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Final report of the HALE (Healthy Ageing: a Longitudinal study in Europe) Project

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Participating countries in the HALE project

Rapport in het kort

Eindrapport van het HALE (Healthy Ageing: a Longitudinal study in Europe) Project

Lichamelijk functioneren, psychisch welzijn, het geheugen en het sociale leven nemen af en ziekte en sterfte nemen toe met het ouder worden. Echter, niet iedereen krijgt te maken met ernstige gezondheidsproblemen op oudere leeftijd. In opeenvolgende generaties worden we steeds gezonder oud. Deze en andere resultaten worden beschreven in het eindrapport van het HALE project (HALE is “Healthy Ageing: a Longitudinal study in Europe”, ofwel “Gezond ouder worden: een langlopende vervolgstudie in Europa”).

De resultaten tonen aan dat de gevolgen van ouder worden te beïnvloeden zijn door voeding en leefstijl (roken, alcohol, bewegen) en daarmee samenhangende factoren. Mediterrane voeding, matig alcoholgebruik, niet roken en regelmatig bewegen dragen ieder afzonderlijk en vooral ook in combinatie bij aan het verlagen van het sterfterisico. Een lagere systolische bloeddruk en minder cholesterol in het bloed zijn ook bij ouderen gerelateerd aan een lager risico op sterfte aan hart- en vaatziekten. Blijven bewegen, matig koffiegebruik, getrouwd zijn of samenwonen verkleinen de kans op achteruitgang in geheugen. Ook bleek dat de huidige epidemie van overgewicht niet iets is van de laatste jaren: het aantal mensen met overgewicht in opeenvolgende generaties neemt al toe sinds 1960.

In dit project stonden voeding en leefstijl centraal. Daarom bevelen we aan om interventies op het gebied van de gezondheidsbevordering te richten op verschillende aspecten van voeding en leefstijl. Daarbij kunnen mensen dan zelf kiezen of ze bijvoorbeeld hun voedingsgewoonten of bewegingspatroon aanpassen, of allebei.

Trefwoorden: gezond ouder worden; ouderen; hart- en vaatziekten; voeding; functioneren.

Abstract

Final report of the HALE (Healthy Ageing: a Longitudinal study in Europe) Project

The HALE project showed an increase in Body Mass Index in the different age cohorts, suggesting that the current obesity epidemic went back as far as the 1960s. In some countries favorable changes in systolic blood pressure and serum cholesterol levels occurred. In general, low systolic blood pressure and serum cholesterol levels were related to a low cardiovascular diseases mortality risk. Consumption of a Mediterranean type of diet, moderate consumption of alcohol, non-smoking and regular physical activity were related to a lower mortality risk. These were taken both separately and in combination, the relationship was even stronger in the latter. In the elderly, health and functional status decreased with age, although in subsequent cohorts the proportion of healthy elderly has increased. Regular physical activity, moderate coffee consumption, being married, and living with others were all associated with a smaller cognitive decline in elderly men.

The aim of the HALE project was to study changes in and determinants of usual and healthy ageing in 13 European countries. For this project longitudinal data were used of three international studies: the Seven Countries Study database (7047 men followed for 35 years in five European countries) and the combined database of the FINE and SENECA Study (3805 elderly men and women followed for 10 years in 12 European countries).

Keywords: healthy ageing; elderly; cardiovascular diseases; diet; functional status.

Preface

Healthy ageing consists of optimising life expectancy and quality of life. The aim of the HALE (Healthy Ageing: Longitudinal study in Europe) project was to study changes in demographic, lifestyle, dietary and biological determinants of usual and healthy ageing in terms of mortality and morbidity outcomes as well as in terms of physical, psychological, cognitive, and social functioning in 13 European countries. The HALE project started on the 1st of July 2001 as a continuation of three longitudinal studies: the Seven Countries Study, the Finland, Italy, Netherlands Elderly (FINE) Study and the Survey Europe on Nutrition in the Elderly: a Concerted Action (SENECA) Study. The HALE project was concerned with data collected in 7047 men aged 40-99 in five European countries (Finland, Greece, Italy, the Netherlands, Serbia) in the period 1959-2000 in the Seven Countries Study. In the period 1988-2000 also data were collected in 3805 men and women aged 70-99 in 12 European countries (Belgium, Denmark, France, Finland, Greece, Hungary, Italy, the Netherlands, Poland, Portugal, Spain and Switzerland). The project was funded by the European Union (QLK6-CT-2000-00211).

Since the start of the project, four workshops were held in 2001 (Wageningen, the Netherlands), 2002 (Bilthoven, the Netherlands), 2003 (Rome, Italy) and 2004 (Toulouse, France). During the final workshop in Toulouse the main findings of the project were discussed as well as the recommendations and the public health implications of the HALE project.

We are very much indebted to Dr. Kremers, Maastricht University, the Netherlands, and Dr. Davies, London, UK, who participated in the final workshop. Dr. Kremers took together with Dr. Van der Waerden the responsibility for chapter 2 of this report. Dr. Davies translated the results of the HALE project in a leaflet for health managers entitled: 'Healthy Ageing: From research to practice'.

On behalf of the editors, D. Kromhout, principal investigator of the HALE project
Bilthoven, Februari 2005

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Summary

The aim of the HALE project was to study changes in and determinants of usual and healthy ageing in 13 European countries. For this project longitudinal data were used of three international studies: the Seven Countries Study (7047 men followed for 35 years in five European countries) and the FINE and SENECA Study (3805 elderly men and women followed for 10 years in 12 European countries).

Results from the HALE project showed that morbidity and mortality as well as physical, psychological, cognitive, and social functioning in elderly men and women from 13 European countries generally decreased in participants getting older, but improved in subsequent generations. Morbidity, mortality and functioning were related to various demographic, lifestyle, dietary and biological factors.

1. Key messages of the HALE project

The results of the HALE project were summarized in the following 9 key messages.

From middle to old age there were different trends in cardiovascular risk factors during 35 years.

- Body Mass Index increased as a result of cohort-related changes.
- Systolic blood pressure increased as a result of age-related changes.
- Systolic blood pressure decreased as a result of cohort-related changes.
- Serum cholesterol decreased in Northern Europe as a result of age-related changes.
- Serum cholesterol increased in Southern and Central Europe as a result of age-related changes.

From middle to old age serum cholesterol and systolic blood pressure predict long-term cardiovascular mortality.

- The level of and change in serum cholesterol in middle-aged men predict coronary heart disease mortality later in life.
- The level of and change in systolic blood pressure in middle-aged men predict cardiovascular mortality later in life.
- Serum cholesterol is related to typical but not to atypical coronary mortality.
- Systolic blood pressure is related to both typical and atypical coronary mortality.

In the elderly weight changes and antioxidant levels in blood are related to mortality.

- Weight loss increases mortality risk: men with a weight loss of 5 kg or more in the first four years of follow-up have a more than twofold increased mortality risk.
- Blood carotene levels are inversely related to cardiovascular, cancer and all-causes mortality. This association is confined to lean subjects ($BMI < 25 \text{ kg/m}^2$).
- Blood α -tocopherol levels are not related to cardiovascular and all-causes mortality.

In the elderly diet but *not* supplements predict health.

- Diet scores measuring agreement with a Mediterranean diet were stronger related to mortality than the WHO's Healthy Diet Indicator.
- A Mediterranean type of diet decreases coronary mortality by about 40% and all-causes mortality by about 20%.
- Moderate coffee consumption is inversely related to cognitive decline.
- General vitamin and mineral supplement use is not related to mortality.

In the elderly non-smoking and moderate alcohol consumption lower mortality risk.

- Non-smoking compared with smoking decreases mortality risk by 35%.
- Moderate alcohol consumption compared with non-drinking decreases mortality risk by about 20%.

In the elderly physical activity lowers mortality risk and improves cognitive and physical functioning.

- Moderate physical activity lowers mortality risk by about 35%.
- Physical activity is inversely associated with cognitive decline.
- Physical activity is positively associated with physical functioning.

In the elderly time trends in physical, psychological and cognitive functioning were observed.

- Physical, psychological and cognitive functioning decreased with increasing age.
- Physical, psychological and cognitive functioning improved in succeeding birth cohorts.

In the elderly social functioning is related to mortality and cognitive functioning.

- Losing a partner is associated with a higher mortality risk in men.
- Losing a partner is associated with a stronger cognitive decline in men.
- Having few social contacts is associated with a higher mortality risk in women.

In the elderly there are regional differences in Europe with respect to health.

- Cardiovascular risk factors are generally in favour of the South.
- Diet is generally in favour of the South.
- Micronutrient status is generally in favour of the South.
- Self-perceived health displays no clear pattern.
- Psychological functioning is in favour of the North, physical functioning in favour of the South.

2. Recommendations for healthy ageing and public health implications

S Kremers, J Van der Waerden, Maastricht University, Maastricht, the Netherlands

The following **recommendations** for healthy ageing were formulated based on the results of the HALE project:

- Maintain body weight in old age.
- Maintain low systolic blood pressure (< 140 mmHg) and serum cholesterol levels (< 5 mmol/L) into old age.
- Use a Mediterranean type of diet.
- Be physically active preferably at least 30 minutes per day.
- If you use alcohol, do so in moderation.
- Do not smoke.

These recommendations do not only apply to elderly but are consistent with those for adults of different ages.

Combined diet and lifestyle approach

Since a major part of these recommendations concern lifestyle and diet, adaptation of a lifestyle approach in health promotion interventions may be useful. The study from Knoops et al. (1) showed cumulative effects of adopting multiple health behaviours. Combining multiple health behaviours in one intervention will have various advantages. On the one hand, a focus on multiple lifestyle behaviours may complicate the prevention of weight gain. Compared to isolated smoking cessation interventions for example, where smoking cessation is the single behavioural goal, changing multiple behaviours may be regarded as much more complex. However, an advantage of the lifestyle approach lies in the fact that some individuals might be interested in reaching changing their dietary behaviour, while others might be more inclined to change their level of physical activity during leisure time. Offering a target group the possibility of choosing how to improve their lifestyle will constitute an attractive feature for intervention designers trying to achieve the prevention of lifestyle-related morbidity and mortality (2, 3).

Additionally, synergetic effects may follow from successful changes in one behaviour with respect to other behaviours that are promoted within the same program. Particularly, changes in dietary behaviour may induce changes in physical activity (2, 4). For example, successfully changing one behaviour could boost motivation for both that behaviour and other behaviours. This, in turn, could enhance the motivation to change the second behaviour (5). The principle of these synergistic effects forms a potentially effective ingredient of health promotion programmes aiming to prevent weight gain. Health promotion interventions have shown that large changes in behaviour cannot be expected. However, the studies carried out within the HALE project have shown that small behavioural changes have the potential to result in large effects on morbidity, functioning and mortality.

Nutrition education

With respect to the findings regarding the Mediterranean type of diet, it is important to realise that the cut-off points used by Knoops et al. (1) do not differ considerably from advice in current nutrition education practice. Nutrition education may therefore focus on the fact that a

Mediterranean type of diet is merely in line with current dietary recommendations. It should also be stressed that these recommendations are even important in later life. Since other healthy diets also exist (e.g. the traditional Japanese diet), we speak of a Mediterranean *type* of diet to indicate certain characteristics of the diet such as a low intake of saturated and trans fat and high consumption of fruit and vegetables. Nutrition education should therefore focus on the fact that there are many possible choices within the current dietary guidelines to come to a healthy diet.

Prevention of mental health problems

The results from the HALE project support the development of physical activity interventions for prevention of mental health problems. Although evidence suggests that exercise interventions may have a preventive as well a therapeutic role in mental health disorders, the use of exercise as a tool to prevent mental health problems has been identified as a neglected intervention in mental health care (6). It reduces anxiety, depression, and negative mood, and improves self-esteem and cognitive functioning (6). Intervention studies have shown that exercise can be as effective in reducing depressive symptoms as psychotherapy (7). However, optimal dose in terms of frequency, duration and intensity needed for treatment and prevention efficacy is not fully defined (8). Intervention designers need to acknowledge that exercise levels that are more intense than participants' habitual level are less likely to improve mood and is liable to worsen it. Strenuous exercise in people who are not having intense exercise habits has commonly found to be unpleasant (9). In intervention studies, participants usually meet in a supervised setting three times a week to exercise with a group for 30 to 60 minutes (6). Supervised settings require interventions to be targeted at specific high-risk groups and to be based on the needs of specific population groups.

Target group segmentation

Target group segmentation can be used as a tool to direct interventions to specific high-risk groups. Although the proportion of healthy elderly increases, absolute demands on health services are not likely to decrease. In order to efficiently use financial resources, specific target groups need to be focused on. The need to define an intervention group means a programmatic need for an epidemiologically and demographically defined population in order to plan effective programs and to measure their effects on morbidity, functioning and mortality (10). Precisely defining the various groups who will benefit from the program enables the planner to know both the people who get the program and the population to whom the program is intended (11). Potential target groups that have been identified in the HALE project are (a) lower SES groups and (b) individuals that are socially deprived. In the past decade, various evidence-based strategies have been developed to reduce health inequalities (12). Ideally, factors targeted by the strategy should be known to contribute to the explanation of health inequalities, and interventions and policies should be known to diminish exposure of socially deprived populations and lower socioeconomic groups to these factors. However, important gaps are present in the knowledge base, both in terms of coverage of various policy options and in terms of strength of evidence (12, 13). Therefore, implementation of theory- and evidence-based interventions with continued evaluation efforts are required.

3. Publications from the HALE project

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4. Introduction to the HALE project

In the past century, the developed world has witnessed a sharp increase in life expectancy. As a result the percentage of those aged 65 years and older represented about 17% of the population in 2003 in the European Union (Figure 1; (14)). This percentage will probably be doubled in about 30 years (15). Since life expectancy in western societies has stretched almost to the limit now, public health focus has shifted to healthy life expectancy (Figure 2).

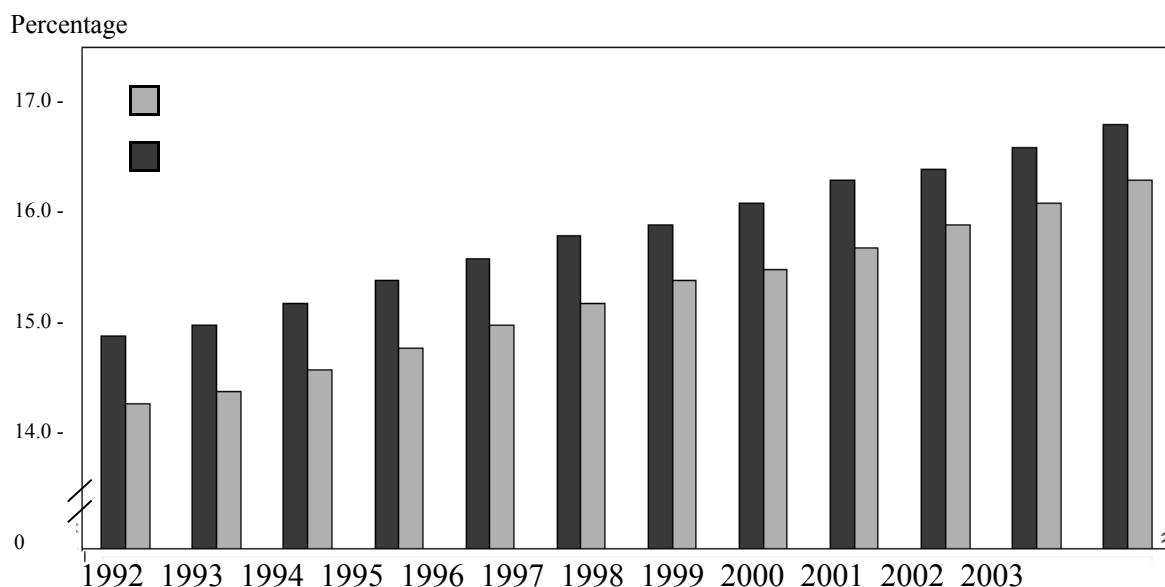


Figure 1. Percentage of population aged 65 and over in the European Union.

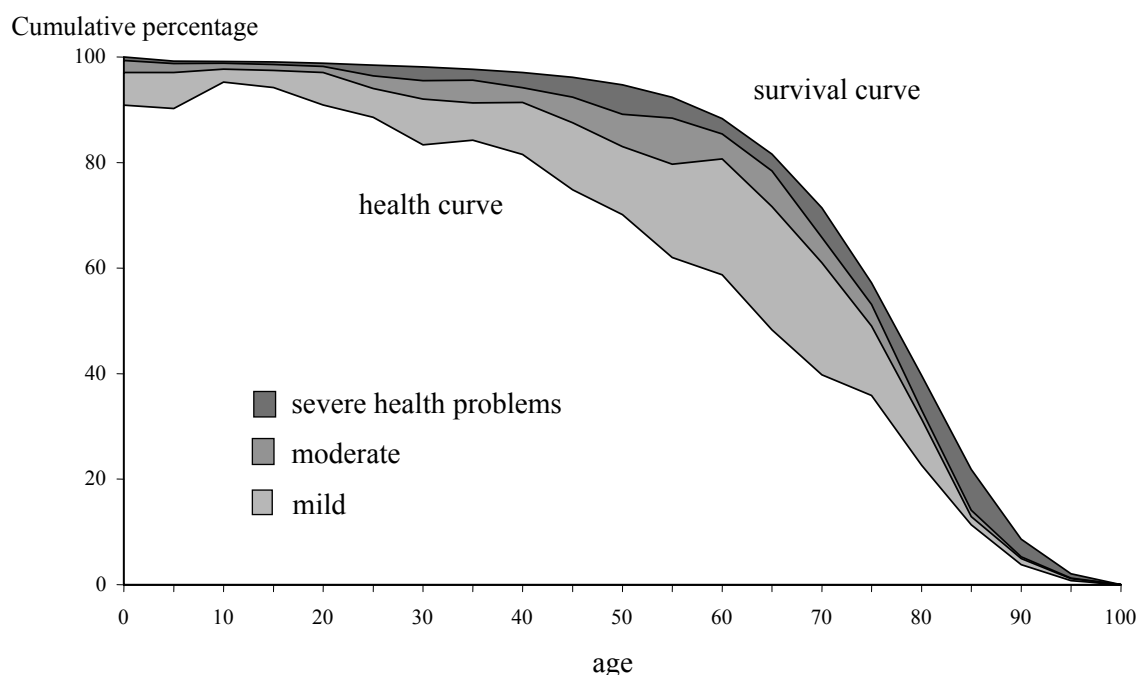


Figure 2. Survival curve and health curves according to health problems for males in 1994 in the Netherlands (Source: CBS-Health Survey; data processed by TNO-PG, Ruwaard and Kramers 1998)

Whether the increase in life expectancy is accompanied by a favourable change in health expectancy is under debate. This discussion relates to compression or expansion of morbidity or an equilibrium. A major challenge for public health in European countries is to maintain health and quality of life in an ageing population. Healthy ageing, viewed from a medical or public health viewpoint, consists of optimising life expectancy, while at the same time minimising physical, psychological and social morbidity (16). It is important to note that in the present project, the concept of healthy ageing includes the total spectrum of mortality, morbidity and health-related quality of life (self-perceived health, physical, psychological, cognitive and social functioning). Apart from healthy ageing we distinguish usual ageing: usual ageing relates to mixed effects of age and chronic diseases, healthy ageing refers to age effects only (17). The connotation of the term “healthy” is regionally dependent in the sense that economic conditions and culture determine the minimum, the maximum, and the optimum in healthy ageing (18).

This project contributes to the cultural aspect of healthy ageing by comparing (changes in) indicators of healthy ageing within and between European countries. Analyses on age, period and cohort differences in determinants of healthy ageing provide information on ageing in different phases of life. Estimation of the impact of biological and lifestyle factors including diet give insight in the preventable proportion of mortality, morbidity and loss in functioning. This project made use of already collected data on 10,852 persons in 13 European countries.

The aim of the HALE project was to study changes in and determinants of usual and healthy ageing in terms of mortality and morbidity outcomes as well as in terms of physical, psychological, cognitive, and social functioning in 13 European countries.

Availability of longitudinal data of three international studies (Seven Countries Study, Finland, Italy, Netherlands Elderly (FINE) Study, Survey Europe on Nutrition in the Elderly: a Concerted Action (SENECA) Study) allowed us to investigate European differences in specific indicators of healthy ageing and their biological, socio-demographic and lifestyle determinants. To be able to study different indicators and the relationships with lifestyle determinants, two databases were constructed ([work package 1](#)). Three other objectives can be distinguished: [work package 2](#) relates to biological determinants of healthy ageing; [work package 3](#) relates to dietary determinants of healthy ageing; and [work package 4](#) relates to age-related changes and cultural differences in indicators of functioning and relationships with lifestyle, socio-demographic factors, morbidity and mortality.

5. Construction of standardized European databases on healthy ageing

5.1. Objectives

1. The finalising of the Seven Countries Study database containing data of 7047 men aged 40-99 years in five European countries (Finland, Greece, Italy, the Netherlands, Serbia) in the period 1959-2000, concerning: biological risk factors (blood pressure, Body Mass Index (BMI), serum cholesterol and heart rate), prevalence data on cardiovascular diseases (CVD), diabetes, cancer, chronic obstructive pulmonary disease (COPD) and asthma, mortality data including cardiovascular mortality.
2. The construction of a database for studying healthy ageing and its determinants with data of two longitudinal studies (FINE and SENECA) of 3805 men and women aged 70-99 years in 12 European countries (Belgium, Denmark, Finland, France, Greece, Hungary, Italy, the Netherlands, Poland, Portugal, Spain, Switzerland) in the period 1988-2000, concerning: indicators of healthy ageing (mortality, morbidity, self-perceived health, physical functioning, psychological functioning, cognitive functioning, social functioning), and determinants of healthy ageing (socio-demographic (country, age, gender, socio-economic status, marital status, living situation), diet (dietary patterns, nutrients, nutritional status), lifestyle (physical activity, smoking, alcohol consumption) and biological determinants (blood pressure, serum cholesterol, BMI)).

5.2. Methodology and study materials

Two databases were constructed combining existing longitudinal data collected in the period 1959-2000 (one on the Seven Countries Study, and the other on the FINE study and the SENECA study) in 13 European countries. The data were collected through physical examinations, blood sampling, interviews, questionnaires and death certificates. Data on indicators of healthy ageing were supplemented by information on determinants, e.g. socio-demographic factors, biological factors, dietary and lifestyle factors.

A systematic search of other relevant studies (involving comparable longitudinal measures of healthy ageing and determinants in the elderly) to incorporate in the database was made using the network of participants and the international literature. Harmonisation of all data was an important and substantial part of the work. Although data had been collected in a standardised way within the three studies, harmonisation was necessary before analyses could take place. First an inventory of all details of the available datasets and the methodology of data collection was made. Second, decisions were taken in collaboration with all participants on how to deal with differences in the analyses of data. All participants in the project delivered local data for the international databases and all details on methodology and variables.

5.3. Results

Two databases were constructed:

- for WP2, a database of European cohorts of the Seven Countries Study on biological determinants of healthy ageing. For the analyses the 35-year mortality data were used

because the database containing the 40-year mortality became only available at the end of the project period.

- for WP3 and WP4, a European database on diet, lifestyle and ageing in terms of functioning based on data of the FINE and SENECA Study. Data of these two databases were combined. The process of harmonisation of the two databases is described below.

5.3.1 Harmonisation of FINE and SENECA databases

The two databases include in total data of 3805 persons from 13 European countries. The process of harmonising data sets started with comparing questionnaires and individual questions in order to define corresponding variables and answer categories. Next, the databases were constructed (as SAS data-files) and described in the HALE manual. In the harmonisation step, variables of the FINE and SENECA Study were compared for the following domains:

- socio-demographic status
- diet and lifestyle factors
- biological risk factors (anthropometric and blood parameters)
- indicators of healthy ageing

The result of the harmonisation activities is summarised per domain. Four possible outcomes were defined:

- variables of FINE and SENECA that are similar
- variables of FINE and SENECA that are not similar
- variables of FINE and SENECA that are available for all centres
- variables of FINE and SENECA that are not available for all centres

Socio-demographic status: the variables marital status, living status, number of children, occupation, country and gender were similar for FINE and SENECA and were available for all centres. The variables income and type of education were similar in both studies but were not available for all centres.

Diet and lifestyle factors: similar variables were available for smoking, dietary intake and alcohol consumption. Data on supplementation practice were not comparable in the FINE and SENECA Study. Harmonising the variables smoking and dietary intake was not possible without losing information in one or two studies. To measure physical activity, different questionnaires were used in FINE and SENECA that could not be harmonised in one format. As part of a MSc project, a student from Wageningen University compared the physical activity questionnaires in one study sample (see below).

Biological factors: the variables height, weight, triceps skinfold, and arm circumference were measured in the same way in both studies. The variables biceps and subscapular skinfold, waist and hip circumference were measured in one of the two studies. The blood parameters total cholesterol, HDL cholesterol and triglycerides are similar in FINE and SENECA, but the variables homocysteine, albumin and vitamin D were measured in a limited number of centres and subjects. Additional blood analyses were performed for homocysteine and –in a limited number of centres and subjects– also for C-reactive protein (CRP).

Health status variables: data on vital status and causes of death were collected in both studies and the data were coded by one experienced clinical epidemiologist according to the ninth

revision of the International Classification of Diseases. Similar questionnaires were used for measuring physical performance, activities of daily living (ADL), and cognitive functioning. However, chronic diseases, self-perceived health and depression were not measured in the same way. For chronic diseases the cumulative prevalence data were calculated for both studies. For self-perceived health and depression two different questions/questionnaires were used. Extra harmonisation activities were necessary for these variables. The Dutch study centre in FINE included the Zung as well as the Geriatric Depression Scale questionnaire. As part of a MSc project, a student from Wageningen University compared both questionnaires (see below).

An overview of all available variables is shown in Appendix I.

Validation of depression and physical activity questionnaires

The validity of two scales for measuring depression and two questionnaires for measuring physical activity, which were used for WP3 and WP4, was determined.

Based on the internal consistencies of the depression scales, the Geriatric Depression Scale appeared more suitable to measure depressive feelings in the elderly than the Zung Self-rating Depression Scale. In diagnosing depressive feelings the two scales classified approximately 20% differently.

Two measures of physical activity, the Voorrips and Morris scores, were compared in 30 men and 60 women participating in the HALE project. The correlation coefficient between the two scores was 0.60. Fifty-seven percent of the 90 participants were classified in the same tertile, and only 6% was classified in opposite tertiles. The Voorrips score correlated better than the Morris score with the physical activity ratio derived from a doubly labelled water estimate of energy expenditure (correlation coefficients were 0.52 and 0.34).

5.3.2 Study population

The study population used in WP2 derives from the European cohorts of the Seven Countries Study consisting of men aged 40-59 years, enrolled and first examined in the early 1960's. They are: the two Finnish cohorts of men living in rural areas of that country (East and West Finland); the cohort of Zutphen, a small commercial town in the Netherlands; the rural cohorts enrolled in the villages of Crevalcore and Montegiorgio in Italy; the three cohorts in Serbia Velika Krsna (a rural village), Zrenjanin (an agro-industrial cooperative) and in Belgrade (the University Faculty); and the rural cohorts on the Greek Islands of Crete and Corfu. Altogether they included 7047 men aged 40-59 years at entry examination. Details on the general characteristics of those cohorts are given elsewhere (19, 20). The baseline response rate was 98.1 % in Finland, 84.3 % in the Netherlands, 98.7% in Italy, 91.4% in Serbia and 96.6% in Greece. From year 0 to year 35 of the follow-up, 5204 men had died, of which 2593 from CVD (table 1).

Table 1: Thirty-five year death rates from CVD and ALL causes of death among middle-aged men in the European cohorts of originally the Seven Countries Study

Country	Denominator	CVD death rate per 1000 in 35 years	ALL death rate per 1000 in 35 years
Finland	1677	439	811
Netherlands	878	347	712
Italy	1712	320	728
Serbia	1565	425	747
Greece	1215	278	661

The study population used in WP3 and WP4 included participants of the SENECA and FINE study. The SENECA study started in 1988 and consisted of a random age- and sex-stratified sample of inhabitants, born between 1913 and 1918, of 19 European towns. In the HALE project, 13 centers that carried out mortality follow-up were included. The original participation rate in the centers varied from 37% to 81%. Surveys were repeated in 1993 and 1999. The response rates for SENECA were 68% in 1993 and 55% in 1999. All men and women of the following towns were included: Hamme, Belgium; Roskilde, Denmark; Marki, Poland; Strasbourg, France; Valence, France; Iraklion, Greece; Monor, Hungary; Padua, Italy; Culemborg, the Netherlands; Vila Franca de Xira, Portugal; Betanzos, Spain; and Yverdon, Burgdorf, and Bellinzona, Switzerland.

The FINE study consists of the survivors of 5 cohorts of the Seven Countries Study: East Finland; West Finland; Crevalcore, Italy; Montegiorgio, Italy; and Zutphen, the Netherlands. The FINE study, which started in 1984 and continued to 2000, recruited men who were born between 1900 and 1920. For the HALE project, we used the 1989-1991 measurements of men aged 70 to 90 years at baseline. Surveys were repeated in the years 1994-1995 and 1999-2000. The response rates in 1989-1991 were 92% for the Finnish cohorts, 74% for the Dutch cohort, and 76% for the Italian cohorts.

The study centers of the FINE Study were also included in the Seven Countries Study. Although this caused some overlap, inclusion of FINE centers in the Seven Countries Study made it possible to look further back in time. Another advantage was that the combination of FINE and SENECA databases allowed a view over more European countries and provided information about both men and women.

Table 2 summarizes information about demographics, diet, lifestyle factors and vital status of the participants of the SENECA and FINE studies.

Table 2: Baseline characteristics of the SENECA and FINE study*

	SENECA		FINE
	Women (n=1,103)	Men (n=1,072)	Men (n=1,058)
Age (years) (mean ± sd)	73 ± 1.8	73 ± 1.8	77 ± 4.4
Never smoked or stopped > 15 years (%) (n)	88 (947)	43 (464)	58 (614)
Smoker or stopped ≤ 15 years (%) (n)	12 (129)	57 (608)	42 (444)
Median Mediterranean diet score	4	4	4
Median components Mediterranean diet score:			
Monounsaturated/saturated fat ratio ¹ (median)	1	1	1
Vegetables/potatoes g/day ¹ (median)	268	319	266
Fruit ¹ g/day ¹ (median)	258	233	212
Legumes/nuts/seeds g/day ¹ (median)	4	5	10
Meat and poultry g/day ¹ (median)	106	138	118
Milk and milk products g/day ¹ (median)	323	326	407
Fish g/day ¹ (median)	24	27	20
Grains g/day ¹ (median)	196	249	228
Mean activity score (mean ± sd)			
Voorrips Score	12 ± 9	18 ± 15	
Morris Score (minutes/week)			633 ± 632
North Europe (%) (n)	42 (462)	45 (477)	65 (692)
South Europe (%) (n)	58 (641)	55 (595)	35 (366)
Alcohol (%) (n)			
Abstainers	53 (583)	20 (206)	25 (264)
Users	47 (520)	80 (866)	75 (794)
Years of education (mean ± sd)	7 ± 3.5	8.5 ± 4	7 ± 4
BMI (%) (n)			
≤ 25 kg/m ²	39 (434)	39 (414)	43 (453)
> 25 kg/m ²	61 (669)	61 (658)	57 (605)
Coronary heart disease at baseline (%) (n)	14 (158)	17 (179)	12 (129)
Stroke (%) (n)	2 (18)	4 (40)	6 (60)
Diabetes (%) (n)	9 (102)	8 (81)	9 (100)
Cancer (%) (n)	2 (24)	1 (15)	8 (93)
died during 10 years follow-up (%) (n)	28 (306)	52 (554)	57 (619)
died from coronary heart disease (%) (n)	13 (41)	14 (79)	19 (113)
died from cardiovascular diseases (%) (n)	42 (128)	35 (194)	50 (309)
died from cancer (%) (n)	16 (50)	23 (128)	27 (169)
died from other causes (%) (n)	13 (38)	14 (79)	16 (97)
died from unknown cause (%) (n)	29 (90)	28 (153)	7 (44)

*The total number of participants was 3805. The table displays only participants without missing data for the variables displayed.

¹grams/day, corrected for 2500 kcal/day in men, 2000 kcal in women

5.3.3 Definition of Southern and Northern Europe

A differentiation was made between Northern, Central and Southern Europe:

- North: Finland (East), Finland (West), Roskilde (Denmark), Hamme (Belgium), Haguenau (France), Zutphen (the Netherlands), Culemborg (the Netherlands), Burgdorf (Switzerland);
- Central: Marki (Poland), Chateau-Renault (France), Belgrade, Velika Krsna, Zrenjanin (Serbia);
- South: Montegiorgio (Italy), Crevalcore (Italy), Romans (France), Renault (France), Bellinzona (Switzerland), Yverdon (Switzerland), Betanzos (Spain), Coimbra (Portugal), Vila Franca de Xira (Portugal), Archanes (Greece), Padua (Italy).

5.4. Conclusion

The construction of the combined SENECA and FINE database was a time-consuming activity, for which it was necessary to employ one person full-time during one year with external funds. Harmonisation of the data involved comparing questionnaires and individual questions, define corresponding variables and answer categories, and validate scales and questionnaires. The resulting database could be used for the analyses of work packages 3 and 4. Since the number of persons in the database amounted to 2589 (of which 1829 free of chronic disease) men and 1216 (of which 918 free of chronic disease) women (FINE and SENECA), and approximately one quarter of the women and half of the men died by the last follow-up, the power of the statistical analyses conducted in WP 3 and 4 was sufficient. For WP 2, data of more than 7000 men followed for 35 years were available. Of those men, 5204 died, of which 2593 from CVD. This is a very powerful database for studying risk factor-disease relationships.

6. Biological determinants of healthy ageing

6.1. Objectives

This work package investigated age, period and cohort analyses of blood pressure, cholesterol and BMI in men followed up from 40 to 99 years of age and the impact of these changes on coronary heart disease (CHD), stroke and all-causes mortality. The key-objectives were:

1. compare the age-related changes in blood pressure, cholesterol and BMI in men aged 40-99 years in Northern and Southern Europe;
2. compare the age-related changes in biological risk factors in healthy men aged 40-99 years in Northern and Southern Europe;
3. investigate the effects of age-related changes in biological risk factors on CHD, stroke and all-causes mortality in Northern and Southern European populations, taking into account the effect of regression dilution bias.

6.2. Methodology and study materials

The biological risk factors were studied in data collected since 1959 in five European countries (Finland, Greece, Italy, The Netherlands, Serbia) participating in the Seven Countries Study. Data on biological risk factors (blood pressure, cholesterol, and BMI) were collected in these countries at baseline, 5 and 10 years of follow-up. Additional data were collected after 25, 30, 35 and 40 years of follow-up. In Crete (Greece), additional data were only collected after 31 and 40 years of follow-up. These data made it possible to study age-related changes in biological risk factors between the ages 40-99. Information on the prevalence of chronic diseases (e.g. CVD, diabetes, cancer, COPD and asthma) has repeatedly been collected in the Seven Countries Study between 1959 and 2000. This information made it possible to study “usual” changes, e.g. changes in biological risk factors with age and “healthy” changes, e.g. changes in biological risk factors with age in “healthy” men. The effect of the age-related changes on CHD, stroke and all-causes mortality was assessed using Cox’s regression. Finally, the amount of measurement error in the data on biological risk factors was estimated based on the repeated measurements made in each study. These estimates were used to correct the observed effect of age-related changes on mortality for regression dilution bias (21). Mortality data have been collected continuously during a 40-year follow-up period. Because the 40-year mortality follow-up could be completed only recently, our data analyses were based on the 35-year mortality data.

6.3. Results

Objective 1: compare the age-related changes in blood pressure, cholesterol and BMI in men aged 40-99 in Northern and Southern Europe.

In nine European cohorts of the Seven Countries Study, average systolic blood pressure increased approximately 15 mm Hg during 25 years, maintaining a steady state thereafter, with the largest increases in Serbia and Greece. Average serum cholesterol varied between approximately 4.5 mmol/l in Serbia and 6.5 mmol/l in Finland around 1960. Twenty-five years later the average level was about 6 mmol/l in all five countries and decreased slightly

thereafter. Average body mass index increased in all countries for 25 years and levelled off thereafter. With respect to the cohort effect, we considered men aged 50-59 years in the period 1960-1970 and men aged 75-84 in the period 1985-1995. Average systolic blood pressure decreased in all countries with the exception of men aged 50-59 in Serbia and men aged 75-84 in The Netherlands. Average serum cholesterol uniformly increased in men aged 50-59 for the younger age class and slightly decreased in men aged 75-84. Average BMI increased systematically in all countries in both age groups (Figure 3) (22).

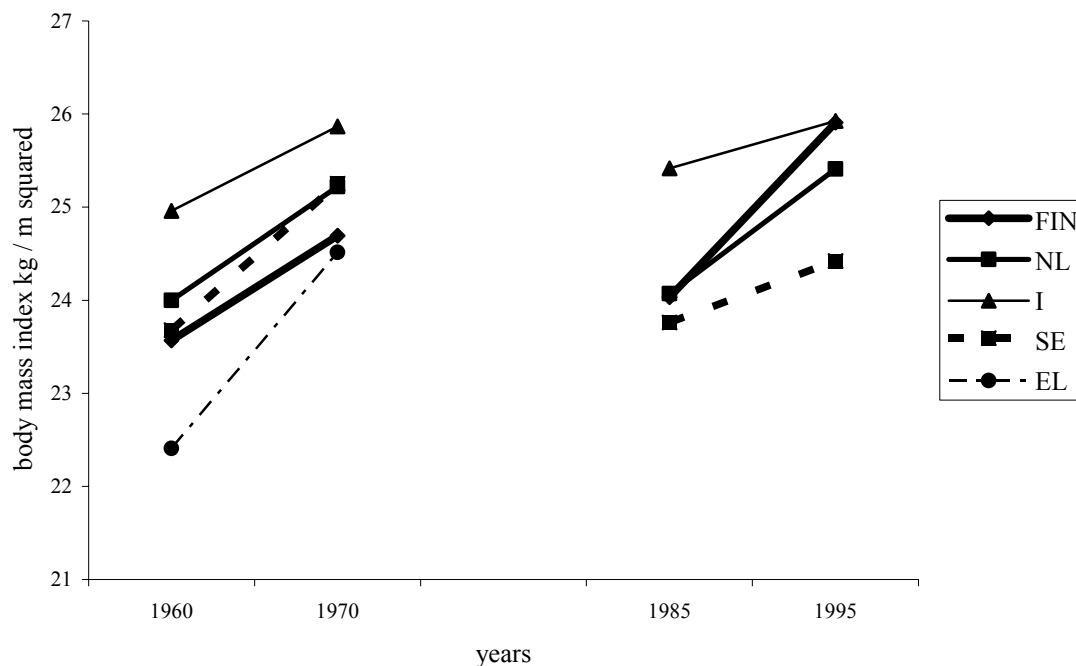


Figure 3. Trends in average body mass index in the generation effect analysis. The period 1960 – 1970 refers to aged 50-59; the period 1985-1995 refers to age 75-84. FIN = Finland; NL= the Netherlands; I = Italy; SE = Serbia; EL = Greece. Data from Greece not available for the period 1985-1995.

Objective 2: compare the age-related changes in biological risk factors in healthy men aged 40-99 in Northern and Southern Europe.

Curves describing time trends in mean risk factor levels, and dealing with the ageing effect, were separately produced for subjects who were still alive at the end of the 35-year follow-up period, and subsequently compared with curves based on all subjects available at each follow-up step. These results are not reported in detail. In all cases, for those surviving 35 years lower levels were seen in the early phase of the follow-up (1960-1970). During the last 10 years of follow-up the differences between the curves were much smaller until they reached the same final levels. This is due to the fact that at the last examination only the survivors are measured. Overall the shape of the curves were similar for the two groups.

Objective 3: investigate the effects of age-related changes in biological risk factors on CHD, stroke and all-causes mortality in Northern and Southern European populations, taking into account the effect of regression dilution bias.

The association between a single baseline serum cholesterol measurement and early and late CHD death risk was studied in men from 10 European cohorts in the Seven Countries Study. After exclusion of the first five years, a relatively constant strength in risk throughout the 35 years of follow-up was shown, although a strong relationship during the first 10-year period was followed by a weaker relationship later on (Figure 4). The pooled estimates for the five countries under study gave a relative risk for 1 mmol/L of serum cholesterol (95% CI) of 1.30 (1.18-1.43) for the first, 1.17 (1.09-1.27) for the second, and 1.20 (1.11-1.29) for the last 10-year period of follow-up (23). Ten-year changes in serum cholesterol concentrations predicted CHD and ACVD (CVD of atherosclerotic origin) mortality: an increase of cholesterol levels of 1 mmol/L corresponded to an increase of 11% (5-18) for CHD risk and 5% (0-10) for ACVD (26).

There was a continuous and significant association of baseline SBP with CVD and all-causes deaths during three decades of follow-up, although the strength of association was significantly declining from the first to the third decade. The relative risk for 20 mmHg of SBP (and its 95% confidence intervals) in predicting CVD deaths was 1.65 (1.54 – 1.77) for the first 10-year block; 1.33 (1.24 – 1.42) for the second block; and 1.22 (1.13 – 1.31) for the last 10 year block. The corresponding levels for all-causes deaths were 1.41 (1.34 – 1.49); 1.26 (1.19 – 1.32); and 1.11 (1.05 – 1.17). Changes in SBP during 10 years (delta-SBP) added predictive power to baseline measurements in a direct and significant way, with a relative risk for a change of 10 mmHg of 1.14 (1.10 – 1.17) for CVD deaths and 1.11 (1.09 – 1.13) for all-causes deaths (24).

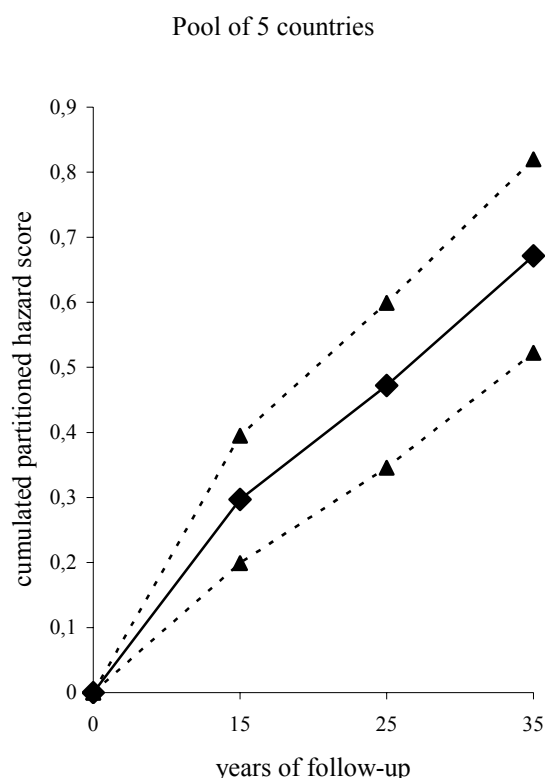


Figure 4. Cumulated partitioned hazard score of serum cholesterol predicting CHD death in 30 years (from year 5 to year 35 of follow-up) in the pool of 5 countries.

*Solid line= hazard score;
dotted lines=95% confidence intervals*

Death rates from typical (myocardial infarction, other forms of ischemia or sudden death) and atypical (chronic arrhythmias, heart blocks or heart failure in the absence of a history of angina, myocardial infarction, other forms of ischemia or sudden death) CHD were inversely related among the five countries. Death rates from typical CHD were highest in Northern Europe and lowest in Southern Europe. For atypical CHD this was the other way around. In the multivariate analysis conducted on pools of 5 countries (adjusted for countries), the relationship of risk factors with typical CHD deaths was direct and significant for age (hazard ratio -HR- for 5 years of age 1.44 (95% CI 1.36 – 1.52)), systolic blood pressure (HR for 20 mmHg, 1.39 (1.32 – 1.47)), serum cholesterol (HR for 1 mmol/l of 1.22 (1.16 – 1.27)) and smoking habits (HR smokers v non smokers of 1.39 (1.24 – 1.57)). For atypical CHD deaths, age had a larger HR of 2.27 (2.05 – 2.52), systolic blood pressure a smaller HR of 1.28 (1.16 – 1.41), serum cholesterol an inverse non-significant HR of 0.90 (0.58 - 1.58) and smoking habits a larger HR of 1.54 (1.26 – 1.89) (25).

Multivariate coefficients for systolic blood pressure and serum cholesterol change in the first 10 years of follow-up were statistically significant in prediction of CHD and ACVD deaths occurring between year 10 and 35, while baseline levels of the same risk factors retained their positive and significant predictive power. An increase of 20 mm Hg in systolic blood pressure was associated with a 22% (95% CI 13 – 31%) increase of risk for CHD death and a 25% (18 – 31%) for ACVD death (figure 1). For serum cholesterol an increase of its levels of 1 mmol/L corresponded to an increase of 11% (5 – 18) for CHD risk and 5% (0 – 10) for ACVD (26).

The role of recent systolic blood pressure and serum total cholesterol values relative to values 25 years earlier on CHD mortality and stroke in subjects aged 65 years and older was re-analysed using a sophisticated method to adjust for regression dilution bias. The results indicated that past systolic blood pressure seems to be more important than more recent systolic blood pressure in its effect on CHD, while for effects of cholesterol on CHD and systolic blood pressure on stroke both recent and past values seem to be important (27).

6.4. Conclusion

Time trends in biological risk factors for CVD studied in five European countries are complex and not univocal, although similarities with other observations have been found. A generalised increase in the levels of BMI (a cohort effect) and of systolic blood pressure (as a consequence of ageing) are the only universal findings. On the other hand, with some exceptions subsequent generations of middle-aged and elderly men tended to have lower average systolic blood pressure levels, which might partly reflect an increased use of anti-hypertensive drugs among hypertensives. Furthermore, between 1960 and 1985 population average serum cholesterol levels increased in Italy, Greece and Serbia, probably as a result of Westernization of Southern and Central European diets. In Finland however, healthy changes in diet may have contributed to a lowering of average serum cholesterol levels.

With respect to changes in cardiovascular risk factors in healthy men, in those surviving 35 years lower levels of systolic blood pressure, serum cholesterol and BMI were seen in the early phase of the follow-up (1960-1970). During the last 10 years of follow-up the differences between the survivors and the total study population were much smaller until the risk factors reached the same final levels. Overall the development in risk factors was similar for the two groups.

High serum cholesterol concentrations in middle-aged men increase the risk of CHD mortality later in life. Changes in cholesterol concentrations during follow-up additionally predict the risk of CHD. It was shown that a single serum cholesterol measurement in middle-

aged men maintains a strong relationship with the occurrence of CHD deaths during 35 years of follow-up, suggesting a long-term biological memory of serum cholesterol levels.

High systolic blood pressure in middle age increases the risk of all-causes mortality, cardiovascular mortality and CHD mortality later in life. Changes in blood pressure during follow-up additionally predict mortality risk.

Finally, the result indicate that serum cholesterol and age are differently related with typical and atypical CHD deaths, suggesting different etiologies for these coronary diseases. This suggests that a heart condition manifest only as heart failure or chronic arrhythmias represents a cause of death occurring, on average, in people older than those with typical coronary disease. Such a condition has no association with preceding levels of serum cholesterol and could represent a disease which should not be necessarily classified as CHD. We conclude from these findings the need to maintain a low serum cholesterol level into old age to keep CHD risk low and a low blood pressure level to keep CVD risk low.

7. Dietary determinants of healthy ageing

7.1. Objectives

This work package investigated gender-specific interrelationships between dietary factors and their impact on healthy ageing in persons aged 70-99 years. The key objectives were:

1. investigate nutrient intake and biomarkers of nutrient intake in relation to self-perceived health, psychological and cognitive functioning and all-causes mortality in elderly in Northern and Southern European populations;
2. investigate relations between nutritional status (body weight and indicators of body composition) and self-perceived health, psychological and cognitive functioning and all-causes mortality in elderly in Northern and Southern European populations;
3. develop a Healthy Diet Score to investigate relations between dietary patterns, self-perceived health and all-causes mortality in elderly in Northern and Southern European populations;
4. investigate the interrelationships between diet, physical activity, smoking and alcohol consumption in relation to self-perceived health, psychological and cognitive functioning and all-causes mortality in elderly in Northern and Southern European populations.

7.2. Methodology and study materials

Associations between diet, (biomarkers of) nutrient intake, nutritional status, health, functioning and all-causes mortality were studied in the FINE and SENECA study. Comparable longitudinal data were available for 13 European countries (FINE: Finland, Italy, the Netherlands; SENECA: Belgium, Switzerland, Denmark, Spain, France, Italy, the Netherlands, Portugal, Poland, Hungary, Greece, Serbia). In the FINE study information on men aged 70-89 years in 1990 was available. In the SENECA Study men and women aged 70-75 years were included at baseline (1988). Since 1988/1990 both studies have collected data on diet, physical activity, smoking, alcohol consumption, self-perceived health, psychological and cognitive functioning repeatedly. Dietary variables have been collected with the dietary history method in both the FINE and SENECA study. Data on biochemical indicators of nutrient intake have mostly been collected in the SENECA study. Repeated measures of diet and nutritional status were related to repeated measures of functioning and 10-year mortality data using Cox regression and repeated measurement models. Cluster and factor analysis in the combined large dataset was used to identify specific dietary patterns related to healthy ageing. Healthy Diet Scores developed for younger adults were evaluated and adapted for older persons. The interrelations of changes in weight, indicators of body composition, diet, physical activity, smoking and alcohol consumption in relation to self-perceived health, different aspects of functioning and mortality were modelled.

7.3. Results

Objective 1: investigate nutrient intake and biomarkers of nutrient intake in relation to self-perceived health, psychological and cognitive functioning and all-causes mortality in elderly in Northern and Southern European populations.

Preliminary analyses indicated that at age 81-86 years, total dietary intake decreased compared to 10 years before in free-living elderly from the SENECA cohorts Haguenau in the north and Romans in the south of France. In all periods daily dietary intake was generally low as compared to the recommended daily intake for elderly subjects (28).

With regard to serum concentrations of homocysteine (tHcy), a north-south gradient was observed. The lowest tHcy levels corresponded to Mediterranean countries (Portugal, Spain and Greece), while in central or northern European countries (the Netherlands, Belgium, and Poland) median values were at least 4 $\mu\text{mol/L}$ higher. Folic acid and vitamin B12 also showed a north-south pattern with generally higher levels in the South. The mean tHcy concentration for all centres was 16.0 $\mu\text{mol/l}$, which is well above the 14.0 $\mu\text{mol/L}$ usually recognised as the high-risk cut-off value. Countries with lower values showed lower concentrations in women than in men. Over a 10-year period, tHcy concentrations increased markedly in centres with high tHcy concentrations, whereas in centres with the lowest concentrations (Spain and Portugal, serum tHcy levels did not increase (29).

Cardiovascular mortality was significantly related to plasma carotene (α -, β - and γ -carotene) concentrations in the SENECA population. The relative risk per increment of 0.5 $\mu\text{mol/l}$ carotene was 0.79 (0.63 – 1.00). Inverse but non-significant associations were found with stroke and heart failure, and no association with CHD. The reduction in cardiovascular death risk was confined only to lean subjects with a BMI $<25 \text{ kg/m}^2$. Plasma levels of α -tocopherol were not significantly associated with cardiovascular mortality. The association between antioxidant levels and cardiovascular mortality did not differ between smokers and non-smokers, and there was no indication of an interaction between plasma levels of carotene and α -tocopherol (30).

General use of vitamin and mineral supplements had no favourable effect on all-causes mortality. Among smoking men there was a higher mortality among supplement users than among non-users (HR (95% CI) = 1.57 (1.08 – 2.29), and a similar tendency was observed for smoking women (HR=1.54 (0.71 – 3.36)). After including potential confounders, a tendency to a higher mortality rate in supplement users among smoking men (adjusted HR = 1.46 (0.95 – 2.26)) and smoking women (adjusted HR=2.58 (0.98 – 6.78)) persisted. In non-smoking men and women no significant relationship between supplement use and risk of mortality was found (HR=0.79 (0.52 – 1.19) for men and 0.90 (0.59 – 1.35) for women) (31).

Objective 2: investigate relationships between nutritional status (body weight and indicators of body composition) and self-perceived health, psychological and cognitive functioning and all-causes mortality in elderly in Northern and Southern European populations.

In the SENECA population, mean changes over a 10-year period in height, weight and circumferences were small to modest. Average height decreased by 1.5 – 2 cm. Overall, the distributions of body weight change were wide with median values close to zero. Clear decreases in body weight of 2.6 – 4.2 kg were observed in only three of the nine towns that were studied, i.e. Betanzos/Spain (in men and women), Yverdon/Switzerland (only in women) and Roskilde/Denmark (only in women). An increase of at least 5 kg of body weight took place in 13% of both men and women, whereas 23% and 27% of men and women lost at least 5 kg of their baseline weight. Such weight loss over the first 4 years of follow-up was significantly associated with higher mortality rates in men (crude RR 2.2; $p < 0.0001$; Figure 5). Serial changes in arm circumferences were small, but waist circumferences increased by 3 – 4 cm (32). Health effects of anthropometric changes will be investigated in future analyses.

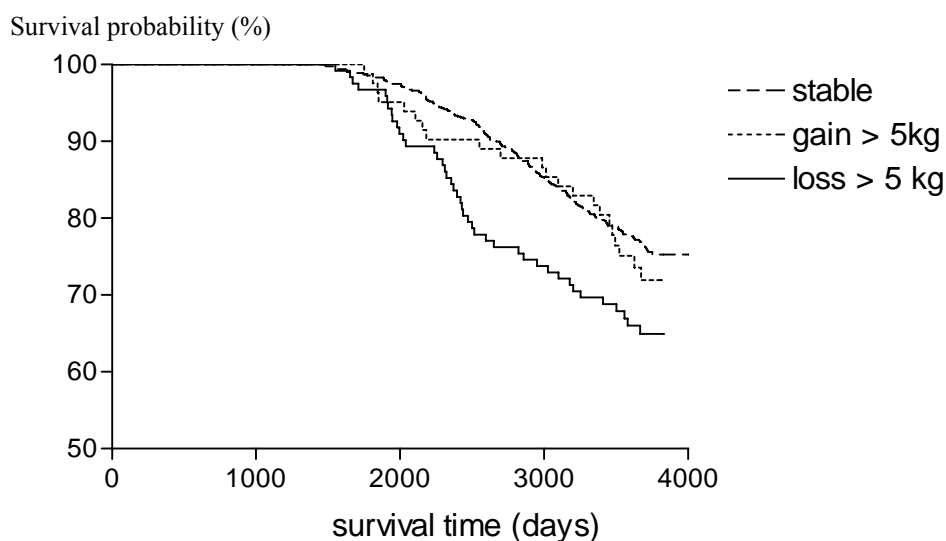


Figure 5. Probability of survival for subjects with and without weight change.

Objective 3: develop a Healthy Diet Score to investigate relationships between dietary patterns, self-perceived health and all-causes mortality in elderly in Northern and Southern European populations.

Three measures of overall dietary quality were composed: the Mediterranean Diet Score (MDS), which measures adherence to the traditional Greek Mediterranean diet; the Mediterranean Adequacy Index (MAI), which assesses how close a diet is to a Reference Italian Mediterranean diet as observed in Nicotera in Southern Italy in 1957; and the Healthy Diet Indicator (HDI), which evaluates the accordance with the WHO-guidelines for the prevention of chronic diseases. For a description of the diet scores the reader is referred to Knoops et al. (33). The association between dietary patterns and mortality was examined using the three indexes. The Mediterranean Diet Score (HR: 0.83 with 95 % CI: 0.75-0.92), the Mediterranean Adequacy Index (HR: 0.80 with 95 % CI: 0.72-0.88) and the Healthy Diet Indicator (HR: 0.89 with 95 % CI: 0.81-0.98) were inversely associated with all-causes mortality. Adjustments were made for age, gender, alcohol consumption, physical activity, smoking, number of years of education, body mass index, chronic diseases at baseline and study centre. The MAI was more strongly related to mortality in Northern than in Southern Europe.

Dietary patterns in the HALE study population were also identified by factor analysis based on 11 items. Three major patterns were identified. Factor 1 was characterised by high intakes of fruit and vegetables, fish and cheese and low intakes of sugar and alcohol. Factor 2 was mainly distinguished by high intakes of sugar and milk products and low intakes of alcohol. Factor 3 was expressive of high intakes of fats/oils, meat and low intakes of grains. These three main patterns were significantly associated with geographical region ($p < 0.001$) and with educational level ($p < 0.001$) (34). There was, however, a statistically significant interaction between geographical region and educational level ($p < 0.001$), indicating that the contribution of these two determinants was not independent. The most interesting results were observed for Factor 1. This pattern was generally privileged by medium and highly educated people, but the effect of educational level was stronger in the South ($p < 0.001$) than in the North ($p = 0.02$). However, the influence of the region was not significant ($p = 0.11$) among the people of low educational level, who were less likely to follow this pattern, whatever their region of origin (18).

Objective 4: investigate the interrelationships between diet, physical activity, smoking and alcohol consumption in relation to self-perceived health, psychological and cognitive functioning and all-causes mortality in elderly in Northern and Southern European populations.

The influence of smoking on plasma antioxidants (carotene, retinol, α -tocopherol and folic acid) was studied in men and women separately in the SENECA baseline sample. In men, smokers had lower concentrations (P50) of carotene ($0.34\mu\text{mol/L}$, $p<0.001$), retinol ($1.98\mu\text{mol/L}$, $p<0.01$), alpha-tocopherol ($26.93\mu\text{mol/L}$, $p<0.1$) and folic acid ($11.78\mu\text{mol/L}$, $p<0.05$) than former smokers (0.46 , 2.15 , 26.68 and $12.14\mu\text{mol/L}$) and non-smokers (0.53 , 2.0 , 28.79 and $12.91\mu\text{mol/L}$), respectively. No significant influence of smoking habit was found in women except for plasma folic acid (12.69 , 13.37 and $14.73\mu\text{mol/L}$ in current, former and non-smokers, respectively). The percentage of the population having an α -tocopherol/cholesterol ratio $> 5.2\text{ mmol/mol}$ was higher among non-smokers (71% for both men and women) than current smokers (58% and 69% for men and women, respectively) (35). Finally, serum homocysteine levels were significantly ($p<0.05$) higher in current (16.6 (0.4) $\mu\text{mol/L}$) and former (16.2 (0.3) $\mu\text{mol/L}$) smokers than in never smokers (13.8 (0.2) $\mu\text{mol/L}$).

After adjustment for confounding factors, homocysteine concentrations were related to total alcohol consumption ($r=0.16$, $p<0.005$), wine consumption ($r=0.15$, $p<0.005$) and spirits consumption ($r=0.07$, $p<0.05$), but not beer consumption ($r=0.02$). When persons were categorized according to their alcohol intake, there was a clear trend of an increase in homocysteine levels with increasing alcohol “status”, and homocysteine levels were significantly higher in those consuming more than 30 g/d alcohol compared to those who drank less. Traditional risk factors for CVD (cholesterol, HDL-cholesterol, triglycerides, albumin) were not associated with homocysteine levels (36).

Predictors of limitations in physical functioning, as measured with a 7-item physical performance test, included age, physical activity, presence of chronic diseases, geographical region and the Mediterranean Diet Score (37).

Among HALE participants, a lower all-causes mortality risk was significantly associated with adherence to a Mediterranean diet ($\text{HR}=0.77$ (95% CI $0.68 - 0.88$)), moderate alcohol use ($\text{HR}=0.78$ ($0.67 - 0.91$)), physical activity ($\text{HR}=0.63$ ($0.55 - 0.72$)) and non-smoking ($\text{HR}=0.65$ ($0.57 - 0.75$)). Similar results were observed for mortality from CHD, CVD and cancer. The combination of four low risk factors lowered the all-causes mortality rate to 0.35 ($0.28 - 0.44$) (see Figure 6). In total, 59% of all deaths, 64% deaths from CHD, 60% from CVD and 60% from cancer could be attributed to lack of adherence to this low-risk pattern (1).

7.4. Conclusion

Whilst small to modest average changes in height, body weight and circumferences emerged over SENECA’s 10-year follow-up period, considerable gains and losses of body weight had occurred in a significant proportion of the population. Early weight loss was predictive for lower subsequent survival.

The mean plasma homocysteine concentration for all study centres was well above the cut-off value that is used to identify subjects at increased risk for CVD. A north-south gradient in homocysteine levels was observed, with the lowest values in Mediterranean countries. Also serum folate and vitamin B12 concentrations followed a north-south pattern, with higher

levels generally found in the South. There were associations between homocysteine levels and total alcohol intake, intake of wine and spirits but not beer, probably due to the folate content of beer. Former and current smokers had higher homocysteine levels than non-smokers. Homocysteine concentrations showed no association with traditional CVD risk factors.

The results suggest that high plasma levels of carotene are associated with a 20% lower cardiovascular death risk in elderly people, especially in lean subjects. Most antioxidants examined in plasma were lowered by smoking in men, but not in women except for folic acid. There was no support for a favourable effect of the use of vitamin and mineral supplements on mortality.

A healthy diet (as determined with the modified Mediterranean Diet Score), moderate consumption of alcohol, non-smoking and being physically active all decrease all-causes and cause-specific mortality risk. The combination of the above low-risk factors is associated with a more than 50% lower rate of all-causes and cause-specific mortality. Since the two diet scores that measure agreement with a Mediterranean diet were stronger related to mortality than the WHO's HDI, those scores seem a better overall indicator of a healthy diet. Dietary patterns identified by factor analysis confirmed the persistence of geographical disparities but also the strong influence of socio-economic status that may modulate the cultural influence in the population of European elderly people.

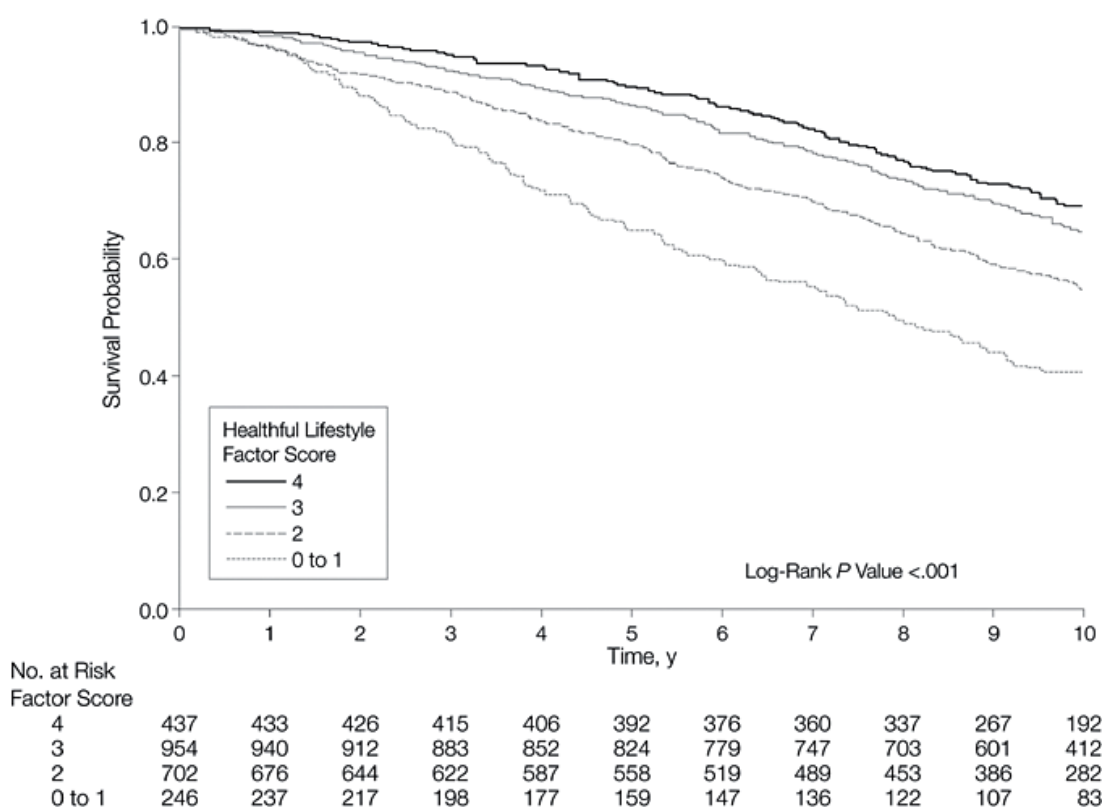


Figure 6. Kaplan-Meier Curves for Number of Healthful Lifestyle Factors

8. Healthy ageing in terms of functioning

8.1. Objectives

This work package investigated gender-specific age-related changes in and determinants of functioning in people aged 70-99 years in 13 European countries. Key objectives were:

1. compare age-related changes in self-perceived health and in physical, psychological, cognitive and social functioning in the elderly in Northern and Southern European populations;
2. compare the effects of socio-demographic and lifestyle determinants on self-perceived health and physical, psychological, cognitive and social functioning in the elderly in Northern and Southern European populations;
3. compare the relationships of different aspects of functioning with morbidity and mortality in the elderly in Northern and Southern European populations.

8.2. Methodology and study materials

Two international prospective studies including 13 European countries with comparable data on health and its determinants were used: the FINE Study (Finland, Italy, the Netherlands) and the SENECA Study (Belgium, Switzerland, Denmark, Spain, France, Italy, the Netherlands, Portugal, Poland, Hungary, Greece, Serbia). Longitudinal data were available for analyses on age-related changes in and determinants of functioning in the elderly within European countries and for comparison between European countries. The FINE Study contributed men aged 70-90 years in 1989-1991 to the HALE project and the SENECA Study men and women aged 70-75 years at baseline (1988-1989). These studies allowed us to operationalise healthy ageing in terms of mortality, morbidity and functioning. Functioning was measured with a generic question on self-perceived health, uni-dimensional measures (physical functioning: physical performance, activities of daily living; psychological functioning: depression; cognitive functioning; social functioning: frequency of contact, memberships) and with multi-dimensional measures. Determinants of functioning included in the studies were age, gender, socio-economic status, marital status, living situation, smoking, alcohol consumption, diet and physical activity. Cox regression analyses and repeated measurement models were used to examine the relationships of different aspects of functioning with morbidity and mortality.

8.3. Results

Objective 1: compare age-related changes in self-perceived health and in physical, psychological, cognitive and social functioning in the elderly in Northern and Southern European populations.

Physical functioning

Age-related changes in physical functioning, measured with a 12-item ADL questionnaire, were investigated using the HALE database. In the course of the 1990's physical functioning (disability and need for help) of European men and women aged 70+ at baseline declined with age, especially among men. Physical functioning was somewhat better in Southern than

in Northern Europe. Functional status ameliorated in succeeding birth cohorts over the 10-year follow-up period. This trend was more pronounced in the South than in the North and it was independent of the effect of age, study and region in self-care disability in both genders (OR 0.85 (0.75 – 0.97) in men and 0.64 (0.43- 0.97) in women) and in self-care need for help in men (OR 0.83 (0.70 – 0.96)) (38).

Self-perceived health

In the SENECA Study, women generally reported to be in good health less often than men. Highest percentages of people in good health were found in two study centres in Switzerland and in the Netherlands. Lowest percentages of people in good health were found in the study centres in Poland, Portugal and Hungary. In the FINE Study, men in Finland reported to be in good health less often than men in Italy and in the Netherlands. The percentage of healthy people decreased with 0.4-0.6% with age (continuous variable, in years) for FINE men. For SENECA men a similar trend was found (decrease of 0.9-1.1%). Effects of birth cohorts and years of study were not statistically significant (39).

Psychological functioning

The prevalence of depression, defined as Zung Self-rating Depression Scale ≥ 48 or Geriatric Depression Scale ≥ 6 , was positively associated with age in both sexes in cross-sectional analyses. The proportion of depressed persons was higher among women (14% – 39%) than men (9% – 32%) in all age groups. There was a higher prevalence of depression in the South than in the North in both genders. Psychological functioning ameliorated in similar age groups during follow-up, more markedly in the South than in the North (40).

Cognitive functioning

The influence of ageing, period and birth cohort on 10-year cognitive decline was studied in European elderly men who participated in the FINE Study. Cognitive functioning decreased with 1.5 points on the Mini-Mental State Examination (MMSE) (score 0-30) during 10 years. This decline was mainly attributable to an age effect, but differences in cognitive decline between birth cohorts were also observed as well as a period effect, indicating that respondents of later birth cohorts and later in time had a better cognition (41).

Social functioning

Regarding social functioning, the majority of men (in SENECA and FINE) had a partner during the 10-year study period and the majority of the women had no partner. The majority of men that lived with others, did so during the entire study period. In women there was more diversity: about 37% lived together with others during the entire study, 29% lived alone during the entire study period, and 21% lost their household members during the study (39).

Objective 2: compare the effects of socio-demographic and lifestyle determinants on self-perceived health and physical, psychological, cognitive and social functioning in the elderly in Northern and Southern European populations

Self-perceived health

Associations between socio-demographic and lifestyle determinants with self-perceived health were studied in the FINE and SENECA population. Cross-sectional analyses showed that being in good (self-perceived) health was associated with younger age, a higher level of education, consuming more alcohol (for men only), being a smoker, being more physically active and not having (had) diabetes, stroke or myocardial infarction. These associations were similar in Northern and Southern Europe. For diet, the associations differed between regions.

Being in good health was related to a healthier diet for FINE men in the North but not in the South. For men and women of the SENECA Study we found an opposite association: being in good health was related to an unhealthy diet in Southern but not in Northern Europe (42). Due to the cross-sectional nature of the above findings no causal inferences can be drawn and therefore the above associations should be interpreted with caution.

Psychological functioning

Associations of vitamin and mineral status with depression were studied in the SENECA population. Of the depressed patients (Geriatric Depression Scale score > 5) 2.4% had vitamin B12 deficiency and 0.3% suffered from folic acid deficiency. In the 1993 follow-up positive correlations between B-vitamin levels and mental health were observed, but no such correlations were found in the finale (1999), which might indicate a survival effect (43). Depressed elderly men in the FINE Study were less educated, showed lower cognitive functioning, were less physically active, had a lower serum cholesterol concentration and had more chronic diseases than the non-depressed ones. The two groups did not differ with respect to weight, total energy intake, alcohol consumption or smoking status. However, the total fat intake was statistically significantly lower and the ratio between monounsaturated and saturated fat intake higher among the depressed than the not depressed. In a follow-up of five years, conjugal loss, level of physical activity, decline in cholesterol levels, lower educational level and lower baseline cognitive functioning showed some association with risk of developing categorically defined depression. When age, education, cognitive functioning, socio-demographic variables and life style-related as well as dietary factors were controlled for, decline in cholesterol levels (1.96, 95% CI 1.12-3.45) and baseline depressive status (OR 1.22, 95% CI 1.13-1.31) were the strongest independent predictors of development of depression. Physical activity showed a weaker but still statistically significant negative association with risk of developing depression. Other life style-related or dietary factors were not independently associated with risk of depression (44).

The temporal relationship of blood pressure and serum cholesterol with late life depression was determined in 374 Finnish men. In 1989, the prevalence of depression, defined as a score of 48 or more on the Zung Self-rating Depression Scale, was 15.7%. When compared with those who did not develop a depression, men who developed depression showed lower mean serum cholesterol levels throughout the follow-up. In all men, aged 40-59 at baseline, the cholesterol levels increased up to the age of 59-74 and started to decline thereafter. In those developing depression the decline was more rapid than in those not developing depression (45). No relationship was found between baseline systolic or diastolic blood pressure and development of depression (46).

Cognitive functioning

Associations of vitamin and mineral status with cognitive function were studied in the SENECA population. Only 2.8% of the participants with a cognitive deficit (MMSE < 23) were deficient for vitamin B12 and none of them had a folic acid deficiency. In the 1993 follow-up positive correlations between B-vitamin levels and mental health were observed, but not in SENECA's finale (1999), which might indicate a survival effect (43). Data of the FINE Study were used to study the influence of marital status and living situation, physical activity and coffee consumption on cognitive function. Men who were married in 1985 and at follow-up in 1990 had a subsequent 10-year cognitive decline of 1.0 point on the MMSE (score 0-30). An additional decline of 1.0 and 1.1 points was observed in men who lost a partner and in unmarried men, respectively (Figure 7). Regarding living situation, men who lived together in 1985 and 1990 had a cognitive decline of 0.9 points. Men who started

to live alone and men who lived alone at both examinations had an additional decline of 1.2 and 2.8, respectively (47).

MMSE score

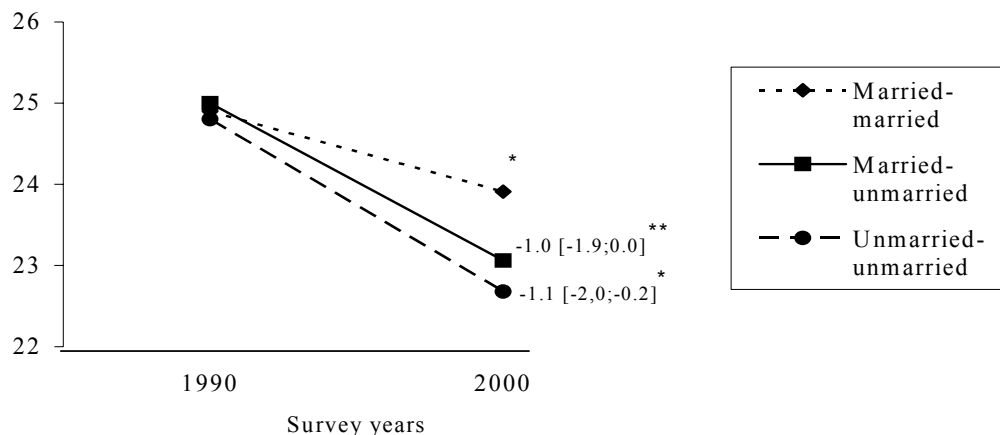


Figure 7. Transition in marital status between 1985 and 1990 with subsequent 10-year cognitive decline for 1121 Finnish, Dutch and Italian men.

* 10-year cognitive decline of the reference group of men who were married-married was 1.0 points (95% CI: [0.7;1.3]).

**Additional cognitive decline and 95% CI between parenthesis compared to reference group.

MMSE-score

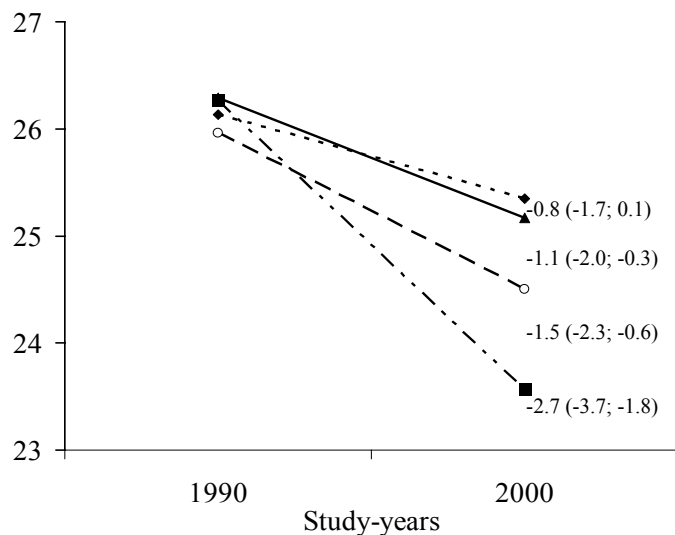


Figure 8. Ten-year cognitive decline per quartile of baseline intensity of physical activity for healthy Finnish, Dutch and Italian survivors.

- ■ — : lowest quartile
- ▲ — : second quartile
- - - ◆ - - - : third quartile
- - - ○ - - - : highest quartile

Mean change in cognitive functioning between 1990 and 2000 (95% CI). Adjusted for age, education, smoking status, alcohol consumption, country, mental activities and duration.

a Reference group

b Borderline significant different from reference group (p=0.07)

c Significant different from reference group (p=0.02)

d Significant different from reference group (p=0.004)

Rates of cognitive decline did not differ among men with a high or low duration of physical activity at baseline. However, a decrease in activity duration of more than 60 minutes per day over 10 years resulted in a decline of 1.7 points, which was 2.6 times stronger than the decline of men who maintained their activity duration. Men in the lowest *intensity* quartile (e.g., playing billiards and walking at lower pace than 3 miles per hour) at baseline had a 1.8 to 3.5 times stronger 10-year cognitive decline than those in the other quartiles (quartile 2 e.g. playing volleyball, walking at 3 mph; quartile 3 e.g. gymnastics and walking at 3.3 mph; quartile 4 e.g. swimming and walking more than 3.3 mph) (Figure 8). A decrease in intensity of physical activity of at least half a SD (corresponding to e.g. the difference between playing volleyball and swimming or with a change in walking velocity of 0.5 mph) was associated with a 3.6 times stronger decline than maintaining the level of intensity (48).

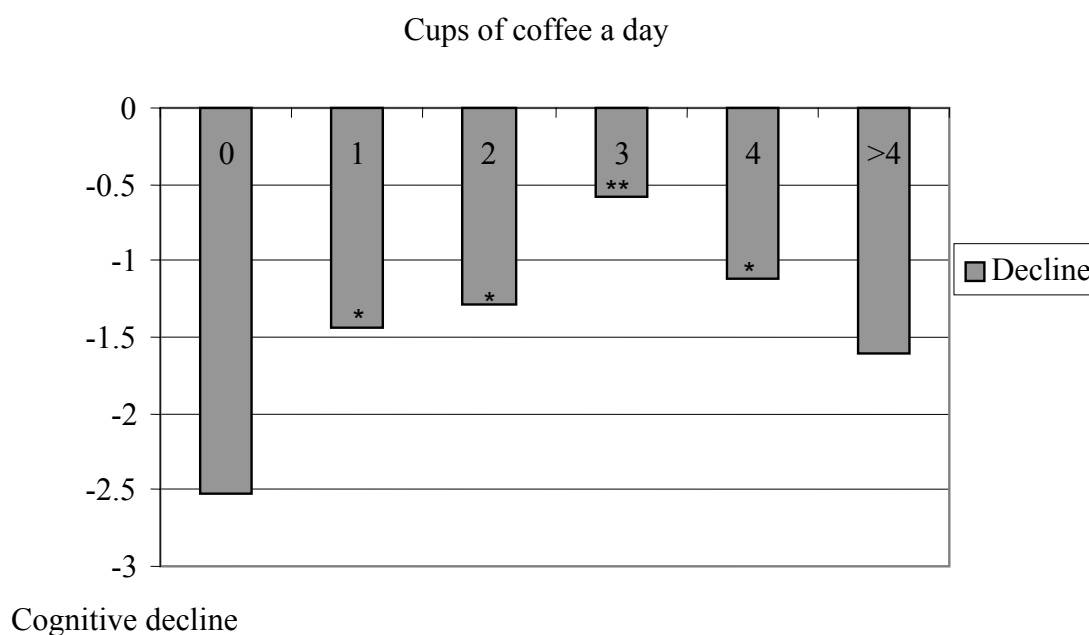


Figure 9. Magnitude of 10-Year Cognitive Decline by Number of Cups of Coffee Consumed at Baseline.

Multivariate adjusted for age, education, country, alcohol consumption, smoking status, physical activity and baseline cognitive functioning.

* Significant different from 0 cups of coffee a day ($p < 0.05$)

** Significant different from 0 cups of coffee a day ($p < 0.001$)

Men who consumed coffee had a 10-year cognitive decline of 1.2 points (4%), and men who did not had an *additional* decline of 1.4 points. A linear dose-response relationship was present up to three cups of coffee a day in such a way that increased coffee consumption was associated with less rapid cognitive decline. Men who consumed three cups of coffee a day had the smallest cognitive decline of 0.6 points, which was 4.3 times smaller than men who did not consume coffee. Men who consumed four or more cups had a stronger decline than men who consumed three cups, but a smaller decline than those who did not consume coffee (Figure 9) (49).

Social functioning

Associations between socio-demographic and lifestyle determinants with social functioning were studied in the FINE and SENECA population. Having few social contacts was related to lower levels of education, and for women also to less physical activity and having (had) diabetes or stroke. In women, having few social contacts was more prevalent in the lowest tertile of alcohol consumption. There was no relationship between social contacts and alcohol consumption for men. There were no striking differences between people from Northern or Southern Europe (42).

Objective 3: compare the relationships of different aspects of functioning with morbidity and mortality in the elderly in Northern and Southern European populations.

Self-perceived health

Being in good health was persistently related to a lower risk of total mortality, CVD-, CVA- and CHD-mortality, but not to cancer mortality. The association was somewhat stronger in Southern Europe for FINE-men and SENECA-women, and in Northern Europe for SENECA-men (42).

Cognitive functioning

The association between (five year change in) cognitive functioning and subsequent (five year) mortality was investigated in 493 men from the Netherlands and Italy. Ten-year mortality rates did not differ between men who were cognitively impaired, borderline impaired or cognitively intact in 1990. However, men whose cognition decreased (more than 1 SD) between 1990 and 1995 had a twofold increased risk of dying compared with men whose cognition was stable (HR_{adjusted}=1.9, 95% CI: [1.4;2.8]). Mortality risk of men whose cognition became better between 1995 and 2000 was not different from men whose cognition was stable (HR_{unadjusted}=1.1, 95% CI: [0.7;1.8] and HR_{adjusted}=1.1, 95% CI: [0.7;1.9]).

Social functioning

Having few social contacts was related to mortality for SENECA-women in Southern Europe. Women with few social contacts had higher risks of total mortality, CVD-, CVA- and CHD-mortality, but not of cancer mortality. The amount of social contact was not related to mortality in men. Having a partner or living with others was related to lower mortality risks for FINE and SENECA-men. This relation was not found in women (42).

8.4. Conclusion

Physical functioning

The results indicate that physical functioning decreases with increasing age. The fact that physical functioning ameliorated in succeeding birth cohorts more in the South than in the North suggests that dynamics of physical functioning in old age may be culturally determined.

Self-perceived health

Self-perceived health was generally better among men. Good self-perceived health was associated with lower age and higher education, more alcohol consumption (for men only), being a smoker, being more physically active and not having (had) diabetes, stroke or myocardial infarct. However, these associations should be interpreted with caution due to

their cross-sectional nature. The relation with diet differed according to study population and region. Self-perceived health decreased with age, and there were no cohort and period effects. Persons with a better self-perceived health have a lower total mortality, CVD-, CVA- and CHD-mortality, but not cancer mortality risk. No differences in self-perceived health between Northern and Southern Europe were observed.

Psychological functioning

Depression was more common among women. There were also regional differences in favour of men and women living in the North. The prevalence of depression was positively associated with age in cross-sectional analyses, but longitudinally decreased in succeeding birth cohorts, more markedly in the South than in the North. Depressed elderly men in the FINE Study were less educated, showed lower cognitive functioning, were less physically active, had a lower total fat intake and a higher monounsaturated/saturated fat intake ratio, a lower serum cholesterol concentration and more chronic diseases than the not depressed. Decline in cholesterol levels and baseline depressive status were the strongest independent predictors of development of depression during five years of follow-up. Physical activity showed a weaker but still statistically significant negative association with risk of developing depression. Positive correlations between B-vitamin levels and psychological functioning were observed, but not in the SENECA finale, possibly as a result of a survival effect. Preliminary results suggest that lower serum cholesterol levels in middle-age and a more rapid decline in cholesterol levels prior to the development of depression might be associated with the development of depression in late life. However, cardiovascular mortality in midlife or chronic diseases may have biased the results. Further analyses are needed to clarify the specificity of serum cholesterol to late life depression. Blood pressure levels did not predict development of depression independently of cognitive functioning and physical illness.

Cognitive function

Cognitive function in elderly men decreased with time. This was attributable to ageing, whereas respondents of later birth cohorts and later in time had a better cognition. Not cognitive functioning measured at one moment, but cognitive decline was associated with a twofold increase in 10-year mortality rates. Cognitive decline was less among men who were physically active, married, lived together and drank coffee. With respect to physical activity, participation in activities with at least a medium-low intensity might postpone cognitive decline even in old age. Maintaining duration or intensity of physical activity resulted in less cognitive decline than decreasing duration or intensity. Coffee consumption might also reduce cognitive decline; three cups of coffee seemed to be the optimum. However, confirmation by other longitudinal studies is needed. The finding that B-vitamin levels were positively correlated with cognitive function in 1993, but not in the finale (1999) might indicate a survival effect.

Social functioning

Women living in the South with more social contacts had lower total mortality, CVD-, CVA- and CHD-mortality, but not cancer mortality rates. In men, having a partner or living with others was associated with lower mortality rates. Differences in (dynamics of) social functioning between men and women were observed. Having few social contacts was related to lower education, and for women also to less physical activity and having (had) diabetes or stroke. In women, having few social contacts was more prevalent in those with a low alcohol consumption, but no relationship was found in men.

9. Summary and conclusions

In summary, results from the HALE project showed that morbidity and mortality as well as physical, psychological, cognitive, and social functioning in elderly men and women from 13 European countries generally decreased in participants getting older, but improved in subsequent generations. Morbidity, mortality and functioning were related to various demographic, lifestyle, dietary and biological factors. The main findings of the HALE project are briefly summarised below.

Construction of standardized European databases on healthy ageing

Work package 1 consisted of the construction of standardized European databases on healthy ageing and the completion of the mortality data. For work package 2, data of more than 7000 men followed for 35 years in the Seven Countries Study were available. Of those men, 5204 died, of which 2593 from CVD. For work packages 3 and 4, harmonization of the data of European elderly present in two databases (FINE and SENECA), was needed. This harmonization consisted of comparing questionnaires and individual questions, defining corresponding variables and answer categories, and validating scales and questionnaires. The number of persons in the combined database amounted to 2589 (of which 1829 free of chronic disease) men and 1216 (of which 918 free of chronic disease) women, and approximately one quarter of the women and half of the men died during 10 years of follow-up. These databases are very powerful for studying risk factor-disease relationships.

Biological risk factors for cardiovascular diseases

Trends in risk factors over a 35-year period were studied in the European cohorts of the Seven Countries Study. The increase in BMI in different age cohorts shows that the current obesity epidemic started already in the 1960's. However, in different countries and age groups favorable changes in serum cholesterol and blood pressure occurred, which might be ascribed to improvements in diet and lifestyle (as in Finland), but also to medication in the case of hypertension.

Systolic blood pressure measured at middle-age predicts CVD mortality even during a long (35 -year) follow-up period. The same holds for serum cholesterol in relation to CHD.

Changes in cholesterol and systolic blood pressure levels during follow-up also influenced cardiovascular mortality. We showed that systolic blood pressure levels are related to both typical and atypical coronary mortality, whereas serum cholesterol levels are related only to typical coronary mortality. These findings emphasize the importance of maintaining low systolic blood pressure (< 140 mmHg) and serum cholesterol levels (< 5 mmol/L).

Diet, risk factors and mortality

We showed that consumption of a Mediterranean type of diet lowers all-causes and cause-specific mortality risk. Further, cardiovascular, cancer and all-causes mortality were related to plasma carotene concentrations, which are partly determined by dietary intake. Blood α -tocopherol levels were not related to cardiovascular, cancer and all-causes mortality. From a public health perspective, these findings indicate that improvements in health can be achieved if more elderly adopt a healthy –Mediterranean type of– diet. Such a diet is characterized by a relatively high consumption of bread, cereals, legumes, vegetables, fruit, fish, vegetable oils and wine, and a relatively low intake of milk, cheese, meat, potatoes, eggs, animal fats and hard margarines, sweet beverages, cakes, pies and cookies, sugar, beer and spirits.

Use of vitamin and mineral supplements had no favorable effect on all-causes mortality. A potential explanation is that we only assessed the use of supplements in general, and no information was available on the use of supplements containing specific micronutrients for which elderly are at risk of having deficiencies. However, while such supplements might have beneficial effects, the need for supplementation in general may have been over advertised because our results showed clearly that a Mediterranean type of diet without adding supplements has the potential to improve health.

Trends in functioning

Physical, psychological, and cognitive functioning decreased as the participants got older. Although functioning decreased with age, in succeeding birth cohorts physical, psychological and cognitive functioning improved, meaning that the proportion of elderly people with functional impairments will decrease. This implies that the need for social and medical services may not increase in phase with ageing of the populations. However, since the number of elderly people will increase in the coming decades, the absolute demands on health services may increase in spite of these positive developments. Policy makers and public health professionals need to be aware of this.

Lifestyle, functioning and mortality

We showed that a lifestyle characterized by moderate consumption of alcohol, non-smoking and being physically active for at least 30 minutes per day (together with consumption of a Mediterranean type of diet) lowers the risk of all-causes and cause-specific mortality. We also found relationships of physical, psychological, cognitive and social functioning and self-perceived health with lifestyle. Especially a combination of healthy lifestyle factors decreased mortality risk. Considerable gains in terms of mortality and functioning could therefore be achieved if elderly change their lifestyle in a healthy way. Moderate consumption of alcohol, non-smoking and being physically active are the lifestyle factors in this context.

Regional differences

Regional differences were observed in terms of micronutrient status (generally in favor of the South), cardiovascular risk factors (generally in favor of the South), self-perceived health (no clear pattern) and functioning (psychological functioning in favor of the North, physical functioning in favor of the South). The observed improvement in functional status in succeeding birth cohorts was more pronounced in the South than in the North.

Overall conclusions

We conclude that maintaining low systolic blood pressure and serum cholesterol levels is important for the prevention of CVD. The increase in BMI in different age cohorts shows that the current obesity epidemic started already in the 1960's. However, in some countries and age groups also favourable changes in serum cholesterol and blood pressure occurred. The elderly form a population group in which health and functional status decrease with age, although in subsequent cohorts the proportion of healthy elderly has increased. When estimating the need for social and medical services, the effects of ageing, a growing elderly population and an improvement of health in subsequent cohorts must be taken into account. The HALE project has identified several determinants of health and functional status that can be targeted in public health interventions. These include consumption of a Mediterranean type of diet, moderate consumption of alcohol, non-smoking and being physically active.

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Appendix II: The HALE database

Basic data	Variables WP 2	Variables WP3	Variables WP 4
ID	Total cholesterol	Total cholesterol	Self-perceived health
Gender	HDL cholesterol	HDL cholesterol	Relative health
Country/region	Blood pressure	Triglycerides	Physical Performance
Date of birth	Anthropometric measures:	Albumin	Test (PPT):
Marital status	Weight	Vitamin D	PPT-tandem stand
Living status	Height	Homocysteine	PPT-measured walk
Number of children	Arm circumference	Anthropometric measures	PPT-single chair stand
Education	Triceps	Physical activity	PPT-repeated chair stand
Occupation		Diet scores:	Activities of Daily Living (ADL):
Income		Healthy Diet Indicator	ADL-Basic
Smoking		Mediterranean Adequacy Index	ADL-Mobility
Alcohol		Mediterranean Diet Score	ADL-Instrumental
Prevalence of:		Milk and milk products	Depression (Zung, GDS)
Myocardial Infarction		Fruits and fruit products	Mini Mental State
Stroke		Eggs	Examination (MMSE)
Diabetes		Poultry and meat	Physical activity
Cancer		Fish	Diet scores:
Causes of death		Vegetables	Healthy Diet Indicator
		Fats/oils	Mediterranean Adequacy Index
		Legumes/nuts/seeds	Mediterranean Diet Score
		Sugar/sweets	
		Grains/bread	
		Energy intake	
		Total protein	
		Animal protein	
		Total fat	
		Polyunsaturated fatty acids	
		Monounsaturated fatty acids	
		Saturated fatty acids	
		Cholesterol	
		Total carbohydrates	
		Mono- and disaccharides	
		Alcohol	
		Vitamin B1	
		Vitamin B2	
		Vitamin B6	
		Vitamin C	
		Vitamin A	
		β -carotene	
		Calcium	
		Iron	