.[69] An overview of the guidelines, average intake per category and percentage of people adhering to the guideline can be found in **Table 1**.

The Health Council of the Netherlands also made guidelines for the amount of physical activity one would have to display in order to optimize health.[71] These state that all adults should "engage in physical activity of moderate intensity for at least 150 minutes every week, spread over several different days." and "Do activities that strengthen your muscles and bones at least twice a week", whilst avoiding sitting down for long periods.[71] In 2020, 52.9% of adults complied with the physical activity guidelines, 58.3% met the amount of minutes of moderate intensity physical activity, while 82.2% of adults complied to doing muscle strengthening activities at least twice a week. Additionally, 52.4% do sports weekly, 25.4% has a subscription to a sports provider, and 18.4% is member of a sports club.[72]

In addition to changing dietary and physical activity habits, also the time of day when individuals display these behaviours is changing rapidly. Occupations with regular working hours from 9:00 to 17:00, from Monday to Friday are less common. In the European working conditions survey, 18% of the Dutch respondents indicated they worked during the night in the last month, 51% worked during the weekend, 14% worked in shifts and 45% worked different hours per week.[73]

Based on the numbers that show an increase in prevalence of NCD's and the numbers showing that only about half of the people meet the guidelines for diet and physical activity set by the Health Council, there may be a lot to gain from a health and lifestyle perspective.

Table 1. Dutch dietary Guidelines according to the Wheel of Five, average intake and percentage of people reaching the recommended intake per product group.[69,70]

Food group	Product group	Recommended intake	Average daily intake (g)	People reaching recommended intake (%)
1	Fruit	200g daily	143	12.9
	Vegetables	200g daily	112	16.4
2	Wholegrain bread & cereal	90g daily	93	47.3
3	Dairy	A few portions daily	333	91
	Nuts (unsalted)	15g daily	2	3.5
	Fish	Once per week	15	34
	Legumes	Once per week	5	2
	Eggs	150g per week	12	35
	Meat	Reduce processed and red meat intake	76	na
4	Fats and Oils	Replace hard fats with soft fats and oils	23	na
5	Drinks	Drink only water or tea and (black) coffee	1302	49
	Tea	450g	252	19

Non-communicable diseases are caused and prevented by lifestyle

A frequently advocated approach for reduction of NCD's is to improve dietary composition, decrease caloric intake, and increase physical activity.[15] Which change in dietary composition should be preferred, remains food for debate. Reducing fat intake has been of great interest since the 1950's. This started with the Framingham study and the Seven Countries study, indicating that fat intake was the cause for the development of CVD.[74,75] Further research showed it was not that straightforward, because the types of fat consumed were related to differences in risk for development of CVD. Trans-fats present in animal and (ultra-)processed foods, with emphasis on industrial trans-fats, were blamed for increasing the risk for development of CVD, whereas intake of unsaturated fat has a protective effect on development of CVD.[76–81] With regards to saturated fat it is less clear whether there is indeed an increased risk for development of CVD. It may well be that the source of saturated fat is more important than the total amount of saturated fat.[82] In any case, to this day the recommendation is to limit fat intake and especially saturated fat as much as possible.

Because initially the consumption of fat was seen as disadvantageous, intake shifted from fats towards carbohydrates.[83,84] This rise in carbohydrate intake over the last few decades is tracked by a rise in prevalence of NCD's. Research then focused more on the possible deleterious effects of consuming high amounts of carbohydrates, which also sparked interest in the effect of low-carbohydrate (LC) diets to improve general health indices. Carbohydrates can be divided into different categories as well, ranging from polysaccharides (long-chain carbohydrates),

and oligosaccharides (short-chain carbohydrates), to mono- or disaccharides (sugars).[85] Especially sugars should be avoided in LC diets, because of their glycaemic effect, meaning that they make carbohydrates available for metabolism, increasing blood glucose levels.[85] More recently the "Paleo" movement has gained considerable attention based on the evolutionary perspective that our bodies are best equipped for consumption of the hunter-gatherer diet. They recommend to lower or avoid consumption of dairy and grains, due to the fact that these were incorporated in our diet during the transition to an agricultural lifestyle.[53] The Mediterranean diet also has been of interest, due to the low prevalence of CVD in the Mediterranean area.[75] The Mediterranean diet has been shown to be protective for the development of CVD[75], cancer, and all-cause mortality.[86] Also of interest are the so-called "blue zones", such as Sardinia (Italy)[87], Ikaria (Greece)[88–90], Okinawa (Japan), Nicoya (Costa Rica) and Loma Linda (California, USA), where people age relatively healthy and gracefully.[91,92] The "blue zones" were identified by Dan Buettner, who described nine common lifestyle characteristics that could improve healthy ageing.[93] These characteristics contain high expression of low level physical activity (like gardening), mindful eating, having a positive outlook on life and connecting with the people around.[93] More recently vegetarian and vegan diets, excluding respectively meat or all animal products, also became of interest. This is partially due to the improvement in cardiovascular risk parameters, like blood pressure, hyperlipidemia[94], and risk for T2D, but also because of the environmental aspect, with plant-based food products having lower environmental impact than animal products.[95] This shift in interest in different diets has also been analysed through Google searches between 2004 to 2019 by Towers et al.[96] All of the abovementioned diets or lifestyles have proven to be effective for weight loss[97–99], reduction of T2D[100,101], CVD[102,103], depression, or markers of MetS.[104,105]

To induce weight loss, reduction of caloric intake and/or increase in physical activity certainly contribute to changes in energy balance but reducing the intake of processed foods may be of importance too. Indeed, a diet consisting of only ultra-processed foods can cause excess calorie intake and lead to weight gain in two weeks. And vice versa, a diet consisting entirely of unprocessed foods can reduce body weight in only two weeks, possibly due to an increase in the appetite-suppressing hormone PYY and a reduction in ghrelin, the hunger hormone. Interestingly, there were no differences observed between the unprocessed and ultra-processed diets in palatability, hunger, fullness or satisfaction.[106]

In addition, physical activity should be increased since reduced physical activity is related to overweight and obesity[107], probably due to a positive energy balance when energy intake from food is higher than energy expenditure. Additionally, sedentary behaviour is related to increased risk of attracting CVD[108,109], and metabolic disease risk.[110] Increasing physical activity is often followed by lower CVD risk, even when sedentary behaviour is present.[108]

What comes before the disease?

In order to alleviate the prevalence of NCD's, identification of people at risk for NCD's is necessary. NCD's do not develop overnight, but slowly develop over the course of several years or even decades. Therefore, early markers should be used that could give a forecast of such a process. This would leave room for lifestyle changes that turn around or slow down the processes that finally lead to NCDs at an early stage. There are several arguments which suggest that this approach may work. For instance, general depressive symptoms are related to

development of depression five years later, and additionally in women somatic symptoms are related to development of depression.[111] Unspecific somatic symptoms are shown to precede development of T2D 16 years later, independent of established cardio-metabolic risk factors.[112] The same is true for myocardial infarction, where exhaustion four years prior to the event is a significant predictor independent of classic risk factors.[113] Also sleep complaints precede obesity[114] and CVD.[114,115] Unexplained somatic symptoms are also related to medical illnesses, anxiety and depression one year later.[116] This shows that clinical manifestation of a disease is preceded by preclinical markers that can be detected years earlier. By timely assessment of these general psychological and somatic symptoms this leaves ample opportunity for lifestyle modification to turn around and prevent the development of NCD's.

From the Forgotten Organ to the Player of Human Health

An potential important modulating factor between lifestyle and health is presented by the trillions of microorganisms, i.e. archaea, bacteria, eukarya, and viruses residing in our gut. Technological advancements of DNA sequencing techniques have made the determination of the (bacterial) gut microbiota composition easier and cheaper over the past years[117], making it a widespread field of research. Because lifestyle (especially diet) is a key player influencing the composition of our gut microbiota, it is worth understanding this relation for potential future health benefits.

Gut microbiota starts to inhabit human the gut probably already in utero.[118] At or after birth, the composition is influenced by mode of delivery, diet (incl. infant feeding method), genetics, geographical location, and use of pharmaceutics (e.g. antibiotics). A hunter-gatherer community, the BaAka in Africa, was found to have significantly different gut microbiota composition than the agricultural community, Bantu, living close to them. They both had significantly different gut microbiota compositions from US Americans, indicating that compositional and functional features of the gut microbiome reflect adaptations to different lifestyles.[119] At three years of age a roughly stable gut microbiota composition is formed[120–122], and can be altered throughout lifespan mostly by environmental factors, such as diet/lifestyle, medication and ageing.[123,124] However, as ageing seems to have a permanent effect on gut microbiota[125,126], alterations in diet or medication, change in physical activity and use of antibiotics, trigger mostly temporal changes.[127,128] E.g. intakes of healthy plant and animal foods are related to presence of specific and different bacterial taxa, which clearly deviate from those found in subjects that eat refined products and meats.[129] Changes in dietary energy content can also influence gut microbiota composition in humans. When caloric content of a diet was increased in lean individuals, the microbiota composition altered and led to increased energy harvest from food and decreased energy content in feces.[130] This demonstrates that gut microbiota is not only influenced by the type of food (animal or plant-based), but also quality of food (ultra-processed or non-processed), and energy content, thus affecting human health.

Due to the metabolic activity of the gut microbiota, which is essential in maintaining host homeostasis and health, and its insufficient recognition in the past decades, gut microbiota is also called "The Forgotten Organ". The high level of interplay between the gut microbiota and host has probably emerged by co-evolution.[131] As such, gut microbiota plays a role in host nutrition by promoting digestion and synthesis of beneficial metabolites like short-chain fatty acids (SCFA) and

vitamins.[132] It also plays a role in the interplay with the immune system and influences pathogen resistance and immune function.[133] It has been shown that 10% of the immune response variability comes directly from interactions associated with the gut microbiota.[134] Lastly, gut microbiota can affect the central nervous system via the microbiome-gut-brain axis and can e.g. affect behaviour and development of psychological symptoms.[135] This communication is facilitated through signalling molecules that can act as local neurotransmitters (such as SCFA's, γ-amino butyrate, serotonin, melatonin, histamine and acetylcholine).[136–140]

Properly functioning gut microbiota is crucial for our health, and there are several indications of the consequences of an unfavourable gut microbiota composition. An example often cited is the transplantation of gut microbiota from adult twins, discordant for obesity, into germ-free mice. Mice receiving gut microbiota transplants from the obese individual gained significantly more weight and had higher adiposity than mice receiving gut microbiota transplants from the lean individual.[141] Cohousing these lean and obese mice (and thus allowing the faecal-oral route) could prevent weight gain in obese mice and change their microbiota to a lean-like state.[141] This prevention of weight gain was achieved when a diet low in saturated fat and high in fruit and vegetables was consumed, but not with a high saturated fat, low fruit and vegetable diet, suggesting a diet-microbiota interaction that influences host biology.[141] In humans faecal microbiota transplantation has been successfully used in the treatment of Clostridium difficile infection, and it's recommended for other conditions such as inflammatory bowel disease, autoimmune disorders, certain allergic diseases, and cardiometabolic disorders associated with obesity.[142] Underlying these recommendations is the prediction that gut dysbiosis underlies the pathogenesis of these diseases.[133,143,144]

Attempts to find gut microbiota markers that could possibly explain obesity led to initial thoughts that the ratio of most prominent phyla in the gastrointestinal tract, the Firmicutes to Bacteroidetes ratio, could be a factor related to obesity.[145] A recent meta-analysis however found no relation between Firmicutes to Bacteroidetes ratio and obesity.[127,146] Another marker, microbiota richness represented by Shannon diversity index, has been shown to be correlated to obesity status, with 7% lower richness associated with obesity.[147] Additionally, individuals with reduced gut microbiota richness, had more adiposity, insulin resistance, dyslipidaemia, and inflammation than people with a high microbial richness.[148] Bacterial composition has also been shown to be related to risk for development of CVD.[149,150] There are even indications that a certain gut microbiota composition is correlated to psychological symptoms or neurological disorders.[151] Dysbiosis could lead to a reduced intestinal barrier (leaky-gut), causing an inflammatory response.[137,152] This in turn can lead to depression or other psychiatric disorders.[153,154] The relation between gut microbiota and mental health, stress, anxiety and depression is well documented in the review by Spichak et al.[155], who found several species that were associated with increased quality of life, whereas other species were depleted in people with depression.[155]

Aim and outline of this thesis

The aim of this thesis is to investigate various aspects of lifestyle on the prevention of NCD's, with the emphasis on the effect of a change in dietary intake, its interaction with gut microbiota and the effect of work environment on health. For this purpose, several studies were performed as outlined in **Figure 4**.

To understand the relation between change in dietary intake and markers of the metabolic syndrome a meta-analysis was performed with studies including subjects with obesity, and the metabolic syndrome (Chapter 2), but without clinically manifested cardiometabolic diseases.

To understand the effect of a change in dietary intake on reduction of general somatic and psychological symptoms in the general population, an online intervention study was designed and performed called "Eten voor de Wetenschap", ("Eating for Science"). In this study individuals were included who followed a self-initiated dietary change, and reported on general symptoms (Chapter 3), and handed in faeces samples for analysis of their gut microbiota composition (Chapter 4).

The designed online intervention was also applied in Bakkeveen, a village in the municipality of Opsterland in eastern Friesland in the Netherlands, where aspects of "blue zone" principles were studied on general symptoms (Chapter 5).

To complement the view of the relation between daily lifestyle and health, the influence of shift work on general symptoms was investigated (Chapter 6).

Lastly, the main findings and implications for future research are discussed (Chapter 7).

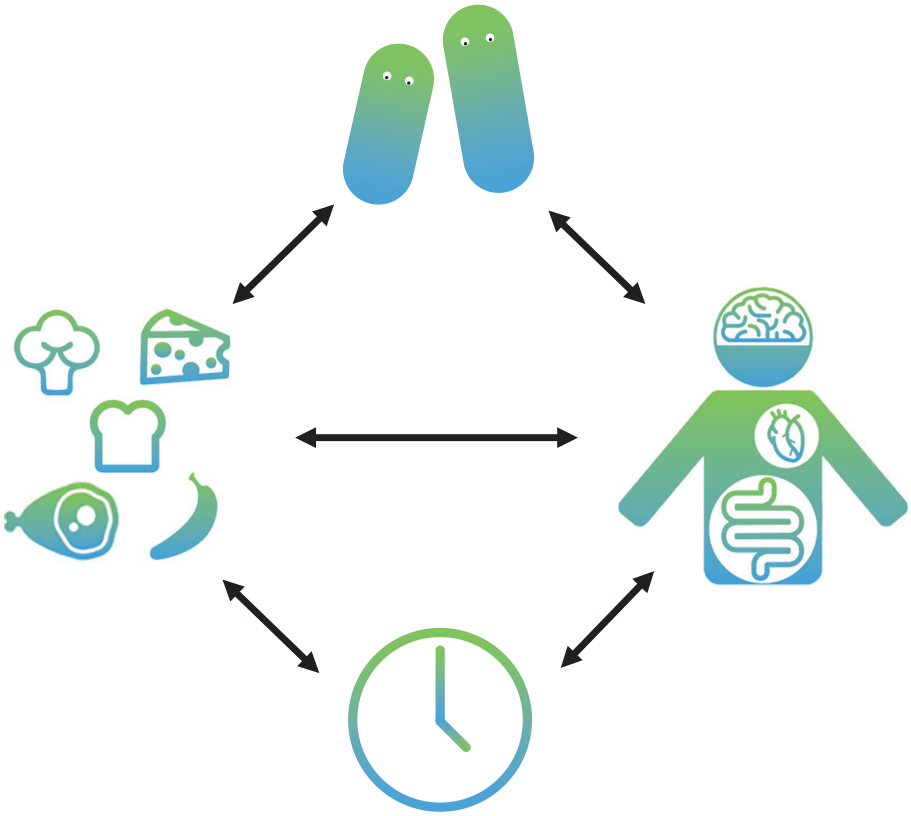

Figure 4. This thesis will focus on the relation between a change in lifestyle, emphasising dietary intake, and human health, with interest in the possible modulating role of the gut microbiota.

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