

How to live until 90 – Factors predicting survival in 75-year-olds from the general population

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Abstract

Background: The objective of the study was to explore potential predictors common in a clinical context, for survival to age 90 among 75-year-olds from Sweden's general population. We performed a prospective community-based cohort study with 15-year follow-up among 75-year-olds from a defined geographical area.

Methods: Of 1,100 inhabitants born in 1922 and living in Västerås in 1997, 618 were invited to participate in a cardiovascular health survey, and 432 individuals accepted participation. Among them, 380 subjects (61% of those originally invited; 191 men and 189 women) had complete records for all examined variables. Variables were categorized into 4 groups: 1) Previous or present disease; 2. Exercise test variables; 3. Conventional risk factors; 4. Other potential risk factors. Through Area Under the Receiver Operating Characteristic (AUROC) curves, strong predictors for survival until age 90 (AUROC \geq 0.60) in men and women were selected.

Results: The strongest individual predictors for reaching the age of 90 were metabolic equivalents and systolic blood pressure (BP) rise during exercise test, QTc interval in resting electrocardiogram (ECG) and peak expiratory flow (PEF) in men, and, for women, white blood cell (WBC) counts and systolic blood pressure BP rise during exercise. The strongest independent predictor in multivariable models were metabolic equivalents in men and WBC counts in women (explained variability 22 and 6%).

Conclusions: High exercise capacity in men and low WBC in women were the strongest independent predictors of reaching age 90 among the clinical predictors at 75. The strongest modifiable predictor was exercise capacity in men, which can be improved by physical training.

Citation: Nilsson G, Hedberg P, Ohrvik J (2014) How to live until 90 – Factors predicting survival in 75-year-olds from the general population. *Healthy Aging Research* 3:5. doi:10.12715/har.2014.3.5

Received: October 7, 2014; **Accepted:** October 21, 2014; **Published:** November 25, 2014

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Competing interests: The authors have declared that no competing interests exist.

Sources of funding: The original cardiovascular health survey was supported by grants from SparbanksstiftelsenNya and the Västmanland's Research Foundation Against Cardiovascular Diseases.

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Introduction

In recent years, many studies have been published on risk factors for overall mortality. With a growing aging population, there is increased interest in the modifiable factors related to survival to very old age. According to Statistics Sweden, the life expectancy has increased by 1.5 and 2 years for women and men,

respectively, during the last decade. We have previously published findings regarding risk factors for overall mortality during 10-year follow-up in a cohort of 75-year-old men and women from the general population in a defined geographical area of Sweden. These factors consisted of low systolic blood pressure (BP) response during exercise [1], prolonged

QTc interval in resting ECG [2], low high density lipoprotein-cholesterol (HDL-c) in men [3], high white blood cell (WBC) count primarily in women [4] and low psychological well-being in men [5].

Each age class represents survivors from younger age classes. Consequently risk factor patterns can be expected to differ between age classes. For example, high blood cholesterol is a strong risk factor of mortality at age 40 but this fact does not imply that it is a risk factor at 75. At this age most individuals sensitive to adverse effects of high cholesterol may have died. Furthermore, individuals suffering adverse effects of abnormally high cholesterol levels may have decreased cholesterol levels due to “reverse causation” [6] from symptomatic or asymptomatic chronic diseases.

A previous report by Wilhelmsen et al. [7] identified non-smoking and low total cholesterol (TC) levels as predictors of survival from 50 to 90 year of age. Similar to our study, their study performed in Gothenburg, Sweden consisted of individuals from a defined geographical area who were invited to participate in a health survey. Conversely to our study, they invited individuals at age 50 and women did not participate in the study. Willcox et al. [8] reported midlife risk factors of dying before age 85 in a male general population living on the Hawaiian island Oahu and identified several risk factors, including hypertension and tobacco smoking. Simons et al. [9,10] examined the relation between survival during 20 years of follow-up and conventional risk factors in non-institutionalized men and women > 60 year of age (mean age=68). Tobacco smoking, hypertension, diabetes and low PEF were prominent risk factors.

Other studies concerning survival to 90 year of age did not select their study population from the general population. These studies include the Physician Health Study that was confined to physicians [11] and did not include women, and the British Whitehall studies [12-14] that had mid-life data collection and mainly behavioral, psychosocial, socioeconomic and cardiovascular profiles of a cohort including civil service employees.

In the present study, we explored the predictive ability of a set of 29 factors for survival to age 90, obtained

in a health survey of 75-year-olds. We also investigated the change in predictive ability over time – predictive ability for 10-year survival and, given 10-year survival, for survival up to 15 years – in a subset of important factors.

Methods

Study population

The city of Västerås (130,000 inhabitants) situated in central Sweden has a population socioeconomically representative of the country. In 1997 a random sample of 618 of the 1,100 inhabitants born in 1922 (i.e. 75 years old) was invited to a cardiovascular health survey. The final number of participants was 432 (70% of those invited; women = 222; men = 210). Reasons for non-participation were: unknown (n=46); never reached (n=29); unwilling due to diseases under treatment (n=54); language or logistical problems (n=27); locomotive impairment (n=28); or died before examination (n=2).

Due to missing values in one or more of the 29 clinical variables the examined cohort finally consisted of 191 men and 189 women (61% of the originally invited individuals). The main reason for missing values was the inability or unwillingness to conduct a bicycle exercise stress test (14 men and 32 women).

The study was approved by the research ethics committee of Uppsala University, Sweden.

Baseline examinations

A total of 29 predictors of survival were included in the study. Diagnosis of previous myocardial infarction (MI), stroke or transitory ischemic attack (TIA), and known angina pectoris, diabetes, and asthma was based on a self-reported history of disease verified by medical records. Hypertension was defined as self-reported physician-diagnosed high blood pressure (BP) in combination with regular antihypertensive treatment. Newly detected diabetes was defined as a fasting plasma glucose ≥ 7.0 mmol/L without a

previous diagnosis of diabetes according to the WHO criteria [15].

Fasting (≥ 10 h) blood samples were collected for biochemical analysis. Serum triglycerides (TG) and HDL-c were determined enzymatically using an automated analyzer system (Hitachi 717, Boehringer Mannheim, Mannheim, Germany). Non-HDL-c was calculated as TC minus HDL-c. The blood glucose samples were treated with a hemolytic reagent (Merck Diagnostica, Darmstadt, Germany) and glucose was determined enzymatically with glucose dehydrogenase using a Cobas Mira analyzer (Roche Diagnostics Ltd, Rotkreuz, Switzerland). Plasma glucose was computed from venous whole blood glucose using the formula: plasma glucose = $0.558 + 1.119 \times \text{whole blood glucose}$ [16].

The brain natriuretic peptide (BNP) analyses were performed at the Western Infirmary, Glasgow UK, using two-site monoclonal antibody immunoradiometric assays (Shionoria BNP kit; Shionogi & Co. Ltd, Osaka, Japan). WBC were counted with an automated blood cell counter, Cell-Dyn 3500 (Abbott). Current smoking was defined as daily smoking during the last month before index examination.

Systolic and diastolic BP were measured with a mercury sphygmomanometer and rounded to the nearest 5 mm Hg, with the subjects in a supine position and having rested for five minutes, which was the clinical practice in Sweden at that time. Waist circumference was measured in the horizontal plane at the midpoint between the lowest rib and the iliac crest [17] and hip circumference at the broadest part of the hip. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Rodby RE 830/990 ergometers (Rodby Innovation AB, Vane, Sweden) were used with workload beginning at 30 Watts (W) and increasing in steps of 10 W per minute. Patients were encouraged to exercise until they experienced limiting symptoms, usually breathlessness or general tiredness. Other reasons for discontinuing the exercise test were chest pain ($n=6$), pain in hip or knee ($n=7$), abnormal blood pressure reaction ($n=6$), frequent ventricular ectopic beats ($n=2$), or development of excessive ST

depression ($n=5$). Heart rate was measured immediately after exercise and at 4 min into recovery. Exercise capacity was measured in Watts (W), which were converted to maximum oxygen consumption calculated as metabolic equivalents (MET) units using the formula:

$$\text{MET} = (13 \times \text{workload (W)} / \text{body weight (kg)} + 3.5) / 3.5$$

A detailed description of the exercise test protocol has previously been published [1,18]. Heart rate recovery (HRR) was measured based on a recovery period of 4 minutes.

A standard 12-lead electrocardiogram (ECG) was registered in the morning after a resting period of at least 10 min using a Siemens Elemi Machine. The QT and QRS intervals were measured by the SICARD 440/740 ECG computer analysis program (Mega cart version 3 V4, 7/2.38/23, Siemens Elemi) [19]. The QT-intervals were corrected for heart rate using Hodges' linear correction formula ($\text{QTc} = \text{QT} + 1.75(\text{heart rate} - 60)$). Peak expiratory flow (PEF) was measured as L/min with a mechanical peak flow meter.

Prospective follow-up

All-cause mortality served as the primary end-point. By means of the Swedish population register, the study cohort was followed for all-cause mortality from the index examination in 1997 until exactly 15-year afterward. The register was linked to the individuals participating in the study via the unique personal identification number that all Swedish citizens possess. Assessment of follow-up survival status was complete for all participants.

Statistical analysis

All analyses were stratified by sex. Continuous variables were characterized by means and standard deviation (SD) or, in cases of markedly skewed distribution, by medians and interquartile ranges. For continuous data the t-test was used to compare groups. Variables with markedly skewed distribution were logarithmically transformed. Categorical data were compared using the Fisher's exact test. The

associations between exercise capacity and HRR and between QTc and BNP were assessed by Pearson's correlation coefficient.

As measure of predictive ability the Area Under the Receiver Operating Characteristic (AUROC) curve was used. By means of AUROC the variables with the strongest predictive ability (AUROC ≥ 0.60 in either sex) were selected and tested for their ability to predict survival until age 90 by means of crude and multivariable logistic regression analyses. Odds ratios were used to estimate relative risks. Both forward and backward stepwise analyses using 0.05 as entry and removal probabilities were used detect problems with potential multi-collinearity. A two-sided p-value < 0.05 was regarded as statistically significant.

Cumulative mortality was estimated by means of a Kaplan-Meier analysis. In order to obtain clinically useful cut-off points for exercise capacity, as reflected by MET units in men and by WBC counts in women for predicting 15-year survival we chose the point on the ROC curve that represented the largest sum of sensitivity and specificity [20]. Ten-fold cross-validation was used to eliminate the influence of the individuals being classified when determining the cut-off points [21]. IBM SPSS Statistics 20 was used for all statistical analysis.

Results

The variables considered for possible predictive ability were categorized into four groups: previous and current diseases, exercise test variables, conventional risk factors, and miscellaneous factors of potential predictive value for survival. The basic characteristics of the examined factors are summarized in Table 1.

The predictive capacity of the variables as measured by the AUROC curve is shown in Table 2. High exercise capacity, high systolic BP rise during exercise, strong HRR, high PEF, low BNP, high HDL-c, short QTc and QRS intervals in resting ECG and absence of known angina pectoris or previous MI performed best as predictors of survival to age 90 among men.

Table 1. Basic characteristics of the selected variables according to survival status

	Men (n=191)		Women (n=189)	
	Survivors (n=47)	Non-survivors (n=144)	Survivors (n=99)	Non-survivors (n=90)
Prevalent or previous disease				
Angina pectoris or previous MI	4 (9)	40 (28)**	8 (8)	15 (17)
Stroke/TIA	0	3 (2)	1 (1)	6 (7)*
Known hypertension	6 (13)	45 (31)**	23 (23)	31 (35)
Known diabetes	3 (6)	10 (7)	5 (5)	8 (9)
Diabetes (previously known or newly detected)	7 (15)	25 (17)	14 (14)	20 (23)
Asthma bronchial	1 (2)	10 (7)	9 (9)	14 (16)
Exercise test				
Metabolic equivalents units	8.2 (1.4)	6.9 (1.4)***	6.4 (1.2)	6.0 (1.5)
Systolic BP rise, mmHg	58 (24)	41 (25)***	42 (23)	33 (22)**
4 minutes heart rate recovery, beats/min	57 (16)	45 (18)***	50 (13)	44 (16)*
Conventional risk factors				
Current smoker	3 (6)	21 (15)	2 (2)	11 (10)**
Total cholesterol†, mmol/L	6.0 (1.0)	6.0 (1.1)	6.6 (1.1)	6.4 (1.2)
HDL-cholesterol, mmol/L	1.50 (0.34)	1.36 (0.29)**	1.73 (0.46)	1.61 (0.55)
Non HDL cholesterol, mmol/L	4.6 (1.1)	4.6 (1.1)	4.9 (1.2)	4.8 (1.1)
Triglycerides, mmol/L	1.4 (1.0–1.8)	1.5 (1.1–2.0)*	1.4 (1.1–2.1)	1.5 (1.2–2.1)
Systolic BP, mmHg	159 (25)	162 (24)	167 (27)	172 (24)
Diastolic BP, mmHg	83 (9)	85 (10)	84 (9)	84 (11)
Body weight, kg	76 (11)	77 (10)	70 (11)	70 (13)
Height, cm	175 (6)	174 (6)	163 (5)	161 (6)
BMI, kg/m ²	24.9 (3.0)	25.3 (2.9)	26.2 (3.8)	26.7 (4.3)
BMI > 25 (yes/no)	24 (51)	73 (51)	57 (58)	60 (67)
Waist, cm	93 (9)	95 (8)	87 (10)	89 (12)
Hip, cm	102 (7)	103 (6)	106 (10)	106 (10)
Waist/hip ratio	0.91 (0.05)	0.92 (0.05)	0.82 (0.05)	0.84 (0.06)*
Miscellaneous factors				
Peak expiratory flow, L/min	484 (89)	415 (110)***	321 (67)	302 (88)
Brain natriuretic peptide, fmol/mL	4.3 (2.8–8.4)	9.5 (3.8–17.7)***	7.3 (4.0–11.9)	8.4 (4.7–15.7)*
Creatinine, µmol/L	107 (13)	106 (21)	87 (11)	87 (14)
White blood cells, 10 ⁹ /L	6.1 (1.1)	6.5 (1.5)	5.5 (1.1)	6.1 (1.5)**
QRS duration ECG, ms	92 (14)	100 (17)**	88 (11)	89 (12)
QTc -interval ECG, ms	409 (24)	421 (25)**	415 (22)	422 (24)

Values are number (%), mean (SD) or median (interquartile range)

*p<0.05, **p<0.01, and ***p<0.001 for difference between survivors and non-survivors within sex

† Seven men and 6 women were on lipid-lowering drugs

All of these predictors reached AUROC ≥ 0.60 . Among women, the predictive ability of the examined factors was generally weaker than in men with exception of low WBC count, which together with high systolic BP, strong HRR at exercise test, and high HDL-c were the only factors reaching AUROC ≥ 0.60 for predicting survival to age 90. At the exercise test, MET units, as opposed to systolic BP rise and HRR, was a statistically significant stronger predictor for 15 year survival in men than women (p=0.006). This was the only statistically significant sex disparity in prognostic ability of the present set of variables.

All variables with AUROC ≥ 0.60 in either sex (Table 2) were analyzed for change in predictive ability over time. The predictive abilities for 10-year survival and for survival up to 15 years given 10-year survival were analyzed separately using logistic regression, as shown in Figure 1. In men, MET units, 4 minute HRR, and PEF were significant (p < 0.05) predictors

for survival to both years 85 and 90, and QTc interval was significant for survival to 85 and reached near significance for survival to 90 years ($p = 0.064$) (Figure 1, upper panel). In women WBC count and 4 minute HRR were significant for survival to 85 and nearly significant for survival to 90 year ($p = 0.077$ and 0.079 , respectively) (Figure 1, lower panel).

Table 2. Predictive ability of examined factors for survival to 90 among 75 years-old by AUROC curve

	Men (n=191)			Women (n=189)		
	AUROC (95%CI)	Direction of association*	p^\dagger	AUROC (95%CI)	Direction of association*	p^\dagger
Prevalent or previous disease						
Angina pectoris or previous MI	0.60 (0.51–0.68)	-	0.048	0.54 (0.46–0.63)	-	
Stroke/TIA	0.51 (0.42–0.61)	-		0.53 (0.45–0.61)	-	
Known hypertension	0.59 (0.50–0.68)	-	0.057	0.56 (0.48–0.64)	-	
Known diabetes	0.50 (0.41–0.60)	-		0.52 (0.44–0.60)	-	
Diabetes (known or previously unknown)	0.51 (0.42–0.61)	-		0.54 (0.46–0.62)	-	
Asthma bronchial	0.52 (0.43–0.62)	-		0.53 (0.45–0.62)	-	
Exercise test						
Metabolic equivalents units	0.75 (0.68–0.83)	+	<0.001	0.59 (0.51–0.68)	+	0.028
Systolic BP rise	0.68 (0.59–0.76)	+	<0.001	0.61 (0.53–0.69)	+	0.009
4 minutes Heart rate recovery	0.70 (0.62–0.78)	+	<0.001	0.62 (0.54–0.70)	+	0.005
Conventional risk factors						
Current smoking	0.54 (0.45–0.63)	-		0.55 (0.46–0.63)	-	
Total cholesterol	0.52 (0.42–0.61)	+		0.55 (0.47–0.64)	+	
HDL-cholesterol	0.62 (0.53–0.72)	+	0.011	0.60 (0.52–0.69)	+	0.014
Non HDL cholesterol	0.52 (0.42–0.61)	-		0.51 (0.43–0.59)	+	
Triglycerides	0.59 (0.50–0.69)	-	0.061	0.52 (0.44–0.61)	+	
Systolic BP	0.54 (0.44–0.63)	-		0.55 (0.47–0.63)	-	
Diastolic BP	0.56 (0.47–0.65)	-		0.51 (0.43–0.60)	-	
Body weight	0.51 (0.41–0.61)	+		0.50 (0.42–0.59)	+	
Height	0.57 (0.47–0.67)	+		0.56 (0.47–0.64)	+	
BMI	0.54 (0.44–0.64)	+		0.54 (0.45–0.62)	-	
BMI > 25	0.50 (0.40–0.59)	+		0.55 (0.47–0.63)	-	
Waist	0.56 (0.45–0.66)	-		0.56 (0.48–0.66)	-	
Hip	0.52 (0.42–0.62)	-		0.51 (0.42–0.59)	-	
Waist/hip ratio	0.57 (0.48–0.66)	-		0.56 (0.48–0.65)	-	
Miscellaneous factors						
Peak expiratory flow	0.70 (0.61–0.78)	+	<0.001	0.57 (0.49–0.65)	+	0.098
Brain natriuretic peptide	0.65 (0.57–0.74)	+	0.001	0.58 (0.50–0.66)	+	0.063
Creatinine	0.56 (0.47–0.65)	+		0.53 (0.45–0.62)	+	
White blood cells	0.58 (0.49–0.67)	-	0.099	0.61 (0.53–0.69)	-	0.010
QRS duration ECG	0.63 (0.55–0.72)	-	0.006	0.53 (0.45–0.61)	-	
QTc -interval ECG	0.64 (0.55–0.73)	-	0.004	0.58 (0.49–0.66)	-	0.074

*Direction of association: + the probability of becoming 90 years is increased for higher values, - the probability of becoming 90 years is decreased for higher values
 $^\dagger p$ -value written out if $p < 0.10$

The AUROC of HRR was high in men (0.70). The absence of HRR in the final multivariate model for men was dependent upon the strong correlation between HRR and MET units (Pearson correlation 0.53; $p < 0.001$ in men and 0.55; $p < 0.001$ in women). Heart rate recovery was included in the final model in men if MET units was excluded from the analysis. Likewise, the absence of BNP from the final models despite its high AUROC value was due to its high correlation with QTc (Pearson correlation 0.30; $p < 0.001$ in men and 0.32; $p < 0.001$ in women).

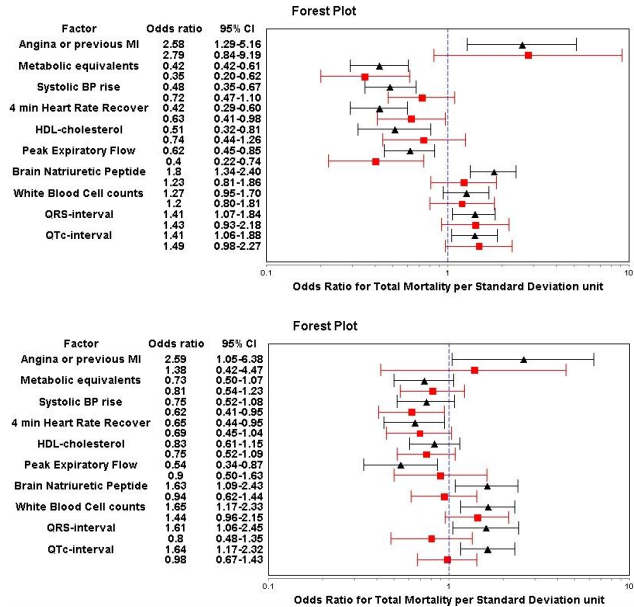


Figure 1. Odds ratios with 95% CI for variables with AUROC ≥ 0.60 in either sex

Ten-year survival is depicted by the black triangles and 15-year survival given 10-year survival is indicated by the red squares. The data for men is shown in the upper panel (deaths/number of men at risk was 83/191 up to 10 years and 62/108 up to 15 years given 10 year survival). The lower panel shows the data for women (deaths/number of women at risk was 48/189 up to 10 year and 45/141 up to 15 year given 10 year survival).

Kaplan-Meier survival curves were produced for the strongest independent predictor in either sex, i.e. exercise capacity (in MET units) among men (log rank test $p < 0.001$) and WBC count among women (log rank test $p < 0.001$), as depicted in Figure 2. The cut-off points for dichotomization were selected as the points with the largest sum of specificity and sensitivity using 10-fold cross-validation.

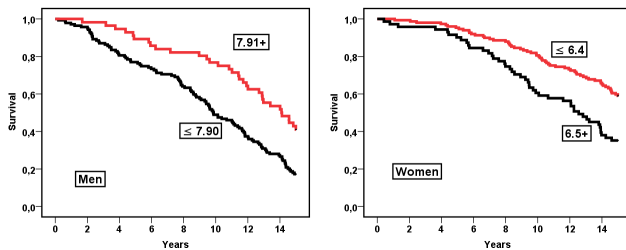


Figure 2. Kaplan-Meier survival curves for men according exercise capacity and for women according to WBC counts

Numbers of men at risk at 0, 3, 6, 9, and 12 years were 191, 173, 147, 122, and 87. Numbers of women at risk at 0, 3, 6, 9 and 12 year were 190, 183, 171, 151, and 129.

Table 3. Best subset logistic regression models for mortality before age of 90, stratified by sex

	OR	95% CI	p
Men (n=191)			
Metabolic equivalents units	0.57	0.42-0.78	<0.001
QTc –interval, 10msec	1.20	1.004-1.43	0.041
Peak expiratory flow, 10L/min	0.95	0.91-0.997	0.031
Systolic BP rise, 10mmHg	0.84	0.70-0.996	0.037
Women (n=189)			
White blood cells, 10 ⁹ /L	1.41	1.12-1.77	0.004
Systolic BP rise, 10mmHg	0.83	0.72-0.95	0.006

Discussion

Principal findings

We report multiple factors that, both individually and jointly, predict survival until 90 years of age among 75 year-old community-dwelling residents from a defined geographical area. The most interesting finding, especially among men, was the strong association between survival and results from the exercise test, including high exercise capacity as measured by MET, high HRR after 4 minutes recovery, and high systolic BP rise during exercise. The prognostic importance of these factors greatly exceeded that of common prevalent diseases such as diabetes, hypertension, asthma, and angina pectoris/previous MI as well as that of conventional risk factors such as smoking, high BP, high level of

TC, low level of HDL-c and obesity. Furthermore, both MET and HRR were significantly related to both shorter (10 year) and longer (10 to 15 year) survival. These findings about the relative importance of factors associated with 15-year survival have clinical implications in terms of the design of appropriate prevention programs for the elderly. The predictive ability for 15-year survival of the examined factor set was generally weaker in women than in men, except for the high independent predictive ability of low WBC count in women; however, in this case, the relationship with longer (10 to 15 year) survival was only borderline significant.

Strengths and limitations

The restriction of our investigation to one age class enables us to leave out age as a confounding factor, creating the possibility of a meaningful estimation of sex-specific relationships between all-cause mortality risk factors despite the relatively small number of participants in the study. Furthermore, the participants are more representative of the population in a defined geographical area than those primarily described in the literature. However, these advantages are offset by the difficulty to generalize our findings to individuals who are 75 years old and to people from other geographical areas. However, it seems likely that our results are applicable to North Europeans and white North Americans in their seventies.

A further strength of the present study is the long follow-up time and the unusually large number of potential predictors of mortality that were studied. A further limitation of the study is the fact that the mortality among invited individuals who did not participate in the study (39%) was considerably higher than among invited individuals who participated (61%), which is primarily reflective of the higher prevalence of diseases under treatment among non-participants. Therefore, the studied population likely consisted of the relatively healthy majority of a general population in a defined geographical area.

Specific causes of death have not been used in the present study in light of the common difficulties in identifying a precise cause of death in very old age even through autopsy [22].

Comparison with other studies

Some of the results presented here confirm previous findings from the present study population with shorter follow-up times. This applies to BP increase during exercise test [1], QTc and QRS intervals in resting ECG [2], TC and HDL-c [3] and WBC counts [4]. The predictive strength of conventional risk factors such as smoking, high BP, obesity, and high TC is generally somewhat lower when registered among the elderly than when registered at midlife [7,12-14]. In an Australian cohort of non-institutionalized men and women aged ≥ 60 years, Simons et al. [9,10] confirmed that smoking, hypertension and diabetes were associated with reduced survival. They also showed that low PEF was associated with poor survival as in our study. The Australian cohort was not examined with an exercise test or WBC counts and is therefore not comparable to our cohort concerning the most important survival predictors.

Exercise capacity

An extensive meta-analysis by Kodama et al. [23] has clearly identified high exercise capacity as measured by an exercise test as a strong predictor of survival in several cohorts with mean ages around 50. However, data for exercise capacity in as advanced an age as 75 were lacking. The present study clearly shows that an exercise stress test, which is a readily available diagnostic procedure, is a good predictor of survival among 75 year-olds, especially in men. In a longitudinal study of the general population, Fleg et al. [24] observed that the age dependent decline of exercise capacity in the general population accelerates, especially in men, in the 70s and beyond. The decline was estimated to $> 20\%$ per 10 years in the 70s. There is clear evidence that high levels of physical activity improves exercise capacity [25] [26] and survival [27,28].

Systolic BP rise

A high systolic BP rise during an exercise test has been previously identified as a strong predictor for survival in the present cohort [1]. The present study

shows that its predictive ability is almost as large as that of exercise capacity among the 75 year-olds. We are not aware of any other reports about the predictive ability of mortality by systolic BP rise among the elderly. The prognostic impact of different degrees of exercise-induced increase in BP is of particular interest concerning women as very few women were included in previous studies on this topic [1]. Among the younger and middle-aged individuals referred to the exercise test for clinical reasons, high systolic BP rise during exercise has been found to be both a predictor for high [29] and low future mortality [30].

Conventional cardiovascular risk factors

With the exception of HDL-c, none of the other blood lipids were significantly associated with survival. This is consistent with our previous report from this cohort [3]. It is well known that the value of obesity, as a risk factor for mortality, weakens and even becomes obsolete among the very elderly [31], which is consistent with the present report. Generally, tobacco smoking, hypertension and obesity had weaker relationships to survival at age 75 than in the midlife [7,12,13] or at a mean age of 68 [10]

WBC counts and other miscellaneous risk factors

As indicated by our results, WBC count has a much stronger prognostic ability for overall mortality and cardiovascular mortality relative to the conventional risk factors among the elderly, such as TC and low-density lipoprotein-cholesterol (LDL-c). The WBC count tends to cluster with other established risk factors such as tobacco smoking [32,33] as well as HDL-c and TG [34,35]. The pathophysiological mechanisms that link elevated WBC count to increased mortality are poorly understood. The increased mortality associated with high WBC counts has previously been demonstrated in elderly men [36] as well as in cohorts consisting of a wide range in age [37-39]. White blood cell counts are increased in vascular diseases but it is unknown whether they are involved in the pathogenesis of such diseases or are merely indicative of other factors causing vascular damage [40].

The QTc interval is an indirect measure of the ventricular action potential, including the depolarization and repolarization of the heart chambers. It is readily obtainable from a standard 12-lead ECG and has a considerably greater prognostic ability than conventional risk factors, such as blood lipids. The present analysis shows a similar prognostic ability for the QTc interval as reflected by the AUROC found for 15-year survival in the present study population. BNP reflects the stretch of cardiac chambers. An additive predictive ability for 6-year survival of BNP and QTc has been described for the present study population [2]. Notably QTc length and serum BNP concentration were strongly positively correlated explaining why BNP was not an independent predictor of 15-year survival despite its high AUROC value.

Conclusions

Further research

The predictive ability of the examined factors was generally higher in men than in women with the exception of WBC count. The mechanisms behind this sex disparity, as well as the adverse prognosis associated with basal WBC counts in the elderly, particularly in women, are poorly understood and deserve further research efforts. The relationship between short QTc and survival should be confirmed in additional cohorts. Furthermore the potential capability of QTc to reflect ECG measures needs to be explored. The strikingly scarce data on factors related to survival among elderly women necessitates greatly expanded research efforts for this group of the population.

Clinical implications

The strongest predictive factor among men, exercise capacity, is clearly modifiable by physical activity, which then can improve both survival and quality of life. In contrast, traditional risk factor interventions such as the reduction of cholesterol levels and BP seem to be less important. Furthermore, exercise capacity clearly exceeds the importance of several

established diseases to life expectancy. Therefore, a physically active lifestyle could compensate well for the prognostically adverse effects of such diseases. Taken together, the results of this analysis are important for preventive health care among the elderly.

Acknowledgments

The authors are grateful to Marja-Leena Ojutkangas for her excellent care of the study participants as well as the data management. We are also grateful to Mattias Rehn for excellent technical support.

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