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TITLE: Self-rated health and all-cause and cause-specific mortality of older adults. Individual data meta-analysis of prospective cohort studies participating in the CHANCES Consortium.

Running Head: Self-rated health and mortality of older adults.

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ABSTRACT (247 words)

Objectives: To evaluate, among the elderly, the association of self-rated health (SRH) with mortality, and to identify determinants of self-rating health as "at-least-good".

Study Design: Individual data on SRH and important covariates were obtained for 424,791 European and Unites States residents, ≥60 years at recruitment (1982-2008) in eight prospective studies of the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES). In each study, adjusted mortality ratios (HRs) in relation to SRH were calculated and subsequently combined with random-effect meta-analyses.

Main outcome measures: All cause, cardiovascular and cancer mortality

Results: Within 12.5 years median follow-up, 93,014 (22%) deaths occurred. SRH "fair" or "poor" vs. "at-least-good" was associated with increased mortality: HRs 1.46 (95% CI 1·23-1.74) and 2.31 (1.79-2.99), respectively. These associations were evident: for cardiovascular and, to a lesser extent, cancer mortality, and, within-study, within-subgroup analyses. Accounting for lifestyle, sociodemographic, somatometric factors and, subsequently, for medical history explained only a modest amount of the unadjusted associations. Factors associated with favourably SRH were: sex (males), age (younger-old), education (high), marital status (married/cohabiting), physical activity (active), body mass index (non-obese), alcohol consumption (low-to-moderate) and previous morbidity (absence).

Conclusion

SRH provides a quick and simple tool for assessing health and identifying groups of elders at risk of early mortality that may be useful also in clinical settings. Modifying determinants of favourably rating health, e.g. by increasing physical activity and/or by eliminating obesity may be important for older adults to “feel healthy” and “be healthy”.

Keywords: self-rated health; all-cause mortality; elderly; ageing; CHANCES; cohort

Abbreviations.

CHANCES: Consortium on Health and Ageing: Network of Cohorts in Europe and the United States;

CI: Confidence Interval;

HR: Hazard Ratio;

OR: Odds Ratio;

SRH: Self-Rated Health;

1. INTRODUCTION

Self-rated health (SRH) has been used as a health indicator since the early 50s by sociologists in health research [1]. SRH is assessed through a single-item question enquiring about a person's health with responses ranging from "excellent/very good" to "poor/very poor" [2-4]. Despite differences across these scales, it has been shown that they provide concordant answers [5].

SRH was firstly used by epidemiologists in the 80s, as a simple, convenient tool to assess health of older individuals [6]. Since then, the association of SRH with mortality has been documented by studies in Western and Asian populations of elders [7-12]. In 2006, a meta-analysis of 22 studies estimated 2-fold higher mortality risk associated with poorer SRH [13]. Several explanations have been proposed for the consistently-shown association of SRH with mortality. It has been argued that SRH among older individuals may reflect gender, education, lifestyle and cultural differences [12]. Nevertheless, studies focusing on subgroups defined by sex [14-18], or education [18-24], showed inconsistent results. Moreover, it has been hypothesized that SRH may be a proxy marker of "true" health [25-27]. SHR, however, remains a predictor of mortality even after controlling for objective assessment of health status [7, 13]. Finally, it has been stated that the association of SRH with all-cause mortality may reflect mortality from chronic diseases with greater impact of daily life, as opposed to mortality due to aggressive diseases with shorter time-to-death intervals; relevant studies are, however, limited [12].

Using centrally harmonized data from eight prospective single- and multi-centre cohort studies participating in the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES), we sought to address the above-indicated issues by evaluating: a) the association of SRH with all-cause, cardiovascular and cancer mortality in older residents of Europe and US, b) the relative merit in the indicated associations of controlling for potential confounders including medical history and, c) common patterns of sociodemographic, lifestyle, somatometric and medical history characteristics that determine the perception of older people's health in this multi-region population. To our knowledge this is the first, prospective investigation of that size that has investigated simultaneously the above-mentioned research questions.

2. METHODS

2.1 Participants

Details on CHANCES (http://www.chancesfp7.eu) have been published [28]. Overall, CHANCES includes fourteen single- or multi-centre on-going prospective cohort studies, undertaken in twenty three European and three non-European countries including the United States. Data collected within each study were harmonised according to pre-agreed harmonisation rules [29]. In total, 683,228 older adults, defined in most cohorts as being $\geq$60 years at recruitment, are included in CHANCES.

For each study, investigators satisfied the local requirements for ethical research, and obtained informed consent from participants.

2.2 Assessment of SRH

SRH at recruitment was assessed in eight of the 14 CHANCES studies. Details are shown in supplementary Table 1.

In each study, the question: "In general how would you rate your health over the last year" (Global SRH) was self-administered at recruitment. In SHARE the question "how would you rate your health in general" was used instead. Answers across studies were categorised in three groups as follows: "Poor" (including also "very poor"); "Fair"; and "at-least-good" (including "Good", "Very good" and "excellent").

2.3 Assessment of lifestyle, anthropometry and medical history

At enrolment, sociodemographic, lifestyle and medical history data were recorded (and subsequently harmonized) in most cohorts and anthropometric measures were undertaken. Physical activity was not assessed in EPIC-Elderly Umea and MORGAM. History of cancer was not available for this analysis in MORGAM.

2.4 Follow-up and death ascertainment

Vital status and cause of death were ascertained through record linkage with official death registries or through active follow-up (death certificates). In SHARE, date and cause of death were obtained from an "end of life interview" with contact persons. Cause-specific mortality, defined as the underlying cause of death was classified as "definite" and "possible" (29).

Primary outcome was all-cause mortality. Secondary outcomes were cardiovascular (CVD) and cancer mortality ("definite"/possible" combined).

From the initial 462,401, individuals, ≥ 60 years at enrolment, 37,610 were excluded due to missing/unreliable information about vital status or SRH. Eventually, 424,791 participants (93,014 deaths) were included in this study.

2.5 Statistical analyses

2.5.1 By participating study. The SRH-mortality associations were estimated through Cox regression models stratified by recruitment age (in age intervals) and cohort of recruitment (in multi-cohort studies). The underlying time scale was age at exit, (age of death or age at last follow-up for participants who were alive or lost from follow-up at last contact (censored)). Age at enrolment was the entry time.

Potential confounders were: sex, physical activity (vigorous physical activity/week, categorically: inactive: 0 hours; active: >0 hours; unknown), current smoking (categorically: non-smoker; daily; unknown), ethanol intake (g/day) at recruitment (categorically: sex-specific tertiles; unknown), body mass index (categorically: <25 kg/m^2; ≥25 to <30 kg/m^2 ; ≥30 kg/m^2; unknown), education (categorically: no formal/primary school; technical/secondary school; college/university/longer; unknown), and marital status (categorically: married/cohabiting; single/divorced/separated; widowed; unknown). Medical history at recruitment was considered through indicators (yes/no) of confirmed/self-reported

diagnosis of major morbidities: coronary heart disease (CHD), stroke, type 2 diabetes (T2D) mellitus, or cancer. A morbidity score indicating the number of these conditions (0-4) was also created.

We evaluated the relative merit of the previously-indicated potential confounders in the SRH-mortality association by fitting: MODEL 1: stratifying for age at recruitment, adjusting for sex; MODEL 2: MODEL 1 *plus* all indicated factors except medical history, and, MODEL 3: MODEL 2 *plus* the four indicators of medical history. The SRH-mortality association was evaluated also in subgroups by: sex; age: ($\leq$70yrs; >70yrs), and; educational attainment: ($\leq$primary school; >primary but <college; $\geq$college). In order to address whether the association of SRH with mortality differentiates across different levels of prevalent morbidity, we also evaluated the indicated association among those with no, 1 of $\geq$2 prevalent health conditions. The same models were fitted for CVD and cancer mortality among participants without CHD, stroke, T2D or cancer at recruitment. The focal event was CVD or cancer death, respectively, and death from other causes was censored.

Determinants of SRH were evaluated by considering SRH as binary outcome ("at-least-good" vs. "fair-or-worse") in logistic regression models including all indicated factors, overall, and in subgroups by morbidity score and sex.

2.5.2 Overall studies. From the eight studies, six shared individual data from selected sub-cohorts which were analysed centrally (Supplementary Table 1). HAPIEE and SENECA analysed their data locally using a common programming code. Meta-analyses were

subsequently performed to calculate overall pooled estimates of study-specific HRs/ORs, using random effects models [30] to account for any statistical between-study heterogeneity [31]. Sensitivity/subgroup analyses were undertaken to further explore heterogeneity (see Results).

Analyses were performed using STATA (Stata Corporation: Stata statistical software, release 11).

3. RESULTS

Mean follow-up ranged from 4.6 (SENECA) to 17.8 years (MORGAM). Based on a total of 4,615,162 person-years of observation, 93,014 deaths were observed among the 175,121 women and 249,670 men of the 8 participating studies. Number of participants/deaths, percentage of individuals > 70 years at recruitment, person-years of follow up and crude mortality rates are shown in Table 1, by study, sex and SRH. The majority of participants - 135,412 (77%) women and 204,061 (82%) men - rated their health as good/very good. Evident in this Table are differences across cohorts with respect to number and age distribution of participants which are reflected in differences in mortality rates. Nevertheless, in the vast majority of the studies a clear trend of increased mortality with lower SRH is evident, in both men and women.

In Table 2 the distribution of the 424,791 individuals from the 8 participating studies across categories of sociodemographic, lifestyle and somatometric variables and SRH are shown.

Men and women of higher education rated their health higher and so did those who were physically active, with ethanol intakes in the 2nd and 3rd tertiles, and married/cohabiting (men only). Of note, ethanol intakes were low with median intakes (g/day): 0.18 (practically non-consumers), 1.87 (low consumers) and 18.93 (moderate consumers) in the 1st, 2nd and 3rd tertiles. SRH of older (≥65 years) and obese men and women, as well as, of smokers (men only) was more often "fair"/"poor" than "at-least-good".

The distribution of individuals across prevalent medical conditions by participating study and SRH is shown in supplementary Table 2. Differences in patterns and frequency of prevalent conditions across studies were evident, reflecting differences in selection criteria and methods of assessment of the indicated conditions. Nevertheless, a notable correlation of SRH with the indicated morbid conditions (increasing percentage of prevalent morbidities by decreasing SRH) was apparent in all cohorts.

The study-specific, as well as, overall (using random-effects models) association of SRH with all-cause mortality is depicted in Figure 1 for each previously-indicated model. HAPIEE included only participants with complete data in all covariates in survival analyses and, therefore, 423,730 participants (92,743 deaths) were analysed. Study-specific HRs indicated increased mortality rates for SRH "fair" vs. "at-least-good" in all models/studies with the exception of the relatively small MORGAM (models 2 and 3). The overall sex-age adjusted HR (95% Confidence Interval (CI)) was 1.69 (1.30, 2.21), and was reduced by 5% (1.60 (1.27, 2.01)) when additional confounders were accounted for, and by another 9% (1.46 (1.23,

1.74)) when medical history was also included. The corresponding HRs for the "poor" vs. "at-least-good" comparison were all indicative of a strong, consistent association with a summary age-sex adjusted HR (95% CI) of 3.09 (2.11, 4.52), which was reduced to 2.73 (1.93, 3.87) in model 2 and to 2.31 (1.79, 2.99) in model 3. Between-studies heterogeneity was substantial (I^2 >90% for all estimates).

The estimated associations between SRH and mortality (model 3) were remarkably consistent in sensitivity analyses: a) restricted to individuals with no missing values in any potential confounder, b) excluding the dominating due to its large sample size NIH-AARP study, c) restricted to six studies which provided individual data, and d) excluding events of the first two years of follow-up – this analysis was undertaken to explore the impact of potential misclassification in self-reported morbidity (a predictor of mortality) which was used as a confounder in the overall analysis. Heterogeneity remained high and was slightly reduced only when NIH-AARP was excluded.

Subgroup analyses provided very similar estimates for the SRH-mortality associations except for the most highly educated people among whom the associations were somehow stronger (Supplementary Table 3). Between-cohort heterogeneity remained generally large, except in subgroups defined by educational attainment (reduction up to 50% in I^2 for the "poor" vs. "at-least-good" comparison) and morbidity score (I^2<1% in the (small) group with $\geq$2 prevalent conditions).

In Table 3 the associations of SRH with CVD and cancer mortality are shown, using studies with consistent data for individuals with no previous CHD, stroke, cancer or T2D which were analysed centrally. For CVD mortality, within-study and overall estimated associations were very similar to those for all-cause mortality but with greater uncertainty (wider confidence intervals) due to the reduction of number of individuals/events. The association with cancer mortality of SRH was evident only for the "poor" vs. "at-least-good" comparison in all studies of modest size and overall. Excluding the dominating NIH-AARP study reduced the SRH-CVD/cancer mortality associations and the between-study heterogeneity, but did not alter the statistical significance of the estimates.

Analysis of determinants of SRH, (supplementary Table 4) revealed that men compared to women had 20% higher odds of rating their health as "at-least-good" rather than "fair-or-worse". Excess in the corresponding odds was also observed for higher education, physical activity, and low-to-moderate ethanol intakes. In contrast, being older, obese (but not overweight) and single/separated decreased the odds of favourably rating health. Finally, having at-least-one of prevalent cancer, CHD, stroke or T2D was associated with a 56% decrease in the odds of higher SRH.

This pattern of determinants of SRH was generally evident a) in study-specific analyses, b) in subgroups by morbidity score and sex, and c) when the largest study (NIH-AARP) was excluded.

4. DISCUSSION

In this large, pooled investigation of eight single- and multi- centre cohort studies, we found that SRH "fair" or "poor" compared to "at-least-good" was associated with a 1.5 and >2 fold increased all-cause mortality, respectively. These associations were only slightly altered after adjustment for sociodemographic, somatometric and lifestyle factors and, subsequently, for medical history, and were consistent: a) in the vast majority of participating studies covering southern, northern, central and eastern European countries, as well as the US, b) in subgroups by sex, age, medical history and educational level, and c) for CVD and, to a lesser extent, cancer mortality. We also identified profiles of people who favourably rated their health, consisting of non-modifiable (sociodemographic) and modifiable (lifestyle) characteristics, as well as, medical history. This is the first multi-region investigation of this size which explored simultaneously the above issues.

Results of our study corroborate and add to existing evidence from studies in Europe, US and Asia regarding the apparent association of SRH with mortality [10-13, 32]. The magnitude of the associations estimated from our data are similar to that of the 2006 meta-analysis [13] and of recent studies in Western countries [10, 11], but higher than those reported in Asian populations- this discrepancy is probably attributed to differences in culture and attitudes regarding the perception and reporting of "health" [12, 18, 33, 34].

Certain questions need to be considered in view of these results: Is SRH a proxy marker of "true" health among older adults, and could SRH substitute for more "objective" measures of health? Is the SRH-mortality association evident only in certain subgroups, and/or, for

specific causes of death? Which characteristics are captured by SRH that may contribute to the apparent survival benefit?

Regarding the first question, it has been shown that SRH is strongly correlated with objective assessment of health such as medically diagnosed conditions [26, 27]. This was also evident in our study regarding SRH and prevalence of serious morbidities. Nevertheless, the association of SRH with mortality was only partly explained when these conditions were taken into account. Although unmeasured and residual confounding cannot be ruled out, SRH appears to capture other dimensions of "true" health and, thus, can supplement, (but not substitute), important, objective health indicators when studying mortality of older adults [33, 35-38].

Regarding the second question, previous studies reported conflicting results for the SRH-mortality association within certain subgroups, or, for cause-specific mortality, partly due to inherent differences with respect to design, populations accrued, and assessment of variables of interest [12, 20-22, 39, 40]. In our study, having the advantage of using harmonized data for exposure/covariates, we found that the SRH-mortality association was consistent in subgroups defined by, sex, age, education and medical history in the majority of studies and overall. Moreover, our analyses confined to apparently healthy individuals, indicated associations of SRH with CVD and cancer mortality – for the latter only for the "poor" (but not "fair") vs. "at- least-good" SRH comparison. SRH has been associated with CVD mortality previously but literature is rather limited [12, 40]. Results regarding cause-specific

mortality, however, should be cautiously interpreted since information on date of diagnosis, type, severity and treatment or either diseases, should be also accounted for. Moreover, SRH was only assessed at recruitment and may have changed in the light of underlying diseases, even before diagnosis. More research is needed towards this direction.

To address the third question, we identified overall profiles of SRH at-least-good. We consistently observed that being male, younger-old, educationally advanced, married or cohabiting, physically active, not obese, low-to-moderate ethanol consumer, and apparently healthy, increases the probability among elders of favourably rating their health. Notably, apart from inherent characteristics (sex and age) and non-modifiable (among older adults) status such as education, the rest are well-documented modifiable risk factors associated with life-expectancy.

To our knowledge, the present work is the largest and most comprehensive study of the association of SRH with mortality of older adults. Other strengths are the multi-region population covered, allowing for broad generalizability of our results, the hard endpoint used, eliminating the role of outcome-misclassification, the harmonised data, ensuring minimal differences in exposures/covariates assessment/recoding, and the high statistical power, allowing for precise estimates and several subgroup analyses. Common analyses were undertaken in all studies increasing the validity of summary estimates as compared to a typical meta-analysis of differently-conducted published studies.

There is also a number of limitations. Despite central harmonization, between-study differences in design and definitions of original variables still exist. Participants may not be representative of the corresponding general populations but this is unlikely to have biased the estimated associations due to the prospective design of studies included. A related issue is the probability of selective mortality in these data, implying that inferences of our study may apply mainly to a "healthy" population of elders. Nevertheless, our results were generally consistent when individuals with serious morbidities at recruitment were analysed. We used only baseline SRH which may have changed during follow-up, although SRH is considered to remain stable even after major health events [41].

A further limitation was the substantial between-study statistical heterogeneity which was, partly, due to the inclusion of larger and smaller cohorts, resulting in variation in the precision of the risk estimates, which may have inflated I^2 values [42]. Repeating the meta-analyses without the dominating NIH-AARP led, generally, to lower but still high I^2 values. Nevertheless, the relative risk estimates appear remarkably consistent in all analyses.

In this large, prospective investigation across Europe and US, we observed increased mortality in people 60 years or older with poorer SRH, consistent across geographical regions, sex, age groups, health status and level of education. We also identified profiles of elderly who favourably rate their health, that include modifiable risk factors such as physical activity and obesity. Our results corroborate and add to existing evidence by supporting the use of SRH as a screening tool to identify groups of elders at higher risk of early mortality which can

be of value even in clinical settings. Given the current trends in demographic ageing and the increased morbidity and mortality among older adults, the shift in the indicated socio-lifestyle factors that determine SRH is important in order for older adults to “feel healthy” and “be healthy”.

4.1 Conclusions

SRH provides a quick and simple tool for assessing health and identifying groups of elders at risk of early mortality. Modifying determinants of favourably rating health, e.g. by increasing physical activity and/or by eliminating obesity may be important for older adults to “feel healthy” and “be healthy”.

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5.2 Compliance with Ethical Standards

5.2.1 Disclosure of potential conflicts of interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare:

Dr. Peasey reports grants from DG-RESEARCH EC-FP7, WELLCOME TRUST, USA National Institute of Aging and MacArthur Foundation during the conduct of the study.

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legally authorized to confirm that Prof. Dimitrios Trichopoulos had no conflict of interest.

The rest of the authors declare that they have no conflict of interest.

5.2.2 Statement of human rights

Ethical approval

For each study, investigators satisfied the local requirements for ethical research.

Informed consent

Informed consent was obtained from all individual participants included in each study.

5.2.3. Authors' contribution:

Christina BAMIA, Philippos ORFANOS, Antonia TRICHOPOULOU and Dimitrios TRICHOPOULOS planned the study. Christina BAMIA carried out the statistical analyses, interpreted the findings and drafted the manuscript. Philippos ORFANOS, Hendrik JUERGES, Ben SCHÖTTKER, Hermann BRENNER, Roberto LORBEER, Mette AADAHL, Charles E. MATTHEWS, Ute MONS, Kai-Uwe SAUM and Antonia TRICHOPOULOU contributed to the writing of the manuscript. All authors revised drafts critically for important intellectual content, and all authors reviewed and approved the final manuscript. All authors, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have seen and approved the final version of the manuscript

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Table 1. Number of Individuals and Deaths, Percentage of Elders (> 70 Years) at Recruitment (1982-2008), and Mortality Rates[a] of the 424,791 Study Participants (93,014 Deaths), per study, sex and Self-Rated Health at Recruitment. The Consortium on Health and Ageing: Network of Cohorts in Europe and the United States Participants.

		Self-Rated Health											
		"At-least-good[b]"				"Fair"				"Poor"			
		Men											
Study/Cohort	**≥70 yrs[c] (%)**	**N**	**Deaths**	**Y[d]**	**MR[a]**	**N**	**Deaths**	**Y[d]**	**MR[a]**	**N**	**Deaths**	**Y[d]**	**MR[a]**
EPIC Elderly	21%	3314	746	37.342	19.98	1650	547	16.984	32.21	321	152	3.0500	49.84
ESTHER	23%	1,834	270	16.328	16.54	721	189	6.082	31.08	61	22	0.457	48.09
HAPIEE	0%	1,909	193	11.361	16.99	4478	754	25.672	29.37	1127	370	5.873	63.00
MORGAM	27%	1,208	715	16.464	43.43	229	96	2.254	42.59	52	37	0.412	89.69
NIH-AARP	6%	188,289	39,254	2177.260	18.03	26,933	12,298	264.340	46.52	4,696	3,233	34.265	94.35

SENECA[e]	100%	745	337	6.065	55.56	317	189	2.190	86.31	101	76	0.599	126.74
SHARE	47%	5,483	442	26.358	16.77	2605	478	11.615	41.15	1089	347	4.283	81.02
TROMSØ	43%	1,279	665	15.126	43.96	1,097	696	11.415	60.97	132	107	1.043	102.59
							Women						
EPIC Elderly	20%	4,046	446	47.343	9.42	2699	411	29.918	13.74	700	151	7.250	20.83
ESTHER	22%	1,979	145	18.290	7.93	878	142	7.866	18.05	41	8	0.360	22.24
HAPIEE	0%	1,432	67	9.132	7.34	5016	361	30.110	11.99	1799	240	10.327	23.24
MORGAM	24%	1,063	462	17.246	26.79	230	66	2.344	28.16	62	38	0.548	69.28
NIH-AARP	6%	119,422	17602	1420.760	12.39	18,291	6,174	195.440	31.59	2,866	1,607	24.500	65.59
SENECA	100%	628	135	5.805	23.26	404	129	3.487	37.00	154	71	1.239	57.31
SHARE	49%	5,568	317	27.116	11.69	3261	394	15.210	25.90	1503	336	6.337	53.02
TROMSØ	50%	1,274	502	16.59	30.26	1,630	868	19.182	45.25	175	129	1.739	74.18

Abbreviations: AT, Austria; BE, Belgium; CH, Switzerland; CZ, Czech Republic; DK, Denmark; EPIC, European Prospective Investigation into Cancer and nutrition; ESTHER, Epidemiological Study on Chances for Prevention. Early Detection. and Optimized THErapy of Chronic Diseases at Old Age; ES, Spain; FR, France; DE, Germany; GR, Greece; HAPIEE, the Health. Alcohol and Psychosocial factors in Eastern Europe; IT, Italy; IL, Israel; LT, Lithuania; MORGAM, MOnica Risk. Genetics. Archiving and Monograph; MR, Mortality Rates; NL, Netherlands; NIH-AARP, National Institutes of Health-American Association of Retired Persons Diet and Health; PL, Poland; RU, Russia; SENECA, Survey Europe on Nutrition in the Elderly: a Concerted Action; SHARE, Survey of Health. Ageing and REtirement in Europe; SE, Sweden;

[a] per 1000 person years

[b] good or very good (including excellent)

[c]Age at recruitment

[d] Y=Person Years/1000

Table 2. Distributions (Numbers and Column %) of the 249,670 Men and 175,121 Women Participating in the 8 Studies, by Certain Characteristics at Enrolment (1982-2008), and Categories of Self-Rated Health. The Consortium on Health and Ageing: Network of Cohorts in Europe and the United States Participants.

Characteristics at recruitment		***Men***				***Women***			
		Self-Rated Health				**Self-Rated Health**			
		"at–least-good[a]"	**"Fair"**	**"Poor"**	**Total**	**"at–least-good[a]"**	**"Fair"**	**"Poor"**	**Total**
Age ≥65 yrs		116,087	23,536	4,696	144,319	74,655	19,520	4,654	98,829
	%	*56.9*	*61.9*	*62.0*	*57.8*	*55.1*	*60.2*	*63.8*	*56.4*
Physical Activity: Active[b]		108,319	13,682	1,691	123,692	59,468	9,137	1,536	70,141
	%	*53.1*	*36.0*	*22.3*	*49.5*	*43.9*	*28.2*	*21.0*	*40.1*
Smoking status: Daily smoker		19,278	6,024	1,316	26,618	16,702	4,139	766	21,607
	%	*9.4*	*15.8*	*17.4*	*10.7*	*12.3*	*12.8*	*10.5*	*12.3*
Ethanol consumption: >1st tertile[c]		135,669	18,946	2,730	157,345	85984	12,009	1,725	99,718

	%	*66.5*	*49.8*	*36.0*	*63.0*	*63.5*	*37.1*	*23.6*	*56.9*
Body Mass Index: ≥ 30 kg/m^2		35,889	10,505	2,045	48,439	26460	11,839	2,944	41,243
	%	*17.6*	*27.6*	*27.0*	*19.4*	*19.5*	*36.5*	*40.3*	*23.6*
Education: > primary education		190,386	31,786	5,923	228,095	122,177	23,794	4,654	150,625
	%	*93.3*	*83.6*	*78.2*	*91.4*	*90.2*	*73.4*	*63.8*	*86.0*
Marital status: married/cohabiting		176,011	31,321	6,127	213,459	60,621	14,845	3,318	78,784
	%	*86.3*	*82.4*	*80.8*	*85.5*	*44.8*	*45.8*	*45.5*	*45.0*
TOTAL		**204,061**	**38,030**	**7,579**	**249,670**	**135,412**	**32,409**	**7,300**	**175,121**

[a] Good or very good (including excellent)

[b] >0 hours of vigorous physical activity/week; EPIC-Elderly UMEA and MORGAM do not have data available on physical activity

[c] Based on sex specific ethanol intake at enrolment

Table 3. Fully Adjusted[a] HR and 95% CI of Cardiovascular and Cancer Mortality Associated with Self-Rated Health, Overall, and by Participating Cohort. The Consortium on Health and Ageing: Network of Cohorts in Europe and the United States Participants.

Cause of death	N	Deaths	$HR_{fair/"at\text{-}least\text{-}good"}$	95% CI		$HR_{poor/"at\text{-}least\text{-}good"}$	95% CI	
				lower	upper		lower	upper
Cardiovascular								
ALL[b]	*280,661*	*12,781*	*1.56[c]*	*1.12*	*2.16*	*2.87[c]*	*1.96*	*4.22*
EPIC-Elderly	10,252	746	1.24	1.06	1.45	2.33	1.83	2.96
ESTHER	3,808	126	1.73	1.19	2.51	1.06[d]	0.25	4.41
MORGAM	2,341	395	1.31	0.92	1.86	3.24	1.87	5.61
NIH-AARP	264,260	11,514	2.03	1.93	2.15	3.82	3.36	4.35
Cancer								
ALL[b]	*280,661*	*20,787*	*1.26[e]*	*0.91*	*1.75*	*2.37[e]*	*1.37*	*4.11*
EPIC-Elderly	10,252	676	0.99	0.84	1.19	1.61	1.22	2.13
ESTHER	3,808	175	1.23	0.88	1.72	1.31[f]	0.47	3.67
MORGAM	2,341	479	1.18	0.845	1.65	3.09	1.85	5.14
NIH-AARP	264,260	19,457	1.68	1.61	1.76	3.67	3.31	4.06

Abbreviations: CI, Confidence Interval; EPIC, European Prospective Investigation into Cancer and nutrition; ESTHER, Epidemiological Study on Chances for Prevention. Early Detection. and Optimized THErapy of Chronic Diseases at Old Age; HAPIEE, the Health. Alcohol and Psychosocial factors in Eastern Europe; HR, Hazard Ratio; MORGAM, MOnica Risk. Genetics. Archiving and Monograph; NIH-AARP, National Institutes of Health-American Association of Retired Persons Diet and Health; SENECA, Survey Europe on Nutrition in the Elderly: a Concerted Action; SHARE, Survey of Health. Ageing and REtirement in Europe;

[a] Only individuals with no history of coronary heart disease, stroke, cancer or type 2 diabetes mellitus were analysed. Adjusting by Model 3

[b] Cohorts with consistent information on cause of death and with available individual data, which were analysed centrally, were included (EPIC-Elderly, ESTHER MORGAM and NIH-AARP).

[c] I^2 for heterogeneity: $\mathbf{HR_{fair/"at\text{-}least\text{-}good"}}$: 92.1%, $\mathbf{HR_{poor\ /\ "at\text{-}least\text{-}good"}}$: 80.4%

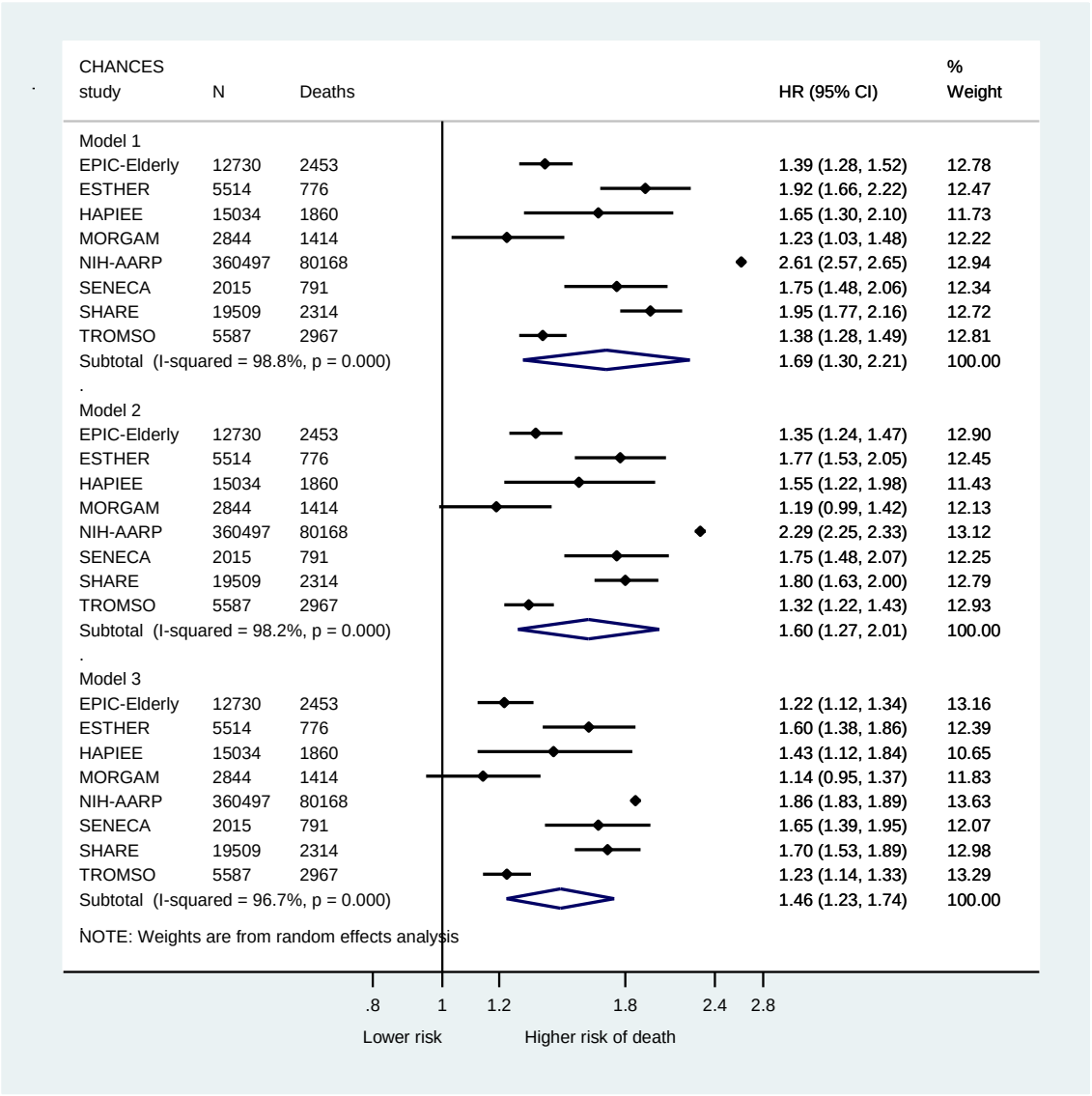
[d] Only 50/3,808 (1.3%) of the ESTHER individuals had self rated heath "poor". Only 2/50 (4%) were dead due to cardiovascular events

[e] I^2 for heterogeneity: $\mathbf{HR_{fair/"at\text{-}least\text{-}good"}}$:92.2% $\mathbf{HR_{poor\ /\ "at\text{-}least\text{-}good"}}$:90.8%

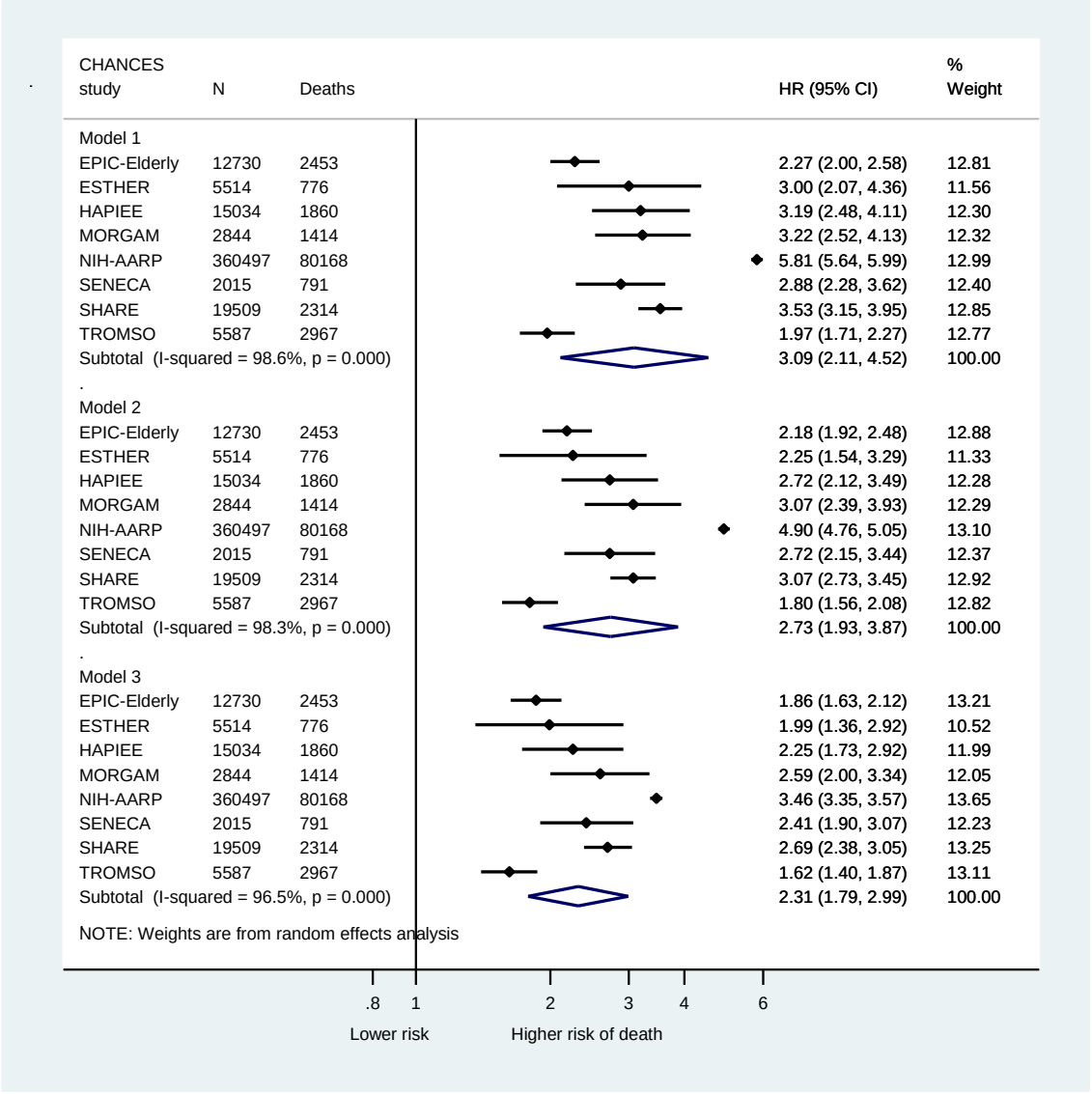
[f] Only 50/3,808 (1.3%) of the ESTHER individuals had self rated heath "poor". Only 4/50 (8%) were dead due to cancer

Figure 1: Meta-Analysis of the Association of Self-Rated Health, with Mortality according to Models 1, 2 and 3. A) HRs for the "fair" vs "at-least-good" comparison; B) HRs for the "poor" vs "at-least-good" comparison. The Consortium on Health and Ageing: Network of Cohorts in Europe and the United States Participants.

A)



B)



Abbreviations: CI, Confidence Interval; EPIC, European Prospective Investigation into Cancer and nutrition; ESTHER, Epidemiological Study on Chances for Prevention. Early Detection. and Optimized THErapy of Chronic Diseases at Old Age; HAPIEE, the Health. Alcohol and Psychosocial factors in Eastern Europe; HR, Hazard Ratio; MORGAM, MOnica Risk. Genetics. Archiving and Monograph; NIH-AARP, National Institutes of Health-American Association of Retired Persons Diet and Health; SENECA, Survey Europe on Nutrition in the Elderly: a Concerted Action; SHARE, Survey of Health. Ageing and REtirement in Europe;

Model 1: Stratified for age and adjusted for sex
Model 2: As in Model 1 and additionally for: physical activity, smoking, ethanol intake, body mass index, education and marital status
Model 3: As in Model 2 and additionally for: Prevalent cancer at recruitment (yes/no); Prevalent coronary heart disease at recruitment (yes/no); Prevalent stroke at recruitment (yes/no); Prevalent type 2 diabetes mellitus at recruitment (yes/no)

Annex

Supplementary Table 1. Selected Characteristics of the Studies and Cohorts Included in the Current Investigation of the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States Participants.

No	Study	Cohorts included in the analysis	Period of enrolment	Period of follow-up	Reference[a]	Individual data analysed centrally
1	EPIC-Elderly (selected centres)	GR. NL. SE	1992-1999	1993-2011	Trichopoulou et al. 2005	Yes
2	ESTHER	DE	2000-2002	2000-2010	Schöttker et al. 2013	Yes
3	HAPIEE	CZ. PL. RU LT	2002-2008	2002-2010	Peasey et al. 2006	No
4	MORGAM[b]	DK. DE.	1982-2001	1983-2010	Evans et al. 2005	Yes
5	NIH-AARP	USA	1995-1997	1995-2008	Schatzkin et al. 2001	Yes
6	SENECA	BE. DK. FR. IT. NL. ES. CH. GR. HU. NO. PT. PL	1988-1989	1993 - 1999	De Groot and van Staveren. 1991	No
7	SHARE[c]	AT. BE. CH. CZ. DE. DK. ES. FR. GR. IL. IT. NL. PL. SE.	2004-2007	2004 - 2012	Börsch-Supan et al. 2013	Yes
8	The Tromsø study	NO	1994-1995	1995-2010	Jacobsen et al. 2012	Yes

Abbreviations: EPIC: European Prospective Investigation into Cancer and nutrition; ESTHER: Epidemiological Study on Chances for Prevention. Early Detection. and Optimized THErapy of Chronic Diseases at Old Age; HAPIEE: the Health. Alcohol and Psychosocial factors in Eastern Europe; MORGAM: MOnica Risk. Genetics. Archiving and Monograph; NIH-AARP: National Institutes of Health-American Association of Retired Persons Diet and Health; SENECA: Survey Europe on Nutrition in the Elderly: a Concerted Action; SHARE: Survey of Health. Ageing and REtirement in Europe; Austria (AT); Belgium (BE); Czech Republic (CZ); Germany (DE); Hungary (HU); Sweden (SE); Switzerland (CH); Denmark (DK); Greece (GR); The Netherlands (NL); Spain (ES); France (FR); Italy (IT); Poland (PL); Portugal (PT); United States of America (USA); Lithuania (LT); Russia (RU); Norway (NO); Israel (IL)

[a] The indicated references are listed below

[b] More cohorts are included in the MORGAM study (http://www.thl.fi/publications/morgam/cohorts/tables/base_summary.htm) but only those indicated in this Table participated in the current study

[c] SHARE conducts end-of-life interviews for deceased respondents. These end-of-life interviews are administered to relatives or other persons close to the deceased.

Supplementary Table 2. Distribution of Participants (Column %) by Medical History and Categories of Self-Rated Health at Recruitment (1982-2008). The Consortium on Health and Ageing: Network of Cohorts in Europe and the United States Participants.

	Self-Rated Health			
STUDY	**"at-least-good[a]"**	**"Fair"**	**"Poor"**	**Total**
EPIC-Elderly (%)				
Prevalent Cancer	3.65	4.62	8.81	4.4
Prevalent coronary heart disease	1.73	6.42	8.33	3.86
Prevalent stroke	0.63	3.63	4.51	1.96
Prevalent diabetes	7.16	16.88	17.24	11.29
At least one of the above	12.49	28.01	33.4	19.47
ESTHER (%)				
Prevalent Cancer	7.29	9.32	8.82	7.91
Prevalent coronary heart disease	5.51	9.44	16.67	6.86
Prevalent stroke	2.99	7.75	15.69	4.61
Prevalent diabetes	14.27	24.89	29.41	17.63
At least one of the above	26.07	41.28	50.98	30.94
HAPIEE (%)				
Prevalent Cancer	4.31	8.04	10.05	6.43
Prevalent coronary heart disease	5.15	10.39	17.98	10.69
Prevalent stroke	1.92	4.28	12.45	5.30
Prevalent diabetes	7.43	12.17	20.34	12.68

At least one of the above	17.11	27.96	46.60	29.07
MORGAM (%)				
Prevalent Cancer[1]				
Prevalent coronary heart disease	5.15	9.59	17.54	6.36
Prevalent stroke	2.86	6.32	13.16	3.83
Prevalent diabetes	7.18	19.17	30.7	10.06
At least one of the above	13.74	30.5	44.74	17.69
NIH_-ARP (%)				
Prevalent Cancer	1.57	3.25	5.57	1.87
Prevalent coronary heart disease	12.91	39.00	53.46	17.03
Prevalent stroke	1.76	7.72	14.65	2.78
Prevalent diabetes	7.57	24.85	33.62	10.28
At least one of the above	21.14	57.12	70.77	26.70
SENECA (%)				
Prevalent Cancer	1.68	2.36	2.35	1.96
Prevalent coronary heart disease	10.92	21.78	26.67	15.96
Prevalent stroke	1.60	3.05	7.45	2.68
Prevalent diabetes	6.12	10.26	15.69	8.43
At least one of the above	18.72	32.04	42.75	25.42
SHARE (%)				

Prevalent Cancer	4.76	7.02	10.73	6.23
Prevalent coronary heart disease	9.31	24.14	36.96	17.44
Prevalent stroke	2.25	6.50	15.93	5.35
Prevalent diabetes	7.54	16.89	23.80	12.51
At least one of the above	20.96	44.82	63.19	33.74
TROMSØ (%)				
Prevalent Cancer	6.70	8.80	13.68	8.11
Prevalent coronary heart disease	5.91	13.64	19.87	10.45
Prevalent stroke	2.82	6.86	14.01	5.41
At least one of the above	16.53	30.84	45.28	25.09

EPIC: European Prospective Investigation into Cancer and nutrition; ESTHER: Epidemiological Study on Chances for Prevention. Early Detection. and Optimized THErapy of Chronic Diseases at Old Age; HAPIEE: the Health. Alcohol and Psychosocial factors in Eastern Europe; MORGAM: MOnica Risk. Genetics. Archiving and Monograph; NIH-AARP: National Institutes of Health-American Association of Retired Persons Diet and Health; SENECA: Survey Europe on Nutrition in the Elderly: a Concerted Action; SHARE: Survey of Health. Ageing and REtirement in Europe

[a] No data available in MORGAM

Supplementary Table 3. Adjusted[a] HR and 95% CI of All-Cause Mortality Associated with Self-Rated Health, in Specific Subgroups. The Consortium on Health and Ageing: Network of Cohorts in Europe and the United States Participants.

Subgroups	N	Deaths	$HR_{fair/"at-least-good"}$	95% CI		$HR_{poor/"at-least-good"}$	95% CI	
				lower	upper		lower	Upper
Morbidity score[b]								
0	309,921	53,875	1.50[c]	1.17	1.91	2.64[c]	1.72	4.03
1	89,322	27,825	1.42[d]	1.22	1.65	2.11[d]	1.57	2.83
≥2	19,587	9,918	1.46[e]	1.40	1.53	2.41[e]	2.27	2.56
Sex								
Males	249,204	62,052	1.44[f]	1.21	1.71	2.30[f]	1.79	2.95
Females	174,526	30,691	1.50[g]	1.26	1.79	2.35[g]	1.77	3.11
Recruitment age (years)[h]								
≤70	369,964	78,483	1.58[i]	1.29	1.93	2.59[i]	2.03	3.32
>70	38,732	12,380	1.39[j]	1.21	1.60	2.14[j]	1.64	2.79
Education[k]								
Up to primary	30,641	7,708	1.39[l]	1.21	1.59	2.04[l]	1.69	2.48
>Primary to < college	112,957	27,147	1.40[m]	1.16	1.68	2.55[m]	1.99	3.27
College or more	251,694	52,123	1.74[n]	1.41	2.15	3.38[n]	2.42	4.73

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval

[a] Adjusted by Model 3.

[b] Sum of indicators (1=yes, 0=no) for the following health conditions: coronary heart disease, stroke, diabetes mellitus, cancer at recruitment. In subgroups with morbidity score 1 or ≥2 HAPPIEE and SENECA were not included due to non-available individual data.

[c] I^2 for heterogeneity: **HR$_{\text{fair/"at-least-good"}}$** ,: 97.3%, **HR$_{\text{poor / "at-least-good"}}$** ,: 97.7%

[d] I^2 for heterogeneity: **HR$_{\text{fair/"at-least-good"}}$** : 82.3%, **HR$_{\text{poor / "at-least-good"}}$**: 89.9%

[e] I^2 for heterogeneity: **HR$_{\text{fair/"at-least-good"}}$**:<1%, **HR$_{\text{poor / "at-least-good"}}$** : <1%

[f] I^2 for heterogeneity: **HR$_{\text{fair/"at-least-good"}}$**:94.1%, **HR$_{\text{poor / "at-least-good"}}$**: 92.6%

[g] I^2 for heterogeneity: **HR$_{\text{fair/"at-least-good"}}$**: 92.2%, **HR$_{\text{poor / "at-least-good"}}$**: 93.2%

[h] HAPPIEE was not included due to non-available individual data.

[i] I^2 for heterogeneity: **HR$_{\text{fair/"at-least-good"}}$**:95.0%, **HR$_{\text{poor / "at-least-good"}}$**: 91.3%

[j] I^2 for heterogeneity: **HR$_{\text{fair/"at-least-good"}}$**: 87.1%, **HR$_{\text{poor / "at-least-good"}}$**: 91.7%

[k] HAPPIEE and SENECA were not included due to non-available individual data

[l] I^2 for heterogeneity: **HR$_{\text{fair/"at-least-good"}}$**: 82.3%, **HR$_{\text{poor / "at-least-good"}}$**: 80.4%

[m] I^2 for heterogeneity: **HR$_{\text{fair/"at-least-good"}}$**: 86.4%, **HR$_{\text{poor / "at-least-good"}}$**: 78.5%

[n] I^2 for heterogeneity: **HR$_{\text{fair/"at-least-good"}}$**: 57.2%, **HR$_{\text{poor / "at-least-good"}}$**: 47.7%

Supplementary Table 4. OR[a] of Self-Rated Health as "at- least-good" rather Than "fair or poor" Associated with Characteristics at Enrolment. The Consortium on Health and Ageing: Network of Cohorts in Europe and the United States Participants.

Characteristics at recruitment	OR	95% CI		I[b]for heterogeneity
		Lower	Upper	
Sex (Reference: Female)				
Males	1.20	1.05	1.37	91%
Age				
Per year increment	0.98	0.97	0.99	85.1%
Body Mass Index				
(Reference: <25 kg/m^2):				
(≥25 – <30) kg/m^2	1.01	0.98	1.03	<1%
≥ 30 kg/m^2	0.75	0.65	0.86	86.6%
Smoking				
(Reference: no smoking)				
Daily	0.92	0.76	1.12	93.9%
Ethanol intake[2]				
(Reference: 1st tertile)				
2nd tertile	1.40	1.28	1.54	81.7%
3rd tertile	1.53	1.38	1.69	76.4%
Marital Status				
(Reference: married/cohabiting)				

single/separated	0.86	0.76	0.97	59.7%
widowed	0.92	0.84	1.00	71.3%
Education				
(Reference: ≤primary)				
>primary - <college	1.47	1.19	1.82	92.9%
≥college	1.96	1.44	2.65	93.1%
Health conditions at recruitment[c]				
(Reference: none)				
At least one	0.44	0.34	0.57	98.5%
Physical Activity[d]:				
(Reference: Inactive)				
Active[4]	1.88	1.53	2.31	96.0%

Abbreviations: OR, Odds Ratio

[a] Estimated from meta-analysis of mutually adjusted ORs, derived from multivariate logistic regressions undertaken in each of the participating studies,

[b] Tertiles estimated from sex and study specific ethanol intake at enrolment,

[c] Health conditions considered at recruitment: cancer, coronary heart disease, stroke, diabetes mellitus

[d] Active: >0 hours of vigorous physical activity/week, Inactive: 0 hours of vigorous physical activity/week.

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