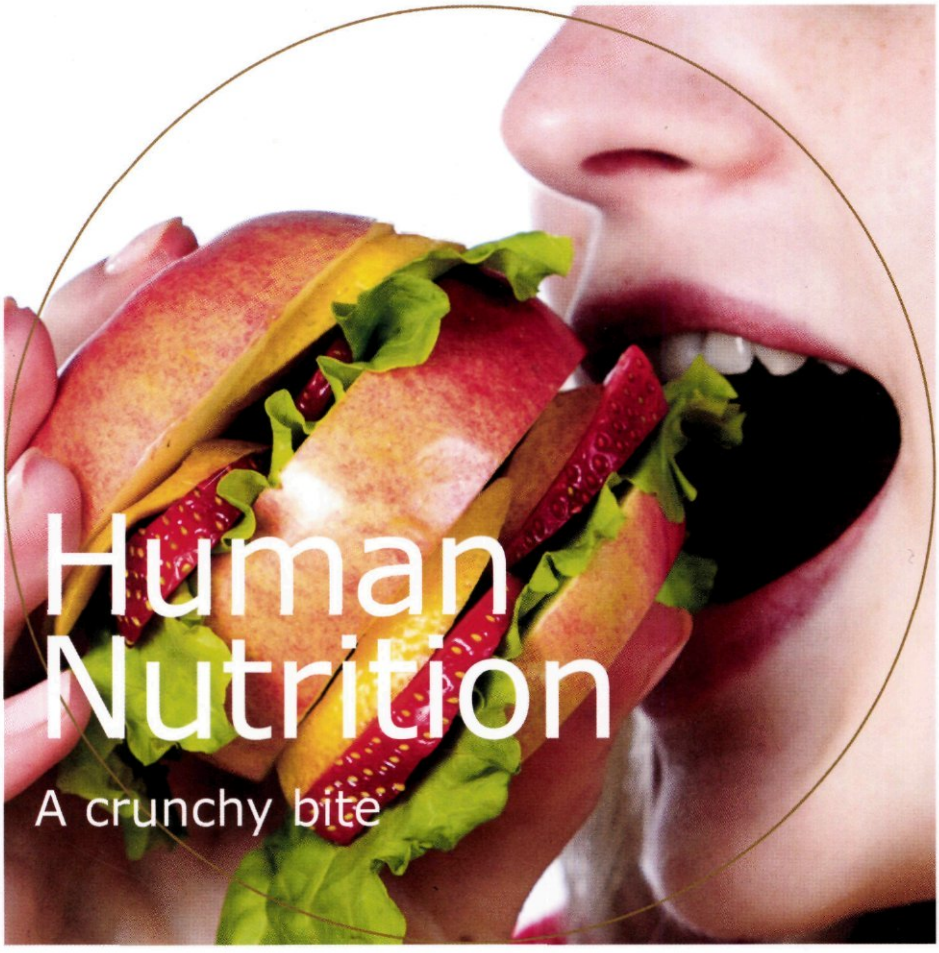

Human Nutrition

A crunchy bite

Prof. dr. Frans J. Kok

Farewell address upon retiring as Professor of Nutrition and Health at Wageningen University on 15 October 2015

WAGENINGEN UNIVERSITY
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Mr. Rector, colleagues, students, family and friends, ladies and gentlemen.

Nutritional science is a young and complex scientific discipline. As an appetizer to this farewell address, I will take you on a short historical journey of this fascinating field, where much is still to be discovered.

Gerrit Jan Mulder, professor of Medicine and Chemistry at Utrecht University was the pioneer of nutrition in The Netherlands. In 1847, he published "De Voeding in Nederland, in verband tot den Volksgeest", setting the first dietary guidelines for the Dutch population (1). Mulder argued, that the poor should eat more protein-rich beans and peas and less potatoes (2). The wealthy were advised to eat less meat and less fat. Mulder died in 1880, just 5-years before Van Gogh painted his famous Potato Eaters, a painting which gives a nice impression of the living standards in rural areas in those days.

Around 1900 onwards, The Vitamin Revolution began. A total of 13 vitamins were discovered, including vitamin D in 1922 (3). The seniors among us, and I am now one of them, will remember the bad tasting cod liver oil preventing us from rickets also known as English disease.

Later, in 1952, at the first International Congress on Nutrition and Dietetics which was held in Amsterdam, the American physiologist Ancel Keys put forward the fat-cholesterol-heart disease hypothesis (4). The role of fatty acids is still keeping us busy today (5).

In the Western world, changes in lifestyle began to have a major health impact. The excess intake of calories combined with a sedentary lifestyle brought us the obesity epidemic.

Here you see the obesity trends over the last 30 years in the US and The Netherlands [Figure 1] (6). Since the 1980s, obesity has doubled in our country and in America 1 in 3 adults are now obese.

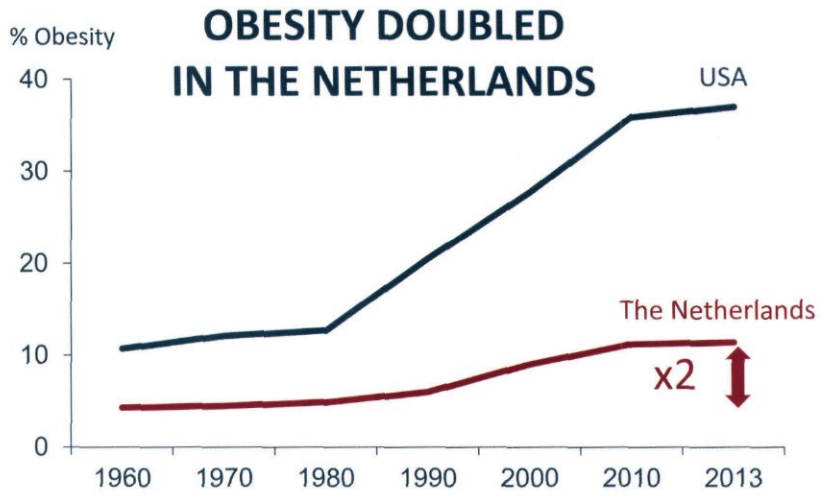

Figure 1

Meanwhile in developing countries hunger rates increased. The last ten years has seen a dramatic rise in "the double burden of malnutrition", where under- and overnutrition coincide (7).
From the 1970s onwards, nutritional epidemiology and dietary intervention studies provided insight into the health effects of total diets, foods and nutrients. And the food industry started, albeit slowly, to reduce or remove less desirable components, such as saturated fat, trans fat, salt and added sugar, from their products [Figure 2].

Technological developments also had a major impact. The human genome project, the omics technology, and the recent mapping of the epigenome, made it possible to study genetic susceptibility and gene expression in relation to diet. Personalized nutrition became the new buzz-word (8).
And now Big Data is trending. The term refers to huge amounts of data from multiple levels that can be obtained for any individual. This includes information from electronic dietary and medical records, sensors, scanners, social media and the various omics (9). Digital technology will definitely become a major driver of nutritional science and public health in the future.
After this flashback, I will offer you a three-course menu: early life nutrition, midlife nutrition and late life nutrition. In our research and academic training in

Wageningen, we cover diet in health and disease over the full lifecycle. International nutrition and metabolic health are chosen as common themes. And we pursue a multidisciplinary approach at the level of the cell, the individual and the population. Time doesn't allow for a complete overview, but I will give you a flavour of our work and some future perspectives.

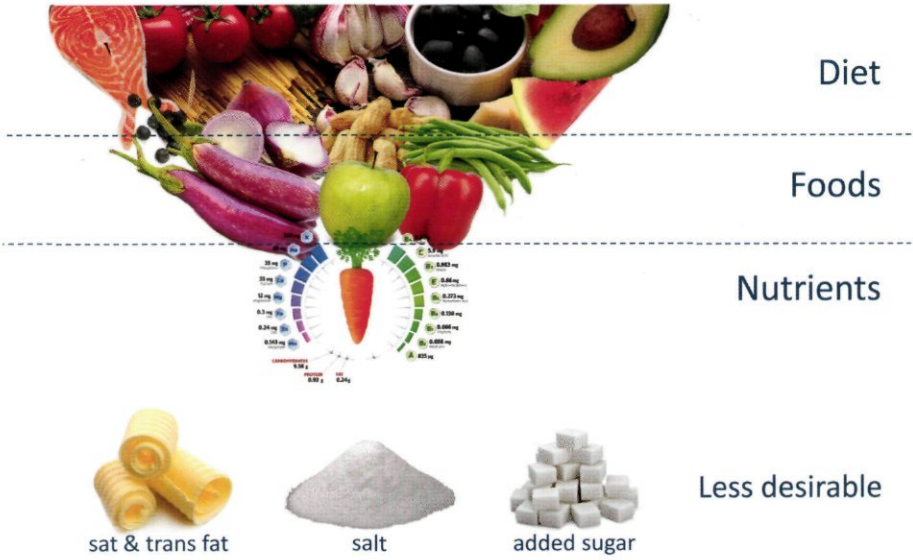

Figure 2

Early Life Nutrition

I will start off with the topic of Early life nutrition.
This map shows the 34 countries that account for 90% of the global burden of malnutrition [Figure 3] (10). The causes are low intake of energy and proteins and "hidden hunger", related to the big five problem nutrients: iron, vitamin A, iodine, zinc and folic acid.

Malnutrition is responsible for almost half of all deaths in children under the age of 5 (11). It causes health problems such as anemia, blindness and birth defects. Later in life we still see the consequences, such as reduced growth, also known as stunting, impaired mental development and lower work productivity. Imagine, the death of 1 million children per year can be prevented if there would be full access to just ten proven nutrition interventions (12).

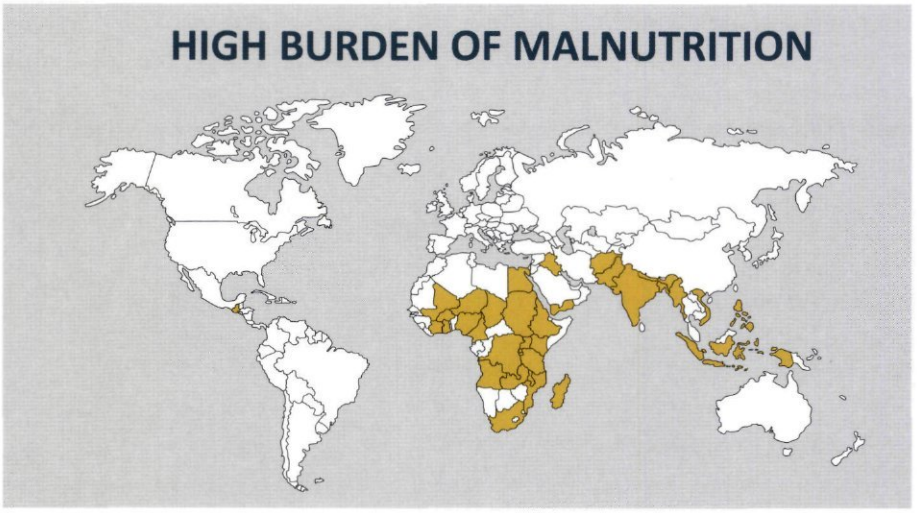

Figure 3

Since the start of our Division in 1969, international nutrition, especially of mother and child, has been a focus area. We have built an extensive network in Africa and Asia, aiming at institutional capacity building through collaborative research and training of local people. Our overall research goal is to provide evidence for the efficacy of nutrition interventions.

Strategies to fight against malnutrition comprise supplementation, fortification, biofortification and dietary diversification (13). To illustrate our research approach, I will give two examples, one on iron and the other on vitamin A.

Iron deficiency is the most common and widespread nutritional disorder worldwide. Iron fortification of a staple food such as maize may be a solution, but the iron form is critical because maize contains high levels of phytate, which inhibits iron absorption. In a randomised controlled trial among 500 Kenyan schoolchildren, one of my PhD graduates showed that iron in the form of ironEDTA, is absorbed better than electrolytic iron [Figure 4] (14). EDTA prevents iron from binding to phytate.

The ironEDTA groups improved their iron-status. The high-dose also significantly decreased anaemia prevalence. Electrolytic iron didn't show any effect. Our findings strongly contributed to a change in fortification policy by the Kenyan authorities. A fine example of Science for Impact, as we like it in Wageningen.

Besides iron, vitamin A is also an area of focus in our Division. Worldwide coverage of vitamin A supplementation is quite good, but deficiency persists and additional food based strategies are still needed (13). The INSTAPA vitamin A study in Africa as shown in the video, is part of a large 6 million euro EU project coordinated by our Division. Nine partners, including 6 from Africa were involved.

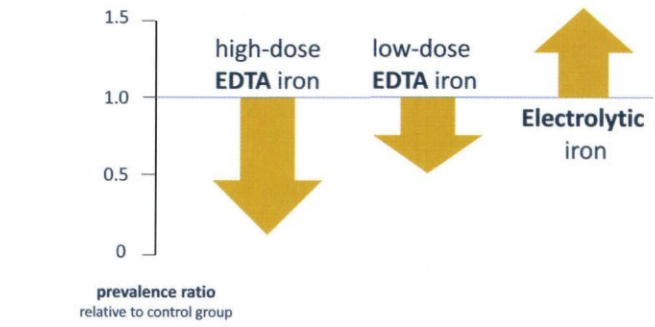

Figure 4

The Kenyan children (video) normally eat white cassava, which is low in vitamin A. To increase vitamin A intake, white cassava was biofortified . This was done by cross breeding vitamin A rich yellow cassava imported from South America to Africa with local crops, resulting in varieties with increased levels. In an 18 weeks trial with 360 Kenyan children, we showed that biofortified cassava increased blood retinol levels significantly and the kids really liked the yellow cassava (15).

An important milestone for improving early life nutrition was the launching of the "1000 Days Initiative" by Hillary Clinton five years ago in Washington [Figure 5].

Figure 5

This partnership of governments as well as the public and private sector calls for action on the first 1000 days of life, when better nutrition can have a lifelong impact on a child's future.

I will illustrate this with iron and brain development. Brain regions involved in cognitive and mental performance, are highly susceptible to iron deficiency, especially from the last trimester of pregnancy until 2 years after birth. Animal studies suggest that insufficient iron during critical periods of brain development is difficult to remedy.

This is also true for humans. In a trial among 6000 pregnant women and 4600 live births in rural western China, one of my Chinese PhDs showed that children had significantly lower mental development at the age of 2, unless sufficient iron was provided during pregnancy (16).

In line with earlier meta-analyses, the China trial confirmed that extra iron decreased infant mortality, and improves several health outcomes, such as birth weight, duration of gestation, and early preterm delivery (17).

Figure 6

This example illustrates that the first 1000 days of life make up a crucial window of opportunity to combat malnutrition, not only for iron but also for energy and other problem nutrients such as iodine and folic acid.

A second window of opportunity is the pre-pregnancy period. Nutritional status of adolescent girls in deprived areas requires much more attention, because first pregnancy under age 18 is highly prevalent. Adolescent girls are in rapid growth and stunting is very common. What they eat affects not only their health, but also the

health of their kids and even their grandkids. These transgenerational effects refer to epigenetics.
Epigenetics describes heritable, but reversible, changes in gene expression mediated primarily by DNA methylation and histone modification. Our environment, from smoking to diet and pollution can leave epigenetic marks on our DNA, silencing or activating genes.

The study among rural Gambian women, presented today in our symposium by professor Andrew Prentice nicely demonstrates that a mother's nutritional status at the time of conception can influence her child's epigenome, with likely lifelong implications [Figure 6]. DNA methylation was higher in children conceived in the rainy ('hungry') season compared to the dry ('harvest') season. Which was in line with the maternal periconceptional status of methyl-donor nutrients (18). The epigenome links nature and nurture. Epigenetic changes occur not just in pregnancy but over the full life span and unravelling the influence of diet will become a major future challenge for nutrition science.
Studying diet-epigenome interactions poses several challenges because diet-induced epigenetic changes occur over time, they can be rapid, temporary or persistent (19). So the timing of assessing exposure, the choice of epigenetic marks and tissue types is critical. And , we need to know the phenotypic consequences of epigenetic marks. Epigenome Wide Association Studies are now underway to identify them.

An alarming phenomenon in Asia and Africa is stunted obesity: the combination of early life undernutrition and subsequent overnutrition. This so-called "double burden of malnutrition" can lead to diabetes and other chronic diseases later in life. We need to understand the risk factors, including genetics and epigenetics, of these Western-type diseases, because they differ in etiology in a non-Western context. Our intervention strategies cannot simply be extrapolated to African or Asian populations.

Several nutrition specific strategies against malnutrition, such as breast feeding and supplementation are effective and necessary but insufficient to completely solve the problem. Equally important are nutrition-sensitive measures, such as agriculture, clean water and sanitation, education and employment. Our biofortified cassava study is a good example of how agriculture can contribute to nutrition security. Being part of an agricultural oriented university, our Division has the unique capacity to study how food systems can promote improved nutrition and health.
For this farewell address, I created a number of one-minute video's. I wrote the scripts and I found a designer at an internet platform who helped me to put it in an

animation. The video's express my view on some societal issues related to nutrition. The first one is on International Food and Nutrition Policy (see Text Box 1).

Text Box 1 International Food and Nutrition Policy

The Sustainable Development Goals will stimulate governments to frame their agendas to achieve food and nutrition security, and promote sustainable agriculture. At present, global Agri&Food industry makes unhealthy foods cheaper and healthy sustainable foods more expensive. A long-term industry strategy, placing consumer and environment at the heart, will better help reaching the development goals. Governments also need to show the political will to secure a healthy and sustainable food supply by international trade, pricing and other measures. And, if self-regulation by industry fails, measures such as taxing junk foods, controlling portion sizes and kids marketing are necessary. It's our world: take care of it.

Midlife Nutrition

Now we move on to the main course, midlife nutrition.

A challenge for many at this stage in life is weight management. Almost half of Dutch adults is overweight and one in 8 is obese (20). Diabetes, a direct consequence of obesity, is projected to increase worldwide by more than 75% in the next 20 years. Largest increases are expected in Asia and India as a result of the "double burden of malnutrition" (21).

Figure 7

Obesity is a massive problem, with many efforts to eat less and move more. The major enemy is our environment with an abundance of low-priced energy-dense foods and drinks, tempting advertising, and sedentary living conditions [Figure 7]. In the 2015 Lancet series on obesity (22) it was stated very clear: "Today's food environments exploit people's biological, psychological, social, and economic vulnerabilities, making it easier for them to eat unhealthy foods."

Results from weight-loss diets are disappointing, regardless whether they emphasize proteins, fats or carbohydrates (23,24). Losing 5% of initial body weight in the long run is what trials at best show. The good news is that losing some kilo's may already have meaningful health benefits (25).
Modern science and technology is in the era of personalized nutrition and Big Data. Integrating multi-level data from genotype to phenotype and the environment is truly a challenge, but it will help to better understand obesity and other nutrition problems [Figure 8]. And if we understand better, we may intervene better.

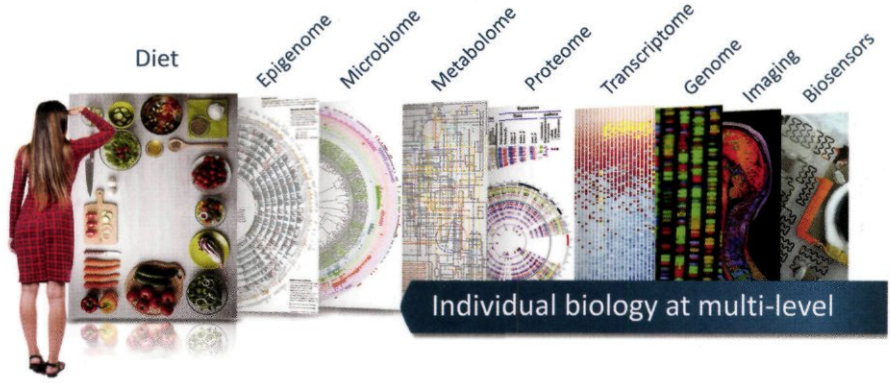

Figure 8

I will take our Wageningen Belly Fat Project to illustrate this multi-level approach. But first, I would like to show you how my own body responds to dietary change. Five years ago, I exposed myself to a self-experiment, being my own guinea pig for two months in a well-designed trial. The first month, I adopted an unhealthy diet and transformed myself into a couch potato. The second month, I changed back to my usual, healthy pattern. At regular intervals, blood and 24 hour urine samples were collected and a series of tests and scans were completed.
In Figure 9 you see all the foods and beverages I consumed in one healthy and one unhealthy week. The unhealthy pattern was not extreme. I didn't go on a McDonalds supersize-me diet, but chose on purpose a pattern reflecting the

habitual Dutch diet. During the healthy period, I followed the Dutch Dietary and Physical Activity Guidelines. At first glance, the diets look quite similar. A closer look shows important differences: more calories, saturated and trans fat, salt and added sugar, and less fibre in the unhealthy period.

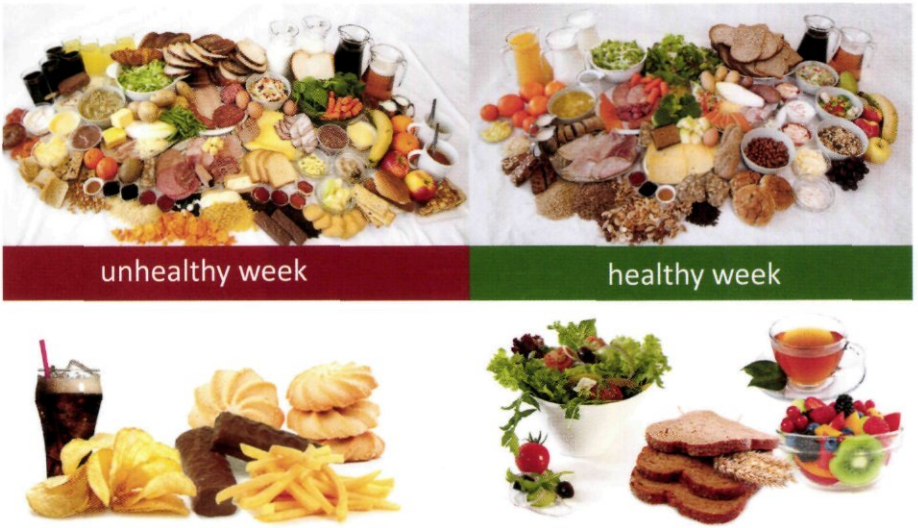

Figure 9

As planned and calculated by our dietician, I gained 2.5 kg in 4 weeks. Most health parameters such as belly fat, body fitness, vascular function and heart rate worsened. Blood lipids, blood pressure, blood insulin and liver enzyme levels increased. In the second healthy month of the trial all indices, including bodyweight returned to normal. Conclusion? I never had expected such fast and dramatic changes. Of course no scientific inference can be made, but the findings convinced me even more how important diet and physical activity are for your health.
Adverse metabolic changes may be more pronounced in overweight and obese subjects. This slide shows body scans of an obese and normal weight person. To reach a BMI of 36.2 I would have to put on 40 kg. During the development of obesity, excess fat which accumulates in and around metabolic organs such as the adipose tissue, liver, and muscle may negatively affect lipid and glucose metabolism.
In Figure 10 you see how it works. The stressed fat cells release signals attracting immune cells that infiltrate the adipose tissue leading to a state of chronic low-grade inflammation. This process may result in insulin resistance eventually causing diabetes and other chronic diseases (26).

The molecular pathways that are activated in obese adipose tissue and lead to insulin resistance are complex. I will not go into the interactions between the immune cell and adipocyte that determine the degree of inflammation (27). Our molecular nutrition group is very active in this exciting field of immuno-metabolism. These mechanistic insights will help us to move forward in designing nutritional interventions, to prevent or treat inflammation, and ultimately improve metabolic health.

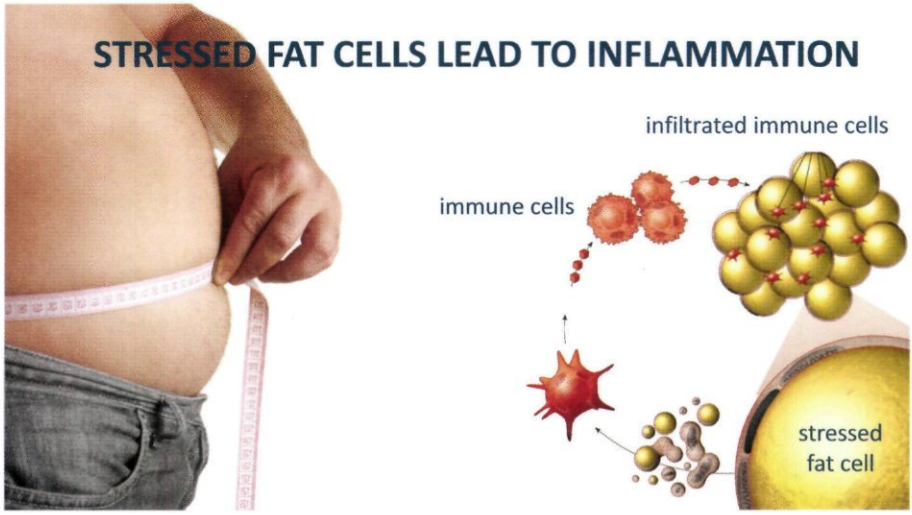

Figure 10

Previous studies have shown that reduction of excess fat in liver and muscle leads to normalization of insulin sensitivity. Even in diabetes patients modest weight loss had a similar effect (28-30).
Our Wageningen Belly Fat Project which I mentioned earlier aims to study the effect of weight loss on metabolic health [Figure 11]. In a 12 weeks controlled trial, 110 overweight subjects, with an average BMI of 31 were randomized into three groups: the first group followed a Western (unhealthy) diet with 30% energy restriction, the second group an optimized (healthy) diet with 30% energy restriction, and the control group consumed their usual diet with no caloric restriction. Subjects in the intervention groups lost as much as 600 kg, mean weight loss in the intervention groups were 6.3 and 8.4 kg. The usual diet group gained 0.8 kg. Primary outcome was liver fat quantified by proton magnetic resonance spectroscopy. It decreased dramatically and significantly between the control and both intervention groups.

Wageningen Belly Fat Project

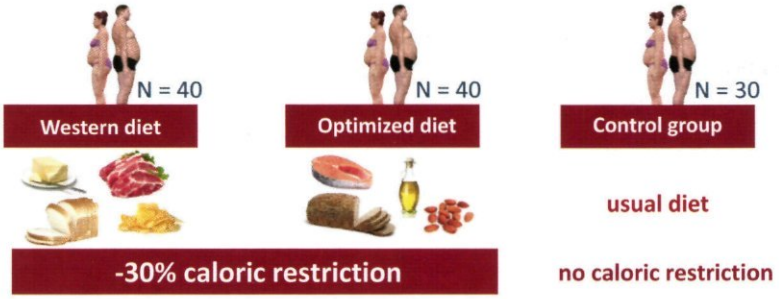

Figure 11

The health effects of weight loss in the Belly fat project is studied by measuring a large set of indices. New sophisticated techniques allow us to collect even more data. For example, we could have looked whether weight loss leads to changes in hunger and satiety and reward activation in the brain.

The neurobiology of eating behaviour is an exciting field. In our Division we are using functional MRI to measure effects of taste and smell exposure. Brain responses may also have been linked to gut hormones and the microbiome, to see how the gut "talks" to the brain. We can easily and locally sample gut content by swallowing the capsule shown left. We are using this device, to study the impact of different diets on the microbiome. Indeed, microbiota is popular nowadays, but one should not forget that it is our diet that drives the gut microbiota.

Dietary intake assessment will also benefit from new technologies. Our new location at the Helix provides facilities for serving meals to 100 study participants at a time. This way dietary intake can be well controlled. In free living settings, however, self-reporting of dietary intake is sensitive to bias and may become the weakest link.

To improve this, we are currently testing web-based tools making use of smartphones and wearable devices [Figure 12], for instance sensors near the ear and throat measuring chewing and swallowing. Ideally we would like to measure real-time validated food intake.

You see there are many ways to collect large amounts of multi-level data from an individual, like we did in the Belly Fat Project.
Integration of the multi-level data in the Belly Fat study requires sophisticated bioinformatics and statistical methods for high dimensional data (31,32). The resulting mechanistic insights will make us better understand why for instance, on the same caloric restriction, one person lost 8 kg whereas another only 2.

Figure 12

The research strategy in our Belly Fat study was hypothesis driven, which implies a concise research question and measuring possible intermediary steps in the causal pathway. Now with Big Data, gigabytes of information become available allowing a data driven, hypothesis generating approach. Information on real-time dietary and medical practices, lifestyle, social contacts, and omics often collected by individuals themselves opens up new possibilities. Big Data, however, also means Big Error, both random and systematic. It enables us to identify a wealth of signals, which should be confirmed in epidemiologically well-characterized populations and finally tested in intervention studies [Figure 13].

As we heard from professor Norbert Stefan today, obesity may not be unhealthy for everyone and future research, including Big Data may identify who is at risk and under what conditions. More complete understanding, will make nutrition research move from a 'one-size-fits all' group level to specific subgroups and ultimately to a 'what's in it for me' personal level.

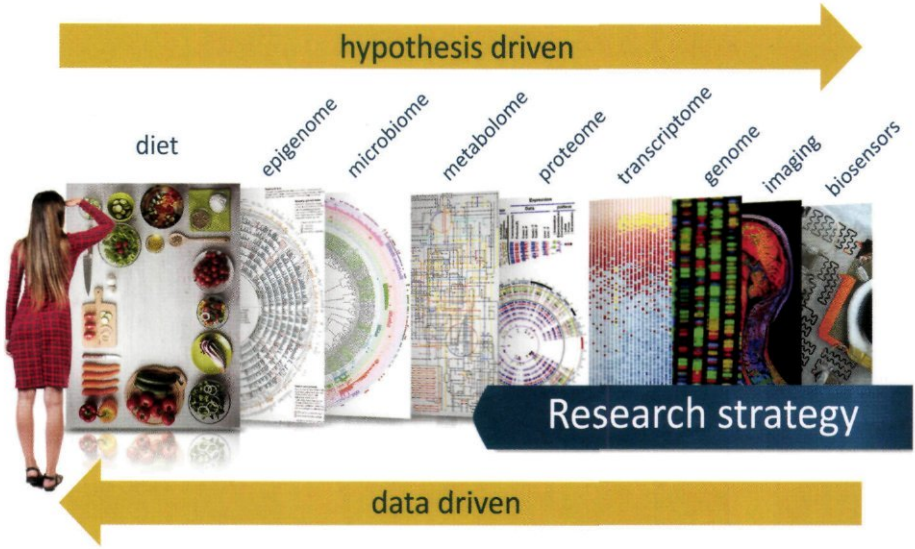

Figure 13

Many overweight people want to lose weight and are browsing the Internet for the latest hypes. As an intermezzo, I will now show you my view on Nutrition and the Media (see Text Box 2).

Text Box 2 Nutrition and the Media.
TV, newspapers, books, internet and social media. Nutrition is everywhere. Diet gurus promise weight losses of 1-2 kg per week, making big money by clever marketing but misleading the public. Other so-called experts glamourize exotic superfoods, bashing basic products such as bread and dairy. Nutrition is entertainment for talk shows. Editors are not interested in the facts. Science journalists are more responsible, providing context in their articles. Good to see that nutrition is hot, but be aware of media seeking for sensation. And for the consumer: rely on authorities and forget about the hypes, that come and go and only cost you money.

Late Life Nutrition

And now for the dessert, late life nutrition

This is Susannah Jones, the oldest verified person in the world. She lives in the US and is 116 years old. Her key to long life: surround yourself with love and positive energy. And on her menu: bacon and eggs every morning for over a century. Not very healthy, but Ms. Jones most probably has strong genes.

Genes account for about one-third of the variation in life expectancy. This is the programmed part of aging. In fact, our DNA is programmed so that we slowly degenerate. Most of the aging process is driven by random damage due to chronic stresses such as inflammation, oxidative and metabolic stress. Many factors, including diet contribute to this damage which may occur in all body cells. As we age, our body's repair machinery can't keep up, and the damage accumulates, resulting in age-related disorders (33,34).
So as we get older, we gradually lose our physiological integrity, leading to loss of organ function, decreased quality of life and higher risk of disease (34) [Figure 14].

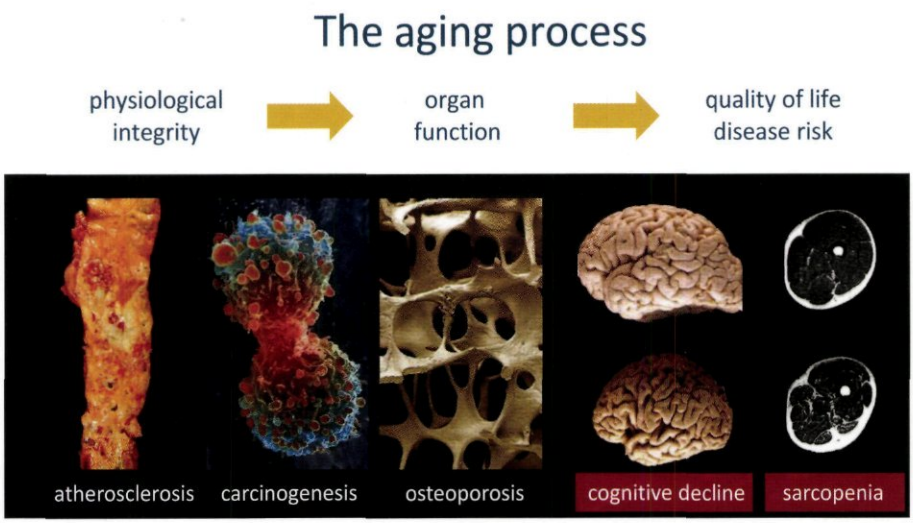

Figure 14

In Wageningen, we have a rich history in research on diet and the prevention of cardiovascular disease, cancer and osteoporotic fractures. All manifestations of the aging process. I will now go into cognitive decline and sarcopenia, topics taken up more recently by our group on nutrition in the elderly.
An aging brain is vulnerable to cognitive decline. Mental processes including memory, information processing speed, and decision making may decrease with age. This process may finally lead to Alzheimer's disease, with 80% of cases, the most common form of dementia. With the aging population, dementia will increase in the coming years, so effective prevention strategies are important.
Using results of meta-analyses it has been estimated that about a third of Alzheimer's disease cases could be attributable to low education and modifiable lifestyle risk factors such as smoking, physical inactivity, hypertension and

depression. This provides opportunities for prevention (35).
Intervention studies on cognitive decline targeting several lifestyle factors were for a long time lacking. Recently a large-scale 2-years randomised trial in Finland, showed that a combined program on healthy eating, exercise training, brain training and vascular risk monitoring was beneficial for cognitive function and dementia risk (36).
Cognition has also been an area of interest at our Division. In a number of trials, we have looked into the effect of individual dietary components on cognition (37-39). Promising candidates such as B-vitamins and omega-3 fatty acids showed mixed results. This may be related to the timing and duration of the intervention or the ability of cognitive tests to pick up subtle differences. Or simply that these nutrients don't have biological relevance.
Scanning of specific brain regions may increase accuracy to spot changes in cognitive function. At the University of Oxford, a 2-year trial with a high dose of B-vitamins in elderly with memory complaints showed a significant reduction of the loss of gray matter (40). Gray matter volume is specifically affected in Alzheimer's disease [Figure 15]. However, we could not confirm these findings in a similar study among 218 elderly subjects (41).

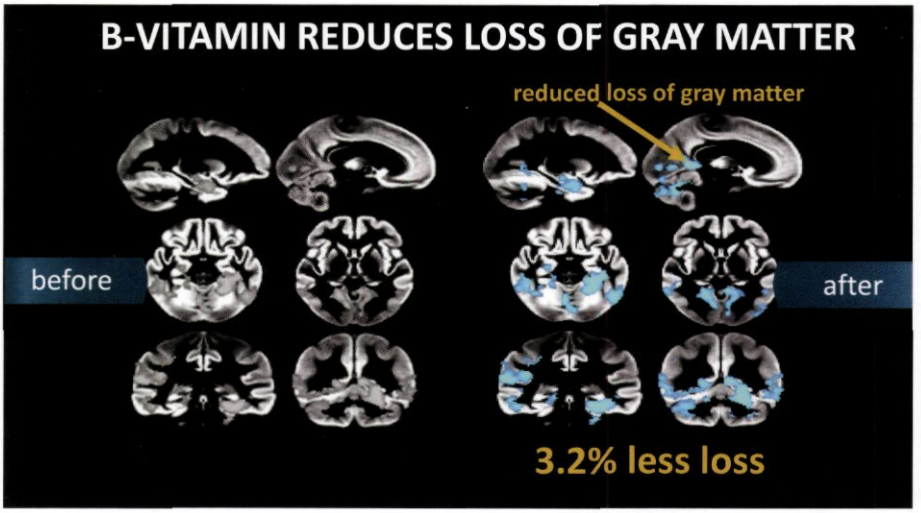

Figure 15

To understand to what extent individual nutrients matter in cognitive performance, functional MRI may be helpful in future studies. A performance task in the scanner before and after a long-term nutrition intervention may better show changes in

neuronal activation in relevant brain regions. For example, with a before/after Stroop test, we could study the effect on brain connectivity of long-term omega-3 fatty acids supplementation. Brain connectivity clarifies how neurons and neural networks process information.

"Use it or lose it" not only holds for the brain, but also for other organs, like your muscles. This brings me to sarcopenia, which is the aging loss of muscle mass and strength. This slide shows a cross section of the upper leg of a 25 year old man and an untrained 63 year old male. The gray area is muscle protein, the white area is fat. With aging, muscle protein turnover decreases. Physical activity stimulates muscle protein synthesis, but dietary proteins are necessary for a positive balance. Elderly people, however, have a diminished response to dietary protein intake. This is called anabolic resistance. An inactive lifestyle combined with anabolic resistance, may lead to substantial loss of muscle mass up to 50% over the years. Sarcopenia is associated with negative outcomes such as falls, immobility, disability, and premature death.

To prevent or counteract loss of muscle mass, resistance exercise training is particularly important, since it stimulates the synthesis of type II muscle fibers, which are most relevant for muscle strength. Besides proteins, vitamin D and omega-3 fatty acids are other promising dietary factors to prevent sarcopenia.

A study at our Division among 62 frail elderly people showed that resistance-type exercise training is an effective strategy to improve strength and physical performance (42) [Figure 16]. And indeed, additional protein was needed at breakfast and lunch to overcome the anabolic resistance to food intake resulting in an increase in muscle mass in the protein supplementation group only.

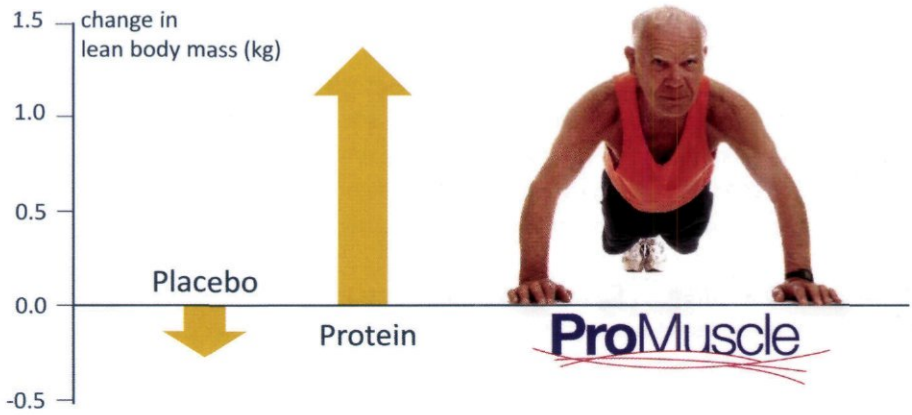

Figure 16

An intriguing next step in sarcopenia research is on muscle functioning, which depends on physiological characteristics as well as neurological factors. The role of nutrition on muscle functioning and the stimulation by the brain is poorly understood. This will be further explored using electromyographic analysis.
In a disease state and after acute inactivity, loss of muscle mass and performance is much more rapid and severe. A hospitalized patient for example, may lose 1 kg of muscle mass in only 7 days. In Dutch hospitals and care institutions, the prevalence of undernutrition, due to protein and energy deficiency, ranges between 20 and 30% (43). This is unacceptable, it raises health care costs due to clinical complications and longer hospital stay.
We could show that undernourished patients receiving protein enriched foods improved physical performance and strength. Bread, juices and desserts with extra protein were provided in the hospital and at home after discharge for a period of 6 months. It resulted in 20 to 30% higher daily protein intake.

Figure 17

The Cater with Care project is one of several spin-offs of the Nutrition Alliance Gelderse Vallei [Figure 17]. Eight years ago, this unique collaboration between the general hospital in Ede and our Division started. Our joint goal is to achieve health benefits for patients by optimizing diet and physical activity before, during and after medical treatment. The hospital developed into the first nutrition hospital in The Netherlands and Europe with an on-demand meal service "At Your Request". Through the Alliance, medical specialists, our academic staff, master and doctoral students, are collaborating in many projects.

To conclude, diet and physical activity are crucial for healthy aging and you're never too old to change. For example, if you start at age 60 you will gain an extra two quality years on top of your life expectancy (44).
Now I show you the final video animation on Public-Private Partnership (see Text Box 3).

Text Box 3 Public-private partnerships
The Cater with Care project is an example of public-private partnership, bringing health benefits to undernourished patients and commercial benefits to food companies. We definitely need research collaboration with the AgriFood industry to solve major societal problems such as hunger and obesity. Current science policy, however, is focusing too much on matching public research funds with industry money. This way, the industry increasingly determines the research agenda with the risk of solely addressing short-term business-focused topics. A better balance between curiosity-driven research and precompetitive research with industry involvement is required. In the long run, this will pay off in terms of economy and public health.

Human Nutrition Training

I come to the last part of my talk.

A few remarks on Nutrition training should not be missing from this farewell lecture. Our bachelor-master program is the only full academic training in human nutrition in the Netherlands. The curriculum is quite flexible as students compile to a great extent their own study profile out of a broad range of courses and practical's.
After the first graduates in the early 1970s, almost 3000 students received their diploma. The last decade we have seen a sharp increase in student applications. To keep up the high standard of education, we had to introduce a numerus fixus for bachelors last year.
In 1972, I started my Wageningen nutrition training [Figure 18]. We were the generation of "eternal students". In the education system nowadays, efficiency thinking is the norm. It's crucial however, that students have sufficient time for personal development to be prepared for their societal role. In the 1970s, I was active in political theatre. We challenged food multinationals in a play entitled The Dessert with the Bad Aftertaste and had heated discussions with the audience. But appropriate in the seventies, we also experienced self-made space cake in the Wageningen Arboretum garden, listening to Lou Reed and the Velvet Underground.

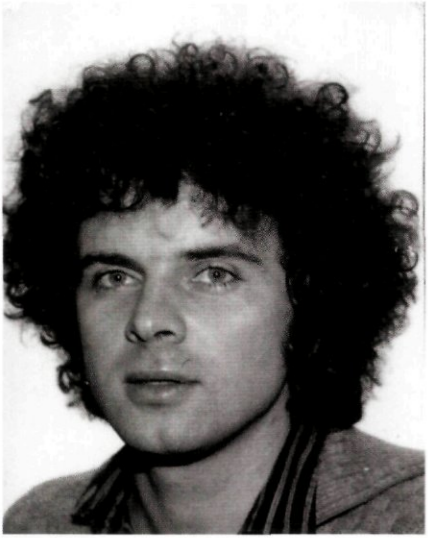

Figure 18

In those days, we were trained as all-round nutritionists, with strong emphasis on research methodology and an explicit connection to foods. Nowadays far-reaching specialisation is inevitable, but research methodology and general knowledge of nutrition and food remains essential, making the curriculum unique and very well placed in Wageningen.

Nutrition and health are now very much global themes and societal and scientific developments continuously demand new and advanced education. For the future, I see epigenetics, big data and sustainability as essential topics for human nutrition training.

Also the mode of delivering education is rapidly changing, with E-learning and flipped teaching, where the traditional lectures are delivered online and reflection and discussion with students takes place face-to-face in class. And the current information revolution requires training in so-called information literacy skills. Students need to recognize when information is needed, and how to find, evaluate, and use it effectively.

Acknowledgements

I was very privileged to have met so many interesting people in my career. And I am very pleased to see so many here today. I look back with satisfaction and harbour many good memories.
First working at the Netherlands Heart Foundation, in the days when egg yolk was seen as poison and was best given to your dog or used as shampoo. But the egg made a comeback and according to the 2015 US Dietary Guidelines, people don't need to worry too much about cholesterol in their diet (45).
Later, I moved to the Erasmus University Medical Center and TNO. While the hot topic at the time was lipids, I kept myself busy with antioxidants and free radicals. This was a very new topic in nutrition research, and I was seriously asked by some well-respected colleagues if I'd started a new political party.
There were also moments when I volunteered myself for research purposes. To convince an EU committee that a fat biopsy from the buttocks wasn't harmful, I volunteered in an instruction video. Years later this video popped up in the US and our students on excursion to the US embarrassed me by asking whether I had become an adult movie star.
I will remember the students and faculty in the many teaching courses here and abroad. It's extremely rewarding to work with young people and I loved the intriguing cultures and amazing landscapes of Africa, Asia and China.

I am very grateful to all my Wageningen Human Nutrition colleagues [Figure 19].

Figure 19

I have very much appreciated the spirit, collaboration and good humour, which has resulted in excellent research and inspired teaching over the years. The move to the beautiful new Helix building will further stimulate creativity and productivity. I wish the entire team all the best, especially the two new chairholders professors Ellen Kampman and Edith Feskens and the new chair of Division professor Kees de Graaf.

Sincere thanks is expressed to the Executive Board of Wageningen University for the trust in me over the near 25 years of my professorship. I am proud of this university, addressing very relevant societal topics. I witnessed and was active in the strategic transformation from agriculture to life sciences, with emphasis now on healthy and safe foods, natural resources and the living environment. I have loved working in science but also in administrative positions as Dean of Science and Member of the Academic Board. And yes, managers could drive me crazy every now and then, I am pretty sure that this was vice versa. But constructive criticism was always my main intention.

For the guidance in my scientific career, I owe thanks to many, but two people deserve special consideration, Professor Jo Hautvast and Professor Walter Willett [Figure 20].
During my one-year master training in epidemiology at Harvard University in 1983, Walter Willett was my tutor. We kept in contact over the years, several of our PhD students went to Boston for data-analysis, and I was very proud to act as honorary promotor, when you Walter were awarded an honorary doctorate by our university in 2003. Walter, you are an exceptional scientist and I admire your integrity, modesty and friendly character. Thank you very much for your support.

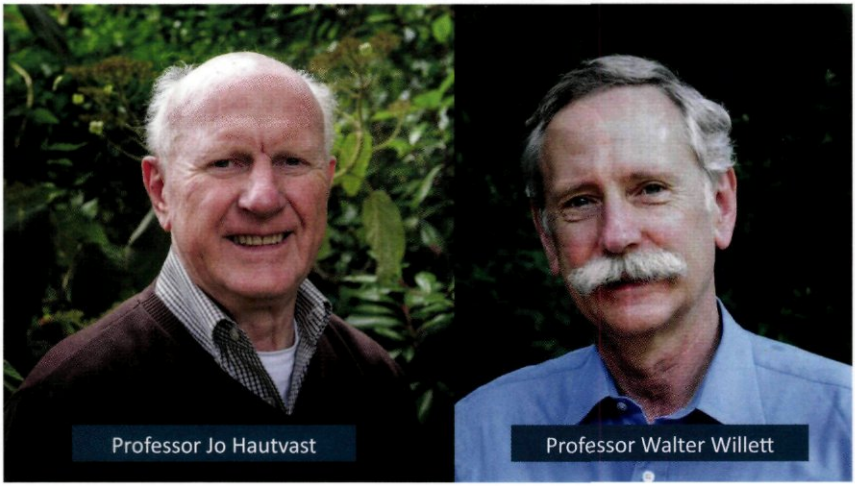

Figure 20

Professor Hautvast, dear Jo, you are a close friend and like a second father to me. Over 40 years, you have been my teacher, supervisor, and mentor, asking me to become your successor 18 years ago. Your wisdom, inspiration, and social abilities are outstanding and served for me as a role model. I am privileged to have met you and thank you for your confidence and belief in me. We are both delighted to see that Human Nutrition in Wageningen is 'alive and kicking'.
The final words are for Anneroos and our two children Fransien and Chris. Thank you for always supporting me to spread my wings. We have a great family, and I am eager to go on a next journey in my life, especially as a very fresh grandfather.
Ladies and gentlemen, thank you for your attention.

Ik heb gezegd.

References

1 Mulder GJ. De Voeding in Nederland, in verband tot den Volksgeest. HA Kramers, publishers 1847.

2 Brouwer E. Gerrit-Jan Mulder (1802-1880). J Nutr 1952; 46: 3-11.

3 Semba RD. The discovery of the vitamins. Int J Vitam Nutr Res 2012; 82: 310-315.

4 Keys A. The cholesterol problem. Voeding 1952; 13: 539-555.

5 Chowdhury R et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: A systematic review and meta-analysis. Ann Intern Med 2014; 160: 398-406.

6 www.zorgatlas.nl en www.cdc.gov/obesity

7 Haddad L for the Independent Expert Group. 2015 Global Nutrition Report: actions and accountability to advance nutrition and sustainable development. International Food Policy Research Institute, Washington 2015.

8 Müller M, Kersten S. Nutrigenomics: Goals and Perspectives. Nature Rev Genet. 2003; 4: 315-322.

9 Khoury MJ, Ioannidis JPA. Big data meets public health. Science 2014; 346: 1954-1055.

10 Bhutta ZA et al. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? The Lancet, 2013; published on-line June 6. http://globalnutritionseries.org/ http://www.who.int/mediacentre/factsheets/fs178/en/

11 UNICEF. Improving child nutrition: the achievable imperative for global progress. UNICEF 2013. www.unicef.org/media/files/nutrition_report_2013.pdf

12 Black RE et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. The Lancet 2013; published on-line June 6. http://globalnutritionseries.org/

13 Brouwer ID. Agriculture and nutrition: Linkages and complementaries. In (eds) Akinyoade A etal. Digging Deeper: Inside Africa's Agricultural, Food and Nutrition Dynamics. Published by Koninklijke Brill NV, Leiden 2014.

14 Andang'o PE et al. Efficacy of iron-fortified whole maize flour on iron status of schoolchildren in Kenya: a randomised controlled trial. The Lancet 2007; 369: 1799-806

15 Talsma EF et al. Biofortified yellow cassava and vitamin A status in Kenyan children: a randomized controlled trial. Submitted.

16 Chang S et al. Effect of iron deficiency anemia in pregnancy on child mental development in rural China. Pediatrics 2013 Mar;131(3):e755-63. doi: 10.1542/peds.2011-3513.

17 Zeng L. Impact of micronutrient supplementation during pregnancy on birth weight, duration of gestation, and perinatal mortality in rural western China: double blind cluster randomised controlled trial. BMJ 2008;337:a2001 doi:10.1136/bmj.a2001

18 Dominguez-Salas P et al. Maternal nutrition at conception modulates DNA methylation of human metastable epialleles. Nature Comm 2014; Apr 29;5:3746. doi: 10.1038/ncomms4746.
19 Mill J et al. From promises to practical strategies in epigenetic epidemiology. Nat Rev Genet 2013; 14: 585-94
20 http://www.nationaalkompas.nl/gezondheidsdeterminanten/persoonsgebonden/overgewicht/
21 (http://www.idf.org/diabetesatlas).
22 Lancet series. Obesity 2015. http://www.thelancet.com/series/obesity-2015
23 Frank M et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009; 360: 859-73.
24 Johnston BC et al. Comparison of weight loss among named diet programs in overweight and obese adults, a meta-analysis. JAMA 2014; 312: 923-33.
25 Wing RR et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care 2011; 34: 1481-1486.
26 Chawla A et al. Macrophage-mediated inflammation in metabolic disease. Nature Rev Immunol 2012; 11: 738–749.
27 Johnson AR et al. The inflammation highway: metabolism accelerates inflammatory traffic in obesity. Immunol Rev 2012; 249: 218–238.
28 Lim EL et al. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia 2011: 54: 2506-14.
29 Petersen KF. PNAS 2012; 109: 8236-40 Reversal of muscle insulin resistance by weight reduction in young, lean, insulin-resistant offspring of parents with type 2 diabetes.
30 Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. N Engl J Med 2014; 371:1131-1141.
31 Topol EJ. Individualized Medicine from Prewomb to Tomb. Cell 2014; 153: 1194–1217.
32 Zhang B et al. Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease Cell 2013; 153: 7070 – 20.
33 Jin K. Modern Biological Theories of Aging. Ageing and Disease 2010; 1: 72-74.
34 López-Otín C et al. The Hallmarks of Aging. Cell 2013; 153: 1194–1217.
35 Norton S et al. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol 2014; 13: 788–94.
36 Ngandu T et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 2015; 385: 2255-63.
37 Durga J et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet 2007; 369:208-16.

38 van de Rest O et al. Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial. Neurology 2008; 71:430-8 .
39 Van der Zwaluw N et al. Results of 2-year vitamin B treatment on cognitive performance: secondary data from an RCT. Neurology 2014; 83:2158-66.
40 Douaud G. Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. Proc Nat Acad Sc 2013; 110: 9523–28.
41 van der Zwaluw N et al. Folate and vitamin B12-related biomarkers in relation to brain MRI volumes. Submitted.
42 Tieland M et al. Protein Supplementation Increases Muscle Mass Gain During Prolonged Resistance-Type Exercise Training in Frail Elderly People: A Randomized, Double-Blind, Placebo-Controlled Trial JAMDA 2012; 13: 713-9.
43 Health Council of the Netherlands. Malnutrition in the elderly. The Hague. Health Council of the Netherlands, 2011; publication no 2011/32.
44 Jankovic N et al. Adherence to a Healthy Diet According to the World Health Organization Guidelines and All-Cause Mortality in Elderly Adults From Europe and the United States. Am J Epidemiol 2014; 180: 978–88.
45 http://health.gov/dietaryguidelines/2015-scientific-report/

Prof. dr. Frans J. Kok

'Nutritional sciences are moving into an era, where advanced technologies allow to comprehensively study the health effects of nutrients, foods and dietary patterns. This will help to solve major societal challenges, such as the double burden of malnutrition and the obesity epidemic. Moreover, better insight into underlying mechanisms, will make nutrition research move from a 'one-size-fits all' group level to specific subgroups and ultimately to a 'what's in it for me' personal level.'

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