Author's response to reviews

Title: Stability of dietary patterns assessed with reduced rank regression; the Zutphen elderly Study

Authors:

Nicole Jankovic (Nicole.Jankovic@wur.nl)
Martinette T Streppel (Martinette.Streppel@wur.nl)
Ellen Kampman (Ellen.kampman@wur.nl)
Lisette CPGM Groot de (Lisette.degroot@wur.nl)
Hendriek C Boshuizen (Hendriek.Boshuizen@wur.nl)
Sabita S Soedamah-Muthu (Sabita.Soedamah-muthu@wur.nl)
Daan Kromhout (Daan.Kromhout@wur.nl)
Edith JM Feskens (Edith.Feskens@wur.nl)

Version: 2
Date: 20 December 2013

Author's response to reviews: see over
Dear Editor,

Thank you very much for the opportunity to revise our manuscript. The valuable comments given by Dr. Gina Leslie Ambrosini and Dr. Fumiaki Imamura gave us the opportunity to review our manuscript with a new perspective. We highly appreciated the suggestions and comments by the reviewers and think that the manuscript gained in quality, now having incorporated most of the suggestions. Please find our point by point answers and the revised manuscript attached. We would like to thank you for the opportunity to adapt our manuscript and we are looking forward to your response.

Yours sincerely,

Nicole Jankovic
Reviewer's report
Title: Stability of dietary patterns assessed with reduced rank regression; the Zutphen elderly Study
Version: 1 Date: 18 October 2013
Reviewer: Fumiaki Imamura

Reviewer's report:
The authors examined 5-year reproducibility of dietary patterns derived from RRR. The message is nicely simple and methodological investigation would benefit readers in a nutrition field.

The followings are comments that are, I believe, important to receive attention, although all most are minor ones.

Major comment:
Limitations should be stated clearly regarding the selection of the healthy elderly population and also dietary data observed in 2 decade ago. Readers should be aware whether or not the findings can be applicable to dietary patterns in this century.

Authors reply: We have added the following sentence to the manuscripts discussion (line 305-308): “However, we do not consider the selection of healthy elderly participants or the information on dietary intake data used from two decades ago as a major limitation. The current manuscript focussed on the methodology of RRR and the potential of RRR to derive stable dietary patterns over time.”

Comparing the food consumption survey (FCS) of the Netherlands in 1987/88 with our results for the main food groups such as bread, potatoes, fruits and vegetables and meat revealed similar estimates regarding food consumption. However, comparisons with the most recent FCS in elderly men of the Netherlands showed large differences in the consumption of these food groups. The derived patterns are therefore probably not applicable to the current situation. However, the focus of this paper was to derive stable dietary patterns over time.

Minor comments:
“RRR derived dietary patterns” and similar expression was confusing, because derived looked both a past-tensed verb and an adjective. Please hyphenate ‘RRR’ and ‘derived’. Too many hyphens are detractive, so state “dietary patterns derived from RRR analysis” whenever appropriate.

Authors reply: Changes were applied to the abstract, the manuscript and the manuscript tables.

Abstract:
"Cross-check" should be clear in the abstract. Cross-check between a participant and an interviewer could be inferred, for example. But it appears not.

Authors reply: The word cross-check has been removed from the abstract as this appears to be more confusing than helpful.
The abstract states use of 19 food groups. This information would raise a question about why the authors came up with the number. As the authors may know, 19 look too few. Thus, the N of food items they had, and the fact of narrowing them down to 19 should be stated briefly in the method.

Authors reply: The following is now included in the subjects/methods section of the abstract line 29-31: "Backwards regression on risk factors and food groups was applied prior to the RRR analysis to exclude food groups with low predictability (from 36 to 19 food groups) for the chosen risk factor profile."

Ones would advise the authors to make the background succinct. The three long sentences are too long. Something like the following would be fine enough. "Reduced rank regression (RRR) has been widely used to derive dietary patterns associated with risk factors for chronic diseases. Long-term stability of RRR-derived dietary patterns remains unknown."

Authors reply: The introduction has been adapted accordingly line 65-68.

Note that examining 5-year stability and some other information are not background and explained in the method.

Authors reply: 5-year stability has been replaced by: “the long-term stability of dietary patterns”

Results should show what percentage of variabilities of dietary factors was explained by each pattern derived by RRR. If readers know RRR, they can guess that a pattern explaining variations of dietary factors well is more stable than others. Second and third patterns are residuals of the first pattern, so not surprising that they had less reproducibility.

Authors reply: Line 206-208 describes now the following: “The 1st derived RRR pattern explained 6.6% (2nd pattern: 5.6%, 3rd pattern 5.5) and 6.0% (2nd pattern: 5.9%, 3rd pattern 5.3) of the variation in dietary variables at baseline and follow-up respectively."

The line 43-44 looks too much selective. Objectivity should be indicated. Also N for adults without chronic diseases and diet prescription (at baseline or at follow-up?) should be presented.

Authors reply: We excluded the sensitivity analysis combining prescribed diet and chronic diseases from the manuscript. However, differentiating between participants with and without chronic diseases at baseline remained in the manuscript (line 234-237). The number of participants free of disease at baseline is now included in the manuscript.

Differentiating participants who had a chronic disease or prescribed diet between 1985 and 1990 revealed the following correlation coefficients between 1985 and 1990 derived diets: Disease yes 1985 and 1990 (0.28) N=160 vs. Disease no (0.55) N= 307
Prescribed diet yes in 1985 or 1990 (0.58) N=60
Prescribed diet no in 1985 or 1990 (0.50) N=407

Diet and chronic diseases yes in 1985 and 1990 (0.34) N=282
Diet and chronic diseases 1985 and 1990 No (0.59) N= 185

However, epidemiological studies usually exclude chronic diseases at baseline. Doing so, the correlation coefficients between dietary patterns derived in 1985 and 1990 for participants without chronic diseases at baseline (N=368) was 0.50.

The parallel composition on line 45-46 says "Dietary patterns... remain an attractive approach" Patterns are not an approach. Make sure of the grammatical structure.

Authors reply: The sentence structure is now changed to (line 39-42): ‘Dietary patterns as measured by RRR after backwards regression are reasonably stable over a period of five years. Thus, RRR appears to be an attractive method to measure long-term dietary exposure for nutritional epidemiological studies with one dietary measurement at baseline.’

RRR is not necessarily sophisticated, compared to the others. As the authors may know, it has a limitation of constraint by response variables. RRR may not be good for describing patterns underlying in a population.

Authors reply: The introduction has changed. The purpose of this paper was not to describe the underlying dietary pattern of this population but to derive stable patterns over time using RRR. We have included the following sentence (line 63,64): ‘In contrast to PCA and factor analysis RRR patterns do not describe naturally occurring patterns of the population under study. Derived patterns from RRR have the purpose to explain variation in biological risk factors.’

Line 63-67 look unnecessary. This study is not intending to compare RRR to PCA.

Authors reply: These lines have now been removed.

on line 72, "reasonably stable" is correct.

Authors reply: Due to changes in the introduction this adaptation becomes unnecessary.

However, we applied the suggestion in the abstract (line 39).

The authors should acknowledge that dietary patterns derived from the other methods, which the authors might know, were examined previously.

Authors reply: The following references are now incorporated in the introduction.


The introduction should include why reproducibility of diets should be examined.

Authors reply: After revision the introduction includes the following sentence (line 68-72): “Cohort studies often lack information on repeated measures over time and need to rely on baseline measurements, assuming stability of long-term exposure. Therefore, we assessed the long-term stability of dietary patterns derived from RRR in elderly men on the population level. This analysis will add to the knowledge and possible implications of RRR analysis in nutritional epidemiology.”

On line 73, the sentence seems broken. Also "applied for descriptive purposes"[7] is not clear. If stability of RRR-derived patterns were examined for descriptive purpose, this would be good. The authors might want to say, explicitly, "the prior study derived dietary patterns by RRR repeatedly but did not examine the reproducibility of any patterns derived."

Authors reply: This part is now deleted.

Methods:

The authors lost more than 50% of the population recruited in the study (939 to 467). It could be possible that the 467 men were particularly healthy, committed to highly stable diets, and reported them very well. The authors should present the difference between the 467 adults evaluated and the others not evaluated.

Authors reply: A section comparing excluded and included participants has been added to the manuscript lines 188-193: “significant differences for BMI (25.2 kg/m$^2$ vs. 25.7 kg/m$^2$, p=0.04) and uric acid (0.37 mmol/l vs. 0.36 mmol/l, p=0.04). Regarding food group consumption we observed significant differences for cereal products, vegetables, cheese, non-alcoholic and alcoholic drinks, which were all consumed more by included participants, and fats were consumed less by included participants.”
on line 121, "correctly" should be rephrased. The authors are never able to correctly rank individuals over time.

Authors reply: The word “correctly” has been replaced by “similarly”

It is not clear how many dietary variables were aggregated into the smaller number of food groups. The aggregation should be as clear as possible, because subjectivity might have been involved and because readers could imagine the effort needed to replicate this study. Looking at the Table 2, it does not make sense to list light and strong alcoholic beverages separately from wine and beer at the first glance. Aggregating them, “liquor or spirits” should be fine. Also it is concerning to aggregate tea, coffee, and other non-caloric beverages. The authors might not need to change it, but what they did is not clear regarding food grouping.

Authors reply: Food grouping was based on previous allocation of food groups as defined by the Dutch food grouping system NEVO of that time. An extensive list of food grouping can be provided in Dutch by contacting the corresponding author (The number of aggregated food groups is now added to table 2).

On line 143, "we calculated exploratory derived RRR dietary pattern scores" is not clear. The point might be whether or not RRR was run independently for the baseline diets and for the diets 5 years after the baseline. Was it?

Authors reply: We replaced the sentence by the following statement. Changes are indicated in bold (line 145-147).

Finally, we ran exploratory RRR analysis independently for 1985 and 1990 and assigned a z-score [...].

On line 163-164, it is not clear why the sample size was 763 here. Did the authors included adults with dietary data but without one of the response variables? Was it 939? More importantly, it is not clear what the authors did after applying the RRR to the 763 adults.

Authors reply: Study population and subject section is revised line 80-84: “Excluding participants with missing data on dietary intake or response variables at baseline reduced the sample from 939 to 763 participants. Excluding participants with missing information at follow-up revealed a sample of 467 men eligible for further analyses.”

This sentence has been added to the Statistical analysis part (lines 172-176): finally, RRR was applied to the full study population of 763 participants in 1985, describing the sample prior exclusion of participants dying between 1985 and 1990. The correlation coefficient between exploratory RRR scores derived in the full study population at baseline and reduced sample of 1985 was calculated for 467 participants.

This sentence has been added to the results section lines (238-243): Correlation coefficients between dietary patterns derived from RRR using 36 food groups in the full (n=763) and
reduced sample (n=467) of 1985 were high (correlation coefficient comparing 467 participants of the full and reduced sample r=0.75). The full study sample of 763 participants showed significant cross validation tests for 36 food groups. However, comparability of the patterns derived in the full and reduced sample increased after backwards regression (r =0.86).

On line 176, statement of this analytic results in the result section is preferred. Please remove the same information from the Method section. In the method section, it would be fine to read just what the authors did.

Lines 141 to 143 were removed “After backwards regression the Van der Voet's test was applied again to the final RRR model which included 19 food groups and six response variables.”

Then not all methods were not necessary, on the next lines.

Authors reply: The following sentence was moved from the results to the methods section: The decision on the number of patterns was based on the results of the cross-validation, the Van der Voet’s test and the comparability between patterns from baseline and follow-up.

Labelling has been removed from the results section and is now described in the methods section lines 152, 153.

The following sentence has been removed: “In an additional analysis we assessed the influence of changes in food group consumption over five years on the stability of the RRR derived dietary patterns.”

On line 212, “exploratory derived” is not clear. The lines would let reviewers expect correlations of the patterns derived from the baseline and applied to dietary data at the baseline and the follow-up, i.e. confirmatory. Why not were the confirmatory ones compared? Although formal test was not performed, greater reproducibility and sensitivity of confirmatory derivation of patterns at 1990 looked better.

Authors reply: These analyses were now added to table 5 and in the results (lines 224 onwards) and discussion lines 280 onwards.

What were the results after evaluating 763 adults, after assigning the RRR-derived patterns to them?

Authors reply: Applying RRR analysis to 763 participants revealed similar dietary pattern scores (r=0.76). After running backwards regression the stability increased (r=0.86). This is now stated in the results section of the manuscript lines 238-243.

Table 2:
“P10” and “p90“ are not clear.

Authors reply: Title has changed to: Median (10th , 90th percentile) of the initial 36 defined food groups at baseline and at follow-up in the Zutphen elderly Study (N=467).
“1985 intake in g/d“ is not clear or incorrect expression.

Authors reply: Changed in table:
Food consumption (g/d) 1985
Food consumption (g/d) 1990

Table 4.
This table should include the confirmatory pattern scores derived from diets in 1990.

Authors reply: Correlation coefficients are now included. Percent variation accounted for is now included in table 3.

Table 5.
“exploratory 1985”, “exploratory 1990”, “confirmatory 1990” should be stated more clearly.

Authors reply: Two separate food notes included instead of one explaining both exploratory and confirmatory.

In the footnote, the authors need to state whether or not means and SDs in 1985 were used or means and SDs at each time point were used.


Discussion:
The following sentence raises a concern of subjectivity. “The highest correlation coefficients between examination rounds for the “low in cereal fibre pattern” were shown in men without chronic disease and prescribed diet.”
This could be said comfortably only if the authors formally tested the correlation among the healthier subgroup was significantly higher than that among the rest. The authors did not test it, and readers would not be sure of the precision of the above statement. The possibility can be discussed in the section, but this statement in the conclusion raises a yellow or red signal.

Authors reply: This part of the analysis has been removed due to reasons explained earlier in this document.

The paragraph beginning from line 235 should present difference in the methods deriving dietary patterns.

Authors reply: The discussion has been revised. For the discussion the suggestion above is not applicable anymore. The difference in methods is described in the introduction line 62-64.
On line 261, “robust dietary patterns” is not clear what the authors want to say. Also, it is not clear why the selection of food groups would be important in a small-sized study. This could be demonstrated in the study population and in other study groups, so the definite statement, without objective view, should not be stated without clear explanation.

Authors reply: The word robust replaced by greater stability.

In the revised version we try to clarify the selection of food groups and importance for a small sized study population starting with the statistical analysis line 140 describing the impact of the non-significant Van der Voet’s test: [...] Derived patterns would highly be influenced by chance findings. Results: line 240 to 243 “The full study sample of 763 participants showed significant cross validation tests for 36 food groups. However, comparability of the patterns derived in the full and reduced sample increased after backwards regression (r =0.86).”

On page 11, the authors characterized their study as small. It is not clear why. But typical dietary studies examining reproducibility of dietary measures had much smaller sizes.

Authors reply: This paragraph has now been changed and the characterization of small has been removed line 301 to 305: “For this study we lost 50 % of the participants from the initial baseline sample as we wanted to measure the same group of people at two different time points. Two reasons were responsible for the loss of participants. Men dying between 1985 and 1990 and men non-responding (22%) at the follow-up examination, which might result in a “more healthy” population in comparison to the general Dutch population.”

On line 276-277, “attenuation factors were low” is not clear what it means. Attenuation for what and which “low” means good or bad should be described.

Authors reply: Attenuation was replaced by a description in more general terms line 309-312: “A reproducibility study on the performance of the cross-check dietary history method examined in the Zutphen Study revealed that measurement error of the a cross-check dietary history method was small.”

Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests.
Reviewer's report

Title: Stability of dietary patterns assessed with reduced rank regression; the Zutphen elderly Study

Version: Date: 21 October 2013

Reviewer: Gina Leslie Ambrosini

Reviewer's report:

OVERALL COMMENTS

This is a small cohort study of elderly men in The Netherlands (n=467). The paper aims to describe the stability of dietary patterns in these men after five years of follow up. The authors attempted to identify dietary patterns using reduced rank regression (RRR). The authors' empirical approach is encouraging. However, what could have been a quite straightforward analysis identifying patterns in food intake associated with a set of CVD risk factors, is a quite complicated manuscript. The main purpose of this paper is lost within the complex and numerous methodologies applied and the point of the RRR analysis is almost lost along the way. This manuscript would benefit from simplification.

MAJOR COMPULSORY REVISIONS

1. My major concerns relate to the reasons for, and approach by which, the authors reduced the number of food groups in their RRR pattern analysis. Firstly, it is not clear why the authors decided to apply the ‘Van de Voet’s test’ to identify the optimal number of dietary patterns in their RRR analysis (initially based on 36 food groups). RRR always produces the same number of patterns as there are response variables. Unlike PCA or FA, decisions regarding the number of patterns are not necessary with RRR, but rather, which of the resulting patterns explain a sufficient amount of variation and are most interpretable, to take forward. In this analysis, six patterns would have been identified, by default.
Authors reply regarding why Van der Voets test was used: As mentioned in the manuscript line 130 Heroux et al. previously used cross validation and the Van der Voet’s test to choose a meaningful number of dietary patterns. A non-significant Van der Voet test indicate that some food groups are irrelevant in explaining variation and cause noise and therefore instability of dietary patterns. This does not necessarily mean that the derived RRR pattern does explain a low percentage in response variables, but excluding irrelevant components from the analysis minimize the noise and result in a significant p-value for Van der Voet’s and presumably result in more stable patterns.

Line 129 is now revised: “Random sample cross-validation and subsequent Van der Voet’s test [...] were used to define the number of dietary patterns, that best predict response variables and exclude chance findings of correlations.”

Regarding reviewer comment:’ RRR produce number of patterns according to response’: We agree that six patterns would have been derived by default of which the first pattern always explains the most variation in response variables. However, the Van der Voet’s test shows how many dietary patterns add significantly to the explanation of response variables.

2. The authors report that ‘ no dietary pattern based on the initial 36 a-priori defined food groups could be derived to explain the six chosen response variables’. This raises concerns about the appropriateness of RRR using the defined response variables, in this dataset. Do the authors mean that no single pattern explained a sufficient amount of variation in all response variables (and by what criteria) ? If so, is this a reasonable expectation, given the number and selected response variables ? Or did none of the patterns explain any/much variation ? These important points are unclear.

Authors reply: We would like to respond to the first statement as the answer connects to the other parts of the comment.

1. Our previous expression ‘ no dietary pattern based on the initial 36 a-priori defined food groups could be derived: ’ is now revised line 138-141: In the initial analyses, the Van der Voet’s test indicated that no dietary pattern, based on 36 a-priori defined food groups, was able to optimally predict the six response variables. Derived patterns were strongly influenced by chance findings.

3. In response to the poor fit of the RRR model (or inability to explain variation in response variables), the authors reduced the number of food groups in the RRR
pattern analysis. They went about identifying those food groups ‘most associated’ with the response variables, by regressing all food groups onto the individual response variables. Food groups were eliminated using a backward regression model. The RRR analysis then attempted to find patterns in the 19 remaining food groups that were associated with the response variables. Line 281 (conclusions): ‘Backwards elimination to select a limited number of food (sub)groups related to the risk factors increased the reproducibility of the procedure and yielded two relatively stable patterns in our dataset’. This is probably not surprising, given that the authors only included food groups in their RRR that had an association with the response variables. I doubt this approach to improve the RRR model is appropriate. Does this potentially circular approach increase the probability of finding similar patterns at both time points? Can the authors assure that this approach does not bias their RRR analysis?

Authors reply: We understand this part of the methods is not clear:

a. We do not believe that the circular approach does bias our result as the only food group included which was found to be important for 1990 and not in 1985 was wine (not included in the manuscript).

b. In the discussion we now mention (line 267-281): The decision for Backwards elimination prior to the RRR analysis was taken based on the result of the Van der Voet’s test and was influenced by the approach chosen by Weismayer et al.[6] and Newby et al.[5]. Both authors applied confirmatory factor analysis, meaning factor analysis was applied twice. After the first run of factor analysis those food groups with highest factor loadings were selected on which the second run of factor analysis was applied. As factor loadings represent the bivariate correlation between food groups and derived food patterns, our backwards approach resembles a simplified form of what is called confirmatory factor analysis. Instead of correlation coefficients (equivalent to loadings), regression coefficients (equivalent to weights) were used. Weismayer et al.[6] reported that confirmed factor scores were slightly stronger correlated over time (healthy pattern 0.57 vs. 0.63 after 5 years) and Newby et al.[5] concluded that confirmatory factor scores were highly correlated with exploratory scores and reproducible over time. Therefore, we assume that our analysis gained in quality by the application of backwards regression. It is important to mention that confirmatory factor analysis should not be mixed with confirmatory RRR as applied for the current analysis.
4. The authors refer to their methods as similar to those applied by Schulze et al (ref 22) to obtain a ‘simplified score’. However, Schulze et al did this for a different purpose: to cross validate a dietary pattern from one subset of participants in the Nurses Health Study (NHS) to two other subgroups that did not have response (biomarkers) data. Furthermore, Schulze applied a ‘simplified score’ in the EPIC Study, but AFTER a PCA analysis using all food groups. The simplified dietary pattern scores were simply based on scoring weights from a smaller number of foods (only those loading highest on the pattern). It appears that the authors have done something very different here.

Author’s reply: We highly appreciate this comment as it appears that in the jungle of vocabulary we might have accidentally chose the wrong reference for the point we wanted to make. Indeed, the references for Schulze et al. should and has now been replaced by Newby et al. (Ref.5) who applied the so called confirmatory factor analysis.

As stated by Newby et al. “In this study, we tried to confirm factors that were suggested both by the exploratory factor analysis [...] We tested each of the explored factors in separate confirmatory models, in which food groups with factor loadings >=0.20 from the exploratory analysis were entered as independent terms. For example, we entered the processed meat, meat, liver, refined grains, legumes, potatoes, eggs, reduced-fat dairy,[...] For both explored and confirmed factors, factor scores were calculated for each participant for each of the factors at each time point. The standardized intakes of each of the food groups (mean 0, SD 1) were weighted by their factor loadings and summed (16). Thus, each individual received a factor score for 4 unique food patterns (i.e., explored in 1987, explored in 1997, confirmed in 1987, and confirmed in 1997).”

5. Line 256 The authors state ‘Regarding the number of food groups we applied an objective method that allowed the inclusion of the most important food groups for CVD risk factors’ in the RRR analysis. If the most important food groups for CVD are identified using this backward regression method, then the RRR analysis appears redundant. What does RRR bring to this analysis if you have already established which food groups are associated with the response variables of interest (CVD risk factors)? This is unclear. Why are dietary patterns
being examined in this study at all? There needs to be a more clear rationale (early in paper).

Author’s reply: We agree with the reviewer that this sentence was confusing. We have eliminated the above mentioned sentence and explained the rational of backwards regression more thoroughly in line 267 onwards as described earlier.

Direct reaction on statements below: Based on backwards regression we were able to minimize the number of food groups to those that are most important regarding the chosen risk factors. A “reduced” pattern as described by Newby et al. would do a similar thing whereas the decision is based on factor loadings (correlation coefficients) instead of regression coefficients.

By simply performing backwards regression we would not know how the single components interact with each other. Furthermore, our objective was to gain knowledge for future epidemiological studies using this method for the assessment of diet disease relationships. RRR would be useless for studies like EPIC having only baseline dietary data assessed. If RRR can produce stable patterns over time this method becomes useful in epidemiological studies.

We have changed our introduction according to the reviewer comments line 68-70.

“Therefore, we assessed the long-term stability of dietary patterns derived from RRR in elderly men on the population level to learn more about RRR analysis and possible implications for nutritional epidemiological research.”

6. Oddly, the resulting RRR patterns (based on 19 food groups) explain so little of the variation in response variables, again, it is questionable whether these data are suitable for the proposed analysis. Only 8% of the variation in all response variables was explained by the dietary patterns – more than the explained variation in food groups, which is concerning, as the aim of RRR is to explain the variation in response variables, not food groups. 8% is also very low, considering that the authors undertook a complicated process to include food groups that had an association with the response variables in their RRR analysis.

Did the authors consider reducing the number of response variables instead of food groups?

Author’s reply: Excluding food groups from the analysis increases stability but does not increase the variation explained. One does expect low percentages of variation explained in response variables if biomarkers are applied. Similar percentages in variation explained were
found by Heroux et al. The first pattern they derived by RRR explained 4.3% of variation in all biomarkers used (uric acid, BMI, HDL-cholesterol, Triglycerides, White blood cells, mean arterial pressure, fasting glucose, total cholesterol).

The decision for the response variables was done a-priori and we did not consider to change the constellation.

7. More detail would be helpful on why the six response variables were chosen together as a response set rather than just individually. For example, what is the rationale for including both total cholesterol and HDL cholesterol as response variables? Uric acid and blood pressure?

Authors reply: All variables are independent risk factors for CVD mortality. We do not expect a higher value for variation explained by reducing the number of biomarkers.

As mentioned in the manuscript: The risk factor selection was based on prior knowledge[19-22] and were also previously applied in studies for the purpose of RRR analysis[23, 24].

8. How were individuals who were taking lipid-lowering drugs or antihypertensives handled in the RRR analysis? How might this impact the RRR dietary patterns?

The number of lipid lowering drug users in 1990 (N=467) was low: 4 lipid lowering drug users. The number of antihypertensive drug users was 143. We do not expect that these numbers would greatly influence our results.

We expect excluding participants with chronic diseases at baseline (sample size after exclusion of chronic diseases N=368) to reduce the number of drug users even more. Lines 235-238 describe that the correlation coefficients between dietary pattern 1985 and 1990 of participants without chronic diseases showed only slightly greater stability in dietary patterns over time (r=0.50 compared to r=0.47 initial sample).

9. Line 64-67 One of the main advantages of RRR is seen as it being a hypothesis testing method i.e. it can be used to test defined pathways between diet and health outcomes (it depends on a-priori information as response variables); it is NOT known as a hypothesis generating method. I am yet to be convinced by the latter viewpoint presented by the authors.

Authors reply: Lines 64 to 67 were excluded as suggested by the other reviewer.

Tucker et al. described RRR as: “maximizes associations between food group intakes and risk markers; as such, it may lead to new hypotheses”.
10. Line 72 – the stability or tracking of an RRR dietary pattern has been reported previously by others (see Ambrosini GL et al. Obesity, 2013). The reference (7) by Wosje reported dietary pattern factor loadings, not correlation coefficients (reflecting stability) over time. Furthermore, Wosje et al inappropriately included their outcomes of interest (bone and fat mass) as response variables in their RRR analysis, which would have biased the observed associations between their dietary patterns and outcomes.

Authors reply: The introduction is now revised and the reference of Wosje et al. has been excluded.

Previously, RRR has been used to derive dietary patterns associated with risk factors from baseline data for the analysis of chronic diseases and for tracking dietary patterns in children[10]

MINOR ESSENTIAL REVISIONS

11. Abstract - RRR incorporates both exploratory and a-priori components

Authors reply: The abstract has been revised. The following background information is now included line 23: “Reduced rank regression (RRR) combines exploratory analysis with a-priori knowledge by including risk factors in the model.”

12. Line 33 is unclear

Authors reply: Line 26 in the updated manuscript (previously line 33) has been adapted to: “Our aim was to assess the stability of dietary patterns derived by RRR and evaluate the use of RRR for subsequent diet disease analysis.”


Authors reply: The abstract mentions the following now line 37, 38: “correlation coefficient of 0.47 (95% CI: 0.38-0.53)”

14. Abstract - Why are these dietary patterns attractive? Are they associated with disease or health outcomes?

Authors reply: The following sentence is included in the abstract line 24-26: “Dietary patterns derived from RRR analysis can be interpreted by the chosen risk factor profile and give an indication of positive or adverse health effects for a specific disease.”

15. Line 59 the RRR method does not ‘belong’ to Hoffman et al. Reduced rank
regression has been around as a statistical method for much longer, and applied in other disciplines.

Authors reply: We included the word to nutritional science to be more concise: “A more sophisticated method to study dietary patterns is called RRR and was introduced to nutritional epidemiology by Hoffmann et al.”

16. Lines 60-68 is confusing to newcomers to RRR and probably not necessary

Authors reply: These lines are now excluded.

17. There could be greater emphasis on the fact this is looking at population level stability, not at the individual level, in the most part. This is not well distinguished at present.

Authors reply: statement about the population level is important and we have added this information in the introduction (page 71, line 69)

18. Was the dietary assessment method validated?

Authors reply: Yes, please find line 311: “A reproducibility study on the performance of the cross-check dietary history method examined in the Zutphen Study revealed that measurement error of the cross-check dietary history method was small [32].”

19. Can the authors consider the impact of including fewer food groups in the RRR analysis, in terms of interpretability of the patterns?

Authors reply: We included the following information in the results (line 239-244); Correlation coefficients between dietary patterns derived from RRR using 36 food groups in the full (n=764) and reduced sample (n=467) of 1985 were high (correlation coefficient comparing 467 participants of the full and reduced sample r=0.75). The full study sample of 764 participants showed significant cross validation tests for 36 food groups. However, comparability of the patterns derived in the full and reduced sample increased after backwards regression (r =0.86).

Line 308, 309: The current manuscript focussed on the methodology of RRR and the potential of RRR to derive stable dietary patterns over time.

20. 143-146 This can be simplified as every individual received a z-score for each of the derived dietary patterns

Authors reply: The above mentioned sentence has been changed as follows: “Finally, we ran exploratory RRR analysis independently for 1985 and 1990 and assigned a z-score per individual for each of the derived patterns for both study years.”
22. Line 150-152 it is not immediately clear why confirmatory RRR was used. Here

Authors reply: The sentence has been replaced by the following line 155, 156: “We ran a confirmatory RRR analysis to differentiate the influence of food group consumption and changes in biomarker profile over time on the stability of dietary patterns.”

23. 159-164 Justification for each sensitivity analysis would be helpful

Authors reply: Different opinions exist whether dietary patterns should be analysed with or without adjustment for energy intake. We elaborate on this issue in the discussion section. As there is still discussion whether dietary patterns need energy adjustment at all, we considered this analysis as an addition to the current discussion.

For the other sensitivity analysis we included the following lines 169 176: “BMI was excluded from the response set to ascertain that dietary patterns derived are not solely BMI driven; separate RRR analyses were performed in participants without chronic diseases (myocardial infarction, stroke, diabetes or cancer) at baseline, as epidemiological studies often exclude participants with prevalent diseases; and finally, to assess the influence of reducing the study sample on the derived dietary patterns, RRR was additionally applied to the full study population of 763 participants in 1985 (describing the sample prior exclusion of participants dying between 1985 and 1990).”

24. What are the implications of using non fasting lipids as response variables?

Authors reply: We expect no different results for the RRR analysis if fasting lipid values were included. Langsted et al. (Langsted A, Freiberg JJ, Nordestgaard BG: Fasting and nonfasting lipid levels influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. Circulation 2008, 118:2047-2056) conclude “Lipid profiles at most change minimally in response to normal food intake in individuals in the general population”.

25. Why was pattern 3 included if it was difficult to interpret and there was no consistency between this pattern at baseline and follow up? Why was this pattern not ignored, like the other three patterns that have not been described.

Authors reply: Indeed, we could have removed the third pattern but we decided to base our decision on the Van der Voets test. By showing 3 dietary patterns instead of one, readers of the manuscript less familiar with RRR can see what factors do influence the stability of dietary patterns. Least explained variation in food groups reveals least stable patterns.

26. Line 191 There is not data in the tables (showing fibre or other nutrient intakes) to support this statement.

Authors reply: Where applicable, the word fibre has been replaced by fibre intake from cereals and bread.
27. The relatively small sample size and the potential limitations of this on the RRR analysis deserves acknowledgement.

Authors reply: We consider the sample for a stability analysis as a reasonable sample size. Previous studies even used smaller sub-samples of about 90 participants like for instance Bountziouka et al. (ref. 3). We give additional explanations for the reasons of the small sample size and implications on the results in line 302 to 306.

28. The authors could consider the potential limitations of using biomarkers as response variables in their RRR analysis.

Authors reply: We first included a thorough paragraph on the disadvantages of biomarkers but finally decided to mention this issue only shortly(line 260-263)”The application of RRR has some disadvantages [...] differences in derived food patterns could be caused by changes in risk factors over time”. The reason for a short sentence was that we consider the biomarker approach overall as an advantage. Even though the variation explained in biomarkers is often low (<10%) the profit is related to the derivation of patterns that are highly likely to be associated with the outcome of interest.

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests