# **Dietary patterns,** biomarkers of atherosclerosis, cardiovascular and all-cause mortality

Femke PC Sijtsma

# **Dietary patterns,** biomarkers of atherosclerosis, cardiovascular and all-cause mortality

Femke PC Sijtsma

## Thesis committee

### Promotors

Prof. Dr Kromhout

*Professor of Public Health Research*
*Wageningen University*

Prof. Dr D.R. Jacobs

*Professor, Epidemiology & Community Health*
*University of Minnesota, Minneapolis, USA*

### Co-promotor

Dr S.S. Soedamah-Muthu

*Assistant professor, Division of Human Nutrition*
*Wageningen University*

### Other members

Prof. Dr P. van 't Veer, *Wageningen University*
Prof. Dr M. Visser, *VU University Amsterdam*
Prof. Dr P.A. van den Brandt, *Maastricht University*
Dr J.A. Iestra, *UMC Utrecht*

This research was conducted under the auspices of the Graduate School VLAG
(Advanced Studies in Food Technology, Agrobiotechnology, Nutrition and Health Sciences)

# **Dietary patterns,**
biomarkers of
atherosclerosis, cardiovascular
and all-cause mortality

Femke PC Sijtsma

**Thesis**
submitted in fulfilment of the requirements for the degree of doctor
at Wageningen University
by the authority of the Rector Magnificus
Prof. Dr A.P.J. Mol,
in the presence of the
Thesis Committee appointed by the Academic Board
to be defended in public
on Thursday 5 November 2015
at 11 a.m. in the Aula.

Femke Sijtsma
Dietary patterns, biomarkers of atherosclerosis,
cardiovascular and all-cause mortality
208 pages.

PhD thesis, Wageningen University, Wageningen, NL (2015)
With references and summary in English

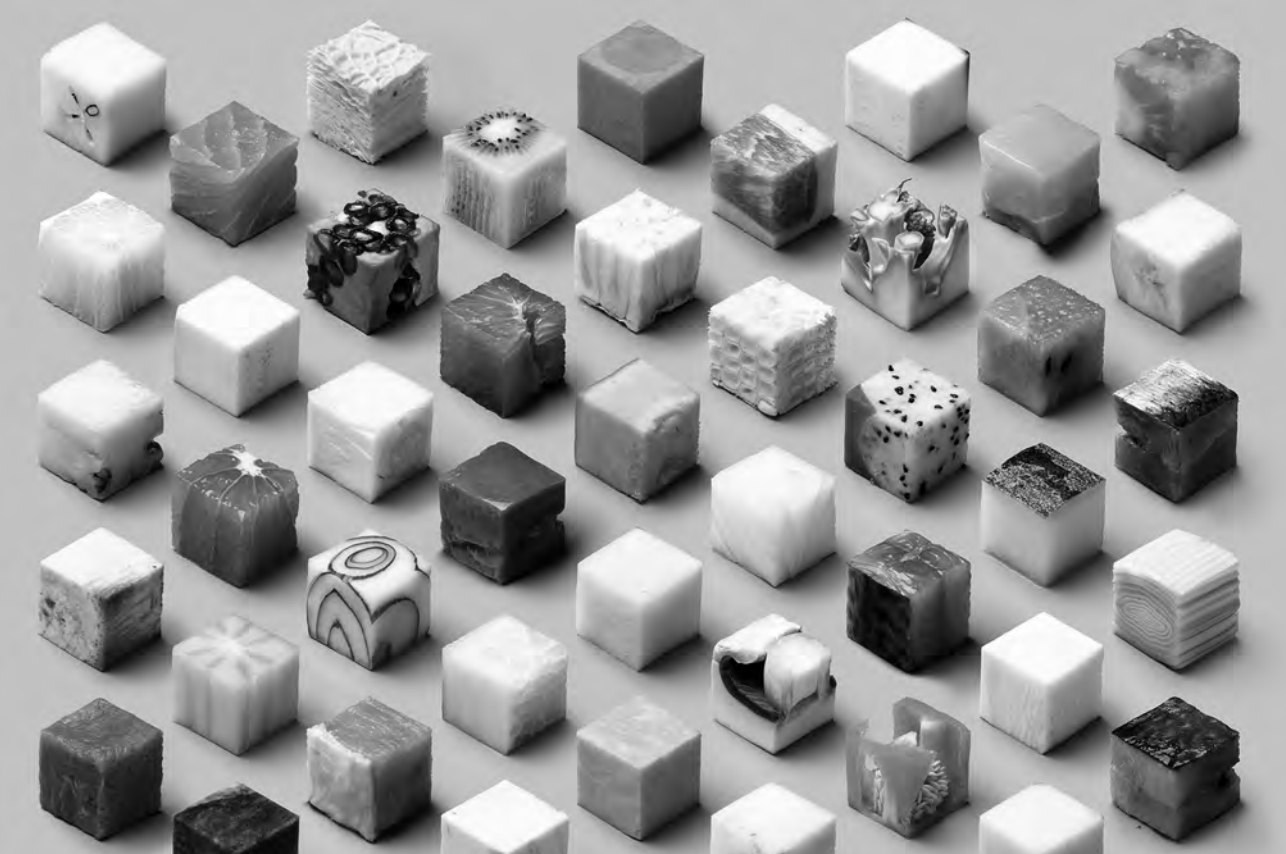
ISBN 978-94-6257-549-3

## CONTENTS


| | | |
|---|---|---|
| **Chapter 1** | General introduction | 7 |
| **Chapter 2** | Longitudinal trends in diet and effects of sex, race, and education on dietary quality score change: the Coronary Artery Risk Development in Young Adults study | 19 |
| | Supplemental Material | 37 |
| **Chapter 3** | Diet quality is prospectively associated with markers of endothelial function: the CARDIA study | 49 |
| | Supplemental Material | 65 |
| **Chapter 4** | Dietary patterns are associated with plasma F2-isoprostanes in an observational cohort study of adults | 71 |
| | Supplemental Material | 93 |
| **Chapter 5** | Classification of foods based on dietary guidelines for nutrition education and food-based dietary scores, an example from the Netherlands | 101 |
| | Supplemental Material | 113 |
| **Chapter 6** | Healthy eating and lower mortality risk in a large cohort of cardiac patients who received state-of-the-art drug-treatment | 121 |
| | Supplemental Material | 138 |
| **Chapter 7** | Healthy eating and survival among elderly men with and without cardiovascular-metabolic diseases | 147 |
| | Supplemental Material | 164 |
| **Chapter 8** | General discussion | 173 |
| | English summary | 187 |
| | Dankwoord \| Acknowledgments | 193 |
| | **About the author** | 201 |
| | Curriculum Vitae | 203 |
| | List of publications | 205 |
| | Overview of completed training activities | 207 |

# 1

# General introduction



Dietary patterns are multiple dietary components operationalized as a single exposure; they reflect entire diets [1, 2]. The long history of epidemiologic study into diet and cardiovascular disease (CVD) has traditionally relied on analysis of specific nutrients or foods [1-3]. Because they reflect real-world dietary preferences, dietary patterns might be easier to interpret and communicate than findings for nutrients or individual foods. The dietary pattern approach, as opposed to nutrient- or individual-food-based analysis, has become increasingly popular over the past decade.

The use of dietary patterns as a single exposure has increased for several reasons. First, it is often difficult to separate the specific effects of nutrients or food groups because of the highly interrelated nature of dietary exposures [4]. Also, neither nutrients nor foods are consumed singly, and important synergy among and within foods likely exists, where the joint effect of the diet's constituent parts may be greater than the individual effects of single foods and nutrients [1, 2].

Furthermore, observational evidence for some specific nutrients have been contradicted by large randomized controlled trials [5, 6] suggesting that findings from observational studies may represent a broader role of diet. However, an intervention trial, the Dietary Approached to Stop Hypertension with an overall diet focus, was successful in demonstrating that dietary patterns can favorably affect blood pressure, a major CVD risk factor [7]. Furthermore, two intervention studies investigating Mediterranean dietary patterns the Lyon Diet-Heart Study [8] and the Prevención con Dieta Mediterránea (PREDIMED) [9] showed protective effects in prevention of cardiovascular events. It has been suggested that, for making public health recommendations, dietary patterns might be easier to interpret or translate into diets than individual foods and nutrients.

## Dietary patterns in epidemiology

In general, two types of methods are used to define dietary patterns: 1) theoretically, or *a priori*, defined dietary scores and 2) empirically, or *a posteriori*, derived dietary patterns.

*A priori* dietary scores have been developed to assess diet quality based on adherence to dietary patterns or recommendations [10, 11]. In addition to dietary-guideline-based indices, such as the 'Healthy Eating Index', examples of other *a priori* patterns include the 'Dietary Approaches to Stop Hypertension index', and cultural diets, such as traditional Mediterranean, Japanese, or vegetarian diets. A review of dietary quality indices documented 20 distinct indices of overall diet quality [10]. Among these, the 'Healthy Eating Index' [12] and 'Alternate Healthy Eating Index' [13], the 'Healthy Diet Indicator' [14], and the 'Mediterranean Diet Score' [15] have been studied most extensively.

Many of the existing diet scores include both nutrient recommendations and foods or food groups. It is recognized that nutrient-based targets are difficult to

interpret by the public, therefore, for dietary guidance at minimum translation of nutrients to foods is needed [16, 17]. As a consequence, food-based *a priori* scores have the advantage that they are easier to translate into diet recommendations. There are several difficulties in creating a food-based dietary score, however, as there are no specific guidelines on which foods should be included or how foods should be scored.

Another way of examining dietary patterns is an '*a posteriori*' approach. Factor analysis (e.g. principal components analysis (PCA)) and cluster analysis [18] are two commonly used methods to derive dietary patterns [19]. Factor analysis reduces data into patterns based upon intercorrelations between dietary items, whereas cluster analysis reduces data into patterns based upon individual differences in mean intakes [19]. Recently, the treelet transform has been introduced as a combination of PCA and cluster analysis [20].

PCA is commonly used to define dietary patterns. PCA derived patterns or components are direct linear relationships of the underlying dietary variables. The derived dietary pattern variables explain as much as possible of the total variation of the original dietary variables [21]. Each participant receives a factor score for each derived pattern representing the level of adherence to that dietary pattern. Because the *a posteriori* approaches generate patterns based on available empirical data without *a priori* hypothesis they do not necessarily represent optimal diets [2]. However, they do allow us to gain insight into existing food consumption patterns within the populations and patterns that may be associated with higher or lower health risk.

## Dietary patterns, endothelial function, oxidative stress, CVD and all-cause mortality

Both *a priori* and *a posteriori* approaches have yielded significant associations with a range of early stage markers of CVD. Generally, the literature supports a role for dietary patterns in CVD-related outcomes, with a protective influence of plant-based diets (e.g., dietary patterns rich in fruit, vegetables, and whole grains, and low in meat and refined grains) and negative influence of diets high in meat and refined grains.

Observational studies showed that higher scores on diet quality indices such as a 'Mediterranean Diet Score' and 'Alternative Healthy Eating Index' were associated with lower concentrations of the endothelial function markers: E-selectin, soluble intercellular cell adhesion molecule 1 (sICAM-1), and soluble vascular cell adhesion molecule 1 (sVCAM-1) [22]. Similarly, an *a posteriori* dietary pattern labelled as 'Prudent' characterized by higher intakes of fruit, vegetables, legumes, fish, poultry, and whole grains was associated with lower concentrations of E-selectin, and a

dietary pattern labelled as 'Western' characterized by higher intakes of red and processed meats, sweets, desserts, French fries, and refined grains was associated with higher concentration of E-selectin, sICAM-1 and s-VCAM-1 [23]. A 'Whole Grain and Fruit' [24] dietary pattern characterized by whole grains, fruit, nuts, and green leafy vegetables was inversely associated with sICAM-1.

There are few studies of oxidative stress and dietary patterns. Two intervention studies provided evidence for the relation of dietary patterns with oxidative stress. Lopes et al. found that among free-living obese hypertensives the 'Dietary Approaches to Stop Hypertension Combination Diet' reduced oxidative stress induced by acute hyperlipidemia [25]. Miller et al. found that modification of diet can favorably affect serum antioxidant capacity and protect against lipid peroxidation in a randomized trial [26]. Furthermore, two studies showed beneficial effects of fruit and vegetable intake on markers of oxidative stress [27, 28].

A lower risk of CVD and all-cause mortality has been associated with several indices of diet quality. For example, in observational studies associations of CVD and all-cause mortality have been shown with the 'Mediterranean Diet Score' [29-31], the 'Alternative Healthy Eating Index' [13], the 'Healthy Diet Indicator' [14, 29] and the 'Recommended Food Score' [13, 32, 33].

## Variability in findings of dietary patterns with early stage markers of CVD and mortality

There remains significant variability across studies in how dietary patterns are operationalized and modeled in statistical analysis. Variability in study findings of dietary patterns and scores with cardiovascular outcomes indicate that additional work is needed to better understand underlying dynamics of dietary patterns.

For example, a study comparing the association of several *a priori* dietary scores with early markers of CVD risk found associations for the 'Alternative Healthy Eating Index' and 'alternate Mediterranean Diet Index' but not for the 'Healthy Eating Index' and 'Diet Quality Index Revised' [22]. Similarly, comparing several *a posteriori* dietary patterns, a principal components analysis-derived 'American Healthy' dietary pattern was not associated, but a 'Western' dietary pattern was positively associated with early stage markers of CVD risk [34].

Studies on dietary indices and CVD outcomes have reported differences in estimates of the strength of the associations comparing two *a priori* patterns. McCullough et al. found that the 'Alternative Healthy Eating Index' was inversely associated with CVD risk in both men and women, whereas the 'Recommended Food Score' was not associated with CVD risk in women [13]. Similarly, Michels et al. showed a significant inverse association for an *a priori* 'Recommended Food Score', but no association for a 'Not Recommended Food Score' with CVD and all-cause mortality [33].

Comparing several *a posteriori* patterns Fung et al. showed that a 'Prudent' dietary pattern was not associated, but a 'Western' dietary pattern was positively associated with stroke risk [35]. Comparing *a priori* and *a posteriori* patterns in the same study sample, Osler et al. found no association for the 'Healthy Food Index' and the PCA derived 'Western' pattern with coronary heart disease. The PCA derived 'Prudent' pattern was associated with a lower risk of coronary heart disease but lost significance after controlling for confounding. Furthermore, the associations with the PCA derived dietary patterns were modified by BMI [36].

Studies that compared multiple diet scores suggested that solely food-based diet scores are better predictors of mortality than scores based predominantly on nutrient intakes, or combination of nutrients and foods [37-39]. Studies in the elderly suggested that dietary patterns were associated with mortality risk in elderly under 80 years of age but not in elderly older than 80 years [40] or only in those aged under 75 years [41].

Therefore, investigations comparing several methodological approaches in a single dataset are needed to better understand the sensitivity of findings to dietary pattern construction and to better understand different dietary patterns with respect to foods, nutrients, and as measures of dietary quality. Furthermore, associations of diet defined by different methodological approaches with CVD outcomes improves insight into the diet and CVD relationships .

## Rationale

Only few studies have evaluated and compared different methodological approaches to define dietary patterns in relation to the development of CVD within one study [42-44]. Also studies on the association of dietary patterns with early stage markers of CVD are limited and diverse in terms of study populations, study design and methods of defining dietary patterns. Further research is needed to investigate and compare several methodological approaches of dietary pattern analysis in predicting early stage markers of CVD and mortality. Furthermore, there are only a few solely food-based dietary scores, further research is needed to investigate methodology for creating food-based dietary scores and to investigate these scores in predicting mortality.

## OUTLINE OF THIS THESIS

The aim of this thesis is to create, examine and compare several dietary patterns and indices and assess these in relationship to both early stage markers of CVD (markers of endothelial function and oxidative stress) and CVD and all-cause mortality.

**Chapter 2** describes the creation of the '*A Priori* Diet Quality Score', representing overall diet quality. Furthermore, the longitudinal trends in diet and the effects of gender, race and education on diet pattern change will also be examined. **Chapter 3** describes prospective associations of the 'A Priori Diet Quality Score' and two dietary patterns derived using principal components analysis the 'Fruit and Vegetables' dietary pattern (characterized by high intakes of fruit, vegetables, and whole grains) and the 'Meat' dietary pattern (characterized by high intakes of red meat, refined grain, and butter) with cellular adhesion molecules (CAMs) E-selectin, P-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule (VCAM). **Chapter 4** describes prospective associations of the 'A Priori Diet Quality Score', 'Fruit and Vegetables' dietary pattern and 'Meat' dietary pattern and a plasma biomarker of lipid peroxidation, $F_2$-isoprostanes. The chapters 2-4 are all based on data from the Coronary Artery Risk Development in Young Adults (CARDIA) study. **Chapter 5** describes a food classification system derived from the Food-based Dietary Guidelines in the Netherlands that can be used to systematically and objectively classify foods in relation to their effects on health. This classification system also provides a framework to create food-based dietary scores for epidemiologic research on diet and chronic disease relationships. **Chapter 6** describes the creation of two dietary scores the 'Dutch Healthy Nutrient and Food Score' (DHNaFS) and the 'Dutch Undesirable Nutrient and Food Score' (DUNaFS) based on the food classification system described in chapter 5 in the Alpha Omega Trial. Furthermore, the association of these dietary scores with CVD and all-cause mortality in cardiac patients will be assessed. Similar food-based dietary scores will be created in the Zutphen Elderly study in **chapter 7**, in which we investigate the associations of the dietary scores with CVD and all-cause mortality in men with and without cardiovascular-metabolic diseases**. Chapter 8** discusses the main findings and implications of the different studies presented in this thesis.

## REFERENCES


1. Jacobs DR, Jr., Steffen LM. Nutrients, foods, and dietary patterns as exposures in research: a framework for food synergy. 2003;78: 508S-513.
2. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 2002;13:3-9.
3. Messina M, Lampe JW, Birt DF, Appel LJ, Pivonka E, Berry B, et al. Reductionism and the narrowing nutrition perspective: time for reevaluation and emphasis on food synergy. J Am Diet Assoc. 2001;101:1416-9.
4. Jacques PF, Tucker KL. Are dietary patterns useful for understanding the role of diet in chronic disease? Am J Clin Nutr. 2001;73:1-2.
5. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med. 1996;334:1145-9.
6. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. N Engl J Med. 1994;330:1029-35.
7. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med. 1997;336:1117-24.
8. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation. 1999;99:779-85.
9. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368:1279-90.
10. Waijers PM, Feskens EJ, Ocke MC. A critical review of predefined diet quality scores. Br J Nutr. 2007;97:219-31.
11. Kant AK. Indexes of overall diet quality: A review. J Am Diet Assoc. 1996;96:785-91.
12. Kennedy ET, Ohls J, Carlson S, Fleming K. The Healthy Eating Index: design and applications. J Am Diet Assoc. 1995;95:1103-8.
13. McCullough ML, Feskanich D, Stampfer MJ, Giovannucci EL, Rimm EB, Hu FB, et al. Diet quality and major chronic disease risk in men and women: moving toward improved dietary guidance. Am J Clin Nutr. 2002;76:1261-71.
14. Huijbregts P, Feskens E, Rasanen L, Fidanza F, Nissinen A, Menotti A, et al. Dietary pattern and 20 year mortality in elderly men in Finland, Italy, and The Netherlands: longitudinal cohort study. BMJ. 1997;315:13-7.
15. Trichopoulou A, Kourisblazos A, Wahlqvist ML, Gnardellis C, Lagiou P, Polychronopoulos E, et al. Diet and Overall Survival in Elderly People. Brit Med J. 1995;311:1457-60.
16. Willett WC, Ludwig DS. The 2010 Dietary Guidelines--the best recipe for health? N Engl J Med. 2011;365:1563-5.
17. Mozaffarian D, Ludwig DS. Dietary guidelines in the 21st century--a time for food. JAMA. 2010;304:681-2.
18. Devlin UM, McNulty BA, Nugent AP, Gibney MJ. The use of cluster analysis to derive dietary patterns: methodological considerations, reproducibility, validity and the effect of energy mis-reporting. Proc Nutr Soc. 2012;71:599-609.
19. Newby PK, Tucker KL. Empirically Derived Eating Patterns Using Factor or Cluster Analysis: A Review. Nutr Rev. 2004;62:177-203.
20. Gorst-Rasmussen A, Dahm CC, Dethlefsen C, Scheike T, Overvad K. Exploring dietary patterns by using the treelet transform. Am J Epidemiol. 2011;173:1097-104.
21. Ocke MC. Evaluation of methodologies for assessing the overall diet: dietary quality scores and dietary pattern analysis. Proc Nutr Soc. 2013;72:191-9.
22. Fung TT, McCullough ML, Newby PK, Manson JE, Meigs JB, Rifai N, et al. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr. 2005;82:163-73.

23. Lopez-Garcia E, Schulze MB, Fung TT, Meigs JB, Rifai N, Manson JE, et al. Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr. 2004;80:1029-35.
24. Nettleton JA, Steffen LM, Mayer-Davis EJ, Jenny NS, Jiang R, Herrington DM, et al. Dietary patterns are associated with biochemical markers of inflammation and endothelial activation in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 2006;83:1369-79.
25. Lopes HF, Martin KL, Nashar K, Morrow JD, Goodfriend TL, Egan BM. DASH diet lowers blood pressure and lipid-induced oxidative stress in obesity. Hypertension. 2003;41:422-30.
26. Miller ER, 3rd, Appel LJ, Risby TH. Effect of dietary patterns on measures of lipid peroxidation: results from a randomized clinical trial. Circulation. 1998;98:2390-5.
27. Holt EM, Steffen LM, Moran A, Basu S, Steinberger J, Ross JA, et al. Fruit and vegetable consumption and its relation to markers of inflammation and oxidative stress in adolescents. J Am Diet Assoc. 2009;109:414-21.
28. Thompson HJ, Heimendinger J, Haegele A, Sedlacek SM, Gillette C, O'Neill C, et al. Effect of increased vegetable and fruit consumption on markers of oxidative cellular damage. Carcinogenesis. 1999;20: 2261-6.
29. Knoops KT, Groot de LC, Fidanza F, Alberti-Fidanza A, Kromhout D, van Staveren WA. Comparison of three different dietary scores in relation to 10-year mortality in elderly European subjects: the HALE project. Eur J Clin Nutr. 2006;60:746-55.
30. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003;348:2599-608.
31. Osler M, Schroll M. Diet and mortality in a cohort of elderly people in a north European community. Int J Epidemiol. 1997;26:155-9.
32. Kant AK, Schatzkin A, Graubard BI, Schairer C. A prospective study of diet quality and mortality in women. JAMA. 2000;283:2109-15.
33. Michels KB, Wolk A. A prospective study of variety of healthy foods and mortality in women. Int J Epidemiol. 2002;31:847-54.
34. Kerver JM, Yang EJ, Bianchi L, Song WO. Dietary patterns associated with risk factors for cardiovascular disease in healthy US adults. Am J Clin Nutr. 2003;78:1103-10.
35. Fung TT, Stampfer MJ, Manson JE, Rexrode KM, Willett WC, Hu FB. Prospective study of major dietary patterns and stroke risk in women. Stroke. 2004;35:2014-9.
36. Osler M, Helms Andreasen A, Heitmann B, Hoidrup S, Gerdes U, Morch Jorgensen L, et al. Food intake patterns and risk of coronary heart disease: a prospective cohort study examining the use of traditional scoring techniques. Eur J Clin Nutr. 2002;56:568-74.
37. Reedy J, Krebs-Smith SM, Miller PE, Liese AD, Kahle LL, Park Y, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. J Nutr. 2014;144:881-9.
38. McNaughton SA, Bates CJ, Mishra GD. Diet quality is associated with all-cause mortality in adults aged 65 years and older. J Nutr. 2012;142:320-5.
39. Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. High diet quality is associated with a lower risk of cardiovascular disease and all-cause mortality in older men. J Nutr. 2014;144:673-80.
40. Lasheras C, Fernandez S, Patterson AM. Mediterranean diet and age with respect to overall survival in institutionalized, nonsmoking elderly people. Am J Clin Nutr. 2000;71:987-92.
41. Hamer M, McNaughton SA, Bates CJ, Mishra GD. Dietary patterns, assessed from a weighed food record, and survival among elderly participants from the United Kingdom. Eur J Clin Nutr. 2010;64:853-61.
42. Nettleton JA, Steffen LM, Schulze MB, Jenny NS, Barr RG, Bertoni AG, et al. Associations between markers of subclinical atherosclerosis and dietary patterns derived by principal components analysis and reduced rank regression in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 2007;85:1615-25.

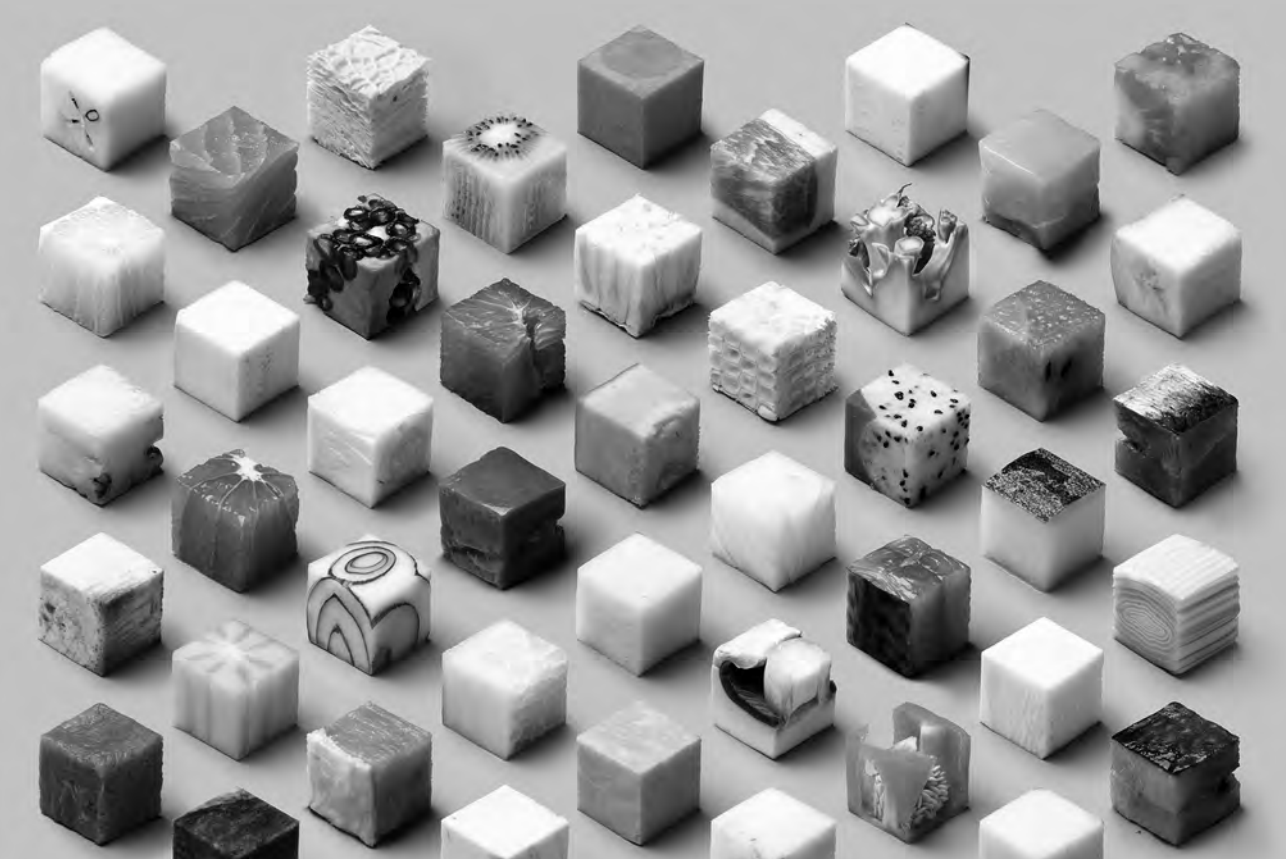
43. Osler M, Heitmann BL, Gerdes LU, Jorgensen LM, Schroll M. Dietary patterns and mortality in Danish men and women: a prospective observational study. Br J Nutr. 2001;85:219-25.
44. Panagiotakos DB, Pitsavos C, Stefanadis C. Alpha-priori and alpha-posterior dietary pattern analyses have similar estimating and discriminating ability in predicting 5-Y incidence of cardiovascular disease: methodological issues in nutrition assessment. J Food Sci. 2009;74:H218-24.

# 2

# Longitudinal trends in diet and effects of sex, race, and education on dietary quality score change: the Coronary Artery Risk Development in Young Adults study

Femke PC Sijtsma, Katie A Meyer, Lyn M Steffen, James M Shikany, Linda Van Horn, Lisa Harnack, Daan Kromhout, David R Jacobs Jr

Am J Clin Nutr 2012;95:580–6.



## ABSTRACT

**Background:** The food supply and dietary preferences have changed in recent decades.

**Objective:** We studied time- and age-related individual and population-wide changes in a dietary quality score and food groups during 1985–2006.

**Design:** The Coronary Artery Risk Development in Young Adults (CARDIA) study of 5115 black and white men and women aged 18–30 y at year 0 (1985–1986) assessed diet at examinations at study years 0, 7 (1992–1993), and 20 (2005–2006). The dietary quality score, which was validated by its inverse association with cardiovascular disease risk, summed 46 food groups rated by investigators as positive or negative on the basis of hypothesized health effects. We used repeated-measures regression to estimate time specific mean diet scores and servings per day of food groups.

**Results:** In 2652 participants with all 3 diet assessments, the mean (±SD) dietary quality score increased from 64.1 ± 13.0 at year 0 to 71.1 ± 12.6 at year 20, which was mostly attributable to increased age. However, the secular trend, which was estimated from differences of dietary quality scores across time at a fixed age (age matched time trend), decreased. The diet score was higher in whites than in blacks and in women than in men and increased with education, but demographic gaps in the score narrowed over 20 y. There tended to be increases in positively rated food groups and decreases in negatively rated food groups, which were generally similar in direction across demographic groups.

**Conclusions:** The CARDIA study showed many age-related, desirable changes in food intake over 20 y of observation, despite a secular trend toward a lower diet quality. Nevertheless, demographic disparities in diet persist.

## INTRODUCTION

Food availability, supply, and environment changed considerably between 1985 and 2006. There have been a variety of international dietary recommendations for reducing risk of ischemic heart disease. Recently, recommendations have begun to emphasize particular food groups, which may be easier for the population to implement. The 1985 US Dietary Guidelines [1] encouraged increased intakes of fruit and vegetables; however, in the 2010 US Dietary Guidelines [2], food-group recommendations have been extended and advise a shift in food intake to a more plant-based diet that emphasizes fruit, vegetables, legumes, whole grains, nuts, and seeds. In addition, increased intakes of seafood and low-fat dairy products and consumption of only moderate amounts of lean meats, poultry, and eggs were likewise recommended [2]. Recommendations are ultimately intended to guide the public to a healthful diet; compared with nutrient recommendations, food recommendations have been more stable and may be easier for the population to implement. However, more information is needed about whether earlier recommendations correspond to actual changes in dietary intakes in the general population and whether changes are different in socio-demographic groups.

Some data suggested that diet quality has improved over recent decades despite population-wide weight gain, but secular trends and age effects were not distinguished [3]. Because people age from young adulthood to middle age, they tend to improve their diet [4–6]. In contrast, one study reported an unfavorable secular diet quality trend and a lower proportion of the population who met the national recommended nutrient and food intakes in 2 cross-sectional studies in 2000 and 2005 [7]. Some reports of trends in food-group and nutrient intakes have focused on differentials by sex [3, 8], race, or education [9]. The Coronary Artery Risk Development in Young Adults (CARDIA) study reported that the Keys score, which is a measure of the tendency of diet to alter serum cholesterol, tended to decrease in young adult between 1985–1986 and 1992–1993, which was similar for black and white men and women and concordant with a secular trend toward lower serum cholesterol, despite increasing obesity [10]. These studies documented demographic differences in diet that did not narrow over time [8–10]. Furthermore, during the last few decades, major societal changes in the food environment have occurred. Fast-food availability and consumption has increased greatly [11], and restaurant portion sizes have increased [12]. The production and availability of processed foods, including boxed or packaged and frozen foods, increased [13].

We used an *a priori* diet score that has been validated as a measure of dietary quality in that it is a predictor of myocardial infarction [14], diabetes [15], and variables that are apparently on the causal pathway for clinical cardiovascular disease [16, 17]. The *A Priori* Diet Quality Score is novel in that it is based on *a priori* reasoning and solely on foods consumed rather than on nutrients.

In light of the societal influences mentioned, we compared CARDIA diet data between 1985–1986 and 2005–2006. We hypothesized that a secular trend toward a worse overall *a priori* diet quality exists but that certain improvements in dietary quality, such as an increased intake of phytochemical-rich plant food and decreased intake of red meat, would be evident and consistent with recent dietary recommendations. In addition, we hypothesized that these improvements in dietary quality would be age related and more common among certain socio-demographic strata, such as higher education, white race, and female sex (i.e. that demographic gaps would widen over 20 y).

## SUBJECTS AND METHODS

### Study sample

The CARDIA study is a multicenter, longitudinal investigation of the evolution of ischemic heart disease risk starting in young adulthood [18]. The CARDIA study began in 1985–1986 with 5115 black and white adults aged 18–30 y from 4 metropolitan areas (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). Study participants were sampled to obtain roughly equal numbers of blacks (51.5%) and whites (48.5%), men (45.5%) and women (54.5%), ages 18–24 y (44.9%) and 25–30 y (55.1%), and with a high school education or less (39.7%) or more than a high school education (60.3%). Among 6 follow-up examinations were those in 1992–1993 (year 7) and 2005–2006 (year 20). A majority of the surviving cohort membership has been examined at each of the follow-up examinations (81% of subjects at year 7 and 72% of subjects at year 20); 87% of subjects have attended ≥ 2 examinations at years 0, 7, and 20, and 63% of subjects attended all 3 examinations. Participants who attended a clinic but had no dietary data (n = 4, 143, and 406 at years 0, 7, and 20, respectively) or an implausibly high or low energy intake (<800 or >8000 kcal/d for men; <600 or >6000 kcal/d for women; n = 128, 94, and 54 at years 0, 7, and 20, respectively) were excluded from analysis. After exclusion, there were 4983, 3849, and 3089 participants with diet measured at years 0, 7, and 20, respectively, and 2652 participants who completed the diet assessment at all 3 examinations. Findings differed little between all available participants and the cohort of 2652 people with complete data. The CARDIA study was approved by the institutional review board of each field center; each study participant provided informed written consent.

### Other baseline measurements

Standard questionnaires were used to obtain self-reported demographic and behavioral information. Sex, race, date of birth, education, and cigarette smoking

were ascertained by a structured interview or self-administered questionnaire at each examination. Self-reported smoking status was classified as never, former, or current smoker. Height and weight were measured at each examination and recorded to the nearest 0.5 cm and 0.2 kg, respectively. BMI was defined as weight (in kg) divided by height squared (in $m^2$). A physical activity score was derived from the CARDIA Physical Activity History, which is a simplified version of the Minnesota Leisure Time Physical Activity Questionnaire [19], at each examination. Educational status was quantified as years attained as reported at each examination (**Table 1**) or as the maximum (at any visit) reported number of years of schooling completed in stratification (**Table 2**).

## Dietary assessment and food-group creation

Diet was assessed at years 0, 7, and 20 by using an interviewer administered CARDIA Diet History [20]. Interviewers asked open-ended questions about dietary consumption in the past month within 100 food categories that referenced 1609 separate food items during years 0 and 7 and many more at year 20. The diet assessment methods were maintained across examinations; despite the increase in the number of food items reported, which was a reflection of the changing food supply. In addition, fast-food restaurant use (visits/wk) was queried at each examination and eating breakfast (d/wk) was queried at years 7 and 20. Foods were assigned in one of 166 food groups by using the food-grouping system devised by the University of Minnesota Nutrition Coordinating Center. Food-group intake was assessed as servings per day of constituent foods. We excluded 6 infant-product food groups (not relevant), unsweetened water (collected at year 20 only), and non-grain flour (rarely consumed). In addition, we collapsed these 158 food groups into 46 food groups, which, in turn, were based on considerations of similar nutrient characteristics, hypothesized biologic effects, and comparability to food groups defined in previous studies [9].

## Description of the *a priori* dietary pattern score

We created a dietary pattern score from the 46 foods groups as done in previous studies [14–17]. The *A Priori* score was created by classifying foods groups according to investigator ratings that matched those established in the initial use of the *A Priori* score [14] as beneficial (n = 20), adverse (n = 13), or neutral (n = 13) in terms of hypothesized health effects. See Table 1 under "Supplemental data" in the online issue for details about the investigator ratings of food groups and the CARDIA *a priori* assignment. Food groups considered beneficial or adverse with respect to health effects were categorized into quintiles of consumption, and study participants received a score of 0–4 for each of the 46 food groups, depending on their amount of consumption. In food groups with large subsets of non-consumers,

non-consumers were coded 0 and consumers were split into quartiles with scores from 1 to 4 to ensure variability across 5 levels of consumption. The *A Priori* dietary pattern score was the sum of category scores 0–4 for the positively rated food groups plus scores in reverse order (4–0) for negatively rated food groups.

Food groups that were considered neutral did not contribute to the overall *A Priori* dietary pattern score. The theoretical maximum score was 132. It was assumed that a higher *A Priori* dietary pattern score indicated better diet quality. A one-unit change in the score was a change of one category (usually one quintile) of one food group in the presumed positive direction. To assess the change in the overall dietary pattern, we scaled the score according to baseline parameters. Specifically, we used the cutoffs of food group categories as determined at year 0, which were then applied to dietary data of years 0, 7, and 20.

A baseline reliability study of nutrient consumption from the diet history showed that sex- and energy-adjusted 1-mo test-retest correlations were lower for blacks (0.27–0.58) than for whites (0.54–0.82). Correlations between mean nutrient intakes from the diet history and 7 random 24-h dietary recalls ranged from 0.50 to 0.86 for white men to 0.20–0.53 for black women, with the exception of carbohydrates in black women, r = 0.04 [21]. Despite the suggestion that the diet history was less reliable in blacks than in whites, the correlations for the *A Priori* diet score tracking over time were high in both races. In blacks, the correlation between years 0 and 7 was 0.51, between years 7 and 20 was 0.52, and between years 0 and 20 was 0.43. These correlations were slightly lower than the corresponding correlations in whites (i.e. 0.62, 0.61, and 0.57, respectively). The diet score tracked over time more highly than did the direct questions about fast food (0.30, 0.27, and 0.18, respectively) and breakfast eating (0.46 between years 7 and 20); in each case, the tracking was somewhat higher in whites than in blacks.

## Statistical analysis

We based most analyses on the cohort of 2652 people with complete data. We used the personal computer version (9.2) of the Statistical Analysis System (SAS Institute Inc.) for all analyses. A longitudinal analysis was conducted by using the 3 repeated measures of the dietary pattern score modeled as the outcome variable in a mixed model (SAS PROC MIXED, n = 2652; SAS Institute Inc.). We examined several regression models with different levels of adjustment. The model included participant sex (male or female sex), study center (Birmingham, Chicago, Minneapolis, or Oakland), race (white or black), total energy intake (kcal/d), age at year 0 (continuous), and time (continuous or discrete, depending on the model). Sensitivity models also included BMI (continuous). SAS PROC MIXED (SAS Institute Inc.) with time modeled as a continuous variable was used to obtain the P-trend. Interactions with race, sex, and maximum achieved education were analyzed by using product terms (e.g.

time x race). To separate secular trends from age effects, we plotted unadjusted means and 95% CIs and included all available participants (n = 4983). A mixed model was also used to estimate the *A Priori* diet score at ages 20 and 50 y by following the linear equation that linked the *A Priori* diet score to age within each examination [12]. In this model, the dependent variable was the repeated *A Priori* diet score, and independent variables were the current age (continuous) and year of examination (0, 7, or 20). The model was repeated with adjustment for race, sex, and time-dependent energy intakes. Statistical significance was considered to be met at $P < 0.05$.

To study changes in food groups over time, we computed mean servings per day for each food group and time point. We assessed the P-trend in a mixed model by using time as a continuous variable. We examined demographic interactions by noting the race x sex or education (high school degree or less compared with any college) interaction with $P < 0.0011$ (Bonferroni adjusted for 46 food-group comparisons). For race and sex, we hierarchically deleted non-significant interaction terms (i.e. we first examined a model with race x time, sex x time, and race x sex x time terms). If the race x sex x time term had a P value ≥ 0.0011, we deleted it and examined lower-order interactions.

## RESULTS

### Sample characteristics

Characteristics of the study participants for each survey are shown in Table 1. Years of education attained increased significantly over 20 y, as did BMI and waist circumference. Physical activity decreased between years 0 and 7, whereas current smoking decreased over 20 y. Total energy intake decreased between years 7 and 20. Carbohydrate intake increased between years 0 and 7 but decreased between years 7 and 20. Protein intake increased between years 7 and 20. Total fat intake decreased between years 0 and 7 but rebounded by year 20, whereas changes in saturated and polyunsaturated fats were monotonically decreasing and increasing, respectively. Participants reported visiting fast-food restaurants, on average, almost twice per week, which decreased to 1.6 times/wk at year 20. Participants reported eating breakfast 4.2 times/wk at year 7, which increased to 4.8 times/wk at year 20.

### Trends in the diet-quality score

The unadjusted mean (±SD) *A Priori* dietary pattern score in the 2652 participants whose diet was assessed on all occasions was 64.1 ± 13.0, 67.5 ± 12.1, and 71.1 ± 12.6 at years 0, 7, and 20, respectively (**Table 2**). Participants who did not attend all

**TABLE 1** Demographic, behavioral, and dietary characteristics of participants in the CARDIA study, 1985–1986 to 2005–2006[1]

| | Year 0 | Year 7 | Year 20 | p-trend |
|---|---|---|---|---|
| Age (y) | 25.2 ± 3.5[2] | 32.2 ± 3.5 | 45.3 ± 3.6 | |
| Female (%) | 57 | | | |
| White (%) | 57 | | | |
| Center (%) | | | | |
| Birmingham | 24 | | | |
| Chicago | 25 | | | |
| Minneapolis | 25 | | | |
| Oakland | 25 | | | |
| Education attained, (y) | 14.2 ± 2.2 | 14.9 ± 2.5 | 15.2 ± 2.6 | <.0001 |
| Body Mass Index (kg/m$^2$) | 24.4 ± 4.8 | 26.5 ± 5.8 | 29.4 ± 7.2 | <.0001 |
| Waist circumference (cm) | 77.4 ± 11.2 | 83.4 ± 13.7 | 91.7 ± 15.3 | <.0001 |
| Physical activity (exercise units) | 419.8 ± 291.6 | 336.9 ± 267.3 | 336.2 ± 265.5 | <.0001 |
| Current smoker (%) | 24.3 | 22.7 | 17.3 | <.0001 |
| Dietary variables (mean, SD) | | | | |
| Mean total energy (kcal/day) | 2681.4 ± 1222 | 2694.4 ± 1157 | 2296.1 ± 999.4 | <.0001 |
| Total carbohydrates (percentage of energy) | 45.9 ± 7.2 | 49.7 ± 8.1 | 47.0 ± 9.6 | 0.04 |
| Total protein (percentage of energy) | 14.9 ± 2.6 | 14.8 ± 2.7 | 15.6 ± 3.6 | <.0001 |
| Total fat (percentage of energy) | 37.6 ± 5.9 | 34.9 ± 6.8 | 36.4 ± 8.4 | <.0001 |
| Saturated fat | 14.1 ± 2.9 | 12.1 ± 3 | 11.5 ± 3.1 | <.0001 |
| Monounsaturated fat | 13.9 ± 2.5 | 12.9 ± 2.9 | 13.9 ± 4 | 0.003 |
| Polyunsaturated fat | 6.9 ± 2 | 7.1 ± 2.2 | 8.1 ± 3.6 | <.0001 |
| Fast food (visits/wk) | 1.9 ± 2.2 | 1.9 ± 2.4 | 1.6 ± 2.2 | <.0001 |
| Eats breakfast (times/wk) | Not asked | 4.2 ± 2.6 | 4.8 ± 2.4 | <.0001 |

[1] n = 2652 participants with dietary assessment at CARDIA years 0, 7, and 20. P-trend values were based on repeated measures regression models with time modeled as a continuous variable. CARDIA, Coronary Artery Risk Development in Young Adults

[2] Mean ± SD (all such values)

**TABLE 2** Changes in the *A Priori* diet score during the CARDIA study, 1985–1986 to 2005–2006 (n = 2652)[1]

| | N | Year 0 | Year7 | Year 20 | P-trend | Adjusted change[2] |
|---|---|---|---|---|---|---|
| *A Priori* diet score | 2652 | 64.1 ± 13.0[3] | 67.5 ± 12.1 | 71.1 ± 12.6 | <.0001 | 6.8 (6.4-7.3) |
| Sex, Race | | | | | | |
| White female | 797 | 71.6 ± 12.6 | 73.7 ± 10.9 | 77.6 ± 11.7 | <.0001 | 5.9 (5.2-6.7) |
| White male | 717 | 66.6 ± 11.8 | 69.4 ± 11.2 | 72.6 ± 11.8 | <.0001 | 5.8 (4.9-6.6) |
| Black female | 713 | 57.9 ± 10.4 | 62.7 ± 10.7 | 66.7 ± 11.1 | <.0001 | 8.6 (7.8-9.5) |
| Black male | 425 | 56.2 ± 10.2 | 60.4 ± 10.8 | 63.8 ± 11.3 | <.0001 | 7.3 (6.2-8.4) |
| Education[4] | | | | | | |
| High school | 369 | 57.3 ± 11.0 | 60.6 ± 11.8 | 64.4 ± 12.3 | <.0001 | 6.9 (5.7-8.0) |
| Some college | 787 | 59.9 ± 11.7 | 64.1 ± 11.3 | 67.6 ± 11.4 | <.0001 | 7.5 (6.7-8.3) |
| College | 662 | 66.1 ± 13.0 | 69.4 ± 11.3 | 72.9 ± 12.5 | <.0001 | 6.7 (5.8-7.6) |
| Post College | 834 | 69.4 ± 12.4 | 72.2 ± 11.2 | 76.0 ± 11.5 | <.0001 | 6.5 (5.7-7.2) |

[1] P-trend values and adjusted mean changes were based on repeated-measures regression models adjusted for sex, race, center, age, and total energy (kcal/d). CARDIA, Coronary Artery Risk Development in Young Adults.
[2] Values are means; 95% CI in parentheses.
[3] Mean ± SD (all such values).
[4] Maximum attained during follow-up.

examinations or who otherwise had missing dietary data at any time point showed significantly lower scores (corresponding values: 61.0 ± 12.8 (n = 2331), 65.4 ± 12.4 (n = 1197), and 66.8 6 13.2 (n = 437); P < 0.0001). The dietary pattern score varied by demographic group and was higher in whites than in blacks and in women than in men. The score was also higher with greater educational attainment. In contrast, changes over time were most positive in groups that initially had lower scores. There was a larger increase in the dietary pattern score in blacks (8 units) than in whites (6 units) (P < 0.0001), and the increase in the score was less with increased educational attainment. Adjustment for sex, race, center, education, age, and total energy intake had little effect on the unadjusted means. Further adjustment for BMI did not change the outcomes.

The variability in score over race, sex, education, and time was substantial. For example, the unadjusted score in participants whose diet was assessed on all occasions was 54.6 ± 9.8 in year 0 in 109 black men who had no education past high school, which increased at year 20 to 61.0 ± 11.3 (P < 0.0001) compared with 72.5 ± 12.3 in year 0 in 726 white women who had more than a college education, which increased at year 20 to 78.3 ± 11.3 (P < 0.0001) (**Figure 1**).

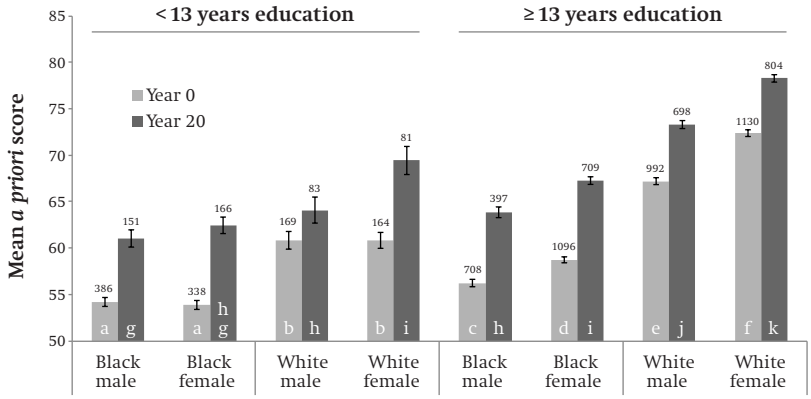



**FIGURE 1** Unadjusted mean (95% CI) *A Priori* diet score according to race, sex, and educational groups; all available diet records: n = 4983 at year 0 (1985–1986) and 3089 at year 20 (2005–2006). Bars with different letters differed significantly from one another (P , 0.05) in pairwise comparisons. The race, sex, and education comparison was done separately for years 0 and 20.

## Aging compared with secular trends

As shown in **Figure 2**, a large part of the change in the *A Priori* diet score was attributable to the increasing age of the sample. On the basis of repeated-measures regression analysis with adjustment for race, sex, maximum achieved education, and time-dependent energy intake, the increase in the score with age was greatest in the earliest examination (when the participants were youngest) at 0.87 ± 0.043 units/y of age observed at year 0, 0.47 ± 0.047 units/y of age observed at year 7, and 0.38 ± 0.051 units/y of age observed at year 20 ($P < 0.0001$ for the time x age interaction).

The secular trend (the average vertical distance between examination-specific curves shown in Figure 2; the so-called age-matched time trend) was negative throughout the study. Between years 0 and 7, people aged 25–30 y in 1992–1993 had a slightly lower mean diet score than did people aged 25–30 y in 1985–1986. Although there were no overlapping ages observed at both years 7 and 20, extrapolation of the curves in Figure 2, with adjustment for race, sex, maximum achieved education, and time-dependent energy intake, suggested a mean *A Priori* diet score of 78.7 at age 50 y if the age pattern at year 0 had been followed, of 68.8 if the age pattern at year 7 had been followed, and of 65.8 if the age pattern at

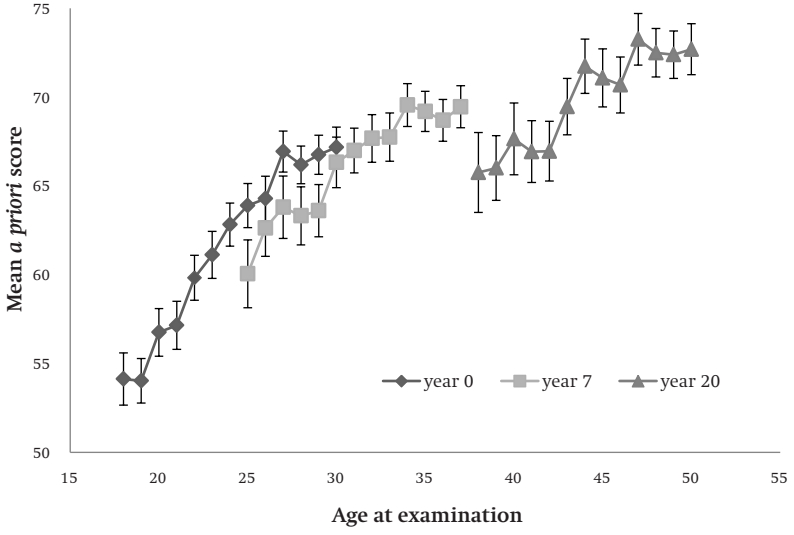



**FIGURE 2** Mean (95% CI) *A Priori* diet score according to current age and year of examination. Adjusted for sex, race, center, age, and total energy (kcal/d); all available diet records: n = 4962 at year 0 (1985–1986), 3803 at year 7 (1992–1993), and 3057 at year 20 (2005–2006).

**TABLE 3** Changes in food groups grouped according to their rating in the *A Priori* diet score in the CARDIA study, 1985–1986 to 2005–2006 (n = 2652)[1]

| Food group | Year 0 | Year 7 | Year 20 | Change in servings/d from years 20 to 0[2] | Percentage change[3] | P-trend |
|---|---|---|---|---|---|---|
| | Servings/d | Servings/d | Servings/d | | | |
| Positively-rated | | | | | | |
| Oil | 1.46 ± 0.02[4] | 3.25 ± 0.05 | 2.75 ± 0.12 | 1.29 | 88 | <.0001 |
| Soy products | 0.23 ± 0.01 | 0.63 ± 0.03 | 0.79 ± 0.04 | 0.56 | 243 | <.0001 |
| Green vegetables | 0.37 ± 0.01 | 0.54 ± 0.01 | 0.79 ± 0.02 | 0.42 | 114 | <.0001 |
| Seeds, nuts | 0.80 ± 0.03 | 0.76 ± 0.04 | 1.15 ± 0.04 | 0.35 | 44 | <.0001 |
| Fruit | 1.43 ± 0.02 | 1.66 ± 0.03 | 1.67 ± 0.03 | 0.24 | 17 | <.0001 |
| Poultry | 1.24 ± 0.02 | 1.47 ± 0.02 | 1.45 ± 0.03 | 0.21 | 17 | <.0001 |
| Low fat dairy | 1.16 ± 0.02 | 1.37 ± 0.03 | 1.30 ± 0.03 | 0.14 | 12 | <.0001 |
| Whole grains | 1.52 ± 0.02 | 1.89 ± 0.03 | 1.61 ± 0.03 | 0.09 | 6 | <.0001 |
| Negatively-rated | | | | | | |
| Salty snacks | 0.04 ± 0.00 | 0.20 ± 0.01 | 0.24 ± 0.01 | 0.20 | 500 | <.0001 |
| Processed meat | 0.90 ± 0.02 | 0.81 ± 0.02 | 0.92 ± 0.02 | 0.02 | 2 | <.0001 |
| Fried potato | 0.36 ± 0.01 | 0.29 ± 0.01 | 0.18 ± 0.01 | -0.18 | -50 | <.0001 |
| Sweet breads | 1.00 ± 0.02 | 0.90 ± 0.02 | 0.77 ± 0.02 | -0.23 | -23 | 0.3676 |
| Soft drink | 1.60 ± 0.03 | 1.41 ± 0.03 | 0.95 ± 0.04 | -0.65 | -41 | <.0001 |
| High fat dairy | 2.07 ± 0.03 | 1.46 ± 0.03 | 1.18 ± 0.03 | -0.89 | -43 | <.0001 |
| Regular red meat | 2.37 ± 0.04 | 2.03 ± 0.03 | 1.40 ± 0.03 | -0.97 | -41 | <.0001 |
| Butter | 4.78 ± 0.07 | 3.88 ± 0.07 | 2.11 ± 0.06 | -2.67 | -56 | <.0001 |
| Neutrally-rated | | | | | | |
| Sugar substitute | 0.06 ± 0.01 | 0.13 ± 0.01 | 0.66 ± 0.05 | 0.60 | 1000 | <.0001 |
| Diet soft drink | 0.38 ± 0.02 | 0.72 ± 0.02 | 0.64 ± 0.03 | 0.26 | 68 | <.0001 |
| Nonfried potatoes | 0.42 ± 0.01 | 0.54 ± 0.01 | 0.29 ± 0.01 | -0.13 | -31 | <.0001 |
| Refined grains | 4.55 ± 0.05 | 5.30 ± 0.06 | 3.55 ± 0.05 | -1.00 | -22 | 0.0005 |

[1] P-trend values were based on repeated-measures regression models adjusted for sex, race, center, age, and total energy (kcal/d). CARDIA, Coronary Artery Risk Development in Young Adults.
[2] All values are means.
[3] (Year 20 − year 0) 4 year 0.
[4] Mean ± SE (all such values).

year 20 had been followed. Although a linear age pattern appears to fit the data in Figure 2 well, we did not have sufficient age range in any examination to completely exclude curvature in the association of the diet-pattern score with age.

## Changes in food groups

Change in selected food groups over 20 y that corresponded to changes in dietary pattern scores is shown in **Table 3**. Changes were more prominent and generally more consistent in negatively rated food groups than in neutrally or positively rated food groups, which were generally in a direction consistent with the philosophy of the *A Priori* diet score. Of the 46 food groups studied, 43 food groups showed a significant trend over 20 y; however, these trends did not always display a monotonic trend over 20 y. Decreases of ≥0.5 servings/d occurred in intakes of butter, regular red meat, whole-fat dairy and soft drinks in the negatively rated food groups. Increases of ≥0.35 servings/d were seen in intakes of seeds and nuts, green vegetables, soy products, and oil in the positively rated food groups. Several substantial changes occurred in neutrally rated food groups as follows: intakes of refined grains decreased by 1.0 serving/d, whereas intakes of sugar substitutes and diet soft drinks increased by ≥0.26 servings/d. (See Table 2 under "Supplemental data" in the online issue for a complete analysis of changes in all 46 food groups that composed the dietary score.)

Differences in food-group time trends over 20 y between demographic groups tended to be concordant in direction. However, a few food groups showed changes in opposite directions. Whole grain food consumption increased in white women (+0.29 servings/d) and showed very little change in all other demographic groups. The consumption of soft drinks increased in men (+0.48 servings/d) but decreased in women (-0.08 servings/d). Processed-meat consumption increased in whites (+0.23 servings/d) and in higher-educated people (+0.12 servings/d) and decreased in blacks (-0.16 servings/d) and lower-educated people (-0.25 servings/d). There was a substantially larger decrease in butter consumption in blacks (-3.5 servings/d) than in whites (-1.7 servings/d) and in lower-educated people (24.3 servings/d) than in people with high education (-2.2 servings/d). (See Tables 3– 4 under "Supplemental data" in the online issue for a complete analysis of changes in all 46 food groups that composed the dietary score by race and sex and education.) The frequency of visits to fast-food restaurants was inversely related to the diet score (age-, race-, and sex-adjusted r = -0.22 at year 0, -0.30 at year 7, and -0.32 at year 20). Corresponding correlations of frequency of eating breakfast with diet score were r = 0.14 at year 7 and 0.18 at year 20.

## DISCUSSION

Over 20 y of follow-up of a cohort of black and white Americans aged from young adulthood to middle age, we observed significant and positive changes in a measure of diet quality. In particular, consumption of plant foods, poultry, and low-fat dairy increased, whereas the consumption of many foods that could be considered health adverse, including fried potatoes, soft drinks, high fat dairy, and red meat, decreased. The consumption of sugar substitutes and diet soft drinks increased. Our data suggested that aging played a major role in diet-quality improvement over the course of follow-up because the diet-quality score increased across age within each examination. However, as hypothesized, the age-matched time trend suggested a secular trend of a decreased diet quality from 1985–1986 to 1992–1993 to 2005–2006 in the population from which the CARDIA sample was drawn. Specifically, on the basis of the slope over age of the diet-quality score in 1985–1986, we estimated that a 50-y-old would have a mean diet-quality score of 78.7, but the observation of 50-y olds in 2005–2006 estimated their diet-quality score to be 65.8. Thus, our data imply that individuals attained improvements in dietary quality despite aspects of the food supply and food choices that applied population wide and became less desirable as decades passed.

Improvements in the overall diet quality were apparent in all demographic groups. Although the diet score at year 0was lower in men, blacks, and subjects with lower educational attainment, those groups tended to show greater increases in the diet score during follow-up. Thus, the substantial demographic gap in diet quality observed at baseline persisted at year 20, but the differences narrowed. Changes in specific food groups generally supported a change in the direction of improved diet quality.

Few studies have examined longitudinal trends in diet quality through adulthood. The 1946 British Birth Cohort of women aged 36 y, who were followed until age 53 y, showed a significantly increased consumption of a dietary pattern derived from principal component analysis [22], which was consistent with our findings of an increased diet-quality score over adulthood. The British Birth Cohort dietary pattern was characterized by a high consumption of fruit, vegetables, and dairy and a deceased consumption of a dietary pattern of meat, potatoes, and sweets. Men seemed to follow similar dietary principles. Because this study covered only a single year of age at each examination, it could not separate age from period effects. In the National Longitudinal Study of Adolescent Health cohort, between 1994 and 2002, as participants aged from between 12–19 to 18–26 y, fast-food consumption significantly declined, whereas breakfast consumption increased [23]; no separation of age from period effects was presented. Two studies from Europe also showed that, as people aged from adolescence to adulthood, they

changed their diet in the direction of dietary recommendations [3, 8]. These studies documented changes over a variety of age ranges, although improvements after adolescence may weaken with increasing age. Our serial cross-sectional data (Figure 2) showed the largest improvement in diet quality per year of age during 1985–1986 (CARDIA year 0) when our participants were 18–30 y old. It is possible that this result indicated an important period of settling in to a stable dietary pattern. We observed a continuing improvement in diet quality in subsequent surveys through age 50 y, albeit at a slower rate than in younger adulthood. It is possible that this trend eventually reverses.

Strengths of our study included the thorough dietary assessment on repeated occasions in a large population-based cohort. The dietary assessment was comprehensive. Although reliability may be have been slightly lower in blacks than in whites, the *A Priori* diet score showed a high level of tracking and expected correlation in both races with other dietary characteristics, including other diet pattern scores, visits to fast-food restaurants, and the frequency of breakfast eating. Although the *A Priori* diet score had an element of subjectivity because it is based on the informed opinions of 4 nutrition scientists, excellent, although not complete, agreement about how to rate the food groups existed across investigators. Ratings were mostly, but not always, in line with official recommendations. The score has functioned well in validity testing. There were also limitations of our study. It is possible that CARDIA participants were particularly aware of their dietary intake because of general study participation and the interviewer-administered dietary history assessments, which resulted in improvements of their diet. However such an intervention seems unlikely because the investigators had little contact with the participants and the dietary emphasis was largely during the 3 dietary assessments, which were 7 and 13 y apart. To examine population-wide secular trends, we used a method that examined the mean dietary score at a fixed age, which was achieved at different calendar times (age-matched time trend) [10]. Consistent with our prior hypothesis and other evidence [6–8], there was a secular decline in diet quality, especially after 1992–1993. Nevertheless, our method should be interpreted with caution for 3 reasons. The method depended on specific ages overlapping between different periods (which did not occur between years 7 and 20), our cohort design represented the underlying population less and less well because there was attrition from our sample, and we could not fully account for the possible curvature in the diet score and age association. As in any observational study, residual confounding could not be ruled out.

During the past decades, dietary recommendations have tended to shift from nutrients to an overall dietary pattern, with emphasis on varied consumption and with specific attention to certain food groups (e.g. consumption of red and processed meats, fruit and vegetables, and whole-grain foods). The *A Priori* diet

score is in line with many dietary guidelines. The improved diet quality with increased age likely resulted from the attention of CARDIA participants to dietary guidelines. At the same time, our suggestion that diet quality in the population at large worsened between 1985–1986 and 2005–2006 is worthy of note. In addition, different demographic sectors have diets of different quality. In a time of a high supply of non-nutrient-dense foods, the person who wishes to improve his or her diet quality may be working at cross-purposes with the general culture. Increasing the desirability of and access to fruit, vegetables, whole grains without added sugars, salt, solid fats, or extra calories, especially in demographic groups with lower *A Priori* diet scores, could help improve these trends.

## ACKNOWLEDGMENTS

The authors' responsibilities were as follows—FPCS: conceptualization, statistical analysis, interpretation, and writing of the manuscript text; KAM: conceptualization, interpretation, and writing and review of the manuscript; LMS: conceptualization, review of the manuscript, and director of the CARDIA Diet Center; JMS, LVH, and LH: review of the manuscript; DK: conceptualization, interpretation, and review of the manuscript; DRJ: securement of funding, collection of data, conceptualization, statistical analysis, interpretation, and writing and review of the manuscript text. None of the authors had a conflict of interest.

Supported by the National Heart, Lung, and Blood Institute, NIH, Coronary Artery Risk Development in Young Adults (contracts N01-HC-95095, N01-HC-48047, N01-HC-48048, N01-HC-48049, and N01-HC-48050 and grant R01-HL-53560) and the National Heart, Lung, and Blood Institute (grant T32 HL07779).

## REFERENCES


1. Dietary Guidelines Advisory Committee. Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 1985, to the Secretary of Agriculture and the Secretary of Health and Human Services. Washington, DC: US Department of Agriculture, Agricultural Research Service, 1985. Available from: http://www.cnpp.usda.gov/Publications/DietaryGuidelines/1985/1985CommitteeReport.pdf (cited 31 January 2011).
2. Dietary Guidelines Advisory Committee. Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2010, to the Secretary of Agriculture and the Secretary of Health and Human Services. Washington, DC: US Department of Agriculture, Agricultural Research Service, 2010. Available from: http://www.cnpp. usda.gov/DGAs2010-DGACReport.htm (cited 31 January 2011).
3. Bertheke Post G, de Vente W, Kemper HC, Twisk JW. Longitudinal trends in and tracking of energy and nutrient intake over 20 years in a Dutch cohort of men and women between 13 and 33 years of age: The Amsterdam Growth and Health Longitudinal Study. Br J Nutr 2001;85:375–85.
4. Hu FB, Rimm EB, Stampfer MJ, Ascherio A, Spiegelman D, Willett WC. Prospective study of major dietary patterns and risk of coronary heart disease in men. Am J Clin Nutr 2000;72:912–21.
5. Wang H, Steffen LM, Jacobs DR, Zhou X, Blackburn H, Berger AK, Filion KB, Luepker RV. Trends in cardiovascular risk factor levels in the Minnesota Heart Survey (1980-2002) as compared with the National Health and Nutrition Examination Survey (1976-2002): a partial explanation for Minnesota's low cardiovascular disease mortality? Am J Epidemiol 2011;173:526–38.
6. Pelucchi C, Galeone C, Negri E, La Vecchia C. Trends in adherence to the Mediterranean diet in an Italian population between 1991 and 2006. Eur J Clin Nutr 2010;64:1052–6.
7. Valde´s J, Grau M, Subirana I, Marrugat J, Covas MI, Schro¨der H. Secular trends in energy intake and diet quality in a Mediterranean population. Ann Nutr Metab 2009;54:177–83.
8. Lake AA, Mathers JC, Rugg-Gunn AJ, Adamson AJ. Longitudinal change in food habits between adolescence (11-12 years) and adulthood (32-33 years): The ASH30 study. J Public Health (Oxf) 2006;28:10–6.
9. Kant AK, Graubard BI, Kumanyika SK. Trends in black-white differentials in dietary intakes of U.S. adults, 1971-2002. Am J Prev Med 2007;32:264–72.
10. Jacobs DR Jr, Hannan PJ, Wallace D, Liu K, Williams OD, Lewis CE. Interpreting age, period and cohort effects in plasma lipids and serum insulin using repeated measures regression analysis: the CARDIA Study. Stat Med 1999;18:655–79.
11. Nielsen SJ, Siega-Riz AM, Popkin BM. Trends in food locations and sources among adolescents and young adults. Prev Med 2002;35:107–13.
12. Nielsen SJ, Popkin BM. Patterns and trends in food portion sizes, 1977-1998. JAMA 2003;289:450–3.
13. Du H, Feskens E. Dietary determinants of obesity. Acta Cardiol 2010; 65:377–86.
14. Lockheart MS, Steffen LM, Rebnord HM, Fimreite RL, Ringstad J, Thelle DS, Pedersen JI, Jacobs DR Jr. Dietary patterns, food groups and myocardial infarction: a case-control study. Br J Nutr 2007;98: 380–7.
15. Nettleton JA, Steffen LM, Ni H, Liu K, Jacobs DR Jr. Dietary patterns and risk of incident type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care 2008;31:1777–82.
16. Nettleton JA, Schulze MB, Jiang R, Jenny NS, Burke GL, Jacobs DR Jr. *A priori* -defined dietary patterns and markers of cardiovascular disease risk in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr 2008;88:185–94.
17. Jacobs DR Jr, Sluik D, Rokling-Andersen MH, Anderssen SA, Drevon CA. Association of 1-y changes in diet pattern with cardiovascular disease risk factors and adipokines: results from the 1-y randomized Oslo Diet and Exercise Study. Am J Clin Nutr 2009;89:509–17.
18. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr, Liu K, Savage PJ. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol 1988;41:1105–16.
19. Jacobs DR Jr, Hahn LP, Haskell WL, Pirie P, Sidney S. Validity and reliability of a short physical activity history: CARDIA and the Minnesota Heart Health Program. J Cardiopulm Rehabil 1989;9:448–59.

20. McDonald A, Van Horn L, Slattery M, Hilner J, Bragg C, Caan B, Jacobs D Jr, Liu K, Hubert H, Gernhofer N, et al. The CARDIA dietary history: development, implementation, and evaluation. J Am Diet Assoc 1991;91:1104–12.
21. Liu K, Slattery M, Jacobs D Jr, Cutter G, McDonald A, Van Horn L, Hilner JE, Caan B, Bragg C, Dyer A, et al. A study of the reliability and comparative validity of the CARDIA dietary history. Ethn Dis 1994;4:15–27.
22. Mishra GD, McNaughton SA, Bramwell GD, Wadsworth ME. Longitudinal changes in dietary patterns during adult life. Br J Nutr 2006; 96:735–44.
23. Harris KM, Gordon-Larsen P, Chantala K, Udry JR. Longitudinal trends in race/ethnic disparities in leading health indicators from adolescence to young adulthood. Arch Pediatr Adolesc Med 2006;160:74–81.

## SUPPLEMENTAL MATERIAL

Details about the investigator ratings of food groups and the CARDIA A Priori diet score assignment derived from the investigator ratings are in Supplemental table 1. Between studies there exist food grouping differences, and few differences in ratings; generally the investigator opinion agreed very closely.

Black participants and those with less educational attainment generally showed more change than whites and more highly educated participants, but this pattern varied across food groups. Those demographic interactions which reached the Bonferroni corrected p-value of <0.0012 are indicated in Supplemental table 2 we considered race and sex differences and education differences, but not race, sex, and education differences.

Differences among demographic groups, Supplemental table 3 (by race and sex) and 4 (by education), were especially prominent and significant for the negative rated food groups. For most food groups changes were in the same direction for both demographic groups however one demographic group showed a larger increase or decrease compared to the other demographic groups.

**SUPPLEMENTAL TABLE 1** Investigator ratings of food groups and comparability to previous studies.

| Cardia food groups | Investigators' independent ratings | | | | CARDIA *A Priori* score | Previous studies' consensus | | |
|---|---|---|---|---|---|---|---|---|
| | FPCS | JAN | DRJ | LMS | | Nettleton et.al.[1] | Lockheart et al.[2] | Jacobs et al.[3] |
| Avocado | + | + | | | + | + | + | + |
| Beans | + | + | | | + | + | | + |
| Beer | + | + | + | + | + | + | + | + |
| Coffee | + | + | - | - | + | + | 0 | - |
| Fatty fish | + | + | + | | + | | + | + |
| Fruit | + | + | + | + | + | + | + | + |
| Green vegetables | + | + | + | + | + | + | + | + |
| Lean fish | + | + | | | + | + | + | + |
| Low fat dairy | + | + | + | + | + | | + | + |
| Liquor | + | + | + | + | + | | + | + |
| Oil | + | + | + | + | + | + | + | + |
| Other vegetables | + | + | + | + | + | + | + | + |
| Poultry | + | 0 | + | + | + | + | + | + |
| Seeds nuts | + | + | + | + | + | + | | + |
| Soy products | + | + | | | + | + | | |
| Tea | + | + | + | + | + | + | + | + |
| Tomato | + | + | + | + | + | + | + | + |
| Whole grains | + | + | + | + | + | + | + | + |
| Wine | + | + | + | + | + | + | + | + |
| Yellow vegetables | + | + | + | + | + | + | + | + |
| Butter | - | - | - | - | - | | - | - |
| Fried poultry and fish | - | - | | | - | | | |
| Fried potato | - | - | | | - | - | - | |
| Grain dessert | - | - | | | - | - | | |
| Organ meat | - | - | - | - | - | 0 | - | - |
| Processed meat | - | - | - | - | - | - | - | - |
| Regular red meat | - | - | - | - | - | | - | - |
| Salty snacks | - | - | - | - | - | - | - | - |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Sauces | 0 | - | + | + | - | | + | + |
| Soft drinks | - | - | - | - | - | - | - | - |
| Sweet breads | - | - | | | - | - | | - |
| Sweet extra's | - | - | - | - | - | - | - | - |
| Whole fat dairy | - | - | - | - | - | - | - | - |
| Chocolate | 0 | 0 | | | 0 | 0 | - | - |
| Diet soft drink | 0 | 0 | + | -,+ | 0 | 0 | 0 | + |
| Eggs | 0 | 0 | | | 0 | 0 | 0 | 0 |
| Fruit juice | 0 | 0 | - | - | 0 | | - | - |
| Lean red meat | + | 0 | | + | 0 | 0 | 0 | + |
| Margarine | 0 | 0 | | | 0 | | | |
| Meal replacements | 0 | 0 | | | 0 | 0 | | |
| Pickled food | 0 | 0 | | | 0 | | | |
| Potatoes | 0 | 0 | | | 0 | 0 | 0 | 0 |
| Refined grains | 0 | 0 | | | 0 | 0 | 0 | 0 |
| Shellfish | + | 0 | | | 0 | | | |
| Soups | 0 | 0 | + | + | 0 | + | + | + |
| Sugar substitutes | 0 | 0 | | | 0 | | | |

[1]Nettleton JA, Schulze MB, Jiang R, Jenny NS, Burke GL, Jacobs DR,Jr. *A Priori* -defined dietary patterns and markers of cardiovascular disease risk in the multi-ethnic study of atherosclerosis (MESA). Am J Clin Nutr. 2008 Jul;88(1):185-94.

[2]Lockheart MS, Steffen LM, Rebnord HM, Fimreite RL, Ringstad J, Thelle DS, et al. Dietary patterns, food groups and myocardial infarction: A case-control study. Br J Nutr. 2007 Aug;98(2):380-7.

[3]Jacobs DR Jr, Sluik D, Rokling-Andersen MH, Anderssen SA, Drevon CA. Association of 1-y changes in diet pattern with cardiovascular disease risk factors and adipokines: results from the 1-y randomized Oslo Diet and Exercise Study. Am J Clin Nutr. 2009 Feb;89(2):509-17.

**SUPPLEMENTAL TABLE 2** Changes in food groups, grouped according to their rating in the *A Priori* diet score, with notations of substantial race-sex and educational attainment differences in change pattern, CARDIA 1985-86 to 2005-06

| Food group | mean sv/d y0 | mean sv/d y7 | mean sv/d y20 | mean change (20 −0) | % change (20 −0/ 0) | p-trend | Demographic groups showing exceptions to the overall trend (p<0.0012 for interaction) |
|---|---|---|---|---|---|---|---|
| Positively rated | | | | | | | |
| Avocado | 0.08 | 0.08 | 0.15 | 0.07 | 88% | <.0001 | Race-sex: White 0.12, others 0.04 |
| Beans | 0.21 | 0.26 | 0.25 | 0.04 | 19% | <.0001 | Race: White 0.07, Black 0.01<br>Education: 13+ 0.05, ≤13 -0.04 |
| Beer | 0.52 | 0.49 | 0.31 | -0.21 | -40% | <.0001 | Sex: -0.36, -0.06 |
| Coffee | 1.12 | 1.22 | 1.47 | 0.35 | 31% | <.0001 | Sex: 0.5, 0.22 |
| Fatty fish | 0.04 | 0.05 | 0.02 | -0.02 | -50% | <.0001 | |
| Fruit | 1.43 | 1.66 | 1.67 | 0.24 | 17% | <.0001 | Sex: 0.13, 0.32 |
| Green vegetables | 0.37 | 0.54 | 0.79 | 0.42 | 114% | <.0001 | Sex: 0.35, 0.47 |
| Lean fish | 0.70 | 0.66 | 0.76 | 0.06 | 9% | 0.0160 | |
| Low fat dairy | 1.16 | 1.37 | 1.30 | 0.14 | 12% | 0.0003 | |
| Liquor | 0.20 | 0.18 | 0.20 | 0.00 | 0% | 0.6400 | |
| Oil | 1.46 | 3.25 | 2.75 | 1.29 | 88% | <.0001 | |
| Other vegetables | 2.10 | 2.32 | 2.03 | -0.07 | -3% | 0.1200 | |
| Poultry | 1.24 | 1.47 | 1.45 | 0.21 | 17% | <.0001 | |
| Seeds nuts | 0.80 | 0.76 | 1.15 | 0.35 | 44% | <.0001 | |
| Soy products | 0.23 | 0.63 | 0.79 | 0.56 | 243% | <.0001 | Sex: 0.42, 0.65 |
| Tea | 0.61 | 0.47 | 0.69 | 0.08 | 13% | 0.3100 | |
| Tomato | 0.49 | 0.64 | 0.54 | 0.05 | 10% | 0.0002 | Sex: 0.01, 0.08 |
| Whole grains | 1.52 | 1.89 | 1.61 | 0.09 | 6% | 0.0030 | Race-Sex: White 0.29, others 0.02 |
| Wine | 0.16 | 0.15 | 0.28 | 0.12 | 75% | <.0001 | Race: White 0.25, Black -0.01<br>Education: 13+ 0.15, ≤13 0.0 |
| Yellow vegetables | 0.26 | 0.25 | 0.25 | -0.01 | -4% | 0.2000 | |
| Negatively rated | | | | | | | |
| Butter | 4.78 | 3.88 | 2.11 | -2.67 | -56% | <.0001 | Race: White -1.7, Black -3.5<br>Sex: -3.5 -2.0<br>Education: 13+ -2.2, ≤13 -4.3 |
| Fried poultry and fish | 4.69 | 3.13 | 2.39 | -2.30 | -49% | <.0001 | Sex: -2.8 -1.8 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Fried potato | 2.37 | 2.03 | 1.40 | -0.97 | -41% | <.0001 | Race: White -0.7, Black -1.2<br>Sex: -1.2 -0.8 |
| Grain dessert | 2.07 | 1.46 | 1.18 | -0.89 | -43% | <.0001 | Race: White -0.6, Black -1.2<br>Sex: -1.3 -0.6 |
| Organ meat | 1.60 | 1.41 | 0.95 | -0.65 | -41% | <.0001 | Race: White -0.5, Black -0.8 |
| Processed meat | 1.00 | 0.9 | 0.77 | -0.23 | -23% | <.0001 | Race: White -0.1, Black -0.4<br>Sex: -0.4 -0.1 |
| Regular red meat | 0.36 | 0.29 | 0.18 | -0.18 | -50% | <.0001 | Race: White -0.1, Black -0.2<br>Sex: -0.2 -0.1 |
| Salty snacks | 0.69 | 0.77 | 0.62 | -0.07 | -10% | 0.0040 | |
| Sauces | 0.05 | 0.04 | 0.02 | -0.03 | -60% | <.0001 | |
| Soft drinks | 0.90 | 0.81 | 0.92 | 0.02 | 2% | 0.0050 | Race: White 0.23, Black -0.16<br>Education: 13+0.12, ≤13 -0.25 |
| Sweet breads | 0.11 | 0.26 | 0.20 | 0.09 | 82% | <.0001 | Race: White -0.04, Black 0.22 |
| Sweet extra's | 1.78 | 1.59 | 1.87 | 0.09 | 5% | 0.007 | Education: 13+0.22, ≤13 -0.29 |
| Whole fat dairy | 0.04 | 0.20 | 0.24 | 0.20 | 500% | <.0001 | |
| Neutrally rated | | | | | | | |
| Chocolate | 4.55 | 5.30 | 3.55 | -1.00 | -22% | <.0001 | Race: White -0.7, Black -1.3<br>Sex: -1.4 -0.7 |
| Diet soft drink | 1.95 | 1.54 | 1.06 | -0.89 | -46% | <.0001 | |
| Eggs | 1.72 | 2.08 | 0.88 | -0.84 | -49% | <.0001 | |
| Fruit juice | 0.82 | 0.54 | 0.44 | -0.38 | -46% | <.0001 | Race: White -0.2, Black -0.6<br>Sex: -0.8 -0.4<br>Education: 13+ -0.3, ≤13 -0.7 |
| Lean red meat | 0.42 | 0.54 | 0.29 | -0.13 | -31% | <.0001 | |
| Margarine | 0.68 | 0.57 | 0.61 | -0.07 | -10% | 0.0400 | Sex: -0.4 -0.2 |
| Meal replacements | 0.19 | 0.19 | 0.19 | 0.00 | 0% | 0.8700 | |
| Pickled food | 0.23 | 0.24 | 0.24 | 0.01 | 4% | 0.1100 | |
| Potatoes | 0.04 | 0.05 | 0.05 | 0.01 | 25% | <.0001 | Education: 13+ 0.02, ≤13 0.0 |
| Refined grains | 0.35 | 0.37 | 0.45 | 0.10 | 29% | <.0001 | |
| Shellfish | 0.01 | 0.05 | 0.14 | 0.13 | 1300% | <.0001 | Race: White 0.09, Black 0.16<br>Sex: 0.21 0.06 |
| Soups | 0.38 | 0.72 | 0.64 | 0.26 | 68% | <.0001 | Sex: 0.48 -0.08 |
| Sugar substitutes | 0.06 | 0.13 | 0.66 | 0.60 | 1000% | <.0001 | Race: White 0.4, Black 0.8<br>Sex: 0.5 0.7 |

**SUPPLEMENTAL TABLE 3** Changes in food groups, grouped according to their rating in the *A Priori* diet score, by race and sex, CARDIA 1985-86 to 2005-06

| | black | | white | | black | |
|---|---|---|---|---|---|---|
| | male | female | male | female | male | female |
| | Mean sv/d year 0 | mean sv/d year 0 | Mean sv/d year 0 | Mean sv/d year 0 | change 0-20 | change 0-20 |
| Positively rated | | | | | | |
| Avocado | 0.03 | 0.04 | 0.12 | 0.13 | 0.04 | 0.04 |
| Beans | 0.32 | 0.18 | 0.22 | 0.15 | -0.01 | 0.03 |
| Beer | 0.92 | 0.16 | 0.87 | 0.26 | -0.34 | 0.00 |
| Coffee | 0.55 | 0.61 | 1.71 | 1.69 | 0.29 | 0.20 |
| Fatty fish | 0.05 | 0.03 | 0.05 | 0.03 | -0.02 | -0.01 |
| Fruit | 1.48 | 1.45 | 1.39 | 1.39 | 0.09 | 0.24 |
| Green vegetables | 0.28 | 0.28 | 0.40 | 0.54 | 0.29 | 0.43 |
| Lean fish | 0.77 | 0.65 | 0.75 | 0.66 | 0.15 | 0.12 |
| Low fat dairy | 0.88 | 0.61 | 1.84 | 1.42 | 0.11 | 0.15 |
| Liquor | 0.27 | 0.12 | 0.27 | 0.17 | 0.02 | 0.01 |
| Oil | 1.73 | 1.19 | 1.73 | 1.29 | 1.51 | 1.08 |
| Other vegetables | 2.22 | 1.74 | 2.43 | 2.12 | -0.05 | 0.03 |
| Poultry | 1.58 | 1.18 | 1.17 | 1.08 | 0.34 | 0.29 |
| Seeds nuts | 0.88 | 0.61 | 1.04 | 0.73 | 0.30 | 0.34 |
| Soy products | 0.16 | 0.19 | 0.27 | 0.32 | 0.46 | 0.63 |
| Tea | 0.36 | 0.36 | 0.87 | 0.88 | 0.05 | 0.12 |
| Tomato | 0.50 | 0.36 | 0.61 | 0.51 | -0.01 | 0.04 |
| Whole grains | 1.75 | 1.07 | 1.99 | 1.41 | 0.07 | 0.08 |
| Wine | 0.14 | 0.12 | 0.15 | 0.21 | -0.04 | 0.01 |
| Yellow vegetables | 0.19 | 0.19 | 0.29 | 0.36 | 0.00 | 0.00 |
| Negatively rated | | | | | | |
| Butter | 7.54 | 4.43 | 4.69 | 2.82 | -4.56 | -2.64 |
| Fried poultry and fish | 0.10 | 0.08 | 0.18 | 0.10 | 0.29 | 0.18 |
| Fried potato | 0.55 | 0.34 | 0.37 | 0.20 | -0.26 | -0.17 |
| Grain dessert | 0.96 | 0.64 | 0.71 | 0.49 | -0.02 | -0.16 |
| Organ meat | 0.07 | 0.07 | 0.03 | 0.02 | -0.02 | -0.03 |
| Processed meat | 1.59 | 0.89 | 0.82 | 0.39 | -0.18 | -0.11 |
| Regular red meat | 3.48 | 2.08 | 2.61 | 1.50 | -1.42 | -0.92 |
| Salty snacks | 0.04 | 0.02 | 0.05 | 0.05 | 0.21 | 0.14 |
| Sauces | 5.82 | 4.07 | 5.35 | 3.78 | -2.75 | -1.76 |
| Soft drinks | 2.29 | 1.89 | 1.41 | 0.83 | -0.70 | -0.75 |
| Sweet breads | 1.65 | 0.88 | 0.99 | 0.58 | -0.46 | -0.26 |
| Sweet extra's | 2.56 | 1.76 | 1.85 | 1.05 | 0.16 | 0.20 |
| Whole fat dairy | 2.85 | 1.79 | 2.28 | 1.49 | -1.51 | -0.85 |

| white | | | | |
|---|---|---|---|---|
| male | female | | | |
| change 0-20 | Change 0-20 | p-value sex*race*time | p value race*time adjusted for race*sex and sex*time | p value sex*time adjusted for race*sex and race*time |
| 0.05 | 0.12 | 0.0540 | 0.0015 | 0.0098 |
| 0.05 | 0.08 | 0.8866 | 0.0008 | 0.1834 |
| -0.38 | -0.11 | 0.5848 | 0.0513 | <.0001 |
| 0.49 | 0.19 | 0.1544 | 0.1348 | 0.0068 |
| -0.02 | -0.02 | 0.4093 | 0.2930 | 0.9845 |
| 0.18 | 0.40 | 0.7415 | 0.2330 | 0.0121 |
| 0.37 | 0.50 | 0.6650 | 0.0180 | 0.0001 |
| 0.01 | -0.01 | 0.8765 | 0.0116 | 0.7634 |
| -0.12 | 0.25 | 0.0126 | 0.1897 | 0.0136 |
| -0.04 | 0.02 | 0.2717 | 0.6679 | 0.5701 |
| 1.50 | 1.23 | 0.4448 | 0.9043 | 0.0355 |
| -0.34 | 0.01 | 0.0344 | 0.0140 | 0.0148 |
| 0.25 | 0.09 | 0.4079 | 0.0134 | 0.0999 |
| 0.26 | 0.48 | 0.2960 | 0.3846 | 0.1327 |
| 0.38 | 0.66 | 0.4430 | 0.9087 | 0.0017 |
| -0.09 | 0.13 | 0.4154 | 0.8724 | 0.1067 |
| 0.02 | 0.11 | 0.3985 | 0.1549 | 0.0022 |
| -0.09 | 0.29 | 0.0035 | 0.8744 | 0.0114 |
| 0.25 | 0.25 | 0.2682 | <.0001 | 0.2469 |
| -0.05 | -0.01 | 0.4334 | 0.1135 | 0.3343 |
| -2.33 | -1.17 | 0.0182 | <.0001 | <.0001 |
| -0.05 | -0.03 | 0.0098 | <.0001 | 0.1145 |
| -0.18 | -0.09 | 0.5511 | <.0001 | <.0001 |
| 0.01 | -0.03 | 0.1696 | 0.0662 | 0.0605 |
| -0.02 | -0.01 | 0.1293 | 0.0166 | 0.3857 |
| 0.25 | 0.21 | 0.4047 | <.0001 | 0.9513 |
| -0.90 | -0.56 | 0.4361 | <.0001 | <.0001 |
| 0.23 | 0.23 | 0.1512 | 0.0263 | 0.0833 |
| -2.80 | -1.86 | 0.9159 | 0.9546 | <.0001 |
| -0.56 | -0.39 | 0.1258 | 0.0034 | 0.5266 |
| -0.17 | 0.03 | 0.7995 | <.0001 | <.0001 |
| -0.09 | 0.28 | 0.2538 | 0.5873 | 0.122 |
| -1.01 | -0.26 | 0.762 | <.0001 | <.0001 |

**SUPPLEMENTAL TABLE 3 (continued)** Changes in food groups, grouped according to their rating in the *A Priori* diet score, by race and sex, CARDIA 1985-86 to 2005-06

| | black | | white | | black | |
|---|---|---|---|---|---|---|
| | male | female | male | female | male | female |
| | Mean sv/d year 0 | mean sv/d year 0 | Mean sv/d year 0 | Mean sv/d year 0 | change 0-20 | change 0-20 |
| Neutrally rated | | | | | | |
| Chocolate | 0.20 | 0.20 | 0.18 | 0.18 | 0.00 | -0.05 |
| Diet soft drink | 0.10 | 0.15 | 0.43 | 0.85 | 0.20 | 0.14 |
| Eggs | 1.07 | 0.58 | 0.68 | 0.44 | -0.14 | -0.03 |
| Fruit juice | 2.69 | 2.04 | 1.78 | 1.33 | -0.99 | -0.94 |
| Lean red meat | 1.28 | 0.63 | 0.99 | 0.48 | -0.80 | -0.33 |
| Margarine | 2.14 | 1.65 | 1.79 | 1.36 | -0.85 | -0.71 |
| Meal replacements | 0.02 | 0.00 | 0.03 | 0.01 | 0.29 | 0.08 |
| Pickled food | 0.35 | 0.30 | 0.44 | 0.33 | 0.05 | 0.09 |
| Potatoes | 0.50 | 0.37 | 0.52 | 0.32 | -0.15 | -0.12 |
| Refined grains | 6.37 | 3.97 | 5.16 | 3.06 | -1.52 | -0.90 |
| Shellfish | 0.24 | 0.21 | 0.28 | 0.19 | 0.04 | 0.02 |
| Soups | 0.03 | 0.03 | 0.05 | 0.04 | 0.02 | 0.01 |
| Sugar substitutes | 0.01 | 0.05 | 0.06 | 0.12 | 0.25 | 0.49 |

| white | | | | |
|---|---|---|---|---|
| male | female | | | |
| change 0-20 | Change 0-20 | p-value sex*race*time | p value race*time adjusted for race*sex and sex*time | p value sex*time adjusted for race*sex and race*time |
| 0.06 | 0.01 | 0.6672 | 0.0047 | 0.0114 |
| 0.54 | 0.09 | 0.0013 | 0.0920 | <.0001 |
| -0.11 | 0.05 | 0.2433 | 0.0202 | 0.0001 |
| -0.68 | -0.77 | 0.5109 | 0.0181 | 0.705 |
| -0.39 | -0.06 | 0.1171 | <.0001 | <.0001 |
| -1.01 | -0.73 | 0.1437 | 0.1896 | 0.0758 |
| 0.14 | 0.04 | 0.0038 | <.0001 | <.0001 |
| 0.07 | 0.17 | 0.3567 | 0.1715 | 0.0502 |
| -0.17 | -0.08 | 0.1174 | 0.9251 | 0.0669 |
| -1.07 | -0.35 | 0.4246 | 0.0002 | <.0001 |
| -0.03 | 0.01 | 0.1200 | 0.0516 | 0.7904 |
| 0.02 | 0.02 | 0.2407 | 0.0693 | 0.3845 |
| 0.61 | 0.91 | 0.6444 | <.0001 | <.0001 |

**SUPPLEMENTAL TABLE 4** Changes in food groups, grouped according to their rating in the *A Priori* diet score, by educational attainment, CARDIA 1985-86 to 2005-06

| | year 0 | | year 7 | | year 20 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean sv/d <13 | Mean sv/d 13+ | Mean sv/d <13 | Mean sv/d 13+ | Mean sv/d <13 | Mean sv/d 13+ | absolute change <13 | absolute change 13+ | p value interaction <13 vs 13+ |
| Positively rated | | | | | | | | | |
| Avocado | 0.04 | 0.09 | 0.04 | 0.09 | 0.07 | 0.16 | 0.03 | 0.07 | 0.1685 |
| Beans | 0.27 | 0.20 | 0.30 | 0.25 | 0.23 | 0.25 | -0.04 | 0.05 | 0.0014 |
| Beer | 0.81 | 0.44 | 0.91 | 0.40 | 0.60 | 0.26 | -0.21 | -0.18 | 0.5568 |
| Coffee | 1.04 | 1.15 | 1.20 | 1.22 | 1.30 | 1.5 | 0.26 | 0.35 | 0.1604 |
| Fatty fish | 0.04 | 0.04 | 0.04 | 0.06 | 0.02 | 0.02 | -0.02 | -0.02 | 0.5961 |
| Fruit | 1.42 | 1.43 | 1.43 | 1.71 | 1.40 | 1.72 | -0.02 | 0.29 | 0.0055 |
| Green vegetables | 0.26 | 0.41 | 0.41 | 0.57 | 0.53 | 0.84 | 0.27 | 0.43 | 0.0012 |
| Lean fish | 0.66 | 0.71 | 0.69 | 0.66 | 0.73 | 0.77 | 0.07 | 0.06 | 0.5444 |
| Low fat dairy | 1.04 | 1.19 | 1.22 | 1.40 | 1.14 | 1.33 | 0.10 | 0.14 | 0.8740 |
| Liquor | 0.27 | 0.18 | 0.31 | 0.15 | 0.26 | 0.19 | -0.01 | 0.01 | 0.7610 |
| Oil | 1.33 | 1.50 | 3.34 | 3.23 | 2.65 | 2.77 | 1.32 | 1.27 | 0.3422 |
| Other vegetables | 2.20 | 2.08 | 2.26 | 2.33 | 1.96 | 2.04 | -0.24 | -0.04 | 0.0376 |
| Poultry | 1.28 | 1.23 | 1.53 | 1.46 | 1.43 | 1.46 | 0.15 | 0.23 | 0.3460 |
| Seeds nuts | 0.78 | 0.81 | 0.96 | 0.72 | 0.96 | 1.19 | 0.18 | 0.38 | 0.1215 |
| Soy products | 0.24 | 0.23 | 0.80 | 0.59 | 0.90 | 0.77 | 0.66 | 0.54 | 0.1475 |
| Tea | 0.51 | 0.64 | 0.39 | 0.48 | 0.51 | 0.72 | 0.00 | 0.08 | 0.4010 |
| Tomato | 0.46 | 0.49 | 0.58 | 0.65 | 0.48 | 0.55 | 0.02 | 0.06 | 0.8663 |
| Whole grains | 1.41 | 1.55 | 1.64 | 1.95 | 1.37 | 1.66 | -0.04 | 0.11 | 0.6243 |
| Wine | 0.12 | 0.17 | 0.08 | 0.17 | 0.12 | 0.32 | 0.00 | 0.15 | 0.0018 |
| Yellow vegetables | 0.2 | 0.27 | 0.18 | 0.26 | 0.19 | 0.26 | -0.01 | -0.01 | 0.9574 |
| Negatively rated | | | | | | | | | |
| Butter | 6.47 | 4.31 | 5.50 | 3.53 | 2.18 | 2.09 | -4.29 | -2.22 | <.0001 |
| Fried poultry and fish | 0.16 | 0.10 | 0.44 | 0.22 | 0.26 | 0.18 | 0.10 | 0.08 | 0.4496 |
| Fried potato | 0.49 | 0.32 | 0.41 | 0.27 | 0.25 | 0.16 | -0.24 | -0.16 | 0.2088 |
| Grain dessert | 0.79 | 0.66 | 0.87 | 0.75 | 0.79 | 0.58 | 0.00 | -0.08 | 0.0686 |

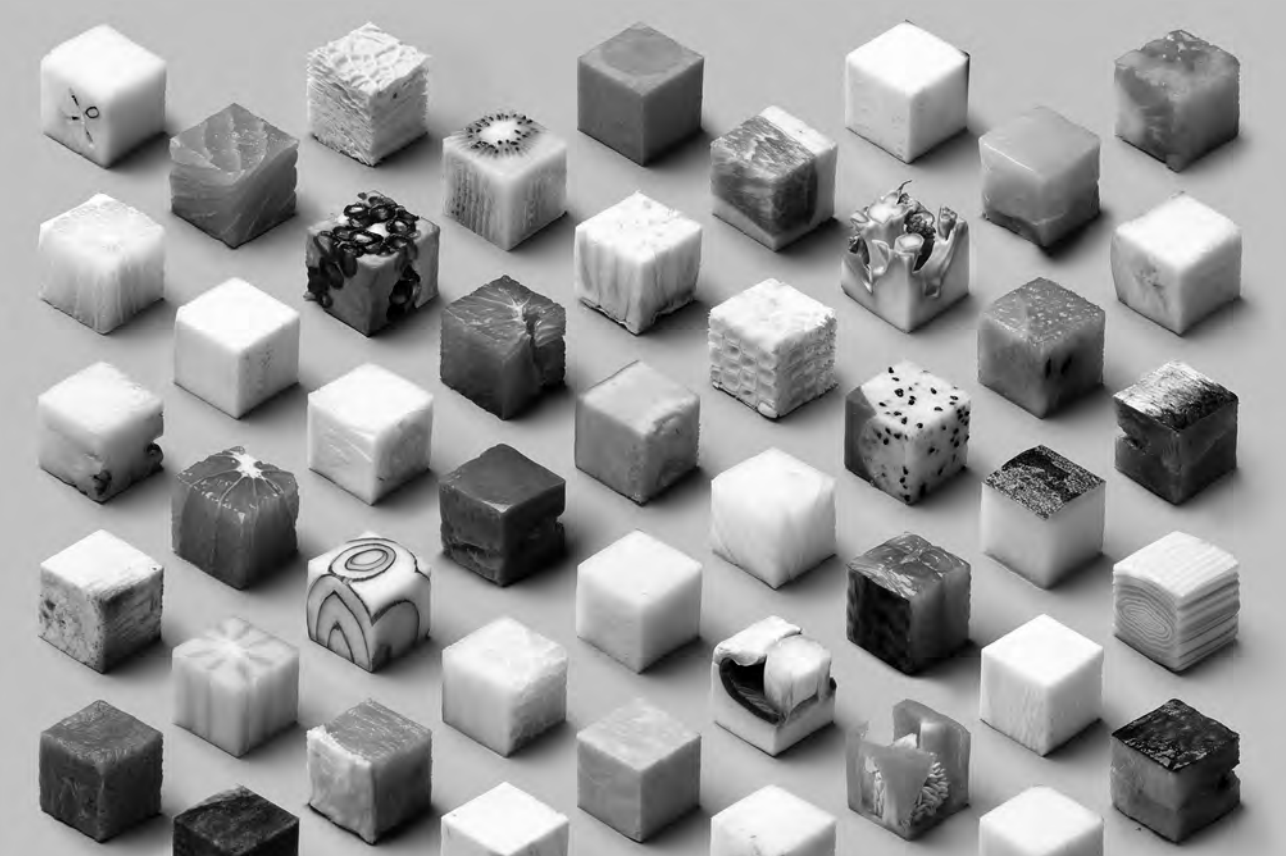
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Organ meat | 0.07 | 0.04 | 0.07 | 0.03 | 0.04 | 0.02 | -0.03 | -0.02 | 0.2845 |
| Processed meat | 1.44 | 0.75 | 1.25 | 0.71 | 1.19 | 0.87 | -0.25 | 0.12 | <.0001 |
| Regular red meat | 3.09 | 2.17 | 2.98 | 1.83 | 1.79 | 1.32 | -1.30 | -0.85 | 0.0245 |
| Salty snacks | 0.04 | 0.04 | 0.15 | 0.21 | 0.29 | 0.23 | 0.25 | 0.19 | 0.0016 |
| Sauces | 5.13 | 4.57 | 3.78 | 2.99 | 2.57 | 2.36 | -2.56 | -2.21 | 0.2393 |
| Soft drinks | 2.52 | 1.34 | 2.21 | 1.24 | 1.66 | 0.82 | -0.86 | -0.52 | 0.0157 |
| Sweet breads | 1.33 | 0.91 | 1.09 | 0.85 | 0.85 | 0.75 | -0.48 | -0.16 | 0.0020 |
| Sweet extra's | 2.33 | 1.62 | 2.07 | 1.48 | 2.04 | 1.84 | -0.29 | 0.22 | 0.0013 |
| Whole fat dairy | 2.58 | 1.92 | 1.78 | 1.39 | 1.15 | 1.18 | -1.43 | -0.74 | <.0001 |
| Neutrally rated | | | | | | | | | |
| Chocolate | 0.24 | 0.18 | 0.23 | 0.18 | 0.19 | 0.19 | -0.05 | 0.01 | 0.0284 |
| Diet soft drink | 0.15 | 0.45 | 0.49 | 0.77 | 0.44 | 0.68 | 0.29 | 0.23 | 0.1290 |
| Eggs | 0.92 | 0.61 | 0.89 | 0.50 | 0.75 | 0.58 | -0.17 | -0.03 | 0.0342 |
| Fruit juice | 2.11 | 1.90 | 1.52 | 1.55 | 1.21 | 1.03 | -0.90 | -0.87 | 0.9473 |
| Lean red meat | 1.11 | 0.74 | 0.76 | 0.50 | 0.39 | 0.45 | -0.72 | -0.29 | <.0001 |
| Margarine | 2.09 | 1.61 | 2.55 | 1.98 | 1.05 | 0.85 | -1.04 | -0.76 | 0.1667 |
| Meal replacements | 0.02 | 0.01 | 0.03 | 0.05 | 0.20 | 0.12 | 0.18 | 0.11 | 0.2217 |
| Pickled food | 0.37 | 0.35 | 0.41 | 0.36 | 0.40 | 0.46 | 0.03 | 0.11 | 0.1538 |
| Potatoes | 0.54 | 0.39 | 0.63 | 0.52 | 0.35 | 0.28 | -0.19 | -0.11 | 0.0752 |
| Refined grains | 5.82 | 4.20 | 6.64 | 5.02 | 4.24 | 3.41 | -1.58 | -0.79 | 0.0294 |
| Shellfish | 0.21 | 0.23 | 0.20 | 0.25 | 0.17 | 0.25 | -0.04 | 0.02 | 0.0495 |
| Soups | 0.04 | 0.04 | 0.05 | 0.05 | 0.04 | 0.06 | 0.00 | 0.02 | <.0001 |
| Sugar substitutes | 0.04 | 0.07 | 0.07 | 0.15 | 0.45 | 0.70 | 0.41 | 0.63 | 0.1368 |

# 3

# Diet quality and markers of endothelial function: The CARDIA study

Femke PC Sijtsma, Katie A Meyer, Lyn M Steffen, James M Shikany, Andrew O Odegaard, Myron D Gross, Daan Kromhout, David R Jacobs Jr

Nutr Metab Cardiovasc Dis 24(6): 632-638.



## ABSTRACT

**Background and aim:** Dietary patterns are associated cross-sectionally with cellular adhesion molecules (CAMs). We studied prospective associations of three dietary patterns with CAMs.

**Methods and results:** In the Coronary Artery Risk Development in Young Adults (CARDIA) study, diet was assessed at years 0 (1985-86) and 7 (1992-93) examinations. Four circulating CAMs (E-selectin, P-selectin, soluble intercellular adhesion molecule 1 (sICAM-1), and vascular cellular adhesion molecule (VCAM)) were assayed at years 7 and 15 (2000-01). We created one index score "*A Priori* Diet Quality Score" and derived dietary patterns using principal components analysis (PCA). Multivariable linear regression models predicted year 15 CAMs from averaged (year 0/7) dietary patterns. The *A Priori* Diet Quality Score rated 46 food groups beneficial, neutral or adverse based on hypothesized health effects. We derived two PCA dietary patterns: "fruit and vegetables (FV)" (high intakes of fruit, vegetables, and whole grains) and "meat" (high intakes of red meat, refined grain, and butter).

All dietary patterns were related to E-selectin and sICAM-1. P-selectin was not related to the FV dietary pattern. VCAM was only related to the *A Priori* Diet Quality Score. Strongest associations were for the meat dietary pattern with E-selectin (effect size 28% of an SD (+3.9/13.7 ng/mL)) and P-selectin (effect size 37% of an SD (+4.1/11.2 ng/mL)) and the *A Priori* Diet Quality Score with sICAM-1 (effect size 34% of an SD (-15.1/44.7 ng/mL)) and VCAM (effect size of 26% of an SD (-45.1/170.3 ng/mL)).

**Conclusion:** This prospective analysis suggests that dietary patterns are associated with CAMs.

## INTRODUCTION

Endothelial dysfunction occurs early in atherosclerotic development [1]. The cellular adhesion molecules (CAMs) E-selectin, P-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cellular adhesion molecule (VCAM), are expressed by inflamed endothelium and participate in recruitment and adhesion of leukocytes to endothelial cells [2]. Higher circulating concentrations of these CAMs indicate endothelial dysfunction, promote atherosclerosis, and associate with subclinical cardiovascular disease [3]. Diet influencing endothelial function may be a mechanism by which dietary quality affects the development of cardiovascular disease.

Clinical and experimental studies suggested that dietary n-3 fatty acids, antioxidant vitamins, folic acid, and L-arginine have beneficial effects on endothelial function, likely through multiple, complex mechanisms. Examples are inhibition of monocyte adhesion and platelet activation, increased nitric-oxide production and improvement of vasodilation, and blockage of lipid oxidation [4]. Randomized cross-over trials showed that Mediterranean-style diets improved endothelial function [5,6]. Cross-sectional studies found inverse associations between principal components analysis (PCA) derived dietary patterns and markers of endothelial function in women [7] and in ethnically diverse men and women [8]. Some, but not all, cross-sectional associations of different prudent dietary patterns were inverse with endothelial function [9]. One longitudinal study investigated consumption of food groups and markers of endothelial function, but overall dietary pattern was not assessed [10]. Associations of dietary patterns with markers of endothelial function have not been investigated in prospective studies.

We hypothesized that the *A Priori* Diet Quality Score and the FV dietary pattern with high loadings on fruit and vegetables is inversely related to E-selectin, P-selectin, sICAM-1, and VCAM. Similarly, we hypothesize that the meat dietary pattern with high loadings of meat, butter, and refined grains is positively related to these CAMs.

## METHODS

### Study sample

The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a multicenter, longitudinal investigation of the evolution of coronary heart disease risk starting in young adulthood [11]. CARDIA recruited a population based sample of 5115 black and white men and women aged 18-30 years in Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. Recruitment achieved roughly equal proportions of blacks (51.5%) and whites (48.5%), men (45.5%) and women

(54.5%), ages 18-24 y (44.9%) and 25-30 y (55.1%), and with ≤high school education (39.7%) or >high school education (60.3%). For the present study, we used dietary data collected at baseline (1985-86) and after 7 years of follow-up (1992-93). The response rates were 81% at year 7 and 74% at year 15 (2000-01). Young Adult Longitudinal Trends in Antioxidants (YALTA) and Circulating CAMs and the Vasculature are CARDIA ancillary studies in which the CAMs E-selectin, P-selectin, sICAM-1, and VCAM were measured in year 7 and year 15. Institutional Review Board approval and informed consent were obtained at each study center at every examination.

Participants who had missing dietary data (n = 4 at year 0 and n = 143 at year 7), or implausibly high or low energy intake (<800 or >8000 kcal/day for men, <600 or >6000 kcal/day for women) (n = 128 at year 0 and n = 94 at year 7) were excluded from analysis. Accounting for analysis-specific exclusions due to missing data for relevant exposures or covariates, we included 2789 participants for the prospective analysis of year 15 values of E-selectin and the average of year 0 and 7 dietary patterns, 2947 for P-selectin, 2911 for sICAM-1, and 2998 for VCAM.

## Blood collection and measurements of biomarkers

Overnight fasting blood samples were processed within 90 min of blood collection and stored at -70C until shipped on dry ice to a central laboratory. Participants were asked to fast ≥12 h and to avoid heavy physical activity and smoking for 2 h before examination. CAMs were assayed at the Molecular Epidemiology and Biomarker Research Laboratory in the University of Minnesota with sandwich ELISA methods from R & D Systems (E-selectin Cat No: DSLE00, P-selectin Cat No: BBE6, sICAM-1 Cat. No. DCD540 (year 7) and DY720 (year 15), and VCAM Cat No. DVC00). Serum (E-selectin) and plasma (P-selectin) samples from year 7 and 15 exams were diluted 10- and 6-fold, respectively. The within plus between day coefficients of variation (CV) were 7.7 and 10.5%, respectively. The E-selectin measurements for years 7 and 15 were performed over a period of several months, and no assay drift was evident during this time.

Serum (sICAM-1) samples from year 7 and 15 exams were diluted 10- and 400-fold and plasma (VCAM) samples 21-fold. The within plus between day CVs were <10% (both sICAM-1 assays) and 9.0% (VCAM). All VCAM analyses of the year 7 and 15 samples were performed over a few months in 2010, and no assay drift was detected during this time. To account for assay drift (P-selectin), assay change and the prevalence of the single nucleotide polymorphism rs5491 T-allele (sICAM-1), P-selectin and sICAM-1 were calibrated (details in the online Supplementary material).

## Other measurements

Standard questionnaires were used to obtain self-reported demographic and behavioral information across CARDIA examinations. Information on sex, race, date of birth, education, and cigarette smoking was collected by structured interview or self-administered questionnaire at each examination. Educational status was quantified as the maximum (at any examination) reported number of years of schooling completed. Self-reported smoking status was classified as never, former, or current. A physical activity score was derived from the CARDIA Physical Activity History. The total exercise score was in exercise units (a sum across 13 activities of frequency times intensity). Height and weight were measured at each examination and recorded to the nearest 0.5 cm and 0.2 kg, respectively. Body mass index (BMI) was calculated as weight(kg)/height$^2$(m).



## Dietary assessment and creation of dietary pattern scores

Diet assessment and the procedure for the creation of dietary patterns were described in detail elsewhere [12,13]. In summary, diet was assessed at years 0 and 7 by interviewer-administered CARDIA Diet History [14].

Foods were assigned to one of 166 food groups using the food grouping system devised by the University of Minnesota Nutrition Coordinating Center (NCC). We further collapsed these food groups into 46 food groups based on similar nutrient characteristics and comparability to food groups defined in previous studies [15-17]. The *A Priori* Diet Quality Score was created by classifying 46 foods groups as beneficial (n = 20), adverse (n = 13), or neutral (n = 13) in terms of hypothesized health effects [15-17]. The *A Priori* assignment for each of the 46 food groups (beneficial = "+", adverse = "-",neutral = "0") was described in detail elsewhere [12,13] and can be found in Supplementary Table 1.

The *A Priori* Diet Quality Score was the sum of category scores 0-4 for the beneficial items plus scores in reverse order (4-0) for adverse foods. Food groups that were considered neutral did not contribute to the overall *A Priori* Diet Quality Score. The theoretical maximum score was 132, higher scores indicating a healthier dietary pattern.

We used PCA with orthogonal rotation to derive uncorrelated dietary patterns and determine factor loadings for each of the 46 food groups. We selected the 2 principal components that explained the most dietary variance (Supplementary Table 1). We refer to these 2 factors as "meat dietary pattern" and "fruit and vegetable (FV) dietary pattern" to reflect their relatively high loadings of red meat (as well as refined grain and butter) or fruits and vegetables (as well as whole grains and lean fish), respectively. Factor loadings were generally consistent across years; factor loadings <0.20 were suppressed in Supplementary Table 1.

## Statistics

Unadjusted means of participant characteristics were calculated by quintiles of *A Priori* Diet Quality Score and the two dietary patterns. Multivariable adjusted linear regression models assessed associations of dietary patterns (averaged year 0 and 7, using 1 exam if the other was missing), each divided into consumption quintiles, to predict E-selectin, P-selectin, sICAM-1, and VCAM prospectively for CAMs at year 15. Parallel cross-sectional analyses for CAMs at year 7 were examined in sensitivity analyses, as was ability to predict change in CAMs between year 7 and year 15.

Separate regression analyses were conducted for each dietary pattern. Tests for trend used multivariable linear regression models with continuous dietary pattern scores. We studied different levels of adjustment. A minimal model (model 1) included sex (male, female), race (black, white), study center (Birmingham, Chicago, Minneapolis, Oakland), year 0 age (continuous), and total energy (continuous). The model was further adjusted for smoking status (current, never, former), educational attainment, and physical activity (model 2). To investigate BMI and waist circumference as potential intermediaries between dietary patterns and endothelial function, we included these variables in a subsequent model (model 3). We used the PC version (9.2) of the Statistical Analysis System (SAS, Cary, NC).

# RESULTS

## Baseline characteristics

Age, white race, and educational attainment were positively associated with the *A Priori* Diet Quality Score and the FV pattern and negatively related to the meat dietary pattern (Table 1). Total energy decreased across quintiles of the *A Priori* Diet Quality Score and increased both in the meat and in the FV dietary patterns. People at higher levels of the *A Priori* Diet Quality Score and FV dietary pattern were less likely to smoke and had a lower waist circumference; the reverse was true for people scoring high on the meat dietary pattern. BMI decreased across quintiles of the *A Priori* Diet Quality Score and FV dietary pattern and was not significantly associated with the meat dietary pattern. Physical activity increased across quintiles of all three dietary patterns.

Unadjusted concentrations of E-selectin, P-selectin, and sICAM-1 were all lower at higher values of the *A Priori* Diet Quality Score and the FV pattern and higher at higher values of the meat dietary pattern. VCAM showed a reverse pattern, being positively related to the *A Priori* Diet Quality Score and the FV pattern, but inversely related to the meat pattern.

Tracking correlation coefficients between year 7 and 15 were 0.57 for P-selectin, 0.77 for E-selectin, 0.59 for sICAM-1, and 0.70 for VCAM. Correlations were 0.39 between E-selectin and P-selectin, 0.44 between E-selectin and sICAM-1, 0.26 between P-selectin and sICAM, and lower than 0.2 for all other combinations.

## Dietary patterns and cellular adhesion molecules

In each multivariable model (Table 2), all three dietary patterns were associated with E-selectin. A strong association was seen with the meat dietary pattern ($p_{trend}$ < 0.001). In model 2, the mean E-selectin was 3.9 ng/mL higher in the highest meat dietary pattern quintile compared to the lowest. This was an effect size of 27% (3.9/13.7 ng/mL) of an SD.

P-selectin was inversely associated with the *A Priori* Diet Quality Score ($p_{trend}$ 0.004) and positively with the meat dietary pattern ($p_{trend}$ 0.02). The strongest association between P-selectin and diet was with the meat dietary pattern. The mean P-selectin was 4.1 ng/mL higher in the highest compared to the lowest meat dietary pattern quintile. This was an effect size of 37% (4.1/11.2 ng/mL) of an SD. P-selectin was not significantly associated with the FV dietary pattern.

All three dietary patterns were associated with sICAM-1. The *A Priori* Diet Quality Score was strongly inversely associated with sICAM-1 ($p_{trend}$ < 0.001). The mean sICAM-1 was 15.1 ng/mL lower in the highest vs. the lowest *A Priori* Diet Quality Score quintile. This was an effect size of 34% of an SD (15.1/44.7 ng/mL) for sICAM-1.

VCAM was inversely associated with the *A Priori* Diet Quality Score ($p_{trend}$ 0.006). The mean VCAM was 45.1 ng/mL lower in the highest vs. the lowest *A Priori* Diet Quality Score quintile. This was an effect size of 26% of an SD (45.1/170.3 ng/mL) for VCAM.

Further adjustment for BMI and waist (model 3) gave qualitatively similar results. Adjustment for plasma lipids (cholesterol, high-density lipoprotein and triglycerides) and measures of glucose metabolism (HOMA, glucose and insulin) did not substantively change the estimates shown in Model 3 of the association of diet with any of the CAMs (data not shown).

In a secondary analysis we examined associations of dietary patterns and CAMs at year 7 (Supplementary Table 2). Cross-sectional associations were generally weaker than the longitudinal analysis presented in Table 2 and in some cases did not reach statistical significance. Cross-sectional associations of dietary patterns formed exclusively from year 7 data with the CAMs were similar to findings in Supplementary Table 2 for the *A Priori* Diet Quality Score, but were somewhat weaker for the two principal components patterns (data not shown). Because the associations with the CAMs at year 15 tended to be stronger than the corresponding associations with CAMs at year 7, we looked at predicting evolution of the CAMs,

**TABLE 1** Characteristics of study sample (mean (SD)) according to quintiles of averaged year 0/7 dietary pattern scores[1,2]

| | *A Priori* Diet Quality Score[3] | | |
|---|---|---|---|
| | Q1 | Q3 | Q5 |
| Dietary pattern score | 48.2 (3.9) | 62.9 (1.9) | 81.2 (4.9) |
| Age (y) | 23.4 (3.8) | 25.0 (3.6) | 26.3 (2.9) |
| Female (%) | 46.7 | 52.6 | 65.7 |
| White (%) | 20.9 | 45.7 | 87.7 |
| Current smoker (%) | 34.0 | 29.0 | 16.3 |
| Education attained (years) | 14.1 (2.2) | 15.3 (2.5) | 16.9 (2.3) |
| Physical activity (exercise units) | 321.8 (248.0) | 362.8 (241.4) | 467.3 (244.5) |
| Mean total energy (kcal/day) | 3149 (1275.7) | 2845.1 (1219.4) | 2520.6 (924.2) |
| Body Mass Index (kg/m$^2$) | 26.1 (5.9) | 25.9 (5.3) | 24.2 (4.2) |
| Waist circumference (cm) | 82.3 (13.1) | 81.6 (12.1) | 76.9 (10.1) |
| E-selectin, year 7 (n=3028) | 36.8 (15.2) | 34.5 (14.6) | 29.5 (13.4) |
| E-selectin, year 15 (n=2789) | 38.7 (14.8) | 36.0 (13.3) | 30.4 (12.2) |
| P-selectin, year 7 (n=3818) | 29.7 (8.8) | 28.5 (8.8) | 26.7 (8.6) |
| P-selectin, year 15 (n=2947) | 38.3 (12.0) | 36.5 (10.2) | 34.3 (10.5) |
| sICAM-1, year 7 (n=2538) | 154.2 (32.2) | 144.0 (34.1) | 126.9 (26.8) |
| sICAM-1, year 15 (n=2911) | 167.1 (49.7) | 158.5 (48.1) | 137.1 (31.5) |
| VCAM, year 7 (n=3809) | 513.6 (202.7) | 516.6 (157.2) | 552.7 (160.7) |
| VCAM, year 15 (n=2998) | 514.6 (210.8) | 512.7 (151.5) | 540.0 (163.6) |

sICAM-1 soluble intercellular adhesion molecule 1, VCAM vascular cellular adhesion molecule.

[1] Data presented were averaged (year 0/7), except education (maximum attained over follow-up) and cellular adhesion molecules (as marked). N Z 3818 for all non CAM variables.

[2] Tests for trend of continuous variables were based on general linear regression with averaged year 0/7 dietary pattern as continuous independent variable adjusted for race sex center and age. Chi-square tests were used for categorical variables across all 5 levels of dietary pattern variables.

[3] Trend across *A Priori* Diet Quality Score significant at <0.05 for all variables except VCAM year 7 (p-value 0.29).

[4] Meat dietary pattern diet and FV dietary pattern are principal components, centered on zero with a standard deviation of 1.0.

[5] Trend FV dietary pattern significant at <0.05 for all variables except VCAM year 7 (p-value 0.48) and VCAM year 15 (p-value 0.64).

[6] Trends across Meat dietary pattern significant at <0.05 for all variables except waist (p-value 0.99), VCAM year 7 (p-value 0.35) and VCAM year 15 (p-value 0.15).

| FV dietary pattern[4,5] | | | Meat dietary pattern [4,6] | | |
|---|---|---|---|---|---|
| Q1 | Q3 | Q5 | Q1 | Q3 | Q5 |
| -1.0 (0.2) | -0.2 (0.1) | 1.3 (0.8) | -1.0 (0.2) | -0.2 (0.1) | 1.5 (0.7) |
| 24.1 (3.9) | 25.2 (3.5) | 25.7 (3.3) | 25.7 (3.4) | 25.1 (3.6) | 24.2 (3.7) |
| 60.1 | 55.5 | 48.3 | 84.9 | 53.9 | 20.7 |
| 22.4 | 57.0 | 73.4 | 74.5 | 54.0 | 28.9 |
| 35.0 | 26.5 | 19.4 | 14.5 | 25.5 | 46.6 |
| 14.2 (2.2) | 15.7 (2.5) | 16.3 (2.6) | 16.4 (2.4) | 15.7 (2.6) | 14.1 (2.3) |
| 269.9 (209.1) | 356.8 (219.7) | 505.1 (269.2) | 372.1 (209.4) | 354.1 (239.8) | 465.7 (275.7) |
| 2346.9 (1032.4) | 2624.7 (1011.2) | 3383.5 (1267.5) | 1743.1 (510.2) | 2554.5 (517.9) | 4582.3 (999.8) |
| 26.4 (5.9) | 25.6 (5.2) | 24.9 (4.8) | 24.7 (5.0) | 25.9 (5.6) | 25.3 (4.8) |
| 81.8 (12.9) | 80.7 (12.0) | 80.0 (11.8) | 75.8 (10.9) | 81.8 (12.4) | 83.0 (11.5) |
| 36.1 (15.6) | 33.7 (14.4) | 31.7 (13.8) | 29.1 (13.0) | 34.1 (14.6) | 38.6 (15.9) |
| 37.6 (14.5) | 35.6 (13.9) | 32.4 (12.5) | 31.0 (13.2) | 35.9 (14.2) | 38.9 (13.9) |
| 29.3 (9.8) | 28.5 (9.1) | 28.0 (9.0) | 25.6 (7.6) | 28.9 (9.2) | 31.9 (10.4) |
| 37.4 (10.7) | 37.2 (12.3) | 35.9 (11.1) | 34.7 (9.9) | 36.9 (11.2) | 39.4 (12.4) |
| 153.4 (32.7) | 140.4 (34.6) | 133.6 (30.7) | 131.6 (31.0) | 141.7 (30.1) | 153.2 (34.1) |
| 168.4 (50.8) | 153.8 (45.3) | 144.9 (35.2) | 143.3 (37.9) | 157.0 (48.9) | 163.8 (41.5) |
| 502.4 (170.5) | 517.9 (156.4) | 544.2 (168.6) | 549.3 (164.0) | 527.8 (163.5) | 512.3 (183.4) |
| 511.1 (195.7) | 519.4 (158.5) | 543.8 (170.8) | 539.2 (154.9) | 535.7 (178.7) | 514.2 (196.7) |

**TABLE 2** Estimates (SE) of year 15 soluble adhesion molecules per quintile of averaged year 0/7 dietary pattern

| | | Quintile of Dietary Pattern Consumption | | | | | |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | P-trend[1] |
| *A Priori* Diet Quality Score | E-selectin year 15 (35.1 (13.7)) | 446 | 514 | 576 | 643 | 639 | |
| | model 1 | 0 | -0.5 (0.8) | -1.3 (0.9) | -1.8 (0.9) | -4.2 (1.0) | <0.001 |
| | model 2 | 0 | -0.3 (0.8) | -0.7 (0.9) | -0.7 (0.9) | -2.4 (1.0) | 0.02 |
| | model 3 | 0 | -0.5 (0.8) | -0.8 (0.8) | -0.6 (0.9) | -1.8 (1.0) | 0.08 |
| | P-selectin year 15 (36.8 (11.2)) | 471 | 537 | 611 | 682 | 646 | |
| | model 1 | 0 | -0.4 (0.7) | -2.0 (0.7) | -1.2 (0.7) | -3.4 (0.8) | <0.001 |
| | model 2 | 0 | -0.3 (0.7) | -1.7 (0.7) | -0.6 (0.7) | -2.6 (0.8) | 0.004 |
| | model 3 | 0 | -0.4 (0.7) | -1.7 (0.7) | -0.6 (0.7) | -2.4 (0.8) | 0.009 |
| | sICAM-1 year 15 (154.7 (44.7)) | 464 | 531 | 603 | 674 | 639 | |
| | model 1 | 0 | -1.2 (2.7) | -5.6 (2.7) | -9.5 (2.8) | -21.2 (3.1) | <0.001 |
| | model 2 | 0 | -0.9 (2.6) | -4.3 (2.7) | -5.9 (2.8) | -15.1 (3.1) | <0.001 |
| | model 3 | 0 | -1.4 (2.6) | -4.3 (2.6) | -5.5 (2.7) | -12.9 (3.1) | <0.001 |
| | VCAM year 15 (525.8 (170.3)) | 417 | 541 | 618 | 657 | 665 | |
| | model 1 | 0 | -19.3 (10.1) | -32.4 (10.1) | -18.7 (10.6) | -45.4 (11.6) | 0.002 |
| | model 2 | 0 | -19.4 (10.2) | -32.1 (10.3) | -18.9 (11.0) | -45.1 (12.4) | 0.006 |
| | model 3 | 0 | -18.9 (10.2) | -31.9 (10.3) | -18.7 (11.0) | -45.5 (12.4) | 0.005 |
| FV dietary pattern | E-selectin year 15 | 495 | 551 | 576 | 583 | 584 | |
| | model 1 | 0 | -0.8 (0.8) | -0.7 (0.8) | -1.3 (0.9) | -3.5 (0.9) | <0.001 |
| | model 2 | 0 | 0.0 (0.8) | 0.4 (0.8) | 0.4 (0.9) | -1.3 (1.0) | 0.03 |
| | model 3 | 0 | 0.0 (0.8) | 0.5 (0.8) | 0.5 (0.9) | -1.2 (1.0) | 0.02 |
| | P-selectin year 15 | 524 | 585 | 600 | 619 | 619 | |
| | model 1 | 0 | -0.4 (0.7) | -0.6 (0.7) | -1.5 (0.7) | -2.2 (0.8) | 0.003 |
| | model 2 | 0 | 0.1 (0.7) | 0.1 (0.7) | -0.4 (0.7) | -0.8 (0.8) | 0.28 |
| | model 3 | 0 | 0.1 (0.7) | 0.2 (0.7) | -0.3 (0.7) | -0.8 (0.8) | 0.26 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | sICAM-1 year 15 | 520 | 574 | 594 | 617 | 606 | |
| | model 1 | 0 | -5.9 (2.6) | -10.2 (2.7) | -14.7 (2.8) | -18.5 (3.0) | <0.001 |
| | model 2 | 0 | -2.2 (2.5) | -4.5 (2.6) | -5.8 (2.8) | -7.5 (3.1) | 0.02 |
| | model 3 | 0 | -2.2 (2.5) | -4.0 (2.6) | -5.3 (2.7) | -7.1 (3.0) | 0.01 |
| | VCAM year 15 | 547 | 609 | 595 | 627 | 620 | |
| | model 1 | 0 | -19.8 (9.9) | -30.7 (10.3) | -26.0 (10.8) | -25.0 (11.6) | 0.18 |
| | model 2 | 0 | -19.7 (9.9) | -30.7 (10.5) | -26.1 (11.2) | -24.8 (12.2) | 0.25 |
| | model 3 | 0 | -19.5 (10.0) | -30.5 (10.5) | -25.8 (11.2) | -24.6 (12.2) | 0.26 |
| Meat dietary pattern | E-selectin year 15 | 570 | 594 | 503 | 561 | 461 | |
| | model 1 | 0 | 1.3 (1.0) | 3.0 (1.2) | 5.5 (1.3) | 6.2 (1.5) | <0.001 |
| | model 2 | 0 | 0.2 (1.0) | 1.5 (1.2) | 3.6 (1.4) | 3.9 (1.5) | <0.001 |
| | model 3 | 0 | 0.7 (1.0) | 1.9 (1.2) | 3.5 (1.3) | 3.3 (1.5) | 0.001 |
| | P-selectin year 15 | 600 | 633 | 637 | 693 | 484 | |
| | model 1 | 0 | 2.4 (0.8) | 3.8 (1.0) | 5.3 (1.1) | 5.7 (1.2) | <0.001 |
| | model 2 | 0 | 1.7 (0.8) | 2.9 (1.0) | 3.9 (1.1) | 4.1 (1.2) | 0.02 |
| | model 3 | 0 | 1.9 (0.8) | 3.0 (1.0) | 3.9 (1.1) | 3.9 (1.2) | 0.02 |
| | sICAM-1 year 15 | 599 | 625 | 634 | 581 | 472 | |
| | model 1 | 0 | 4.3 (3.3) | 12.7 (3.8) | 21.5 (4.4) | 26.7 (4.8) | <0.001 |
| | model 2 | 0 | -1.9 (3.2) | 3.9 (3.7) | 9.0 (4.3) | 11.9 (4.8) | 0.02 |
| | model 3 | 0 | -0.5 (3.1) | 4.9 (3.7) | 8.5 (4.2) | 9.8 (4.7) | 0.04 |
| | VCAM year 15 | 641 | 641 | 635 | 570 | 511 | |
| | model 1 | 0 | 10.1 (12.2) | -6.8 (14.4) | 14.8 (16.3) | 7.3 (18.2) | 0.73 |
| | model 2 | 0 | 10.5 (12.3) | -6.5 (14.6) | 16.2 (16.7) | 7.3 (18.8) | 0.67 |
| | model 3 | 0 | 9.9 (12.3) | -7.2 (14.7) | 15.7 (16.7) | 7.0 (18.8) | 0.67 |

sICAM-1 soluble intercellular adhesion molecule 1, VCAM vascular cellular adhesion molecule
Model 1: covariates include, race, sex, center, age, energy.
Model 2: model 1 plus smoking status, educational attainment and physical activity.
Model 3: model 2 plus BMI and waist.
[1] P-value for trend based on multivariate adjusted regression analysis with dietary pattern as a continuous values

using the full adjustment of model 3. Dependent variables were the year 15 CAM concentrations, co-varying the year 7 CAM concentrations. For the *A Priori* Diet Quality Score, these associations were in the expected direction, that is better diet predicted less increase in each CAM, but p-values were generally not significant (E-selectin n = 1941, t = 1.83, p = 0.07; P-selectin n = 2545, t = 1.56, p = 0.12; sICAM-1 n = 1698, t = 0.66, p = 0.51; VCAM n = 2580, t = 2.04, p = 0.04).

## DISCUSSION

We showed that CAMs are related longitudinally to dietary patterns. The *A Priori* Diet Quality Score was inversely related to E-selectin, P-selectin, sICAM-1, and VCAM. Using PCA, we identified an FV and a meat dietary pattern, which were, respectively, positively and inversely correlated with the *A Priori* Diet Quality Score. The FV dietary pattern was inversely associated with E-selectin and sICAM-1 but not with P-selectin and VCAM. The meat dietary pattern was positively associated with E-selectin, P-selectin, and sICAM-1, but not with VCAM. Although CAMs are related to adiposity, blood lipids, and insulin resistance, adjustment for the year 7 values of these variables did not suggest mediation of the diet-CAM associations.

Previous studies investigated cross-sectional associations of PCA-derived dietary patterns with CAMs. Nettleton et al. found that sICAM-1 was inversely associated with a "whole grain and fruit" pattern and positively related to a "bean, tomatoes and refined grain" pattern. "Fats and processed meats" and "vegetables and fish" patterns were not associated with sICAM-1, and E-selectin was not associated with any of the dietary patterns [8]. Similarly, Lopez-Garcia et al. found that E-selectin, sICAM-1, and VCAM were positively associated with a PCA-derived Western diet. A prudent diet was only inversely associated with E-selectin [7]. Fung et al. compared several diet quality scores and found E-selectin was inversely associated with all diet quality scores. sICAM-1 was inversely associated with the Alternate Healthy Eating Index (AHEI) [18] and Alternate Mediterranean Diet Index (aMED), and VCAM was only inversely associated to aMED [9].

This suggests that including different nutrients or food groups or different weightings of food groups included in the dietary patterns may affect the strength of the diet pattern associations with circulating markers of endothelial dysfunction. Diet quality scores are a stable characteristic compared to food groups or nutrients and are therefore a useful approach to study relations with CAMs. Although the findings are robust and in expected directions, there are differences in the strength of the associations of the CAMs and the three dietary patterns. All three dietary patterns were created using the same food groups, but the weightings of

the food groups differ between the two methods. The PCA approach weights each food group, normalized to its standard deviation. The *A Priori* Diet Quality Score first sorts food groups into beneficial, adverse, or neutral, then weights them by their quintile position in the intake distribution. The *A Priori* Diet Quality Score emphasized more beneficial food groups (n = 20) than adverse food groups (n = 13). In terms of the *a priori* ratings of food groups as beneficial or adverse, the FV pattern emphasized the beneficial groups, whereas the meat dietary pattern emphasized the adverse food groups.

Our study sample was relatively young (mean age 32 at year 7, and 40 in year 15), and had lower concentrations of CAMs compared to previous studies [7-9], which could in part explain why our cross-sectional analysis showed weaker associations than our longitudinal associations.

CAMs have an important role in the accumulation of circulating leukocytes at sites of injury, infection, and inflammation. This accumulation of leukocytes involves several steps (known as the leukocyte adhesion cascade) and cell types including T and B cells, monocytes and macrophages, dendritic cells, and natural killer cells. In the cascade, cells undergo tethering, rolling, activation, arrest, tight adhesion, and diapedesis. Unique combinations of endothelial adhesion molecules and chemokines direct tissue specific migration of leukocytes and control the various steps in the cascade [19-21]. For example, P and E-selectin are involved in the tethering, rolling, and activation of leukocytes. ICAM-1 facilitates monocyte/macrophage migration and adherence to endothelial cells. VCAM facilitates macrophage uptake into the subintimal space. Together, the CAMs form an integrated and overlapping system for the transport of leukocytes into the vascular wall and have an active role in the development of atherosclerotic plaque [22].

Our study has several strengths. First, repeated measurements of diet averaged for analysis may increase the reliability of our data. Second, because of the large CARDIA sample and extensive data we could adjust for important confounding variables. Third, our study included two primary methods to create dietary patterns. The *A Priori* Diet Quality Score is based on current judgment whereas the PCA patterns are based on correlations among food groups, as consumed by the participants. Fourth, repeated measurements of cellular adhesion molecules allowed us to investigate associations of dietary patterns with these markers both cross-sectionally and longitudinally.

Our study also has limitations. Although we accounted for many possible confounders, as in every observational study, we cannot rule out residual confounding.

In conclusion, both an *a priori* dietary score and *a posteriori* dietary patterns were related to endothelial function and support protective effects of a prudent dietary pattern high in fruits and vegetables and low in red meats, processed meats, and refined grains on health of the endothelium. The association of higher

diet quality with biomarkers of endothelial function should be considered as a possible pathway through which diet may affect the development of cardiovascular disease.

## ACKNOWLEDGMENTS

The authors' responsibilities were as follows: FPCS: Conceptualization, statistical analysis, interpretation, wrote and reviewed manuscript; KAM: Conceptualization, interpretation, wrote and reviewed manuscript; LMS: reviewed manuscript; director of CARDIA Diet Center; LvH, and JMS reviewed manuscript; MDG Secured funding, collected data, wrote and reviewed manuscript; AOO statistical analysis, wrote and reviewed manuscript; DK: conceptualization, interpretation, reviewed manuscript; DRJ: Secured funding, collected data, conceptualization, statistical analysis, interpretation, wrote and reviewed manuscript. FPCS, KAM, LMS, LvH, JMS, MDG, AOO, and DK declare no conflict of interest; DRJ is a member of the Scientific Advisory Board of the California Walnut Commission.

Source of Funding: Supported by contracts N01-HC-95095, N01-HC-48047, N01-HC-48048, N01-HC-48049 and N01-HC-48050 (CARDIA Study) and grants R01-HL-53560 (Young Adult Longitudinal Trends in Antioxidants), R01 HL093077 (Circulating CAMs and the Vasculature), and T32 HL07779, all from the National Heart, Lung, and Blood Institute, National Institutes of Health.

## REFERENCES


1. Ross R. Atherosclerosis an inflammatory disease. N Engl J Med 1999;340(2):115e26.
2. Calder PC, Ahluwalia N, Albers R, Bosco N, Bourdet-Sicard R, Haller D, et al. A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. Br J Nutr 2013;109(Suppl. 1):S1e34
3. Gross MD, Bielinski SJ, Suarez-Lopez JR, Reiner AP, Bailey K, Thyagarajan B, et al. Circulating soluble intercellular adhesion molecule 1 (sICAM-1) and subclinical atherosclerosis: the coronary artery risk development in young adults (CARDIA) study. Clin Chem. 2012;58(2):411e20
4. Brown AA, Hu FB. Dietary modulation of endothelial function: implications for cardiovascular disease. Am J Clin Nutr 2001;73(4): 673e86.
5. Marin C, Ramirez R, Delgado-Lista J, Yubero-Serrano EM, Perez- Martinez P, Carracedo J, et al. Mediterranean diet reduces endothelial damage and improves the regenerative capacity of endothelium. Am J Clin Nutr 2011;93(2):267e74.
6. Fuentes F, Lopez-Miranda J, Perez-Martinez P, Jimenez Y, Marin C, Gomez P, et al. Chronic effects of a high-fat diet enriched with virgin olive oil and a low-fat diet enriched with alphalinolenic acid on postprandial endothelial function in healthy men. Br J Nutr 2008;100(1):159e65.
7. Lopez-Garcia E, Schulze MB, Fung TT, Meigs JB, Rifai N, Manson JE, et al. Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr 2004;80(4):1029e35.
8. Nettleton JA, Steffen LM, Mayer-Davis EJ, Jenny NS, Jiang R, Herrington DM, et al. Dietary patterns are associated with biochemical markers of inflammation and endothelial activation in the multi-ethnic study of atherosclerosis (MESA). Am J Clin Nutr 2006;83(6):1369e79.
9. Fung TT, McCullough ML, Newby PK, Manson JE, Meigs JB, Rifai N, et al. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr 2005; 82(1):163e73.
10. van Bussel BC, Henry RM, Schalkwijk CG, Ferreira I, Feskens EJ, Streppel MT, et al. Fish consumption in healthy adults is associated with decreased circulating biomarkers of endothelial dysfunction and inflammation during a 6-year follow-up. J Nutr 2011 Sep; 141(9):1719e25.
11. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol 1988; 41(11):1105e16.
12. Meyer KA, Sijtsma FPC, Nettleton JA, Steffen LM, Van Horn L, Shikany JM, et al. Dietary patterns are associated with plasma F(2)-isoprostanes in an observational cohort study of adults. Radic Biol Med. 2013 Apr;57:201e9.
13. Sijtsma FP, Meyer KA, Steffen LM, Shikany JM, Van Horn L, Harnack L, et al. Longitudinal trends in diet and effects of sex, race, and education on dietary quality score change: the coronary artery risk development in young adults study. Am J Clin Nutr 2012; 95(3):580e6.
14. McDonald A, Van Horn L, Slattery M, Hilner J, Bragg C, Caan B, et al. The CARDIA dietary history: development, implementation, and evaluation. J Am Diet Assoc 1991;91(9):1104e12.
15. Jacobs DR, Sluik D, Rokling-Andersen MH, Anderssen SA, Drevon CA. Association of 1-y changes in diet pattern with cardiovascular disease risk factors and adipokines: results from the 1-y randomized Oslo diet and exercise study. Am J Clin Nutr 2009; 89(2):509e17.
16. Lockheart MS, Steffen LM, Rebnord HM, Fimreite RL, Ringstad J, Thelle DS, et al. Dietary patterns, food groups and myocardial infarction: a case-control study. Br J Nutr 2007; 98(2):380e7.
17. Nettleton JA, Schulze MB, Jiang R, Jenny NS, Burke GL, Jacobs Jr DR. *A Priori* -defined dietary patterns and markers of cardiovascular disease risk in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr 2008;88(1):185e94.
18. McCullough ML, Feskanich D, Stampfer MJ, Giovannucci EL, Rimm EB, Hu FB, et al. Diet quality and major chronic disease risk in men ad women: moving toward improved dietary guidance. Am J Clin Nutr 2002;76(6):1261e71.
19. von Andrian UH, Mackay CR. T-cell function and migration. Two sides of the same coin. N Engl J Med 2000;343(14):1020e34.

20. Cyster JG. Homing of antibody secreting cells. Immunol Rev 2003; 194:48e60.
21. Campbell DJ, Kim CH, Butcher EC. Chemokines in the systemic organization of immunity. Immunol Rev 2003;195:58e71.
22. Galkina E, Ley K. Leukocyte influx in atherosclerosis. Curr Drug Targets 2007;8(12):1239e48.

## SUPPLEMENTAL MATERIAL

### Calibration of P-selectin and sICAM-1

The P-selectin measurement for year 15 was performed in 2003, while that for year 7 was performed in 2010. Although the method was the same for both years, assay drift was noted and an adjustment was made to account for it, calibrating based on sample reruns in 2012. The calibration was year 7 P-selectin in year 15 scaling = 2.1336 + 1.1812 * year 7 P-selectin as measured in 2010.

The assay used for the year 7 samples for sICAM-1 was affected by the prevalence of the single nucleotide polymorphism (SNP) rs5491 T-allele, which is common in blacks and rare in whites. It produces an isoform of sICAM-1 that was detectable using the year 15 assay, but was not detectable using the year 7 assay. Therefore the amount of detectable sICAM-1 was reduced in heterozygotes for this SNP. Genotype information was available for the participants and the year 7 results could be adjusted both for the assay change and for the presence of the genetic variant. Based on sample reruns in 2012, in homozygous A-allele blacks, year 7 sICAM-1 recalibrated to the year 15 scale = 60.9559 + 0.3876 * year 7 sICAM-1 as measured in 2010. In homozygous rs5491 A-allele whites, the recalibration was year 7 sICAM-1 recalibrated to the year 15 scale = 24.5845 + 0.5138 * year 7 sICAM-1 as measured in 2010. In heterozygous blacks, year 7 sICAM-1 recalibrated to the year 15 scale = 86.0227 + 0.6374 * year 7 sICAM-1 as measured in 2010. In heterozygous rs5491 whites, the recalibration was year 7 sICAM-1 recalibrated to the year 15 scale = 26.2139 + 0.8449 * year 7 sICAM-1 as measured in 2010. sICAM-1 was not detectable in the few rs5491 T homozygotes, who were omitted.

### Dietary patterns

At baseline the mean (SD) *A Priori* Diet Quality Score was 64.1(13.0) and 67.5(12.1) in year 7. We derived two PCA dietary patterns: "fruit and vegetables (FV)" (high intakes of fruit, vegetables, and whole grains) and "meat" (high intakes of red meat, refined grain, and butter). At year 0, eigenvalues for the meat and FV dietary pattern were 4.7 and 2.8, respectively, with proportion of variance explained of 10.3% for the meat dietary pattern and 6.1% for the FV dietary pattern.

Tracking correlations coefficients between year 0 and 7 were 0.66 for the *A Priori* Diet Quality Score, 0.50 for the FV dietary pattern, and 0.59 for the meat dietary pattern. The averaged (year 0 and 7) *A Priori* Diet Quality Score correlated positively with the averaged FV dietary pattern score (r = 0.64) and negatively with the averaged meat dietary pattern score (r = -0.32); the multiple correlation coefficient of the *A Priori* Diet Quality Score regressed on both of the principal components scores was 0.80.

**SUPPLEMENTAL TABLE 1** Description of the *A Priori* Diet Quality Score and the PCA-derived meat and FV dietary pattern factor loadings.

| CARDIA Food Groups | *A Priori* Diet Quality Score | FV dietary pattern[1] | | Meat dietary pattern[1] | |
|---|---|---|---|---|---|
| | Rating | Year 0 | Year 7 | Year 0 | Year 7 |
| Avocado | + | 0.44 | 0.27 | | |
| Beans | + | | 0.35 | 0.29 | |
| Beer | + | | | 0.25 | 0.32 |
| Coffee | + | | | | |
| Fish | + | | | | |
| Fruit | + | 0.49 | 0.51 | | |
| Green vegetables | + | 0.56 | 0.64 | | |
| Lean fish | + | 0.38 | 0.35 | | |
| Low fat dairy | + | 0.28 | 0.27 | | |
| Liquor | + | | | | 0.20 |
| Oil | + | 0.45 | 0.40 | 0.25 | 0.38 |
| Other vegetables | + | 0.69 | 0.73 | 0.23 | |
| Poultry | + | 0.20 | 0.26 | 0.25 | 0.31 |
| Seeds, nuts | + | 0.34 | | | |
| Soy products | + | | | | |
| Tea | + | | | | |
| Tomato | + | 0.53 | 0.59 | | |
| Whole grains | + | 0.40 | 0.42 | | |
| Wine | + | 0.21 | 0.20 | | |
| Yellow vegetables | + | 0.47 | 0.54 | | |
| Butter | - | | | 0.70 | 0.65 |
| Fried foods | - | | | | 0.35 |
| Fried potatoes | - | | | 0.54 | 0.52 |
| Grain dessert | - | | | 0.39 | 0.39 |
| Organ meat | - | | | | 0.22 |
| Processed meat | - | | | 0.58 | 0.54 |
| Regular red meat | - | | | 0.60 | 0.71 |
| Salty snacks | - | | 0.27 | | |
| Sauces | - | 0.32 | 0.31 | 0.34 | 0.59 |
| Soft drink | - | -0.21 | -0.22 | 0.41 | 0.43 |
| Sweet breads | - | | | 0.58 | 0.43 |
| Sweet extras | - | | | 0.39 | 0.32 |
| Whole fat dairy | - | | | 0.43 | 0.44 |

**SUPPLEMENTAL TABLE 1 (continued)** Description of the *A Priori* Diet Quality Score and the PCA-derived meat and FV dietary pattern factor loadings.

| CARDIA Food Groups | *A Priori* Diet Quality Score | FV dietary pattern[1] | | Meat dietary pattern[1] | |
|---|---|---|---|---|---|
| | Rating | Year 0 | Year 7 | Year 0 | Year 7 |
| Chocolate | 0 | | | | |
| Diet soft drink | 0 | | 0.21 | | |
| Eggs | 0 | | | 0.50 | 0.53 |
| Fruit juice | 0 | 0.21 | 0.22 | 0.20 | |
| Lean red meat | 0 | | | 0.36 | 0.34 |
| Margarine | 0 | | | 0.27 | 0.33 |
| Meal replacement | 0 | | | | |
| Pickled foods | 0 | 0.34 | 0.35 | | 0.23 |
| Potatoes | 0 | 0.22 | | 0.34 | 0.27 |
| Refined grains | 0 | | | 0.72 | 0.71 |
| Shellfish | 0 | 0.24 | 0.29 | | |
| Soups | 0 | | 0.30 | | |

[1] Factor loadings <0.20 are suppressed.

**SUPPLEMENTAL TABLE 2** Estimates (SE) of year 7 soluble adhesion molecules per quintile of averaged year 0/7 dietary pattern

| | | | Quintile of Dietary Pattern Consumption | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | 5 | Ptrend[1] |
| *A Priori* Diet Quality Score | E-selectin year 7 (33.8 (14.7)) | | 471 | 584 | 634 | 692 | 647 | |
| | | model 1 | 0 | -0.4 (0.9) | -1.2 (0.9) | -1.4 (0.9) | -4.0 (1.0) | <0.001 |
| | | model 2 | 0 | 0.0 (0.9) | -0.5 (0.9) | -0.1 (0.9) | -2.1 (1.1) | 0.10 |
| | | model 3 | 0 | -0.3 (0.8) | -0.6 (0.9) | 0.0 (0.9) | -1.2 (1.0) | 0.50 |
| | P-selectin year 7 (28.6 (9.3)) | | 621 | 720 | 794 | 855 | 828 | |
| | | model 1 | 0 | 0.5 (0.5) | -1.1 (0.5) | -1.2 (0.5) | -2.3 (0.6) | <0.001 |
| | | model 2 | 0 | 0.6 (0.5) | -0.9 (0.5) | -0.9 (0.5) | -1.8 (0.6) | <0.001 |
| | | model 3 | 0 | 0.6 (0.5) | -0.9 (0.5) | -0.8 (0.5) | -1.5 (0.6) | <0.001 |
| | sICAM-1 year 7 (141.1 (32.6)) | | 371 | 465 | 515 | 605 | 582 | |
| | | model 1 | 0 | -4.3 (2.2) | -7.3 (2.2) | -9.4 (2.2) | -19.2 (2.4) | <0.001 |
| | | model 2 | 0 | -2.9 (2.0) | -3.9 (2.0) | -4.1 (2.1) | -10.8 (2.4) | <0.001 |
| | | model 3 | 0 | -3.4 (2.0) | -3.9 (2.0) | -3.9 (2.1) | -9.6 (2.3) | 0.001 |
| | VCAM year 7 (526.4 (170.0)) | | 621 | 721 | 792 | 849 | 826 | |
| | | model 1 | 0 | -21.2 (8.9) | -17.8 (9.0) | -13.2 (9.3) | -18.8 (10.2) | 0.40 |
| | | model 2 | 0 | -21.3 (9.0) | -19.0 (9.1) | -15.3 (9.6) | -21.7 (10.8) | 0.27 |
| | | model 3 | 0 | -20.5 (8.9) | -19.0 (9.1) | -15.6 (9.6) | -24.9 (10.8) | 0.15 |
| FV dietary pattern | E-selectin year 7 | | 543 | 600 | 606 | 660 | 619 | |
| | | model 1 | 0 | -1.1 (0.8) | -2.0 (0.9) | -2.7 (0.9) | -4.4 (1) | <0.001 |
| | | model 2 | 0 | -0.4 (0.8) | -0.8 (0.9) | -1.2 (0.9) | -2.2 (1) | 0.07 |
| | | model 3 | 0 | -0.4 (0.8) | -0.8 (0.9) | -1.1 (0.9) | -2.2 (1) | 0.05 |
| | P-selectin year 7 | | 698 | 748 | 767 | 823 | 782 | |
| | | model 1 | 0 | -0.9 (0.5) | -1.4 (0.5) | -1.9 (0.5) | -2.8 (0.6) | <0.001 |
| | | model 2 | 0 | -0.6 (0.5) | -1.0 (0.5) | -1.3 (0.5) | -2.0 (0.6) | <0.001 |
| | | model 3 | 0 | -0.6 (0.5) | -1.0 (0.5) | -1.3 (0.5) | -2.0 (0.6) | <0.001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | sICAM-1 year 7 | | 441 | 495 | 498 | 569 | 535 | |
| | | model 1 | 0 | -7.4 (2.0) | -9.6 (2.1) | -13.9 (2.1) | -18.0 (2.3) | <0.001 |
| | | model 2 | 0 | -3.3 (1.9) | -4.0 (2.0) | -6.1 (2.1) | -7.3 (2.3) | 0.12 |
| | | model 3 | 0 | -3.0 (1.9) | -4.0 (2.0) | -5.9 (2.0) | -7.1 (2.3) | 0.13 |
| | VCAM year 7 | | 698 | 747 | 764 | 823 | 777 | |
| | | model 1 | 0 | 0.3 (8.7) | -16.3 (8.9) | 0.3 (9.2) | -4.7 (10.1) | 0.58 |
| | | model 2 | 0 | -1.7 (8.7) | -19.2 (9.1) | -3.5 (9.6) | -10.0 (10.7) | 0.89 |
| | | model 3 | 0 | -1.8 (8.7) | -19.3 (9.1) | -3.9 (9.5) | -10.1 (10.7) | 0.89 |
| Meat dietary pattern | E-selectin year 7 | | 603 | 634 | 637 | 591 | 563 | |
| | | model 1 | 0 | 2.6 (1.0) | 4.3 (1.2) | 6.0 (1.3) | 7.7 (1.5) | <0.001 |
| | | model 2 | 0 | 1.6 (1.0) | 2.7 (1.2) | 3.9 (1.4) | 5.2 (1.6) | 0.001 |
| | | model 3 | 0 | 2.3 (1.0) | 2.9 (1.2) | 3.7 (1.3) | 4.4 (1.5) | 0.002 |
| | P-selectin year 7 | | 775 | 796 | 794 | 751 | 702 | |
| | | model 1 | 0 | 2.5 (0.6) | 3.3 (0.7) | 4.7 (0.8) | 5.7 (0.9) | <0.001 |
| | | model 2 | 0 | 2.1 (0.6) | 2.7 (0.7) | 3.8 (0.8) | 4.8 (0.9) | 0.002 |
| | | model 3 | 0 | 2.3 (0.6) | 2.8 (0.7) | 3.9 (0.8) | 4.6 (0.9) | 0.002 |
| | sICAM-1 year 7 | | 541 | 532 | 541 | 492 | 432 | |
| | | model 1 | 0 | 7.5 (2.4) | 16.0 (2.8) | 25.0 (3.2) | 27.0 (3.6) | <0.001 |
| | | model 2 | 0 | 2.4 (2.3) | 6.5 (2.7) | 12.2 (3.1) | 11.8 (3.5) | 0.20 |
| | | model 3 | 0 | 2.8 (2.3) | 6.1 (2.7) | 11.2 (3.1) | 10.0 (3.4) | 0.34 |
| | VCAM year 7 | | 772 | 794 | 793 | 749 | 701 | |
| | | model 1 | 0 | 0.3 (10.5) | -8.8 (12.3) | -6.0 (14.0) | 22.8 (15.6) | 0.006 |
| | | model 2 | 0 | 2.8 (10.6) | -4.3 (12.6) | 0.6 (14.3) | 16.5 (16.2) | 0.02 |
| | | model 3 | 0 | 0.0 (10.6) | -6.1 (12.5) | 0.1 (14.3) | 15.1 (16.1) | 0.02 |

sICAM-1 soluble intercellular adhesion molecule 1, VCAM vascular cellular adhesion molecule 1

[1]P-value for trend based on multivariate adjusted regression analysis with dietary pattern as a continuous value

Model 1: covariates include, race, sex, center, age, energy

Model 2: model 1 plus smoking status, educational attainment and physical activity

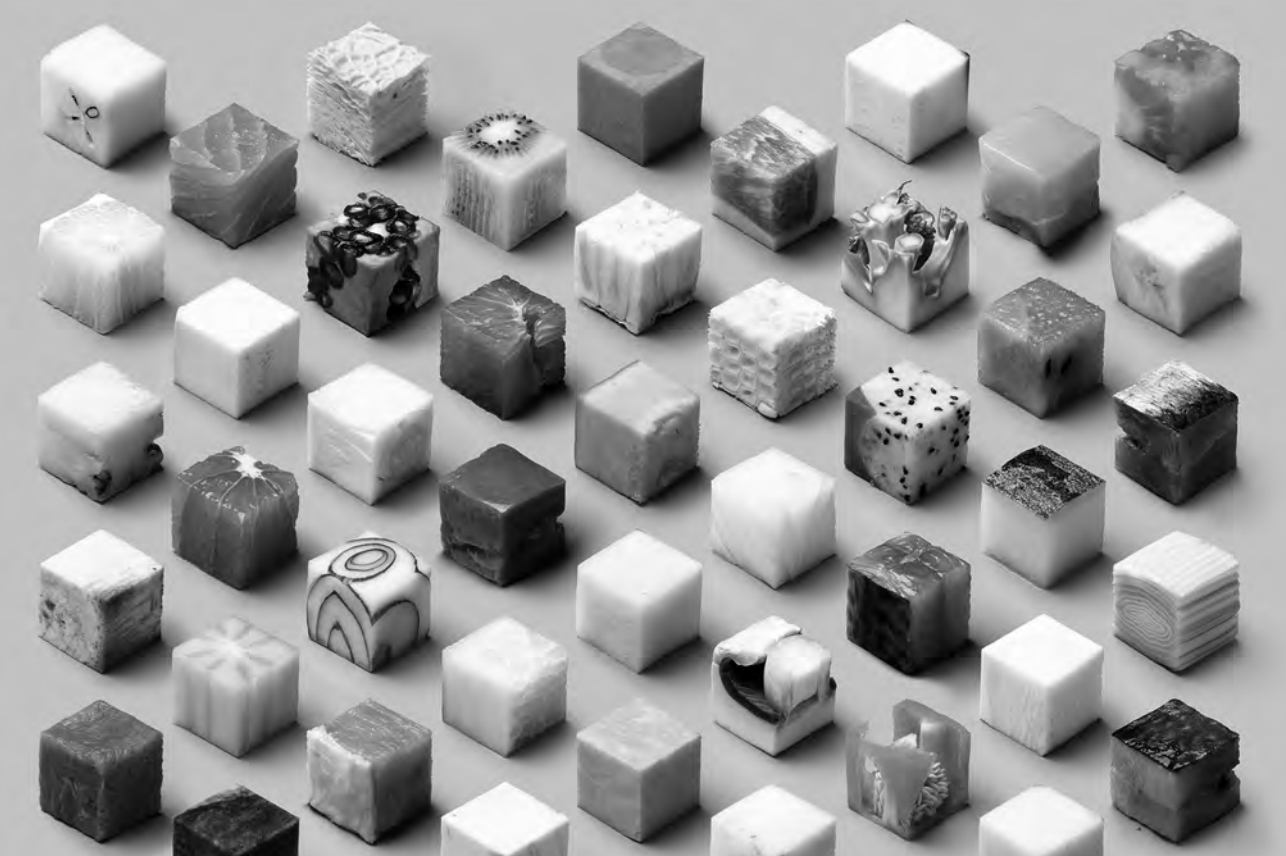
Model 3: model 2 plus BMI and waist

# 4

# Dietary patterns are associated with plasma F2-isoprostanes in an observational cohort study of adults

Katie A. Meyer, Femke P.C. Sijtsma, Jennifer A. Nettleton, Lyn M. Steffen, Linda Van Horn, James M. Shikany, Myron D. Gross, Jaakko Mursu, Maret G. Traber, David R. Jacobs Jr.

Free radical biology & medicine 57(0): 201-209.



## ABSTRACT

Associations between individual foods or nutrients and oxidative markers have been reported. Comprehensive measures of food intake may be uniquely informative, given the complexity of oxidative systems and the possibility of antioxidant synergies. We quantified associations over a 20-year history between three food-based dietary patterns (summary measures of whole diet) and a plasma biomarker of lipid peroxidation, $F_2$-isoprostanes, in a cohort of Americans ages 18–30 at year 0 (1985–1986). We assessed diet at years 0, 7, and 20 through a detailed history of past-month food consumption and supplement use and measured plasma $F_2$-isoprostanes at years 15 and 20. We created three dietary patterns: (1) *a priori* ("*A Priori* Diet Quality Score") based on hypothesized healthfulness of foods, (2) an empirical pattern reflecting high fruit and vegetable intake ("fruit–veg"), and (3) an empirical pattern reflecting high meat intake ("meat"). We used linear regression to estimate associations between each dietary pattern and plasma $F_2$-isoprostanes cross-sectionally (at year 20, n=2736) and prospectively (year 0/7 average diet and year 15/20 average $F_2$-isoprostanes, n=2718), adjusting for age, sex, race, total energy intake, education, smoking, body mass index, waist circumference, physical activity, and supplement use. In multivariable-adjusted cross-sectional analysis, the *A Priori* Diet Quality Score and the fruit–veg diet pattern were negatively, and the meat pattern was positively, associated with $F_2$-isoprostanes (all p values <0.001). These associations remained statistically significant in prospective analysis. Our findings suggest that long-term adherence to a diet rich in fruits and vegetables and low in red meat may decrease lipid peroxidation.

## INTRODUCTION

Oxidative stress is hypothesized to play a role in the pathogenesis of cardiovascular and other chronic diseases [1,2]. Oxidative stress is a dynamic and complex biologic process, making its direct assessment challenging. Various markers of oxidative damage have been proposed, of which $F_2$-isoprostanes, a measure of lipid peroxidation, are considered the most reliable [3-5]. Findings from observational and intervention studies have been mixed with respect to the association between diet and $F_2$-isoprostanes [6-9]. Studies have generally focused on individual foods or nutrients, however, and very little is known about the effects of diet as a whole on $F_2$-isoprostanes [10, 11].

We considered that a whole-diet approach might be particularly well-suited to the study of oxidative processes, which are possibly influenced by a range of foods. The notion that studying diet comprehensively, rather than through isolated foods and nutrients, may yield unique information is not new [12], but has gained traction in the past decade among nutritional epidemiologists [13, 14]. Dietary patterns, summary measures of whole diet, may better reflect the complexity of diet, may better capture synergistic aspects of dietary components, and may be more powerful and reliable measures in observational epidemiology, in which dietary exposures are prone to larger measurement errors [12-14].

In this study, we quantified the associations of three dietary patterns and plasma $F_2$-isoprostanes in the Coronary Artery Risk Development in Young Adults (CARDIA) study, a large, longitudinal cohort study of black and white Americans. We hypothesized that dietary patterns reflective of a high diet quality (rich in plant foods, low in red meat) would be inversely associated with plasma $F_2$-isoprostanes and that these associations would be observable over long-term follow-up. We further hypothesized that whole-diet associations would not be completely explained by consumption of dietary antioxidant nutrients or supplement use.

## MATERIALS AND METHODS

### Study sample

CARDIA is a multicenter, longitudinal study of the evolution of coronary heart disease risk starting in young adulthood [15]. CARDIA began in 1985–1986 with a group of 5115 black and white adults ages 18–30 years from four metropolitan areas (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA, USA). Study participants were sampled to obtain roughly equal numbers of blacks (51.5%) and whites (48.5%), men (45.5%) and women (54.5%), and ages 18–24 (44.9%) and 25–30 years (55.1%), and those with a high school education or less (39.7%) or more

than a high school education (60.3%). Follow-up examinations were conducted during 1987–1988 (Year 2), 1990–1991 (Year 5), 1992–1993 (Year 7), 1995–1996 (Year 10), 2000–2001 (Year 15), and 2005–2006 (Year 20). A majority of the surviving cohort membership has been examined at each of the follow-up examinations (91, 86, 81, 79, 74, and 72%, respectively). The Young Adult Longitudinal Trends in Antioxidants (YALTA) ancillary study assayed $F_2$-isoprostanes in year 15 and 20 CARDIA plasma samples. CARDIA and YALTA were approved by the institutional review board of each field center; each study participant provided informed written consent.

## Clinical measures

Participants were asked to fast for ≥12 h and to avoid heavy physical activity and smoking for the 2 h before each CARDIA exam. Blood was collected from participants in EDTA-containing and serum Vacutainer tubes and stored at 4 °C. Within 90 min of collection, blood samples were separated through centrifugation, aliquotted into airtight vials, flash-frozen, and stored at −70 °C until shipped. Samples were delivered overnight on dry ice to a central laboratory and stored at −70 °C until analysis.

In years 15 and 20, plasma free $F_2$-isoprostanes were measured with a gas chromatography–mass spectrometry-based method [16] by the Molecular Epidemiology and Biomarker Research Laboratory at the University of Minnesota (Minneapolis, MN, USA), as previously described [17]. All samples were analyzed within 1 year of collection. Substudies demonstrated the stability of $F_2$-isoprostanes (no ex vivo loss or formation) during blood collection and processing procedures. Analytical variation of the method was 10% for each of three control pools assembled in 2000 and assayed repeatedly between October 2000 and August 2007; the values of these control pools were stable over time, implying that both assay and stored samples were stable. Thus year 15 and 20 plasma $F_2$-isoprostane concentrations are directly comparable (Figure 1). A separate quality control approach used 368 blind duplicate pairs (which included non-assay variance attributable to phlebotomy, sample handling, and labeling, as well as to chemical analysis). In the blind duplicate analysis, the overall technical error was 20.1% and the test–retest correlation was 0.84.

## Other baseline measurements

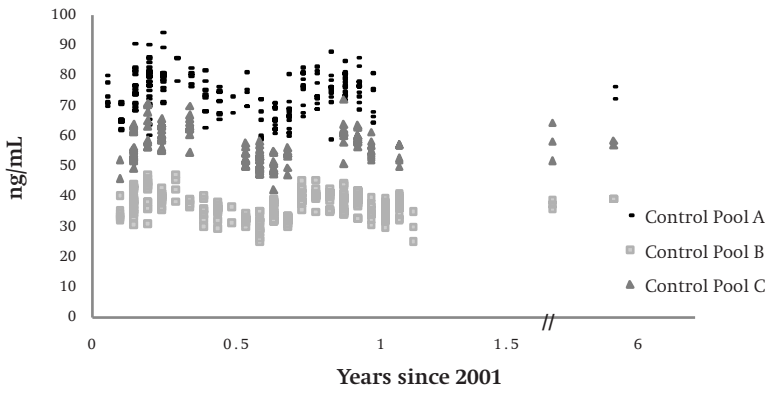
Standard questionnaires were used to obtain self-reported demographic and behavioral information across CARDIA examinations. Sex, race, date of birth, education, cigarette smoking, weekly alcohol consumption, and vitamin supplement use were ascertained by structured interview or self-administered questionnaire at each examination. Educational status was quantified as the maximum (at any visit) reported number of years of schooling completed.

Self-reported smoking status was classified as never, former, or current smoker. Alcohol consumption in drinks per week was computed from self-reported frequency of beer, wine, and liquor consumption. Participants reported their use of dietary supplements, including brand, dose, and frequency of use. Physical activity was assessed with the validated interview-administered CARDIA Physical Activity History, a simplified version of the Minnesota Leisure Time Physical Activity Questionnaire [18], from which a score was calculated by multiplying participants' self-reported activity frequency by the activity intensity and summing over activities. Height and weight were measured by study staff at each examination and recorded to the nearest 0.5 cm and 0.2 kg, respectively. Body mass index (BMI) was defined as weight (kg) divided by height squared ($m^2$).

## Dietary assessment and food group creation

Diet was assessed at years 0, 7, and 20 by participant self-report to an interviewer-administered validated diet history. Interviewers asked study participants open-ended questions about dietary consumption in the past month within 100 food categories, referencing 1609 separate food items in years 0 and 7 and several thousand separate food items in year 20. For example, an affirmative response to the question: "Do you usually eat bread?" was followed with open-ended questions






| | Control Pool B | Control Pool C | Control Pool A |
|---|---|---|---|
| N | 233 | 142 | 209 |
| Mean | 36.7 | 56.6 | 73.7 |
| CV | 11.1% | 10.0% | 9.4% |

**FIGURE 1** $F_2$-isoprostane concentrations 2000–2007 in repeatedly measured control pools stored at −70 °C since 2000

about the type of bread (e.g., white, whole wheat/mixed grains, rye) and, for each bread type, the frequency of consumption (as servings per day, week, or month). The complete CARDIA diet history can be viewed online at http://www.cardia.dopm.uab.edu/images/more/doc/D10006.PDF.

Detailed diet history data were coded by the University of Minnesota Nutrition Coordinating Center (NCC). Recipes were decomposed into constituent foods and assigned a number of servings per day. Foods were placed into 166 food groups using the food grouping system devised by the NCC. Food group intake was calculated as the total number of servings per day each food within the food group was consumed. From the 166 food groups within the NCC system, we excluded 6 infant products (not relevant), unsweetened water, and nongrain flour (rarely consumed). We further collapsed the remaining 158 food groups into 46 food groups, as shown in Supplementary Table 1, to approximate those previously established by study coauthors [19, 20]. Food groups were created based on considerations of similar nutrient characteristics, hypothesized biologic effects, and comparability to food groups defined in previous studies [19, 20].

## Description of dietary patterns

We created a dietary pattern, *a priori*, by classifying foods groups as beneficial (n=20), adverse (n=13), or neutral (n=13) in terms of hypothesized health effects (Supplementary Table 2) [19, 20]. We categorized the 33 non-neutral food groups into quintiles of consumption, scored the food group consumption as 0 to 4 for beneficial or 4 to 0 (the reverse) for adverse foods, depending on the study participant's quintile level of consumption, and summed across all 33 food groups. For food groups with a large proportion of non-consumers, we coded non-consumers as 0 and consumers were categorized into quartiles. The theoretical maximum score was 132, with a baseline mean of 64 (SD 13, range 25–110). Higher scores indicate higher hypothesized diet quality (1 point corresponds to a shift in a single food group to the next higher quintile), and we thus refer to this summary measure as the "*A Priori* Diet Quality Score."

We additionally derived two dietary patterns empirically, based on the study participants' self-reported dietary consumption. We used principal components analysis (PCA) with orthogonal rotation to derive uncorrelated dietary patterns from the 46 food groups. This is an established approach to studying dietary patterns [13, 21]. We refer to these dietary patterns as the "fruit–veg" and "meat" diet patterns to reflect dietary consumption patterns that were relatively high in fruits and vegetables or meat, respectively. PCA results, presented as factor loadings, were generally consistent across years 0 and 7 (Supplementary Table 2).

The two methods for constructing dietary patterns differ conceptually. The *A Priori* Diet Quality Score is based on our beliefs, guided by the scientific literature,

about the health effects of foods, whereas the two empirically derived dietary patterns are based on a statistical correlation structure of food consumption, based on CARDIA participants' reported consumption. We note that the PCA still incorporates *a priori* considerations about diet and nutrition reflected in decisions about diet assessment and food group creation. All three dietary patterns are completely food-based, and in this way differ from approaches to dietary pattern construction that incorporate both foods and nutrients [12, 13].

## Reliability of dietary data

A baseline reliability study of nutrient consumption comparing two CARDIA diet histories administered 1 month apart found substantial sex- and energy-adjusted test–retest correlations, ranging from 0.27 (polyunsaturated fat) to 0.82 (saturated fat) [22]. We lack reliability data for foods and dietary patterns in the CARDIA diet validation study. However, in another large prospective cohort study, short-term reliability coefficients for dietary patterns [23] were generally in the same range as for foods [24] and nutrients [25]. In our data, participants' dietary patterns were characterized by long-term stability exceeding that observed for food or nutrient consumption. Correlation coefficients for dietary patterns at years 0 and 7 were 0.66 for the *A Priori* Diet Quality Score, 0.50 for the fruit–veg diet pattern, and 0.59 for the meat diet pattern, whereas correlation coefficients for nutrients or foods were generally lower than 0.40. For example, the correlation coefficient for years 0 and 7 dietary α-tocopherol was 0.24 and the coefficient for years 0 and 7 fruit consumption was 0.33.

## Statistical analysis

We used linear regression to quantify cross-sectional and prospective associations between dietary patterns and plasma $F_2$-isoprostanes. In the prospective analyses, we calculated averages of each of the three dietary patterns assessed at years 0 and 7 and of $F_2$-isoprostanes measured at years 15 and 20. We averaged diet and biomarker data because: 1) there was no biologic reason for choosing specific years for prospective analysis, 2) averaging across examination years increased the sample size (by including people for whom only one measure was available), and 3) averaging may improve the stability of dietary [26] and biomarker [27] data obtained in epidemiologic studies. However, we note that findings for prediction of year 20 $F_2$-isoprostanes from year 0 diet patterns did not yield substantially different findings from those presented (data not shown).

Separate regression analyses were conducted for each of the three dietary patterns, as independent variables, and plasma $F_2$-isoprostanes. Dietary patterns were modeled as quintiles of consumption and continuously, using the p value from the continuous model to assess linear trend. All regression models adjusted

for participant sex (male, female), study center (Birmingham, Chicago, Minneapolis, Oakland), race (white, black), age (continuous), and total energy (continuous). A fuller model included educational attainment (≤high school, some college, ≥college), current cigarette smoking (current, never/former), supplement use (yes/no), physical activity (continuous exercise units), BMI (continuous), and waist circumference (continuous). In subsequent analysis, we additionally adjusted for dietary consumption of several antioxidants, including α-tocopherol, ascorbic acid, vitamin A, and α- and β-carotene. We included the nutrient-adjusted analysis to examine the extent to which antioxidant nutrients appeared to account for associations between dietary patterns and $F_2$-isoprostanes. We also quantified associations between dietary patterns and $F_2$-isoprostanes separately among supplement users and nonusers. For cross-sectional analysis, we adjusted for year 20 covariate values; for prospective analysis, we adjusted for covariate values averaged across years 0 and 7. If dietary, covariate, or $F_2$-isoprostanes data were available for only 1 of the 2 years (year 0 or 7), we used the single year's value in the analysis. Potential intermediates were handled the same. To address possible non-normality in $F_2$-isoprostanes, we included linear regression analysis of natural logarithm-transformed $F_2$-isoprostanes. We also considered the possibility that associations may differ for high values of $F_2$-isoprostanes, and thus included logistic regression analysis of those at or above vs below the 75th percentile of $F_2$-isoprostanes. All analyses were completed with the PC version (9.2) of SAS (Cary, NC, USA).

We excluded from analysis clinic attendees who had missing dietary data (n=4 at year 0, 143 at year 7, and 406 at year 20) or who reported implausibly high or low energy intake (<800 or >8000 kcal/day for men, <600 or >6000 kcal/day for women) (n=128 at year 0, 94 at year 7, and 54 at year 20). Data on plasma $F_2$-isoprostanes were missing for 670 participants at year 15 and 486 at year 20. After exclusions and accounting for missing data, we had 2736 participants available for year 20 cross-sectional analysis and 2718 available for prospective analysis. Other exclusions were analysis-specific, based on missing data for covariates.

## RESULTS

### Dietary patterns

The *A Priori* Diet Quality Score, created from hypothesized health effects of foods, reflected a diet consistent with dietary guidelines, with low consumption of red meat and refined grains and high consumption of fruits and vegetables and whole grains. For example, among participants in the 1st, 3rd, and 5th quintiles of the *A Priori* Diet Quality Score, the respective mean daily servings of red meat were 2.1,

1.4, and 0.8; whole grains were 0.9, 1.6, and 2.2; and green vegetables were 0.2, 0.6, and 1.6. The *A Priori* Diet Quality Score was not low fat, but had fat consumption consistent with a Mediterranean diet, with higher consumption of oil (2.1, 2.1, and 3.8 servings/day within 1st, 3rd, and 5th quintiles) and nuts and seeds (0.6, 1.0, and 1.9) and lower consumption of fried potatoes (0.3, 0.2, and 0.1) and butter (2.5, 2.0, 1.4).

Principal components analysis revealed two major patterns of dietary consumption among CARDIA participants. One pattern, the fruit–veg diet, was characterized by higher consumption of fruit, green vegetables, yellow vegetables, whole grains, and nuts and seeds (Table 1). The meat diet was characterized by higher consumption of red meat, processed meat, butter, fried potatoes, and refined grains (Table 1). Food-specific loading scores for each pattern are shown in Supplementary Table 2. The fruit–veg diet was positively correlated and the meat diet was negatively correlated with the *A Priori* Diet Quality Score (respectively, at year 20, r=0.69 and r=−0.42). The meat and fruit–veg dietary patterns were the first two principal components and together explained 7.5% of the total variance in the 46 food groups at year 0, 8.1% at year 7, and 7.3% at year 20. The meat diet explained slightly more of the variance than the fruit–veg diet (4.4% vs 3.2%, 4.6% vs 3.5%, and 3.9% vs 3.4% from orthogonal rotated analysis of year 0, 7, and 20 data, respectively). Other factors explained less than 2% each of the total variance. In addition to explaining the most variance, the first two factors were conceptually appealing: the patterns distinguished participants on consumption of major food groups and are broadly consistent with other studies reporting results for "Western" and "prudent" dietary patterns derived from PCA.

## Year 20 characteristics of the study sample according to dietary patterns

Dietary patterns were associated with participant characteristics (Table 1). People who ranked high on the *A Priori* Diet Quality Score or the fruit–veg diet pattern were more likely to be white, have a college degree, and use supplements. They were less likely to smoke. In contrast, participants who ranked high on the meat diet were more likely to be black or to smoke and were less likely to have a college degree or use supplements. BMI and waist circumference decreased across quintiles of the *A Priori* Diet Quality Score and fruit–veg pattern and increased across quintiles of the meat dietary pattern. Physical activity increased across quintiles of the *A Priori* Diet Quality Score and the fruit–veg pattern, but was stable across quintiles of the meat pattern. We note that in energy-adjusted models, exercise decreased across quintiles of the meat dietary pattern.

**TABLE 1** Characteristics of study sample at year 20 according to quintiles of year 20 dietary pattern scores, CARDIA 2005–2006, n=2736[1]

| | *A Priori* Diet Quality Score[2,3] | | |
|---|---|---|---|
| | Q1 | Q3 | Q5 |
| n | 540 | 614 | 571 |
| Dietary pattern score (mean (SD)) | 3.4 (0.4) | 4.7 (0.2) | 6.2 (0.4) |
| $F_2$-isoprostanes (pg/ml) | 63.0 (35.4) | 56.2 (31.9) | 43.5 (17.6) |
| Age, years | 24.2 (3.8) | 25.2 (3.5) | 26.0 (3.3) |
| Female (%) | 49.3 | 54.4 | 66.0 |
| White (%) | 31.3 | 54.9 | 81.3 |
| College degree (%) | 32.8 | 50.7 | 77.1 |
| Current smoker (%) | 28.4 | 20.9 | 9.2 |
| Supplement user (%) | 32.6 | 52.9 | 67.6 |
| Body mass index (kg/m2) | 30.6 (7.3) | 29.8 (6.8) | 27.0 (5.7) |
| Waist circumference, cm | 95.1 (15.7) | 92.9 (15) | 85.9 (13.6) |
| Physical activity (exercise units) | 240 (233) | 332 (275) | 452 (297) |
| Mean total energy (kcal/day) | 2495 (1185) | 2251 (1039) | 2292 (806) |
| Dietary α-tocopherol (mg/day) | 8.4 (6.5) | 9.9 (8.5) | 15.4 (10.6) |
| Dietary ascorbic acid (mg/day) | 114 (124) | 163 (251) | 204 (177) |
| Dietary vitamin A (IU/day) | 5320 (3653) | 8636 (6326) | 15,168 (10,784) |
| Dietary α-carotene (μg/day) | 282 (433) | 564 (997) | 1113 (1472) |
| Dietary β-carotene (μg/day) | 1953 (1759) | 3679 (3094) | 7439 (5850) |
| Fruit (sv/day) | 0.8 (1) | 1.6 (1.9) | 2.5 (2.0) |
| Green vegetables (sv/day) | 0.2 (0.3) | 0.6 (0.6) | 1.6 (1.3) |
| Yellow vegetables (sv/day) | 0.1 (0.2) | 0.2 (0.3) | 0.5 (0.6) |
| Oil (sv/day) | 2.1 (4.6) | 2.1 (4.1) | 3.8 (6.0) |
| Refined grains (sv/day) | 4.6 (3) | 3.5 (2.5) | 2.5 (1.7) |
| Red meat (sv/day) | 2.1 (1.9) | 1.4 (1.3) | 0.8 (0.9) |
| Whole grains (sv/day) | 0.9 (1.1) | 1.6 (1.4) | 2.2 (1.5) |
| Seeds and nuts (sv/day) | 0.6 (1.4) | 1.0 (1.6) | 1.9 (2.3) |
| Processed meat (sv/day) | 1.3 (1.1) | 0.9 (0.9) | 0.6 (0.8) |
| Fried potatoes (sv/day) | 0.3 (0.4) | 0.2 (0.2) | 0.1 (0.1) |
| Butter (sv/day) | 2.5 (2.6) | 2.0 (2.2) | 1.4 (1.9) |

sv/day, servings per day.

[1] Tests for trend of continuous variables were based on general linear regression with dietary pattern as continuous independent variable. $\chi 2$ tests were used for categorical variables across all five levels of the dietary pattern.

[2] *A Priori* score is expressed in standard deviation (SD) units to facilitate comparison with the PCA scores. The overall mean (SD) of the *A Priori* Diet Quality Score at year 20 was 70.3 (12.8).

[3] All variables significant at $p < 0.01$

[4] Meat diet and fruit–vegetable diet scores are principal components, centered on 0 with a standard deviation of 1.0.

[5] All variables significant at $p < 0.01$ except gender (0.39) and processed meat (0.021).

[6] All variables significant at $p < 0.01$ except physical activity (p=0.22), dietary vitamin A (0.21), dietary α-carotene (0.25), dietary β-carotene (0.036), whole grains (0.34), and seeds and nuts (0.33).

| Fruit–veg dietary pattern[4,5] | | | Meat dietary pattern[4,6] | | |
|---|---|---|---|---|---|
| Q1 | Q3 | Q5 | Q1 | Q3 | Q5 |
| 547 | 548 | 547 | 547 | 548 | 547 |
| −1.1 (0.2) | −0.2(0.1) | 1.5 (0.9) | −1.0 (0.2) | −0.2(0.1) | 1.6 (1.0) |
| 64.0 (35.5) | 53.7 (28.5) | 44.6 (19.7) | 51.2 (28.6) | 53.2 (28.6) | 56.5 (29.6) |
| 24.1 (3.9) | 25.3 (3.5) | 25.6 (3.4) | 25.8 (3.4) | 25.2 (3.7) | 24.8 (3.6) |
| 56.1 | 55.1 | 54.3 | 82.1 | 60.0 | 28.0 |
| 27.6 | 62.2 | 70.6 | 62.9 | 56.6 | 41.3 |
| 28.9 | 58 | 68.7 | 64.4 | 54.7 | 35.8 |
| 27.4 | 15.1 | 12.7 | 9.4 | 15.2 | 32.1 |
| 30.9 | 55.3 | 62.9 | 62.2 | 53.5 | 36.9 |
| 30.6 (7.3) | 29.4 (6.9) | 28.3 (6.3) | 27.8 (6.3) | 29.6 (6.4) | 30.4 (7.6) |
| 93.9 (15.3) | 92.0 (15.4) | 89.6 (15.2) | 85.3 (13.9) | 92 (13.9) | 97.2 (16.6) |
| 221 (217) | 340 (264) | 459 (308) | 351 (272) | 305 (255) | 353 (305) |
| 2035 (1019) | 2252 (1001) | 2927 (1104) | 1539 (574) | 2121 (542) | 3718 (1111) |
| 6.2 (3.5) | 10.4 (10.7) | 18.7 (11.3) | 10.1 (10.4) | 10.3 (9.2) | 14.3 (8.6) |
| 95.3 (182.5) | 165 (232) | 261 (220) | 139 (134) | 161 (217) | 207 (234) |
| 4228 (2683) | 8107 (4061) | 19,122 (14,153) | 11,242 (13,012) | 8774 (6850) | 10,688 (8012) |
| 207 (306) | 507 (621) | 1498 (2292) | 845 (189) | 553 (757) | 673 (995) |
| 1541 (1300) | 3406 (2020) | 9347 (7533) | 5462 (6934) | 3900 (3620) | 4395 (4158) |
| 0.6 (0.7) | 1.4 (1.1) | 3.0 (2.6) | 2.1 (2.4) | 1.6 (1.7) | 1.5 (1.6) |
| 0.2 (0.2) | 0.6 (0.5) | 1.8 (1.4) | 1.1 (1.3) | 0.7 (0.8) | 0.6 (0.7) |
| 0.1 (0.1) | 0.2 (0.2) | 0.6 (0.7) | 0.4 (0.6) | 0.2 (0.3) | 0.2 (0.3) |
| 1.6 (3.2) | 2.0 (4.0) | 4.2 (6.8) | 1.7 (3.1) | 2.4 (4.5) | 4.4 (8.7) |
| 3.8 (2.6) | 3.5 (2.5) | 3.3 (2.5) | 1.5 (0.9) | 3.0 (1.3) | 6.4 (3.1) |
| 1.7 (1.7) | 1.4 (1.4) | 1.3 (1.4) | 0.5 (0.4) | 1.1 (0.7) | 3.0 (2.1) |
| 0.7 (0.9) | 1.6 (1.2) | 2.5 (2.0) | 1.6 (1.4) | 1.6 (1.5) | 1.5 (1.5) |
| 0.4 (0.8) | 1.0 (1.5) | 2.3 (3.0) | 1.2 (2.0) | 1.0 (1.6) | 1.0 (1.9) |
| 1.0 (1.0) | 0.8 (0.8) | 0.9 (1.1) | 0.3 (0.3) | 0.8 (0.7) | 1.8 (1.5) |
| 0.3 (0.4) | 0.2 (0.2) | 0.1 (0.2) | 0.1 (0.1) | 0.1 (0.1) | 0.4 (0.5) |
| 1.7 (2.0) | 2.1 (2.4) | 2.3 (2.7) | 0.9 (0.9) | 1.8 (1.8) | 3.7 (3.3) |

## Year 20 characteristics of the study sample according to plasma $F_2$-isoprostanes

Plasma $F_2$-isoprostanes were negatively associated with physical activity, supplement use, and educational attainment and were positively associated with cigarette smoking, BMI, and waist circumference (Table 2). Across quintiles of $F_2$-isoprostanes, dietary intake of α-tocopherol, ascorbic acid, vitamin A, and α- and β-carotene decreased (Table 2). Year 15 and 20 $F_2$-isoprostanes were correlated at 0.62. The distribution of $F_2$-isoprostanes was left-skewed, as evidenced by the large standard deviation for the 5th quintile of $F_2$-isoprostanes.

## Cross-sectional associations between dietary patterns and plasma $F_2$-isoprostanes

At year 20, plasma $F_2$-isoprostane concentrations were associated with each of the three diet measures (Figure 2), in multivariable-adjusted regression models (adjusted for age, gender, race, study center, total energy consumption, smoking, education, supplement use, physical activity, BMI, and waist circumference). $F_2$-isoprostane concentrations decreased across quintiles of the *A Priori* Diet Quality Score (mean 61.6, 56.7, 56.6, 50.0, and 44.3 pg/ml, $p_{trend}$ ≤0.0001) and the fruit–veg dietary pattern (mean 62.1, 55.2, 54.6, 51.5, and 45.7 pg/ml, $p_{trend}$ ≤0.0001), whereas they increased across quintiles of the meat dietary pattern (mean 48.0, 53.1, 52.4, 55.3, and 60.4 pg/ml, $p_{trend}$ ≤0.0001). Findings were materially similar from regression analysis of natural logarithm-transformed $F_2$-isoprostanes, though the transformation yielded a smaller range of geometric mean values from the 1st to the 5th quintile of dietary pattern (Supplementary Table 3). Logistic regression analysis of those at or above vs those below the 75th percentile did not reveal anomalous associations between diet and high $F_2$-isoprostanes (data not shown).

The associations between dietary pattern and $F_2$-isoprostanes were similar among supplement nonusers and users: $F_2$-isoprostanes were negatively associated with the *A Priori* Diet Quality Score and the fruit–veg pattern and positively associated with the meat pattern (Table 3).

Additional adjustment for dietary antioxidant nutrients, including α-tocopherol, ascorbic acid, vitamin A, and α- and β-carotene, did not materially change estimated mean $F_2$-isoprostanes across quintiles of consumption of the *A Priori* Diet Quality Score or the fruit–veg dietary pattern among supplement nonusers and users. The association between the meat dietary pattern and $F_2$-isoprostanes was attenuated to a greater extent upon adjustment for dietary antioxidants, particularly among supplement users. For example, among supplement users, comparing the 1st and 5th quintiles of meat dietary pattern consumption, the estimated $F_2$-isoprostanes means were 44.8 (41.6, 48.0) and 58.0 (53.2, 62.7) before adjustment for dietary antioxidant nutrients and 47.0 (43.8, 50.3) and 53.8 (48.8, 58.7) after adjustment

**TABLE 2** Characteristics of study sample at year 20 according to quintiles of year 20 plasma $F_2$-isoprostanes, CARDIA 2005–2006.

| | Quintile of $F_2$-isoprostanes | | | | | p value[1] |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | |
| n | 547 | 547 | 550 | 545 | 547 | |
| $F_2$-isoprostanes (pg/ml) | 28.1 (3.9) | 37.5 (2.3) | 46.2 (3.0) | 58.4 (4.3) | 98.9 (36.0) | |
| Age at baseline (years) | 25.6 (3.4) | 24.9 (3.5) | 25.1 (3.5) | 24.9 (3.7) | 25.1 (3.7) | 0.34 |
| Female (%) | 48.1 | 45.2 | 51.5 | 61.5 | 75.9 | <0.0001 |
| White (%) | 60.9 | 58.3 | 57.1 | 49.2 | 51.0 | 0.0010 |
| College degree (%) | 65.5 | 60.5 | 52.9 | 47.7 | 41.1 | <0.0001 |
| Current smoker (%) | 11.2 | 16.0 | 18.7 | 22.6 | 25.3 | <0.0001 |
| Supplement user (%) | 65.3 | 52.8 | 52.0 | 40.9 | 44.2 | <0.0001 |
| Body mass index (kg/m2) | 26.7 (4.6) | 27.7 (5.6) | 28.7 (6.4) | 30.7 (7.1) | 32.9 (8.2) | <0.0001 |
| Waist circumference (cm) | 86.9 (12.5) | 89.1 (13.5) | 90.7 (15.2) | 94.6 (16.4) | 97.3 (16.5) | <0.0001 |
| Physical activity (exercise units) | 396 (284) | 386 (287) | 375 (290) | 285 (248) | 242 (229) | <0.0001 |
| Dietary α-tocopherol (mg/day) | 13.7 (11.0) | 11.8 (10.0) | 10.8 (7.1) | 9.9 (6.2) | 9.3 (9.6) | <0.0001 |
| Dietary ascorbic acid (mg/day) | 184 (206) | 175 (231) | 166 (153) | 142 (122) | 138 (203) | 0.0066 |
| Dietary vitamin A (IU/day) | 11,458 (9911) | 10,040 (9030) | 9839 (8272) | 9033 (10,308) | 7780 (6231) | <0.0001 |
| Dietary α-carotene (μg/day) | 838 (1418) | 678 (1202) | 681 (1083) | 608 (1599) | 462 (716) | <0.0001 |
| Dietary β-carotene (μg/day) | 5264 (5294) | 4575 (4783) | 4405 (4312) | 3896 (5388) | 3345 (3229) | <0.0001 |

[1]Tests for trend of continuous variables were based on general linear regression with $F_2$-isoprostanes as continuous independent variable. $\chi 2$ tests were used for categorical variables across all five levels of $F_2$-isoprostanes.

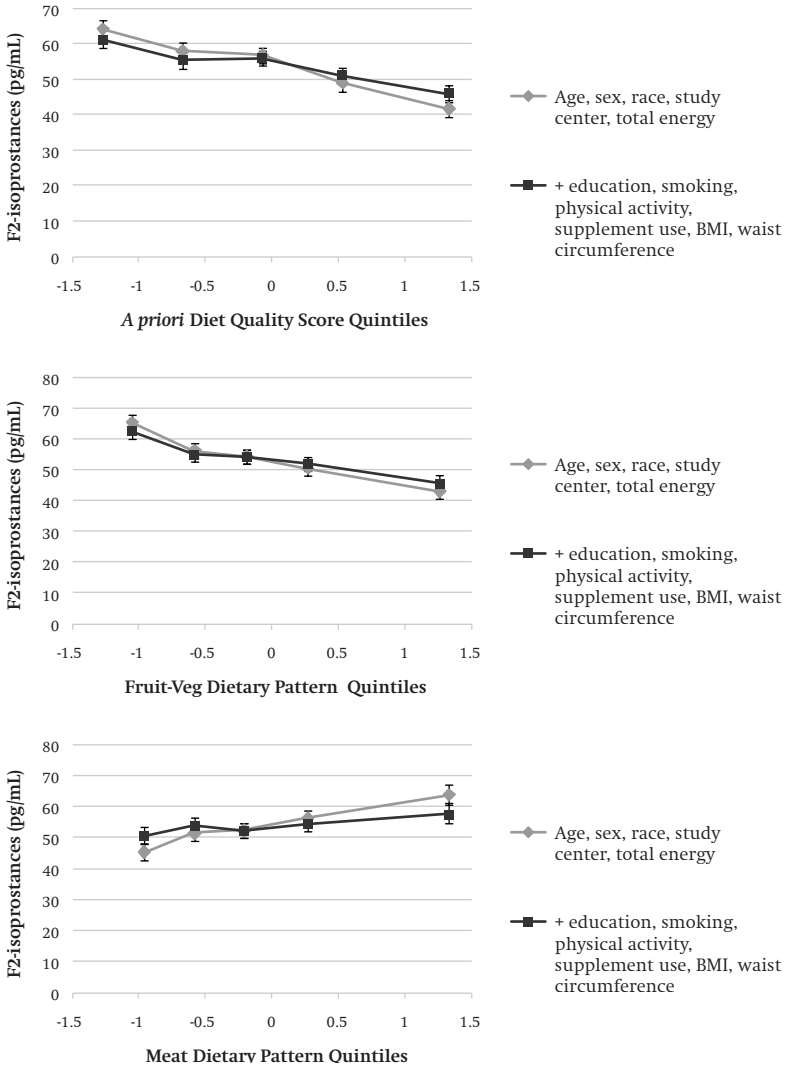



**FIGURE 2** Multivariable-adjusted mean year 20 $F_2$-isoprostanes (pg/ml) according to quintiles of year 20 (a) *A Priori* Diet Quality Score, (b) fruit–veg dietary pattern, and (c) meat dietary pattern. Estimated mean $F_2$-isoprostanes are plotted on dietary pattern quintile medians. For graphical purposes, the *A Priori* Diet Quality Score is centered at its mean. All $p < 0.0001$ for the trend in $F_2$-isoprostanes across quintiles of dietary patterns.

**TABLE 3** Year 20 multivariable (MV)-adjusted mean $F_2$-isoprostanes (95% confidence interval) according to year 20 quintile of dietary patterns, among supplement nonusers and users, CARDIA 2005–2006.

| | Quintile of dietary pattern | | | | | p value trend |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | |
| Supplement nonusers | | | | | | |
| *A Priori* Diet Quality Score | | | | | | |
| n | 364 | 296 | 289 | 205 | 185 | |
| MV-adjusted[1] | 63.5 (60.2, 66.8) | 60.0 (56.5, 63.4) | 60.7 (57.2, 64.1) | 51.1 (46.9, 55.3) | 44.6 (40.0, 49.3) | <0.0001 |
| +Dietary nutrients[2] | 62.6 (59.2, 66.0) | 59.5 (56.1, 63.0) | 60.8 (57.4, 64.3) | 52.0 (47.7, 56.3) | 45.9 (41.0, 50.7) | <0.0001 |
| Fruit–veg dietary pattern | | | | | | |
| n | 378 | 289 | 245 | 224 | 203 | |
| MV-adjusted | 65.5 (62.2, 68.9) | 56.4 (52.9, 59.9) | 56.7 (52.9, 60.5) | 56.5 (52.4, 60.5) | 46.8 (42.3, 51.3) | <0.0001 |
| +Dietary nutrients | 64.5 (61.0, 68.1) | 55.9 (52.4, 59.5) | 56.9 (53.1, 60.7) | 57.0 (52.9, 61.0) | 48.6 (43.5, 53.8) | <0.0001 |
| Meat dietary pattern | | | | | | |
| n | 207 | 236 | 255 | 296 | 345 | |
| MV-adjusted | 51.7 (46.9, 56.5) | 55.0 (50.7, 59.2) | 54.9 (51.1, 58.7) | 59.6 (56.1, 63.1) | 63.3 (58.8, 67.8) | <0.0001 |
| +Dietary nutrients | 53.7 (48.8, 58.6) | 55.6 (51.3, 59.9) | 55.4 (51.6, 59.2) | 59.2 (55.7, 62.6) | 61.7 (57.1, 66.3) | 0.0057 |
| Supplement users | | | | | | |
| *A Priori* Diet Quality Score | | | | | | |
| n | 176 | 214 | 325 | 296 | 386 | |
| MV-adjusted | 60.4 (56.5, 64.4) | 53.3 (49.8, 56.7) | 52.4 (49.6, 55.1) | 48.4 (45.6, 51.3) | 43.3 (40.6, 46.0) | <0.0001 |
| +Dietary nutrients | 59.0 (54.9, 63.1) | 52.5 (49.0, 56.0) | 51.7 (48.9, 54.5) | 48.6 (45.7, 51.4) | 44.9 (41.9, 47.8) | <0.0001 |
| Fruit–veg dietary pattern | | | | | | |
| n | 169 | 258 | 303 | 323 | 344 | |
| MV-adjusted | 58.8 (54.7, 63.0) | 53.6 (50.4, 56.8) | 52.2 (49.4, 55.1) | 47.3 (44.5, 50.0) | 44.4 (41.4, 47.3) | <0.0001 |
| +Dietary nutrients | 56.8 (52.5, 61.2) | 52.6 (49.3, 55.8) | 51.5 (48.6, 54.3) | 47.3 (44.5, 50.1) | 46.8 (43.4, 50.2) | 0.0001 |
| Meat dietary pattern | | | | | | |
| n | 340 | 311 | 293 | 251 | 202 | |
| MV-adjusted | 44.8 (41.6, 48.0) | 50.9 (47.9, 53.8) | 49.6 (46.7, 52.5) | 51.0 (47.8, 54.3) | 58.0 (53.2, 62.7) | <0.0001 |
| +Dietary nutrients | 47.0 (43.8, 50.3) | 52.0 (49.0, 54.9) | 49.3 (46.4, 52.3) | 50.4 (47.2, 53.7) | 53.8 (48.8, 58.7) | 0.032 |

[1] Adjusted for age, sex, race, study center, total energy consumption, education, smoking, physical activity, BMI, and waist circumference.
[2] Additionally adjusted for dietary α-tocopherol, ascorbic acid, vitamin A, and α- and β-carotene.

(Table 3). Similarly, in the analysis of natural logarithm-transformed $F_2$-isoprostanes, the *A Priori* Diet Quality Score and fruit–veg dietary pattern displayed stronger associations with $F_2$-isoprostanes in supplement-stratified multivariable-adjusted analysis that included adjustment for dietary nutrients than did the meat dietary pattern (Supplementary Table 3). In separate models of possible statistical interaction, we did not find evidence that associations between dietary patterns and $F_2$-isoprostanes differed according to smoking status (data not shown).

We obtained multivariable-adjusted standardized regression coefficients for individual antioxidant nutrients in the total sample. These findings indicate that the regression coefficient for the association between the *A Priori* Diet Quality Score and $F_2$-isoprostanes was stronger (−6.1; 95% CI −7.4, −4.8) than those for dietary α-tocopherol (−3.8; −5.0, −2.6), ascorbic acid (−0.2; −1.3, 0.9), vitamin A (−2.9; −4.0, −1.7), α-carotene (−1.6; −2.6, −0.5), or β-carotene (−2.9; −4.0, −1.7).

## Prospective associations between dietary patterns and plasma $F_2$-isoprostanes

In multivariable-adjusted analysis, the year 0/7 average *A Priori* Diet Quality Score and fruit–veg dietary pattern were both negatively associated, and the year 0/7 average meat dietary pattern was positively associated, with year 15/20 average $F_2$-isoprostanes (Figure 3a). We next looked at whether year 0/7 diet was associated with the change in $F_2$-isoprostanes between years 15 and 20. We note that in our data year 20 $F_2$-isoprostanes were on average lower than year 15 concentrations. In multivariable-adjusted analysis, year 15 to 20 changes in $F_2$-isoprostanes were inversely associated with the year 0/7 *A Priori* Diet Quality Score and fruit–veg dietary pattern and positively associated with the year 0/7 meat dietary pattern (Figure 3b).

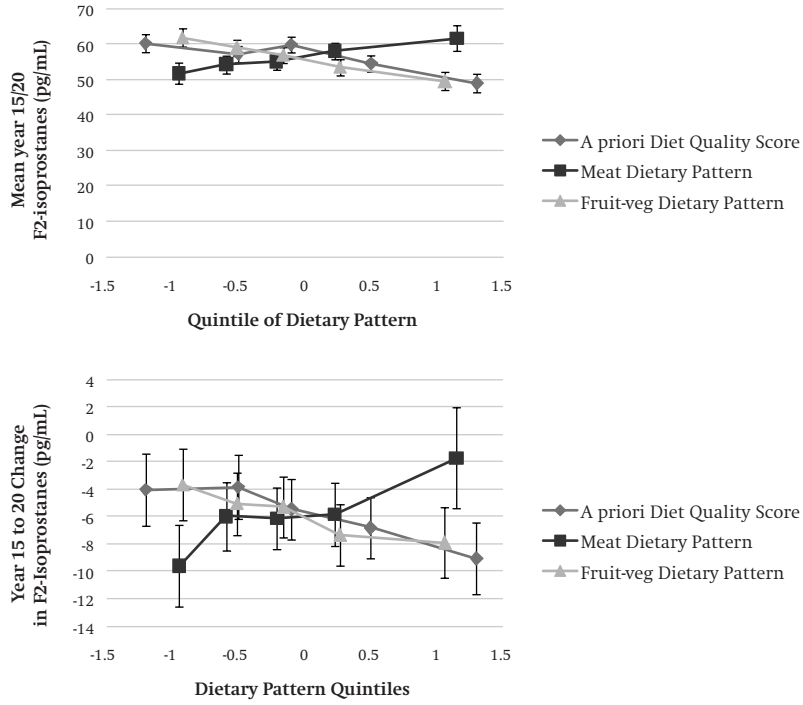



**FIGURE 3** (a) Multivariable-adjusted mean year 15/20 F2-isoprostanes (pg/ml) and (b) mean change in $F_2$-isoprostanes (pg/ml) from year 15 to 20 according to quintiles of year 0/7 average dietary patterns. Data were adjusted for age, sex, race, study center, total energy consumption, education, smoking, physical activity, supplement use, BMI, and waist circumference. Year 15 to 20 change analysis was also adjusted for year 15 $F_2$-isoprostanes. $F_2$-isoprostanes are plotted at dietary pattern quintile medians. The *A Priori* Diet Quality Score is centered for graphical purposes. All $p < 0.01$ for trend.

## DISCUSSION

In this cohort of young and middle-aged black and white Americans, we found significant associations among three food-based dietary patterns and plasma $F_2$-isoprostanes. Our findings suggest that diets high in plant foods and low in red meat may decrease systemic oxidative stress. These associations could not be explained by differences in demographic variables, smoking, physical activity, BMI, waist circumference, or supplement use. This study demonstrates the utility of summary measures of diet –dietary patterns– to assess associations between diet and $F_2$-isoprostanes.

In this analysis, we studied summary measures of whole diet (dietary patterns), rather than individual nutrients or foods. The use of dietary patterns has grown over the past decade, and our findings contribute to a literature showing that dietary patterns provide a powerful method for studying diet and health. Dietary patterns may better allow for the complexity of food and food synergy [13, 14] and may be especially well-suited to the study of oxidative stress –a complex biologic process that is probably influenced by a variety of dietary components [6]. The benefit of studying diet comprehensively is supported by the strength of dietary pattern associations after accounting for vitamin supplement use and dietary antioxidant nutrient consumption. Although there are few studies of oxidative stress and dietary patterns, our data are consistent with data from observational [9] and intervention [7, 11] studies showing an inverse association between plant-based diets and $F_2$-isoprostanes.

In our data, the apparent benefit conferred by plant-based diets on $F_2$-isoprostane concentrations could not be explained by vitamin supplement use or by the consumption of dietary antioxidants, including α-tocopherol, ascorbic acid, vitamin A, and α- and β-carotene. These findings may indicate that plant-based diets affect oxidative stress through dietary components that have not been identified or measured or through complex pathways involving dietary synergy. In contrast, dietary antioxidants seemed to account for more of the association between the meat dietary pattern and $F_2$-isoprostanes among supplement users and, to a lesser extent, supplement nonusers. These findings may reflect the greater variability in phytochemical-rich plant foods in the *A Priori* Diet Quality Score and the fruit–veg dietary pattern, compared to the meat dietary pattern, seen, for example, in the consumption of whole grains, nuts and seeds, and green and yellow vegetables across quintiles of dietary pattern in Table 1.

Our analysis included the two primary methods for dietary pattern construction: 1: a pattern based on *a priori* considerations of the health effects of foods and 2: patterns empirically derived from dietary consumption of the study sample. Each approach provides an overall summary of dietary consumption, and, in the present analysis, all three summaries are purely foods-based. Dietary patterns derived from principal components analysis generally do not incorporate nutrients, but, to our knowledge, our *A Priori* Diet Quality Score is the first *a priori* pattern that does not incorporate nutrient or supplement use and is comprehensive in scope of foods included, in contrast to other published *a priori* dietary patterns, such as the Mediterranean diet [28] and the Alternate Health Eating Index [29]. Our focus on foods is consistent with our support for a greater emphasis on foods in dietary research [14, 30], as well as with calls for a foods-based approach to dietary recommendations [31].

Dietary patterns research has been critiqued for the variability in published approaches to defining patterns. In addition to a focus on foods-based diet summaries, our selection of dietary patterns was motivated by an interest in testing the stability of diet–isoprostanes associations with several patterns and to restrict analysis to approaches that have been established in the literature. Our two PCA-derived patterns can be considered conceptually comparable to "Western" and "prudent" patterns in publications from other cohort studies [32, 33], although we recognize that the exact weighting of foods will vary among study samples and depending on foods included in the dietary assessment. The approach used to create the *A Priori* Diet Quality Score has also been previously published and has been shown to predict a range of cardiometabolic outcomes in other samples [19, 20]. From our reading of the dietary patterns literature, we believe that specific approaches to variable construction may be less relevant than the finding that studying whole diets is a powerful method to verify the importance of food in physiologic processes. Still, the field of dietary patterns is new and future research will benefit from work focused on elucidating important distinctions among patterns.



Our study has several strengths and limitations. The large CARDIA study sample and extensive covariate data enable us to provide effect estimates that are stable and adjusted for important confounding variables. Applying both *a priori* and principal component analysis approaches allowed us to test the robustness of findings despite differences in approaches to construct dietary patterns. The repeated measurement of diet and biologic markers allowed us to average diet and biomarker data, which increases the reliability of our prospective analysis. Our longitudinal design also enabled us to include both cross-sectional and prospective analysis. Cross-sectional results do not temporally distinguish the measurement of diet and $F_2$-isoprostanes, both of which were assessed at year 20, whereas prospective analysis included assessment of diet and co-variables that preceded the measurement of $F_2$-isoprostanes. The prospective associations may mean that the conditions for midlife oxidative stress exist many years before midlife. The timing of data collection was not planned with the current study in mind, and although the analysis was prospective in nature, we were unable to examine concurrent change in diet and $F_2$-isoprostances, which weakens our ability to make causal statements. Our study sample was relatively young (ages 38–50 in year 20) and limited to black and white race groups, and it is possible that our findings may not represent older or more diverse populations.

Our analysis was limited to a single measure of oxidative damage, lipid peroxidation. Among available markers, $F_2$-isoprostanes are considered the gold standard for assessing lipid peroxidation [3-5]. A study of experimentally induced oxidative damage supports the use of either urinary or plasma $F_2$-isoprostanes as

reliable time- and dose-dependent markers of general oxidative status in vivo [34]. Evidence from many, but not all, epidemiologic studies supports higher $F_2$-isoprostanes in physiologic states consistent with the oxidative stress hypothesis [3]. In the CARDIA sample, $F_2$-isoprostanes have been inversely associated with circulating carotenoids [35] and positively associated with smoking, BMI, coronary artery calcification [17], and insulin resistance [36].

In conclusion, our data support cross-sectional and prospective associations between foods-based dietary patterns and plasma concentrations of $F_2$-isoprostanes, a biomarker of lipid peroxidation. Associations were robust to the method of dietary pattern creation, with both *a priori* and principal components analysis-derived patterns showing relations to plasma $F_2$-isoprostanes, and to multivariable-adjustment for BMI, waist circumference, smoking, and physical activity. These findings could not be explained by vitamin supplement use or by dietary consumption of antioxidant nutrients. These data support protective effects of a diet high in fruits, vegetables, nuts, seeds, and whole grains and low in red and processed meats and refined grains against oxidative damage.

## REFERENCES


1. Griendling KK, FitzGerald GA. Oxidative stress and cardiovascular injury: Part I: basic mechanisms and in vivo monitoring of ROS. Circulation. 2003;108:1912-6.
2. Griendling KK, FitzGerald GA. Oxidative stress and cardiovascular injury: Part II: animal and human studies. Circulation. 2003;108:2034-40.
3. Basu S. F2-isoprostanes in human health and diseases: from molecular mechanisms to clinical implications. Antioxidants & redox signaling. 2008;10:1405-34.
4. Milne GL, Yin H, Morrow JD. Human biochemistry of the isoprostane pathway. J Biol Chem. 2008;283:15533-7.
5. Stephens JW, Khanolkar MP, Bain SC. The biological relevance and measurement of plasma markers of oxidative stress in diabetes and cardiovascular disease. Atherosclerosis. 2009;202:321-9.
6. Hollman PC, Cassidy A, Comte B, Heinonen M, Richelle M, Richling E, et al. The biological relevance of direct antioxidant effects of polyphenols for cardiovascular health in humans is not established. J Nutr. 2011;141:989S-1009S.
7. Roberts CK, Vaziri ND, Barnard RJ. Effect of diet and exercise intervention on blood pressure, insulin, oxidative stress, and nitric oxide availability. Circulation. 2002;106:2530-2.
8. Thompson HJ, Heimendinger J, Haegele A, Sedlacek SM, Gillette C, O'Neill C, et al. Effect of increased vegetable and fruit consumption on markers of oxidative cellular damage. Carcinogenesis. 1999;20:2261-6.
9. Holt EM, Steffen LM, Moran A, Basu S, Steinberger J, Ross JA, et al. Fruit and vegetable consumption and its relation to markers of inflammation and oxidative stress in adolescents. J Am Diet Assoc. 2009;109:414-21.
10. Lopes HF, Martin KL, Nashar K, Morrow JD, Goodfriend TL, Egan BM. DASH diet lowers blood pressure and lipid-induced oxidative stress in obesity. Hypertension. 2003;41:422-30.
11. Miller ER, 3rd, Appel LJ, Risby TH. Effect of dietary patterns on measures of lipid peroxidation: results from a randomized clinical trial. Circulation. 1998;98:2390-5.
12. Kant AK. Indexes of overall diet quality: a review. J Am Diet Assoc. 1996;96:785-91.
13. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 2002;13:3-9.
14. Jacobs DR, Jr., Steffen LM. Nutrients, foods, and dietary patterns as exposures in research: a framework for food synergy. Am J Clin Nutr. 2003;78:508S-13S.
15. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR, et al. Cardia - Study Design, Recruitment, and Some Characteristics of the Examined Subjects. Journal of Clinical Epidemiology. 1988;41:1105-16.
16. Morrow JD, Roberts LJ, 2nd. Mass spectrometric quantification of F2-isoprostanes in biological fluids and tissues as measure of oxidant stress. Methods Enzymol. 1999;300:3-12.
17. Gross M, Steffes M, Jacobs DR, Jr., Yu X, Lewis L, Lewis CE, et al. Plasma F2-isoprostanes and coronary artery calcification: the CARDIA Study. Clin Chem. 2005;51:125-31.
18. Jacobs DR, Jr, Hahn LP, Haskell WL, Pirie P, Sidney S. Validity and reliability of a short physical activity history: CARDIA and the Minnesota Heart Health Program. J Cardiopulm Rehabil. 1989;1989;9:448-459.
19. Lockheart MS, Steffen LM, Rebnord HM, Fimreite RL, Ringstad J, Thelle DS, et al. Dietary patterns, food groups and myocardial infarction: a case-control study. Br J Nutr. 2007;98:380-7.
20. Nettleton JA, Schulze MB, Jiang R, Jenny NS, Burke GL, Jacobs DR, Jr. A priori-defined dietary patterns and markers of cardiovascular disease risk in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 2008;88:185-94.
21. Kant AK. Dietary patterns and health outcomes. J Am Diet Assoc. 2004;104:615-35.
22. Liu K, Slattery M, Jacobs D, Jr., Cutter G, McDonald A, Van Horn L, et al. A study of the reliability and comparative validity of the cardia dietary history. Ethn Dis. 1994;4:15-27.
23. Hu FB, Rimm E, Smith-Warner SA, Feskanich D, Stampfer MJ, Ascherio A, et al. Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. Am J Clin Nutr. 1999; 69:243-9.

24. Feskanich D, Rimm EB, Giovannucci EL, Colditz GA, Stampfer MJ, Litin LB, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc. 1993;93:790-6.
25. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and Validity of an Expanded Self-Administered Semiquantitative Food Frequency Questionnaire among Male Health-Professionals. AmJEpidemiol. 1992;135:1114-26.
26. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol. 1999;149:531-40.
27. Block G, Dietrich M, Norkus E, Jensen C, Benowitz NL, Morrow JD, et al. Intraindividual variability of plasma antioxidants, markers of oxidative stress, C-reactive protein, cotinine, and other biomarkers. Epidemiology. 2006;17:404-12.
28. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003;348:2599-608.
29. Willett WC, McCullough ML. Dietary pattern analysis for the evaluation of dietary guidelines. Asia Pacific journal of clinical nutrition. 2008;17 Suppl 1:75-8.
30. Jacobs DR, Jr., Tapsell LC. Food, not nutrients, is the fundamental unit in nutrition. Nutr Rev. 2007;65:439-50.
31. Mozaffarian D, Ludwig DS. Dietary guidelines in the 21st century--a time for food. JAMA. 2010;304:681-2.
32. Hu FB, Rimm EB, Stampfer MJ, Ascherio A, Spiegelman D, Willett WC. Prospective study of major dietary patterns and risk of coronary heart disease in men. Am J Clin Nutr. 2000;72:912-21.
33. Fung TT, Stampfer MJ, Manson JE, Rexrode KM, Willett WC, Hu FB. Prospective study of major dietary patterns and stroke risk in women. Stroke. 2004;35:2014-9.
34. Kadiiska MB, Gladen BC, Baird DD, Graham LB, Parker CE, Ames BN, et al. Biomarkers of oxidative stress study III. Effects of the nonsteroidal anti-inflammatory agents indomethacin and meclofenamic acid on measurements of oxidative products of lipids in CCl4 poisoning. Free Radic Biol Med. 2005;38:711-8.
35. Hozawa A, Jacobs DR, Jr., Steffes MW, Gross MD, Steffen LM, Lee DH. Relationships of circulating carotenoid concentrations with several markers of inflammation, oxidative stress, and endothelial dysfunction: the Coronary Artery Risk Development in Young Adults (CARDIA)/Young Adult Longitudinal Trends in Antioxidants (YALTA) study. Clin Chem. 2007;53:447-55.
36. Park K, Gross M, Lee DH, Holvoet P, Himes JH, Shikany JM, et al. Oxidative stress and insulin resistance: the coronary artery risk development in young adults study. Diabetes Care. 2009;32:1302-7.

## SUPPLEMENTAL MATERIAL

**SUPPLEMENTAL TABLE 1** CARDIA food groups and their constituent Nutrition Coordinating Center (NCC) food subgroups.

| | |
|---|---|
| Food group 1: Fruit | Citrus fruit |
| | Fruit excluding citrus fruit |
| | Fried fruits |
| | Fruit-based savory snack |
| Food group 2: Fruit Juices | Citrus juice |
| | Fruit juice excluding citrus juice |
| Food group 3: Eggs/Omelettes | Eggs |
| | Egg substitute |
| Food group 4: Whole grain foods | Grains, flour and dry mixes - some whole grain |
| | Loaf-type bread and plain rolls - some whole grain |
| | Crackers - some whole grain |
| | Pasta - some whole grain |
| | Ready-to-eat cereal (not presweetened) - some whole grain |
| | Ready-to-eat cereal (presweetened) - whole grain |
| | Grains, flour and dry mixes - whole grain |
| | Loaf-type bread and plain rolls - whole grain |
| | Crackers - whole grain |
| | Pasta - whole grain |
| | Ready-to-eat cereal (not presweetened) - whole grain |
| | Ready-to-eat cereal (presweetened) - whole grain |
| | Popcorn |
| | Flavored popcorn |
| | Snack bars - some whole grain |
| | Snack bars - whole grain |
| Food group 5: Sweet breads | Other breads (quick breads, corn muffins, tortillas) - whole grain |
| | Other breads (quick breads, corn muffins, tortillas) - some whole grain |
| | Other breads (quick breads, corn muffins, tortillas) - refined grain |
| Food group 6: Salty snacks | Snack chips - whole grain |
| | Snack chips - some whole grain |
| | Snack chips - refined grain |
| Food group 7: Refined grains | Ready-to-eat cereal (not presweetened) - refined grain |
| | Ready-to-eat cereal (presweetened) - refined grain |
| | Crackers - refined grain |
| | Pasta - refined grain |
| | Grains, flour and dry mixes - refined grain |
| | Loaf-type bread and plain rolls - refined grain |
| | Snack bars - refined grain |
| Food group 8: Grain desserts | Cakes, cookies, pies, pastries, danish, doughnuts and cobblers - whole grain |
| | Cakes, cookies, pies, pastries, danish, doughnuts and cobblers - some whole grain |
| | Cakes, cookies, pies, pastries, danish, doughnuts and cobblers - refined grain |
| | Miscellaneous dessert |

**SUPPLEMENTAL TABLE 1 (Continued)** CARDIA food groups and their constituent Nutrition Coordinating Center (NCC) food subgroups.

| | |
|---|---|
| Food group 9: Chocolate | Chocolate candy |
| Food group 10: Seeds, nuts and peanut butter | Nuts and seeds<br>Nut and seed butters |
| Food group 11: Dairy low fat | Yogurt - sweetened low fat<br>Yogurt - sweetened fat free<br>Yogurt - artificially sweetened low fat<br>Yogurt - artificially sweetened fat free<br>Milk - reduced fat<br>Milk - low fat and fat free<br>Ready-to-drink flavored milk - reduced fat<br>Ready-to-drink flavored milk - low fat and fat free<br>Sweetened flavored milk beverage powder with non-fat dry milk<br>Artificially sweetened flavored milk beverage powder with non-fat dry milk<br>Cream - reduced fat<br>Cream - low fat and fat free<br>Cheese - reduced fat<br>Cheese - low fat and fat free |
| Food group 12: Dairy whole fat | Yogurt - sweetened whole milk<br>Yogurt - artificially sweetened whole milk<br>Frozen dairy dessert<br>Pudding and other dairy dessert<br>Artificially sweetened pudding and other dairy dessert<br>Cream<br>Milk – whole<br>Ready-to-drink flavored milk – whole<br>Sweetened flavored milk beverage powder without non-fat dry milk<br>Artificially sweetened flavored milk beverage powder without non-fat dry milk<br>Cheese - full fat |
| Food group 13: Soups | Soup broth |
| Food group 14: Beans | Legumes (cooked dried beans) |
| Food group 15: Vegetables- green leafy | Dark-green vegetables |
| Food group 16: Vegetables- dark-yellow | Deep-yellow vegetables |
| Food group 17: Vegetables- potatoes | White potatoes |
| Food group 18: Other vegetables | Other starchy vegetables<br>Other vegetables<br>Fried vegetables<br>Vegetable juice<br>Vegetable-based savory snack |

**SUPPLEMENTAL TABLE 1 (Continued)** CARDIA food groups and their constituent Nutrition Coordinating Center (NCC) food subgroups.

| | |
|---|---|
| Food group 19: Avocados/ guacamole | Avocado and similar |
| Food group 20: Tomatoes | Tomato |
| Food group 21: Fried potatoes | Fried potatoes |
| Food group 22: Processed meats | Cold cuts and sausage<br>Lean cold cuts and sausage<br>Meat-based savory snack |
| Food group 23: Red meat lean | Beef<br>Veal<br>Lamb<br>Cured pork<br>Fresh pork |
| Food group 24: Red meat regular | Lean fresh pork<br>Lean lamb<br>Lean cured pork<br>Game<br>Lean veal<br>Lean beef<br>Food group 25: Organ meat<br>Organ meats<br>Food group 26: Poultry<br>Poultry<br>Lean poultry |
| Food group 27: Fried foods | Fried chicken - commercial entrée and fast food<br>Fried fish - commercial entrée and fast food<br>Fried shellfish - commercial entrée and fast food |
| Food group 28: Fish | Fish - fresh and smoked |
| Food group 29: Lean fish | Lean fish - fresh and smoked |
| Food group 30: Shellfish | Shellfish |
| Food group 31: Sweet extras | Sugar<br>Syrup, honey, jam, jelly, preserves<br>Non-chocolate candy<br>Frosting or glaze |
| Food group 32: Sugar substitute | Sugar substitute |
| Food group 33: Margarine | Margarine - regular<br>Margarine - reduced fat |
| Food group 34: Oil | Oil<br>Fried vegetables |
| Food group 35: Butter | Butter and other animal fats – regular<br>Butter and other animal fats - reduced fat<br>Shortening |

**SUPPLEMENTAL TABLE 1 (Continued)** CARDIA food groups and their constituent Nutrition Coordinating Center (NCC) food subgroups.

| | |
|---|---|
| Food group 36: Meal replacement drinks | Dairy-based sweetened meal replacement/supplement<br>Dairy-based artificially sweetened meal replacement/supplement<br>Nondairy-based sweetened meal replacement/supplement<br>Nondairy-based artificially sweetened meal replacement/supplement<br>Nondairy-based unsweetened meal replacement/supplement |
| Food group 37: Coffee | Sweetened coffee<br>Artificially sweetened coffee<br>Unsweetened coffee<br>Sweetened coffee substitutes<br>Artificially sweetened coffee substitutes<br>Unsweetened coffee substitutes |
| Food group 38: Tea | Sweetened tea<br>Artificially sweetened tea<br>Unsweetened tea<br>Nondairy-based artificially sweetened meal replacement/supplement |
| Food group 39: Sugar-sweetened soft drinks | Sweetened soft drinks<br>Sweetened water<br>Sweetened fruit drinks<br>Non-alcoholic beer<br>Non-alcoholic light beer |
| Food group 40: Diet soft drinks | Artificially sweetened soft drinks<br>Unsweetened soft drinks<br>Artificially sweetened water<br>Artificially sweetened fruit drinks |
| Food group 41: Beer | Beer and ales |
| Food group 42: Liquor | Cordial and liqueur<br>Distilled liquor |
| Food group 43: Wine | Wine |
| Food group 44: Salad dressing/ sauces | Salad dressing – regular<br>Salad dressing - reduced fat/reduced calorie/fat free<br>Sauces, sweet – regular<br>Sauces, sweet - reduced fat/reduced calorie/fat free<br>Sauces and condiments - regular<br>Sauces and condiments - reduced fat<br>Gravy – regular<br>Gravy - reduced fat/fat free |
| Food group 45: Soy/non-dairy products | Meat alternatives<br>Milk – nondairy<br>Cheese – nondairy<br>Yogurt – nondairy<br>Frozen nondairy dessert<br>Cream – nondairy |
| Food group 46: Pickled foods | Pickled foods |

**SUPPLEMENTAL TABLE 2** Description of the *A Priori* Diet Quality Score and PCA-derived dietary pattern scoring algorithms*. For the *A Priori* Diet Quality Score, CARDIA food groups were scored as positive, negative, or neutral for health. PCA-derived pattern descriptions are given as factor loadings from the PCA.

| CARDIA Food Groups | *A Priori* Diet Quality Score | Meat Diet Pattern | | FV Diet Pattern | |
|---|---|---|---|---|---|
| | Health Impact | Year 0 | Year 7 | Year 0 | Year 7 |
| Avocado | + | | | 0.44 | 0.27 |
| Beans | + | 0.29 | | | 0.35 |
| Beer | + | 0.25 | 0.32 | | |
| Butter | - | 0.70 | 0.65 | | |
| Chocolate | 0 | | | | |
| Coffee | + | | | | |
| Diet soft drink | 0 | | | | 0.21 |
| Eggs | 0 | 0.50 | 0.53 | | |
| Fish | + | | | | |
| Fried foods | - | | 0.35 | | |
| Fried potatoes | - | 0.54 | 0.52 | | |
| Fruit | + | | | 0.49 | 0.51 |
| Fruit juice | 0 | 0.20 | | 0.21 | 0.22 |
| Grain dessert | - | 0.39 | 0.39 | | |
| Green vegetables | + | | | 0.56 | 0.64 |
| Lean fish | + | | | 0.38 | 0.35 |
| Lean red meat | 0 | 0.36 | 0.34 | | |
| Low fat dairy | + | | | 0.28 | 0.27 |
| Liquor | + | | 0.20 | | |
| Margarine | 0 | 0.27 | 0.33 | | |
| Meal replacement | 0 | | | | |
| Oil | + | 0.25 | 0.38 | 0.45 | 0.40 |
| Organ meat | - | | 0.22 | | |
| Other vegetables | + | 0.23 | | 0.69 | 0.73 |
| Pickled foods | 0 | | 0.23 | 0.34 | 0.35 |
| Potatoes | 0 | 0.34 | 0.27 | 0.22 | |
| Poultry | + | 0.25 | 0.31 | 0.20 | 0.26 |
| Processed meat | - | 0.58 | 0.54 | | |
| Regular red meat | - | 0.60 | 0.71 | | |
| Refined grains | 0 | 0.72 | 0.71 | | |
| Salty snacks | - | | | | 0.27 |
| Sauces | - | 0.34 | 0.59 | 0.32 | 0.31 |
| Seeds, nuts | + | | | 0.34 | |
| Shellfish | 0 | | | 0.24 | 0.29 |
| Soft drink | - | 0.41 | 0.43 | -0.21 | -0.22 |
| Soups | 0 | | | | 0.30 |

**SUPPLEMENTAL TABLE 2 (Continued)** Description of the *A Priori* Diet Quality Score and PCA-derived dietary pattern scoring algorithms*. For the *A Priori* Diet Quality Score, CARDIA food groups were scored as positive, negative, or neutral for health. PCA-derived pattern descriptions are given as factor loadings from the PCA.

| CARDIA Food Groups | *A Priori* Diet Quality Score | Meat Diet Pattern | | FV Diet Pattern | |
|---|---|---|---|---|---|
| | Health Impact | Year 0 | Year 7 | Year 0 | Year 7 |
| Soy products | + | | | | |
| Sugar substitutes | 0 | | | | |
| Sweet breads | - | 0.58 | 0.43 | | |
| Sweet extra | - | 0.39 | 0.32 | | |
| Tea | + | | | | |
| Tomato | + | | | 0.53 | 0.59 |
| Whole fat dairy | - | 0.43 | 0.44 | | |
| Whole grains | + | | | 0.40 | 0.42 |
| Wine | + | | | 0.21 | 0.20 |
| Yellow vegetables | + | | | 0.47 | 0.54 |

*Factor loadings <0.20 are suppressed

**SUPPLEMENTAL TABLE 3** Year 20 multivariable-adjusted geometric mean $F_2$-isoprostanes (95% confidence interval) according to year 20 quintiles of dietary patterns, CARDIA 2005/06.

| | Quintile of dietary pattern | | | | | p-value trend |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | |
| **Supplement non-users** | | | | | | |
| *A Priori* Diet Quality Score | | | | | | |
| MV-adjusted[1] | 56.6 (54.3, 59.1) | 53.2 (50.9, 55.6) | 53.6 (51.3, 56.0) | 47.5 (45.0, 50.1) | 43.4 (40.9, 46.0) | <0.0001 |
| +dietary nutrients[2] | 55.8 (53.4, 58.3) | 52.8 (50.5, 55.2) | 53.7 (51.4, 56.1) | 48.2 (45.7, 50.9) | 44.4 (41.7, 47.3) | <0.0001 |
| Fruit-veg dietary pattern | | | | | | |
| MV-adjusted | 58.8 (56.4, 61.3) | 51.2 (49.0, 53.6) | 51.6 (49.2, 54.2) | 50.0 (47.5, 52.6) | 43.2 (40.9, 45.7) | <0.0001 |
| +dietary nutrients | 58.2 (55.6, 60.8) | 50.9 (48.7, 53.3) | 51.7 (49.3, 54.3) | 50.3 (47.8, 53.0) | 44.1 (41.3, 47.0) | <0.0001 |
| Meat dietary pattern | | | | | | |
| MV-adjusted | 48.7 (45.8, 51.9) | 49.8 (47.1, 52.6) | 50.3 (48.0, 52.9) | 52.5 (50.2, 54.9) | 55.7 (52.6, 59.0) | <0.0001 |
| +dietary nutrients | 50.4 (47.3, 53.6) | 50.3 (47.6, 53.1) | 50.7 (48.3, 53.2) | 52.1 (49.8, 54.4) | 54.3 (51.2, 57.5) | 0.011 |
| **Supplement users** | | | | | | |
| *A Priori* Diet Quality Score | | | | | | |
| MV-adjusted | 53.0 (49.8, 56.4) | 46.7 (44.3, 49.3) | 46.3 (44.4, 48.3) | 44.4 (42.5, 46.5) | 40.9 (39.2, 42.7) | <0.0001 |
| +dietary nutrients | 51.1 (47.9, 54.4) | 45.9 (43.5, 48.4) | 45.7 (43.8, 47.7) | 44.5 (42.6, 46.6) | 42.4 (40.5, 44.4) | <0.0001 |
| Fruit-veg dietary pattern | | | | | | |
| MV-adjusted | 52.6 (49.4, 56.1) | 48.2 (45.9, 50.6) | 46.3 (44.3, 48.4) | 43.4 (41.6, 45.3) | 40.5 (38.7, 42.4) | <0.0001 |
| +dietary nutrients | 50.9 (47.6, 54.4) | 47.2 (44.9, 49.7) | 45.7 (43.7, 47.8) | 43.4 (41.6, 45.3) | 42.4 (40.2, 44.6) | <0.0001 |
| Meat dietary pattern | | | | | | |
| MV-adjusted | 41.8 (39.8, 43.9) | 45.8 (43.8, 48.0) | 43.8 (41.9, 45.9) | 46.3 (44.1, 48.7) | 50.9 (47.2, 54.8) | <0.0001 |
| +dietary nutrients | 43.8 (41.6, 46.0) | 46.9 (44.8, 49.1) | 43.7 (41.7, 45.7) | 45.7 (43.4, 48.0) | 46.6 (43.1, 50.4) | 0.11 |

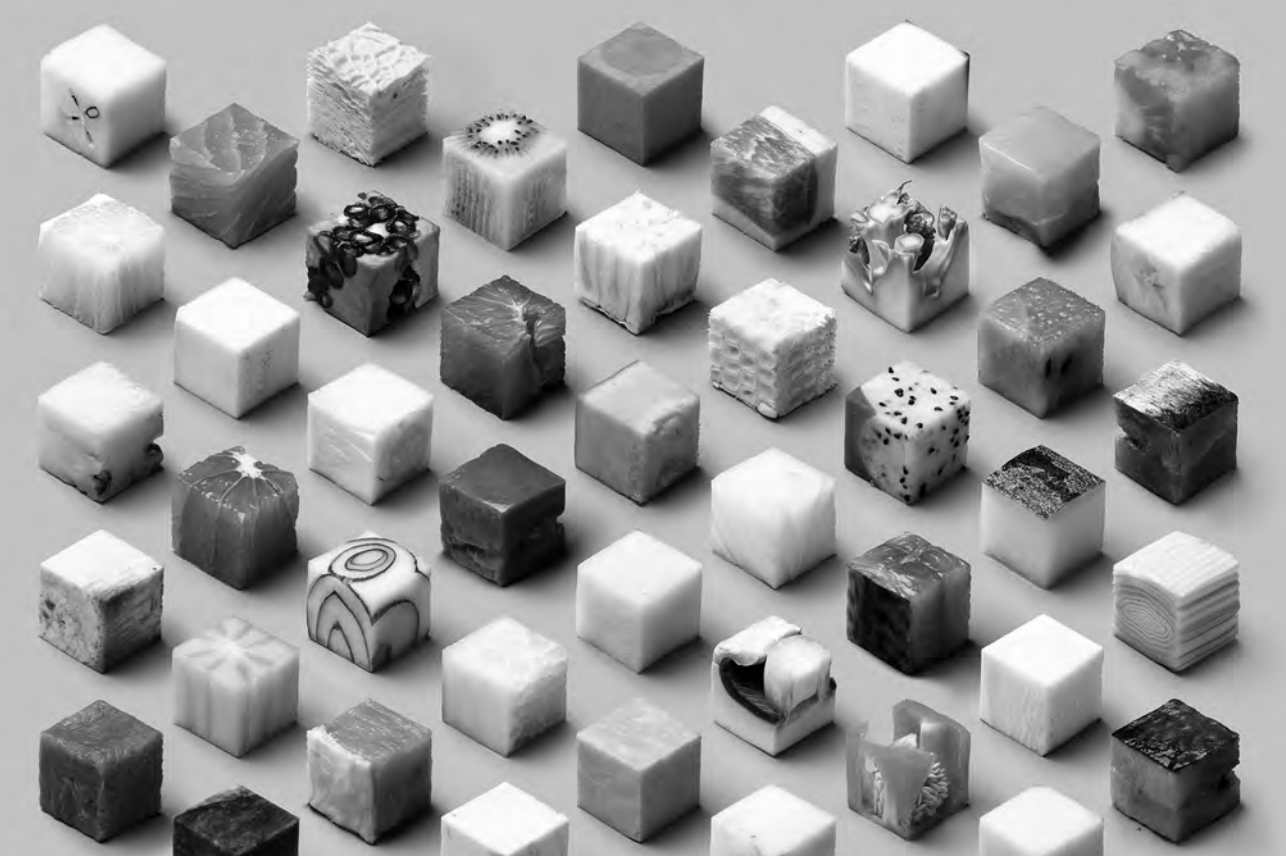
[1]Adjusted for age, gender, race, study center, total energy consumption, education, smoking, physical activity, BMI, and waist circumference.
[2]Additionally adjusted for dietary consumption of alpha-tocopherol, ascorbic acid, vitamin A, and alpha- and beta-carotene.

# 5

# Classification of foods based on dietary guidelines for nutrition education and food-based dietary scores, an example from the Netherlands

Femke P.C.Sijtsma, Sabita S. Soedamah-Muthu, Andrea Werkman, Astrid Postma-Smeets, Danielle Wolvers, David R. Jacobs Jr, Daan Kromhout

Submitted



## ABSTRACT

**Objective** Despite much research on nutrients and chronic diseases, a preferable method does not exist for making food classifications that satisfy multiple nutrient criteria.

**Design** We developed a system to classify all foods in the diet based on their nutrient content and their likely chronic disease effects.

**Setting** In collaboration with the Netherland Nutrition Center.

**Subjects** not applicable.

**Results** First, each food was divided into basic foods, non-basic foods and ready meals. Basic foods are nutrient-rich foods that are typical for the Dutch diet. Non-basic foods are generally energy-dense foods and rich in solid fats, sodium and/or sugar. Second, several food groups were created within each broad category. Classification criteria for each food group were developed based on presumed positive, neutral or negative effects on chronic diseases of five nutrients: four that likely increase (saturated fatty acids, mono-*trans* unsaturated fatty acids, sodium, and added sugar) and one that likely decreases (dietary fiber) the risk of chronic diseases. Third, each food was classified on the most adverse interpretation of any of the criteria. For further evaluation of the food classification system, we formed two groups of foods: those with presumed positive or neutral chronic disease effects and those with presumed negative effects.

**Conclusions** We have provided a method for classifying every food in a transparent and novel way using multiple nutrient criteria. Although this system needs validation, resulting food classification can be used in nutritional education and epidemiological studies on dietary quality scores and chronic disease incidence.

## INTRODUCTION

Nutrient-based targets are difficult to interpret by the public, therefore at minimum translation of nutrients to foods is needed. In an ideal situation food-based dietary guidelines should correspond with scientific evidence on chronic disease prevention by recognizing each food as a complex unit of which the health effect may not be fully described by its individual nutrients and bioactive compounds [1, 2]. Research on diet and disease relationships traditionally relied on analysis of specific nutrients but has more recently shifted to foods and dietary (quality) scores. Studies that compared multiple dietary scores suggested that dietary scores solely based on foods or food groups are better predictors of mortality than those based predominantly on nutrient intakes, or combination of nutrients and foods [3-5]. However, specific criteria do not exist on which foods or food groups should be included, or how they should be scored.

In the Netherlands two organizations are responsible for developing dietary guidelines. The process is depicted in **Figure 1.** The Health Council of the Netherlands reviews the evidence on nutrition and chronic diseases regularly to establish Guidelines for a Healthy Diet [6]. The Netherlands Nutrition Centre translates these guidelines into the Food Choice Guidelines [7]. These guidelines are formulated in terms of foods and serve two goals, first to provide a nutritionally adequate diet containing all recommended macro and micronutrients and second to contribute to the prevention of chronic diseases.



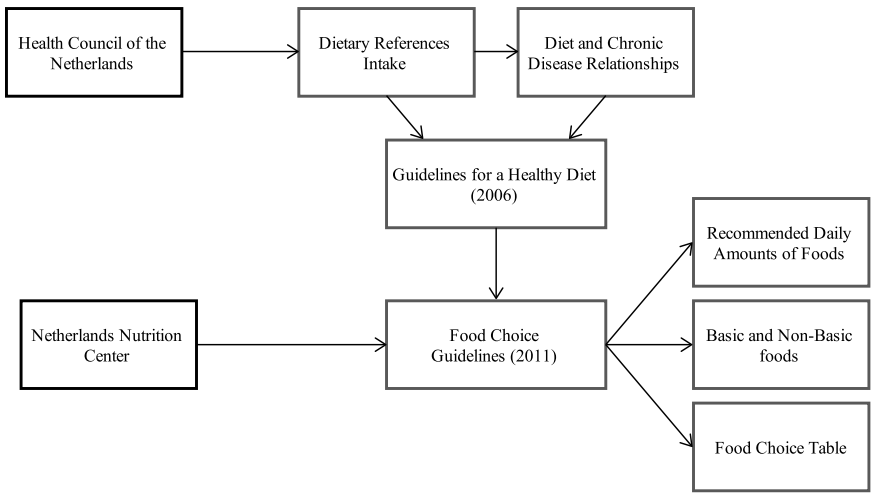



**FIGURE 1** Organizations and process for developing food-based dietary guidelines.

Nutrient and energy-based criteria for classification of foods are used for compiling a Food Choice Table corresponding to the Guidelines. The main purpose of this Table is nutrition education, however other applications can be envisioned. A second purpose could be to stimulate the food industry to develop or reformulate products for a healthy diet. Finally, the criteria for classifying foods could be used to develop food-based dietary scores for evaluation of the dietary guidelines and epidemiologic research on diet and the incidence of chronic diseases.

This paper describes a system for classification of foods using multiple, food group specific nutrient-based criteria that are based on state-of-the-art knowledge of nutrients in foods and their potential effects on chronic diseases and current consumption patterns in the Netherlands. Furthermore, the criteria also provide an evidence-based framework for food-based dietary pattern scores to be used in epidemiologic research.

## Dietary guidelines

In the Netherlands the evidence on diet and chronic disease relationships is evaluated by the Health Council. To develop the Guidelines for a Healthy Diet [6], information on Dietary Reference Intakes of nutrients is also taken into account [8-10]. The most recent version of the Guidelines dates from 2006 and currently a revision is taking place. The Guidelines apply to the apparently healthy Dutch population from the age of 12 months onwards.

Relative to the current Dutch diet the 2006 Guidelines are targeted at increasing the consumption of dietary fiber-rich foods such as fruit, vegetables, and whole grain bread, and cis-unsaturated fatty acids in plant oils and fish. A low intake is advised for saturated fatty acid, mono-*trans* unsaturated fatty acids, foods and beverages that contain easily fermentable sugars, drinks high in food acids, alcoholic beverages and salt. Finally the report emphasizes that, in the context of diet-related chronic diseases, the focus should be on dietary patterns and not on individual foods. As stated by the Health Council these guidelines need to be translated into quantitative advice on food consumption: the so-called food-based dietary guidelines [11].

Food-based dietary guidelines are generally broad and nonspecific such as ‘eat a variety of foods each day’ or ‘eat plenty of fruits and vegetables’ or more specific such as ‘eat five portions of fruits and vegetables a day’. Messages may also indicate the type of food, such as ‘eat low-fat dairy products and drink low-fat milk’, or are meal specific such as ‘eat breakfast every day’ [12]. These simple messages are generally illustrated for nutrition education purposes. Examples are the United States My Plate [13] and the Food Pyramid which is used in many European countries [12].

## Classification of foods to the effects of nutrients on health

The classification of foods in the Netherlands was done in two steps. Firstly, a distinction was made among basic and non-basic foods and ready meals. The basic foods are illustrated using a food wheel, the center of which is used for the most important messages on foods **(Figure 2)**. The food wheel itself consists of five broad food groups i.e. "bread, cereals, legumes and potatoes", "fruit and vegetables", "dairy, meat, fish and eggs", "fats and oils", and "beverages". These five broad food groups are subdivided into 16 basic food groups consisting of nutrient-dense foods that are typical for the Dutch diet and are important contributors to the nutrient supply of the consumers. Non-basic foods and ready meals, are usually energy-dense and and/or high in solid fats, sodium and/or added sugar, are subdivided in nine food groups (**Table 1)**.

In the second step each food group was divided into three subgroups, foods with a positive, neutral or negative effect on health. This is similar to a strategy that has been developed in the USA by Sijtsma et al. [14]. The five main criteria for the classification of the individual foods within the broad basic foods category were based on the most important nutrients for prevention of chronic diseases, according to the Guidelines for a Healthy Diet. These are four nutrients that increase the risk of chronic diseases: saturated fatty acids, *trans* unsaturated fatty acids, added sugar and sodium, and one nutrient that decreases the risk of chronic diseases: dietary fiber.


**FIGURE 2** Wheel of five.

**TABLE 1.** Overview of food groups within the broad categories of basic foods, non-basic foods, and ready meals

| Basic foods | Non-basic foods | Ready Meals |
|---|---|---|
| Vegetables and fruit | Soups | Warm meals/main courses |
| Fruit juices | Sauces | Mixed salads |
| Legumes | Snacks | Lunch dishes/sandwiches |
| Potatoes, pasta | Sugar sweetened beverages | |
| Rice | Spreads | |
| Bread | Other foods | |
| Breakfast cereals | | |
| Other grain products | | |
| Milk and milk products | | |
| Cheese | | |
| Unprocessed meat | | |
| Processed meat | | |
| Eggs | | |
| Fish | | |
| Fats and oils | | |
| Water | | |

A few exceptions to these nutrient criteria exist. Vegetable and fruit consumption should be stimulated, therefore all unprocessed vegetable and fruits are classified positive. This includes frozen, canned or jarred vegetables and fruits provided that the total edible portion is present in de final product. More processed vegetables or fruits (i.e. pureed, juiced) are classified neutral, additions to vegetables and fruits classifies for a negative rating (i.e. à la crème versions of vegetables). For eggs there are no classification criteria, they are nutrient rich but also contain cholesterol, this is not rated in the criteria, therefore maximum recommended amount is set at 3 eggs per week. Processed fish e.g. salted and pickled herring, smoked and steamed fish, were classified as positive regardless of these five nutrients. The reason is that fish consumption is low in the Netherlands (<1 serving per week) and needs to be stimulated to achieve an adequate intake of the essential n-3 poly-unsaturated fatty acids.

There was no energy criterion for basic foods, instead daily recommended amounts, stratified by age and gender, are available for each basic food group [15]. For non-basic foods and ready meals an energy criterion was added to limit the risk of a positive energy balance. For ready meals a vegetable component was also added because in the Dutch dietary pattern most of the vegetables are consumed with meals. A description of how the criteria for a positive, neutral or negative rating

were derived with an example for the classification of breads, snacks and ready meals, and criteria points for all foods are described in the supplemental material.

## Food-based dietary scores based on the classification system

Based on the classification system described above an evidence-based framework was created to create food-based dietary scores to be used in epidemiologic research. This is needed because existing dietary scores have disadvantages. Firstly, a limited selection of food groups is included, secondly, food groups are generally broadly defined and thirdly, many scores include both food and nutrient-based scoring components.

Because of the detailed classification system several issues should be kept in mind in preparing food-based dietary scores. Firstly, depending on the dietary assessment method food groupings can be based on several foods, for example when a food frequency questionnaire is used. Secondly, each food group will be not be consumed in sufficient amounts in every population to stand alone. For example, in the Dutch elderly population the consumption of low-fat cheese is very low, therefore, the criteria for a positive rating of cheese might not be applicable. Thirdly, with respect to scoring, dietary pattern choices have to be made regarding the neutral rated foods. Different options are possible; excluding neutral food groups from an overall dietary score as done in previous studies [14, 16-18] or combining positive and neutral foods in one score.

We created two dietary scores, one scoring positive and neutral basic foods and another one scoring negative including refined or processed basic foods, non-basic foods and ready meals (Table 2). In the positive and neutral scored basic food groups there should be considerable variety and sufficient intake of foods based on the Dutch consumption pattern. We used either the cut off points for a neutral rating (whole grains, low-fat milk and yoghurt, oils and soft margarines and the non-caloric drinks) or the cut off point for a positive rating (unprocessed) vegetables, fruit, potatoes, lean meat) to decide to which score a specific food was added. For some food groups we did not use classification criteria because 1) the nutrients were not applicable (eggs), 2) the consumption of the specific food group should be stimulated (fish), 3) overall consumption of the food group is not sufficient to further divide the food group into positive or negative foods (protein rich plant foods). The negative scored high fat, refined, and processed basic foods, the non-basic foods and ready meals are generally energy dense, low in nutrients and/or high in solid fats, sodium and added sugar. For the high-fat, refined and processed basic foods the criteria for solid fats, sodium added sugar and dietary fiber are specified in table 2. Because of the high energy density and/or the high content of solid fats, sodium and added sugar and/or low content of dietary fiber we did not use the classification criteria for non-basic foods and ready meals.

**TABLE 2** Simplified classification of foods for the purpose of creating food-based dietary scores

| Positive and neutral rated basic food groups | Examples of foods | Criteria |
|---|---|---|
| Vegetables | Lettuce, tomatoes, cauliflower, green beans, leeks etc. | Unprocessed vegetables |
| Fruit | Apple, orange, bananas, grapes, strawberries etc. | Unprocessed fruit |
| Whole grains | Whole wheat bread, crackers, cereals, brown rice | Bread[1]:<br>SFA: ≤ 1.1g/100g<br>TF: ≤ 0.1g/100g<br>DF: ≥ 1.3g/100kcal<br>Na: ≤ 500mg/100g<br>AS: ≤ 13en% |
| Potatoes | All potatoes and potato products regardless of preparation method | SFA: ≤ 1.1g/100g<br>TF: ≤ 0.1g/100g<br>DF: ≥ 1.7g/100kcal<br>Na: ≤ 100mg/100g |
| Protein rich plant foods | Peas, broad beans, tofu, nuts and seeds | All legumes, nuts and seeds |
| Lean meat | Beef, chicken or turkey breast, ham | SFA: ≤ 4g/100g<br>Na: ≤ 100mg/100g<br>AS: not added |
| Fish | Trout, salmon, herring, pollock, shellfish | All fish |
| Eggs | | All eggs |
| Low fat milk and yoghurt | Skimmed and semi-skimmed milk, yoghurt, buttermilk | SFA: ≤ 1.3g/100g<br>Na: ≤ 100mg/100g<br>AS: ≤ 5g/100g |
| Oils and soft margarines | Vegetable oils, (diet) low-fat margarines | SFA: ≤ 30% of total fat<br>TF: ≤ 1.3en%<br>Na: ≤ 160mg/100g |
| Non caloric drinks | Water, tea, coffee, | SFA: ≤ 1.0g/100g<br>TF: ≤ 0.1g/100g<br>Na: ≤ 20mg/100ml<br>AS: not added |
| Negatively rated basic and non-basic food groups | | |
| Processed vegetables | Canned or jarred vegetables, spinach a la crème, pickled vegetables, sauerkraut | n.a. |
| Processed fruit | Fruit or vegetable juice, applesauce | n.a. |

**TABLE 2 (Continued)** Simplified classification of foods for the purpose of creating food-based dietary scores

| Negatively rated basic and non-basic food groups | Examples of foods | Criteria |
|---|---|---|
| Refined grains | Refined bread, cornflakes, white rice | Refined bread[1]<br>SFA: > 1.1g/100g<br>TF: > 0.1g/100g<br>DF: < 1.3g/100 kcal<br>Na: > 500mg/100g<br>AS: > 13en% |
| High-fat meat | Hamburger, chicken or turkey with skin, minced meat, pork sirloin | SFA: > 13en%<br>Na: > 100mg/100g<br>AS: added |
| Processed meat | Cold cuts (bacon, sliced ham, salami) | SFA: > 13en%<br>Na: > 900mg/100g<br>AS: > 2.5g/100g |
| Full-fat milk and yoghurt | Full-fat milk, chocolate milk, yoghurt, coffee cream | SFA: > 1.3g/100g<br>Na: > 100mg/100g<br>AS: > 5g/100g |
| Negatively rated basic and non-basic food groups | Examples of foods | Criteria |
| Full-fat cheese | Hard cheeses (e.g. Gouda, cheddar), soft cheeses (e.g. brie, camembert), cream cheese | SFA: > 16g/100g<br>Na: > 900mg/100g |
| Butter and hard margarines | Butter, margarine | SFA: > 30% of total fat<br>TF: > 1.3en%<br>Na: > 160mg/100g |
| Soups | Vegetable soup, stock/broth | n.a. |
| Sauces | Mayonnaise, ketchup, gravy, hollandaise, béarnaise | n.a. |
| Spreads | Peanut butter, jam, chocolate-hazelnut spreads | n.a. |
| Ready meals | Pizza, quiche, lasagne | n.a. |
| Sweet snacks | Ice cream, cookies, candy bars, chocolate | n.a. |
| Savory snacks | Crisps, chips, deep fried snacks, döner kebab, condiments | n.a. |
| Sugar sweetened beverages | Soda's, ice tea, lemonade, cappuccino | n.a. |

SFA:= saturated fatty acids, TF:= trans fat, DF= fiber, Na= sodium, AS= added sugar, EN= energy kcal; general criteria, tolerance levels, food group specific criteria

Each specific food is first classified according to the criteria for a positive classification. If any criterion is not satisfied the neutral criterion is checked. If all neutral criteria are not satisfied the food is classified negative

[1]Classification criteria for bread are shown, different criteria should be used for rice and cereals

## DISCUSSION

We described a food classification system in which all foods were initially categorized into basic and non-basic foods, and ready meals. Within these broad categories food groups were created, and then individual foods were classified as having a positive, neutral or negative effect on health. Criteria to classify foods were based on four nutrients that increase the risk of chronic diseases: saturated fatty acids, *trans* unsaturated fatty acids, sodium, and added sugar and one nutrient that decrease the risk of chronic diseases: dietary fiber. For non-basic foods and ready meals the same five nutrients were used plus energy content. Finally two dietary scores were created, one scoring positive and neutral foods and another scoring negative foods to be used in epidemiological research.

Although the criteria were developed using state-of-the-art knowledge of nutrition they may change because of advancing knowledge and changes in the Dutch food consumption pattern. The current criteria may not be optimal for the prevention of chronic diseases because what is desired can be compromised by which foods are available, i.e. there should be a variety of choice in foods in each category. For example the lower threshold for fiber is based on an international recommendation (3.0 mg/MJ). This is lower than the recommendation of the Health Council of the Netherlands (3.4 mg/MJ). Sodium thresholds are based on the current sodium content of foods. Therefore, it is not possible to realize the current recommendation of less than 6g salt per day. This recommendation can only be realized if the food industry lowers sodium content of foods. Instead of added sugar it might be better to define criteria based on free sugars since they are of greatest interest in relation to a positive energy balance [19]. These criteria should be evaluated regularly and possibilities to re-formulate the criteria more strictly should be considered.

An important limitation of the present classification system is that the criteria were developed specifically for the Dutch situation. These criteria are not necessarily directly applicable in other countries with different foods and food consumption patterns. Other or additional public health goals may be important for developing food-based dietary guidelines in other countries. For most Western countries however, dietary goals are quite similar, i.e. stimulating fiber intake, and discouraging the intake of saturated fat, *trans* unsaturated fat, sodium, and added sugar. Therefore, the general principles of classifying foods may also be applicable in other countries.

Only a few nutrients were used to classify foods. This raises the question of the importance of other nutrients and of energy in classifying foods. Nutrients in foods are, however, highly correlated e.g. fiber rich foods are often also rich in vitamins and minerals (e.g. whole grain breads, fruits, vegetables). There is no

energy criterion for basic foods that are important contributors of essential nutrients and trace elements and therefore less important with regards to energy content. To avoid overconsumption of high fat, refined and processed basic foods it is important to stress appropriate portion sizes and recommended daily amounts.

The classification criteria are not only important for nutrition education, but also for investigating dietary patterns in relation to chronic diseases. Dietary pattern scores based on current food-based dietary guidelines are useful not only for assessing diet and chronic disease relationships but also for evaluating dietary guidelines. In this context the definition of a dietary pattern is an important question. Up to now, most dietary patterns scores are based on both nutrients and foods and few scores are solely based on foods. Published food-based dietary pattern scores generally included only a few broad food groups [20, 21] or recommended foods [22] and may not capture all dietary information. Furthermore, *A priori* Diet Quality Scores were created based on evaluation of food-disease relationships by individual researchers [14, 17, 18, 23]. The criteria described in the present paper provide an evidence-based approach for creating food groups and classifying foods which can be combined into a food-based dietary pattern score.

In conclusion, the described system can be used to systematically and objectively classify each food in relation to their likely effects on health. This is not only important for nutrition education but could also provide a framework for epidemiologic research on diet and chronic disease relationships. Further research is needed to validate the classification system and to assess whether food-based dietary scores based on this system predict disease.



## ACKNOWLEDGMENTS

F.P.C.S., S.S.S.M. and D.K. identified the study topic and design. F.P.C.S. wrote the first draft of the manuscript. S.S.S.M., A.W., A.P.S., D.W., D.R.J. and D.K. reviewed the manuscript. All authors contributed to and approved the final draft of the paper. F.P.C.S., A.W., A.P.S., D.W., and D.K. declare no conflict of interest. S.S.S.M. received unrestricted research grants from the Dutch Dairy Association and Global Dairy Platform to carry out meta-analyses on the association between dairy products and cardiovascular diseases. D.R.J. is a member of the Scientific Advisory Board of the California Walnut Commission.

The contributions of F.P.C.S., S.S.S.M. and D.K. to this article were funded by the Royal Netherlands Academy of Arts and Sciences.

## REFERENCES


1. Mozaffarian D, Ludwig DS. Dietary guidelines in the 21st century--a time for food. JAMA. 2010;304:681-2.
2. Willett WC, Ludwig DS. The 2010 Dietary Guidelines--the best recipe for health? N Engl J Med. 2011;365:1563-5.
3. Reedy J, Krebs-Smith SM, Miller PE, Liese AD, Kahle LL, Park Y, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. J Nutr. 2014;144:881-9.
4. McNaughton SA, Bates CJ, Mishra GD. Diet quality is associated with all-cause mortality in adults aged 65 years and older. J Nutr. 2012;142:320-5.
5. Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. High diet quality is associated with a lower risk of cardiovascular disease and all-cause mortality in older men. J Nutr. 2014;144:673-80.
6. Health Council of the Netherlands. Guidelines for a healthy diet 2006. The Hague: Health Council of the Netherlands. publication no. 2006/21.
7. Netherlands Nutrition Center, Guidelines Food Choice. http://www.voedingscentrum.nl/Assets/Uploads/Documents/Voedingsvoorlichters/Richtlijnen_voedselkeuze_2011.pdf. (accessed June 4th, 2012)
8. Health Council of the Netherlands. Dietary reference intakes: calcium, vitamin D, thiamin, riboflavin, niacin, pantothenic acid, and biotin. The Hague publication no. 2000/12.
9. Health Council of the Netherlands. Dietary Reference Intakes: vitamin B6, folic acid, and vitamin B12. The Hague publication no.2003/04.
10. Health Council of the Netherlands. Dietary Reference Intakes: energy, proteins, fats and digestible carbohydrates. The Hague publication no. 2001/19R (corrected edition: June 2002).
11. Health Council of the Netherlands. Healthy Nutrition. http://www.gezondheidsraad.nl/en/task-and-procedure/areas-of-activity/healthy-nutrition. (accessed March 5th, 2015)
12. The European Food Information Council (EUFIC). Food-Based Dietary Guidelines in Europe. http://www.eufic.org/article/en/expid/food-based-dietary-guidelines-in-europe. (accessed June 4th, 2012).
13. United States Department of Agriculture, The Center for Nutrition Policy and Promotion. MyPlate. http://www.choosemyplate.gov/. (accessed June 4th, 2012)
14. Sijtsma FP, Meyer KA, Steffen LM, Shikany JM, Van Horn L, Harnack L, et al. Longitudinal trends in diet and effects of sex, race, and education on dietary quality score change: the Coronary Artery Risk Development in Young Adults study. Am J Clin Nutr. 2012;95:580-6.
15. Netherlands Nutrition Center, Wheel of Five. http://www.voedingscentrum.nl/nl/schijf-van-vijf/schijf.aspx. (accessed June 4th, 2012)
16. Nettleton JA, Schulze MB, Jiang R, Jenny NS, Burke GL, Jacobs DR, Jr. A priori-defined dietary patterns and markers of cardiovascular disease risk in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 2008;88:185-94.
17. Lockheart MS, Steffen LM, Rebnord HM, Fimreite RL, Ringstad J, Thelle DS, et al. Dietary patterns, food groups and myocardial infarction: a case-control study. Br J Nutr. 2007;98:380-7.
18. Jacobs DR, Jr., Sluik D, Rokling-Andersen MH, Anderssen SA, Drevon CA. Association of 1-y changes in diet pattern with cardiovascular disease risk factors and adipokines: results from the 1-y randomized Oslo Diet and Exercise Study. Am J Clin Nutr. 2009;89:509-17.
19. World Health Organization. Diet, Nutrition and the Prevention of Chronic Diseases. Joint WHO/FAO Expert Consultation. 2003.
20. Lowik MRH, Hulshof KFAM, Brussaard JH. Food-based dietary guidelines: some assumptions tested for the Netherlands. Brit J Nutr. 1999;81:S143-S9.
21. Osler M, Heitmann BL, Gerdes LU, Jorgensen LM, Schroll M. Dietary patterns and mortality in Danish men and women: a prospective observational study. Br J Nutr. 2001;85:219-25.
22. Kant AK, Schatzkin A, Graubard BI, Schairer C. A prospective study of diet quality and mortality in women. JAMA. 2000;283:2109-15.
23. Nettleton JA, Schulze MB, Jiang R, Jenny NS, Burke GL, Jacobs DR, Jr. A priori-defined dietary patterns and markers of cardiovascular disease risk in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 2008;88:185-94

## SUPPLEMENTAL MATERIAL

### Details of the classification of foods to the effects of nutrients on health.

To be able to classify each food based on the five nutrients, energy, and vegetable intake, three sets of criteria were developed i.e. general criteria, food group specific criteria and tolerance levels.

Each food was first classified using the general criteria. General criteria for saturated fat, *trans* fat, and sodium were derived from the Guidelines for a Healthy Diet. For added sugar the criterion was based on international recommendations [1]. For the nutrients that needed to be restricted there was a difference between average and recommended intake of approximately 30%. This difference was used as a general criterion. An exception was the intake of dietary fiber which needs to be encouraged, therefore there was no upper limit. The lower limit for the general criterion was 1.3 g/100 kcal based on international recommendations [1].

Food group specific criteria were derived if the general criteria were insufficient to classify foods. To distinguish neutral from negative classified foods, food group specific criteria were based on the average current intake of a given nutrient (taken from the third Dutch National Food Consumption Survey) expressed per 100g of the food [2]. To distinguish positive from neutral foods the desired change for the five main nutrients was taken into account. For example, compared to the current intake a decrease of 30% for saturated fat and an increase of 30% for fiber was used.

Tolerance levels were determined for nutrients with a negative influence on health i.e. saturated fat, *trans* fat, sodium and added sugar. These levels were defined as at maximum 5% of the guideline for the relevant nutrients in 100g of the food. The tolerance levels serve two aims, firstly to discourage the food industry to add these nutrients to foods and secondly to allow traces of these nutrients in specific foods.

### Three examples of classifying foods

For bread, general criteria were applied to distinguish neutral foods from negative foods. A food group specific criterion was derived for fiber: currently in the Netherlands, bread consumption provides on average 1.8g fiber per 100kcal. The limit for a positive classification was set approximately 30% higher than current intake and thus at 2.4 g/100 kcal. Sodium levels in all breads were higher than the general criterion; therefore a food group specific criterion was derived of at most 500 mg/100g for positive and neutral classification of breads and more than 500 mg/100 g for negative classified breads. Bread contains only traces of saturated and *trans* fat and therefore tolerance levels were applied for these nutrients. It is possible that a food would be positively categorized for one criterion and neutral or negative

for another one. In that case the food would be classified based on the worst health effect.

Energy was the main criterion for non-basic foods such as snacks. An overall diet based on the daily recommended amounts of basic foods would add up to approximately 1650 kcal and based on an average total energy intake of 2000 kcal about 350 kcal per day are available in the Dutch dietary pattern for non- basic foods consumed during three or four snacking occasions per day. Therefore a limit of 110 kcal per serving was used to distinguish neutral from negative classified snacks and less than 75 kcal per serving for positive classified snacks. Criteria for saturated and *trans* fat were based on general criteria. Sodium and added sugar criteria were based on food specific criteria.

The energy criterion for ready meals was derived from the average energy content of meals reported in the third Dutch National Food Consumption Survey (1998) [2], adding a margin of 25%. The limit for saturated fat and *trans* fat to distinguish neutral from negative classified ready meals was derived from the general criteria. The limit to distinguish positive from neutral ready meals was based on a lower food specific criterion, enabling classifying composite meals in the positive category. For sodium, food group specific criteria were used. General criteria were used for fiber. For vegetables, the lower recommendation of the Guidelines for a Healthy Diet of 150 gram was used. **Supplemental table 1** lists the criteria for all foods.

**SUPPLEMENTAL TABLE 1** Criteria for classifying all foods on their effect of health

| | Positive | Neutral | Negative |
|---|---|---|---|
| Basic foods | | | |
| Vegetables and fruit | Unprocessed vegetables and fruit[1] | Processed vegetables and fruit | Processed vegetables and fruit |
| | | SFA: ≤ 1.1g/100g | SFA: > 1.1g/100g |
| | | TF: ≤ 0.1g/100g | TF: > 0.1g/100g |
| | | DF: ≥ 1.3g/100kcal | DF: < 1.3g/100 kcal |
| | | Na: ≤ 200mg/100g | Na: > 200mg/100g |
| | | AS: ≤ 2.5g/100g | AS: > 2.5g/100g |
| Fruit juices | Fruit juices cannot be classified positive because not all edible parts of the original fruit are present in the juice. | EN: ≤ 50kcal/100ml | EN: > 50kcal/100ml |
| | | SFA: ≤ 1.1g/100g | SFA: > 1.1g/100g |
| | | TF: ≤ 0.1g/100g | TF: > 0.1g/100g |
| | | DF: ≥ 0.75g/100kcal | DF: < 0.75g/100 kcal |
| | | Na: ≤ 100mg/100g | Na: > 100mg/100g |
| | | AS: not added | AS: added |
| Legumes | SFA: ≤ 1.1g/100g | SFA: ≤ 1.1g/100g | SFA: > 1.1g/100g |
| | TF: ≤ 0.1g/100g | TF: ≤ 0.1g/100g | TF: > 0.1g/100g |
| | DF: ≥ 2.4g/100kcal | DF: ≥ 1.3g/100kcal | DF: < 1.3g/100kcal |
| | Na: ≤ 100mg/100g | Na: ≤ 200mg/100g | Na: > 200mg/100g |
| | AS: ≤ 2.5g/100g | AS: ≤ 2.5g/100g | AS: > 2.5g/100g |
| Potatoes, pasta | SFA: ≤ 1.1g/100g | SFA: ≤ 1.1g/100g | SFA: > 1.1g/100g |
| | TF: ≤ 0.1g/100g | TF: ≤ 0.1g/100g | TF: > 0.1g/100g |
| | DF: ≥ 1.7g/100kcal | DF: ≥ 1.3g/100kcal | DF: < 1.3g/100kcal |
| | Na: ≤ 100g/100g | Na: ≤ 100mg/100g | Na: > 100mg/100g |
| | AS: not added | AS: not added | AS: added |
| Rice | SFA: ≤ 1.1g/100g | SFA: ≤ 1.1g/100g | SFA: > 1.1g/100g |
| | TF: ≤ 0.1g/100g | TF: ≤ 0.1g/100g | TF: > 0.1g/100g |
| | DF: ≥ 1.3g/100kcal | DF: ≥ 0.7g/100kcal | DF: < 0.7g/100 kcal |
| | Na: ≤ 100mg/100g | Na: ≤ 100mg/100g | Na: > 100mg/100g |
| | AS: not added | AS: not added | AS: added |

**SUPPLEMENTAL TABLE 1 (Continued)** Criteria for classifying all foods on their effect of health

| | Positive | Neutral | Negative |
|---|---|---|---|
| Basic foods | | | |
| Bread | SFA: ≤ 1.1g/100g | SFA: ≤ 1.1g/100g | SFA: > 1.1g/100g |
| | TF: ≤ 0.1g/100g | TF: ≤ 0.1g/100g | TF: > 0.1g/100g |
| | DF: ≥ 2.4g/100kcal | DF: ≥ 1.3g/100kcal | DF: < 0.7g/100 kcal |
| | Na: ≤ 500mg/100g | Na: ≤ 500g/100g | Na: > 500g/100g |
| | AS: ≤ 2.5g/100g | AS: ≤ 13en% | AS: > 13en% |
| Breakfast cereals | SFA: ≤ 1.1g/100g | SFA: ≤ 3.0g/100g | SFA: > 3.0g/100g |
| | TF: ≤ 0.1g/100g | TF: ≤ 0.1g/100g | TF: > 0.1g/100g |
| | DF: ≥ 2.4g/100kcal | DF: ≥ 1.3g/100kcal | DF: < 1.3g/100kcal |
| | Na: ≤ 500mg/100g | Na: ≤ 500mg/100g | Na: > 500mg/100g |
| | AS: ≤ 2.5g/100g | AS: ≤ 20g/100g | AS: > 20g/100g |
| Other grain products (e.g. flour) | n/a | SFA: ≤ 1.1g/100g | SFA: > 1.1g/100g |
| | | TF: ≤ 0.1g/100g | TF: > 0.1g/100g |
| | | DF: ≥ 1.3g/100kcal | DF: < 1.3g/100kcal |
| | | Na: ≤ 100mg/100g | Na: > 100mg/100g |
| | | AS: ≤ 2.5g/100g | AS: > 2.5g/100g |
| Milk and milk products | SFA: ≤ 0.5g/100g | SFA: ≤ 1.3g/100g | SFA: > 1.3g/100g |
| | TF: not added | TF: not added | TF: added |
| | Na: ≤ 100mg/100g | Na: ≤ 100mg/100g | Na: > 100mg/100g |
| | AS: not added | AS: ≤ 5g/100g | AS: > 5g/100g |
| Cheese | SFA: ≤ 12g/100g | SFA: ≤ 16g/100g | SFA: > 16g/100g |
| | TF: not added | TF: not added | TF: added |
| | Na: ≤ 900mg/100g | Na: ≤ 900mg/100g | Na: > 900mg/100g |
| | AS: not added | AS: not added | AS: added |
| Unprocessed meat | SFA: ≤ 4g/100g | SFA: ≤ 13en% | SFA: > 13en% |
| | TF: not added | TF: not added | TF: added |
| | Na: ≤ 100mg/100g | Na: ≤ 100mg/100g | Na: > 100mg/100g |
| | AS: not added | AS: not added | AS: added |
| Processed meat | SFA: ≤ 4g/100g | SFA: ≤ 13en% | SFA: > 13en% |
| | TF: not added | TF: not added | TF: not added |
| | Na: ≤ 900mg/100g | Na: ≤ 900mg/100g | Na: > 900mg/100g |
| | AS: ≤ 2.5g/100g | AS: ≤ 2.5g/100g | AS: > 2.5g/100g |

| | | | |
|---|---|---|---|
| Eggs | | | |
| Fish | Unprocessed fish and shellfish | Processed fish and shellfish | Processed fish and shellfish |
| | | SFA: ≤ 30en% of total fat | SFA: > 30en% of total fat |
| | | TF: ≤ 0.1g/100g | TF: > 0.1g/100g |
| | | Na: ≤ 450mg/100g | Na: > 450mg/100g |
| | | AS: not added | AS: added |
| Fats and oils | SFA: ≤ 16g/100g | SFA: ≤ 30% of total fat | SFA: > 30% of total fat |
| | TF: ≤ 1.3en% or 1g/100g | TF: ≤ 1.3en% | TF: > 1.3en% |
| | Na: ≤ 160mg/100g | Na: ≤ 160mg/100g | Na: > 160mg/100g |
| | AS: not added | AS: not added | AS: added |
| Water, coffee and tea | n/a | SFA: ≤ 1.0g/100g | SFA: > 1.0g/100g |
| | | TF: ≤ 0.1g/100g | TF: > 0.1g/100g |
| | | Na: ≤ 20mg/100ml | Na: > 20mg/100ml |
| | | AS: not added | AS: added |
| Non-Basic foods | | | |
| Soups | EN: ≤ 30kcal/100g | EN: ≤ 100kcal/100g | EN: > 100kcal/100g |
| | SFA: ≤ 1.1g/100g | SFA: ≤ 1.1g/100g | SFA: > 1.1g/100g |
| | TF: ≤ 0.1g/100g | TF: ≤ 0.1g/100g | TF: > 0.1g/100g |
| | Na: ≤ 350mg/100g | Na: ≤ 350mg/100g | Na: > 350mg/100g |
| | AS: ≤ 2.5g/100g | AS: ≤ 2.5g/100g | AS: > 2.5g/100g |
| Sauces | EN: ≤ 100kcal/100g | EN: ≤ 350kcal/100g | EN: > 350kcal/100g |
| | SFA: ≤ 1.1g/100g | SFA: ≤ 30 % of total fat | SFA: > 30% of total fat |
| | TF: ≤ 0.1g/100g | TF: ≤ 1.3en% | TF: > 1.3en% |
| | Na: ≤ 450mg/100g | Na: ≤ 750mg/100g | Na: > 750mg/100g |
| | AS: ≤ 2.5g/100g | AS: ≤ 11g/100g | AS: > 11g/100g |
| Snacks | EN: ≤ 75kcal/portion | EN: ≤ 110kcal/portion | EN: > 110kcal/portion |
| | SFA: ≤ 13en% | SFA: ≤ 13en% | SFA: > 13en% |
| | TF: ≤ 1.3g/100g | TF: ≤ 1.3en% | TF: > 1.3en% |
| | Na: ≤ 400mg/100g | Na: ≤ 400mg/100g | Na: > 400mg/100g |
| | AS: ≤ 20g/100g | AS: ≤ 20g/100g | AS: > 20g/100g |
| Sugar Sweetened Beverages | EN: ≤ 4kcal/100ml | EN:≤ 30kcal/100ml | EN: > 30kcal/100ml |
| | SFA: not added | SFA: ≤ 1.1g/100g | SFA: ≤1.1 g/100g |
| | TF: not added | TF: ≤ 0.1g/100g | TF: > 0.1g/100g |
| | Na: ≤ 20mg/100g | Na: ≤ 20mg/100g | Na: > 20mg/100g |
| | Alcohol: <0.5% | Alcohol: <0.5% | Alcohol: ≥0.5% |

**SUPPLEMENTAL TABLE 1 (Continued)** Criteria for classifying all foods on their effect of health

| | Positive | Neutral | Negative |
|---|---|---|---|
| Non-Basic foods | | | |
| Spreads | EN: ≤ 200kcal/100 g | EN: ≤ 350kcal/100g | EN: > 350kcal/100g |
| | SFA: ≤ 13en% | SFA: ≤ 13en% | SFA: > 13en% |
| | TF: ≤ 1.3g/100g | TF: ≤ 1.3en% | TF: > 1.3en% |
| | Na: ≤ 400mg/100g | Na: ≤ 400mg/100g | Na: > 400mg/100g |
| | AS: ≤ 2.5g/100g | AS: ≤ 30g/100g | AS: > 30g/100g |
| Other foods | EN: ≤ 200kcal/100g | | |
| | SFA: ≤ 13en% | SFA: ≤ 13en% | SFA: > 13en% |
| | TF: ≤ 1.3g/100g | TF: ≤ 1.3en% | TF: > 1.3en% |
| | Na: ≤ 350mg/100g | Na: ≤ 1.3mg/kcal | Na: > 1.3mg/kcal |
| | AS: not added | AS: ≤ 13en% | AS: > 13en% |
| Ready Meals | | | |
| Warm meals/ main courses | EN: 400-700kcal/portion | EN: 400-700kcal/portion | EN: < 400 or > 700kcal/portion |
| | EN: 550-950kcal/meal | EN: 550-950kcal/meal | EN: < 550 or > 950kcal/meal |
| | SFA: ≤ 10en% | SFA:≤ 13en% | SFA: > 13en% |
| | TF: ≤ 1.0en% | TF:≤ 1.3en% | TF: > 1.3en% |
| | DF: ≥ 1.3g/100kcal | DF≥ 1.3g/100kcal | DF: < 1.3g/100kcal |
| | Na: ≤ 160mg/100g | Na≤ 2.2mg/kcal | Na: > 2.2mg/100kcal |
| | AS: ≤ 10en% | AS≤ 13en% | AS: > 13en% |
| | Vegetables: ≥ 150g/portion | Vegetables: ≥ 150g/portion | Vegetables: < 150g/portion |
| Mixed Salads | EN: ≤ 110kcal/100g | EN≤ 110kcal/100g | EN: > 110 kcal/100g |
| | SFA: ≤ 1.8g/100g | SFA:≤ 2.6g/100g | SFA: > 2.6g/100g |
| | TF: ≤ 0.1g/100g | TF:≤ 0.1g/100g | TF: > 0.1 g/100g |
| | DF: ≥ 1g/100kcal | DF≥ 0.8g/100kcal | DF: < 0.8 g/100kcal |
| | Na: ≤ 100mg/100g | Na≤ 170mg/100g | Na: > 170 mg/100g |
| | AS: ≤ 10en% | AS≤ 13en% | AS: > 13 en% |
| Lunch dishes/ sandwiches | Sandwich: ≤350kcal/portion | Sandwich: ≤ 350kcal/portion | Sandwich: > 350kcal/portion |
| | Breakfast: 200-350kcal | Breakfast: 200-350kcal | Breakfast: < 200 or >350kcal |
| | Lunch: 350-600kcal | Lunch: 350-600kcal | Lunch: > 350 or > 600kcal |
| | SFA: ≤ 9en% | SFA:≤ 13en% | SFA: > 13en% |

| | | |
|---|---|---|
| TF: ≤ 1.3en% | TF:≤ 1.3en% | TF: > 1.3en% |
| DF: ≥ 1.3g/100kcal | DF≥ 0.8g/100kcal | DF: < 0.8g/100kcal |
| Na: ≤ 160mg/100g | Na≤ 1.9mg/kcal | Na: > 1.9mg/100g |
| AS: ≤ 10en% | AS≤ 13en% | AS: > 13en% |
| Vegetables: ≥ 50g/portion | | |

SFA= saturated fatty acids, TF= *trans* fat, DF= fibre, Na= sodium, AS= added sugar, EN= energy kcal;
Each specific food is first classified according to the criteria for a positive classification. If any criterion is not satisfied the neutral criterion is checked. If all neutral criteria are not satisfied the food is classified negative.
[1]All fruit and vegetables in which all edible parts are present in the final product

## REFERENCES SUPPLEMENTAL MATERIAL

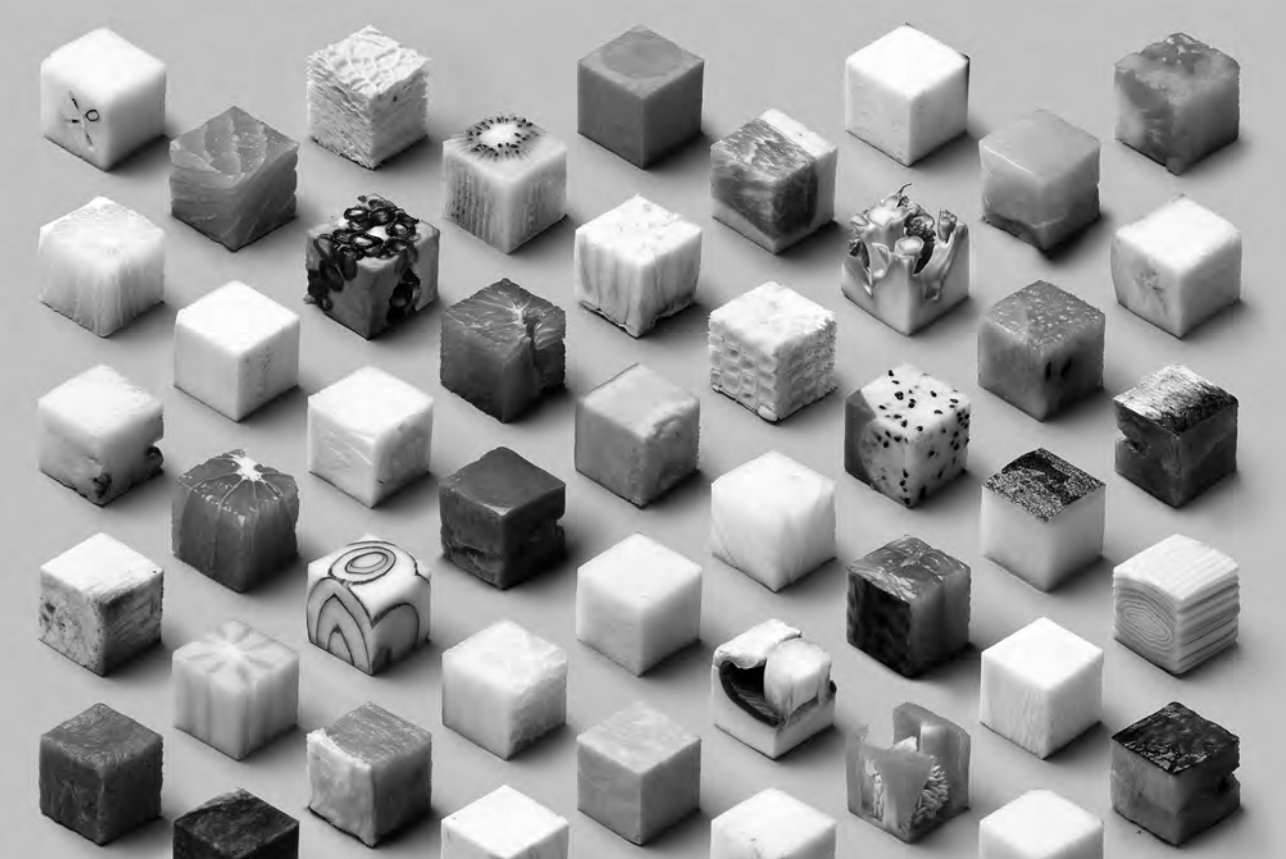
1. World Health Organization (2003) Diet, Nutrition and the Prevention of Chronic Diseases. Joint WHO/FAO Expert Consultation.
2. Netherlands Nutrition Center (1998) Zo eet Nederland: resultaten van de Voedselconsumptiepeiling 1997-1998. Den Haag.

# 6

# Healthy eating and lower mortality risk in a large cohort of cardiac patients who received state-of-the-art drug-treatment

Femke PC Sijtsma, Sabita S Soedamah-Muthu, Janette de Goede, Linda M Oude Griep, Johanna M Geleijnse, Erik J Giltay, Menko Jan de Boer, David R Jacobs Jr, Daan Kromhout

Accepted for publication in Am J Clin Nutr



## ABSTRACT

**Background** Little is known about dietary scores and mortality risk in cardiac patients who are well treated with drugs, with attendant relatively low risk of cardiovascular diseases.

**Objective** We assessed whether healthy eating lowers the risk of CVD and all-cause mortality in cardiac patients.

**Design** We included 4307 patients from the Alpha Omega Trial aged 60-80 years with a clinically diagnosed myocardial infarction and monitored mortality for 10 years. Diet was assessed at baseline (2002-2006) with a validated 203-item Food Frequency Questionnaire. We created two dietary scores based on non-overlapping sets of foods: "Dutch Healthy Nutrient and Food Score (DHNaFS)" and the "Dutch Undesirable Nutrient and Food Score (DUNaFS)". The associations of both dietary scores with CVD and all-cause mortality were assessed using multivariable adjusted Cox regression models.

**Results** Median time after myocardial infarction at baseline was 3.7 y (IQR:1.7-6.3). During median 6.5 y follow-up (IQR: 5.3-7.6) 801 patients died, of whom 342 from CVD. One patient was lost to follow up. A substantially higher average amount of DHNaFS foods (≈1750g/d) than DUNaFS foods (≈ 650g/d) was consumed. Almost all patients received drug-treatment: 86% used statins, 90% anti-hypertensive and 98% anti-thrombotic medication. Patients in the fifth quintile of the DHNaFS had 30% (Hazard Ratio (HR) 0.70; 95% Confidence interval (CI) 0.55,0.91) lower CVD and 32% (HR 0.68; 95%CI 0.47,0.99) lower all-cause mortality risk compared to patients in the first quintile. The DUNaFS was unrelated to both CVD and all-cause mortality.

**Conclusions** Beyond state-of-the-art drug treatment, healthy eating was associated with lower risk of CVD and all-cause mortality in cardiac patients.

## INTRODUCTION

Diet is an important modifiable risk factor for cardiovascular diseases (CVD) and all-cause mortality. Systematic reviews and a meta-analysis showed a lower risk of CVD and all-cause mortality for healthy dietary scores in general populations [1, 2]. Secondary prevention studies on diet quality in relation to CVD mortality were carried out mostly in study populations that were receiving limited state-of-the-art CVD drug [3-7]. One study showed that a higher quality diet was associated with a lower CVD mortality in patients taking secondary preventive drugs, but used a short and limited food frequency questionnaire (FFQ) [8]. Information is therefore needed about whether healthy eating can further lower the risk of CVD and all-cause mortality in patients, beyond state-of-the-art drug treatment.

Previous prospective cohort studies used dietary scores such as the Mediterranean Diet Score (MDS) [4, 5, 7] and the (modified) Alternative Healthy Eating Index (AHEI) [6, 8] that are based on nutrients as well as a limited number of broadly-defined food groups. Consequently, these scores do not reflect the overall dietary pattern since they include mostly nutrient-dense foods but not snacks, ready meals, and drinks such as tea and coffee. Dietary scores that are solely based on a broad set of more narrowly defined food groups have the advantage that they are easier to translate into dietary recommendations.

The objective of the present study was to assess the associations of two food-based dietary scores with CVD and all-cause mortality in cardiac patients who received state-of-the-art drug treatment. The classification of foods in each score was based on 5 nutrient criteria. We hypothesized that a dietary score higher in healthy nutrients and foods is associated with lower CVD and all-cause mortality risk and a dietary score higher in undesirable nutrients and foods is associated with a greater mortality risk in these patients.

## METHODS

### Patients and study design

The Alpha Omega Trial, a randomized placebo-controlled double-blind intervention study designed to investigate the effect of the omega-3 fatty acids on CVD incidence has been described in detail previously [9, 10]. Patients were men and women aged 60-80 years with a verified clinically diagnosed MI up to 10 y before randomization. Between 2002 and 2006, 4837 post-myocardial infarction patients were included in the trial. All patients provided written informed consent. The trial was approved by a central medical ethics committee (Haga Hospital, Leyenburg, The Hague, The Netherlands) and by the ethics committee at each participating hospital.

Patients who had missing dietary (n= 453) data or implausibly high or low energy intake (<800 or >8000 kcal/day for men, <600 or >6000 kcal/day for women: n= 27) were excluded. Physical activity was missing for 25 patients, smoking status for 1 patient and education level for 24 patients. Accounting for analysis-specific exclusions due to missing data for covariates, we included 4307 patients in the fully adjusted Cox proportional hazards models.

## Dietary data

Dietary data were collected at baseline and at the final examination (after on average 41 months) by a 203-item FFQ developed for the Alpha Omega Trial. The FFQ was an extended and adapted version of a reproducible and biomarker validated FFQ. The Pearson's correlation coefficient of intake determined by the FFQ and the dietary history was 0.83 for energy intake [11]. The (8 week) reproducibility was high for the food groups consumed daily such as bread, butter/margarine with Spearman correlation coefficients up to 0.92 [12]. Patients were asked to report the usual intake of foods consumed during the previous month; questions on the frequency, amount, and type of foods, as well as preparation methods were included. Trained dieticians checked the returned questionnaires and obtained additional information on unclear or missing items by phone. Quality assurance procedures included double entry of the FFQ data. Food consumption data were converted into energy and nutrient intake by using the 2006 Dutch food composition database [13].

The 203 food items were collapsed into 24 food groups according to nutrient and energy criteria derived from the Netherlands Food Based Dietary Guidelines [14]. Classification criteria for each food were based on presumed positive, neutral or negative effects on chronic diseases of five nutrients: four that likely increase (saturated fatty acids, mono-*trans* unsaturated fatty acids, sodium, and added sugar) and one that likely decreases (dietary fiber) the risk of chronic diseases, and for some food groups energy. A few whole food groups were classified regardless of nutrients and energy. Each food was classified on the most adverse interpretation of any of the criteria. Details about the classification of foods and food groups are reported in **supplemental Table 1**. We made a distinction between food groups consisting of healthy nutrients and foods that contribute importantly to the nutrient supply and are typical for the Dutch diet and food groups that are high in undesirable nutrients and foods.

## Dietary scores

To create two food-based dietary scores, food groups were categorized into quintiles of consumption. The Dutch Healthy Nutrient and Food score (DHNaFS) included 11 nutrient-dense food groups; vegetables, fruit, whole grains, protein-rich plant

foods (mostly legumes), potatoes, lean meat, fish, eggs, low-fat milk and yogurt, oils and soft margarines, and non-caloric drinks.

The Dutch Undesirable Nutrient and Food score (DUNaFS) included 13 food groups that were high in solid fats, sodium and/or added sugar; processed fruit, high-fat meat, processed meat, full-fat milk, cheese, refined grains, butter and hard margarines, soups, spreads, ready meals, savory snacks, sweet snacks and sugar sweetened beverages.

The scores were calculated by summing the category scores (0-4) of the food groups. Eggs had a large subset of non-consumers, therefore in this food group non-consumers were coded 0 and consumers were split into quartiles with scores from 1 to 4 to ensure variability across 5 levels of consumption. The theoretical maximum for the DHNaFS was 44 and for the DUNaFS was 52. The correlation between the two scores was 0.25.

Baseline mean(SD) was 22.4(6.1) for the DHNaFS and 25.8(7.0) for the DUNaFS based on 4357 FFQs, after 41 months the mean (SD) was 22.3(6.2) for the DHNaFS and 25.9(7.1) for the DUNaFS based on 2219 FFQs. Tracking correlations between baseline scores and the scores after 41 months were 0.57 for the DHNaFS and 0.61 for the DUNaFS.

## Ascertainment and classification of mortality

Vital status and causes of death were monitored through a computerized link with municipal registries. The median follow-up was 6.5 year (IQR: 5.3-7.6) and only one patient was lost to follow-up (censored after 2.9 years).

Information on the causes of death was obtained from the Dutch National Mortality Registry (Statistics Netherlands [CBS]) from May 2002 through January 2012. Causes of death were coded according to the International Classification of Diseases, 10$^{th}$ revision. Cardiovascular mortality included ischemic heart diseases (codes: I20-I25), cardiac arrest (I46), sudden death undefined (R96), heart failure (I50), and stroke (I60-I69) as primary or secondary causes of death.

The classifications of the causes of death by the Endpoint Adjudication Committee (EAC) of the Alpha Omega Trial and CBS were compared for the first 41 months. Based on EAC classification there were 162 CVD events that occurred in the first 41 months, post trial there were 180 CVD events based on less complete information of the CBS. Cardiovascular mortality data showed that there was 80% agreement between the two classifications when the primary and/or secondary cause of death were used. In total we observed 801 deaths of which 342 were CVD deaths. Of the CVD deaths, 265 (77%) had CVD coded as the primary cause of death.

**TABLE 1** Median intake (IQR) of food groups in grams/day of 4357 cardiac patients of the Alpha Omega Trial across quintiles of the Dutch Healthy Nutrient and Food Score (DHNaFS) and the Dutch Undesirable Nutrient and Food Score (DUNaFS)

| | Dutch Healthy Nutrient and Food score[1,2] | | | Dutch Undesirable Nutrient and Food score[1,3] | | |
|---|---|---|---|---|---|---|
| | Q1 | Q3 | Q5 | Q1 | Q3 | Q5 |
| DHNaFS food groups[4] | | | | | | |
| Vegetables | 48 (35- 67) | 77 (62- 98) | 105 (86- 131) | 69 (45- 94) | 77 (58- 100) | 85 (63- 110) |
| Fruit | 47 (14- 114) | 108 (43- 217) | 239 (111- 310) | 106 (35- 254) | 116 (46- 264) | 110 (69- 255) |
| Whole grains | 88 (66- 130) | 118 (88- 158) | 158 (111- 181) | 94 (88- 158) | 111 (88- 158) | 138 (88- 167) |
| Potatoes | 50 (47- 99) | 99 (50- 99) | 99 (99- 140) | 70 (50- 99) | 99 (50- 99) | 99 (70- 132) |
| Protein-rich plant foods | 6 (3- 11) | 12 (7- 18) | 18 (12- 26) | 9 (4- 15) | 12 (7- 19) | 14 (9- 21) |
| Lean meat | 15 (3- 27) | 27 (14- 40) | 36 (25- 47) | 19 (3- 36) | 25 (12- 39) | 30 (17- 40) |
| Eggs | 7 (3- 18) | 18 (7- 18) | 18 (7- 18) | 7 (3- 18) | 7 (7- 18) | 18 (7- 18) |
| Fish | 5 (0- 14) | 14 (4- 17) | 16 (13- 38) | 12 (2- 18) | 12 (4- 17) | 15 (8- 22) |
| Low fat milk and yogurt | 106 (21- 171) | 160 (95- 300) | 300 (150- 396) | 150 (71- 300) | 166 (106- 300) | 167 (87- 300) |
| Oils and soft margarines | 0 (0- 1) | 2 (0- 5) | 4 (1- 9) | 1 (0- 5) | 1 (0- 5) | 2 (0- 5) |
| Non-caloric drinks | 750 (502- 1006) | 931 (676- 1250) | 1175 (892- 1500) | 900 (570- 1275) | 954 (712- 1275) | 949 (713- 1250) |
| DUNaFS food groups | | | | | | |
| Processed fruit | 73 (20- 156) | 95 (29- 176) | 127 (42- 212) | 50 (0- 127) | 94 (21- 168) | 148 (73- 237) |
| Refined grains | 39 (17- 80) | 37 (20- 67) | 41 (23- 68) | 21 (10- 41) | 40 (23- 66) | 67 (42- 97) |
| High-fat meat | 17 (3- 34) | 24 (10- 40) | 31 (17- 43) | 12 (0- 26) | 23 (11- 40) | 35 (21- 48) |
| Processed meat | 12 (6- 18) | 16 (6- 41) | 18 (7- 43) | 7 (3- 17) | 13 (6- 40) | 18 (13- 43) |
| Full-fat milk and yogurt | 48 (11- 128) | 38 (6- 106) | 28 (2- 82) | 11 (0- 45) | 39 (11- 103) | 75 (36- 153) |
| Cheese | 14 (7- 21) | 19 (8- 31) | 20 (14- 49) | 10 (7- 20) | 19 (8- 28) | 21 (14- 50) |
| Butter and hard margarines | 9 (2- 22) | 10 (1- 22) | 9 (1- 22) | 2 (0- 11) | 10 (2- 21) | 18 (8- 31) |
| Soups | 31 (12- 79) | 35 (17- 90) | 35 (17- 90) | 17 (0- 35) | 35 (17- 90) | 67 (35- 124) |
| Spreads | 10 (2- 17) | 13 (4- 20) | 15 (6- 30) | 5 (2- 15) | 13 (5- 20) | 18 (11- 36) |
| Ready meals | 35 (10- 69) | 45 (18- 77) | 59 (25- 92) | 22 (6- 48) | 49 (21- 75) | 80 (48- 113) |
| Sweet snacks | 44 (23- 76) | 51 (31- 83) | 57 (36- 86) | 27 (14- 45) | 51 (33- 77) | 84 (59- 113) |
| Savory snacks | 14 (7- 24) | 18 (9- 29) | 17 (10- 29) | 8 (4- 14) | 17 (9- 26) | 29 (19- 39) |
| Sugar-sweetened beverages | 21 (0- 108) | 28 (0- 106) | 25 (0- 92) | 0 (0- 30) | 21 (0- 82) | 75 (21- 160) |

[1] Tests for trend based on general linear regression with dietary scores as continuous independent variable.

[2] p-trend across quintiles of the Dutch Healthy Nutrient and Food score <0.05 for all food groups except solid fats

[3] p-trend across quintiles of the Dutch Undesirable Nutrient and Food score <0.05 for all food groups except fruit, low-fat milk, vegetable oils and fats

[4] foods included in each food group can be found in supplemental table 1

## Other measurements

Information on risk factor measurements has been described in detail in previous publications (9, 10). In summary, body weight and height were measured and body mass index (BMI) was calculated as weight (kg)/ height$^2$ (m). Systolic and diastolic (1st and 5th Korotkoff sound, respectively) blood pressure were measured twice with an automatic device, with the patient seated, after a 10-minute rest. Blood lipids and glucose were analyzed by standard kits using an autoanalyzer (Hitachi 912, Roche Diagnostics, Basel, Switzerland).

Information on chronic disease history, smoking habits (never/former/current), and educational level (low/moderate/high) was collected by a self-administered questionnaire. Alcohol intake was derived from the FFQ data and categorized as 0 g/d, >0-10 g/d, >10-≤20 g/d or >20 g/d alcohol. Physical activity was assessed by the validated Physical Activity Scale for the Elderly (PASE) (15) and categorized as no activity or only light activity (≤ 3MET), >0 to <5 days/week moderate or vigorous active (>3MET) or ≥5 days/week moderate or vigorous active (>3MET). Self-reported medication of the patients was coded according to the Anatomical Therapeutic Chemical Classification System (ATC). ATC codes were C02, C03, C07, C08, and C09 for blood pressure-lowering medication, C10AA for statins and B01 for anti-thrombotic medication.

## Statistical analysis

Although the Alpha Omega Trial has an experimental design the current analyses were done as in observational prospective cohort studies (with adjustment for intervention groups).

Unadjusted means of patient characteristics were calculated across quintiles of both dietary scores. To investigate the association of the baseline DHNaFS and DUNaFS with CVD and all-cause mortality we used Cox proportional hazard models including both scores simultaneously in the model. Proportional hazards assumptions were examined by a log–minus–log plot and the assumptions were met. Survival time was defined as the period (in days) between assessment date at baseline and date of death (CVD or all-cause) or end of follow-up (for participants that survived). For the patient who was lost to follow up survival time was defined as the period in days between baseline and last available update of CBS data for that patient. We studied different levels of adjustment. A minimal model (model 1) included sex and age (in years) and intervention groups (Placebo, EPA-DHA and ALA, EPA-DHA, ALA). Model 2 was further adjusted for energy (energy (kcal)/ standard deviation), alcohol intake(0g/d, >0-10g/d, >10-≤20 g/d, >20g/d), level of education (low, moderate, high), physical activity (no activity or only light activity (≤ 3MET), >0 to <5 days/week moderate or vigorous active (>3MET) or ≥5 days/week moderate or vigorous active (>3MET)) and smoking status (never, former, current).

Model 3 was additionally adjusted for BMI (kg/m$^2$), systolic blood pressure (mm Hg), total cholesterol/HDL (mmol/l) and prevalence of diabetes.
Sensitivity analysis included stratification models by sex (male vs. female), age (<65vs. ≥65), BMI (<30 vs. ≥30 kg/m$^2$), physical activity (no or only light activity vs. moderate to vigorous physical activity), alcohol (consumers; alcohol intake > 0 g/day vs non-consumers; alcohol intake = 0g/day) and smoking (ever vs. never). For these analyses the DHNaFS was dichotomized at the median.

Data were analyzed using used the PC version (9.3) of the Statistical Analysis System (SAS, Cary, NC).

## RESULTS

### Dietary scores

The participants in this study consumed on average a substantially higher amount of the foods in the DHNaFS (approximately 1750 g/d) than of the foods in the DUNaFS (approximately 650 g/d) resulting in an overall ratio of 2.9.

The gram weight consumption of food groups generally increased across quintiles of both scores with the exception of full-fat milk in the DHNaFS. The medians (Q3) of the food groups in the DHNaFS and DUNaFS were similar but the range of intake (Q5 vs. Q1) of the DHNaFS food groups was at least 2 times greater across quintiles of the DHNaFS compared to the DUNaFS **(Table 1)**. Across quintiles of both scores the absolute intake of energy and nutrients increased, however the macro-nutrients expressed relative to energy as energy-percentage decreased across quintiles of the DHNaFS and increased across quintiles of the DUNaFS **(Table 2)**. There was a smaller range of intake (Q5-Q1) in saturated fat (5g vs. 14g), sodium (762mg vs. 1090mg) and added sugar (31g vs. 67g), and a larger range of intake of dietary fiber (12g vs. 7g) across quintiles of the DHNaFS compared to quintiles of the DUNaFS.

Baseline characteristics were generally similar across the quintiles of the two dietary scores **(Table 2)**. Patients in the highest quintile of both scores were more likely to be male and had a lower prevalence of diabetes. Blood pressure and serum lipids did not differ across quintiles. Almost all patients received state-of-the-art antithrombotic, antihypertensive, and statin therapy. Patients in the highest quintile of both scores were more likely to be moderate to vigorously active, non-smokers, higher educated and alcohol consumers. Differences for these lifestyle variables were generally smaller across quintiles of the DUNaFS.

**TABLE 2** Baseline characteristics of 4357 cardiac patients of the Alpha Omega Trial across quintiles of the Dutch Healthy Nutrient and Food Score and the Dutch Undesirable Nutrient and Food Score [12]

| | Dutch Healthy Nutrient and Food Score[3] | | | Dutch Undesirable Nutrient and Food Score[4] | | |
|---|---|---|---|---|---|---|
| | Q1 | Q3 | Q5 | Q1 | Q3 | Q5 |
| Energy (kcal/d) | 1509 (4423) | 1811 (446) | 2129 (470) | 1327 (323) | 1790 (334) | 2317 (416) |
| Saturated fat (g) | 21.2 (9.9) | 23.8 (9.9) | 26.2 (9.7) | 15.3 (6.1) | 23.1 (7.7) | 32.3 (9.4) |
| Trans fat(g) | 1.2 (0.6) | 1.4 (0.6) | 1.5 (0.6) | 0.9 (0.4) | 1.3 (0.4) | 1.9 (0.5) |
| Sodium(mg) | 1829.9 (595.0) | 2174.9 (621.0) | 2591.6 (643.9) | 1670.0 (465.9) | 2121.9 (529.7) | 2760.4 (634.6) |
| Fiber(g) | 15.7 (5.0) | 21.0 (5.1) | 27.6 (6.3) | 18.2 (6.3) | 21.2 (6.4) | 24.8 (7.2) |
| Added sugar (g) | 87.0 (47.6) | 100.5 (46.3) | 118.0 (45.7) | 69.7 (34.2) | 100.0 (40.0) | 136.9 (47.7) |
| Gender | | | | | | |
| Female | 290 (30.7) | 219 (20.2) | 142 (15.4) | 297 (36.2) | 198 (20.7) | 97 (10.5) |
| Male | 656 (69.3) | 864 (79.8) | 783 (84.7) | 523 (63.8) | 759 (79.3) | 831 (89.6) |
| Age (years) | 69.6 (5.5) | 68.9 (5.5) | 68.7 (5.5) | 69.5 (5.5) | 69.2 (5.5) | 68.6 (5.7) |
| BMI (kg/m$^2$) | 27.8 (4.2) | 27.7 (3.8) | 27.5 (3.7) | 28.2 (4.1) | 27.7 (3.8) | 27.4 (3.6) |
| BMI ≥ 30 | 252 (26.6) | 246 (22.7) | 186 (20.1) | 229 (27.9) | 221 (23.1) | 180 (19.4) |
| Time since myocardial infarction | 4.3 (3) | 4.2 (3.1) | 4.2 (3.3) | 4.4 (3.5) | 4.4 (3.2) | 4.2 (3.2) |
| Anti-thrombotic drugs[5] | 918 (97) | 1056 (97.5) | 910 (98.4) | 790 (96.3) | 933 (97.5) | 911 (98.2) |
| Antihypertensive drugs[6] | 858 (90.7) | 961 (88.7) | 834 (90.2) | 739 (90.1) | 851 (88.9) | 829 (89.3) |
| Statins | 785 (83.0) | 924 (85.3) | 810 (87.6) | 724 (87.1) | 827 (86.1) | 766 (83.4) |
| Prevalent Diabetes Mellitus | 211 (22.3) | 210 (19.4) | 182 (19.7) | 216 (26.3) | 181 (18.9) | 146 (15.7) |
| Systolic blood pressure | 142.5 (22.6) | 141.2 (21.2) | 140.4 (21) | 142.7 (22.4) | 141.8 (20.8) | 139.8 (21.3) |
| Diastolic blood pressure | 79.8 (11.3) | 80.2 (10.8) | 79.8 (10.5) | 79.5 (11.4) | 80.4 (11.1) | 80 (11.3) |
| Serum lipids mmol/liter[7] | | | | | | |
| Total cholesterol | 4.79 (1.00) | 4.69 (0.91) | 4.59 (0.87) | 4.81 (0.99) | 4.73 (0.94) | 4.64 (0.91) |
| LDL cholesterol | 2.62 (0.87) | 2.56 (0.78) | 2.51 (0.75) | 2.61 (0.87) | 2.58 (0.79) | 2.57 (0.81) |
| HDL cholesterol | 1.30 (0.36) | 1.28 (0.34) | 1.28 (0.32) | 1.33 (0.37) | 1.29 (0.34) | 1.25 (0.31) |
| Triglycerides | 1.98 (1.11) | 1.90 (1.06) | 1.79 (0.93) | 1.96 (1.08) | 1.93 (1.00) | 1.85 (0.97) |

**TABLE 2 (Continued)** Baseline characteristics of 4357 cardiac patients of the Alpha Omega Trial across quintiles of the Dutch Healthy Nutrient and Food Score and the Dutch Undesirable Nutrient and Food Score [12]

| | Dutch Healthy Nutrient and Food Score[3] | | | Dutch Undesirable Nutrient and Food Score[4] | | |
|---|---|---|---|---|---|---|
| | Q1 | Q3 | Q5 | Q1 | Q3 | Q5 |
| Physical activity | | | | | | |
| No activity or only light activity | 502 (53.5) | 450 (41.8) | 284 (30.9) | 367 (45.1) | 381 (40) | 354 (38.2) |
| 0-5 d/w moderate or vigorous active (>3MET) | 292 (31.1) | 401 (37.3) | 388 (42.2) | 261 (32.1) | 366 (38.4) | 382 (41.3) |
| ≥5 d/w moderate or vigorous active (>3MET) | 144 (15.4) | 225 (20.9) | 248 (27) | 185 (22.8) | 206 (21.6) | 190 (20.5) |
| Smoking | | | | | | |
| Never | 158 (16.7) | 162 (15) | 174 (18.8) | 155 (18.9) | 154 (16.1) | 154 (16.6) |
| Former | 556 (58.8) | 739 (68.2) | 668 (72.2) | 525 (64) | 640 (66.9) | 638 (68.8) |
| Current | 232 (24.5) | 182 (16.8) | 83 (9) | 140 (17.1) | 163 (17) | 136 (14.7) |
| Education | | | | | | |
| Low | 610 (65) | 615 (57.2) | 444 (48.1) | 497 (61.4) | 537 (56.4) | 482 (52.2) |
| Moderate | 265 (28.2) | 334 (31.1) | 313 (33.9) | 249 (30.7) | 290 (30.4) | 317 (34.3) |
| High | 64 (6.8) | 126 (11.7) | 166 (18) | 64 (7.9) | 126 (13.2) | 125 (13.5) |
| Alcohol consumption | | | | | | |
| 0 g/d alcohol | 286 (30.2) | 187 (17.3) | 127 (13.7) | 247 (30.1) | 176 (18.4) | 119 (12.8) |
| >0 - 10 g/d alcohol | 373 (39.4) | 421 (38.9) | 365 (39.5) | 311 (37.9) | 366 (38.2) | 374 (40.3) |
| >10-≤20 g/d alcohol | 112 (11.8) | 207 (19.1) | 204 (22.1) | 105 (12.8) | 185 (19.3) | 205 (22.1) |
| > 20 g/d alcohol | 175 (18.5) | 268 (24.8) | 229 (24.8) | 157 (19.2) | 230 (24) | 230 (24.8) |

[1] Values are presented as mean (SD) for continuous variables or n (%) for categorical variables, except for triglycerides median (IQR)

[2] Tests for trend of continuous variables were based on general linear regression with dietary scores as continuous independent variable. Chi-square tests were used for categorical variables across all 5 levels of dietary scores

[3] p-trend across quintiles of the Dutch Healthy Nutrient and Food Score <0.05 for all characteristics except time since myocardial infarction, prevalent diabetes mellitus, diastolic blood pressure, HDL cholesterol, anti-hypertensive drugs and anti-thrombotic drugs

[4] p-trend across quintiles of the Dutch Undesirable Nutrient and Food Score <0.05 for all characteristics except time since myocardial infarction, diastolic blood pressure, triglycerides, LDL cholesterol, smoking and anti-hypertensive drugs

[5] ATC codes B01

[6] ATC codes C02, C03, C07, C08 and C09

[7] To convert the values for serum cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for serum triglycerides to milligrams per deciliter, divide by 0.01129.

## Dietary scores, CVD and all-cause mortality

Cox proportional hazard ratios (HRs) for CVD and all-cause mortality across quintiles of the DHNaFS and DUNaFS simultaneously modelled are presented in **Table 3**. A higher DHNaFS was significantly associated with a lower all-cause mortality risk (p-trend 0.0006). In the fully adjusted model, patients in the highest quintile of the DHNaFS had 30% lower all-cause mortality risk compared to patients in the lowest quintile. A higher DHNaFS was also significantly associated with a lower CVD mortality risk. Patients in the highest quintile of the DHNaFS had 32% lower CVD mortality risk compared to patients in the lowest quintile. The DUNaFS was not associated with all-cause or CVD mortality.

In sensitivity analysis we stratified patients for gender, age, prevalent diabetes, BMI, smoking, physical activity and alcohol consumption and no major differences were observed between strata, except for alcohol which only showed an inverse association in the consumers (**supplemental table 2**). In the adjusted model (model 3) the first alcohol category (>0-10g/d alcohol) compared to no alcohol consumption (0 g/d alcohol) predicted lower all-cause mortality. Few individual food groups (adjusted for the dietary scores minus that specific food group) were associated with the outcomes. Whole grain modelled together with the DHNaFS (without whole grain) and the DUNaFS predicted mortality, however the DHNaFS (without whole grain) remained significantly associated (data not shown). Sandwich spreads was also inversely associated with the outcomes but did not change associations with the dietary scores (data not shown).

**TABLE 3** Multivariable adjusted HRs for all-cause and CVD Mortality across quintiles of the Dutch Healthy Nutrient and Food Score and the Dutch Undesirable Nutrient and Food Score[1]

| | Q1 | Q2 | Q3 | Q4 | Q5 | P-trend |
|---|---|---|---|---|---|---|
| Dutch Healthy Nutrient and Food Score | 14 (12-16) | 20 (19-21) | 23 (22-24) | 27 (26-28) | 31 (30-34) | |
| N | 946 | 667 | 1083 | 736 | 925 | |
| Person-years | 5966.8 | 4204.3 | 6896.3 | 4475 | 4759.5 | |
| No. of cases all-cause mortality | 228 | 137 | 193 | 120 | 123 | |
| AR per 1000 py all-cause mortality | 38.2 | 32.6 | 28 | 26.8 | 25.8 | |
| No. of cases CVD mortality | 102 | 58 | 73 | 48 | 61 | |
| AR per 1000 py CVD mortality | 17.1 | 13.8 | 10.6 | 10.7 | 12.8 | |
| Dutch Undesirable Nutrient and Food Score | 17 (14- 18) | 22 (21- 23) | 26 (25- 27) | 29 (29- 30) | 35 (33- 37) | |
| N | 831 | 791 | 961 | 855 | 919 | |
| Person-years | 5363.2 | 4987.1 | 6074.8 | 5411.6 | 5865.4 | |
| No. of cases all-cause mortality | 165 | 159 | 177 | 156 | 144 | |
| AR per 1000 py all-cause mortality | 30.8 | 31.9 | 29.1 | 28.8 | 24.6 | |
| No. of cases CVD mortality | 70 | 70 | 65 | 69 | 68 | |
| AR per 1000 py CVD mortality | 13.1 | 14 | 10.7 | 12.8 | 11.6 | |
| | | | | | | |
| All-Cause Mortality | | | | | | |
| Dutch Healthy Nutrient and Food Score | | | | | | |
| Model 1[2] | 1 | 0.89 (0.72-1.10) | 0.74 (0.61-0.9) | 0.67 (0.54-0.84) | 0.57 (0.45-0.71) | <0.0001 |
| Model 2[3] | 1 | 0.97 (0.78-1.20) | 0.81 (0.66-0.99) | 0.78 (0.62-0.99) | 0.72 (0.56-0.93) | 0.0015 |
| Model 3[4] | 1 | 0.95 (0.76-1.18) | 0.77 (0.63-0.95) | 0.76 (0.60-0.97) | 0.70 (0.55-0.91) | 0.0006 |
| Dutch Undesirable Nutrient and Food Score | | | | | | |
| Model 1[2] | 1 | 1.12 (0.9-1.39) | 1.03 (0.83-1.27) | 1.09 (0.87-1.36) | 0.95 (0.75-1.20) | 0.552 |
| Model 2[3] | 1 | 1.19 (0.94-1.49) | 1.10 (0.87-1.39) | 1.24 (0.95-1.62) | 1.08 (0.79-1.48) | 0.857 |
| Model 3[4] | 1 | 1.22 (0.97-1.54) | 1.14 (0.89-1.45) | 1.28 (0.98-1.68) | 1.15 (0.84-1.58) | 0.702 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Cardiovascular Mortality | | | | | | |
| Dutch Healthy Nutrient and Food Score | | | | | | |
| Model 1[2] | 1 | 0.84 (0.60-1.16) | 0.62 (0.46-0.84) | 0.59 (0.41-0.83) | 0.61 (0.44-0.85) | <.0001 |
| Model 2[3] | 1 | 0.88 (0.63-1.23) | 0.63 (0.46-0.87) | 0.65 (0.45-0.94) | 0.72 (0.50-1.03) | 0.008 |
| Model 3[4] | 1 | 0.88 (0.63-1.23) | 0.59 (0.43-0.82) | 0.59 (0.41-0.87) | 0.68 (0.47-0.99) | 0.0002 |
| Dutch Undesirable Nutrient and Food Score | | | | | | |
| Model 1[2] | 1 | 1.17 (0.83-1.63) | 0.90 (0.64-1.26) | 1.14 (0.81-1.61) | 1.05 (0.74-1.48) | 0.99 |
| Model 2[3] | 1 | 1.1 9 (0.84-1.68) | 0.87 (0.60-1.27) | 1.17 (0.78-1.76) | 1.09 (0.68-1.74) | 0.651 |
| Model 3[4] | 1 | 1.22 (0.86-1.73) | 0.92 (0.63-1.34) | 1.23 (0.82-1.85) | 1.15 (0.72-1.84) | 0.759 |

HR hazard ratio, AR absolute risk

[1] Hazard ratios (and 95% CIs) generated by Cox proportional hazards regression including both scores simultaneously in the model, with Q1 as the referent.

[2] Model 1 adjusted for age (in years) and sex (male, female) and intervention group (Placebo, EPA-DHA and ALA, EPA-DHA, ALA)

[3] Model 2 additionally adjusted for energy (energy(kcal)/SD), alcohol intake (0g/d, >0-10g/d, >10-≤20 g/d, >20g/d), level of education (low, moderate, high), physical activity (no physical activity, 0-5 d/w moderate or vigorous active (>3MET), >=5 d/w moderate or vigorous active (>3 MET)) and smoking status (never, former, current)

[4] Model 3 additionally adjusted for BMI (kg/m2 ), prevalent diabetes, systolic blood pressure and total cholesterol/HDL cholesterol

## DISCUSSION

Cardiac patients consumed 3 times more (by gram weight) of the foods in the DHNaFS compared to foods high in solid fats, sodium and/or added sugar that were included in the DUNaFS. The DHNaFS was associated with ca. 30% lower risk of all-cause and CVD mortality, comparing the extreme score quintiles. The DUNaFS was not associated with all-cause and CVD mortality.

Dietary quality scores solely based on food groups have the advantage that they are easier to understand and implement compared to existing mixed food group and nutrients scores such as AHEI or MDS. In addition, our nutrient-based method of rating food groups mimics what a consumer would do if selecting foods to eat based primarily on 5 nutrient criteria and energy content. Furthermore, our DHNaFS and DUNaFS include all food groups that are part of the Dutch dietary pattern. In contrast, in the MDS, for example, only a few, broadly defined, nutrient-dense food groups are rated (e.g. total dairy and total meat), which are not easily translated in to a healthy dietary pattern. Creating two dietary scores one with nutrient rich foods and one with foods high in solid fats, sodium, and/or added sugar allowed easy comparison of the value of higher intake of foods considered by our criteria to be healthier versus lower intake of foods considered not to be healthy.

As in the present study, the Nurses' Health Study and the Health Professionals Follow-Up Study observed a lower risk of all-cause mortality in patients with prior CVD in the multivariable adjusted pooled HR in the highest quintile of the AHEI and MDS (HR 0.76 (95%CI 0.60,0.96) and 0.81 (95%CI 0.72,0.91) respectively). Neither score reached statistical significance for the association with CVD mortality in the pooled analysis (HR 0.73 (95%CI 0.51,1.04) and 0.85 (95%CI 0.67,1.09) respectively). Furthermore, after excluding the alcohol component from AHEI and MDS results attenuated suggesting that moderate alcohol intake was an important health contributor to both scores [6, 7]. This was confirmed by both Trichoupoulou et al. and Hoevenaar et al. who showed that alcohol contributed most to the inverse association of MDS with CVD and all-cause mortality [16, 17]. In our study, we excluded alcohol from our scores and nevertheless found associations of the DHNaFS score with CVD and all-cause mortality.

The food groups scored in the DUNaFS score were generally high in solid fats, sodium and/or added sugar. Therefore we hypothesized an unfavorable effect on health: however, this dietary score was not associated with mortality. Patients in the highest quintiles of the DUNaFS also consumed a substantial amount of DHNaFS foods; however, the ratio between DHNaFS and DUNaFS food groups was greater for the highest quintiles of the DHNaFS compared to DUNaFS which may partly explain the lack of association with mortality for the DUNaFS. Furthermore,

some food groups may have been misclassified, for example we found that sandwich fillings were inversely associated with the outcomes. This could relate to healthful effects of peanut butter [18] or chocolate [19], but we could not clearly isolate a reason for this finding.

Our study has limitations. The patients in the Alpha Omega Trial received additional amounts of omega-3 fatty acids [10]. However, adjustment for intervention groups did not change our results. Patients may have received dietary advice to improve their diet after their first MI and could have made changes in their diet during follow-up. The tracking correlation of the DHNaFS over 41 months indicate that the score was tracked over time and was similar to the tracking correlations of the *a priori* diet quality score observed in the population-based CARDIA study over 7 and 20 years [20]. As our study population included only patients our results are not generalizable to the general 'healthy' population. Although we accounted for many possible confounders, as in every observational analysis, we cannot rule out residual confounding.

Our study also has several strengths. We realized a complete mortality follow-up of the vital status and causes of death of the patients. We used an extensive and detailed FFQ which enabled us to define food groups objectively and systematically using classification criteria for foods derived from the Netherlands' Food-Based Dietary Guidelines [14]. Also, we assessed the association of diet quality in a cohort in which almost all patients received state-of-the-art antithrombotic, antihypertensive, and statin therapy. Previous studies assessed diet quality in populations that did not receive adequate statin-treatment [3-5], or were hetero-geneous for statin treatment [6,7].

In conclusion, our results suggest that cardiac patients who consumed a nutrient rich diet have lower all-cause and CVD mortality risk. Despite the fact that our patients received state-of-the-art drug treatment, we observed an additional beneficial effect on mortality of a high quality diet.



## ACKNOWLEDGMENTS

F.P.C.S.: conceptualization, statistical analysis, interpretation, and writing of the manuscript; S.S.S.M.: conceptualization, interpretation, writing and critical review of the manuscript; J.d.G., L.M.O.G., J.M.G., E.J.G.: substantial contributions to conception and design, acquisition of data and critical review of the manuscript; M.J.d.B.: acquisition of data and critical review; D.R.J.: conceptualization and critical review of the manuscript; D.K.: conception and design of the study, conceptualization, interpretation, writing and critical review of the manuscript. See online supplemental material for list of committees and collaborators.

F.P.C.S, L.M.O.G, E.J.G, M.J.d.B and D.K declare no conflict of interest. S.S.S.M., J.d.G and J.M.G received unrestricted research grants from the Dutch Dairy Association and Global Dairy Platform to carry out meta-analyses on the association between dairy products and cardiovascular diseases. D.R.J. is a consultant of the California Walnut Commission

## REFERENCES


1. Kant AK. Dietary patterns and health outcomes. J Am Diet Assoc. 2004;104:615-35.
2. Martinez-Gonzalez MA, Bes-Rastrollo M. Dietary patterns, Mediterranean diet, and cardiovascular disease. Curr Opin Lipidol. 2014;25:20-6.
3. Barzi F, Woodward M, Marfisi RM, Tavazzi L, Valagussa F, Marchioli R, et al. Mediterranean diet and all-causes mortality after myocardial infarction: results from the GISSI-Prevenzione trial. Eur J Clin Nutr. 2003;57:604-11.
4. Iestra J, Knoops K, Kromhout D, de Groot L, Grobbee D, van Staveren W. Lifestyle, Mediterranean diet and survival in European post-myocardial infarction patients. Eur J Cardiovasc Prev Rehabil. 2006;13:894-900.
5. Trichopoulou A, Orfanos P, Norat T, Bueno-de-Mesquita B, Ocke MC, Peeters PH, et al. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. BMJ. 2005;330:991.
6. Li S, Chiuve SE, Flint A, Pai JK, Forman JP, Hu FB, et al. Better diet quality and decreased mortality among myocardial infarction survivors. JAMA Intern Med. 2013;173:1808-18.
7. Lopez-Garcia E, Rodriguez-Artalejo F, Li TY, Fung TT, Li S, Willett WC, et al. The Mediterranean-style dietary pattern and mortality among men and women with cardiovascular disease. Am J Clin Nutr. 2014;99:172-80.
8. Dehghan M, Mente A, Teo KK, Gao P, Sleight P, Dagenais G, et al. Relationship between healthy diet and risk of cardiovascular disease among patients on drug therapies for secondary prevention: a prospective cohort study of 31 546 high-risk individuals from 40 countries. Circulation. 2012;126:2705-12.
9. Geleijnse JM, Giltay EJ, Schouten EG, de Goede J, Griep LMO, Teitsma-Jansen AM, et al. Effect of low doses of n-3 fatty acids on cardiovascular diseases in 4,837 post-myocardial infarction patients: Design and baseline characteristics of the Alpha Omega Trial. Am Heart J. 2010;159:539-46.e2.
10. Kromhout D, Giltay EJ, Geleijnse JM, Alpha Omega Trial G. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med. 2010;363:2015-26.
11. Feunekes GI, Van Staveren WA, De Vries JH, Burema J, Hautvast JG. Relative and biomarker-based validity of a food-frequency questionnaire estimating intake of fats and cholesterol. Am J Clin Nutr. 1993;58:489-96.
12. Feunekes IJ, Van Staveren WA, Graveland F, De Vos J, Burema J. Reproducibility of a semiquantitative food frequency questionnaire to assess the intake of fats and cholesterol in The Netherlands. Int J Food Sci Nutr. 1995;46:117-23.
13. Netherlands Nutrition Centre. NEVO-tabel: Nederlands Voedingsstoffenbestand 2006/Stichting Nederlands Voedingsstoffenbestand. Den Haag; 2006.
14. Netherlands Nutrition Centre. Guidelines Food Choice. Den Haag, 2011. http://www.voedingscentrum.nl/Assets/Uploads/Documents/Voedingsvoorlichters/Richtlijnen_voedselkeuze_2011.pdf. (4 June 2012).
15. Schuit AJ, Schouten EG, Westerterp KR, Saris WH. Validity of the Physical Activity Scale for the Elderly (PASE): according to energy expenditure assessed by the doubly labeled water method. J Clin Epidemiol. 1997;50:541-6.
16. Trichopoulou A, Bamia C, Trichopoulos D. Anatomy of health effects of Mediterranean diet: Greek EPIC prospective cohort study. BMJ. 2009;338:b2337.
17. Hoevenaar-Blom MP, Nooyens AC, Kromhout D, Spijkerman AM, Beulens JW, van der Schouw YT, et al. Mediterranean style diet and 12-year incidence of cardiovascular diseases: the EPIC-NL cohort study. PloS One. 2012;7:e45458.
18. Blomhoff R, Carlsen MH, Andersen LF, Jacobs DR, Jr. Health benefits of nuts: potential role of antioxidants. Br J Nutr. 2006;96 Suppl 2:S52-60.
19. Hooper L, Kay C, Abdelhamid A, Kroon PA, Cohn JS, Rimm EB, et al. Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. Am J Clin Nutr. 2012;95:740-51.
20. Sijtsma FP, Meyer KA, Steffen LM, Shikany JM, Van Horn L, Harnack L, et al. Longitudinal trends in diet and effects of sex, race, and education on dietary quality score change: the Coronary Artery Risk Development in Young Adults study. Am J Clin Nutr. 2012;95:580-6.

## SUPPLEMENTAL MATERIAL

### Classification of foods and food groups

The Netherlands Nutrition Centre developed criteria for classifying foods on their effect on chronic diseases in the Netherlands Food Based Dietary Guidelines1. To create and classify food groups from the FFQ, criteria (primarily the lowest category to fit 5 nutrient and energy guidelines except for some whole food groups that were classified regardless of their nutrient and energy contents) derived from the Food Based Dietary Guidelines were used.

The main reasons for deviation from the classification criteria were:

- Lack of specificity of the FFQ e.g. all vegetables were combined in one food group because the FFQ did not make a distinction between fresh or processed vegetables.
- Low consumption of foods e.g. all cheeses were combined into one food group instead of making a distinction between the fat content of different cheeses because of very low consumption of low-fat cheese.
- Infrequently reported foods e.g. legumes and meat substitutes were combined into 1 food group

**SUPPLEMENTAL TABLE 1** Food groups and criteria[1] for food group assignment to the Dutch Healthy Nutrient and Food Score (DHNaFS) and the Dutch Undesirable Nutrient and Food Score (DUNaFS) in the Alpha Omega Trial

| Food Score | Food group in the indicated Food Score | Foods included in food group | Criteria for Classification of Individual Foods |
|---|---|---|---|
| Dutch Healthy Nutrient and Food Score (DHNaFS)[2] | Vegetables | Lettuce, tomatoes, cauliflower, green beans, leeks etc. | Unprocessed vegetables |
| | Fruits | Apple, orange, bananas, grapes, strawberries etc. | Unprocessed fruit |
| | Whole grains | Whole wheat bread, crackers, cereals, brown rice | Bread[2]:<br>SFA: ≤ 1.1g/100g<br>TF: ≤ 0.1g/100g<br>DF: ≥ 1.3g/100kcal<br>Na: ≤ 500mg/100g<br>AS: ≤ 13en% |
| | Protein rich plant foods | Peas, broad beans, tofu, nuts and seeds | All legumes, nuts and seeds |
| | Potatoes | Potatoes | SFA: ≤ 1.1g/100g<br>TF: ≤ 0.1g/100g<br>DF: ≥ 1.7g/100kcal<br>Na: ≤ 100mg/100g |
| | Lean meat | Beef, chicken or turkey breast, ham | SFA: ≤ 4g/100g<br>Na: ≤ 100mg/100g<br>AS: not added |
| | Fish | Trout, herring, pollock, shellfish | All fish |
| | Eggs | | All eggs |
| | Low-fat milk and yoghurt | Skimmed and semi-skimmed milk, yoghurt, buttermilk | SFA: ≤ 1.3g/100g<br>Na: ≤ 100mg/100g<br>AS: ≤ 5g/100g |
| | Oils and soft margarines | Vegetable oils, (diet) low-fat margarines | SFA: ≤ 30% of total fat<br>TF: ≤ 1.3en%<br>Na: ≤ 160mg/100g |

**SUPPLEMENTAL TABLE 1 (Continued)** Food groups and criteria[1] for food group assignment to the Dutch Healthy Nutrient and Food Score (DHNaFS) and the Dutch Undesirable Nutrient and Food Score (DUNaFS) in the Alpha Omega Trial

| Food Score | Food group in the indicated Food Score | Foods included in food group | Criteria for Classification of Individual Foods |
|---|---|---|---|
| | Non-caloric drinks | Water, tea, coffee, diet soft drinks | SFA: ≤ 1.0g/100g<br>TF: ≤ 0.1g/100g<br>Na: ≤ 20mg/100ml<br>AS: not added |
| Dutch Undesirable Nutrient and Food Score (DUNaFS)[2] | Processed fruit | Fruit or vegetable juice, applesauce | All processed fruits |
| | High-fat meat | Hamburger, chicken or turkey with skin, minced meat, pork sirloin | SFA: > 13en%<br>Na: > 100mg/100g<br>AS: added |
| | Processed meat | Cold cuts (bacon, sliced ham, salami) | SFA: > 13en%<br>Na: > 900mg/100g<br>AS: > 2.5g/100g |
| | Full-fat milk and yoghurt | Full-fat milk, chocolate milk, yoghurt, coffee cream | SFA: > 1.3g/100g<br>Na: > 100mg/100g<br>AS: > 5g/100g |
| | Cheese | Hard cheeses (e.g. Gouda, cheddar), soft cheeses (e.g. brie, camembert), cream cheese | SFA: > 16g/100g<br>Na: > 900mg/100g |
| | Refined grains | Refined bread, cornflakes, white rice | Refined bread[3]<br>SFA: > 1.1g/100g<br>TF: > 0.1g/100g<br>DF: < 1.3g/100 kcal<br>Na: > 500mg/100g<br>AS: > 13en% |
| | Soup | Vegetable soup, stock/broth | EN: > 100kcal/100g<br>SFA: > 1.1g/100g<br>TF: > 0.1g/100g<br>Na: > 350mg/100g<br>AS: > 2.5g/100g |
| | Spreads | Peanut butter, jam, chocolate-hazelnut spreads | EN: > 350kcal/100g<br>SFA: > 13en%<br>TF: > 1.3en% |

| | | |
|---|---|---|
| | | Na: > 400mg/100g |
| | | AS: > 30g/100g |
| Butter and hard margarines | Butter, margarine | SFA: > 30% of total fat |
| | | TF: > 1.3en% |
| | | Na: > 160mg/100g |
| Sweets snacks | Ice cream, cookies, candy bars, chocolate | EN: > 110kcal/portion |
| | | SFA: > 13en% |
| | | TF: > 1.3en% |
| | | Na: > 400mg/100g |
| | | AS: > 20g/100g |
| Savoury snacks | Fries, chips, deep fried snacks, döner kebab, condiments | EN: > 110kcal/portion |
| | | SFA: > 13en% |
| | | TF: > 1.3en% |
| | | Na: > 400mg/100g |
| | | AS: > 20g/100g |
| Sugar sweetened beverages | Soda's, ice tea, lemonade, cappuccino | EN: > 30kcal/100ml |
| | | SFA: ≤1.1 g/100g |
| | | TF: > 0.1g/100g |
| | | Na: > 20mg/100g |
| Ready meals | Pizza, quiche, lasagne | EN: < 400 or > 700kcal/portion |
| | | EN: < 550 or > 950kcal/meal |
| | | SFA: > 13en% |
| | | TF: > 1.3en% |
| | | DF: < 1.3g/100kcal |
| | | Na: > 2.2mg/100kcal |
| | | AS: > 13en% |
| | | Vegetables: < 150g/portion |

SFA:= saturated fatty acids, TF:= *trans* fat, DF= fibre, Na= sodium, AS= added sugar, EN= energy kcal;

[1]The complete list with criteria can be found online in the Netherlands Food Based Dietary Guidelines[1]

[2]To create the DHNaFS and DUNaFS, food groups were first categorized into quintiles of consumption and then the scores were calculated by summing the category scores (0-4) of the food groups.

[3]Classification criteria for bread are shown, different criteria were used for rice and cereals

**SUPPLEMENTAL TABLE 2**. Multivariable adjusted HRs[1] for all-cause and CVD mortality of the dichotomized Dutch Healthy Nutrient and Food Score (DHNaFS) stratified by major risk factors

| | | All-cause mortality | p-value interaction | CVD mortality | p- value interaction |
|---|---|---|---|---|---|
| Diabetes | no | 0.77 (0.65-0.93) | 0.44 | 0.66 (0.50-0.87) | 0.04 |
| | yes | 0.78 (0.57-1.08) | | 0.87 (0.56-1.39) | |
| BMI | <30 | 0.81 (0.68-0.97) | 0.48 | 0.72 (0.55-0.94) | 0.66 |
| | ≥30 | 0.69 (0.49-0.97) | | 0.69 (0.42-1.14) | |
| Gender | male | 0.82 (0.69-0.98) | 0.32 | 0.76 (0.59-0.99) | 0.20 |
| | female | 0.63 (0.44-0.91) | | 0.54 (0.30-0.98) | |
| Smoking | never | 0.59 (0.37-0.97) | 0.30 | 0.71 (0.37-1.36) | 0.98 |
| | ever | 0.78 (0.66-0.92) | | 0.70 (0.54-0.90) | |
| Age | <65 | 0.96 (0.65-1.42) | 0.55 | 0.79 (0.43-1.46) | 0.98 |
| | ≥65 | 0.73 (0.62-0.88) | | 0.69 (0.53-0.89) | |
| Physical activity | no-mild | 0.78 (0.63-0.96) | 0.77 | 0.73 (0.56-1.04) | 0.40 |
| | moderate-vigorous | 0.80 (0.64-1.01) | | 0.70 (0.49-1.00) | |
| Alcohol | non-consumer | 1.12 (0.81-1.56) | 0.004 | 1.00 (0.58-1.72) | 0.12 |
| | consumer | 0.72 (0.60-0.85) | | 0.67 (0.68-0.97) | |
| Statins | no | 0.76 (0.54-1.07) | 0.56 | 0.70 (0.40-1.23) | 0.73 |
| | yes | 0.81 (0.68-0.97) | | 0.74 (0.57-0.96) | |

HR hazard ratio

[1] HRs for the comparison of scores above vs. below the median DHNaFS

Models adjusted for age, gender, energy (energy(kcal)/SD), alcohol intake (0g/d, >0-10g/d, >10-≤20 g/d, >20g/d), level of education (low, moderate, high), physical activity (no physical activity, >0-5 d/w moderate or vigorous active (>3MET), ≥5 d/w moderate or vigorous active (>3 MET)) and smoking status (never, former, current). The confounder variable was excluded from the model when used for stratification.

## List of collaborators Alpha Omega Trial Group

**Executive Committee**

D. Kromhout, Principal Investigator, Division of Human Nutrition, Wageningen University
E.G. Schouten (from 2002-2005), Co-Principal Investigator, Division of Human Nutrition, Wageningen University
J.M. Geleijnse, Trial Coordinator, Division of Human Nutrition, Wageningen University
E.J. Giltay, Study Physician, Department of Psychiatry, Leiden University Medical Centre, Leiden
J. de Goede, Trial Assistant, Division of Human Nutrition, Wageningen University
L.M. Oude Griep, Data Quality Monitor, Division of Human Nutrition, Wageningen University
A.M. Teitsma-Jansen, Logistics Manager, Division of Human Nutrition, Wageningen University
E. Waterham, Data Manager, Division of Human Nutrition, Wageningen University

**Steering Committee Voting members:**

B.J.M. Mulder (chair), Academic Medical Centre, Amsterdam
J.W. Deckers, Erasmus Medical Centre, Rotterdam
M.B. Katan, VU University, Institute for Health Sciences, Amsterdam
P.L. Zock, Division of Human Nutrition, Wageningen University (until January 2004) Observers:
M.J. de Boer, Isala Clinics, Zwolle
H. de Leeuw, Netherlands Heart Foundation, The Hague
E.G. Schouten, Food and Consumer Product Safety Authority, The Hague (since January 2005)
P.L. Zock, Unilever R&D, Vlaardingen (since January 2004)

**Data and Safety Monitoring Board**

E. Boersma (chair), Erasmus Medical Centre, Rotterdam
J.W. Jukema, Leiden University Medical Centre, Leiden
J.J. van Binsbergen, Radboud University Medical Centre, Nijmegen

**Endpoint Adjudication Committee**

D.A.M. van der Kuip (chair), Rotterdam
K. Thomas, Diaconessenhuis, Meppel

M. Rivero-Ayerza (until January 2009), Erasmus Medical Centre, Rotterdam
A.M. Vollaard (since January 2009), Academic Medical Centre, Amsterdam

**Independent physician**
C.J. Fieren, Wageningen

**Participating cardiology centres**
Alysis Zorggroep, Kliniek Velp, Velp: L.H.J. van Kempen
BovenIJ Ziekenhuis, Amsterdam: A. Bakx
Bronovo Ziekenhuis, The Hague: M.I. Sedney
Canisius Wilhelmina Ziekenhuis, Nijmegen: D.P. Hertzberger
Catharina-ziekenhuis, Eindhoven: H.R. Michels
Diaconessenhuis, Leiden: A.A. de Rotte, R.P. van Rugge
Erasmus Medisch Centrum, Rotterdam: A. Klootwijk
Flevoziekenhuis, Almere: J.A. Verheul
Gelre Ziekenhuizen, Apeldoorn: D.M. Nicastia
Haga Ziekenhuis, location Leyweg, The Hague: R. Robles de Medina
Haga Ziekenhuis, location Sportlaan, The Hague: M. van Rossem
Havenziekenhuis, Rotterdam: C.M. Leenders
Isala Klinieken, location De Weezenlanden, Zwolle: M.J. de Boer
't Lange Land Ziekenhuis, Zoetermeer: P. van der Meer
Lievensberg Ziekenhuis, Bergen op Zoom: S.C. Uppal, J.G. Blok
Máxima Medisch Centrum, Veldhoven: R.F. Visser
Meander Medisch Centrum, Amersfoort: A. Mosterd
Medisch Centrum Alkmaar, Alkmaar: V.A.W.M. Umans, C.L.A. Reichert
Medisch Spectrum Twente, Enschede: J.W. Louwerenburg
Oosterscheldeziekenhuis, Goes: A.H. Liem
Rijnland Ziekenhuis, Leiderdorp: C. van Rees, C.J.H.J. Kirchhof
Rode Kruis Ziekenhuis, Beverwijk: L. Konst
Slingeland Ziekenhuis, Doetinchem: H. Drost
Slotervaartziekenhuis, Amsterdam: R.A.M. van Liebergen
St. Anna Ziekenhuis, Geldrop: P.E. Polak
St. Antonius Ziekenhuis, Nieuwegein: H.W.M. Plokker
St. Lucas Andreas Ziekenhuis, Amsterdam: J. Schroeder-Tanka
Tergooi ziekenhuis, Hilversum: P. de Milliano
Twee Steden Ziekenhuis, Tilburg: H. van Kesteren
IJsselland Ziekenhuis, Capelle a/d IJssel: B.J. van den Berg
Zaans Medisch Centrum, Zaandam: P.N.A. Bronzwaer
Ziekenhuis Gelderse Vallei, Ede: T.T. van Loenhout

**Laboratories**

National Institute of Public Health and the Environment (RIVM), Bilthoven: E.H.J.M. Jansen

Stichting Huisartsenlaboratorium Oost (SHO), Velp: W. Grootaarts, D. van Rumpt

Wageningen University, Division of Human Nutrition, Wageningen: P.J.M. Hulshof, H.M. van der Struijs-van de Putte, P. Versloot, R. Hovenier.

**Dietetics**

Wageningen University, Division of Human Nutrition, Wageningen: J.H.M. de Vries, E. Siebelink

**Trial margarines**

Unilever R&D, Vlaardingen: O.E. Rosier, J.L. Zevenbergen

## REFERENCES SUPPLEMENTAL MATERIAL

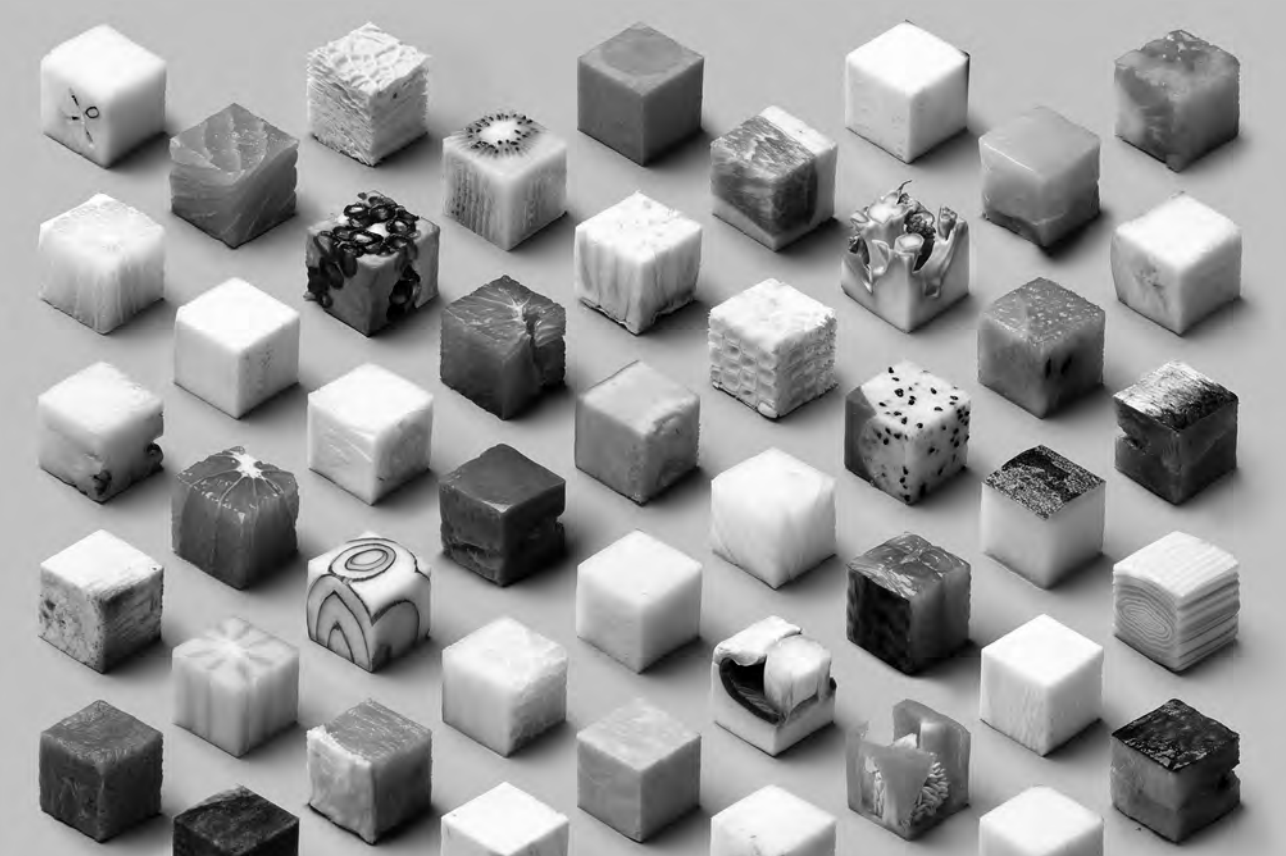
1. Netherlands Nutrition Centre. Guidelines Food Choice. Den Haag, 2011. http://www.voedingscentrum.nl/Assets/Uploads/Documents/Voedingsvoorlichters/Richtlijnen_voedselkeuze_2011.pdf. (accessed 4 June 2012).

# 7

# Healthy eating and survival among elderly men with and without cardiovascular-metabolic diseases

Femke PC Sijtsma, Sabita S Soedamah-Muthu, Sabine EM de Hoon, David R Jacobs Jr , Daan Kromhout

Accepted for publication in Nutr Metab Cardiovasc Dis



## ABSTRACT

**Background and Aims** The strength of the associations of dietary scores with cardiovascular disease (CVD) and all-cause mortality in elderly vary considerably between *a priori* scores. We assessed whether healthy eating lowers the risk of CVD and all-cause mortality among elderly men.

**Methods and Results** The Zutphen Elderly Study (age 65-84 years) was divided into men with (n=210) and without (n=616) cardiovascular-metabolic diseases at baseline in 1985. Diet was assessed with the cross-check dietary history method. We created the "Dutch Healthy Nutrient and Food Score" (DHNaFS) and the "Dutch Undesirable Nutrient and Food Score" (DUNaFS). Associations of the scores with CVD and all-cause mortality were assessed using multivariable Cox regression models. Associations of scores with life years gained used general linear models.
During a median follow-up of 10.6 years (IQR 5.8-15.9) 806 participants died, of whom 359 from CVD. Over all men, diet scores did not predict death. Among men with cardiovascular-metabolic diseases, DHNaFS was associated with lower CVD (HR: 0.57; 95%CI: 0.35-0.93) and all-cause mortality risk (HR: 0.64; 95% CI: 0.44-0.94) comparing highest vs. lowest score tertiles. Men with cardiovascular-metabolic diseases in the highest vs. lowest tertile of the DHNaFS lived 2.5 year longer. The DHNaFS was not associated with CVD and all-cause mortality in men without cardiovascular-metabolic diseases. The DUNaFS was not associated with any of the outcomes.

**Conclusion** A high quality diet was associated with a 40% lower mortality risk and 2.5 year longer life expectancy in elderly men with, but not without, cardiovascular-metabolic diseases.

## INTRODUCTION

Several *a priori* dietary scores have been developed to assess diet quality based on adherence to dietary patterns or recommendations [1, 2]. The strengths of association between diet quality and cardiovascular disease (CVD) and all-cause mortality in the elderly vary considerably between a *priori* scores [3]. Studies that compared multiple dietary scores suggest that food-based dietary scores are better predictors of mortality than scores based predominantly on nutrient intakes [4-6]. Furthermore, food-based *a priori* scores have the advantage that they are easier to translate into diet recommendations. Existing scores have some disadvantages. First, a limited selection of food groups is included, second, food groups are generally broadly defined and third, many scores include both food and nutrient-based scoring components.

Studies in populations free from cardiovascular-metabolic diseases at baseline reported lower risk of CVD and all-cause mortality with higher dietary scores indicating a healthier diet [4, 5, 7]. Several studies did not adjust for prevalent diseases in elderly people [6, 8-10]. The association of dietary scores with mortality in populations with cardiovascular-metabolic diseases at baseline have only been investigated in men and women aged 60 to 70 [11-14] and in a small population aged 70+ [15].

We hypothesized that a nutrient-rich dietary score is associated with lower CVD and all-cause mortality risk. Because the prevalence of cardiovascular-metabolic diseases increases with age and may be associated with dietary modifications, we stratified our sample into men with and without cardiovascular-metabolic diseases at baseline. In 2010, 98% of the Zutphen Elderly cohort had died, providing a unique opportunity both to study the predictive value of a nutrient-rich dietary score for CVD and all-cause mortality risk and for life years gained.

## METHODS

### Study population

The prospective Zutphen Elderly Study started in 1985, collecting information on risk factors for CVD and health in elderly men. At baseline, 555 survivors of the initial Zutphen Study [16] were invited and re-examined in 1985. Additionally, a random sample was selected of all men of the same birth cohort (age 65-84, living at least five years in Zutphen), who were not part of the original cohort. In total 1266 men were invited of whom 939 participated (74%).

Men with missing dietary data in 1985 and 1990 (n=41) or cancer at baseline (n=76) were excluded from the analysis, resulting in 826 men available for analysis. Two groups were derived, a diseased population (n=210) of men with prevalent

cardiovascular-metabolic diseases at baseline: myocardial infarction (n=97) or stroke (n=26) or diabetes mellitus (n=66) or any combination (n=21), and a healthy population (n=616) of men without any of these prevalent diseases at baseline. The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the University of Leiden, the Netherlands in 1985 and 1990. Written informed consent was obtained from all participants.

## Dietary data

Information on usual dietary intake of the last month was collected by trained dieticians, applying the cross-check dietary history method, adapted to the usual Dutch diet [17]. Each participant, if possible in the presence of his wife, was interviewed about his usual food consumption during weekdays and weekends. Based on this daily pattern, average food consumption during a day or week was estimated (first check) and the quantity of foods bought per week (second check) was used to verify the participants' food consumption. Daily intake of energy, nutrients and alcohol was calculated using an updated Dutch Food Composition Table close to the year of measurement [18]. The reproducibility of the dietary history method was tested three months and twelve months after the start of the Zutphen Study. Reproducibility of major food groups was assessed with the highest Spearman correlation coefficients for bread (0.83), and milk products (0.72) and the lowest for meat (0.49) and vegetables (0.49) [17].

The 782 food items were collapsed into 22 food groups according to criteria derived from the Netherlands Food Based Dietary Guidelines. Details about the classification of foods and food groups are summarized in **supplemental Table 1**. We made a distinction between food groups consisting of nutrient-rich foods that contribute importantly to the nutrient supply and food groups that are high in solid fats, sodium and/or added sugar.

## Dietary scores

We created 2 food-based dietary scores. The Dutch Healthy Nutrient and Food Score (DHNaFS) included 11 nutrient-dense food groups; vegetables, fruit, whole grains, protein-rich plant foods (mostly legumes), potatoes, lean meat, fish, eggs, low-fat milk and yoghurt, vegetable oils and soft margarines, and non-caloric drinks (tea, coffee, water). The Dutch Undesirable Nutrient and Food Score (DUNaFS) included 11 food groups that were high in solid fats, sodium and/or added sugar; processed vegetables, fruit juice and sugar sweetened beverages, high-fat meat, processed meat, full-fat milk, cheese, refined grains, butter and hard margarines, ready meals and soups, spreads and snacks.

All food groups were categorized into tertiles of consumption. Subsequently, the two dietary scores were calculated by summing the tertile scores (0, 1 or 2) of the food groups included in the score. The theoretical maximum for both scores was 22. Finally, both food-based dietary scores were categorized into tertiles. The correlation between the two dietary scores was -0.05. Tracking correlations between baseline scores and the scores after 5 years were 0.51 for the DHNaFS and 0.46 for the DUNaFS in the healthy men and 0.64 for the DHNaFS and 0.38 for the DUNaFS in the cardiovascular-metabolic diseased men.

## Ascertainment and classification of mortality

Participants were followed until death or censored in 2010 (July 1). Vital status was obtained from municipal registries. The median follow-up was 10.7 (IQR 5.9-15.9) and only 2 men were lost to follow-up and censored after their last physical examination. Information on the causes of death was obtained from Statistics Netherlands and was verified by the general practitioners of the participants and hospital discharge data and data of the Dutch cancer registry. Coding of the causes of death followed the International Classification of Diseases, ninth revision (ICD-9) [19]. With codes 390-459 plus 798.2 (sudden death) referring to CVD. The first cause of death was included in the analysis.

## Other measurements

Data on socioeconomic status (low/moderate/high), physical activity (0/1-150/ >150 minutes at ≥4 MET per week) [20], smoking status (never/former/current), and medication use were collected by questionnaire. Medication use was coded according to the Anatomical Therapeutic Chemical Classification System (ATC). Alcohol intake (0/<20/≥20 g/d) was derived from the dietary history. Height and body weight were measured according to standardized procedures. BMI was calculated as weight (kg) divided by height squared (m2). Blood pressure was measured twice at the right arm with the men in supine position, using a random zero sphygmomanometer. Mean value of the measurements were calculated. Non-fasting venous blood samples were taken to determine total and high-density lipoprotein (HDL) cholesterol levels using standard validated methods [21-23]. Questionnaires were used to obtain information about the physicians' conclusions on history of myocardial infarction, stroke, diabetes mellitus and cancer.

## Statistical analysis

Statistical analyses were conducted using the PC version of Statistical Analysis System (version 9.3) SAS Institute, Cary, NC, USA. Baseline characteristics across tertiles of the dietary scores were calculated using simple descriptive statistics. Cox's proportional hazard regression models were used to investigate the association

of the dietary scores with CVD and all-cause mortality. Proportional hazards assumptions were examined by a log–minus–log plot and the assumptions were met. Different levels of adjustment were studied. A minimum model (model 1) included age (continuous) and energy intake per standard deviation (continuous). This model was further adjusted for smoking (never, former, current), physical activity (no, 1-150 min/week, >150 min/week), SES (low, medium, high), and alcohol intake (0, <20, ≥20 g/d) (model 2). To the final model (model 3), medication (anti-thrombotics, anti-diabetics and anti-hypertensives) were added. Sensitivity analysis included BMI, cholesterol levels and blood pressure in the model.

General linear models with the same adjustment levels were used to assess the association of life years gained (modeled as the difference between age at baseline and age at death) with both dietary scores. For this analysis we excluded men that were alive in 2010 (n=2 in men with and n=33 in men without cardiovascular-metabolic diseases) and the 2 men that were lost to follow-up.

## RESULTS

### Dutch Healthy Nutrient and Food Score

Overall, the participants in this study consumed a substantially higher amount of DHNaFS food groups (approximately 1700 g/d) than DUNaFS food groups (approximately 600 g/d) resulting in an overall ratio of 2.9. This ratio was similar in healthy and diseased men in the first tertile of the DHNaFS, but increased more across tertiles in the diseased men (2.4 to 4.2) than in the healthy men (2.1 to 3.7). The diseased men consumed approximately 75 g/d more of the DHNaFS food groups and 60 g/d less of the DUNaFS food groups compared to the healthy men **(Table 1)**. Total median intake of food groups in grams across tertiles of the DUNaFS can be found in the **supplemental table 2**.

### Baseline characteristics

Healthy and diseased men in the highest tertile of the DHNaFS were more likely to be younger, had a higher energy intake, consumed more fiber and sodium compared to the lowest tertile **(Table 2)**. Added sugar intake was lower across tertiles in the diseased men (47.5 g/d to 50.4 g/d) compared to healthy men (67.4 g/d to 60.8 g/d)

Healthy men in the highest tertile of the DHNaFS were more physically active and consumed more alcohol. There were no differences across tertiles of the DHNaFS for physical activity and alcohol consumption in the diseased men. None of BMI, blood pressure, cholesterol, smoking, SES, saturated fat and trans fat intake and medication use differed across DHNaFS in either healthy or diseased men.

**TABLE 1** Median intake (IQR) of food groups across tertiles of the Dutch Healthy Nutrient and Food Score of 616 healthy and 210 diseased participants of the Zutphen Study[1]

| | healthy men | | | Cardiovascular-metabolic diseased men | | |
|---|---|---|---|---|---|---|
| | DHNaFS | | | DHNaFS | | |
| Tertile | 1 | 2 | 3 | 1 | 2 | 3 |
| N | 196 | 239 | 181 | 68 | 61 | 81 |
| DHNaFS food groups (g/day) | | | | | | |
| Vegetables | 118 (90-153) | 143 (109-184) | 176 (144-217) | 125.5 (88-155) | 120 (93-162) | 174 (147-201) |
| Fruits | 101 (33-157) | 133 (70-212) | 174 (120-268) | 104.5 (35-178) | 128 (88-205) | 222 (143-274) |
| Whole grains | 60 (9-106) | 96 (41-140) | 122 (88-172) | 61 (6-104) | 99 (70-140) | 135 (100-170) |
| Potatoes | 129 (91-180) | 160 (116-232) | 186 (134-252) | 117.5 (84-150) | 160 (96-200) | 164 (139-220) |
| Protein rich plant foods | 10 (0-24) | 19 (7-30) | 22 (10-36) | 11.5 (0-24) | 16 (6-31) | 24 (12-42) |
| Lean meat | 15 (0-32) | 24 (9-42) | 32 (17-52) | 16 (11-32) | 31 (18-52) | 36 (15-56) |
| Eggs | 11 (4-20) | 16 (7-23) | 20 (14-27) | 11 (7-16) | 14 (9-23) | 21 (12-22) |
| Fish | 6 (0-18) | 13 (0-23) | 21 (9-35) | 4.5 (0-17) | 15 (4-28) | 15 (2-29) |
| Oils and soft margarines | 0 (0-4) | 1 (0-20) | 14 (0-24) | 0 (0-11) | 1 (0-19) | 21 (3-32) |
| Non-caloric drinks (water, tea, coffee) | 746 (550-923) | 834 (658-1061) | 973 (788-1160) | 698 (568-903) | 864 (720-1050) | 1046 (758-1250) |
| Low fat milk and yoghurt | 0 (0-110) | 84 (0-249) | 195 (14-340) | 20 (0-184) | 71 (0-271) | 202 (33-398) |
| DUNaFS food groups (g/day) | | | | | | |
| Processed vegetables | 9 (0-20) | 7 (0-20) | 8 (0-18) | 11.5 (0-27) | 6 (0-19) | 4 (0-18) |
| Fruit juice and sugar sweetened beverages | 41 (0-100) | 29 (2-88) | 26 (1-85) | 21 (0-104) | 21 (0-72) | 21 (0-71) |
| Refined grains | 61 (27-110) | 40 (17-86) | 35 (19-68) | 46.5 (16-115) | 43 (16-87) | 41 (17-68) |
| High-fat meat | 54 (34-72) | 52 (33-73) | 51 (36-74) | 52.5 (34-72) | 51 (29-71) | 54 (34-69) |
| Processed meat | 23 (10-40) | 26 (11-41) | 29 (14-44) | 19 (10-33) | 20 (11-36) | 25 (6-40) |
| Full-fat milk and yogurt | 138 (48-331) | 132 (33-273) | 85 (24-232) | 169 (48-263) | 124 (24-269) | 68 (14-192) |
| Cheese | 21 (11.5-37) | 27 (15-42) | 31 (18-47) | 23.5 (11-45) | 26 (16-47) | 32 (20-54) |
| Butter and hard margarines | 40 (24-56) | 37 (22-57) | 32 (18-54) | 35.5 (22-49) | 36 (19-55) | 22 (12-38) |
| Extras | 42 (21-68) | 46 (24-73) | 49 (27-73) | 30 (16-54) | 41 (15-59) | 42 (19-74) |
| Spreads | 7 (0-20) | 10 (0-20) | 8 (0-20) | 5 (0-15) | 10 (1-17) | 10 (0-21) |
| Ready meals | 23 (0-71) | 24 (0-71) | 18 (0-71) | 18 (0-72) | 18 (0-71) | 18 (0-71) |

DHNaFS Dutch Healthy Nutrient and Food Score, DUNaFS Dutch Undesirable Nutrient and Food Score

[1]p-trend across tertiles of the DHNaFS <0.05

**TABLE 2** Baseline characteristics across tertiles of the Dutch Healthy Nutrient and Food Score of 616 healthy and 210 diseased participants of the Zutphen Study[1,2]

| | healthy men[3] | | | Cardiovascular-metabolic diseased men[4] | | |
|---|---|---|---|---|---|---|
| | DHNaFS | | | DHNaFS | | |
| Tertile | 1 | 2 | 3 | 1 | 2 | 3 |
| N | 196 | 239 | 181 | 68 | 61 | 81 |
| Age in 1985 in years | 72.5 (5.4) | 72.1 (5.2) | 70.9 (4.9) | 73.2 (5.3) | 73.7 (5.5) | 71.1 (5.1) |
| BMI | 25.7 (3.4) | 25.4 (2.6) | 25.9 (3.4) | 26.2 (3.1) | 25.1 (2.9) | 25.6 (3.2) |
| Systolic blood pressure | 150.7 (18.4) | 150.3 (22.5) | 150.7 (21.2) | 151.8 (17.7) | 149.7 (23.3) | 151.6 (24.3) |
| Diastolic blood pressure | 84.9 (11.1) | 85.7 (11.1) | 86.2 (11.8) | 85.9 (10.8) | 83.3 (11.3) | 85.3 (12) |
| Serum lipids mmol/liter[5] | | | | | | |
| Total cholesterol | 6.1 (1.1) | 6.1 (1) | 6.1 (1) | 6.2 (1.6) | 6 (1.1) | 6.2 (1.1) |
| HDL cholesterol | 1.1 (0.3) | 1.1 (0.3) | 1.2 (0.3) | 1.1 (0.3) | 1.1 (0.3) | 1.1 (0.3) |
| Physical activity | | | | | | |
| No | 115 (61.2) | 106 (46.1) | 65 (36.5) | 49 (72.1) | 42 (68.9) | 51 (64.6) |
| 1-150 min/week at ≥ 4 MET | 34 (18.1) | 60 (26.1) | 52 (29.2) | 5 (7.4) | 6 (9.8) | 11 (13.9) |
| >150 min/week at ≥ 4 MET | 39 (20.7) | 64 (27.8) | 61 (34.3) | 14 (20.6) | 13 (21.3) | 17 (21.5) |
| Smoking | | | | | | |
| Never | 33 (18.3) | 41 (18.3) | 33 (18.9) | 14 (21.9) | 10 (17.2) | 18 (22.8) |
| Former | 82 (45.6) | 116 (51.8) | 92 (52.6) | 31 (48.4) | 31 (53.5) | 43 (54.4) |
| Current | 65 (36.1) | 67 (29.9) | 50 (28.6) | 19 (29.7) | 17 (29.3) | 18 (22.8) |
| SES | | | | | | |
| Low | 45 (23.9) | 67 (29.4) | 45 (25.3) | 28 (41.8) | 20 (32.8) | 18 (22.8) |
| Medium | 128 (68.1) | 133 (58.3) | 113 (63.5) | 33 (49.3) | 39 (63.9) | 52 (65.8) |
| High | 15 (8) | 28 (12.3) | 20 (11.2) | 6 (9) | 2 (3.3) | 9 (11.4) |
| Alcohol consumption | | | | | | |
| 0 g/day | 60 (31.8) | 43 (18.6) | 34 (19) | 23 (34.9) | 21 (35) | 25 (31.7) |
| <20 g/day | 82 (43.4) | 131 (56.7) | 91 (50.8) | 25 (37.9) | 24 (40) | 43 (54.4) |
| ≥20 g/day | 47 (24.9) | 57 (24.7) | 54 (30.2) | 18 (27.3) | 15 (25) | 11 (13.9) |
| Prescribed diet | 32 (16.9) | 39 (16.9) | 31 (17.3) | 33 (50) | 31 (51.7) | 51 (64.6) |
| Energy (kcal/d) | 2125.2 (511.8) | 2285.7 (499.3) | 2434.2 (492.5) | 1888.2 (396.8) | 2133 (518.6) | 2301.1 (465.9) |
| Dietary fiber, g | 20.3 (5.6) | 24.9 (5.9) | 29 (6) | 19.5 (5.7) | 23.9 (7.6) | 30.3 (7.8) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Saturated fat, g | 42.7 (15) | 44 (14.6) | 44.4 (15) | 38.6 (11.3) | 42.3 (16) | 38.4 (13.6) |
| Trans fatty acid, g | 10.5 (5.6) | 11 (6.5) | 11.2 (6.4) | 8.3 (4.2) | 9.5 (5.5) | 10 (5.7) |
| Sodium, mg | 2213.3 (586.2) | 2457.1 (645.9) | 2743 (687.9) | 2115.4 (667) | 2417.4 (599.3) | 2771.4 (811.6) |
| Added sugar, g | 67.4 (40.8) | 64.6 (38) | 60.8 (36.2) | 47.5 (31.9) | 47.3 (42.3) | 50.4 (39.7) |
| Medication | | | | | | |
| Antithrombotic agents | 6 (3.3) | 12 (5.3) | 12 (6.9) | 15 (23.4) | 11 (19) | 21 (26.6) |
| Lipid lowering drugs | 1 (0.6) | 1 (0.4) | 1 (0.6) | 0 (0) | 1 (1.7) | 2 (2.5) |
| Antidiabetic drugs | 0 (0) | 0 (0) | 0 (0) | 4 (6.3) | 11 (19) | 15 (19) |
| Antihypertensive drugs | 29 (16.1) | 38 (16.9) | 36 (20.6) | 22 (34.4) | 24 (41.4) | 32 (40.5) |
| Prevalent diseases | | | | | | |
| Myocardial infarction | | | | 27 (39.7) | 31 (50.8) | 39 (48.1) |
| Stroke | | | | 11 (16.2) | 5 (8.2) | 10 (12.3) |
| Diabetes mellitus | | | | 23 (33.8) | 21 (34.4) | 22 (27.2) |
| Any combination of the above | | | | 7 (10.3) | 4 (6.6) | 10 (12.3) |

DHNaFS Dutch Healthy Nutrient and Food Score

[1]Values are presented as mean (SD) for continuous variables or n (%) for categorical variables

[2]Tests for trend of continuous variables were based on general linear regression with dietary scores as continuous independent variable. Chi-square tests were used for categorical variables across all 5 levels of dietary scores

[3]p-trend across tertiles of the Dutch Healthy Nutrient and Food Score <0.05 for age, HDL cholesterol, physical activity, alcohol consumption, energy (kcal/d), dietary fiber, sodium, added sugar

[4]p-trend across tertiles of the Dutch Healthy Nutrient and Food Score <0.05 for age, energy (kcal/d), dietary fiber, trans fatty acids, sodium, added sugar

[5]To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586.

## Dietary scores and CVD mortality

In the total sample we observed 789 deaths of which 354 were from CVD. In the total sample the DHNaFS was not significantly associated with CVD and all-cause mortality. Because there was significant interaction between healthy and diseased men with the DHNaFS (p-value 0.02 and 0.05 in the fully adjusted models for CVD and all-cause mortality respectively) we further stratified all analysis.

We observed 225 CVD deaths in the healthy men and 129 in the diseased men. The absolute risk of CVD mortality was 2 to 3 times lower in healthy than in diseased men and relatively stable across tertiles of the DHNaFS in healthy men but decreased across tertiles of the DHNaFS in the diseased men **(Table 3)**. The DHNaFS was not associated with CVD mortality in the total sample and the healthy men. Diseased men in the highest tertile of the DHNaFS had 43% (HR 0.57; CI

**TABLE 3** Multivariable adjusted HRs (95% CI) for CVD mortality across tertiles of the Dutch Healthy Nutrient and Food Score

| | | T1 | T2 | T3 | P-trend |
|---|---|---|---|---|---|
| Healthy men | | | | | |
| DHNaFS | (median IQR) | 8 (7-9) | 11 (10-12) | 14 (13-15) | |
| N | | 196 | 239 | 181 | |
| Person-years | | 2281 | 2891 | 2345 | |
| No. of cases | | 68 | 90 | 67 | |
| AR per 1000 py | | 29.8 | 31.1 | 28.6 | |
| Model 1 | | 1 | 1.07 (0.78-1.47) | 1.03 (0.73-1.47) | 0.48 |
| Model 2 | | 1 | 1.09 (0.77-1.53) | 1.06 (0.74-1.54) | 0.38 |
| Model 3 | | 1 | 1.06 (0.76-1.49) | 0.99 (0.68-1.44) | 0.53 |
| Cardiovascular-metabolic diseased men | | | | | |
| DHNaFS | (median IQR) | 8 (7-9) | 11 (10-12) | 14 (13-15) | |
| N | | 68 | 61 | 81 | |
| Person-years | | 473 | 562 | 775 | |
| No. of cases | | 46 | 39 | 44 | |
| AR per 100 py | | 97.2 | 69.4 | 56.8 | |
| Model 1 | | 1 | 0.61 (0.40-0.95) | 0.63 (0.40-0.99) | 0.03 |
| Model 2 | | 1 | 0.63 (0.40-1.01) | 0.69 (0.43-1.10) | 0.11 |
| Model 3 | | 1 | 0.54 (0.33-0.88) | 0.57 (0.34-0.93) | 0.02 |

HR hazard ratio, CI confidence interval, DHNaFS Dutch Healthy Nutrient and Food Score, AR absolute risk
model 1 adjusted for age and energy (kcal)/SD
model 2 additionally adjusted for alcohol intake (0, <20, ≥20 g/d), SES (low, moderate, high), physical activity (0/1-150/>150 minutes at ≥ 4 MET per week) and smoking status (never, former, current)
model 3 additionally adjusted for medication (antithrombotic agents, anti-diabetic drugs, anti-hypertensive drugs)

0.34-0.93) lower CVD mortality risk compared to patients in the lowest tertile. Further adjustment for BMI, blood pressure and cholesterol did not change the results (data not shown).The DUNaFS was not associated with CVD mortality risk **(supplemental table 4)**.

## Dietary scores and all-cause mortality

From the 616 healthy men 583 died and from the 210 diseased men 208 died. The absolute risk for all-cause mortality was 1.7 times lower in healthy than in diseased men in the first tertile and 1.4 times lower in the second and third tertile. The absolute risk decreased across tertiles of the DHNaFS in the total sample, was relatively stable across tertiles of the DHNaFS in healthy men but decreased across tertiles of the DHNaFS in the diseased men **(Table 4)**. In the fully adjusted model,

**TABLE 4** Multivariable adjusted HRs (95% CI) for All-Cause mortality across tertiles of the Dutch Healthy Nutrient and Food Score

| | | T1 | T2 | T3 | P-trend |
|---|---|---|---|---|---|
| Healthy men | | | | | |
| DHNaFS | (median IQR) | 8 (7-9) | 11 (10-12) | 14 (13-15) | |
| N | | 196 | 239 | 181 | |
| Person-years | | 2281 | 2891 | 2345 | |
| No. of cases | | 187 | 227 | 168 | |
| AR per 1000 py | | 82.0 | 78.5 | 71.6 | |
| Model 1 | | 1 | 0.96 (0.78-1.16) | 0.89 (0.72-1.11) | 0.50 |
| Model 2 | | 1 | 1.06 (0.85-1.31) | 1.02 (0.81-1.28) | 0.63 |
| Model 3 | | 1 | 1.04 (0.84-1.29) | 0.97 (0.76-1.23) | 0.82 |
| Cardiovascular-metabolic diseased men | | | | | |
| DHNaFS | (median IQR) | 8 (7-9) | 11 (10-12) | 14 (13-15) | |
| N | | 68 | 61 | 81 | |
| Person-years | | 473 | 562 | 775 | |
| No. of cases | | 46 | 39 | 44 | |
| AR per 1000 py | | 143.8 | 108.5 | 100.6 | |
| Model 1 | | 1 | 0.64 (0.45-0.91) | 0.73 (0.51-1.05) | 0.15 |
| Model 2 | | 1 | 0.67 (0.45-0.97) | 0.79 (0.54-1.15) | 0.47 |
| Model 3 | | 1 | 0.58 (0.39-0.86) | 0.67 (0.45-0.99) | 0.11 |

HR hazard ratio, CI confidence interval, DHNaFS Dutch Healthy Nutrient and Food Score, AR absolute risk
model 1 adjusted for age and energy (kcal)/SD
model 2 additionally adjusted for alcohol intake (0, <20, ≥20 g/d), SES (low, moderate, high), physical activity (0/1-150/>150 minutes at ≥ 4 MET per week) and smoking status (never, former, current)
model 3 additionally adjusted for medication (antithrombotic agents, anti-diabetic drugs, anti-hypertensive drugs)

**TABLE 5** Life years gained1 (95% CI) across tertiles of the Dutch Healthy Nutrient and Food Score

| | | healthy men | | | Cardiovascular-metabolic diseased men | | |
|---|---|---|---|---|---|---|---|
| | | DHNaFS | | | DHNaFS | | |
| Tertile | | 1 | 2 | 3 | 1 | 2 | 3 |
| N | | 187 | 227 | 168 | 68 | 61 | 78 |
| Age at examination 19852 | | 72.7 (5.4) | 72.3 (5.2) | 71.2 (4.9) | 73.2 (5.3) | 73.7 (5.5) | 71.2 (5.1) |
| Age at death | | 83.8 (6.4) | 83.7 (6.4) | 83.2 (6.9) | 80.1 (6.4) | 82.9 (6.5) | 80.5 (6.0) |
| Age difference | | 11.1 (5.7) | 11.4 (6.1) | 12.0 (6.2) | 6.9 (5.3) | 9.2 (6.0) | 9.2 (5.5) |
| Life years gained | | | | | | | |
| | Model 1 | ref | 0.3 (-0.9-1.5) | 0.9 (-0.4-2.2) | ref | 2.2 (0.2-4.2) | 2.1 (0.2-4.1) |
| | Model 2 | ref | -0.1 (-1.4-1.1) | 0.2 (-1.1-1.5) | ref | 2.3 (0.3-4.4) | 2.0 (0.0-4.0) |
| | Model 3 | ref | 0.0 (-1.3-1.2) | 0.4 (-0.9-1.8) | ref | 2.6 (0.6-4.6) | 2.4 (0.4-4.5) |

DHNaFS Dutch Healthy Nutrient and Food Score

[1] number of life years gained is based on years lived since baseline examination

[2] mean (SD)

model 1 adjusted for energy (kcal)/SD

model 2 additionally adjusted for alcohol intake (0, <20, ≥20 g/d), SES (low, moderate, high), physical activity (0/1-150/>150 minutes at ≥ 4 MET per week) and smoking status (never, former, current)

model 3 additionally adjusted for medication (antithrombotic agents, anti-diabetic drugs, anti-hypertensive drugs)

diseased men in the highest tertile of the DHNaFS had 33% (HR 0.67; CI0.45-0.99) lower all-cause mortality risk compared to diseased men in the lowest tertile. The DUNaFS was not associated with all-cause mortality risk **(supplemental table 5)**.

### Dietary scores and life years gained

Age at baseline did not differ much between healthy and diseased men. After adjustment for lifestyle factors diseased men in the highest tertiles of the DHNaFS lived more than 2.5 years longer compared to diseased men in the lowest tertile. In the healthy men there was no difference in life years gained across tertiles. The DUNaFS was not associated with life years gained (data not shown).

## DISCUSSION

We assessed two food-based dietary scores in an elderly sample of men with and without cardiovascular-metabolic diseases. The DHNaFS was associated with approximately 40% lower CVD and all-cause mortality risk comparing the extreme score tertiles of cardiovascular-metabolic diseased men but not in healthy men. Diseased men in the top two tertiles of the DHNaFS lived 2.5 year longer compared to those in the lowest tertile. The DUNaFS was not associated with CVD and all-cause mortality.

Our results of the DHNaFS in the men with cardiovascular-metabolic diseases are consistent with those of the cardiac patients the HALE project [15]. In that study a higher MDS-score was associated with lower all-cause mortality risk in cardiac patients [15]. In the Health Professionals Follow-up study the Mediterranean Diet Score (MDS) was associated with lower all-cause and CVD mortality risk in men with a previous CVD event [11]. However, that study showed that the associations of the MDS score with mortality attenuated after removal of the alcohol component from the score [11]. In the present study there was no alcohol component included in the dietary scores, instead we adjusted for alcohol consumption.

Several studies reported significant inverse associations of dietary scores with CVD and all-cause mortality in elderly men free from cardiovascular-metabolic diseases [4, 5, 7]. Our results in healthy men are in line with those of Hamer et al. on a Mediterranean-style dietary pattern [10] and Streppel et al. on the NRF9.3 score who observed no association with all-cause mortality in healthy men [24]. One explanation for the different associations in men with and without cardiovascular-metabolic diseases could be that only 17% of the healthy men were on a prescribed diet compared to more than 54% of the diseased men. The diet quality of the diseased men likely improved because of the dietary advice and showed a stronger contrast in dietary fiber and sodium intake compared to the healthy men.

This could be an explanation for the association observed in the diseased men and the absence of an association in healthy men. The dietary advice in the diseased men may be reflected in the lower intake of added sugar in this group.

The food groups scored in the DUNaFS were generally high in solid fats, sodium and/or added sugar and therefore we hypothesized an unfavorable effect on health, however, we did not find associations of this dietary score with mortality. A reason for this null-finding could be that two dietary scores are not mutually exclusive. The men consumed on average 2000-2500 grams across tertiles of the DUNaFS, of which approximately 1700 gram was derived from the DHNaFS food groups. This suggests that even though men score high on the DUNaFS they can still have a reasonable healthy overall diet and could be a reason for the null-findings with the DUNaFS.

The dietary scores were relatively stable characteristics with good 5-year tracking correlations, although we observed stronger correlation coefficients for the DHNaFS than for the DUNaFS. Both dietary scores do not take into account secular trends such as dietary modifications by the food-industry. We showed previously that between 1985 to 1995 trans fatty acid intake decreased in the Zutphen elderly [25]. This suggests that although the participants kept a similar dietary pattern over the years the nutritional composition improved. More specifically this affected food groups (i.e. snacks and butter and margarines) included in the DUNaFS. This could be another explanation for the lack of association of this dietary score and mortality.

Our study has limitations. Our sample size was relatively small, especially the diseased men. Our study sample comprised elderly Dutch men and therefore might not be generalizable to younger populations and women. Although we accounted for several possible confounding variables residual confounding cannot be ruled out. Our study has several strengths. Diet was assessed with the cross check dietary history method, which provides detailed information regarding the types of food and beverages consumed, which enabled us to define food groups objectively and systematically using classification criteria for foods derived from the Netherlands' Food-Based Dietary Guidelines [26]. Follow up was long and almost complete resulting in a large number of person years and only 2 persons were lost to follow up. Because our population was almost followed until extinction we had a unique opportunity to assess life years gained. To the best of our knowledge no previous study assessed the amount of life years gained with healthy eating.

In conclusion, our results suggest that a high quality diet is associated with 40% lower mortality risk and longer life expectancy in elderly men with cardiovascular-metabolic diseases, but not in elderly men without these diseases. These results need replication in other and larger studies. Also, research on the impact

of diet in elderly is needed to make more accurate food-based recommendations and should take into account not only life expectancy but also quality of life.

## ACKNOWLEDGMENTS

F.P.C.S.: conceptualization, statistical analysis, interpretation, and writing of the manuscript text; S.S.S.M.: conceptualization, interpretation, writing and review of the manuscript; S.E.M.d.H.: statistical analysis, interpretation, writing and review of the manuscript; D.R.J.: statistical analysis, interpretation and review of the manuscript, D.K.: conceptualization, interpretation, writing and review of the manuscript text F.P.C.S., S.E.M.d.H. and D.K. declare no conflict of interest. S.S.S.M received unrestricted grants from the Dutch Dairy Association and Global Dairy Platform to carry out meta-analysis on the association between dairy products and cardiovascular diseases. D.R.J. is a consultant for the California Walnut Commission.

The contributions of F.P.C.S., S.S.S.M. and D.K. to this article were funded by the Royal Netherlands Academy of Arts and Sciences. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## REFERENCES


1. Waijers PM, Feskens EJ, Ocke MC. A critical review of predefined diet quality scores. Br J Nutr. 2007; 97:219-31.
2. Kant AK. Dietary patterns and health outcomes. J Am Diet Assoc. 2004;104:615-35.
3. Ford DW, Jensen GL, Hartman TJ, Wray L, Smiciklas-Wright H. Association between dietary quality and mortality in older adults: a review of the epidemiological evidence. J Nutr Gerontol Geriatr. 2013; 32:85-105.
4. Reedy J, Krebs-Smith SM, Miller PE, Liese AD, Kahle LL, Park Y, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. J Nutr. 2014;144:881-9.
5. Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. High diet quality is associated with a lower risk of cardiovascular disease and all-cause mortality in older men. J Nutr. 2014;144:673-80.
6. McNaughton SA, Bates CJ, Mishra GD. Diet quality is associated with all-cause mortality in adults aged 65 years and older. J Nutr. 2012;142:320-5.
7. Knoops KT, de Groot LC, Kromhout D, Perrin AE, Moreiras-Varela O, Menotti A, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. JAMA. 2004;292:1433-9.
8. Lee MS, Huang YC, Su HH, Lee MZ, Wahlqvist ML. A simple food quality index predicts mortality in elderly Taiwanese. J Nutr Health Aging. 2011;15:815-21.
9. Lasheras C, Fernandez S, Patterson AM. Mediterranean diet and age with respect to overall survival in institutionalized, nonsmoking elderly people. Am J Clin Nutr. 2000;71:987-92.
10. Hamer M, McNaughton SA, Bates CJ, Mishra GD. Dietary patterns, assessed from a weighed food record, and survival among elderly participants from the United Kingdom. Eur J Clin Nutr. 2010; 64:853-61.
11. Lopez-Garcia E, Rodriguez-Artalejo F, Li TY, Fung TT, Li S, Willett WC, et al. The Mediterranean-style dietary pattern and mortality among men and women with cardiovascular disease. Am J Clin Nutr. 2014;99:172-80.
12. Li S, Chiuve SE, Flint A, Pai JK, Forman JP, Hu FB, et al. Better diet quality and decreased mortality among myocardial infarction survivors. JAMA Intern Med. 2013;173:1808-18.
13. Dehghan M, Mente A, Teo KK, Gao P, Sleight P, Dagenais G, et al. Relationship between healthy diet and risk of cardiovascular disease among patients on drug therapies for secondary prevention: a prospective cohort study of 31 546 high-risk individuals from 40 countries. Circulation. 2012;126:2705-12.
14. Barzi F, Woodward M, Marfisi RM, Tavazzi L, Valagussa F, Marchioli R, et al. Mediterranean diet and all-causes mortality after myocardial infarction: results from the GISSI-Prevenzione trial. Eur J Clin Nutr. 2003;57:604-11.
15. Iestra J, Knoops K, Kromhout D, de Groot L, Grobbee D, van Staveren W. Lifestyle, Mediterranean diet and survival in European post-myocardial infarction patients. EurJCardiovascPrevRehabil. 2006;13: 894-900.
16. Keys A. Seven countries. A multivariate analysis of death and coronary heart disease. : Harvard University Press; 1980.
17. Bloemberg BP, Kromhout D, Obermann-De Boer GL, Van Kampen-Donker M. The reproducibility of dietary intake data assessed with the cross-check dietary history method. Am J Epidemiol. 1989;130:1047-56.
18. Stichting Nederlands Voedingsstoffenbestand, NEVO-tabel: Nederlands Voedingsstoffenbestand 1986–1987, 1989–1990. Den Haag: Voorlichtingsbureau voor de Voeding.
19. Organization WH. International Classification of Diseases, Ninth Revision (ICD-9). Geneva: Switzerland World Health Organization1977.
20. Caspersen CJ, Bloemberg BP, Saris WH, Merritt RK, Kromhout D. The prevalence of selected physical activities and their relation with coronary heart disease risk factors in elderly men: the Zutphen Study, 1985. Am J Epidemiol. 1991;133:1078-92.

21. Siedel J, Schlumberger H, Klose S, Ziegenhorn J, Wahlefeld AW. Improved Reagent for the Enzymatic Determination of Serum-Cholesterol. J Clin Chem Clin Bio. 1981;19:838-9.
22. Stahler F, Gruber W, Stinshoff K, Roschlau P. [A practical enzymatic cholesterol determination]. Med Lab (Stuttg). 1977;30:29-37.
23. Warnick GR, Benderson J, Albers JJ. Dextran sulfate-Mg2+ precipitation procedure for quantitation of high-density-lipoprotein cholesterol. Clin Chem. 1982;28:1379-88.
24. Streppel MT, Sluik D, van Yperen JF, Geelen A, Hofman A, Franco OH, et al. Nutrient-rich foods, cardiovascular diseases and all-cause mortality: the Rotterdam study. Eur J Clin Nutr. 2014;68:741-7.
25. Oomen CM, Ocke MC, Feskens EJM, van Erp-Baart MAJ, Kok FJ, Kromhout D. Association between trans fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study. Lancet. 2001;357:746-51.
26. Netherlands Nutrition Centre. Guidelines Food Choice. Den Haag, 2011. http://www.voedingscentrum.nl/Assets/Uploads/Documents/Voedingsvoorlichters/Richtlijnen_voedselkeuze_2011.pdf. (4 June 2012).

**SUPPLEMENTAL TABLE 1** Food groups and criteria[1] for food group assignment to the Dutch Healthy Nutrient and Food Score and the Dutch Undesirable Nutrient and Food Score in the Zutphen Elderly Study

| Food Score | Food group | Foods included in food groups | Criteria for Classification |
|---|---|---|---|
| Dutch Healthy Nutrient and Food Score (DHNaFS) | Vegetables | Lettuce, tomatoes, cauliflower, green beans, leeks etc. | Unprocessed vegetables |
| | Fruits | Apple, orange, bananas, grapes, strawberries etc. | Unprocessed fruit |
| | Whole grains | Whole wheat bread, crackers, cereals, brown rice | Bread[2]:<br>SFA: ≤ 1.1g/100g<br>TF: ≤ 0.1g/100g<br>DF: ≥ 1.3g/100kcal<br>Na: ≤ 500mg/100g<br>AS: ≤ 13en% |
| | Protein rich plant foods | Peas, broad beans, tofu, nuts and seeds | |
| | Potatoes | Potatoes | SFA: ≤ 1.1g/100g<br>TF: ≤ 0.1g/100g<br>DF: ≥ 1.7g/100kcal<br>Na: ≤ 100mg/100g |
| | Lean meat | Beef, chicken or turkey breast, ham | SFA: ≤ 4g/100g<br>Na: ≤ 100mg/100g<br>AS: not added |
| | Fish | Trout, salmon, herring, pollock, shellfish | All fish |
| | Eggs | | All eggs |
| | Low-fat milk and yoghurt | Skimmed and semi-skimmed milk, yoghurt, buttermilk | SFA: ≤ 1.3g/100g<br>Na: ≤ 100mg/100g<br>AS: ≤ 5g/100g |
| | Oils and soft margarines | Vegetable oils, (diet) low-fat margarines | SFA: ≤ 30% of total fat<br>TF: ≤ 1.3en%<br>Na: ≤ 160mg/100g |
| | Non-caloric drinks | Water, tea, coffee, | SFA: ≤ 1.0g/100g<br>TF: ≤ 0.1g/100g<br>Na: ≤ 20mg/100ml<br>AS: not added |

| | | | |
|---|---|---|---|
| Dutch Undesirable Nutrient and Food Score (DUNaFS) | Processed vegetables | Canned or jarred vegetables, spinach a la creme, pickeled vegetables, sauerkraut | |
| | Fruit juice and sugar sweetened beverages | Orange juice, grape juice, apple sauce, canned or jarred fruits in syrup | |
| | High-fat meat | Hamburger, chicken or turkey with skin, minced meat, pork sirloin | SFA: > 13en%<br>Na: > 100mg/100g<br>AS: adde |
| | Processed meat | Cold cuts (bacon, sliced ham, salami) | SFA: > 13en%<br>Na: > 900mg/100g<br>AS: > 2.5g/100g |
| | Full-fat milk and yoghurt | Full-fat milk, chocolate milk, yoghurt, coffee cream | SFA: > 1.3g/100g<br>Na: > 100mg/100g<br>AS: > 5g/100g |
| | Cheese | Hard cheeses (e.g. Gouda, cheddar), soft cheeses (e.g. brie, camembert), cream cheese | SFA: > 16g/100g<br>Na: > 900mg/100g |
| | Refined grains | Refined bread, cornflakes, white rice | Refined bread[2]<br>SFA: > 1.1g/100g<br>TF: > 0.1g/100g<br>DF: < 1.3g/100 kcal<br>Na: > 500mg/100g<br>AS: > 13en% |
| | Spreads | Peanut butter, jam, chocolate-hazelnut spreads | EN: > 350kcal/100g<br>SFA: > 13en%<br>TF: > 1.3en%<br>Na: > 400mg/100g<br>AS: > 30g/100g |
| | Butter and hard margarines | Butter, margarine | SFA: > 30% of total fat<br>TF: > 1.3en%<br>Na: > 160mg/100g |
| | Extras | Ice cream, cookies, candy bars, chocolate, Fries, chips, deep fried snacks, condiments, sauces | EN: > 110kcal/portion<br>SFA: > 13en%<br>TF: > 1.3en%<br>Na: > 400mg/100g<br>AS: > 20g/100g |
| | Ready meals | Mixed dishes, pizza, soups | |

**SUPPLEMENTAL TABLE 2** Total median intake (IQR) of food groups in grams across tertiles of the Dutch Undesirable Nutrient and Food Score (DUNaFS) of 616 healthy and 210 diseased participants of the Zutphen Study

| | healthy men | | | Cardiovascular-metabolic diseased men | | |
|---|---|---|---|---|---|---|
| | DUNaFS | | | DUNaFS | | |
| Tertile | 1 | 2 | 3 | 1 | 2 | 3 |
| N | 197 | 226 | 193 | 85 | 75 | 50 |
| DHNaFS food groups | | | | | | |
| Vegetables | 153 (120-202) | 147 (108-184) | 137 (101-173) | 153 (103-182) | 144 (100-197) | 142 (106-163) |
| Fruits | 130 (63-222) | 121 (59-212) | 143 (90-228) | 143 (83-222) | 130 (69-251) | 185 (113-248) |
| Whole grains | 105 (60-140) | 96 (54-135) | 77 (13-136) | 93 (70-150) | 110 (59-144) | 96 (6-154) |
| Potatoes | 140 (93-200) | 167 (119-229) | 170 (124-238) | 140 (89-190) | 150 (111-200) | 161 (118-210) |
| Protein rich plant foods | 13 (1-29) | 19 (6-32) | 18 (7-32) | 14 (0-37) | 19 (9-32) | 18 (9-35) |
| Lean meat | 27 (10-44) | 24 (8-46) | 21 (7-37) | 32 (13-55) | 28 (12-52) | 24 (10-39) |
| Eggs | 14 (7-22) | 16 (8-23) | 18 (7-25) | 14 (7-21) | 14 (7-22) | 15 (11-22) |
| Fish | 12 (0-26) | 16 (3-29) | 13 (0-24) | 13 (0-22) | 13 (0-32) | 11 (0-23) |
| Oils and soft margarines | 4 (0-18) | 1 (0-17) | 0 (0-19) | 13 (0-27) | 4 (0-28) | 1 (0-16) |
| Non-caloric drinks | 781 (630-1000) | 853 (653-1075) | 867 (660-1100) | 795 (630-1050) | 831 (640-1080) | 905 (720-1140) |
| Low fat milk and yoghurt | 97 (0-296) | 85 (0-250) | 26 (0-194) | 107 (0-364) | 100 (0-232) | 45 (0-203) |
| DUNaFS food groups | | | | | | |
| Processed vegetables | 0 (0-14) | 8 (0-18) | 16 (3-26) | 0 (0-18) | 9 (0-19) | 18 (7-29) |
| Fruit juice and sugar sweetened beverages | 6 (0-52) | 29 (3-85) | 65 (19-125) | 0 (0-24) | 32 (5-122) | 51 (21-126) |
| Refined grains | 23 (9-47) | 45 (22-82) | 75 (38-119) | 23 (6-47) | 45 (19-82) | 87 (54-129) |
| High-fat meat | 43 (27-65) | 54 (35-73) | 60 (42-77) | 50 (26-69) | 53 (39-69) | 60 (34-78) |
| Processed meat | 16 (6-31) | 26 (14-43) | 33 (19-46) | 14 (3-33) | 23 (12-36) | 31 (17-38) |
| Full-fat milk and yoghurt | 48 (15-160) | 127 (33-240) | 229 (107-382) | 50 (3-192) | 124 (30-262) | 236 (66-334) |
| Cheese | 21 (14-36) | 26 (15-40) | 34 (20-51) | 20 (11-32) | 29 (17-49) | 45 (27-60) |
| Butter and hard margarines | 25 (11-42) | 37 (23-54) | 49 (29-63) | 19 (11-34) | 37 (19-48) | 41 (29-58) |
| Extras | 30 (17-56) | 45 (25-65) | 66 (40-93) | 21 (10-33) | 47 (27-66) | 54 (34-91) |
| Spreads | 3 (0-14) | 7 (0-20) | 15 (2-30) | 8 (0-15) | 9 (0-22) | 15 (2-25) |
| Ready meals | 0 (0-36) | 24 (0-72) | 54 (11-96) | 0 (0-43) | 18 (0-87) | 71 (9-102) |

p-trend across quintiles of the DUNaFS <0.05

DHNaFS Dutch Healthy Nutrient and Food Score

**SUPPLEMENTAL TABLE 3** Baseline characteristics across tertiles of the Dutch Undesirable Nutrient and Food Score of 616 healthy and 210 diseased participants of the Zutphen Study[1,2]

| | healthy men[3] | | | Cardiovascular-metabolic diseased men[4] | | |
|---|---|---|---|---|---|---|
| | DUNaFS | | | DUNaFS | | |
| | 1 | 2 | 3 | 1 | 2 | 3 |
| N | 197 | 226 | 193 | 85 | 75 | 50 |
| Age in 1985 in years | 71.8 (5) | 71.8 (5.5) | 71.9 (5.1) | 72.5 (5.3) | 72.6 (5.6) | 72.4 (5.2) |
| BMI | 25.5 (3) | 25.8 (3.2) | 25.5 (3.3) | 25.4 (3.2) | 25.9 (3) | 25.7 (3.2) |
| Systolic blood pressure | 152.9 (23.3) | 148.9 (19) | 150 (20.1) | 152.1 (23.9) | 151 (21.4) | 149.7 (19.8) |
| Diastolic blood pressure | 85.9 (11.5) | 85 (11.5) | 85.9 (11) | 83.3 (11.1) | 86.5 (11.5) | 85.2 (11.7) |
| Serum lipids mmol/liter[5] | | | | | | |
| Total cholesterol | 6.1 (1) | 6.2 (1) | 6 (1.1) | 6.4 (1.4) | 6 (1.1) | 6 (1.2) |
| HDL cholesterol | 1.2 (0.3) | 1.1 (0.3) | 1.1 (0.3) | 1.1 (0.3) | 1 (0.2) | 1.1 (0.2) |
| Physical activity | | | | | | |
| No | 97 (50.5) | 102 (47.2) | 87 (46.3) | 61 (72.6) | 47 (62.7) | 34 (69.4) |
| 1-150 min/week at ≥ 4 MET | 44 (22.9) | 55 (25.5) | 47 (25) | 8 (9.5) | 10 (13.3) | 4 (8.2) |
| >150 min/week at ≥ 4 MET | 51 (26.6) | 59 (27.3) | 54 (28.7) | 15 (17.9) | 18 (24) | 11 (22.5) |
| Smoking | | | | | | |
| Never | 39 (20.6) | 36 (17.1) | 32 (17.8) | 19 (24.1) | 13 (18.1) | 10 (20) |
| Former | 90 (47.6) | 108 (51.4) | 92 (51.1) | 46 (58.2) | 35 (48.6) | 24 (48) |
| Current | 60 (31.8) | 66 (31.4) | 56 (31.1) | 14 (17.7) | 24 (33.3) | 16 (32) |
| SES | | | | | | |
| Low | 48 (25) | 51 (23.7) | 58 (31) | 28 (33.3) | 24 (32.4) | 14 (28.6) |
| Medium | 123 (64.1) | 142 (66.1) | 109 (58.3) | 49 (58.3) | 44 (59.5) | 31 (63.3) |
| High | 21 (10.9) | 22 (10.2) | 20 (10.7) | 7 (8.3) | 6 (8.1) | 4 (8.2) |
| Alcohol consumption | | | | | | |
| 0 g/day | 53 (27.9) | 48 (21.7) | 36 (19.2) | 31 (38.3) | 25 (33.3) | 13 (26.5) |
| <20 g/day | 70 (36.8) | 120 (54.3) | 114 (60.6) | 27 (33.3) | 37 (49.3) | 28 (57.1) |
| ≥20 g/day | 67 (35.3) | 53 (24) | 38 (20.2) | 23 (28.4) | 13 (17.3) | 8 (16.3) |

**SUPPLEMENTAL TABLE 3** Baseline characteristics across tertiles of the Dutch Undesirable Nutrient and Food Score of 616 healthy and 210 diseased participants of the Zutphen Study[1,2]

| | healthy men[3] | | | Cardiovascular-metabolic diseased men[4] | | |
|---|---|---|---|---|---|---|
| | DUNaFS | | | DUNaFS | | |
| | 1 | 2 | 3 | 1 | 2 | 3 |
| Prescribed diet | 43 (22.6) | 36 (16.3) | 23 (12.2) | 52 (64.2) | 37 (49.3) | 26 (53.1) |
| Energy (kcal/d) | 1960 (431.7) | 2255.2 (415.1) | 2630.1 (477.7) | 1825.3 (442.9) | 2210.2 (358.2) | 2479.6 (450.5) |
| Dietary fiber, g | 23.5 (7) | 24.6 (6.3) | 25.9 (6.8) | 23.4 (8) | 25.2 (8.1) | 27.2 (9.4) |
| Saturated fat, g | 34.4 (12.2) | 43.3 (12.3) | 53.6 (13.6) | 32.1 (13.1) | 41 (9.9) | 50.1 (12.3) |
| Trans fatty acid, g | 8.2 (5) | 11 (6.2) | 13.6 (6.2) | 7.1 (5) | 10.2 (4.8) | 11.7 (4.7) |
| Sodium, mg | 2102.2 (567.2) | 2435 (582.9) | 2865.9 (650.5) | 2131.8 (575.8) | 2512.4 (786.2) | 2923.2 (734.3) |
| Added sugar, g | 52.7 (39.1) | 63.6 (36.1) | 77.3 (36.5) | 33.6 (35.7) | 62.4 (37.1) | 53.1 (34.6) |
| Medication | | | | | | |
| Antithrombotic agents | 14 (7.4) | 10 (4.8) | 6 (3.3) | 18 (22.8) | 21 (29.2) | 8 (16) |
| Lipid lowering drugs | 1 (0.5) | 2 (1) | 0 (0) | 2 (2.5) | 0 (0) | 1 (2) |
| Antidiabetic drugs | 0 (0) | 0 (0) | 0 (0) | 16 (20.3) | 8 (11.1) | 6 (12) |
| Antihypertensive drugs | 43 (22.8) | 33 (15.7) | 27 (14.9) | 33 (41.8) | 30 (41.7) | 15 (30) |
| Prevalent diseases | | | | | | |
| Myocardial infarction | | | | 37 (43.5) | 37 (49.3) | 23 (46) |
| Stroke | | | | 13 (15.3) | 9 (12) | 4 (8) |
| Diabetes mellitus | | | | 26 (30.6) | 21 (28) | 19 (38) |
| Any combination | | | | 9 (10.6) | 8 (10.7) | 4 (8) |

DUNaFS Dutch Undesirable Nutrient and Food Score

1 Values are presented as mean (SD) for continuous variables or n (%) for categorical variables, except for triglycerides median (IQR)

2 Tests for trend of continuous variables were based on general linear regression with dietary scores as continuous independent variable. Chi-square tests were used for categorical variables across all 5 levels of dietary scores

3 p-trend across tertiles of the Dutch Healthy Nutrient and Food Score <0.05 for age, HDL cholesterol, physical activity, alcohol consumption, energy (kcal/d), dietary fiber, sodium, added sugar

4 p-trend across tertiles of the Dutch Healthy Nutrient and Food Score <0.05 for age, energy (kcal/d), dietary fiber, trans fatty acids, sodium, added sugar

5 To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586.

**SUPPLEMENTAL TABLE 4** Multivariable adjusted HRs for CVD Mortality across tertiles of the Dutch Undesirable Nutrient and Food Score

| | | T1 | T2 | T3 | P-trend |
|---|---|---|---|---|---|
| Healthy men | | | | | |
| DUNaFS | median (IQR) | 8 (7-9) | 11 (10-12) | 14 (13-16) | |
| N | | 197 | 226 | 193 | |
| Person-years | | 2309.6 | 2864.4 | 2342.1 | |
| No. of cases | | 72 | 84 | 69 | |
| AR per 1000 py | | 3.1 | 2.9 | 2.9 | |
| | | | | | |
| Model 1 | | 1 | 0.90 (0.65-1.25) | 0.91 (0.62-1.32) | 0.6782 |
| Model 2 | | 1 | 0.91 (0.65-1.28) | 0.94 (0.63-1.40) | 0.7485 |
| Model 3 | | 1 | 0.89 (0.64-1.26) | 0.91 (0.61-1.35) | 0.5692 |
| | | | | | |
| Cardiovascular-metabolic diseased men | | | | | |
| DUNaFS | median (IQR) | 8 (6-9) | 11 (10-12) | 14 (13-16) | |
| N | | 85 | 75 | 50 | |
| Person-years | | 699.4 | 607.8 | 502.5 | |
| No. of cases | | 51 | 46 | 32 | |
| AR per 100 py | | 7.3 | 7.6 | 6.4 | |
| | | | | | |
| Model 1 | | 1 | 1.13 (0.73-1.74) | 0.98 (0.58-1.67) | 0.8202 |
| Model 2 | | 1 | 1.16 (0.72-1.84) | 1.03 (0.59-1.79) | 0.9833 |
| Model 3 | | 1 | 1.11 (0.69-1.80) | 1.06 (0.60-1.87) | 0.7708 |

HR hazard ratio, AR absolute risk
model 1 adjusted for age and energy (kcal)/SD
model 2 additionally adjusted for alcohol intake (0, <20, ≥20 g/d), SES (low, moderate, high), physical activity (0/1-150/>150 minutes at ≥ 4 MET per week) and smoking status (never, former, current)
model 3 additionally adjusted for medication (antithrombotic agents, anti-diabetic drugs, anti-hypertensive drugs)

**SUPPLEMENTAL TABLE 5** Multivariable adjusted HRs for All-Cause Mortality across tertiles of the Dutch Undesirable Nutrient and Food Score

| | | T1 | T2 | T3 | P-trend |
|---|---|---|---|---|---|
| Healthy men | | | | | |
| DUNaFS | median (IQR) | 8 (7-9) | 11 (10-12) | 14 (13-16) | |
| N | | 197 | 226 | 193 | |
| Person-years | | 2309.6 | 2864.4 | 2342.1 | |
| No. of cases | | 191 | 208 | 183 | |
| AR per 100 py | | 8.3 | 7.3 | 7.8 | |
| | | | | | |
| Model 1 | | 1 | 0.82 (0.67-1.00) | 0.86 (0.68-1.09) | 0.2632 |
| Model 2 | | 1 | 0.80 (0.65-0.99) | 0.86 (0.67-1.10) | 0.1629 |
| Model 3 | | 1 | 0.81 (0.65-1.00) | 0.86 (0.67-1.10) | 0.1588 |
| | | | | | |
| Cardiovascular-metabolic diseased men | | | | | |
| DUNaFS | median (IQR) | 8 (6-9) | 11 (10-12) | 14 (13-16) | |
| N | | 85 | 75 | 50 | |
| Person-years | | 699.4 | 607.8 | 502.5 | |
| No. of cases | | 84 | 74 | 49 | |
| AR per 100 py | | 12.0 | 12.2 | 9.8 | |
| | | | | | |
| Model 1 | | 1 | 1.05 (0.75-1.46) | 0.80(0.52-1.22) | 0.3333 |
| Model 2 | | 1 | 0.99 (0.68-1.42) | 0.75 (0.48-1.19) | 0.3273 |
| Model 3 | | 1 | 0.98 (0.67-1.42) | 0.79 (0.50-1.24) | 0.5258 |

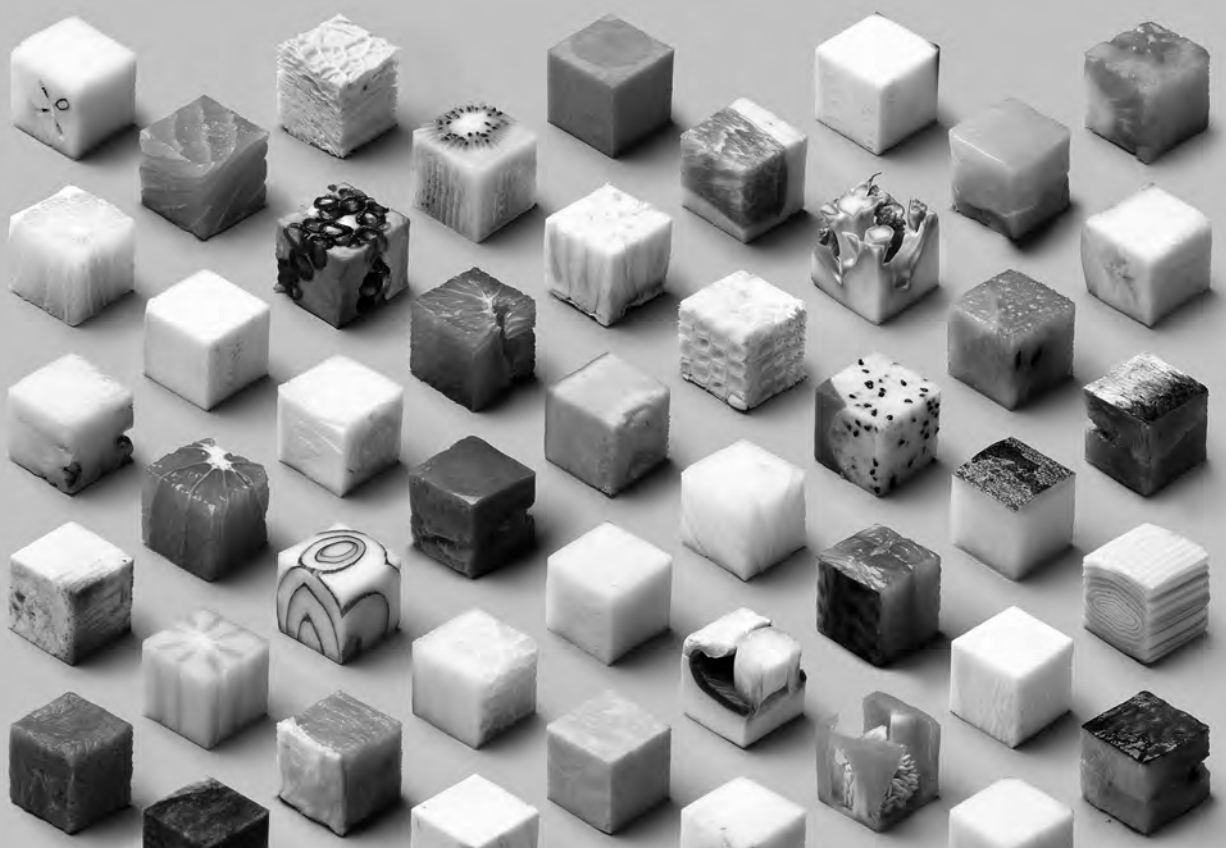
HR hazard ratio, AR absolute risk
model 1 adjusted for age and energy (kcal)/SD
model 2 additionally adjusted for alcohol intake (0, <20, ≥20 g/d), SES (low, moderate, high), physical activity (0/1-150/>150 minutes at ≥ 4 MET per week) and smoking status (never, former, current)
model 3 additionally adjusted for medication (antithrombotic agents, anti-diabetic drugs, anti-hypertensive drugs)

## REFERENCES SUPPLEMENTAL MATERIAL

1. Netherlands Nutrition Centre. Guidelines Food Choice. Den Haag, 2011. http://www.voedingscentrum.nl/Assets/Uploads/Documents/Voedingsvoorlichters/Richtlijnen_voedselkeuze_2011.pdf. (4 June 2012).

# 8

# General discussion



The aim of this thesis was to create, examine and compare several dietary patterns and scores and assess these in relation to both early stage markers of cardiovascular disease (CVD) (markers of endothelial function and oxidative stress) and CVD and all-cause mortality.

This chapter describes the main findings, followed by a discussion of the main findings, methodological considerations, implications and recommendations for further research.

## MAIN FINDINGS

The *A Priori* Diet Quality Score created in the CARDIA study showed many age-related, desirable changes in food intake over 20 years of observation, despite a secular trend towards a lower overall diet score (chapter 2). A higher score on the *A Priori* Diet Quality Score was prospectively associated with less oxidative stress and better endothelial function. The principal component analysis (PCA) based 'Fruit and Vegetable' dietary pattern was inversely associated with oxidative stress but not with all markers of endothelial function. The 'Meat' dietary pattern was positively associated with all markers except VCAM (chapter 3 and 4). Based on the classification system of foods of the Netherland Nutrition Center we created two food-based dietary scores (chapter 5). The 'Dutch Healthy Nutrient and Food Score' was associated with lower risk of CVD and all-cause mortality in cardiac patients aged 60-80 years, and in elderly (65-84) men with, but not without, cardiovascular-metabolic diseases (chapter 6 and 7). The 'Dutch Undesirable Nutrients and Foods Score was not associated with CVD and all-cause mortality (chapter 6 and 7). Overall our findings suggest that dietary patterns are important for both early stage markers of CVD and mortality. We observed differences in the strength of the associations between and within methods of dietary pattern creation.

Two different approaches were used to study dietary patterns in this thesis; 1) theoretically, or *'a priori'* dietary scores and 2) empirically, or *'a posteriori'* derived dietary patterns. We used *'a priori'* food-based dietary scores in each chapter of this thesis. We used principal components analysis (PCA) to derive 'a posteriori' dietary patterns in chapter 3 and 4.

There are many existing *'a priori'* scores [1, 2] which are based on existing knowledge and therefore limited by the current knowledge of diet-disease relationships, and healthy intake levels of nutrients and foods. Many studies compared several *a priori* scores in relation to all-cause mortality in one study [3-10] but several differences were noted in the strength of associations. Generally, (largely) food-based dietary scores predicted mortality better than dietary scores

based on nutrients [3, 11]. In this thesis we created several food-based dietary scores based on different strategies for classifying foods and food groups.

The *A Priori* Diet Quality Score in chapters 2-4 was created by classifying food groups according to considerations of similar nutrient characteristics, hypothesized biologic effects, and comparability to food groups defined in previous studies [12-14]. Mursu et al. showed that the *A Priori* Diet Quality Score correlates highly with Alternative Healthy Eating Index-2010 [15], that both scores predicted mortality and that both scores complemented each other when modeled together [9]. Furthermore, the *A Priori* Diet Quality Score has similarities with the Dietary Approaches to Stop Hypertension index and the Mediterranean Diet Score comparing food groups assignment of "beneficial" and "adverse".

An alternate *a priori* method is to incorporate evidence on food groups and nutrients. The Netherlands Nutrition Center translated the recommended intake for presumed beneficial (i.e dietary fiber) nutrients and upper limits for presumed adverse nutrients (i.e. saturated fatty acids, trans unsaturated fatty acids, added sugar and sodium) to nutrient criteria for each food [16, 17]. To create the Dutch Healthy Nutrient and Food Score and the Dutch Undesirable Nutrient and Food Score these nutrient criteria were used for the classification of food groups. We showed that the 'Dutch Healthy Nutrient and Food Score' was associated with CVD and all-cause mortality in cardiac patients and in elderly men with cardiovascular metabolic disease. The 'Dutch Undesirable Nutrient and Food Score' was not associated with mortality.

A similar approach was used creating the 'Nutrient-Rich Food 9.3-index' scoring each food on nine beneficial nutrients (protein, fiber, vitamins and minerals) and three adverse nutrients (saturated fat, sugar and sodium) [18]. Streppel et al. showed that elderly with a higher 'Nutrient-Rich Food 9.3-index' score had a lower risk of all-cause mortality. There was, however, significant interaction for gender and the association was statistically significant for women but not for men [19].

The 'Dietary Inflammatory Index' uses a similar approach to define a food score based on "inflammatory nutrients". Briefly, the 'Dietary Inflammatory Index' was derived after a literature review from 1950 to 2010, including all articles that assessed the role of whole foods and dietary constituents on interleukins, Tumor Necrosis Factor-alpha and highly sensitive C-Reactive Protein. Overall 'Dietary Inflammatory Index' scores for each participant represent the sum of each of the 'Dietary Inflammatory Index' components in relation to the comparison global diet database [20]. Garcia-Arellano et al. provided evidence for a direct prospective association of a higher 'Dietary Inflammatory Index' with a higher risk of CVD [21].

In conclusion, although dietary pattern defined by dietary scores are based on guidelines or recommendations there are still many decisions to be made to create

a dietary score. The different approaches have shown to be associated with cardiovascular outcomes and mortality, therefore the choice of approach depends on the aim of the study.

Dietary patterns derived by PCA provided insight into existing food consumption patterns in the CARDIA study. There are several decisions in the analysis that may significantly affect the results, i.e. the dietary patterns derived. Some key aspects that the researcher need to decide on are the number of food items or groups to include, adjustment of input variables before analysis (i.e. energy adjustment), the criteria for the number of factors to retain, the rotation method and the labelling of the dietary patterns (quantitatively or qualitatively) [22, 23]. How these choices affect the outcome is unclear.

Dietary patterns derived from PCA will not be the same across studies because they are based on different food consumption data, however, several studies find similar dietary patterns using PCA [22]. Similarly to the PCA derived dietary patterns in CARDIA other studies find a healthful often labelled 'prudent' dietary pattern and a less-healthful often labelled 'Western' dietary pattern. The healthful dietary pattern is often characterized by high loadings of vegetables, fruit, legumes, whole grains and fish, whereas the less-healthful dietary pattern is often characterized by high loadings of red meat, processed meat, butter, potatoes, refined grains and high-fat dairy [22, 24-27].

PCA may well be able to identify dietary patterns in a sample, however, these patterns may not necessarily represent healthful diets as they are based on correlation of intakes between foods. Although this method may therefore not be useful to evaluate diet quality, it provides insight into existing food consumption patterns within a population and reveals dietary patterns that are associated with higher (or lower) health risks [28, 29].

## Comparison of *a priori* dietary scores and *a posteriori* dietary patterns

In chapter 3 and 4 we compared differences in associations between the two dietary pattern methodologies described above. We found differences in strength of associations between the *A Priori* Diet Quality Score and the PCA derived dietary patterns with early markers of endothelial function and oxidative stress. The *A Priori* Diet Quality Score presented in chapter 2-4 emphasized more beneficial food groups (i.e. 20 food groups were rated beneficial) than adverse food groups (i.e. 13 food groups were rated adverse). Compared to the *a priori* ratings of food groups as beneficial or adverse, the PCA derived 'Fruit and Vegetable' dietary pattern emphasized the beneficial groups, whereas the 'Meat' dietary pattern emphasized the adverse food groups.

Few studies compared both methods in one study, however similar to the studies in this thesis, Osler et al. compared both *a posteriori* and *a priori* scores in

one study and found that an *a priori* Healthy Food Index and PCA derived 'Western' dietary pattern were not associated but a PCA derived 'Prudent' dietary pattern was associated with lower all-cause mortality risk after adjustment for important confounders [27].

Nettleton et al. studied two PCA derived dietary patterns the 'Beans, Tomatoes, and Refined Grains' dietary pattern and the 'Whole Grains and Fruit' dietary pattern and one *a priori* 'Low-Risk' dietary score (defined as the weighted sum of whole grains, vegetables, nuts/seeds, low-fat dairy, coffee (positively weighted), red meat, processed meat, high-fat dairy, and soda (negatively weighted)) in relation to type 2 diabetes. The 'Beans, Tomatoes, and Refined Grains' dietary pattern was positively associated and the 'Whole grains and fruit' dietary pattern and the 'Low-Risk' score were inversely associated with incidence of type 2 diabetes [30]. In this study it was noted that although beans and tomatoes contain positive nutrients the PCA-analysis revealed that these foods were correlated with less-favorable food groups such as refined grains, high-fat dairy foods, and red-meat [30].

In conclusion, *a priori* dietary pattern scores and *a posteriori* PCA derived dietary patterns serve different purposes in nutrition research. However, they may inform each other in investigating diet and chronic disease relationships. *A posteriori* PCA derived patterns could inform which food groups and patterns are relevant in a population. Dietary pattern scores based on *a priori* knowledge about food groups may inform which food groups could be included in the PCA.

## DEFINING FOOD-BASED DIETARY PATTERN SCORES IN EPIDEMIOLOGY

Many aspects should be considered when dietary pattern scores are developed in epidemiological studies. The most important ones are which components should be included in the score, the scoring of food groups, weighing of foods and dietary patterns in different populations.

In the several *a priori* dietary pattern scores used in this thesis similar food groups have been rated differently in each score, other food groups were included as a component in one dietary score but not in the other. For example, in this thesis eggs were considered neutral in '*A Priori* Diet Quality Score' and positive in 'Dutch Healthy Nutrient and Food Score'. Although eggs are an important source of many nutrients such as minerals, folate, B vitamins, proteins, and monounsaturated fatty acids they contain also a considerable amount of cholesterol, a risk factor for CVD. It is known that dietary cholesterol raises the ratio of total to HDL cholesterol

and, therefore, adversely affects the cholesterol profile [31]. A recent meta-analysis of prospective cohort studies showed that egg consumption was not associated with the risk of CVD and cardiac mortality in the general population [32]. However, egg consumption may be associated with an increased incidence of type 2 diabetes among the general population and CVD comorbidity in diabetic patients [32]. Furthermore, in the US regular egg consumption tends to be associated with unhealthy lifestyle factors such as smoking and physical inactivity and higher consumption of eggs was likely to be associated with increased consumption of red and processed meats [33].

Similarly, potatoes were considered neutral in in '*A Priori* Diet Quality Score' and positive in 'Dutch Healthy Nutrient and Food Score'. Potatoes were part of the 'Dutch Healthy Nutrient and Food Score' score as in the Netherlands boiled potatoes are an important component of warm meals, especially in the elderly, furthermore potatoes have a relatively high nutrient density because they are a concentrated source of dietary fiber, vitamin C and potassium [34]. However, beneficial nutrients may be counteracted by preparation method [13] which may be relevant in US populations where a large proportion of the potatoes is consumed as chips or fries.

Alcohol was included in the '*A Priori* Diet Quality Score', but not in the 'Dutch Healthy Nutrient and Food Score' or the 'Dutch Undesirable Nutrient and Food Score', where we instead adjusted for alcohol consumption. Although alcohol is included in many dietary scores such as the Mediterranean Diet Score and the Alternate Healthy Eating Index-2010 we decided to exclude it from the dietary scores because various studies showed that the association of dietary scores with CVD and all-cause mortality were attenuated after removing the alcohol component [35, 36]. Furthermore, alternate exclusion of components of the Mediterranean Diet Score showed that alcohol contributed most to the inverse association between Mediterranean Diet Score and CVD and all-cause mortality [37, 38]. Because the inverse association of alcohol with CVD is well established [39] and we were interested a dietary pattern that predicted mortality regardless of alcohol consumption we decided to adjust for it in stead of including alcohol consumption as a component of the dietary pattern.

Finally, chocolate was rated neutral in the '*A Priori* Diet Quality Score' and part of the snack food group in the 'Dutch Undesirable Nutrient and Food Score'. However, evidence suggest that chocolate could be considered positive because of the beneficial cardiovascular effects of cocoa and chocolate [40] and the inverse association of chocolate with CVD [41]. However, the cocoa content of commercial available chocolate varies considerably and potential benefits may be diminished through the excess caloric intake [42] which shows the difficulty of rating chocolate.

In conclusion, depending on the study populations, the position of food groups in the dietary pattern, the outcomes studied, food groups may differ with regards to their *a priori* rating. Furthermore, as the body of evidence is growing with respect to the relation of food groups with health outcomes, the food groups included in dietary pattern scores may change.

Generally, all food groups in the dietary scores are scored proportionally according to quintiles or tertiles of intake. This raises the question whether each food group shows a similar linear relation with CVD or that different cut off points should be incorporated in a dietary score. It is also possible that associations of food groups with diseases are non-linear e.g. U-shaped. For example, the 'Alternate Healthy Eating Index' and 'Mediterranean Diet Score' include alcohol as one of the components but give most points for moderate alcohol consumption. In the '*A Priori* Diet Quality Score' higher intakes of beer, wine and liquor were rated positively with no upper limit, based partly on the rarity of heavy alcohol consumption in the studies which utilized the '*A Priori* Diet Quality Score'.

Furthermore, in each dietary score all components receive equal weight which assumes that each component contributes equally to the development of CVD. Several authors proposed the incorporation of weighing factors for diet quality indicators [2, 43]. Suggested weighing factors include relative risks or odd ratios for different food groups and health outcomes. In practice, this approach would likely result in different weighing factors for each health outcome studied. This would result in outcome specific dietary scores which is undesirable with respect to comparability of dietary patterns between studies.

In this thesis weighing factors were not applied in the dietary scores, however there were components that were correlated (e.g vegetables and fruit) with each other in each dietary score or that were included as several food groups (e.g. yellow vegetables, green vegetables and other vegetables in the '*A Priori* Diet Quality Score') and indirectly weighted more heavily. Furthermore, it has been shown that alternately excluding components from a score did not change the result [37, 38] suggesting the overall score is not driven by one of its single components.

Finally, food groups that are not included in the dietary score are weighted indirectly by the fact that generally the more of these neutral food groups are consumed the less of the rated food groups are consumed and vice versa.

## Dietary patterns in elderly

We observed an inverse association with the 'Dutch Healthy Nutrient and Food Score' in elderly men with cardiovascular-metabolic diseases but not in the healthy elderly men. Studying elderly represents a challenge for epidemiological studies. An important aspect of aging is the long-term exposure to many risk factors that

might influence health status later in life [44]. Furthermore it is likely that there are certain periods in life that the dietary patterns are important in relation to morbidity and mortality [45]. Particularly in the oldest old, simply getting sufficient energy intake is to be very important; however this is confounded with the general state of health, including the ability of the person to feed himself or herself.

Another aspect in elderly is the survivor bias, the healthy elderly men in the Zutphen study have survived a long range of exposures without events. Therefore, this selected group of elderly might have been less susceptible to external exposures. Furthermore, this may have resulted in a homogenous group of healthy participants and low levels of exposure which might be another explanation for the null finding in the elderly men.

Further research should examine the associations of dietary patterns with mortality outcomes to find out whether dietary patterns are relevant for health outcomes in the elderly.

## FURTHER RESEARCH ON THE DEFINITION OF DIETARY SCORES.

The evidence on the dietary patterns and health relationships is continuously growing, therefore it is recommended to update dietary scores according to the latest research with respect to food groups. With regards to the '*A Priori* Diet Quality Score' and the 'Dutch Healthy Nutrient and Food Score' this means that food groups might move from being negative to neutral or positive or vice versa.

The 'Dutch Healthy Nutrient and Food Score' specifically is based on the Dutch Guidelines for a Healthy diet 2006 [16] that was largely based on nutrient recommendations. Currently, a revision is undertaken that focuses on the association of basic food groups with chronic diseases. The (food-based) Food Choice Guidelines [17] will be updated as well and used for nutrition education in The Netherlands. When the Food Choice Guidelines are updated the 'Dutch Healthy Nutrient and Food Score' and 'Dutch Undesirable Nutrient and Food Score' should be updated and subsequently evaluated. Newly developed dietary scores should be evaluated regarding their validity [23]. Suggested evaluation strategies include examining the relationship of the dietary score with foods or nutrient intakes, validity and reliability [23, 46]. Ultimately, all dietary patterns and scores used in this thesis were evaluated by quantifying longitudinal associations with early stage markers of CVD and mortality. Additionally, because the 'Dutch Healthy Nutrient and Food Score' and 'Dutch Undesirable Nutrient and Food Score' were developed from the food-based dietary guidelines, associations of these scores with chronic diseases provide also information on the validity of these dietary guidelines.

## CONCLUSIONS AND IMPLICATIONS

Adherence to a healthy diet is inversely associated with early stage markers of CVD (markers of endothelial function and oxidative stress), CVD and all-cause mortality. Although many differences exist between methodologies and populations studied in this thesis, taking all evidence together several components are consistent among the different dietary patterns. Dietary pattern scores studied in this thesis are also in line with the results for other dietary scores.

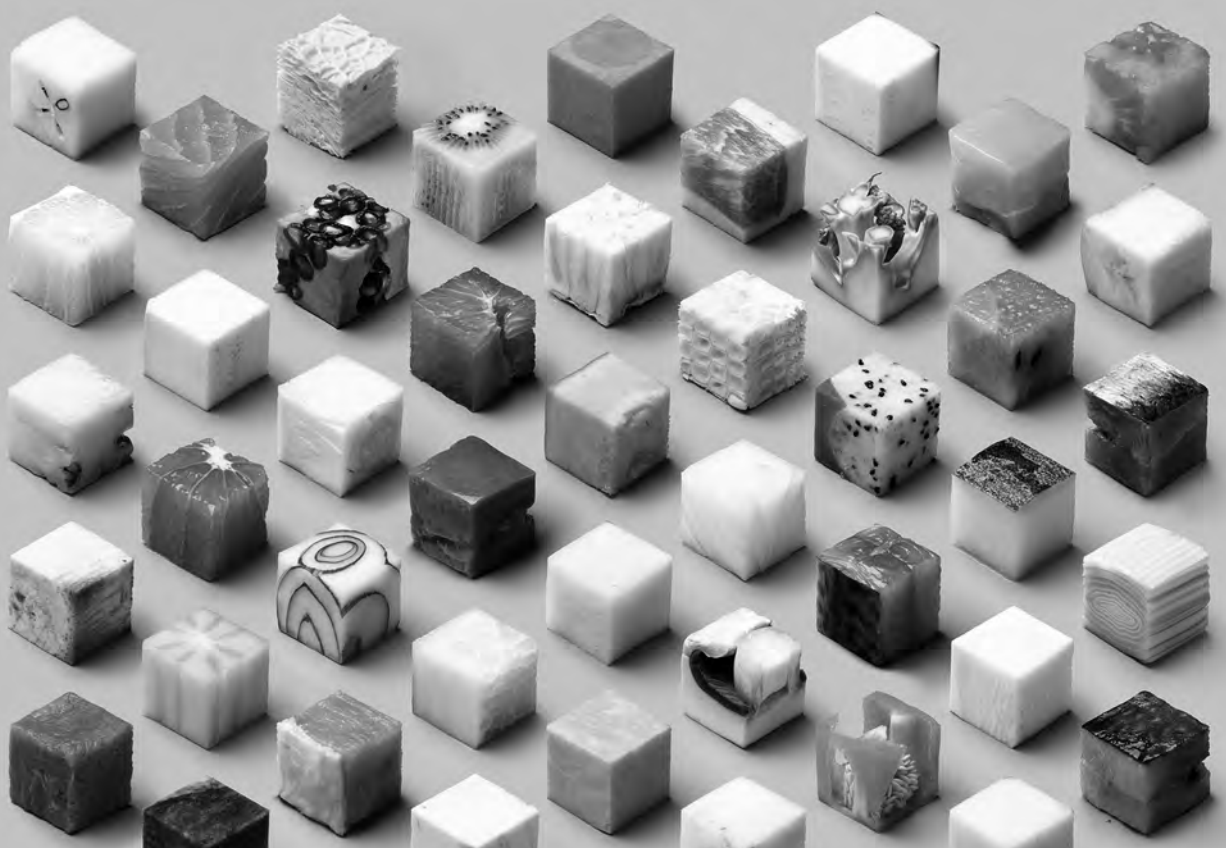
In summary a healthy diet consists of plenty of vegetables and fruit, whole grains, legumes, nuts and seeds, moderate intake of fish/poultry/lean meats, low fat dairy, and limited intake of processed meats, refined grains, sugar sweetened beverages, ready meals and snacks. However, this thesis also showed that a high-quality dietary pattern can be achieved in several different ways, and may vary in different populations. Finally, for nutrition education it is important that research on food-based dietary scores and chronic disease eventually will be translated into food-based dietary guidelines.

## REFERENCES


1. Kant AK. Indexes of overall diet quality: A review. J Am Diet Assoc. 1996;96:785-91.
2. Waijers PM, Feskens EJ, Ocke MC. A critical review of predefined diet quality scores. Br J Nutr. 2007;97:219-31.
3. Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. High diet quality is associated with a lower risk of cardiovascular disease and all-cause mortality in older men. J Nutr. 2014;144:673-80.
4. Harmon BE, Boushey CJ, Shvetsov YB, Ettienne R, Reedy J, Wilkens LR, et al. Associations of key diet-quality indexes with mortality in the Multiethnic Cohort: the Dietary Patterns Methods Project. Am J Clin Nutr. 2015;101:587-97.
5. Knoops KT, Groot de LC, Fidanza F, Alberti-Fidanza A, Kromhout D, van Staveren WA. Comparison of three different dietary scores in relation to 10-year mortality in elderly European subjects: the HALE project. Eur J Clin Nutr. 2006;60:746-55.
6. Lee MS, Huang YC, Su HH, Lee MZ, Wahlqvist ML. A simple food quality index predicts mortality in elderly Taiwanese. J Nutr Health Aging. 2011;15:815-21.
7. Liese AD, Krebs-Smith SM, Subar AF, George SM, Harmon BE, Neuhouser ML, et al. The Dietary Patterns Methods Project: synthesis of findings across cohorts and relevance to dietary guidance. J Nutr. 2015;145:393-402.
8. McNaughton SA, Bates CJ, Mishra GD. Diet quality is associated with all-cause mortality in adults aged 65 years and older. J Nutr. 2012;142:320-5.
9. Mursu J, Steffen LM, Meyer KA, Duprez D, Jacobs DR, Jr. Diet quality indexes and mortality in postmenopausal women: the Iowa Women's Health Study. Am J Clin Nutr. 2013;98:444-53.
10. Reedy J, Krebs-Smith SM, Miller PE, Liese AD, Kahle LL, Park Y, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. J Nutr. 2014;144:881-9.
11. Struijk EA, May AM, Wezenbeek NL, Fransen HP, Soedamah-Muthu SS, Geelen A, et al. Adherence to dietary guidelines and cardiovascular disease risk in the EPIC-NL cohort. Int J Cardiol. 2014;176:354-9.
12. Jacobs DR, Jr., Sluik D, Rokling-Andersen MH, Anderssen SA, Drevon CA. Association of 1-y changes in diet pattern with cardiovascular disease risk factors and adipokines: results from the 1-y randomized Oslo Diet and Exercise Study. Am J Clin Nutr. 2009;89:509-17.
13. Lockheart MS, Steffen LM, Rebnord HM, Fimreite RL, Ringstad J, Thelle DS, et al. Dietary patterns, food groups and myocardial infarction: a case-control study. Br J Nutr. 2007;98:380-7.
14. Nettleton JA, Schulze MB, Jiang R, Jenny NS, Burke GL, Jacobs DR, Jr. A priori-defined dietary patterns and markers of cardiovascular disease risk in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 2008;88:185-94.
15. McCullough ML, Feskanich D, Stampfer MJ, Giovannucci EL, Rimm EB, Hu FB, et al. Diet quality and major chronic disease risk in men and women: moving toward improved dietary guidance. Am J Clin Nutr. 2002;76:1261-71.
16. Health Council of the Netherlands. Guidelines for a Healthy Diet 2006. publication no. 2006/21. The Hague: Health Council of the Netherlands. 2006.
17. Netherlands Nutrition Centre. Guidelines Food Choice. Den Haag, 2011. http://www.voedingscentrum.nl/Assets/Uploads/Documents/Voedingsvoorlichters/Richtlijnen_voedselkeuze_2011.pdf. (4 June 2012).
18. Fulgoni VL, 3rd, Keast DR, Drewnowski A. Development and validation of the nutrient-rich foods index: a tool to measure nutritional quality of foods. J Nutr. 2009;139:1549-54.
19. Streppel MT, Sluik D, van Yperen JF, Geelen A, Hofman A, Franco OH, et al. Nutrient-rich foods, cardiovascular diseases and all-cause mortality: the Rotterdam study. Eur J Clin Nutr. 2014;68:741-7.
20. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr. 2014;17:1689-96.
21. Garcia-Arellano A, Ramallal R, Ruiz-Canela M, Salas-Salvado J, Corella D, Shivappa N, et al. Dietary Inflammatory Index and Incidence of Cardiovascular Disease in the PREDIMED Study. Nutrients. 2015;7:4124-38.

22. Newby PK, Tucker KL. Empirically Derived Eating Patterns Using Factor or Cluster Analysis: A Review. Nutr Rev. 2004;62:177-203.
23. Ocke MC. Evaluation of methodologies for assessing the overall diet: dietary quality scores and dietary pattern analysis. Proc Nutr Soc. 2013;72:191-9.
24. Fung TT, Willett WC, Stampfer MJ, Manson JE, Hu FB. Dietary patterns and the risk of coronary heart disease in women. Arch Intern Med. 2001;161:1857-62.
25. Hu FB, Rimm EB, Stampfer MJ, Ascherio A, Spiegelman D, Willett WC. Prospective study of major dietary patterns and risk of coronary heart disease in men. Am J Clin Nutr. 2000;72:912-21.
26. Kerver JM, Yang EJ, Bianchi L, Song WO. Dietary patterns associated with risk factors for cardiovascular disease in healthy US adults. Am J Clin Nutr. 2003;78:1103-10.
27. Osler M, Heitmann BL, Gerdes LU, Jorgensen LM, Schroll M. Dietary patterns and mortality in Danish men and women: a prospective observational study. Br J Nutr. 2001;85:219-25.
28. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 2002;13:3-9.
29. Kant AK. Dietary patterns and health outcomes. J Am Diet Assoc. 2004;104:615-35.
30. Nettleton JA, Steffen LM, Ni H, Liu K, Jacobs DR, Jr. Dietary patterns and risk of incident type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care. 2008;31:1777-82.
31. Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: a meta-analysis. Am J Clin Nutr. 2001;73:885-91.
32. Shin JY, Xun P, Nakamura Y, He K. Egg consumption in relation to risk of cardiovascular disease and diabetes: a systematic review and meta-analysis. Am J Clin Nutr. 2013;98:146-59.
33. Rong Y, Chen L, Zhu T, Song Y, Yu M, Shan Z, et al. Egg consumption and risk of coronary heart disease and stroke: dose-response meta-analysis of prospective cohort studies. BMJ. 2013;346:e8539.
34. King JC, Slavin JL. White potatoes, human health, and dietary guidance. Adv Nutr. 2013;4(3):393S-401S.
35. Li S, Chiuve SE, Flint A, Pai JK, Forman JP, Hu FB, et al. Better diet quality and decreased mortality among myocardial infarction survivors. JAMA Intern Med. 2013;173:1808-18.
36. Lopez-Garcia E, Rodriguez-Artalejo F, Li TY, Fung TT, Li S, Willett WC, et al. The Mediterranean-style dietary pattern and mortality among men and women with cardiovascular disease. Am J Clin Nutr. 2014;99:172-80.
37. Hoevenaar-Blom MP, Nooyens AC, Kromhout D, Spijkerman AM, Beulens JW, van der Schouw YT, et al. Mediterranean style diet and 12-year incidence of cardiovascular diseases: the EPIC-NL cohort study. PloS One. 2012;7:e45458.
38. Trichopoulou A, Bamia C, Trichopoulos D. Anatomy of health effects of Mediterranean diet: Greek EPIC prospective cohort study. BMJ. 2009;338:b2337.
39. Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ. 2011;342:d671.
40. Hooper L, Kay C, Abdelhamid A, Kroon PA, Cohn JS, Rimm EB, et al. Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. Am J Clin Nutr. 2012;95:740-51.
41. Buitrago-Lopez A, Sanderson J, Johnson L, Warnakula S, Wood A, Di Angelantonio E, et al. Chocolate consumption and cardiometabolic disorders: systematic review and meta-analysis. BMJ. 2011;343:d4488.
42. Latham LS, Hensen ZK, Minor DS. Chocolate--guilty pleasure or healthy supplement? J Clin Hypertens (Greenwich). 2014;16:101-6.
43. Kourlaba G, Panagiotakos DB. Dietary quality indices and human health: A review. Maturitas. 2009;62:1-8.
44. Brenner H, Arndt V. Epidemiology in aging research. Exp Gerontol. 2004;39:679-86.
45. Lasheras C, Fernandez S, Patterson AM. Mediterranean diet and age with respect to overall survival in institutionalized, nonsmoking elderly people. Am J Clin Nutr. 2000;71:987-92.
46. Guenther PM, Reedy J, Krebs-Smith SM, Reeve BB. Evaluation of the Healthy Eating Index-2005. J Am Diet Assoc. 2008;108:1854-64.

# English Summary



The long history of epidemiologic studies on diet and cardiovascular disease (CVD) has traditionally relied on analysis of specific nutrients or foods. Dietary patterns are multiple dietary components operationalized as a single exposure; they reflect the entire diet. In general, two methods are used to define dietary patterns: 1) theoretically, or *a priori*, defined dietary scores and 2) empirically, or *a posteriori*, derived dietary patterns. *A priori* dietary scores were developed to assess diet quality based on adherence to dietary patterns or recommendations. An example of an '*a posteriori*' approach is factor analysis (e.g. principal components analysis (PCA)). Factor analysis reduces data into patterns based upon intercorrelations between nutrients or foods. The aim of this thesis was to create, examine and compare several dietary patterns and indices and assess these in relation to both early stage markers of CVD (markers of endothelial function and oxidative stress) and to mortality from CVD and all-causes.

In **chapter 2** we described the creation of the *A Priori* Diet Quality Score, representing overall diet quality in the Coronary Artery Risk Development in Young Adults (CARDIA) study. The CARDIA study included 5115 black and white men and women, aged 18-30 at baseline (1985-86). Diet was assessed diet at baseline, year 7(1992-93) and 20 (2005-06) examinations. The A Priori Diet Quality Score summed 46 food groups rated by investigators as positive or negative on the basis of hypothesized health effects. In 2652 participants with 3 diet assessments, the mean (±SD) *A Priori* Diet Quality Score increased from 64.1± 13.0 at year 0 to 71.1 ± 12.6 at year 20, which was primarily attributable to increased age. However, the secular trend, which was estimated from differences of dietary quality scores across time at a fixed age (age matched time trend), decreased. The diet score was higher in whites than in blacks and in women than in men and increased with education, but demographic gaps in the score narrowed over 20 y. Consumption of positively rated food groups tended to increase and negatively rated food groups tended to decrease, and were similar in direction across demographic groups.

In **chapter 3** we used the '*A Priori* Diet Quality Score' and two dietary patterns derived using principal components analysis (PCA) the 'Fruit and Vegetables' dietary pattern and the 'Meat' dietary pattern in the CARDIA study. We studied prospective associations of the '*A Priori* Diet Quality Score', the 'Fruit and Vegetables' dietary pattern and the 'Meat' dietary pattern with cellular adhesion molecules (CAMs). The 'Fruit and Vegetables' dietary pattern was characterized by high intakes of fruit, vegetables, and whole grains and the 'Meat' dietary pattern by high intakes of red meat, refined grain, and butter. The '*A Priori* Diet Quality Score' was related to all CAMs. The 'Fruit and Vegetables' dietary pattern was related to

E-selectin and sICAM-1 but not to P-selectin and VCAM. The 'Meat' dietary pattern was related to all CAMs except VCAM. Strongest associations were for the 'Meat' dietary pattern with E-selectin (effect size 28% of an SD (+3.9/13.7 ng/mL)) and P-selectin (effect size 37% of an SD (+4.1/11.2 ng/mL)) and the 'A Priori Diet Quality Score' with sICAM-1 (effect size 34% of an SD (-15.1/44.7 ng/mL)) and VCAM (effect size of 26% of an SD (-45.1/170.3 ng/mL)).

**Chapter 4** described prospective associations of the *A Priori* Diet Quality Score, 'Fruit and Vegetables' dietary pattern and 'Meat' dietary pattern and a plasma biomarker of lipid peroxidation, $F_2$-isoprostanes also in the CARDIA study. We estimated associations between each dietary pattern and plasma $F_2$-isoprostanes cross-sectionally (at year 20, n=2736) and prospectively (year 0/7 average diet and year 15/20 average $F_2$-isoprostanes, n=2718). In the cross-sectional analysis, the *A Priori* Diet Quality Score and the 'Fruit and Vegetables' dietary pattern were inversely, and the 'Meat' dietary pattern was positively, associated with $F_2$-isoprostanes (all p values <0.001). These associations were also statistically significant in prospective analysis.

In **chapter 5** we described a food classification system derived from the Food-based Dietary Guidelines in the Netherlands that can be used to systematically and objectively classify foods in relation to their effects on health. Classification criteria for each food group were developed based on presumed positive, neutral or negative effects on chronic diseases of five nutrients: four that likely increase (saturated fatty acids, mono-*trans* unsaturated fatty acids, sodium, and added sugar) and one that likely decreases (dietary fiber) the risk of chronic diseases. This classification system also provided a framework to create food-based dietary scores for epidemiologic research on diet and chronic disease relationships.

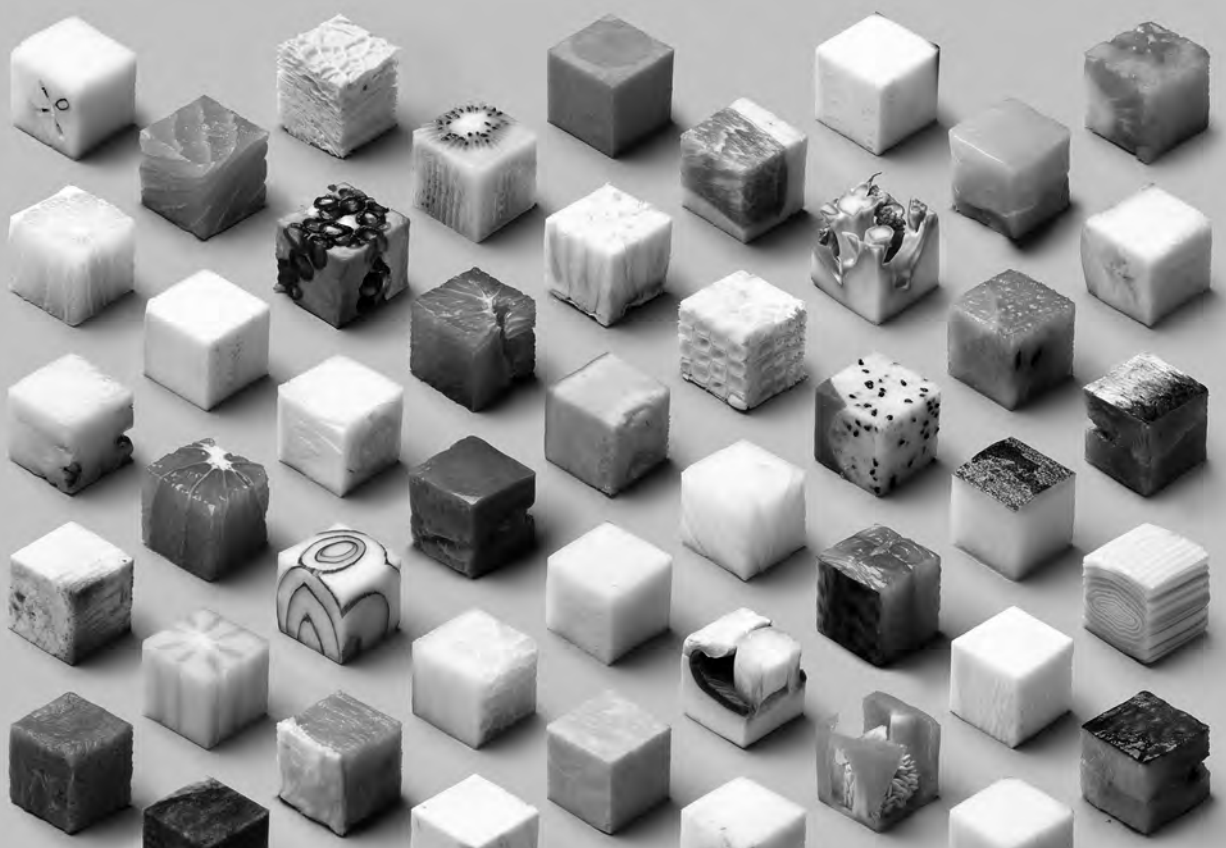
**Chapter 6** describes the creation of two dietary scores the 'Dutch Healthy Nutrient and Food Score' and the 'Dutch Undesirable Nutrient and Food Score' based on the food classification system described in chapter 5 in the Alpha Omega Trial. The Alpha Omega Trial is a randomized controlled trial; however the current analyses were done from an observational prospective cohort perspective (with adjustment for intervention groups). We included 4307 cardiac patients aged 60-80 years and monitored mortality for 10 years. Patients in the highest quintile of the 'Dutch Healthy Nutrient and Food Score' had 30% (HR 0.70; 95% CI 0.55-0.91) lower CVD and 32% (HR 0.68; 95%CI 0.47-0.99) lower all-cause mortality risk compared to patients in the first quintile. The 'Dutch Undesirable Nutrient and Food Score' was unrelated to both CVD and all-cause mortality.

In **Chapter 7** we also created a 'Dutch Healthy Nutrient and Food Score' and a 'Dutch Undesirable Nutrient and Food Score' in the Zutphen Elderly Study. We assessed the association of these scores with 25 year CVD and all-cause mortality and life-years gained. We divided the men (age 65-84 years) into those with (n=210) and without (n=616) cardiovascular-metabolic diseases at baseline in 1985. During a median follow-up of 10.6 years (IQR 5.8-15.9) 806 participants died, of whom 359 from CVD. Diet scores did not predict death in all men. Among men with cardiovascular-metabolic diseases, 'Dutch Healthy Nutrient and Food Score' was associated with lower CVD (HR: 0.57; 95%CI: 0.35-0.93) and all-cause mortality risk (HR: 0.64; 95% CI: 0.44-0.94) comparing highest vs. lowest tertiles of the score. Men with cardiovascular-metabolic diseases in the highest vs. lowest tertile of the 'Dutch Healthy Nutrient and Food Score' lived 2.5 year longer. The 'Dutch Healthy Nutrient and Food Score' was not associated with CVD and all-cause mortality in men without cardiovascular-metabolic diseases. The 'Dutch Undesirable Nutrient and Food Score' was not associated with any of the outcomes.

In **Chapter 8** we summarized the main findings of this thesis and reflected on some methodological considerations. First, we discussed the different approaches to derive dietary scores and patterns and the advantages and disadvantages of these methods. Second, we reflected on important aspects for creating *a priori* dietary scores and on further research. Finally, the general conclusions and implications were presented.

From the results presented in this thesis we conclude that adherence to a healthy diet is inversely associated with early stage markers of CVD (markers of endothelial function and oxidative stress), CVD and all-cause mortality. In summary, a healthy diet consists of plenty of vegetables and fruit, legumes, whole grains, nuts and seeds, moderate intake of fish/poultry/lean meats and low fat dairy, and limited intake of processed meats, refined grains, sugar sweetened beverages, ready meals and snacks. However, this thesis also showed that a high quality dietary pattern can be achieved in several different ways, and may differ among populations.

# Dankwoord | Acknowledgments



## DANKWOORD | ACKNOWLEDGMENTS

Yes!! Mijn proefschrift is af! Dit heb ik zeker niet alleen voor elkaar gekregen, graag wil ik iedereen bedanken die heeft bijgedragen aan dit proefschrift.

First my supervisors! **David and Daan**, thank you for your trust in me and giving me the opportunity to start with my PhD. **David,** who would have thought that an internship in Minneapolis would lead to 6 years of close collaboration! You mentored me throughout the years both scientifically and personally. It was always a pleasure to work with you in Minneapolis, during your visits in Wageningen, but also through email and skype. Thank you for your patience with me, I hope that we'll stay in touch and keep exchanging ideas. Beste **Daan**, wat geweldig dat ik het project waar ik in Minneapolis mee begonnen was kon voortzetten in Wageningen! Ik heb ontzettend veel geleerd van onze besprekingen die je altijd goed voorbereid had (tot in de details!) mét uitgeprinte versie van het te bespreken document met aantekeningen (waaruit je soms zelf ook niet meer helemaal wijs kon worden). Je eindeloze interesse én enthousiasme met betrekking tot de resultaten hebben me vaak opgepept op het moment dat ik zelf wat minder energie had! Daarnaast natuurlijk ook mijn co-promotor, **Sabita** bedankt voor je begeleiding en input, maar vooral je persoonlijke betrokkenheid. Het was fijn dat je aan me kon zien hoe het met me ging en dat ik altijd even bij je langs kon komen voor hulp, ideeën, advies of om gewoon even gezellig bij te kletsen.

Ook wil ik de leden van de promotiecommissie **Pieter van 't Veer**, **Marjolein Visser**, **Piet van den Brandt** en **Jolein Iestra** voor het lezen en beoordelen van het manuscript en het deelnemen aan de oppositie op 5 november.

**Simone** en **James** ik ben ontzettend blij dat jullie mijn paranimfen willen zijn! Lieve **Simone** wat fijn om al zo lang (27 jaar!) vriendinnen te zijn. Leven op verschillende continenten is eerder een kans voor een leuk tripje dan een obstakel voor onze vriendschap! De flexibiliteit van beiden in het onderzoek werkzaam zijn is daarbij ook een erg handige bijkomstigheid. **James,** kamer 116-roomie! Bedankt voor je gezelligheid, het meedenken over kromme Engelse zinnen en in welk thema we ons kantoor moeten versieren, het mede in elkaar knutselen van afkruiskalenders en ideale koffie houders, het organiseren van kamer 116 uitjes, bbq's en borrels! Het was tof om 4,5 jaar 4 dagen per week naast je te zitten en promotie stress maar vooral ook veel plezier met je te delen!

Kamer 116 heeft veel bewoners gehad gedurende mijn promotie naast de 'harde kern' **Eveline, Lieke, Susanne** en **James** waren er ook 'niet zo tijdelijke bewoners'

**Harrie en Jaike** 'tijdelijke bewoners' **Sabine, Danielle, Fabian, Niels, Inge, Marleen, Sifra, Rianne, Lisette en Lisa** en nog 2 'recente bewoners' **Elly en Claudia.** Ik kijk terug op een fantastische tijd met jullie allemaal!
Lieve **Eveline** bedankt voor al je gezelligheid, leuke gesprekken over van alles en nog wat en geweldige SAS tips en trucs! **Lieke** het is altijd een mooi begin van de week als we gezamenlijk onze weekenden 'even' doornemen! Heel leuk om nu samen ook nog met dezelfde data te ploeteren! **Susanne** ik heb altijd super veel plezier met je gehad op het werk en op congres (en vakantie!). Heel leuk om ook nog even aan een gezamenlijk project te werken (ook al staat het inmiddels al weer op een laag pitje)! **Jaike,** gezellig dat je zo lang bij ons op de kamer bleef hangen, we hebben veel hilarische momenten gehad waar ik met veel plezier op terug kijk!
**Sabine,** bedankt voor je werk aan de Zutphen studie, het was leuk je te begeleiden. Gezellig dat je na je afstuderen nog een projectje kwam doen op kamer 116! **Danielle,** je zat maar kort bij ons op de kamer voor je naar Brisbane vertrok, leuk om toch nog steeds contact te hebben en ik voel me vereerd dat je naar mijn promotie komt! **Fabian, Niels, Inge en Marleen** 'minions ;-)' bedankt voor het dubbel invoeren van de FFQ data maar ook voor de gezellige drukte in kamer 116, alle plekken bezet!!

Andere mensen van de afdeling Humane Voeding, **Marianne** bedankt voor je interesse in mijn project en hoe het met mij ging. **Janette** bedankt voor alle 'hoe kan ik mijn promotie regelen' tips! **Adrienne** fijn dat je meedacht over hoe het verder moest toen ik ziek was. Mede **PhD-ers** het was leuk om tijdens de PhD-tour, lunches en events jullie beter te leren kennen! **Els** bedankt voor je hulp met de Alpha Omega FFQ! **Corine,** hoewel we al een poos niet meer carpoolen, vind ik het toch altijd erg leuk om weer even met je bij te kletsen!

**Katie, Na and Jaakko** working in WBOB wouldn't have been the same without you! **Katie** thank you so much for your help and support. **Jaakko and Na** thank you for essential lunch and coffee breaks, it was fun to hang out with you at work and even more outside work!

Lieve vrienden en vriendinnen **Simone, José, Bram, Gert & Manon, Harrie, Ingrid, Paulette.** Bedankt voor alle gezelligheid de afgelopen jaren. **José** wat hebben we veel beleefd de afgelopen jaren, geweldige vakanties, vele borrels, sauna's en verhuizingen (nou ja dat laatste jij vooral dan), fijn dat we zulke goede vriendinnen zijn. **Brammie!** We hebben verschillende ups en downs gedeeld de afgelopen 13 jaar! Ik ben blij met zo'n goede vriend als jij! **Mr G.** en **Manon** (en Tijn) bedankt voor alle 'duffe' avondjes met slechte tv-programma's en heerlijke drop! Het is altijd fijn om met jullie bij te kletsen en lekker te ontspannen. **Harrie** sja...waar zal ik

beginnen.. bedankt voor je vrolijke chaos, je voor velen onbegrijpelijke humor, je eindeloze uiteenzettingen over fietsen en of wifi nou internet is of niet (snurk)! We hebben een unieke vriendschap, bedankt daarvoor! **Ingrid** ik ben blij dat we tegelijk aan het afstuderen waren, het werd gelijk een stuk leuker! Ik heb de afgelopen jaren graag gebruik gemaakt van je geweldige kookkunsten en je inzichten in het daten met een techneut (of misschien meer aanmoedigingen ;-)). **Paulette** jaren samen op en neer naar Wageningen reizen heeft geleid tot een geweldige vriendschap! Jammer dat we niet meer samen kunnen rennen, hopelijk kunnen we de Koolhydraten toch weer een keer nieuw leven inblazen!
Dear **Liz and Angie (& Brooks)** you were the best roommates I could've wished for! Thanks for all the good times in Minneapolis. **Jack and Sayem** thank you for your friendship, I enjoyed hanging out with you! I miss you and I hope we can catch up in real life sometime again!

Dan zijn er nog een aantal mensen die ik niet vaak genoeg zie, maar als we elkaar zien is het weer als vanouds, **Hil-May, Suzanne, Hanneke, Eline & Frank, Daantje en Daan** bedankt voor jullie gezelligheid bij feestjes, borrels en sinterklaasavonden! **Lizzy** so much fun to meet up in so many different places in the world, I wonder where we'll meet up next!

**Karel en Marlies, Mariken en Paul** ondanks dat jullie eigenlijk pas in de laatste fase van mijn promotie erbij kwamen, heb ik me erg gesteund gevoeld door jullie. Bedankt voor jullie interesse in mijn onderzoek en het meedenken over stellingen, maar vooral voor de ontspannende, vakantie-achtige (en vooral ook lekkere!) weekenden in Zeeuws Vlaanderen.

Lieve broers, (schoon) zus(sen), zwager, nichten en neefjes wat ben ik blij met jullie allemaal! **André** (Anniepannie) **en Antine** jullie hebben me misschien wel het meest van allemaal gesteund, lieve broer hoe bitterzoet het ook is het is fijn om een 'medekneus' in de familie te hebben die meer ervaring heeft met ziek zijn en die snapt hoe ontzettend irritant het kan zijn! **Antine** super leuk dat we samen al aan zoveel hardloop wedstrijdjes meegedaan hebben, ideale ontspanning en gezelligheid, het is wel weer tijd voor een pak wasmiddel ;-)! **Marijke en Johan** hoewel ik de drukte van jullie gezin niet altijd even goed aan kon heb ik altijd genoten van de gezellige chaos bij jullie thuis! Bedankt voor jullie meeleven en steun. Lieve **Marijke**, je bent de beste zus die ik me maar kan wensen! **Bart en Jenny** ik heb me ook door jullie 'buutegeweun' gesteund gevoeld!
**Lieke en Rinske, Gert-Jan, Rianne, Sytske en Thomas, Huib en Meike,** bedankt voor alle knuffels en gezelligheid, jullie zijn de leukste en liefste neefjes en nichtjes!

M'n lieve **Allard** ik ben zo ontzettend blij met jou!! Bedankt voor je onvoorwaardelijke steun, je nuchtere blik en je zorgzaamheid als het weer even wat minder ging. De afgelopen anderhalf jaar waren geweldig en ik hoop dat er nog veel meer geweldige jaren bij zullen komen!

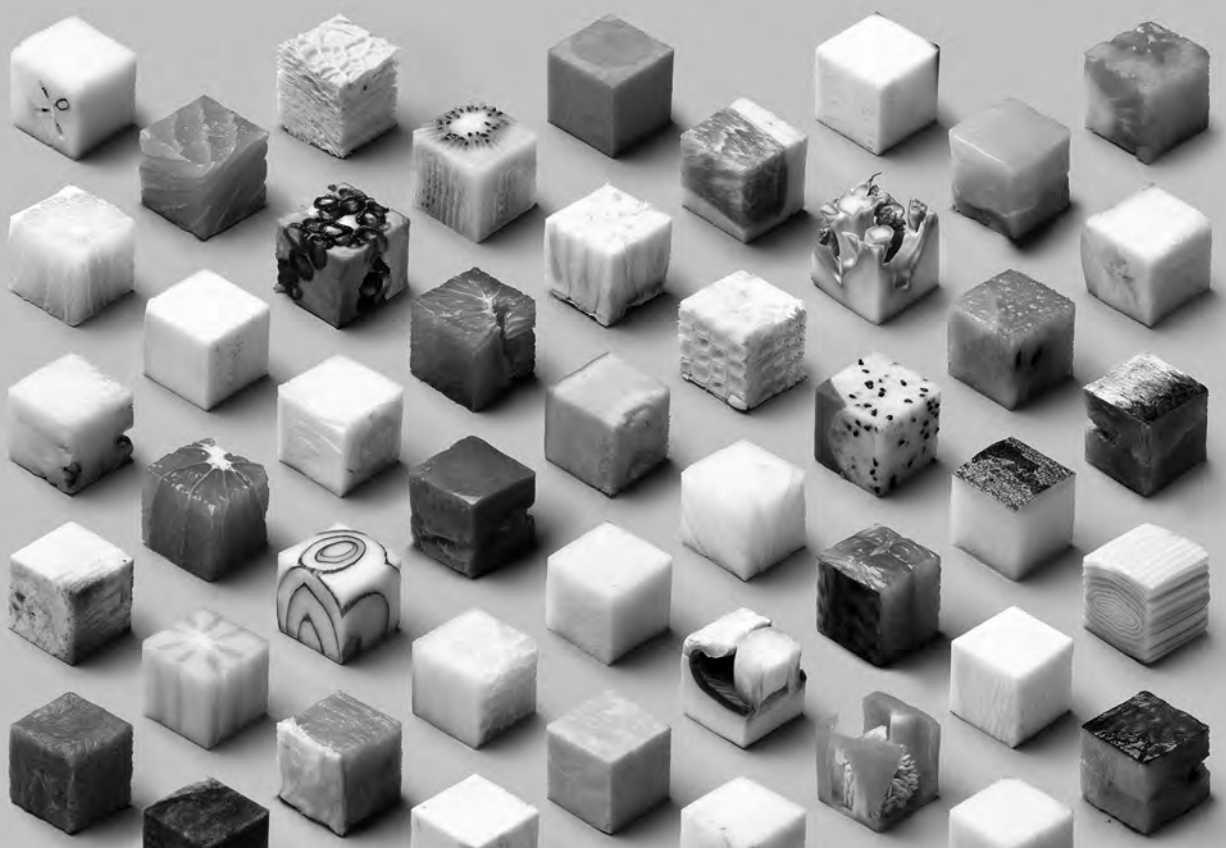
Ik prijs me gelukkig met de allerliefste **papa en mama!** Zonder jullie was ik niet zover gekomen. Bedankt voor jullie steun en interesse in waar ik mee bezig ben! Het was zo ontzettend fijn dat jullie anderhalf jaar lang dag in dag uit met de computer aan geleefd hebben zodat ik ondanks het tijdverschil op ieder moment even jullie gezichten kon zien en kon bijkletsen of uithuilen. Het is heerlijk om weer even thuis te komen in Heerde, waar ik dan verwend word met lekker eten, even helemaal niets meer hoef te doen, echt kan ontspannen en kan genieten van de gezelligheid.

Bedankt allemaal!!

Femke

## About the author

Curriculum Vitae
List of publications
Overview of completed training activities



## CURRICULUM VITAE

Femke Sijtsma was born on April 30, 1984 in Heerde, the Netherlands. After graduating with a VWO degree (university preparatory education) from CC de Noordgouw in 2002, she started her BSc study in Nutrition and Dietetics at the Hogeschool van Arnhem en Nijmegen. She obtained her degree in 2007 and decided to continue her education in Nutrition and Health at Wageningen University. In 2009 Femke completed her MSc thesis entitled: 'Fish and EPA+DHA intake in relation to mental well-being in Dutch coronary heart patients'. After that she did an internship at the Division of Epidemiology and Community Health of the University of Minnesota in Minneapolis where she performed epidemiological research on dietary patterns and biomarkers of cardiovascular diseases. After graduating, Femke started working as a PhD student in Minneapolis for a year, which she continued in 2011 at the Division of Human Nutrition of Wageningen University. During her PhD she attended several conferences and courses within the education program of the VLAG graduate school. Currently, Femke is appointed as a postdoctoral researcher at the Division of Human Nutrition, Wageningen University working on a project about sugar sweetened beverages.

# LIST OF PUBLICATIONS

**FPC Sijtsma**, SS Soedamah-Muthu, S de Hoon, DR Jacobs Jr, D Kromhout. Healthy eating and survival among elderly men with and without cardio-metabolic diseases. Nutr Metab Cardiovasc Dis, In press, DOI:10.1016/j.numecd.2015.08.008

**FPC Sijtsma**, SS Soedamah-Muthu, J de Goede, LM Oude Griep, JM Geleijnse, EJ Giltay, MJ de Boer, DR Jacobs Jr, D Kromhout,. Healthy eating and lower mortality risk in a large cohort of cardiac patients who received state-of-the-art drug-treatment. Accepted for publication in Am J Clin Nutr, In press

**FPC Sijtsma**, SS Soedamah-Muthu, A Werkman, A Postma-Smeets, D Wolvers, DR Jacobs Jr, D Kromhout. Classification of foods based on dietary guidelines for nutrition education and food-based dietary scores, an example from the Netherlands. Submitted

**Sijtsma FP**, Meyer KA, Steffen LM, Van Horn L, Shikany JM, Odegaard AO, et al. Diet quality and markers of endothelial function: the CARDIA study. Nutr Metab Cardiovasc Dis. 2014;24(6):632-8

Meyer KA, **Sijtsma FP**, Nettleton JA, Steffen LM, Van Horn L, Shikany JM, et al. Dietary patterns are associated with plasma F(2)-isoprostanes in an observational cohort study of adults. Free Radic Biol Med. 2013;57:201-9

Gaffo AL, Jacobs DR, Jr., **Sijtsma F**, Lewis CE, Mikuls TR, Saag KG. Serum urate association with hypertension in young adults: analysis from the Coronary Artery Risk Development in Young Adults cohort. Ann Rheum Dis. 2013;72(8):1321-7

**Sijtsma FP**, Meyer KA, Steffen LM, Shikany JM, Van Horn L, Harnack L, et al. Longitudinal trends in diet and effects of sex, race, and education on dietary quality score change: the Coronary Artery Risk Development in Young Adults study. Am J Clin Nutr. 2012;95(3):580-6

van de Rest O, de Goede J, **Sytsma F**, Oude Griep LM, Geleijnse JM, Kromhout D, et al. Association of n-3 long-chain PUFA and fish intake with depressive symptoms and low dispositional optimism in older subjects with a history of myocardial infarction. Br J Nutr. 2010;103(9):1381-7

Widome R, Jacobs DR, Jr., Hozawa A, **Sijtsma F**, Gross M, Schreiner PJ, et al. Passive smoke exposure and circulating carotenoids in the CARDIA study. AnnNutrMetab. 2010;56(2):113-8

## Published Abstracts

**Femke PC Sijtsma**, Andrea Werkman, Sabita S Soedamah-Muthu, Boudewijn C Breedveld, David R Jacobs, Daan Kromhout. Classification of Foods - An Example from the Netherlands. Circulation. 2013; 127: AP106

**Femke PC Sijtsma**, Katie A Meyer, Jennifer A Nettleton, Lyn M Steffen, Linda Van Horn, James M Shikany, Paul Holvoet, Myron D Gross, Daan Kromhout, David R Jacobs. Higher Diet quality is Prospectively Associated with Markers of Endothelial Dysfunction: The Coronary Artery Risk Development in Young Adults Study. Circulation 125 (10 Supplement), AP369

# OVERVIEW OF COMPLETED TRAINING ACTIVITIES

## Discipline specific activities

- Master Class, Longitudinal data analysis (Mixed Models), Graduate school VLAG, Wageningen, The Netherlands, 2014
- Master Class, Confounding in epidemiological research, Graduate school VLAG, Wageningen, The Netherlands, 2014
- Annual meeting of the Netherlands Epidemiology Society (WEON), Vereniging voor Epidemiologie, Utrecht, The Netherlands, 2013
- Conference on Cardiovascular Disease Epidemiology and Prevention/Nutrition, Physical Activity and Metabolism, American Heart Association, New Orleans, USA, 2013
- Annual meeting of NWO Nutrition, Nationale Academie van Voedingswetenschappen, Deurne, The Netherlands, 2012
- Conference on Cardiovascular Disease Epidemiology and Prevention/Nutrition, Physical Activity and Metabolism, American Heart Association, San Diego, USA, 2012
- 43rd Ten Day International teaching seminar on Cardiovascular disease Epidemiology and Prevention, World Heart Foundation, Saint George, Grenada, 2011
- Nutritional and Lifestyle Epidemiology, Graduate school VLAG, Wageningen, The Netherlands, 2011
- Vascular Biology (PhD- training course, ), Dutch Heart Foundation, Arnhem, The Netherlands, 2011
- Principles of Research in Medicine and Epidemiology, Netherlands Institute for Health Sciences (NIHES), Rotterdam, The Netherlands, 2011
- Introduction to Data Analysis, Netherlands Institute for Health Sciences (NIHES), Rotterdam, The Netherlands, 2011
- Regression Analysis, Netherlands Institute for Health Sciences (NIHES), Rotterdam, The Netherlands, 2011
- Survival Analysis, Netherlands Institute for Health Sciences (NIHES), Rotterdam, The Netherlands, 2011

## General Courses

- Philosophy and Ethics of Food Science and Technology, Wageningen Graduate Schools, Wageningen, The Netherlands, 2014
- Scientific Writing, Language Services of Wageningen University and Research Centre, Wageningen, The Netherlands, 2013
- Career Perspectives, Wageningen Graduate Schools, Wageningen, THE NETHERLANDS, 2013
- Techniques for Writing and Presenting a Scientific Paper, Wageningen Graduate Schools, Wageningen, The Netherlands, 2012

## Optionals

- Epi-research meetings/methodology club, Division of Human Nutrition, Wageningen, The Netherlands, 2011-2015
- PhD tour, Division of Human Nutrition, Melbourne/Sydney, Australia, 2013
- Concepts and methods in Epidemiology, Division of Human Nutrition, Wageningen, The Netherlands, 2011-2013
- EpiCH Division Seminar, Division of Epidemiology & Community Health, Minneapolis, USA, 2010-2011
- Preparation PhD research proposal, Wageningen, The Netherlands, 2010

The research described in this thesis was financially supported by Royal Netherlands Academy of Arts and Sciences.

Financial support from Wageningen University for printing this thesis is gratefully acknowledged.

**Cover art**: Lernert & Sander
**Cover design**: Promotie In Zicht, Arnhem
**Layout design**: Promotie In Zicht, Arnhem
**Printed by**: Ipskamp Drukkers, Nijmegen