Healthy aging through a healthy diet

Never too old to eat healthy?!

Nicole Jankovic

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Thesis

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Für meine Familie,
insbesondere für die,
die schon früher gehen mussten.

Studying the elderly

"Think of it this way.

You woke up this morning to what is effectively a 29-hour day. Twenty-four of those hours, you will use now; the other five will be put by for later. The challenge posed by population ageing translates into ensuring that these extra hours will be as good as possible, free from high-cost dependency, when in time we come to use them."

Thomas B. L. Kirkwood

Abstract

Background: The world's population is aging and with it the prevalence of chronic diseases, especially cardiovascular diseases and cancer, increases. A long lasting life is envisaged without the burden of disease. Therefore, current research focuses on risk factors, such as a healthy diet, which may decrease the occurrence of chronic diseases even at advanced age. Earlier studies, examining the role of a healthy diet in the elderly, applied different analysis strategies. In consequence, comparability across studies is limited and prevent an overall conclusion on the role of a healthy diet in elderly.

Methods and subjects: Eleven prospective cohort studies among elderly people (N = 396,391) from Europe and the United States, collaborating in the CHANCES consortium, were analysed. Most cohorts eligible for our analysis, assessed diet once at baseline. Therefore, we first assessed the stability of dietary patterns, derived with reduced rank regression (RRR), in the Zutphen Elderly Study. In the remainder of this thesis, healthy diets were defined based on the 2003 World Health Organization (WHO) "nutrient intake goals" and the 2007 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) food group recommendations. The recommendations were operationalized, using the Healthy Diet Indicator (HDI) and the WCRF/AICR diet score. The association between a healthy diet and risk of all-cause mortality and CVD mortality, was studied using the WHO recommendations, which aim at the prevention of chronic diseases in general. The cancer specific WCRF/AICR recommendations were applied to study the association between a healthy diet and cancer risk. Diet disease associations were assessed in each cohort separately, using Cox-proportional hazards regression. Cohort specific hazard ratios (HR) were pooled by random effects meta-analysis.

Results: The results of the Zutphen Elderly Study showed that dietary patterns, derived by RRR, remained stable over a period of five years. In the CHANCES project a total of 84,978 person years were accumulated, during a median follow-up time ranging between 7 and 15 years across cohorts. An increase of 10 HDI points (range total score 0 to 70 points) was significantly associated with a decreased risk of all-cause mortality (HR: 0.90 and 95% confidence interval (CI): 0.87-0.93). The HR estimate was equivalent to a two year increase in life expectancy. We found a significant inverse association between an increase of 10 HDI points and CVD mortality for Southern European countries and the US (HR: 0.85, 95 % CI: 0.83-0.87), whereas no significant association was found for Northern and Central and Eastern Europe. An increase of 1 point for the WCRF/AICR diet score (range 0-4) was associated with a significantly 6% decreased risk in developing any type of

cancer. Greatest risk reduction was found between a 1 point increase in WCRF/AICR diet score and colorectal cancer (HR: 0.84, 95% CI:0.80-0.89).

Conclusion: Dietary indices based on globally defined dietary recommendations by WHO and WCRF/AICR were found to be associated with all-cause and CVD mortality and cancer risk in old age. Public health interventions targeted on the elderly should not focus on one definition of a "healthy diet" but rather a smart combination of available evidence, to optimally account for CVD as well as cancer specific outcomes.

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Chapter 1

General Introduction

Introduction

The recognition of diet and its importance for health is probably as old as the human race. The first written records on the relationship between diet and human diseases date back to Hippocrates. Throughout the human history dietary exposure changed and so did disease profiles. In the early 20th century nutrient deficiencies caused diseases such as pellagra, beriberi and goitre.[3, 4] After World War II, excess supply of foods in high income countries diminished the number of nutrient deficiencies and increased the number of chronic diseases.[5-11] The most dominant chronic conditions, with greatest public health impact in the western hemisphere, are cardiovascular diseases (CVD) and cancer.[12]

Another observation is the increase in life expectancy, resulting from societal efforts such as; better living standards, access to nutritious diets and medical support[13]. Estimates for life expectancy in the year 2000, for someone aged 60 years in Europe and the US, were about 20 years[14] and forecasts expect the number in life years to increase even more in the future[15, 16]. Approximately 77% of the total life expectancy can be lived disease free. This means, the onset of chronic diseases starts approximately at the age of 62.[17]

Extended life expectancy will lead to longer periods of suffering from chronic diseases in the elderly. The challenge is to increase the number of life years lived in good health. Whether a healthy diet followed at advanced age is associated with an increase in life expectancy and a decrease in chronic diseases, has not yet entirely been answered. Improving the knowledge, on the role of diet later in life, is crucial in developing strategies which enable older people to enjoy the gain in extra life years and continue to make active contributions to society.

Successful aging and diet

The three pillars of successful aging are defined as a low risk of disease and disease related disability, high mental as well as physical function and the active engagement with life.[18] Nutrition represents a major determinant for successful aging,[19] a fact which has been reinforced by numerous publications.[15, 20-23] However, most evidence is derived from the middle-aged population.[24] Therefore, previous health campaigns mainly targeted this specific age group.[25-27]

Previous review papers specifically focussing on the elderly, suggest that healthy diets increase longevity and prevent chronic diseases.[15, 20, 24, 25, 28-33] However, differences in analysis strategies across cohorts limit comparability and prevent an overall conclusion on the association between a healthy diet and the prevention of

chronic diseases later in life.[21, 32, 34] The requirements to fill this knowledge gap are twofold. First, single high quality longitudinal cohort studies need to be analysed in a comparable way. Second, these results need to be summarized by means of meta-analysis. Within the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES), access to individual participant data (IPD) was provided, which allowed for a so called "two stage IPD meta-analysis".[35]

Challenges in aging research

Old age represents a challenge for epidemiological studies. An important aspect of aging is the long term exposure to a variety of risk factors. All of them might, in theory, have an influence on the health status later in life. Therefore, controlling for confounding (e.g. smoking: never, former current) is crucial,[6] especially in old age.

Furthermore, the group of older people could be defined as "successful survivors", as such; risk factors known to be predictive in younger age groups, might lose their importance in the elderly to a certain extent.[36]

CHANCES cohort data revisited

CHANCES is a collaborative, large-scale, integrating project funded by the European Commission, within the Seventh Framework Programme (http://www.chancesfp7.eu/). It consists of 16 partners from Europe and the United States. All collaborators provide prospective cohort data from elderly, aged 60 years and above. This definition of elderly was set a priori by the CHANCES consortium. The aim of CHANCES was to generate high-quality, scientific evidence on risk factors for chronic diseases in the elderly.

Data from the cohorts of the CHANCES project were used to assess the association between a healthy diet (measured by globally applicable dietary pattern scores) and all-cause mortality, CVD mortality and cancer risk. The focus on CVD and cancer was chosen, due to the importance of preventing these diseases. Both conditions represent leading causes of mortality (30% of deaths attributable to CVD[37] and about 25% to cancer[38] of which colorectal cancer is the third leading cause of cancer death)[39] and a threat to healthy life years.[40] All variables used for the data analysis were harmonized according to pre-defined rules (Box 1.1).

Dietary pattern analysis

Studying a whole diet, instead of single foods or nutrients, is called dietary pattern analysis. The advantage of dietary patterns is the integration of complex, interactive effects of more than one dietary exposure.[41] Humans do not consume single foods

or nutrients but rather complete diets.[42] Therefore, dietary patterns reflect real-life circumstances more efficiently in comparison to single foods and nutrients. Two main approaches of dietary pattern analysis can be distinguished: the a-posteriori and a-priori methods.

1

Box 1.1 Data assessment and harmonization in CHANCES

The data in the CHANCES project have been collected within the framework of independent cohorts, with different protocols for data collection and distinct original research foci. Therefore, data standardization and harmonization was a major priority task of the consortium.

Standardization and harmonization procedures were largely based on the experience from the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) project.[1] Harmonization of dietary variables was carried out using the experience from the HECTOR (Healthy Eating Out) study[2] and other studies on nutrition and health. Data assessment procedures included examination of: availability and comparability of data from each cohort; questionnaires and measurement procedures used (e.g. dietary assessment methods, nutrient databases) in the individual cohorts; indicators of the quality of the existing data (e.g. validation studies for dietary intake data). The harmonization procedure is an on-going process which mainly includes the definitions of new harmonized variables for the data analyses to be carried out in CHANCES.

For the harmonization of food groups, a CHANCES specific food classification tree trunk was applied using the experience from EPIC as an example. All cohorts with dietary data were asked to provide additional information on foods, that were contributing to a specific food group. Where necessary, cohorts were asked to re-group foods into another food group category to ascertain a high level of comparability across studies.

The calculation of nutrients was based on food groups, assessed from different questionnaires and cohort specific food composition tables (e.g. EURONUT for SENECA, McCance and Widdowson's for HAPIEE) were applied.

Furthermore, availability and the characteristics of the data on each research area of CHANCES (e.g. CVD, cancer, all-cause mortality, diet) were assessed for all cohort. Joint variables were defined based on the results of the assessment and research interests. A wiki site was used for collecting relevant information from the centres and documenting the cohort descriptions, availability and assessment of the data, the CHANCES variable definitions and the rules for deriving the common (harmonized) variables from the local data sets. The wiki site, where all CHANCES investigators from the different centres had writing access, has been a powerful tool for drafting, commenting, and finalizing the various documents. The wiki website summarize a total number of about 325 variables for use in research projects of which 38 of these variables relate to nutrition. A publication on "Data harmonization and pooled analytical approaches for large-scale research on epidemiology of ageing: The CHANCES (Consortium on Health and Ageing: Network of Cohorts in Europe and the United States) project" is under preparation and expected to be available in 2015.

A-posteriori or data based dietary patterns

The definition of healthy diets requires knowledge on foods and nutrients that prevent the occurrence of chronic diseases. Such information can, for example, be derived with a-posteriori dietary patterns. One such method is called Reduced Rank Regression (RRR).[43] The difference between RRR and other a-posteriori analysis methods, such as Principal Component Analysis (PCA) or factor analysis, relates to the incorporation of biological risk factors, which increases the probability of finding meaningful dietary patterns for the disease under study.[41, 44-46] The applicability of RRR, for an exclusively elderly population, in multiple cohorts,[47, 48] is not well understood. Therefore, RRR was first applied for a descriptive analysis to assess its strengths and weaknesses.

After the inventory of CHANCES cohorts, with sufficient dietary data (supplement 1.1), it was evident that most cohorts had baseline and no repeated measurements of dietary intake available. The lack of repeated measures of dietary intake could be a potential source for misclassification of the exposure. Hence, diet-disease associations would be biased. Therefore, the stability of RRR derived dietary patterns in one CHANCES cohort with available repeated measurements was assessed first. Advantages and disadvantages of RRR will be elaborated on in detail in chapter 2.

A-priori or knowledge based dietary pattern

A-priori dietary patterns can be defined based on observations of a healthy diet found in specific regions, such as the Mediterranean diet,[30] or in the context of a Randomized Controlled Trial (RCT), like the Dietary Approaches to Stop Hypertension (DASH).[49]

Another possibility is to measure the adherence to existing dietary recommendations. The measurement instrument is called dietary indices. Well known examples of dietary indices are the (Alternative) Healthy Eating Index ((A)-HEI)[50, 51] which are based on dietary guidelines for Americans.[52] The Healthy Diet Indicator (HDI),[53] which measures the adherence to the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) nutrient intake goals (recommendations) and the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) score which is based recommendations for cancer prevention.[54]

Dietary indices used in this thesis

Dietary recommendations represent the main exposure of interest in this thesis. Therefore, they will be explained briefly below. The WHO/FAO and WCRF/AICR aimed to formulate worldwide applicable recommendations. The WHO/FAO recommendations were defined in order to decrease the occurrence of chronic diseases in general, whereas the WCRF/AICR recommendations were particularly

provided to reduce the risk of cancer. Evidence for recommendations is mainly derived from observational and human experimental studies with additional mechanistic evidence from animal experiments and in-vitro studies.[5, 55]

The WHO recommendations were applied in subsequent analyses of all-cause mortality and CVD mortality in the CHANCES consortium. Earlier studies suggested that the HDI may not be specific enough to be associated with the occurrence of cancer.[54, 56] Therefore, the association between the WHO recommendations and cancer risk was only assessed in a sensitivity analysis. For the main analysis, the WCRF/AICR cancer-specific recommendations were applied to study the association between a healthy diet and cancer risk. The HDI and WCRF/AICR score were applied earlier to assess diet disease associations in multiple countries.[53, 54, 57-61]

The components, scoring standards and modifications performed on the HDI and WCRF/AICR diet score are summarized in Table 1.1 and Table 1.2.

Aim of the current thesis

The overall aim of this thesis is to assess the associations between a healthy diet, chronic diseases, all-cause mortality and longevity in the elderly. The analysis included harmonized data from different elderly cohorts (minimum of 7 to a maximum of 11 cohorts per analysis) from Europe and the United States. No previous studies reported the association between dietary patterns, chronic diseases and longevity in elderly by means of a "two-stage IPD meta-analysis". This thesis will add to the knowledge regarding the association of existing dietary guidelines and successful aging, in terms of expanding life expectancy and the time span lived disease free. The results of this thesis provide evidence, that can be used to improve health of the aging population by implementing successful interventions.

Outline of the thesis

The first part of the thesis describes the stability of RRR derived dietary patterns over five years in the Zutphen elderly study (chapter 2). The second part of the thesis focuses on nutrient intake goals as defined by WHO, designed to prevent chronic diseases worldwide, and lastly on the food based dietary guidelines defined by WCRF/AICR to prevent cancer risk. In chapter 3 the association is examined between WHO nutrient intake goals and all-cause mortality in eleven cohort studies of the CHANCES consortium. The association between WHO nutrient intake goals and cause specific mortality by CVD is investigated in chapter 4, using 10 cohorts of the CHANCES consortium. The association between the WCRF/AICR guidelines and cancer risk is assessed in seven cohort studies and is elaborated in chapter 5. In the general discussion (chapter 6), the main findings are discussed, methodological restrictions are addressed and results are placed into broader perspective, public health implications are described and suggestions for future research are provided.

Table 1.1 Comparing the HDI scores defined by Huijbregts *et al.* 1997[53] and Jankovic *et al.* (this thesis)

Nutrient or food group recommendations	WHO recommendations 1990[1]	WHO recommendations 2003[1]	HDI Huijbregts dichotomous (0,1) scoring	HDI Jankovic continuous (0-10) scoring
Saturated fatty acids	<10 en%	<10 en%	1 point if 0-10 en% 0 points if >10 en%	10 points if 0-10 en% 1-10 points if <15 en% or >10 0 points if > 15 en%[2]
Polyunsaturated fatty acids	3-7 en%	6-10 en%	1 point if 3-7 en% 0 points if <3 or 7	10 points if 6-10 en% 1-10 points if <6 en% or >0 en% 0 points if > 10 en%[2] or 0 en%
Complex carbohydrates	50-70 en%	No recommendation	1 point if 50-70 en% 0 points if <50 or >70 en%	Not defined in the 2003 WHO nutrient intake goals
Dietary fibre	27-40 g/ day	From foods	1 point if 27-40 g/d 0 points if <27 or >40 g/d	10 points if >25 g/d 1-10 points if <25 g/d 0 points if 0 g/d
Fruits and vegetables	≥400 g/day	≥400 g/day	1 point if >400 g/d 0 points if <400 g/d	10 points if >400 g/d 1-10 points if <400 g/d 0 points if 0 g/d
Pulses, nuts and seeds	≥30g/day (as part of the 400 g/day fruits and vegetables)		1 point if >30 g/d 0 points if <30 g/d	Not defined in the 2003 WHO nutrient intake goals
Mono- and disaccharides	< 10 en%	< 10 en%	1 point if 0-10 en% 0 points if >10 en%	10 points if <10 en% 1-10 points if >10 en% or <30 en% 0 points if > 30en%[2]
Cholesterol	<300 mg/day	<300 mg/day	1 point if 0-300 mg/d 0 points if >300 mg/d	10 points if <300 g/d 1-10 points if >300 and less than 400 g/d 0 point if >400 g/d[2]

[1]Only operationalized foods and nutrients were included in this table. A complete overview of WHO nutrient intake goals in 1990 and 2003 can be found elsewhere.[62]
[2]The upper cut-off value at which a participant scored 0 points was based on the 85th percentile of the population's intake distribution.

Table 1.2 The WCRF score, defined by Romaguera *et al.* 2012[54], as applied by Jankovic *et al.* (this thesis)

WCRF/AICR diet recommendations 2003[1]	WCRF/AICR Romaguera (0, 0.5, 1) scoring[2]
FOODS AND DRINKS THAT PROMOTE WEIGHT GAIN **Limit consumption of energy-dense foods; avoid sugary drinks**	1 point if energy density ≤125 kcal/100g/day 0.5 points if energy density >125 - <175kcal/100g/day 0 points if energy density >175 kcal/100g/day 1 point if sugary drinks intake = 0 g/ day 0.5 points if sugary drinks intake ≤250 g/ day 0 points if sugary drinks intake >250 g/ day
PLANT FOODS **Eat mostly foods of plant origin**	1 point if fruits and vegetable intake ≥400 g/ day 0.5 points if fruits and vegetable intake 200 - <400 g/ day 0 points if fruits and vegetable intake <200 g/ day 1 point if dietary fiber intake ≥25 g/ day 0.5 points if dietary fiber intake 12.5- <25 g/ day 0 points if dietary fiber intake <12.5 g/ day
ANIMAL FOODS **Limit intake of red meat and avoid processed meat**	1 point if red and processed meat <500 g/week and processed meat intake <3 g/ day 0.5 points if red and processed meat <500 g/week and processed meat intake 3 - <50 g/ day 0 points if Red and processed meat ≥500 g/week or processed meat intake ≥50 g/ day
ALCOHOLIC DRINKS **Limit alcoholic drinks**	1 point if ethanol intake ≤20 g/ day (♂) 1 point if ethanol intake ≤10 g/ day (♀) 0.5 points if Ethanol intake >20-30 g/ day (♂) 0.5 points if Ethanol intake >10-20 g/ day (♀) 0 points if Ethanol intake >30 g/ day (♂) 0 points if Ethanol intake >20 g/ day (♀)

[1]Only operationalized foods were included in this table. A complete overview of WCRF/AICR 2003 recommendations and operationalization can be found elsewhere.[54]
[2]The operationalization and scoring of the WCRF/AICR recommendations by Romaguera *et al.*[54] were used for this thesis.

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Supplementary material

Supplement 1.1 Cohort description of CHANCES cohorts with sufficient dietary intake data

EPIC-Elderly (European Prospective Investigation into Cancer and Nutrition)
EPIC-Elderly consists of approximately 100,000 voluntary participants (aged 60 years and older at recruitment) from the EPIC study. EPIC is an on-going, multi-centre, prospective cohort study aiming to investigate the role of biological, dietary, lifestyle, and environmental factors in the aetiology of cancer and other chronic diseases. Twenty three research centres from 10 European countries participate in EPIC (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom). In this study, 5 EPIC-Elderly cohorts (Greece; Bilthoven and Utrecht, the Netherlands; Umea, Sweden and Spain) provided data.

The study recruitments took place from 1992 to 2000 via administration of baseline questionnaires and interviews. After enrolment, participants were contacted at regular intervals every 3-4 years. Mortality was assessed differently in different countries and included record linkages as well as active follow-up procedures.

NIH-AARP (National Institutes of Health-AARP)
The cohort study was initiated in 1995–1996 when a baseline questionnaire eliciting information on usual dietary intake, physical activity, and other health-related behaviours was sent to 3.5 million American Association of Retired Persons (AARP members) aged 50–71 years who resided in one of six US states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) or two US metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). A total of 617,119 men and women returned the baseline questionnaire, a response rate of 17%.

In late 1996, a supplementary questionnaire was mailed to participants who satisfactorily completed the baseline questionnaire, who still lived in the study area, and who did not have prevalent cancer of the colon, breast, or prostate. The supplementary questionnaire inquired about history of hypertension and weight at age 18 years, among other health-related questions. In total, 334,908 participants responded to the supplementary questionnaire An additional follow-up questionnaire was assessed in 2004-2005. All-cause mortality was assessed via record linkage to Cancer Registry and National Death Index.

SENECA (Survey in Europe on Nutrition and the Elderly; a Concerted Action)
SENECA is a multi-centre European prospective mixed cross-sectional and longitudinal study that recruited randomly in 1988/89 around 2000 individuals

from 12 countries (Belgium, Denmark, France, Italy, the Netherlands, Portugal, Spain, Switzerland, Poland, Hungary, Norway and Greece) born between 1913 and 1918 (70-75 years old at baseline). Response rates varied from 37% to 81%. Information on the dietary intake, nutritional status, physical activity, lifestyle and health status were collected through standardised interviews, examinations of blood and anthropometric measurements. Two follow-ups with 5-year intervals were performed after the baseline. Vital status of participants was assessed via municipal registries. Assessments were repeated and extended for the survivors at follow-ups.

HAPIEE (Health, Alcohol and Psychological factors in Eastern Europe)
The **H**ealth, **A**lcohol and **Ps**ychological factors **i**n **E**astern **E**urope (HAPIEE) study comprises four cohorts in four countries: six towns in the Czech Republic (Havirov/ Karvina, Hradec Kralove, Jihlava, Kromeriz, Liberec and Usti and Labem), Krakow (Poland), Kaunas (Lithuania) and Novosibirsk (Russia); each consists of a random sample of men and women, aged 45–69 years old at baseline, stratified by gender and 5 year age groups, and selected from population registers (electoral list in Russia). The response rate was about 60%. The baseline sample sizes were 8,857, 10,728, 7,134 and 9,360 for Czech Republic, Poland, Lithuania and Russia, respectively. Baseline information from the Czech Republic, Russia and Poland was collected in 2002–2005 and in Lithuania 2006-2008 and includes data on health, lifestyle, diet (food frequency), socioeconomic circumstances and psychosocial factors. For these analyses, we used followed up for total mortality by official country-wide (Czech Republic, Russia) or regional mortality registers (Poland) until end of 2011. Data from Lithuania was not included because dietary variables were not available.

Rotterdam Study

The Rotterdam Study is a prospective cohort study among 7,983 persons living in the Ommoord district in the city of Rotterdam. All participants were aged 55 years or over at inclusion and the oldest participant was 106 years old at inclusion.

Two additional cohorts have been defined. Another cohort of 55 years and over was assessed a couple of years later with 3,011 participants. More recently, a third cohort was added with 3,932 participants aged 45 years and over at inclusion. This brings the total Rotterdam Study (RS-I, RS-II and RS-III) to 14,926 participants.

All inhabitants of the Ommoord district of 55 years and over (RS-I and RS-II) or 45 years and over (RS-III) were invited to join the study. Of the total of 20,744 invitees 72% joined the study (14926 participants).

Baseline assessment in the first RS cohort (RS-I) took place between 1989 and 1993. RS-II recruitment started in the beginning of 2000 and ended at the end of 2001. RS-III recruitment started in 2006 and ended in 2008.

All examinations were repeated every 3-4 years in characteristics that could change over time. Examination cycles were from 1990 to 1993 (baseline RS-I), from 1993 to 1995 (RS-I-2), from 1997 to 1999 (RS-I-3), from 2000 to 2001 (baseline RS-II), from 2002 to 2004 (RS-I-4), from 2004 to 2005 (RS-II-2) and from 2006 to 2008 (baseline RS-III). Currently re-examination of RS-I and RS-II is underway.

All surviving members of the cohort were invited to join the investigation at the centre at each follow up. All participants are interviewed at home and come to the centre on 2 different occasions where they are examined in detail.

Participants were followed in particular for diseases that are frequent in the elderly: coronary heart disease, heart failure and stroke, Parkinson, Alzheimer, other dementias, depression, anxiety disorders, macular degeneration and glaucoma, respiratory diseases, liver diseases, diabetes mellitus and osteoporosis. For all analyses we used data of RS-I.

Zutphen Elderly Study

The Zutphen Elderly Study is a prospective cohort study of men born between 1900 and 1920 who lived in Zutphen, a town in the eastern part of the Netherlands. A random sample of men aged 65-84 years in 1985 (response rate 72%) were recruited through March-May 1985. Participants were re-contacted in 1990, 1995 and 2000. The interviews, dietary assessments and medical examinations were conducted at homes and at a study centre. Factors were measured repeatedly with the same methodology and questions. Municipal registries provided information on vital status and were checked at 5-year intervals.

Chapter 2

Stability of Dietary Patterns Assessed with Reduced Rank Regression; the Zutphen Elderly Study

Jankovic N, Streppel MT, Kampman E, de Groot LCPGM, Boshuizen HC, Soedamah-Muthu SS, Kromhout D, Feskens EJM (2014) Nutr J doi: 10.1186/1475-2891-13-30.

Abstract

Background: Reduced rank regression (RRR) combines exploratory analysis with a-priori knowledge by including risk factors in the model. Dietary patterns, derived from RRR analysis, can be interpreted by the chosen risk factor profile and give an indication of positive or adverse health effects for a specific disease. Our aim was to assess the stability of dietary patterns derived by RRR over time. **Methods:** We used data from 467 men, aged 64–85 years, participating in the 1985 and 1990 examination rounds of the Zutphen Elderly Study. Backwards regression on risk factors and food groups was applied prior to the RRR analysis to exclude food groups with low predictability (from 36 to 19 food groups) for the chosen risk factor profile. For the final RRR analysis, dietary intake data from 19 food groups as predictor variables and 6 established risk factors for cardiovascular diseases (body mass index, systolic and diastolic blood pressure, high density lipoprotein and total cholesterol levels, and uric acid) were used. **Results:** Three RRR dietary patterns were derived for both examination years: a "(low in) cereal fibre pattern", an "alcohol pattern" and an "inconsistent pattern". The "(low in) cereal fibre pattern" was most stable over time, with a correlation coefficient of 0.47 (95% CI: 0.38-0.53) between 1985 and 1990 measurements. **Conclusion:** Dietary patterns as measured by RRR, after backwards regression, are reasonably stable over a period of five years. Thus, RRR appears to be an attractive method to measure long-term dietary exposure for nutritional epidemiological studies, with one dietary measurement at baseline.

Keywords

Dietary pattern, Stability, Elderly, Exploratory reduced rank regression analyses, Confirmatory reduced rank regression analyses

Background

Two main approaches exist to derive dietary patterns: the a-priori and the a-posteriori approach. While a-priori defined dietary indices give an indication of a populations diet quality, the a-posteriori approach uses available dietary data to describe a populations diet. Such data reduction methods are principal component (PCA) or factor analysis and cluster analysis. Factors derived from these analyses represent actual dietary patterns of the studied population.[1] Both methods have widely been applied in nutritional epidemiology, and the stability of dietary patterns derived from PCA and factor analysis was examined previously.[2-6]

Another a-posteriori method to study dietary patterns is called reduced rank regression (RRR) and was introduced to nutritional epidemiology by Hoffmann *et al.*[7] RRR finds dietary patterns that are potentially relevant for a disease by using a-priori knowledge, for example on biological risk factors or nutrients relevant for the disease of interest. The initial idea of analysing food groups in relation to risk factors, was to explain, describe and interpret diet-disease relationships based on changes in the chosen risk factors.[8,9] In contrast to PCA and factor analysis, RRR does not describe naturally occurring patterns of the population under study but explain variation in biologically important risk factors.[9] Previously, RRR has been used to derive dietary patterns associated with risk factors from baseline data for the analysis of chronic diseases and for tracking dietary patterns in children.[10] The stability of RRR patterns over time in elderly participants remain unknown.[11,12] Cohort studies often lack information on repeated measures over time and need to rely on baseline measurements, assuming stability of long-term exposure. Therefore, we assessed the long-term stability of dietary patterns, derived from RRR, in elderly men on the population level. This analysis will add to the knowledge and possible implications of RRR analysis in nutritional epidemiology.

Methods

Study population

The Zutphen Elderly Study started in 1985 to collect longitudinal population-based data on risk factors of cardiovascular diseases and health in elderly men living in the town of Zutphen, in the eastern part of The Netherlands. At baseline, 939 elderly Dutch men, aged 64–85 years (response rate 74%), participated in this study. Every five years from 1985 until 2000, the subjects' dietary intake and cardiovascular disease risk factors were measured.[13,14] Excluding participants with missing data on dietary intake or response variables, reduced the sample from 939 to 763 participants. Five years after baseline, measurements were collected from

560 elderly men (response rate 78%). Additional exclusion of participants with missing information at follow-up resulted in a sample of 467 men eligible for further analyses.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Medical Ethics Committee of the Leiden University, The Netherlands in 1985 and 1990. Written informed consent was obtained from all participants.

Assessment of dietary intake

The usual dietary intake of the last 2 to 4 weeks was assessed at the home of the participant by dieticians, applying the cross-check dietary history method,[15] which was adapted to the Dutch situation. The dietary survey took place between March and June in 1985 and 1990, respectively. If possible, the partner/housemate who usually cooked the meals was present during the interview which consisted of two parts. For the first check, the dietician interviewed the participant about his usual food intake on weekdays and weekends. For the second check, the dietician quantified the foods bought per week and compared these values with the participants report. Both sources of information were used to estimate the participant's usual food and alcohol consumption, energy and nutrient intake. Consumed foods were encoded by the dieticians, according to the Uniform Food Encoding System developed in the Netherlands.[16] After the coding, the foods were categorized into 36 food groups. Prevalent chronic diseases,[13] were assessed by questionnaire information and confirmed by letters from general practitioners.

Collection of response variables

According to a standardized protocol, height and weight were measured by a physician. Results were rounded to the nearest millimeter. Weight was recorded to the nearest 0.5 kg.[14] Body mass index (BMI) was calculated by dividing weight in kilograms by the height in meters^2 (kg/m^2). Systolic and diastolic (Korotkoff phase five) blood pressure were measured while participants were in supine position. Blood pressure measurements were taken twice at the end of the physical examination using a random-zero sphygmomanometer (Hawksley & Sons Ltd, West Sussex, United Kingdom).[14,17] The mean value of the repeated measurements was used in the analyses. Non-fasting venous blood samples were used to determine total and high-density lipoprotein (HDL) cholesterol levels in the standardized Lipid Laboratory of our Division.[18] Uric acid was analysed by a standard procedure of an autoanalyser at the Central Clinical and Chemical Laboratory of the University Hospital of Leiden, The Netherlands (SMAC, Technicon).

Statistical analyses

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina, United States) and a two-sided p-value <0.05 was considered statistically significant.

To assess the stability of dietary intake over a period of five years, median food group intakes in grams per day were compared between baseline and five years of follow-up. Correlation coefficients were calculated to examine the ability to rank participants food group intake similarly over time. Due to the skewed distribution of food groups, Spearman correlations were used.

We started the RRR dietary pattern analyses, including six CVD risk factors as response variables: BMI, systolic and diastolic blood pressure, serum total, HDL cholesterol, and uric acid. The risk factor selection was based on prior knowledge[19-22] and the chosen risk factors were also applied previously in studies for the purpose of RRR analysis.[23,24]

Random sample cross-validation and subsequent Van der Voet's test as previously applied by Heroux *et al.*[23], were used, to define the number of dietary patterns, that best predict response variables and exclude chance findings of correlations. Cross-validation was performed on initially, 36 defined food groups and six risk factors. Both methods are described in detail elsewhere.[25,26] In short, random sample cross-validation forms 1000 random test sets of the initial dataset in which the RRR analyses is performed. The predictive power of the dietary patterns derived in each of the test sets, is summarized as the predicted residual sum of squares (PRESS). Based on the PRESS estimates, the Van der Voet's test identifies the optimal number of dietary patterns. Each additional derived pattern would not contribute significantly to the explained variation in risk factors. In the initial analyses, the Van der Voet's test indicated that no dietary pattern, based on 36 a-priori defined food groups, was able to predict the six response variables sufficiently. Derived patterns were strongly influenced by chance findings. Therefore, we reduced the number of food groups by applying backwards regression on the baseline and follow-up single response variables and corresponding food group data. Food groups that were important for baseline and for more than two response variables ($p = 0.05$) either in 1985 or 1990 were included in the model. Food groups not contributing to the explained variation in response variables would be eliminated. Finally, we ran exploratory RRR analysis independently for 1985 and 1990 and assigned a z-score per individual for each of the derived patterns for both study years.[24] The stability of dietary patterns derived from RRR was examined by comparing the food groups with a high weight (> 0.10 or < -0.10) in each pattern at baseline and follow-up, the direction of the weights and the ability of the patterns to classify individuals similarly over time. As RRR

z-scores are normally distributed, Pearson correlation coefficients were calculated between baseline and follow-up dietary patterns. Labelling of the derived food patterns was performed by using the highest positive or inverse food group weight of each dietary pattern at baseline and follow-up.

We ran a confirmatory RRR analysis to differentiate the influence of food group consumption and changes in biomarker profile over time, on the stability of dietary patterns. With this approach food group- and risk factor weights were fixed, which is different from the exploratory analysis where weights were first established through RRR.[5,24] Confirmatory factor scores were calculated by multiplying the fixed food group factor weights derived in 1985, with the standardized dietary intake data of 1990 and vice versa. For the assessment of diet changes, Pearson correlation coefficients were calculated between exploratory and confirmatory dietary pattern scores using dietary intake of the other year. The influence of biomarkers can partially (as RRR weights are influenced by food groups and response variables) be examined by the correlation coefficient between exploratory and confirmatory dietary pattern scores using dietary intake of the same year. For reasons of simplicity, we will only discuss correlation coefficients for exploratory pattern 1985 with confirmatory 1990 (change in diet) and confirmatory 1985 (change in weights).

The following sensitivity analysis were performed to assess the influence on stability: food groups were energy-adjusted prior to the RRR analysis using the residual method;[27] BMI was excluded from the response set to ascertain that dietary patterns derived are not solely BMI driven; separate RRR analyses were performed in participants without chronic diseases (myocardial infarction, stroke, diabetes or cancer) at baseline, as epidemiological studies often exclude participants with prevalent diseases; and finally, to assess the influence of reducing the study sample on the derived dietary patterns, RRR was additionally applied to the full study population of 763 participants in 1985 (describing the sample prior exclusion of participants dying between 1985 and 1990). The correlation coefficient between the exploratory RRR score derived in the full study population at baseline and reduced sample of 1985, was calculated for 467 participants.

Results

Table 2.1 describes the characteristics of the study population which included 467 men (aged 64–85 years at baseline). Substantial changes between baseline and follow-up were observed for several CVD risk factors. Mean diastolic blood pressure decreased by 3.8 mmHg and energy intake decreased by 844 kJ (correlation coefficients between response variables of 1985 and 1990 are presented in Supplementary Table

2.1). The prevalence of chronic diseases (myocardial infarction, stroke, diabetes or cancer) increased with at least four percentage points for each disease.

Table 2.1 Demographic and lifestyle characteristics of elderly men (N = 467), aged 64–85 years, participating in the Zutphen Elderly Study in 1985 and 1990

Characteristics	1985	1990
BMI (kg/m^2) *	25.7 ± 3.0	25.5 ± 3.2
Systolic blood pressure (mmHg) *	150.0 ± 20.2	149.4 ± 21.4
Diastolic blood pressure (mmHg) *	85.5 ± 11.1	81.7 ± 11.8
Total-cholesterol (mmol/l) *	6.13 ± 1.07	6.07 ± 1.13
HDL-cholesterol (mmol/l) *	1.11 ± 0.26	1.14 ± 0.29
Uric acid (mmol/l) *	0.36 ± 0.07	0.35 ± 0.08
Energy (kJ/ day)	9430 ± 2052	8586 ± 1962
Prevalence of chronic disease (%)+		
Myocardial infarction	11	15
Stroke	2	6
Diabetes	5	10
Cancer	5	12

* Expressed as mean and standard deviation
+ The categorical variable chronic diseases (yes/no) had no missing values

Greatest median increases between baseline and follow-up in food group consumption were observed for fruits and low-fat milk products, whereas the consumption of potatoes, vegetables, high-fat milk products, unhealthy fats and energy free drinks decreased (Table 2.2). Spearman correlation coefficients between food groups of the two measurement rounds ranged from 0.14 for potato products to 0.71 for strong alcoholic beverages.

Comparison of excluded and included participants showed significant differences for BMI (25.2 kg/m^2 vs. 25.7 kg/m^2, p = 0.04) and uric acid (0.37 mmol/l vs. 0.36 mmol/l, p = 0.04). Regarding food group consumption we observed significant differences for cereal products, vegetables, cheese, non-alcoholic and alcoholic drinks, which were all consumed more by included participants, and fats were consumed less by included participants (data not shown).

After backwards regression 19 food groups remained for further RRR analysis. Based on the results of the Van der Voet's test three dietary patterns were derived from RRR for both examination years. Table 2.3 shows the three exploratory RRR patterns and percentage of variation explained. Dietary pattern 1 derived in 1985 and 1990 could best be described as the "(low in) cereal fibre pattern". The characteristics of this pattern were a low intake of high-fibre bread and cereals and

a high consumption of fruit juices and sugar sweetened beverages. Pattern 2 was labelled as an "alcohol pattern" showing consistent positive associations with beer wine and strong alcoholic beverages at baseline and follow-up. Pattern 3 did not contain consistent food groups at baseline and after 5 years of follow-up and was therefore labelled "inconsistent". Percentages in explained variation in single risk factors were slightly different over time, resulting from a slightly different food group composition over the years. The percentage of variation explained in total risk factors and in the 19 food groups were similar over time. The 1st derived RRR pattern explained 6.6% (2nd pattern: 5.6%, 3rd pattern 5.5%) and 6.0% (2nd pattern: 5.9%, 3rd pattern 5.3%) of the variation in dietary variables at baseline and follow-up respectively. The sum of explained variation by all 3 dietary patterns was about 17% in food groups and about 8% in CVD risk factors for both examination years.

Table 2.4 shows significant consistent positive correlations with the "(low in) cereal fibre pattern" for all risk factors except for HDL-cholesterol in 1990. The adherence to the "(low in) cereal fibre pattern" resulted in lower fibre intake from cereals and bread and a higher risk factor profile. The "alcohol pattern" showed significant positive associations with HDL-cholesterol at both time points. Also the "inconsistent pattern" showed a positive association with HDL-cholesterol at baseline and follow-up. However, in contrast to the other two patterns, this association might be caused by different food groups in 1985 and 1990 as the food group weights were different in these years. The confirmatory 1990 and 1985 "low in cereal fibre" dietary patterns showed correlation coefficients with risk factors similar to the exploratory RRR scores (Table 2.4)

Table 2.5 shows the correlation coefficients between the derived dietary patterns at baseline and follow-up. The strongest correlation between exploratory derived dietary patterns at baseline and follow-up was observed for the "(low-in) cereal fibre pattern". Confirming the "(low in) cereal fibre pattern" using 1990s diet and 1985 derived RRR weights, showed a slightly stronger correlation with the "(low-in) cereal fibre pattern" derived with loadings and diet of 1985 (0.60 vs. 0.47). Correlation coefficients between confirmatory pattern 1985 and exploratory 1985 showed a correlation coefficient close to 1. The correlation coefficient between the 1985 and 1990 confirmatory scores was slightly lower compared to the correlation coefficient between exploratory patterns derived in 1985 and 1990.

Table 2.2 Median (10th , 90th percentile) of the initial 36 defined food groups at baseline and at follow-up in the Zutphen Elderly Study (N = 467)

Food groups (number of aggregated food groups)*	Food consumption (g/d) 1985	Food consumption (g/d) 1990	Spearman correlation
Low-fibre bread (17)	**20 (0,113)**	**21 (0,100)**	**0.55**
High-fibre bread (21)	**99 (0,183)**	**102 (10,188)**	**0.65**
Low-fibre cereals (28)	**8 (0,41)**	**10 (0,46)**	**0.26**
High-fibre cereals (29)	**0 (0,13)**	**0 (0,23)**	**0.38**
Potatoes (4)	154 (69,286)	125 (63,212)	0.51
Potato products (24)	0 (0,5)	0 (0,11)	0.14
Legumes (31)	0 (0,26)	0 (0,26)	0.28
Vegetables (190)	173 (105,266)	151 (91,234)	0.38
Fruit (82)	**143 (26,328)**	**174 (42,361)**	**0.49**
Fruit juices (23)	**0 (0,120)**	**0 (0,120)**	**0.31**
High-fat meat (64)	**29 (0,61)**	**20 (0,50)**	**0.38**
Low-fat meat (88)	54 (20,102)	56 (23,101)	0.36
Meat products (87) +	20 (1,50)	18 (0,47)	0.44
Organ meat (8)	0 (0,5)	0 (0,2)	0.17
Fatty fish (9)	**0 (0,18)**	**0 (0,16)**	**0.40**
Lean fish (35)	8 (0,31)	5 (0,29)	0.43
Egg and egg products (7)	**16 (2,35)**	**14 (4,31)**	**0.47**
Cheese (44)	**29 (8,65)**	**22 (6,59)**	**0.37**
High-fat milk products (57)	**109 (0,450)**	**92 (1,418)**	**0.48**
Low-fat milk products (56)	86 (0,470)	161 (0,543)	0.56
Healthy fats (3)‡	2 (0,31)	10 (0,40)	0.46
Unhealthy fats (33)‡	**33 (9,71)**	**22 (6,53)**	**0.50**
Soup (37)	18 (0,114)	9 (0,98)	0.24
Sauce (39)	0 (0,5)	1 (0,8)	0.19
Ready to eat meat snacks (20)	0 (0,1)	0 (0,8)	0.24
Ready to eat meals (83)	**0 (0,10)**	**0 (0,28)**	**0.19**
Sugar and sweets (117)	**51 (10,109)**	**51 (11,108)**	**0.59**
Cake and biscuits (64)	34 (3,78)	32 (7,71)	0.58
Savoury snacks (13)	0 (0,3)	0 (0,4)	0.34
Nuts and seeds (21)	0 (0,20)	1 (0,13)	0.40
Energy free beverages (19)§	**856 (500,1375)**	**823 (468,1272)**	**0.54**
Sugar sweetened beverages (16)	**0 (0,71)**	**0 (0,101)**	**0.30**
Beer (3)	**0 (0,149)**	**0 (0,129)**	**0.52**
Wine (6)	**0 (0,50)**	**0 (0,64)**	**0.53**
Light alcoholic beverages (10)|	0 (0,15)	0 (0,11)	0.54
Strong alcoholic beverages (11)¶	**10 (0,100)**	**1 (0,70)**	**0.71**

* Food groups included in the final RRR analyses after backwards regression are presented in bold (an extensive list of food grouping can be provided by contacting the corresponding author).
+ Meat products include products e.g. salami, ham, bacon.
‡ Healthy fats are defined as fats high in linoleic acid and unhealthy fats as high in saturated fatty acids and trans fatty acids.
§ Energy free beverages include e.g. water, coffee, tea and light drinks.
| Light alcoholic beverages include e.g. Campari, Port, Sherry, Shandy.
¶Strong alcoholic beverages include e.g. Jenever, whiskey, rum, cognac.

Table 2.3 Exploratory RRR dietary pattern weights* in the Zutphen Elderly Study (N = 467)

	RRR dietary pattern weights+							
	Pattern 1 (low in cereal fibre)		Pattern 2 (alcohol)		Pattern 3 (inconsistent)			
	Baseline (1985)	Follow-up (1990)	Baseline (1985)	Follow-up (1990)	Baseline (1985)	Follow-up (1990)		
Food groups+								
Low-fibre bread	−0.05	−0.05	−0.09	−0.07	−0.03	0.04		
High-fibre bread	**−0.20**	**−0.27**	0.05	−0.05	0.01	0.09		
Low-fibre cereals	0.08	−0.08	0.02	0.04	**−0.12**	−0.04		
High-fibre cereals	**−0.16**	**−0.25**	0.06	−0.03	−0.02	−0.02		
Fruits	−0.05	−0.04	−0.04	0.03	−0.08	**−0.13**		
Fruit juices	**0.12**	**0.14**	−0.04	−0.02	−0.01	0.03		
High-fat meat	0.00	0.09	−0.03	0.01	0.08	−0.03		
Fatty fish	0.04	**0.11**	−0.04	0.02	**0.13**	0.01		
Egg and egg products	−0.05	0.04	0.04	−0.04	0.07	0.09		
Cheese	**−0.10**	0.03	0.03	0.06	**0.18**	**−0.13**		
High-fat milk products	**−0.12**	−0.08	0.08	**−0.14**	−0.05	**0.10**		
Unhealthy fats	0.00	**−0.17**	0.00	**0.15**	0.01	**−0.12**		
Ready to eat meals	**0.10**	0.00	**0.10**	0.05	0.01	**0.10**		
Energy free beverages	0.07	0.09	−0.04	0.02	−0.06	−0.06		
Sugar and sweets	−0.09	**−0.10**	0.08	0.04	**−0.15**	0.03		
Sugar sweetened beverages	**0.16**	0.06	−0.07	−0.04	−0.07	−0.07		
Beer	**0.14**	**0.12**	**0.12**	**0.11**	−0.05	0.03		
Wine	**0.12**	**0.10**	**0.10**	**0.14**	0.03	0.08		
Strong alcoholic beverages	0.07	−0.05	**0.26**	**0.13**	−0.01	**0.14**		
% explained variation in							**Total‡ 1985**	**Total ‡ 1990**
BMI	5.1	12.1	2.8	0.0	2.3	0.5	10.2	12.6
Total cholesterol	2.3	3.5	0.1	1.2	3.4	0.3	5.8	5.0
HDL cholesterol	0.1	2.2	8.6	7.3	1.8	1.1	10.5	10.7
Systolic BP	4.5	1.1	2.0	0.1	0.3	3.7	6.8	4.8
Diastolic BP	4.9	2.9	0.8	0.3	0.7	4.9	6.4	8.2
Uric acid	7.0	4.2	0.3	2.7	1.8	0.1	9.1	7.0
All six risk factors	4.0	4.3	2.5	1.9	1.7	1. 8	8.2	8.0
All nineteen food groups	6.6	6.0	5.6	5.9	5.5	5.3	17.7	17.2

* For this analyses we relied on the factor weights (regression coefficient in the RRR model) instead of loadings (correlation coefficient between the food pattern and the food groups) as suggested by Imamura *et al.*.[24]

+ A negative dietary pattern weight reflects a low intake of this food group, whereas a positive dietary pattern weight reflects high intakes of this food group for a person that scores high on the specific dietary pattern.

‡ Total variation explained in CVD risk factors equals the cumulative percentage in explained variation of all three food patterns derived from RRR.

Table 2.4 Pearson correlation coefficients of the food patterns derived from RRR with cardiovascular risk factors and percentage variation in food group intakes and risk factors explained by the food patterns in the Zutphen Elderly Study (N = 467)

	Pattern 1 (low in cereal fibre) *		Pattern 2 (alcohol) *		Pattern 3 (inconsistent) *		Pattern 1 (low in cereal fibre) +		Pattern 1 (low in cereal fibre) +	
	Baseline (1985)	Follow-up (1990)	Baseline (1985)	Follow-up (1990)	Baseline (1985)	Follow-up (1990)	Confirmatory (1990)		Confirmatory (1985)	
CVD risk factors	**1985**	**1990**	**1985**	**1990**	**1985**	**1990**	**1990**	**1985**	**1990**	**1985**
BMI	0.23‡	0.35‡	−0.17‡	0.00	0.15‡	−0.07	0.21‡	0.21‡	0.26‡	0.28‡
Total cholesterol	0.15‡	0.19‡	−0.04	0.11‡	0.18‡	−0.05	0.13‡	0.15‡	0.11‡	0.15‡
HDL cholesterol	0.03	−0.15‡	0.29‡	0.27‡	0.14‡	0.11‡	0.07	0.01	−0.09	−0.09
Systolic BP	0.21‡	0.10‡	0.14‡	−0.03	−0.05	0.19‡	0.19‡	0.12‡	0.10‡	0.11‡
Diastolic BP	0.22‡	0.17‡	0.09	−0.06	−0.08	0.22‡	0.21‡	0.14‡	0.09	0.12‡
Uric acid	0.26‡	0.20‡	−0.05	0.16‡	−0.13‡	−0.03	0.24‡	0.24‡	0.11‡	0.16‡

* Exploratory dietary pattern scores were calculated at baseline and follow-up by summing the product of the standardized (mean = 0 and standard deviation = 1) food group weight and the individual's standardized food group intake (score = Σ (weight(x) * consumption(x) (g/d));[24] For the RRR analysis in 1985 means and standard deviations of that year were used. For Exploratory 1990 means and standard deviations of 1990 were used.
+ Confirmatory 1990 used standardized dietary intake data of 1990 and weights derived in 1985.Confirmatory 1985 used standardized dietary intake data of 1985 and weights derived in 1990.
‡ Significant correlation $p < 0.05$.

Several sensitivity analyses were performed on the first derived pattern as this pattern by definition explains most variation in the chosen risk factors, and is therefore most stable over time. Energy adjustment of the food group intakes as well as the exclusion of BMI from the response variables resulted in similar dietary patterns compared to the initially derived patterns at baseline and follow-up (data not shown). Limiting our population to those who had no chronic diseases (n = 368 participants without myocardial infarction, stroke, diabetes or cancer) at baseline showed a similar correlation coefficient for the exploratory derived "(low in) cereal fibre pattern" between baseline and follow-up (r = 0.50) compared to r = 0.47 in Table 2.5. Correlation coefficients between dietary patterns derived from RRR using 36 food groups in the full (n = 763) and reduced sample (n = 467) of 1985 were high (correlation coefficient comparing 467 participants of the full and reduced sample r = 0.75). The full study sample of 763 participants showed significant cross validation tests for 36 food groups. Comparability of the patterns derived in the full and reduced sample increased after backwards regression (r = 0.86).

Discussion

Three exploratory dietary patterns were derived from RRR at baseline and at follow-up in a male Dutch elderly population. We labelled the dietary patterns as a "(low in) cereal fibre pattern", an "alcohol pattern" and an "inconsistent pattern". The exploratory "(low in) cereal fibre pattern" was relatively stable over time. Stability was represented by a similar pattern structure of high weighing food groups at baseline and follow-up, consistent associations between the derived patterns and CVD risk factors and a moderate correlation coefficient of the "(low in) cereal fibre pattern" between baseline and follow-up.

A trend towards a healthier diet over time was observed by a significant decrease in high-fat meat and meat products and a significant increase in fruit intake, low-fat milk products and healthy fats. Furthermore, we found a decrease in energy intake, as reported by other investigators studying elderly populations.[28-31] Correlation coefficients for the main food groups were comparable to those of the Zutphen Elderly Study obtained after one year of follow-up.[32] This suggests that, in the Zutphen Elderly Study, the relative position of the participants in the distribution of the food groups was relatively stable during follow-up.

The application of RRR has some disadvantages. RRR requires a reasonable sample size for an appropriate examination. Reducing our sample size to 467 participants has likely influenced the non-significant results for the Van der Voet's test. Furthermore, RRR is linked to two arbitrary choices: 1) the selection of risk factors

as response variables and 2) the selection of food groups. We applied known risk factors for CVD available in the Zutphen Elderly Study. Choosing risk factors based on literature is associated with limitations, as these risk factors might not necessarily be highly correlated with each other. Low correlations might result in the derivation of dietary patterns with a low predictability for the chosen risk factors. Bias towards a positive finding related to stability of dietary patterns seems unlikely but the influence of response variables on dietary patterns should be taken into account in studies focussing on the interpretation of dietary patterns.

The decision for backwards elimination of food groups prior to the RRR analysis was taken based on the result of the Van der Voet's test and was influenced by the approach chosen by Weismayer *et al.*[6] and Newby *et al.*[5] Both authors applied confirmatory factor analysis, meaning factor analysis was applied twice.

After the first run of factor analysis, those food groups with highest factor loadings were selected, on which the second run of factor analysis was applied. As factor loadings represent the bivariate correlation between food groups and derived food patterns, our backwards approach resembles a simplified form of what is called confirmatory factor analysis. Instead of correlation coefficients (equivalent to loadings), regression coefficients (equivalent to weights) were used. Weismayer *et al.*[6] reported that confirmed factor scores were slightly stronger correlated over time (healthy pattern 0.57 vs. 0.63 after 5 years) and Newby *et al.*[5] concluded that confirmatory factor scores were highly correlated with exploratory scores and reproducible over time. Therefore, we assume that our analysis gained in quality by the application of backwards regression. However, bias towards better reproducibility in the Zutphen Elderly Study cannot be excluded as food groups were selected because of good predictability on the selected response variables across the study years 1985 and 1990. Potential bias is expected to be small as only one variable (wine) was included in the set of food groups that was important for 1990 and not 1985. However, ideally one would test the selection of food groups in an independent study sample.

Examining the influence of change in diet (keeping weights constant for 1985 and 1990) increased the correlation coefficients only slightly to 0.60. Changing the weights but keeping the same foods increased the correlation to 0.73. The reason for a correlation of smaller than 1, is likely influenced by changes in food groups and small changes in biomarkers. A slight influence of biomarkers on the stability of dietary patterns was expected, given that changes over time in response variables were only observed in diastolic blood pressure. Furthermore, we ran several sensitivity analyses to examine the influence of the subjective decisions taken. Regarding the risk factors used, we expected BMI to play an important role in the

formulation of RRR food patterns, due to the association with CVD.[19] Additional sensitivity analysis showed that dietary patterns remained essentially similar after the exclusion of BMI. This is in line with the results obtained by Schulze *et al.*[33] and indicates that the correlation between BMI and food groups on one hand and BMI and the chosen risk factors on the other hand, did not corrupt the pattern structure and did not influence the stability of the patterns.

Additional energy adjustment on predictor variables did not change the dietary pattern structure in our population. The reason for this could be the homogeneous character of the Zutphen Elderly population regarding energy intake, age and sex. After energy adjustment, Kröger *et al.*[34] found a decrease of about 15 percentage points in total explained nutrient variation by the first pattern derived from RRR. Our results for the percentage in explained CVD risk factor variation was similar before and after energy adjustment. Whether energy adjustment should be performed depends on the research question and on the population under study.[23,24,35]

Table 2.5 Pearson correlation coefficients between exploratory and confirmatory dietary patterns in 1985 and 1990 in the Zutphen Elderly Study (N = 467)

Dietary patterns	**Exploratory* 1990**			**Confirmatory⁺ 1990 (diet (D) 1990, loading (L) 1985)**	**Confirmatory 1985 (D: 1985, L: 1990)**
Exploratory 1985	Pattern 1 Low in cereal fibre	Pattern 2 Alcohol	Pattern 3 Inconsistent	Pattern 1 Low in cereal fibre	Pattern 1 Low in cereal fibre
Pattern 1	0.47‡	0.31‡	0.05	0.60‡	0.73‡
Pattern 2	−0.22‡	0.34‡	0.35‡	0.11	−0.41‡
Pattern 3	0.08	0.16	−0.04	0.05	0.20‡
Confirmatory⁺ 1985 (D: 1985, L: 1990)	0.55‡	0.06	−0.09	0.43‡	1.00
Confirmatory 1990 (D: 1990, L: 1985)	0.71‡	0.40‡	0.24‡	1.00	0.43‡

* See footnote * Table 2.4.
⁺ See footnote ⁺ Table 2.4.
‡ Significant at $p < 0.0001$.

For this study we lost 50% of the participants from the initial baseline sample, as we wanted to measure the same group of people at two different time points. Two reasons were responsible for the loss of participants. Men dying between 1985 and 1990 and men non-responding (22%) at the follow-up examination, which might result in a "more healthy" population in comparison to the general Dutch population. However, we do not consider the selection of healthy elderly participants or the

information on dietary intake data used from two decades ago as a major limitation. The current manuscript focussed on the methodology of RRR and the potential of RRR to derive stable dietary patterns over time. The advantage of the present study was the assessment of diet by a cross-check dietary history method at both examination years. A reproducibility study on the performance of the cross-check dietary history method examined in the Zutphen Study revealed that measurement error of the cross-check dietary history method was small.[32] Therefore, we assume that correlations between food groups and response variables in the present study were slightly underestimated and affected the dietary patterns derived from RRR only marginally.

In conclusion, the results of the present study on the stability of dietary patterns are in accordance with those reported in the literature. The "(low in) cereal fibre pattern" was the most stable pattern especially in apparently healthy elderly men. RRR analysis remains an attractive approach for nutritional epidemiology and the validity of this pattern should be further evaluated in subsequent diet-disease analyses.

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Supplementary material

Supplementary Table 2.1 Pearson correlation coefficients between CVD risk factors of 1985 and 1990 in the Zutphen Elderly Study (N = 467)

1985	1990					
Response variables	BMI	Total cholesterol	HDL cholesterol	Systolic BP	Diastolic BP	Uric acid
BMI	0.87*	0.12*	-0.26*	0.15*	0.29*	0.16*
Total cholesterol	0.13*	0.78*	0.08	0.07	0.05	0.11*
HDL cholesterol	-0.22*	0.12*	0.79*	0.03	-0.06	-0.22*
Systolic BP	0.07	0.03	0.06	0.62*	0.63*	-0.05
Diastolic BP	0.23*	0.04	0.02	0.63*	0.53*	0.04
Uric acid	0.18*	0.11*	-0.21*	0.05	0.12*	0.68*

*Significant at p = 0.05

chapter 3

Adherence to a Healthy Diet According to the World Health Organization Guidelines and All-Cause Mortality in Elderly Adults from Europe and the United States

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Abstract

The World Health Organization (WHO) has formulated guidelines for a healthy diet to prevent chronic diseases and postpone death worldwide. Our objective was to investigate the association between the WHO guidelines, measured using the Healthy Diet Indicator (HDI), and all-cause mortality in elderly men and women from Europe and the United States. We analyzed data from 396,391 participants (42% women) in 11 prospective cohort studies who were 60 years of age or older at enrollment (in 1988–2005). HDI scores were based on 6 nutrients and 1 food group and ranged from 0 (least healthy diet) to 70 (healthiest diet). Adjusted cohort-specific hazard ratios were derived by using Cox proportional hazards regression and subsequently pooled using random-effects meta-analysis. During 4,497,957 person-years of follow-up, 84,978 deaths occurred. Median HDI scores ranged from 40 to 54 points across cohorts. For a 10-point increase in HDI score (representing adherence to an additional WHO guideline), the pooled adjusted hazard ratios were 0.90 (95% confidence interval (CI): 0.87, 0.93) for men and women combined, 0.89 (95% CI: 0.85, 0.92) for men, and 0.90 (95% CI: 0.85, 0.95) for women. These estimates translate to an increased life expectancy of 2 years at the age of 60 years. Greater adherence to the WHO guidelines is associated with greater longevity in elderly men and women in Europe and the United States.

Keywords

Aging, cohort, Consortium on Health and Ageing: Network of Cohorts in Europe and the United States, diet; longevity, meta-analysis

Introduction

The elderly population is growing, and we need to understand which factors contribute to an increase in lifespan.[1] Diet plays an important role in extending life expectancy,[2] but more research is required to quantify the magnitude of its role. Studying diet by means of dietary pattern analysis is an appealing method to assess the association with longevity because humans do not consume single foods or nutrients, but rather complex diets.[3] A well-known example of a healthy dietary pattern is the Mediterranean diet, which is known to reduce the risk of premature death.[4] The latest scientific evidence on the association of diet with chronic diseases and death is summarized in population-specific dietary guidelines, which aim to help people make informed "healthy" choices. The adherence to dietary guidelines can be measured by diet quality indices. One example of a dietary index is the American Healthy Eating Index, which defines adherence to the US dietary guidelines.[5] The Healthy Eating Index–2010 was found to be inversely associated with all-cause mortality in elderly participants in the United States.[6] However, studies on an international level require the operationalization of globally applicable dietary guidelines. Therefore, the 1990 World Health Organization (WHO) guidelines for a healthy diet for the prevention of chronic diseases and subsequent increase of life expectancy[7] were translated into the Healthy Diet Indicator (HDI).[8, 9]

In 2003, the WHO updated the dietary guidelines according to the latest scientific evidence.[10] The association between survival and a healthy diet that accords with the latest WHO guidelines has not been quantified. Combining all causes of death as a single outcome measure is of great interest for the population under study, because comorbid conditions frequently prevent identification of the primary causes of death.[11] Our hypothesis was that greater adherence to the WHO guidelines is associated with greater longevity. We tested this hypothesis and quantified the number of years of life gained by following the WHO guidelines in 11 prospective cohort studies of participants aged 60 years or older from Europe and the United States.

Methods

We conducted a meta-analysis of individual participant data from 11 population-based cohorts of the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES). Its aim is to combine and integrate prospective cohort studies to produce, improve, and clarify the evidence on the distribution and risk factors of chronic diseases in the elderly and their socioeconomic implications (www.chancesfp7.eu). The CHANCES cohorts were chosen because all variables

needed for this project were harmonized according to predefined rules. The harmonization rules were discussed among the CHANCES partners until a consensus was reached.

We included participants 60 years of age or older from the European Prospective Investigation Into Cancer and Nutrition–Elderly (EPIC-Elderly) Study[12] from Spain, the Netherlands, Greece, Sweden, and Denmark; the Health, Alcohol, and Psychosocial Factors in Eastern European Countries (HAPIEE) Study[13] from Czech Republic, Russia, and Poland; the National Institutes of Health–AARP Diet and Health (NIH-AARP) Study from the United States[14]; the Rotterdam Elderly Study (RES)[15] from the Netherlands; and the Survey in Europe on Nutrition and the Elderly, a Concerted Action (SENECA) Study[16] from Europe. Baseline data were collected between 1988 and 2005. Before the analysis, we excluded participants with incomplete follow-up information relevant for the analysis. We also excluded participants with missing information on age or death status, as well those who had missing or unrealistic information on body mass index (BMI) (weight (kg)/ height (m)^2) (i.e., BMI values of >60 or <10) at baseline and those with extreme energy intakes. The RES and the NIH-AARP Study had dietary intake outliers that we removed by Box-Cox transformation.

Main characteristics of the cohorts have been previously described in the literature[12–15, 17–19] and are summarized in Supplementary Table 3.1, available at http://aje.oxfordjournals.org/. In all cohorts, the collaborative research procedures were in accordance with the ethical standards of the responsible institutional or regional committees on human experimentation, and all participants gave written informed consent.

All-cause mortality

Information on vital status was almost complete across cohorts (Supplementary Table 3.1). The start of follow-up was defined as age at baseline, and the end of follow-up was defined as the age of the participant at last linkage with the death registry.

Dietary assessment

Different dietary assessment methods were used in each cohort. Most cohorts applied a validated food frequency questionnaire.[12–18] The SENECA Study used a validated dietary history method.[19] The total numbers of food frequency questionnaire or dietary history items, reference periods, and interview-derived or self-reported dietary assessments differed across cohorts. Translation of foods into nutrients was performed by using cohort-specific food composition tables.

Healthy Diet Indicator (HDI)

We substituted the WHO guidelines on the HDI score that were introduced by Huijbregts *et al.*[8] with the updated WHO guidelines from 2003 on diet and nutrition to prevent chronic diseases. The initial dichotomous scoring system[8] was replaced by a continuous scoring system, because this deals more efficiently with between-person variation and can better reveal diet-disease associations.[20] WHO components, as updated in 2003, and HDI scoring standards are shown in Table 3.1. All cohorts had information on 9 nutrients and 1 food group of the 14 WHO guideline goals. Five of the 11 cohorts (3 cohorts of the HAPIEE Study plus the NIH-AARP Study and the RES) had information on all dietary intake goals. To improve the comparability with previous studies,[6] we focused on the following 7 HDI components, which were available in all cohorts: percentages of energy intake from saturated fatty acids, polyunsaturated fatty acids (PUFAs), mono- and disaccharides, and protein; and intakes of cholesterol (mg/day), fruits and vegetables combined (g/day), and either total dietary fiber or nonstarch polysaccharides (g/day). The intakes of *n*-3 PUFAs, *n*-6 PUFAs, *trans*-fatty acids, and sodium were not included in the score for the main analysis. Furthermore, as suggested before,[8] we excluded total fat and total carbohydrates from the HDI score calculation to avoid duplicating weights for these 2 components. We did not include monounsaturated fatty acids because the WHO guidelines do not take them into account. Dietary fiber was used for the HDI score calculation in all cohorts except the HAPIEE Study, in which only information on intake of nonstarch polysaccharide was available. Data on intake of free sugars were not available in all cohorts and were replaced by data on mono- and disaccharides. In accordance with the WHO guidelines, all macronutrients were expressed as a percentage of energy intake. For the calculation of nutrient densities, we excluded energy provided by ethanol.[8]

The HDI includes 3 categories of guidelines ("moderation," "moderation range," and "adequacy") with accompanying scoring systems (Table 3.1). The maximum score of 10 points was allocated if the intake was in accordance with the WHO guidelines. For the moderation category, (saturated fatty acids, mono- and disaccharides, and cholesterol) participants with higher intakes than recommended received proportionally fewer points, with a minimum of 0 points at the upper limit. The upper limit was defined as the 85th percentile of the combined cohort-specific population distribution.[21] The "moderation range" components (6%–10% of energy intake from PUFAs and 10%–15% from protein) were scored with a maximum of 10 points if intake was within the recommended range. A score of 0 corresponded to an intake of 0 at the lower limit or the 85th percentile at the upper limit. Regarding PUFAs, 85% of our participants met the WHO guidelines (i.e., the upper limit was included in the recommended range). Therefore, all participants with PUFA intakes

above the recommended range received 0 points. For the "adequacy" components (>25g/day of fiber and >400g/day of fruits and vegetables), participants with lower intakes were allocated proportionately fewer points, with 0g/day as the minimum.

After all individual scores were summed, participants received the maximum HDI score of 70 points if all guidelines were met; the minimum HDI score was 0.

Table 3.1 Healthy Diet Indicator Components Based on the World Health Organization's 2003 Recommendations[a,b] and Operationalization as Applied in the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States, 1988–2011

HDI component	Standard for minimum score of zero points lower limit[c]	Standard for maximum number of 10 points[d]	Standard for minimum score of zero points upper limit[e]
"Moderation" components			
Saturated fatty acids (en%[e])	n.a	<10	>15
Mono-and disaccharides (en%)[f]	n.a	<10	>30
Cholesterol (mg/d)	n.a	<300	>400
"Moderation range" components			
Polyunsaturated fatty acids(en %)	0	6-10	>10
Protein (en %)	0	10-15	>20
"Adequacy" components			
Total dietary fiber (g/d)[g]	0	>25	n.a
Fruits and vegetable (g/d)	0	>400	n.a

Abbreviations: WHO, World Health Organization; HDI, Healthy Diet Indicator, en, Energy; n. a, not applicable; d, day

[a] The following WHO guidelines were not scored due to overlap with included components: Total fat, total carbohydrates

[b] The following WHO guidelines were not scored due to lack of information: Monounsaturated fatty acids, N-6, N-3 polyunsaturated fatty acids, *Trans*-fatty acids, Sodium

[c] Calculation of points for dietary intake between the lower limit and the standard intake for maximum number of points: (Intake/standard lower limit)*10.

[d] Standard in accordance with WHO guidelines. The joint WHO Food and Agriculture organization of the United Nations (FAO) guidelines of 2003 do not indicate clear fiber cut-off values. Fulfillment of the fruit and vegetable recommendation and consumption of whole grains should sum up to 20 g non-starch polysaccharides (NSP) which equals approximately 25 g of dietary fiber.

[e] The upper cut-off value at which a participant could score more than 0 points was based on percentile 85 of the population's intake distribution. Calculation of points for dietary intake between the upper limit and the standard intake for maximum number of points: 10-(intake-10)*10/standard upper limit-10)).

[e] En% was calculated without energy from alcohol

[f] Free sugars were replaced by mono-and disaccharides.

[g] Fiber was not available for Health, Alcohol and Psychosocial factors in Eastern European countries (HAPIEE). Therefore, we applied non-starch polysaccharides instead for that cohort with a standard maximum score of 20.

Covariates

We used similar statistical models for each of the cohorts. Data on measured height and weight were available for EPIC-Elderly Study, the RES, and the SENECA Study; self-reported data were used for the NIH-AARP Study and the HAPIEE Study. In the RES, no baseline measurements of physical activity were available. As a proxy measure, physical activity assessed 6 years after baseline was used. Information on physical activity in the Swedish cohort of the EPIC-Elderly Study was not provided. Potential confounding variables were selected based on their associations with dietary patterns and all-cause mortality.

Statistical analysis

This meta-analysis of individual participant data followed a 2-step approach by first analyzing each of the 11 CHANCES cohorts individually using the same analysis script, and then conducting meta-analyses of the obtained hazard ratio estimates. We applied Cox proportional hazard models, using age as the underlying time variable, to assess the association between the continuously scored HDI (per 10-point increment) and all-cause mortality. Hazard ratio estimates were summarized by random-effects meta-analysis to take into account differences in sample size and the possibility of statistical heterogeneity among the studies. Between-study heterogeneity was determined by I^2 statistics.[22] The final hazard ratio was adjusted for sex; educational level (primary or less (low), more than primary but less than college or university (medium), or college or university (high)); alcohol consumption (low (0g/day), medium (for men, >0–40g/day; for women, >0–20g/day), or high (for men, >40g/day; for women, >20g/day); smoking status (never, former, or current); energy intake (kcal/day); and vigorous physical activity (yes or no). Participants with missing data for the confounding variables were assigned to a separate category for each of these variables. BMI and BMI^2 (to account for a potential U-shaped association with death) were not included in the main model for their potential influence on the association as a mediator, but additional analyses showed that inclusion of BMI and BMI^2 did not change the hazard ratio estimate. We included study center for the HAPIEE Study and the EPIC-Elderly multicenter cohorts (Spain, the Netherlands, and Denmark) and region for the SENECA Study in all models to adjust for potential differences in baseline hazards across centers or regions.

Potential effect modifications by age, sex, BMI (<27 or ≥27), which is considered the upper range of normal for elderly persons[23], smoking, educational level, alcohol consumption, and chronic disease at baseline were investigated by including an interaction term in the models and by conducting stratified analysis. To examine the importance of excluded HDI components (*n*-3 and *n*-6 as separate components, *trans*-

fatty acids, and sodium) to the association between WHO guidelines and all-cause mortality, we additionally investigated the complete HDI score based on 10 WHO components in the HAPIEE Study, the NIH-AARP Study, and the RES. Sensitivity analyses were performed by excluding missing covariates, data on chronic diseases at baseline, and data from participants who died during the first 2 years of follow-up. To examine the relative importance of the single HDI components, we excluded 1 HDI component at a time while including this component as a covariate in the model. Finally, we calculated population-attributable risk[24] and life expectancy. [25] To estimate the years gained by adhering to a healthy diet, we used data on life expectancy at age 60 years for Europeans in the year 2000 from the WHO data base.[26]

Cohort-specific data were analyzed using SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina). For random-effects meta-analysis, we used the *metafor* package in R, version 2.15.0 (R Foundation for Statistical Computing, Vienna, Austria). *P* values of less than 0.05 were considered statistically significant.

3

Results

Median length of follow-up ranged from 5 to 15 years across cohorts (Table 3.2). During that time, a total of 84,978 deaths occurred (Table 3.3). Median HDI scores ranged from 40 (interquartile range, 35–45) in the EPIC-Elderly cohort in Denmark to 54 (interquartile range, 49–59) in the EPIC-Elderly cohort in Greece. We obtained low (unhealthy) median HDI component scores for saturated fatty acids for all cohorts except the EPIC-Elderly cohorts in Spain and Greece and the NIH-AARP cohort. A low score for dietary cholesterol was observed in the EPIC-Elderly cohort in Denmark and the HAPIEE cohort in Russia. Protein scores ranged from very low (0 points) in the EPIC-Elderly cohort in Spain to very high (10 points) in the EPIC-Elderly cohort in Sweden and in the SENECA cohort. All cohorts scored high on PUFAs, dietary fiber, and fruits and vegetables combined, except the EPIC-Elderly cohort in Sweden, with a score of 5 points for fruits and vegetables, and the RES cohort, with a low score for dietary fiber (Table 3.4).

Mean age at baseline ranged from 60 years in the EPIC-Elderly cohort in Sweden to 73 years in the SENECA cohort (data not shown). In all cohorts, mean age, BMI values, and proportions of men and women were comparable across HDI quartiles (Supplementary Table 3.2). Participants in the highest HDI quartile (representing the greatest adherence to WHO guidelines) were more likely to be highly educated, never or former smokers, and physically active, and they were less likely to drink large amounts of alcohol. The associations between HDI and mean energy intake and mean scores for PUFAs and mono- and disaccharides differed across cohorts.

Table 3.2 Follow-up Information on 396,391 Participants in the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States, 1988–2011

CHANCES cohorts		Start of follow-up (year)	End of follow-up (year)	Median follow-up (years)
EPIC ELDERLY	Spain	1992-96	2009	14
	Netherlands	1993-97	2009	13
	Greece	1994-99	2011	11
	Sweden	1992-96	2009	14
HAPIEE	Denmark	1993-97	2007	12
	Czech Republic	2002-05	2011	8
	Russia	2002-05	2010	7
	Poland	2002-05	2009	5
NIH-AARP	United States	1995-96	2008	13
Rotterdam Study	The Netherlands	1989-93	2010	15
SENECA	Europe	1988	1998	10

Abbreviations: CHANCES, Consortium on Health and Ageing: Network of Cohorts in Europe and the United States; EPIC-Elderly, European Prospective Investigation Into Cancer and Nutrition–Elderly Study; HAPIEE, Health, Alcohol, and Psychosocial Factors in Eastern European Countries Study; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; SENECA, Survey in Europe on Nutrition and the Elderly, a Concerted Action.

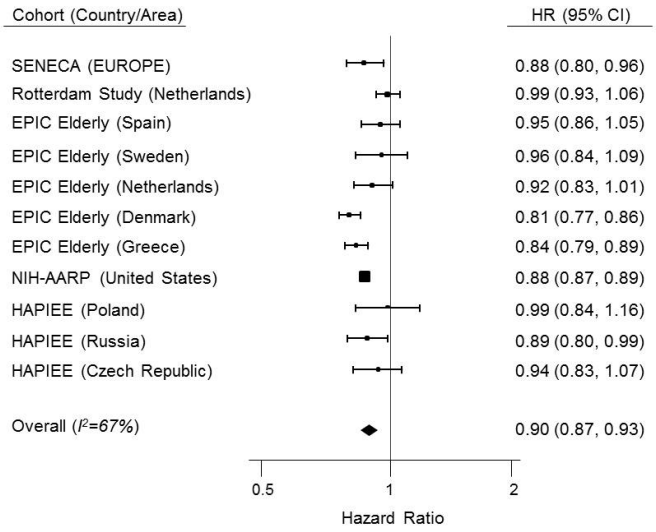


Figure 3.1 Cohort-specific and pooled hazard ratios (HRs) of all-cause mortality in relation to a 10-point increase in Healthy Diet Indicator (HDI) score, adjusted for sex, educational level, smoking status, energy intake, alcohol consumption, and physical activity level in the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES), 1988–2011. Bars, 95% confidence intervals (CIs). Cohorts are ordered according to year of baseline assessment, beginning with the oldest. I2 value is expressed as the percentage of total variability caused by heterogeneity. All datawere obtained from CHANCES (www.chancesfp7.eu). EPIC-Elderly, European Prospective Investigation Into Cancer and Nutrition–Elderly Study; HAPIEE, Health, Alcohol, and Psychosocial Factors in Eastern European Countries Study; NIH-AARP, National Institutes of Health–American Association of Retired Persons Diet and Health Study; SENECA, Survey in Europe on Nutrition and the Elderly, a Concerted Action.

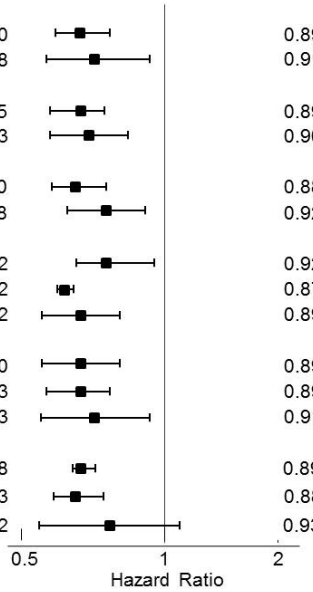
Figure 3.1 shows the hazard ratios after adjustment for sex, educational level, smoking status, energy intake, alcohol consumption, and physical activity. The hazard ratios per 10 units ranged from 0.81 for the EPIC-Elderly cohort in Denmark to 0.99 for the RES cohort. Overall, the results showed a 10% reduction (hazard ratio = 0.90, 95% CI: 0.87, 0.93, I^2 = 67%) in all-cause mortality for each 10-point increase in HDI score. The inclusion of the covariates weakened the association slightly compared with the age- and sex-adjusted model (hazard ratio = 0.86, 95% CI: 0.82, 0.90, I^2 = 85%).

Stratifying the included cohorts by potential effect modifiers (Figure 3.2A) and cohort-specific characteristics (Figure 3.2B), as well as excluding participants with chronic diseases at baseline or those who died within the first 2 years of follow-up (Figure 3.2C) produced hazard ratios similar to the summary hazard ratio of 0.90. However, inclusion of all 10 HDI components changed the pooled hazard ratio estimate slightly, which had wider confidence intervals and a greater level of heterogeneity (Figure 3.2B). Excluding single components of the HDI and adding them instead as confounders produced little difference in pooled hazard ratio estimates compared with the overall result. All summary estimates remained statistically significant, ranging from 0.87 (95% CI: 0.86, 0.88) to 0.93 (95% CI: 0.90, 0.97) (Supplementary Table 3.3).

Finally, the calculation of the population-attributable risk based on the adjusted analyses showed that 2% (in the RES) to 18% (in the EPIC-Elderly cohort in Denmark) of deaths could be attributed to unhealthy diets. The overall population-attributable risk estimate across cohorts derived by meta-analysis was 10% (95% CI: 0.08, 0.12). On the basis of WHO life expectancy data, the overall hazard ratio of 0.90 would translate to an increase in life expectancy of approximately 2 years for someone who was 60 years of age in 2000.

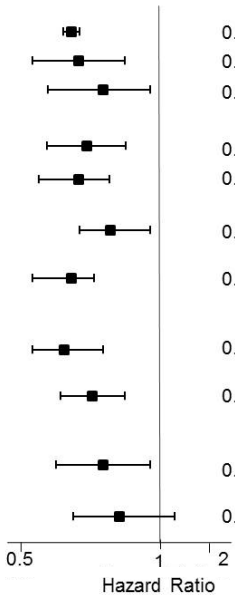
A) Potential Effect Modifiers

	No. Deaths	HR (95% CI)	I^2
Age category, years			
60-70	76,070	0.89 (0.86, 0.93)	58
>70	8,908	0.91 (0.85, 0.98)	64
Sex			
Male	56,095	0.89 (0.85, 0.92)	42
Female	28,883	0.90 (0.85, 0.95)	66
BMI			
<27	45,720	0.88 (0.85, 0.92)	43
≥27	39,258	0.92 (0.87, 0.97)	70
Smoking			
Never	20,292	0.92 (0.88, 0.98)	51
Former	44,872	0.87 (0.86, 0.88)	<1
Current	16,452	0.89 (0.84, 0.94)	52
Education			
Low	6,720	0.89 (0.84, 0.94)	49
Medium	25,783	0.89 (0.85, 0.93)	28
High	49,423	0.91 (0.84, 0.98)	20
Alcohol			
None	74,758	0.89 (0.88, 0.91)	0
Medium	50,143	0.88 (0.85, 0.92)	54
High	9,722	0.93 (0.84, 1.02)	56



B) Cohort-Specific Characteristics

	Cohort	HR (95% CI)	I^2
Location			
United States	NIH	0.89 (0.88, 0.90)	n.a.
Europe	EPIC E (all), S, RS	0.90 (0.84, 0.96)	78
Eastern Europe	H	0.93 (0.86, 0.99)	0
Median Follow-Up, years			
≤10	H (all), S	0.91 (0.86, 0.96)	0
>10	RS, EPIC E (all), NIH	0.90 (0.85, 0.94)	78
% Cases			
≤15	EPIC E (ES, NL, SE), H (CZ, PL)	0.94 (0.90, 0.99)	0
>15	RS, EPIC E (GR, DK), H (RU), NIH, S	0.89 (0.84, 0.92)	79
Dietary Assessment			
Self-report	RS, EPIC E (NL, DK), H (CZ, PL), NIH	0.88 (0.84, 0.93)	66
Interview	EPIC E (ES, GR, SE), H (RU), S	0.92 (0.87, 0.97)	31
HDI score			
Based on 7 Components	RS, NIH, H (all)	0.93 (0.87, 0.99)	49
Based on 10 Components	RS, NIH, H (all)	0.95 (0.89, 1.02)	83



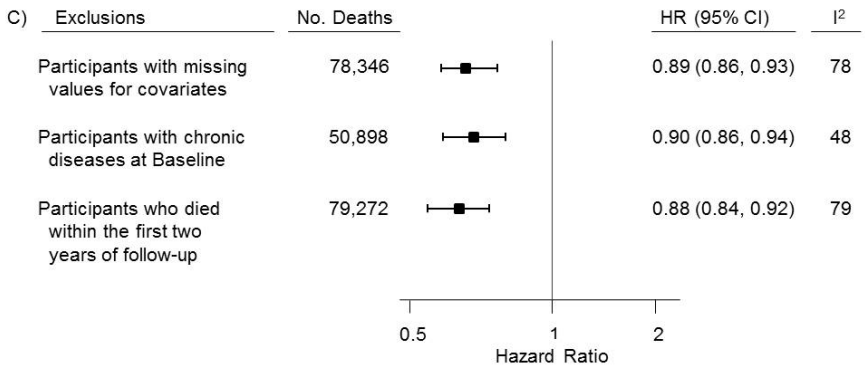


Figure 3.2 Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) in theConsortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES), 1988–2011, for the association between a 10-point increase in Healthy Diet Indicator (HDI) score and all-cause mortality A) stratified for potential effect modifiers; B) stratified for cohort-specific characteristics; and C) after several exclusion criteria have been applied. Body mass index (BMI) is weight (kg)/height (m)^2. I^2 values are expressed as percentages of total variability caused by heterogeneity. CZ, Czech Republic; DK, Denmark; EPIC-E, European Prospective Investigation into Cancer and Nutrition–Elderly Study; GR, Greece; HAPIEE, Health, Alcohol, and Psychosocial Factors in Eastern European Countries Study; NA, not applicable; NIH-AARP, National Institutes of Health–American Association of Retired Persons Diet and Health Study; NL, Netherlands; PL, Poland; RES, Rotterdam Elderly Study; RU, Russia; SENECA, Survey in Europe on Nutrition and the Elderly, a Concerted Action; SP, Spain; SW, Sweden.

Table 3.3 CHANCES baseline characteristics of N = 396,391 participants, 1988-2011

CHANCES cohorts	EPIC ELDERLY					HAPIEE			NIH-AARP	Rotterdam Study	SENECA
	Spain	Netherlands	Greece	Sweden	Denmark	Czech Republic	Russia	Poland	United States	The Netherlands	Europe
Characteristics	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.
Participants prior exclusions (age ≥ 60 years)	5,185	6,896	9,863	3,364	15,355	3,442	3,796	3,877	349,047	4,320	2,251
Participants eligible for analysis	5,168	6,730	9,531	3,263	15,264	3,376	3,794	3,859	339,182	4,160	2,064
Causes of death											
All deaths	643	1,010	2,006	499	2,438	411	590	305	73,883	2,397	796
Death due to CVD	179	295	932	154	556	153	319	102	22,993	707	286
Death due to cancer	284	408	608	193	973	193	131	136	27034	n.a.	169
Men[2]	2,228	309	3,824	1,541	7,083	1,642	1,755	1,967	205,174	1,709	1,028
Disease at baseline											
Stroke	71	127	246	n.a.	339	167	275	126	8,806	91	51
CHD	71	211	388	90	536	281	401	495	57,309	604	324
Diabetes	592	300	1,373	100	449	569	275	612	34,221	428	174
Cancer	74	489	336	n.a.	193	235	128	235	6,374	n.a.	38

Table 3.3 to be continued

Table 3.3 continued

Education[1]											
Low	4,423	2,252	8,664	1,802	6,280	499	693	655	2,747	1,514	1,356
Medium	841	3,710	522	1,069	6,558	2,402	2,134	2,213	90,079	2,310	537
High	318	735	304	363	2,384	460	967	987	23,6076	314	167
Alcohol[2]											
Low	2,136	1,492	3,306	418	439	1,248	2,867	2,706	85,066	852	762
Medium	2,351	4,333	5,772	2,844	11,514	1,701	855	803	221,760	2,878	1,048
High	681	905	453	1	3311	366	71	316	32,356	430	254
Smoking											
Never	3,460	3,178	6,439	1,952	4,685	1,628	2,475	1,792	115,863	1,427	1,069
Former	841	2,349	1,739	691	5,472	1,090	546	1,224	176,036	1,825	604
Current	862	1,175	1,093	535	5,063	633	773	829	34,619	883	364
Vigorous physical active[3]											
Yes	268	3,810	1,949	n.a.	6,821	2,245	1,180	2,596	161,882	865	519
No	4,864	2,695	7,434		2,651	996	2,612	1,065	173,492	1,068	1,016

Abbreviations: CVD, Cardiovascular disease; n.a., not available as no data was provided; CHD, Coronary heart disease; kcal, kilocalories; d, day
[1]Education: Low = Primary or less, medium = more than primary but less than college or university, high = college or university
[2]Alcohol: low = 0g of alcohol/d), medium = men > 0-40g/d and women > 0-20g/d, high = men > 40g/d and women > 20g/d
[3] Vigorous physical active: Yes = being vigorous physically active, no = not being vigorous physically active

Table 3.4 Median and Interquartile Range of the HDI and its components of N = 396,391 CHANCES participants,1988-2011

Cohort	EPIC Elderly						HAPIEE		NIH-AARP	Rotterdam Study	SENECA
Country	Spain	The Netherlands	Greece	Sweden	Denmark	Czech Republic	Russia	Poland	United States	The Netherlands	Europe
Total HDI and component points	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Total HDI (max. 70 points)	46 (40,51)	45 (40,49)	54 (49,59)	46 (41,51)	40 (35,45)	48 (42,53)	42 (37,47)	42 (37,47)	53 (47,57)	44 (39,48)	47 (42,53)
Saturated fatty acids	9 (4,10)	2 (0,5)	6 (3,9)	2 (0,5)	1 (0,5)	3 (0,6)	2 (0,5)	1 (0,5)	10 (7,10)	0 (0,4)	1 (0,8)
Polyunsaturated fatty acids	8 (6,10)	10 (8,10)	7 (6,8)	7 (6,8)	9 (8,10)	10 (9,10)	10 (0,10)	8 (7,9)	10 (8,10)	9 (6,10)	7 (5,10)
Protein	0 (0,4)	4 (0,7)	9 (6,10)	10 (7,10)	3 (0,7)	5 (1,8)	5 (2,9)	3 (0,6)	8 (4,10)	6 (2,10)	10 (6,10)
Mono and disaccharides	6 (4,8)	2 (0,4)	7 (5,8)	5 (3,6)	5 (3,7)	5 (3,8)	7 (5,8)	5 (3,7)	3 (0,5)	4 (2,6)	6 (3,8)
Cholesterol	8 (0,10)	10 (10,10)	10 (10,10)	10 10,10)	1 (0,10)	10 (5,10)	2 (0,10)	6 (0,10)	10 (10,10)	10 (10,10)	10 (3,10)
Fiber	9 (7,10)	9 (7,10)	8 (6,9)	7 (6,9)	10 (8,10)	9 (7,10)	8 (7,10)	9 (7,10)	7 (5,9)	6 (5,8)	8 (6,10)
Fruits and vegetables	10 (9,10)	9 (6,10)	10 (10,10)	5 (3,9)	8 (5,10)	10 (9,10)	10 (7,10)	10 (8,10)	10 (10,10)	10 (8,10)	10 (9,10)

Abbreviations: HDI, Healthy Diet Indicator; CHANCES, Consortium on Health and Ageing: Network of Cohorts in Europe and the United States; IQR Interquartile Range; EPIC, European Prospective Investigation into Cancer and Nutrition elderly study; HAPIEE, Health, Alcohol and Psychosocial factors in Eastern European countries; NIH-AARP, National Institutes of Health – American Association of Retired People; SENECA, Survey in Europe on Nutrition and the Elderly.

Discussion

Our study included 11 cohorts from Europe and the United States and comprised a total sample of 396,391 elderly participants with 84,978 deaths. Overall, we found that a healthier diet according to WHO guidelines was associated with lower risk of death. These results did not appear to be explained by other risk factors or by specific components of the HDI, and they were similar among different age groups, between men and women, and across geographical locations. Excluding participants with chronic diseases at baseline did not change the overall pooled association between HDI score and all-cause mortality. Depending on the cohort, up to 18% of deaths could be attributed to unhealthy diet, and an increase in 10 HDI points was associated with a 2-year increase in life expectancy for a person 60 years of age.

An increase of 10 HDI points represents adherence to 1 additional WHO guideline. However, improving dietary quality should be achieved by following a balanced diet. For example, avoiding the consumption of potato chips and sweets, reducing the consumption of meat during the main meal by introducing 1 (additional) day of fish intake, and replacing full-fat milk with low-fat milk would add approximately 6 points to the total HDI score (2 points for saturated fat, 1 point for PUFAs, 2 points for mono- and disaccharides, and 1 point for cholesterol). Together with eating 2 additional servings of fruits or vegetables daily (approximately 2 points) and replacing white rolls and cereals with whole-grain alternatives (approximately 2 points for fiber), this would result in an increase of 10 HDI points. Our results show that such a difference in dietary quality would translate to a 10% lower mortality rate in an elderly population. Three previous studies[8, 9, 27] assessed the WHO recommendations from 1990, measured by the original dichotomous HDI scoring system, in relation to all-cause mortality. Huijbregts *et al.*[8] included a population-based random sample of 3,045 men aged 50–70 years from the Finnish, Italian, and Dutch cohorts of the Seven Countries Study, who were followed for 20 years. The pooled hazard ratio was 0.87 (95% CI: 0.77, 0.98) when comparing the bottom tertile versus the top tertile. Knoops *et al.*[9] analyzed data from Healthy Ageing: a Longitudinal Study in Europe, including 3,117 men and women aged 70–90 years who were followed for 10 years. The HDI scores showed an inverse association with mortality risk of 0.89 (95% CI: 0.81, 0.98) comparing HDI scores above the median with those below the median. Finally, Sjögren *et al.*[27] reported an inverse but nonsignificant hazard ratio estimate of 0.96 (95% CI: 0.77, 1.19) per 1–standard deviation increase between the HDI score and total mortality risk in a population of elderly Swedish men after 10 years of follow-up. Our results strengthen these findings by using updated dietary guidelines and enlarging the cohort size by pooling and extending the coverage of the countries across Europe and the United States. Also, we applied a continuous

HDI score and not a dichotomous one as in the previous HDI studies, which might have improved the power of our study.[20] Combining prospective cohort studies in a meta-analysis to examine the association between nutrient-based dietary patterns and all-cause mortality typically introduces heterogeneity.[28] Reasons for this might be related to, for example, the use of different dietary questionnaires (assessment of dietary intake) and food composition tables (translation of food groups into nutrients). As expected, the levels of heterogeneity and uncertainty increased after the additional inclusion of *n*-6 PUFAs, *n*-3 PUFAs, *trans*-fatty acids, and sodium. We considered the result of our main analysis on the association between the HDI and all-cause mortality based on 7 instead of 10 HDI components to be reliable and more precise. An advantage of the current meta-analysis was the use of the same analysis script across cohorts and the use of harmonized variables, enabling the reduction of heterogeneity. The overall I^2 value was interpreted as being moderate in size. All hazard ratio estimates pointed in the same direction, which shows that the level of heterogeneity was driven by differences in strength of the association rather than by the direction.[29] Another advantage of the present study is the large sample size and diversity of the populations.

Limitations of our study are partly related to differences in cohort design, such as differences in length of follow-up, dietary assessment methods, and comparability of specific dietary variables. However, despite cohort differences, we found similar results across cohorts, which strengthens our overall finding. We performed stratified analyses by region to ensure that the large NIH-AARP Study did not dominate the overall result, and we found stable significant inverse associations between HDI and all-cause mortality across strata.

A single dietary intake measurement at baseline assumes a constant diet over time. To partially reduce potential bias from dietary changes between baseline and follow-up, we excluded all deaths occurring within 2 years after baseline in an additional analysis. This resulted in a slightly stronger association between the HDI score and all-cause mortality, which might indicate an underestimation of our overall association. We tried to differentiate between a healthy diet and a healthy lifestyle by including the most important risk factors for all-cause mortality. However, residual confounding by unmeasured or imprecisely measured covariates remains possible. The HDI score, as a measure of dietary quality, appears to be a useful tool for international comparison studies, but its associations with health outcomes may be weaker compared with associations with specifically tailored diet scores such as, for instance, the Dietary Approaches to Stop Hypertension diet[30] to prevent cardiometabolic diseases or a score tailored to a specific study population, such as the Healthy Eating Index. [31, 32] In addition, our results need to be confirmed in future studies examining non-Western populations, such as those from Asia, Africa, and

South America, with different dietary patterns.

The results of the present study showed that a healthy diet based on the globally defined dietary guidelines of the WHO is associated with greater survival in elderly populations in Europe and the United States. This analysis confirms that the WHO dietary guidelines are valuable to promote overall good health.

Acknowledgements

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Supplementary Table 3.1 Characteristics of the 11 cohort studies for the analysis on dietary quality and all-cause mortality, CHANCES

Cohort	N men and women prior exclusion of age below 60 years	Percentage above age 60	Baseline period	Median follow-up time (person years)	Percentage mortality ascertainment	Dietary assessment method	Total number of dietary history/FFQ items	Reference period (months)	Food composition table used	Dietary data expression	Food group Fruits and vegetables
EPIC-elderly Spain	2,228 men and 2,940 women	100%	1992-1996	14 (67900)	100%	Interviewer administered quantitative dietary history questionnaire	736 food items (open ended)	Previous year	The EPIC Nutrient Database (ENDB)[1-3]	cooked	• Excludes legumes & white potatoes-all preparations • Excludes fruit juice
EPIC-elderly Nether-lands	309 men and 6,421 women	100%	1993-1997	13 (86168)	>98%	Self-administered quantitative diet-questionnaire	213 food items	Previous year	The EPIC Nutrient Database (ENDB)[1-3]	cooked	• Excludes legumes & white potatoes-all preparations • Excludes fruit juice
EPIC-elderly Greece	3,824 men, 5,707 women	100%	1994-1999	11 (98300)	>97%	Interviewer administered quantitative diet-questionnaire	260 food items (open ended)	Previous year	The EPIC Nutrient Database (ENDB)[1-3]	cooked	• Excludes legumes & white potatoes-all preparations • Excludes fruit juice
EPIC-elderly Sweden (North)	1,541 men and 1,722 women	100%	1992-1996	14 (43921)	98%	Interview based semi-quantitative FFQ	84 food items	Previous year	The EPIC Nutrient Database (ENDB)[1-3]	cooked	• Excludes legumes & white potatoes-all preparations • Excludes fruit juice
EPIC-elderly Denmark	7,083 men and 8,181 women	100%	1993-1997	12 (173753)	100%	Self-administered semi-quantitative FFQ	173 food items	Previous year		cooked	

Supplementary Table 3.1 to be continued

Supplementary Table 3.1 continued

Cohort	N men and women prior exclusion of age below 60 years	Percentage above age 60	Baseline period	Median follow-up time (person years)	Percentage mortality ascertainment	Dietary assessment method	Total number of dietary history/FFQ items	Reference period (months)	Food composition table used	Dietary data expression	Food group Fruits and vegetables
HAPIEE Czech Republic	1,642 men and 1,782 women	43%	2002-2005	8 (26291)	100%	Self-administered FFQ	136 food and drink items	3 months	McCance& Widdowson[4]	cooked	• Excludes legumes & white potatoes- all preparations • Excludes fruit juice
HAPIEE Russia	1,755 men and 2,041 women	42%	2002-2005	7 years (23813)	100%	interview based FFQ	147 food and drink items	3 months	McCance& Widdowson[4]	cooked	• Excludes legumes & white potatoes- all preparations • Excludes fruit juice
HAPIEE Poland	1,969 men and 1,901women	39%	2002-2005	5 (19528)	100%	interview based FFQ	148 food and drink items	3 months	McCance& Widdowson[4]	cooked	• Excludes legumes & white potatoes- all preparations • Excludes fruit juice
NIH-AARP United States	205,174 men and 134,008	61%	1995-1996	13 years (3885719)	100%	Self-administered FFQ	124	Previous year	USDA[5]	cooked	• Potatoes and legumes not excluded • Fruit juice not excluded
Rotterdam Study Netherlands	1,709 men and 2,451	80%	1989 and 1993	15 years (55477)	>97%	Self-report and interview based semi-quantitative FFQ	170 items 20 main food groups	Previous year	NEVO[6]	cooked	• Excludes legumes & white potatoes- all preparations • Excludes fruit juice
SENECA* Europe	1,028 men and 1,036 women	100% (all participants aged 70 and above)	1988	10 years (17088)	>91%	Interview based dietary history method	131 (including drinks = 142) main groups = 14	1 month	Eurocode coding system 1993[7]	raw	• Excludes legumes. Potatoes not excluded • Includes fruit and fruit products

*Belgium, Denmark, France, Greece, Italy. The Netherland, Portugal, Spain, Switzerland

Supplementary Table 3.2 Baseline characteristics (from 1988-2005) by highest and lowest HDI quartile per CHANCES cohort

Cohort/Country	EPIC Elderly (ES)		EPIC Elderly (NL)		EPIC Elderly (GR)		EPIC Elderly (SE)		EPIC Elderly (DK)	
Highest and lowest quartile	Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4
HDI	35 ± 4	55 ± 3	36 ± 4	52 ± 3	44 ± 4	62 ± 2	37 ± 3	54 ± 3	31 ± 4	50 ± 4
N	1292	1292	1682	1682	2382	2383	815	815	3815	3816
Covariates	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std
Age at baseline	63 ± 2	63 ± 2	65 ± 3	64 ± 3	65 ± 3	65 ± 3	60 ± 1	60 ± 0	63 ± 2	63 ± 2
BMI (kg/m^2)	30 ± 4	30 ± 4	27 ± 4	25 ± 4	29 ± 5	29 ± 5	26 ± 4	26 ± 4	27 ± 4	26 ± 4
Energy without alcohol (kcal/d)	1968 ± 626	1852 ± 473	1606 ± 484	1792 ± 408	1704 ± 785	1796± 517	1407 ± 643	1741 ± 493	2089 ± 585	1854 ± 403
Energy(kcal/d)	2067 ± 695	1921 ± 520	1669 ± 490	1837 ± 419	1776 ± 854	1852 ± 549	1423 ± 648	1761 ± 501	2238 ± 611	1953 ± 426
Saturated fatty acids (en%)	13.9 ± 3.4	9.1 ±2.1	15.9 ± 2.5	11.8 ± 2.2	15.3 ± 2.3	11.2 ± 2.0	16.4 ± 3.0	11.8 ± 2.4	15.9 ± 2.3	10.9 ± 2.4
Polyunsaturated fatty acids (en%)	6.2 ± 3.5	5.6 ± 1.8	5.7 ± 2.2	7 ± 1.5	10.4 ± 4.3	5.7 ± 2.6	3.9 ± 0.9	4.6 ± 1.1	5.3 ± 1.3	6.1 ± 1.5
Protein (en%)	21 ± 3.3	18.6 ± 2.9	20.1 ± 2.7	15.7 ± 1.9	18.2 ± 1.7	15.1 ± 1.5	16.3 ± 2.6	14.5 ± 1.6	19.3 ± 2.5	16.7 ± 2.5
Mono-and disaccharides (en%)	18.8 ± 6.7	18.3 ± 5.9	24.1 ± 5.8	28.3 ± 6.3	16 ± 4.7	17 ± 4.3	21.8 ± 5.5	21 ± 5.3	19.7 ± 5.7	22 ± 6.3
Cholesterol (mg/d)	426 ± 151	243 ± 89	237 ± 105	164 ± 56.4	241 ± 140	154 ± 66.1	174.4 ± 107.8	151.9 ± 58	484.3 ± 175	248 ± 65.6
Fibre (g/d)	20.3 ± 8.2	26.9 ± 7.7	17.8 ± 5.3	26.7 ± 5.4	15.3 ± 7.2	21.7 ± 6.3	12.7 ± 5.2	25.4 ± 6.1	22 ± 7.5	30.5 ± 7.3
Fruits and vegetables (g/d)	466 ± 306	643 ± 287	278 ± 128	481 ± 191	562 ± 351	795 ± 293	132 ± 89	411 ± 195	292 ± 187	495 ± 224
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Men	557 (43)	557 (43)	77 (5)	77 (5)	956 (40)	956 (40)	385 (47)	385 (47)	1770 (46)	1771 (46)
Education primary or less	1076 (83)	1128 (87)	638 (38)	500 (30)	2207(93)	2122 (89)	499 (61)	404 (50)	1677 (44)	1623 (43)
Education more than primary but less than college	106 (8)	77 (6)	874 (52)	942 (56)	107 (4)	155 (7)	238 (29)	268 (33)	1632 (43)	1584 (42)
Education college or university	92 (7)	71 (6)	160 (10)	232 (14)	50 (2)	103 (4)	68 (8)	139 (17)	496 (13)	597 (16)
Smoking status never	848 (66)	864 (67)	697 (41)	837 (50)	1600 (67)	1613 (68)	441 (54)	541 (66)	990 (26)	1140 (30)
Smoking status former	196 (15)	234 (18)	570 (34)	625 (37)	419 (18)	470 (20)	147 (18)	175 (21)	1168 (31)	1317 (35)
Smoking status current	247 (19)	193 (15)	405 (24)	214 (13)	296 (12)	246 (10)	201 (25)	82 (10)	1644 (43)	1343 (35)
Alcohol consumption low	503 (39)	561 (43)	387 (23)	369 (22)	920 (39)	774 (32)	108 (13)	86 (11)	120 (3)	91 (2)
Alcohol consumption medium	588 (46)	619 (48)	986 (59)	1139 (68)	1332 (56)	1485 (62)	707 (87)	728 (89)	2614 (69)	2924 (77)
Alcohol consumption high	201 (16)	112 (9)	309 (18)	174 (10)	130 (5)	124 (5)	n.a. n.a.	1 (0)	1081 (28)	801 (21)
Vigorous physical activity Yes	58 (4)	75 (6)	919 (55)	978 (58)	489 (21)	488 (20)	n.a. n.a.	n.a. n.a.	1515 (40)	1709 (45)
Dead due to all causes	163 (13)	154 (12)	287 (17)	237 (14)	577 (24)	437(18)	156 (19)	109 (13)	819 (21)	605 (16)

Supplementary Table 3.2 to be continued

Supplementary Table 3.2 continued

Cohort/Country	HAPIEE (CZ)		HAPIEE (RU)		HAPIEE (PL)		NIH_AARP (US)		RS (NL)		SENECA (Europe)	
Highest and lowest quartile	Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4
HDI	37 ± 4	57 ± 3	33 ± 4	53 ± 4	33 ± 3	51 ± 3	42 ± 5	60 ± 2	36 ± 3	51 ± 3	37 ± 4	57 ± 3
N	585	586	709	710	659	659	81329	87095	1039	1040	516	516
Covariates	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std
Age at baseline	64 ± 3	65 ± 3	65 ± 3	65 ± 2	65 ± 3	65 ± 3	65 ± 3	66 ± 3	70 ± 7	69 ± 6	73 ± 2	73 ± 2
BMI (kg/m^2)	28 ± 4	27 ± 4	28 ± 5	28 ± 5	27 ± 4	27 ± 4	27 ± 5	27 ± 4	27 ± 4	26 ± 3	27 ± 5	26 ± 4
Energy without alcohol (kcal/d)	2074 ± 773	1978 ± 621	2468 ± 649	2132 ± 623	2232 ± 658	1925± 469	1691 ± 850	1846 ± 557	1822 ± 495	1973 ± 403	1964 ± 643	2042 ± 574
Energy(kcal/d)	2147 ± 782	2020 ± 626	2504 ± 666	2158 ± 640	2251 ± 669	1940 ± 476	1786 ± 899	1937 ± 639	1909 ± 514	2031 ± 411	2067 ± 687	2136 ± 599
Saturated fatty acids (en%)	15.4 ± 2.0	11.4±2.2	15.7 ± 2.2	12.0 ± 2.2	16.2 ± 2.3	12.5 ± 2.6	12.1 ± 3.3	8.5 ± 1.9	16.5 ± 3.0	13.4 ± 3.1	16.5 ± 3.8	11.2 ± 4.0
Polyunsaturated fatty acids (en%)	6.9 ± 1.8	6.8 ± 1.6	8.8 ± 2.6	8.9 ± 2.4	4.7 ± 1.1	5.1 ± 1.2	7.9 ± 2.9	7.3 ± 1.5	6.9 ± 3.8	7.6 ± 1.8	6.9 ± 4.2	5.8 ± 2.9
Protein (en%)	19.4 ± 3.0	15.7 ± 2.2	18.7 ± 2.5	15.9 ± 2.6	19.4 ± 2.1	17.3 ± 2.3	17.3 ± 3.5	14.8 ± 1.9	18.3 ± 3.2	16.3 ± 2.7	16.7 ± 3.7	14.5 ± 2.2
Mono-and disaccharides (en%)	18.6 ± 6.1	22.1 ± 7.9	17.2 ± 4.7	17.7 ± 5.0	20.1 ± 5.5	20.5 ± 6.6	23.2 ± 8.4	24.4± 6.8	22.0 ± 6.0	23.3 ± 6.0	19.3 ± 7.1	17.2 ± 7.6
Cholesterol (mg/d)	379.4 ± 154.2	223.0 ± 69.6	496.6± 178.5	290.1 ± 124.8	446.7 ± 173.1	270.5± 72.1	256.6 ± 160.3	165.5 ± 71.0	257.4 ± 91.9	207.1 ± 59.0	378.9 ± 149.0	225.3 ± 71.1
Fibre (g/d)	16.1 ± 9.2	25.0 ± 14.7	15.7 ± 5.9	18.0 ± 6.2	17.6 ± 7.7	20.6 ± 7.0	14.7 ± 8.4	24.6 ± 8.3	14.0 ± 3.8	19.2 ± 4.2	17.5 ± 7.9	24.2 ± 10.7
Fruits and vegetables (g/d)	504 ± 476	858 ± 756	385 ± 278	466 ± 276	453 ± 290	588 ± 280	480 ± 335	818 ± 388	383 ± 159	495 ± 146	479 ± 253	613 ± 282
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Men	262 (45)	262 (45)	319 (45)	319 (48)	319 (48)	319 (48)	48703 (60)	53178 (61)	427 (41)	427 (41)	257 (50)	257 (50)
Education primary or less	82 (14)	84 (14)	135 (19)	124 (17)	117 (18)	96 (15)	775 (1)	698 (1)	402 (39)	358 (34)	340 (66)	354 (69)
Education more than primary but less than college	407 (70)	427 (73)	401 (57)	389 (55)	360 (55)	373 (57)	23378 (29)	22557 (26)	565 (54)	587 (56)	138 (27)	113 (22)
Education college or university	93 (16)	74 (13)	173 (24)	197 (28)	182 (28)	189 (29)	54497 (67)	61324 (70)	66 (6)	89 (9)	37 (7)	48 (9)
Smoking status never	274 (47)	318 (54)	447 (63)	506 (71)	323 (49)	335 (51)	23856 (29)	32281 (37)	335 (32)	369 (35)	261 (51)	268 (52)
Smoking status former	152 (26)	173 (30)	77 (11)	84 (12)	149 (23)	200 (30)	40477 (50)	46255 (53)	401 (39)	476 (46)	143 (28)	160 (31)
Smoking status current	153 (26)	92 (16)	185 (26)	120 (17)	183 (28)	121 (18)	13666 (17)	5549 (6)	297 (29)	188 (18)	110 (21)	76 (15)
Alcohol consumption low	179 (27)	245 (42)	514 (73)	575 (81)	437 (66)	448 (68)	20543 (25)	22529 (26)	206 (20)	220 (21)	175 (34)	214 (41)
Alcohol consumption medium	302 (31)	283 (48)	171 (24)	129 (18)	153 (23)	150 (23)	51150 (63)	57078 (66)	686 (66)	746 (72)	278 (54)	235 (46)
Alcohol consumption high	96 (52)	44 (8)	24 (3)	5 (1)	67 (10)	54 (8)	9636 (12)	7488 (9)	147 (14)	74 (7)	63 (12)	67 (13)
Vigorous physical activity Yes	374 (64)	426 (73)	229 (32)	206 (29)	419 (64)	495 (75)	31722 (39)	47236 (54)	212 (20)	236 (23)	144 (28)	201 (39)
Dead due to all causes	69 (12)	52 (9)	89 (13)	71 (10)	38 (6)	35 (5)	21199 (26)	16570 (19)	646 (62)	570 (55)	231 (45)	174 (34)

Supplementary Table 3.3 Association between a 10 point increment in HDI score and all-cause mortality[1] excluding one HDI component at a time, CHANCES

Excluded component	Pooled HR estimate and 95% CI random effects model[2]
Saturated fatty acids	0.90 (0.84, 0.96)
Polyunsaturated fatty acids	0.87 (0.86, 0.88)
Protein	0.91 (0.86, 0.95)
Mono- and disaccharides	0.90 (0.86, 0.94)
Cholesterol	0.89 (0.84, 0.95)
Fiber	0.93 (0.90, 0.97)
Fruits and vegetables	0.91 (0.87, 0.94)

[1]all models are adjusted for sex, education, smoking status, energy intake, alcohol consumption and physical activity

[2]models were additionally adjusted for the excluded HDI component

References supplementary material

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Chapter 4

WHO Guidelines for a Healthy Diet and Mortality from Cardiovascular Disease in European and American Elderly: the CHANCES Project

Jankovic N, Geelen A, Streppel MT, de Groot LCPGM, Kiefte de Jong J, Orfanos P, Bamia C, Trichopoulou A, Boffetta P, Bobak M, Pikhart H, Kee F, O' Doherty MG, Buckland G, Woodside J, Franco OH, Ikram MA, Struijk EA, Pajak A, Malyutina S, Kubinova R, Wennberg M, Park Y, Kampman E, Feskens EJ

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Abstract

Background: The Healthy Diet Indicator (HDI) measures adherence to the WHO dietary guidelines, which are formulated to assist in the prevention of chronic diseases globally. **Objective:** Generate evidence on the association between the HDI and mortality from cardiovascular disease (CVD), coronary heart disease (CHD) and stroke to guide preventive strategies. **Design:** We analyzed data of ten prospective cohort studies from Europe and the US, comprising a total sample of 281,874 men and women (age ≥60 years) free from chronic diseases at baseline. Components of the HDI included saturated fatty acids, polyunsaturated fatty acids, mono- and disaccharides, protein, cholesterol, dietary fiber and fruits and vegetables. Cohort specific hazard ratios (HR) adjusted for age, sex, education, smoking, physical activity, energy and alcohol intake, were pooled using a random-effects model. **Results:** During 3,322,768 person-years of follow-up, 12,492 people died from CVD. An increase by 10 HDI points (complete adherence to an additional WHO guideline) was not associated with CVD mortality (HR: 0.94, 95% CI: 0.86-1.03), CHD mortality (HR: 0.99, 95% CI: 0.85-1.14) and stroke mortality (HR: 0.95, 95% CI: 0.88-1.03). However, stratifying the data by geographical region showed significant inverse associations between HDI and CVD mortality in Southern European cohorts (HR 0.87, 95% CI: 0.79-0.96) and the US (HR: 0.85, 95% CI: 0.83-0.87). **Conclusion**: Overall, greater adherence to the WHO dietary guidelines was not significantly associated with CVD mortality, but the results varied across regions, with clear inverse associations in elderly populations in Southern Europe and the US.

Keywords

CHANCES, ageing, cohort, diet, mortality, cardiovascular disease, meta-analysis

Introduction

The prevention of cardiovascular disease (CVD) later in life is of increasing interest, as the number of elderly people is growing constantly and occurrence of CVD increases with advancing age.[1] Diet is an important modifiable risk factor for CVD incidence[2] even in old age.[1, 3] To maximize the reduction of CVD through diet, evidence based country specific dietary guidelines were formulated and operationalized into healthy diet scores. Examples for such dietary pattern indices are the Healthy Eating Index of the United States[4] or the Dutch Healthy Eating Index,[5] which are applicable to investigate country specific associations between dietary quality and CVD. The combination of results on the association between dietary quality and CVD mortality in multiple countries, generates the greatest level of evidence. Deriving comparable data on dietary quality across cohorts, requires a globally applicable dietary quality score.[6, 7] The Healthy Diet indicator (HDI),[8] based on WHO's 2003[9] nutrient intake goals to prevent chronic diseases worldwide, represents a globally applicable diet quality index. The indicator includes recommendations on the intake of dietary fatty acids (affecting plasma lipids and lipoproteins),[10] total carbohydrates and free sugars (mainly affecting body fatness),[11] cholesterol (as a marker for animal products),[12] protein (potentially influencing blood lipid levels, blood pressure and body weight),[13] sodium (affecting blood pressure),[10] fruits and vegetables (anti-inflammatory and antioxidant effects), and dietary fiber (affecting insulin sensitivity, blood pressure, lipids and inflammation).[14]

The aim of this meta-analysis was to add to the current knowledge regarding the potential benefits of adhering to a healthy diet (HDI) by preventing CVD mortality in old age. Furthermore, we evaluated whether this association would differ by age, gender and geographical location.

Subjects and methods

We conducted an individual participant based meta-analysis within the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES; www.chancesfp7.eu). Its aim is to combine and integrate prospective cohort studies to produce, improve and clarify the evidence on risk factors for chronic diseases in the elderly, and their socio-economic implications. The cohorts of the CHANCES consortium were chosen because they undertook the efforts to harmonize all variables needed for this project according to pre-defined rules. The harmonization rules were discussed among the CHANCES partners until a consensus was reached.

We included participants aged 60 years and above from the **E**uropean **P**rospective **I**nvestigation into **C**ancer and Nutrition elderly study (EPIC Elderly)[15] [Spain (ES), the Netherlands (NL), Greece (GR), the Northern part of EPIC Elderly Sweden (SE)]; the **H**ealth, **A**lcohol and **P**sychosocial factors **i**n **E**astern **E**uropean countries (HAPIEE)[16] [Czech Republic (CZ), Russia (RU), and Poland (PL)]; the **N**ational **I**nstitutes of **H**ealth **(NIH)- A**merican **A**ssociation of **R**etired **P**eople **(**AARP**)** Diet and Health Study United States (US) including the following US regions: California, Louisiana, Florida, Atlanta, North Carolina, New Jersey, Pennsylvania and Detroit,[17] the Rotterdam Study[18] [The Netherlands (NL)] and the **S**urvey in **E**urope on **N**utrition and the **E**lderly; a **C**oncerted **A**ction **(**SENECA)[19] [multi-center European Study (EU)]. Prior to the analysis, we excluded participants with incomplete follow-up information relevant for the analysis. We also excluded participants with missing information on age, chronic diseases (CVD, diabetes, cancer), missing or implausible information on BMI (if BMI >60 kg/m^2 or <10 kg/m^2) and unknown cause of death. The Rotterdam Study and NIH-AARP showed dietary intake outliers which we removed by Box-Cox transformation (i.e. excluding participants beyond twice the interquartile range above the 75th or below the 25th percentile of sex-specific Box-Cox transformed energy intake).

The main characteristics of the cohorts have been described previously[15-17, 19-23] and were summarized in Supplementary Table 3.1 (chapter 3). In all of the cohorts the procedures followed were in accordance with the ethical standards of the responsible institutional or regional committee on human experimentation, and all participants gave written informed consent.

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CVD mortality

CVD cause of death were defined by ICD codes: ICD8: 390-458, ICD 9: 390-459, ICD10: 100-199. CHD was defined by the following codes: ICD8: 410-414, ICD 9: 410-414, ICD10: 120-125; and stroke by: ICD8: 430-438, ICD 9: 430-438, ICD10: 160-169. Missing values for specific causes of death were below 8% across cohorts. Start of follow-up was defined as age at baseline and end of follow-up was defined as age of the participant at last linkage with the death registry.

Dietary assessment

Different dietary assessment methods were applied in each cohort. Most cohorts applied a validated Food Frequency Questionnaire (FFQ).[15-17, 19, 21-23] SENECA and EPIC Elderly ES used a validated dietary history method.[24] The total number of either FFQ or dietary history items, reference periods and interview or self-reported

assessments differed across cohorts. Translation of foods into nutrients was performed by using country specific food composition tables. The cohort specific definition for the food group "fruits and vegetables" is given in Supplementary Table 3.1 (chapter 3).

Healthy Diet Indicator (HDI)

Huijbregts *et al.*[8] introduced the HDI for assessing the level of dietary quality within a population according to the WHO dietary guidelines as published in 1990.[11] We substituted the WHO guidelines published in 1990 with the updated 2003 WHO guidelines on diet and nutrition to prevent chronic disease.[9] The initial dichotomous scoring system[8] was replaced by a continuous scoring system, as this deals more efficiently with between person variation and can better reveal diet-disease associations.[25, 26] HDI components as updated in 2003 and scoring standards were presented earlier in chapter 3 (Table 3.1). All cohorts had information on nine nutrients and one food group out of the 14 WHO goals. Five of the 11 cohorts had information on all dietary intake goals. To increase comparability across cohorts and with previous publications,[8, 27-29] we focused on the following HDI components: percentage of energy intake from saturated fatty acids (SFA en%), polyunsaturated fatty acids (PUFA en%), mono- and disaccharides (en%), protein (en%), cholesterol (mg/d), fruits and vegetables combined (g/d) and either total dietary fiber or non-starch polysaccharides (g/d). The intake of n-3 PUFA, n-6 PUFA, trans-fatty acids and sodium were not included in the score. Furthermore, as suggested before,[8] we excluded total fat and total carbohydrates from the HDI score calculation to avoid duplicating weights for these two components. We excluded monounsaturated fatty acids (MUFAs) as the WHO guideline does not take the intake of MUFAs into account. Dietary fiber was used for the HDI calculation in all cohorts except HAPIEE, where only non-starch polysaccharide was available. Free sugars were not available in all cohorts and were replaced by mono- and disaccharides. According to the WHO guidelines, all macronutrients were expressed as percentage of energy intake. For the calculation of nutrient densities, we excluded energy provided by ethanol, as performed earlier.[8]

The HDI includes three different categories of guideline ("moderation", "moderation range", "adequacy") with accompanying scoring system. The maximum score of ten points was allocated if the intake was in accordance with the WHO guideline. For the moderation category (SFA, mono- and disaccharides, cholesterol) participants with a higher intake than recommended received proportionally fewer points, with a minimum of 0 points at the upper limit. The upper limit was defined as the 85th percentile of the combined cohort-specific population distribution.[30] The

"moderation range" components (PUFA 6-10 en%, protein 10-15 en%) were scored with a maximum of 10 points if intake was within the recommended range. A score of zero corresponded to an intake of zero at the lower limit or the $>85^{th}$ percentile at the upper end. Regarding PUFA, 85% of our participants met the WHO guidelines, i.e. the upper limit was included in the recommended range. Therefore, all participants with a PUFA intake above the recommended range received 0 points. For the "adequacy" components (fiber >25g/d and fruits and vegetables >400g/d), participants received 10 points when meeting the guidelines whereas participants with lower intakes were allocated proportionately fewer points, with 0 g/d as minimum.

After summing up all individual scores, a participant would receive the maximum HDI score of 70 points if all of the guidelines were met and the minimum HDI score of 0 if none was met.[31]

Covariates

Sex, education, alcohol consumption, smoking status and energy intake were assessed by study specific questionnaires and were available for all cohorts. In the Rotterdam Study no baseline measure for physical activity was available. For participants of the Rotterdam Study we used physical activity assessed seven years after baseline as a proxy measure for physical activity at baseline. Physical activity, for participants dying within the first seven years after baseline, was coded as missing. Data on physical activity in EPIC-elderly SE was not available for this study and was therefore not included as a covariate for any analysis performed in EPIC-elderly SE. The following variables were available in some but not all cohorts and were therefore additionally included in the multivariate model but not considered for the pooled analysis: use of lipid-lowering drugs was available in EPIC-elderly GR and Rotterdam Study, history of hypertension (self-reported or documented) was known for EPIC-elderly (ES, NL, GR and SE), Rotterdam Study and SENECA. Information on multivitamin use was available for the Rotterdam Study only. Potential confounders were selected based on prior knowledge regarding their association with dietary patterns and CVD risk.

Statistical analysis

This meta-analysis of individual participant data followed a two-step approach by analysing each of the ten cohorts individually first, using the same analysis script, and conducting meta-analyses of the obtained effect estimates thereafter.

All analyses were performed using the same analysis script. Cox proportional hazard models, applying age as the underlying time variable, were used to assess the association between the HDI score (per 10 point increment, approximately equivalent to the inter-quartile range) and subsequent CVD, CHD and stroke mortality. SENECA was analyzed as one cohort because of the low number of cases per participating country. The cohort-specific hazard ratios (HR) were summarized by random-effects meta-analysis, to take differences in sample size and the possibility of statistical heterogeneity among the studies into account. Between-study heterogeneity was judged by I^2 statistics.[32] To verify that our result was not solely driven by NIH-AARP, we ran random-effects meta-analysis and additionally stratified by region.

The final HR was adjusted for sex, education (primary or less, more than primary but less than college or university, college or university), alcohol consumption [low (0g/d), medium (men > 0-40g/d and women > 0-20g/d), high (men > 40g/d and women > 20g/d)], smoking status (never, former, current), energy intake (kcal/d), vigorous physical activity (yes, no). Participants with missing data for the confounding variables were included by a separate category for these variables. BMI (kg/m^2) was initially not included in the main model because of its potential influence on the association as an intermediate factor. However, to assess whether BMI had any influence on the pooled results, additional adjustment was performed in a sensitivity analysis. We included "center" for the EPIC-elderly multicenter cohorts (ES and NL) and "region" for SENECA in all models to adjust for potential differences in baseline hazards across centers or regions.

In a sensitivity analysis we ran additional models for the Rotterdam Study, EPIC-elderly GR and NIH-AARP for which we had additional data available on hypertension at baseline, use of statins, and multivitamins. Inclusion of those variables did not change the hazard estimates to any material extent. Potential effect modification by age, sex, BMI, smoking, education and alcohol consumption was investigated in each cohort, by including an interaction term between these variables and the HDI score.

For the examination of possible sources of heterogeneity, we compared the pooled HR estimates for CVD mortality with the HR estimates of the stratified analyses by the potential effect modifier (as named above). Stratified analyses by potential effect modifiers were limited to CVD mortality, as numbers of CHD and stroke cases were too small for cohort-specific subgroup analyses. For the stratified analysis by geographical region we categorized SENECA cohorts into Northern (Belgium, Denmark, France (Hagenau), Netherlands, Switzerland Burgdorf) and Southern (France (Romans), Greece, Italy, Portugal, Spain, Switzerland (Yverdon and Bellinzona)) European countries. EPIC-elderly ES and GR were classified as

Southern Europe and EPIC-elderly NL and SE as Northern Europe.

In a sensitivity analysis we studied the influence of possible dietary changes after disease occurrence on the HR. Therefore, we excluded participants who died within the first two years of follow-up as performed earlier.[33] To investigate the importance of specific HDI components, we excluded one HDI component at a time and included them as a co-variable instead.[34]

Cohort specific data were analyzed using SAS version 9.2. For random-effects meta-analysis, the metafor package in R (version 2.15.0) was used. A p-value of <0.05 was considered as statistically significant.

Results

Table 4.1 shows the baseline characteristics of the 281,874 included CHANCES participants. A total of 3,322,768 person-years were accumulated across studies. During that time 12,492, 6,004 and 2,401 people died from CVD, CHD and stroke, respectively. The proportion of deaths due to CVD, CHD and stroke was highest in SENECA (all participants aged ≥ 70 years), followed by Rotterdam Study (longest follow-up). At baseline, mean age ranged from 60 years in EPIC-elderly SE to 73 years in SENECA (Table 4.1). Mean BMI ranged from 26 kg/m^2 in the two Northern European EPIC-elderly cohorts (NL and SE) and Rotterdam Study to 29 kg/m^2 in EPIC-elderly ES and GR. Median HDI scores (max = 70 points) ranged from 42 (interquartile range 37-47) in HAPIEE (RUS, PL) to 54 (interquartile range 49-59) in EPIC-elderly GR.

Table 4.2 shows the overall HDI score and its components for the lowest and highest HDI quartile per cohort. Differences in HDI component scores across cohorts were observed for PUFA and mono- and disaccharides. We observed a positive association between HDI and mean PUFA intake comparing the highest vs. the lowest HDI quartile in EPIC-elderly (NL, SE), Rotterdam Study and HAPIEE (PL), an inverse association in EPIC-elderly (ES, GR), HAPIEE CZ, NIH-AARP and SENECA and no difference in the highest vs. the lowest HDI quartile for HAPIEE (RUS). We observed a positive association between HDI and mean mono- and disaccharide intake in EPIC-elderly (NL), Rotterdam Study, HAPIEE (CZ) and NIH-AARP, an inverse association in EPIC elderly (ES, GR, SE) and SENECA and no difference in the highest vs. the lowest HDI quartile for HAPIEE (RUS, PL).

Table 4.1 Baseline characteristics, Healthy Diet Indicator (HDI) and components of N= 281,874 CHANCES participants

Cohort	**EPIC ELDERLY**			**Rotterdam Study**	**HAPIEE**				**NIH-AARP**	**SENECA**
Country	Spain	Netherlands	Greece	Sweden	Netherlands	Czech Republic	Russia	Poland	United States	Europe
N	4,382	5,711	7,400	3,087	2,970	2,345	2,389	2,639	249,568	1,383
Start of follow-up	1992-96	1993-97	1994-99	1992-96	1989-93	2002-05	2002-05	2002-05	1995-96	1988
End of follow-up	2009	2009	2011	2009	2010	2011	2010	2009	2008	1998
Person-years	58,287	74,024	77,923	58,287	44,309	18,628	18,314	18,630	2,942,034	12,332
Deaths[*]										
Cardiovascular disease	123 (3)	208 (4)	567 (8)	124 (4)	521 (18)	66 (3)	182 (6)	33 (1)	10,498 (4)	170 (12)
Coronary heart disease	54 (1)	61 (1)	173 (2)	66 (2)	79 (3)	28 (1)	107 (4)	14 (1)	5,366 (2)	56 (4)
Stroke	29 (1)	67 (1)	180 (2)	26 (1)	158 (5)	9 (0)	61 (2)	4 (0)	1,811 (1)	56 (4)
Women[*]	2,493 (57)	5,451 (95)	4,559 (62)	1,681 (54)	1,846 (62)	1,295 (55)	1,563 (55)	1,361 (52)	108,536 (43)	734 (53)
Age at baseline[†]	63±2	64±3	67±5	60±1	69±6	65±3	65±3	65±3	65±3	73±2
BMI (kg/m^2)[†]	29 ± 4	26 ± 4	29 ± 5	26 ± 4	26 ± 4	28 ± 4	28 ± 4	27 ± 4	27 ± 4	27 ± 4
Education[*]										
Primary or less	3741 (85)	1,862 (33)	6,726 (91)	1,678 (54)	1,050 (35)	327 (14)	492 (17)	422 (16)	1,797 (1)	921 (66)
More than primary	314 (7)	3,176 (56)	405 (6)	1,018 (33)	1,687 (57)	1,664 (71)	1,609 (57)	1,492 (57)	65,170 (26)	357 (26)
College or University	277 (6)	640 (11)	239 (3)	365 (12)	215 (7)	344 (15)	738 (26)	722 (27)	175,263 (70)	110 (8)
Smoking status[*]										
Never	2,949 (67)	2,734 (48)	5,131 (69)	1,870 (61)	1,073 (36)	1,209 (52)	1,894 (67)	1,300 (49)	90,634 (36)	763 (55)
Former	690 (16)	1,928 (34)	1,220 (16)	630 (20)	1,271 (43)	659 (28)	361 (13)	747 (28)	122,634 (49)	381 (28)
Current	738 (17)	1,021 (18)	839 (11)	508 (16)	606 (20)	459 (20)	584 (22)	582 (22)	26,796 (11)	239 (17)

Table 4.1 to be continued

Table 4.1 continued

Alcohol consumption*										
No	1,760 (40)	1,178 (21)	2,410 (33)	400 (13)	550 (19)	846 (36)	2,122 (75)	1,799 (68)	56,446 (23)	488 (35)
Medium	2,012 (46)	3,743 (66)	4,598 (62)	2,686 (87)	2,114 (71)	1,191 (51)	660 (23)	594 (23)	167,751 (67)	707 (51)
High	610 (14)	790 (14)	392 (5)	1 (0)	306 (10)	268 (11)	56 (2)	223 (8)	25,371 (10)	180 (13)
Vigorous physically active*	227 (5)	3,201 (56)	1,574 (21)	n.a.	692 (23)	1,624 (69)	890 (31)	1,841 (70)	120,064 (48)	492 (36)
Energy intake (kcal/d)†	1,937 ± 602	1,720 ± 423	1,791 ± 547	1,616 ± 587	1,886 ± 444	1,968 ± 679	2,414 ± 739	2,118 ± 683	1,786 ± 742	2,007 ± 624
Total HDI score (max. 70 points)‡	46 (40,51)	45 (40,49)	54 (49,59)	46 (41,51)	44 (39,48)	47 (42,53)	42 (37,47)	42 (37,47)	53 (47,57)	47 (42,53)

*N and percentage
†Mean and standard deviation
‡Median and interquartile range

Table 4.2 Mean and standard deviations of the Healthy Diet Indicator (HDI), its components and energy presented by the lowest and highest HDI quartile (Q), CHANCES

Cohort	**EPIC ELDERLY**								**Rotterdam Study**	
Country	Spain		Netherlands		Greece		Sweden		Netherlands	
Variable	Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4
N	1095	1095	1427	1428	1849	1850	771	771	742	742
HDI score (points)	35 ± 4	55 ± 3	36 ± 4	52 ± 3	44 ± 4	62.2 ± 2	37 ± 3	54 ± 3	36 ± 3	52 ± 3
Saturated fatty acids (en%)	13.5 ± 3.5	9.2 ± 2.1	15.8 ± 2.4	12.6 ± 2.5	14.0 ± 2.2	10.2 ± 1.4	16.2 ± 3.0	12.0 ± 2.4	16.5 ± 2.9	13.4 ± 3.0
PUFA (en%)	6.3 ± 3.5	5.6 ± 1.8	5.7 ± 2.1	7.0 ± 1.5	8.8 ± 4.5	5.4 ± 1.6	3.9 ± 0.8	4.6 ± 1.1	6.7 ± 3.8	7.6 ± 1.8
Protein (en%)	20.9 ± 3.3	18.6 ± 2.9	19.9 ± 2.7	16.2 ± 2.3	16.9 ± 1.7	14.4 ± 1.3	15.8 ± 2.5	14.5 ± 1.6	18.2 ± 3.1	16.2 ± 2.6
Mono-and disaccharides (en%)	18.7 ± 6.7	18.4 ± 6.0	24.1 ± 5.7	27.3 ± 5.9	17.4 ± 4.4	16.7 ± 3.7	21.7 ± 5.5	21.1 ± 5.3	22.3 ± 5.9	23.5 ± 5.9
Cholesterol (mg/d)	427.9 ± 151.4	249.5 ± 90.7	235.5 ± 99.4	178.8 ± 60.2	208.3 ± 105.9	140.0 ± 59.0	177.2 ± 108.2	156.9 ± 59.6	260.2 ± 90.2	207.7 ± 58.8
Fiber (g/d)	21.0 ± 8.4	26.7 ± 7.9	18.1 ± 5.2	26.0 ± 5.2	17.7 ± 6.1	23.4 ± 6.4	13.6 ± 6.0	25.1 ± 6.1	14.1 ± 3.8	19.3 ± 4.0
Fruits and vegetables	471.1 ± 297.0	630.0 ± 282.7	281.0 ± 130.2	457.7 ± 173.5	651.5 ± 267.4	837.3 ± 290.2	141.6 ± 101.4	388.8 ± 190.1	390.2 ± 162.7	500.4 ± 149.4

Table 4.2 to be continued

Table 4.2 continued

Cohort	HAPIEE						NIH-AARP		SENECA	
Country	Czech Republic		Russia		Poland		United States		Europe	
Variable	Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4
N	585	586	709	710	659	659	62,392	62,392	345	345
HDI score (points)	37 ± 4	57 ± 3	33 ± 4	53 ± 4	33 ± 3	62.2 ± 2	42 ± 5	60 ± 2	33 ± 4	54 ± 3
Saturated fatty acids (en%)	15.3 ± 3.5	11.5 ± 2.2	15.7 ± 2.2	12.1 ± 2.4	16.1 ± 2.3	10.2 ± 1.4	12.1 ± 3.3	8.5 ± 1.9	16.9 ± 3.8	10.8 ± 3.7
PUFA (en%)	6.8 ± 1.9	6.7 ± 1.5	8.7 ± 2.6	8.9 ± 2.4	4.7 ± 1.1	5.4 ± 1.6	7.9 ± 2.9	7.3 ± 1.4	6.7 ± 4.2	5.5 ± 2.8
Protein (en%)	19.2 ± 2.9	15.7 ± 2.2	18.7 ± 2.5	15.9 ± 2.5	19.4 ± 2.1	14.4 ± 1.3	17.0 ± 3.5	14.7 ± 1.9	16.4 ± 3.6	14.3 ± 1.9
Mono-and disaccharides (en%)	19.0 ± 6.2	21.9 ± 7.8	17.3 ± 4.8	17.5 ± 4.9	20.2 ± 5.6	16.7 ± 3.7	23.5 ± 8.4	24.6 ± 6.7	19.0 ± 7.2	18.3 ± 8.2
Cholesterol (mg/d)	379.4 ± 154.2	223.2 ± 69.5	496.6 ± 178.5	290.1 ± 124.8	446.7 ± 173.1	140.0 ± 59.0	252.9 ± 158.2	165.8 ± 70.5	380.5 ± 132.8	229.0 ± 76.1
Fiber (g/d)	16.3 ± 9.9	24.4 ± 14.3	15.8 ± 6.0	18.3 ± 6.3	17.5 ± 7.6	23.4 ± 6.4	14.7 ± 8.4	24.6 ± 8.3	17.0 ± 7.4	24.9 ± 11.5
Fruits and vegetables (g/d)	503.5 ± 475.6	857.6 ± 756.4	385.4 ± 278.0	465.8 ± 275.7	453.5 ± 290.4	837.3 ± 290.2	479.7 ± 334.8	821.9 ± 389..9	483.6 ± 244.9	617.8 ± 273.1

Figure 4.1 shows the cohort-specific and pooled HRs for CVD, CHD and stroke mortality per 10 points increase of the HDI (representing the adherence to an additional WHO guideline), after adjustment for sex, education, smoking status, energy intake, alcohol consumption and physical activity. For CVD mortality, HRs per 10 points ranged from 0.84 for EPIC-elderly GR to 1.21 for EPIC-elderly SE. In the pooled data, a non-significant reduction of 6% (HR: 0.94, 95% CI: 0.86-1.03) in CVD mortality was observed per 10 points of HDI. Heterogeneity was high (I^2 = 68%). Additional adjustment for BMI (kg/m^2) did not influence the pooled HR estimate.

For CHD mortality, HRs ranged from 0.75 for EPIC-elderly GR and HAPIEE (RUS) to 1.40 for EPIC-elderly NL, showing no association across cohorts (HR: 0.99 0.95, 95% CI 0.85-1.14, I^2 = 67%). HR estimates for stroke mortality ranged from 0.74 for HAPIEE (CZ) to 1.23 for the Rotterdam Study. Overall risk reductions for stroke mortality amounted to 5% (HR: 0.95, 95% CI 0.88-1.03, I^2 = 7%).

For CVD deaths the HRs were similar for men and women (Table 4.3). Participants aged 70 and above showed a slightly stronger association with a HR of 0.91 compared to the overall estimate of 0.94. A significant inverse association (HR: 0.89, 95% CI 0.83-0.96, I^2 = 24%) between HDI and CVD mortality was observed for participants with BMI ≥ 27 kg/m^2 but not for participants with a BMI < 27 kg/m^2. Significant inverse associations with low heterogeneity were observed in former smokers, medium level educated subjects, and no or high alcohol users.

Stratification by geographical region revealed a significant inverse association between the HDI and CVD mortality in the US (HR NIH-AARP: 0.85, 95% CI 0.83-0.87) and Southern European cohorts (HR 0.87, 95% CI 0.79-0.96 (I^2 = 0%)) but not in Central and Eastern European (HR 0.96, 95% CI 0.70-1.31 (I^2 = 67%)) and Northern European cohorts (HR 1.02, 95% CI 0.85-1.24 (I^2 = 63%)) (Table 4.3). HDI showed a strong inverse association with CHD and stroke mortality in the US and slightly stronger albeit non-significant inverse associations in the Southern European cohorts compared to the overall pooled results for CHD and stroke. The Northern European and Eastern cohorts showed no significant associations between HDI and any of the mortality outcomes. Excluding the first two years of follow-up revealed similar results compared to the main analysis.

Finally, further sensitivity analyses were carried out to investigate the importance of the single HDI components by excluding them one at a time from the HDI and including them as a co-variable instead (Supplementary Table 4.1). The analysis revealed robust pooled HR estimates for CVD and stroke mortality ranging from 0.93 for CVD and 0.94 for stroke mortality (excluding SFA, PUFA or mono- and disaccharides) to 0.96 for CVD (excluding fruits and vegetables) and 0.97 for stroke

mortality (excluding PUFA and fruits and vegetables). HR estimates for CHD were less robust and mostly influenced by PUFA (HR: 0.92) and cholesterol (HR: 0.91).

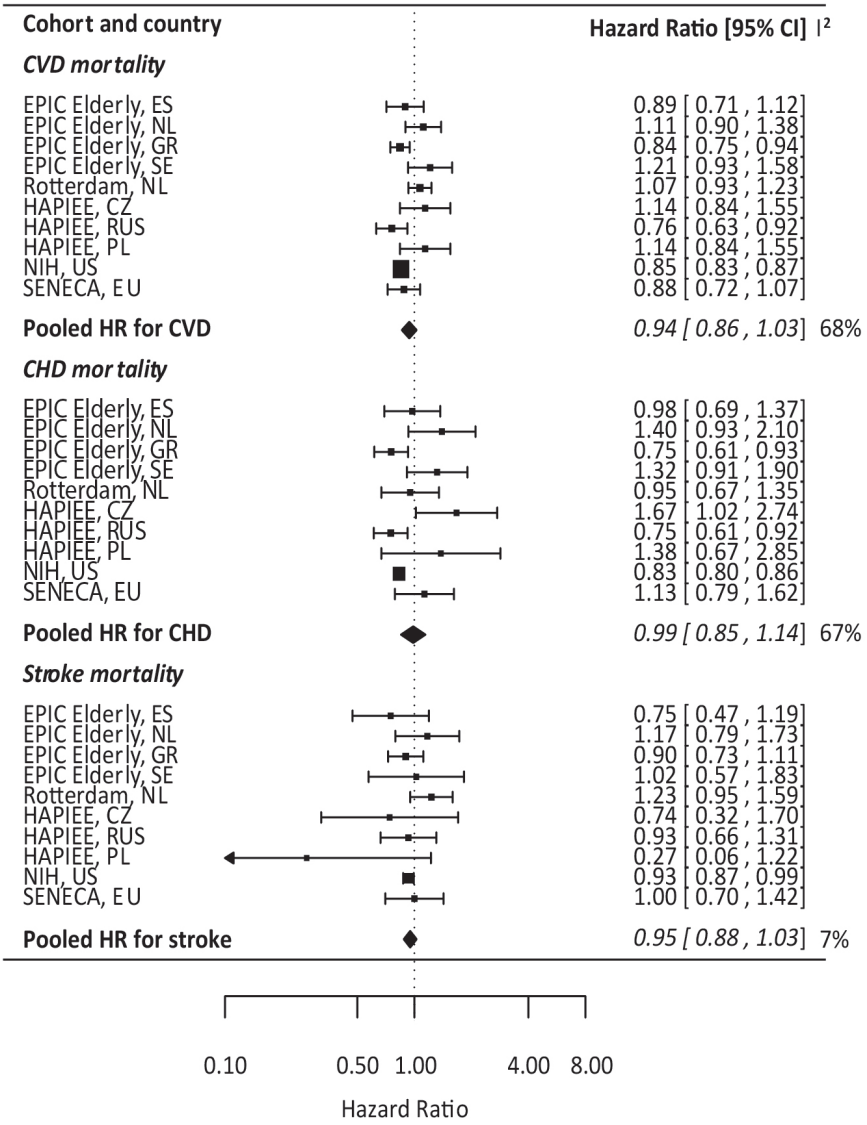

Figure 4.1 Cohort-specific and pooled adjusted hazard ratios (HRs) of CVD, CHD and stroke mortality relation to a 10 point increase in HDI score, in the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES), 1988–2011. Bars, 95% confidence intervals (CIs). I^2 value is expressed as the percentage of total variability caused by heterogeneity. All data were obtained from CHANCES (www.chancesfp7.eu). EPIC-Elderly, European Prospective Investigation Into Cancer and Nutrition–Elderly Study; ES, Spain; NL, Netherlands; GR, Greece; SE, Sweden; HAPIEE, Health, Alcohol and Psychological factors in Eastern Europe; CZ Czech Republic; RUS, Russia; PL, Poland; NIH-AARP, National Institutes of Health–American Association of Retired Persons Diet and Health Study; US, United States; SENECA, Survey in Europe on Nutrition and the Elderly; a Concerted Action; EU, Europe

Table 4.3 Hazard ratios and 95% CI stratified by potential effect modifiers and cohort specific characteristics for the association of a 10 point increment in Healthy Diet Indicator and mortality due to CVD, CHD and stroke, CHANCES

Outcome variable and strata	N CVD deaths/ N participants	HR and 95% CI	I^2 (%)
Stratified analysis by potential effect modifiers CVD only			
Sex			
Men	7,938/152,804	0.93 (0.84, 1.04)	56
Women	4,554/127,976	0.93 (0.82, 1.05)	63
Age group			
Age 60-70	10,914/265,707	0.94 (0.84, 1.04)	72
Age >70	1,576/1,628	0.91 (0.83, 1.00)	19
BMI			
<27 (kg/m^2)	6,730/166,661	0.98 (0.87, 1.11)	66
>27 (kg/m^2)	5,762 / 115,655	0.89 (0.83, 0.96)	24
Smoking			
Never	3,528/109,543	0.95 (0.84, 1.08)	64
Former	5,711/130,518	0.84 (0.81, 0.87)	0
Current	2,709/32,371	0.93 (0.84, 1.04)	32
Education			
Primary or less	1,339/19,002	0.91 (0.79, 1.05)	68
More than primary	3,726/76,891	0.88 (0.84, 0.92)	0
College or University	7,035/178,911	1.07 (0.78, 1.48)	55
Geographical Region			
CVD			
US	10,498/249,568	0.85 (0.83, 0.87)	n.a.
EU	1,994/32,306	0.96 (0.87, 1.06)	55
CEE	281/7,373	0.96 (0.70, 1.31)	67
Southern Europe	790/12,640	0.87 (0.79, 0.96)	0
Northern Europe	923/12,293	1.02 (0.85, 1.24)	63
CHD			
US	5,366/249,568	0.83 (0.80, 0.86)	n.a.
EU	638/32,306	1.00 (0.85, 1.18)	52
CEE	149 /7,373	1.15 (0.64, 2.06)	79
Southern Europe	262/12,640	0.88 (0.72, 1.08)	44
Northern Europe	227/12,293	1.16 (0.94, 1.42)	0
Stroke			
US	6,811/249,568	0.93 (0.87, 0.99)	n.a.
EU	590/32,306	0.99 (0.87, 1.12)	5
CEE	74/7,373	0.80 (0.51, 1.24)	22
Southern Europe	248/12,640	0.90 (0.76, 1.08)	0
Northern Europe	268/12,293	1.14 (0.95, 1.35)	0
Additional analysis excluding participants who died within 2 years of follow-up			
CVD	11,482 /266,860	0.95 (0.86, 1.04)	69
CHD	5,501 / 272,841	0.99 (0.85, 1.14)	62
Stroke	2,247/ 276,095	0.95 (0.89, 1.00)	0

US = NIH-AARP; EU = HAPIEE (all), EPIC Elderly (all), SENECA, Rotterdam Study; CEE = HAPIEE (all); Southern Europe = EPIC Elderly (GR, ES), SENECA (South); Northern Europe = EPIC Elderly (NL, SE), RS[1], Seneca (North)

*All models were adjusted for potential confounding variables

Discussion

Our study included ten cohorts from Europe and the United States, and comprised a total sample of 281,874 elderly participants, free of disease at baseline, with 12,492 CVD deaths, 6,004 CHD deaths and 2,401 stroke deaths. The overall results for the association between the HDI guidelines and CVD, CHD and stroke mortality showed no significant associations. HRs were similar in men and women, but varied across BMI, smoking, alcohol use and education categories. Geographical region appeared to be of importance. Based on our data the inverse association of HDI and CVD mortality appears convincing for Southern European countries and the US, whereas the absence of an association in Northern and Central and Eastern Europe was unexpected.

For the first time, a diet quality index was examined in relation to CVD mortality in a broad range of different cohorts using the same analytical approach. The interpretation of the results will mainly focus on CVD mortality as these results were found to be most robust by means of sensitivity analysis. It appears that the HDI is well able to distinguish underlying food patterns. Differences in food patterns across cohorts might explain the heterogeneous results in HR estimates. Southern European diets (ES, GR) are characterized by a high consumption of plant foods whereas Northern European diets (NL, SE) include a higher consumption of margarine, dairy, sugar, potato and processed meat.[35] For EPIC-elderly ES, GR and the Southern part of SENECA, we assumed to have measured a more traditional/ Mediterranean diet with increasing HDI score. The Mediterranean diet is known to be inversely associated with CVD mortality, which might explain the significant inverse associations found for Southern Europe in the current study.[36] The Northern European countries showed no association between WHO guidelines and CVD. One important food group from the Northern diet are margarines, which in the past were a potential source of *trans*-fatty acids[37, 38] shown to increase the risk for CVD.[37-39]

Central and Eastern European countries are known for unhealthy dietary patterns resulting in high rates of CVD.[21] The underlying food pattern of Central and Eastern European countries might have caused lacking associations between the HDI and CVD mortality for the current study. One exception was HAPIEE RUS showing a significant inverse association for CVD mortality. This exception was likely related to the missing association between HDI, PUFA and mono- and disaccharides we found in HAPIEE RUS.

The NIH-AARP study represents a more health conscious US population as shown in the baseline characteristics. Therefore, greater adherence to the HDI likely indicates a healthier underlying dietary pattern. This pattern might be in accordance to the

US Department of Agriculture (USDA) guidelines for a healthy diet for Americans.[40] Previous studies showed the USDA guidelines to be significantly associated with CVD mortality in the NIH-AARP study.[41] The lack of significant associations for CHD and stroke mortality in Southern European countries could be related to a smaller number of cases across cohorts which makes significant findings less likely.

Results published previously on the association between the HDI and CVD mortality in the elderly are partly in line with our findings. Huijbregts *et al.*[8] examined the adherence to previous WHO recommendations in men aged 50 to 70 years from the Seven Countries Study in relation to 20 year mortality. Participants from Finland, Italy and the Netherlands whose diet was closest to the WHO guidelines had a significantly 18% lower risk of dying due to CVD compared to the group with lowest adherence. Differences in outcomes between our study and the one performed by Huijbregts *et al.* could be related to different consumption levels of processed foods in Northern European countries to that time. Slimani at al.[42] reported a greater amount of manufactured food consumption in Northern Europe around 1990. We expect the consumption of manufactured foods in Northern countries to have been lower in the 1960's (baseline Seven Countries Study) which might explain the inverse associations across cohorts. In line with our findings for Northern Europe, previous studies showed no significant association between the HDI and CVD mortality in elderly men from Sweden and the United Kingdom.[29, 43]

Strengths of our study were the large sample size and the diversity of the population. We had the possibility to examine the HDI in different countries and increase our knowledge regarding the interpretation of the index. Combining cohort studies in a meta-analysis typically results in a high level of heterogeneity.[44] The advantage of this meta-analysis was the use of harmonized variables and identical analysis scripts across cohorts. The overall level of heterogeneity as measured by I^2 was high but fell considerably after stratification. Differences found in BMI were mainly driven by SENECA and EPIC-Elderly SE, which both presented a positive association in the low BMI group and an inverse association in the high BMI group which could also be driven by chance findings. Divergent associations across smoking, alcohol use and education categories showed small levels of heterogeneity due to large CI overlapping all point estimates.

Limitations of our study may be related to differences in cohort design, such as population characteristics, length of follow-up and dietary assessment method. However, this level of heterogeneity across cohorts also provides a unique dataset providing strong evidence on the meta-analysis level. Another disadvantage relates to the assessment of dietary intake taken at baseline. Generally, single dietary measurements assume a stable diet over time and are thus more susceptible to

misclassification of long-term dietary intake from reporting bias and changes occurring in the diet.[45, 46] How stable dietary patterns are in the elderly[47] and whether repeated measures over time improve the estimate of association is not yet clarified.[48, 49] Our sensitivity analysis excluding participants dying within the first two years of follow-up, to reduce the chance for reverse causation, showed similar results compared to the main analysis. Therefore, we can conclude that reverse causation was likely not present. We tried to differentiate between a healthy diet and a healthy lifestyle by including most important risk factors for all-cause mortality but residual confounding by (un)measured covariates may still be possible.

In conclusion, the results of this study show that a healthy diet, based on the WHO guidelines, is significantly associated with decreased CVD mortality in US and Southern European elderly. Non-significant associations found for the Northern European countries are possibly attributable to a less healthy underlying food pattern in comparison to the US and Southern European cohorts. Future studies using the HDI should additionally focus on the underlying food pattern of the studied population. Overall, we consider the HDI as a good measure to assess dietary quality and prevent CVD mortality in an elderly population if the contribution of the single WHO guidelines is well balanced.

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Supplementary material

Supplementary Table 4.1 Additional analysis of the association between a 10 point increment in HDI score and CVD mortality[1] excluding one HDI component at a time, CHANCES.

One component out at a time	HR[2]	(	95% CI		)	I^2
CVD						
Overall	**0.94**	**(**	**0.86,**	**1.03**	**)**	**68**
Saturated fatty acids	0.93	(	0.84,	1.03	)	66
PUFA	0.93	(	0.85,	1.01	)	60
Protein	0.95	(	0.86,	1.06	)	74
Mono- and disaccharides	0.93	(	0.86,	1.02	)	68
Dietary cholesterol	0.94	(	0.85,	1.04	)	68
Fiber	0.95	(	0.88,	1.04	)	51
Fruit and vegetables	0.96	(	0.87,	1.06	)	70
CHD						
Overall	**0.99**	**(**	**0.85,**	**1.14**	**)**	**67**
Saturated fatty acids	1.01	(	0.85,	1.19	)	63
PUFA	0.92	(	0.81,	1.05	)	52
Protein	0.98	(	0.85,	1.14	)	61
Mono- and disaccharides	0.95	(	0.83,	1.09	)	64
Dietary cholesterol	0.91	(	0.81,	1.02	)	37
Fiber	0.97	(	0.85,	1.11	)	42
Fruit and vegetables	0.96	(	0.84,	1.11	)	59
Stroke						
Overall	**0.95**	**(**	**0.88,**	**1.03**	**)**	**7**
Saturated fatty acids	0.94	(	0.87,	1.01	)	2
PUFA	0.97	(	0.84,	1.11	)	42
Protein	0.94	(	0.88,	1.00	)	0
Mono- and disaccharides	0.94	(	0.88,	0.99	)	0
Dietary cholesterol	0.96	(	0.86,	1.06	)	18
Fiber	0.95	(	0.85,	1.07	)	23
Fruit and vegetables	0.97	(	0.89,	1.07	)	16

[1]All models are adjusted for sex, education, smoking status, energy intake, alcohol consumption and physical activity
[2]Models were additionally adjusted for the excluded HDI component

chapter 5

Adhering to the WCRF/AICR Dietary Recommendations for Cancer Prevention and Risk of Cancer in Elderly from Europe and the United States, the CHANCES Consortium

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Preliminary list of co-authors. The final list of co-authors will be announced after all co-authors have reviewed and commented on the manuscript

Abstract

Background: In 2007, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) formulated specific dietary recommendations for cancer prevention. We examined the association between these recommendations and cancer risk in elderly from Europe and the US. **Methods:** This study included 362,114 participants (43% women), from seven prospective cohort studies, who were 60 years of age and above and free from cancer at enrolment. The WCRF/AICR diet score was constructed based on the WCRF/AICR recommendations regarding: 1) energy-dense foods and sugary drinks, 2) plant foods, 3) red and processed meat, and 4) alcoholic drinks. Cox proportional hazards regression was used to examine the association between the WCRF/AICR diet score and cancer risk. Adjusted, cohort-specific hazard ratios (HR) were pooled using random-effects meta-analysis. Risk Advancement Periods (RAP) were calculated to quantify the time period by which the risk of cancer was postponed among those adhering to a healthy diet. **Results:** After a median follow-up of 11 to 15 years across cohorts, 69,708 cancer cases were identified. A one point increase in the WCRF/AICR diet score (range 0 (no adherence) to 4 (complete adherence)) was significantly associated with a reduced risk of total (HR: 0.94, 95% CI: 0.92-0.97), colorectal (HR: 0.84, 95% CI: 0.80-0.89) and prostate cancer (HR:0.94, 95% CI: 0.92-0.97), but not with breast or lung cancer. The decrease in cancer risk translates to a RAP of -1.6 (95% CI: -4.09 to -2.16) years. **Conclusion**: Adherence to the WCRF/AICR dietary recommendations is associated with decreased risk of cancer, later in life.

Keywords

CHANCES, ageing, cohort, cancer risk, diet, WCRF/AICR score

5

Introduction

The elderly population, 60 years of age and above, is increasing[1] and with it, the incidence of cancer increases.[2] For this reason, preventive strategies, postponing the onset of cancer, are necessary and require a solid base of scientific evidence. Results from epidemiological studies, derived in elderly, may encourage public health interventions focusing on those aged 60 years and above.

In 2007, the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) formulated recommendations to prevent cancer.[3] The guidelines are based on quantitative meta-analyses of the most comprehensible collection of available evidence on physical activity, weight management and diet for cancer prevention. Physical activity and BMI are convincingly associated with cancer risk,[3, 4] even in advanced age,[5] whereas, a healthy diet showed, at best, weak associations with the prevention of cancer.[5-9] Interestingly, Romaguera *et al.*[10] found a significant inverse association between the 2007 WCRF/AICR dietary recommendations and cancer risk independent of physical activity and BMI, in participants aged 25 to 70 years. This may suggest that a focus on healthy diets based on cancer specific dietary recommendations in public health practice, could help to decrease the number of cancer cases. Whether the WCRF/AICR dietary recommendations are equally applicable to an exclusively elderly population remains unknown. A matter of concern, in the elderly, is related to the critical window for cancer prevention, which might have passed after the age of 60 years.[5]

The aim of the current research was to confirm the association between the 2007 WCRF/AICR dietary guidelines with total and site specific cancer risk in elderly populations. In contrast to earlier studies, this analysis was performed in a large number of cohorts from Europe and the United States. In addition, this association is quantified as the time period by which the risk of cancer in elderly is postponed among those adhering to a healthy diet.

Subjects and methods

Study population

This meta-analysis was conducted using data from collaborating cohorts of the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES). The aim of the CHANCES consortium was to combine and integrate prospective cohort studies to produce, improve and clarify the evidence on risk factors of chronic diseases in the elderly and their socioeconomic implications (www.chancesfp7.eu). Elderly were defined by the CHANCES consortium as being aged 60 years and above.

We included elderly participants from the **E**uropean **P**rospective **I**nvestigation into **C**ancer and Nutrition Elderly (EPIC Elderly) Study[11] from Spain, the Netherlands, Greece, Sweden and Denmark; the **N**ational **I**nstitutes of **H**ealth-**A**merican **A**ssociation of **R**etired **P**eople Diet and Health **(**NIH-AARP**)** Study, from California, Louisiana, Florida, Atlanta, North Carolina, New Jersey, Pennsylvania and Detroit, United States;[12] the Rotterdam Study[13] from the Netherlands (NL). We excluded participants with incomplete follow-up information relevant for the analysis and participants with missing information on age, those with prevalent cancer at baseline and those who developed cancer during the first year of follow-up, as well as those with unrealistic information on BMI (>60 kg/m^2 or <10 kg/m^2). NIH-AARP showed dietary intake outliers which were identified using Box-Cox transformation. Outliers were defined as being below the 25th percentile minus two interquartile ranges or above the 75th percentile plus two interquartile ranges of intake on the logarithmic scale.[14]

Main characteristics of the cohorts were described previously.[11, 12, 15-19] The research procedures in all cohorts were in accordance with the ethical standards of the responsible institutional or regional committees. All participants gave written informed consent.

Cancer ascertainment

Cancer cases across cohorts were assessed by linkage to population cancer registries. Active follow-up was performed in EPIC Elderly Greece including inquiries by email or telephone to participants, municipal registries, regional health departments, physicians and hospitals. Start of follow-up was defined as the date of enrolment and end of follow-up was defined as the date of cancer diagnosis, death or last completion of follow-up. Data on cancer incidence were coded according to the 9th (Rotterdam Study),10th (EPIC Elderly) and O-3 (NIH-AARP) revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD) codes. The first primary carcinoma was considered for analysis. In EPIC Elderly and NIH-AARP total cancer was defined as any incident cancer occurring. For the Rotterdam Study the variable total cancer summarized incident cases of colon and rectum, lung, breast and prostate cancer.

Collection of covariates

Baseline data from medical, dietary and lifestyle questionnaires were available in all cohorts. EPIC Elderly provided data on measured height and weight. For the Rotterdam Study and NIH-AARP Study, self-reported data on height and weight was used. In the Rotterdam Study no baseline measurements of physical activity were available. Therefore, physical activity assessed 6 years after baseline was used as

a proxy measure for physical activity at baseline. Information on physical activity in the Swedish and Danish cohorts of the EPIC Elderly Study was not provided. Potential confounding variables were selected based on their associations with the WCRF/AICR diet score and cancer risk.[20]

Dietary assessment

Most cohorts applied a validated Food Frequency Questionnaire (FFQ) for the assessment of dietary intake.[11, 12, 15-19] EPIC Elderly Spain assessed dietary intake with a validated diet history questionnaire.[21] The total number of FFQ items, reference period and mode of administration (interview or self-reported) differed across cohorts.[22] The translation of foods into nutrients was performed by using national food composition tables (NIH-AARP,[23] Rotterdam Study)[24] or the EPIC Nutrient Database (EPIC Elderly).[25]

WCRF/AICR score

The WCRF/AICR issued 10 recommendations for the prevention of cancer. Five recommendations relate to dietary intake of which we were able to include the following four in our data analysis: 1) Limit the consumption of energy-dense foods and avoid sugary drinks; 2) eat mostly foods of plant origin; 3) limit the intake of red meat and avoid the consumption of processed meat; 4) limit alcoholic drinks. The fifth recommendation to limit the consumption of salt, and to avoid moldy cereals (grains) or pulses (legumes) will not be applied for the following analysis because of insufficient available data in the CHANCES cohorts. The remaining 4 dietary recommendations (components) were scored according to the operationalization system introduced earlier by Romaguera *et al.*[10] (Table 5.1). The scoring for the single WCRF/AICR categories ranged from 0 (not adhering to the recommendation) with an intermediate category of 0.5 (describing partial adherence, created to apprise a greater proportion of variability in the population) and a maximum value of 1 (meeting the recommendation). The total WCRF/AICR diet score ranges from 0 to 4. A higher WCRF/AICR diet score represents greater adherence to the recommendations. Details on the score construction have been described earlier.[10] Recommendations 1 and 2, respectively were based on two sub-recommendations, see Table 5.1. Each sub-recommendation was scored first and averaged afterwards. The total WCRF/AICR diet score for each CHANCES participant was calculated by summing-up all component scores.

In addition to the WCRF/AICR diet score a WCRF/AICR diet plus score, including BMI and physical activity was derived (range 0 to 6 points). The following cut-off values, based on the operationalization by Romaguera *et al.* were applied for BMI

(in kg/m^2): 18.8-24.9 = 1 point, 25-29.9 = 0.5 points, < 18.5 or > 30 = 0 points. The scoring for physical activity was based on the harmonized CHANCES variable vigorous physical active yes (= 1 point) or no (= 0 points) which was different from the scoring standards applied earlier.[10]

Statistical analysis

Each of the seven cohorts (Rotterdam Study, EPIC Elderly Spain, Sweden, Greece, Netherlands, Denmark and NIH-AARP), was analysed separately using the same a-priori defined analysis script. We applied Cox proportional hazard models to examine the associations between a one point increase in WCRF/AICR diet score and total and site specific cancer risks. The WCRF/AICR diet score was additionally expressed as a categorical variable defined as ≤ 1.75 points; > 1.75 or ≤ 2.25 points; > 2.25 or ≤ 4 points. The median WCRF/AICR scores per category were included in the Cox regression model as a continuous variable to estimate the p-for trend. The final hazard ratio (HR) and 95% Confidence Intervals (95%CI) for the association between the WCRF/AICR diet score and cancer risk was adjusted for age, sex, educational level (primary or less (low), more than primary but less than college or university (medium), and college or university (high)); chronic diseases at baseline (type 2 diabetes, cardiovascular disease, stroke); energy intake in kcal/d (continuous); vigorous physical activity (yes, no); BMI (continuous); smoking status (never, former, current) and intensity of smoking (former: 1 to15 years; 16 to 30 years; more than 30 years of smoking and current: ≤ 15 cigarettes/d; 15-25 cigarettes/d; > 25 cigarettes/d). The variable duration of smoking was not assessed in the NIH-AARP Study and was substituted by the number of years since quitting smoking (≥ 10 years; < 10 years). EPIC Elderly Spain and Netherlands consisted of more than one centre. Analyses in these two cohorts were adjusted for centre to correct for potential differences in baseline hazards within the cohorts. Participants with missing data for the confounding variables were assigned to a separate category for each of these variables.

In a sensitivity analysis, all HR models in the Rotterdam Study and NIH-AARP Study, were additionally adjusted for co-variables specific for women: menopausal status, use of contraceptives, parity and hormone replacement therapy. The EPIC Elderly Study had insufficient data regarding women specific covariates. All HR estimates including additional adjustments of the women specific confounding variables, showed no marked differences compared with the results of the main analysis observed in the Rotterdam Study and NIH-AARP Study. Thus, residual confounding by these covariates on our overall HR estimates of the main analysis is unlikely.

Adjusted HR estimates were summarized by random-effects meta-analysis. Between-study heterogeneity was determined by the I^2 statistic.[26] The following analyses were performed on the associations between a healthy diet and total and colorectal cancer risk. In a sensitivity analyses the NIH-AARP Study was excluded from the random effects meta-analysis, to verify that our results were not solely driven by the results of this large cohort. Risk advancement periods (RAPs) and 95% CI were calculated from the results of multivariable regression models.[27] In short, RAPs are calculated by dividing the regression coefficient of the association between the WCRF/AICR diet score and cancer risk by the regression coefficient of the association between age in years and cancer risk. This measure can be understood as the time period by which the risk of cancer could be postponed through the adherence to an additional recommendation of WCRF/AICR.

Potential effect modifications were assessed by the inclusion of an interaction term between the WCRF/AICR diet score (continuous) and baseline age (60-65 and >65 years), sex, smoking (never, former, current smoker), and chronic diseases at baseline (CVD, diabetes) and by conducting stratified analyses. To examine the relative importance of the single WCRF/AICR diet components, we excluded one WCRF/AICR diet component at a time from the WCRF/AICR diet score, while including this component as a covariate in the model. Furthermore, the WCRF/AICR recommendations on BMI and physical activity were removed from the HR model and included in the score (WCRF/AICR diet plus score), to assess the additional impact of BMI and physical activity on cancer risk. The WCRF/AICR diet plus score was applied in all CHANCES cohorts besides EPIC Elderly Denmark and Sweden as these two cohorts did not provide information on physical activity. Comparisons between pooled HR estimates derived from the WCRF/AICR diet score and plus score were made using the same set of cohorts.

All analyses were performed using SAS version 9.2. For random-effects meta-analysis, we used the metafor package in R (version 2.15.0). P-values of less than 0.05 were considered statistically significant.

Results

Median length of follow-up ranged between 11 and 15 years. During that time, 69,708 total, 6,994 breast, 8,083 lung, 4,527 prostate and 6,550 colorectal cancer cases were identified, see Table 5.2. Mean age at baseline ranged from 60 years in EPIC Elderly Sweden to 70 years in the Rotterdam Study. Baseline characteristics for physical activity and education, differed between cohorts. A large proportion of people with low physical activity levels and a low level of education was observed

in EPIC Elderly Spain and Greece. Figures 5.1 a) to e) show the forest plots for the association between a one point increase in WCRF/AICR diet score and total cancer and cancer specific risk. A one point increase in the WCRF/AICR diet score was significantly inversely associated with total, colorectal and prostate cancer risk. The strongest association was found between the WCRF/AICR diet score and colorectal cancer risk (HR 0.84; 95 CI: 0.80, 0.89). The association between a healthy diet and total and colorectal cancer risk was found to be linear (test for trend was not assessed for prostate cancer risk).

Heterogeneity was low ($I^2 < 20\%$), except for the pooled estimate on the WCRF/AICR diet score and lung cancer risk. The large amount of heterogeneity found for lung cancer was removed after the exclusion of the NIH-AARP Study (HR lung cancer: 1.10; 95% CI: 0.97,1.25, $I^2 = 0\%$). Excluding NIH-AARP from the meta-analyses changed the HR estimates for total (HR: 0.96; 95% CI: 0.93, 1.00, $I^2 = 0\%$), breast (HR: 0.99; 95% CI: 0.86, 1.13, $I^2 = 2\%$) and prostate cancer (HR: 0.95: 95% CI: 0.81-1.12, $I^2 = 0\%$). Only the the association for colorectal cancer remained statistically significant (HR colorectal cancer: 0.83 (95% CI: 0.73, 0.96, $I^2 = 19\%$)).

The pooled RAP estimate for total cancer was -1.57 years (95% CI: -4.09, 2.16) and -3.13 years (95% CI: -1.86, -1.29) for colorectal cancer. This result means that the risk of cancer could be postponed by about 1.6 years, in elderly aged 60 years and above, for each additional WCRF/AICR recommendation followed. No significant effect modification was observed.

The following results base on the analysis of the association between the WCRF/AICR dietary recommendations and total and colorectal cancer risk. The exclusion of single WCRF/AICR dietary components changed the HR estimates for total and colorectal cancer marginally (≤ 0.03 above or below the initial HR estimate). The comparison between the WCRF/AICR diet score and the diet plus score derived in the Rotterdam Study, EPIC Elderly Spain, Greece and Netherlands and NIH-AARP revealed similar pooled HR estimates. The WCRF/AICR diet score showed a HR of 0.95 (0.91-1.00) and 0.84 (95% CI: 0.81-0.88) and the diet plus score showed a HR of 0.98 (0.92-1.04) and 0.85 (0.83-0.88) for total and colorectal cancer, respectively.

Discussion

In this meta-analysis of seven prospective cohort studies from Europe and the United States, with a median follow-up of 11 to 15 years, we found that elderly who adhered to one additional WCRF/AICR dietary recommendation for cancer prevention, were at 6% lower risk to develop any kind of cancer after the age of 60 years. The greatest risk reduction of 16% was shown for colorectal cancer. This

estimate is equivalent to a postponed risk for colorectal cancer of about 3 years, in elderly, for each additional WCRF/AICR recommendation followed.

We found one earlier study that investigated the association between the 2007 WCRF/AICR dietary recommendations and cancer risk in a sensitivity analysis. Romaguera *et al.*[10] analyzed data of subjects aged 25 to 70 years at baseline in the EPIC Study. The HR association between the WCRF/AICR recommendations and cancer risk was 0.92 (95% CI: 0.89, 0.96). They reported similar HR estimates for the association between the WCRF/AICR dietary recommendations and cancer risk. In line with our results, the strongest association was shown for risk of colorectal cancer. This was not surprising given the convincing level of evidence on the association between colorectal cancer and diet, reported by WCRF/AICR.[3] A significant inverse association was found between the WCRF/AICR score and lung cancer risk in a group of middle aged participants from the EPIC Study. The difference observed for lung cancer risk may be related to the age distribution of the populations. HR estimates in elderly are expected to be weaker.[28]

Earlier dietary recommendations of the WCRF/AICR released in 1997 were not associated with cancer risk in a population of older women (aged between 55 and 69 at baseline).[5] The difference in results between the 2007 and 1997 WCRF/AICR diet recommendation may be related to an extended formulation of dietary guidelines in the 2007 release of the WCRF/AICR diet recommendations. New developments of the WCRF/AICR score were the inclusion of dietary fiber instead of complex carbohydrates, more refined definitions of alcohol and red meat intake and consideration of energy density and sugary drinks.

In addition to HRs, we calculated RAPs to enhance the quantification and communication of the impact on cancer risk through the adherence to a healthy diet, as defined by WCRF/AICR, later in life. To the best of our knowledge, no earlier study reported RAP estimates for the association between the WCRF/AICR recommendations and cancer risk. However, one earlier study on the association between a 1 point increase in the WCRF/AICR score and all-cause mortality showed a RAP of +1.2 years.[29] Comparisons of RAPs with earlier studies require a cautious interpretation as the exposure and outcome measures are different.

For the present study the WCRF/AICR recommendation for sodium and moldy foods was not scored.[10, 29] Sodium is of importance for stomach cancer whereas moldy foods are important for liver cancer.[3] None of these cancer outcomes were considered in the current analysis. Therefore, HR estimates are not expected to change if this component would have been additionally included in the score.

This meta-analysis of individual participant data has several strengths. The broad

range of prospective cohort studies represents a wide coverage of populations, and led to HR estimates, which are likely transferable to the general population of elderly participants in Europe and a relatively high educated group of elderly from the US. Other advantages of the present study were the use of harmonized variables and the application of the same analysis script across cohorts.

The assessment of diet and other lifestyle factors once at baseline represents a limitation of this study and most large cohort studies. Diet, lifestyle and other risk factors for disease occurrence might change during follow-up, which could introduce bias.[30] An earlier study in elderly reported relatively stable dietary patterns over a period of 5 years.[31] However, a final conclusion on the strength of potential bias, caused by diet changes later in life, cannot be drawn.[32, 33] Also, residual confounding by unmeasured or imprecisely measured covariates remains possible. Finally, even the application of standardized dietary assessment methods can result in measurement error and misclassification which may have weakened the observed association.

In conclusion, adherence to the WCRF/AICR dietary guidelines is associated with a reduced risk of developing diet related cancers in elderly from Europe and the United States. Our results suggest that the adherence to an additional WCRF/AICR dietary guideline increases the number of years lived with decreased risk of developing overall cancer by 1.5 and for colorectal cancer with 3 years. This suggests that, also among elderly, adherence to the WCRF/AICR dietary recommendations contributes to a lower burden of cancer.

Table 5.1 Operationalization of and adherence to the WCRF/AICR dietary recommendations for cancer prevention in the CHANCES consortium

Operationalization of WCRF dietary recommendations	Scoring	Rotterdam Study N (%)	EPIC Elderly					NIH-AARP Study N (%)
			Spain N (%)	Sweden N (%)	Netherlands N (%)	Denmark N (%)	Greece N (%)	
Total WCRF/AICR diet score:								
Greatest adherence	> 2.25	1833 (47)	3143 (63)	1347 (43)	2577 (42)	3116 (21)	7770 (86)	139649 (44)
Median adherence	1.75-2.25	1248 (32)	854 (17)	1280 (41)	1903 (31)	3984 (27)	920 (10)	101813 (32)
Low adherence	≤ 1.75	793 (20)	959 (19)	487 (16)	1670 (27)	7665 (52)	351 (4)	78254 (24)
Limit the consumption of energy dense foods and avoid sugary drinks								
Energy density:								
< =125Kcal/100 g/d	1.0	2019 (52)	1689 (34)	639 (21)	969 (16)	963 (6)	2790 (31)	94689 (30)
125 to <175 Kcal/100 g/d	0.5	1572 (41)	2616 (53)	1769 (57)	3952 (64)	7927 (54)	6019 (67)	171733 (54)
>175Kcal/100 g/d	0.0	283 (7)	651 (13)	706 (23)	1229 (20)	5875 (40)	232 (3)	53294 (17)
Sugary drink intake:								
0 g/d	1.0	2068 (53)	1839 (37)	54 (2)	590 (10)	384 (3)	none	2971 (1)
< = 250 g/d	0.5	1712 (44)	2884 (58)	2698 (87)	4361 (71)	11941 (81)	8435 (93)	107467 (34)
>250 g/d	0.0	94 (2)	233 (5)	362 (12)	1199 (20)	2440 (17)	606 (7)	209278 (65)
Eat mostly foods of plant origin								
Fruit and vegetable intake:								
≥400 g/d	1.0	2188 (56)	3519 (71)	493 (16)	2355 (38)	4952 (34)	8266 (91)	236467 (74)
200- 400 g/d	0.5	1491 (38)	1109 (22)	1210 (39)	3118 (51)	6334 (43)	706 (8)	66817 (21)
< 200 g/d	0.0	195 (5)	328 (7)	1411 (45)	677 (11)	3479 (24)	69 (1)	16432 (5)
Dietary fiber intake:								
≥ 25 g/d	1.0	175 (5)	2011 (41)	571 (18)	1761 (29)	6817 (46)	1604 (18)	68055 (21)
≥ 12.5-25 g/d	0.5	2988 (77)	2693 (54)	2028 (65)	4174 (68)	7361 (50)	6641 (73)	175280 (55)
<12.5 g/d	0.0	711 (18)	252 (5)	515 (17)	215 (4)	587 (4)	796 (9)	76381 (24)

Table 5.1 to be continued

Table 5.1 continued

Operationalization of WCRF dietary recommendations	**Scoring**	**Rotterdam Study** N (%)	**Spain** N (%)	**Sweden** N (%)	**Netherlands** N (%)	**Denmark** N (%)	**Greece** N (%)	**NIH-AARP Study** N (%)
Limit the intake of red meat and avoid processed meat								
Red and processed meat intake:								
Red meat <500 g/wk and processed meat < 3 g/d	1.0	408 (11)	599 (12)	49 (2)	671 (11)	372 (3)	6882 (76)	30264 (9)
Red meat <500 g/wk and processed meat 3 to 50 g/d	0.5	682 (18)	2405 (49)	2511 (81)	2445 (40)	3788 (26)	935 (10)	175467 (55)
Red meat ≥ 500 g/wk or processed meat >5g/d	0.0	2784 (72)	1952 (39)	554 (18)	3031 (49)	10605 (72)	1224 (14)	113985 (36)
Limit alcoholic drinks								
Ethanol intake: ≤20 g/d (men) Ethanol intake: ≤ 10 g/d (women)	1.0	2864 (74)	3563 (72)	3063 (98)	4560 (74)	8097 (55)	7884 (87)	256907 (80)
Ethanol intake : 20 to ≤ 30 g/d (men) Ethanol intake: 10 to ≤20 g/d (women)	0.5	513 (13)	491 (10)	45 (1)	744 (12)	2701 (18)	519 (6)	25866 (8)
Ethanol intake : >30 g/d (men) Ethanol intake: >20 g/d (women)	0.0	497 (13)	902 (18)	6 (0.2)	846 (14)	3967 (27)	638 (7)	36943 (12)

Table 5.2 Baseline characteristics, follow-up and cancer incidence of participants in the seven cohorts of the CHANCES consortium

Cohort	Rotterdam Study	EPIC Elderly					NIH-AARP
		Spain	Sweden	Greece	Netherlands	Denmark	
N	3,874	4,956	3,114	9,041	6,150	14,765	319,716
Follow-up (years)[1]	15	13	13	10	12	11	11
Cancer incidence[2]							
Total cancers	557 (14)	755 (15)	571 (18)	733 (8)	1024 (17)	3134 (21)	64103 (20)
Breast	120 (3)	55 (1)	55 (2)	63 (1)	203 (3)	321 (2)	6114 (2)
Lung	136 (4)	48 (1)	24 (1)	119 (1)	63 (1)	333 (2)	7470 (2)
Prostate	134 (3)	123 (3)	132 (4)	58 (1)	16 (0.3)	314 (2)	4198 (5)
Colorectal	171 (4)	81 (2)	61 (2)	85 (1)	136 (2)	300 (2)	5673 (2)
Women[2]	2,327 (60)	2,813 (57)	1,604 (52)	5,433 (60)	5,855 (95)	7,872 (53)	128,259 (40)
Age (years)[3]	70 ± 7	63 ± 2	60 ± 1	67 ± 5	64 ± 3	63 ± 2	66 ± 3
BMI	27 ± 4	30 ± 4	26 ± 4	29 ± 5	26 ± 4	26 ± 4	27 ± 5
Being vigorous physically activity[2]							
No	408 (11)	4666 (94)	n.a.	7051 (78)	2488 (40)	n.a.	163006 (51)
Yes	2151 (56)	257 (5)	n.a.	1851 (20)	3450 (56)	n.a.	153179 (48)
Education[2]							
Low	1428 (37)	4240 (86)	1707 (55)	8238 (91)	2054 (33)	6064 (41)	2549 (1)
Medium	2144 (55)	349 (7)	1019 (33)	493 (5)	3400 (55)	6354 (43)	84994 (27)
High	284 (7)	310 (6)	361 (12)	275 (3)	665 (11)	2308 (16)	222546 (70)
Smoking[2]							
Never	1352 (35)	3319 (67)	1861 (60)	6119 (68)	2932 (48)	4547 (31)	110304 (35)
Former	1691 (44)	806 (16)	671 (22)	1641 (18)	2108 (34)	5294 (36)	165161 (52)
Current	810 (21)	827 (17)	504 (17)	1042 (12)	1084 (18)	4878 (33)	32413 (10)

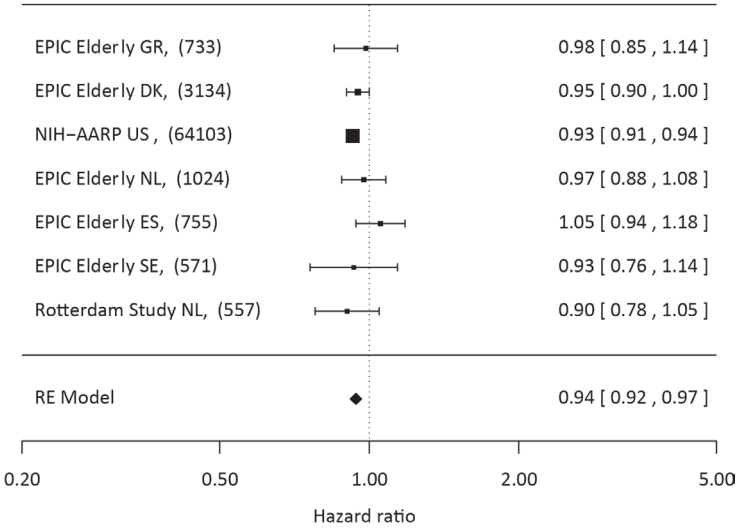
Table 5.2 to be continued

Table 5.2 continued

Cohort	Rotterdam Study	ES	SE	GR	NL	DK	NIH-AARP
Duration of smoking[2,4]							
1-15 years	364 (9)	157 (3)	151 (5)	287 (3)	526 (9)	1290 (9)	126079 (40)
16-30 years	517 (13)	337 (7)	287 (9)	506 (6)	862 (14)	1796 (12)	39082 (12)
>30 years	810 (21)	1115 (23)	628 (20)	1831 (20)	1682 (27)	6614 (45)	n.a.
Number of cigarettes smoked per day[2]							
1-15	488 (13)	334 (7)	n.a	596 (39)	788 (13)	2846 (19)	21731 (7)
16-25	218 (6)	196 (4)		325 (25)	233 (4)	1184 (8)	6628 (2)
>25	29 (1)	53 (1)		217 (61)	23 (0.4)	194 (1)	4054 (1)

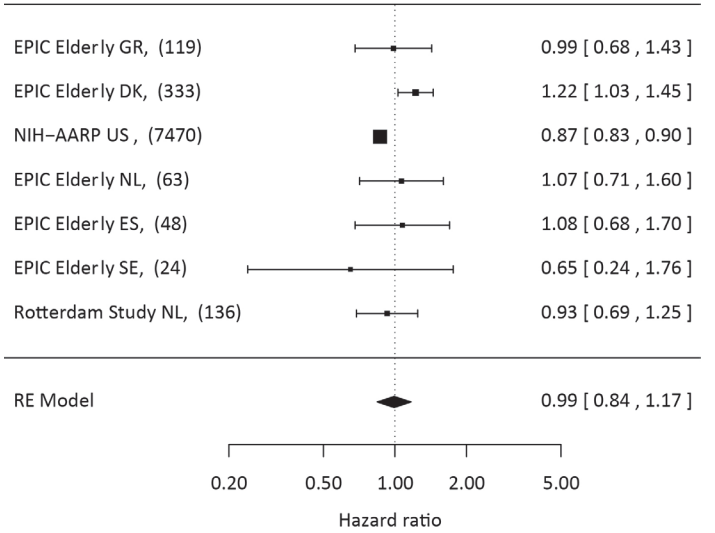
[1] Median and percentile 25, 75
[2] N (%), numbers do not add up to 100 %. The category including missing values is not presented in the Table.
[3] Mean and standard deviation
[4] Duration of smoking 1-15 years = <10 years in NIH-AARP; 16-30 years= >10 years in NIH-AARP; >30 = not applicable to NIH-AARP

a) Total cancer incidence



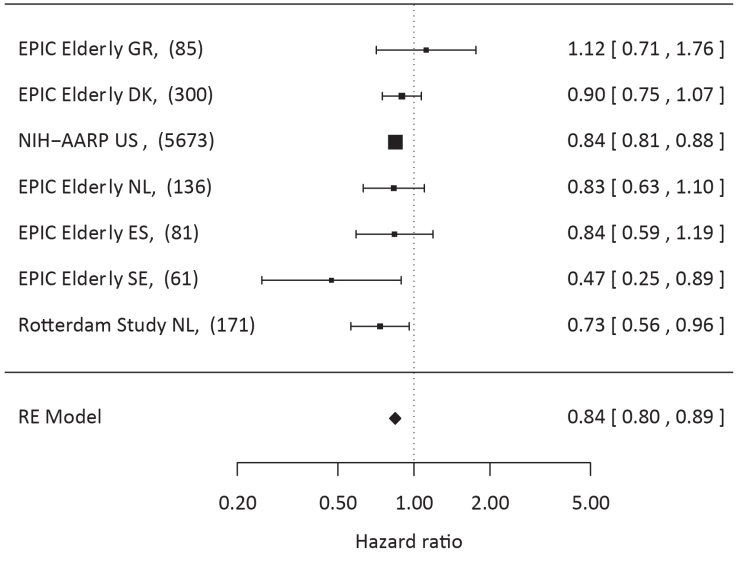
I^2 total cancer incidence = 16%

b) Lung cancer incidence



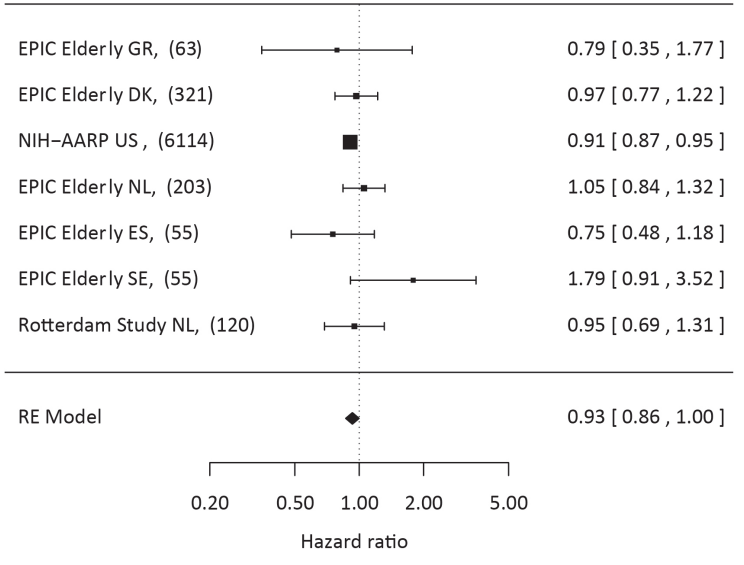
I^2 lung cancer incidence = 65%

c) Colorectal cancer incidence



I^2 colorectal cancer incidence = 3%

d) Breast cancer incidence



I^2 breast cancer incidence = 8%

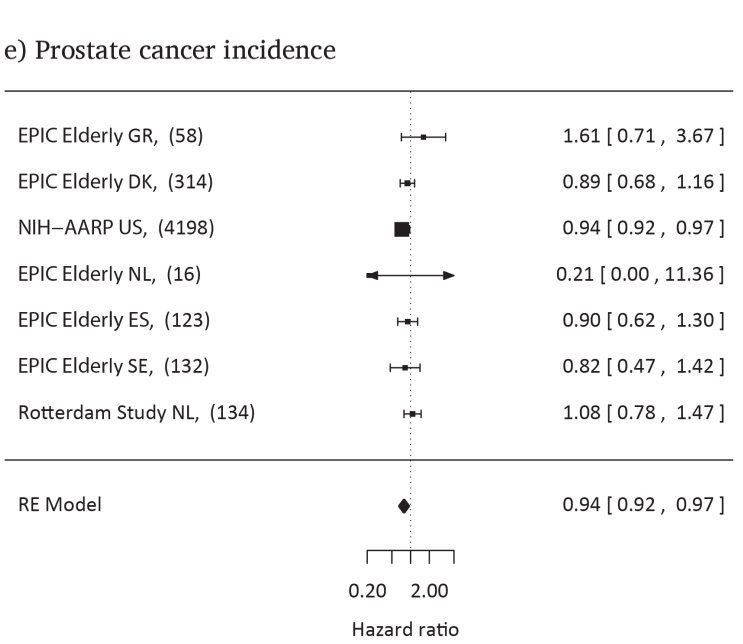


Figure 5.1 Cohort-specific and pooled adjusted hazard ratios (HRs) of total and site-specific cancer risk in relation to a 1 point increase in WCRF/AICR score, in the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES), 1988–2011. Bars, 95% confidence intervals (CIs). I^2 value is expressed as the percentage of total variability caused by heterogeneity. All data were obtained from CHANCES (www.chancesfp7.eu). EPIC-Elderly, European Prospective Investigation Into Cancer and Nutrition–Elderly Study; NIH-AARP, National Institutes of Health–American Association of Retired Persons Diet and Health Study; GR, Greece; DK, Denmark; US, United States; NL, Netherlands; ES, Spain; SE, Sweden

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Chapter 6

General Discussion

Summary of the main findings

The results from prospective cohort studies of the CHANCES consortium, focused on elderly populations, demonstrated that adherence to globally applicable dietary guidelines (WHO and WCRF/AICR) later in life was inversely associated with the incidence of chronic diseases, all-cause mortality and an increase in life expectancy.

The main findings of this thesis are summarized in Table 6.1. An increase of 10 Healthy Diet Indicator (HDI) points (range 0-70) equals the adherence to an additional WHO recommendation and was significantly inversely associated with all-cause mortality. The level of heterogeneity for the pooled estimate was high ($I^2 = 67\%$). However, all risk estimates pointed in the same direction, which indicates heterogeneity in the strength of the association, rather than differences in the direction of the association. The observed hazard ratio (HR) of 0.90, for the association between a 10 point increase in HDI and all-cause mortality, was equivalent to an increase in life expectancy of two years at the age of 60.

The pooled association between an increase of 10 HDI points and CVD mortality was not statistically significant (HR: 0.94 and 95% CI: 0.86-1.03) and showed again a high level of heterogeneity ($I^2 = 68\%$). Stratification by region showed a significant risk reduction for CVD mortality of 15% (95% CI: 13-17%) in the US and 13% (95% CI: 4-21%, $I^2 = 0\%$) in Southern European countries. No association was observed in Northern and Central and Eastern Europe, where heterogeneity remained high ($I^2 > 60\%$). Stratifying CVD mortality, for the analysis of cause specific mortality from coronary heart diseases and stroke, revealed no significant associations with the HDI score (Table 6.1).

An increase of 1 point in the WCRF/AICR diet score (range 1-4) represented the adherence to an additional WCRF/AICR dietary recommendation and was significantly inversely associated with total, colorectal and prostate cancer risk. The strongest association was found with colorectal cancer (HR: 0.84 and 95% CI: 0.80-0.89, $I^2 = 0\%$), while no association was observed between the WCRF/AICR diet score and risk of breast or lung cancer.

Table 6.1 Association between HDI and WCRF/AICR diet scores with mortality and chronic diseases

Outcome (and strata)	HR and 95% CI	I^2 (%)[1]
HDI by 10 points increase[2]		
All-cause mortality **($n_{\text{cohort studies}} = 11$)**	0.90 (0.87-0.93)	67
Stratified by region		
United States	0.89 (0.88-0.90)	n.a.
Europe	0.90 (0.84-0.96)	78
Southern Europe	0.88 (0.82-0.95)	53
Northern Europe	0.91 (0.82-1.02)	87
Central and Eastern Europe	0.93 (0.86-0.99)	0
CVD mortality **($n_{\text{cohort studies}} = 10$)**	0.94 (0.86-1.03)	68
Stratified by region		
United States	0.85 (0.83, 0.87)	n.a.
Southern Europe	0.87 (0.79-0.96)	0
Northern Europe	1.02 (0.85-1.24)	63
Central and Eastern Europe	0.96 (0.70, 1.31)	67
Stratified by outcome		
CHD	0.99 (0.85-1.14)	67
Stroke	0.95 (0.88-1.03)	7
WCRF/AICR diet score by one point increase[3]		
Total cancer risk **($n_{\text{cohort studies}} = 7$)**	0.94 (0.92-0.97)	16
Stratified by cancer site		
Breast	0.93 (0.86-1.00)	8
Colorectal	0.84 (0.80-0.89)	3
Lung	0.99 (0.84-1.17)	65
Prostate	0.94 (0.92-0.97)	0

[1] I^2 describes the variability among studies.
[2] The mean and standard deviation for the HDI ranged from 5.3 ± 0.7 to 4.0 ± 0.8 across cohorts.
[3] The mean and standard deviation for the WCRF/AICR score ranged from 3.0 ± 0.5 to 1.8 ± 0.7 across cohorts.

Reduced Rank Regression and implications for further results

Before analysing the association between a healthy diet and disease, dietary patterns were first assessed regarding their stability over time. Reduced rank regression (RRR) was applied in the Zutphen Elderly Study to derive dietary patterns. The result showed that dietary patterns derived from RRR were stable on the population level over a period of 5 years (chapter 2). Based on the results described in chapter 2 and earlier studies on the stability of dietary patterns over time,[6-8] the use of baseline dietary data is expected to provide a reasonable estimation for long term exposure (at least 5 years). This was an important finding for the interpretation of the results shown in chapter 3 to 5. The majority of CHANCES studies eligible for analysis, assessed dietary intake at baseline; no repeated measurements for diet were taken. Median follow-up periods ranged from 5 to 15 years. Hence, the derived HR estimates described in chapter 3 to 5 are assumed to be reliable. However, if repeated measurements of dietary exposure are available, it is recommended to use this information for association studies, to increase the precision of the association.[9-12]

The overall aim of this thesis was to provide evidence on the association between a healthy diet followed later in life, all-cause mortality and chronic diseases. The ability of RRR to discriminate a "healthy" from an "unhealthy" dietary pattern, in the Zutphen Elderly study, was low. Therefore, RRR was not considered for further analysis of diet disease associations described in this thesis.

Methodological considerations (internal and external validity)

The discussion sections of chapter 3 to 5 included methodological considerations, specifically relevant for the interpretation of the results described in these chapters. Differences in study design across cohorts, such as follow-up periods and dietary assessment methods (which might have influenced the overall HR estimates and the level of heterogeneity) were already discussed. The following pages address some generic methodological questions related to meta-analysis, confounding, studying older populations and dietary pattern analysis, relevant to chapters 3 to 5.

Methodological considerations regarding meta-analysis

Different approaches exist to summarize cohort data and derive an overall summary estimate.[13] Pooled analysis, for instance, requires a single dataset that includes all cohort data. After the investigation of the single cohorts contributing to the CHANCES project, it was concluded that study designs and assessment methods across cohorts were too different to derive a pooled dataset. Therefore, "two-step random effects meta-analysis" was chosen instead.

The analysis of single cohorts was expected to show a smaller amount of variation in dietary exposure in comparison to pooled analysis.[14] However, large variation in dietary intake was observed in several cohorts, i.e. SENECA and NIH-AARP, which included data of cohorts across Europe and the United States, respectively.

All CHANCES variables used for the data analysis were harmonized. The standardization procedure was performed by each cohort separately, following a well-defined standardization protocol. The standardization of variables enabled maximal comparability across cohorts and permitted application of the same analysis script in each of the cohorts. These procedures ascertained the validity of the overall pooled HR estimate.

Selection of cohorts included for analysis

The CHANCES consortium represents a selection of cohort studies, with a large number of participants aged 60 years and above. All results derived in the single cohort studies, independent of their outcome, were presented and included in the subsequent meta-analysis. Therefore, positive publication bias[15] towards a significant result, was not an issue. Eleven of 15 CHANCES cohorts (http://www.chancesfp7.eu/cohorts.html) had sufficient information on dietary data. The number of cohorts, available for analysis, decreased for disease-specific outcomes. The lowest number of seven cohorts was available for the analysis of cancer risk. CHANCES focussed on cohorts from Europe and the US. Fortunately, both regions were represented in each of the analyses, which made it possible to draw an overall conclusion for Europe and the US.

Final considerations for meta-analysis

The quality of the meta-analysis depends on the quality of the included cohort studies.[15] All except one cohort (HAPIEE) used a dietary assessment method, that was validated in their cohort. All-cause mortality and CVD mortality were derived from death registers and cancer outcomes were derived from cancer registries. Thus, the overall pooled results are considered to be valid and reliable. For the analysis in chapter 3 to 5, latest updates on mortality and cancer incidence were used, which ensured currentness of the data. Furthermore, a large number of cases assured sufficient power of the study.

Methodological considerations regarding studying the elderly

A recent policy report by the joint research centre of the European commission[16] addressed the need for epidemiological evidence to improve the aging process. This statement should provide encouragement to perform research in the elderly population despite methodological challenges that are related to this age group.[17]

In the following, age-specific characteristics with potential influence on the results will be addressed.

Multi-morbidity is of specific concern in the elderly. Older participants often suffer from more than one disease. These multi-morbidities may act in combination and result in differing risk estimates, when compared to someone without additional diseases. Multiple morbidities may also lead to the prescription of medical drugs or dietary restrictions which could result in a person's initial risk profile being changed.[17] Repeated measures, would have been required in chapter 4 (CVD mortality) and 5 (cancer risk) to account for the potential error introduced by multi-morbidities in the data analysis. However, no such data were available for the data analyses.

Associations between diet and disease are expected to be weaker in the elderly in comparison to younger age groups. The reason may be related to a larger number of incident cases at baseline, in older adults. The sensitivity analysis of chapter 3 on the association between a healthy diet and all-cause mortality, stratified by age (60-69 and above 70), showed a weaker HR estimate in those aged 70 and above compared to those aged between 60 and 69. Therefore, especially the cohorts including the oldest participants (EPIC Elderly Greece, Rotterdam Study and SENECA), may have underestimated the associations between a healthy diet, all-cause mortality and chronic diseases.

Performing research in the elderly population also has advantages, in comparison to a middle aged group of participants.[18] For example, dietary exposure is expected to be relatively stable with advanced age, which has been shown in earlier studies[6-8] and in chapter 2. Endpoints (like CVD and cancer) occur more frequently among the elderly in comparison to younger age groups.

Generalizability (external validity)

Selection bias is of particular importance in aging research. It can be introduced by a chronic disease occurring later in life which disables participants from joining the study. As a consequence, derived results might become less generalizable to the average elderly population.

From all CHANCES cohorts, the NIH-AARP study was considered to be least generalizable to an overall elderly population. The NIH-AARP study solely invited members of the American Association of Retired Persons (AARP). The response rate was only 18%. In comparison, the largest response rate of 72% was reported in the Rotterdam Study. The recruitment from the group of AARP members resulted in a dataset of participants with a considerably better health profile (e.g. high education level, low proportion of smokers), in comparison to the other cohorts. Even though the cohort specific outcomes might have limitations regarding generalizability,

overall pooled results are expected to cover a broad range of free living elderly, aged 60 years and above. This was additionally confirmed in a sensitivity analysis, by excluding the NIH-AARP study from the overall pooled HR estimate (chapter 3 and 4), which showed similar estimates in comparison to the overall pooled result.

Selection bias may introduce a phenomenon called "survival of the fittest". This theory states that elderly people have survived a range of exposures without dying. Hence, this selected group of the elderly might be less susceptible to external exposures. Likewise, this group of elderly participants might have had a lower exposure to risk factors contributing to the development of diseases later in life, which ascertained their survival. Selection bias and survival of the fittest may result in a homogeneous group of participants and a low variation in exposure, which could have weakened the association between diet and chronic diseases in some CHANCES cohorts.[19]

Methodological considerations regarding dietary pattern analysis

Similar to the analysis of single foods and nutrients, dietary pattern analysis is not free of confounding. The following paragraph will highlight some considerations regarding the use of confounding variables, energy adjustment and the potential influence of weighing factors on the association between a healthy diet on all-cause mortality and chronic diseases.

Confounding

The use of harmonized co-variables and identical Cox proportional hazards regression models, assured a great level of comparability of the analyses across studies. The degree of comparability differed between harmonized covariates. For instance, the definition of smoking in never, former and current was straight forward and highly comparable across cohorts, unlike the variable physical activity for example. The use of different methods (questionnaires) to assess physical activity, only allowed a crude categorization of this variable (e.g. vigorous physical activity yes or no).

Another limitation of a large consortium like CHANCES relates to the applicability of harmonized covariates for the Cox proportional hazards regression model. Education (high, medium, low), might not have been the best proxy to adjust for socioeconomic status in an elderly population. School education did not necessarily reflect the level of socioeconomic status, for those participants included in the analysis. The adjustment for education in the HR models did not result in a material change in HR estimate for either of the disease outcomes examined in chapter 3 to 5. The level of income or pension may have provided a better indicator for differences in socioeconomic status within a country. Unfortunately, information on pensions

or incomes was not provided by the CHANCES cohorts.

Not all confounding variables of interest such as drug use, multivitamin use or women specific covariates (e.g. menopausal status and number of children) were available in all cohorts. Therefore, these variables were not included in the main analysis. Implications for the results, by unconsidered covariates, were examined by sensitivity analyses. The results of the sensitivity analyses in previous chapters, on the association between the HDI and CVD mortality and the WCRF/AICR score and cancer risk, showed no substantial deviations from the overall results, when additional confounders were included for a subset of cohorts. All confounding variables included in the models were defined a-priori based on their association with the exposure and risk profile of the disease (triangle approach).[20]

Role of energy intake

All models were adjusted for total energy intake, though the HDI and the WCRF/AICR scores already account for total energy. The HDI expresses all macronutrients as energy percentages, while one of the WCRF/AICR recommendations suggests to limit the consumption of energy dense foods. As a result, there was no association between energy intake and the health outcomes while adjusting for the diet score. The inclusion of total energy in the Cox proportional hazards models did not change the HR estimates. However, including total energy in the model increased the comparability with previous studies, which adjusted for total energy.[21-23] Furthermore, energy intake and physical activity are highly correlated. The inclusion of total energy intake in the Cox proportional hazards model was expected to remove some extraneous variation related to physical activity.[24] Lastly, the aim of this thesis was to assess dietary quality instead of dietary quantity, which justifies the adjustment for energy intake.

Weighing factors

Previous research papers suggest the incorporation of weighing factors for diet quality indicators.[25] The rationale for weighing factors is based on the assumption that each component contributes differently to the development of chronic diseases. This was not confirmed in chapter 3 to 5, as the exclusion of one component at a time did not substantially affect the score. This shows that the overall pattern is not driven by one of its single components.[26, 27] Nevertheless, weighing factors may help to fine-tune a dietary pattern and increase predictability for a specific disease. However, more scientific evidence is required before weighing factors for specific recommendations or food groups can be assigned.[26]

Methodological considerations regarding the use of public health relevant measures in epidemiological studies

Standard measures derived in epidemiological studies, such as HRs, cannot be directly used to provide public health relevant messages. A broad range of alternative methods has been suggested in the literature.[27-31] In chapter 3, HRs were additionally expressed as Population Attributable Risk (PAR) and life expectancy. In chapter 5 cancer specific Risk Advancement Periods (RAP) were additionally provided (Box 6.1).

Box 6.1 Summary of public health relevant measures used in chapters 3 and 5

Population Attributable Risk (PAR): Number of deaths attributable to the adherence to a non-healthy diet.[1-3]

Life expectancy: Additional years to life while adhering to a healthy diet.[4]

Risk Advancement Periods (RAP): Number of years lived with a decreased risk to develop cancer while adhering to a healthy diet.[5]

The advantage of all these measures is the additional value they add to an epidemiological study. The major limitations of the chosen methods will shortly be discussed. The PAR estimate is based on a hypothetical construct in which all participants would adhere to a healthy diet. This extreme example reflects the percentage of deaths, attributable to the adherence to a non-healthy diet. Hence, PAR describes an unrealistic scenario, because a situation in which everybody would adhere to a healthy diet is unlikely to occur.[32] More limitations related to PAR were illustrated earlier.[33] The calculation of RAPs was described in chapter 5. The interpretation of this result is more complex in comparison to PAR or the increase in life years. RAPs describe the time period by which the risk of cancer is advanced among participants consuming an unhealthy diet conditional on disease-free survival to some baseline age.[5] The clause “disease-free survival” requires the RAP estimate to be treated with caution. Especially elderly participants suffer from multiple diseases. Thus, the calculated RAP for a single cause, excluding those participants with multiple incident diseases, may be weaker than presented in chapter 5. In contrast to PAR and RAP, the calculation of life expectancy requires more assumptions to make. Information on life expectancy of the average population is provided for instance by the WHO.[34] The use of an external data source assumes similar life trends in the average population and the data at hand, which does not necessarily have to be the case. Life expectancy provides a rough estimate of the true expectation. These limitations should be considered whenever public health relevant messages are provided.

The association between WHO recommendations and cancer risk

The WCRF/AICR dietary recommendations were regarded as most relevant for cancer outcomes and were therefore applied in chapter 5 to assess the association between a healthy diet and cancer risk. To complement the evidence for the WHO recommendations, regarding their aim to prevent chronic disease in general, an additional analysis on the association between the HDI and cancer risk was performed.

The HDI score was significantly inversely associated with risk for colorectal and lung cancer (Table 6.2). No association was observed with risk for total, breast or prostate cancer. A healthy diet was most likely to be associated with colorectal cancer risk. The link between diet and colorectal cancer has been well described,[37, 38, 39] while the association between diet and lung cancer remains less well established. However, fruits and foods containing beta-carotenes were convincingly associated with lung cancer.[35] Hence, the WHO recommendation on fruits and vegetables may drive the significant inverse association with lung cancer risk.

Table 6.2 Association between an increase of 10 HDI points and cancer risk, in CHANCES

Outcome	HR and 95% CI[1]
Overall cancer risk	0.97 (0.95-1.00)[2]
($n_{\text{cohort studies}} = 7$)	
Stratified by cancer site	
Breast	0.99 (0.96-1.03)[2]
Colorectal	0.96 (0.93-0.99)[2]
Lung	0.92 (0.90-0.95)[2]
Prostate	0.99 (0.97-1.01)[2]

[1] All models were adjusted for sex, age, education, physical activity, BMI, smoking status and intensity, alcohol, chronic diseases at baseline (diabetes, CHD, stroke) and total energy intake.
[2] These values are not part of the chapters in this thesis, but were derived to provide additional information for the WHO recommendations, with the aim of the prevention of chronic diseases.

The WHO recommendations appeared not specific enough to be associated with a decreased risk for total, breast and prostate cancer. The lack of association for breast and prostate cancer might be due to a lack of specific dietary recommendations for these cancers, such as limiting the consumption of alcohol to zero intake for breast cancer or consumption of foods high in selenium (e.g. nuts and cereals) and lycopene (e.g. tomatoes) for prostate cancer.[35] The inclusion of these recommendations may change the aim of WHO recommendations from prevention of overall chronic disease, to prevention of specific cancer outcomes.

Main findings in comparison with other studies published

The current work focussed on the association between globally applicable diet scores, all-cause and CVD mortality and cancer risk in elderly from Europe and the United States. To our knowledge, no such efforts were performed earlier, allowing limited comparison with previous studies. The results presented in chapters 3 to 5 can best be compared with review papers and multi-centre studies like EPIC. The largest amount of previous evidence was derived from middle-aged populations. The most important findings from previous research are described below. The evidence of this thesis, in combination with results reported in earlier studies, will be used to derive an overall conclusion.

Overall conclusion of review papers on the association between a healthy diet and risk of chronic diseases and all-cause mortality in the elderly

Previous review papers on the association between diet, chronic diseases and longevity in the elderly, concluded that most dietary pattern scores (Alternative Healthy Eating Index (AHEI), Healthy Eating Index (HEI), Dietary Approaches to Stop Hypertension (DASH), different versions of a Mediterranean diet score and HDI) showed an inverse association with chronic disease risk and mortality.[36-41] The major problem with previous dietary pattern analyses was the use of different analysis strategies. Therefore, comparisons across studies were limited, preventing an overall conclusion.[42]

Association between a healthy diet and mortality from all-causes and CVD mortality

The following paragraph summarizes a selection of previous, prospective cohort studies, on the association between a healthy diet and chronic diseases. Evidence for the HDI and its association with chronic diseases is limited. Therefore, other dietary pattern scores were included for the comparison with results reported earlier. The differences found in HR estimates, between Southern and Northern Europe (chapter 4), will be placed into broader perspective.

The EPIC study is one of the best known multi-centre cohort studies in Europe. The HDI was not applied earlier in the EPIC study. However, previous results on the association between the Mediterranean diet and all-cause mortality in the EPIC Elderly study showed a stronger, though non-significant, association for Southern European countries (France, Italy, Spain, Greece: HR 0.87 and 95% (0.79-1.01)), compared to Northern European countries (United Kingdom, Netherlands, Germany, Sweden, Denmark: HR 0.93 and 95% CI (0.89-0.97)).[43]

Previous multi-centre studies of Southern and Northern European cohorts, investigating the association between the HDI, all-cause and CVD mortality, showed

significant inverse associations.[44-46] In contrast, previous studies on the association between the HDI and risk of CVD,[22] cancer[47, 48] and all-cause mortality[22, 49, 50] performed in single cohort studies of Northern European countries did not show significant inverse associations. A possible explanation for the North-South gradient found in European countries, was given in chapter 4. In short, real differences in nutrient profiles[51] and food patterns[52-55] between European countries may cause different results in Northern and Southern Europe.[56]

Recently, Struijk *et al.*[57] made an interesting observation in the EPIC NL study. The HDI, as well as the Dutch Healthy Diet Index (DHD-Index), were not significantly associated with CVD risk in Dutch participants. The DASH score, however, was significantly associated with CVD risk. Food groups included in the DASH score, but not in the HDI score are: use of nuts, legumes and low-fat dairy products. The lack of these food components may have influenced the non-significant association found between the HDI and CVD mortality presented in chapter 4.

Association between the WCRF/AICR score, the HDI score and cancer risk

In this thesis the WCRF/AICR score was significantly inversely associated with total, colorectal and prostate cancer risk. Our findings fit very well with the results published earlier on the association between the WCRF/AICR recommendations and cancer risk.[21, 58, 59] Regarding the HDI, only one previous study was identified that investigated adherence to the HDI score and cancer risk.[48] In the Dutch cohorts of the EPIC study, no significant association was reported for a one point increase in HDI score and total cancer risk. The HR estimate and 95% CI for men was 0.96 (95% CI 0.89-1.03) and for women was 1.00 (95% CI 0.96-1.04).[48] These results are in accordance with the HR estimates presented in Table 6.2. The risks for breast, colorectal, lung or prostate cancer were not reported separately earlier, likely, due to a lack in number of cases.

WHO and WCRF/AICR recommendations

The aim of the WHO is to prevent chronic diseases globally. The results of this thesis showed that the WHO recommendations are inversely associated with the risk of CVD and all-cause mortality, and developing cancer. The primary aim of WCRF/AICR recommendations is to prevent cancer. A significant inverse association between the WCRF/AICR dietary recommendations and cancer risk was shown in chapter 5. A secondary aim was to prevent other chronic diseases, such as CVD.[35] Therefore, the WCRF/AICR recommendation on alcohol takes the inverse association between limited alcohol consumption and specific cardiovascular diseases into account, instead of stating that alcohol should be completely abandoned. Vergnaud *et al.*[60] showed that participants of the EPIC study, with the highest WCRF/AICR scores

(5-7 points), had a 34% lower risk of dying from any cause (95% CI: 0.59, 0.75) as compared with those with the lowest scores (0-3 points). Significant inverse associations were observed in all countries. Furthermore the WCRF/AICR score was significantly associated with a lower risk of dying from cancer and CVD.[60]

Both sets of recommendations are based on scientific evidence mainly derived from the middle-aged population. This thesis has shown that WHO and WCRF/AICR recommendations also apply to an elderly population. Globally applicable recommendations are supposed to support national guidelines.[35] Targeted dietary recommendations for a specific group or outcome would result in greatest benefits for disease prevention.[61] However, countries lacking national guidelines could, for example, rely on a combination of WHO and WCRF/AICR recommendations to formulate national dietary advice.

Randomized Controlled Trials

Benefits of a healthy diet on risk markers for disease have often been reported in randomized controlled trials[62-65] and support the results of this thesis. However, earlier studies did not consider globally applicable recommendations such as the ones by WHO or WCRF/AICR. Furthermore, they did not specifically target elderly participants.

The "New dietary strategies addressing the specific needs of elderly population for a healthy ageing in Europe" (NU-AGE) project, covers an internationally applicable diet plan, targeted on elderly participants, 65 to 80 years of age. The results of the NU-AGE trial would serve as an additional comparison to the findings presented in this thesis.[66] First results of the NU-AGE trial are expected to be published in the second half of 2015. The NU-AGE trial will also enable the researchers to answer the question, whether dietary changes towards a healthier diet later in life beneficially influence risk markers for chronic diseases. This is an important question in understanding the impact of dietary interventions performed in the elderly population which remains to be answered by RCTs (risk factors) and cohort studies (hard endpoints).[67, 68]

Conclusion on the comparison with previous research

The results derived from this thesis are in line with results from previous research. Adhering to a healthy diet, later in life, is associated with a reduced risk of diseases. This thesis showed that both globally defined nutrient intake recommendations and food recommendations prevent premature mortality and the occurrence of chronic diseases, even when applied to elderly people.

Suggestions for future research

Old age cannot easily be defined with clear cut-off points, due to the heterogeneity of this age group.[18, 69] The cut-off value for age of 60 years and above was assigned a priori by CHANCES. Future cohort studies should consider assessing additional measures on physiology (e.g. taste, appetite) and social life (e.g. living situation, loneliness) to enable a finer categorization of the elderly.[74, 75] This additional information may improve the data analysis (e.g. confounding variables) and interpretation of the results derived in elderly cohorts.

Furthermore, it might be of interest to assess the association between globally applicable dietary pattern scores, such as the HDI and WCRF/AICR score, and chronic diseases and all-cause mortality in non-westernized countries to assess worldwide applicability of the recommendations.

WHO and WCRF/AICR additionally suggest, one should be physically active and maintain a "normal" BMI over the lifespan. Both components could be added to the score as performed in chapter 5 on cancer risk. However, it should be noticed that BMI may not be the right indicator for health in older persons.[70, 71] Rather stable body weight, as suggested by WCRF/AICR, may be of greater importance. BMI history was not assessed in the CHANCES cohorts and could not be considered for sensitivity analysis. Future cohort studies may consider to ask for BMI history in their questionnaires. Additional benefits regarding the inclusion of BMI and physical activity, were not indicated in this thesis (chapter 5). The reason could be related to 1) the strong correlation between these components and diet, 2) defined cut-off values for BMI which may not be applicable to elderly and 3) a crude definition of the harmonized variable to define physical activity, as applied in this thesis. The combination of diet, physical activity and stable body weight (or a substitute) is most likely to achieve the greatest benefits in the prevention of chronic disease occurrences. This assumption is based on the strong scientific background for the preventive capacities of BMI and physical activity[72] on chronic disease development.[35, 73] Other risk factors such as smoking, stress, sleep deprivation were not examined in the current thesis and were therefore not specifically discussed. Generally speaking, the "healthier" one's behaviour, the lower the risk to develop diseases.[74-76]

Diet in the elderly offers a broad range of future research activities. The results of this work should encourage the use of the HDI and WCRF scores in research (to examine healthy diets) and in practice (to promote dietary guidance).

Public health implications

PAR, life expectancy and RAPs enabled the translation of the HR estimates to public health relevant messages. The calculation of PAR (chapter 3) showed that 2% (Rotterdam Study) to 18% (Epic Elderly Denmark) of deaths in these cohorts were attributable to a diet which was not in accordance with the WHO recommendations. Life expectancy for someone adhering to the WHO recommendations was increased by about 2 years for a person at the age of 60 years as compared to someone not adhering to the recommendations. The RAP estimates showed 1.5 additional years to live with a low risk to develop total cancer and 3 additional years for colorectal cancer while adhering to the WCRF/AICR recommendations.

These numbers may not appear to be large, however, it should be recognized, life expectancy and RAP estimates increase with increasing levels of dietary quality. Estimates on life expectancy and RAP suggest that the aim of the European commission to increase the healthy life span of elderly people by 2 additional years by the year 2020,[16] is a realistic goal.

The results of this thesis should encourage public health efforts to implement dietary interventions focussed on the elderly. Dietary advice can be guided by the recommendations of for example WHO and WCRF/AICR.

Taking all evidence into consideration, the following components may be incorporated in dietary advice. Based on the WHO recommendations: fruits, vegetables, dietary fibre, cholesterol, protein, sodium and trans-fatty acids. Polyunsaturated fatty acids are excluded from the consideration due to inconsistencies found with CVD mortality in Northern and Southern Europe which requires more scientific evidence. From the WCRF/AICR recommendations: Foods and drinks promoting weight gain, red and processed meat and alcohol. It should be noticed that recommendations for alcohol should be set deliberately. Low to moderate alcohol consumption is supposed to decrease the risk for CVD[77, 78] whereas the risk of cancer[79, 80] increases. To complement these scores, some additional components of the DASH score[81, 82] could be taken under consideration: nuts and legumes, and low-fat dairy.[57] However, the latter requires more scientific evidence before formulating sound recommendations on dairy foods.

In practice, healthy eating could be stimulated by restricting food marketing of certain foods (e.g. high caloric foods or foods high in sodium), improving the provision of nutrition information to the elderly and raising standards for foods provided in public institutions.[83, 84] For the elderly this should also cover home-delivered meals.[85] Susceptibility for behavioural changes is a pre-requisite for a successful intervention. Earlier studies have shown willingness of older adults to change existent behaviours.[86-88]

Overall conclusion

Adherence to a healthy diet, even at advanced age, is inversely associated with cancer risk, CVD and all-cause mortality. Dietary advice should be based on a large amount of evidence. This will result in greatest benefits to health. The importance of a healthy diet, in the elderly, to prevent chronic diseases, has been shown repeatedly. The recognition of the importance of a healthy diet in the elderly is necessary in order to plan and implement efficient public health interventions.

To finalize: One is never too old to eat healthy!!!

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Epilogue

It is a fact that our society is aging. The wish for a vital, long-lasting life is omnipresent in each of us and healthy diet, as defined by WHO and WCRF/AICR, helps to promote overall good health. Efforts to further refine the nutrient goals and guidelines are essential in reaching the greatest achievable outcome. The general guidelines seem to apply not only to middle age but also to elderly people. The circumstances for current generations allow for a long-lasting life. The next step is to define effective interventions, which decrease the number of chronic diseases and increase the years lived, disease free. Aging is likely to remain a hot research topic in the foreseeable future and aging without chronic diseases, will depend on the long-term success of public health interventions.

Summary

Samenvatting

Acknowledgments

Summary

Background

Current life circumstances allow a long lasting life and so, the group of elderly people, is growing constantly. Unfortunately, aging and chronic diseases are closely related. An important factor contributing to the development of chronic diseases is diet. Earlier studies, specifically examining the role of a healthy diet in the elderly, applied various analysis strategies. In consequence, comparability across studies is limited and prevents an overall conclusion on the role of a healthy diet in older adults.

Aim

The aim of this thesis was to assess the associations between a healthy diet, chronic diseases, all-cause mortality and longevity in the elderly. The analysis included harmonized data of different cohorts from Europe and the United States participating in the "Consortium on Health and Ageing: Network of Cohorts in Europe and the United States" (CHANCES). Within the CHANCES consortium elderly people were defined as being 60 years of age or older. No previous studies reported the association between dietary patterns, chronic diseases and mortality in elderly by means of a "two-stage Individual Participant Data meta-analysis", as performed in the current thesis. This thesis will add to the knowledge regarding the association of existing dietary guidelines and successful aging, in terms of expanding life expectancy and the time span lived disease free. The results of this thesis provide evidence, that can be used to improve health of the aging population by implementing successful interventions.

Results

Before analysing the association between a healthy diet and disease, dietary patterns were first assessed regarding their stability over time. Reduced Rank Regression (RRR) was applied in the Zutphen Elderly Study to derive dietary patterns. The result showed that dietary patterns derived from RRR were stable on the population level, over a period of 5 years, in elderly men aged 64 to 85 years (**chapter 2**). Based on the results described in chapter 2, the use of baseline dietary data provides a reasonable estimation for long term exposure (at least 5 years). The ability of RRR to discriminate a "healthy" from an "unhealthy" dietary pattern, in the Zutphen Elderly study was low. Therefore, RRR was not considered for further analysis of diet disease associations described in this thesis. Instead, diet indices were applied to assess adherence to a healthy diet in the elderly. The Healthy Diet Indicator (HDI) measures the adherence to the WHO nutrient intake recommendations, which intend to prevent the occurrence of chronic diseases worldwide. The recommendations of

the Word Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) aim at the prevention of cancer and were operationalized as the WCRF/AICR diet score.

Chapter 3 assessed the association between the HDI and all-cause mortality in 11 cohorts from Europe and the United States. A total of 396,391 participants were included for analysis. Greater adherence to the HDI was significantly inversely associated with all-cause mortality and showed an increase in life expectancy of 2 years at the age of 60.

In **chapter 4** the WHO nutrient intake recommendations were used to examine the association with cardiovascular disease (CVD), coronary heart diseases (CHD) and stroke mortality in 10 cohorts of the CHANCES consortium. The overall pooled results showed no association between the adherence to a healthy diet and cardiovascular disease mortality. The same results were observed for coronary heart diseases and stroke. However, stratifying the cohorts by region, showed a reduced risk of dying due to CVD in Southern Europe and the United States while adhering to a healthy diet. No association was found in Northern Europe and Central and Eastern Europe.

The study in **chapter 5** examined cancer specific recommendations and their association with overall, colorectal, lung, breast and prostate cancer risk in 7 cohort studies from Europe and the United States of the CHANCES consortium. A significant inverse association between the WCRF/AICR dietary recommendations and overall, colorectal and prostate cancer was observed. The strongest association was shown between the WCRF/AICR dietary recommendations and colorectal cancer risk. The results showed that the risk for the diagnosis of colorectal cancer could be postponed by about 3 years, in an older adult, for each additional WCRF/AICR recommendation followed. No association was found between the WCRF/AICR dietary recommendations and breast and lung cancer risk.

Conclusion

A healthy diet based on globally defined dietary recommendations by WHO and WCRF/AICR were found to be associated with all-cause and CVD mortality and cancer risk in elderly from Europe and the United States. Public health interventions targeted on the elderly should not focus on one definition of a “healthy diet” but rather on a smart combination of available evidence, to optimally account for CVD as well as cancer specific outcomes.

Samenvatting

Achtergrond

De huidige levensomstandigheden maken het mogelijk om lang te leven, waardoor de groep oudere mensen groeit. Helaas gaat een hogere leeftijd vaak samen met het ontwikkelen van chronische ziekten. Voeding speelt een belangrijke rol in het risico op chronische ziekten. Eerdere studies die hebben gekeken naar de rol van voeding bij ouderen, hebben verschillende methoden gebruikt. Daardoor is het lastig om deze studies met elkaar te vergelijken en was het eerder nog niet mogelijk om conclusies te trekken over de rol van gezonde voeding bij het voorkomen van chronische ziekten bij ouderen.

Doel

Het doel van dit proefschrift was om te bepalen wat het verband is tussen gezonde voeding, chronische ziekten, sterfte en levensverwachting bij ouderen vanaf 60 jaar. Voor de analyses is data gecombineerd van verschillende cohorten uit Europa en de Verenigde Staten. Dit onderzoek maakt deel uit van het "Consortium on Health and Ageing: Network of Cohorts in Europe and the United States" (CHANCES). In dit proefschrift wordt de relatie onderzocht tussen gezonde voeding, chronische ziekten en sterfte bij ouderen met behulp van een "two stage individual participant data meta-analysis", een methode die nog niet eerder is gebruikt in dit type onderzoek. Deze methode houdt in dat data van eerdere, langlopende studies wordt geanalyseerd en gecombineerd waarbij de individuele deelnemers worden gevolgd in de tijd. Dit proefschrift levert een bijdrage aan de kennis over het verband tussen gezonde voeding volgens voedingsrichtlijnen en succesvol ouder worden, wat in dit geval gedefinieerd wordt als het behalen van een hogere leeftijd en een kortere periode met chronische ziekten. De resultaten uit dit proefschrift kunnen bijdragen aan het verbeteren van de gezondheid van de ouder wordende populatie, bijvoorbeeld door het inzetten van voedingsgerichte interventies.

Resultaten

Om de relatie tussen voeding en ziekten te analyseren werd eerst de stabiliteit van voedingspatronen bekeken. Reduced Rank Regression (RRR) werd gebruikt om verschillende voedingspatronen in kaart te brengen bij mannen van de Zutphen Elderly Study met een leeftijd tussen 64 en 85 jaar. Het resultaat van deze analyse liet zien dat de verkregen RRR voedingspatronen over een periode van vijf jaar redelijk stabiel waren op populatieniveau (**hoofdstuk 2**). Op basis van deze bevinding leek het acceptabel om baseline voedingsgegevens te gebruiken voor longitudinale data-analyses (in ieder geval over een periode van 5 jaar). Met RRR was het in de Zutphense populatie niet goed mogelijk om een onderscheid te maken tussen

gezonde en ongezonde voedingspatronen. Om die reden is RRR niet meer gebruikt in de volgende hoofdstukken. In plaats van RRR, is er gebruik gemaakt van twee voedingsindices om te bepalen hoe gezond de voedingsinname van de ouderen was: de Healthy Diet Indicator (HDI) en de richtlijnen van het World Cancer Research Fund / American Institute of Cancer Research (WCRF/AICR). De HDI meet in hoeverre mensen zich aan de richtlijnen van de World Health Organization (WHO) houden. Het voldoen aan deze richtlijnen zou het ontstaan van chronische ziekten moeten voorkomen. De richtlijnen van het World Cancer Research Fund/American Institute of Cancer Research zijn bedoeld om het ontstaan van kanker te voorkomen.

In **hoofdstuk 3** werd het verband tussen de HDI en sterfte in 11 cohorten uit Europa en de Verenigde Staten bestudeerd. In deze analyse zijn de gegevens van 396,391 ouderen gebruikt. De resultaten van deze analyse lieten zien dat mensen die zich aan de WHO richtlijnen hielden minder snel dood gingen en een 2 jaar hogere levensverwachting hadden op een leeftijd van 60 jaar dan mensen die zich minder goed aan de richtlijnen hielden.

Hoofdstuk 4 beschrijft het verband tussen de HDI en sterfte door hart- en vaatziekten (HVZ), coronaire hartziekten (CHZ) en beroerte. De analyses werden uitgevoerd in 10 cohorten van het CHANCES consortium. Het resultaat liet zien dat er geen verband was tussen het volgen van de richtlijnen en het voorkomen van sterfte door HVZ, CHZ en beroerte. Het verband tussen de HDI en sterfte door HVZ was wel aanwezig na het stratificeren van de data naar regio. Er werd gevonden dat een betere HDI score (meer punten) geassocieerd was met minder sterfte door HVZ in Zuid-Europa en de Verenigde Staten. Er werd geen verband gevonden tussen HDI en sterfte door HVZ in landen in Noord-, Centraal- en Oost-Europa.

In **hoofdstuk 5** werd gekeken naar het verband tussen de kanker-specifieke voedingsrichtlijnen en het risico op kanker in het algemeen en darm-, long-, borst- en prostaatkanker in het bijzonder. In deze studie zijn 7 CHANCES cohorten uit Europa en de Verenigde Staten betrokken. Er werd aangetoond dat het volgen van de WCRF/AICR richtlijnen het risico vermindert op kanker in het algemeen en darm- en prostaatkanker in het bijzonder. Het sterkste verband werd gevonden tussen het volgen van de richtlijnen en risico op darmkanker. Het effect werd groter naarmate er aan meer richtlijnen werd voldaan: voor elke extra richtlijn van WCRF/AICR waaraan een persoon voldeed, werd het risico op de diagnose van darmkanker 3 jaar uitgesteld in vergelijking met personen die aan geen enkele van de kanker-specifieke voedingsrichtlijnen voldeden. Er werd geen verband gevonden tussen gezonde voeding en het risico op borst- en longkanker.

Conclusie

Gezonde voeding, zoals gedefinieerd door WHO en WCRF/AICR, was op latere leeftijd geassocieerd met een langer leven, minder totaalsterfte, minder sterfte door HVZ en een lager risico op verschillende soorten kanker. Interventies gericht op het verbeteren van de volksgezondheid door voeding zouden bij voorkeur de verschillende richtlijnen moeten combineren om zo verschillende chronische ziekten op latere leeftijd zo goed mogelijk te voorkomen.

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I want to finalize my acknowledgements with a thought to my father. He always said “you can reach whatever you want if your wish is strong enough”. Today, I know he was right and I am looking forward to work on the realization of my future wishes.

November 2014

Nicole

About the author

About the Author

Nicole Jankovic was born on 6th of April 1985 in Hann. Münden, Germany. She grew up in Hann. Münden and finished high school in 2004. Subsequently, Nicole started her studies in Nutrition and Home Economics at the Justus-Liebig University, Giessen, Germany. Besides her studies, she worked part-time as a student assistant at the Institute of Household Economics and Consumer Studies, in the years 2007 to 2008, and at the Institute of Agricultural Policy and Marketing research in 2007. Additionally, she was an active member of the Industrial Union Agriculture, Nutrition, Environment, Hessen (VDL), Germany. In September 2008, Nicole went to Wageningen, the Netherlands to start her MSc study on Nutritional and Public Health Epidemiology. Her MSc thesis was embedded in the large European Prospective Investigation into Cancer and Nutrition (EPIC) study. The topic of the thesis was on "The association between different types of protein and incidence of type 2 diabetes in the EPIC study". For her internship she went to the Institute of Child Nutrition (FKE) in Dortmund, Germany. There, she worked again with data of multiple cohorts of the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study. The topic of her internship thesis was related to dietary quality in adolescents from different countries in Europe. Next to her studies in Wageningen, she was an editor of the Wageningen website http://www.food-info.net/nl/index.htm and involved in the German Recruitment Team of Wageningen, University. In 2010, Nicole graduated in Wageningen and started her PhD studies together with Ellen Kampman, Edith Feskens and Lisette de Groot on the association between a healthful diet, chronic diseases and mortality in elderly from Europe and the United States. She participated as well in teaching activities and supervised thesis students. In 2012 she participated in the 3rd International Course in Nutritional Epidemiology, Imperial College London, United Kingdom and in 2014 she joined the European Nutritional Leader Platform Programme in Luxembourg. Currently, Nicole is working as a researcher at the University Duisburg-Essen in Essen, Germany at the Institute of Medical Informatics, Biometrics and Epidemiology. There she coordinates the development of a MSc degree programme in epidemiology, works on scientific publications and is involved in teaching activities at the University.

List of publications

Publications in peer-reviewed journals

Jankovic N, Geelen A, Streppel MT, de Groot LC, Orfanos P, van den Hooven EH, Pikhart H, Boffetta P, Trichopoulou A, Bobak M, Bueno-de-Mesquita HB, Kee F, Franco OH, Park Y, Hallmans G, Tjønneland A, May AM, Pajak A, Malyutina S, Kubinova R, Amiano P, Kampman E, Feskens EJ. Adherence to a Healthy Diet According to the World Health Organization Guidelines and All-Cause Mortality in Elderly Adults From Europe and the United States. Am J Epidemiol. 2014 Nov 15; 180(10): 978-88

Stefler D, Pikhart H, **Jankovic N**, Kubinova R, Pajak A, Malyutina S, Simonova G, Feskens EJ, Peasey A, Bobak M. Healthy Diet Indicator and mortality in Central and Eastern European populations: prospective evidence from the HAPIEE cohort. Eur J Clin Nutr. 2014 Dec; 68(12): 1346-52

Jankovic N, Streppel MT, Kampman E, de Groot LC, Boshuizen HC, Soedamah-Muthu SS, Kromhout D, Feskens EJ. Stability of dietary patterns assessed with reduced rank regression; the Zutphen Elderly Study. Nutr J. 2014 Apr 1;13:30. doi: 10.1186/1475-2891-13-30.

Diethelm K, **Jankovic N**, Moreno LA, Huybrechts I, De Henauw S, De Vriendt T, González-Gross M, Leclercq C, Gottrand F, Gilbert CC, Dallongeville J, Cuenca-Garcia M, Manios Y, Kafatos A, Plada M, Kersting M. Food intake of European adolescents in the light of different food-based dietary guidelines: results of the HELENA (Healthy Lifestyle in Europe by Nutrition in Adolescence) Study. Public Health Nutr. 2012 Mar;15(3):386-98

Publications in peer-reviewed journals named as collaborator

Schöttker B, Jorde R, Peasey A, Thorand B, Jansen EH, Groot Ld, Streppel M, Gardiner J, Ordóñez-Mena JM, Perna L, Wilsgaard T, Rathmann W, Feskens E, Kampman E, Siganos G, Njølstad I, Mathiesen EB, Kubínová R, Pająk A, Topor-Madry R, Tamosiunas A, Hughes M, Kee F, Bobak M, Trichopoulou A, Boffetta P, Brenner H. Consistent associations of low 25-hydroxyvitamin D concentrations with all-cause and cause-specific mortality in a large consortium of cohort studies from Europe and the United States. BMJ. 2014 Jun 17;348:g3656. doi: 10.1136/bmj.g3656

Submitted publications

Jankovic N, Geelen A, Streppel MT, de Groot CPGM Lisette, Kiefte de Jong J, Orfanos P, Bamia C, Trichopoulou A, Boffetta P, Bobak M, Pikhart H, Kee F, O' Doherty MG, Buckland G, Woodside J, Franco OH, Ikram MA, Struijk EA, Pajak A, Malyutina S, Kubinova R, Wennberg M, Park P, Kampman E, Feskens EJ. WHO guidelines for a healthy diet and mortality from cardiovascular disease in European and American elderly: the CHANCES project.

van Lee L; Geelen A; Kiefte-de Jong JC; Hofman A; Witteman JCM; Vonk N; **Jankovic N**; Hooft van Huysduynen E; de Vries JHM; van 't Veer P; Franco OH; Feskens EJM. Adherence to the Dutch dietary guidelines is inversely associated with 20-year mortality in a large prospective cohort study.

Aysel Müezzinler, Carolin Gellert, Ute Mons, et al. Smoking and All-cause Mortality in Older Adults - Results from the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES)

Conference abstracts

Jankovic N, Geelen A, Streppel MT, et al. dietary quality and all-cause mortality, CHANCES consortium. Focus on epidemiology at the Deutsche Gesellschaft für Epidemiologie (DGEpi) Jahrestagung in Leipzig, Germany; September 2013 (Oral presentation)

Jankovic N, Geelen A, Streppel MT, et al. dietary quality and all-cause mortality, CHANCES consortium. Focus on nutrition at International Congress of Nutrition (IUNS), Granada, Spain; September 2013 (Oral presentation)

Jankovic N, Geelen A, Streppel MT, et al. dietary quality and all-cause mortality, SENECA Study. Nederlandse Organisatie voor Wetenschappelijke Onderzoek (NWO), Deurne, The Netherlands; October 2012 (Oral presentation)

Jankovic N, Steppel MT, Kampman E, et al. The reproducibility of dietary patterns in an elderly Dutch population. Werkgroep Epidemiologisch Onderzoek Nederland (WEON), Rotterdam, The Netherlands; June 2012 (Poster presentation)

Jankovic N, Steppel MT, Kampman E, et al. The reproducibility of dietary patterns in an elderly Dutch population. International Conference on Diet and Nutritional Methods (ICDAM), Rome, Italy; May 2012 (Poster presentation)

Overview of completed training activities

Description	Location	Year
1. Discipline specific activities		
Courses		
Nutritional and lifestyle epidemiology	Wageningen, the Netherlands	2011
Masterclass multi-level analysis	Wageningen, the Netherlands	2011
International Course in Nutritional Epidemiology	London, United Kingdom	2012
Summer school "why we age"	Leyden, the Netherlands	2011
Masterclass longitudinal analysis	Wageningen, the Netherlands	2013
Symposium: 25 jaar voedingsonderzoek bij ouderen	Wageningen, the Netherlands	2013
Masterclass confounding	Wageningen, the Netherlands	2014
KLV lezing en discussie avond over kanker	Wageningen, the Netherlands	2012
Conferences and meetings		
Annual CHANCES project board meeting[1]	Heidelberg, Germany	2011
Annual meeting NWO nutrition	Deurne, the Netherlands	2011
Annual meeting NWO nutrition[1]	Deurne, the Netherlands	2012
Annual CHANCES project board meeting[1]	London, United Kingdom	2012
International Conference on diet and Activity Methods (ICDAM) [2]	Rome Italy	2012
WEON (vereniging voor epidemiologie) conference[2]	Rotterdam, the Netherlands	2012
Annual CHANCES project board meeting[1]	Rotterdam, the Netherlands	2013
International Congress of Nutrition (IUNS) [1]	Granada, Spain	2013
Deutsche Gesellschaft für Epidemiologie (DGEpi) [1]	Leipzig, Germany	2013
Annual CHANCES project board meeting[1]	Paris, France	2014

2. **General courses**

PhD competence assessment	Wageningen, the Netherlands	2011
Philosophy and Ethics of Food Science and Technology (6th edition)	Wageningen, the Netherlands	2011
VLAG PhD week	Baarlo, the Netherlands	2011
Successful presenting	Wageningen, the Netherlands	2011
Teaching and supervising thesis students	Wageningen, the Netherlands	2011
Interpersonal Communication for PhD Students (ICPS)	Wageningen, the Netherlands	2012
Scientific writing	Wageningen, the Netherlands	2012
European Nutritional Leadership Programme	Luxembourg, Luxembourg	2014

3. **Optional courses and activities**

Preparation research proposal	Wageningen, the Netherlands	2010
Literature and discussion groups: "Epi-research", "a bite into cancer", "methodology club", "oldsmobiles", "dietary patterns club" and "Rothman lunch"	Wageningen, the Netherlands	2010-2014
Staff seminars and student presentations of the division	Wageningen, the Netherlands	2010-2014
PhD study tour[1, 2]	Wageningen, the Netherlands	2011
How to write a world class paper	Wageningen, the Netherlands	2011

[1] Oral presentation given; [2] Poster presentation given

Notes/Notities/Notizen

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