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2 Midlife cardiovascular status and old age physical functioning trajectories
3 in older business men
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40   ABSTRACT

41   Background. The associations between cardiovascular disease (CVD) risk and later physical

42   functioning have been observed, but few studies with follow-up into old age exist. We

43   investigated the association between cardiovascular status in midlife and physical functioning

44   trajectories in old age.

45   Methods. In the Helsinki Businessmen Study cohort (Caucasian men born in 1919-1934) three

46   CVD status groups were formed based on clinical measurements carried out in 1974: signs of

47   CVD (diagnosed clinically or with changes in ECG, chronic disease present or used medication,

48   n=563); healthy and low CVD risk (n=593) and high CVD risk (n= 1222). Of them, 1560 men had

49   data on physical functioning from at least one of four data collection waves between 2000-

50   2010. Ten questions from the RAND-36 (SF-36) survey were used to construct physical

51   functioning trajectories with latent class growth mixture models. Mortality was accounted for

52   in competing risk models.

53   Results. A five-class solution provided the optimal number of trajectories: 'intact', 'high stable',

54   'high and declining', 'intermediate and declining' and 'consistently low' functioning. Compared

55   to low CVD risk, high CVD risk in midlife decreased the risk of being classified into the 'intact'

56   (fully adjusted β -3.98, SE 2.0, p=0.046) relative to 'consistently low' physical functioning

57   trajectory. Compared to low CVD risk, those with signs of CVD were less likely to follow the

58   'intact', 'high stable' or 'high and declining' relative to the 'consistently low' trajectory (all

59   p<0.018).

60   Conclusions. Among businessmen, a more favorable CVD profile in midlife was associated with

61   better development of physical functioning in old age.

62   Key words: Cardiovascular health, physical functioning trajectories, growth mixture model,

63   life course epidemiology, healthy ageing

64 INTRODUCTION

65 Adequate physical functioning is important in maintaining independence and quality of life with

66 advancing age.[1] Associations between poor physical functioning and adverse outcomes such as

67 geriatric syndromes, nursing home admission and premature mortality[2-6] stress the importance

68 of identifying modifiable risk factors in time. Knowledge on these risk factors may help in

69 designing interventions aimed at maintaining the ability to actively engage in society and live

70 independently.[7]

71

72 Evidence from longitudinal studies suggests that individual modifiable cardiovascular risk

73 factors such as high blood pressure and cholesterol, smoking, obesity and hyperglycemia are

74 linked with later physical functioning.[8-12] While the association of clusters of three or four CVD

75 risk factors[13-15] and established composite CVD risk indices[16-19] and later physical functioning

76 measures have been studied, only few studies with follow-up from midlife into old age

77 exist.[15,16,18,19] Furthermore, little is known about whether and how midlife cardiovascular status

78 is associated with various trajectories of physical functioning in old age. There is marked

79 heterogeneity in the progression of physical functioning with advancing age[20] and it is

80 influenced by current, but also past risk factors. More information on early risk factors for

81 patterns of physical functioning in older age would provide insight into more targeted

82 promotion of functioning. We investigated the association between modifiable midlife

83 cardiovascular risk factors measured in the year 1974 and physical functioning trajectories in

84 old age, which had been assessed at four time points over a 10-year period between 2000 and

85 2010.

86

87

88 MATERIALS AND METHODS

89 Study population

90 The Helsinki Businessmen Study (HBS) cohort has been described in detail earlier.[21] Briefly, the

91 present study population consisted of white men born between 1919 and 1934. They shared a

92 similar working status and belonged to the highest socioeconomic class. Between the years

93 1964 and 1973, 3490 men participated in voluntary health check-ups at the Finnish Institute of

94 Occupational Health that included measurements on CVD risk factors which were considered

95 to be important at that time. Of these men, 3309 formed the baseline cohort for later

96 examinations, see Figure 1. During the years 1972-73 these men were screened for eligibility

97 for a CVD primary prevention trial and in 1974, 1222 men were assessed as having high or low

98 CVD risk or signs of CVD (see below for definitions of CVD risk).[21] During 1974-1980, 1222 high

99 CVD risk men participated in a multifactorial prevention trial,[22] but participation in the trial did

100 not affect the present analyses and all men were included to improve statistical power. Of the

101 2378 men who had data on CVD status in 1974, 1560 had data on physical functioning from at

102 least one of the four subsequent data collection waves carried out in the years 2000, 2003, 2007

103 and 2010 (response rates were 81.5%, 66.3%, 65.1%, 67.8%, respectively) and they formed the

104 analytical sample of this study. The follow-up studies of the HBS have been approved by the

105 Ethics Committee of the Department of Medicine, Helsinki University Hospital, Finland and the

106 study has been registered as Clinical Trials.gov identifier: NCT02526082.

107

108 Cardiovascular status and risk definitions in midlife

109 Examinations for CVD risk factors and health status were carried out in 1974 at a mean age of

110 47.3 (SD 4.0) years. Overweight was determined by relative body weight (%) (body weight in

111 kilograms x 100 divided by height in centimeters minus 105).[23] Smoking was inquired in a

112 questionnaire asking how many cigarettes per day they smoked. Blood pressure was measured

113 in a sitting position after 10 min rest using a mercury sphygmomanometer. Fasting serum

114 cholesterol and triglycerides were measured using standard methods. Blood glucose (mmol/L)

115 was measured 1 hour after a glucose load of 1g/kg of body weight administered orally. Resting

116 and exercise electrocardiograms were taken at the laboratory and medical history was

117 recorded. In 1974, cohort members were classified into groups according to risk factors and

118 possible signs of CVD and other chronic diseases.[22] The CVD risk factors and cut-offs were

119 defined as follows: 1) relative body weight ≥120% (corresponds to BMI ≥27.8 kg/m^2); 2) smoking

120 >10 cigarettes/day; 3) blood pressure ≥160/95 mmHg; 4) serum cholesterol ≥7.0 mmol/L

121 (corresponds to 6.4 mmol/L with current laboratory methods); 5) serum triglycerides ≥1.7

122 mmol/L; and 6) 1-hour post-load glucose ≥9.0 mmol/L.[22] The distribution of risk factors in our

123 analytical sample (according to cut-offs described above) was as follows: 41.4% had one, 32.2%

124 had two, 17.0% had three and 9.4% four or more CVD risk factors. It is of note that risk

125 definitions reflected the situation in the 1970´s. Albeit according to current standards, low-risk

126 men would rather be defined to be at "intermediate" risk, we wanted to use the original CVD

127 grouping that has been reported in several papers.[22,24]

128

129 Three CVD status groups were formed: 1) low CVD risk (n=593, healthy, no signs of CVD, none

130 of the aforementioned risk factors); 2) high CVD risk (n=1222, healthy, no signs of CVD, but had

131 at least one of the CVD risk factors, mean 2.1 risk factors); and 3) signs of CVD (n=563, CVD

132 diagnosed either clinically or with changes in ECG, receiving regular medication for

133 hypertension, hyperlipidemia or diabetes, or having been diagnosed with serious non-CVD). The

134 last group was named 'signs of CVD' while the majority of the conditions that the men had were

135 cardiovascular diseases or related to the metabolic system.

136

137 Physical functioning

138 In the year 2000 at a mean age of 73.3 (SD 4.1) years, physical functioning was assessed using

139 ten items included in the physical functioning domain from the validated RAND-36 Health

140 Survey (Version 1.0) (identical with the Short Form SF-36).[25,26] Cohort members were asked to

141 what extent their health limited daily activities such as walking two or half a kilometer or 100

142 meters or climbing 1 or several flight of stairs. If the participants had no difficulties, some

143 difficulties or they were unable to perform a task, these were coded as 100, 50 and 0,

144 respectively, they were summed up and divided by 10. Scores range from 0 to 100 and a higher

145 score indicated better physical functioning. For each data collection wave, 7 out of the 10

146 physical functioning items were required for the score to be calculated (and in that case the

147 summed score was divided by the respective number of answered items). The proportion of

148 those who had data missing on three items at most ranged between 1.0 and 1.7% across the

149 four data collection waves and when considering all four follow-ups the percentage of those

150 with 7 out of 10 answers for each follow-up we were able to include 48 persons (3.1%).

151

152 Health characteristics in midlife and old age

153 The cohort members were inquired in 1974 about self-rated health with response alternatives:

154 very good, fairly good, average, fairly poor and very poor. For the analyses, two latter ones were

155 coded into one category "poor" due to few cases in the very poor category.[27] In the year 2000,

156 the participants were asked about physician-diagnosed illnesses in a mailed questionnaire. The

157 men who reported having at least one of the following diseases: stroke, transient ischemic

158 attack, high blood pressure, coronary artery disease, heart failure, or dysfunction in

159 cerebrovascular or lower extremity circulation were classified as having CVD. Dates of death

160   were retrieved from the Finnish Population Register Center for the entire cohort between 1974

161   and 2010.

162

163   Statistical methods

164   We identified different physical functioning trajectories by fitting latent class growth mixture

165   models (LGMM) to all available physical functioning data of the 1560 cohort members from the

166   years 2000, 2003, 2007 and 2010 using Mplus version 7.0.[28] In the analyses, we used LGMM

167   with Full Information Maximum Likelihood, in order to capture unobserved subpopulations

168   (latent groups) in all available data with similar physical functioning trajectories, but which were

169   distinct across the latent groups over the follow-up time. Grouping was based on the likelihood

170   of the membership calculated for each individual's own trajectory. Each latent group had their

171   own growth parameters, intercept (indicating similar trajectories over time) and slope

172   (indicating changes in physical functioning scores over time). We estimated the quadratic and

173   cubic shapes of the trajectories in order to identify all potential differences in the development

174   of physical functioning. We used several model fit indices to determine the optimal number of

175   latent groups.[28] For Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC),

176   lower values indicate a better fit of the model. Clarity of classification into trajectory classes

177   was assessed with 1) high percentage of individuals falling into the latent class based on the

178   posterior probabilities (indicates the probability of a participant belonging in a given trajectory

179   class) and 2) high model entropy (an aggregate of posterior probabilities), which ranges

180   between 0 and 1, with values near 1 indicating clear classification.

181

182   The conceptual model for investigating the association between CVD status in midlife and

183   physical functioning trajectories in old age is presented in Figure 2. We constructed a competing

184 risks multinomial regression model to model the risk related to physical functioning trajectory

185 class membership while simultaneously accounting for mortality risk during the physical

186 functioning assessments between the years 2000 and 2010. Kaplan-Meier survival curves did

187 not cross for the major part of time thus supporting proportionality. The proportionality of

188 hazards was tested using the scaled Schoenfeld residuals, where non-significant p-values lend

189 support for the proportionality assumption. The proportionality was supported for all

190 covariates with an effect in the mortality part of the model: CVD status in y. 1974 (high risk vs.

191 rest, p=0.575; sick vs. rest, p = 0.797), self-rated health in y. 1974 (p=0.629), CVD in y. 2000

192 (p=0.669) and the global estimate of proportionality (p=0.875). We estimated unstandardized

193 regression coefficients (β), their mean errors (SE) and related p-values for the associations.

194 Based on the proportional hazards model, the latent effect of excess mortality risk was used to

195 adjust the physical functioning trajectory class for mortality risk. In addition, the model was

196 adjusted for birth year, self-rated health in midlife and self-reported CVD in the year 2000. 71

197 (4.6%) individuals had missing data for self-rated health, which were imputed using multiple

198 imputation in SPSS with data on all intact variables included in the prediction of missing values.

199 Significance level was set at 0.05 and tests were two sided.

200

201 RESULTS

202 The model fit indices used to determine the best model fit for the physical functioning data in

203 the 10-year follow-up indicating the optimal number of latent classes, i.e. physical functioning

204 trajectories, are presented in the Supplementary Table S1. BIC was lowest for the five-class

205 solution. Average membership probabilities in the five latent classes ranged between 0.78 and

206 0.88, while model entropy was 0.71 indicating reasonable classification clarity. The five physical

207 functioning trajectories were named 'intact' (approximately 10% of the cohort belonged to this

208   class), 'high stable' (32%), 'high and declining' (29%), 'intermediate and declining' (23%), and

209   'consistently low' (6%) (Figure 3). Individual observations belonging to each physical functioning

210   trajectory are presented in Supplementary Figure S1.

211

212   There were statistically significant differences in the characteristics of the cohort members

213   across the physical functioning trajectories presented in Table 1. The men classified into the

214   'intact' and 'high stable' trajectory were younger at baseline, 45.2 (SD 3.6) and 46.5 (SD 3.9)

215   years, respectively, whereas those in the 'consistently low' trajectory were the oldest 49.0 (3.8)

216   years. The proportion of men with signs of CVD was higher in the poorer physical functioning

217   trajectories (7.7% in the 'intact' vs. 33.7% in the 'consistently low' trajectory). There were also

218   differences for self-rated health in midlife across the trajectories; of those in the 'intact'

219   trajectory, 44.0% rated their health very good or fairly good, whereas the corresponding

220   proportion was 19.0% in the 'consistently low' trajectory. The prevalence of CVD in the year

221   2000 was 31.0% for the men assigned to the 'intact' trajectory and increased in the poorer

222   physical functioning trajectories being 85.4% in men belonging to the 'consistently low'

223   trajectory. Out of the 1560 cohort members, 539 (34.6%) died between the years 2000 and

224   2010. Mortality during ten years was higher among those who were classified into the poorer

225   physical functioning trajectories (17.6% in the 'intact' trajectory vs. 84.3% in the 'consistently

226   low' trajectory).

227

228

229   The results of the associations between midlife CVD status and physical functioning trajectories

230   in old age for the competing risk multinomial regression models are presented in Table 2.

231   Compared to those with low CVD risk in midlife, those with high CVD risk were less likely to be

232   classified into the 'intact' (fully adjusted β -3.98, SE 2.0, p=0.046) trajectory relative to

233   'consistently low' physical functioning trajectory. In terms of effect size, the associations were

234   parallel for the 'high stable' and 'high and declining' trajectories but not statistically significant.

235   Compared to the men with low CVD risk, those with signs of CVD in midlife were also less likely

236   to be classified into the 'intact', 'high stable' and 'high and declining' physical functioning

237   trajectory relative to the 'consistently low' trajectory, all p-values <0.018. The association was

238   also parallel but statistically non-significant for the 'intermediate and declining' trajectory. The

239   proportion of those who died during the follow-up increased gradually with declining physical

240   functioning trajectories. The prevalence of mortality was lowest among those in the 'intact'

241   trajectory (approximately 18%) and highest among those in the 'intermediate and declining'

242   (54%) and 'consistently low' trajectories (84%), p-value <0.001.

243

244   DISCUSSION

245   We identified five distinct physical functioning trajectories during a 10-year period in a cohort

246   of old business executives who have been followed up from midlife. Albeit around forty percent

247   of the men were classified into the 'intact' or 'high stable' physical functioning trajectory, a fair

248   number of cohort members showed signs of declining physical functioning which progressed

249   during the follow-up period in old age. A clinically significant decrease of 5 or more points[29] in

250   the RAND-36 physical functioning sub-category score was observed in all other trajectories

251   expect for the 'intact' trajectory. A more favorable CVD profile in midlife was associated with

252   better development of physical functioning in old age. Compared to low CVD risk, those with

253   high CVD risk or signs of CVD were less likely to follow one of the four more favorable physical

254   functioning trajectories. The association persisted after adjustment for CVD in old age and also

255   after accounting for mortality as a competing risk. Our findings provide new evidence on the

256   long-term association between modifiable CVD risk factors and subsequent patterns of physical

257   functioning.

258

259   Previous studies have found that higher CVD risk scores, indicating impaired cardiovascular

260   health, are related to poorer subsequent physical functioning.[16-19] However, to the best of our

261   knowledge, there are no previous studies on the patterns of physical functioning that are

262   related to earlier CVD status. In the present study, high CVD risk in midlife decreased the

263   probability of being assigned to a physical functioning trajectory that was intact across the 10-

264   year follow-up of physical functioning in old age. For the men with signs of CVD in midlife, i.e.

265   CVD diagnosed either clinically or with changes in ECG, receiving regular medication for

266   hypertension, hyperlipidemia or diabetes, or having been diagnosed with serious non-CVD, the

267   association was more pronounced. Signs of CVD decreased the probability of being assigned to

268   a more favorable physical functioning trajectory in old age. This association was observed for

269   those men who were assigned to the 'consistently low', 'high and declining' and 'high stable'

270   functioning trajectories compared to those in the 'intact' trajectory. This might be due to

271   disease-related impairments and decreased level of reserve capacity and compensation ability

272   in midlife which may have later led to functional decline.[30]

273

274   The mechanisms underlying impaired physical functioning are complex and may include many

275   physiological changes related to disease processes and geriatric syndromes.[6,31] For example,

276   smoking and hypertension may lead to peripheral artery disease which predisposes to declining

277   physical functioning.[32] Furthermore, damage to the musculoskeletal and peripheral nervous

278   systems start to occur well before the consequences for physical functioning can be detected.

279   Evidence that the onset of the chronic disease burden starts already early on in life is growing.[33]

280   Notably, early detection of risk factors that are known to subsequently be related to disability

281   later in life help to identify individuals who potentially stand to gain from preventive health care

282   measures.[30] Modelling physical functioning trajectories provide more knowledge on the

283   progress of limitation and the timing of preventive measures for maintaining physical capability.

284

285   The strengths of our study include the well-characterized sample of businessmen and

286   executives who came from a homogenous background and who have been followed up across

287   several decades. Midlife cardiovascular status was determined based on

288   measurement/assessment of several CVD risk factors which is similar to other established CVD

289   risk scores such as the Framingham Risk Score.[34] Physical functioning was assessed using the

290   ten items included in the sub-scale of physical functioning from the validated RAND-36 Health

291   Survey questionnaire[25] and having several data collection waves allowed for modeling

292   trajectories over time. GMM analyses are data-driven and a person-centered approach to

293   classifying study participants into sub-groups in a post-hoc manner. The method can be used to

294   describe differences in longitudinal change between and within the unobserved groups. We

295   used a competing risk model to account for mortality that occurred during the 10-year physical

296   functioning follow-up among the old businessmen.

297

298   Some limitations of the study should be recognized. The cohort comprised of men only and

299   included individuals belonging to the highest socioeconomic strata which limits generalizability.

300   The business executives and managers at that time worked typically long hours and the work

301   was often stressful. These aspects of work have been shown to contribute to a higher

302   prevalence of CVD.[35] We did not have the same measures of CVD risk available in old age that

303   we had in midlife and were not able to investigate the long-term association between CVD risk

304 status and later outcomes. During the follow-up of physical functioning between the years 2000

305 and 2010, mortality was relatively high. Using a maximum likelihood method in the GMM

306 analyses, which uses all existing information and does not require complete data, we accounted

307 for non-random missingness related to mortality. We also further accounted for mortality

308 during the follow-up by using a competing risk model in the multinomial regression analyses.

309 We did not have data on physical functioning in midlife and thus adjusted for self-rated health,

310 which is a good general measure of health and is related to adverse outcomes in later life such

311 as frailty.[36]

312

313 In conclusion, in a cohort of older businessmen and executives, midlife cardiovascular status

314 was related to physical functioning patterns in old age which varied greatly among the men.

315 Trajectories that indicate stability/maintenance of physical functioning into old age are markers

316 for healthy ageing and quality of life and important outcomes in terms of the individual's ability

317 to lead an independent and active life. Our results indicate that CVD risk status in midlife is a

318 useful measure in determining the risk of poor physical functioning decades later. Furthermore,

319 intervening in these modifiable risk factors already in midlife might help mitigate decline in

320 physical functioning in older age.

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329 Author contributions

330 MBvB drafted the paper, analyzed the data, designed the study; MJH interpreted the data,

331 designed the study, revised the paper critically for important intellectual content; TT

332 interpreted the data, designed the study, revised the paper critically for important intellectual

333 content; KP interpreted the data, designed the study, revised the paper critically for important

334 intellectual content; SS interpreted the data, designed the study, revised the paper critically

335 for important intellectual content; TS responsible for data acquisition, interpreted the data,

336 designed the study, revised the paper critically for important intellectual content.

337

338 Sponsor's Role

343

344

345

346   LEGENDS

347

348   Figure 1 Study flowchart.

349

350   Figure 2 Conceptual model for assessment of midlife CVD status and physical functioning

351   trajectories in old age when accounting for birth year, self-rated health in midlife, CVD in older

352   age and excess mortality risk. Squares are observed values and circles are latent values.

353

354   Figure 3 Identified physical functioning trajectories over the 10-year follow-up from the year

355   2000 to 2010.

356

357   Supplementary Figure S1 Individual observations belonging to each physical functioning

358   trajectory.

359

360   Supplementary Table S1. Model Fit Statistics, Group Sizes and Average Latent Class

361   Probabilities for Most Likely Class Membership.

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450

Table 1 Characteristics of the Cohort Members According to Physical Functioning Trajectories

	Physical functioning trajectories[*]					p-value
	Intact	High stable	High and declining	Intermediate and declining	Consistently low	
	n=142	n=518	n=440	n=371	n=89	
Birth year, %						<0.001
1919-1925	20.4	31.1	40.2	54.2	53.9	
1926-1933	79.6	68.9	59.8	45.8	46.1	
Age in 1974, years, mean (SD)	45.1 (3.6)	46.5 (3.9)	47.6 (3.9)	48.5 (3.8)	49.0 (3.8)	<0.001
CVD status in 1974, %						<0.001
Low risk	43.0	33.6	32.7	18.6	13.5	
High risk	49.3	51.5	51.1	57.1	52.8	
Signs of CVD	7.7	14.9	16.2	24.3	33.7	
Self-rated health in 1974, %						<0.001
Very good	13.9	3.9	3.8	1.7	0.0	
Fairly good	40.1	35.1	32.9	22.7	19.0	
Average	40.9	50.8	52.6	54.3	51.2	
Poor	5.1	10.2	10.7	21.3	29.8	
CVD[*] in year 2000, %	31.0	52.1	62.7	69.0	85.4	<0.001
Died between 2000 and 2010, %	17.6	21.4	28.9	54.2	84.3	<0.001

SD= standard deviation

[*] Assessed between 2000 and 2010

[†]CVD included self-reported prevalence of stroke, transient ischemic attack, high blood pressure, coronary artery disease, heart failure, or dysfunction in cerebrovascular or lower extremity circulation.

Table 2 Unstandardized Betas, Standard Errors and P-values for Path Coefficients of Models for Midlife CVD Status Predicting Physical Functioning Trajectories in Old Age in the Helsinki Businessmen Study

	Intact vs. Consistently low			High stable vs. Consistently low			High and declining vs. Consistently low			Intermediate and declining vs. Consistently low		
	β	S.E.	p-value	β	S.E.	p-value	β	S.E.	p-value	β	S.E.	p-value
CVD status in midlife[*]												
Low CVD risk	ref.			ref.			ref.			ref.		
High CVD risk	-3.981	1.991	0.046	-3.768	1.984	0.058	-3.697	1.968	0.060	-2.311	1.841	0.209
Signs of CVD	-6.291	2.425	0.009	-5.752	2.402	0.017	-5.634	2.375	0.018	-3.812	2.198	0.083

CVD=cardiovascular disease

[*]Estimated with adjustment for birth year, self-rated health in midlife, CVD status in the year 2000 and excess mortality risk between 2000 and 2010.
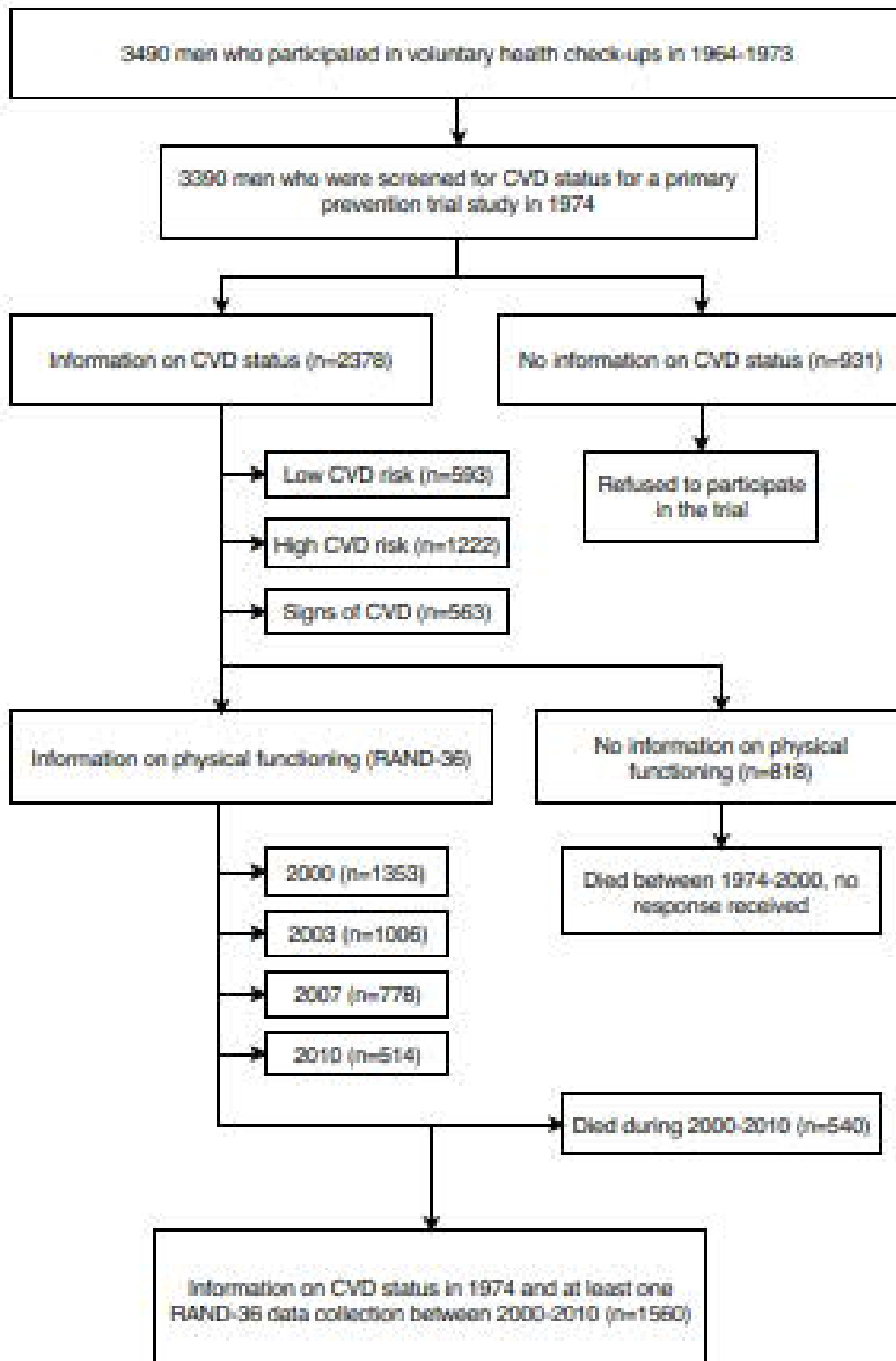
Figure 1


```
┌─────────────────────────────────────────────────────────────┐
│  3490 men who participated in voluntary health check-ups     │
│  in 1964-1973                                                 │
└─────────────────────────────────────────────────────────────┘
                            │
                            ▼
┌─────────────────────────────────────────────────────────────┐
│  3390 men who were screened for CVD status for a primary     │
│  prevention trial study in 1974                              │
└─────────────────────────────────────────────────────────────┘
            │                                   │
            ▼                                   ▼
┌──────────────────────────────┐   ┌──────────────────────────────┐
│ Information on CVD status     │   │ No information on CVD status  │
│ (n=2378)                      │   │ (n=931)                       │
└──────────────────────────────┘   └──────────────────────────────┘
            │                                   │
            │  ┌─────────────────────────┐      ▼
            ├─►│ Low CVD risk (n=593)     │   ┌──────────────────────────┐
            │  └─────────────────────────┘   │ Refused to participate   │
            │  ┌─────────────────────────┐   │ in the trial             │
            ├─►│ High CVD risk (n=1222)   │   └──────────────────────────┘
            │  └─────────────────────────┘
            │  ┌─────────────────────────┐
            └─►│ Signs of CVD (n=563)     │
               └─────────────────────────┘
            │                                   │
            ▼                                   ▼
┌──────────────────────────────┐   ┌──────────────────────────────┐
│ Information on physical       │   │ No information on physical    │
│ functioning (RAND-36)         │   │ functioning (n=818)           │
└──────────────────────────────┘   └──────────────────────────────┘
            │                                   │
            │  ┌──────────────────┐             ▼
            ├─►│ 2000 (n=1353)    │   ┌──────────────────────────┐
            │  └──────────────────┘   │ Died between 1974-2000,  │
            │  ┌──────────────────┐   │ no response received     │
            ├─►│ 2003 (n=1006)    │   └──────────────────────────┘
            │  └──────────────────┘
            │  ┌──────────────────┐
            ├─►│ 2007 (n=778)     │
            │  └──────────────────┘
            │  ┌──────────────────┐
            └─►│ 2010 (n=514)     │
               └──────────────────┘
            │                       │
            │                       ▼
            │          ┌──────────────────────────────┐
            │          │ Died during 2000-2010 (n=540)│
            │          └──────────────────────────────┘
            ▼
┌─────────────────────────────────────────────────────────────┐
│  Information on CVD status in 1974 and at least one          │
│  RAND-36 data collection between 2000-2010 (n=1560)         │
└─────────────────────────────────────────────────────────────┘
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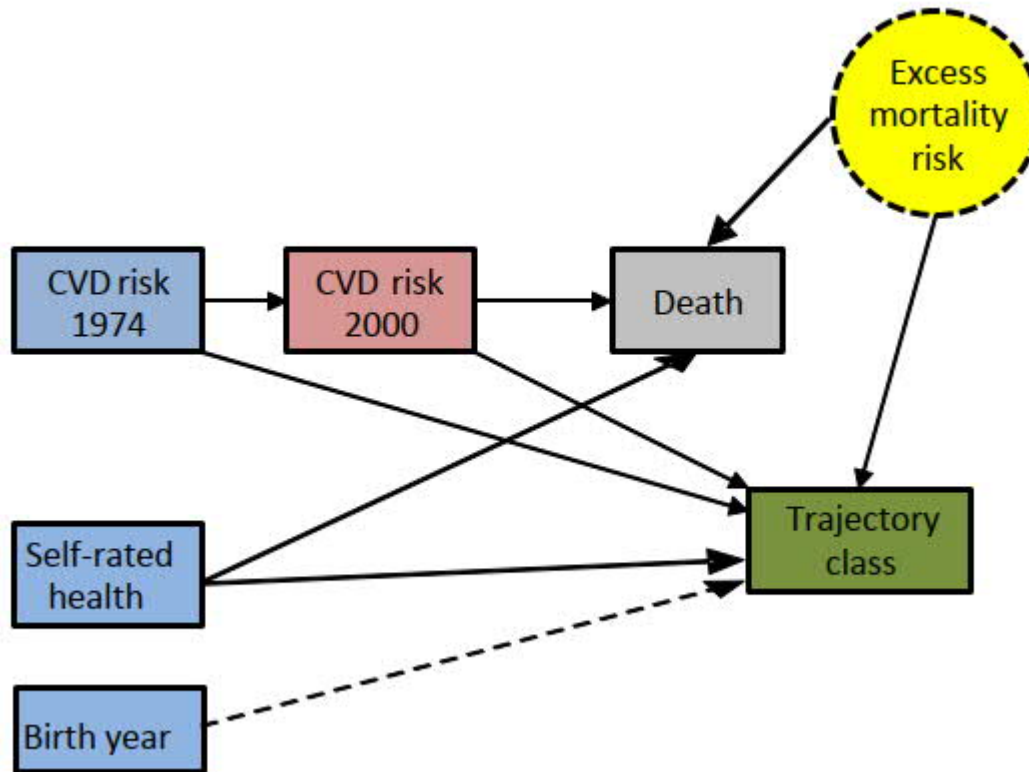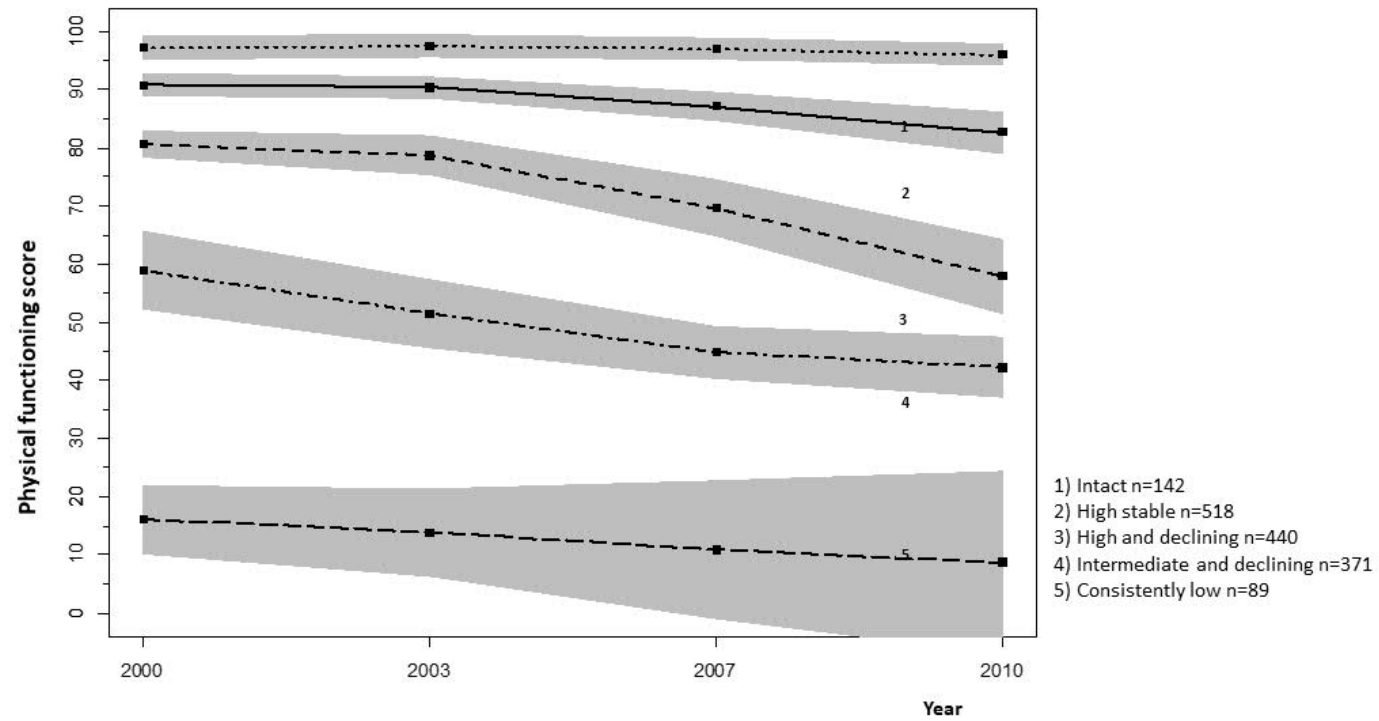
Figure 2.

Figure 3

1) Intact n=142
2) High stable n=518
3) High and declining n=440
4) Intermediate and declining n=371
5) Consistently low n=89

Supplementary Table S1. Model Fit Statistics, Group Sizes and Average Latent Class Probabilities for Most Likely Class Membership.

Classes	LL	Scaling	Free parameters	Information criteria			Entropy	Group size (Average latent class probability for most likely latent class membership)					
				AIC	BIC	aBIC		n_1	n_2	n_3	n_4	n_5	n_6
1	-21939	1.88	13	43904	43977	43935	1.000	1991 (1.00)					
2	-20815	1.26	27	41684	41835	41749	0.742	960 (0.95)	1031 (0.91)				
3[b]	-20597	1.49	38	41270	41483	41362	0.712	742 (0.93)	818 (0.84)	431 (0.81)			
4[c]	-20495	1.31	49	41087	41361	41206	0.691	610 (0.78)	198 (0.80)	517 (0.92)	666 (0.78)		
5[d]	-20453	1.24	54	41009	41312	41140	0.712	556 (0.78)	191 (0.79)	461 (0.84)	631 (0.78)	152 (0.88)	
6[e]	-20422	1.18	65	40973	41337	41131	0.658	535 (0.73)	189 (0.78)	139 (0.66)	619 (0.79)	377 (0.66)	132 (0.79)

Note. LL = loglikelihood, scaling = Robust maximum likelihood scaling factor, AIC = Akaike information criterion, BIC = Bayesian information criterion, aBIC = sample size adjusted Bayesian information criterion.
[b]Parameter restrictions in class 3: var(Q)=0, cov(I,Q)=0, cov(S,Q)=0.
[c]Parameter restrictions in class 2: var(Q)=0, cov(I,Q)=0, cov(S,Q)=0, and in class 3: var(Q)=0, cov(I,Q)=0, cov(S,Q)=0.
[d]Parameter restrictions in class 2: var(Q)=0, cov(I,Q)=0, cov(S,Q)=0, and in class 3: var(I) = 0, var(S), var(Q)=0, cov(I,Q)=0, cov(I,S) = 0, cov(S,Q)=0, and in class 4: intercept(Q)=0, var(I) = 0, var(Q)=0, cov(I,Q)=0, cov(I,S) = 0, cov(S,Q)=0.
[e]Parameter restrictions in class

Supplementary Figure S1