Voed je Beter

Interventiestudie bij Hart- en vaatziekten

Data analysis plan

Primary outcome

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Preliminary title:

The effects of 6 months dietetic counselling in clinical care on the cardiometabolic risk profile and diet quality of cardiovascular patients.

1. Introduction

This data analysis plan (DAP) is developed to guide the statistical analysis of the Voed je Beter trial data. The DAP provides detailed information of the populations that will be analyzed, the parameters that will be evaluated and the specific statistical methods that will be applied. This version of the DAP is designed to evaluate the primary outcome of the trial: the difference in 10-year recurrent cardiovascular risk (%) between the two study arms. For the secondary outcomes, separate DAPs will be created.

1.1 Role of the funding sources

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

2. Protocol summary

2.1 Development of protocol

The Voed je Beter trial is registered at clinicaltrials.gov as study NCT05071092 (see https://classic.clinicaltrials.gov/ct2/show/NCT05071092). The original protocol was approved by the Medical Ethical Committee (NL73021.091.20), in December 2020, and underwent minor changes since then that were all approved by the Medical Ethical Committee. All participants provided written informed consent.

2.2 Rationale

For individuals with a diagnosis of cardiovascular disease (CVD), the estimated five-year rate of experiencing recurrent myocardial infarction, stroke, heart failure, or cardiovascular-related death is 20-30%(1). The risk of getting a cardiovascular event is five times higher in people with CVD compared to those without CVD (1). Lowering the probability of recurrent cardiovascular events in patients with known CVD is referred to as secondary cardiovascular prevention. Secondary cardiovascular prevention consists of both medication use and behavioral strategies for risk factor management, including lifestyle interventions like smoking cessation, physical activity and healthy diet.

Many risk factors for CVD are closely linked to diet, including high blood pressure, high low-density cholesterol (LDL), low high-density cholesterol (HDL), and type 2 diabetes. Substantial evidence from prospective cohort studies shows that higher diet quality is associated with a 14–29% lower risk of CVD and 0.5–2.2 years greater CVD-free survival time (2, 3). Furthermore, the PREDIMED trial showed that

adhering to a Mediterranean diet resulted in less cardiovascular events (myocardial infarction, stroke or death from cardiovascular causes) compared to a control diet (4). However, whether such dietary interventions are equally effective in secondary prevention, has been less well researched.

The large CORDIOPREV trial showed that adhering to a Mediterranean diet appears to be beneficial for people with CVD. In this trial in which more than 1,000 Spanish CVD patients participated, the group that followed a Mediterranean diet appeared to have a 25-30% lower risk of a cardiovascular event (5). It must be noted here that the CORDIOPREV study was conducted in a Mediterranean country with a high acceptance for the Mediterranean lifestyle intervention. It can be questioned if dietary interventions are effective in clinical practice, where cardiovascular patients are not always adequately guided in adjusting their diet. It is well known that adhering to a healthy dietary pattern is difficult (6, 7). There is need for more research that confirms the effectiveness of dietary interventions in secondary prevention of CVD in a clinical care setting.

Besides the Mediterranean diet, dietary patterns with high diet quality are known to be beneficial for CVD risk factors. Especially increasing dietary fiber and reducing salt intake have the potential to improve the risk profile and lower the risk of recurrent CVD. Increasing dietary fiber intake is associated with reductions in low density lipoprotein (LDL)-cholesterol levels (8) and even modest reductions in salt intake cause important reductions in blood pressure (9). An intervention that focuses on improving fiber and salt intake could therefore potentially reduce the risk recurrent events.

However, to investigate this, it is important to not only look at individual risk factors, but at their combination. It is precisely about the presence of a combination of risk factors that determine the cardiovascular risk profile. To assess individual risk profiles, prediction tools can be used. The SMART (Second Manifestations of Arterial Disease) risk score takes into account multiple risk factors and is designed to estimate the 10-year risk for myocardial infarction, stroke or vascular death in individual patients with clinically manifest atherosclerotic vascular disease (10).

To assess the impact of incorporating dietary changes alongside medication on the risk of cardiovascular disease in cardiovascular patients, we performed a randomized controlled trial in a Dutch health care setting. By doing so, we also aimed to investigate whether it is possible to better implement dietary counselling in the current care pathway for people with CVD.

2.3 Objective

With the Voed je beter trial, we aim to investigate the effects of dietetic counselling in clinical care on the cardiometabolic risk profile and diet quality of patients with established CVD. The dietary counselling focused on improving the adherence to the Dutch dietary guidelines.

2.3 Population

Study participants were identified and recruited from two hospitals in the Netherlands (Gelderse Vallei, Ede and Rijnstate, Arnhem, the Netherlands). Eligible for participation were individuals with a

diagnosis of cardiovascular disease, including acute coronary disease syndrome, angina, coronary revascularization, TIA or stroke, symptomatic aortic iliofemoral atherosclerosis, aortic aneurysm, intermittent claudication, or peripheral revascularization. Patients were excluded from participation if they were <18 years old, used medication for the treatment of diabetes, had a known hereditary form of CVD, had an eGFR <30ml/min, were participating in another study that interfered with the outcomes of the current study, or were not able to speak and understand Dutch.

2.4 Design

The Voed je Beter trial is a multicenter, randomized, controlled trial with two parallel arms. Patients were randomly assigned in a 1:1 ratio to usual care or the intervention group. The allocation sequence was computer-generated using block-randomization with variable block sizes (4, 6, 8). Allocation was stratified by hospital.

The intervention period was set at six months. Patients in the intervention group were referred to a dietitian close to their home address or, if that was not available, an online dietitian practice. Patients met with the dietitian seven times within six months with a maximum of 5 clock hours in total. Dietitians were instructed to guide the patients in improving adherence to the Dutch Dietary Guidelines (11). The Dutch Dietary Guidelines include recommendations on 16 components, including salt, vegetables, fruit, whole grain products, legumes, nuts, dairy, fish, tea, fats and oils, coffee, red meat, processed meat, sweetened beverages and fruit juices, and alcohol. Together with the dietitian, patients chose themselves which components they were going to improve. The diet in the study was therefore not prescriptive; goals were negotiated individually with each participant during their first session with the dietitian and were reviewed at each visit. Dietitians were instructed to at least set a goal on improving the intake of salt, fruit or vegetables as these are hypothesized to be the most relevant components for patients with cardiovascular diseases. Due to the nature of the intervention, blinding of dietitians, researchers, and patients was not possible. To limit bias during data analysis, an independent researcher will recode the groups in a way it is no longer possible to determine which group is intervention and which is control. The unblinding of the groups will take place after analyzing the primary outcome.

2.5 Data collection

At baseline, data were collected on demographic factors, lifestyle and medical history. Current age and lifestyle information such as smoking were self-reported by the participant through questionnaires.

Information on dietary quality was collected by an abbreviated food frequency questionnaire (FFQ), consisting of questions about the habitual food intake of the last month (12). This FFQ was used to assess the Dutch Healthy Diet Index which examines adherence to the Dutch Dietary Guidelines. For each component of the dietary guidelines, patients received score ranging from 0 to 10, leading to a total score from 0 to 160 with higher scores indicting better adherence. More information about the Dutch Healthy Diet Index is described elsewhere (13).

Physical activity was assessed using the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH). Participants were asked about physical activity during commuting, activities at work/school, household activity and leisure time activity including sports in a usual week during the past month in days per week, and hours and minutes per day (14). Data from the SQUASH was used to calculate minutes per week moderate to vigorous physical activity (MVPA). The intensity of the specific activities is based on a combination of metabolic equivalent (MET) scores according to the compendium of Ainsworth (15) and self-reported intensity. Activities with a MET score of ≥4.0 or ≥3.0 were scored as MVPA for participants younger than 55 years and participants of 55 years and older respectively.

Self-reported medication of the participants was coded according to the Anatomical Therapeutic Chemical Classification System (ATC). The summary of cardiovascular medication use will include the following drugs, ordered by ATC code:

- B01 Antithrombotic agents
- C02 Antihypertensives
- C03 Diuretics
- C07 Beta-blocking agents
- C08 Calcium-channel blocking agents
- C09 Agents acting on the renin-angiotensin in system
- C10 Lipid lowering
- C10AA Statins

Results will be shown as proportion of patients taking lipid lowering agents (C10), antiplatelet or anticoagulant agents (B01) or blood pressure lowering agents (C02 + C03 + C07 + C08 + C09).

Information about the type of cardiovascular disease and time since the last cardiovascular event were retrieved from electronic patients records. Type of CVD was classified according to the following (non-mutually exclusive) CVD types:

- Coronary Artery Disease
- Cerebrovascular Disease
- Aortic Aneurysm
- Peripheral Artery Disease
- Other

In case people fall into the high-risk category but cannot be classified into one of the four diseases, they are classified as Other.

During a study visit, subjects were physically examined by a trained researcher in the hospital and a nurse obtained a blood sample. Physical examination included measurement of body weight (kg) and height (cm) with the subject wearing indoor clothing. If people were weighed wearing shoes, the weight was subtracted with 1.5 kg to correct for this. Body mass index was computed by dividing the weight in kilograms by height in meters squared. Waist circumference was measured at the midpoint between the bottom rib and the top of the hipbone. Systolic and diastolic blood pressures were

measured with the subject seated, after a 5-minute rest. Measurements were performed trice on the non-dominant upper arm with an automatic device (Microlife WatchBP home A) and values were averaged. Venous blood was drawn for the assessment of serum lipids and biomarkers of nutritional intake. Besides, participants were asked to collect 24-hour urine samples for determination of sodium, potassium and albuminuria.

All measurements were repeated after 3, 6 and 12 months. For the analysis of the primary results, only the 6-month measurements will be used.

2.7 Primary endpoints

The primary outcome of this study is change in 10-year CVD risk as predicted with the SMART risk score (10). The SMART risk score is a model to estimate 10-year recurrent cardiovascular risk expressed as percentage and to predict the effect of treatments such as smoking cessation, blood pressure lowering or lowering LDL-cholesterol (10). To assess the SMART risk score at baseline, we will use the model as shown in figure 1 below and described in (10). The model considers age (y), time since last cardiovascular event (y), type of CVD, having diabetes (y/n) smoking status (y/n), total cholesterol (mmol/l), high-density lipoprotein cholesterol (mmol/l), low-density lipoprotein cholesterol (mmol/l), triglycerides (mmol/l), C-reactive protein (CRP, mg/L), systolic blood pressure (mmHg), estimated Glomerular Filtration rate (eGFR) and anticoagulant (ATC code B01) use to estimate the 10-year recurrent cardiovascular risk. For type of CVD, the original formula includes factors for four different CVDs (coronary artery disease, cerebrovascular disease, aortic aneurysm and peripheral artery disease). For other CVDs, a factor representing the average of the factors associated with these four diseases is used.

Figure 1 Calculation of 10-year CVD risk according to the SMART risk score

10-year CVD risk (%) = $(1-0.81066^{\exp(\text{linear predictor} + 2.099)}) \times 100\%$

In which Linear predictor =

```
-0.0349602236 * age +
0.0005510715 * age^2 +
ifelse(sex=="M", 0.2876587433, 0) +
0.3455832714 * isSmoking +
0.0018913154 * sbp +
0.3181706587 * diabetesDiagnosis +
0.2947019539 * coronaryArteryDisease +
0.3483178604 * cerebrovascularDisease +
0.3303566308 * aorticAneurysm +
0.2244665798 * peripheralArteryDisease +
0.2994607562 * otherDisease +
0.0476995851 * yearsSinceFirstDiagnosis -
0.0016497342 * yearsSinceFirstDiagnosis^2 +
0.5403642493 * log(nonHdl) -
```

0.0396752081 * egfr +
0.0002186126 * egfr^2 +
0.1517601731 * log(crp) -
0.2107210313 * usingAnticoag

To estimate the change in 10-year risk during the 6 months of the study, we will consider changes in LDL cholesterol and systolic blood pressure as these are causal risk factors known to be influenced by diet (16, 17). With the SMART risk model, the effect of changes in these risk factor can be estimated by using a Hazard Ratio (HR) related to these risk factors (10). Every decrease of 1.0 mmol/L in LDL-cholesterol is shown to reduce an individual's cardiovascular risk with 20%, corresponding to an HR of 0.80 (18). Per decrease of 10 mmHg for systolic blood pressure, cardiovascular risk is estimated to be reduced with 22%, hence a HR of 0.78 is used (19). Multiplying the effects of the changes in LDL-cholesterol and systolic blood pressure with the baseline risk, gives us the predicted change in 10-year risk at the end of the intervention.

In short, 10-year CVD risk at six months is calculated as 10-year CVD risk at baseline * $(0.78^{\text{LDL-c end - LDL-c baseline}})$ * $(0.8^{(\text{SBP end – SBP baseline})/10})$. By subtracting the 10-year CVD risk at six months from the 10-year CVD risk at baseline, the change in SMART risk score will be calculated.

Table 1 Example calculation of 10-year CVD risk at six months using changes in LDL-cholesterol and systolic blood pressure

Baseline risk	Change in LDL-c	Change in SBP	6 months risk	Change in risk
1%	increased with 1mmol/l	increased with 3 mmHg	$1*(0.78^{-1})*(0.8^{3/10})$ = 1.2%	+0.2%
20%	decreased with 1mmol/l	decreased with 5 mmHg	$20*(0.78^{1})*(0.8^{5/10})$ = 13.9%	-6.1%
20%	decreased with 0.5 mmol/l	decreased with 2 mmHg	$20*(0.78^{0.5})*(0.8^{2/10})$ = 17.3%	-2.7%
80%	no change	increased with 1 mmHg	$80*(0.78^{0})*(0.8^{1/10})$ = 80.9%	+0.9%

2.8 Secondary endpoints

As secondary outcomes, changes in LDL-cholesterol, body weight, CRP and systolic blood pressure will be presented and compared between groups. Similarly, the change in proportion of individuals using lipid lowering agents, antiplatelet or anticoagulant agents, or blood pressure lowering agents will be presented and compared between groups.

Changes in diet quality, as assessed with the Dutch Healthy Diet index, will be presented for the total population and for the two groups separately but will not be compared with statistical tests. Changes in smoking habits will be presented for the total population and for the two groups separately as % of individuals smoking at baseline and at 6 months.

2.9 Sample size calculation

The study was powered to detect a difference in estimated 10-year CVD risk between the intervention and control group at 6 months of 3.3% (20), with an assumed standard deviation of 6.3% (21). Based on those numbers, a sample size of 114 patients (57 patients per group) was needed to provide a

power of 80% with an alpha 0.05. Considering a possible 20% dropouts, the required sample was increased to 144 patients.

3. Population and variables

3.1 Analysis population

The patient populations to be studied are defined as follows:

3.1.1 Intention-to-treat

The intention-to-treat (ITT) population includes all subjects who were assigned a randomization number. The ITT population is considered the main analysis population. Missing data necessary for the calculation of the primary outcome will be imputed (see 4.4 Missing data for an explanation of procedures).

3.1.2 Per protocol

The following per protocol (PP) populations have been defined:

- PP-Comp: This population includes all subjects in the ITT population who visited the dietitian 5 times or more in the intervention group.
- PP-Diet: This population includes all subjects in the ITT population who improved ≥1 SD on Eetscore compared to baseline in the intervention group, and excludes all subjects who improved ≥1 SD on Eetscore compared to baseline in the control group.

3.2 Subject demographics and pre-treatment characteristics

Subject demographics and pre-treatment characteristics will be summarized for the ITT and PP populations and presented per treatment group and for all subjects.

3.2.1 Demographics

The summary of demographics will include gender, age at randomization, origin of parents and educational level. Educational level will be shown in categories as defined by the Centraal Bureau voor Statistiek (CBS).

3.2.2 Medical history and risk factors

The summary of medical history (type of CVD and time since last event) and CVD risk factors will include body weight, body mass index, waist circumference, total cholesterol (mmol/L), high-density lipoprotein cholesterol (mmol/l), low-density lipoprotein cholesterol (mmol/l), triglycerides (mmol/l), C-reactive protein (mg/L), diastolic blood pressure (mmHg), systolic blood pressure (mmHg), time since last event (y), type of CVD, smoking, alcohol use, level of physical activity.

Smoking status will be shown as percentage of people being current, former, and never smokers. Level of physical activity will be presented as minutes per week moderate to vigorous physical activity (MVPA). Alcohol use will be presented as alcohol consumptions per week. Type of CVD will be shown in categories (n, %) as used in the SMART-risk predictor tool:

- Coronary Artery Disease
- Cerebrovascular Disease
- Aortic Aneurysm
- Peripheral Artery Disease
- Other

3.2.3 Medication

The summary of medication use will be shown as proportion (n, %) of patients taking lipid lowering agents (C10), antiplatelet or anticoagulant agents (B01) or blood pressure lowering agents (C02 + C03 + C07 + C08 + C09).

4. Statistical analysis

4.1 Significance

All statistical tests will use a significance level of α=0.05. Two-tailed tests will be performed for all analyses involving statistical testing. Confidence intervals will be presented with a 95% degree of confidence.

4.2 Multiplicity

No adjustment for multiplicity is planned within any of the analysis performed.

4.3 Data summarization

Summary statistics will consist of the number and percentage of responses in each category for discrete variables, and the mean ± standard deviation (SD), or the median and interquartile range for continuous variables. All percentages will be rounded to one decimal place. All analysis and summary tables will show the population sample sizes in the column headings.

4.4 Missing data

Researchers were instructed to obtain complete CRFs, but participants dropping out of the study resulted in missing data. Data is assumed to be missing at random (MAR). Missing data necessary for the calculation of the primary outcome will be imputed by chained equations with the MICE package for R software (m=10 imputations, iterations =10) (22). In more detail, with this method missing values are imputed by using a model that incorporates random variation. Every variable (except for personID) in the dataset is considered a potential predictor for imputing missing values in other variables.

For the imputation, ten datasets will be created and the data analysis will be performed on these ten datasets. After performing the data-analysis on the ten datasets containing the imputed data, the ten coefficients are estimated by the imputed dataset into one final regression coefficient. The variance will be estimated using the pool() function. To obtain the final coefficients we take the mean of the ten values. We calculate the variance of the estimated coefficient by factoring in the within (accounting

for differences in predicted values from the dataset regarding each observation) and between (accounting for differences between ten datasets) imputation variance. If convergence is not achieved after 10 iterations, more iterations will be used to improve convergence.

4.5 Data distribution and model checking

Analysis of covariance (ANCOVA) will be used to compare continuous data between the intervention and control group. For the primary outcome, SMART risk score at 6 months is considered the dependent variable, and the categorical grouping variable (intervention or control) will be added as independent variable. As covariates, the SMART risk score at baseline and hospital will be added. The ANCOVA model will be implemented using the lm function in R. Assumptions of homogeneity of regression slopes and homogeneity of variances will be checked with the imputed data sets.

For comparison of changes in LDL, body weight, CRP and systolic blood pressure, similar ANCOVAs will be performed with adjustment for study site and baseline values.

Chi-Square tests will be used for the analysis of medication use as this is presented as dichotomous data. The 95% CI will be presented for the difference in proportions. If expected cell frequencies are less than 5, Fisher's exact tests will be used.

If the assumptions underlying ANCOVA (normal distribution of residuals, homogeneity of variances) are not satisfied, data will be transformed. If data is still not normally distributed, linear mixed models will be used. This model will include fixed effects for the SMART risk score, and a random intercept for the grouping variable to account for individual variability within each group. The models will be implemented using the 'lme4' package in R.

4.6 Software

For all data summaries, listings, statistical analyses and graphs, R® version 4.1 or later will be the statistical software package used.

5. Presentation of results

- Figure 2. Flow chart
- Table 1. Baseline table
- Table 2. Cardiovascular risk outcomes
- Table 3. Diet quality outcomes
- Supplementary Table 1. Sample size calculation
- Supplementary Table 2. Cardiovascular risk outcomes within complete cases
- Supplementary Table 3. Diet quality outcomes within complete cases

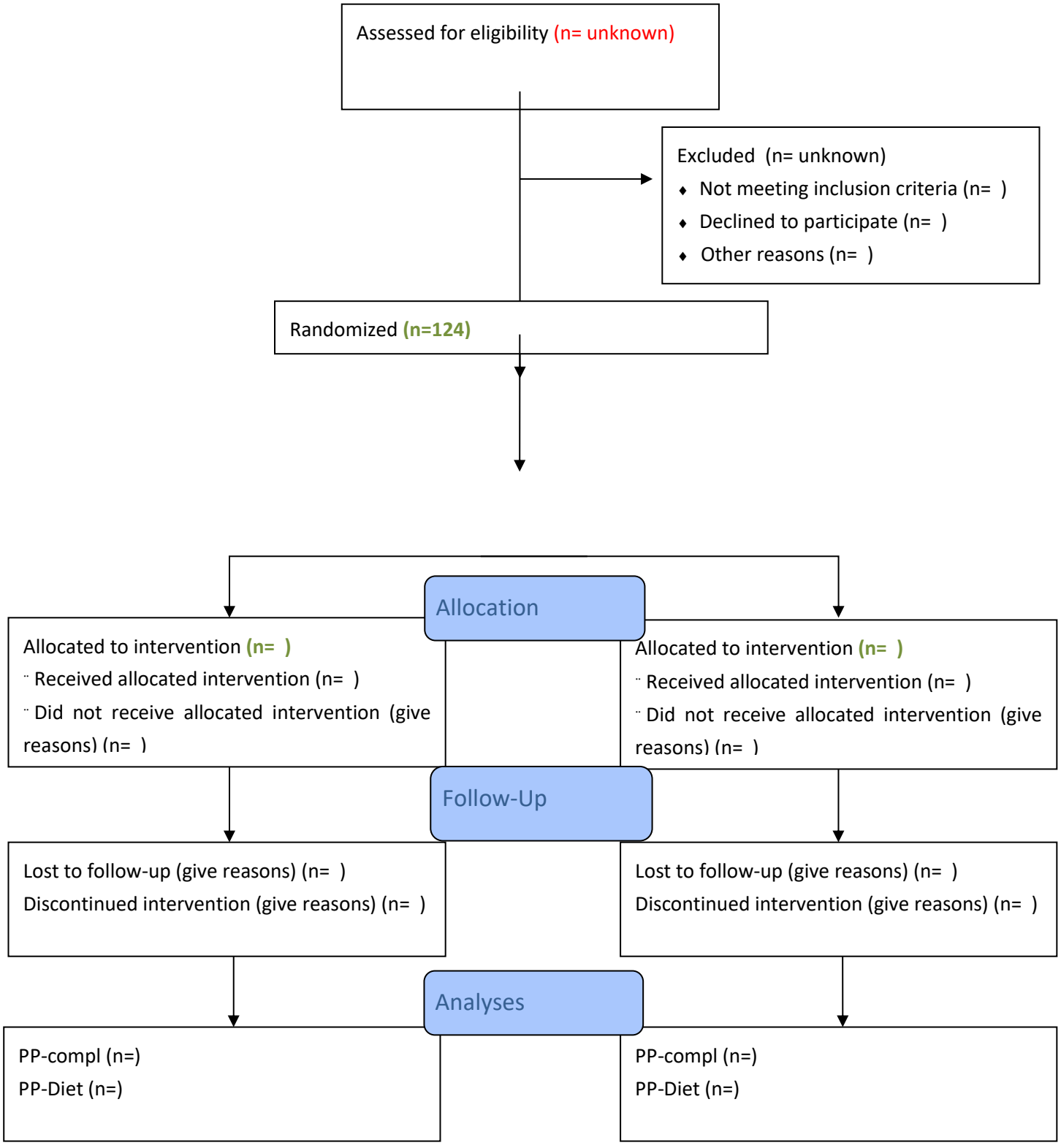

Figure 2. Flow chart of participants in the Voed je Beter CVD trial

Table 1. Baseline characteristics

Characteristics of enrolled patients are shown in table 1. Patients were on average 68 years old and had a BMI of 27.2 kg/m^2.

Table 1. Baseline descriptives participants from the VJB-HVZ trial

	Total (N=124)	Intervention group (n=?)	Control group (n=?)
Female, n (%)			
Education, n (%)			
Low			
Medium			
High			
Smoking, n (%)			
Current			
Former			
Never			
Parents origin, n (%)			
Dutch parents			
No Dutch parents			
Age (years)			
Weight (kg)			
BMI (kg/m2)			
Waist circumference (cm)			
Systolic blood pressure (mmHg)			
Diastolic blood pressure (mmHg)			
Total cholesterol (mmol/l)			
HDL-cholesterol (mmol/l)			
LDL-cholesterol (mmol/l)			
Triglycerides (mmol/l)			
hsCRP (mg/L)			
Diet quality score (DHD15-index)			
Physical activity (min per week)			
Type of CVD, n (%)			
coronary artery disease			
cerebrovascular disease			
abdominal aortic aneurysm			
peripheral artery disease			
other			
Time since first CVD diagnosis (years)			
Antihypertensive drugs, n (%)			
Antiplatelet drugs, n (%)			
Lipid lowering drugs, n (%)			

Table 2. Cardiovascular risk outcomes of the Voed je Beter trial

	n	Baseline	6 months	Change	Mean difference
Intention to treat					
10-year CVD risk (%)					
Group A					
Group B					
Systolic blood pressure (mmHg)					
Group A					
Group B					
LDL-cholesterol (mmol/l)					
Group A					
Group B					
Body weight (kg)					
Group A					
Group B					
Per protocol-based on number of sessions with dietitians					
10-year CVD risk (%)					
Group A					
Group B					
Systolic blood pressure (mmHg)					
Group A					
Group B					
LDL-cholesterol (mmol/l)					
Group A					
Group B					
Body weight (kg)					
Group A					
Group B					
Per protocol- based on improvement in DHD-15					
10-year CVD risk (%)					
Group A					
Group B					
Systolic blood pressure (mmHg)					
Group A					
Group B					
LDL-cholesterol (mmol/l)					
Group A					
Group B					
Body weight (kg)					
Group A					
Group B					

Table 3. Changes in diet quality of the Voed je Beter trial

	n	Baseline	6 months	Change
DHD-15 total				
Group A				
Group B				
Vegetables				
Group A				
Group B				
Fruit				
Group A				
Group B				
Grain products				
Group A				
Group B				
Legumes				
Group A				
Group B				
Nuts				
Group A				
Group B				
Dairy				
Group A				
Group B				
Fish				
Group A				
Group B				
Tea				
Group A				
Group B				
Coffee				
Group A				
Group B				
Oil and fats				
Group A				
Group B				
Red meat				
Group A				
Group B				
Processed meat				
Group A				
Group B				
Sugar-sweetened beverages				
Group A				
Group B				
Salt				
Group A				
Group B				
Alcohol				
Group A				
Group B				

6. References

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