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Predicting survival and morbidity-free survival to very old age

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Abstract As life expectancy continually increases, it is imperative to identify determinants of survival to the extreme end of the lifespan and more importantly to identify factors that increase the chance of survival free of major morbidities. As such, the current study assessed 45 common disease factors as predictors of survival and morbidity-free survival to age 85 years. Within the Rotterdam Study, a population-based cohort, we evaluated morbidity-free participants who were able to attain age 85 within the study duration (n=2,008). Risk factors were assessed at baseline (1990–1993), and mortality and morbidities were then collected continuously until mortality or the occurrence of their 85th birthday (average time of 7.9 years). Risk factors included demographic and lifestyle variables, health and morbidity indicators and physiological makers. Major morbidities examined included dementia, cancer, cerebrovascular accident, heart failure and myocardial infarction. Logistic regression analyses demonstrated that many of the variables were independently predictive for survival and for morbidity-free ageing to 85 years. These included being female, absence of left ventricular abnormalities, stable body weight, unimpaired instrumental activities of daily living, lower C-RP levels and higher levels of femoral neck bone mineral density and albumin. Relative to non-survival, predictors were stronger for morbidity-free survival than for total survival or survival with morbidity. This suggests that lifespan and healthy survival to older age can be relatively well predicted. Understanding predictors of a long and healthy lifespan is vital for developing primary and secondary preventions to help improve the quality of life of older adults and for reducing the financial burden of the rapidly escalating ageing population.

Keywords Healthy ageing · Oldest-old · Risk factors · Mortality · Morbidity

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Introduction

Current longevity studies have documented that numerous demographic and lifestyle, health and

morbidity indicators and physiological factors are protective or disadvantageous for a long life (Fried et al. 1998; Scotta et al. 1997; Terracciano et al. 2008). Indeed, studies have developed indices to predict longevity, comprising morbidities (Newman et al. 2008) and frailty (Mitnitski et al. 2002). The survival characteristics of the exceptionally long-lived, octogenarians and centenarians, are also being identified (Aevarsson et al. 1998; Lagaay et al. 1992; Willcox et al. 2007). However, the fastest-growing sub-group of the elderly population is now the so called oldest-old, those that age to 85 years (Tas and Alders 2001). Identifying factors that predict attaining oldest-old status is vital for developing effective clinical interventions and public health strategies for this burgeoning population. Benetos et al. (2005) examined cardiovascular risk factors of oldest-old status. In 7,467 older adults, they found that only heart rate, pulse pressure, physical activity and glycemia were predictive of survival. This is similar to other studies which have found that factors which are predictive of mortality and morbidities in younger-old adults may not be so predictive for the oldest-old (Lam et al. 2007; Rapp et al. 2008; van Bemmel et al. 2006). Therefore, it is unclear which factors predict survival to oldest-old status and if researchers can accurately predict survival to age 85 years.

In addition to examining survival to oldest-old status, it is important to examine factors that predict healthy survival to 85. Living to this age healthily improves quality of life and reduces the growing economic burden of ageing (Franco et al. 2009). However, few studies have examined healthy survival in oldest-old adults, and many studies predicting healthy ageing examine predictors of specific morbidities (e.g. heart failure) and do not examine survival free of multiple morbidities related to ageing. Examining predictors of survival free of multiple morbidities could be useful for identifying risk factors that can protect against more than one disease and increase chances of improving the healthy ageing of the population as a whole. Furthermore, prevalence of morbidities in the oldest-old is higher than that for younger-old adults (Lagaay et al. 1992). As such, it is important to identify how oldest-old adults can age to 85 free of multiple morbidities.

Using data from the Framingham Heart Study, Terry et al. (2005) examined cardiovascular risk factors of survival to 85 years and morbidity-free survival and found that gender, blood pressure, serum cholesterol, glucose, smoking and education were all predictive of survival and morbidity-free survival to 85. These findings demonstrate that different factors can potentially predict survival, and morbidity-free survival, at the extreme end of the lifespan. Nevertheless, it is essential to examine variables beyond traditional cardiovascular risk factors, as these are more strongly linked to vascular disease than morbidities and healthy ageing. Furthermore, the authors evaluated historical data from the Framingham Heart Study (from 1946) that may not necessarily apply to contemporary populations.

Yates et al. (2008) examined whether health, lifestyle and biological variables predict health and functional status in men to 90 years. They found that smoking, diabetes, obesity, hypertension and sedentary lifestyle were associated with survival to 90 years. The results from this study establish a link between broader predictors and morbidity-free survival; however, the study was only conducted in men and the majority of determinants and the outcomes were self-reported. In older adults, self-report frequently does not correlate well with objective measures and is influenced by several confounding factors such as difficulties managing health (Hong et al. 2005; Schneider et al. 2004). In order to further elucidate predictors of ageing to 85, morbidity-free studies are required which identify a broader range of risk factors, examine both genders, use objective measures, assess multiple morbidities and are based in large, healthy cohorts.

The present study sought to address these issues by prospectively examining a large population-based sample of older adults. First, we aimed to identify what determines survival to the extreme end of the lifespan by examining a broad range of variables predictive of survival to age 85 years. Secondly, we aimed to determine whether we could predict healthy ageing at the extreme end of the lifespan by identifying whether variables could predict survival to 85 years free of multiple major morbidities (cancer, dementia, cerebrovascular accident, heart failure, myocardial infarction).

Methods

Study population and case ascertainment

The project was conducted within the Rotterdam Study, a prospective population-based cohort study

designed to examine the occurrence and risk factors of chronic diseases in older adults. The study design and objectives of the Rotterdam Study are described elsewhere (Hofman et al. 2007). Informed consent was obtained from all participants, and the Medical Ethics Committee of Erasmus Medical Centre approved the study. From 1990 to 1993, all inhabitants aged over 55 years living in the Ommoord district of Rotterdam were invited to participate and of these 7,983 (78%) agreed to participate. Baseline data including demographics, lifestyle, medical history and family history were collected during a home interview. Anthropometrical and physiological measures were obtained during a subsequent visit to the research centre. Follow-up data on mortality and morbidities were collected continuously from baseline onwards, and data are currently available until 01 January 2007.

All participants from baseline who were aged over 85 years (n=783) or born after 01 January 1922 (n=4,116) were excluded from the current study as they could not have achieved the age of 85 years within the study time frame. Participants with prevalent morbidities (n=861), including dementia, cancer (breast, rectal and colon, prostate and lung), cerebrovascular accident, heart failure, myocardial infarction or missing prevalent information (n=215), were excluded from analyses. This resulted in 2,008 participants available for the current study (684 men).

Mortality and morbidity assessment

Mortality status of participants was acquired on a bi-weekly basis from the municipal authorities of Rotterdam. Additionally, the general practitioners in the suburb of Ommoord reported deaths on a continuous basis. Reported deaths were verified by specially trained study personnel who checked the medical records. Information on morbidities was obtained continuously through automated linkage with files from general practitioners and letters and discharge reports from medical specialists. When an event was reported, additional information was then collected (e.g. hospital records, nursing home records). Two research physicians coded all reported events and in the case of disagreement they consulted an expert in the field. Events were coded according to the *International Classification of Diseases, Tenth Revision* (ICD-10; World Health Organisation 1992). Morbidities were selected based on the main causes of hospitalisation and mortality of older adults (Desai et al. 1999). Diabetes is also an important morbidity associated with the ageing process; however, in the current study, it was treated as a predictor. This is because diabetes has little effect on mortality independent of cardiovascular disease and, although diabetes may trigger hospitalisation, it is not usually the primary morbidity associated with admission. Participants were considered to have a major morbidity if they experienced a health event before their 85th birthday. Events selected include (with ICD-10 codes) dementia (F00, F01, F02), cancer—breast, rectal and colon, prostate and lung cancers (C33, C34, C18–C21, C50, C61, C53, C43)—cerebrovascular accident (I61, I63, I64), heart failure (I50) and myocardial infarction (I21). Mortality and morbidity data were available until January 2007.

Assessment of predictors

Predictors were selected based on a review of literature identifying factors that are common predictors of disease in younger-old and oldest-old adults (e.g. Fried et al. 1998; Terry et al. 2005; Yates et al. 2008) and on the availability of data in our sample. Determinants were grouped into demographic and lifestyle, health and morbidity indicators and physiological makers. All determinants were assessed at baseline.

Demographic and lifestyle

Age and sex were recorded. Education was grouped according to the *Dutch Standard Classification of Education*. We applied the ratings from primary education (1) to university level (7) as a continuous variable so that each increase in odds ration (OR) reflected an increase in one category of education. The number of first-degree relatives was a continuous variable. Spousal death was recorded as present vs. absent; living status was coded as living alone compared to living with one or more people. Income was calculated as the equivalent household monthly income (euros). Health insurance was assessed as public vs. private health insurance. Height (m) and weight (kg) were measured, and body mass index was calculated as kilogramme per square metre. Energy intake, fruit and vegetable consumption and alcohol were assessed with the semi-quantitative food fre-

quency questionnaire (Klipstein-Grobusch et al. 1998). Participants indicated all foods and drinks that they consumed more than once a month during the preceding year. During a subsequent visit to the centre, participants completed a structured interview with a trained dietician based on the answers to the SFFQ. The data were then converted to nutrient intake using Dutch Food Composition Tables (Voedingsraad 1993). Total energy intake was calculated as kilojoules consumed on average per day. Fruit and vegetable intake was based on the average grammes consumed per day. Alcohol intake was reported as an average consumption in grammes per day. Smoking was assessed during the interview and defined as never smoking vs. smoking (current or former).

Health and morbidity indicators

Diabetes mellitus was determined if participants reported using anti-diabetic medication or if their non-fasting random or post-load blood glucose concentrations were 11.1 mmol/l or higher. Medication usage was obtained via digital pharmacy records from all pharmacies that serve the Ommoord area and was utilised continuously as the total number of current medications. Anti-hypertensive use was derived in the same manner and coded as absent vs. present. Left ventricular hypertrophy and atrial fibrillation (Heeringa et al. 2006) were assessed with 10-s 12-lead electrocardiograms (ECG) recorded at the research centre with an ACTA Gnosis IV ECG recorder (EsaOte, Florence, Italy), stored digitally and analysed with the Modular ECG Analysis System (van Bemmel et al. 1990). When a positive case was indicated, two research physicians and a cardiologist verified the information. Family history of age-related morbidities, depression history, hospitalisation in the past 12 months, hip fracture and vertebral fracture were assessed with self-report and coded as absent vs. present.

Self-rated health was assessed with the question: 'How is your general health compared to members of your age group?' Scores were 1, worse; 2, same; or 3, better and was applied as a continuous variable. Cognitive capacity was assessed with the Mini Mental State Examination, which assesses six broad areas of daily cognitive functions (Folstein et al. 1975). A cutoff of 26 indicated adequate cognitive capacity vs. impaired cognitive capacity. Memory complaints were recorded in reply to the question: "do you have any memory complaints" and was coded as absent (no complaints) vs. present (mild to severe complaints). Disability, or Activities of Daily Living, was assessed with the Stanford Health Assessment Questionnaire (Fries et al. 1982). This measures disability in eight fields (e.g. hygiene, eating, walking) with a responses ranging from 0, perform without difficulty, to 3, unable to do independently. The mean score of all fields constitutes the Disability Index, and the standard cutoff of 0.5 indicated no disability vs. mild to severe disability. An adaptation of the Instrumental Activities of Daily Living (Lawton and Brody 1969) assessed functioning in basic daily activities. Six areas were assessed (e.g. maintaining finances, meal preparation) with responses ranging from 0, perform without difficulty, to 3, unable to do independently. The mean score of the six items was calculated, and a cutoff of 1.00 (upper quartile) was selected to distinguish between no instrumental disability vs. mild to severe instrumental disability. Unintentional weight loss was defined as at least 3 kg in the past 3 months and recorded as absent vs. present on a self-report basis.

Physiological markers

A venipuncture was performed and non-fasting blood samples were drawn and immediately frozen (−20°C) for haematological variables. Leucocyte count was assessed in citrate plasma using a Coulter Counter T540 (Coulter Electronics). C-reactive protein was measured using a nephelometric method (Immage, Beckman Coulter). High-sensitivity C-reactive protein was measured using a rate near-infrared particle immunoassay method (Immage, Beckman Coulter). Glucose levels were measured by the glucose hexokinase method. Albumin level was assessed with a colourimetric method (Hitachi 747 Böhringer). Creatinine level was assessed by a non-kinetic alkaline picrate method (Kone autoanalyzer). Uric acid was measured with a Kone Diagnostica reagent kit and a Kone autoanalyzer. Total cholesterol and high-density lipoprotein cholesterol (HDL) values were determined with an automated enzymatic procedure (Boehringer Mannheim System).

Systolic and diastolic blood pressures were measured twice by a trained research assistant with a random-zero sphygmomanometer after the subjects

had rested for 5 min. For analyses, we calculated the mean of the two blood pressure measurements. Heart rate was also measured with the aforementioned ECG, and RR intervals (time duration between two consecutive R waves) were measured using MEANS. The median RR interval was computed for analyses. Femoral neck and lumbar spine (vertebrae L2 to L4) bone mineral density measurements were performed by dual-energy X-ray absorptiometry (Lunar DPX-L densitometer). Peripheral artery disease was assessed with ankle brachial blood pressure. This was measured as the ratio of the lowest systolic blood pressure from the left or right posterior tibial artery, measured in supine position (8-MHz continuous-wave Doppler probe: Huntleigh 500D) to the systolic blood pressure in the arm. Aortic calcification of the posterior abdominal aortic wall was determined with a lateral X-ray of the lumbar spine (L1–L4). Calcification was considered present when linear densities were seen in an area parallel and anterior to the lumbar spine. Calcified plaques were scored according to the length of the involved area along the lumbar spine (L1–L4) with scores of 0–5 corresponding to 0, >0 to ≤1, >1.0 to <2.5, ≥2.5 to <5.0, ≥5.0 to <10.0 and ≥10 cm, respectively. Intima media thickness of the common carotid artery was measured on the left and right carotid arteries by ultrasonography, using a 7.5-MHz linear-array transducer (ATL Ultra-Mark IV). We calculated the mean intima media thickness as the mean of the far wall of both the right and left common carotid artery. Carotid plaques were assessed by ultrasound at the common, internal and bifurcation sites of the carotid artery for the presence of atherosclerotic lesions. A point was added to a plaque score if each location was positive for the presence of atherosclerotic plaque (irrespective of plaque size), giving a score range of 0–6.

Statistical analysis

Participants were followed from baseline until their 85th birthday or until death. On average, participants were followed for an average of 7.89 years (SD= 4.21). Survivors with morbidity were followed for 9.50 years (SD=3.80) and morbidity-free survivors for 8.50 years (SD=4.26) Descriptive statistics are presented for all participants at baseline. As participants entered the study at varying ages and thus had different time periods to attain 85 years, baseline age was controlled for in all analyses. Age was therefore analysed as a confounder and not as a predictor in analyses.

Variables that were proposed to predict longevity were grouped into three themes: demographic and lifestyle factors, health and morbidity indicators and physiological makers. Alcohol intake, energy intake, fruit and vegetable intake, relatives, medication usage, self-rated health, aortic calcification and carotid plaques were analysed in their raw format as continuous variables to preserve their original meaning. To assist comparability, the remaining physiological markers were assessed as continuous variables and calculated so that an increase in odds ratios reflected a one standard deviation increase in the predictor. Missing values on predictors were minimal; however, to ensure that analyses were comparable, retained power and were conducted across equal sample sizes, missing values were imputed using single imputation with expectation maximisation algorithm (Arnold and Kronmal 2003). Variables were imputed using the entire population (n=7,983) and a large array of variables available from the Rotterdam Study (Hofman et al. 2007).

The first analysis assessed *predictors of survival to 85* using two sets of logistic regression: (a) a separate univariate model for each predictor to examine the independent contribution, controlling for age and sex; and (b) a full model allowing all significant univariate predictors to compete against each other to determine joint predictors of survival. A backwards stepwise logistic regression was used for the full model as we had no a priori theory on the joint contribution of these variables; this method allows variables to compete for entry and removes predictors that do not improve model fit, thus improving the predictability of the model. The validity of the full logistic regression model predicting survival to age 85 years was determined by examining goodness of fit and discriminatory capacity. The Hosmer–Lemeshow test assessed goodness of fit of the overall model; this estimates the difference between the observed and expected values for survival to 85 at the different levels of predictors. A p value>0.05 indicates that the models fits the data well and is a good predictor of survival. The discriminatory capacity of the model to predict accurately those that survive to 85 and those that do not was determined using the predicted probabilities derived from the Logistic Regression with which the area under the receiver operating

characteristic (ROC) curve was calculated (AUC). A value of 0.5 indicates that the model does not have good predictive ability and 1.0 indicates that it is a perfect prediction model. Sex-pooled analyses were presented to improve power; however, the statistical significance of effect modification by sex for significant predictors was examined as a secondary analysis using interaction terms in the logistic regression models; however, results should be interpreted with caution due to lesser case numbers.

The second analysis sought to examine whether these variables could also *predict survival to 85 morbidity free*. As such, we partitioned the total survival group from the prior analysis into those that survived to 85 with morbidity and those that survived morbidity free. We included the survivors with morbidity in this analysis to reduce bias but partitioned them through using a multinomial logistic regression. This provided us with two sets of odds ratios (survival with morbidity: non-survival; survival morbidity free: non-survival). As such, we are able to remove the influence of people who survive with morbidity from the analysis of morbidity-free survival, but without losing their influence in analyses. As in the first analysis, we conducted two sets of logistic regressions, one to examine each predictor separately controlling for age and sex and one as a full model to examine joint predictors. Only variables which were significant in the first full model predicting survival were assessed and as such the second full model was based on a prior theory so we employed a standard logistic regression.

Results

The mean age of participants at baseline was 75.83 (SD=4.15)years. Of the 2,008 participants, 639 (32%) did not survive to age 85 years. Of the 1,369 subjects that did survive to 85 years, 960 (70%) survived morbidity free. Background characteristics of the sample for those who did not survive to 85 years and those that did survive to 85 years are presented in Table 1. The survival to 85 years group is further divided into those that survived to 85 with morbidity and those that survived to 85 morbidity free. Females were more likely than males to survive to 85 years and to survive morbidity free. Overall, in comparison to the survivors, non-survivors were younger, had less relatives, were more likely to live alone, experienced more spousal deaths, had a higher energy intake, had lower body mass index, consume more alcohol, had a higher percentage of former or current smokers and performed worse on most health indicators and physiological markers than those that did survive. Socioeconomic status (income and education) was comparable. A similar pattern was observed between those that survived with morbidity and those that survived morbidity free.

Predictors of survival to age 85 years

The first analysis examined predictors of survival to 85 years. Initially, we determined independent predictors of survival to age 85 years using logistic regression controlling for age and sex (Table 2, left data block). Of the 45 predictors examined, 28 were independently predictive of survival to 85 years. Non-significant predictors were not presented in Table 2. Significant predictors included measures from all the groups we hypothesised to be related to survival to 85 years: lifestyle and demographics, health indicators and physiological markers. Additionally, we conducted a backward stepwise logistic regression using all predictors significant in the age- and sex-adjusted analyses to determine joint predictors of survival to age 85 years (Table 2, right data block). Fifteen of the predictors remained significant in this full model. Additionally, as the current study presented sex-pooled analyses to improve statistical power, a sub-analysis was conducted to test sex by variable interactions (full data not presented). Leucocytes (p=0.019), diastolic blood pressure (p=0.024) and total cholesterol (p=0.010) were the only significant predictor by sex interactions. However, given the smaller numbers in the analysis, these findings should be interpreted with caution.

Several findings were of consequence. Being female, normal left ventricular functioning, freedom from memory complaints and unimpaired instrumental activities of daily living were the strongest predictors of survival. With the exception of freedom from memory complaints, these factors all remained significant in the full model. Absence of negative life events and higher socioeconomic indicators were also predictive of survival (e.g. lack of spousal death, higher education, absence of hypertensive use). An elevated level of most physiological

Table 1 Baseline characteristics by survival and morbidity status (n=2,008)

	Not survived	Survived to 85		
	Total (n=639)	Total (n=1,369)	With morbidity (n=409)	Morbidity-free 1 (n=960)
Demographic and lifestyle				
Sex (female)	343 (53.7)	981 (71.7)	269 (65.8)	712 (74.2)
Education (range 1–7)	3.00±1.85	2.94±1.84	2.98±1.82	2.92±1.85
Relatives (number of relatives)	8.40 (3.47)	8.78 (3.64)	8.85 (3.66)	8.75 (3.63)
Spousal death (absent)	570 (89.2)	1,266 (92.5)	383 (93.6)	883 (92.0)
Living status (with partner)	228 (35.7)	635 (46.4)	164 (40.1)	471 (49.1)
Income (euro per month)	1,884.64±750.11	1,806.31±814.86	1,804.40±922.51	1,807.13±764.94
Health insurance (private)	278 (43.5)	498 (36.4)	150 (36.7)	348 (36.3)
Body mass index (kg/m^2)	26.10±3.60	26.59±3.73	26.74±3.79	26.53±3.70
Energy intake (kJ/day)	8,340.75±1,709.88	7,903.31±1,623.01	7,972.80±1,602.31	7,873.70±1,631.67
Fruit and vegetable intake (g/day)	556.71±151.42	563.98±168.68	561.74±162.91	564.93±171.15
Alcohol (g/day)	9.84±13.29	7.33±10.61	8.01±11.28	7.04±10.31
Smoking (non-smoker)	207 (32.4)	691 (50.5)	201 (49.1)	490 (51.0)
Health and morbidity indicators				
Diabetes mellitus (absent)	558 (87.3)	1,206 (88.1)	348 (85.1)	858 (89.4)
Medication usage (number of medications)	2.38±2.25	2.15±2.06	2.28±2.15	2.09±2.01
Anti-hypertensive use (none recorded)	539 (84.4)	1,196 (87.4)	352 (86.1)	844 (87.9)
Left ventricular function (normal)	591 (92.5)	1,328 (97.0)	392 (95.8)	936 (97.5)
Atrial fibrillation (absent)	614 (96.1)	1,330 (97.2)	399 (97.6)	931 (97.0)
Family history (free from morbidity)	315 (49.3)	651 (47.6)	187 (45.7)	464 (48.3)
Depression history (no events recorded)	453 (70.9)	957 (69.9)	274 (67.0)	683 (71.1)
Hospitalisation (none past 12 months)	517 (80.9)	1,137 (83.1)	340 (83.1)	797 (83.0)
Hip function (absence of fractures)	627 (98.1)	1,347 (98.4)	402 (98.3)	945 (98.4)
Vertebral function (absence of fractures)	610 (95.5)	1,271 (92.8)	385 (94.1)	886 (92.3)
Self-rated health (1: worse to 3: better)	2.35±0.68	2.51±0.61	2.44±0.62	2.53±0.60
Cognitive status (intact: MMSE≥26)	531 (83.1)	1,183 (86.4)	345 (84.4)	838 (87.3)
Memory (no problems reported)	591 (92.5)	1,302 (95.1)	381 (93.2)	921 (95.9)
ADL (unimpaired: HAQ score≤0.5)	417 (65.3)	918 (67.1)	269 (65.8)	649 (67.6)
IADL (unimpaired: IADL score <1.0)	503 (78.7)	1,180 (86.2)	351 (85.8)	829 (86.4)
Stability in body weight (past 12 months)	546 (85.4)	1,222 (89.3)	369 (90.2)	853 (88.9)
Physiological markers				
Leucocytes (10^9/l)	7.07±3.32	6.66±1.80	6.76±1.79	6.62±1.80
C-reactive protein (g/l)	4.39±5.53	3.05±4.66	3.12±4.72	3.02±4.64
Glucose (mmol/l)	7.12±2.70	6.97±2.77	7.19±3.33	6.87±2.49
Albumin (g/l)	42.12±2.34	42.40±2.26	42.69±2.21	42.28±2.28
Creatinine (μmol/l)	85.66±21.77	82.26±13.65	83.62±14.76	81.68±13.11
Uric acid (μmol/l)	330.50±73.08	316.58±67.99	324.99±70.43	313.00±66.63
Total cholesterol (mmol/l)	6.46±1.27	6.66±1.17	6.64±1.16	6.67±1.17
HDL cholesterol (mmol/l)	1.34±0.39	1.37±0.34	1.35±0.35	1.38±0.34
Systolic blood pressure (mmHg)	144.54±22.03	144.21±20.41	147.36±19.64	142.87±20.60
Diastolic blood pressure (mmHg)	73.76±11.67	72.48±10.81	73.50±11.13	72.04±10.65
Heart rate (median RR interval)	72.52±11.68	72.21±10.31	72.11±10.29	72.25±10.33

Table 1 (continued)

	Not survived	Survived to 85		
	Total (n=639)	Total (n=1,369)	With morbidity (n=409)	Morbidity-free 1 (n=960)
Femoral neck bone mineral density (g/cm^2)	0.80±0.12	0.80±0.12	0.81±0.12	0.79±0.13
Lumbar spine bone mineral density (g/cm^2)	1.09±0.19	1.07±0.19	1.08±0.19	1.06±0.19
Ankle brachial index (ratio)	1.02±0.23	1.04±0.22	1.02±0.22	1.05±0.22
Aortic calcification (plaque length 0–5)	2.18±1.27	2.10±1.29	2.23±1.31	2.04±1.28
Intima media thickness (mm)	0.88±0.14	0.86±0.12	0.88±0.12	0.86±0.12
Carotid plaques (plaque sites 0–6)	2.02±1.64	1.72±1.50	1.89±1.54	1.65±1.48

Values are mean±SD or n (%). All values are from baseline measurements

MMSE Mini Mental State Examination, *ADL* activities of daily living, *HAQ* Health Assessment Questionnaire, *IADL* instrumental activities of daily living

markers decreased the chance of survival to age 85 years. The presence of atherosclerosis indicators also decreased the odds of surviving to age 85 years. However, higher albumin level and femoral neck bone mineral density and total cholesterol increased the odds of survival to age 85.

The full model for predicting survival (Table 2, right data block) was found to have a satisfactory goodness of fit (Hosmer–Lemeshow statistic=9.93, p=0.27), indicating that it has a good capacity to predict survival to 85 years. The discriminatory capacity of the model to predict accurately those that survive to 85 and those that did not was additionally determined using the predicted probabilities derived from the full model logistic regression to calculate the AUC in ROC models. For the full model, the AUC was 0.75 (95% confidence interval (CI), 0.73–0.77), indicating that it was an adequate prediction model. The AUC for age and sex alone, 0.67 (95% CI, 0.65–0.70), was comparable to the AUC for all variables combined, excluding age and sex, 0.67 (95% CI, 0.65–0.70). The AUC was also calculated for the three sub-groups of predictors. The AUC for physiological markers was the largest, 0.73 (95% CI, 0.71–0.75). Followed by health indicators, 0.72 (95% CI, 0.69–0.74), and lifestyle and demographic variables, 0.68 (95% CI, 0.66–0.71).

Predictors of morbidity-free survival to age 85 years

To determine predictors of morbidity-free survival, we partitioned the survival group into those that survived to age 85 with morbidity and those that survived morbidity free. We then conducted multinomial logistic regressions to compare non-survivors (reference group) to survivors to 85 with morbidity and to morbidity-free survivors (Table 3). Age- and sex-adjusted and full models were assessed on variables significant in the previous full model (Table 2) for total survival.

Many of the variables which were previously predictive of total survival (Table 2) were not predictive of survival with morbidity (Table 3, left data block), indicating that these variables were not able to discriminate well between non-survival and survival with morbidity in the oldest-old. All variables which were predictive of total survival were predictive of morbidity-free survival, with the exception of smoking. Notably, these analyses showed that odds ratios for predicting morbidity-free survival were overall stronger (Table 3, right data block) than for total survival (Table 2). Age- and sex-adjusted and full model analyses demonstrated that being female and having normal left ventricular function, higher level of self-rated health, intact cognitive status and unimpaired instrumental activities of daily living were more predictive of morbidity-free survival than total survival. Elevated levels of C-reactive protein, uric acid, diastolic blood pressure, ankle brachial index and carotid plaques were also more predictive of morbidity-free survival than total survival.

Discussion

The current prospective study demonstrated that 960 (48% of total sample) of the oldest-old adults in the

Table 2 Logistic regression with OR and CI for survival to age 85 (n=2,008)

Survived to 85 years (n=1,369)						
Predictor	Age- and sex-adjusted[a]			Stepwise full model[b]		
	OR	(95% CI)	p value	OR	(95% CI)	p value
Demographic and demographic						
Sex (female)	2.13	(1.74–2.60)	<0.001	1.72	(1.29-2.27)	<0.001
Education (per category increase)	1.07	(1.01–1.13)	0.022	–	–	–
Spousal death (absent)	1.59	(1.13–2.22)	0.007	–	–	–
Smoking (non-smoker)	1.49	(1.17–1.88)	0.001	1.36	(1.06–1.75)	0.015
Health and morbidity indicators						
Any medication usage (per medication increase)	0.88	(0.84–0.92)	<0.001	–	–	–
Anti-hypertensive usage (none recorded)	1.42	(1.08–1.88)	0.013	–	–	–
Left ventricular function (normal)	2.69	(1.70–4.24)	<0.001	2.23	(1.38–3.60)	0.001
Self-rated health (1: worse to 3: better)	1.54	(1.32–1.79)	<0.001	1.31	(1.10–1.54)	0.002
Cognitive status (intact)	1.77	(1.34–2.33)	<0.001	1.52	(1.13–2.03)	0.005
Memory (no problems reported)	2.19	(1.46–3.29)	<0.001	–	–	–
ADL (unimpaired)	1.85	(1.47–2.31)	<0.001	–	–	–
IADL (unimpaired)	2.31	(1.75–3.05)	<0.001	1.58	(1.17–2.14)	0.003
Stability in body weight (past 12 months)	1.64	(1.22–2.20)	0.001	1.42	(1.04–1.94)	0.028
Physiological markers						
Leucocytes (per 1-SD increase)	0.81	(0.71–0.91)	0.001	–	–	–
C-RP (per 1-SD increase)	0.74	(0.67–0.83)	<0.001	0.86	(0.77–0.96)	0.007
Glucose (per 1-SD increase)	0.91	(0.82–1.00)	0.046	–	–	–
Creatinine (per 1-SD increase)	0.83	(0.74–0.93)	0.002	–	–	–
Uric acid (per 1-SD increase)	0.86	(0.78–0.96)	0.005	0.87	(0.78–0.97)	0.013
Albumin (per 1-SD increase)	1.31	(1.18–1.45)	<0.001	1.27	(1.14–1.43)	<0.001
Femoral neck BMD (per 1-SD increase)	1.17	(1.06–1.30)	0.002	1.18	(1.06–1.31)	0.003
Systolic BP (per 1-SD increase)	0.90	(0.82–1.00)	0.040	–	–	–
Diastolic BP (per 1-SD increase)	0.90	(0.81–0.99)	0.035	0.89	(0.80–0.99)	0.026
Heart rate (per 1-SD increase)	0.88	(0.80–0.97)	0.013	–	–	–
Total cholesterol (per 1-SD increase)	1.14	(1.03–1.27)	0.015	–	–	–
Ankle brachial index (per 1-SD increase)	1.34	(1.21–1.48)	<0.001	1.19	(1.06–1.33)	0.002
Aortic calcification (one category increase)	0.88	(0.81–0.95)	0.001	–	–	–
Intima media thickness (per 1-SD increase)	0.83	(0.75–0.92)	<0.001	–	–	–
Carotid plaques (one category increase)	0.85	(0.80–0.91)	<0.001	0.91	(0.85–0.98)	0.008

All odds ratios with respect to reference group of non-survival to 85 years (n=639). Variables in each group which were entered, but not significant in any models include: *lifestyle and demographics*: relatives, living status, income, health insurance, body mass index, energy intake, fruit and vegetable intake, alcohol intake; *health and health indicators*: diabetes mellitus, atrial fibrillation, family history of morbidities, depression history, hospitalisation, hip fracture, vertebral fracture; *physiological markers*: glucose, HDL cholesterol, lumbar spine BMD

– variables which were not retained in the most parsimonious model, *ADL* activities of daily living, *IADL* instrumental activities of daily living, *C-RP* C-reactive protein, *BMD* bone mineral density, *BP* blood pressure

[a] Adjusted for age and sex where appropriate

[b] Stepwise full model is a backwards stepwise logistic regression adjusted for variables significant in age- and sex-adjusted analyses

Table 3 Multinomial logistic regression with OR and CI for survival with morbidity and morbidity free (n=2,008)

Survived to 85 years

Predictor	With morbidity (n=409)						Morbidity free (n=960)					
	Age- and sex-adjusted[a]			Standard full model[b]			Age- and sex-adjusted[a]			Standard full model[b]		
	OR	(95% CI)	p value	OR	(95% CI)	p value	OR	(95% CI)	p value	OR	(95% CI)	p value
Demographic and lifestyle												
Sex (female)	1.64	(1.27–2.13)	<0.001	*1.33*	(*0.94–1.87*)	*0.104*	2.44	(1.95–3.04)	<0.001	2.20	(1.64–2.94)	<0.001
Smoking (non-smoker)	1.74	(1.29–2.36)	<0.001	1.64	(1.20–2.24)	0.002	1.38	(1.07–1.77)	0.013	*1.26*	(*0.97–1.65*)	*0.087*
Health and morbidity indicators												
Left ventricular function (normal)	1.88	(1.06–3.34)	0.032	1.84	(1.01–3.33)	0.045	3.38	(1.98–5.77)	<0.001	2.62	(1.49–4.61)	0.001
Self-rated health (1: worse to 3: better)	1.29	(1.06–1.57)	0.011	*1.14*	(*0.93–1.40*)	*0.210*	1.69	(1.43–2.00)	<0.001	1.45	(1.21–1.74)	<0.001
Intact cognitive status (intact)	*1.32*	(*0.94–1.87*)	0.114	*1.22*	(*0.85–1.74*)	*0.285*	2.05	(1.51–2.78)	<0.001	1.71	(1.24–2.35)	0.001
IADL (unimpaired)	1.93	(1.34–2.76)	<0.001	1.51	(1.03–2.21)	0.035	2.54	(1.86–3.45)	<0.001	1.63	(1.17–2.27)	0.004
Stability in body weight (past 12 months)	1.71	(1.15–2.55)	0.008	1.51	(1.00–2.28)	0.049	1.61	(1.17–2.21)	0.003	1.41	(1.00–1.97)	0.049
Physiological markers												
C-RP (per 1-SD increase)	0.78	(0.67–0.90)	0.001	0.86	(0.74–0.99)	0.042	0.73	(0.64–0.82)	<0.000	0.84	(0.74–0.94)	0.004
Uric acid (per 1-SD increase)	*0.96*	(*0.85–1.10*)	*0.581*	*0.93*	(*0.81–1.07*)	*0.296*	0.81	(0.73–0.91)	<0.000	0.84	(0.74–0.94)	0.004
Albumin (per 1-SD increase)	1.40	(1.23–1.59)	<0.001	1.36	(1.19–1.57)	0.000	1.27	(1.13–1.41)	<0.000	1.26	(1.11–1.42)	<0.001
Femoral neck BMD (per 1-SD increase)	1.21	(1.06–1.37)	0.004	1.19	(1.04–1.35)	0.012	1.16	(1.04–1.29)	0.008	1.17	(1.04–1.32)	0.007
Diastolic BP (per 1-SD increase)	*0.98*	(*0.86–1.11*)	*0.741*	*0.95*	(*0.84–1.08*)	*0.462*	0.86	(0.77–0.96)	0.006	0.86	(0.77–0.97)	0.011
Ankle brachial index (per 1-SD increase)	*1.13*	(*1.00–1.28*)	*0.054*	*1.06*	(*0.92–1.21*)	*0.422*	1.46	(1.31–1.64)	0.000	1.26	(1.12–1.43)	<0.001
Carotid plaques (one category increase)	*0.93*	(*0.86–1.01*)	*0.080*	*0.97*	(*0.89–1.06*)	*0.543*	0.81	(0.76–0.87)	0.000	0.88	(0.82–0.95)	0.001

All odds ratios with respect to reference group of non-survival to 85 years (n=639). Italicised values are not significant at $p<0.05$

IADL instrumental activities of daily living, *C-RP* C-reactive protein, *BMD* bone mineral density, *BP* blood pressure

[a] Adjusted for age and sex where appropriate

[b] Standard full model is a forward entry logistic regression adjusted for all variables in the age- and sex-adjusted models

current population survived to 85 morbidity free. Several lifestyle, health and health indicators and physiological markers were predictive of survival to age 85 years. Further, we found that when people who survived to 85 with morbidity were partitioned from analyses, variables were stronger predictors. This suggests that we can predict healthy survival to 85 years.

The first aim of the study was to identify what determines survival to the extreme end of the lifespan, we achieved this by examining variables predictive of survival to age 85 years. We found that several factors were predictive of survival and that jointly the variables could discriminate well between those that did and did not survive to 85. On a grouped variable basis, the AUC showed that physiological markers were the strongest predictors compared to lifestyle and health, accounting for nearly as much variance in survival as all factors combined.

Consistent with prior research on lifestyle risk factors for older adults, being female, having a high level of education, not experiencing adverse life events and abstaining from smoking increased the chance of survival to 85 years (Fried et al. 1998; Lam et al. 2007; Terry et al. 2005; Tucker et al. 1996). In harmony with other longitudinal studies, low medication usage, absence of anti-hypertensive usage (both indicative of underlying mild morbidities), normal left ventricular function, higher level of self-rated health and stable weight all increased the odds of survival to age 85 (Fried et al. 1998; Terry et al. 2005). Intact cognitive status, freedom from memory complaints and unimpaired instrumental and activities of daily living also strongly increased the odds of survival to age 85 years. Although a link has been shown between activities of daily living and mortality (Newman et al. 2006), intact cognitive and memory status have not previously been shown as predictors of mortality. Although it is unlikely that these factors directly cause mortality, it is an important observation as these are readily assessed by health care professionals. Consistent with previous biomarker research, elevated levels of leucocyctes, C-reactive protein, glucose, creatinine, uric acid and systolic and diastolic blood pressure decreased the chance of survival to age 85 years (de Ruijter et al. 2008; Fried et al. 1998). Interestingly, higher total cholesterol and albumin levels increased the odds of survival to age 85 years. However, this finding is consistent with recent controversial research findings on all-cause mortality (Okamura et al. 2008) and contributes to the growing debate of the role of total cholesterol in health (Weverling-Rijnsburger et al. 1997). Higher levels of atherosclerosis also decreased the risk of survival to 85, which aligns with findings from cardiovascular studies of all-cause mortality (Ostrom et al. 2008). These findings demonstrate that risk factors shown in younger adults can also predict survival to age 85, although perhaps to a lesser extent.

Several factors which were significant in independent analyses were not significant in the full model, such as education, heart rate and serum glucose. It is possible that these factors are still important for predicting survival; however, their influence may occur near the inception of the causal pathway and as such adjusting for other variables in the same causal pathway reduces their contribution. The current study did not seek to examine causal pathways, so we are unable to interpret this more fully. These results also demonstrated that the predictive ability of all factors combined (excluding age and sex) was comparable to the variance attributable to age and sex alone. This reflects that age and sex are key predictors of many variables in the current study. Although it is tempting to conclude that age and sex are the strongest predictors of age-related chances and focus on this, it is important to identify risk factors to enable us to identify variables we can target for interventions and also further understand the mechanisms of ageing.

The second aim of the study was to determine if we could predict healthy ageing at the extreme end of the lifespan, we accomplished this by identifying whether variables could predict survival to 85 years morbidity free. Using factors demonstrated as predictors of survival to 85, we found that, with the exception of smoking, variables were better or equivalent predictors of morbidity-free survival than for total survival. The odds ratios we found for morbidity-free survival were more similar to what has previously been reported for younger-old adults for total survival. In our analyses of total survival, we found that variables exhibited less predictive capacity relative to reported predictability for younger-old adults. We considered these results as normal for the oldest-old as they align with other ageing researchers who have often been unable to identify common disease risk factors as risk factors in oldest-old adults (Lam et al. 2007; Rapp et al. 2008; van Bemmel et al.

2006). However, in the current study, we find that when we removed those with morbidity from our analyses, in order to examine healthy ageing, we actually increased the predictability of the variables to a level similar to that reported for younger-old adults.

A plausible explanation for this phenomenon is that younger-old adults exhibit a lower proportion of morbidities relative to the oldest-old. Thus, in analyses of younger-old adults, when those that survive with and without morbidity are combined into total survival, the results are not influenced to a large extent. However, when trying to examine predictors in oldest-old adults, where there is a much higher proportion of morbidities (Lagaay et al. 1992), we may inadvertently dilute results by combining these two groups of survivors as they evidently exhibit substantially different characteristics. In support of this proposition, the current study demonstrated that many variables were not predictive of survival with morbidity relative to non-survival in oldest-old adults. These findings reveal that we can predict survival and morbidity-free survival in the oldest-old. However, when examining survival in the oldest-old, we recommend partitioning the survival group into those that survive with and without a morbidity to provide more homogenous outcome groups and therefore increase the capacity of identifying risk factors of survival in the oldest-old.

The present study has several advantages which strengthen the findings. First, our study was based in a large population-based cohort of community-dwelling older adults, providing us with adequate statistical power and making the result generalisable to a wide range of populations. Second, the current sample contained a large group of participants that aged to 85 morbidity free, increasing the chance of finding predictors of healthy ageing. Third, we used prospective longitudinal information validated across multiple studies and proximal predictors as baseline measures which were taken when adults had already entered older age and thus less susceptible to changes. Fourth, we employed a broad range of indicators measured by standardised assessments and where possible objective measurements, which are less open to recall bias. Finally, we had continuous monitoring of morbidity events (verified by experts in the field) and multiple informant mortality data.

A limitation of the current study was the absence of a physical activity measure. Physical activity in older adults has consistently been linked to mortality and morbidity (Bembom et al. 2009; Benetos et al. 2005; Blair and Brodney 1999; Yates et al. 2008). Additionally, risk factors occurring between the baseline and incidence of non-survival or survival to age 85 were not examined which may have led to an underestimation of associations. This factor is potentially more important for health and health indicators which do alter in older adults. However, lifestyle factors (such as smoking, body mass index) do not tend to change in the elderly, with the exception of the incurrence of a health event which can dramatically change behaviour, such as a incidence of coronary heart disease reducing smoking (Quist-Paulsen and Gallefoss 2003).

The practical implication of examining predictors of survival and morbidity-free survival in the oldest-old goes far beyond simply furthering knowledge; it also has key clinical applications. To date, researchers have found it difficult to identify factors that promote healthy ageing in oldest-old adults. This study identifies several key factors which are predictive of survival to 85 and are readily modifiable. If appropriately targeted in a clinical setting, these could promote healthy ageing which would lead to an improvement in the quality of life of older adults. As an example, consistent with prior findings, lowering blood pressure (Boshuizen et al. 1998) and ceasing smoking (Frosch et al. 2009) increased the odds of surviving to age 85 morbidity free. Given that these two factors were recently cited as responsible for the largest number of deaths in the USA (Danaei et al. 2009), a change in these variables could make a large difference in the lives of older adults. Modification of these factors can arise with self-help, assistance from clinically trained personnel, community-based programmes or medication (Chipperfield and Havens 2001; Dickerson and Gibson 2005; Doolan and Froelicher 2008). Other factors such as cognitive status and disability are not as readily modifiable; nevertheless, lifestyle factors (such as physical activity) have been associated with cognitive performance (Newson and Kemps 2006) and absence of disability (Nusselder et al. 2008) and could provide an adequate means to their optimal maintenance. Lifestyle moderation is a particularly appealing clinical intervention for older adults as this can often be achieved relatively inexpensively, does not require supervision or professional assistance and

can be accessed by the majority of older adults within the privacy of their own homes.

This research also has pertinent public health implications. Given the rapidly escalating ageing population, it is imperative for governments to reduce the economic burden of ageing. The most effective mechanism to achieve this is to increase the longevity of the workforce and to reduce health care and assisted living costs (Murphy and Topel 2003). To do this, the healthy lifespan of older adults must be increased, and the first step in achieving this is identifying factors that predict healthy survival to oldest-old status, as was achieved for the first time in the present study. The current study is also unique in that it identifies factors that not only reduce the incidence of one disease in older adults, but multiple diseases. From a public health standpoint, this provides an appreciably more cost-effective intervention compared to a treatment which influences only one of the multiple morbidities associated with ageing.

In conclusion, we found that several lifestyle factors, health indicators and physiological markers independently predicted survival to 85 years. Examination of joint predictors revealed that some common markers of mortality were not significant predictors of survival to 85. However, this may be due to their primary location in the pathway of ageing being masked in the current model, rather than their lack of effect. Overall, the variables in the joint predictors model were able to predict survival to age 85 years. Interestingly, we found that when those that survive to 85 with morbidity are partitioned from analyses we were better able to predict survival. On the basis of these findings, we conclude that we are able to predict healthy survival in the oldest-old. These findings are useful in a clinical setting where modifiable factors can be targeted to improve the health and quality of life of older adults and in a public health setting where increasing the healthy lifespan of older adults can help to reduce the growing economic burden of ageing. Further research should focus on understanding the causal pathways of the individual risk factors involved in survival and morbidity-free survival to age 85 years.

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