UNIVERSITE PARIS 13

« EQUIPE DE RECHERCHE EN EPIDEMIOLOGIE NUTRITIONNELLE »

Année 2016

THESE

Pour obtenir le grade de

DOCTEUR DE L'UNIVERSITE PARIS 13

Discipline : Biologie - Santé Publique

Présentée et soutenue publiquement le 27 mai 2016 par

Karen Elena ASSMANN

Née le 15 mai 1987 à Marl (Allemagne)

***Titre en français* : Étude des déterminants nutritionnels (nutriments, aliments et alimentation globale) du vieillissement en bonne santé. Analyse dans la cohorte SU.VI.MAX 2.**

***Titre en anglais* : Investigation of nutritional determinants (nutrients, foods, and overall diet) of healthy aging. Analysis in the SU.VI.MAX 2 cohort.**

Thèse dirigée par :

Dr. Emmanuelle KESSE-GUYOT

JURY:

Madame le Docteur Claire SULMONT-ROSSE	Rapporteur
Madame le Docteur Raphaëlle VARRASO	Rapporteur
Monsieur le Professeur Pierre LOMBRAIL	Examinateur
Monsieur le Professeur Serge HERCBERG	Examinateur
Madame le Docteur Catherine FEART	Examinateur
Madame le Docteur Emmanuelle KESSE-GUYOT	Directeur de thèse

ACKNOWLEDGEMENTS

First of all, I would like to express my deep gratitude to my doctoral supervisor **Dr. Emmanuelle Kesse-Guyot**. I am especially thankful for her continuous encouragement and her enormous reactivity that have allowed me to conduct my work under very favourable conditions. I have not only benefited from her great scientific qualities, but also learned a lot from her on rigorous organization, project coordination, and self-confidence. It was a pleasure to have such an outstanding supervisor who is genuinely passionate about her work and very kind, open, and humorous on the personal level.

I would also like to thank **Professor Serge Hercberg**, the director of our research team, for creating a very stimulating research culture, for his continuous interest in my work, for his valuable advice, kindness, and encouragement. In addition, I am grateful for his advice and support during my search of a position as a postdoctoral research fellow. I am honoured to have worked in a research team that, under his guidance, continues to produce excellent scientific work and that seeks to advance projects with direct public health impacts.

Furthermore, I thank **Dr. Raphaëlle Varraso** and **Dr. Claire Sulmont-Rossé**. I am honoured that they have accepted to be the principal examiners (*rapporteurs*) of my thesis, and thus to take the time to evaluate my work.

I also thank **Professor Pierre Lombrail** and **Dr. Catherine Feart** who have kindly accepted to examine my thesis as members of my evaluation committee (*jury*).

In addition, I would like to express my thanks to Dr. Tasnime Akbaraly for the exchanges that we have had during my thesis, notably for her valuable comments and advice concerning my work on healthy aging.

I thank Dr. Pilar Galan, the co-director of our research team, for her valuable scientific advice, her kind encouragement, her friendliness, and her ongoing support – notably concerning my search of a postdoctoral research position.

Moreover, I thank Dr. Valentina Andreeva who was involved in many of the projects of my thesis, notably the development of a healthy aging questionnaire for the NutriNet-Santé study. I would like to thank her for her valuable advice, kindness, and support of my work.

I also thank Dr. Mathilde Touvier for her friendliness and support and for her helpful scientific advice – notably concerning my work on vitamin D and cognition, but also concerning other of my research projects.

Special thanks also go to Amandine Lecoffre, a psychologist who was an intern in our research team in 2013. Amandine has conducted an extensive bibliographic work on the different neuropsychological tests used in the NutriNet-Santé study (and, in part, in the SU.VI.MAX study). I have much profited from this work – and from further valuable advice that she has given me even after the end of her internship – for the drafting of my two cognition-related articles and of this thesis manuscript.

I would also like to thank Professor Hélène Amieva, who has provided very helpful critical comments and suggestions concerning the methodological article on the NutriCog test battery which I have drafted.

Furthermore, I am grateful to Dr. Eric Verger, for his very helpful comments and suggestions concerning my work on a priori dietary scores and healthy aging, and for his advice during my search of a position as a postdoctoral researcher.

I thank Dr. Benjamin Allès, Dr. Camille de Brauer Buscail, Dr. Valérie Deschamps, Dr. Léopold Fezeu, Dr. Chantal Julia, Dr. Katia Castetbon, Dr. Paule Martel, Dr. Caroline Méjean, Dr. Sandrine Péneau, Dr. Marie-Françoise Rolland-Cachera, Dr. Benoît Salanave, and Dr. Charlotte Verdot for the numerous interesting scientific exchanges that we have had since my arrival in our research team, for their openness, kindness, and humour which makes our research team a very pleasant place to work at.

Furthermore, I would like to thank the data managers, statisticians, informaticians, dieticians, technicians, and administrative personnel of our research team, especially Jagatjit Mohinder, Mohand Aït Oufella, Younes Esseddik, Yasmina Chelghoum, Rose Aris-Verrier, Marie Ajanohun, Nazneen Badroudine, Nathalie Arnault, Laurent Bourhis, and Charlie Menard, who have provided practical help and advice concerning my work.

Very special thanks go to present and former PhD candidates and post-doctoral researchers of our research team (and of the Unité Surveillance Périnatale et Nutritionnelle): Moufidath Adjibade, Solia Adriouch, Julia Baudry, Marc Benard, Julie Boudet, Mélanie Deschasaux, Abou Diallo, Pauline Ducrot, Philippine Fassier, Aurélie Lampuré, Dr. Camille Lassale, Hélène Lelong, Dr. Mehdi Menai, Dr. Camille Pouchieu, Wendy SiHassen, and Dr. Marion Torres. I am very thankful for our culture of mutual help, encouragement, and openness. I

owe a lot of the knowledge and skills that I have acquired during my thesis to you – and especially to Dr. Camille Lassale who has co-supervised the internship that I have conducted at the EREN prior to my thesis. To my office mates: the cheerful and humorous ambiance in our little “bureau des doctorants” is something that I will miss immensely.

I also thank Caroline Collin and Lola Neufcourt, two interns with whom I had chance to collaborate with in 2015, for their friendliness, the enthusiasm that they have put into their projects, and the great quality of their work.

Moreover, I am very grateful to Dr. Anette Buyken and to Professor Mariette Mercier, for their great support and encouragement during my studies. Dr. Anette Buyken was the supervisor of my German Diploma internship. She has been a great inspiration and role model for me, has taught me many things about nutritional epidemiology, and was a very pleasant person to work with – thanks to her kindness and openness. Professor Mariette Mercier was in charge of a master’s program in Public Health in Besancon that I attended as an Erasmus exchange student. She provided me with a very warm welcome in France, and her kind support and encouragement have helped me gain confidence in my capacities as an epidemiologist. In addition, her outstanding courses have largely contributed to my enthusiasm about epidemiological and clinical research.

I am deeply thankful to my large family, especially to my parents who have contributed to the proof-reading of my thesis and who have always supported and encouraged me. Moreover, I am thankful to my grandmother Irmgard, who – to me – is a truly outstanding model of healthy aging, ‘wise’ aging, and ‘positive’ aging. I am thankful to my grandfather Gerd who has been an enormous inspiration to me throughout my life. Moreover, I am thankful to my grandmother Elli for all her kindness and encouragement.

Finally, I would like to thank Eva, Heiner, Meike, and Aurélien for proof-reading my thesis and for always being there for me.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

25(OH)D, 25(OH)- vitamin D

95%-CI, 95%- confidence interval

A-MeDi, Alternate Mediterranean Diet score

ANCOVA, Analysis of Variance and Covariance

ADL, Activities of Daily Living

AGS, Abstracts in Social Gerontology

AHEI, Alternate Healthy Eating Index

ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention

CARET, Beta-Carotene and Retinol Efficacy Trial

CCPPRB, Comité Consultatif pour la Protection des Personnes se prêtant à la Recherche Biomédicale

CES-D, Center for Epidemiologic Studies Depression Scale

CFI, Comparative Fit Index

CNIL, Comité National Informatique et Liberté

CRP, C-reactive Protein

CUP, Continuous Update Project

DGAI, Dietary Guidelines for Americans Index

DK-TMT, Delis-Kaplan version of the Trail-making test

DNA, Deoxyribonucleic acid

DQI-I, Dietary Quality Index- International

EuroQoL, EuroQoL Quality of Life Scale

FOXO, class O- forkhead box transcription factors

GI, Glycemic Index

GL, Glycemic Load

HDL, High Density Lipoprotein cholesterol

HEI, Healthy Eating Index

ICD, International Classification of Diseases

IADL, Instrumental activities of daily living

IL, Interleukin

INSEE, Institut National de la Statistique et des Etudes Economiques (French National Institute of Statistics and Economic Studies)

JMIR, Journal of Medical Internet Research

LAMD, Literature-based Adherence Score to the Mediterranean Diet

LDL, Low Density Lipoprotein cholesterol

LPS, Lipopolysaccharid

MDS, Mediterranean Diet Scale

MMSE, Mini Mental State Examination

MSDPS, Mediterranean-Style Dietary Pattern Score

mPNNS-GS, modified Programme National Nutrition Santé- Guideline Score

OECD, Organisation for Economic Co-operation and Development

PANDiet, Probability of Adequate Nutrient Intake Dietary Score

PNNS-GS, Programme National Nutrition Santé- Guideline Score

PPARγ, Peroxisome Proliferator-Activated Receptor gamma

OR, Odds Ratio

RI-48, Rappel Indicé-48 items test

rMed, relative Mediterranean Diet Score

RR, Relative Risk

SF-6D, Short Form-6D healthy survey

SF-12, Short Form-12 healthy survey

SF-36, Medical Outcome Study Short Form-36

SOC, Selection-Optimization-Compensation

RMSEA, root mean square error of approximation

SPPB, Short Physical Performance Battery

SRMR, standardized root mean square residual

SU.VI.MAX, SUpplémentation en VItamines et Minéraux AntioXydants

TDS, Total Diet Score

TMT, Trail Making Test

TNF, Tumor Necrosis Factor

USDA, United States Department of Agriculture

WHO, World Health Organization

WHODAS, World Health Organization Disability Assessment Schedule

PREAMBLE

In the context of the immense demographic changes characterized as 'population aging' **(Wiener and Tilly 2002)** that are taking place worldwide, the prevention of age-related decline in health is a highly important challenge for modern societies.

Two important conceptual frameworks have been developed that permit the consideration of health during aging in a holistic, multidimensional manner – instead of considering isolated diseases and body functions: the concept of "frailty" and the concept of "successful aging" or "healthy aging". While frailty focuses on the "increased vulnerability" that is acquired in the course of age-related health decline **(Cosco et al. 2015a; de Vries et al. 2011)**, successful or healthy aging focuses on the presence of positive health aspects. Moreover, frailty- concepts cover primordially "biomedical" aspects, while a rather large proportion of successful or healthy aging concepts also cover psychosocial aspects **(Cosco et al. 2015a)**.

The healthy or successful aging- framework has notably been popularized by the conceptual work published by John W. Rowe and Robert L. Kahn on the basis of data from the MacArthur Foundation Study of Aging in America **(Rowe and Kahn 1987; Rowe and Kahn 1997)**. The "successful aging"- concept proposed by Rowe and Kahn includes three dimensions: "avoidance of disease and disability", "maintenance of high physical and cognitive function", and "sustained engagement in social and productive activities" **(Rowe and Kahn 1987)**.

One of the modifiable factors that have been suggested to have an important potential for the maintenance of good overall health status during aging is nutrition **(Kiefte-de Jong et al. 2014)**. The general objective of this thesis was thus to investigate the association of different types of nutritional factors (nutrients, foods, and indicators of overall dietary quality) with overall healthy aging – and with a component of healthy aging that has a particularly high public health relevance: cognitive functioning.

This thesis comprises one study that investigated the long-term association of antioxidant supplementation at nutritional doses with overall healthy aging, two studies that investigated different indicators of overall dietary quality in relation to later overall healthy aging, and one study that examined the long-term association of vitamin D status with cognitive functioning.

The first part of this thesis manuscript describes the state of knowledge, the second part specifies the specific objectives and research questions of this thesis, and the third part presents the general methodology that was applied in the different studies.

The central (fourth) part of the thesis manuscript comprises the published (or submitted) versions of the original articles that were drafted in the context of this study – as well as short summaries of these original articles.

Finally, this thesis manuscript includes a detailed discussion of the different findings of this thesis in the light of similar studies and of potential underlying mechanisms, as well as a final conclusion.

PUBLICATIONS AND COMMUNICATIONS

I. Original scientific articles

I.A Articles that are part of this thesis

Assmann KE, Andreeva VA, Jeandel C, Hercberg S, Galan P, Kesse-Guyot E. 2015. Healthy aging five years after a period of daily supplementation with antioxidant nutrients: a post hoc analysis of the French randomised trial SU.VI.MAX. Am J Epidemiol 182(8):694-704.

Assmann KE , Lassale C, Andreeva VA , Jeandel C, Hercberg S, Galan P, Kesse-Guyot E. 2015. A Healthy Dietary Pattern at Midlife, Combined with a Regulated Energy Intake, Is Related to Increased Odds for Healthy Aging. J Nutr 145(9):2139-2145.

Assmann KE, Andreeva VA , Camilleri JM, Verger EO, Jeandel C, Hercberg S, Galan P, Kesse-Guyot E. 2016. Dietary scores at midlife and healthy aging in a French prospective cohort. Br J Nutr. DOI: 10.1017/S0007114516002233, 11 pages [epub ahead of print].

Assmann KE, Touvier M, Andreeva VA, Deschassaux D, Constans T, Hercberg S, Galan P, Kesse-Guyot E. 2015. Midlife plasma vitamin D concentrations and performance in different cognitive domains assessed 13 years later. Br J Nutr 113(10):1628-1637.

I.B Articles that are not directly part of this thesis

Assmann KE, Bailet M, Amandine Lecoffre A, Galan P, Hercberg S, Amieva H, Kesse-Guyot E . 2016. Comparison between a self-administered and supervised version of a web-based cognitive test battery: results from the NutriNet-Santé cohort study. J Med Internet Res 18(4):e68.

Kesse-Guyot E, **Assmann KE**, Andreeva VAA, Castetbon K, Méjean C, Touvier M, Salanave B, Deschamps V, Péneau S, Fezeu L, Julia C, Allès B, Galan P, Hercberg S. 2016. Lessons learned from methodological validation research in e-epidemiology. [Under review]

Kesse-Guyot E, **Assmann KE**, Andreeva VAA, Touvier M, Neufcourt L, Shivappa N, Hébert JR, Wirth MD, Hercberg S, Galan P, Julia C. 2016. Long-term association between the dietary inflammatory index and cognitive functioning. Eur J Nutr. DOI: 10.1007/ s00394-016-1211-3, 9 pages [epub ahead of print].

Neufcourt L, **Assmann KE**, Fézeu LK, Touvier M, Graffouillère L, Shivappa N, Hébert JR, Wirth MD, Hercberg S, Galan P, Julia C, Kesse-Guyot E. 2015. Prospective association between the dietary inflammatory index and metabolic syndrome: findings from the SU.VI.MAX study. Nutr Metab Cardiovasc Dis 25, 988-96.

Kesse-Guyot E, **Assmann KE**, Andreeva VA, Ferry M, Hercberg S, Galan P. 2016. Consumption of dairy products and cognitive functioning: findings from the SU.VI.MAX 2 study. J Nutr Health Aging 20,128-37.

Kesse-Guyot E, Lassale C, **Assmann KE**, Andreeva VA, Julia C, Blacher J, Fezeu L, Hercberg S, Galan P. 2015. Are different vascular risk scores calculated at midlife uniformly associated with subsequent poor cognitive performance? Atherosclerosis 243, 286-292.

Neufcourt L, **Assmann KE**, Fézeu LK, Touvier M, Graffouillère L, Shivappa N, Hébert JR, Wirth MD, Hercberg S, Galan P, Julia C, Kesse-Guyot E. 2016. Prospective association between the dietary inflammatory index and cardiovascular diseases in the SU.VI.MAX cohort. J Am Heart Assoc 4(3):e002735.

Assmann KE, Lassale C, Galan P, Hercberg S & Kesse-Guyot E. 2014. Dietary quality and 6-year anthropometric changes in a sample of French middle-aged overweight and obese adults. PLoS One 9, e87083.

Andreeva VA, Whegang-Youdom S, Touvier M, **Assmann KE**, Fezeu L, Hercberg S, Galan P, Kesse-Guyot E. 2014. Midlife dietary vitamin D intake and subsequent performance in different cognitive domains. Ann Nutr Metab 65, 81-89.

Touvier M, Deschasaux M, Montourcy M, **et al.** 2014. Determinants of Vitamin D Status in Caucasian Adults: Influence of Sun Exposure, Dietary Intake, Sociodemographic, Lifestyle, Anthropometric, and Genetic Factors. J Invest Dermatol 135, 378-88.

Assmann KE, Joslowski G, Buyken AE, Cheng G, Remer T, Kroke A, Gunther AL. 2013. Prospective association of protein intake during puberty with body composition in young adulthood. Obesity (Silver Spring) 21, E782-E789.

Joslowski G, Remer T, **Assmann KE**, Krupp D, Cheng G, Garnett SP, Kroke A, Wudy SA, Gunther AL, Buyken AE. 2013. Animal protein intakes during early life and adolescence differ in their relation to the growth hormone-insulin-like-growth-factor axis in young adulthood. J Nutr 143, 1147-1154.

II. Communications at scientific conferences

II A 1. Oral communications

Journées Francophones de Nutrition (JFN) 09.-11. December 2015 – Marseille, France

Neufcourt L, **Assmann KE**, Fézeu LK, Touvier M, Graffouillère L, Shivappa N, Hébert JR, Wirth MD, Hercberg S, Galan P, Julia C, Kesse-Guyot E. Association prospective entre le Dietary Inflammatory Index et le syndrome métabolique : résultats de l'étude SU.VI.MAX. [Presented by **Assmann KE**]

12th European Nutrition Conference FENS 20.-23. October 2015 – Berlin, Germany

Assmann KE , Lassale C, Andreeva VA , Jeandel C, Hercberg S, Galan P, Kesse-Guyot E. Midlife dietary patterns and healthy aging among French adults: a prospective study.

12th European Nutrition Conference FENS 20.-23. October 2015 – Berlin, Germany

Assmann KE, Andreeva VA , Camilleri JM, Verger EO, Jeandel C, Hercberg S, Galan P, Kesse-Guyot E. Dietary scores at midlife and healthy aging in a French prospective cohort.

International Academy Nutrition and Aging (IANA) 18.-19. June 2015 – Barcelona, Spain

Assmann KE, Andreeva VA, Jeandel C, Hercberg S, Galan P, Kesse-Guyot E. 2015. Healthy aging five years after a period of daily supplementation with antioxidant nutrients: a post hoc analysis of the French randomised trial SU.VI.MAX. J Nutr Health Aging 19, Supplement 1, 18.

Journées Francophones de Nutrition (JFN) 10.-12. December 2014 – Bruxelles, Belgique

Assmann KE, Touvier M, Andreeva VA, Deschassaux D, Constans T, Hercberg S, Galan P, Kesse-Guyot E. Midlife plasma vitamin D and performance in different cognitive domains assessed 13 years later.

Annual congress of the German Society for Epidemiology (DGEpi) 17.-20. September 2014 – Ulm, Germany

Assmann KE, Andreeva VA, Jeandel C, Hercberg S, Galan P, Kesse-Guyot E. Daily supplementation with antioxidant vitamins and minerals in French middle-aged adults and successful aging: a post hoc analysis of the SUpplémentation en Vitamines et Minéraux AntioXydants (SU.VI.MAX) trial.

Annual congress of the German Society for Epidemiology (DGEpi) 26.-29. September 2012 – Regensburg, Germany

Assmann KE, Joslowski G, Buyken AE, Cheng G, Remer T, Kroke A, Gunther AL. Prospective association of protein intake during puberty with body composition in young adulthood.

II A 2. Poster communications

Journées Francophones de Nutrition (JFN) 09.-11. December 2015 – Marseille, France

Assmann KE, Andreeva VA, Hercberg S, Galan P, Kesse-Guyot E. Association prospective entre l'adhérence à la diète méditerranéenne et un concept multidimensionnel du vieillissement en bonne santé.

Journées Francophones de Nutrition (JFN) 09.-11. December 2015 – Marseille, France

Collin C, **Assmann KE**, Deschasaux M, Andreeva VA, Lemogne C, Charnaux N Sutton A, Hercberg S, Galan P, Touvier M, Kesse-Guyot E. Statut en vitamine D et symptômes dépressifs récurrents dans la cohorte française SU.VI.MAX. [Presented by **Assmann KE**]

Journées Francophones de Nutrition (JFN) 09.-11. December 2015 – Marseille, France

Collin C, **Assmann KE**, Andreeva VA, Lemogne C, Hercberg S, Galan P, Kesse-Guyot E. Adéquation aux recommandations nutritionnelles : un facteur protecteur vis-à-vis des symptômes dépressifs chroniques ou récurrents dans la cohorte française SU.VI.MAX. [Presented by **Assmann KE**]

Journées Francophones de Nutrition (JFN) 09.-11. December 2015 – Marseille, France

Neufcourt L, **Assmann KE**, Fézeu LK, Touvier M, Graffouillère L, Shivappa N, Hébert JR, Wirth MD, Hercberg S, Galan P, Julia C, Kesse-Guyot E. Association prospective entre le Dietary Inflammatory Index et les maladies cardiovasculaires dans la cohorte SU.VI.MAX. [Presented by **Assmann KE**]

International Academy Nutrition and Aging (IANA) 18.-19. June 2015 – Barcelona, Spain

Assmann KE, Andreeva VA, Camilleri GM, Verger EO, Jeandel C, Hercberg S, Galan P, Kesse-Guyot E. 2015. Dietary scores at midlife and healthy aging in the French prospective cohort SUpplémentation en Vitamines et Minéraux AntioXydants (SU.VI.MAX). J Nutr Health Aging 19, Supplement 1, 26-27.

International Academy Nutrition and Aging (IANA) 18.-19. June 2015 – Barcelona, Spain

Assmann KE, Lassale C, Andreeva VA, Jeandel C, Hercberg S, Galan P, Kesse-Guyot E. 2015. Midlife dietary patterns and healthy aging among French adults: a prospective study. J Nutr Health Aging 19, Supplement 1, 26.

International Academy Nutrition and Aging (IANA) 18.-19. June 2015 – Barcelona, Spain

Assmann KE, Touvier M, Andreeva VA, Deschassaux D, Constans T, Hercberg S, Galan P, Kesse-Guyot E. 2015. Midlife plasma vitamin D and performance in different cognitive domains assessed 13 years later. J Nutr Health Aging 19, Supplement 1, 27.

Journées Francophones de Nutrition (JFN) 10.-12. December 2014 – Brussels, Belgium

Assmann KE, Andreeva VA, Jeandel C, Hercberg S, Galan P, Kesse-Guyot E. Healthy aging five years after a period of daily supplementation with antioxidant nutrients: a post hoc analysis of the French randomised trial SU.VI.MAX.

STATE OF KNOWLEDGE

I. Population aging as a challenge for modern societies

I.A Worldwide demographic changes

According to estimates reported in the 2015-revision of the United Nations World Population Prospects **(United Nations 2015)**, the proportion of individuals aged 60 years or over will be almost a quarter or more in all main world regions except Africa by 2050 – and even higher than 30% in regions such as Europe, North America, China, or Russia. In France, 31% of the population will be aged 60 years or older by 2035 already, according to projections of the French National Institute of Statistics and Economic Studies (INSEE) **(Blanpain et al. 2010)**.

The 2011-report of the World Health Organization (WHO) on Global Health and Aging points out that while important demographic changes are occurring all over the world, these changes will be the most drastic in less developed countries, where the number of individuals aged 65 years or older is projected to increase by more than 250% **(World Health Organization 2011)**. In developed countries, this proportion is also projected to show a major increase, yet much smaller in magnitude as compared to less developed countries (71%) **(World Health Organization 2011)**. Within the European Union, the 'demographic old-age dependency ratio' (the ratio of individuals aged 65 years or older relative to individuals aged 15 to 64 years) has been projected to increase from 28% in 2013 to 50% in 2060 **(European Commission 2015)**.

I.B Increases in the burden of non-communicable diseases and disability

According to the WHO, the largest part of the disease burden that concerns elderly individuals worldwide is attributable to non-communicable diseases **(Beard 2015)**. Thus, the above-described drastic worldwide demographic changes are expected to be accompanied by an increase in the burden of age-related non-communicable diseases such as diabetes, cardiovascular disease, and different types of cancer **(World Health Organization 2011)**. Moreover, the prevalence of multimorbidity ("the presence of multiple chronic conditions at the same time") increases with age, and is associated with elevated health care costs **(Beard 2015)**.

According to estimations of the WHO **(Beard 2015)**, the largest burden of disability among individuals older than 60 years is attributable to impairments of sensory functions (notably in countries with rather low incomes), pain in back and neck, chronic obstructive pulmonary disease (notably in countries with rather low incomes), depression, falls, diabetes, neurodegenerative disease (especially in countries with higher incomes), and osteoarthritis.

I.C Dementia as a particular age-related public health problem

Dementia is a particularly important age-related public health problem as it is closely related to dependence and disability **(World Health Organization 2011)**. According to a "Delphi consensus study" published in 2005 **(Ferri et al. 2005)**, over 24 million individuals worldwide had dementia in 2005, and this number was estimated to "double every 20 years", so that in 2040, over 80 million individuals may be affected.

According to a report issued by the Organisation for Economic Co-operation and Development (OECD) in 2007, Alzheimer's disease is the most frequent form of dementia, as it accounted for approximately 75% of all dementia cases in an investigation of data from 12 countries. Moreover, less than 3% of individuals aged 65 to 69 years were affected by Alzheimer's disease, against nearly 30% among individuals aged 85 to 89 years. **(Lafortune and Balestat 2007; World Health Organization 2011)**

Alzheimer's disease has a long pre-clinical phase, during which early cognitive changes are detectable **(Amieva et al. 2008; Bäckman et al. 2005; Elias et al. 2000; Ritchie et al. 2016)**. This phase is also called the "predementia phase" of Alzheimer's disease **(Amieva et al. 2008)**. A nested case-control study published by Amieva et al in 2008 included repeated measurements of cognitive functioning over 14 years, and was thus able to closely investigate this predementia phase **(Amieva et al. 2008)**. The first detectable functional declines related to developing Alzheimer's disease later on were related to semantic memory (amongst others to "verbal concept formation"). These changes occurred as early as 12 years before diagnosis of clinical dementia. Approximately 8 to 9 years before diagnosis, functional decline was also observed concerning working memory (a subdomain of executive functioning, see Figure 7).

In a meta-analysis of 47 studies with much shorter follow-up periods (ranging from 1.1 to 6.7 years), preclinical "deficits" were notably observed for "global cognitive availability", "episodic memory", "perceptual speed", and "executive functioning", and to a "somewhat

smaller" degree for "verbal ability" and other aspects of cognitive functioning **(Bäckman et al. 2005)**.

Two elements that have been described as key histopathological characteristics of brains of Alzheimer's disease patients, and which have thus been proposed to be "hallmark lesions", are neurofibrillary tangles, which are aggregates of hyperphosphorylated forms of the microtubule-associated protein tau, and plaques containing amyloid-β **(Binder et al. 2005; Braskie et al. 2010; Brion 1998; Ittner and Gotz 2011)** . The specificity of very early changes to semantic memory that was observed by Amieva et al. is in line with the observation that temporal brain areas are specifically susceptible to the development of neurofibrillary tangle accumulation **(Amieva et al. 2008; Hof et al. 1992)**.

Curative treatment for Alzheimer's disease is currently not available **(Coley et al. 2008; de la Torre 2010)**. Thus, much emphasis has been put on the possibility of preventing or delaying its onset during – or before – the predementia phrase of the disease, notably by targeting different types of lifestyle factors, such as diet **(Coley et al. 2008; Creegan et al. 2015; Middleton and Yaffe 2009; Pope et al. 2003)** and physical activity **(Arenaza-Urquijo et al. 2015; Coley et al. 2008; Middleton and Yaffe 2009; Pope et al. 2003)**, as well as cognitive and social activities **(Arenaza-Urquijo et al. 2015; Coley et al. 2008; Middleton and Yaffe 2009; Pope et al. 2003)**. Singh-Manoux and Kivimäki have notably insisted on the need to investigate continuous changes in cognitive performances starting from early midlife – instead of only focusing on dementia incidence or other binary outcomes – in order to better understand the "cognitive aging process", and to identify "risk factors for unfavourable ageing trajectories" **(Singh-Manoux and Kivimaki 2010)**.

II. The concept of 'healthy' or successful' aging

This thesis refers to 'healthy aging' or 'successful aging' as multidimensional concepts which aim to characterize human health during aging as a whole. Such concepts have become popular objects of research in the last years **(Bülow and Söderqvist 2014; Cosco et al. 2014a)**; however, there is currently no consensus on how exactly 'healthy' or 'successful' aging should be defined **(Bülow and Söderqvist 2014; Cosco et al. 2014a; Martinson and Berridge 2015).**

II.A Terminology issues

Different terms are currently used to describe the above-described multidimensional concepts. The term that was proposed originally, "successful aging", has been criticised for having a

discriminatory connotation, because the concept that is generally considered the opposite of success is "failure" (Bülow and Söderqvist 2014). Thus, a separation of elderly individuals into those who age 'successfully' – and those who do not – can be perceived as degrading for the 'unsuccessful' group **(Bülow and Söderqvist 2014; Martinson and Berridge 2015; Scheidt R.J. et al. 1999)**.

In response to this criticism, a large number of alternative names has been proposed, including "successful aging", "healthy aging", "active aging", "active and healthy aging", "robust aging", "productive aging", "effective aging", "positive aging", "optimal aging", and "aging well" **(Bousquet et al. 2015a; Bülow and Söderqvist 2014; Depp and Jeste 2006; Katz and Calasanti 2014)**.

For the work included in this thesis, we have chosen to adapt the term "healthy aging" in order to avoid possible discriminatory connotations. Thus, this term is preferentially used throughout this thesis manuscript, except in the "State of knowledge"- section that describes the historical development of the concept, criticisms made concerning the most popular version of the concept, and a description of the heterogeneity of available definitions. In this section, many references to "successful aging" are made, since this is the term was proposed originally, and is still used by many authors.

II.B Historical overview

Figure 1 presents a timeline that illustrates some key aspects of the historical development of multidimensional concepts of successful aging or healthy aging.

Figure 1. Timeline illustrating key aspects of the historical development of the successful aging- framework (in part based on (Bülow and Söderqvist 2014)

II.B.1 Rowe and Kahn's model of successful aging

The scientific work that has led to a large dissemination of the 'healthy'/ 'successful' aging – concept, and that established it as a key theoretical framework in geriatric research, was the set-up of the McArthur Foundation Study on Successful Aging **(Bülow and Söderqvist 2014)**. In 1987, the principal investigator of the study, Robert W. Rowe, and his colleague Robert L. Kahn published an article titled "Human Aging: Usual and Successful" in the high-ranking generalist journal Science **(Rowe and Kahn 1987)**.

As highlighted by Bülow et al., the ideas published in this article should be seen, amongst others, as a reaction to rising criticisms with respect to "disengagement theory" **(Cumming and Henry 1961)**, which had been a key concept used in geriatric research **(Bülow and Söderqvist 2014)**. While disengagement theory postulated that "aging naturally and inevitably entailed a gradual withdrawal from society and social relations" **(Bülow and Söderqvist 2014)**, Rowe and Kahn's publication underlined that **age-related decline should not too readily accepted as fate**, stating that too much emphasis had been put on the "role of aging *per se*" when trying to explain health-decline during life.

Rowe and Kahn underlined the existence of "substantial heterogeneity within age groups" with respect to health status, which even appeared "to increase with increasing age". In this context, they insisted on the possibility of prevention, while highlighting that lifestyle factors such as diet and psychosocial factors made up a large part of the causal explanation for health deterioration during aging. Their hypothesis that 'successful aging' was indeed possible was derived from observations that within groups of elderly people, individuals existed that showed "minimal physiologic loss".

Ten years later, in 1997, Rowe and Kahn published another article in which they further developed their idea of 'successful aging' **(Rowe and Kahn 1997)**. It was in this article that they highlighted the multidimensional nature of their successful aging- construct, and defined its different dimensions: "avoidance of disease and disability", "maintenance of high physical and cognitive function", and "sustained engagement in social and productive activities".

II.B.2 Other early concepts

In 1961, Havighurst proposed a concept of successful aging that can be regarded as a multidimensional model of happiness and satisfaction with life:

> "A theory of successful aging is a statement of the conditions of individual and social life under which the individual person gets a maximum of satisfaction and happiness and society maintains an appropriate balance among satisfactions for the various groups which make it up". **(Havighurst 1961)**

The proposed components of happiness and satisfaction with life were "zest", "resolution and fortitude", "goodness of fit between desired and achieved goals", "positive self-concept", and a happy and optimistic "mood tone". Rowe and Kahn's model can be considered as very different from this framework, as it does not include any explicit notion of happiness and satisfaction with life.

Rowe and Kahn's concept is also quite different from an early framework of successful aging developed within the Kansas City Study of Adult Life **(Williams and Wirths 1965)**, which includes "the amount of activity in which the individual engages, his ability to disengage, his satisfaction with life, and the maturity or integration of his personality" as well as being persistently autonomous, with autonomy defined as giving at least the same amount of "input" or "energy" to others as received.

On the other hand, Rowe and Kahn's model is rather similar to two to other earlier concepts, proposed in 1974 by deCarlo ("able to carry on daily routine and absence from more than mild illness which would not impair one's daily routine" as well as good cognitive and mental health) **(DeCarlo 1974)**, and in 1979 by Palmore (surviving to 75 years of age, good physical function/ low disability, and happiness) **(Palmore 1979)**.

An important psychological model published in 1989, thus shortly after Rowe and Kahn's first article, is the "Selection, Optimization, and Compensation (SOC)"- model developed by Paul B. Baltes and Margret M. Baltes **(Baltes and Baltes 1989)**. This model postulates that successful aging involves "efforts at maintaining and achieving high levels of functioning by promoting an adequate level of general reserve capacity" (optimization), "reduction in the number of high-efficacy domains" (selection), and "compensatory skills and activities that become necessary when the required behavioural skills, capacities, and resources are no longer available" (compensation). This model is quite different from Rowe and Kahn's approach, since adaptive efforts of aging individuals are stressed, rather than external factors, and since it does not include the notion of avoiding disease.

II.B.3 The rising popularity of the successful aging- framework in research

Since Rowe and Kahn's publications on successful aging, a very large number of scientific articles have adopted or discussed this concept. Bülow et al. have counted 2,050 citations of Rowe and Kahn's 1987- paper by the 31st December 2013 using Google Scholar, and 998 citations using Web of Science **(Bülow and Söderqvist 2014)**. By the 29th of January 2016, these numbers had already risen to 2570 citations in Google Scholar, and 1,214 citations in Web of Science. Katz et al. have called the successful aging- framework "one of gerontology's most successful ideas" **(Katz and Calasanti 2014)**, and Holstein et al. stated that "the new gerontology" was "built on the concept of successful aging" **(Holstein and Minkler 2003)**, underlining the immense influence of Rowe and Kahn's work and of its adaption by other authors.

II.C Criticisms of Rowe and Kahn's concept

II.C.1 Themes of criticism

A large number of review articles or editorials on the healthy/ successful aging- framework have been published **(Angus and Reeve 2006; Anton et al. 2015; Belgrave and Sayed 2013; Bülow and Söderqvist 2014; Butler et al. 2011; Calasanti et al. 2006; Coleman 1992; Cosco et al. 2013a; Cosco et al. 2013b; Cosco et al. 2014a; Cosco et al. 2014b; Cosco et al. 2015a; Cosco 2015; Crowther et al. 2002; Depp et al. 2010; Depp et al. 2012; Depp and Jeste 2006; Dillaway and Byrnes 2009; Friedman et al. 2015; Fries 2002; Hansen-Kyle 2005; Holstein and Minkler 2003; Jeste et al. 2010; Kahana et al. 2014; Katz and Calasanti 2014; Katz 2013; Khaw 1997; Kivimäki and Ferrie 2011; Kuh 2007; Lamb 2014; Liang and Luo 2012; Martin et al. 2014; McKee and Schutz 2015; Minkler 1990; Morley 2009; Ouwehand et al. 2007; Peel et al. 2004; Peterson and Martin 2015; Phelan and Larson 2002; Pruchno 2015; Rubinstein and deMedeiros 2015; Ryff 1982; Scheidt R.J. et al. 1999; Schulz and Heckhausen 1996; Stowe and Cooney 2015; Tavel 2008; Topaz et al. 2014; Young et al. 2009)**, most of which made suggestions on how the concept proposed by Rowe and Kahn could be improved, or simply expressed concerns about the relevance of the successful aging- framework as it had been developed in geriatric research.

In 2014, Martinson and Berridge published a review of the literature that attempted to summarize the different critiques and suggestions for improvement stated in scientific publications between 1987 and 2013, which were listed in a specific gerontology-related

scientific database, the "Abstracts in Social Gerontology (AGS) database" **(Martinson and Berridge 2015)**.

Several critical reviews of the successful aging concept were not included in Martinson and Berridge's analysis, either because they were published later or because their abstracts had not been referenced in the above-mentioned AGS- database **(Belgrave and Sayed 2013; Bowling and Dieppe 2005; Bülow and Söderqvist 2014; Calasanti et al. 2006; Cosco et al. 2013a; Cosco et al. 2013b; Cosco et al. 2014a; Cosco et al. 2014b; Cosco 2015; Depp and Jeste 2006; Kahana et al. 2014; Katz and Calasanti 2014; Katz 2013; Kuh 2007; Lamb 2014; Martin 2001; Morley 2009; Ouwehand et al. 2007; Peel et al. 2004; Peterson and Martin 2015; Phelan and Larson 2002; Pruchno 2015; Rubinstein and deMedeiros 2015; Ryff 1982; Schulz and Heckhausen 1996; Stowe and Cooney 2015)**. Yet, the different themes of criticism revealed by Martinson and Berridge provide a very complete overview, as criticisms expressed in other publications were largely redundant with what had already been highlighted by Martinson and Berridge.

The following paragraphs, as well as **Figure 2**, which illustrates the different aspects of criticism of Rowe and Kahn's model in a visual manner, are thus largely based on the review article by Martinson and Berridge **(Martinson and Berridge 2015)**.

Figure 2. Summary of criticisms of Rowe and Kahn's successful aging- model (largely based on (Martinson and Berridge 2015))

a) Low proportions of successful aging

A further identified theme of criticism was related to the generally rather low proportions of healthy aging reported by studies that applied definitions based on Rowe and Kahn's model **(Martinson and Berridge 2015)**. Martinson and Berridge notably cited McLaughlin et al., who have suggested adapting the criteria and thresholds for successful aging definitions so as to not "limit the study of healthy aging to those with near-perfect health" **(McLaughlin et al. 2012)**. Several other authors (notably Cosco and Schulz (Cosco et al. 2014b; Schulz and Heckhausen 1996)) have highlighted this issue by stating that, especially for the oldest-old, Rowe and Kahn's criteria were unrealistic to achieve. Of note, proportions obtained when applying Rowe and Kahn's criteria tend to be much lower than proportions of self-rated successful aging **(Cosco et al. 2014a)**.

b) Too little emphasis on psychosocial factors, subjective factors, and 'positive' factors

Several of the identified studies underlined that Rowe and Kahn's concept was lacking one or more important aspects. Very general suggestions were to put more emphasis on psychological and social factors, subjective factors, and to use "positive as opposed to pathological health characteristics". **(Martinson and Berridge 2015)**

The need to put more emphasis on 'subjective' factors was, amongst others, stressed by Cosco et al. who highlighted that "augmenting objective components with subjective components provides a more holistic conceptualization" of successful aging **(Cosco et al. 2014a)**, and by Pruchno et al. who proposed a "Two-Factor Model of Successful Aging", including both objective and subjective measures **(Pruchno et al. 2010)**.

c) Too little emphasis on criteria that matter to elderly individuals

A further type of criticism was that the Rowe and Kahn- model was not sufficiently based on criteria that actually matter to elderly individuals, i.e. aspects that they perceive as important for their own successful aging. The criteria identified by Martinson et al. as having been reported to be part of older adults' subjective representations of successful aging include "emotional well-being", "spirituality", "comportment", "acceptance of change"/ "accepting the aging process", "self-acceptance and self-contentment", "self-care", "financial well-being", "living with family" and "emotional care". **(Martinson and Berridge 2015)**

The importance of giving more weight to criteria of successful aging that matter to aging individuals themselves has been stressed by various authors, such as Cosco **(Cosco et al. 2013a)**, Bowling **(Bowling and Dieppe 2005)**, Cernin **(Cernin et al. 2011)**, Jopp **(Jopp et al. 2015)**, and Troutman **(Troutman et al. 2011; Troutman-Jordan and Staples 2014)**. Cosco et al., who have conducted a systematic review on studies reporting lay perspectives of successful aging, have concluded that the most recurrent elements of lay perspectives were "attitudinal and engagement components", as well as "external factors, such as finances and environment" **(Cosco et al. 2013a)**.

d) Specific missing components

Martinson and Berridge also identified voices which proposed to add various rather specific components to the successful aging- framework, in order to obtain a more complete and

holistic concept. The listed components were "spirituality", "marital status and quality", "affective status", "life satisfaction", and "leisure activity". **(Martinson and Berridge 2015)**

e) Dichotomous nature of the construct

The dichotomous nature of Rowe and Kahn's successful aging concept has notably been criticised by Cosco **(Cosco et al. 2014b)** and Schulz **(Schulz and Heckhausen 1996)**. Schulz and Heckhausen underlined that a binary vision of successful aging prevented researchers from considering the "large heterogeneity within the normal category", that is, the variety of health states among 'usual agers'. **(Martinson and Berridge 2015)**

f) Problematic basic philosophy

Martinson and Berridge also identified publications that fundamentally challenged the relevance of Rowe and Kahn's successful aging- concept for various different reasons. One major reason was the **lack of consideration of socioeconomic and political factors**, such as social injustice, as important determinants of successful aging (i.e. an overestimation of the capability of individuals to be in control of their own fate by adopting a healthy lifestyle). **(Martinson and Berridge 2015)**

This point was notably stressed by Rubinstein **(Rubinstein and deMedeiros 2015)**. According to them, Rowe and Kahn's model showed an exaggerated focus on the possibilities of the individual to change its fate, which revealed a spirit of neoliberalism and "Western possessive individualism". For the authors, an immense problem of Rowe and Kahn's concept is that external factors related to the socioeconomic and political environment, such as social inequalities, are not accounted for.

Another important aspect revealed by Martinson and Berridge was that the **exclusiveness** of the concept, related to its binary approach, which leads to labelling the presence of disability as 'non-successful' aging. Since this can be perceived as discriminatory and judgemental, suggestions were made to create concepts that avoid creating groups of individuals that, by definition, do no longer have the chance to "age successfully" because they have disability or chronic illness. One example is a model of "resilient aging" which represents, according to the authors, a more inclusive concept as resilience was "attainable by all older adults". **(Martinson and Berridge 2015)**

Moreover, Rowe and Kahn's objective to mark a clear depart from disengagement theory has led to the fact that the reality of death, and thus the **inevitability of health decline at some**

point is missing from their concept. This has notably been criticised by Cosco **(Cosco et al. 2013a)** and by Lamb **(Lamb 2014)**.

g) Lacking life-course perspective

A final critically viewed aspect of Rowe and Kahn's model is the fact that it does not explicitly take a life-course perspective. Stowe et al. stated that it thus failed "to capture developmental processes and trajectories of continuity and change in function over time" **(Stowe and Cooney 2015)**. Further advocates for integrating a life-course perspective into concepts of successful or healthy aging are Pruchno **(Pruchno and Wilson-Genderson 2014)**, Kuh **(Kuh 2007)**, and Schulz **(Schulz and Heckhausen 1996)**.

II.C.2 Reaction of Rowe and Kahn to these criticisms

Rowe and Kahn have, in part, reacted to these different elements of criticism in an article published in 2015: "Successful Aging 2.0: Conceptual Expansions for the 21st Century". They clarify that in their view, models with a psychological focus that adopt life-course perspectives - such as the SOC- model developed by Baltes and Baltes **(Baltes and Baltes 1989)** - indicated the "how" of successful aging, while Rowe and Kahn's model indicated the "what". They also underline that their concept did not view the opposite of "successful aging" as "unsuccessful aging", but as "usual aging", stating that the terminology that was used during early phases of the development of their concept was "usual aging" versus "better than usual aging". With respect to criticisms stating that their model was "too biomedical", they pointed out that there were other voices that suggested focusing more - and not less - on aspects such as "biomarkers and genetics" as factors with a role for healthy aging **(Silverstein 2015)**.

A theme of criticism that appears to be of great importance to Rowe and Kahn is the lack of consideration of social, societal, and political factors in their initial successful aging model. A large part of their 2015- article is dedicated to this issue, underlining that they do consider these factors to be of major importance, and have thus, in 2007, assembled a research network dedicated, amongst others, to "recommend specific policies to facilitate emergence of a successfully aging society". This research network developed several important aspects of successful aging "at the society level": "productivity and engagement", "cohesion, including the degree of synergy or tension between generations and socioeconomic strata", "balance in dealing with the risks and benefits of demographic change", "resilience", and "sustainability" **(Rowe 2010)**. Moreover, Rowe and Kahn make three suggestions for research perspectives aimed at developing a successful aging concept that includes societal aspects: "re-engineering

core societal institutions", "adopting a life-course perspective", and "focusing on human capital". Research on societal institutions should cover aspects such as the identification of "institutional or structural obstacles to successful aging". In Rowe and Kahn's view, the adoption of a life-course perspective should include discussions on how different life tasks (raising children, professional activities, etc.) could be better distributed across lifespan. "Focusing on human capital" makes reference to using the talent of older individuals.

Rowe and Kahn also note that calls for completely abandoning their successful aging concept in response to the numerous criticisms were the "minority", and refer to Stowe and Cooney who suggested that the immense popularity and the large use of the concept in scientific research warranted "modification over disposal" **(Stowe and Cooney 2015)**.

II.D The heterogeneity of available definitions

II.D.1 Heterogeneity with respect to the included criteria

a) Description of the broad range of applied criteria

In 2006, Depp and Jeste conducted a comprehensive review of the literature in which they considered "published English-language peer-reviewed reports of data-based studies" on adults older than 60 years, which contained operationalized concepts of successful aging, and which "examined successful aging as a dependent variable" **(Depp and Jeste 2006)**. They retrieved 28 studies that included 29 different successful aging- definitions. The authors concluded that there was a large heterogeneity among the retrieved definitions, but that most concepts included the notion of "absence of disability" or good "physical performance", and (although to a lesser degree), the "absence of cognitive impairment".

The most recent systematic review of the literature was publish by Cosco et al. in 2014 **(Cosco et al. 2014a)**, and included original, peer-reviewed scientific articles that contained an operational definition of successful aging, which was not a "single-item self-report" measure of successful aging, and which did not use "previously identified operational definitions". A total of 84 studies met these criteria – and as some studies reported multiple definitions, a total of 105 different definitions were identified. A large majority (over 90%) of the definitions contained factors related to physiological health (such as "physical functioning"), and almost 50% contained elements related to engagement with life. Factors related to "well-being" were also found in almost 50% of definitions, and more than a quarter of operationalized definitions contained aspects related to "personal resources", such as

resilience. Only a small fraction (about 5%) included external factors such as an individual's financial situation. Three of the 84 studies also included self-rated successful aging as part of a multidimensional model.

Figure 3 illustrates the general groups of healthy/ successful aging- components identified by Cosco et al. **(Cosco et al. 2014a)**, as well as the more concrete criteria with which the components were operationalized. In addition, a number of concrete criteria that were not explicitly mentioned in Cosco's review (mostly because the respective studies had not yet been published, or because they did not provide data-based operationalized definitions, but rather suggestions for definitions) are listed.

The main categories of healthy/ successful aging- criteria identified by Cosco et al. ("physiological" criteria, "well-being", "engagement", "personal resources", and "extrinsic factors") are represented as central dark blue ellipses in the Figure. In addition, these main categories are discussed in the manuscript text below the Figure.

Figure 3. Components of published operational definitions of healthy or successful aging (largely based on (Cosco et al. 2014a))

Elements identified in the review of the literature published by Cosco et al. are displayed in circles or rectangles with a dark-blue background; additional elements are displayed in circles or rectangles with a light-blue background.

Physiological factors

Concerning the general component "physiological factors", Cosco et al. mentioned the concrete criteria "longevity", "physical function/ disability", "health status", "illness/ disease presence", and "mental health". Cosco et al. have not listed examples in order to detail what kind of specific criteria were summarized under the headings "longevity" and "health status". However, it can be hypothesized that "longevity" referred to survival up to a specific age (as used by authors such as Sabia et al. **(Sabia et al. 2012)** or Vaillant and Mukamal **(Vaillant and Mukamal 2001)**). Concerning "health status", it can be hypothesized that this category referred to indicators that were not directly related to physical functioning, cognitive functioning, diseases, or mental health – such as self-rated overall health status (as used by authors such as Roos and Havens **(Roos and Havens 1991)** or Hamid et al. **(Hamid et al. 2012)**).

In Figure 3, "illness/ disease presence" is generalized as "absence/ small number of (chronic) diseases" as some authors do not insist on the absence of disease, but rather on the presence of few diseases **(Pruchno et al. 2010)**. In an article titled "A proposed panel of biomarkers of healthy ageing", Lara et al. furthermore proposed to include metabolic health (including glucose metabolism and body composition), as well as endocrine function and immune function **(Lara et al. 2015)**.

Personal resources

With respect to the general component "personal resources", Rowe and Kahn mentioned the concrete criteria "resilience", "coping", and "independence/ autonomy". Other studies have operationalized this element with the factors "self-efficacy" **(Bowling and Iliffe 2006)**, "optimism" **(Bowling and Iliffe 2006; Cosco et al. 2015b)**, "education" **(Tyrovolas et al. 2015)**, "geotranscendence" **(Troutman et al. 2011)**, "spirituality" **(Araujo et al. 2016; Crowther et al. 2002; Troutman et al. 2011; Young et al. 2009)** and "health behaviours" (such as high dietary quality and physical activity) **(Tyrovolas et al. 2015; Zolnikov 2015)**.

Gerotranscendence is a concept developed by Tornstam, which has been summarized as "a shift in meta-perspective, from a materialistic and rationalistic perspective to a more mature and existential one" by Troutman et al. **(Troutman et al. 2011)**.

Extrinsic factors

Specifications concerning the component "extrinsic factors" in Cosco's review article included "environment" and "finances". A more concrete criterion related to "environment"

was mentioned by Zolnikov et al.: "environment free of contaminants" **(Zolnikov 2015)**. Zolnikov et al. also included the factor "healthcare framework" into their successful aging concept.

Engagement

The component "engagement" has been operationalized as "active life" and "social engagement", as well as "support system", and "voluntary work" according to Cosco et al. Further authors have also considered the factors "few sedentary activities" and "sense of belonging to a local community" **(Weir et al. 2010)**.

Well-being

Concerning "well-being", Cosco et al. have identified the concrete criteria "affective status" and "life satisfaction". Others have suggested the factors "little or no pain" **(Kaplan et al. 2008; Pruchno et al. 2010; Troutman et al. 2011)** and "quality of life" **(Bousquet et al. 2015a)**, including self-perceived health **(Cernin et al. 2011; Cho et al. 2012; Cosco et al. 2015b; Holden et al. 2014; Kok et al. 2015; Roos and Havens 1991; Thielke and Diehr 2012)**.

Subjective rating

As mentioned above, a final general component identified by Cosco et al. was "subjective rating of successful aging".

While the general categories of successful aging- components identified by Cosco et al. are very useful for comparing different definitions in a structured manner, it is evident that many of the various 'concrete criteria' listed above could be connected to multiple 'general categories'. For example, "little or no pain" could be interpreted as a factor related to well-being, but also as a factor related to physiological health. "Education" can be seen as a personal resource, but also as an external factor **(Lara et al. 2015)**. Moreover, "mental health", which has been classified among the physiological factors by Cosco **(Cosco et al. 2014a)**, is closely related to "affective status", which Cosco et al. have related to well-being.

b) Reasons for the observed differences in definitions

Overall, Depp's and Cosco's systematic reviews above all underline the large heterogeneity in operationalized definitions of healthy or successful aging **(Cosco et al. 2014a; Depp and Jeste 2006)**. This heterogeneity is largely related to the criticisms made with respect to Rowe and Kahn's concept. For example, many authors perceived a lack of emphasis on psychosocial dimensions, and thus added factors such as "resilience", "optimism", "spirituality", or

"purposefulness" – while others did not. Furthermore, the missing consideration of external factors/ societal determinants such as financial situation and education caused some authors to directly include such elements into their successful aging- definitions **(Cheung and Lau 2015; Tyrovolas et al. 2015; Wang and Lin 2012)** – while others preferred to study such factors as predictors, and not inherent components, of healthy or successful aging **(Arias-Merino et al. 2012; Avlund et al. 1999; Bell et al. 2014; Berkman et al. 1993; Britton et al. 2008; Chou and Chi 2002; Formiga et al. 2012; Hamid et al. 2012; Hank 2011; Jang et al. 2009; Kaplan et al. 2008; McLaughlin et al. 2010; Ng et al. 2009; Nosraty et al. 2012; Pruchno et al. 2010; Pruchno and Wilson-Genderson 2014; Strawbridge et al. 2002; White et al. 2015; Willcox et al. 2006)**.

In their 1997-article, Rowe and Kahn had explained that avoidance of disease referred "not only to absence or presence of disease itself, but also to absence, presence, or severity of risk factors for disease" **(Rowe and Kahn 1997)**. This explains why some authors included components such as body composition or body mass index **(Lara et al. 2015; Tyrovolas et al. 2015)**, blood pressure **(Cho et al. 2012; Gureje et al. 2014; Hamid et al. 2012; Holden et al. 2014; Jang et al. 2009; Pruchno et al. 2010; Pruchno and Wilson-Genderson 2014; Strawbridge et al. 2002)** or even health behaviours such as favourable eating habits and physical exercise **(Tyrovolas et al. 2015; Zolnikov 2015)**. However, most authors did not follow the suggestion to also include risk factors, and focused on the simple absence of disease and disability **(Cosco et al. 2014a; Depp and Jeste 2006)**.

In addition, it is natural that operationalized, data-based definitions of healthy or successful aging can only account for indicators for which data is available. Thus, an important reason for differences in available healthy aging definitions is probably related to data availability.

II.D.2 Heterogeneity with respect to chosen cut-offs

Even when using the same variables to define certain components of successful aging, operationalized definitions can differ with respect to the chosen instruments to measure particular indicators, and with respect to the chosen cut-offs for continuous variables. Notably, a large proportion of studies that use components based on cognitive and physical functioning tests use fixed cut-offs to define cognitive health **(Almeida et al. 2014; Andrews et al. 2002; Arias-Merino et al. 2012; Cernin et al. 2011; Chaves et al. 2009; Cho et al. 2012; Edwards et al. 2011; Formiga et al. 2012; Hsu 2011; Jorm et al. 1998; Li et al. 2006; Newman et al. 2003; Ng et al. 2009; Puig-Domingo et al. 2008; Reed et al. 1998; Roos and Havens 1991; Samieri et al. 2013; Sarnak et al. 2008; Sun et al. 2011; Tyas et al. 2007; von Faber et al. 2001; White et al. 2015; Willcox et al. 2006; Young et al.**

2009) and physical health (Andrews et al. 2002; Cernin et al. 2011; Edwards et al. 2011; Hamer et al. 2014; Reed et al. 1998; Strawbridge et al. 2002).

On the other hand, other studies use distribution-based cut-offs for cognitive functioning (Akbaraly et al. 2013a; Akbaraly et al. 2013b; Hamer et al. 2014; Hank 2011; Jang et al. 2009; McLaughlin et al. 2010; Sabia et al. 2012; Singh-Manoux et al. 2014) and physical functioning (Akbaraly et al. 2013a; Akbaraly et al. 2013b; Sabia et al. 2012; Singh-Manoux et al. 2014; von Faber et al. 2001) – especially studies based on the Whitehall II cohort (Akbaraly et al. 2013a; Akbaraly et al. 2013b; Sabia et al. 2012; Singh-Manoux et al. 2014).

II.D.3 Heterogeneity with respect to proportions of healthy or successful aging

In the systematic review of the literature published by Cosco et al. (Cosco et al. 2014a), there were 69 studies that reported percentages of successful aging, and 115 distinct groups of "successful agers". Healthy or successful aging- proportions ranged from less than 0.5% to about 92%. The median was 23%, and the mean was 28%. Among the six identified studies that investigated self-rated successful aging, however, as many as 71% were – on average – classified as "successful agers".

A number of studies have created multiple models of healthy or successful aging and have reported such proportions for each of their models. For instance, Nosraty et al. (Nosraty et al. 2012) have investigated successful aging among Finish individuals aged ≥ 90 years, using six different operationalized definitions. The definition that yielded the highest proportion of 'successful agers' (18%) included a specific component on physical health (absence of dementia, good vision and hearing, independence in three mobility activities and in two activities of daily living (ADL) - activities), as well as a social component ("having met one's children and having talked on the phone with family members/ friends during the past two weeks"). The definition that yielded the lowest proportion (1.6%) differed from the former definition with respect to the physical health-component ("no dementia" was replaced by "absence of disease"), and included an additional component referring to psychological health ("absence of depressiveness, average or good self-rated health, and agreement with the view that it is good to live to be 100").

Another example is a study published by Cho et al. (Cho et al. 2012), in which a definition based on Rowe and Kahn's concept (absence of five specific chronic diseases as well as of

high blood pressure, no limitations in instrumental activities of daily living (IADL) and in physical activities of daily living, Mini Mental State Examination (MMSE) score ≥ 23, and active engagement with life) was compared with a definition focused on psychosocial factors (good or excellent self-rated health, good perceived financial situation, and 'happiness'). Within a sample of octogenarians, only 15% met the criteria of the first definition, while as many as 62% met the criteria of the second definition. Among a sample of centenarians, no individual met the criteria of the first definition, while 48% met the criteria of the second definition.

A very similar approach was taken by Cernin et al. **(Cernin et al. 2011)**, who compared an "objective definition" (good physical and cognitive functioning, independence in terms of IADL) with a "self-rated definition" (at least "good" self-rated overall health status). The mean age of the study sample was 73 years, and 30% of participants met the criteria of the "objective definition", while 63% met the criteria of the "self-rated definition".

Tyas et al. **(Tyas et al. 2007)** have attempted to take a non-binary approach at healthy aging by defining four different groups instead of two: non- healthy aging, "good" healthy aging, "very good" healthy aging, and "excellent" healthy aging. The definition of these groups depended on the choice of cut-offs for the different criteria (good cognitive functioning - as assessed by the MMSE and a Delayed Word Recall- test, basic activities of daily living, IADL, and "self-rated function"). For example, to be classified into the category "excellent" healthy aging, an individual had to have ≥ 28 points on the MMSE and to be independent in terms of all IADL. To fall into the category "good" healthy aging, ≥ 24 points on the MMSE and having a score ≥ 3 on the IADL- scale was sufficient. Finally, 6% of participants were classified as 'excellent agers', 14% as 'very good agers', and 18% as 'good agers'.

These different examples illustrate that multiple factors have an influence on the observed proportions of healthy or successful aging: the age of the participants, the types of components chosen (i.e. rather biomedical components of rather psychosocial components, or self-rated measures of healthy or successful aging), the variables chosen to operationalize these general components, and the applied cut-offs. These aspects are illustrated in **Figure 4**.

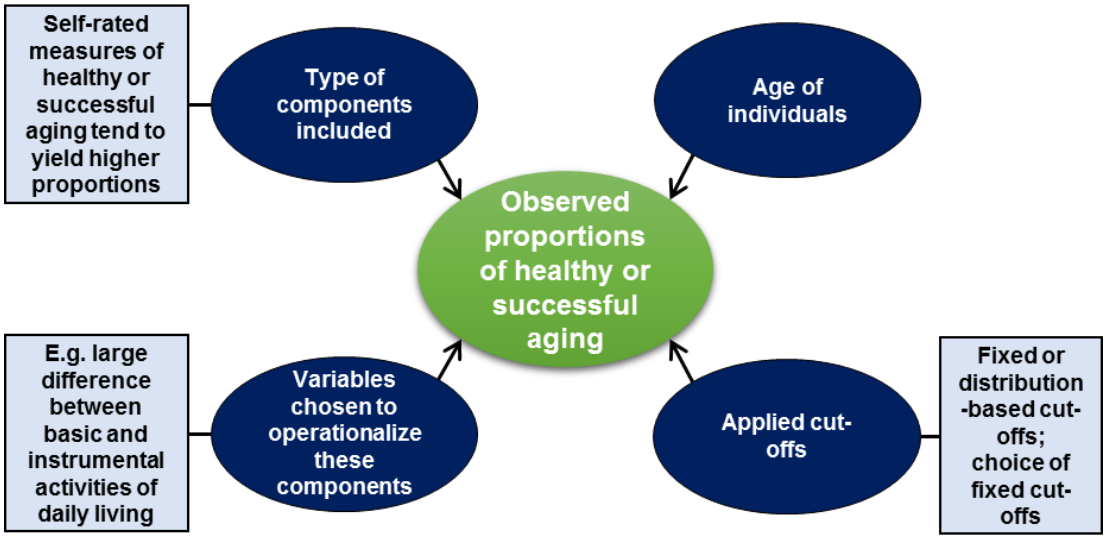

Figure 4. Factors related to observed proportions of healthy or successful aging

II.E Attempts to create consensus definitions

II.E.1 Workshop organized by German researchers (Regensburg, Germany, 2012)

Attempts have been made to create consensus definitions of healthy or successful aging, or at least to make progress on the way of obtaining such consensus definitions. A group of German researchers has organized a workshop in 2012 that aimed to investigate health indicators related to aging that are used in German research projects, with the final objective to help develop "a set of indicators for the assessment of healthy ageing". The results of the workshop were published in the form of a scientific article in 2013 **(Fuchs et al. 2013)**, which concluded, amongst others, that taking a multidimensional approach was crucial. Such an approach should include "a comprehensive assessment of resources, diseases and complaints, cognitive and functional capacities, and limitations and disability". Moreover, "environmental, sociodemographic, and socioeconomic factors and biological/genetic determinants" should be taken into account. A key objective of the publication was to encourage further collaborative discussions in order to develop "an agreed-upon basic set of instruments" for research projects on the health of elderly individuals.

II.E.2 European workshop (Montpellier, France, 2014)

In October 2014, a workshop with similar objectives was also organized on an international level, in the context of the annual conference of the European Innovative Partnership on Active and Healthy Aging in Montpellier, France. On the basis of the discussions during this workshop, two scientific publications have been drafted and published **(Bousquet et al. 2015a; Bousquet et al. 2015b)**.

The first publication **(Bousquet et al. 2015a)** focused on the proposed framework for defining "active and healthy aging", which was based on previous work by Kuh et al. **(Kuh et al. 2014)**. This framework included both proposed inherent components of active and healthy aging, and factors suggested to have a major role in the development of active and healthy aging. The inherent components were "physical and cognitive capability", "psychological and social wellbeing, mental health and quality of life", and "functioning of underlying physiological systems […], preventing or delaying onset of chronic diseases, frailty and disability". It was underlined that all three components should be considered throughout the life course, not only punctually at one point during aging. The suggested factors with an influence on active and healthy aging were "education, lifelong learning, working and caring", "lifetime lifestyles", and "lifetime social, economic, and physical environment".

The second publication **(Bousquet et al. 2015b)** focused on means of assessing these different proposed components. The proposed instruments included two "core" questionnaires, and a number of optional questionnaires. The first proposed core questionnaire was the World Health Organization Disability Assessment Schedule (WHODAS) 2.0. The second core domain was quality of life. Rather than proposing one single most pertinent measure of quality of life, a number of potentially adequate instruments were proposed: the EuroQoL Quality of Life Scale 5 (EuroQoL 5), the Short Form-12 healthy survey (SF-12), and the Short Form-6D healthy survey (SF-6D).

II.F Concepts developed by the WHO

The WHO has developed two concepts that can be regarded as closely related to multidimensional concepts of healthy or successful aging: "active aging", and "healthy aging". The "active aging"- concept has been developed within a very policy- and society-oriented framework, published in a 2002- report titled "Active Aging – A Policy Framework" **(World Health Organization 2002)**.

The WHO's "healthy aging"- concept, on the other hand, has been developed in the context of the "World Report on Ageing and Health" published in 2015, and presents a model which is (as its name indicates) more directly focused on concrete health- aspects **(Beard 2015)**.

The following chapter is entirely dedicated to these two concepts for two reasons. First, the WHO is an authority with immense importance for public health research and action. Second, the "healthy aging"- concept developed by the WHO provides a very holistic framework that in a certain manner responds to many criticisms expressed with respect to Rowe and Kahn's concept (such as a missing life-course approach, the missing consideration of external factors, and the missing consideration of resilience as an important modulator of the aging process). It should be noted, however, that the consideration of such a large number of different factors renders the concept difficult to implement into cohort studies with a biomedical focus such as the SU.VI.MAX study.

II.F.1 The WHO's "active aging"- framework

a) Core definition

The concept of "active ageing" proposed by the WHO in 2002 **(World Health Organization 2002)** should not be understood as a health outcome, but rather as a continuous process: "Active ageing is the process of optimizing opportunities for health, participation, and security in order to enhance quality of life as people age".

a) Specifications

This process should permit individuals to "realize their potential for physical, social, and mental well being throughout the life course" and also assure "adequate protection, security and care". It is underlined that 'activity' does not only refer to physical exercise, or to professional activity, but to involvement in a large number of different domains ("social, economic, cultural, spiritual, and civic affairs"). In line with above-mentioned voices that insist on the development of inclusive concepts of healthy aging, the WHO's concept explicitly "aims to extend healthy life expectancy and quality of life for all people as they age, including those who are frail, disabled and in need of care". **(World Health Organization 2002)**

b) Proposed determinants of active aging

Proposed determinants of active aging are the "cross-cutting determinants" culture and gender, and other elements, including economic, social, behavioural, and personal factors, as

well as "health and social services" and the "physical environment". **(World Health Organization 2002)**

c) Proposals for policies that facilitate active aging

The key policy proposal made in order to facilitate active aging for individuals worldwide were constructed around three "pillars": health, participation, and security. Key policy proposals concerning health were related to **(World Health Organization 2002)**:

- diminishing the burden of chronic illness and premature maturity,
- diminishing major health risk factors (such as low dietary quality, smoking, and psychological factors),
- assuring the accessibility, quality, and 'age-friendliness' of social services, and
- providing training for "caregivers".

Proposals with respect to participation were related to:

- improving "basic education" and possibilities for "lifelong learning",
- assuring secured incomes, and augmenting possibilities for professional and volunteer work, and
- continued involvement in family and community life.

Suggestions concerning security were related to:

- assuring "protection, safety and dignity" (especially for vulnerable groups such as HIV-infected individuals, and people in emergency situations), and
- improving gender equality.

II.F.2 The WHO's "healthy ageing"- framework

a) Definition of healthy aging

In their 2015-report "World Report on Ageing and Health" **(Beard 2015)**, the WHO defined healthy aging as "the process of developing and maintaining the functional ability that enables well-being in older age".

"Functional ability" was defined as involving "the health-related attributes that enable people to be and to do what they have reason to value". This concept does not only refer to the

individual's "physical and mental capacities", but also to external environmental factors (related to the individual's home, its community, and the society it lives in) and the interaction between these internal and external elements. The WHO underlines that "well-being" should be "considered in the broadest sense", involving elements like "happiness", "satisfaction", and "fulfilment".

a) Healthy aging as a process

The WHO explicitly states that their concept of healthy aging takes on a life-course perspective. Healthy aging is thus considered as a continuous process, during which multiple factors play a role. According to the framework proposed by the WHO, an individual's physical and mental capacities are influenced by the following factors **(Beard 2015)**:

- genes,
- gene-environment interactions before and after birth,
- non-modifiable "personal characteristics" (sex, ethnicity),
- partly modifiable "personal characteristics" (socio-professional status, education, gender, financial/ material situation),
- different "exposures", "opportunities", "barriers", and "access to resources", which depend on the above-mentioned personal characteristics (sex, education, financial situation, etc.)
- accumulating damage on the molecular and cellular level, which can result in lowered "physiological reserves", and shifts in homeostasis (these changes are considered as "largely inevitable", but subject to substantial variations concerning their magnitude),
- other characteristics related to health (which are, themselves, influenced by various environmental factors):
    - specific behaviours, personality traits, and competences related to health,
    - factors that augment the risk for diseases (such as hypertension),
    - diseases or injuries,
    - "broader geriatric syndromes".

As described under "a) Definition of healthy aging", the "functional ability" of an individual is then influenced by both its above-mentioned physical and mental capacities, environmental factors, and the interaction between personal capacities and the environment.

The process of healthy aging is further shaped by an individual's "resilience", which the WHO defines as "the ability to maintain or improve a level of functional ability in the face of adversity". According to the WHO, resilience comprises both internal factors (such as personality characteristics and "physiological reserves") and external factors (such as good social integration).

As stated above, the WHO defines "functional ability" as "the health-related attributes that enable people to be and to do what they have reason to value". In this light, considering healthy aging in a life-course perspective is crucial, as "the beings and doings that people have reason to value differ among individuals, and change over the course of people's lives".

The life-course approach taken by the WHO also considers the inevitability of death. Instead of regarding healthy aging as a punctual outcome, "trajectories of healthy aging" are considered, which end – as all human biological life – with death. An "optimal" trajectory distinguishes itself from suboptimal trajectories personal capacities that "remain high until the end of life".

b) Suggested "key issues for public-health action"

As stated above, the "active ageing"- framework proposed by the WHO was a much more policy- and society- oriented approach than the "healthy ageing"- framework. The "healthy ageing"- framework does not include equally detailed policy suggestions, but proposed "key issues for public-health action". These issues are grouped according to four main themes: "dealing with diversity", "reducing inequity", "enabling choice", and "ageing in place". **(Beard 2015)**

The first aspect refers to developing research that helps to increase the understanding of "diverse pathways" of healthy aging, but also to changing health services so that "people have access to health services that respond to their preferences" and are "coordinated around their needs".

The aspect "reducing inequity" includes, amongst others, the notion of reaching "groups that are particularly disadvantaged". The WHO notably suggested that public health programs should be evaluated with respect to their potential to reduce inequalities.

"Enable choice" refers to helping individuals develop the competences that are necessary to make choices that are beneficial for their health and lives. This aspect is, according to the WHO, strongly connected with "reducing inequity", as disadvantaged groups tended to have

less access to the resources that are important for developing the ability to make favourable choices.

The final aspect, “ageing in place”, refers to improve the possibilities for elderly individuals to keep living in their own homes, and to further develop “new forms of assisted living and nursing-home care”.

Figure 5 attempts to visualize key aspects of the very complex "healthy ageing"- framework proposed by the WHO.

Figure 5. Illustration of the framework of healthy aging developed by the World Health Organization (based on (Beard 2015))

III. Nutritional epidemiology

Multiple definitions of "epidemiology" have been proposed. A frequently used and well-accepted definition is the one proposed by Brian MacMahon, a former director of the Havard School of Public Health's Department of Epidemiology. According to MacMahon, epidemiology is "the study of the distribution and determinants of disease frequency in man" **(MacMahon and Pugh 1970)**.

The WHO defines epidemiology as:

> "[…] the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems. Various methods can be used to carry out epidemiological investigations: surveillance and descriptive studies can be used to study distribution; analytical studies are used to study determinants". **(World Health Organization 2016)**

Nutritional epidemiology can be considered as a sub-discipline of epidemiology, which specifically focuses on nutritional determinants of health (including dietary factors and physical activity, which contributes to a regulated overall energy balance).

III.A Assessment of dietary consumption

Methods of assessment used in nutritional epidemiology can be roughly divided into methods that aim to assess the foods that are "actually consumed by an individual on one or more specific days" (24-hour recalls and dietary records), and into methods that "report usual intake over longer periods of time" (food frequency questionnaires and diet histories) **(Willett 1998)**.

The principal of 24-hour recalls is the conduction of a detailed interview by a trained examiner, during which participants report all food consumption from "midnight to midnight of the previous day" or "over the past 24-hour period" **(Willett 1998)**.

Dietary records consist of "a detailed listing of all foods consumed on one or more days". Participants of studies conduct the work of noting details on food consumption themselves, ideally shortly after food or beverage consumption takes place. The assessment of the consumed quantities relies either on standard portion sizes or on household measuring tools, or the participants are encouraged to weigh the foods and beverages they eat. **(Willett 1998)**

Food frequency questionnaires are composed of two elements: a "food list" (containing the names of various foods and/ or food groups) and a "frequency response section" (inquiring

information on the frequency of consumption of these foods/ food groups). Food lists can be specific (thus not covering the overall diet, but only specific aspects) or comprehensive (the latter option has the advantage that overall energy intake can be estimated). **(Willett 1998)**

The diet history method developed by Burke includes one self-administered 3-day food diary, a list of usually consumed foods, and a detailed interview, which is to be carried out by highly qualified professionals. Given the large efforts needed to complete such a dietary history, this method is not often used in nutritional epidemiology **(Shim et al. 2014)**.

Advantages of 24-hour recalls or dietary records covering a 24-hour period ('24-hour dietary records') include the precise assessment of the consumed quantities over a 24-hour period **(Andreeva and Kesse-Guyot 2015)**. Food frequency questionnaires, on the other hand, provide less precision concerning the consumed quantities, and are thus more susceptible to misreporting ('overreporting' or 'underreporting') **(Andreeva and Kesse-Guyot 2015)**. The advantage of this method is that habitual food intakes can be obtained via a single administration of the tool, while 24-hour recalls or 24h-dietary records require repeated administration over sufficiently long time periods (in a non-consecutive manner, i.e. distributed across the different days of the week and seasons of the year) in order to supply reliable estimates of usual dietary intakes **(Andreeva and Kesse-Guyot 2015; Willett 1998)**.

Food composition tables are necessary in order to calculate nutrient intake from information on food or food group consumption. Measurement errors related to this procedure are related to the variation of food composition according to "environmental conditions, geographical location, food production and preparation methods". **(Andreeva and Kesse-Guyot 2015)**.

Further types of bias related to dietary assessment in nutritional epidemiology include memory-related bias ("recall bias"), social desirability bias (leading, for example, to general energy underreporting or to the underreporting of foods perceived as 'unhealthy'), as well as measurement errors related to the portion size estimation **(Andreeva and Kesse-Guyot 2015; Gibson 2005; Hebert et al. 1995; Thompson and Byers 1994)**.

III.B Investigation of specific dietary factors

The investigation of the relation between single nutrients, foods, or food groups with biological indicators or health outcomes is highly important for the development and confirmation of mechanistic hypothesis concerning the aetiology of diseases, and to better understand general aspects of human physiology and metabolism. However, an immense

challenge for such analysis is that the presence of specific nutrients and other constituents (such as fibres or polyphenols) in specific foods or food groups is highly correlated with the presence of other constituents (one example is the fact that milk products are important sources of both animal protein and easily absorbable calcium **(Bonjour et al. 2013; Pereira 2014)**). Moreover, specific food constituents show strong interactions (both antagonism and synergism). Examples include interactions of the minerals copper and zinc or manganese and iron with respect to their absorption in the intestine, or effects of alcohol on iron metabolism **(Jacobs, Jr. et al. 2009)**.

Moreover, it has been suggested that the association of single nutrients with health outcomes may be of too small magnitude to be detectable in epidemiologic studies, while the cumulative effect of diverse nutrients and other dietary components could be identified more easily **(Hu 2002; Jacobs, Jr. et al. 2009).**

III.C The 'whole diet'- approach

In response to the above-mentioned limitations of the traditionally applied approach to focus on specific dietary factors such as nutrients, foods, and food groups, an alternative approach has been developed in nutritional epidemiology: the 'whole diet'- or 'overall diet'- approach, which has also been named "dietary pattern analysis" **(Hu 2002)**.

In nutritional epidemiology, historically, two main types of methodologies have been developed in order to consider the diet of an individual as a whole.

The first method involves the construction of scores or indices based on existing knowledge and/or hypothesis. This method is also referred to as "*a priori*" dietary pattern analysis. The second method involves the extraction of dietary patterns by empirical, data-based methods such as principal component analysis or cluster analysis, and is also referred to as "*a posteriori*" dietary pattern analysis. **(Andreeva and Kesse-Guyot 2015; Hu 2002; Kant 2004)**

With the application of reduced rank regression to nutritional epidemiology, a method has been introduced that can be seen as a hybrid method (i.e. a method sharing both elements of the *a priori*- and the *a posteriori*- approach), as this method is essentially data-driven, but also requires reflection on specific mechanistic hypotheses by which diet may affect health outcomes **(Andreeva and Kesse-Guyot 2015; Hoffmann et al. 2004)**.

III.C.1 *A priori* dietary scores

A large variety of different *a priori* – dietary scores has been developed to this day **(Andreeva and Kesse-Guyot 2015; Kant 2004; Kourlaba and Panagiotakos 2009; Waijers et al. 2007; Wirt and Collins 2009)**. Many of these scores have been designed to measure adherence to national nutritional guidelines, such as the Healthy Eating Index (HEI), and its updated version, the HEI-2010 **(Guenther et al. 2013; Kennedy et al. 1995)**, the Alternate Healthy Eating Index (AHEI) **(McCullough et al. 2002)** and its updated version, the AHEI-10 **(Chiuve et al. 2012)**, the Dietary Guidelines for Americans Index (DGAI) **(Fogli-Cawley et al. 2006)**, the Healthy Eating Index for Australians **(Roy et al. 2015)** and its modified version, the Total Diet Score (TDS), or the French Programme National Nutrition Santé- Guideline Score (PNNS-GS) **(Estaquio et al. 2009)**.

Other scores reflect adherence to specific forms of diet such as the Mediterranean diet (Buckland et al. 2010; Patterson et al. 1994; Rumawas et al. 2009; Sofi et al. 2014; Trichopoulou et al. 2003), measure dietary diversity **(Drescher et al. 2007; Drewnowski et al. 1997; Kant et al. 1991; Krebs-Smith et al. 1987)**, or the adequacy of the diet to nutrient reference values **(Krebs-Smith et al. 1987; Verger et al. 2012).**

Moreover, particular scores have been developed to reflect a diet that is hypothesized to be beneficial concerning specific health outcomes, such as cardiovascular health **(Appel et al. 1997)** or cognitive health **(Morris et al. 2015)**, based on available evidence and hypotheses.

Finally, a number of scores have been designed to generally reflect a type of diet that is thought to be beneficial for overall health, such as the AHEI **(McCullough et al. 2002)** or the Dietary Quality Index- International (DQI-I) **(Kim et al. 2003)**.

III.C.2 *A posteriori* dietary patterns

A posteriori dietary patterns have the advantage that they can reveal new interesting aspects, since their construction is data-based, and not dependent on the existing state of knowledge and specific hypotheses **(Hu 2002)**. On the other hand, subjective decisions have to be made in the phase of food group- construction, which precedes the application of data-reduction methods **(Andreeva and Kesse-Guyot 2015; Newby and Tucker 2004)**. Further subjective decisions concern potential transformations of the dietary "input" variables (i.e. the food groups), and the number of dietary patterns to retain **(Newby and Tucker 2004)**.

Two frequently applied data-reduction methods are principal component analysis (or more generally factor analysis) and cluster analysis **(Newby and Tucker 2004)**. In the case of principal

component analysis, the aim is to "construct linear combinations of food intakes, which explain a high proportion of the variation in food intakes" **(Wirfalt et al. 2013)**. Cluster analysis, on the other hand, "aggregates individuals into relatively homogeneous subgroups (clusters) with similar diets" **(Hu 2002)**.

While *a priori dietary* scores mostly serve to confirm specific hypotheses (for example on the relevance of national dietary guidelines for disease prevention), a *posteriori dietary* patterns rather serve exploratory purposes **(Andreeva and Kesse-Guyot 2015)**. A disadvantage of *a posteriori* dietary patterns is that the extracted patterns are specific to the investigated population, and may be difficult to reproduce in other study samples **(Jacques and Tucker 2001; Schulze et al. 2003)**. Schulze et al. have developed a more robust methodological approach that consists of computing "simplified pattern variables" that can be better applied to study samples other than the sample that served for the extraction of the dietary pattern scores **(Schulze et al. 2003)**. These simplified patterns are obtained by calculating the sum of those "unweighted standardised food variables" that were highly correlated with a specific pattern **(Schulze et al. 2003)**. Usual dietary pattern scores are a linear combination of *all* initial food variables (and the different food variables have different 'weights' according to the magnitude of their correlation with the dietary pattern).

Two frequently identified dietary patterns are 'healthy' dietary patterns characterized by a high consumption of "plants foods", "fish and seafood", "vegetable oils" and "low-fat dairy products" on the one hand, and 'Western' dietary patterns characterized by a high consumption of "food products low in essential nutrients and high in energy", and "red and processed meats". **(Wirfalt et al. 2013)**

IV. Diet and healthy aging

IV.A Diet in relation with multidimensional healthy aging concepts

IV.A.1 Studies investigating overall dietary quality

Four studies **(Akbaraly et al. 2013a; Gopinath et al. 2015; Hodge et al. 2014; Samieri et al. 2013)** investigated the relation between *a priori* dietary scores or *a posteriori dietary* patterns with multidimensional constructs of healthy aging. The names of the chosen constructs already indicate conceptual differences: while Hodge, Samieri, and Gopinath used the terms "successful aging" or "healthy aging", Akbaraly et al. employed the term "ideal aging", which suggests the identification of a group with particularly high levels of functioning.

Akbaraly et al. **(Akbaraly et al. 2013a)** employed the term "ideal aging", which well describes the fact that the applied construct identified a small group (4%) of individuals who had maintained very high levels of functioning during aging, as compared to their peers. In order to be considered as showing 'good functioning' in the areas cognition, physical health, respiratory health, and cardiovascular health, individuals had to present scores above the sex- and age- specific median. Further criteria of the definition chosen by Akbaraly et al. were that an individual had to survive to age 60, present no major chronic disease (coronary heart disease, stroke, cancer, or diabetes), not present any limitations in IADL, and have a score higher than 42 points on the mental health subscore of the Medical Outcome Study Short Form-36 (SF-36) questionnaire. After a mean follow-up of 16 years, the average age of participants at follow-up was approximately 67 years. Lower scores on the AHEI were associated with a higher probability for cardiovascular and non-cardiovascular death, but not with a higher probability for ideal aging. On the other hand, of two dietary patterns extracted by principal component analysis, named "healthy foods"-pattern and "Western-type"-pattern, the Western-type pattern showed a significant (inverse) association with ideal aging. This dietary pattern was positively correlated with intakes of fried and sweet food, processed food and red meat, refined grains, as well as high-fat dairy products.

Samieri et al. **(Samieri et al. 2013)** considered the updated version of the AHEI (the AHEI-2010) as an exposition variable, and observed – in contrast to Akbaraly et al. – a positive relation between higher scores on this index and higher odds of "healthy aging". An additional exposition variable investigated by Samieri et al. was adherence to the

Mediterranean diet, as measured by the Alternate Mediterranean Diet Score. The observed odds ratios (OR) were somewhat higher for the Alternate Mediterranean Diet Score than for the AHEI (the respective OR and 95% -confidence intervals (95%-CI) were 1.46 [1.17, 1.83] and 1.34 [1.09, 1.66]). Participants in this study were, on average, substantially older at follow-up than in the study by Akbaraly et al. (approximately 74 years). Moreover, the chosen healthy aging definition was quite different as a distribution-based cut-off was only applied for one variable (the SF-36 mental health subscore). Further criteria were survival to 70 years, the absence of 11 different types of chronic disease, no major impairments in cognitive function (as defined by a score higher than 31 points on the telephone adaption of the MMSE), and no major impairments in physical function. The observed proportion of successful aging was quite low (11.0%), which may be related to the fact that the absence of a rather large number of chronic conditions was required, and that the participants were rather old at follow-up.

Much higher proportions of "successful aging" (18.9% among men and 18.4% among women) were observed in the study published by **Hodge et al.** **(Hodge et al. 2014)**, although the average age at follow-up (approximately 75 years) is comparable to that in Samieri et al.'s study. Successful aging was defined as survival to 70 years, absence of major chronic disease (diabetes, cancer, and three different types of severe cardiovascular events), no impairment or perceived major difficulty concerning physical functioning, and having at least 20 points on the Kessler psychological distress scale (Hodge et al. 2014). Hodge et al. observed significant relations with two out of four dietary patterns extracted by principal component analyses: a pattern correlated with high fruit intake (positive association with odds for healthy aging), and a pattern correlated with high intakes of meat and fatty foods (inverse association with odds for healthy aging).

Finally, **Gopinath et al.** **(Gopinath et al. 2015)** observed a positive association of higher adherence to the Australian Dietary Guidelines, as measured by the TDS, with odds for "successful aging". Successful aging was defined as the absence of major chronic disease (cancer, coronary artery disease, stroke, angina [pectoris], acute myocardial infarction), absence of observed walking difficulties and of limitations in IADL, functional independence (assessed by a larger number of indicators), and having a score of at least 24 on the MMSE. Compared to the above-mentioned studies, the observed proportion of successful aging was of intermediate size (15.5%). The average age at follow-up was about 72 years for 'normal agers' and about 70 years for 'successful agers'.

Thus, overall, studies investigating measures of the overall diet with respect to healthy aging generally identified higher dietary quality as a beneficial factor, and "Western-type" dietary patterns as a detrimental factor. However, only one of two studies that investigated the AHEI obtained significant results, and not all data-based dietary patterns were significantly associated with healthy aging.

A further study that investigated a variable that could be considered as an indicator of dietary quality was published by **Britton et al.** **(Britton et al. 2008)**. However, dietary quality was only one among many investigated exposition variables, and the chosen indicator was of very simple nature: "not having a poor diet" was defined as showing at least two of the following three criteria: "most frequently used bread was white", "usually used milk was whole"; "fruit or vegetables were eaten less often than daily". A further issue that makes it difficult to draw valid conclusions from this study is that only a very restricted statistical adjustment (for age and socioeconomic category) was applied. The study's findings concerning diet were that "not having a poor diet" was associated with higher odds for healthy aging among men, but not among women.

Tables 1 provides an overview of these different studies, which are all prospective cohort studies with varying times of mean or median follow-up (10 to 16 years).

Table 1. Observational studies on the relation between *a priori* dietary scores and multidimensional concepts of healthy aging

Article, Study	Country, sex, number	Baseline age (y, mean ± SD)	Follow-up age (y, mean)	Follow-up (y)	Definition of successful aging and further comments	Further comments	% Healthy aging	Dietary factors showing a significant association with healthy aging (OR [95%-CI])
(Akbaraly et al. 2013a) Whitehall II study	United Kingdom, ♂♀, n=5,350	51.3±5.3	≈67	Mean: 16	**"Ideal aging":** - aged ≥ 60 years and survived - no coronary artery disease, stroke, cancer, diabetes - < 1 difficulty in IADL - no mental health problems (> 42 points on mental health component of the SF-36) - good functioning in the following areas: * cognition: score of global cognition calculated from 5 cognitive tests * physical health: walking speed measured over an 8-footlong course * respiratory health: forced expiratory volume in 1 second * cardiovascular health: blood pressure	The % healthy aging was computed among survivors and deceased *Good functioning:* scores > sex- and age- standardized median (≥ median for blood pressure)	4%	**No association** Overall dietary quality, as assessed by the AHEI **(-) Higher scores on a "Western-type" dietary pattern** (extracted via principal component analyses) $OR_{highest\ vs.\ lowest\ tertile}$: 0.58 [0.36-0.94]
(Samieri et al. 2013) Nurses' Health Study	USA, ♀, n=10,670	59.1±2.5: usual agers 58.6±2.5: healthy agers	≈74: both groups	Mean: 15	**"Healthy aging":** - aged ≥ 70 years and survived - no chronic disease - no major impairments in cognitive function: telephone adaption of MMSE ≥ 31 points - no major impairments in physical function (*impairment:* limited at least "a little" on moderate activities (items of the SF-36) or limited "a lot" on more difficult items) - good mental health: SF-36 mental health index score >84 (the median value in the cohort)	The % healthy aging was computed among survivors only	11.0%	**(+) Higher scores on the AHEI-2010, and on the Alternate Mediterranean Diet score (A-MeDi)** $OR_{highest\ vs.\ lowest\ quintile}$: AHEI-2010: 1.34 [1.09, 1.66] A-MeDi: 1.46 [1.17, 1.83]

Article, Study	**Country, sex, number**	**Baseline age (y, mean ± SD)**	**Follow-up age (y, mean)**	**Follow-up (y)**	**Definition of successful aging and further comments**	**Further comments**	**% Healthy aging**	**Dietary factors showing a significant association with healthy aging (**OR [95%-CI])
(Hodge et al. 2014) Melbourne Collabor-ative Cohort Study	Australia, ♂♀, n=6,308	64.0±3.3: usual agers 63.4±3.2: successful agers	≈75.7: usual agers; ≈75.1: successful agers	Median: 11.7 for survivors 6.4 for deceased	**"Successful aging":** - aged ≥ 70 years and survived - no diabetes, heart attack, coronary artery bypass graft surgery, angioplasty, stroke, cancer - no impairment, perceived major difficulty with physical functioning (criteria based on the questionnaires SF-12, ADL, and IADL) - low risk of psychological distress (≥ 20 points on the Kessler psychological distress scale)	The % healthy aging were computed among survivors and deceased	♂18.9%; ♀18.4%	**(+/-) 2 of 4 dietary patterns** extracted via factor analysis**: a pattern high in fruits (+), and a pattern high in meat and fatty foods (-)** $OR_{highest\ vs.\ lowest\ quintile}$: 1.31 [1.05, 1.63] and 0.69 [0.55, 0.86]
(Gopinath et al. 2015) Blue Mountains Eye Study	Australia, ♂♀, n=1,609	Mean±SE: 61.9±0.3: normal agers 59.9±0.5: successful agers	≈72: normal agers ≈70: successful agers	10 (unclear if mean or median)	**"Successful aging":** - no cancer, coronary artery disease, stroke, angina, acute myocardial infarction, or diabetes - no disability (no observation of walking difficulties by trained examiner and <1 limitation in IADL) - functional independence (various criteria) - good cognitive functioning (MMSE ≥24) - good respiratory functioning - good cardiovascular functioning (blood pressure) - good mental health (≥59 points on the MHI of the SF-36; <10 points on the CES-D-10)	The % healthy aging was computed among survivors and deceased *Respiratory functioning:* no continual shortness of breath/ coughing, heart or lung problems	15.5%	**(+) Higher adherence to the Australian dietary guidelines** (as measured by the "Total Diet Score" TDS) $OR_{highest\ vs.\ lowest\ quartile}$: 1.58 [1.02–2.46]

Article, Study	Country, sex, number	Baseline age (y, mean ± SD)	Follow-up age (y, mean)	Follow-up (y)	Definition of successful aging and further comments	Further comments	% Healthy aging	Dietary factors showing a significant association with healthy aging (OR [95%-CI])
(Britton et al. 2008) Whitehall II study	United Kingdom, ♂♀, 5,823	♂ 43.8±5.9 ♀ 44.3±5.9	≈61: both groups	Median: 17	**"Successful aging":** - no major disease - good functioning in the following areas: * cognition: Alice Heim 4-I cognitive test * physical health: walking speed measured over an 8-footlong course; physical component score of the SF-36 * respiratory health: forced expiratory volume *Good functioning*: being in the highest sex-specific tertile for at least three of the "functioning components"	- **Very restricted adjustment of analyses** (only for age and socioeconomic category) The % healthy aging was computed among survivors only	♂12.8%; ♀14.6%	**(+ among men only)** **"Not having a poor diet"** (≥2 criteria: "most frequently used bread was white", "usually used milk was whole"; "fruit or vegetables were eaten less often than daily") ♂ 1.4 [1.1–1.7] ♀ 1.1 [0.8–1.6]

Abbreviations: ADL, activities of daily living; AHEI, Alternative Healthy Eating Index; A-MeDi, Alternate Mediterranean Diet score; CES-D, Center for Epidemiological Studies Depression Scale; GDS, Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living; IPAQ, International Physical Activity Questionnaire; MHI, Mental Health Index; MMSE, Mini Mental State Examination; SD, standard deviation; SE, standard error; SF, Short Form Healthy Survey.

IV.A.2 Studies investigating specific dietary factors

Three studies considered specific components of the diet: the frequency of fruit and vegetable consumption **(Sabia et al. 2012)**, dietary flavonoid intake **(Samieri et al. 2014)**, and overall energy intake **(Tyrovolas et al. 2015)**. **Sabia et al.** **(Sabia et al. 2012)** used a definition that is very similar to that employed by Akbaraly et al., as both investigations were based on the British Whitehall II cohort. However, cut-offs for functioning measures were chosen differently. High function was defined as not being in the lowest age- and sex-specific quintile (as opposed to 'not as having scores above the median'). This lead to a healthy aging proportion that was much higher than in the study by Akbaraly et al. (21%). The main diet-related finding of the study was that consuming fruits and vegetables everyday was related to higher odds of "successful aging".

For their investigation on the relation between dietary flavonoid intake and healthy aging, **Samieri et al.** **(Samieri et al. 2014)** used the same definition as in their study on overall dietary quality and healthy aging. They identified a significant positive relation of the consumption of four groups of flavonoids (flavones, flavanones, anthocyanins, and flavonol) with healthy aging.

The "successful aging"- definition used by **Tyrovolas et al.** **(Tyrovolas et al. 2015)** is very different from those used in the other studies that have investigated dietary factors in relation to healthy aging. In fact, a measure of dietary quality (adherence to the Mediterranean diet) was an integral part of the definition. Moreover, two elements that can be considered 'external' factors were integrated into the successful aging- concept: education and financial status. The definition included no notion of absence of disease, but factors that can be considered disease risk factors (body mass index and a cardiovascular risk score). Further components were physical activity, mental health, social activities and excursions. An additional fundamental difference with respect to the other concepts is that successful aging is not considered as a binary variable, but as a continuous construct. Finally, the study is of cross-sectional nature. Its main findings were that an overall energy intake higher than 1,700 kcal (corresponding to the upper tertile cut-off) and a positive energy balance were associated with lower scores on the developed successful aging index.

Tables 2 provides an overview of these different investigations. All of the studies but one **(Tyrovolas et al. 2015)** are based on prospective cohorts with mean or median follow-up periods ranging from 15.2 to 17 years.

Table 2. Observational studies on the relation between specific dietary factors and multidimensional concepts of healthy aging

Article, Study	Country, sex, number	Baseline age (y, mean ± SD)	Follow-up age (y, mean)	Follow-up (y)	Definition of successful aging and further comments	Further comments	% Healthy aging	Dietary factors showing a significant association with healthy aging (OR [95%-CI])
(Samieri et al. 2014) Nurses' Health Study	USA, ♀, n=13,818	59.1±2.5: usual agers 58.6±2.5: healthy agers	≈74: both groups	Mean: 15.2	**"Healthy aging":** Same definition as Samieri et al. 2014	The % healthy aging was computed among survivors only	11.0%	**(+) Higher intakes of multiple classes of flavonoids** OR highest vs. lowest quintile: Flavones: 1.32 [1.10, 1.58] Flavanones: 1.28 [1.08, 1.53] Anthocyanins: 1.25 [1.04, 1.50] Flavonol : 1.18 [0.98, 1.42]
(Sabia et al. 2009) Whitehall II study	United Kingdom, ♂♀, n= 5,100	51.3 (SD 5.3)	≈68	Median: 16.3	**"Successful aging":** Same definition as Akbaraly et al. 2013a, except: - survival is considered separately - cut-off for functioning measures chosen differently: "not being in the lowest quintile"	The % healthy aging was computed among survivors and deceased	21%	**(+) Daily consumption of fruits and vegetables (yes/no)** 1.35 [1.15–1.58]
(Tyrovolas et al. 2015) MEDIS Study (more details given in (Tyrovolas et al. 2014))	Mediter-ranean islands (various countries) ♂♀, n=2,663	Range: 65-100 years (no mean/ median values provided)	None (cross-sectional)	None	**Continuous "successful aging index", based on:** - education (years of school) - financial status - physical activity (measured via the IPAQ) - body mass index - mental health (measured via the GDS): - participation in social activities - yearly excursions - cardiovascular risk score (criteria: hypertension, hypercholesterolemia, diabetes and obesity) - adherence to the Mediterranean diet (MedDiet score)	-> Assignment of 0 to 1 points to each component -> Final score: 0-10 points	-	**(-) high energy intake** (>1,700 kcal/day vs. ≤ 1,700 kcal/d); **positive** (vs. negative) **energy balance** β [95%-CI] = −0.21[−0.37, −0.05], and = −0.21 [−0.37, −0.05], respectively.

Abbreviations: ADL, activities of daily living; AHEI, Alternative Healthy Eating Index; CES-D, Center for Epidemiological Studies Depression Scale; GDS, Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living; IPAQ, International Physical Activity Questionnaire; MMSE, Mini Mental State Examination; SD, standard deviation; SE, standard error; SF, Short Form Healthy Survey.

IV.B Nutritional components associated with healthy aging criteria

This section will notably focus on what is known on the association of dietary factors with three main components of Rowe and Kahn's model of healthy/ successful aging: the absence of disease (interpreted here as the absence of three major chronic diseases: cardiovascular disease, diabetes, and cancer), good physical functioning, and good cognitive functioning. The relation between diet and cognitive functioning will be considered in a particularly detailed manner, as this thesis has a particular focus on cognitive health during aging.

IV.B.1 General considerations

The specific relations between diet and healthy aging largely depend on how exactly healthy aging is defined. Within the framework proposed by the WHO **(Beard 2015)**, diet is considered as a "health characteristic", which interacts with other health characteristics such as diseases, injuries, "geriatric syndromes", disease risk factors, and notably with "physiological reserves" and "shifts in homeostasis", which are provoked by growing molecular damage during aging (see Figure 5).

These different health characteristics then influence an individual's physical and mental capacities, which, in interaction with various external factors, make up a person's general "functional ability". In turn, overall well-being, which includes the possibility to carry out activities that are valued as important, is then influenced by functional ability.

With respect to Rowe and Kahn's framework, the role of nutrition would not be fundamentally different, except that "functional ability" and "well-being" as defined by the WHO are not explicitly part of the Rowe and Kahn- model. Moreover, rather than being health characteristics among others, the presence of disease has the role of an "outcome" in Rowe and Kahn's framework. In their model, the indicator that most closely resembles the "functional ability"- and "well-being" components of the WHO- framework is "active engagement with life", which can be considered as a consequence of the absence of disease and disability and the presence of good cognitive and physical functioning **(Rowe and Kahn 1997)**.

IV.B.2 Diet and chronic diseases

a) Cardiovascular disease

A systematic review of the literature on the link between dietary factors and coronary heart disease **(Mente et al. 2009)** concluded that there was "strong evidence" (notably among investigations with good methodologic quality) for a beneficial role of vegetables, nuts, monounsaturated fatty acids, adherence to the Mediterranean diet and to other "high-quality dietary patterns", and for a detrimental role of trans-fatty acids, foods with an elevated glycaemic index or glycaemic load, and adherence to 'Western-type' dietary patterns.

An important role of overall diet for the prevention of cardiovascular disease has also been highlighted in a review of the literature published by Mozaffarian et al., who concluded that "a focus on foods and overall dietary patterns rather than individual nutrients or supplements" was warranted **(Mozaffarian et al. 2011)**. They underline, however, that public health prevention strategies should also target specific selected nutrients – notably "sodium and industrially produced *trans* fats", whose consumption should be limited.

Furthermore, a systematic review and meta-analysis of observational studies on the link between dietary fibre intake and cardiovascular disease concluded that higher consumption of dietary fibre appeared to have a preventive role with respect to cardiovascular disease and coronary heart disease **(Threapleton et al. 2013)**.

In addition, the United States Department of Agriculture (USDA) has recently published a report on the relation between overall dietary quality and three health outcomes: body weight and obesity, cardiovascular disease, and diabetes **(United States Department of Agriculture 2014)**. Concerning cardiovascular disease, the authors concluded that there was "strong and consistent evidence" concerning a beneficial role of adherence to *a priori* dietary patterns characterized by:

- a high consumption of "fruits, vegetables, whole grains, nuts, legumes, unsaturated oils, low-fat dairy, poultry, and fish",
- a low consumption of "red and processed meat, high-fat dairy, and sugar-sweetened foods and drinks",
- and a moderate consumption of alcohol.

a) Diabetes type 2

Concerning diabetes type 2, the above-mentioned USDA-report **(United States Department of Agriculture 2014)** concluded that there was "limited evidence" concerning a beneficial role of adherence to *a priori* dietary patterns characterized by:

- a high consumption of "fruits, vegetables, legumes, cereals/whole grains, nuts, fish, and unsaturated oils",
- a low consumption of "meat and high-fat dairy".

With respect to *a posteriori* dietary patterns, the available evidence was labelled as "limited and inconsistent". Concerning particular types of diet, the report concluded that there was "insufficient evidence" as regards Mediterranean-style or vegetarian diet patterns in relation to diabetes type 2 risk, and "limited, inconsistent evidence" concerning the relation between specific types of diet and improved glucose tolerance and insulin resistance.

Among specific dietary factors, one of the most discussed elements is dietary glycaemic index (GI) or dietary glycaemic load (GL). A recent systematic review of observational studies has concluded that the observed findings were "consistent with protective effects of low dietary GI and GL" **(Greenwood et al. 2013)**. In addition, a systematic review and meta-analysis on the association between fruit and vegetable intake and the incidence of type 2- diabetes has come to the conclusion that an elevated consumption of green leafy vegetables could have an important preventive role **(Carter et al. 2010)**.

b) Cancer

Concerning cancer, the available evidence with respect to overall dietary quality is less consistent than concerning cardiovascular disease **(Kant 2010)**. However, various specific dietary factors have consistently been shown to be associated with particular locations of cancer. A recent systematic review of the literature has identified a number of detrimental factors with respect to overall cancer risk: "alcoholic beverages, overweight and obesity, red meat and processed meat, salt and salted foods and beta-carotene supplements". Factors that were identified as beneficial were: "physical activity, fruits and vegetables, dietary fiber, dairy products and breastfeeding". **(Latino-Martel et al. 2016)**

Moreover, the "Continuous Update Project (CUP) matrix" of the World Cancer Research fund provides updated summary of evidence for the relation between specific nutritional factors and cancer **(World Cancer Research Fund International 2016)**. A "convincing decreased risk" for

colorectal cancer is attributed to foods containing dietary fibre, as well as to lactation. For postmenopausal breast cancer, lactation is also attributed this high level of evidence. "Probable decreased risk" for various cancer types is attributed to non-starchy vegetables, fruits, garlic, diets high in calcium, coffee, and physical activity. On the other hand, "convincing increased risk" for different types of cancer is attributed to aflatoxins, red meat, processed meat, alcoholic drinks, beta-carotene, and body fatness and adult attained height; and "probable increased risk" to "cantonese-style salted fish", salt, salted and salty foods, glycaemic load, arsenic in drinking water, maté, and greater birth weight.

IV.B.3 Diet and physical functioning

A review of the literature on the role of dietary factors for mobility concluded that current evidence was in favour of a beneficial role of adequate intakes of micronutrients, especially antioxidants and vitamins **(Milaneschi et al. 2010)**. Moreover, a recent study published by the same author indicates that higher adherence to the Mediterranean diet may be associated with slower decline in mobility among elderly individuals **(Milaneschi et al. 2011)**.

In addition, malnutrition is discussed as a key factor for the development of mobility limitations **(Cederholm et al. 2014)**, which has led to the development of the "Mini Nutritional Assessment"- tool in order to screen individuals at risk for malnutrition in clinical settings **(Guigoz et al. 2002)**.

IV.B.4 Diet and cognitive functioning

Various systematic reviews of the literature on the association between diet (or modifiable risk factors in general) and neurodegenerative diseases (or cognitive decline) have been conducted **(Lehert et al. 2015; Lafortune et al. 2016; Deckers et al. 2014; Plassman et al. 2010; Berendsen et al. 2015; Lourida et al. 2013)**.

a) General conclusions from systematic reviews of observational studies

A recent systematic review and "Delphi consensus study" on the link between lifestyle factors and dementia has concluded that the "strongest support" was identified for "depression, (midlife) hypertension, physical inactivity, diabetes, (midlife) obesity, hyperlipidemia, and smoking" and that concerning diet and other aspects (coronary heart disease, renal illness, and "cognitive activity"), more research was needed **(Deckers et al. 2015)**. A systematic review published by Plassman et al. came to a similar conclusion, stating that evidence on the link between nutritional factors was "limited" **(Plassman et al. 2010)**. In line with this, Lafortune et

al. concluded that there was "limited evidence' that overall dietary quality in midlife was related to later risk of dementia or overall cognitive functioning **(Lafortune et al. 2016)**.

a) The Mediterranean diet and other overall dietary patterns

A systematic review of available randomized controlled trials conducted by Lehert et al. underlined, above all, the preventive potential of interventions based on a Mediterranean diet supplemented with olive oil (although this conclusion was only grounded on one randomized controlled study, the PREDIMED trial) **(Lehert et al. 2015).**

In line with this, a systematic review on the association between the overall diet and cognitive decline or dementia in both observational and intervention studies highlights the available evidence for a beneficial role of adherence to the Mediterranean diet (which had been identified in "4 of 6 cross-sectional studies, 6 of 12 longitudinal studies, 1 trial, and 3 meta-analyses") **(van de Rest et al. 2015)**. In the same systematic review, evidence for a favourable role of other types of measures of overall dietary quality – both *a priori* dietary scores and *a posteriori* dietary patterns – was found in all 6 investigated cross-sectional studies and in 6 of 8 prospective observational studies.

A review of the literature published by Gu et al. has concluded that *a priori* or *a posteriori* dietary patterns reflecting "higher intake of fruits, vegetables, fish, nuts and legumes, and lower intake of meats, high fat dairy, and sweets" appeared to have a beneficial role in the prevention of Alzheimer's disease **(Gu and Scarmeas 2011)**. Of note, the above-described pattern is rather close to general representations of the Mediterranean diet. This is in line with a review published by Allès et al., which stated that the areas that were, at present, regarded to provide "the most promising leads" included Mediterranean-type dietary patterns and "any diets high in vegetables" or in omega-3 polyunsaturated fatty acids **(Allès et al. 2012)**.

A recent review of the literature that specifically focused on the relation between adherence to the Mediterranean diet and cognitive outcomes has concluded that there was a strong "biological rationale" for a beneficial role of the Mediterranean diet, but that results from observational studies were "mixed", especially when considering the findings of the most recently published investigations **(Feart et al. 2015)**.

b) Omega-3 fatty acids

With respect to **omage-3 fatty acids**, Lehert et al. **(Lehert et al. 2015)** stated that their meta-analysis "confirmed the absence of cognitive effect", citing a Cochrane review that had not

found a "clear role" of omega-3 fatty acids for dementia prevention **(Sydenham et al. 2012)**. This is in contradiction with a statement of a "National Institutes of Health State-of-the-Science Conference" on the prevention of Alzheimer's disease and cognitive decline, which underlined that "the most consistent evidence" (based on observational studies) concerning the prevention of cognitive decline was available for long-chain omega-3 fatty acids **(Daviglus et al. 2011)**.

c) Vitamin D

Lehert et al. also found no indication for a protective role of **vitamin D**; however, this observation was only based on one single randomized controlled trial **(Lehert et al. 2015)**. Similar to the evidence available for omega-3 fatty acids, there is a large divergence between results from observational studies and from intervention trials with respect to vitamin D. While the randomized controlled trials included intro Lehert et al.'s review **(Lehert et al. 2015)** and other intervention trials **(Anastasiou et al. 2014)** have, overall, obtained rather discouraging results, findings from observational studies tend to suggest a beneficial role of an adequate vitamin D status. In a systematic review of epidemiological studies on vitamin D and cognition **(van der Schaft et al. 2013)**, 18 out of 25 cross-sectional studies have found a significant link between lower vitamin D concentrations or intake and worse cognitive performance or a higher prevalence of dementia. Out of six prospective studies, four have found that lower vitamin D concentrations were related to an increased risk of cognitive decline.

d) B-vitamins and antioxidants

With respect to **B-vitamins**, Lehert et al. highlighted that although observational studies had indicated possible relations with Alzheimer's disease, the results from randomized controlled trials have been mixed **(Lehert et al. 2015)**.

Concerning **antioxidants**, current evidence from randomized controlled trials is not in favour of a beneficial role for cognitive outcomes **(Daffner 2010)**. Yet, the SU.VI.MAX trial showed a beneficial role of antioxidant supplemental for later episodic memory performances, and verbal memory scores were higher among supplemented individuals as compared to non-supplemented individuals in two subgoups: non-smokers, and individuals with low baseline serum- vitamin C concentrations **(Kesse-Guyot et al. 2011b)**.

A systematic review on antioxidant nutrients in relation to age-related cognitive decline, based on observational studies, has concluded that there was "a possibility for protective effects of antioxidant nutrients against decline in cognition in older people although the supportive evidence is still limited in number" **(Rafnsson et al. 2013)**. A review that specifically focused on vitamin C and Alzheimer's disease highlighted that there was "a large body of evidence" for a protective role of "maintaining healthy vitamin C levels", but that the avoidance of deficiency was probably more favourable than the consumption of supplements in addition to generally healthy dietary habits **(Harrison 2012)**. Among the different types of dietary antioxidants, notably polyphenols have been identified to have a positive role for the prevention of dementia or the maintenance of good cognitive functioning during aging **(Commenges et al. 2000; Kesse-Guyot et al. 2012; Letenneur et al. 2007; Nooyens et al. 2015)**.

IV.B.5 Mechanisms relating diet to general age-related health decline

In line with the WHO's suggestion that accumulating "molecular and cellular damage" as a key underlying mechanism of age-related decline, two major biological pathways have been suggested by which diet could, in part, counteract (or help to not accelerate) this decline: the prevention of low-grade chronic inflammation **(Barbaresko et al. 2013; Shivappa et al. 2014; Szarc vel et al. 2015),** and the prevention of damages provoked by excessive oxidative stress **(Harman 1992; Yoshihara et al. 2010)**. These two pathways are linked, as oxidative stress can be a cause and consequence of inflammation **(Khansari et al. 2009; Reuter et al. 2010)**.

The important role of inflammation a number of researchers now use the term "inflammaging processes for age-related decline is underlined by the fact that" **(Franceschi and Campisi 2014)**. A large number of specific dietary components **(Shivappa et al. 2014)** - such as fibre, different vitamins and minerals, spices like garlic and ginger, polyunsaturated fatty acids, and polyphenols – as well as overall dietary patterns **(Barbaresko et al. 2013)**, have been shown to be associated with biomarkers of chronic low-grade inflammation.

With respect to oxidative stress, dietary antioxidants and antioxidants supplied by supplements have been in the centre of attention with respect to age-related disease prevention for a long time **(Ames et al. 1993)**. Yet, the current evidence makes it difficult to draw firm conclusions – especially concerning antioxidant supplements, which have yielded

disappointing results in the context of prevention trials **(Biesalski et al. 2010; Bjelakovic et al. 2012; Hemilä and Kaprio 2011a; Myung et al. 2010; Myung et al. 2013)**.

A further key mechanism that has been suggested to be related to longevity and healthy aging in animal models is caloric restriction **(Fontana and Partridge 2015)**. However, the relevance of this pathway for humans is still under debate.

Other biological mechanisms that have been suggested to relate nutritional factors with the prevention of age-related decline in health include:

- the prevention of telomere shortening **(Shammas 2011)**,
- the prevention of genomic instability via the maintenance of well-functioning DNA repair mechanisms **(Choi and Mason 2000),**
- the prevention of metabolic disorders **(Calcada et al. 2014)**,
- the modulation of epigenetic alterations **(Szarc vel et al. 2015)**,
- and the modulation of changes related to gut microbiota **(Claesson et al. 2012).**

Mechanisms that are specific to the prevention of cognitive decline include the maintenance of well-functioning membrane structures in the brain (which notably include omega-3 fatty acids) **(Andreeva and Kesse-Guyot 2015)**, the regulation of neurotransmitters **(Andreeva and Kesse-Guyot 2015; Gomez-Pinilla 2008)**, and an enhancement of autophagy of misfolded or damaged proteins (such as amyloid β protein) **(Banerjee et al. 2015)**.

OBJECTIVES

As explained in the "State of knowledge"- section of this thesis, a healthy diet has been suggested to be a key factor that could help maintain a good overall health status during the process of aging, and delay the onset of chronic disease, functional impairment, and disability. Notably, a rather large body of research on the relation between dietary factors and chronic diseases is available. However, only very few studies have, to this day, evaluated the relation between dietary factors and multidimensional models of healthy or successful aging. This is of interest for multiple reasons. Practically, public health initiatives should not aim to prevent or delay the onset of specific health conditions, but help improve the overall health status of the population (and in particular of elderly individuals). Thus, results on the relation between modifiable risk factors and multidimensional concepts of healthy or successful aging are a valuable complement to available function- and disease- specific research. Furthermore, in a similar manner as overall diet- approaches, the use of multidimensional models of healthy aging may help to identify associations that are too small to be detected when analysed separately, but become detectable when considered in the context of an 'overall health'-framework. Finally, the aetiology of age-related chronic diseases and functional decline is probably, at least in part, related to common underlying biological mechanisms, such as oxidative stress and chronic low-grade inflammation.

Thus, the **first objective** of this thesis was to investigate the effect of antioxidant supplementation (i.e. the initial main exposition factor of the SU.VI.MAX trial) in order to provide more data suitable to confirm – or to not confirm – the hypothesis according to which antioxidant nutrients have a protective role against age-related decline by counteracting the detrimental effects of excessive oxidative stress. We furthermore aimed to determine whether the tested antioxidant supplementation was more effective (or only effective) among individuals with initially low levels of the tested antioxidants and in those with a lower consumption of foods that are rich in antioxidants. In addition, we aimed to determine whether the efficacy of the supplementation also depended on smoking status and alcohol consumption, two lifestyle factors that are known to influence antioxidant status and metabolism **(Stryker et al. 1988)**, and on age.

The **second objective** was to investigate the relation between nutritional factors and a multidimensional model of healthy aging. In particular, we chose to use two different 'overall

diet'- approaches (*a posteriori* dietary patterns and *a priori* dietary scores), given the multiple advantages of these approaches over traditional 'single food'- or 'single nutrient'- approaches, which we have listed in the "State of knowledge"- section of this thesis. Concerning the '*a posteriori'*- approach, we chose to apply principal component analysis in order to obtain data-driven dietary patterns, which we then aimed to examine concerning their relation to overall healthy aging. Concerning the '*a priori'*- approach, we took a special focus on the role of adherence to nutritional recommendations, and questioned whether both food-based and nutrient-based recommendations were pertinent for the maintenance of good overall health during aging.

The *a priori*- dietary scores that we investigated, the modified Programme National Nutrition Santé- Guideline Score (mPNNS-GS), the Probability of Adequate Nutrient Intake Dietary Score (PANDiet), and the Dietary Quality- International score either directly penalize excessive total energy intakes (mPNNS-GS) or at least put substantial emphasis on 'moderation' (i.e. consumption of specific macronutrients, micronutrients, or food groups in limited amounts). Data-reduction methods that are used to extract *a posteriori*- dietary patterns (such as principal component analysis) do not have such inherent control elements. We thus chose to not only investigate the simple adherence to specific *a posteriori*- dietary patterns with respect to healthy aging, but also to specifically investigate whether the highest probability for healthy aging would be observed among individuals with both regulated overall energy intakes and high adherence to *a posteriori*- dietary patterns that would potentially indicate higher overall dietary quality.

The **third objective** of this thesis was to more specifically investigate the relation between diet and the maintenance of high levels of cognitive functioning during aging. The prevention of age-related cognitive decline and dementia is a major public health challenge, given the immense impact of these conditions on an individual's autonomy. We more specifically investigated the relation between midlife vitamin D status and later cognitive functioning. Obtaining more knowledge on potential detrimental health effects of vitamin D deficiency and insufficiency is of high importance, as large proportions of populations worldwide have low circulating vitamin D levels. In France, for example, more than 45% of the population is estimated to have vitamin D 'insufficiency' (or 'moderate deficiency', depending on the chosen terminology).

Table 3 details the different objectives of this thesis and the corresponding concrete research questions.

Table 3. Objectives and research questions of this thesis

	Objective	**Research questions**
Objective 1	To examine the prospective association between daily supplementation with antioxidant vitamins and minerals, over a period of 8 years, with a multidimensional concept of healthy aging, in a population of French adults	**Research question 1.1:** Is there a long-term association of antioxidant nutrient supplementation with respect to the probability of healthy aging, as assessed with the help of a multidimensional model? Is such a supplementation more effective among individuals with initially low levels of the tested antioxidants and in those with a lower consumption of foods that are rich in antioxidants?
Objective 2	To examine the prospective association between overall dietary quality at midlife and a multidimensional concept of healthy aging in a population of French adults	**Research question 2.1:** Is adherence to different *a posteriori* dietary patterns at midlife, extracted by principal component analysis, prospectively associated with a multidimensional concept of healthy aging? Is this association modulated by overall energy intake? **Research question 2.2:** Are higher adherence to the French official food-based dietary guidelines (as measured by the mPNNS-GS), higher adequacy of the diet to the French nutrient reference values (as measured by the PANDiet), and higher adherence to both food-based and nutrient-based dietary guidelines of different countries (as measured by the Dietary Quality- International score) at midlife prospectively associated with a multidimensional concept of healthy aging?
Objective 3	To examine the prospective association between plasma vitamin D status at midlife and later cognitive functioning	**Research question 3.1:** Is there a prospective association between plasma vitamin D status at midlife and cognitive functioning in different domains assessed 13 years later?

GENERAL METHODOLOGY

I. The SU.VI.MAX and SU.VI.MAX 2 studies

I A. The SU.VI.MAX study

I.A.1 Basic design

The SU.VI.MAX study was a primary prevention trial with a randomized, placebo-controlled, double-blind design and a follow-up- period of 8 **years (Hercberg et al. 1998; Hercberg et al. 2004)**. The trial had the objective to evaluate the effect "of a combination of antioxidant vitamins and minerals, namely beta-carotene, vitamin C, vitamin E, selenium, and zinc at doses considered to be nutritional and nonpharmacologic" on the incidence of fatal or non-fatal ischemic heart disease (International Classification of Diseases (ICD-10) codes I20-I24) and cancer at all sites (ICD-10 codes C00-C97) **(Hercberg et al. 2004)**, among adults recruited from the general population. The pre-specified secondary study objectives were to evaluate the effect of antioxidant supplementation on "the main localizations of cancers and infectious diseases, overall and cause-specific mortality, and perceived health and health-care consumption". **(Hercberg et al. 1998; Hercberg et al. 2004)**

I.A.2 Ethical approval

The ethical committee for studies with human subjects (i.e. the "Comité Consultatif pour la Protection des Personnes se prêtant à la Recherche Biomédicale" (CCPPRB)) of Paris-Cochin has given approval to the SU.VI.MAX study (approval number 706). Moreover, the study has received approval by the Comité National Informatique et Liberté (CNIL, number 334641). **(Hercberg et al. 1998; Hercberg et al. 2004)**

I.A.3 Recruitment and eligibility criteria

Recruitment was based on multiple channels that were used nationwide (in France): television, radio, and newspapers. Eligibility criteria were **(Hercberg et al. 1998; Hercberg et al. 2004)**:

- Provision of written informed consent, and completion of a screening questionnaire
- Absence of diseases "likely to hinder active participation or threatened 5-year survival

- Acceptance of participation constraints (amongst others the possibility to receive a placebo rather than antioxidant supplementation)
- No previous regular consumption of supplements containing the antioxidants that were tested in the trial
- No "extreme beliefs or behaviour" concerning diet
- Aged 35–60 years (women) or 45–60 years (men)

Before inclusion, potential participants received 15 'test capsules' in order to 'simulate' the study protocol and thus to help them decide whether the protocol was acceptable for them. The justification for the differential pre-defined age-ranges according to sex was that breast and uterine cancers already occur with substantial frequency at relatively young ages. The final study sample of the SU.VI.MAX trial contained 12,741 individuals. **(Hercberg et al. 1998; Hercberg et al. 2004)**

I.A.4 Intervention

The finally enrolled participants were randomly assigned to the intervention- or the placebo-group, according to a stratified randomization strategy, accounting for sex, age group, smoking status, and area of residence. The administered doses of the different antioxidants were as follows: 6000 mg of beta-carotene, 120 mg of vitamin C, 30 mg of vitamin E, 100 mg of selenium, 100 mg of selenium, and 20 mg of zinc. **(Hercberg et al. 1998; Hercberg et al. 2004)**.

Figure 6 presents multiple aspects of the design of the SU.VI.MAX trial, notably the different elements of follow-up.

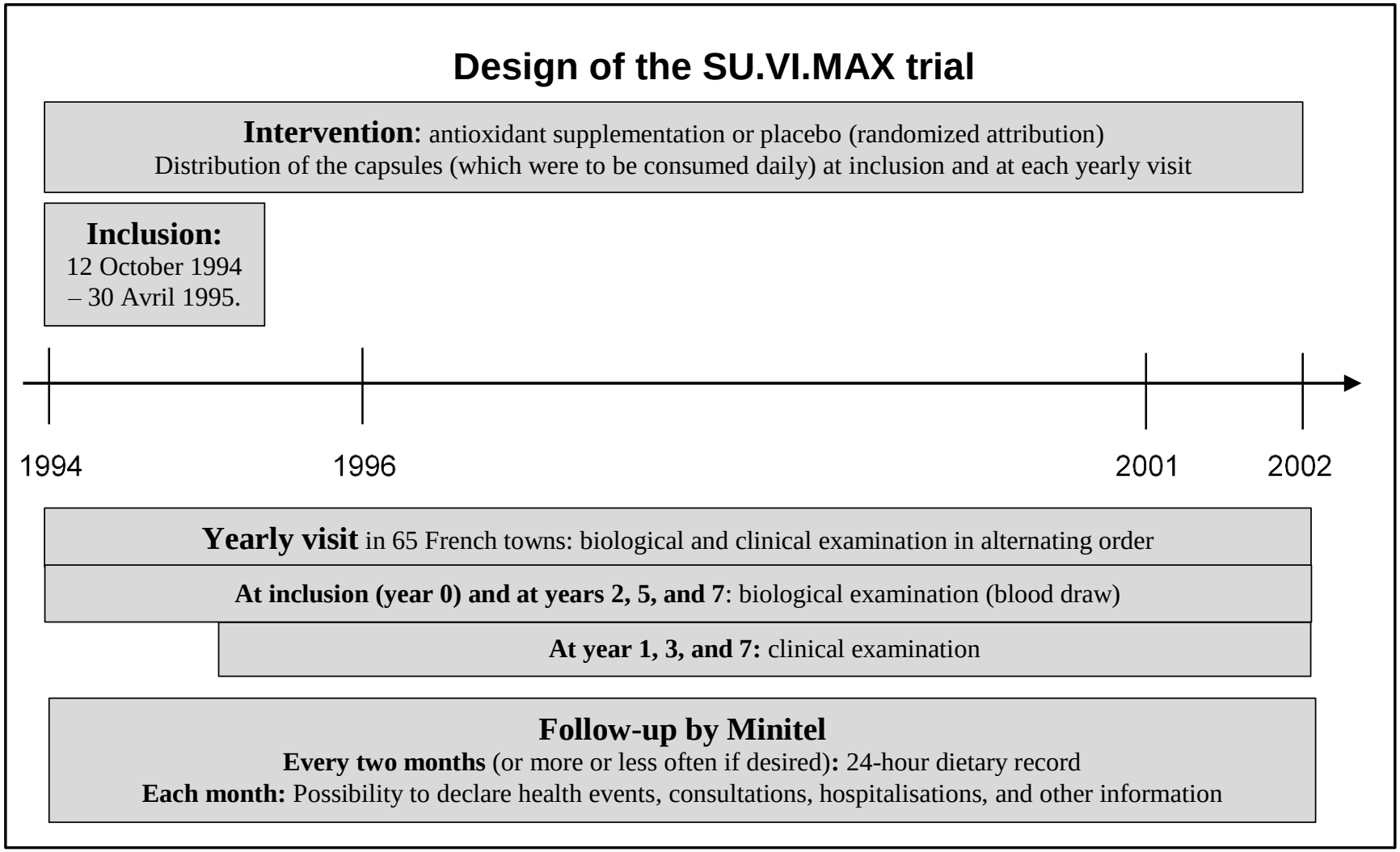

Figure 6. Design of the SU.VI.MAX trial

I.A.5 Collection of sociodemographic and other data

The obligatory SU.VI.MAX inclusion- questionnaire inquired information on sociodemographic indicators such as sex, date of birth, marital status, occupation, and education level, and on other indicators, such as tobacco consumption and medication use **(Kesse-Guyot et al. 2011c)**.

I.A.6 Collection of data on health events

In addition to yearly visits, which consisted of a blood-draw or a clinical examination in alternating order, participants were followed via Minitel, a "French telephone-based terminal" that was frequently used in France at the time of the study. By the means of these terminals, participants were notably asked to declare occurring health events, medical consultations, and hospitalizations. **(Hercberg et al. 1998; Hercberg et al. 2004)**

The ascertainment of health relied both on self-reporting by participants themselves, or on inquiries to the participant's neighbours or physician. A detailed medical file was created for all participants with suspected health events, and event validation was then conducted by a blinded expert committee on the basis of all pertinent records (such as histologic records for cancers, or radiologic records and other criteria for ischemic disease). By the end of the follow-up period, vital status and causes of death for all participants were compared with data from the national death registry. **(Hercberg et al. 1998; Hercberg et al. 2004)**

I.A.7 Collection of data on blood pressure, weight and height

Clinical examinations took place one year after inclusion (at year 1) and then at years 3 and 7. They notably included the measurement of blood pressure at both arms according to a standardized protocol (with the help of a mercury sphygmomanometer, after a period of lying down for at least 10 minutes), and the measurement of weight (with an electronic scale; participants did not wear shoes and only indoor clothing) and height (with a wall-mounted stadiometer; participants did not wear shoes). In addition, clinical examinations also included specific investigations, for instance thyroid ultrasound examinations, or mammography for women. **(Hercberg et al. 2004; Kesse-Guyot et al. 2011d)**

I.A.8 Collection of biological data

Draws of 35 ml- venous blood samples were carried out at inclusion (year 0), and then at years 2, 5, and 7, after a 12-hour fast. All blood draws at baseline (year 0) occurred between

October 1994 and April 1995. After the blood draw, the samples were instantly centrifuged. Within less than 1 hour after the blood draw, aliquots of plasma were stored in dry ice, and then, within a period of no more than 24 hours, shipped to a central biobank. In this central biobank, the aliquots were stored frozen in liquid nitrogen, at a temperature of minus 196°C. For vitamin C measurements, the procedure was slightly different: "before freezing, whole venous blood was collected in heparinized tubes and immediately centrifuged for 20 minutes at 3000 x g and 4°C, and 0.5 mL plasma was diluted 1-in-10 with 4.5 mL of an aqueous 5% metaphosphoric acid solution"**(Czernichow et al. 2006)**. **Table 4** summarizes the different biological measures that were included in the analyses of this thesis, and the respective measurement procedures.

Table 4. Summary of the biological measures included in the analyses of this thesis

Measured molecule	Serum/ plasma	Measurement method
vitamin C (i.e. ascorbic acid)	serum	"automated method based on the principle of continuous flow segmented by air bubbles" **(Bourgeois CF et al. 1989)**
retinol	serum	high-performance liquid chromatography; Biotek-Kontron HPLC system (Biotek-Kontron, Montigny-le-Bretonneux, France) **(Vuilleumier et al. 1983)**
beta-carotene	serum	
vitamin E (i.e. tocopherol)	serum	
zinc	serum	flame atomic absorption spectrometry (Perkin Elmer 3110 spectrometer for zinc and selenium; Perkin Elmer 4100 ZL for selenium) (Perkin Elmer, Norwalk, Conn) **(Arnaud et al. 1991; Nève et al. 1987)**
selenium	serum	
total cholesterol	serum	enzymatic method (Technicon flow analysis device; Technicon DAX-24; Bayer Diagnostic, Pittsburgh, PA)
fasting glucose	serum	
25-hydroxy-vitamin D	plasma	Roche Cobas electrochemoluminescent total 25-hydroxy-vitamin D assay **(Knudsen et al. 2012; Touvier et al. 2014)** *measured in the context of a nested case-control study on the link between vitamin D and cancer*

I.A.9 Collection of dietary data

Participants were invited to complete one 24-hour dietary record every two months, via Minitel. The specific week days were randomly chosen in order to cover each day of the week and all seasons of the year. (Kesse-Guyot et al. 2013)

In order to code food portions in the context of the 24-hour dietary records, assistance was provided to participants by the means of an instruction manual that contained "validated photographs of over 250 foods represented in 3 different portion sizes". In addition, participants could select 2 different "intermediate" and 2 different "extreme" portion sizes; thus, a total number of 7 different portion sizes was available. **(Le Moullec et al. 1996)**

The estimation of nutrient intake on the basis of the 24-hour dietary records was implemented with the help of a food-composition table developed specifically for the SU.VI.MAX study **(Hercberg S 2005; Kesse-Guyot et al. 2013)**. For all analyses included in this thesis, usual dietary intakes at baseline were defined as the average intakes of a person across all available 24-h dietary records that were provided during the first 2 years of follow-up. In order to obtain sufficiently precise estimates, dietary data were only calculated for participants who had provided at least 3 dietary records during this period. Moreover, dietary records that were characterized by a reported overall energy intake of less than 100 kcal per day or of more than 6000 kcal per day were excluded. In addition, men reporting less than 800 kcal per day and women reporting less than 500 kcal per day across at least one third of their 24-hour dietary records were excluded from analyses. This procedure is usually applied for studies based on data of the SU.VI.MAX study **(Kesse-Guyot et al. 2011d; Lassale et al. 2012)**.

For alcohol and fish, which tend to be consumed with very varying frequency, or infrequently by large groups of the population, data was collected from questionnaires in addition to the information provided by the 24h- dietary records. The usual consumption of alcohol was also assessed with the help of a validated semi-quantitative questionnaire **(Lasfargues et al. 1990)**, and usual consumption of seafood was also assessed via a specific item of a general baseline-questionnaire **(Kesse-Guyot et al. 2011d)**.

I.A.10 Collection of data on physical activity

Two types of information on physical activity were collected: an item of the inclusion-questionnaire inquired whether participants had a regular physical activity, and if yes, whether this activity corresponded to more than 1 hour of walking per day. Moreover, in 1998, the validated French version of the Modifiable Activity Questionnaire was administered to the participants of the SU.VI.MAX study **(Kriska et al. 1990; Schulz et al. 1994; Vuillemin et al. 2000)**.

I B. The SU.VI.MAX 2 study

In 2007–2009, all participants of the SU.VI.MAX trial were invited to be part of the observational SU.VI.MAX 2 study, which can be considered as a supplemental follow-up point.

The SU.VI.MAX 2 study was approved by the CCPPRB of Paris-Cochin Hospital (no. 2,364) and the CNIL(no. 907,094). Written informed consent was obtained from each subject.

This supplemental follow-up point included a clinical examination (which notably included the physical functioning tests that are part of the Short Physical Performance Battery (SPPB) **(Guralnik et al. 1994)**), a neuropsychological evaluation that was carried out by trained neuropsychologists, and the completion of additional questionnaires, notably the SF-36 questionnaire **(Leplege et al. 1998)**, and the Lawton Instrumental Activities of Daily Living-scale **(Graf 2008)**. In addition, the participants were also presented with the MMSE **(Folstein et al. 1975)**, and were asked to complete the Center for Epidemiological Studies- Depression Scale (CES-D) **(Morin et al. 2011)**. In addition the above-listed aspects of data collection during the SU.VI.MAX 2 follow-up point that are directly relevant for this thesis, a variety of other data were collected, such as dietary data (via a food frequency questionnaire), anthropometric measurements, measurement of blood pressure, and audiometric measures.

The final study sample of the SU.VI.MAX 2 observational follow-up point contained 6,850 individuals. The rather large difference between the sample sizes of the original SU.VI.MAX trial and the SU.VI.MAX 2 study can be explained by the fact that participation in the SU.VI.MAX 2 study was completely facultative, and had in no way been presented as a condition for participation in the original SU.VI.MAX trial.

The neuropsychological evaluation included a number of different tests and was carried out in a subsample of about 5000 participants. The **RI-48** (Rappel Indicé-48 items test), designed to assess **episodic memory** function, is based on a list of 48 words that belong to 12 different categories. For the analyses included in this thesis, we used the delayed cued-recall, which corresponds to recalling the words after a certain amount of time, after being presented with a "cue", i.e. after being asked to name words belonging to a specific category. The final test score corresponds to the number of correctly recalled words (the score thus has a maximum of 48 points). **(Adam et al. 2007; Kesse-Guyot et al. 2013)**

Lexical-semantic memory was evaluated with the help of **verbal-fluency tasks.** The first task was a "semantic fluency task", during which participants were asked to name as many animals as possible. The second task was a "phonemic fluency task", during which participants were asked to name words starting with the letter "P." The final test score corresponded to the number of correct words listed during a period of 2 minutes for each of the tasks. **(Kesse-Guyot et al. 2013; Lezak et al. 2004)**

Short-term and working memory was evaluated with the help of **forward and backward digit span- tests.** These tests consisted of repeating sequences of digits forward or backward. The number of digits was continuously augmented "by one unit" until the individual was not able to correctly complete two "consecutive trials of the same digit-span length". For each sequence that was correctly repeated, one point was attributed. Each of the two digit span-tests had a maximum score of 14 points. **(Kesse-Guyot et al. 2013; Wechsler 1981)**

Mental flexibility was evaluated via **condition 4 ("number-letter switching") of the Delis-Kaplan Trail Making test (DK-TMT)**. This condition is similar to "Part B" of the original version of the TMT, which was designed for the U.S. "Army Individual Test Battery" **(Tombaugh 2004)**. For this test, participants were asked to connect numbers and letters in alternating order. The final test score corresponds to the time (in seconds) that was needed to complete the task (thus, lower scores were indicative of higher performance). According to the conversion tables provided by Delis and Kaplan, "scaled scores" corrected for age-group were also calculated. These scaled score were reverse-coded so that higher scores were indicative of higher performance. **(Delis et al. 2001a; Delis et al. 2001b)**

Figure 7 presents the different domain-specific tests included in the neuropsychological evaluation, and their interpretation with respect to different domains of cognitive functioning.

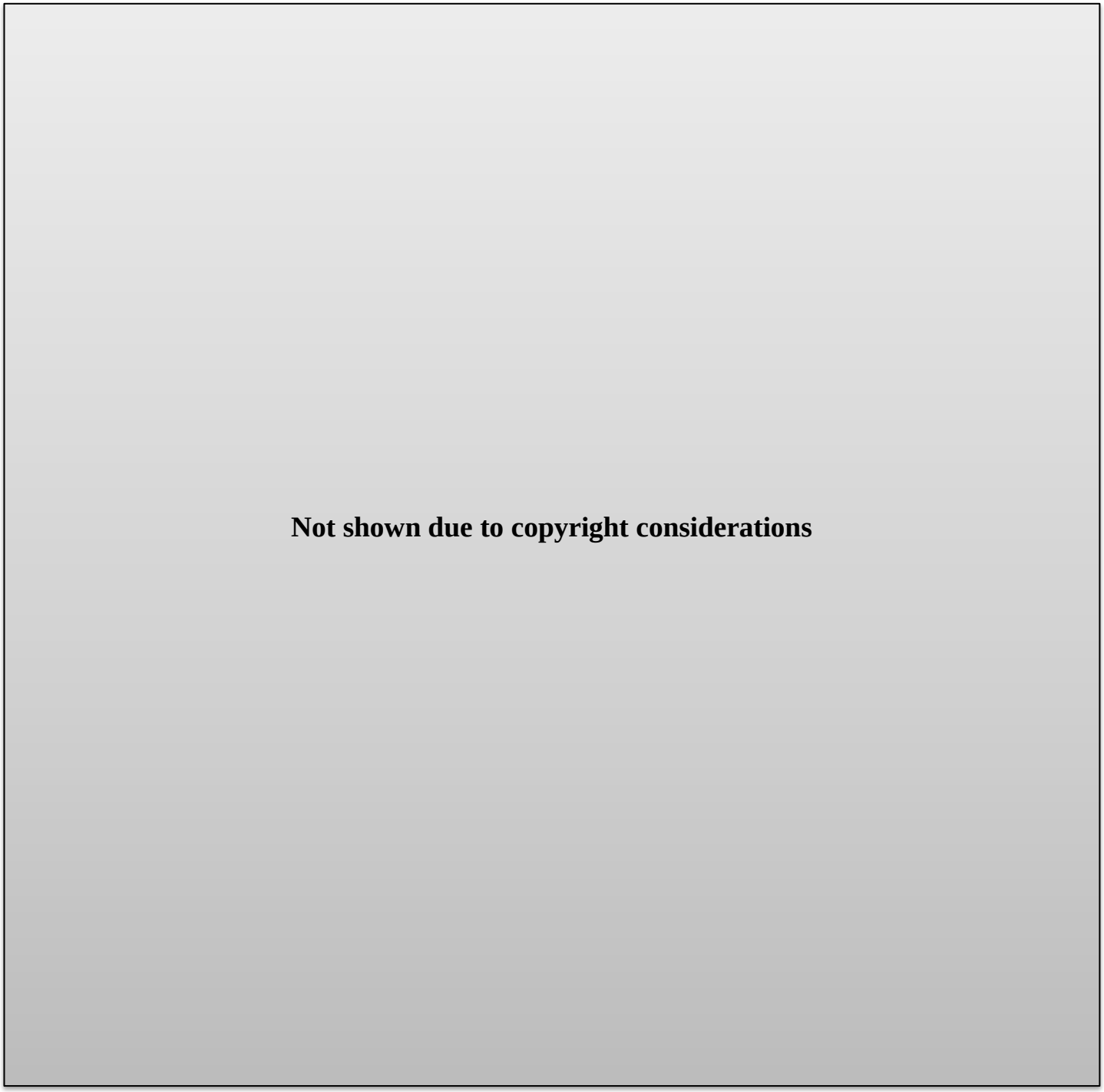

Figure 7. Presentation of the different tests used in the neuropsychological evaluation, in the context of the different domains of cognitive functioning

The Figure was created on the basis of the following references: **(Cowan 2008)**, **(Elliott 2003)**, **(Baddeley 2010)**, **(Deschamps and Moulignier 2005)**, *(Gazzaniga et al. 2000). The names of the cognitive tests are displayed in green. Abbreviations: DCR: delayed cued recall; RI-48: rappel indicé- 48 items; TMT, Trail Making Test.*

II. Development of an operational definition of healthy aging

II.A General rationale

When developing an operationalized definition of healthy aging for the SU.VI.MAX and SU.VI.MAX 2 studies, we considered the following criteria:

1) In order to obtain results that would be well comparable with those of other studies, we aimed to create a definition that would generally fit the framework proposed by Rowe and Kahn, as their model has served as a reference for most existing definitions. Furthermore, we aimed to model healthy aging as a binary variable, in line with the majority of available studies (although more and more studies with continuous indices have been published since we have developed our definition for the SU.VI.MAX study).
2) Our definition had to fit the variables available in the SU.VI.MAX and SU.VI.MAX 2 studies, and the age-range of participants
3) We aimed to take into account two of the most frequent criticisms expressed with respect to the Rowe and Kahn- model:
    a. The need for more emphasis on subjective criteria, such as perceived health status
    b. The need for more emphasis on mental health

In line with our aim to obtain a definition that would reflect elements of health that matter to individuals and/or have a direct impact on their everyday lives, we decided not to include risk factors for health deterioration (such as high body mass index, high blood pressure, or high blood cholesterol).

Furthermore, when determining cut-offs for transforming continuous variables into binary constructs (in order to obtain an overall binary “healthy aging”- indicator), we used cut-offs with a clinical significance whenever possible. Thus, our strategy was to consider that an individual was “aging healthily” with respect to a specific criterion as long as the individual did not show test results or questionnaire scores that indicated a probably meaningful impairment.

II.B Presentation of the chosen criteria and cut-offs

We defined healthy aging as follows:

- The absence of:
    - incident major chronic disease (cancer, cardiovascular disease or diabetes) during follow-up,
    - limitations in IADL,
    - function-limiting pain,
    - depressive symptomatology,
    - and health-related limitations in social life;
- the presence of:
    - good physical functioning,
    - good cognitive functioning,
    - and good overall self-perceived health.

Healthy aging was operationalized as a binary variable: individuals who met all of the above criteria were considered to show healthy aging, while individuals who did not meet at least one of the above criteria were considered to not show healthy aging.

II.B.1 Avoidance of disease and disability

We decided to operationalize Rowe and Kahn's criterion "avoidance of disease and disability" by 'absence of incident cancer, cardiovascular disease, or diabetes', and 'no limitations in IADL' (the latter of the two as a proxy for absence of disability).

II.B.2 Good cognitive functioning

Concerning Rowe and Kahn's criterion 'good cognitive functioning' we decided to not include all of the neuropsychological variables available in the SU.VI.MAX study – in order to avoid giving a disproportionate weight to this dimension of healthy aging with respect to the other dimensions. First, we aimed to choose variables that would both allow a good comparison with the results of other studies. We thus included the MMSE, which has been used in a rather large number of operationalized definitions of healthy or successful aging **(Almeida et al. 2014; Andrews et al. 2002; Arias-Merino et al. 2012; Cernin et al. 2011; Chaves et al. 2009; Cho et al. 2012; Formiga et al. 2012; Jorm et al. 1998; Li et al. 2006; Newman et al. 2003; Ng et al. 2009; Puig-Domingo et al. 2008; Samieri et al. 2013; Sarnak et al. 2008; Tyas et al. 2007; von Faber et al. 2001; Young et al. 2009)**. Second, given the rather young age-range of our study population at follow-

up (as compared to other studies on healthy aging or cognitive decline), we aimed to include variables that would limit ceiling effects, and that would be sensitive to early detrimental cognitive changes. We have thus included the RI-48 test, which measures episodic memory and is used for the detection of early Alzheimer's disease **(Adam et al. 2007),** and the TMT, which measures mental flexibility. Mental flexibility is a subcategory of executive functioning, a domain that is thought to also be affected in preclinical Alzheimer's disease **(Bäckman et al. 2005)**.

We considered a cut-off of ≥ 27/30 points on the Mini-Mental State Examination, which has been referenced in the literature **(O'Bryant et al. 2008; Pendlebury et al. 2010)**, and appeared to us as sufficiently high considering the age-range of our study population. For the RI-48 test, we considered the cut-off of ≥ 19/48 points suggested by the authors **(Adam et al. 2007)**. For condition 4 of the DK-TMT, no fixed cut-off has been suggested in the literature. We thus chose the 10. percentile (i.e. the mean minus 1.29 standard deviations, which corresponds to 5.5 points) on the scaled (i.e. age-corrected and reverse-coded) score of the Delis-Kaplan reference population aged 50-89 years **(Delis et al. 2001a; Delis et al. 2001b)**. Within the above-mentioned Delis-Kaplan reference population, the mean ± the standard deviation of the 'DK-TMT scaled score' is 9.82 ± 3.37, and its range is 1-19.

II.B.3 Good physical functioning

Concerning the criterion 'good physical functioning', the principal measure available in the SUVI.MAX/ SU.VI.MAX 2 study was the SPPB. As for the MMSE, we chose a cut-off that was referenced in the literature **(Bogin et al. 2014; Cavallari et al. 2013; Hugenschmidt et al. 2014; Wakefield et al. 2010)**, but sufficiently high when considering the age-range of our study population: 11/12 points.

II.B.4 Engagement in social and productive activities

Concerning the criterion "Sustained engagement in social and productive activities", the only relevant information that was available in the SU.VI.MAX study were the items concerning health-related limitations in social life in the SF-36 questionnaire. We thus included a component "no health-related limitations in social life" into our definition. Individuals were considered to not present health-related limitations in social life if they reported that their health affected their social life only slightly or not at all (in the negative way) and that the frequency of such limitations was no higher than "some of the time".

II.B.5 Further components on mental and self-perceived health

As stated above, we aimed to enrich Rowe and Kahn's original concept by further components on mental health and on self-perceived health. We chose to define the component "good mental health (no depressive symptoms)" as having less than 16 points on the CES-D, which is the internationally applied cut-off for the presence of depressive symptoms **(Langevin et al. 2011; Radloff 1977)**.

A further component "good overall self-perceived health" was defined as judging one's own health status as 'excellent', 'very good', or 'good' in the SF-36 questionnaire.

Finally, as we considered pain to be a highly important determinant of overall well-being, we included a component "no function-limiting pain". Individuals were considered to not present function-limiting pain if they stated having experienced no more than "mild" physical pain in the previous month and if the experienced pain had no impact or only a limited impact on their daily activities.

Table 5 presents the specific variables and the chosen-cut offs that were used to define each criterion.

Table 5. Criteria used to define "healthy aging" in the SU.VI.MAX study

Not shown due to copyright considerations

II.C Descriptive data concerning the chosen healthy aging definition

II.C.1 Data availability

In the SU.VI.MAX/ SU.VI.MAX 2 studies, data on healthy aging status were available for 3,966 individuals. Information on healthy aging status was collected at the SU.VI.MAX 2 observational follow-up point (2007-2009), in which 6,850 SU.VI.MAX participants were included on a voluntary basis. We decided to only determine healthy aging status among individuals aged at least 45 years at inclusion (1994-1995). Hence, we excluded participants who were still rather young at baseline (the SU.VI.MAX cohort comprised men aged 45-60 years at inclusion and women aged 35-60 years at inclusion; we thus excluded women aged 35-44 years at inclusion). Since our healthy aging definition included the absence of incident major chronic disease, we excluded participants who already had such chronic disease (diabetes, cancer, cardiovascular disease) at inclusion. Out of these 5,243 participants, 3,966 individuals had full information on all variables needed to compute healthy aging status, based on our definition. **Figure 8** illustrates the above-explained details on data availability and participant selection.

Figure 8. SU.VI.MAX participants with available information on healthy aging status

The information given in Figure 8 corresponds to the sample- selection flowchart of our investigation on the association between antioxidant supplementation and later healthy aging, since antioxidant supplementation status (supplementation vs. placebo) was known for all of the 3,966 participants with available information on healthy aging status. Of these participants, 1,466 (37.0%) presented healthy aging according to our criteria, and 2,500 (63.0%) did not present healthy aging according to our criteria.

For our investigations on the association of *a posteriori* dietary patterns and *a priori* dietary scores with later healthy aging, the respective flowcharts are different, since not all of the 3,966 participants with available information on healthy aging status had available dietary data at baseline.

II.C.2 Distribution of the chosen criteria in the SU.VI.MAX study

Table 6 presents, for each criterion of our healthy aging definition:

- the proportion of all participants who corresponded to this criterion;
- the proportion of all participants who did not correspond to this criterion;
- the proportion of participants classified as 'non-healthy' agers who did not correspond to this criterion;
- the proportion of participants classified as 'non-healthy' agers who did not correspond to this criterion – but who corresponded to all other criteria (and who were thus only classified as 'non-healthy' agers due to this specific criterion).

In Table 5, the specific criteria of our definition have been grouped according to their correspondence to the criteria of the concept developed by Rowe and Kahn. However, this correspondence is ambiguous. For example, we chose to group "no function-limiting pain" together with another variable issued from the SF-36 questionnaire ("good perceived health") and with "good mental health (no depressive symptoms)".

We are aware that "no function-limiting pain" may as well have been grouped together with "absence of major chronic disease" and "no limitations in IADL". Yet, the information given in Table 6 is of purely descriptive nature and thus only provides information that can help to better understand and interpret the results of our analysis in which "healthy aging" was investigated as a binary variable.

Table 6. Distribution of healthy aging criteria in the SU.VI.MAX study (n=3,966 with available information on healthy aging status in 2007-2009)

Criterion of Rowe and Kahn's concept of successful aging	Criterion of the SU.VI.MAX- definition of healthy aging	% corresponding to criterion	% not corresponding to criterion	% of 'non-healthy agers' not corresponding to criterion	% of 'non-healthy agers' who corresponded to all healthy aging criteria except this specific one
Avoidance of disease and disability	No diabetes, cancer, cardiovascular disease, or limitations in instrumental activities of daily living	79.4	20.7	67.2	12.2
	Absence of disease (i.e. no incident diabetes, cancer, or cardiovascular disease)	**85.5**	**14.5**	**77.0**	**8.7**
	No incident diabetes	96.9	3.1	95.1	1.6
	No incident cardiovascular disease	96.4	3.6	94.3	1.9
	No incident cancer	96.4	3.6	86.5	4.9
	No limitations in instrumental activities of daily living	**92.6**	**7.4**	**88.3**	**3.0**
Maintenance of high physical and cognitive function	**Good physical functioning**	**73.2**	**26.8**	**57.5**	**17.1**
	Good cognitive functioning	**79.9**	**20.1**	**68.1**	**12.9**
Sustained engagement in social and productive activities	**No health-related limitations in social life**	**90.3**	**9.7**	**84.7**	**1.5**
None	Other criteria	73.8	26.3	58.4	11.6
	Good mental health (no depressive symptoms)	**83.6**	**16.4**	**74.0**	**6.1**
	No function-limiting pain	**87.1**	**12.9**	**79.5**	**3.2**
	Good perceived health	**94.5**	**5.5**	**91.3**	**0.6**

Of the 3,966 individuals with information on healthy aging status, 26.8% did not correspond to the "good physical functioning"- criterion, 20.1% did not correspond to the "good cognitive functioning"- criterion, 16.4% presented depressive symptoms, 14.5% were not free of major chronic disease, 12.9% were not free of function-limiting pain, 9.7% did not correspond to the "no health-related limitations in social life"- criterion, 7.4% were not free of limitations in IADL, and 5.5% did not report good perceived overall health.

Of the 2,500 participants who did not present healthy aging according to our criteria, 17.1% were only classified as 'non-healthy' agers because they did not present good physical functioning, 12.9% only because they did not present good cognitive functioning, 8.7% only because they were not free of major chronic disease, 6.1% only because they did not present good mental health, 3.2% only because they were not free of function-limiting pain, 3.0% only because they were not free of limitations in IADL, 1.5% only because they were not free of health-related limitations in social life, and 0.6% only because they did not report a good overall perceived health status.

In order to better understand how often – and to what degree – individuals cumulated different 'health impairments' (i.e. lacking correspondence to a criterion), we counted the frequency of such 'health impairments' with respect to the 8 different criteria (absence of major chronic disease, no limitations in IADL, good physical functioning, good cognitive functioning, no health-related limitations in social life, good mental health, no function-limiting pain, and good perceived health).

The following frequency distribution was observed:

- 1466 participants (37.0%) had no 'health impairments' (i.e. those individuals that were classified as 'healthy agers'),
- 1326 participants (33.4%) had 1 'health impairment',
- 677 participants (17.1%) had 2 'health impairments',
- 286 participants (7.2%) had 3 'health impairments',
- 135 participants (3.4%) had 4 'health impairments',
- 51 participants (1.3%) had 5 'health impairments',
- 20 participants (0.5%) had 6 'health impairments', and
- 5 participants (0.1%) had 7 'health impairments.

No participant had 'impairments' with respect to all 8 criteria of our definition.

III. Statistical analyses

III.A Multivariable analyses: types of statistical models and adjustment

Analyses concerning the relation between dietary factors and healthy aging were generally implemented with the help of multivariable logistic regression models, as healthy aging was conceptualized as a binary outcome.

For analyses on the relation between antioxidant supplementation and healthy aging, however, the initial randomized design of the SU.VI.MAX trial allowed us to simply compute unadjusted relative risks (RR) as main statistical analyses. As the proportion of healthy aging was relatively elevated in our study population, OR cannot be interpreted in the same manner as RR **(Ragland 1992; Zhang and Yu 1998)**. Thus, the computation of RR as main statistical analyses had the advantage that the magnitude of the observed effect was estimated in a more realistic manner. Because RR are not dependent on the 'baseline risk' p0 (i.e. the risk in the 'control' or 'reference' group) **(Grant 2014)**, which can differ across studies, the use of RR permits a better comparison of results across studies than the use of OR.

Sensitivity analyses in which we conducted unadjusted as well as extensively adjusted logistic regression models confirmed that potential confounding variables had no substantial influence on our results.

Analyses on the relation between midlife vitamin D status and later cognitive functioning were carried out with the help of multivariable regression models and analyses of variance and covariance (ANCOVA), since all cognitive test variables were of continuous nature. The variables for which all main models (except the computation of RR in the analyses on antioxidant supplementation and healthy aging) were adjusted are listed below:

- Sociodemographic factors:
    - Sex,
    - Age,
    - Educational level,
    - Occupation,
    - Family situation/ living arrangement;
- Factors related to the design of the study:

  - Follow-up time,
  - Intervention group (antioxidant supplementation or placebo);
- Lifestyle factors;
  - Smoking status,
  - Physical activity level (except for analyses on the nutritional score PNNS-GS, which already contains a physical activity component).

In addition, statistical multivariable models were adjusted for specific factors that were identified as potential confounders concerning the specific association of interest.

III.B Inverse probability weighting

Inverse probability weighting is a statistical method that allows to partially account for selection bias that is related to missing data at follow-up **(Cole and Hernan 2008; Seaman and White 2011)**. The strategy of the method is to attribute more weight to individuals who have similar characteristics as those individuals who were excluded from analyses. Its implementation includes the following steps:

1. Creation of a logistic regression model that predicts the probability to be included into the study sample with a maximum of accuracy (i.e. with a maximal area under the curve- value), and a Hosmer-Lemeshow-test indicating adequate fit (i.e. $p > 0.05$);
2. Extraction of the predicted probabilities for inclusion into the study sample for each participant;
3. Verification that the highest 10% predicted probabilities are not larger than 50% of the sum of all probabilities;
4. Computation of the inverse of the predicted probabilities (1/probability);
5. Computation of 'stabilized weights': multiplication of each "1/probability" with the sampling proportion (i.e. the proportion of included participants among all participants of the 'source' population);
6. Inclusion of these stabilized weights into the desired statistical analysis (using, for example, the 'weight'- statement of SAS proc logistic).

In the case of our analyses, the probability to be included in the study sample notably corresponded to the probability to have data on healthy aging at follow-up. The basic logistic regression model comprised 'inclusion in our final study sample (yes/ no)' as the dependent variable, and the exposition variable of interest as an independent variable. Further

independent variables to be included were chosen from the different available sociodemographic, lifestyle, and health- variables on the basis of descriptive tables comparing included and excluded participants: variables that showed a significant (or nearly significant) difference between included and excluded participants were included in the logistic regression model. Moreover, interaction terms were tested in order to improve the predictive potential of the model.

PUBLICATIONS

The chapter “Publications” concerns the main original scientific articles that have been drafted in the context of this thesis, and includes both already published articles (n=3) and articles that have not yet been published (n=1). For each article, a short summary of the scientific background, objectives, methods, and results is presented. The discussion of the findings of each article is included in the chapter “Discussion” of this thesis manuscript. For more detailed information, please refer to the original articles that are included in the form of screenshots for the already published articles, and as conventional text for the other article. **Table 7** presents the different scientific articles and their correspondence to the research questions stated in the chapter “Objectives”.

Table 7. List of scientific articles included in this thesis

Research questions	Drafted scientific articles
Research question 1.1: Is there a long-term association of antioxidant nutrient supplementation with the probability of healthy aging, as assessed with the help of a multidimensional model? Is such a supplementation more effective among individuals with initially low levels of the tested antioxidants and among those with a lower consumption of foods that are rich in antioxidants?	**Publication 1**: Healthy aging 5 years after a period of daily supplementation with antioxidant nutrients: a post hoc analysis of the French randomized trial SU.VI.MAX (published in the American Journal of Epidemiology)
Research question 2.1: Is the adherence to different *a posteriori* dietary patterns at midlife, extracted by principal component analysis, prospectively associated with a multidimensional concept of healthy aging? Is this association modulated by overall energy intake?	**Publication 2**: A healthy dietary pattern at midlife, combined with a regulated energy intake, is related to increased odds for healthy aging" (published in the Journal of Nutrition)
Research question 2.2: Are higher adherence to the French official food-based dietary guidelines (as measured by the mPNNS-GS), higher adequacy of the diet to the French nutrient reference values (as measured by the PANDiet), and higher adherence to both food-based and nutrient-based dietary guidelines of different countries (as measured by the Dietary Quality Index- International) at midlife prospectively associated with a multidimensional concept of healthy aging?	**Publication 3**: Dietary scores at midlife and healthy aging in a French prospective cohort (in revision at the British Journal of Nutrition)
Research question 3.1: Is there a prospective association between plasma vitamin D status at midlife and cognitive functioning in different domains assessed 13 years later?	**Publication 4**: Midlife plasma vitamin D concentrations and performance in different cognitive domains assessed 13 years later (published in the British Journal of Nutrition)

I. Publication 1: Antioxidant supplementation and healthy aging

Title: Healthy aging 5 years after a period of daily supplementation with antioxidant nutrients: a post hoc analysis of the French randomized trial SU.VI.MAX

Authors: Assmann KE, Andreeva VA, Jeandel C, Hercberg S, Galan P, Kesse-Guyot E

Publication details: Am J Epidemiol 2015;182(8):694-704. doi: 10.1093/aje/kwv105

Not shown due to copyright considerations

II. Publication 2: *A posteriori* dietary patterns and healthy aging

Title: A healthy dietary pattern at midlife, combined with a regulated energy intake, is related to increased odds for healthy aging

Authors: Assmann KE, Lassale C, Andreeva VA, Jeandel C, Hercberg S, Galan P, Kesse-Guyot E

Publication details: J Nutr 2015;145(9):2139-45. doi: 10.3945/jn.115.210740

Not shown due to copyright considerations

III. Publication 3: *A priori* dietary scores and healthy aging

Title: Dietary scores at midlife and healthy aging in a French prospective cohort

Authors: Assmann KE, Andreeva VA, Camilleri GM, Verger EO, Jeandel C, Hercberg S, Galan P, Kesse-Guyot E

Publication details: Br J Nutr 2016. doi: 10.1017/S0007114516002233, 11 pages [epub ahead of print].

Not shown due to copyright considerations

IV. Publication 4: Plasma vitamin D and later cognitive functioning

Title: Midlife plasma vitamin D and performance in different cognitive domains assessed 13 years later

Authors: Assmann KE, Touvier M, Andreeva VA, Deschasaux M, Constans T, Hercberg S, Galan P, Kesse-Guyot E

Publication details: Br J Nutr 2015;113(10):1628-37. doi: 10.1017/S0007114515001051

Not shown due to copyright considerations

DISCUSSION

The objective of this thesis was to investigate the role of different dietary factors for healthy aging. Overall healthy aging was examined with the help of a multidimensional model largely based on the framework proposed by Rowe and Kahn. The maintenance of high levels of cognitive functioning throughout aging was examined with the help of results of a neuropsychological test battery, which were modelled as 'synthetic cognitive factors' derived by principal component analysis.

The "Discussion"- section of this thesis includes the following elements:

1. a discussion of the main results of the conducted studies in relation to the research questions specified in the "Objectives"-section, and in the light of other investigations referenced in the literature;
2. an overall discussion of the potential underlying factors related to our different findings, including an examination of the interrelations of the specific results – and their consideration within a general framework on the beneficial potential of diet for healthy aging;
3. an examination of the methodological strengths and limitations of the studies conducted within this thesis;
4. a discussion of perspectives for future research and a final conclusion, including the public health impacts of our findings.

I. Critical discussion of the main findings of this thesis

Table 8 summarizes the main elements of discussion that will be highlighted in this chapter (i.e. a summary of the main results corresponding to each research question, a discussion of the observed specificities of these results to certain subgroups of our study population - or to specific dietary indicators -, and a comparison with other studies).

Table 8. Summary of basic discussion elements for each of this thesis' research questions

Research question	Summary of results	Hypotheses for specificities	Comparison with other studies
Research question 1.1: - Long-term association of antioxidant nutrient supplementation with HA? - Effect modification by initial levels of the tested antioxidants and by initial consumption of foods rich in antioxidants?	- No overall association among all participants - Interaction with sex: significant association among men only - In addition, significant beneficial effects among participants with low baseline vitamin C or zinc concentrations, or with low baseline fruit and vegetable consumption	- Men had lower baseline vitamin C concentrations then women - Among women with low baseline vitamin C levels, the observed effect size (RR for HA) was even larger than among men with low initial vitamin C (but not significant, probably due to the small number of women with low initial vitamin C levels) → Possibly, the observed sex-specificity largely reflects a specificity to low baseline vitamin C. However, additional mechanisms may be involved.	- Available meta-analyses do not suggest a beneficial effect of antioxidant supplementation on mortality or chronic disease - Hypotheses that have been made to explain this: relatively short treatment and follow-up duration of many trials; dependency of the supplementation effect on specific baseline characteristics (antioxidant levels, smoking, exercise); specific combinations of antioxidants may be particularly effective (and others not)
Research question 2.1: - Prospective association between different *a posteriori* dietary patterns at midlife and HA? - Effect modification by overall energy intake?	- Identified *a posteriori* dietary patterns: a "western pattern" and a "healthy pattern" - No overall association between either dietary pattern and HA - Interaction between overall energy intake and the "healthy pattern": significant association with HA among individuals with energy intakes < sex-specific median	- High energy intake may 'counterbalance' beneficial effects of "healthy" dietary patterns - A previous study has shown an inverse relation between relatively high energy intakes and HA - The "caloric restriction"- hypothesis suggests a beneficial effect of rather low energy intakes on the aging process	- **(Akbaraly et al. 2013a)**: 2 dietary patterns were extracted: ''healthy foods'' and ''Western-type.'' Only the Western-type pattern was (inversely) associated with ''ideal aging.'' - **(Hodge et al. 2014)**: inverse association between a "meat and fatty foods"- pattern and HA, and positive association between a "fruit"-dietary pattern and HA.

Research question	Summary of results	Hypotheses for specificities	Comparison with other studies
Research question 2.2: - Prospective association between adherence to the French food-based guidelines, higher adequacy to the French nutrient reference values, and higher adherence to both food- and nutrient-based guidelines of different countries with HA?	- Positive association between quartiles of the mPNNS-GS, the PNNS-GS and the PANDiet and odds of HA - Investigation of continuous scores: significant results only observed for the mPNNS-GS and the PNNS-GS	- Main difference in the conception of the scores: only the (m)PNNS-GS entirely reflects food-based nutritional guidelines - Moreover, only the (m)PNNS-GS considers alcohol consumption - Specific technical details of score construction may also play a role	- **(Samieri et al. 2013)**: positive association of the AHEI-2010 and the AMDS with HA - **(Gopinath et al. 2015)**: positive association of the TDS with HA - **(Akbaraly et al. 2013a)**: no relation of the AHEI with HA
Research question 3.1: - Prospective association between plasma vitD status and cognitive functioning in different domains?	- No overall relation between plasma vitD status at midlife and later HA - Interaction with educational level: significant results concerning the main cognitive outcomes for participants with a low educational level only - Specificity of this relation to short-term and working memory	- According to the literature, higher educated individuals may have higher 'cognitive reserve', and thus an improved ability to cope with potential neurologic damage → impairments of brain function were potentially only measurable in participants with lower cognitive reserve	Out of the n=14 prospective studies that have been published to this day[1]: - n=6: lower risk of negative cognitive outcomes or less cognitive decline - n=3: subgroup-specific positive associations or an association between outcomes at follow-up but not with changes in cognitive functioning during follow-up - n=5: no statistically significant longitudinal associations Little evidence for a protective role of vitamin D supplementation from intervention studies

Abbreviations: AHEI-2010, Alternate Healthy Eating Index-2010; AMDS, Alternate Mediterranean Diet Score; HA, Healthy Aging; mPNNS-GS, modified Programme National Nutrition Santé- Guideline Score; PNNS-GS, Programme National Nutrition Santé- Guideline Score; RR, Relative Risk; TDS, Total Diet Score, VitD: vitamin D.
[1]To the best of our knowledge.

I.A Objective 1

Objective 1 of this thesis was to examine the prospective association between daily supplementation with antioxidant vitamins and minerals, over a period of 8 years, with a multidimensional concept of healthy aging measured 5 years later. This objective included only one specific research question (divided into a primary and a secondary research question), which is detailed below.

I.A.1 Basic discussion of the study findings

Research question 1.1 focused on whether there was a long-term association of antioxidant nutrient supplementation with the probability of healthy aging, as assessed with the help of a multidimensional model. A secondary question was whether such a supplementation was more effective (or only effective) among individuals with initially low levels of the tested antioxidants and among those with a lower consumption of foods that are rich in antioxidants.

This research question was addressed by publication 1: "Healthy aging 5 years after a period of daily supplementation with antioxidant nutrients: a post hoc analysis of the French randomized trial SU.VI.MAX", published in the American Journal of Epidemiology.

Brief summary of the results in relation to the specified research questions

Not shown due to copyright considerations

Hypotheses concerning the observed specificity of our results to men

Not shown due to copyright considerations

I.A.2 Comparison with other studies

Not shown due to copyright considerations

Potential reasons for the limited evidence of beneficial effects of antioxidant supplementation

Not shown due to copyright considerations

I.B Objective 2

Objective 2 of this thesis was to examine the prospective association between overall dietary quality at midlife and a multidimensional concept of healthy aging in a population of French adults. This objective included two specific research questions, as detailed below.

I.B.1 Basic discussion of the study findings

a) Research question 2.1

Research question 2.1 focused on whether a higher adherence to different a posteriori dietary patterns at midlife, extracted by principal component analysis, was prospectively associated with a multidimensional concept of healthy aging. A secondary research question was whether this association was modulated by overall energy intake.

This research question was addressed by publication 2: "A healthy dietary pattern at midlife, combined with a regulated energy intake, is related to increased odds for healthy aging", published in the Journal of Nutrition.

Brief summary of the results in relation to the specified research questions

Not shown due to copyright considerations

Hypotheses concerning the specificity of our results to participants with relatively low overall energy intakes

Not shown due to copyright considerations

b) Research question 2.2

Research question 2.2 focused on whether a higher adherence to the French official food-based dietary guidelines (as measured by the mPNNS-GS), a higher adequacy of the diet to the French nutrient reference values (as measured by the PANDiet) and a higher adherence to both food-based and nutrient-based dietary guidelines of different countries (as measured by the DQI-I) at midlife was prospectively associated with a multidimensional concept of healthy aging.

Brief summary of the results in relation to the specified research question

Not shown due to copyright considerations

Hypotheses concerning the heterogeneous magnitude of the observed association according to the type of dietary recommendation investigated

Not shown due to copyright considerations

I.B.2 Comparison with other studies

a) General comparison of the different studies' findings

To the knowledge of the author of this thesis, only four other studies have investigated the association between *a priori* dietary scores or *a posteriori* dietary patterns and healthy aging.

***A priori* dietary scores and healthy aging**

Not shown due to copyright considerations

***A posteriori* dietary patterns and healthy aging**

Not shown due to copyright considerations

b) Comparison of the indicators of the overall diet used in the different studies

Table 9 provides a brief overview of the basic characteristics of the different *a priori* dietary scores and *a posteriori* dietary patterns investigated in the above-discussed studies, in comparison with the scores and pattern used or extracted in our analyses.

The AHEI-2010, which has – in contrast to the original AHEI **(Akbaraly et al. 2013a)** – been positively related to a multidimensional concept of healthy aging **(Samieri et al. 2013)**, differs from the original AHEI in multiple aspects **(Chiuve et al. 2012; McCullough et al. 2002)**. First, the group of 'components to limit' has been enlarged from "*trans* fat" to "sugar sweetened drinks and fruit juice", "red and processed meat", "*trans* fat", and "sodium". Second, three 'components to increase' have been modified: "cereal fiber" has become "whole grains", "nuts and soy protein" has become "nuts and legumes", and the "ratio of polyunsaturated to saturated fatty acids" has become simply "polyunsaturated fatty acids" and "long chain omega-3 fats". Finally, "multivitamin use" has been deleted from the list of 'components to increase'. These differences may be one potential explanation concerning the different conclusions of the studies published by Samieri et al. **(Samieri et al. 2013)** and by Akbaraly et al.

(Akbaraly et al. 2013a). However, the characteristics of the study samples and the differences in healthy aging definitions have probably also played a role.

The mPNNS-GS **(Assmann et al. 2014)** and the PNNS-GS **(Estaquio et al. 2009)** can be considered as closer to the AHEI-2010 than to the AHEI, as these scores also put an emphasis on the limitation of sweetened beverages and of salt. Moreover, the components "vegetable added fat" and "seafood" (whose consumption should be increased) imply an increase of polyunsaturated fatty acids and of long chain omega-3 fatty acids. The TDS **(Russell et al. 2013)** (which has as well been positively associated with healthy aging) also puts an emphasis on an increased consumption of whole grains and of fish (thus a source of long chain omega-3 fatty acids), and a limited consumption of sodium and added sugars.

A large difference between the different whole-diet approaches concerns the consideration of overall energy intake. Neither the AHEI **(McCullough et al. 2002)**, nor the AHEI-2010 **(Chiuve et al. 2012)** or the PANDiet **(Verger et al. 2012)** or DQI-I **(Kim et al. 2003)** include an explicit mechanism to account for overall energy intake – in contrast to the PNNS-GS **(Estaquio et al. 2009)**, the mPNNS-GS **(Assmann et al. 2014)**, and the TDS **(Russell et al. 2013)**. Out of the different studies that have investigated *a posteriori* dietary patterns, only our study has stratified analyses according to overall energy intake.

Common characteristics of the *a priori* dietary scores and the *a posteriori* dietary patterns that have been positively related to multidimensional concepts of healthy aging are:

- a high consumption of fruits and vegetables,
- a high consumption of whole grains or fibre,
- a high consumption of fish or long chain omega-3 fatty acids,
- a low consumption of sweetened products (sweetened beverages, added sugars, sweetened desserts or chocolates,
- a low consumption of salt or sodium (or of "processed food" that tends to be high in sodium **(Webster et al. 2010)**).

Not all of these characteristics are present in all scores or patterns that have been associated with healthy aging (in particular, the PANDiet as a nutrient-based score includes only nutrient components).

Table 9. Brief overview of the characteristics of the dietary scores and dietary patterns investigated in other studies, as compared to those investigated in our analyses

Study	Overall diet- indicators	Characteristics
(Samieri et al. 2013)	**AHEI-2010**	+ vegetables, fruit, whole grains, nuts and legumes, long chain omega-3 fats, polyunsaturated fatty acids ± alcohol – sugar sweetened drinks and fruit juice, red and processed meat, *trans* fat, sodium
	A-MeDi	+ fruits, vegetables (excluding potatoes), whole grains, nuts, legumes, fish, ratio of MUFA to SFA ± alcohol – red meat or processed meat
(Gopinath et al. 2015)	**TDS**	+ vegetables, legumes, fruit, cereals (preferably wholegrain), fish, physical activity ± lean meats, fish, poultry and/ or alternatives, dairy products, **ratio of energy intake to energy expenditure** – saturated fat, sodium, alcohol, added sugars, "extra food" (i.e. snacks)
(Akbaraly et al. 2013a)	AHEI	+ vegetables, fruit, cereal fibre, nuts and soy protein, multivitamin use, ratio of white to red meat, ratio of polyunsaturated to saturated fatty acids ± alcohol – *trans* fat
	"healthy foods"- pattern	+ vegetables, fruits, fish
	"Western-type" pattern	+ fried food, processed food, red meat, pies, sweetened desserts, chocolates, refined grains, high-fat dairy products, condiments
(Hodge et al. 2014)	**"fruit"-pattern**	+ fruit
	"vegetables"-pattern	+ vegetables
	"southern European"-pattern	+ feta, legumes, salad, olive oil, and inverse loadings for tea, margarine, cake, sweet biscuits and puddings
	"meat and fatty foods"-pattern	+ meat, white bread, savoury pastry dishes and fried foods

Study	Overall diet- indicators	Characteristics
Our analyses on *a posteriori* dietary patterns and healthy aging **(Assmann et al. 2015b)**	**"healthy"-pattern**	+ vegetables, vegetable fat, fruit, whole grains, fish, sweetening products, soup, and fresh dairy products
	"western"-pattern	+ alcoholic beverages, meat and poultry, processed meat, refined grains, cheese, potatoes, and salted snacks; – fresh dairy products
Our analyses on *a priori* dietary scores and healthy aging	**PNNS-GS**	+ fruit & vegetables, water, vegetable added fat, seafood, whole grain, physical activity ± starchy foods, dairy products, non-dairy sources of animal protein, **overall energy intake (penalization for excessive overall energy intakes)** – added fat, sweets, sweetened beverages, alcohol, salt
	mPNNS-GS	equal to the PNNS-GS, except that there is no physical activity- component
	PANDiet	+ polyunsaturated fatty acids, fibre, specific vitamins and minerals ± total carbohydrates, total fats, total protein, various vitamins and minerals – saturated fatty acids, cholesterol, sodium
	DQI-I	+ overall food group variety, protein source variety, vegetables, fruits, cereals, fibre, protein, Fe, Ca, vitamin C "balance": ratios "carbohydrate : protein : fat" and "PUFA : MUFA : SFA" – total fat, saturated fat, cholesterol, Na, empty-energy foods

Abbreviations: AHEI, Alternative Healthy Eating Index; DQI-I, Dietary Quality Index- International; HEI, Healthy Eating Index; mPNNS-GS, modified Programme National Nutrition Santé- Guideline Score; MUFA, monounsaturated fatty acids; PANDiet, Probability of Adequate Nutrient Intake Dietary Score; PNNS-GS, Programme National Nutrition Santé- Guideline Score; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TDS, Total Diet Score.

+: The highest number of points is attributed if consumption of the respective component is increased (or if a ratio of different components is increased).
±: The highest number of points is attributed if the consumption of the respective component (or a ratio of components) is within a certain range.
–: The highest number of points is attributed if consumption of the respective component is decreased.

Indicators of the overall diet that have shown significant associations with multidimensional concepts of healthy aging are shown in orange, bold font.
Of note, the "healthy" dietary pattern in our study was only associated with healthy aging among individuals with low overall energy intakes.

Discussion of the differences in applied healthy aging definitions

Not shown due to copyright considerations

I.C Objective 3

Objective 3 of this thesis was to examine the prospective association between plasma vitamin D status at midlife and later cognitive functioning. This objective included only one specific research question, which is detailed below.

I.C.1 Basic discussion of the study findings

Research question 3.1 focused on whether there was a prospective association between plasma vitamin D status at midlife and later cognitive functioning in different domains assessed 13 years later. This research question was addressed by publication 4: "Midlife plasma vitamin D concentrations and performance in different cognitive domains assessed 13 years later", published in the British Journal of Nutrition.

Brief summary of the results in relation to the specified research question

Not shown due to copyright considerations

Hypotheses concerning the specificity of our findings to participants with a low educational level

Not shown due to copyright considerations

Discussion of potential mediation effects by vascular health and diabetes

Not shown due to copyright considerations

I.C.2 Comparison with other studies

Prospective observational studies

Not shown due to copyright considerations

Intervention studies on the effect of vitamin D supplementation

Not shown due to copyright considerations

Domain-specific associations of vitamin D with cognition

Not shown due to copyright considerations

II. Synthetic discussion of the findings in the context of potential mechanistic pathways

As detailed in the "Introduction"- section, a number of theories exist that aim to describe general underlying mechanisms for age-related health decline. Thus, shared pathways may exist by which different nutritional factors influence the aetiology of specific age-related chronic diseases and functional decline. Figure 8 illustrates a hypothetical framework for the role of dietary factors in the prevention of age-related health decline, and places this thesis' main results into the context of this general framework. The mechanistic pathways that are shown in **Figure 9** are by no means a complete list of all of the different pathways that have been discussed in the literature. The aim of the Figure is rather to propose a framework that is specific to the studies included in this thesis and sufficiently simple to provide a structured and comprehensive overview.

The associations that were observed between dietary factors (i.e. antioxidant supplementation, different indicators of overall dietary quality, and vitamin D status) and global healthy aging or cognitive functioning may notably have been mediated by the following mechanisms.

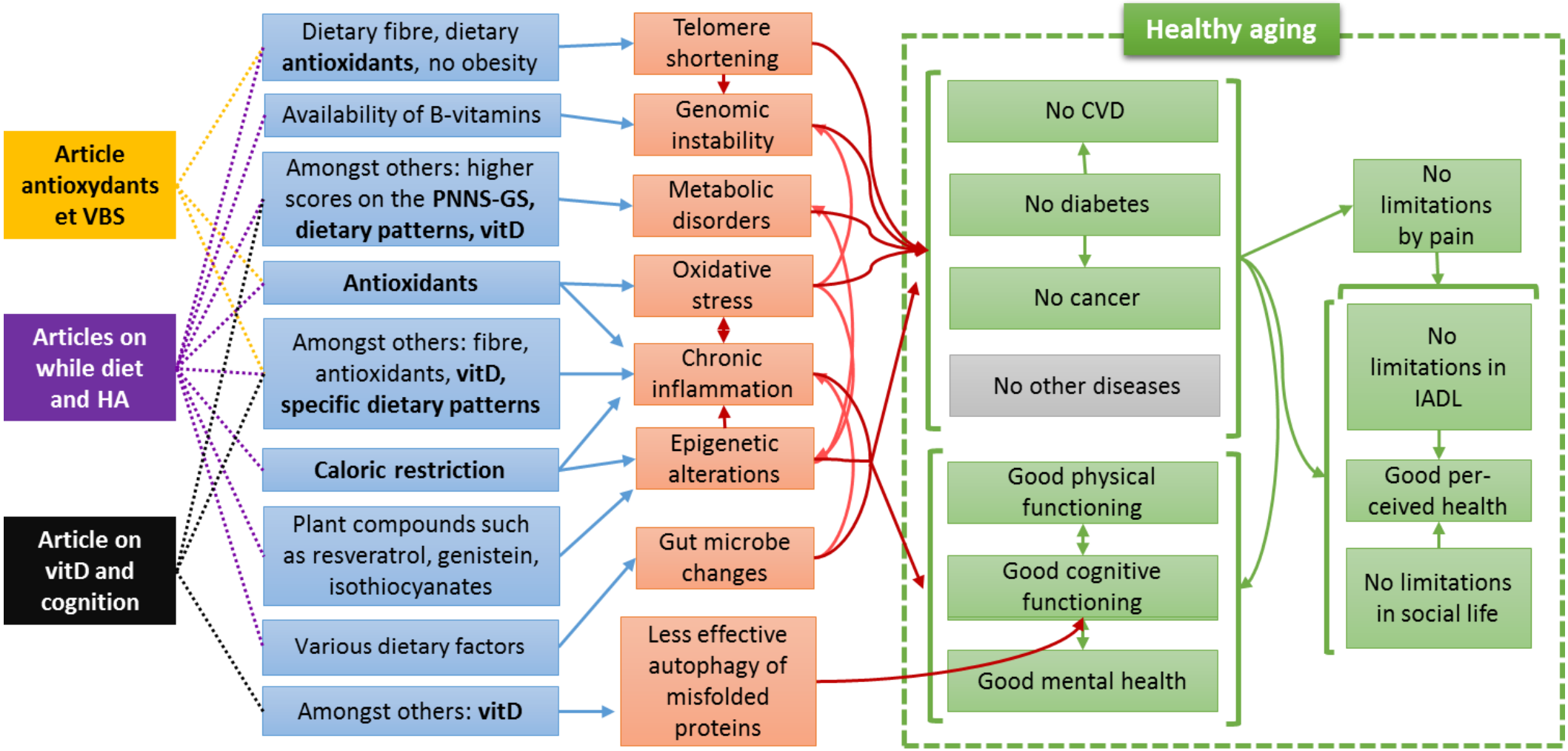

Figure 9. Hypothetical framework for the role of dietary factors in the prevention of age-related health decline

II.A Oxidative stress, xenohormesis, and genomic instability

The ”oxidative stress theory of aging”, which is notably based on the work of Denham Harman **(Harman 1992; Salmon et al. 2010)** , suggests that an “accumulation of oxidative damage to cellular macromolecules” contributed “ to a progressive decline in the function of cellular process”, amongst others due to the accrual of genomic instability (related to DNA-damage). According to the “Mitochondrial Free Radical Theory of Aging”, oxidative damage is especially induced by “mitochondrial free radicals, produced as by-products during normal metabolism” **(Sanz and Stefanatos 2008)**.

Various authors insist on the importance of an adequate redox homeostasis, instead of a general limitation of any oxidative stress for healthy aging **(Poljsak et al. 2013; Ristow et al. 2009; Sohal and Orr 2012)**. For instance, Poljsak et al. have proposed that “both extremes, oxidative and antioxidative stress” were “damaging”. In a study published by Ristow et al., an exercise intervention among 29 healthy young men was not beneficial with respect to indicators of insulin sensitivity among participants who had been supplemented with high-dose vitamin C and vitamin E – while a beneficial role was seen among participants who had received a placebo **(Ristow et al. 2009)**. Moreover, an augmented expression of transcription factors that are sensitive to reactive oxygen species and at the same time regulate insulin sensitivity (amongst others peroxisome proliferator-activated receptor gamma (PPARγ)) was only observed in the placebo-group. This indicates that limited amounts of oxidative stress (induced by physical exercise) may be beneficial for the maintenance of an adapted glucose metabolism.

The Mitochondrial Free Radical Theory of Aging and similar theories have recently been the object of much criticism **(Gladyshev 2014; Liochev 2013; Sanz and Stefanatos 2008; Stuart et al. 2014)**. While Gladyshev has postulated that the free radical theory of aging was “dead”, other authors have simply concluded that the current available evidence did not permit to draw firm conclusions **(Liochev 2013; Sanz and Stefanatos 2008).** Finally, it has been suggested that the potential of such theories to explain the origins of age-related decline should not be overstated – and that these theories should be refined and put into a broader context of other explanative approaches **(Liochev 2013; Stuart et al. 2014)**.

Despite the generally disappointing findings of randomized controlled trials that have tested the effect of antioxidant supplementation on mortality and chronic disease incidence **(Bjelakovic et al. 2012; Myung et al. 2010; Myung et al. 2013)**, various authors still suggest a

potentially important role of antioxidants in the prevention of age-related diseases **(Andreeva and Kesse-Guyot 2015; Chatzianagnostou et al. 2015; Shammas 2011; Vasto et al. 2014)**.

As suggested by our study on the long-term association between antioxidant supplementation and healthy aging, as well as by other studies **(Biesalski et al. 2010; Hemilä and Kaprio 2011a; Hemilä and Kaprio 2009; Hemilä and Kaprio 2011b)**, the effect of antioxidant supplementation may strongly depend on participant characteristics, including baseline antioxidant levels, physical activity level, and smoking status.

The oxidative stress theory of aging is not only relevant with respect to our article on antioxidant supplementation and healthy aging, but also with respect to our articles on *a posteriori* dietary patterns and *a priori* dietary scores in relation to healthy aging. Both the identified 'healthy' dietary pattern and the scores mPNNS-GS and PNNS-GS account for fruit and vegetable intake (thus important dietary sources of antioxidants), and the PANDiet accounts for the intake of various antioxidant vitamins and minerals. Thus, the observed relations of these dietary patterns and scores with healthy aging may, in part, have been mediated by a reduction of oxidative stress. On the other hand, it has been suggested that plant components that have antioxidant functions may, in reality, have health effects that are mainly mediated via pathways other than oxidative stress reduction (despite the fact that the compounds also have antioxidant properties). Notably, the "xenohormesis hypothesis" suggests that phytochemicals that are produced by plants in response to stress may modulate "enzymes and receptors of stress-response pathways in mammals" **(Howitz and Sinclair 2008; Szarc vel et al. 2015)**. In particular, it has been suggested that compounds such as resveratrol may increase lifespan by mimicking caloric restriction. **(Howitz and Sinclair 2008; Szarc vel et al. 2015)**

Apart from DNA damage caused by oxidative stress, genomic instability is also related to a generally lowered functionality of DNA repair mechanisms in old age **(Gorbunova et al. 2007; Mathers 2013)**. DNA repair mechanisms notably depend on the availability of folate (in the form of 5,10-Methylenetetrahydrofolate), which is implicated in the conversion of uracil to thymine **(Duthie 2011)**. In addition, folate – along with vitamin B12 – is involved in the regeneration of methionine from homocysteine **(Miller 2003)**. Experimental evidence suggests that homocysteine may impair DNA repair in the brain **(Kruman et al. 2002)**. Moreover, higher circulating homocysteine has been associated with worse cardiovascular and cognitive outcomes **(Gallucci et al. 2004; Malaguarnera et al. 2004; Quadri et al. 2004)**.

II.B The "inflammaging" concept

Another thoroughly discussed framework that attempts to explain part of the age-related decline in health has been named "inflammaging", and refers to "low-grade, chronic, systemic inflammation in aging, in the absence of overt infection" **(Franceschi and Campisi 2014)**. Chronic inflammation and oxidative stress are linked, as oxidative stress can be a cause and consequence of inflammation **(Khansari et al. 2009; Reuter et al. 2010)**. Thus, the term "oxi-inflammaging theory" has also been used **(Szarc vel et al. 2015)**.

This framework is notably grounded on the observation that elderly individuals tend to show "mildly elevated" circulating concentrations of inflammation mediators (such as interleukin (IL)-6, IL-1, tumor necrosis factor (TNF), and C-reactive protein (CRP)) **(Calcada et al. 2014) (Szarc vel et al. 2015)**, and on the fact that inflammatory mediators have been associated with a number of age-related diseases, such as arthritis, cardiovascular disease, diabetes, dementia, and cancer **(Calcada et al. 2014)**.

The proposed specific mechanisms include "persistent production of reactive molecules by infiltrating leukocytes", which can lead to damage on the cellular and tissue- level, "production of cytokines that amplify or modulate the inflammatory response and alter the phenotypes of nearby cells", and the crosstalk with other signalling pathways. **(Franceschi and Campisi 2014)**

A large number of specific dietary components **(Shivappa et al. 2014)** - such as fibre, different vitamins and minerals, spices like garlic and ginger, polyunsaturated fatty acids, and polyphenols – as well as overall dietary patterns **(Barbaresko et al. 2013)**, have been shown to be associated with biomarkers of chronic low-grade inflammation. In particular, "Western"- *a posteriori* dietary patterns or patterns characterized by high intakes of meat have been (cross-sectionally) associated with higher concentrations of pro-inflammatory mediators such as CRP. On the other hand, "healthy"- *a posteriori* dietary patterns involving high intakes of fruits and vegetables have been associated with lower circulating concentrations of such mediators in cross-sectional studies **(Barbaresko et al. 2013)**. In the SU.VI.MAX study, higher midlife adherence to an *a posteriori* dietary pattern characterized by a high consumption of vegetables and vegetable oils was inversely associated with circulating CRP 12 years later **(Julia et al. 2013)**.

Hence, our findings concerning a positive association of higher adherence to the French food-based dietary guidelines and higher scores on an *a posteriori*- dietary pattern may also be explained by a positive role of such patterns for the prevention of low-grade chronic inflammation. Our results concerning antioxidant supplementation and healthy aging may also be interpreted in the context of 'inflammaging', as vitamin C and zinc have been suggested to be involved in the prevention of chronic inflammation **(Shivappa et al. 2014)**. In addition, vitamin D has been suggested to have an anti-inflammatory role, notably in the brain – via the "suppression of proinflammatory cytokines" **(Banerjee et al. 2015)**. Hence, our results on the relation between midlife vitamin D status and later cognitive performances may also be related to a potential prevention of detrimental effects mediated by excessive inflammation.

II.C Epigenetic changes and caloric restriction

One underlying mechanism related to "inflammaging" may be age-related **epigenetic alterations**, including changes in "DNA methylation patterns", "posttranslational modification of histones", and "chromatin remodeling" **(Szarc vel et al. 2015)**. A number of plant compounds such as resveratrol, epigallocatechin gallate and isothiocyanates have been suggested to have an effect on "epigenetic modulators", such as histone deacetylase, DNA methyltransferase, and Histone acetyltransferase.

In addition, the potentially beneficial effects of **caloric restriction**, which has been shown to increase lifespan in various animal models **(Fontana and Partridge 2015)**, may notably be mediated by epigenetic mechanisms, such as the activation of Sirtuin 1 **(Li et al. 2011; Szarc vel et al. 2015)**. This biological mechanism is potentially of interest with respect to our finding that only the combination of high adherence to a 'healthy' dietary pattern was associated with a higher probability of healthy aging. However, it is unclear whether among humans, caloric restriction has the same effect on longevity and overall healthy aging as in specific animal models **(Fontana and Partridge 2015)**.

II.D Changes in gut microbiota

Apart from epigenetic changes, age-related alterations with respect to gut microbiota may also have a role for "inflammaging". Amongst others, bacterial lipopolysaccharid (LPS) can 'leak' from the gut into the circulation, which can then trigger low-grade inflammation **(Hakansson and Molin 2011)**. The intestinal barrier can, in turn, be modulated by dietary factors. Diets with

a high fat content have, for instance, been associated with higher LPS leakage **(Hakansson and Molin 2011)**.

In addition, imbalances in the composition of the gut microbiota ("dysbiosis") have been associated with cardiometabolic diseases, and animal models have indicated that high-fat diets may trigger alterations of the microbiota, which may influence the metabolism of the host, in particular insulin sensitivity **(Aron-Wisnewsky and Clement 2016)**.

A recent cross-sectional study indicated a relation of gut microbiota composition with both dietary patterns with differing contents of fat and health characteristics such as frailty markers and inflammation **(Claesson et al. 2012)**. Findings from longitudinal studies are necessary to elucidate whether gut microbiota composition is a mediator, or rather a marker of this association. Under the hypothesis that gut microbiota are important mediators of associations between diet and health, the findings of this thesis may also be partly explained by microbiota-related mechanisms.

II.E Metabolic disorders and vascular health

A metabolic concept that links two major chronic diseases, diabetes and cardiovascular disease, is the "metabolic syndrome", which involves elevated fasting glucose levels, high circulating triglycerides, low circulating high density lipoprotein (HDL)- cholesterol, high blood pressure, and an elevated waist circumference **(Alberti et al. 2009)**. It has been suggested that metabolic disorders can further trigger inflammation, which has led to the creation of the term "metaflammation" **(Calcada et al. 2014)**.

A preventive role of higher adherence to the French food-based dietary guidelines has been suggested by a previous investigation of data from the SUV.I.MAX study **(Kesse-Guyot et al. 2011a)**, which is in line with the fact that various other *a priori* and *a posteriori* dietary patterns have been associated with the risk to develop a metabolic syndrome **(United States Department of Agriculture 2014)**. Thus, the association between higher adherence to these guidelines and healthy aging, which has been observed in one of the studies included in this thesis, may in part be mediated by a positive role of higher dietary quality for a balanced metabolic state.

Our finding that both high dietary quality (as measured by adherence to a "healthy"- *a posteriori* dietary pattern) and a regulated overall energy intake are necessary for healthy aging can also be interpreted in the context of metabolic disorders. It has been suggested that

the production of "adipokines" such as adiponectin or IL-6 by the visceral adipose tissue may induce reduced insulin sensitivity and dysfunction of the endothelium of blood vessels **(Ritchie and Connell 2007)**, which can lead to vascular damage. Hence, a regulated overall energy intake may affect overall healthy aging via the prevention of central obesity and related metabolic disorders.

In addition, low vitamin D status has been linked to an altered glucose metabolism (notably a reduced insulin sensitivity), which is an important component of the metabolic syndrome **(Teegarden and Donkin 2009)**. As diabetes and impaired glucose tolerance appear to be risk factors for dementia **(Banerjee et al. 2015; Meneilly and Tessier 2016; Messier 2005)**, the mechanistic pathway "metabolic disorders" is also of relevance for the interpretation of our results on vitamin D status and cognitive functioning.

II.F Autophagy of damaged and misfolded proteins

A further pathway that is relevant to our findings concerning vitamin D and cognition is the prevention of the accumulation of damaged and misfolded proteins, notably of amyloid beta. It has been suggested that 1,25(OH)2D may be able to recover the capability of "macrophages to phagocytose soluble amyloid β protein", and thus to prevent the formation of plaques **(Banerjee et al. 2015)**, which is one of the two major hallmarks of Alzheimer's disease **(Binder et al. 2005; Braskie et al. 2010; Brion 1998; Ittner and Gotz 2011)**.

II.G Telomere shortening

A further crucial mechanism related to age-related decline in health is telomere shortening **(Shammas 2011)**. Telomere length may predict longevity and overall healthy aging – notably due to the fact that cells with telomeres that have become too short initiate apoptosis or become "senescent" **(Shammas 2011)**. The term "senescent cell" refers to cells that have adopted "a state of permanent cell-cycle arrest" **(Campisi and d'Adda di 2007)**. Lifestyle factors that have been associated with a slower pace of telomere shortening include the avoidance of obesity, high consumption of dietary fibre, and high consumption of dietary antioxidants **(Shammas 2011)**. As the 'healthy' dietary pattern identified in our study focusing on *a posteriori* dietary patterns, and the *a priori* dietary score PNNS-GS are both characterized by a higher intake of dietary fibre and dietary antioxidants, the respective study findings of our thesis can also be interpreted in the context of telomere shortening prevention. In addition, the

results obtained in our study on antioxidant supplementation and healthy aging may also be explained in the context of this mechanism.

III. Methodological considerations

III.A General methodological aspects related to nutritional epidemiology

As detailed in the "Introduction"-section of this thesis, the methods of nutritional assessment applied in nutritional epidemiology are subject to a number of potential biases – and particular types of assessment are characterized by specific strengths and limitations.

III.A.1 24-hour dietary records

The nutritional data that were used in the studies included in this thesis were obtained with the help of 24-hour dietary records. In comparison with food frequency questionnaires, this method permits a much more precise assessment of the consumed quantities over a 24-hour period **(Andreeva and Kesse-Guyot 2015)**.

However, habitual food intakes can only be estimated in a reliable manner via repeated administration over sufficiently long time periods **(Andreeva and Kesse-Guyot 2015; Willett 1998)**. Thus, the procedure used for the presented studies was to calculate mean intakes across all available dietary records during the first two years of follow-up, which were obtained in a manner that permitted the coverage of the different days of the week and the different seasons of the year.

Participants who had completed less than 3 dietary records during this period were excluded from analyses. This decision is a compromise between obtaining maximal precision for nutritional data, and excluding a minimal number of participants from analyses in order to limit selection bias. The limitation of selection bias is important in the context of nutritional epidemiology, as it can be hypothesized that participants with enough motivation to complete a large number of dietary records likely have personality characteristics that also cause them to put much effort into dietary habits that they consider as "healthy".

It has been suggested that three 24-hour dietary recalls (or 24-hour dietary records in our case) provide reasonably reliable estimates of overall energy intake **(Ma et al. 2009)**. A methodological article based on data from the SU.VI.MAX study has suggested that at least 8

dietary records were necessary for obtaining high-precision estimates for usual intakes of most of the investigated nutrients **(Mennen et al. 2002)**. High-precision estimates were defined as an accuracy of 0.9, i.e. a misclassification of less than 10% of participants "in the extreme fraction, opposite to the true intakes when nutrient intake would be divided into quintiles".

Thus, the exclusion of participants with less than 3 dietary records (instead of, for example, with less than 8 dietary records) may appear problematic. However, as reported in the publications included in this thesis, the average number of dietary records provided was generally 10. In the study sample used to carry out our analyses on *a priori* dietary scores and healthy aging, only 21.1% of participants had completed less than 8 dietary records, and only 12.1% had completed less than 6 dietary records [data not shown]. Similar proportions were observed in the study sample for analyses on *a posteriori* dietary patterns and healthy aging. Thus, a large majority of participants had provided sufficient dietary records for the estimation of both overall energy intake and specific nutrient intakes with high accuracy.

A further factor that is in favour of a high quality of the available nutritional data is the dispersion of dietary records over the different days of the week and seasons of the year **(Kesse-Guyot et al. 2013)**. In addition, the coding of food portions was carried out with the help of an instruction manual with validated photographs **(Le Moullec et al. 1996)**.

Finally, a standardized procedure **(Kesse-Guyot et al. 2011d; Lassale et al. 2012)** for the exclusion of participants with implausible overall energy intakes was applied. Dietary records reporting overall energy intakes of less than 100 kcal per day or of more than 6000 kcal per day were excluded. Furthermore, men reporting less than 800 kcal per day and women reporting less than 500 kcal per day across at least one third of their 24-hour dietary records were considered as energy underreporters and thus excluded.

III.A.2 Food composition tables

As mentioned in the "Introduction"-section, measurement errors related to the computation of nutrient intakes on the basis of food composition tables are related to the variation of food composition according to "environmental conditions, geographical location, food production and preparation methods" **(Andreeva and Kesse-Guyot 2015)**. Such variations apply to all types of food composition tables, and thus also have to be considered as a potential source of measurement error with respect to the results of this thesis.

On the other hand, the food composition table used in the SU.VI.MAX study was developed especially for the study and published in the form of a book **(Hercberg S 2005)** and contains a very large number of different foods (over 900). This can be regarded as a particular strength of our analysis, implying a high quality of our nutritional data.

III.A.3 Recall bias and social desirability

Memory-related bias ("recall bias") is probably generally of smaller magnitude in 24-hour dietary records as compared to other methods such as food frequency questionnaires, which inquire food consumption over larger periods of time. However, the high level of details of information inquired by 24-hour dietary records is probably also susceptible to inaccurate memories.

Social desirability bias is important to consider when interpreting nutritional data obtained from all types of nutritional assessment. Examples for such bias are underreporting of overall energy intake and fat intake, and overreporting of the consumption of fruits and vegetables **(Hebert et al. 1995; Hebert et al. 2008)**. It has been shown that women are more likely to show such differential misreporting **(Hebert et al. 1995)**.

III.B Confounding bias and adjustment

All observational studies are subject to potential confounding bias. Such bias implies a factor that is related to both the exposure variable and the investigated outcome, without being a mediating factor of the association between exposure and outcome **(McNamee 2003)**. While such bias can be reduced by the adjustment for variables that have been identified as confounding factors in the literature, unmeasured factors cannot be adjusted for **(Greenland and Morgenstern 2001; McNamee 2003)**. Furthermore, the impact of statistical of adjustment is limited to the degree of detail and accuracy of the measured variables. Thus, the possibility of residual confounding cannot be excluded and should be taken into account when interpreting the findings of this thesis.

In conclusion, the observational design of our analyses must be regarded as an important limitation of our analyses. The extensive adjustment for potential confounding factors, on the other hand, can be seen as a particular strength of our studies. An additional strength of our analyses pertains to the prospective design of the SU.VI.MAX and SU.VI.MAX 2 studies, which notably limits reverse causality bias.

III.C Generalizability

The recruitment of participants of the SU.VI.MAX study relied on the willingness of participants to be part of a in a long-term prevention trial, and thus to accept a larger number of constraints (daily intake of a capsule containing a combination of antioxidants or a placebo, the completion of questionnaires, participation at annual visits, reporting of information via Minitel). It is probable that individuals with a particular interest for diet and health were overrepresented in the cohort, and that individuals with a particularly low overall dietary quality were underrepresented.

Thus, the generalizability of our results may be limited. However, limitations in representativeness do not necessarily lead to bias concerning observed associations between specific exposures and outcomes **(Nohr et al. 2006)** – although they may lead to a reduced variability of the exposure variable of interest. It can be hypothesized that a within study sample including more individuals with very low overall dietary quality, the observed associations concerning *a priori* and *a posteriori* indicators of the overall diet may have been even stronger (under the hypothesis that very low dietary quality has a particularly detrimental role for health outcomes).

III.D Selection bias and inverse probability weighting

Another type of selection bias is related to the availability of data on the investigated exposure variables and outcome variables among participants of a cohort.

The analyses presented in this thesis manuscript have the particularity that the outcome variables were only assessed in a clearly defined subsample of the original SU.VI.MAX cohort: participants of the SU.VI.MAX 2 cohort. As the SU.VI.MAX 2 cohort (n=6,850) only makes up 54% of the original SU.VI.MAX cohort (n=12,741), we chose to only evaluate healthy aging among participants who were part of the SU.VI.MAX 2 cohort, and thus had available information on health status at follow-up. We could have also 'included' deceased individuals into our analyses, by classifying them into the 'non-healthy aging' category. However, given the fact that death was only a minor reason for non-participation in the SU.VI.MAX 2 (as explained in the "Methods"-section of the article "Dietary scores at midlife and healthy aging in a French prospective cohort"), this did not appear to us as a reasonable choice. 'Re-including' deceased individuals would have led to an overrepresentation of

participants who had not survived during follow-up, with respect to individuals who had survived but were simply not motivated to participate in the SU.VI.MAX 2 study.

In order to address the problem that we thus, however, underrepresented (i.e. completely excluded) deceased individuals, and potentially individuals who did not want to participate in the SU.VI.MAX 2 study because they were ill, we conducted inverse probability weighting either as sensitivity analyses or applied this methodology to our main models. Like statistical adjustment for confounding, inverse probability weighting is, however, no guarantee for complete neutralization of any potential selection bias.

Thus, the fact that our study samples only made up rather small proportions of the original SU.VI.MAX cohort must be considered as an important limitation of our analyses, while the use of an innovative statistical method for the consideration of selection bias can be regarded as a strength.

III.E Aspects related to the chosen healthy aging definition

III.E.1 Comparability with other studies

As outlined in the "Introduction"-section, a large heterogeneity in available definitions exists. This has large implications on the comparability of different studies. For example, the study by Tyrovolas et al. that found an inverse association between higher overall energy intakes **(Tyrovolas et al. 2015)** is highly relevant for the interpretations of our finding that a 'healthy'- *a posteriori* dietary pattern was only associated with healthy aging among individuals with rather low energy intakes. Yet, the difference between our healthy aging concept and that of Tyrovolas et al. is immense. Amongst others Tyrovolas et al. included a measure of adherence to the Mediterranean Diet into their concept, along with educational level, financial status, and body mass index. In our framework, all of these indicators are considered as predictors and not as inherent components of healthy aging.

In order to develop a definition that would be easily comparable, we largely based our concept on the model published by Rowe and Kahn, as its three components are those which are the most frequently included into operationalized definitions of healthy or successful aging **(Cosco et al. 2014a)**.

Thus, while the general heterogeneity of available healthy aging definitions must be regarded as a limitation of our analyses, our choice to develop a definition with maximal compatibility can be regarded as a strength with respect to comparability aspects.

III.E.2 Data availability

Most variables composing our healthy aging-definition were only available at follow-up. Thus, we were not able to formally investigate health decline in the course of aging. This is problematic because individuals that have been classified into the category "non-healthy aging" for specific components of our definition (such as physical and cognitive functioning, limitations of social life, pain-related limitations, or mental health) may in reality already have been in this category at baseline. Thus, the hypothesized temporal association of midlife diet with later health outcomes, may not reflect the true processes for all participants. This could mean that for some participants, dietary factors in earlier phases than midlife may be of importance. Moreover, reverse causality cannot be excluded.

However, our study sample was initially middle-aged (thus rather young) and (according to the eligibility criteria of the SU.VI.MAX trial) free of any disease likely to hinder study participation. Hence, we consider that our working hypothesis that subjects were globally healthy at baseline is generally plausible.

III.E.3 Healthy aging as a process

As detailed in the "Introduction"-section, many authors have underlined the need to consider healthy aging as a process, and not as an outcome measured at a single time point. However, in the SU.VI.MAX study, such repeated measures of healthy aging were not possible – which should be regarded as a limitation of our analyses.

Very frequent repetitions of measures require immense human and financial resources and very highly motivated participants. Thus, capturing the 'true' process of healthy aging, including all possible events that may influence the transition of an individual between different states, is generally difficult in epidemiological studies.

III.F Statistical analyses

For our analyses on a multidimensional concept of healthy aging, multivariable logistic regression was used to analyse the relation with dietary factors. However, the overall proportion of healthy aging in our studies was quite high (almost 40%). With such high

proportions of outcome variables, OR cannot be interpreted in the same manner as RR, but are inflated **(Ragland 1992; Zhang and Yu 1998)**.

Our analyses on antioxidant supplementation and healthy aging – for which we calculated both RR and OR – provide an idea of the magnitude of this inflation effect. While the unadjusted OR observed among individuals with a low baseline vitamin C status was as large as 1.48. However, the corresponding RR was only 1.28.

This is in line with a formula published by Robert Grant **(Grant 2014)**, which permits the conversion of OR to RR for a given 'baseline risk' p0 (i.e. the risk in the 'control group'): "RR = OR /(1−p0 +(p0 × OR))".

When applying this conversion formula to the above-mentioned OR observed for individuals with a low baseline vitamin C status (OR = 1.48, baseline risk, i.e. healthy aging proportion among participants in the placebo group = 0.32), the result is exactly equal to the observed RR (1.28).

However, as the author has pointed out, there is no 'shared' baseline risk for all subjects when confounding is an issue and OR have thus been obtained by multivariable logistic regression. In this case, Grant suggested calculating an 'average baseline risk' by entering the observed average of each covariable into the regression equation
"$\ln(\frac{p}{1-p}) = \alpha + \beta_1 E + \sum \beta_i A_i$", in order to obtain an approximation for the 'baseline risk' p0.

In more detail, the following procedure has to be followed:

- The observed mean values of each covariable have to be multiplied with the respective beta-parameters, and then summed.
- Next, the value of the intercept α has to be added to this sum. If the 'control group' or 'reference group' has been coded as the reference level, no additional step is necessary.
- The obtained result is to the average "logit" (or "log odds", i.e. $\ln(\frac{p}{1-p})$).
- To obtain the "average odds", the exponential of the value has to be calculated.
- The average risk "p" (i.e. an approximation for the 'baseline risk' p0) is then obtained with the formula p=odds/(1+odds).
- Finally, this approximation of p0 has to be inserted into the formula

"RR= OR /(1−p0 +(p0 × OR))"

This strategy can be applied to our results concerning *a posteriori* dietary patterns and *a priori* dietary scores. The OR for being in the third versus in the first tertile of the 'healthy'-dietary pattern – among individuals with energy intakes below the sex-specific median was 1.49. With the help of Grant's formula, this number can be converted to a RR of 1.28.

Similarly, the OR for being in highest versus the lowest quartile of the mPNNS-GS, PANDiet, and PNNS-GS can be converted as follows:

- mPNNS-GS: OR of 1.44 → RR of 1.25 (calculated with a p0 of 0.34),
- PANDiet: OR of 1.28 → RR of 1.16 (calculated with a p0 of 0.35),
- PNNS-GS: OR of 1.64 → RR of 1.36 (calculated with a p0 of 0.32).

III.G Specific aspects concerning our analyses on antioxidant supplementation and on vitamin D

a) Analysis on antioxidant supplementation and healthy aging

The main limitation related to our analyses concerning antioxidant supplementation and healthy aging is that a multidimensional concept of healthy aging was not a pre-specified primary endpoint of the SU.VI.MAX trial. Thus, our analysis must be regarded as a post-hoc analysis of a randomized controlled trial, which means that its results cannot be considered to have the same level of evidence as the results concerning the primary endpoints (the incidence of cancer and cardiovascular disease). In addition, the subgroup-analyses that we conducted were not pre-planned and thus of exploratory nature. As a consequence, no causal inference can be made with respect to our results, and further trials are necessary to confirm our findings.

On the other hand, the initial randomized controlled design of the SU.VI.MAX trial remains an important strength of our study – increasing the trustworthiness of its results with respect to the results of purely observational studies. A further strength is the fact that high compliance of the SU.VI.MAX participants with the allocated treatment was observed **(Hercberg et al. 2004; Hercberg et al. 2010b)**. In addition, the realization of subgroup analyses can be regarded as a strength – even given their exploratory nature. The stratification variables had been determined with respect to existing hypotheses, and our subgroup analyses can be regarded as important elements of evidence as few other trials have published similar stratified results.

b) Analyses on baseline vitamin D status and healthy aging

Several specific limitations with respect to our analyses on baseline vitamin D status and healthy aging should be noted.

- There was no cognitive assessment at baseline, which prevented us from formally investigating cognitive decline. It is possible that individuals with low vitamin D status already had worse cognitive performance at baseline, thus leading to an overestimation of the identified association. The fact that we adjusted for self-reported memory complaints at baseline, educational level and baseline- occupational category may partly attenuate such potential bias.
- No data on vitamin D status at follow-up (2007-09) was available, and only a single baseline measurement of 25(OH)D was available for each participant. A recent study indicated that, depending on the season of blood draw, a single sample can provide a reasonable average for 25(OH)D over a 1-yr period **(Major et al. 2013)**. Since in our study, blood samples were drawn between October and April, the samples that were obtained at time points with a largest distance from summer do probably not correspond to the average 25(OH)D concentration of an individual across the year. However, we adjusted for season of blood draw, in order to partly account for this issue.
- No data on dietary supplement use (including vitamin D supplements) after the end of the SU.VI.MAX trial phase were available.

Specific strengths concerning our analyses on vitamin D status and later healthy aging included:

- the use of a neuropsychological battery including validated cognitive tests designed to limit floor and ceiling effects, and
- the use of a large number of different cognitive tests, which permitted us to report specific results on different cognitive domains (in contrast to many other studies on vitamin D and cognition).

IV. Perspectives for future research

IV.A Development of a healthy aging definition for the NutriNet-Santé study

IV.A.1 Development of a web-questionnaire

The NutriNet-Santé study is a "web-based prospective cohort study" with a planned follow-up period of 10 years, which has two main objectives: the investigation of the association of nutrition with mortality and health outcomes, and the investigation of the "determinants of dietary patterns and nutritional status" **(Hercberg et al. 2010a)**. Data assessment relies on web-based tools, except for biochemical samples and clinical examinations, which have been conducted within a subsample of the cohort (n≈ 19,500) **(Hercberg et al. 2010a)**. To date, more than 150,000 individuals have been included into the cohort.

In order to implement a multidimensional concept of healthy aging for the NutriNet-Santé cohort, a specific questionnaire has been developed in the context of this thesis, in cooperation with Dr. Emmanuelle Kesse-Guyot and Dr. Valentina Andreeva.

The questionnaire inquires information on the following elements:

- perceived general health,
- life satisfaction,
- health-related limitations of social life,
- pain and pain-related limitations,
- leisure activities (including social activities),
- limitations in IADL,
- social environment,
- diseases (including information on treatment and limitations related to the diseases),
- number of prescribed and usually taken medications,
- physical capacities,
- mental health,
- change in memory capacities over time,
- stress (events, emotions, and reactions),
- optimism,
- resilience,

- sleep duration, and
- perceived overall dietary quality.

Not all elements will be included into the definition of healthy aging. Aspects such as optimism, stress, social environment, and resilience will rather be used to examine determinants and correlates of healthy aging in a more holistic manner than this has been possible in the SU.VI.MAX study (where less data were available).

As the NutriNet-Santé study is an ongoing cohort, the questionnaire will be administered multiple times in order to better consider healthy aging as a continuous process. We are currently working on the development of the operationalized definition of healthy aging for the NutriNet-Santé study and will provide more information in the context of a first publication.

IV.A.2 Validation of an online- cognitive test battery

In addition to the self-reported data on changes in memory capacities over time, which will be available via the above-described questionnaire, an online cognitive test battery has been developed for the NutriNet-Santé study.

A methodological study has been conducted with the objective to compare self-administration of the web-based test battery with traditional means of administration (i.e. administration by a neuropsychologist). This comparison study can be considered as a partial validation of the cognitive test battery. The author of this thesis has conducted the management of the data of this comparison study as well as the statistical analyses, and has drafted a scientific article describing the results of the study. A copy of this article, which has been accepted by the Journal of Medical Internet Research (JMIR), is included in **Appendix 1** of this thesis.

Table 10 gives an overview of the different tests included into the battery, and the cognitive processes that they were designed to measure.

On the basis of the data obtained via this web-based cognitive test battery, a more accurate indicator of overall cognitive capacities will thus be created and compared to the self-reported data that are part of the healthy aging questionnaire. Moreover, it will be possible to investigate a definition of healthy aging that includes these more accurate cognitive data within the subgroup of NutriNet-Santé participants who have completed the online cognitive test battery.

Table 10. Description of the cognitive test battery designed for the NutriNet-Santé Study

Not shown due to copyright considerations

IV.A.3 Development of one or multiple healthy aging concepts

The exact nature of the healthy aging definition for the NutriNet-Santé study has not yet been determined. In addition to the development of a binary concept, it will be possible to also develop a continuous score.

Furthermore, as the WHODAS 2.0- questionnaire has also been administered to the participants of the NutriNet-Santé cohort, it will be possible to develop an additional concept of "active and healthy aging", following the guidelines developed during the 2014-conference of the European Innovative Partnership on Active and Healthy Aging **(Bousquet et al. 2015a; Bousquet et al. 2015b)** (see the State of knowledge- section of this thesis). This will help provide comparable data across various European studies on healthy aging determinants.

IV.B The association between adherence to the Mediterranean diet and healthy aging

A Mediterranean-style diet is commonly defined as a dietary pattern characterized by a consumption of rather large amounts of cereals, vegetables, legumes, fruits, fish, nuts, and olive oil and only moderated amounts of meat and dairy products **(Davis et al. 2015)**. This type of diet has been suggested as a key dietary pattern with an important role in the prevention of age-related health decline **(Chatzianagnostou et al. 2015; United States Department of Agriculture 2014; Vasto et al. 2014)**.

Thus, we have also begun to investigate the relation between adherence to the Mediterranean diet, as measured by four different *a priori*- dietary scores and healthy aging. The scores that we have chosen to investigate are the Mediterranean Diet Scale (MDS) **(Trichopoulou et al. 2003)**, the Mediterranean Style Dietary Pattern Score (MSDPS) **(Rumawas et al. 2009)**, the relative Mediterranean Diet Score (rMed) **(Buckland et al. 2010)**, and the Literature-based Adherence Score to the Mediterranean Diet (LAMD) **(Sofi et al. 2013)**. Preliminary findings on the association of these scores with healthy aging in the SU.VI.MAX study are included in **Appendix 2**. These results have also been presented in the form of a poster at a French-language annual nutrition congress ("Journées Francophones de Nutrition") in December 2015 **(Assmann et al. 2015a)**. The drafting of a scientific article is in progress.

IV.C The association between anthropometric indicators, metabolic disorders, and healthy aging

Our finding that adherence to a "healthy"- dietary pattern was only associated with healthy aging when combined with a regulated energy intake indicates that the prevention of overweight and obesity may be important for a healthy aging process. This is in line with several of the mechanisms relating diet to healthy aging that were detailed in the chapter "Synthetic discussion of the different findings in the context of potential mechanistic pathways". Moreover, an elevated body mass index and an elevated waist circumference were significantly associated with lower odds of "successful aging" in a recent investigation of data from the Whitehall II cohort **(Singh-Manoux et al. 2014)**.

We have thus decided to examine the association of anthropometric indicators (notably body mass index and waist circumference) and of metabolic disorders with healthy aging in the SU.VI.MAX study, in the context of an internship of a student enrolled in a Master's degree-program. This internship will take place between April and September 2016, and will be supervised by Dr. Emmanuelle Kesse-Guyot and the author of this thesis.

V. Final conclusion

The results of the studies presented in this thesis contribute to a better understanding of the potential role of dietary factors for an overall healthy aging process, and for healthy cognitive aging in particular. Given the drastic demographic changes that are occurring worldwide and the related increase in the burden of non-communicable diseases **(World Health Organization 2011)**, the development of holistic approaches of preventing global age-related health decline is an immense public health challenge. Dementia is a particularly important public health problem in this context as it is closely related to the loss of autonomy **(World Health Organization 2011)**.

Our studies' results confirm the importance of targeting midlife lifestyles, in particular diet. The importance of prevention strategies that are focused on the midlife period has been especially highlighted with respect to dementia (given the long latency period of neurodegenerative diseases) **(Coley et al. 2008; de la Torre 2010; Rooney 2014; Singh-Manoux and Kivimaki 2010)**, but also concerning general age-related health decline **(Harlow and Derby 2015)** or specific diseases such as cancer **(Ory et al. 2014)**.

A recent publication reporting key elements of a conference symposium on "Nutrition and healthy aging" – "Epidemiology of human aging" has proposed a number of "key ingredients" for healthy aging, derived from studies on indicators of the overall diet – in relation to mortality, chronic diseases, and cognitive health **(Kiefte-de Jong et al. 2014)**. The proposed beneficial key ingredients are "fruits", "vegetables", "(whole) grains", "fish", and "legumes, pulses and potatoes", and the proposed detrimental factors are "red meat" and "sugar-rich foods". The results of our studies are largely in agreement with this proposition (except for the factor "red meat" as no significant association of our "western"- dietary pattern, characterized by high consumption of meat and processed meat, with healthy aging was observed). Our results thus contribute to the identification of evidence-based nutritional strategies for the prevention of overall age-related health decline – and provide new arguments for the promotion of a healthy diet.

Within the context of the WHO-framework of healthy aging, well-targeted nutritional strategies could help individuals to maintain high "physical and mental capacities" during aging. These capacities then determine, in interaction with external factors (such as transport options), the "functional ability" of an individual. An individual with high functional ability,

living within a favourable environment, will then “be able to do what they have reason to value”, and find life satisfaction and fulfilment.

REFERENCES

Adam,S., Van der Linden,M., Ivanoiu,A., Juillerat,A.C., Bechet,S., and Salmon,E. 2007. Optimization of encoding specificity for the diagnosis of early AD: the RI-48 task. J Clin Exp Neuropsychol. 29(5):477-487.

Akbaraly,T., Sabia,S., Hagger-Johnson,G., Tabak,A.G., Shipley,M.J., Jokela,M. et al. 2013a. Does overall diet in midlife predict future aging phenotypes? A cohort study. Am J Med. 126(5):411-419.

Akbaraly,T.N., Hamer,M., Ferrie,J.E., Lowe,G., Batty,G.D., Hagger-Johnson,G. et al. 2013b. Chronic inflammation as a determinant of future aging phenotypes. CMAJ. 185(16):E763-E770.

Alberti,K.G., Eckel,R.H., Grundy,S.M., Zimmet,P.Z., Cleeman,J.I., Donato,K.A. et al. 2009. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 120(16):1640-1645.

Allès,B., Samieri,C., Feart,C., Jutand,M.A., Laurin,D., and Barberger-Gateau,P. 2012. Dietary patterns: a novel approach to examine the link between nutrition and cognitive function in older individuals. Nutr Res Rev. 25(2):207-222.

Almeida,O.P., Khan,K.M., Hankey,G.J., Yeap,B.B., Golledge,J., and Flicker,L. 2014. 150 minutes of vigorous physical activity per week predicts survival and successful ageing: a population-based 11-year longitudinal study of 12 201 older Australian men. Br J Sports Med. 48(3):220-225.

Ames,B.N., Shigenaga,M.K., and Hagen,T.M. 1993. Oxidants, antioxidants, and the degenerative diseases of aging. Proc Natl Acad Sci USA. 90(17):7915-7922.

Amieva,H., Le Goff,M., Millet,X., Orgogozo,J.M., Peres,K., Barberger-Gateau,P. et al. 2008. Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. Ann Neurol. 64(5):492-498.

Anastasiou,C.A., Yannakoulia,M., and Scarmeas,N. 2014. Vitamin D and Cognition: An Update of the Current Evidence. J Alzheimers Dis. 42 Suppl 3:S71-S80.

Andreeva, V. A. and Kesse-Guyot, E. K. Nutrition and cognition in the context of ageing: Role of dietary patterns. 2015. Boca Raton, FL, CRC Press, Taylor & Francis Group. Nutrition for brain health and cognitive performance.

Andreeva,V.A., Whegang-Youdom,S., Touvier,M., Assmann,K.E., Fezeu,L., Hercberg,S. et al. 2014. Midlife dietary vitamin D intake and subsequent performance in different cognitive domains. Ann Nutr Metab. 65(1):81-89.

Andrews,G., Clark,M., and Luszcz,M. 2002. Successful aging in the Australian Longitudinal Study of Aging: Applying the MacArthur model cross-nationally. Journal of Social Issues 58(4):749-765.

Angus,J. and Reeve,P. 2006. Ageism: A Threat to "Aging Well" in the 21st Century. Journal of Applied Gerontology 25(2):137-152.

Annweiler,C., Fantino,B., Gautier,J., Beaudenon,M., Thiery,S., and Beauchet,O. 2012. Cognitive effects of vitamin D supplementation in older outpatients visiting a memory clinic: a pre-post study. J Am Geriatr Soc. 60(4):793-795.

Annweiler,C., Llewellyn,D.J., and Beauchet,O. 2013a. Low serum vitamin D concentrations in Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 33(3):659-674.

Annweiler,C., Montero-Odasso,M., Llewellyn,D.J., Richard-Devantoy,S., Duque,G., and Beauchet,O. 2013b. Meta-analysis of memory and executive dysfunctions in relation to vitamin D. J Alzheimers Dis. 37(1):147-171.

Annweiler,C., Rolland,Y., Schott,A.M., Blain,H., Vellas,B., and Beauchet,O. 2011. Serum vitamin D deficiency as a predictor of incident non-Alzheimer dementias: a 7-year longitudinal study. Dement Geriatr Cogn Disord. 32(4):273-278.

Anton,S.D., Woods,A.J., Ashizawa,T., Barb,D., Buford,T.W., Carter,C.S. et al. 2015. Successful aging: Advancing the science of physical independence in older adults. Ageing Res Rev. 24(Pt B):304-327.

Appel,L.J., Moore,T.J., Obarzanek,E., Vollmer,W.M., Svetkey,L.P., Sacks,F.M. et al. 1997. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med. 336(16):1117-1124.

Araujo,L., Ribeiro,O., Teixeira,L., and Paul,C. 2016. Successful aging at 100 years: the relevance of subjectivity and psychological resources. Int Psychogeriatr. 28(2):179-188.

Arenaza-Urquijo,E.M., Wirth,M., and Chetelat,G. 2015. Cognitive reserve and lifestyle: moving towards preclinical Alzheimer's disease. Front Aging Neurosci. 7:134. doi: 10.3389/fnagi.2015.00134.

Arias-Merino,E.D., Mendoza-Ruvalcaba,N.M., Arias-Merino,M.J., Cueva-Contreras,J., and Vazquez,A.C. 2012. Prevalence of successful aging in the elderly in Western Mexico. Curr Gerontol Geriatr Res. Volume 2012 (2012), Article ID 460249, 6 pages.

Arnaud,J., Fortis,I., Blachier,S., Kia,D., and Favier,A. 1991. Simultaneous determination of retinol, alpha-tocopherol and beta-carotene in serum by isocratic high-performance liquid chromatography. J Chromatogr. 572(1-2):103-116.

Aron-Wisnewsky,J. and Clement,K. 2016. The gut microbiome, diet, and links to cardiometabolic and chronic disorders. Nat Rev Nephrol. 12(3):169-181.

Assmann, K. E., Andreeva, V. A., Hercberg, S., Galan, P., and Kesse-Guyot, E. 2015a. P332: Association prospective entre l'adhérence à la diète méditerranéenne et un concept multidimensionnel du vieillissement en bonne santé. Journées Francophones de Nutrition (JFN) 09.-11. December 2015 - Marseille, France.

Assmann,K.E., Lassale,C., Andreeva,V.A., Jeandel,C., Hercberg,S., Galan,P. et al. 2015b. A Healthy Dietary Pattern at Midlife, Combined with a Regulated Energy Intake, Is Related to Increased Odds for Healthy Aging. J Nutr. 145(9):2139-2145.

Assmann,K.E., Lassale,C., Galan,P., Hercberg,S., and Kesse-Guyot,E. 2014. Dietary quality and 6-year anthropometric changes in a sample of French middle-aged overweight and obese adults. PLoS One. 9(2):e87083.

Avlund,K., Holstein,B.E., Mortensen,E.L., and Schroll,M. 1999. Active life in old age. Combining measures of functional ability and social participation. Dan.Med Bull. 46(4):345-349.

Bäckman,L., Jones,S., Berger,A.K., Laukka,E.J., and Small,B.J. 2005. Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis. Neuropsychology. 19(4):520-531.

Baddeley,A. 2010. Working memory. Current Biology 20(4):R136-R140.

Balion,C., Griffith,L.E., Strifler,L., Henderson,M., Patterson,C., Heckman,G. et al. 2012. Vitamin D, cognition, and dementia: a systematic review and meta-analysis. Neurology 79(13):1397-1405.

Baltes,P.B. and Baltes,M.M. 1989. Optimierung durch Selektion und Kompensation. Ein psychologisches Modell erfolgreichen Alterns [Optimization by selection and compensation. A psychological model of successful aging]. Zeitschrift für Pädagogik 35:85-105.

Banerjee,A., Khemka,V.K., Ganguly,A., Roy,D., Ganguly,U., and Chakrabarti,S. 2015. Vitamin D and Alzheimer's Disease: Neurocognition to Therapeutics. Int J Alzheimers Dis. Volume 2015 (2015), Article ID 192747, 11 pages:192747.

Barbaresko,J., Koch,M., Schulze,M.B., and Nothlings,U. 2013. Dietary pattern analysis and biomarkers of low-grade inflammation: a systematic literature review. Nutr Rev. 71(8):511-527.

Bartali,B., Devore,E., Grodstein,F., and Kang,J.H. 2014. Plasma vitamin D levels and cognitive function in aging women: the nurses' health study. J Nutr Health Aging. 18(4):400-406.

Beard, J. Officer A. Cassels A. World report on ageing and health. 2015. Geneva, World Health Organization.

Belgrave, Linda Liska and Sayed, Bisma Ali. Successful/Productive Aging, Responsibility, and Reflection. Arxer, L. Steven and Murphy, W. John. The Symbolism of Globalization, Development, and Aging. 91-107. 2013. New York, NY, Springer New York.

Bell,C.L., Chen,R., Masaki,K., Yee,P., He,Q., Grove,J. et al. 2014. Late-life factors associated with healthy aging in older men. J Am Geriatr.Soc. 62(5):880-888.

Berkman,L.F., Seeman,T.E., Albert,M., Blazer,D., Kahn,R., Mohs,R. et al. 1993. High, Usual and Impaired Functioning in Community-Dwelling Older Men and Women - Findings from the Macarthur Foundation Research Network on Successful Aging. Journal of Clinical Epidemiology 46(10):1129-1140.

Beydoun,M.A., Beydoun,H.A., Boueiz,A., Shroff,M.R., and Zonderman,A.B. 2013. Antioxidant status and its association with elevated depressive symptoms among US adults: National Health and Nutrition Examination Surveys 2005-6. Br J Nutr. 109(9):1714-1729.

Biesalski,H.K., Grune,T., Tinz,J., Zollner,I., and Blumberg,J.B. 2010. Reexamination of a meta-analysis of the effect of antioxidant supplementation on mortality and health in randomized trials. Nutrients. 2(9):929-949.

Binder,L.I., Guillozet-Bongaarts,A.L., Garcia-Sierra,F., and Berry,R.W. 2005. Tau, tangles, and Alzheimer's disease. Biochim.Biophys.Acta. 1739(2-3):216-223.

Bjelakovic,G., Nikolova,D., Gluud,L.L., Simonetti,R.G., and Gluud,C. 2012. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst.Rev. doi: 10.1002/14651858.CD007176.pub2.

Blanpain,N., Chardon,O., division Enquêtes et études démographiques, and INSEE. 2010. Projections de population à l'horizon 2060 . INSEE Première 1320.

Bogin,B., Harper,D., Merrell,J., Chowdhury,J., Heinrich,M., Garaj,V. et al. 2014. Influence of Adult Knee Height, Age at First Birth, Migration, and Current Age on Adult Physical Function of Bangladeshi Mothers and Daughters in the United Kingdom and Bangladesh. Journal of Anthropology vol. 2014, Article ID 808634, 14 pages, 2014. doi:10.1155/2014/808634.

Bonjour,J.P., Kraenzlin,M., Levasseur,R., Warren,M., and Whiting,S. 2013. Dairy in adulthood: from foods to nutrient interactions on bone and skeletal muscle health. J Am Coll.Nutr. 32(4):251-263.

Bourgeois CF, Chartois RR, Counstans MF, and Georges PR. 1989. Automated determination of vitamin C in foodstuffs and biological tissues. Analysis 9:519-525.

Bousquet,J., Kuh,D., Bewick,M., Standberg,T., Farrell,J., Pengelly,R. et al. 2015a. Operational Definition of Active and Healthy Ageing (AHA): A Conceptual Framework. J Nutr Health Aging. 19(9):955-960.

Bousquet,J., Malva,J., Nogues,M., Manas,L.R., Vellas,B., and Farrell,J. 2015b. Operational Definition of Active and Healthy Aging (AHA): The European Innovation Partnership (EIP) on AHA Reference Site Questionnaire: Montpellier October 20-21, 2014, Lisbon July 2, 2015. J Am Med Dir.Assoc. 16(12):1020-1026.

Bowling,A. and Dieppe,P. 2005. What is successful ageing and who should define it? BMJ. 331(7531):1548-1551.

Bowling,A. and Iliffe,S. 2006. Which model of successful ageing should be used? Baseline findings from a British longitudinal survey of ageing. Age and Ageing 35(6):607-614.

Braskie,M.N., Klunder,A.D., Hayashi,K.M., Protas,H., Kepe,V., Miller,K.J. et al. 2010. Plaque and tangle imaging and cognition in normal aging and Alzheimer's disease. Neurobiol.Aging. 31(10):1669-1678.

Breitling,L.P., Perna,L., Muller,H., Raum,E., Kliegel,M., and Brenner,H. 2012. Vitamin D and cognitive functioning in the elderly population in Germany. Exp Gerontol. 47(1):122-127.

Brion,J.P. 1998. Neurofibrillary tangles and Alzheimer's disease. Eur Neurol. 40(3):130-140.

Britton,A., Shipley,M., Singh-Manoux,A., and Marmot,M.G. 2008. Successful aging: the contribution of early-life and midlife risk factors. J Am Geriatr.Soc. 56(6):1098-1105.

Buckland,G., Agudo,A., Lujan,L., Jakszyn,P., Bueno-de-Mesquita,H.B., Palli,D. et al. 2010. Adherence to a Mediterranean diet and risk of gastric adenocarcinoma within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. Am J Clin Nutr. 91(2):381-390.

Buell,J.S., Dawson-Hughes,B., Scott,T.M., Weiner,D.E., Dallal,G.E., Qui,W.Q. et al. 2010. 25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services. Neurology 74(1):18-26.

Bülow,M.H. and Söderqvist,T. 2014. Successful ageing: a historical overview and critical analysis of a successful concept. J Aging Stud. 31:139-149.

Butler,J.P., Fujii,M., and Sasaki,H. 2011. Balanced aging, or successful aging? Geriatr.Gerontol.Int. 11(1):1-2.

Caballero,B., Rubio-Gonzalez,A., Potes,Y., Martinez-Reig,M., Sanchez-Jurado,P.M., Romero,L. et al. 2014. Associations of the antioxidant capacity and hemoglobin levels with functional physical performance of the upper and lower body limbs. Age (Dordr.). 36(2):851-867.

Calasanti,T., Slevin,K., and King,N. 2006. Ageism and Feminism: From "Et Cetera" to Center. 18(1):13-30.

Calcada,D., Vianello,D., Giampieri,E., Sala,C., Castellani,G., de,G.A. et al. 2014. The role of low-grade inflammation and metabolic flexibility in aging and nutritional modulation thereof: a systems biology approach. Mech.Ageing Dev. Volumes 136-137:138-147.

Campisi,J. and d'Adda di,F.F. 2007. Cellular senescence: when bad things happen to good cells. Nat Rev Mol.Cell Biol. 8(9):729-740.

Carter,P., Gray,L.J., Troughton,J., Khunti,K., and Davies,M.J. 2010. Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis. BMJ. 341:c4229. doi: 10.1136/bmj.c4229.:c4229.

Cavallari,M., Moscufo,N., Skudlarski,P., Meier,D., Panzer,V.P., Pearlson,G.D. et al. 2013. Mobility impairment is associated with reduced microstructural integrity of the inferior and superior cerebellar peduncles in elderly with no clinical signs of cerebellar dysfunction. Neuroimage.Clin. 2:332-340.

Cederholm,T., Nouvenne,A., Ticinesi,A., Maggio,M., Lauretani,F., Ceda,G.P. et al. 2014. The role of malnutrition in older persons with mobility limitations. Curr Pharm.Des. 20(19):3173-3177.

Cernin,P.A., Lysack,C., and Lichtenberg,P.A. 2011. A Comparison of Self-Rated and Objectively Measured Successful Aging Constructs in an Urban Sample of African American Older Adults. Clin Gerontol. 34(2):89-102.

Chatzianagnostou,K., Del,T.S., Pingitore,A., Sabatino,L., and Vassalle,C. 2015. The Mediterranean Lifestyle as a Non-Pharmacological and Natural Antioxidant for Healthy Aging. Antioxidants.(Basel). 4(4):719-736.

Chaves,M.L., Camozzato,A.L., Eizirik,C.L., and Kaye,J. 2009. Predictors of normal and successful aging among urban-dwelling elderly Brazilians. J Gerontol.B Psychol.Sci Soc Sci. 64(5):597-602.

Cheung,K.S. and Lau,B.H. 2015. Successful aging among Chinese near-centenarians and centenarians in Hong Kong: a multidimensional and interdisciplinary approach. Aging Ment.Health. [epub ahead of print. DOI:10.1080/13607863.2015.1078281].

Cheung,S.T. 2000. Possible dangers in a low fat diet: some evidence reviewed. Nutr Health 14(4):171-280.

Chiuve,S.E., Fung,T.T., Rimm,E.B., Hu,F.B., McCullough,M.L., Wang,M. et al. 2012. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr. 142(6):1009-1018.

Cho,J., Martin,P., and Poon,L.W. 2012. The Older They Are, the Less Successful They Become? Findings from the Georgia Centenarian Study. Journal of Aging Research Volume 2012 (2012), Article ID 695854, 8 pages.

Choi,S.W. and Mason,J.B. 2000. Folate and carcinogenesis: an integrated scheme. J Nutr. 130(2):129-132.

Chou,K.L. and Chi,I. 2002. Successful aging among the young-old, old-old, and oldest-old Chinese. Int J Aging Hum Dev. 54(1):1-14.

Claesson,M.J., Jeffery,I.B., Conde,S., Power,S.E., O'Connor,E.M., Cusack,S. et al. 2012. Gut microbiota composition correlates with diet and health in the elderly. Nature. 488(7410):178-184.

Cole,S.R. and Hernan,M.A. 2008. Constructing inverse probability weights for marginal structural models. Am.J.Epidemiol. 168(6):656-664.

Coleman,P.G. 1992. Personal adjustment in late life: Successful aging. Reviews in Clinical Gerontology 2(1):67-78.

Coley,N., Andrieu,S., Gardette,V., Gillette-Guyonnet,S., Sanz,C., Vellas,B. et al. 2008. Dementia prevention: methodological explanations for inconsistent results. Epidemiol.Rev. 30:35-66.

Commenges,D., Scotet,V., Renaud,S., Jacqmin-Gadda,H., Barberger-Gateau,P., and Dartigues,J.F. 2000. Intake of flavonoids and risk of dementia. Eur J Epidemiol. 16(4):357-363.

Cosco,T.D. 2015. Successfully aging predicts successful aging in successful agers: further definitional issues. Int Psychogeriatr. 27(1):170-171.

Cosco,T.D., Armstrong,J.J., Stephan,B.C., and Brayne,C. 2015a. Successful aging and frailty: mutually exclusive paradigms or two ends of a shared continuum? Can.Geriatr.J. 18(1):35-36.

Cosco,T.D., Prina,A.M., Perales,J., Stephan,B.C., and Brayne,C. 2013a. Lay perspectives of successful ageing: a systematic review and meta-ethnography. BMJ Open. 3(6):pii: e002710.

Cosco,T.D., Prina,A.M., Perales,J., Stephan,B.C., and Brayne,C. 2014a. Operational definitions of successful aging: a systematic review. Int Psychogeriatr. 26(3):373-381.

Cosco,T.D., Stephan,B.C., and Brayne,C. 2013b. On the success of the successful aging paradigm. J Appl.Gerontol. 32(3):275-276.

Cosco,T.D., Stephan,B.C., and Brayne,C. 2014b. (Unsuccessful) binary modeling of successful aging in the oldest-old adults: a call for continuum-based measures. J Am Geriatr.Soc. 62(8):1597-1598.

Cosco,T.D., Stephan,B.C., and Brayne,C. 2015b. Validation of an a priori, index model of successful aging in a population-based cohort study: the successful aging index. Int Psychogeriatr. 27(12):1971-1977.

Cowan,N. 2008. What are the differences between long-term, short-term, and working memory? Prog.Brain Res. 169:323-328.

Creegan,R., Hunt,W., McManus,A., and Rainey-Smith,S.R. 2015. Diet, nutrients and metabolism: cogs in the wheel driving Alzheimer's disease pathology? Br J Nutr. 113(10):1499-1517.

Crowther,M.R., Parker,M.W., Achenbaum,W.A., Larimore,W.L., and Koenig,H.G. 2002. Rowe and Kahn's model of successful aging revisited: positive spirituality--the forgotten factor. Gerontologist. 42(5):613-620.

Cumming,E. and Henry,W.E. 1961. Growing old: The process of disengagement. New York: Basic Books.

Czernichow,S., Couthouis,A., Bertrais,S., Vergnaud,A.C., Dauchet,L., Galan,P. et al. 2006. Antioxidant supplementation does not affect fasting plasma glucose in the Supplementation with Antioxidant Vitamins and Minerals (SU.VI.MAX) study in France: association with dietary intake and plasma concentrations. Am J Clin Nutr. 84(2):395-399.

Daffner,K.R. 2010. Promoting successful cognitive aging: a comprehensive review. J Alzheimers Dis. 19(4):1101-1122.

Daviglus,M.L., Plassman,B.L., Pirzada,A., Bell,C.C., Bowen,P.E., Burke,J.R. et al. 2011. Risk factors and preventive interventions for Alzheimer disease: state of the science. Arch.Neurol. 68(9):1185-1190.

Davis,C., Bryan,J., Hodgson,J., and Murphy,K. 2015. Definition of the Mediterranean Diet; a Literature Review. Nutrients. 7(11):9139-9153.

de la Torre,J.C. 2010. Alzheimer's disease is incurable but preventable. J.Alzheimers.Dis. 20(3):861-870.

De Luca,L.M. and Ross,S.A. 1996. Beta-carotene increases lung cancer incidence in cigarette smokers. Nutr Rev. 54(6):178-180.

de Vries,N.M., Staal,J.B., van Ravensberg,C.D., Hobbelen,J.S., Olde Rikkert,M.G., and Nijhuis-van der Sanden MW. 2011. Outcome instruments to measure frailty: a systematic review. Ageing Res Rev. 10(1):104-114.

DeCarlo,T.J. 1974. Recreation paricipation patterns and successful aging. J Gerontol. 29(4):416-422.

Deckers,K., van Boxtel,M.P., Schiepers,O.J., de,V.M., Munoz Sanchez,J.L., Anstey,K.J. et al. 2015. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. Int J Geriatr.Psychiatry. 30(3):234-246.

Delis,D.C., Kaplan,E., and Kramer,J.H. 2001a. Delis-Kaplan Executive Function System (D-KEFS) examiner's manual. San Antonio, TX: The Psychological Corporation.

Delis,D.C., Kaplan,E., and Kramer,J.H. 2001b. Delis-Kaplan Executive Function System (D-KEFS) technical manual. San Antonio, TX: The Psychological Corporation.

Depp,C., Vahia,I.V., and Jeste,D. 2010. Successful aging: focus on cognitive and emotional health. Annu.Rev.Clin.Psychol. 6:527-550.

Depp,C.A., Harmell,A., and Vahia,I.V. 2012. Successful cognitive aging. Curr Top.Behav.Neurosci. 10:35-50.

Depp,C.A. and Jeste,D.V. 2006. Definitions and predictors of successful aging: a comprehensive review of larger quantitative studies. Am J Geriatr.Psychiatry. 14(1):6-20.

Deschamps,R. and Moulignier,A. 2005. La mémoire et ses troubles. EMC - Neurologie 2(4):505-525.

Dillaway,H.E. and Byrnes,M. 2009. Reconsidering Successful Aging A Call for Renewed and Expanded Academic Critiques and Conceptualizations. Journal of Aging and Health 28(6):702-722.

Drescher,L.S., Thiele,S., and Mensink,G.B. 2007. A new index to measure healthy food diversity better reflects a healthy diet than traditional measures. J Nutr. 137(3):647-651.

Drewnowski,A., Henderson,S.A., Driscoll,A., and Rolls,B.J. 1997. The Dietary Variety Score: assessing diet quality in healthy young and older adults. J Am Diet.Assoc. 97(3):266-271.

Duthie,S.J. 2011. Folate and cancer: how DNA damage, repair and methylation impact on colon carcinogenesis. J Inherit.Metab Dis. 34(1):101-109.

Edwards,D.R., Gilbert,J.R., Jiang,L., Gallins,P.J., Caywood,L., Creason,M. et al. 2011. Successful aging shows linkage to chromosomes 6, 7, and 14 in the Amish. Ann.Hum Genet. 75(4):516-528.

Elias,M.F., Beiser,A., Wolf,P.A., Au,R., White,R.F., and D'Agostino,R.B. 2000. The preclinical phase of alzheimer disease: A 22-year prospective study of the Framingham Cohort. Arch.Neurol. 57(6):808-813.

Elliott,R. 2003. Executive functions and their disorders. Br Med Bull. 65:49-59.:49-59.

Epstein,K.R. 2003. The role of carotenoids on the risk of lung cancer. Semin Oncol. 30(1):86-93.

Estaquio,C., Kesse-Guyot,E., Deschamps,V., Bertrais,S., Dauchet,L., Galan,P. et al. 2009. Adherence to the French Programme National Nutrition Sante Guideline Score is associated with better nutrient intake and nutritional status. J Am Diet.Assoc. 109(6):1031-1041.

Etgen,T., Sander,D., Bickel,H., Sander,K., and Forstl,H. 2012. Vitamin D deficiency, cognitive impairment and dementia: a systematic review and meta-analysis. Dement.Geriatr.Cogn Disord. 33(5):297-305.

European Commission. The 2015 Ageing Report: Economic and budgetary projections for the 28 EU Member States (2013-2060). European Economy 3. 2015. Brussels.

Feart,C., Samieri,C., and Barberger-Gateau,P. 2015. Mediterranean diet and cognitive health: an update of available knowledge. Curr Opin Clin Nutr Metab Care. 18(1):51-62.

Ferri,C.P., Prince,M., Brayne,C., Brodaty,H., Fratiglioni,L., Ganguli,M. et al. 2005. Global prevalence of dementia: a Delphi consensus study. Lancet. 366(9503):2112-2117.

Fogli-Cawley,J.J., Dwyer,J.T., Saltzman,E., McCullough,M.L., Troy,L.M., and Jacques,P.F. 2006. The 2005 Dietary Guidelines for Americans Adherence Index: development and application. J Nutr. 136(11):2908-2915.

Folstein,M.F., Folstein,S.E., and McHugh,P.R. 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr.Res. 12(3):189-198.

Fontana,L. and Partridge,L. 2015. Promoting Health and Longevity through Diet: From Model Organisms to Humans. Cell. 161(1):106-118.

Formiga,F., Ferrer,A., Alburquerque,J., Fernandez-Quevedo,M., Royo,C., and Pujol,R. 2012. The challenge of maintaining successful aging at 87 years old: the Octabaix study two-year follow-up. Rejuvenation.Res. 15(6):584-589.

Franceschi,C. and Campisi,J. 2014. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol.A Biol.Sci Med Sci. 69 Suppl 1:S4-9. doi: 10.1093/gerona/glu057.:S4-S9.

Friedman,S.M., Shah,K., and Hall,W.J. 2015. Failing to Focus on Healthy Aging: A Frailty of Our Discipline? J Am Geriatr.Soc. 63(7):1459-1462.

Fries,J.F. 2002. Successful aging--an emerging paradigm of gerontology. Clin Geriatr.Med. 18(3):371-382.

Fuchs,J., Scheidt-Nave,C., Hinrichs,T., Mergenthaler,A., Stein,J., Riedel-Heller,S.G. et al. 2013. Indicators for healthy ageing--a debate. Int J Environ.Res Public Health. 10(12):6630-6644.

Fusco,D., Colloca,G., Lo Monaco,M.R., and Cesari,M. 2007. Effects of antioxidant supplementation on the aging process. Clin Interv.Aging. 2(3):377-387.

Gallagher, J. C. and Sai, A. J. Vitamin D insufficiency, deficiency, and bone health. J Clin Endocrinol Metab. 95, 2630-2633. 2010. United States.

Gallucci,M., Zanardo,A., De,V.L., and Vianello,A. 2004. Homocysteine in Alzheimer disease and vascular dementia. Arch.Gerontol.Geriatr.Suppl. (9):195-200.

Gazzaniga,M., Coquery,J.M., and Macar,F. 2000. Neurosciences cognitives, la biologie de l'esprit. Brussels: De Boeck.

Gibson,R.S. 2005. Principles of nutritional assessment, 2nd ed. New York: Oxford University Press.

Ginde,A.A., Liu,M.C., and Camargo,C.A., Jr. 2009. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. Archives of Internal Medicine 2009/03/25(6):626-632.

Gladyshev,V.N. 2014. The free radical theory of aging is dead. Long live the damage theory! Antioxid.Redox.Signal. 20(4):727-731.

Gomez-Pinilla,F. 2008. Brain foods: the effects of nutrients on brain function. Nature reviews 9(7):568-578.

Goodman,M., Bostick,R.M., Kucuk,O., and Jones,D.P. 2011. Clinical trials of antioxidants as cancer prevention agents: past, present, and future. Free Radic.Biol.Med. 51(5):1068-1084.

Gopinath,B., Russell,J., Kifley,A., Flood,V.M., and Mitchell,P. 2015. Adherence to Dietary Guidelines and Successful Aging Over 10 Years. J Gerontol.A Biol.Sci Med Sci. glv189.

Goralczyk,R. 2009. Beta-carotene and lung cancer in smokers: review of hypotheses and status of research. Nutr Cancer. 61(6):767-774.

Gorbunova,V., Seluanov,A., Mao,Z., and Hine,C. 2007. Changes in DNA repair during aging. Nucleic Acids Res. 35(22):7466-7474.

Gosney,M.A., Hammond,M.F., Shenkin,A., and Allsup,S. 2008. Effect of micronutrient supplementation on mood in nursing home residents. Gerontology. 54(5):292-299.

Graf,C. 2008. The Lawton instrumental activities of daily living (IADL) scale. Medsurg.Nurs. 17(5):343-344.

Graf,C.E., Rossi,C., Giannelli,S.V., Nobari,B.H., Gold,G., Herrmann,F.R. et al. 2014. Vitamin D is not associated with cognitive status in a cohort of very old hospitalized patients. J Alzheimers Dis 42 Suppl 3:S53-S61.

Granic,A., Hill,T.R., Kirkwood,T.B., Davies,K., Collerton,J., Martin-Ruiz,C. et al. 2015. Serum 25-hydroxyvitamin D and cognitive decline in the very old: the Newcastle 85+ Study. Eur J Neurol. 22(1):106-107.

Grant,R.L. 2014. Converting an odds ratio to a range of plausible relative risks for better communication of research findings. BMJ. 348:f7450. doi: 10.1136/bmj.f7450.:f7450.

Greenland,S. and Morgenstern,H. 2001. Confounding in health research. Annu.Rev Public Health. 22:189-212.:189-212.

Greenwood,D.C., Threapleton,D.E., Evans,C.E., Cleghorn,C.L., Nykjaer,C., Woodhead,C. et al. 2013. Glycemic index, glycemic load, carbohydrates, and type 2 diabetes: systematic review and dose-response meta-analysis of prospective studies. Diabetes Care. 36(12):4166-4171.

Grodstein,F., Kang,J.H., Glynn,R.J., Cook,N.R., and Gaziano,J.M. 2007. A randomized trial of beta carotene supplementation and cognitive function in men: the Physicians' Health Study II. Arch.Intern.Med. 167(20):2184-2190.

Gu,Y. and Scarmeas,N. 2011. Dietary patterns in Alzheimer's disease and cognitive aging. Curr.Alzheimer Res. 8(5):510-519.

Guenther,P.M., Casavale,K.O., Reedy,J., Kirkpatrick,S.I., Hiza,H.A., Kuczynski,K.J. et al. 2013. Update of the Healthy Eating Index: HEI-2010. J Acad Nutr Diet. 113(4):569-580.

Guigoz,Y., Lauque,S., and Vellas,B.J. 2002. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. Clin Geriatr.Med. 18(4):737-757.

Guralnik,J.M., Simonsick,E.M., Ferrucci,L., Glynn,R.J., Berkman,L.F., Blazer,D.G. et al. 1994. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 49(2):M85-M94.

Gureje,O., Oladeji,B.D., Abiona,T., and Chatterji,S. 2014. Profile and determinants of successful aging in the Ibadan Study of Ageing. J Am Geriatr.Soc. 62(5):836-842.

Hakansson,A. and Molin,G. 2011. Gut microbiota and inflammation. Nutrients. 3(6):637-682.

Hamer,M., Lavoie,K.L., and Bacon,S.L. 2014. Taking up physical activity in later life and healthy ageing: the English longitudinal study of ageing. Br J Sports Med. 48(3):239-243.

Hamid,T.A., Momtaz,Y.A., and Ibrahim,R. 2012. Predictors and prevalence of successful aging among older Malaysians. Gerontology. 58(4):366-370.

Hank,K. 2011. How "successful" do older Europeans age? Findings from SHARE. J Gerontol.B Psychol.Sci Soc Sci 66(2):230-236.

Hansen-Kyle,L. 2005. A concept analysis of healthy aging. Nurs.Forum. 40(2):45-57.

Harlow,S.D. and Derby,C.A. 2015. Women's Midlife Health: Why the Midlife Matters. Women's Midlife Health 1(5):1-3.

Harman,D. 1992. Free radical theory of aging. Mutat.Res. 275(3-6):257-266.

Harrison,F.E. 2012. A Critical Review of Vitamin C for the Prevention of Age-Related Cognitive Decline and Alzheimer's Disease. J Alzheimers Dis. 29(4):711-726.

Havighurst,R.J. 1961. Successful aging. The Gerontologist 1(1):8-13.

Hebert,J.R., Clemow,L., Pbert,L., Ockene,I.S., and Ockene,J.K. 1995. Social desirability bias in dietary self-report may compromise the validity of dietary intake measures. Int J Epidemiol. 24(2):389-398.

Hebert,J.R., Hurley,T.G., Peterson,K.E., Resnicow,K., Thompson,F.E., Yaroch,A.L. et al. 2008. Social desirability trait influences on self-reported dietary measures among diverse participants in a multicenter multiple risk factor trial. J Nutr. 138(1):226S-234S.

Hemilä,H. and Kaprio,J. 2011a. Subgroup analysis of large trials can guide further research: a case study of vitamin E and pneumonia. Clin Epidemiol 3(1):51-59.

Hemilä,H. and Kaprio,J. 2009. Modification of the effect of vitamin E supplementation on the mortality of male smokers by age and dietary vitamin C. Am J Epidemiol. 169(8):946-953.

Hemilä,H. and Kaprio,J. 2011b. Vitamin E may affect the life expectancy of men, depending on dietary vitamin C intake and smoking. Age Ageing. 40(2):215-220.

Hercberg S. 2005. Table de composition SU.VI.MAX des aliments. Paris: Les éditions INSERM/Economica.

Hercberg,S., Castetbon,K., Czernichow,S., Malon,A., Mejean,C., Kesse,E. et al. 2010a. The Nutrinet-Sante Study: a web-based prospective study on the relationship between nutrition and health and determinants of dietary patterns and nutritional status. BMC.Public Health 10(1):242.

Hercberg,S., Chat-Yung,S., and Chaulia,M. 2008. The French National Nutrition and Health Program: 2001-2006-2010. Int J Public Health. 53(2):68-77.

Hercberg,S., Galan,P., Preziosi,P., Bertrais,S., Mennen,L., Malvy,D. et al. 2004. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. Arch.Intern.Med. 164(21):2335-2342.

Hercberg,S., Kesse-Guyot,E., Druesne-Pecollo,N., Touvier,M., Favier,A., Latino-Martel,P. et al. 2010b. Incidence of cancers, ischemic cardiovascular diseases and mortality during 5-year follow-up after stopping antioxidant vitamins and minerals supplements: a postintervention follow-up in the SU.VI.MAX Study. Int J Cancer. 127(8):1875-1881.

Hercberg,S., Preziosi,P., Briancon,S., Galan,P., Triol,I., Malvy,D. et al. 1998. A primary prevention trial using nutritional doses of antioxidant vitamins and minerals in cardiovascular diseases and cancers in a general population: the SU.VI.MAX study--design, methods, and participant characteristics. SUpplementation en VItamines et Mineraux AntioXydants. Control Clin Trials. 19(4):336-351.

Hodge,A.M., O'Dea,K., English,D.R., Giles,G.G., and Flicker,L. 2014. Dietary patterns as predictors of successful ageing. J Nutr Health Aging. 18(3):221-227.

Hof,P.R., Bierer,L.M., Perl,D.P., Delacourte,A., Buee,L., Bouras,C. et al. 1992. Evidence for early vulnerability of the medial and inferior aspects of the temporal lobe in an 82-year-old patient with preclinical signs of dementia. Regional and laminar distribution of neurofibrillary tangles and senile plaques. Arch.Neurol. 49(9):946-953.

Hoffmann,K., Schulze,M.B., Schienkiewitz,A., Nothlings,U., and Boeing,H. 2004. Application of a new statistical method to derive dietary patterns in nutritional epidemiology. American journal of epidemiology 159(10):935-944.

Holden,C.A., Collins,V.R., Handelsman,D.J., Jolley,D., and Pitts,M. 2014. Healthy aging in a cross-sectional study of Australian men: what has sex got to do with it? Aging Male. 17(1):25-29.

Holick,M.F. 2007. Vitamin D deficiency. N.Engl.J.Med. 357(3):266-281.

Holstein,M.B. and Minkler,M. 2003. Self, society, and the "new gerontology". Gerontologist. 43(6):787-796.

Hossein-nezhad,A. and Holick,M.F. 2013. Vitamin D for health: a global perspective. 88(7):720-755.

Howitz,K.T. and Sinclair,D.A. 2008. Xenohormesis: sensing the chemical cues of other species. Cell. 133(3):387-391.

Hsu,H.C. 2011. Impact of morbidity and life events on successful aging. Asia Pac.J Public Health. 23(4):458-469.

Hu,F.B. 2002. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 13(1):3-9.

Hugenschmidt,C.E., Burdette,J.H., Morgan,A.R., Williamson,J.D., Kritchevsky,S.B., and Laurienti,P.J. 2014. Graph Theory Analysis of Functional Brain Networks and Mobility Disability in Older Adults. J Gerontol.A Biol.Sci Med Sci. 69(11):1399-1406.

Ittner,L.M. and Gotz,J. 2011. Amyloid-beta and tau--a toxic pas de deux in Alzheimer's disease. Nat Rev Neurosci. 12(2):65-72.

Jacobs,D.R., Jr., Gross,M.D., and Tapsell,L.C. 2009. Food synergy: an operational concept for understanding nutrition. Am.J.Clin.Nutr. 89(5):1543S-1548S.

Jacques,P.F. and Tucker,K.L. 2001. Are dietary patterns useful for understanding the role of diet in chronic disease? Am J Clin Nutr. 73(1):1-2.

Jang,S.N., Choi,Y.J., and Kim,D.H. 2009. Association of socioeconomic status with successful ageing: differences in the components of successful ageing. J Biosoc.Sci. 41(2):207-219.

Jeste,D.V., Depp,C.A., and Vahia,I.V. 2010. Successful cognitive and emotional aging. World Psychiatry. 9(2):78-84.

Jopp,D.S., Wozniak,D., Damarin,A.K., De,F.M., Jung,S., and Jeswani,S. 2015. How could lay perspectives on successful aging complement scientific theory? Findings from a u.s. And a German life-span sample. Gerontologist. 55(1):91-106.

Jorm,A.F., Christensen,H., Henderson,A.S., Jacomb,P.A., Korten,A.E., and Mackinnon,A. 1998. Factors Associated with Successful Ageing. Australasian Journal on Ageing 17(1):33-37.

Julia,C., Meunier,N., Touvier,M., Ahluwalia,N., Sapin,V., Papet,I. et al. 2013. Dietary patterns and risk of elevated C-reactive protein concentrations 12 years later. Br J Nutr. 110(4):747-754.

Kahana,E., Kahana,B., and Lee,J.E. 2014. Proactive Approaches to Successful Aging: One Clear Path through the Forest. Gerontology. 60(5):466-474.

Kant,A.K. 2004. Dietary patterns and health outcomes. J.Am.Diet.Assoc. 104(4):615-635.

Kant,A.K. 2010. Dietary patterns: biomarkers and chronic disease risk. Appl.Physiol Nutr Metab. 35(2):199-206.

Kant,A.K., Block,G., Schatzkin,A., Ziegler,R.G., and Nestle,M. 1991. Dietary diversity in the US population, NHANES II, 1976-1980. J Am Diet.Assoc. 91(12):1526-1531.

Kaplan,M.S., Huguet,N., Orpana,H., Feeny,D., McFarland,B.H., and Ross,N. 2008. Prevalence and factors associated with thriving in older adulthood: a 10-year population-based study. J Gerontol.A Biol.Sci Med Sci. 63(10):1097-1104.

Katz,S. and Calasanti,T. 2014. Critical Perspectives on Successful Aging: Does It "Appeal More Than It Illuminates"? Gerontologist. 55(1):26-33.

Katz,S. 2013. Active and Successful Aging. Lifestyle as a Gerontological Idea. Recherches sociologiques et anthropologiques 44(1):33-49.

Kennedy,E.T., Ohls,J., Carlson,S., and Fleming,K. 1995. The Healthy Eating Index: design and applications. Journal of the American Dietetic Association 95(10):1103-1108.

Kesse-Guyot,E., Andreeva,V.A., Lassale,C., Ferry,M., Jeandel,C., Hercberg,S. et al. 2013. Mediterranean diet and cognitive function: a French study. Am J Clin Nutr. 97(2):369-376.

Kesse-Guyot,E., Fezeu,L., Andreeva,V.A., Touvier,M., Scalbert,A., Hercberg,S. et al. 2012. Total and specific polyphenol intakes in midlife are associated with cognitive function measured 13 years later. J.Nutr. 142(1):76-83.

Kesse-Guyot,E., Fezeu,L., Galan,P., Hercberg,S., Czernichow,S., and Castetbon,K. 2011a. Adherence to French nutritional guidelines is associated with lower risk of metabolic syndrome. J Nutr. 141(6):1134-1139.

Kesse-Guyot,E., Fezeu,L., Jeandel,C., Ferry,M., Andreeva,V., Amieva,H. et al. 2011b. French adults' cognitive performance after daily supplementation with antioxidant vitamins and minerals at nutritional doses: a post hoc analysis of the Supplementation in Vitamins and Mineral Antioxidants (SU.VI.MAX) trial. Am J Clin Nutr. 94(3):892-899.

Kesse-Guyot,E., Fezeu,L., Jeandel,C., Ferry,M., Andreeva,V., Amieva,H. et al. 2011c. French adults' cognitive performance after daily supplementation with antioxidant vitamins and minerals at nutritional doses: a post hoc analysis of the Supplementation in Vitamins and Mineral Antioxidants (SU.VI.MAX) trial. Am J Clin Nutr. 94(3):892-899.

Kesse-Guyot,E., Touvier,M., Henegar,A., Czernichow,S., Galan,P., Hercberg,S. et al. 2011d. Higher adherence to French dietary guidelines and chronic diseases in the prospective SU.VI.MAX cohort. Eur.J.Clin.Nutr. 65(8):887-894.

Khansari,N., Shakiba,Y., and Mahmoudi,M. 2009. Chronic inflammation and oxidative stress as a major cause of age-related diseases and cancer. Recent Pat Inflamm.Allergy Drug Discov. 3(1):73-80.

Khaw,K.T. 1997. Healthy aging. British Medical Journal 315(7115):1090-1096.

Kiefte-de Jong,J.C., Mathers,J.C., and Franco,O.H. 2014. Nutrition and healthy ageing: the key ingredients. Proc.Nutr.Soc. 73(2):249-259.

Kim,S., Haines,P.S., Siega-Riz,A.M., and Popkin,B.M. 2003. The Diet Quality Index-International (DQI-I) provides an effective tool for cross-national comparison of diet quality as illustrated by China and the United States. J Nutr. 133(11):3476-3484.

Kivimäki,M. and Ferrie,J.E. 2011. Epidemiology of healthy ageing and the idea of more refined outcome measures. International Journal of Epidemiology 40(4):845-847.

Knekt,P., Sääksjärvi,K., Järvinen,R., Marniemi,J., Männistö,S., Kanerva,N. et al. 2014. Serum 25-hydroxyvitamin d concentration and risk of dementia. Epidemiology 25(6):799-804.

Knudsen,C.S., Nexo,E., Hojskov,C.S., and Heickendorff,L. 2012. Analytical validation of the Roche 25-OH Vitamin D Total assay. 50(11):1965-1968.

Kok,A.A., Aartsen,M.J., Deeg,D.J., and Huisman,M. 2015. Capturing the Diversity of Successful Aging: An Operational Definition Based on 16-Year Trajectories of Functioning. Gerontologist. [epub ahead of print. DOI: 10.1093/geront/gnv127].

Kontogianni,M.D. and Panagiotakos,D.B. 2014. Dietary patterns and stroke: A systematic review and re-meta-analysis. Maturitas 79(1):41-47.

Kourlaba,G. and Panagiotakos,D.B. 2009. Dietary quality indices and human health: a review. Maturitas 62(1):1-8.

Krebs-Smith,S.M., Smiciklas-Wright,H., Guthrie,H.A., and Krebs-Smith,J. 1987. The effects of variety in food choices on dietary quality. J Am Diet.Assoc. 87(7):897-903.

Kriska,A.M., Knowler,W.C., LaPorte,R.E., Drash,A.L., Wing,R.R., Blair,S.N. et al. 1990. Development of questionnaire to examine relationship of physical activity and diabetes in Pima Indians. Diabetes Care. 13(4):401-411.

Kruman,I.I., Kumaravel,T.S., Lohani,A., Pedersen,W.A., Cutler,R.G., Kruman,Y. et al. 2002. Folic acid deficiency and homocysteine impair DNA repair in hippocampal neurons and sensitize them to amyloid toxicity in experimental models of Alzheimer's disease. J Neurosci. 22(5):1752-1762.

Kuh,D. 2007. A life course approach to healthy aging, frailty, and capability. J Gerontol.A Biol.Sci Med Sci. 62(7):717-721.

Kuh,D., Copper,R., Hardy,R., Richards,M., and Ben-Shlomo,Y. 2014. A Life Course Approach to Healthy Ageing (Life Course Approach to Adult Health). Oxford: Oxford University Press.

Lafortune, G. and Balestat, G. Trends in severe disability among elderly people. Assessing the evidence in 12 OECD countries and the future implications. Organization for Economic Cooperation and Development. 2007. Paris.

Lafortune,L., Martin,S., Kelly,S., Kuhn,I., Remes,O., Cowan,A. et al. 2016. Behavioural Risk Factors in Mid-Life Associated with Successful Ageing, Disability, Dementia and Frailty in Later Life: A Rapid Systematic Review. PLoS One. 11(2):e0144405.

Lamb,S. 2014. Permanent personhood or meaningful decline? Toward a critical anthropology of successful aging. J Aging Stud. 29:41-52. doi: 10.1016/j.jaging.2013.12.006. Epub;%2014 Jan 31.:41-52.

Langevin,V., François,M., Boini,S., and Riou,A. 2011. Center for Epidemiologic Studies-Depression Scale (CES-D). Documents pour le Médecin du Travail 127:475-480.

Lara,J., Cooper,R., Nissan,J., Ginty,A.T., Khaw,K.T., Deary,I.J. et al. 2015. A proposed panel of biomarkers of healthy ageing. BMC Med. 13:222. doi: 10.1186/s12916-015-0470-9.:222-0470.

Lasfargues,G., Vol,S., Le,C.H., Bedouet,M., Hagel,L., Constans,T. et al. 1990. Validity of a short self-administered dietary questionnaire compared with a dietetic interview [in French]. Presse Med. 19(20):953-957.

Lassale,C., Fezeu,L., Andreeva,V.A., Hercberg,S., Kengne,A.P., Czernichow,S. et al. 2012. Association between dietary scores and 13-year weight change and obesity risk in a French prospective cohort. Int J Obes (Lond). 36(11):1455-1462.

Latino-Martel,P., Cottet,V., Druesne-Pecollo,N., Pierre,F.H., Touillaud,M., Touvier,M. et al. 2016. Alcoholic beverages, obesity, physical activity and other nutritional factors, and cancer risk: A review of the evidence. Crit Rev Oncol.Hematol. (16):10.

Le Moullec,N., Deheeger,M., Preziosi,P., Montero,P., Valeix,P., Rolland-Cachera,M.F. et al. 1996. Validation du manuel photos utilisé pour l'enquête alimentaire de l'étude SU.VI.MAX. Cahier de Nutrition et de Diététique 31(3):158-164.

Lee,Y.H., Kim,J.H., and Song,G.G. 2014. Vitamin D receptor polymorphisms and susceptibility to Parkinson's disease and Alzheimer's disease: a meta-analysis. Neurol.Sci. 35(12):1947-1953.

Lehert,P., Villaseca,P., Hogervorst,E., Maki,P.M., and Henderson,V.W. 2015. Individually modifiable risk factors to ameliorate cognitive aging: a systematic review and meta-analysis. Climacteric. 18(5):678-689.

Leplege,A., Ecosse,E., Verdier,A., and Perneger,T.V. 1998. The French SF-36 Health Survey: translation, cultural adaptation and preliminary psychometric evaluation. J Clin Epidemiol. 51(11):1013-1023.

Letenneur,L., Proust-Lima,C., Le,G.A., Dartigues,J.F., and Barberger-Gateau,P. 2007. Flavonoid intake and cognitive decline over a 10-year period. Am J Epidemiol. 165(12):1364-1371.

Lezak,M.D., Howieson,D.B., and Loring,D.W. 2004. Neuropsychological Assessment. New York, NY: Oxford University Press.

Li,C., Wu,W., Jin,H., Zhang,X., Xue,H., He,Y. et al. 2006. Successful aging in Shanghai, China: definition, distribution and related factors. Int Psychogeriatr. 18(3):551-563.

Li,Y., Daniel,M., and Tollefsbol,T.O. 2011. Epigenetic regulation of caloric restriction in aging. BMC Med. 9:98. doi: 10.1186/1741-7015-9-98.:98-99.

Liang,J. and Luo,B. 2012. Toward a discourse shift in social gerontology: From successful aging to harmonious aging. Journal of Aging Studies 26(3):327-334.

Liochev,S.I. 2013. Reactive oxygen species and the free radical theory of aging. Free Radic.Biol.Med. 60:1-4.

Littlejohns,T.J., Henley,W.E., Lang,I.A., Annweiler,C., Beauchet,O., Chaves,P.H. et al. 2014. Vitamin D and the risk of dementia and Alzheimer disease. Neurology. 83(10):920-928.

Llewellyn,D.J., Lang,I.A., Langa,K.M., Muniz-Terrera,G., Phillips,C.L., Cherubini,A. et al. 2010. Vitamin D and risk of cognitive decline in elderly persons. Arch.Intern.Med. 170(13):1135-1141.

Ma,Y., Olendzki,B.C., Pagoto,S.L., Hurley,T.G., Magner,R.P., Ockene,I.S. et al. 2009. Number of 24-hour diet recalls needed to estimate energy intake. Ann.Epidemiol. 19(8):553-559.

MacMahon,B. and Pugh,T.F. 1970. Epidemiology: principles and methods. Boston: Little Brown and Compagny.

Major,J.M., Graubard,B.I., Dodd,K.W., Iwan,A., Alexander,B.H., Linet,M.S. et al. 2013. Variability and reproducibility of circulating vitamin D in a nationwide U.S. population. 98(1):97-104.

Malaguarnera,M., Ferri,R., Bella,R., Alagona,G., Carnemolla,A., and Pennisi,G. 2004. Homocysteine, vitamin B12 and folate in vascular dementia and in Alzheimer disease. Clin Chem Lab Med. 42(9):1032-1035.

Martin,A. 2001. Apports nutritionnels conseillés pour la population Française. Paris: Tec & Doc, Lavoisier.

Martin,P., Kelly,N., Kahana,B., Kahana,E., Willcox,J., Willcox,D.C. et al. 2014. Defining Successful Aging: A Tangible or Elusive Concept? Gerontologist. gnu044.

Martinson,M. and Berridge,C. 2015. Successful Aging and Its Discontents: A Systematic Review of the Social Gerontology Literature. Gerontologist. 55(1):58-69.

Maserejian,N.N., Hall,S.A., and McKinlay,J.B. 2012. Low dietary or supplemental zinc is associated with depression symptoms among women, but not men, in a population-based epidemiological survey. J Affect.Disord. 136(3):781-788.

Mathers,J.C. 2013. Nutrition and ageing: knowledge, gaps and research priorities. Proc Nutr Soc. 72(2):246-250.

McCullough,M.L., Feskanich,D., Stampfer,M.J., Giovannucci,E.L., Rimm,E.B., Hu,F.B. et al. 2002. Diet quality and major chronic disease risk in men and women: moving toward improved dietary guidance. Am J Clin Nutr. 76(6):1261-1271.

McKee,K.J. and Schutz,B. 2015. Psychosocial factors in healthy ageing. Psychology & Health 30(6):607-626.

McLaughlin,S.J., Connell,C.M., Heeringa,S.G., Li,L.W., and Roberts,J.S. 2010. Successful aging in the United States: prevalence estimates from a national sample of older adults. J Gerontol.B Psychol.Sci Soc Sci. 65B(2):216-226.

McLaughlin,S.J., Jette,A.M., and Connell,C.M. 2012. An examination of healthy aging across a conceptual continuum: prevalence estimates, demographic patterns, and validity. J Gerontol.A Biol.Sci Med Sci 67(7):783-789.

McNamee,R. 2003. Confounding and confounders. Occup.Environ.Med. 60(3):227-234.

Meneilly,G.S. and Tessier,D.M. 2016. Diabetes, Dementia and Hypoglycemia. Can.J Diabetes. 40(1):73-76.

Mennen,L.I., Bertrais,S., Galan,P., Arnault,N., Potier de,C.G., and Hercberg,S. 2002. The use of computerised 24 h dietary recalls in the French SU.VI.MAX Study: number of recalls required. Eur J Clin Nutr. 56(7):659-665.

Mente,A., de,K.L., Shannon,H.S., and Anand,S.S. 2009. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Arch.Intern.Med. 169(7):659-669.

Messier,C. 2005. Impact of impaired glucose tolerance and type 2 diabetes on cognitive aging. Neurobiol.Aging. 26 Suppl 1:26-30.

Middleton,L.E. and Yaffe,K. 2009. Promising strategies for the prevention of dementia. Arch.Neurol. 66(10):1210-1215.

Milaneschi,Y., Bandinelli,S., Corsi,A.M., Lauretani,F., Paolisso,G., Dominguez,L.J. et al. 2011. Mediterranean diet and mobility decline in older persons. Exp Gerontol. 46(4):303-308.

Milaneschi,Y., Tanaka,T., and Ferrucci,L. 2010. Nutritional determinants of mobility. Curr Opin Clin Nutr Metab Care. 13(6):625-629.

Miller,A.L. 2003. The methionine-homocysteine cycle and its effects on cognitive diseases. Altern.Med Rev. 8(1):7-19.

Minkler,M. 1990. Aging and disability: Behind and beyond the stereotypes. Journal of Aging Studies 4(3):245-260.

Moon,J.H., Lim,S., Han,J.W., Kim,K.M., Choi,S.H., Kim,K.W. et al. 2015. Serum 25-hydroxyvitamin D level and the risk of mild cognitive impairment and dementia: the Korean Longitudinal Study on Health and Aging (KLoSHA). Clin Endocrinol.(Oxf). 83(1):36-42.

Morin,A.J., Moullec,G., Maiano,C., Layet,L., Just,J.L., and Ninot,G. 2011. Psychometric properties of the Center for Epidemiologic Studies Depression Scale (CES-D) in French clinical and nonclinical adults. Rev Epidemiol Sante Publique. 59(5):327-340.

Morley,J.E. 2009. Successful aging or aging successfully. J Am Med Dir.Assoc. 10(2):85-86.

Morris,M.C., Tangney,C.C., Wang,Y., Sacks,F.M., Barnes,L.L., Bennett,D.A. et al. 2015. MIND diet slows cognitive decline with aging. Alzheimers Dement. 11(9):1015-1022.

Mozaffarian,D., Appel,L.J., and Van Horn,L. 2011. Components of a cardioprotective diet: new insights. Circulation 123(24):2870-2891.

Myung,S.K., Ju,W., Cho,B., Oh,S.W., Park,S.M., Koo,B.K. et al. 2013. Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials. BMJ. 346:f10.

Myung,S.K., Kim,Y., Ju,W., Choi,H.J., and Bae,W.K. 2010. Effects of antioxidant supplements on cancer prevention: meta-analysis of randomized controlled trials. Ann.Oncol. 21(1):166-179.

Nève, J., Chamart, S., and Molle, L. Optimisation of a direct procedure of selenium in plasma and erythrocyte using Zeeman effect atomic absorption spectrometry. Bratter, P. and Schamer, P. Trace Element Analytical Chemistry in Medicine and Biology. 4, 1-10. 1987. Berlin, Walter de Gruyter.

Newby,P.K. and Tucker,K.L. 2004. Empirically derived eating patterns using factor or cluster analysis: a review. Nutr Rev. 62(5):177-203.

Newman,A.B., Arnold,A.M., Naydeck,B.L., Fried,L.P., Burke,G.L., Enright,P. et al. 2003. "Successful aging": effect of subclinical cardiovascular disease. Arch.Intern.Med. 163(19):2315-2322.

Ng,T.P., Broekman,B.F., Niti,M., Gwee,X., and Kua,E.H. 2009. Determinants of successful aging using a multidimensional definition among Chinese elderly in Singapore. Am J Geriatr.Psychiatry. 17(5):407-416.

Nohr,E.A., Frydenberg,M., Henriksen,T.B., and Olsen,J. 2006. Does low participation in cohort studies induce bias? Epidemiology. 17(4):413-418.

Nooyens,A.C., Milder,I.E., van Gelder,B.M., Bueno-de-Mesquita,H.B., van Boxtel,M.P., and Verschuren,W.M. 2015. Diet and cognitive decline at middle age: the role of antioxidants. Br J Nutr. 113(9):1410-1417.

Nosraty,L., Sarkeala,T., Hervonen,A., and Jylha,M. 2012. Is there successful aging for nonagenarians? The vitality 90+ study. J Aging Res. Volume 2012 (2012), Article ID 868797, 9 pages.

O'Bryant,S.E., Humphreys,J.D., Smith,G.E., Ivnik,R.J., Graff-Radford,N.R., Petersen,R.C. et al. 2008. Detecting dementia with the mini-mental state examination in highly educated individuals. Arch.Neurol. 65(7):963-967.

Ocké,M.C. 2013. Evaluation of methodologies for assessing the overall diet: dietary quality scores and dietary pattern analysis. Proc.Nutr.Soc. 72(2):191-199.

Ory,M.G., Anderson,L.A., Friedman,D.B., Pulczinski,J.C., Eugene,N., and Satariano,W.A. 2014. Cancer prevention among adults aged 45-64 years: setting the stage. Am J Prev.Med. 46(3 Suppl 1):S1-S6.

Ouwehand,C., de Ridder,D.T., and Bensing,J.M. 2007. A review of successful aging models: proposing proactive coping as an important additional strategy. Clin Psychol.Rev. 27(8):873-884.

Palmore,E. 1979. Predictors of successful aging. Gerontologist. 19(5 Pt 1):427-431.

Patterson,R.E., Haines,P.S., and Popkin,B.M. 1994. Diet quality index: capturing a multidimensional behavior. Journal of the American Dietetic Association 94(1):57-64.

Peel,N., Bartlett,H., and McClure,R. 2004. Healthy ageing: how is it defined and measured? Australasian Journal on Ageing 23(3):115-119.

Pendlebury,S.T., Cuthbertson,F.C., Welch,S.J., Mehta,Z., and Rothwell,P.M. 2010. Underestimation of cognitive impairment by Mini-Mental State Examination versus the Montreal Cognitive Assessment in patients with transient ischemic attack and stroke: a population-based study. Stroke. 41(6):1290-1293.

Pereira,P.C. 2014. Milk nutritional composition and its role in human health. Nutrition. 30(6):619-627.

Perez-Lopez,F.R., Chedraui,P., and Fernandez-Alonso,A.M. 2011. Vitamin D and aging: beyond calcium and bone metabolism. Maturitas 69(1):27-36.

Perna,L., Mons,U., Kliegel,M., and Brenner,H. 2014. Serum 25-hydroxyvitamin D and cognitive decline: a longitudinal study among non-demented older adults. Dement.Geriatr.Cogn Disord. 38(3-4):254-263.

Peterson,N.M. and Martin,P. 2015. Tracing the origins of success: implications for successful aging. Gerontologist. 55(1):5-13.

Phelan,E.A. and Larson,E.B. 2002. "Successful aging"--where next? J Am Geriatr.Soc 50(7):1306-1308.

Pietrzak,R.H., Maruff,P., Mayes,L.C., Roman,S.A., Sosa,J.A., and Snyder,P.J. 2008. An examination of the construct validity and factor structure of the Groton Maze Learning Test, a new measure of spatial working memory, learning efficiency, and error monitoring. Arch.Clin Neuropsychol. 23(4):433-445.

Plassman,B.L., Williams,J.W., Jr., Burke,J.R., Holsinger,T., and Benjamin,S. 2010. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. Ann.Intern.Med. 153(3):182-193.

Poljsak,B., Suput,D., and Milisav,I. 2013. Achieving the balance between ROS and antioxidants: when to use the synthetic antioxidants. Oxid.Med Cell Longev. Volume 2013 (2013), Article ID 956792, 11 pages.

Pope,S.K., Shue,V.M., and Beck,C. 2003. Will a healthy lifestyle help prevent Alzheimer's disease? Annu.Rev.Public Health 24:111-132.

Pruchno,R. 2015. Successful aging: contentious past, productive future. Gerontologist. 55(1):1-4.

Pruchno,R.A. and Wilson-Genderson,M. 2014. A Longitudinal Examination of the Effects of Early Influences and Midlife Characteristics on Successful Aging. J Gerontol.B Psychol.Sci Soc Sci. 70(6):850-859.

Pruchno,R.A., Wilson-Genderson,M., and Cartwright,F. 2010. A two-factor model of successful aging. J Gerontol.B Psychol.Sci Soc Sci. 65(6):671-679.

Puig-Domingo,M., Serra-Prat,M., Merino,M.J., Pubill,M., Burdoy,E., and Papiol,M. 2008. Muscle strength in the Mataro aging study participants and its relationship to successful aging. Aging Clin Exp Res. 20(5):439-446.

Quadri,P., Fragiacomo,C., Pezzati,R., Zanda,E., Forloni,G., Tettamanti,M. et al. 2004. Homocysteine, folate, and vitamin B-12 in mild cognitive impairment, Alzheimer disease, and vascular dementia. Am J Clin Nutr. 80(1):114-122.

Radloff,L. 1977. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Appl.Psychol.Meas. 1:385-401.

Rafnsson,S.B., Dilis,V., and Trichopoulou,A. 2013. Antioxidant nutrients and age-related cognitive decline: a systematic review of population-based cohort studies. Eur J Nutr. 52(6):1553-1567.

Ragland,D.R. 1992. Dichotomizing continuous outcome variables: dependence of the magnitude of association and statistical power on the cutpoint. Epidemiology. 3(5):434-440.

Reed,D.M., Foley,D.J., White,L.R., Heimovitz,H., Burchfiel,C.M., and Masaki,K. 1998. Predictors of healthy aging in men with high life expectancies. Am J Public Health. 88(10):1463-1468.

Reuter,S., Gupta,S.C., Chaturvedi,M.M., and Aggarwal,B.B. 2010. Oxidative stress, inflammation, and cancer: how are they linked? Free Radic.Biol.Med. 49(11):1603-1616.

Ristow,M., Zarse,K., Oberbach,A., Kloting,N., Birringer,M., Kiehntopf,M. et al. 2009. Antioxidants prevent health-promoting effects of physical exercise in humans. Proc Natl Acad Sci U S A. 106(21):8665-8670.

Ritchie,K., Carriere,I., Berr,C., Amieva,H., Dartigues,J.F., Ancelin,M.L. et al. 2016. The clinical picture of Alzheimer's disease in the decade before diagnosis: clinical and biomarker trajectories. J Clin Psychiatry. [epub ahead of print. DOI: 10.4088/JCP.15m09989].

Ritchie,S.A. and Connell,J.M. 2007. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. Nutr Metab Cardiovasc Dis. 17(4):319-326.

Rooney,R.F. 2014. Preventing dementia: how lifestyle in midlife affects risk. Curr Opin Psychiatry. 27(2):149-157.

Roos,N.P. and Havens,B. 1991. Predictors of successful aging: a twelve-year study of Manitoba elderly. Am J Public Health. 81(1):63-68.

Rowe,J.W. and Kahn,R.L. 1987. Human Aging - Usual and Successful. Science 237(4811):143-149.

Rowe,J.W. and Kahn,R.L. 1997. Successful aging. Gerontologist 37(4):433-440.

Rowe,J.W.B.L.F.B.R.B.-S.A.C.J.C.L. 2010. Policies and politics for an aging America. The MacArthur Foundation Research Network on an Aging Society: Contexts 9:22-27.

Roy,R., Hebden,L., Rangan,A., and Allman-Farinelli,M. 2015. The development, application, and validation of a Healthy eating index for Australian Adults (HEIFA-2013). Nutrition. (15):10.

Rubinstein,R.L. and deMedeiros,K. 2015. "Successful aging," gerontological theory and neoliberalism: a qualitative critique. Gerontologist. 55(1):34-42.

Rumawas,M.E., Meigs,J.B., Dwyer,J.T., McKeown,N.M., and Jacques,P.F. 2009. Mediterranean-style dietary pattern, reduced risk of metabolic syndrome traits, and incidence in the Framingham Offspring Cohort. The American journal of clinical nutrition 90(6):1608-1614.

Russell,J., Flood,V., Rochtchina,E., Gopinath,B., Allman-Farinelli,M., Bauman,A. et al. 2013. Adherence to dietary guidelines and 15-year risk of all-cause mortality. Br J Nutr. 109(3):547-555.

Russell,R.M. 2004. The enigma of beta-carotene in carcinogenesis: what can be learned from animal studies. J Nutr. 134(1):262S-268S.

Ryff,C.D. 1982. Successful Aging - A Developmental-Approach. Gerontologist 22(2):209-214.

Sabia,S., Nabi,H., Kivimaki,M., Shipley,M.J., Marmot,M.G., and Singh-Manoux,A. 2009. Health behaviors from early to late midlife as predictors of cognitive function: The Whitehall II study. Am.J Epidemiol. 170(4):428-437.

Sabia,S., Singh-Manoux,A., Hagger-Johnson,G., Cambois,E., Brunner,E.J., and Kivimaki,M. 2012. Influence of individual and combined healthy behaviours on successful aging. CMAJ. 184(18):1985-1992.

Salmon,A.B., Richardson,A., and Perez,V.I. 2010. Update on the oxidative stress theory of aging: does oxidative stress play a role in aging or healthy aging? Free Radic.Biol.Med. 48(5):642-655.

Samieri,C., Sun,Q., Townsend,M.K., Chiuve,S.E., Okereke,O.I., Willett,W.C. et al. 2013. The association between dietary patterns at midlife and health in aging: an observational study. Ann.Intern.Med. 159(9):584-591.

Samieri,C., Sun,Q., Townsend,M.K., Rimm,E.B., and Grodstein,F. 2014. Dietary flavonoid intake at midlife and healthy aging in women. Am J Clin Nutr. 100(6):1489-1497.

Sanders,T.A. 2003. High- versus low-fat diets in human diseases. Curr Opin Clin Nutr Metab Care 6(2):151-155.

Sanz,A. and Stefanatos,R.K. 2008. The mitochondrial free radical theory of aging: a critical view. Curr Aging Sci. 1(1):10-21.

Sarnak,M.J., Katz,R., Fried,L.F., Siscovick,D., Kestenbaum,B., Seliger,S. et al. 2008. Cystatin C and aging success. Arch.Intern.Med. 168(2):147-153.

Scheidt R.J., Humpherys,D.R., and Yorgason J.B. 1999. Successful Aging: What's Not to Like? Journal of Applied Gerontology 18(3):277-282.

Schneider,A.L., Lutsey,P.L., Alonso,A., Gottesman,R.F., Sharrett,A.R., Carson,K.A. et al. 2014. Vitamin D and cognitive function and dementia risk in a biracial cohort: the ARIC Brain MRI Study. 21(9):1211-8, e69.

Schulz,L.O., Harper,I.T., Smith,C.J., Kriska,A.M., and Ravussin,E. 1994. Energy intake and physical activity in Pima Indians: comparison with energy expenditure measured by doubly-labeled water. Obes Res. 2(6):541-548.

Schulz,R. and Heckhausen,J. 1996. A life span model of successful aging. American Psychologist 51(7):702-714.

Schulze,M.B., Hoffmann,K., Kroke,A., and Boeing,H. 2003. An approach to construct simplified measures of dietary patterns from exploratory factor analysis. Br.J Nutr 89(3):409-419.

Seaman,S.R. and White,I.R. 2011. Review of inverse probability weighting for dealing with missing data. Stat.Methods Med.Res. 22(3):278-295.

Shammas,M.A. 2011. Telomeres, lifestyle, cancer, and aging. Curr Opin Clin Nutr Metab Care. 14(1):28-34.

Shim,J.S., Oh,K., and Kim,H.C. 2014. Dietary assessment methods in epidemiologic studies. Epidemiol Health. Volume: 36, Article ID: e2014009, 8 pages.

Shivappa,N., Steck,S.E., Hurley,T.G., Hussey,J.R., and Hebert,J.R. 2014. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr. 17(8):1689-1696.

Silverstein,M. 2015. Foreword (and farewell). J Gerontol.B Psychol.Sci Soc Sci. 70(1):85-86.

Singh-Manoux,A. and Kivimaki,M. 2010. The importance of cognitive aging for understanding dementia. Age (Dordr.) 32(4):509-512.

Singh-Manoux,A., Sabia,S., Bouillon,K., Brunner,E.J., Grodstein,F., Elbaz,A. et al. 2014. Association of body mass index and waist circumference with successful aging. Obesity (Silver.Spring). 22(4):1172-1178.

Slinin,Y., Paudel,M., Taylor,B.C., Ishani,A., Rossom,R., Yaffe,K. et al. 2012. Association between serum 25(OH) vitamin D and the risk of cognitive decline in older women. J Gerontol.A Biol.Sci Med Sci. 67(10):1092-1098.

Slinin,Y., Paudel,M.L., Taylor,B.C., Fink,H.A., Ishani,A., Canales,M.T. et al. 2010. 25-Hydroxyvitamin D levels and cognitive performance and decline in elderly men. Neurology. 74(1):33-41.

Sofi,F., Abbate,R., Gensini,G.F., and Casini,A. 2010. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. Am.J.Clin.Nutr. 92(5):1189-1196.

Sofi,F., Macchi,C., Abbate,R., Gensini,G.F., and Casini,A. 2013. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public health nutrition 17(12):2769-2782.

Sofi,F., Macchi,C., Abbate,R., Gensini,G.F., and Casini,A. 2014. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr. 17(12):2769-2782.

Sohal,R.S. and Orr,W.C. 2012. The redox stress hypothesis of aging. Free Radic.Biol.Med. 52(3):539-555.

Song,Y., Wang,L., Pittas,A.G., Del Gobbo,L.C., Zhang,C., Manson,J.E. et al. 2013. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: a meta-analysis of prospective studies. Diabetes care 36(5):1422-1428.

Stern,Y. 2009. Cognitive reserve. Neuropsychologia 47(10):2015-2028.

Stowe,J.D. and Cooney,T.M. 2015. Examining Rowe and Kahn's Concept of Successful Aging: Importance of Taking a Life Course Perspective. Gerontologist. 55(1):43-50.

Strawbridge,W.J., Wallhagen,M.I., and Cohen,R.D. 2002. Successful aging and well-being: Self-rated compared with Rowe and Kahn. Gerontologist 42(6):727-733.

Stryker,W.S., Kaplan,L.A., Stein,E.A., Stampfer,M.J., Sober,A., and Willett,W.C. 1988. The relation of diet, cigarette smoking, and alcohol consumption to plasma beta-carotene and alpha-tocopherol levels. Am J Epidemiol. 127(2):283-296.

Stuart,J.A., Maddalena,L.A., Merilovich,M., and Robb,E.L. 2014. A midlife crisis for the mitochondrial free radical theory of aging. Longev.Healthspan. 3(1):4-3.

Sun,Q., Townsend,M.K., Okereke,O.I., Rimm,E.B., Hu,F.B., Stampfer,M.J. et al. 2011. Alcohol consumption at midlife and successful ageing in women: a prospective cohort analysis in the nurses' health study. PLoS Med. 8(9):e1001090.

Sydenham,E., Dangour,A.D., and Lim,W.S. 2012. Omega 3 fatty acid for the prevention of cognitive decline and dementia. Cochrane Database Syst.Rev. 6:CD005379. doi: 10.1002/14651858.CD005379.pub3.:CD005379.

Szarc vel,S.K., Declerck,K., Vidakovic,M., and Vanden Berghe,W. 2015. From inflammaging to healthy aging by dietary lifestyle choices: is epigenetics the key to personalized nutrition? Clin Epigenetics. 7(1):33-0068.

Tagliabue,E., Raimondi,S., and Gandini,S. 2015. Vitamin D, Cancer Risk, and Mortality. Adv.Food Nutr Res. 75:1-52.

Tavel,P. 2008. Successful Ageing A Survey of the Most Important Theories. Human Affairs 18(2):183-196.

Teegarden,D. and Donkin,S.S. 2009. Vitamin D: emerging new roles in insulin sensitivity. Nutr Res Rev. 22(1):82-92.

Thielke,S. and Diehr,P. 2012. Transitions among Health States Using 12 Measures of Successful Aging in Men and Women: Results from the Cardiovascular Health Study. J Aging Res. Volume 2012 (2012), Article ID 243263, 9 pages.

Thompson,F.E. and Byers,T. 1994. Dietary assessment resource manual. The Journal of nutrition 124(11 Suppl):2245S-2317S.

Threapleton,D.E., Greenwood,D.C., Evans,C.E., Cleghorn,C.L., Nykjaer,C., Woodhead,C. et al. 2013. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. BMJ. 347:f6879. DOI: 10.1136/bmj.f6879.

Toffanello,E.D., Coin,A., Perissinotto,E., Zambon,S., Sarti,S., Veronese,N. et al. 2014. Vitamin D deficiency predicts cognitive decline in older men and women: The Pro.V.A. Study. 83(24):2292-2298.

Tombaugh,T.N. 2004. Trail Making Test A and B: normative data stratified by age and education. Arch.Clin Neuropsychol. 19(2):203-214.

Topaz,M., Troutman-Jordan,M., and MacKenzie,M. 2014. Construction, Deconstruction, and Reconstruction: The Roots of Successful Aging Theories. Nurs.Sci Q. 27(3):226-233.

Touvier,M., Deschasaux,M., Montourcy,M., Sutton,A., Charnaux,N., Kesse-Guyot,E. et al. 2014. Determinants of Vitamin D Status in Caucasian Adults: Influence of Sun Exposure, Dietary Intake, Sociodemographic, Lifestyle, Anthropometric, and Genetic Factors. J Invest Dermatol. 135(2):378-388.

Trichopoulou,A., Costacou,T., Bamia,C., and Trichopoulos,D. 2003. Adherence to a Mediterranean diet and survival in a Greek population. N.Engl.J Med. 348(26):2599-2608.

Troutman,M., Nies,M.A., Small,S., and Bates,A. 2011. The development and testing of an instrument to measure successful aging. Res Gerontol.Nurs. 4(3):221-232.

Troutman-Jordan,M. and Staples,J. 2014. Successful aging from the viewpoint of older adults. Res Theory.Nurs.Pract. 28(1):87-104.

Tyas,S.L., Snowdon,D.A., Desrosiers,M.F., Riley,K.P., and Markesbery,W.R. 2007. Healthy ageing in the Nun Study: definition and neuropathologic correlates. Age Ageing. 36(6):650-655.

Tyrovolas,S., Haro,J.M., Mariolis,A., Piscopo,S., Valacchi,G., Makri,K. et al. 2015. The Role of Energy Balance in Successful Aging Among Elderly Individuals: The Multinational MEDIS Study. J Aging Health. 27(8):1375-1391.

Tyrovolas,S., Haro,J.M., Mariolis,A., Piscopo,S., Valacchi,G., Tsakountakis,N. et al. 2014. Successful aging, dietary habits and health status of elderly individuals: a k-dimensional approach within the multi-national MEDIS study. Exp Gerontol. 60:57-63.

United Nations, Department of Economic and Social Affairs Population Division. World Population Prospects - The 2015 Revision. Key Findings and Advances Tables. Working Paper No. ESA/P/WP.241. 2015.

United States Department of Agriculture. A Series of Systematic Reviews on the Relationship Between Dietary Patterns and Health Outcomes. 2014. Alexandria, Virginia.

Vaillant,G.E. and Mukamal,K. 2001. Successful aging. American Journal of Psychiatry 158(6):839-847.

van de Rest,O., Berendsen,A.A., Haveman-Nies,A., and de Groot,L.C. 2015. Dietary patterns, cognitive decline, and dementia: a systematic review. Adv.Nutr. 6(2):154-168.

van der Schaft,J., Koek,H.L., Dijkstra,E., Verhaar,H.J., van der Schouw,Y.T., and Emmelot-Vonk,M.H. 2013. The association between vitamin D and cognition: A systematic review. Ageing research reviews 12(4):1013-1023.

Vasto,S., Buscemi,S., Barera,A., Di,C.M., Accardi,G., and Caruso,C. 2014. Mediterranean diet and healthy ageing: a Sicilian perspective. Gerontology. 60(6):508-518.

Verger,E.O., Mariotti,F., Holmes,B.A., Paineau,D., and Huneau,J.F. 2012. Evaluation of a diet quality index based on the probability of adequate nutrient intake (PANDiet) using national French and US dietary surveys. PLoS One. 7(8):e42155.

Vernay,M., Sponga,M., Salanave,B.t., OlÃ©ko,A., Deschamps,V.r., Malon,A.l. et al. 2012. Statut en vitamine D de la population adulte en France: l'étude nationale nutrition santé (ENNS, 2006-2007). Bulletin Epidémiologique hebdomadaire n° 16-17:189-194.

von Faber,M., Bootsma-van der Wiel,A., van Exel,E., Gussekloo,J., Lagaay,A.M., van Dongen,E. et al. 2001. Successful aging in the oldest old - Who can be characterized as successfully aged? Archives of Internal Medicine 161(22):2694-2700.

Vuillemin,A., Oppert,J.M., Guillemin,F., Essermeant,L., Fontvieille,A.M., Galan,P. et al. 2000. Self-administered questionnaire compared with interview to assess past-year physical activity. Med Sci Sports Exerc. 32(6):1119-1124.

Vuilleumier,J.P., Keller,H.E., Gysel,D., and Hunziker,F. 1983. Clinical chemical methods for the routine assessment of the vitamin status in human populations. Part I: The fat-soluble vitamins A and E, and beta-carotene. Int J Vitam.Nutr Res. 53(3):265-272.

Waijers,P.M., Feskens,E.J., and Ocke,M.C. 2007. A critical review of predefined diet quality scores. Br.J.Nutr. 97(2):219-231.

Wakefield,D.B., Moscufo,N., Guttmann,C.R., Kuchel,G.A., Kaplan,R.F., Pearlson,G. et al. 2010. White matter hyperintensities predict functional decline in voiding, mobility, and cognition in older adults. J Am Geriatr.Soc. 58(2):275-281.

Wang,Y.T. and Lin,W.I. 2012. Successful ageing: the case of Taiwan. Australas.J Ageing. 31(3):141-146.

Webster,J.L., Dunford,E.K., and Neal,B.C. 2010. A systematic survey of the sodium contents of processed foods. Am J Clin Nutr. 91(2):413-420.

Wechsler,D. 1981. Wechsler Adult Intelligence Scale-Revised. New York, NY: Psychological Corporation.

Weir,P.L., Meisner,B.A., and Baker,J. 2010. Successful aging across the years: does one model fit everyone? J Health Psychol. 15(5):680-687.

White,C.M., St John,P.D., Cheverie,M.R., Iraniparast,M., and Tyas,S.L. 2015. The role of income and occupation in the association of education with healthy aging: results from a population-based, prospective cohort study. BMC Public Health. 15(1):1181-2504.

Wiener,J.M. and Tilly,J. 2002. Population ageing in the United States of America: implications for public programmes. Int J Epidemiol. 31(4):776-781.

Willcox,B.J., He,Q., Chen,R., Yano,K., Masaki,K.H., Grove,J.S. et al. 2006. Midlife risk factors and healthy survival in men. JAMA. 296(19):2343-2350.

Willett,W. 1998. Nutritional Epidemiology, 2nd ed. Oxford, UK: Oxford University Press.

Williams, R. H. and Wirths, C. G. Lives through the years. Styles of life and successful aging. 1965. New York, Atherton Press.

Wilson,V.K., Houston,D.K., Kilpatrick,L., Lovato,J., Yaffe,K., Cauley,J.A. et al. 2014. Relationship Between 25-Hydroxyvitamin D and Cognitive Function in Older Adults: The Health, Aging and Body Composition Study. J Am Geriatr Soc 62(4):636-614.

Wirfalt,E., Drake,I., and Wallstrom,P. 2013. What do review papers conclude about food and dietary patterns? Food Nutr Res. 57: 20523. DOI:10.3402/fnr.v57i0.20523.

Wirt,A. and Collins,C.E. 2009. Diet quality--what is it and does it matter? Public Health Nutr. 12(12):2473-2492.

World Cancer Research Fund International. 2016. Summary of strong evidence from our analysis of worldwide research on diet, nutrition, physical activity & preventing cancer. Available from: http://www.wcrf.org/int/research-we-fund/continuous-update-project-findings-reports/continuous-update-project-cup-matrix. Accessed on the: 22-2-2016.

World Health Organization. Active ageing: a policy framework. 2002. Geneva.

World Health Organization. 2016. Health topics: Epidemiology. Available from: http://www.who.int/topics/epidemiology/en/. Accessed on the: 10-2-2016.

World Health Organization, National Institute on Aging National Institues of Health and U. S. Department of Health and Human Services. Global Health and Aging. NIH Publication no. 11-7737. 2011. Geneva.

Yaffe,K., Clemons,T.E., McBee,W.L., and Lindblad,A.S. 2004. Impact of antioxidants, zinc, and copper on cognition in the elderly: a randomized, controlled trial. Neurology. 63(9):1705-1707.

Yoshihara,D., Fujiwara,N., and Suzuki,K. 2010. Antioxidants: benefits and risks for long-term health. Maturitas. 67(2):103-107.

Young,Y., Frick,K.D., and Phelan,E.A. 2009. Can Successful Aging and Chronic Illness Coexist in the Same Individual? A Multidimensional Concept of Successful Aging. Journal of the American Medical Directors Association 10(2):87-92.

Zhang,J. and Yu,K.F. 1998. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA. 280(19):1690-1691.

Zolnikov,T.R. 2015. Proposing a re-adapted successful aging model addressing chronic diseases in low- and middle-income countries. Qual.Life Res. 24(12):2945-2949.

APPENDICES

I. Appendix 1: Methodological article on the NutriNet-Santé cognitive test battery

Not shown due to copyright considerations

II. Appendix 2: Preliminary results on the relation between adherence to the Mediterranean diet and healthy aging

II.A Abstract

Background: The Mediterranean diet has been suggested as a key element for the prevention of age-related chronic disease. However, very few studies have examined its relation with multidimensional concepts of healthy aging.

Objective: We aimed to investigate the association between adherence to the Mediterranean diet at midlife, as assessed by four scores, and healthy aging. A secondary objective was to conduct an exploratory investigation of potential underlying pathways involving indicators related to the metabolic syndrome.

Methods: We analyzed data from 3,012 participants of the *SUpplémentation en Vitamines et Minéraux AntioXydants* study aged 45-60 years at baseline (1994-1995) and initially free of major chronic disease, with available data on HA status in 2007-2009. We defined healthy aging as not developing any major chronic disease, good physical and cognitive functioning, independence in instrumental activities of daily living, no depressive symptoms, good social functioning, good self-perceived health and no function-limiting pain. The Mediterranean Diet Scale (MDS), the Mediterranean Style Dietary Pattern Score (MSDPS), the relative Mediterranean Diet Score (rMed), and the Literature-based Adherence Score to the Mediterranean Diet (LAMD) were calculated using baseline data from repeated 24-h dietary records. The association of these scores with healthy aging was analyzed using logistic regression. Structural equation modelling was applied to conduct exploratory analyses with respect to potential underlying pathways.

Results: In 2007-2009, 38% of participants met our healthy aging criteria. After adjustment for potential confounders, higher scores on the rMed ($OR_{tertile\ 3versus\ quartile\ 1}$=1.42 [95%-CI=1.16; 1.73]; p_{trend}=0.0007) and LASMD (1.36 [1.12; 1.65]; p_{trend}=0.002) were associated with higher odds of healthy aging. We observed no association between the MDS (1.20 [0.97; 1.49]; p_{trend}=0.09) or the MSDPS (1.20 [0.99; 1.45]; p_{trend}=0.07) and healthy aging.

Structural equation modelling yielded a model in which the rMed was both directly and indirectly related to a latent "healthy aging"- construct. The indirect link involved an association of the rMed with a latent "intermediate factors"- construct, which was – in turn – associated with the "healthy aging"- construct.

This "intermediate factors"- construct was characterized by indicators related to the metabolic syndrome that were measured in 2001-2002 (waist-to-hip-ratio, HDL, fasting blood glucose, triglycerides, systolic blood pressure, and LDL). The "healthy aging"- construct was characterized by higher levels of cognitive functioning, less limitations in instrumental activities of daily living, a higher probability for the absence of major chronic disease, higher levels of physical functioning, and higher perceived global health.

Conclusion: Our results suggest a favourable role of high adherence to the Mediterranean diet at midlife for maintaining good overall health during aging. One potential underlying pathway may be an association of the Mediterranean diet with more beneficial metabolic profiles.

References:

MDS: **Trichopoulou,A. et al. 2003. Adherence to a Mediterranean diet and survival in a Greek population. N.Engl.J Med. 348(26):2599-2608;**

MSDPS: **Rumawas,M.E. et al. 2009. Mediterranean-style dietary pattern, reduced risk of metabolic syndrome traits, and incidence in the Framingham Offspring Cohort. The American journal of clinical nutrition 90(6):1608-1614.**

rMed: **Buckland,G. et al. 2010. Adherence to a Mediterranean diet and risk of gastric adenocarcinoma within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. Am J Clin Nutr. 91(2):381-390;**

LASMD: **Sofi,F. et al. 2013. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public health nutrition :1-14;**

II.B Results obtained with a structural equation modelling- approach

Not shown due to copyright considerations

III. Appendix 3: Supervision of interns

6-months internship of Caroline Collin

Karen Assmann has co-supervised a 6-month internship (March - August 2015) of a last-year student enrolled in an engineer's degree program in life sciences, agronomy, and nutrition. The student (Caroline Collin) has investigated the long-term association of vitamin D status and adherence to the French food-based dietary guidelines with chronic or recurrent depressive symptoms in the SU.VI.MAX study.

Two original scientific articles have been drafted in this context. These articles, of which Karen Assmann is the second author, are currently under review. Moreover, Karen Assmann has presented two posters on these studies at the Journées Francophones de Nutrition (JFN) 2015, a French-language annual nutrition congress.

6-months internship of Lola Neufcourt

Karen Assmann has moreover contributed to the supervision of the 6-month internship (March - August 2015) of Lola Neufcourt, who was also enrolled in an engineer's degree program in life sciences. The student has investigated the prospective association of the inflammatory potential of the diet (measured via a specific *a priori* dietary score, the Dietary Inflammatory Index) with the risk of developing cardiovascular disease or the metabolic syndrome in the SU.VI.MAX study.

Lola Neufcourt has published two original scientific articles, of which Karen Assmann is the second author. In addition, Karen Assmann has given an oral presentation on the association of the Dietary Inflammatory Index with the risk of developing the metabolic syndrome at the Journées Francophones de Nutrition (JFN) 2015.

6-months internship of Indunil Ruhunuhewa

Indunil Ruhunuhewa is a last-year student enrolled in a master's degree program in Methodology and Statistics in Biomedical Research. She will conduct an internship of 6 months in April - September 2016 on the association between anthropometric indicators and metabolic health at midlife with later healthy aging in the SU.VI.MAX study. This internship will be co-supervised by Karen Assmann.

IV. Appendix 4: Scientific collaborations

Karen Assmann has participated in a long-term collaborative scientific training program on structural equation modelling and multi-block analysis. The training program was funded in the context of a call for projects embedded in the meta-program “DID’IT” (Diet impact and determinants - Interactions and transitions) of the French National Institute for Agricultural Research (INRA). Participants of this training program took an active role by presenting ongoing work and critically discussing the ongoing analyses of other participants. The session comprised, in total, 10 days of training, which took place from January 2014 to April 2015.

V. Appendix 5: Summary (in English & French)

Summary: Investigation of nutritional determinants (nutrients, foods, and overall diet) of healthy aging. Analysis in the SU.VI.MAX 2 cohort.

The aim of this thesis was to investigate nutritional determinants of a multidimensional concept of healthy aging in the French SU.VI.MAX study, which contains dietary data measured in 1994-95, and health data measured in 2007-09. The specific aims were: to examine the relation of an 8-year antioxidant supplementation with later healthy aging; to investigate midlife overall dietary quality with respect to later healthy aging; and to examine circulating midlife vitamin D status with respect to later cognitive performances.

No overall effect of antioxidant supplementation was observed. However, in subgroup analyses, a beneficial effect was seen among men, participants with low baseline vitamin C or zinc concentrations, or with a low fruit and vegetable consumption. Moreover, a beneficial role of higher adherence to the French nutrition guidelines and higher adequacy to the French nutrient reference values was observed. Next, we observed a positive role of higher adherence to a "healthy" empirically derived dietary pattern among participants with low overall energy intakes. Finally, we found a relation of higher vitamin D- levels with better outcomes related to short term- and working memory, among participants with low education only.

Our results support a beneficial role of a well-balanced intake of antioxidant nutrients for healthy aging, and underline the pertinence of the French nutrition guidelines and nutrient reference values. They moreover indicate that both a high dietary quality and an adequate energy intake are of importance. Finally, our results partly support a beneficial role of an adequate vitamin D status for preserving good cognitive health during aging.

Keywords: Nutrition, diet, prevention, aging, cognition, epidemiology

Résumé : Étude des déterminants nutritionnels (nutriments, aliments et alimentation globale) du vieillissement en bonne santé. Analyse dans la cohorte SU.VI.MAX 2.

Nous avons investigué les déterminants nutritionnels d'un modèle multidimensionnel du vieillissement en bonne santé (VBS) dans la cohorte SU.VI.MAX, qui contient des données nutritionnelles collectées en 1994-96, et des données de santé collectées en 2007-09. Les déterminants étudiés étaient une supplémentation en antioxydants, et la qualité globale de l'alimentation. Un objectif supplémentaire était d'étudier le rôle du statut plasmatique en vitamine D pour la santé cognitive.

Il n'y avait pas d'effet global de la supplémentation en antioxydants. Dans des analyses stratifiées, un effet bénéfique était observé chez les hommes et chez ceux ayant un statut sérique bas en vitamine C ou en zinc, ou ayant une consommation faible de fruits et légumes. De plus, le VBS était associé à une bonne adéquation aux recommandations nutritionnelles françaises et aux apports nutritionnels conseillés. Nous avons également identifié un rôle bénéfique d'une typologie alimentaire a posteriori 'saine' chez ceux ayant un faible apport énergétique. Enfin, nous avons observé une relation entre un statut plus élevé en vitamine D et de meilleures performances de la mémoire à court terme et de travail chez ceux ayant un niveau d'éducation faible.

Nos résultats indiquent un rôle bénéfique d'un apport équilibré en nutriments antioxydants, et d'une bonne adéquation aux recommandations nutritionnelles françaises et aux apports nutritionnels conseillés pour le VBS. De plus, ils soulignent l'importance de présenter à la fois une bonne qualité alimentaire et un apport adéquat en énergie. Enfin, nos résultats indiquent en partie un rôle bénéfique d'un bon statut en vitamine D pour la santé cognitive.

Discipline : Biologie – Épidémiologie – Santé Publique

Mots-clés : Nutrition, alimentation, prévention, vieillissement, cognition, épidémiologie

Laboratoire d'accueil : Équipe de Recherche en Epidémiologie Nutritionnelle, UMR U1153 Inserm/ U1125 Inra/ Cnam/ Université Paris 13, Centre de Recherche en Epidémiologie et Statistiques Sorbonne Paris Cité, 74 rue Marcel Cachin, 93017 Bobigny, France