Dietary measures in the battle against prediabetes

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Abstract :

Type 2 diabetes is a well-known chronic condition, estimated to affect more than 500 millions of people all over the world. This disease seems to be preceded by a period of glucose dysregulation, called prediabetes, not yet fulfilling the diagnostic criteria for diabetes however. In this preliminary state we can still delay and even reverse the progression to diabetes without the use of medication, but by altering the patients' lifestyle, meaning healthier food and increasing the physical activity.

In our literature study, we examined nine randomized controlled trials focusing on the content of the dietary advice, the way of giving the advice, the observed parameters and the follow-up time. The diagnostic criteria for (pre)diabetes have changed over time, so this is clearly reflected in the RCT's. Two of them also used a screening tool to select patients previous to blood withdrawal. The overall food goals were all quite similar and the interventions itself all pretty intensive, using dieticians or other trained healthcare professionals. Globally, even if proven successful, the interventions used in the RCT's cannot be implemented that easily in our routine healthcare. This all requires a lot of extra man-hours and money, not only for society, but for the patient as well. There is no proper refunding for prediabetic patients, even in countries as Belgium, which already has an extensive healthcare system.

Nowadays it is the responsibility of the own family doctor to advice the patients with prediabetes to change their lifestyle. Yet, the content and extent of information given about diet and exercise is not fixed and might differ a lot if we compare between various general practitioners.

In our protocol we want to develop an intervention in which the own family doctor gives the dietary advice to their own prediabetic patients in a series of consultations.

Patients will be screened using the FINDRISC to subsequently draw blood in those with a score ≥ 12. Patients may be included with fasting plasma glucose of 100 - 125 mg/dl or with an HbA1c of 5.7% - 6.4%.

For our intervention, we must consider that, firstly, a general practitioner obviously doesn't have a degree in nutrition, so the information they will have to provide should be more basic. Secondly, we want to come up with a less intensive, in terms of man-hours, and less expensive intervention, so we should focus more on triggering behavioral changes and personal reflection to make healthier food choices. That is why, we will use the Food Triangle, the visual representation of the Flemish Dietary Guidelines, in our intervention as a basis for the dietary advice given during seven fixed consultations over a period of eighteen weeks, supplemented with the Nutri-Score.

To use this protocol, as much as possible general practitioners should be recruited and afterwards randomized in control or intervention group. Practitioners in the control group will just be ordered to give the advice as they normally do to patients with prediabetes, as practitioners in the intervention group will have to follow the intervention and series of consultations as discussed in the protocol. Repeat blood testing will be executed at six and twelve months.

The main goal of the intervention is obviously to prevent the progression to diabetes, but we also want to develop an intervention that is easily implemented in our standard health care, if proven successful.

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1. Literature study as a preparation for our study protocol

1.1 Introduction

Type 2 diabetes is a chronic disease that is affecting a large amount of people all over the world(1). In 2021, the number of people who were struggling with this disease was estimated around 537 million people by the International Diabetes Federation, and this number is increasing at an alarming rate(2,3). Patients with diabetes mellitus have not only a higher morbidity, but also an increased mortality, which implies that people suffering from this disease must be followed up meticulously to delay these complications or detect and treat them as soon as possible(1,4). Additionally there are many patients who are not diagnosed on time and present for the first time with already very serious complications of type II diabetes(3,5,6). All of this is not only a threat to the quality of life of diabetes patients, but it also poses a serious burden to our health system(4).

That is why an early detection and treatment of the patients at risk to develop diabetes imposes himself(7). Prediabetes is the term used for patients in an intermediate glycemic state, which means that their glycemic parameters are too low to be diagnosed as diabetic, but too high to be considered as normal(4). Sadly every year five to ten percent of these patients progress to a diabetic state(8). Secondly, these patients seem to be, in their prediabetic state and thus prior to the development of diabetes, already at higher risk to suffer from nephropathy, neuropathy and macrovascular diseases(4,6,8,9). All of these known to be complications of diabetes itself(1). In other words, they are in need of urgent interventions to stop any further progression or even return to euglycemic state in best cases. Several studies have demonstrated the positive effect of lifestyle measures(3,4,9–11). So in the first part of this paper, we will update the search from the systematic review and also examine the past randomized controlled trials on strengths and weaknesses, to conclude in the second part with a new study protocol using diet to treat prediabetics in Belgium(10).

1.2 Methods

In 2022 we updated the search, previously executed by Poncelet M. and Schutyser D., to discover any more randomized controlled trials and thereby any further evidence and updates on how to implement diet and exercise in the treatment of prediabetes(10). Obviously, we used the same MESH terms in PubMed as in the systematic review mentioned above, namely:

“Prediabetes” OR “Impaired Fasting Glucose” OR “Impaired Glucose Tolerance” OR “Glucose Intolerance” OR “Insulin Resistance” OR “Prediabetic State”
AND
“Exercise” OR “Physical Activity” OR “Physical Fitness” OR “Diet” OR “Lifestyle” OR “Life-Style”

The randomized controlled trials were withholden according to the same criteria, so patients had to be diagnosed with prediabetes, a diagnosis of metabolic syndrome or gestational diabetes was not enough to be included. The intervention had to consist of diet and/or physical activity compared to standard care or no intervention at all and needed a minimal duration of two years. Studies using medication or supplement dietary changes as an

intervention were not allowed. The studied primary outcome had to be the progression of the prediabetic patients to diabetes mellitus type 2 when treated with these lifestyle interventions compared to standard care or no intervention. The randomized controlled trials had to be published between September 2019 and June 2022. Using these filters, we searched the database and ended up with 796 articles.
We carried out a first screening based on title and abstract to come up with ten studies that could match with our population, intervention, comparison and outcome. After reading the full length articles we ended up with only one study to add with the previous studies already assessed and discussed by Poncelet M. and Schutyser D.

1.3 Results

So as a preparation for our study protocol, we compared the different approaches in the studies described in the systematic review (10).We also updated the search in June 2022 to end up with one additional study to compare and discuss(12). Not only the dietary recommendations varied in these seven studies, but they also differed in ways of including patients, manner of giving dietary advice and duration of follow-up. Our findings are summarized in table 1.

Secondly we also assessed the two studies that were the inspiration for almost all later studies, summarized in table 2(13–15).

Table 1: The seven RCT's included

	Identification of prediabetic patients	Overall food goals	Control vs Intervention	Keeping track of dietary intake	Primary endpoint	Follow-up time	Special remarks
Ram J. et al. India 2014 537 patients (16,17)	Two step identification - capillary glucose ≥160 mg/dL 2hPG (75g) - confirmative OGTT after 1 week: venous samples taken at fasting, 30 min and 2h after 75g glucose ingestion.	- Avoiding simple sugars and refined carbohydrates, - Reducing total fat intake to less than twenty grams a day, - Restricting the usage of saturated fat - And augmenting the intake of fiber-rich food like whole grains, vegetables and fruits.	**Control** At baseline: - Personalized standard advice - Printed educational information about a healthy lifestyle **Intervention** Same as control group plus -Text messages with principles about healthy lifestyle practice /motivation (2-4/week for 2 years)	- 24h dietary recall method - by dietician - at baseline and every six months	Incidence of diabetes based on - annual OGTT Or - semi-annual 2h post glucose load test	24 months	All male participants
Davies M.J. et al. 'Let's Prevent' Program United Kingdom 2015 637 patients (18)	Two step identification 1. Leicester Diabetes Practice Risk Score: The 10% with the highest scores were screened using a OGTT 2. IFG: 110-125 mg/dl and/or IGT: 140-199 mg/dl	- Total fat intake < 30% of total energy intake - Saturated fat intake < 10% of total energy intake - Fiber intake > 15g/1000kcal (The same as in the Finnish Diabetes Prevention Program and the Diabetes Prevention Program in the USA (13,14).)	**Control** Booklet including - Risk factors for diabetes - Information on dietary changes and physical activity to prevent diabetes **Intervention** Same as control group plus - Six hours long educational group session (10 persons/group) - Fifteen minute motivational telephone call every 3 months by a trained nurse. - Three hours long recapitulation lessons at months 12 and 24.	- DINE food frequency questionnaire - at baseline and at 6, 12, 24 and 36 months during the study.	Progression to T2DM diagnosed with - symptoms + OGTT - no symptoms but 2 OGTT - (from January 2013) HbA1c ≥ 6.5%	Three years	Usage of the Desmond model: - goes out from the idea that the patient has the capacity to make its own lifestyle choices and is responsible for its own health, - they wanted to initiate, motivate, and facilitate behavioral changes in the intervention group This way a more cost-effective and long-lasting effect was intended.

Shahbazi S. et al. Iran 2018 322 patients (19)	- FPG of 100-125 mg/dl or - IGT: OGTT 2-h PG 140-199 mg/dl Confirmed by two tests	Different in the three groups: * Control group: - fat intake < 30% (saturated fat < 10%) of total energy intake - follow the Food Guide Pyramid * HMD Intervention group: - 15% from protein, - 45 % from fat (specifically 25% MUFA, 10% PUFA and 10% SFA) - and 40% from carbohydrate * NFD Intervention group: - 15% from protein, - 30% from fat (specifically 10% MUFA, 10% PUFA and 10% SFA) - and 55% from carbohydrate.	**Control** Subjects in de control group were only encouraged to follow the USDA Food Guide Pyramid and to reduce their saturated fat intake and overall energy consumption(19). **Intervention** Written diet regimen by a registered dietician. + Dietary advice every six months after.	- The three-consecutive-day food diary of which one day was a holiday - By a dietician - Every six months	Incidence of T2DM with - fasting glucose of ≥ 126 mg/dL Or - 2-h post glucose challenge of ≥200 mg/dL confirmed by two tests. Both tests were repeated annually at 12 and 24 months.	2 years	Diet alone, no physical activity included!
Barengo N.C. et al. DEMOJUAN Project Colombia 2019 390 patients (20)	Two step identification - Finnish Diabetes Risk Score(20) ≥ 13: considered to be at high risk of having IGT, IFG or even diabetes. - Followed by OGTT after at least 12h of fasting IGT: 2hPG 140 – 199 mg/dl or IFG: FPG 100 -125 mg/dl	- a total fat intake < 30% of the energy consumed -a saturated fat intake < 10% of the energy consumed - minimum 500 g of fruit/ vegetable intake a day	**Control** Standard treatment: lifestyle advice given by their own physician **Intervention** Group seminars - monthly in the first year, bimonthly in the last year, - led by a nutritionist and physical activity specialist, - ten participants/group - most of them included a cooking workshop Individual sessions - with the nutritionist, - six times over 2 years, - discuss eating patterns and habits, - a meal plan adjusted to their own personal goals	Baseline dietary habits: A questionnaire consisting of sixteen questions.	Reversion to normoglycemia = FPG < 100 mg/dL and 2hPG< 140 mg/dL OGTT was executed again at month 1 and month 24.	24 months	

Dai X. et al. China 2019 137 patients (21)	Compared the effects of different types of exercise on people with prediabetes. There was no dietary intervention however.						
Khalangot M.D. et al. Ukraine 2019 123 patients (22)	IFG: FPG 110 -125 mg/dl or/and 2hPG ≥ 140 mg/dL, but < 200 mg/dl	- basic recommendations based of the IMAGE toolkit for the prevention of Type 2 Diabetes in Europe(7) - to consume around 200g of low fat dairy products - to consume less than 25 g of sugar daily	All of them received the same information at baseline.	A questionnaire to discover in which extent they followed the given advice on dietary measures after an average of 2.8 years.	Screen-detected diabetes mellitus diagnosed with a fasting capillary blood glucose of ≥ 110 mg/dL.	2.8 years	This was no RCT, as all of the participants were given the same recommendations. They investigated if participants who reported to be adherent to the given recommendations had lower risk in developing diabetes compared to the participants with low adherence.
Sampson M, et al. The Norfolk Diabetes Prevention Study England 2020 1028 patients (23)	IFG: FPG 110-125 mg/dl Or HbA1c 6-6.4% and FPG 100 -109 mg/dl Tested two times.	Reduction of total and saturated fat intake.	**Control** - 2-hour session to discuss the risks of diabetes and how to prevent with lifestyle changes - Written information **Intervention 1** - six 2-hour long educational group sessions over a period of twelve weeks followed by up to fifteen maintenance sessions every eight weeks. - fifteen patients /group - by trained healthcare professionals **Intervention 2** - same as intervention 1 - additional individual phone calls by trained volunteers with diabetes to motivate them	Usage of a Diet Behavior Questionnaire to report about their dietary fat and fiber intake at baseline and repeated at months 6, 12, 24, 36, 40 and 46.	Progression to T2DM measuring FPG and HbA1c levels at months 6, 12, 24, 36, 40 and 46.	Up to 46 months	They acknowledged that the costs were high and therefore difficult to translate into standard clinical care.

IGT: Impaired glucose tolerance // OGTT: Oral glucose tolerance test // IFG: Impaired fasting glucose // DINE: Dietary Instrument for Nutritional Education // T2DM: Type 2 diabetes mellitus // HMD: High monosaturated fat diet // MUFA: Monosaturated fatty acid // PUFA: Polyunsaturated fatty acid // SFA: Saturated fatty acid // NFD: Normal fat diet // FPG: Fasting plasma glucose

Table 2 : The Diabetes Prevention Program and Finnish Diabetes Prevention Study

	Identification of patients with prediabetes	Overall food goals	Control vs Intervention	How to follow dietary intake	Outcome	Follow-up time	Special Remarks
Diabetes Prevention Program (DPP) 1999 USA 3234 patients (14,15,24)	First screening : fasting glucose - with glucose meter on capillary blood: 76 -140 mg/dl or, - with glucose meter on venous blood: 65-140 mg/dl or, - with glucose analyzer, FPG: 81-140 mg/dl Afterwards: Before June 1997 - IFG: FPG 100-139 mg/dl or, - IGT: OGTT 2hPG 140-199 mg/dl After June 1997 - IFG: FPG 95-125 mg/dl and - IGT: OGTT 2hPg 140-199 mg/dl	Reduction of total fat was more important than a reduction of calories. - Calories: daily calorie intake estimated using the initial weight minus 500-1000 calories /day to achieve weight loss - Fats < 25% of total calories a day (ranging from 1200 kcal/d= 33 g fat/d to 2000 kcal/d=55 g fat/d depending on their weight)	**Control** Written information about a healthy lifestyle and a 20- to 30-min individual session with their case manager encouraged to follow the Food Pyramid Guidelines + Placebo tablets twice a day **Intervention 1** Core curriculum 24 weeks: - min 16 sessions with the individual case manager (30-60 min) - daily self-monitoring fat and energy intake (booklet) Maintenance period: - face-to-face contact min every two months - min one telephone contact in between **(Intervention 2)** 850 mg metformin twice a day	Provided with: - a food scale, measuring cups and spoons. - 'the DPP Lifestyle Balance Fat Counter booklet' which included > 1500 types of food with its estimated fat and calorie content During first 24 weeks: daily food records During maintenance: minimum one week/month	Diabetes Mellitus diagnosed with - FPG semi-annual ≥ 126 mg/dl - OGTT annual 2hPG ≥ 200 mg/dl - repeated once to confirm within six weeks.	Between 3 1/3 and 6 years.	Very individualized The prescribed food goals were rather used to achieve the weight loss of > 7% body weight than a goal on itself.
The Finnish Diabetes Prevention Study (DPS) 2001 Finland 522 patients (13,25)	IGT: OGTT 2hPG 140-199 mg/dl Repeated once	- Fat intake < 30% of total energy intake - Saturated fat < 10% of total energy intake - Fiber intake > 15g/1000kcal	**Control** - 30 min -1 hour session about lifestyle and diabetes risk. - Printed, general information. **Intervention** - Seven individual sessions with the nutritionist during the first year. Followed by one session every three months during the two years after - Group sessions/ lectures/ cooking lessons on a voluntary basis	3-day food record every three months	Diabetes Mellitus diagnosed with OGTT 2hPG ≥ 200 mg/dl Every year Repeated once after one week for confirmation	3 years	

1.4 Discussion

First, while the identification of prediabetic patients relied in most studies on solely testing all patients for IGT or IFG, two RCT's initially screened for 'patients at risk' with the Leicester Diabetes Practice Risk Score or with the Finnish Diabetes Risk Score, before taking blood samples(18,20). This way, not just everyone needs a blood sample taken, which not only saves time but saves money as well. We can also notice the definition of a prediabetes has changed a few times, especially when we take a closer look at the cut-off values for IFG. In some studies fasting glucose levels starting from 100 mg/dl define as being prediabetic, and others use the higher threshold of 110 mg/dl. The most recent study also made a partial use of HbA1c to include patients(23).

The overall food goals are quite similar in all studies and most of them are derived from the Finnish Diabetes Prevention Program or the Diabetes Prevention Program in the USA(13,15). Only one of them, differed a great deal as a special diet regarding fat intake had to be followed in the two intervention groups(19). When we compare the interventions in the different RCT's, we can conclude that they are (almost) all very intensive, combining group and individual sessions, two of them with supplemental phone calls and only one using less invasive text messages.

Eventually the outcome in all of them was the progression to diabetes mellitus, where only two of them used HbA1c as a tool to diagnose this chronic disease(18,23).

So a lot of studies based their dietary recommendations and goals on the Diabetes Prevention Program (DPP) in the US or The Finnish Diabetes Prevention Study (DPS) (13,15). Both with a rather individualized and pretty intensive approach. These strategies proved to be successful, however it is very time-consuming for both participants as caregivers and more importantly quite expensive to provide such individualized and intensive help for every person with prediabetes.

If we examine the available guidelines, the NICE guideline states some clear aims in terms of diet and activity to achieve and maintain a healthy weight. Although slight changes can be accomplished in some motivated patients individually, they acknowledge the scope of change must be broadened. Therefore the necessity arises to have national (and even international) initiatives to support and facilitate such changes(4). The American Diabetes Association recommends to lose and maintain a 7% of initial body weight and to increase the physical activity to a minimum of 150 minutes/week (grade A recommendation). Although there is grade B evidence to use a diet to prevent diabetes, they do not give any details on how this diet should be balanced in terms of calories from proteins, fat and carbohydrates, as the evidence shows that the perfect formula does not exist(26).

1.5 Conclusion

In conclusion, the biggest problem with these study protocols is the implementation into routine care because this requires a lot of extra consults with dieticians, physicians, physiotherapists or exercise instructors etc., and therefore time and money that even the best healthcare system cannot provide on such large scale. Therefore the focus has to shift to behavioral changes in the patient in order to diminish the total of consults and costs.

Additionally the question arises if a more basic advice concerning diet, given and monitored by a physician alone, could work to prevent diabetes in the population at risk. A consult with a dietician in Belgium is financially not possible for all of us, in fact you must take into account that this costs at least fifty euros for a one hour session, and prices are variable. The health insurance fund only pays back a small part, again variable in total amount and total of session's paid back.

Is it possible to come up with a less costly, less intensive intervention focusing on dietary changes in patients with prediabetes to effectively prevent the progression to type 2 diabetes? We will do a proposition in the next part of this paper.

2. Clinical Trial Protocol: Dietary measures for prediabetic patients in the general practice to prevent diabetes

2.1 Background and Rationale

Diabetes is a well-known chronic condition in the Western World(1). Already a dazzling 537 million of adults were estimated to suffer from this condition worldwide in 2021 and it is feared that this number will increase with nothing less than a fifth by 2030 by the International Diabetes Federation(2). This disease does not only pose a serious burden mentally, physically and financially to the patient her- or himself, but it is also associated with a huge cost for our whole health system. Diabetes Mellitus Type II seems to be preceded by a period of dysregulated glucose metabolism, called prediabetes. These patients are not only at high risk to develop diabetes, but this state is also associated with some well-known complications from diabetes, such as nephropathy, neuropathy and macrovascular disease(9). Shouldn't we be focusing more on treating prediabetes, and therefore preventing diabetes instead of merely treating diabetes, the risk factors and the subsequent complications? Lifestyle intervention programs including dietary measures and augmented physical activity have already been proven efficient in the treatment of prediabetic patients.

However the implementation of lifestyle interventions as described and executed in the past randomized controlled trials in our general health care seems to be very difficult. Dietary programs in clinical studies, for example, were individualized and almost every time in collaboration with a dietician(27). To provide this type of care, it requires a lot of extra man hours from dieticians, physicians and physical therapists and therefore a lot of extra money. And even in our country with a good healthcare system, this seems to be too expensive, both for the health system as for the patient.

One other way to provide nutritional information and to help the population to pick the 'healthier' options is the so called front-of-pack nutritional labels. One of those is the Nutri-Score, developed in France, but nowadays also used in other European countries, such as Belgium, Luxembourg, the Netherlands, Spain, etc. (28). The underlying labeling system, the modified Food Standard Agency Nutrient Profiling System (FSAm-NPS), takes into account the negative components (energy density, simple sugars, sodium and saturated fats) and the positive components (fibers, protein, proportions of fruit, vegetables or legumes, nuts and certain oils) of the food products to calculate a score ranging from -15 to +40, or from most healthy to least healthy pick respectively. This score is subsequently used to provide a letter and color code to the food product, marking the lowest nutritional products with an E/red, and the highest nutritional ones with an A/green (Fig 1.). Studies showed that the Nutri-Score was easy to recognize and understand, and therefore useful for the consumer to choose the 'healthier' option within one and the same food group(28–30).



Figure 1: The Nutri-Score Label



Figure 2: The Food pyramid

Research shows that a daily intake of food products with a higher FSAm-NPS Dietary Index, thus the consumption of products with lower nutritional quality, is associated with unfavorable changes in CVD risk factors, more particularly changes in BMI, waist circumference, plasma glucose levels and triglycerides, but also with overall cancer incidence and death(31–34). These findings support the use of Nutri-Score to achieve a healthier eating pattern for us all.

Unfortunately the Nutri-Score has been criticized as well and knows its flaws. The most important comments are about the labeling being based on 100g/100ml of product rather than on portion size, the fact that vitamins and minerals are not integrated in the calculation, and about that all fatty acids are assumed harmful, nevertheless some of these are beneficial and even necessary for the body to function (essential fatty acids and fat-soluble vitamins, for example in fatty fish)(35).

That is why, in Belgium, it is recommended to not solely rely on the Nutri-Score itself, but to see it as an addition to the Flemish Dietary Guidelines. The Food Triangle is the visual representation of these guidelines and should be consulted first. This inverted pyramid is divided into four sections with from the wide top, the drinks and food groups we should consume more of (dark green), to the narrow bottom the type of food we should consume less of (orange). Next to the inverted pyramid itself, there is a red circle that depicts types of food or beverages, junk food, that should be avoided as much as possible, as these are not at all nourishing.

Firstly the consumer should consult the food pyramid to see where their type of food is located, so in other words if is recommended to eat this more often or less. Secondly, consumers can compare the Nutri-Score of the food products within one and the same food group, to make the healthiest choice.

Nowadays it is the responsibility of the patients' family doctor to give prediabetic patients the information about diabetes, its complications and how progression to the diabetic state can be prevented. However there are no precise guidelines about this topic. So the extent of the information about diet and exercise given to the patients very much differs from each other.

In this writing we want to develop a protocol focusing on dietary guidance for prediabetic patients. The intervention group will get dietary guidance in a series of one-on-one appointments with their own family doctor as well as written information about the topic. This dietary guidance consists of giving patients a basic understanding of the Flemish Food Pyramid and the Nutri-Score. The focus will be more on the personal reflection and triggering behavioral changes.
The control group however will only receive the standard information their own family doctor is used to provide when diagnosing prediabetes.
Can we find a significant difference in the incidence of diabetes mellitus type 2 when we compare both groups? If so, we might have an intervention that is easy to integrate in our health system.

2.2 Trial Objectives and Design

2.2.1 Trial Objectives

Lifestyle changes have already been proven efficient in the treatment of prediabetes and therefore prevention of diabetes type 2. But expanding from a small study population, to offering this intensive type of care to prediabetic patients worldwide, seems to be difficult.

In this study we want to make use of less costly measures to delay or stop the progression to type two diabetes, by providing standardized information about the Food Triangle and Nutri-

Score during a series of consultations with the own family doctor. This to eventually empower patients to make healthy changes to their diet by themselves.

So our primary research question is the following:

Can we, in our function as a family doctor, prevent the progression to diabetes mellitus type 2 in prediabetic patients by providing information about the Food Pyramid to use in combination with the Nutri-Score and thus find a significant difference in the incidence of diabetes mellitus type 2 when we compare the control and the intervention group?

Secondary research questions are:

- If our intervention might have significant influence on their HbA1c of fasting glucose levels
- If our intervention might trigger changes in weight and subsequently BMI in the prediabetic patients in the intervention group compared to these in the control group.
- If our intervention changes the FINDRISC more of a patient in the intervention group compared to the patients in the control group.

2.2.2 Primary Endpoints

The incidence of type 2 diabetes, diagnosed with the following parameters:

- Fasting Glucose Levels of ≥126 mg/dl measured semi-annual and confirmed by a second test on a different day,
- Or with a HbA1c of 6.5% or more, measured annually(36).

2.2.3 Secondary Endpoints

Secondary endpoints are as following:

- Changes in HbA1c and fasting glucose levels
- Changes in BMI, measured semi-annual:
  BMI = weight (in kg) / (height (in m) x height (in m))
- Changes in weight: semi-annual
- Changes in FINDRISC: calculated and evaluated semi-annual

2.2.4 Trial Design, randomization and blinding

In this randomized controlled trial, we have to use a parallel group design as our intervention consists mainly out of delivering information and empowering patients to make healthier dietary choices. However this makes it possible to run the intervention and collect the data in the intervention and control group at the same time on very different locations.

Secondly, blinding is not an option here, because of the nature of our intervention, as the person delivering the information and involved in the follow-up and data-collecting is one and the same, thus the investigator or the family doctor. Blinding patients is not possible too, as the whole point of our intervention is to empower the patients in the intervention group to change their dietary lifestyle to avoid diabetes.

Finally, randomization in this trial will not be focusing on the patient, but rather on the family doctor or practice. So in other words, firstly we must recruit as many family doctors/practices as possible. We can order these alphabetically and give them a number, to subsequently

randomize the even numbers in the control group and the uneven numbers in the intervention group.

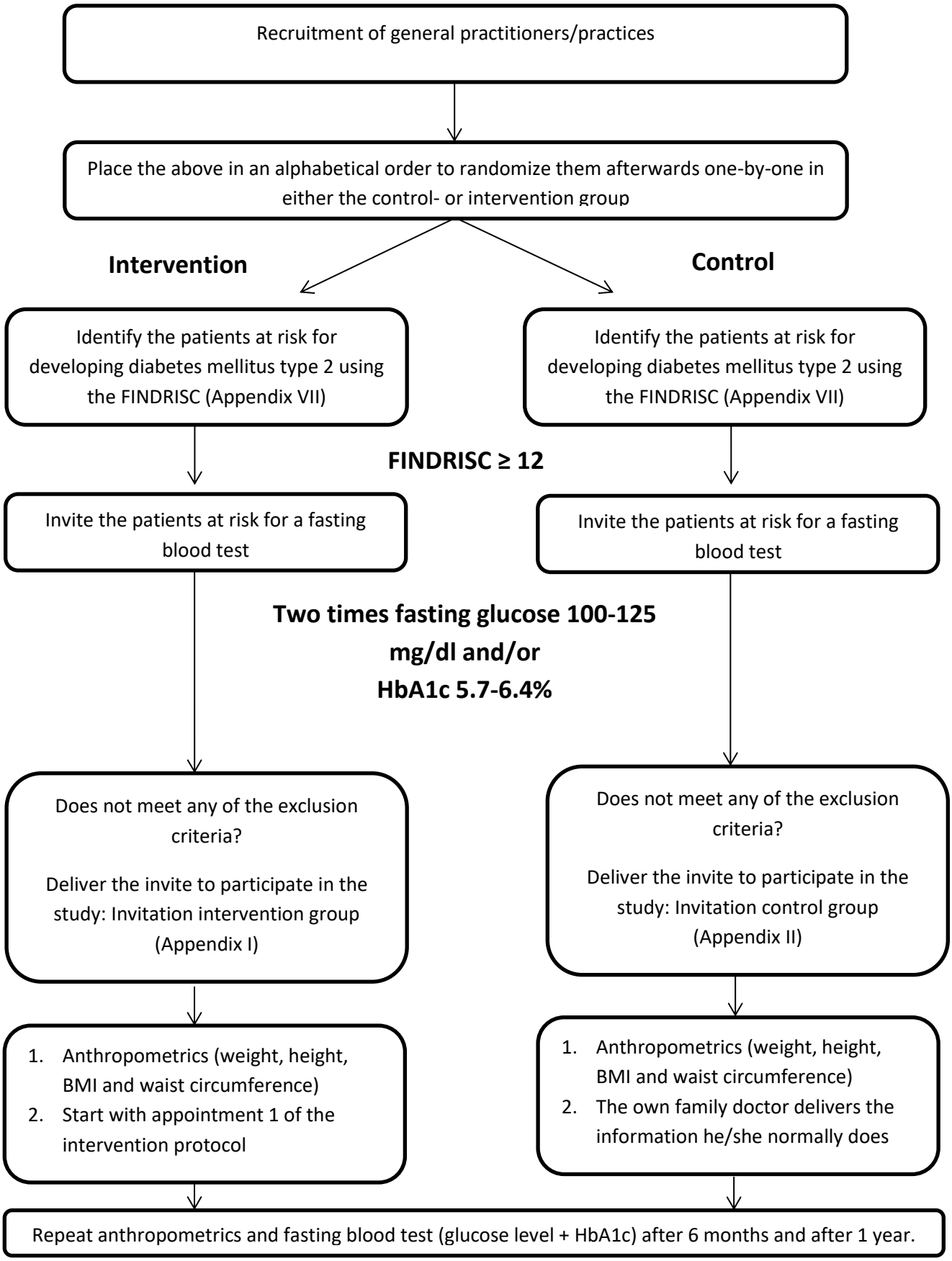
Problems that may occur with this type of randomization is that the study groups may differ a great deal in number of patients observed. To avoid this, we can give them a fixed number of patients to include, not too high to make it possible for everyone to reach this number without a problem, 3 for example.

Another problem we may encounter, is that the general practitioner in the control group may (unconsciously) give more information than he or she normally does, just because they are in a RCT. We can only give the advice to treat their patients as they normally do, and behave as they are not in this RCT. But completely rule out this type of bias doesn't seem to be possible.

2.2.5 Expected Duration of the Trial

We expect that this trial will have a minimal duration of a year, considering that the information given to the patients is spread out over a period of three to four months, change of weight and definitely HbA1c takes time and that every year an estimate of five to ten percent of prediabetic patients progresses to a diabetic state.

To see the full timeline of this RCT, please consult the following figure:


Recruitment of general practitioners/practices
Place the above in an alphabetical order to randomize them afterwards one-by-one in either the control- or intervention group
Intervention
Control
Identify the patients at risk for developing diabetes mellitus type 2 using the FINDRISC (Appendix VII)
Identify the patients at risk for developing diabetes mellitus type 2 using the FINDRISC (Appendix VII)
FINDRISC ≥ 12
Invite the patients at risk for a fasting blood test
Invite the patients at risk for a fasting blood test
Two times fasting glucose 100-125 mg/dl and/or HbA1c 5.7-6.4%
Does not meet any of the exclusion criteria?
Deliver the invite to participate in the study: Invitation intervention group (Appendix I)
Does not meet any of the exclusion criteria?
Deliver the invite to participate in the study: Invitation control group (Appendix II)
1. Anthropometrics (weight, height, BMI and waist circumference)
2. Start with appointment 1 of the intervention protocol
1. Anthropometrics (weight, height, BMI and waist circumference)
2. The own family doctor delivers the information he/she normally does
Repeat anthropometrics and fasting blood test (glucose level + HbA1c) after 6 months and after 1 year.

2.3 Trial Population / Eligibility Criteria

2.3.1 Inclusion criteria

Participants eligible for inclusion in this Trial must meet **all** of the following criteria:

1. A written informed consent of the participant has been obtained, completely voluntarily.

2. Use of highly effective methods of birth control that result in low failure rate (i.e., less than 1% per year) when used consistently and correctly; such as implants, injectables, combined oral contraceptives, some IUDs, true sexual abstinence, or commitment to a vasectomized partner.

3. Participants selected by the FINDRISC test (≥12) and afterwards identified as being prediabetic according to the latest American Diabetes Association and World Health Organization criteria, being a fasting glucose level of 100-125 mg/dl confirmed by two tests on two separate days or a HbA1c of 5.7-6.4%.

2.3.2 Exclusion criteria

Participants eligible for this Trial must **not** meet any of the following criteria:

1. The participant has a history of

- Diabetes
- Or major illnesses (such as cancer, cardiopulmonary disease, chronic liver or kidney disease) which drastically reduces their life expectancy or intervenes with their capability to follow such lifestyle program.
- Or psychological disorders such as depression, schizophrenia,..
- Or cognitive impairment
- Or physical disabilities that would prevent him or her from doing the physical training.

2. Any disorder, which in the Investigator's opinion might jeopardize the participant's safety or compliance with the protocol.

3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate, highly effective contraceptive.

4. Participation in an interventional Trial with an investigational medicinal product (IMP) or device.

5. Participants using any form of weight lowering drugs, currently following a strict diet, or going into consult with a dietitian.

6. Participants using one of the following: glucocorticoids, anti-psychotics, metformin, or any other anti-diabetic drug.

7. Participants younger than 18 years or older than 70 years.

2.4 Trial Procedures

2.4.1 Participant consent and withdrawal of consent

Each participant, in both the intervention as control group, will receive an informed consent form. No trial-related procedure will be conducted prior to obtaining written informed consent from potential trial participants.

Participants can withdraw consent at any time and for any reason during this study, without any further consequences. Trial data and samples before withdrawal can be used in the trial, but no new trial data or samples can be collected after.

Potential trial participant will receive an information sheet prior to giving consent, these forms are slightly different in the control and intervention group. You can find both of the information sheets as well as the informed consent form in the appendices (appendices I-III)

2.4.2 Selection of Participants/Recruitment

We intend to use the FINDRISC test as a first screening in our practice(7). Using these eight questions patients are selected and invited for further blood tests if they have a score of ≥ 12 (appendix VII). The subsequent fasting blood sample is tested for FPG and HbA1c.

Prediabetes is defined as

- An HbA1c of 5.7 – 6.4%, or
- A fasting glucose level of 100 – 125mg/dl, or
- with oral glucose tolerance test (OGTT) and 2-hour glucose levels between 140 to 199 mg/dl. But we will not be using this last test.

Patients can be included in the study with FPG of 100 mg/dl to 125 mg/dl or with HbA1c of 5.7% to 6.4%.

2.4.3 Premature discontinuation of Trial treatment

Every participant has the right to end their participation in the trial for any reason at any time. Data collected before the drop-out may be used, but no new data concerning this patient may be collected.

Participants may also require discontinuation of the trial because of some of the following circumstances:

- Development of diseases or conditions as listed above in the exclusion criteria.
- No – shows for trial visits, without clearly stating discontinuation by the participant.

The development of diabetes is our primary endpoint, patients then should be treated accordingly. Obviously, data collected, regarding weight, HbA1c, glucose levels and BMI after starting glucose-regulating medication cannot be used in the trial.

2.5 Trial Treatment

This intervention consists of giving information to prediabetic patients regarding a healthy diet using the Food Pyramid and the Nutri-Score. This information will be given during a series of consultations with their own general practitioner. The information given verbally to

the patients will also be handed out on paper (appendices IV and VI). The point of the intervention is encouraging patients to think about their dietary choices and to empower them to make healthier choices, keeping in mind the Food Pyramid and Nutri-Score.

Every consultation will focus on a prefixed subject as shown below.

Appointment 1 – week 1:	What must be discussed? • Explanation about prediabetes, diabetes, risk factors. • Explanation about the study, goals, timeline of consultations (appendix IV) • Paper food diary (appendix V) Take-home messages and homework? • Deciding if they want to participate in this study • Signing of the informed consent • Filling out the food diary for a minimum of 5 days • Making an appointment if they want to join, bringing both their informed consent as well as their food diary
Appointment 2 – week 2-3:	What must be discussed? • Discussing the food diary: ▪ Does the patient see any room for improvement? ▪ What can we do better? • Discussing the food-triangle (appendix VI) ▪ What changes should and can we make now if we look at our food diary again? • Explaining the Nutri-Score (appendix VI) Take-home messages and homework? • Keep the food diary for a minimum of three days every week • Write next to every meal/snack where it is located in the Food Pyramid
Appointment 3 – week 5:	What must be discussed? • Where is our food located in the Food Pyramid, how often do we eat or drink things that are located in the red circle? • Discussing breakfast ▪ Can we make some alterations? ▪ Refer to the following website https://www.gezondleven.be/themas/voeding/evenwichtige-gezonde-maaltijd/gezond-ontbijt Take-home messages and homework? • Can we make alterations to our breakfast in real life? • Keep the food diary for a minimum of three days every week
Appointment 4 – week 8:	What must be discussed? • Discussing breakfast: changes made? Difficulties? • Discussing lunch ▪ Can we make some alterations? ▪ Refer to the following website https://www.gezondleven.be/themas/voeding/evenwichtige-gezonde-

	maaltijd/gezond-middageten • Measuring weight Take-home messages and homework? • Can we make alterations to our lunch in real life? • Keep the food diary for a minimum of three days every week
Appointment 5 – week 11:	What must be discussed? • Discussing lunch: changes made? Difficulties? • Discussing supper ▪ Can we make some alterations? ▪ Refer to the following website https://www.gezondleven.be/themas/voeding/evenwichtige-gezonde-maaltijd/gezonde-warme-maaltijd Take-home messages and homework? • Can we make alterations to our supper in real life? • Keep the food diary for a minimum of three days every week
Appointment 6 – week 14:	What must be discussed? • Discussing supper: changes made? Difficulties? • Discussing snacks ▪ Can we make some alterations? ▪ Refer to the following website https://www.gezondleven.be/themas/voeding/evenwichtige-gezonde-maaltijd/gezond-tussendoortje • Measuring weight Take-home messages and homework? • Can we make alterations to our snacks in real life? • Keep the food diary for a minimum of two days every week
Appointment 7 – week 18:	What must be discussed? • Discussing our food diary: can we still make improvements? Are there any difficulties? Questions?

2.6 Safety

No safety issues are foreseen with this type of intervention.

2.7 Statistics and Data Analysis

To test the differences in our primary outcome, the development of diabetes, in both groups, we'll be using the χ^2 test. Linear regression can be used subsequently to adjust for any baseline imbalances. The differences between numeral data at baseline and follow-up at 6 and 12 months within one group will be analyzed using the paired t test, as differences in mean change of BMI, weight, HbA1c and fasting glucose level from baseline to 6 or 12 months between the intervention and control group will be tested using the unpaired t test. The statistical significance is set at 5%.

3. References

1. World Health Organisation. Diabetes [Internet]. [cited 2023 Jan 14]. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes

2. Federation ID. Diabetes: Facts & figures [Internet]. Diabetes Atlas. 2021 [cited 2022 Oct 16]. Available from: https://www.idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html

3. Tinajero MG, Malik VS. An Update on the Epidemiology of Type 2 Diabetes: A Global Perspective. Endocrinol Metab Clin North Am. 2021 Sep 1;50(3):337–55.

4. National Institute for Health and Care Excellence. Type 2 diabetes prevention: population and community-level interventions. 2011 [cited 2022 Oct 16];85. Available from: www.nice.org.uk/guidance/ph35

5. Schlienger JL. Complications du diabète de type 2. Press Medicale [Internet]. 2013 May [cited 2022 May 13];42(5):839–48. Available from: http://dx.doi.org/10.1016/j.lpm.2013.02.313

6. Liu Y, Guo H, Wang Q, Chen J, Xuan Y, Xu J, et al. Short-term effects of lifestyle intervention in the reversion to normoglycemia in people with prediabetes. Prim Care Diabetes [Internet]. 2022 [cited 2022 Jun 21];16:168–72. Available from: https://doi.org/10.1016/j.pcd.2021.12.009

7. Lindström J, Neumann A, Sheppard KE, Gilis-Januszewska A, Greaves CJ, Handke U, et al. Take action to prevent diabetes- The IMAGE toolkit for the prevention of type 2 diabetes in Europe. Horm Metab Res [Internet]. 2010 [cited 2023 Jan 3];42(SUPPL. 1):S37–55. Available from: http://www.thieme-connect.com/products/ejournals/html/10.1055/s-0029-1240975

8. Bansal N. Prediabetes diagnosis and treatment: A review. World J Diabetes [Internet]. 2015 [cited 2022 Oct 16];6(2):296. Available from: https://www.wjgnet.com/1948-9358/full/v6/i2/296.htm

9. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020 Jan 1;41(2):255–323.

10. Margot P, Dieter S, Leuven KU, Prof P, Bert A, Leuven KU. The Effect of Lifestyle Interventions on the Progression towards Type 2 Diabetes Mellitus in Prediabetic Patients : A Systematic Review. 2020;1–19.

11. Roncero-Ramos I, Alcala-Diaz JF, Rangel-Zuñiga OA, Gomez-Delgado F, Jimenez-Lucena R, García-Rios A, et al. Prediabetes diagnosis criteria, type 2 diabetes risk and dietary modulation: The CORDIOPREV study. Clin Nutr [Internet]. 2020 Feb 1 [cited 2022 Mar 2];39(2):492–500. Available from: https://pubmed.ncbi.nlm.nih.gov/30852029/

12. Sampson M, Clark A, Bachmann M, Garner N, Irvine L, Howe A, et al. Lifestyle Intervention With or Without Lay Volunteers to Prevent Type 2 Diabetes in People With Impaired Fasting Glucose and/or Nondiabetic Hyperglycemia A Randomized Clinical Trial. 2020; Available from: https://jamanetwork.com/

13. Lindström J, Louheranta A, Eriksson J, Uusitupa M, Tuomilehto J. The Finnish Diabetes Prevention Study (DPS) Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care [Internet]. 2003 [cited 2022 May 10];26(12):3230–6. Available from: http://diabetesjournals.org/care/article-pdf/26/12/3230/590993/dc1203003230.pdf

14. The Diabetes Prevention Program Research Group. The Diabetes Prevention Program (DPP): Description of lifestyle intervention. Diabetes Care [Internet]. 2002 [cited 2022 May 10];25(12):2165–71. Available from: http://www.bsc.gwu.edu/dpp/manuals.htmlvdoc.

15. The Diabetes Prevention Program Research Group. The Diabetes Prevention Program: Design and methods for a clinical trial in the prevention of type 2 diabetes. Diabetes Care [Internet]. 1999 Apr [cited 2023 Jan 22];623–34. Available from: https://diabetesjournals.org/care/article/22/4/623/19111/The-Diabetes-Prevention-Program-Design-

and-methods

16. Ram J, Selvam S, Snehalatha C, Nanditha A, Simon M, Samith Shetty A, et al. Improvement in diet habits, independent of physical activity helps to reduce incident diabetes among prediabetic Asian Indian men. 2014 [cited 2022 Apr 12]; Available from: http://dx.doi.org/10.1016/j.diabres.2014.09.043

17. Ramachandran A, Snehalatha C, Ram J, Selvam S, Simon M, Nanditha A, et al. Eff ectiveness of mobile phone messaging in prevention of type 2 diabetes by lifestyle modifi cation in men in India: a prospective, parallel-group, randomised controlled trial. diabetes-endocrinology [Internet]. 2013 [cited 2022 Apr 12];1. Available from: www.thelancet.com/

18. Davies MJ, Gray LJ, Ahrabian D, Carey M, Farooqi A, Gray A, et al. A community-based primary prevention programme for type 2 diabetes mellitus integrating identification and lifestyle intervention for prevention: a cluster randomised controlled trial. Program Grants Appl Res. 2017 Jan;5(2):1–290.

19. Shahbazi S, Vahdat Shariatpanahi Z. Prevention of type 2 diabetes mellitus by changes in diet among subjects with abnormal glucose metabolism: a randomized clinical trial.

20. Barengo NC, Acosta T, Arrieta A, Ricaurte C, Florez K, Tuomilehto JO. Early Lifestyle Interventions in People with Impaired Glucose Tolerance in Northern Colombia: The DEMOJUAN Project. Int J Environ Res Public Heal Artic [Internet]. Available from: www.mdpi.com/journal/ijerph

21. Dai X, Zhai | Lu, Chen | Qingyun, Miller JD, Lirong Lu |, Hsue C, et al. Two-year-supervised resistance training prevented diabetes incidence in people with prediabetes: A randomised control trial. 2019 [cited 2022 May 10]; Available from: https://doi.org/10.1002/dmrr.3143

22. Khalangot MD, Kovtun VA, Gurianov VG, Pysarenko YM, Kravchenko VI. Evaluation of type 2 diabetes prevention through diet modification in people with impaired glucose regulation: A population-based study. Prim Care Diabetes [Internet]. 2019 Dec 1 [cited 2022 May 10];13(6):535–41. Available from: https://doi.org/10.1016/j.pcd.2019.03.011

23. Sampson M, Clark A, Bachmann M, Garner N, Irvine L, Howe A, et al. Lifestyle Intervention With or Without Lay Volunteers to Prevent Type 2 Diabetes in People With Impaired Fasting Glucose and/or Nondiabetic Hyperglycemia A Randomized Clinical Trial. 2020 [cited 2022 Oct 16]; Available from: https://jamanetwork.com/

24. The Diabetes Prevention Program Research Group. The Diabetes Prevention Program: Baseline characteristics of the randomized cohort. Diabetes Care [Internet]. 2000 Nov [cited 2023 Jan 22];1619–29. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1360735/pdf/nihms5312.pdf

25. Eriksson J, Lindström J, Valle T, Aunola S, Hämäläinen H, Ilanne-Parikka P, et al. Prevention of Type II diabetes in subjects with impaired glucose tolerance: The Diabetes Prevention Study (DPS) in Finland. Study design and 1-year interim report on the feasibility of the lifestyle intervention programme. Diabetologia [Internet]. 1999 [cited 2023 Feb 1];42(7):793–801. Available from: https://link.springer.com/article/10.1007/s001250051229

26. Association AD. Standards of Medical Care in Diabetes—2022 Abridged for Primary Care Providers. Clin Diabetes [Internet]. 2022 Jan 1 [cited 2023 Jan 17];40(1):10–38. Available from: https://diabetesjournals.org/clinical/article/40/1/10/139035/Standards-of-Medical-Care-in-Diabetes-2022

27. Ford CN, Weber MB, Staimez LR, Anjana RM, Lakshmi K, Mohan V, et al. Dietary changes in a diabetes prevention intervention among people with prediabetes: the Diabetes Community Lifestyle Improvement Program trial. Acta Diabetol [Internet]. 2019 Feb 6 [cited 2022 Mar 2];56(2):197–209. Available from: https://link.springer.com/article/10.1007/s00592-018-1249-1

28. Andreeva VA, Egnell M, Touvier M, Galan P, Julia C, Hercberg S. International evidence for the effectiveness of the front-of-package nutrition label called nutri-score. Cent Eur J Public Health [Internet]. 2021 [cited 2023 Feb 21];29(1):76–9. Available from:

http://cejph.szu.cz/doi/10.21101/cejph.a6239.html

29. De Temmerman J, Heeremans E, Slabbinck H, Vermeir I. The impact of the Nutri-Score nutrition label on perceived healthiness and purchase intentions. Appetite. 2021 Feb 1;157.

30. van den Akker K, Bartelet D, Brouwer L, Luijpers S, Nap T, Havermans R. The impact of the nutri-score on food choice: A choice experiment in a Dutch supermarket. Appetite. 2022 Jan 1;168.

31. Gómez-Donoso C, Martínez-González MÁ, Perez-Cornago A, Sayón-Orea C, Martínez JA, Bes-Rastrollo M. Association between the nutrient profile system underpinning the Nutri-Score front-of-pack nutrition label and mortality in the SUN project: A prospective cohort study. Clin Nutr [Internet]. 2021 Mar 1 [cited 2023 Mar 5];40(3):1085–94. Available from: https://pubmed.ncbi.nlm.nih.gov/32768318/

32. Khoury N, Gómez-Donoso C, Martínez MÁ, Martínez-González MÁ, Corella D, Fitó M, et al. Associations Between the Modified Food Standard Agency Nutrient Profiling System Dietary Index and Cardiovascular Risk Factors in an Elderly Population. Front Nutr. 2022 Jul 14;9:1546.

33. Egnell M, Crosetto P, D'Almeida T, Kesse-Guyot E, Touvier M, Ruffieux B, et al. Modelling the impact of different front-of-package nutrition labels on mortality from non-communicable chronic disease. Int J Behav Nutr Phys Act [Internet]. 2019 Jul 15 [cited 2023 Mar 7];16(1):1–11. Available from: https://ijbnpa.biomedcentral.com/articles/10.1186/s12966-019-0817-2

34. Deschasaux M, Huybrechts I, Murphy N, Julia C, Hercberg S, Srour B, et al. Nutritional quality of food as represented by the FSAm-NPS nutrient profiling system underlying the Nutri-Score label and cancer risk in Europe: Results from the EPIC prospective cohort study. Antonia Trichopoulou [Internet]. 2018 [cited 2023 Mar 7];10(9). Available from: https://doi.org/10.1371/journal.pmed.1002651

35. Włodarek D, Dobrowolski H. Fantastic Foods and Where to Find Them-Advantages and Disadvantages of Nutri-Score in the Search for Healthier Food. Nutrients [Internet]. 2022 Nov 1 [cited 2023 Feb 21];14(22). Available from: https://pubmed.ncbi.nlm.nih.gov/36432529/

36. World Health Organisation. HEARTS D: diagnosis and management of type 2 diabetes [Internet]. 2020 [cited 2023 Mar 14]. Available from: https://www.who.int/publications/i/item/who-ucn-ncd-20.1

4. Appendices

4.1 Appendix I: Information sheet for the prediabetic patient (Intervention group)

De strijd tegen prediabetes met een gezond dieet!

Beste Mevrouw/Meneer,

U wordt uitgenodigd om deel te nemen aan een medisch-wetenschappelijk onderzoek betreffende prediabetes. De beslissing of u wel of niet wil deelnemen, is geheel uw keuze. Voordat u een beslissing kan nemen, is het echter wel belangrijk dat u weet wat het onderzoek net inhoudt. Daarom hebben wij deze informatiebrief opgesteld. Heeft u na het doornemen van deze brief nog vragen? Contacteer ons dan gerust!

Waarom dit onderzoek?

Diabetes of suikerziekte is een chronische aandoening die wereldwijd al meer dan 500 miljoen mensen treft en dit aantal is de laatste jaren erg snel aan het toenemen. Diabetes wordt voorafgegaan door een periode van glucose dysregulatie, met andere woorden een periode waarin er reeds een licht toegenomen hoeveelheid suiker in het bloed te vinden is, maar echter nog niet de hoge niveaus die we zien bij echte suikerziekte. Deze toestand heten we prediabetes. Helaas evolueert vijf tot tien procent van de patiënten met prediabetes jaarlijks naar diabetes of suikerziekte.

Het goede nieuws is dat we deze evolutie kunnen afremmen of zelfs stoppen! Dit kan met behulp van levensstijlaanpassingen, namelijk een gezond dieet en een toename in de fysieke activiteit, en behoeft dus geen medicatie.

Wat verwachten we van U?

Op basis van een screeningsvragenlijst konden wij vaststellen dat u een hoog risico heeft op het ontwikkelen/hebben van suikerziekte. Daarom werd u uitgenodigd voor aanvullende bloedonderzoeken. Na deze onderzoeken stellen we helaas vast dat u reeds prediabetes ontwikkeld heeft. Om verdere evolutie een halt toe te roepen, nodigen wij u uit bij ons in de praktijk om in onze studie te stappen.

In deze studie willen we met informatie over gezonde voeding, de voedingsdriehoek en de Nutri-Score samen met u een gezonder voedingspatroon bereiken. Dergelijke veranderingen hebben echter tijd nodig, en daarom voorzien wij de nodige opvolging over het komende jaar. Na verloop van tijd wordt u opnieuw uitgenodigd voor controle bloedonderzoeken.

Er zijn helemaal geen risico's verbonden bij deelname aan dit onderzoek.
Indien u toestemt om deel te nemen aan dit onderzoek dienen wij natuurlijk de nodige gegevens van uw dossier te verwerken in deze studie. Deze gegevens zullen vanzelfsprekend, in overeenstemming met de Belgische Wetgeving betreffende bescherming van natuurlijke personen en verwerking van persoonsgegevens, vertrouwelijke behandeld en geanonimiseerd worden.

➔ Heeft u nog vragen? Of bent u bereid om deel te nemen?

Maak dan een afspraak zodat we het nogmaals persoonlijk met u kunnen doornemen!

4.2 Appendix II: Information sheet for the prediabetic patient (Control group)

De strijd tegen prediabetes met een gezond dieet!

Beste Mevrouw/Meneer,

U wordt uitgenodigd om deel te nemen aan een medisch-wetenschappelijk onderzoek betreffende prediabetes. De beslissing of u wel of niet wil deelnemen, is geheel uw keuze. Voordat u een beslissing kan nemen, is het echter wel belangrijk dat u weet wat het onderzoek net inhoudt. Daarom hebben wij deze informatiebrief opgesteld. Heeft u na het doornemen van deze brief nog vragen? Contacteer ons dan gerust!

Waarom dit onderzoek?

Diabetes of suikerziekte is een chronische aandoening die wereldwijd al meer dan 500 miljoen mensen treft en dit aantal is de laatste jaren erg snel aan het toenemen. Diabetes wordt voorafgegaan door een periode van glucose dysregulatie, met andere woorden een periode waarin er reeds een licht toegenomen hoeveelheid suiker in het bloed te vinden is, maar echter nog niet de hoge niveaus die we zien bij echte suikerziekte. Deze toestand heten we prediabetes. Helaas evolueert vijf tot tien procent van de patiënten met prediabetes jaarlijks naar diabetes of suikerziekte.

Het goede nieuws is dat we deze evolutie kunnen afremmen of zelfs stoppen! Dit kan met behulp van levensstijlaanpassingen, namelijk een gezond dieet en een toename in de fysieke activiteit, en behoeft dus geen medicatie.

Wat verwachten we van U?

Op basis van een screeningsvragenlijst konden wij vaststellen dat u een hoog risico heeft op het ontwikkelen/hebben van suikerziekte. Daarom werd u uitgenodigd voor aanvullende bloedonderzoeken. Na deze onderzoeken stellen we helaas vast dat u reeds prediabetes ontwikkeld heeft. Een gezonde voeding en toename in fysieke activiteit zou ervoor kunnen zorgen dat de evolutie naar diabetes wordt afgeremd of zelfs wordt gestopt! Uw arts geeft u de nodige informatie hieromtrent.

Wij nodigen u graag uit na 6 en 12 maanden om terug een bloedafname te plannen om uw suikerwaardes verder op te volgen.

Er zijn helemaal geen risico's verbonden bij deelname aan dit onderzoek.
Indien u toestemt om deel te nemen aan dit onderzoek dienen wij natuurlijk de nodige gegevens van uw dossier te verwerken in deze studie. Deze gegevens zullen vanzelfsprekend, in overeenstemming met de Belgische Wetgeving betreffende bescherming van natuurlijke personen en verwerking van persoonsgegevens, vertrouwelijke behandeld en geanonimiseerd worden.

➔ Heeft u nog vragen? Of bent u bereid om deel te nemen?

Maak dan een afspraak zodat we het nogmaals persoonlijk met u kunnen doornemen!

4.3 Appendix III: Informed Consent

De strijd tegen prediabetes met een gezond dieet!

Beste,

U werd uitgenodigd deel te nemen aan een klinische studie met betrekking tot prediabetes. Deelname aan dit onderzoek is volledig vrijwillig. Bovendien kunt u op gelijk welk tijdstip zich later alsnog terugtrekken uit deze studie, zonder enige consequenties.

Met het ondertekenen van dit formulier geeft u ons de toestemming om de nodige gegevens te verzamelen, verwerken en gebruiken en gaat u dus akkoord om mee te werken aan deze studie.

(Goedkeuring Commissie Medische Ethiek nog aan te vragen bij aanvang van de studie.)

Ik, ……., verklaar dat

- ik op voldoende wijze geïnformeerd ben, zowel schriftelijk als mondeling, over het belang en het verloop van deze studie,
- ik voldoende tijd gekregen om hierover te kunnen nadenken en op eventuele vragen duidelijke antwoorden heb gekregen,
- ik begrijp dat mijn toestemming volledig vrijwillig is en dat ik op gelijk welk tijdstip alsnog kan beslissen deze terug in te trekken.

Ondergetekende verklaart hierbij akkoord te gaan met de deelname aan bovengenoemd onderzoek.

Datum:

Naam deelnemer: Handtekening:

Naam huisarts: Handtekening:

4.4 Appendix IV: Information sheet for the patient during consult 1 (Intervention group)

Beste,

U gaf zich op om deel te nemen aan onze studie betreffende prediabetes. Hieronder nogmaals de informatie over (pre)diabetes, het doel van deze studie en wanneer we u verwachten het komende jaar!

Wat is diabetes?

Ons lichaam en dus onze organen kunnen niet werken zonder brandstof. Hiervoor gebruiken we koolhydraten of suikers uit onze voeding. Die suikers komen, na inname, terecht in onze bloedbaan, maar moeten dan nog onze cellen binnenraken. En hier zit het probleem: suiker heeft insuline nodig als soort van sleutel om deze cel binnen te komen. Insuline wordt echter bij mensen met suikerziekte te weinig (of zelfs helemaal niet meer) geproduceerd door onze pancreas, waardoor suikers zich opstapelen in onze bloedbaan.

Te hoge suikerhoeveelheden leidt tot schade verspreidt over ons ganse lichaam. Uiteindelijk kan dit resulteren in nierfunctieachteruitgang of dialyse, gezichtsvermindering of blindheid, chronische wonden of amputatie, hartinfarcten, beroertes,… Ongetwijfeld kent u wel iemand die suikerziekte of diabetes heeft en dus dagelijks medicatie moet nemen of zelfs insuline moet inspuiten om deze verwikkelingen tegen te gaan.

Prediabetes?

U heeft prediabetes en zit met andere woorden nog in een voorstadium van diabetes, waardoor we bij u nog de mogelijkheid hebben om deze ziekte af te remmen en zelfs volledig te stoppen. Maar daarvoor zult u uw levensstijl moeten aanpassen, dat wil zeggen kiezen voor een gezondere voeding en meer lichaamsbeweging! Samen met u nemen we, in deze studie, uw voedingsgewoontes onder de loep en bekijken we waar we gezonde aanpassingen kunnen maken.

Korte tijdlijn van de studie

Start	- Informatie over (pre)diabetes, deze studie, verwachtingen - Ondertekenen geïnformeerde toestemming - **Opdracht:** Minimum 5 dagen bijhouden van voedingsdagboek
Week 2-3	- Voedingsdriehoek en Nutri-Score - **Opdracht:** Minimum 3 dagen/week bijhouden van voedingsdagboek + neerschrijven waar in de voedingsdriehoek zich hun voeding bevindt
Week 5	- Ontbijt - **Opdracht:** Minimum 3 dagen/week bijhouden van voedingsdagboek + aanpassingen maken aan ontbijt
Week 8	- Middagmaal - **Opdracht:** Minimum 3 dagen/week bijhouden van voedingsdagboek + aanpassingen maken aan middagmaal
Week 11	- Avondmaal - **Opdracht:** Minimum 3 dagen/week bijhouden van voedingsdagboek + aanpassingen maken aan avondmaal
Week 14	- Tussendoortjes - **Opdracht:** Minimum 2 dagen/week bijhouden van

	voedingsdagboek + aanpassingen maken aan tussendoortjes
Week 18	- Moeilijkheden? - Bespreken van voedingsdagboek en aanpassingen tot nu toe.
Maand 6 of week 26	- Lichaamsmetingen - Nuchtere bloedafname
1 jaar	- Lichaamsmetingen - Nuchtere bloedafname

Het is belangrijk om deze terugkomdata strikt na te komen, anders kunnen wij uw data misschien niet gebruiken en zal u niet langer tot deze studie worden toegelaten. Bovendien is het in uw eigen belang uw gezondheid en zeker uw suikerwaarden met regelmaat te laten controleren.

Bedankt alvast voor uw medewerking en samen gaan we ervoor!

4.5 Appendix V: Food diary

Voedingsdagboek

Datum ……

Naam ……

Verandering begint met het in kaart brengen van wat we nu gewoon zijn. Wees eerlijk, schrijf zo uitgebreid mogelijk neer wat en hoeveel u net at. Doe dit zo snel mogelijk, anders loopt u al snel het risico een deel te vergeten.

Ontbijt:

…… sneden klein/groot …… brood OF ……....

besmeerd met …….. of belegd met ……

Ik dronk …… ……

met volle/halfvolle/magere melk of …. suikerklontjes

Andere: ……

Tussendoortje voormiddag:

Ik dronk …….

Ik at ……

Warme maaltijd:

Soep of andere warme dranken: ……..

……. gr vlees/vis: ……..

met ……. gr groenten/fruit: ……

met ……. gr aardappelen/rijst/pasta: ……...

Frituurvet/Bakvet/andere: ……..

Drank: ……

Dessert: ……

Tussendoortje namiddag:

Ik dronk …….

Ik at ……

Broodmaaltijd:

…… sneden klein/groot …… brood OF ……....

besmeerd met …….. of belegd met ……

Andere: ……

Ik dronk …….

Tussendoortje avond:

Ik dronk……..

Ik at ……

Samengevat:

Hoeveel fruit en groenten at ik vandaag?.....

Dronk ik voldoende water? ……..

At of dronk ik zaken die niet tot de voedingsdriehoek behoren?
……

4.6 Appendix VI: Gezond(er) eten

Gezond(er) eten

Bij de behandeling van prediabetes ligt de focus op gezonder leven. Met een gezond eetpatroon en voldoende lichaamsbeweging krijgen we deze aandoening onder controle!
Het is echter niet nodig om een streng dieet te volgen, met gezonde en gevarieerde voeding zoals weergegeven in de voedingsdriehoek kunnen we al heel wat bereiken. Bovendien moeten onze dieetaanpassingen natuurlijk ook op lange termijn vol te houden zijn.

Voedingsstoffen: macro- en micronutriënten

1. **Koolhydraten: suikers, zetmeel, en vezels**
   Koolhydraten zijn de belangrijkste brandstof voor ons lichaam. Deze worden omgezet naar glucose en dankzij insuline opgenomen in onze lichaamscellen.
   Belangrijk is echter dat:
   - we niet meer innemen dan we verbruiken, anders verhoogt ons gewicht.
   - we op regelmatige tijdstippen eten om een goede spreiding te verkrijgen over de dag.
   - we kiezen voor trage koolhydraten, met andere woorden koolhydraten of suikers die TRAAG worden vrijgezet:
     - Slechte of snelle koolhydraten: snoep, koekjes, wit brood, cornflakes, witte rijst, frisdrank,…
     - Goede of trage koolhydraten: volkoren product, fruit, groenten, peulvruchten,…
2. **Vetten: verzadigd of onverzadigd**
   Vetten behoren ook tot een gezonde voeding, belangrijk is echter goed op te letten welke soorten vet je net inneemt.
   - Slechte of VERZADIGDE vetzuren: gebak, snoep, producten van dierlijke oorsprong (kaas, boter, vlees, …)
   - Goede of ONVERZADIGDE vetzuren: vetstoffen op plantaardige basis (zonnebloemolie/maïsolie/olijfolie/…), vis, walnoten,…
3. **Eiwitten: dierlijke en plantaardige eiwitten.**
   Eiwitten zijn eveneens belangrijke bouwstoffen voor ons lichaam. Eiwitten zijn zowel in dierlijke als plantaardige voeding te vinden. Omdat dierlijke producten (vlees, vis, melkproducten, kaas en eieren) ook vaak veel verzadigde of dus slechtere vetzuren bevatten, is het belangrijk om regelmatig plantaardige producten (peulvruchten, graanproducten, noten) te nuttigen om zo een perfecte balans te vinden.
4. **Vitamines en mineralen**

Voedingsdriehoek

De voedingsdriehoek is een belangrijk hulpmiddel om een gezond en gevarieerd eetpatroon te bereiken.

Helemaal bovenaan prijkt water als onze belangrijkste bron van vocht.

Verder toont deze ‘omgekeerde’ driehoek aan de brede bovenzijde welke voeding meer mag worden ingenomen en aan de smalle punt onderaan welke voeding in beperktere mate moet worden ingenomen. Elke laag heeft dan ook een andere kleur afhankelijk van het effect op uw gezondheid.

In de **donkergroene zone:** voedingsproducten van plantaardige origine met een gunstig effect op uw gezondheid.

In de **lichtgroene zone:** dierlijke voedingsproducten met een vrij gunstig tot neutraal effect.

In de **oranje zone:** de producten van zowel dierlijke als plantaardige oorsprong met een ongunstig effect op onze gezondheid, maar die mogelijks enkele nuttige voedingsstoffen bevatten.

Daarnaast kunnen we ook nog **de rode bol** terugvinden naast onze driehoek. Dit zijn sterk bewerkt producten die duidelijk ongezond zijn en daarenboven overbodig. Deze moeten dus zoveel als mogelijk uit onze voeding worden geschrapt.



Hieronder vind je, volgens de kleuren van de voedingsdriehoek, welke voedingsproducten wel aangeraden worden (met een **groene RAND**) en welke voedingsproducten niet aangeraden worden (met een **rode RAND**).

Drank: **drink vooral water**	• Water (kraan – mineraal – bron – gearomatiseerd zonder suiker) • Thee /Gefilterde koffie zonder suiker/zoetstof • Groentesoep (vers – blik - brik) zonder room/vlees • Melk (mager- halfvol) • Soja natuur	• Kant-en-klare gesuikerde drank obv thee of koffie (zoals ijsthee/ijskoffie) • Soep obv pakjes/bouillon • Vruchtenlimonade • Alcohol (≤ 1 glas/dag) • Frisdrank • Energiedrank • Sportdrank • Vers geperst fruitsap
	• Light frisdrank (< 5kcal/100ml) max ½ liter per dag	
Groenten: **Varieer** **Min 300g over 2 innames/dag**	• Groenten (vers – diepvries – blik - bokaal) zonder room of saus toegevoegd • Groentesoep (vers – brik – blik) zonder room of vlees	• Soep op basis van pakjes of bouillon • Groentechips
Fruit: **Min 2 st/dag**	• Fruit (vers – diepvries – blik – bokaal) zonder toevoegingen	• Vruchtenlimonade • Confituur (met verlaagd suikergehalte) • Grenadine • Fruitsap • Gedroogd fruit • Smoothie
Peulvruchten: **1x/week** (kikkererwten, spliterwten, linzen, bonen: wit/bruin/zwart/kidney/soja/ tuin/lima/lupine…)	• Peulvruchten (gedroogd/blik) • Vleesvervangers (zoals tofu, tempe, seitan,…)	• Kant-en-klare vleesvervangers: Gebruik de Nutri-Score om de beste keuze te maken

Brood, Graanproducten en aardappelen:

Min 125g/dag

- Volkoren/Bruin (> 50% volle granen)
  - Brood/pistolet/ stokbrood
  - Cracker/beschuit /rijstwafel
  - Rijst/deegwaren
- Havermout/muesli/ granola
- Gekookte aardappelen/ Puree zonder toevoegingen

- Wit/Bruin (≤ 50% volle granen)
  - Brood/pistolet/ stokbrood
  - Cracker/beschuit /rijstwafel
  - Rijst/deegwaren
- Havermout/muesli/ granola met toevoeging van chocolade of suiker (Gebruik Nutri-Score!)
- Gebak/(koffie)koeken
- Frieten/kroketten (max 1x/2 weken)
- Chips (light)
- Puree in poedervorm

Oliën en vetten:

- Verkies zachte/vloeibare vetten boven harde
- 1 mespunt/snede brood
- 1 el/persoon in bereidingen

Rijk aan onverzadigde Vetzuren:

- Oliën op plantaardige basis
- Zacht bak- of braadvet
- Zachte margarine
- Minarine
- (Frituurolie)

- (Halfvolle) boter
- Kokos-/palm-vet
- Frituurvet
- Harde margarine (in blok of wikkel verpakt
- Mayonaise/dressing

Onverzadigd vet ≥ 2/3 van totaal vet? → GOED!

Noten en zaden:

Handvol/dag

<u>Ongezouten noten/zaden</u>

- Puur
- In pasta zonder toevoeging

<u>Noten/zaden</u>

- met krokantjes/ chocolade
- met toevoeging van suiker/zout

Vis:

1-2x/week

- Vis (vers/in blik op eigen nat/diepvries) Zonder toevoeging van olie/saus

- Gefrituurde visproducten
- Gepaneerde visproducten
- Gerookte visproducten

Melk en alternatieven:

250-500 ml melk/dag

- (Karne)Melk natuur
- Yoghurt natuur
- Plattekaas natuur
- Sojadrink natuur

- Dessert obv room
- (Karne)melk/yoghurt/ plattekaas/sojadrink met toevoeging van suiker/zoetstof

Kaas:

1 snede kaas/2 sneden brood

Max 20g vet/100g kaas

- Magere/halfvolle plattekaas
- Magere smeerkaas
- Verse light kaas
- Mozzarella/ricotta
- Verse geitenkaas

≥ 21g vet/100g kaas

- Franse zachte kaas
- Geitenkaas/emmentaler/ kruidenkaas/mascarpone

Eieren: < 6/ week (incl. in bereidingen)

Wit vlees:

Beperk tot 1 maaltijd met vlees per dag

Vers gevogelte

- Kalkoenborst
- (Soep)Kip/kippenborst/ kippenbout
- Wild gevogelte
- Struisvogel-filet/-steak
- Duif

Bewerkt gevogelte

- Kippensalade
- Kip nuggets
- Kippen ham/kalkoen ham/kalkoensalami
- (Gepaneerde bereidingen/gehakt)

Rood vlees:

Beperkt tot 1 maaltijd met vlees per dag

Max 300g rood vlees per week

Vers vlees

- Rundvlees/kalfsvlees
- Paardenvlees
- Schapenvlees
- Mager/halfvet lamsvlees (bv lamsbout(lapje), lamsfilet, lamskotelet, lamskarbonade)
- Mager/halfvet varkensvlees (bv mignonette, filetkotelet, karbonade)

Bewerkt vlees

- Ham (gekookt/rauw)
- Gerookte vleeswaren
- Bacon/spek
- Filet americain
- Charcuterie: paté, vleessalade
- Worst

Behoort niet tot de voedingsdriehoek en dus zoveel mogelijk te mijden:

(Light/groente)chips, fastfood, koeken, gebak, snoep, bewerkt vlees, chocopasta, pizza,…

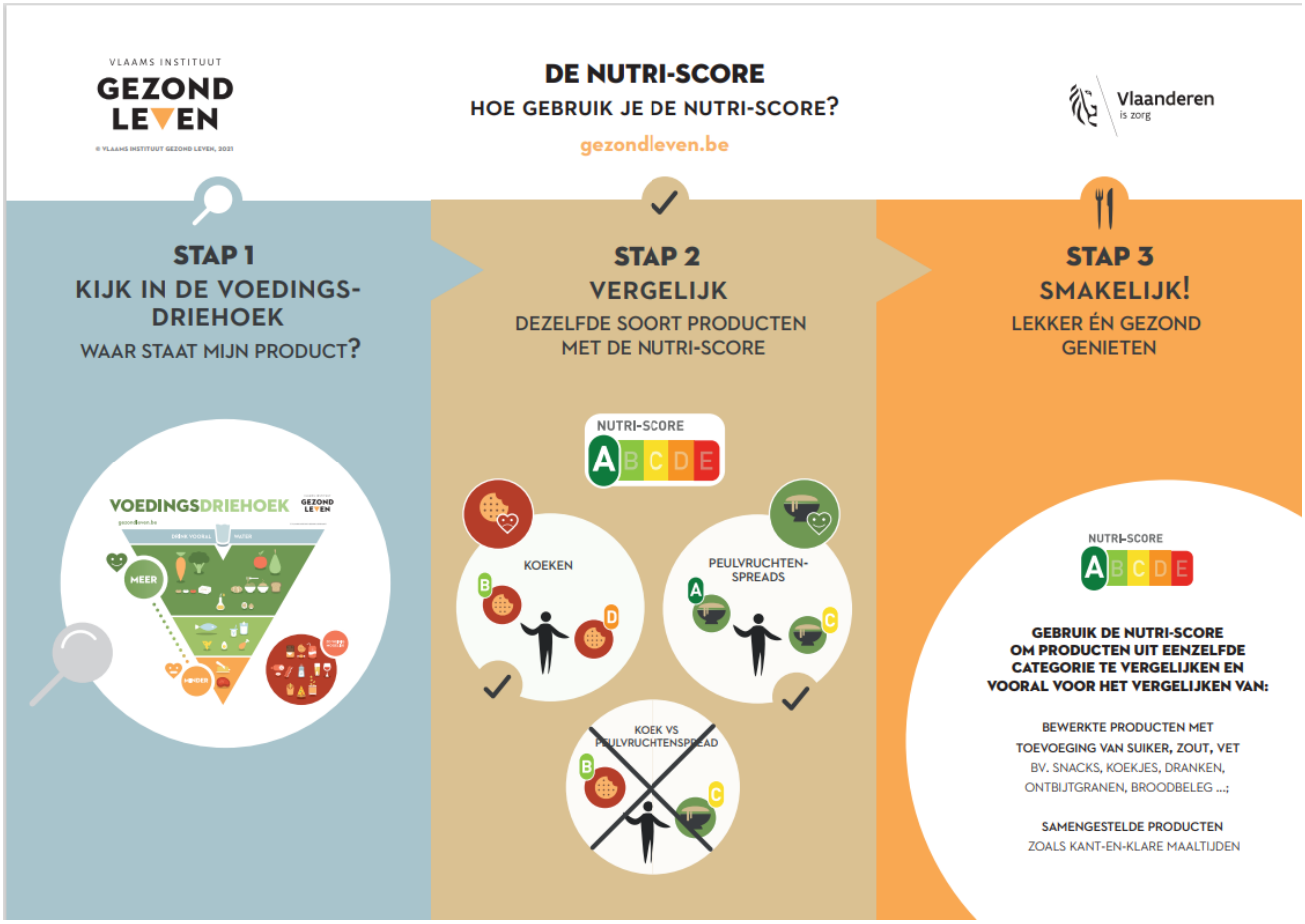
Zo toch eens gegeten/gedronken: Vergelijk de Nutri-Score binnen dezelfde voedingsgroep om de minst ongezonde keuze te maken!

Nutri-Score

Tenslotte vinden we nu op heel wat producten in de winkel de Nutri-Score terug. Deze score is het resultaat van de balans tussen de positieve en de negatieve eigenschappen van het voedingsmiddel. Zo krijgen de voedingsmiddelen met meer gezonde kenmerken (eiwit, vezels, fruit, …) het label A in het groen, en de voedingsmiddelen met meer ongezonde kenmerken (vetten, suikers, …) het label E in het rood. Dit toont op een makkelijke manier aan welke de gezondere optie is wanneer we producten willen vergelijken uit dezelfde categorie.

Wil je de dus voor gezonde voeding kiezen?

1. **Kijk eerst naar de voedingsdriehoek! Waar staat mijn voedingsmiddel?**
2. **Gebruik in tweede plaats de Nutri-Score en vergelijk producten uit eenzelfde groep om zo de meest gezonde keuze te maken.**



Nuttige websites

- www.gezondleven.be
- www.zekergezond.be

Bronnen:

1. Voeding – Gezond Leven. https://www.gezondleven.be/themas/voeding.
2. Vlaams Instituut Gezond Leven (2017): Onderbouwing inhoudelijke visie voeding en gezondheid. Achtergronddocument bij vernieuwde richtlijnen en visuele voorstelling van de voedingsdriehoek. Laken (Brussel), Online: gezondleven.be.
3. Diabetes Fonds (2021): Lekker en gezond eten met diabetes. (Amersfoort)(verkrijgbaar via www.diabetesfonds.nl).
4. Diabetes Liga (2019): Voedingsprotocol bij diabetes. (Gent)(verkrijgbaar via www.shop.diabetes.be).

4.7 Appendix VII: FINDRISC (Nederlandstalig – Domus Medica)

1. **Leeftijd**

   Hoe oud ben je?

   - Jonger dan 45 jaar 0p.
   - Tussen 45 en 54 jaar 2p.
   - Tussen 55 en 64 jaar 3p.
   - 65 jaar of ouder 4p.

2. **Gewicht**

   Hoe hoog is je BMI?

   - Lager dan 25 0p.
   - Tussen 25 en 30 1p.
   - Meer dan 30 3p.

3. **Buikomtrek**

   Wat is je buikomtrek?

	Vrouw	Man	
○	< 80 cm	< 94 cm	0p.
○	80-88 cm	94-102 cm	3p.
○	> 88 cm	> 102 cm	4p.

4. **Beweging**

   Beweeg je dagelijks minimum een half uur?

   - Ja 0p.
   - Nee 2p.

5. **Gezonde voeding**

   Eet je dagelijks groenten en fruit?

   - Ja 0p.
   - Nee 1p.

6. **Bloeddruk**

   Neem je of heb je ooit medicatie tegen hoge bloeddruk genomen?

   - Ja 2p.
   - Nee 0p.

7. **Bloedsuikerwaarde**

   Werd er ooit een verhoogde bloedsuikerwaarde bij u vastgesteld (bv. Tijdens ziekenhuisopname, routinecontrole of tijdens zwangerschap)

   - Ja 5p.
   - Nee 0p.

8. **Erfelijkheid**

   Heb je familieleden met diabetes type 1 of type 2?

   - Nee 0p.
   - Ja, grootouder(s), oom(s)/tante(s), neven/nichten in de eerste graad, maar geen ouder(s), broer(s), zus(sen) of kind(eren) 3p.
   - Ja, ouder(s), broer(s), zus(sen) of kind(eren) 5p.

Totaal: …

4.8 Appendix 8: Spirit Checklist



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	13
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	TBD
	2b	All items from the World Health Organization Trial Registration Data Set	TBD
Protocol version	3	Date and version identifier	TBD
Funding	4	Sources and types of financial, material, and other support	TBD
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	TBD
	5b	Name and contact information for the trial sponsor	TBD
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	TBD
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	TBD

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	13-14
	6b	Explanation for choice of comparators	14
Objectives	7	Specific objectives or hypotheses	14-15
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	15-16

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	TBD
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	15-19
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	19-21
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	19
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	18
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	16-17

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	TBD
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15-16

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	15-16
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	15-16
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	TBD
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15-16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	TBD

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	TBD
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	TBD
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	TBD

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	TBD
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	TBD
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	TBD

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	TBD
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	TBD

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	TBD
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	TBD
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	TBD
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	TBD
	31b	Authorship eligibility guidelines and any intended use of professional writers	TBD
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	TBD
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	25-27
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	TBD

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.