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Aging and Survival

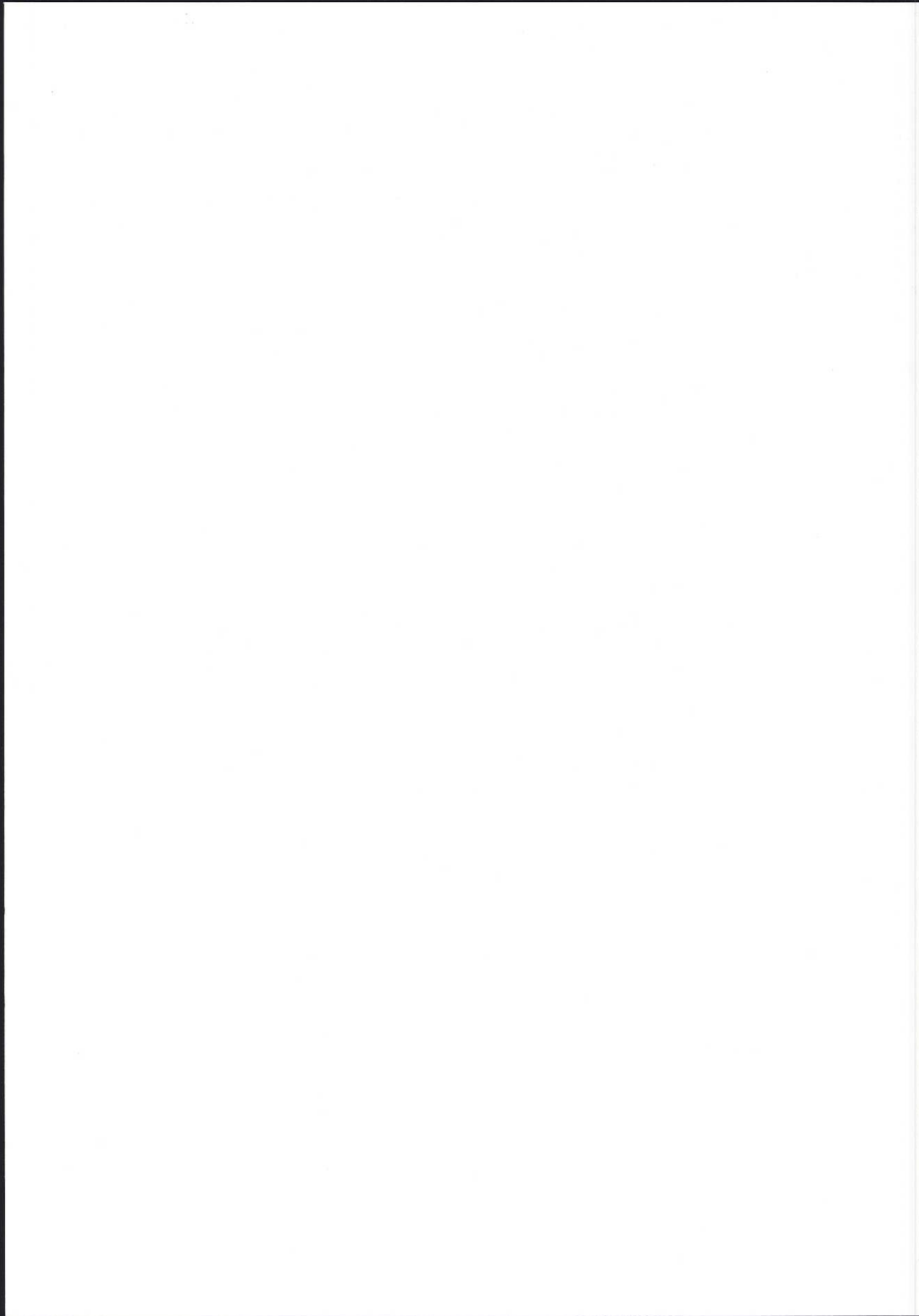
Studies of Social, Biobehavioural, and Genetic Correlates

Birgit Ljungquist



GÖTEBORG, SWEDEN 1996

**FROM THE DEPARTMENT OF GERIATRIC MEDICINE,
GÖTEBORG UNIVERSITY, GÖTEBORG
SWEDEN**



Aging and Survival
Studies of Social, Biobehavioural, and Genetic Correlates

av

Birgit Ljungquist
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AKADEMISK AVHANDLING

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- Study I.** Ljungquist B., Sundström G. Health and social networks as predictors of survival in old age. *Scandinavian Journal of Social Medicine*, in press 1996.
- Study II.** Ljungquist B., Berg S., Steen B. Determinants of survival: An analysis of the effects of age at observation and length of the predictive period. *Aging Clinical and Experimental Research* 1996; 8:22-31.
- Study III.** Ljungquist B., Berg S., Steen B. Prediction of survival in 70-year olds. *Archives of Gerontology and Geriatrics* 1995; 20: 295-307.
- Study IV.** Ljungquist B., Lanke J. Seasonal variations in mortality rates: A comparison between centenarians and the general population. (Submitted).
- Study V.** Ljungquist B., Berg S., Lanke J., McClearn G., Pedersen N. The effect of genetic factors for longevity: A comparison of identical and fraternal twins in the Swedish Twin Registry. (Submitted).

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Birgit Ljungquist, Department of Geriatric Medicine, Göteborg University, Göteborg, Sweden

ABSTRACT

The aim of this thesis was to explore the influence of social, biobehavioural, and genetic factors on survival in old age.

Three large databases comprising Swedish elderly were analysed. Study I was performed on a nation-wide random sample originally collected in 1954 by Statistics Sweden for a government commission on elderly affairs. It comprised non-institutionalised persons, 67 years and older. Study II and Study III were based on data from the prospective longitudinal population study of elderly in Göteborg, the H70-investigation. The analyses were performed mainly on a random sample of 70-year-old persons, which was compiled in 1971/1972. In Study IV, data on centenarians were collected from official publications from Statistics Sweden. Data from the oldest part of the Swedish Twin Registry was used in Study V. This registry was compiled in 1961 and includes like sexed twins born between 1886 and 1925 of which 10,505 twin pairs were included.

The common objective for all studies in this thesis is survival, expressed as length of life or as age at death.

The results show that there is no single factor nor is there a specific set of factors that can be identified as the best predictor of survival. Related variables can be systematised into higher level domains. As an alternative to the use of a set of specific variables for predicting survival/death, a number of risk domains can be utilised. Survival capacity is dependent on the shared influence of factors from various domains like health, cognition, mobility, lifestyle, activities, social networks, etc. Deficits in one domain can be compensated by great capacities in other domains. A good predictor of survival reflects the effects of a complex network of factors. A measure of lung capacity proved to possess this quality and was the single best variable to predict survival among all those variables included in these studies.

Among the centenarians an increased mortality rate was observed during the winter season. At these high ages the level of vigour is low and minor environmental stress will be enough to cause death.

The twin studies showed that about one third of the variance in longevity can be explained by genetic effects, and two thirds of the variance are due to environmental effects. The genetic effect seems to diminish in importance in old ages.

Key words: Aging, survival, elderly, twins, genetic, biobehavioural, social, risk domain, predictor of survival, seasonal.

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INTRODUCTION

Aging and survival are central elements in the science of gerontology. It is a matter of great importance to achieve a better understanding of the mechanisms that regulate our aging, and finally our death. The established view, that science may affect human longevity favourably by postponing the ageing process and thereby the onset of diseases and finally death, still persists as a challenge for gerontological research to evaluate.

There is no general or universal definition of aging. Researchers have used different definitions depending on their own theoretical bases. A widely accepted definition is given by Strehler (106) and according to him changes must be deleterious, progressive, intrinsic and universal to be defined as aging changes. Arking (3) has developed this definition when describing aging as "those series of cumulative, universal, progressive, intrinsic, and deleterious functional and structural changes that usually begin to manifest themselves at reproductive maturity and eventually culminate in death."

The biological definitions usually underline functional decline terminating in death. Comfort (12) thus proposed aging to be "an increased liability to die, or an increasing loss of vigour, with increasing chronological age, or with the passage of the life cycle." Schroots and Birren (97) have given a broader definition of aging. In addition to biological aging, which they called senescing, they also identified social aging, called eldering, and psychological aging, called geronting. Among these three components is senescing, the only one necessarily related to declining capacity.

As the biological definitions state, aging is a detrimental process. In young individuals there is a great amount of reserve capacity in vital organs to handle external and internal stress. At higher ages, though, these reserves have diminished and a minor quantity of stress can be enough to cause death.

Age is by convention measured in time units, but the pace of the aging process varies widely among individuals. Age-related changes arise from a

variety of sources and two individuals of the same age can be extremely far apart in their aging processes. This heterogeneity is a problem that must be considered in all aging studies, but the variance is far more pronounced in old ages than in younger ages. In a review of biological periodicities (52) was stated that, "Time is inseparable from aging; it may be, therefore, useful in organizing our thoughts about aging to consider the role of time in some biological processes."

Many investigations have been performed with the objective to gain knowledge of survival and predictors of survival, but it is evident from the literature that there is a great amount of variation in the results and in the conclusions drawn from the results. There might be a number of reasons for this variability. It is likely that predictors shift in their significance over the life cycle, which was already pointed out in one of the first textbooks on the methodology of longevity predictions (92) but has not been frequently discussed since.

Mortality studies are performed most often on both left and right censored data. Those who have died earlier, possibly for other reasons than those being studied, are not at all included in the study, and those who are still alive when the study is finished, or have for some reason been lost or dropped out during the study, have an unknown remaining survival time and unknown cause of death. Censoring may affect results in ways that are not easily interpreted.

Factors that appear important over short time spans may be less important in a life-time perspective, which affects the results when different prediction intervals are used. The effect of the length of the predictive period has rarely been discussed. The Bonn Longitudinal study (57) is one of the few studies which has discussed the importance of the length of the predictive period for the selection of significant indicators of survival and for the strength of the correlation between predictors and longevity.

The age of the individuals at observation is another seldom discussed aspect. The few investigations that have considered age are mainly within the cognitive domain and the discussions have primarily been focused on whether the correlation between survival and cognitive tests are stronger

among middle-aged and young old-aged individuals than among the oldest-old ones (90, 15).

Another aspect that ought to be considered regarding age concerns gender differences. In Sweden in 1990, the expected remaining length of life at birth was almost six years higher among women than among men, and the male mortality rate is higher than the female mortality rate at all ages. Part of the gender differences found in the power of different factors as predictors of mortality may be explained by the shorter average distance to death among men compared to women, which exists at any age.

Some of the most frequently examined predictors of survival will be discussed in the following paragraphs.

Socio-economic factors

Factors describing social class have been found in a number of studies (21, 22, 114, 110) to be of importance for health and survival, but the impact seems to vary among countries. Not only a person's own social class but also that of the parents has proved to be of importance for a person's longevity (111). Class differences have in most studies (13, 94) been found to be of greater significance in the middle-aged groups and thereafter diminish by age. An exception to this was a British study (100) in which socio-economic factors were found to be influential on survival not only for the middle-aged ones, but also for those who reached an advanced age and a curvilinear dependence was suggested. Even in a Swedish study (77), social class differences were found to influence survival with effects that were increasing with age for women but not for men.

Social networks

In a number of studies (81, 31, 116), various indicators of social networks have been found to be correlated with survival, and social networks have proved to be as important as health for predicting survival (37). Exceptions from these findings have been reported, however. In a British study (100), social network factors were found not to be influential on survival. This was also the result of a 14-year follow-up Danish study (74). But social networks have been measured in different ways which may explain some of the divergence in the importance of social networks as a predictor of longevity (76). It has also been suggested that social support has different significance as a predictor depending on what specific risks and illnesses the individuals are coping with (59). Another reason for divergent results can be that the correlation between social network and survival is dependent on age. Social networks are possibly more important among younger individuals than among elderly ones and they should not be operationalized in the same way for all ages (73). A large Swedish study (75) identified social networks as the single most important factor for early death, particularly among men in younger age cohorts. In the Alameda County study (99), in contrast, mortality risk was found to be strongly correlated with a network index over a long time span (17 years).

Life style

Life style is a highly multidimensional category which has been represented in various studies by a great number of divergent factors. Life style can include factors that are generally well known to shorten length of life (e.g., smoking, excessive eating, use of alcohol and drugs) which are supposed to have an influence on length of life by their effects on health in general and their relationship to certain diseases (lung cancer, cardiovascular diseases, etc.) (28). But life style can also include factors describing attitudes to religion or politics, leisure activities (e.g., reading, performing or listening to music, watching television), and physical activities (e.g., gardening, sports activities) as well as a number of other

hobbies. Different kinds of activities have been found in several studies to be of importance for longevity (79, 99, 47). But there are exceptions; in the Bonn longitudinal study no significant differences were found between survivors and non survivors for leisure activities (56).

Physical functional ability, measured by ADL (Activity of daily living) or IADL (Instrumental activity of daily living) represents another dimension of activity and these factors have also been found in a number of studies to be correlated with mortality over both short and long time spans (81, 64, 51, 109). Activity factors, of any kind, probably reflect the importance of staying active and the benefit this has on mobility and on mental and physical health. On the other hand, activities often require good health!

Physical health

Physical health, obviously, is closely related to the presence of diseases. The influence of various diseases on longevity is a large subject to discuss but it is not an aim for this thesis to analyse the correlation between longevity and various diseases. Physical health can be specified differently. Not only objectively measured health status but also self-rated health has proven to be useful in predicting survival. In the Duke Longitudinal Study (80) in which health variables proved to be the strongest predictors of survival, self-rated health was an even better predictor than was an objective measure of health. A prospective study of the health of elderly people in New Haven, Connecticut, USA (39) gave similar results. When controlling for other risk factors, the effects of subjective health proved to be even stronger in a healthy cohort than in a less healthy cohort (96), and it was hypothesised that one reason for this could be that persons with perceived poor health were less likely to undertake health protective behaviours. Self-perceived health was also found to be correlated with longevity in the Alameda County study (46).

A range of physiological variables have been recognised as predictors of survival. In the Baltimore Longitudinal Study (108) a number of health-related variables were identified as predictors of survival, e.g., systolic

blood pressure, forced expiratory capacity, and creatinine clearance. Those variables have often been classified as biomarkers of aging (3, 70). Other examples of biomarkers and other variables associated to health, identified as predictors of survival, are weight changes, height, body mass index, serum cholesterol, etc. (16, 58, 54, 24, 65, 25, 34).

The fact that extreme hot or cold periods are related to increased mortality has been verified in several studies (4, 49, 14, 120). Excess winter mortality caused by respiratory diseases, influenza, infections, and cardiovascular diseases has been reported in several studies and, as explanations to the seasonal variations in mortality, have been discussed not only temperature but also the corresponding seasonal variations in blood pressure, serum cholesterol, serum triglycerides, and plasma fibrinogen concentrations. The greatest seasonal variations in mortality have been found in vulnerable groups like new-born children and the oldest-old ones (32, 72, 82).

Cognitive functioning and dementia

Cognitive functioning, both experience related crystallised intelligence and information processing related fluid intelligence, has been found in a great number of studies to be correlated to longevity (79, 6, 61, 55). Some findings suggest that the rate of change in cognitive function is a more powerful predictor of survival than the level of cognitive function (15, 86). In contrast, other studies report that no decline in cognitive function in older ages can be found in healthy individuals (e.g. 63), which would indicate that correlation between cognitive functioning and survival is mainly reflecting illness. Other studies again suggest that intellectual changes are not at all related to distance to death (117). Twin studies show that most of the variance in general cognitive abilities among older people is due to genetic differences (85).

A population-based longitudinal study (42) has reported an increased mortality risk in the demented, twice the risk in the non-demented, over a follow-up period of 4 years. In a number of studies on individuals with

diagnosed dementia of Alzheimer type or with vascular dementia correlations have been found between cognitive functioning and survival (26, 33).

Genetics

An early observation found that mortality rates among men are higher than among women, and that this difference is maintained through the life span. This might be caused by chromosomal differences or sex-specific hormone differences which explicitly, or implicitly by influences on gender related behaviours, might affect longevity. Very little is known, however, about the mechanisms underlying these gender differences in mortality rates and to what extent they could be modified. According to recent studies, men seem to have a survival advantage over women among the most extremely aged, and this has in the literature been referred to as a gender crossover (87). Gender differences in aging have only rarely been addressed in a systematic way in gerontological research.

Studies on the influence of genetic factors on health and longevity generally show a genetic effect. Only limited information is available, however, on the relative importance of genetic and environmental factors on longevity. According to evolution theories, there is a limited life span, with the limit set by genes (50). Early genealogical studies found significant parent-offspring correlations in longevity (83, 11). Studies on twins provide a strong design for investigating the genetic effects on longevity. Data from the Swedish Twin Registry (44,9), the Danish Twin Registry (36), and the New York State Twin Registry (41) all show that there are less differences in longevity within identical (MZ) twin pairs than within fraternal (DZ) like-sexed twin pairs. The relative effects of genetic and environmental factors on longevity have been studied using data from the Danish Twin Registry (69). The results suggested that environmental factors account for most of the variance in age at death and that it is mainly nonshared environmental factors that are of importance. The genetic effects were interpreted as nonadditive rather than additive.

As can be seen from the discussions above, conclusions drawn in the studies demonstrate both similarities and discrepancies. As the designs differ considerably across studies, it is likely that age at observation as well as the length of the observation period might explain some of the divergence. In addition, there might be differences among the studies concerning inclusion criteria, sample sizes, variable definition, etc. that might have had an impact on the results. Finally, it must be remembered that analyses performed on a sample of individuals will provide us with knowledge on an average level valid only for this sample. General conclusions can be drawn with an uncertainty that can be specified, but conclusions on an individual level can never be drawn based on results from of a sample study.

AIMS

General

- to explore the influence of social, biobehavioural, and genetic factors and their interactions on survival in old age.

Specific

- to investigate the importance for survival of factors describing social status and social networks compared with the importance of health factors and study how the influences vary with age, social class, marital status, and health status at examination (Study I)
- to analyse the effects of age at examination, length of predictive period, and physical health for selection of predictors of survival (Study II)
- to investigate whether there is one set of overall best predictors of survival, or whether correlated variables could be exchanged without significant loss of predictive power, or whether prediction of survival could be performed on basis of a less detailed domain level (Study III)
- to describe seasonal variations in mortality among centenarians (Study IV)
- to examine the relative importance of genetic and environmental effects on longevity (Study V).

MATERIAL AND METHODS

SUBJECTS

Study I

Study I was performed on a nation-wide random sample originally collected in 1954 by Statistics Sweden for a government commission on elderly affairs (103). It comprised 1,151 non-institutionalised persons, 67 years and older. At the time of the interview, 21 persons were dead and 57 were institutionalised, and because of that, excluded. Only nine persons refused participation. Dates of death were collected for survival analyses, using personal code numbers as identifiers. Only one person could not be identified and was therefore excluded from the study. Another person, still alive, was also excluded. The total number of non-respondents was thus 11, an extremely low figure. Study I was performed on a total of 1,062 persons, 491 men and 571 women. The age range at the interview was 67 - 97 years for men and 67 - 95 years for women. The median age was 75 years for men and 74 years for women. The age at death ranged from 69 to 100 years for men and from 68 to 104 years for women, and the median age at death was 83 years for men and 85 years for women. The range of the observation period was 0 - 28 years for men with a median period length of 7 years. For women, the range of the observation period was 0 - 31 years with a median period length of 8 years. The age and sex distribution is shown in Figure 1.

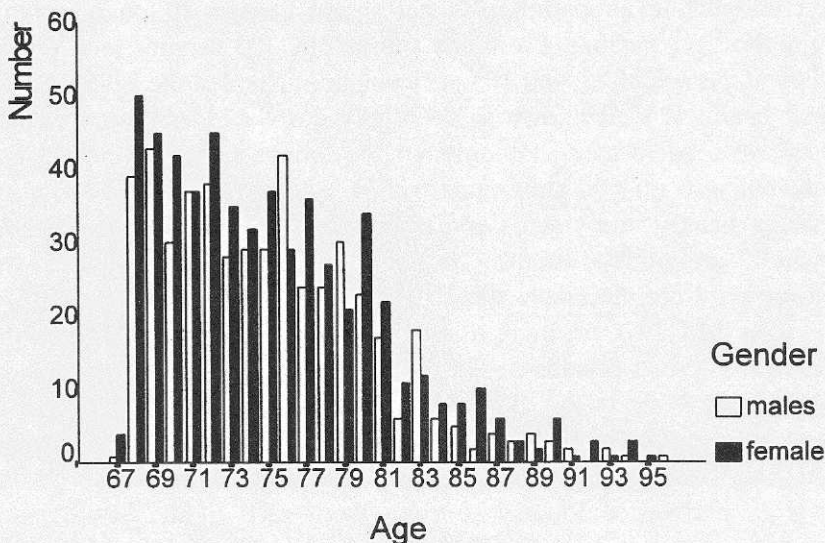


Figure 1. Distribution of gender and age in Study I.

Study II

Study II was based on data from the prospective longitudinal population study of elderly in Göteborg, the H70-investigation (91, 107, 5, 105). The first birth cohort in this investigation was born in 1901/1902. From a random sample of 1,148 persons who were 70 years old in 1971/1972, 975 individuals (84,8%) agreed to participate in the H70-investigation. One person was excluded in Study II because no questions of interest for the study had been answered. Study II thus comprised 974 individuals, 449 men and 525 women. The non-respondents did not significantly differ from the respondents in sex, marital status, or income. The survivors were asked to participate in similar investigations at the ages of 75 and 79. Five years later, at the age of 75, 744 out of 825 survivors participated and at the age of 79, 432 out of the 660 survivors agreed to participate. There has been a number of follow-ups after the age of 79, but information from these has not been used in this study.

A psychological examination was performed at age 70 on a random subsample of 391 persons. From this subsample, 303 persons took part in the study at the age of 75, and 165 persons participated at the age of 79. As physical health is well known to be highly correlated with survival, all analyses were performed, not only on the whole samples of men and women, but also on two subgroups within each sex, with one subgroup comprising healthy individuals and the other comprising the remaining, less healthy individuals. Healthy individuals were defined as those who had no or only one definable disease as diagnosed by a physician (53). Those who had two or more diseases were defined as less healthy individuals. Survival periods of five, nine, 15 and, 20 years were studied. Figures 2 and 3 show the flow of the individuals between groups of healthy, less healthy and deceased individuals during the two follow-up examination periods and the percentage of deceased persons at the observation periods of 15 and 20 years from each of the health-status groups defined at the age of 79. Figure 2 shows the flow of the men, and Figure 3 shows the flow of the women.

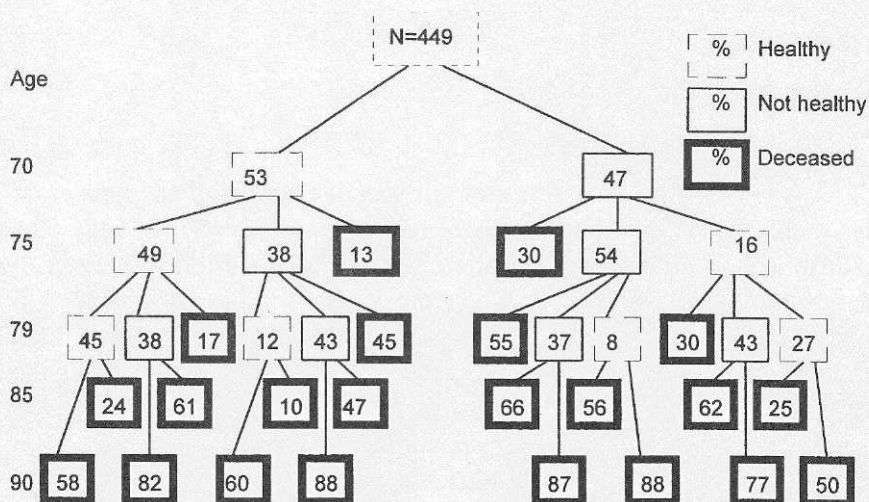


Figure 2. Percentages of healthy, non-healthy, and deceased men at the examinations at 70, 75, and 79 years of age and percentages of deceased men at the ages of 85 and 90.

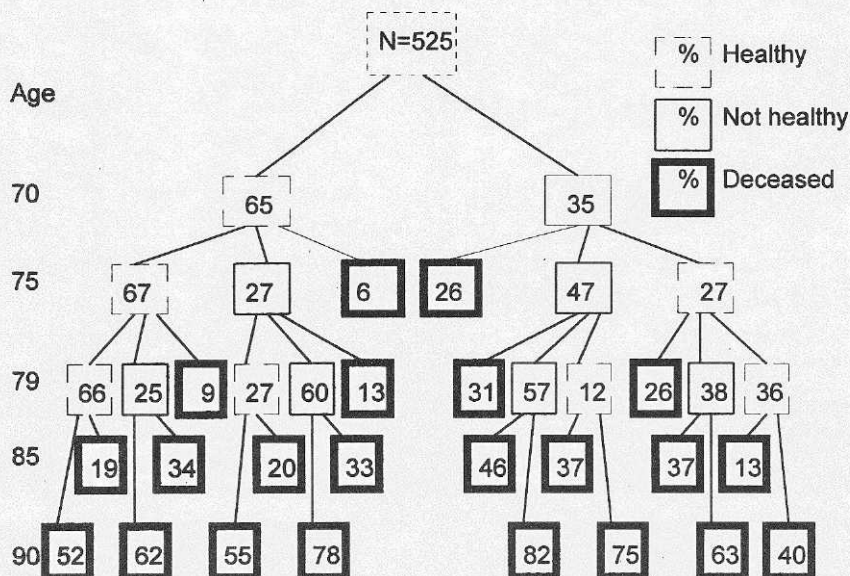


Figure 3. Percentages of healthy, non-healthy, and deceased women at the examinations at 70, 75, and 79 years of age and percentages of deceased women at the ages of 85 and 90.

Study III

Study III, like Study II, was based on data from the H70-investigation. Analyses were performed on data from the first birth cohort at the age of 70, thus the same 974 individuals (449 men and 525 women) used in Study II were also used in Study III. In addition to this first cohort, a second birth cohort in the H70-investigation, born five years later, was also used. From this cohort a sample consisting of 1,036 persons (474 men and 562 women, 70 year of age), was used, primarily to replicate the analyses performed on the first birth cohort. The non-respondents in the two cohorts

did not significantly differ from the respondents in sex, marital status, and income.

Study IV

In Study IV, data on date of birth, sex, and date of death were collected from official publications from Statistics Sweden (104). Information could be obtained on every person who died at an age of 100 years or more, during the period of 1911 - 1970. Only birth cohorts with no remaining survivors at the end of 1970 could be used and, therefore, the population in this study comprised 1,137 women born between 1811 and 1865 and 509 men born between 1811 and 1864. The total Swedish population was used as a reference set. In Population Changes, Statistics Sweden, information has been published since 1963 on the number of deaths during each calendar month (88), listing men and women separately.

Study V

Data from the Swedish Twin Registry was used in Study V. The oldest part of this registry was compiled in 1961 and includes like sexed twins born between 1886 and 1925. The age range at data collection in 1961 was 37 to 76 years. Only complete twin pairs were recorded in the registry, that is, both twins in a pair had to be alive and, moreover, their addresses were known and they had both answered a mailed questionnaire. The registry comprises about 95% of all complete twin pairs living in Sweden in 1961 who belonged to these age cohorts. The zygosity was determined on basis of the twins' own answers on questions on their physical similarity as children. If the two twins in a pair both judged themselves to be "as like as two peas in a pod" when they were children, they were classified as monozygotic twins. If they both answered that they were only of ordinary family likeness, they were classified as dizygotic twins. Those twin pairs in which the two twins gave different answers remained unclassified. To test the validity in this method of determining zygosity, a serological

examination was performed on 200 twin pairs. This test showed an agreement with the twins' own judgement in 99% of the twin pairs who were preliminary classified as monozygotic (MZ) twins and in 91% among the pairs preliminary classified as dizygotic (DZ) twins. Further details of this portion of the registry have been presented elsewhere (10). Study V included 3,656 MZ twin pairs (2007 female pairs, 1649 male pairs) and 6,849 DZ twin pairs (3866 female pairs, 2983 male pairs). Age and sex distributions are shown in Figures 4 and 5.

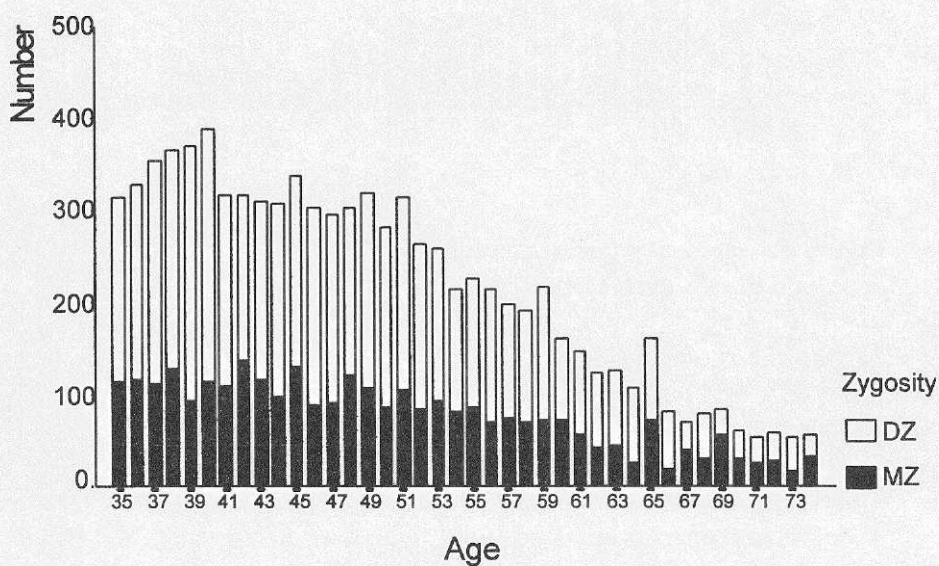


Figure 4. Age and zygosity distribution among male twin pairs at their entry into the Swedish Twin Registry.

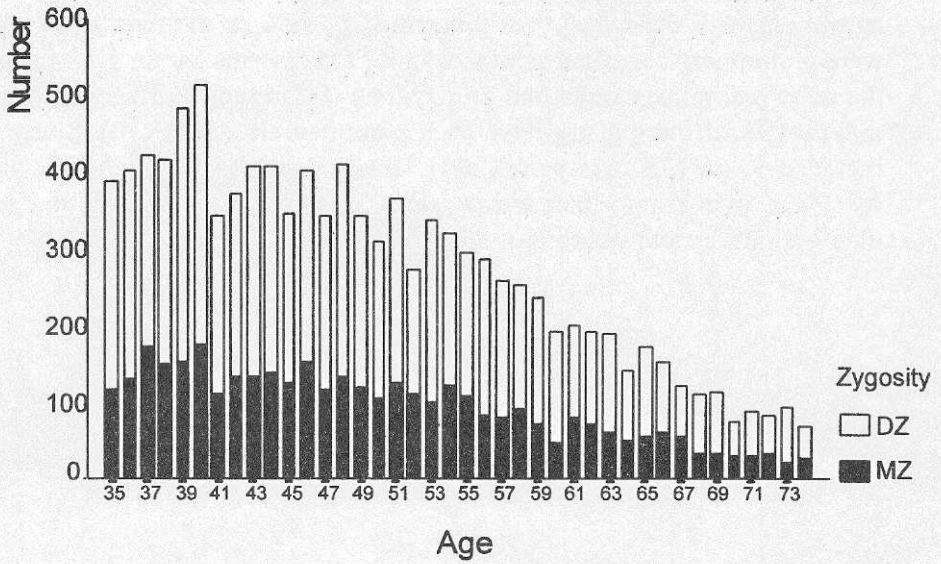


Figure 5. Age and zygosity distribution among female twin pairs at their entry into the Swedish Twin Registry.

Among these twin pairs there were a number of pairs who were reared apart: 179 MZ pairs (82 male pairs, 97 female pairs) and 446 DZ pairs (169 male pairs and 277 female pairs). They were all separated before the age of 12 and 46% of them were separated before the age of two. In Figures 5 and 6 the distributions of their ages at separation are presented. Twins reared apart primarily belong to another aging study, the Swedish Adoption/Twin Study of Aging (SATSA) (84).

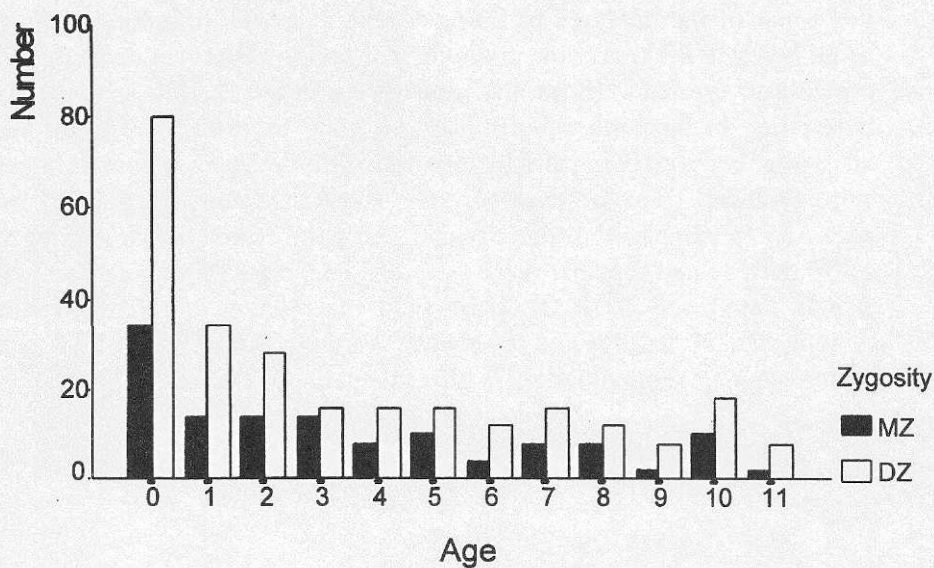


Figure 6. Age at separation among the male twins reared apart.

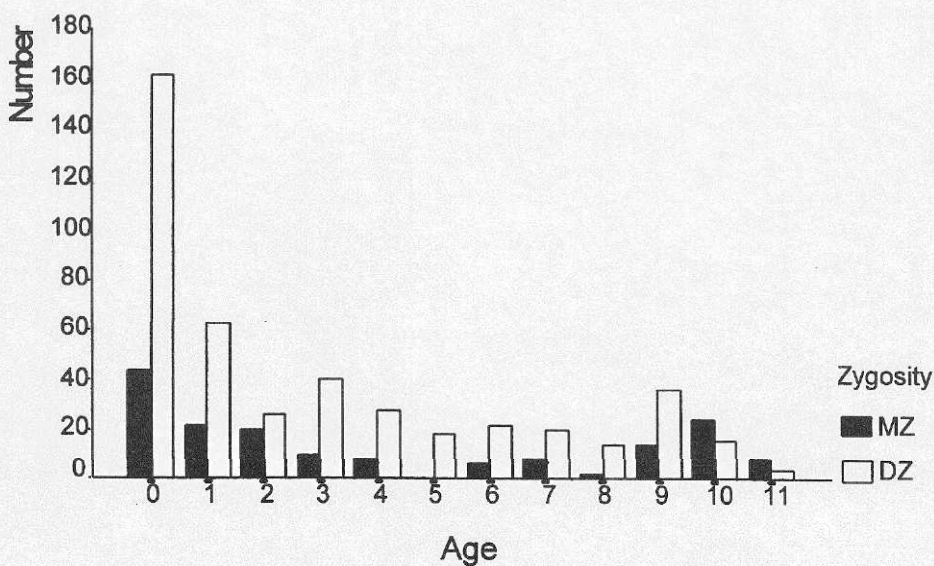


Figure 7. Age at separation among the female twins reared apart.

For some of the analyses in Study V, the absolute difference in age at death between the two twins in a twin pair had to be known or, at least, be possible to estimate. Those analyses were performed on a subsample of twin pairs. In the birth cohorts between 1886 to 1900, both twins were alive in only seven twin pairs by the time Study V began. Those twin pairs were excluded from the analyses. The subsample comprised 1,864 twin pairs, 1,734 pairs reared together and 130 pairs reared apart. Among the 1,734 pairs reared together there were 662 MZ pairs (304 male pairs, 358 female pairs) and 1072 DZ pairs (415 male pairs, 657 female pairs). Among the 130 pairs reared apart there were 40 MZ pairs (19 male pairs, 21 female pairs) and 90 DZ pairs (25 male pairs, 65 female pairs).

DEPENDENT VARIABLES

The common objective for all studies in this thesis is the study of survival, expressed as length of life or as age at death. When a sample comprises individuals from the same one-year birth cohort, the conventional way to describe age in time units (in years, months and days) will be satisfactory enough. This is the situation in Studies II and III.

In a sample comprising individuals from different one-year birth cohorts, this measure of age, however, is less appropriate to use. The challenge to survive a year at a certain age in 1900 was greater than the challenge to survive a year at the same age in 1995. To survive one year at the age of 90 is also a greater challenge than to survive one year at the age of 70 as the risk of death increases with age. Gompertz found that the age-specific mortality rate increased as an exponential function of age, $q_x = q_0 e^{bx}$. In this function, q_0 is the mortality rate at age $x=0$, representing the standard or age-independent mortality rate, which could be interpreted as the genetically determined vitality of the genotype. The age-dependent mortality rate constant is given by b , and bx measures the rate of increase in mortality and represents the rate of aging. The ratio q/q_0 of a person's mortality rate, q , to a standard mortality rate, q_0 , can be interpreted as a person's frailty. This ratio is assumed to be independent of age. The age-specific mortality is defined as the probability of dying at a certain age among those individuals, who have already survived until that age. The validity of the Gompertz survival model is, however, nowadays frequently discussed and a number of generalised Gompertzian models have been proposed (66, 60). At ages above about 95 years, Gompertz function is proved not to be adequate as the rate of increase in mortality lessens. This decrease could be due to the existence of a small subpopulation of survivors who age differently (66). According to recent studies, there also seems to be a gender crossover at the highest ages when men seem to have a survival advantage over women (87).

According to reasons given above, ages at death or numbers of years survived are not convenient measures to be used for describing survival, when a sample comprises individuals of different ages at entry, which is

the situation in Studies I and V. There are, however, a number of alternatives to handle this situation. Palmore (79) has introduced a measure called the longevity quotient, LQ that is the ratio of the actual length of survival to the expected survival as computed from life tables. LQ assigns, however, equal weight to all survival times, no matter if they are short, average, or long. Another measure of survival time that gives a result, which is not confounding by age, is proposed by Deeg (17). This is a measure of realised probability to die (RPD). For each individual, the probability of being alive up to the age of death is computed as a product of the yearly probabilities of survival over the period from examination until death. A similar measure of survival was used in Study I and in Study V. Here the integrated mortality risk (IMR) was used. For each individual the mortality risk was computed as a sum of risks over the period from date of observation until date of death. Information on mortality risks for each sex, age, and calendar year was collected from official publications of Statistics Sweden.

In some of the analyses in Study V, still another approach was used. In those analyses, the distance in age at death between the two twins in a pair was the variable under study. A great number of individuals are still alive and therefore the exact age at death was not known and, consequently, could not be used as a measure. The only essential information available was how many individuals, that had been deceased between the first twin in a pair to die and the second twin in the same pair to die, or alternatively, to the end of the study. In these analyses could, therefore, rank numbers of deaths be used as a substitute for exact ages at death.

EXPLANATORY VARIABLES

The independent variables in the first three studies, I-III, were chosen from different domains. The main aim in these studies was to evaluate survival from a multidimensional point of view and describe the overall effect on longevity of social factors, biobehavioral factors, genetic factors, and interactions between factors. The objective was to perform multivariate examinations of survival by using representative samples of predictors belonging to different domains. The aim was not to include every possible predictor of survival in the investigations. Most of the variables included have been found in previous studies to be reliable predictors of survival. The number of explanation variables, that could potentially be included, was limited by the sample sizes. Another restriction in the selection and definition of predictors was that all studies were secondary analyses and the variables had to be chosen among those which were available.

The categorical variables were, in most cases, dichotomised for primarily two reasons. The first arises from a qualitative point of view. An answer is less reliable when there has been a great number of closely related alternatives to choose among, and uniting close alternatives of answers will increase the reliability of the answer. The second reason arises from a quantitative point of view as the power of a test is dependent on the number of cases in each category. The continuous variables in some analyses were entered unclassified while in some other analyses they were dichotomised or trichotomised. How to define interval limits when categorising continuous variables can always be discussed. The intervals in these studies were chosen according to general consensus, but in most cases no entire agreement for definition of class limits can be found. The main objective when classifying was to find a cut that was justifiable from a general perspective, it was not a primary objective to find the cut giving the highest possible discrimination effect.

Study I

The main aim in Study I was to examine the importance of social status and social networks on survival in relation to health factors. The explanatory variables in Study I mainly reflected these domains. Health was described by perceived health and by interviewer-rated physical health, mental health, and mobility. The respondents were classified into social groups according to a standardised Swedish classification model (20). Social network was described by marital status, whether the respondents lived alone or together with one or more persons, and whether they had any children or not. The frequency of contacts with children, relatives or friends, and activities in associations were also considered. As a measure of the respondent's subjective judgements of whether the network was satisfactory, he/she was asked about perceived loneliness and desire for more contacts. Life style was described by reading habits and frequency of outdoor stays and the attitude to religiosity expressed by how frequently the respondent attended service in church or listened to radio services, and whether he/she read religious books or magazines. Independence level was estimated by the respondent's ability to perform daily chores and household work, or if he/she had any paid occupation.

Study II

The aim of Study II was to analyse the importance of age at observation and length of the predictive period on selection of predictors for survival, using data from the Swedish H70-investigation. Compared to study I, Study II was based on a smaller number of explanatory variables, but the variables were chosen to reflect a somewhat broader perspective. In addition to variable domains used in Study I, describing health, social status, network, life style, and independence, Study II also comprised variables that could be considered as biomarkers of aging and variables giving information about dementia and cognitive functioning. In Study II, health was represented by self-rated health, and by the number of definable diseases diagnosed by a physician. Dementia was classified according to

DSM-III R (1). Social status was expressed by number of years at school and by yearly income. Network was described by self-rated feeling of loneliness and by the frequency of contacts with children, friends and neighbours. Life style was described by the frequency of reading newspapers or books or performing some other type of hobby activity. Independence was defined as a non-institutionalised living, without need of any help with household duties or personal hygiene. Body mass index and a measure of lung capacity were used as biomarkers of aging.

Study III

One aim of Study III was to investigate whether prediction of survival could be performed on basis of factors on a domain level without any loss of efficiency. Therefore, a greater number of variables were applied in Study III and the variables were classified into seven domains. There is no commonly accepted classification system and it was not an aim for this thesis to invent and introduce a classification system. How to classify variables into a number of domains is by no means obvious. Some variables could have been placed in more than one domain and then a choice was inevitable. However, my conviction is that this choice of domains is not a crucial point as far as the choices can be reasonably justified. The seven domains which were defined were labelled I. Socio-economic status; II. Life style; III. Social network; IV. Need of help; V. Biomarkers of aging; VI. Physical health and VII. Cognition and mental health.

I. Socio-economic status

The first domain reflects the respondent's social background. This domain comprises variables that describe education, current income, marital status, and whether or not the respondent has or have had any children.

II. Life style

Life style will focus on the respondent's habits. It includes performance of activities like reading newspapers and books or other types of hobby activities. This domain also includes attitudes to religion, smoking habits, and alcohol abuse.

III. Social networks

The third domain, social networks, comprises variables which, in an objective or subjective sense, describe the respondent's social networks. The variables give information about the number of co-residents, frequencies of contacts with children, relatives, and friends, active memberships in associations, and the respondent's subjective feelings of loneliness and boredom.

IV. Need of help

The respondent's need of help, which constitutes domain four, is defined by living conditions, i.e., whether the respondent lives in his/her own dwelling or if he/she is institutionalised. Need of help is defined by the respondent's need for assistance with household chores or with personal hygiene and by whom this help is received. This domain also includes two variables measured on scales: a nursing load scale and an activity of daily living (ADL) scale (27). The nursing load scale comprises three components: viz. time-consumption, and physical and mental demands on staff. It is influenced by factors such as impaired mobility, incontinence, and demands on supervision. The scale range is 0-41, with the latter figure referring to a patient with maximum requirements on nursing load. As a measure of ADL a test of mobility is used. The respondent was given a value of 0 if he/she was able to walk, a value of 10 if chair bound and a

value of 20 if bedridden. In addition to these values, points were given for functions the respondent was not able to perform. The scale range is 0-32.

V. Biomarkers of aging

Domain five consists of variables which often are classified as biomarkers of aging. As representatives for this domain variables are chosen which measure weight, body mass index (BMI), blood pressure (systolic and diastolic) and lung functioning expressed by peak flow measure.

VI. Physical health

The number of prescribed drugs, the number of definable diseases diagnosed by a physician, and the frequencies of visits at a doctor are used as objective measures of physical health. Subjective measures of physical health are the respondent's own judgement of his/her health and whether he/she feels tired.

VII. Cognition

Variables describing cognitive functioning are included in the last domain. Cognition or intelligence is a multidimensional variable comprising a great number of entities which can be clustered into a few higher level groups. Two important groups, crystallised intelligence and fluid intelligence, are represented with one variable each, in the seventh domain. Crystallised intelligence comprises abilities based on previous knowledge and experiences, like word comprehension, and to measure verbal ability a test called "Synonymer" was used (18). Fluid intelligence comprises abilities of perceptual speed and problem solving like spatial orientation and

inductive reasoning and to measure these abilities a test called "Figurklassifikation" was used (18).

All explanatory variables included in Studies I, II or III, and how they have been categorised, are described in detail in the Appendix.

Study IV

The main aim of Study IV was to study the effect of seasonal variations on survival among centenarians. No further information on the individuals was known other than what was given in the statistical abstracts from Statistic Sweden: gender, date of birth, and date of death.

Study V

In Study V, variables that describe genetic and environmental effects on survival were evaluated. The only information available for this study was sex, dates of birth and death, zygosity and a notation of whether the two twins in a twin pair were reared together and, in case of separation, at what age they were separated.

STATISTICAL METHODS

There were some methodological difficulties due to the structure of the samples used. This was solved by use of a number of different statistical methods. The samples in Study I and Study V comprised individuals that entered the studies at different ages, that is, the observations were left censored which had to be considered in the analyses. Moreover, most individuals in Study V are still alive and analyses of length of life thus had to be performed on ranked deaths instead of on ages at death. In Study V latent variables were studied which required a special methodology.

Correlations between integrated mortality risk and independent indices were calculated using Spearman's (r_s) ranked correlation (I).

Student's t-test was used to test for differences in integrated mortality risks between subgroups of respondents (I) and to test for differences in continuous covariates between groups of survivors and non-survivors (III).

Pearson's chi-square test was used to test for differences in categorical covariates between groups of survivors and non-survivors (III).

To identify predictors of survival, univariate and stepwise multivariate analyses were used. Univariate analyses were used to discover correlations between survival and single explanatory variables without considering the influence of correlated covariates. When the dependent variable was continuous with no censored observations, ordinary regression analyses were used (I). In cases with right censored observations Cox regression analyses were used (II and III) (2, 93). When the dependent variable was dichotomised (alive - dead), logistic regression analyses were used (III) and odds ratios were computed to measure the importance of the covariates (35).

Kaplan-Meier survival functions were estimated to describe survival in different subgroups of individuals, and Mantel-Cox log rank tests were used to test for overall differences between survival curves (II, III) (2, 93).

Chi-square tests were used on likelihood ratio statistics to test for differences in seasonal pattern of mortality between sexes or periods (IV).

Wilcoxon signed rank test was used to test for differences in mortality rates between centenarians and the general population (IV).

Differences in survival rates between MZ and DZ twins, for a number of specified ages, were tested by Kaplan-Meier analyses, considering left truncated observations, and the overall differences were tested by a log-rank test, also considering left truncations (V).

Rank intraclass correlations of Spearman-type (95) were computed on right and left censored observations as a measure of correlation within twin pairs (V).

In samples without censored observations, ordinary intraclass correlation, according to Pearson, was used (V).

Cox regression analyses, considering time-dependent covariates and right and left censored observations, were used to describe the effect of the death of one twin in a twin pair on the surviving twin partner (V).

The LISREL program (43) was used to obtain maximum-likelihood estimates of the contribution to the variance in survival from different environmental and genetic factors. The fits of the models were tested by chi-square-statistics (V).

The path diagram in Figure 8 specifies how each type of factors contributes to the twin similarity for integrated mortality risk. The environmental and genetic effects are not measured directly; they are latent variables. The different kinds of effects are:

- Nonshared environmental effects (E_n) are effects unique to individuals that make twins different from each other.
- Rearing environmental effects (E_r) are effects that contribute to twin similarity because the twins are reared in the same family. The correlation between E_r factors is 1.0 for twins reared together and 0 for twins reared apart.

- Shared environmental effects are various common environmental experiences, shared by the twins. These effects contribute to similarity in twins, regardless of rearing status and are called correlated environments (Ec).
- Additive genetic effects (Ga). Identical twins (MZ) share all their genes while fraternal twins (DZ) share, on average, 50% of the genes with additive effect. The correlation between Ga factors is 1.0 for MZ twins and 0.5 for DZ twins.
- Dominant genetic effects (Gd). Fraternal twins (DZ) share, on average 25% of the genes with dominant effects. The correlation between Gd factors is 1.0 for MZ twins and 0.25 for DZ twins.

The corresponding factor loadings, en, er, ec, ga, and gd, estimate the importance of each factor on the observed variable, which, in this study, was integrated mortality risk.

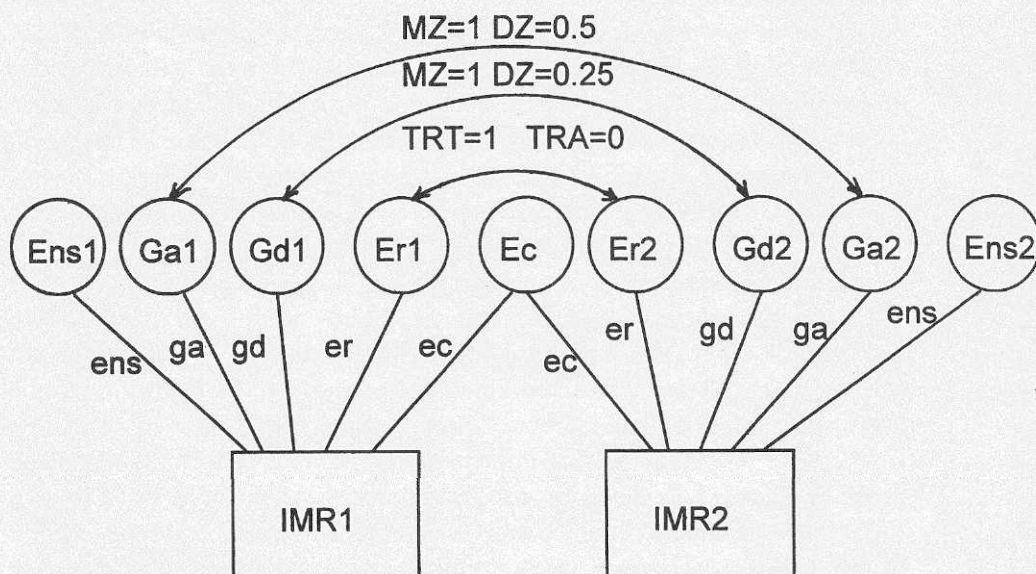


Figure 8. Path diagram of model of twin resemblance for identical (MZ) and fraternal (DZ) twins reared apart or reared together.

RESULTS

Study I

Study I was performed on a Swedish, nation-wide sample from 1954 comprising 1,062 men and women, aged 67 and above. The complete samples of men and women were analysed, and also a number of sub-samples. As a measure of survival capacity the endured integrated mortality risk (EMR) was used.

When the sample was split into subgroups depending on age at examination, EMR proved to be somewhat higher in the oldest age group than in younger ones, but the differences were not statistically significant. The main reason for this increased EMR by age is not that the oldest ones belong to an exclusive group of survivors. Rather, the higher median value was reflecting the inclusion criteria of the study. The most vulnerable part of the oldest ones lived in an institution and were thus excluded. The same pattern was found when the sample was split on marital status. Those who were not married at examination had a somewhat higher survival capacity compared to the married ones, despite a higher median age in the not married subgroup. Living alone was also found as a predictor of survival in the subgroup of the oldest male participants. This is probably a bias effect as presumably many of those who were married and/or lived together with a spouse or other relatives could stay in their homes even if their health was declining. Those who lived alone had to move to an institution when they could not look after themselves and were thus excluded from this study. A very simple measure to be used for survival capacity is self-rated health but nevertheless it proved to be remarkably useful. The difference in EMR between the subgroup of individuals, rating themselves to be in good health and the subgroup of individuals who rated themselves as less healthy, was statistically highly significant ($p < 0.0001$) for both sexes.

Socio-economic status

There were no statistically significant differences in mortality risk between persons who were married or not at the time of the interview. Few persons belonged to the upper social classes, and social class was only discovered as a significant predictor in one subgroup, among those aged 81 and above. A gender difference was found here, it was a benefit to women to belong to the upper social classes while it was an advantage for men to belong to the lowest social class.

Social networks

The importance for survival of an active membership in associations showed large gender differences. This factor was not important in any subgroup among men but was significant among the subgroup of all women, as well as in every female subgroup, with exception for the two oldest ones and the subgroup comprising the upper social classes. As mentioned above, living alone was a significant predictor of survival among men in the oldest agegroup, but not among women. Men were obviously taken care of by their wives and could stay in their homes even with frail health. Older women often do not have husbands to look after them.

Physical health

In the whole sample and in most subgroups, with only a few exceptions health factors were the overall most important factors of all for predicting survival. These exceptions were found among both sexes in the oldest agegroup, 81 years of age and above, among women 71-75 years of age and among men 76-80 years of age. Self-rated health was a better indicator of survival among men than among women, and, in most cases, a better

indicator than the interviewer rated health. In the youngest agegroup and among the not married ones, mental health was of greater importance for survival than physical health. Among women with perceived good health, no other significant predictors for survival were found.

Life style

Activity factors proved to be good predictors in most of the subgroups among women, expressed primarily by household work or daily chores. Activity was not a significant predictor among men in the oldest agegroup, nor among married men or men in the upper social classes. The most important activity factor among men was outdoor stays, and this was the only significant factor among men with perceived good health. Gainful work was a highly significant predictor of survival in the oldest male agegroup. Religiosity was of some importance for survival among women, statistically significantly in the lowest social class, but not in the upper social classes. Churchgoing was a significant predictor of survival mainly among married men and among not married women and women in the lowest social class. Churchgoing might be a sign of religiosity but could also be an expression of good health and mobility.

The ability to perform daily chores or household work were important predictors of survival among women in all subgroups except, of course, in the group of healthy women. Among men, these variables were less important as predictors of survival.

Study II

The main aim in Study II was to evaluate the effects of age at observation and length of the predictive period on the choice of significant predictors for survival. As physical health is known to be of great importance for survival all analyses were also performed on two subgroups of individuals,

those who had one disease, at most, diagnosed by a physician (health group I) and those with two or more diagnosed diseases (health group II).

Socio-economic status

Income proved to be important for survival among all women, and mainly among women in good health (health group I), over both a short and a long predictive period. Among men, income was not at all a significant indicator of long life. Education was of some importance over a short period among healthy men at the highest age, i.e., 79 years.

Social networks

Social networks was of importance for survival only at the age of 70. Among women it was significant only in health group I and over a period of 10-15 years. Among men social networks was a significant predictor of survival during a short prediction period both among all men and in the less healthy group (health group II).

Perceived feeling of loneliness had a predictive power among the healthy 70-year-old men over a 10-year period and among 75-year-old men in health group II over a 5-year period. Among women 70 and 75 year of age, it had a long-term predictive value mainly among the healthy ones.

Physical health

Beside the diagnosed diseases, which here were used to split the observations into two health groups, the individual's own judgement of his/her health status was registered. This perceived health factor was mainly an indicator for survival/death among men, in both health groups and over prediction periods of different lengths.

Dementia and cognitive functioning

Dementia was a significant predictor at the age of 79 among women in the whole sample, but not in the specific subgroups. The prevalence of dementia was, however, low. Among men, dementia was found to be significant at the age of 75, and then in health group I and over a long prediction interval.

Cognitive functioning proved to be a good indicator for survival, for men at the ages of 70 and 75 and for women at the age of 75, both in the whole sample and in the two subgroups.

Biomarkers of aging

As representatives of biomarkers of aging, lung capacity and body mass index were entered. Lung capacity, measured as peak flow volume, proved to be a good predictor of survival. It significantly indicated survival at all ages and over periods of different lengths, but mainly for women in health group I (the healthy ones) and for men in health group II (the less healthy ones).

Body mass index (BMI) was most important at the age of 70, when a low value indicating malnutrition, was a predictor for death in health group II over a short period of time for both sexes. A high BMI value was an indicator for death among women in health group I over a long prediction period.

Activity and need of help

At the age of 70 activity was a significant predictor among men in both health groups over short as well longer periods, and among women mainly in health group II and over a shorter period. At the age of 75, activity was primarily important among women over a short interval for health group II and over longer intervals for health group I. Also at the ages of 75 and 79 activity had a certain amount of predictive power for both sexes.

At the age of 70 need of help was a very good indicator for death over both shorter and longer periods among men in both health groups, and among women in health group II.

The importance of controlling for the length of the predictive period can be illustrated by the survival functions in Figures 9 and 10, based on data from Study II. The Figures show the survival functions for healthy 70-year-old men and women, respectively, with good and bad quality of their networks. After a 5-year period, at 75 years of age, differences in network was not a significant predictor for survival among women but was among men, as can be seen in Figures 9 and 10. After a 10-year period, network differences were significant predictors for both sexes. A study over 15 years should conclude that networks was a significant predictor for survival among women but not among men. Entirely different conclusions would thus have been drawn on the same observations from three studies of different prediction periods.

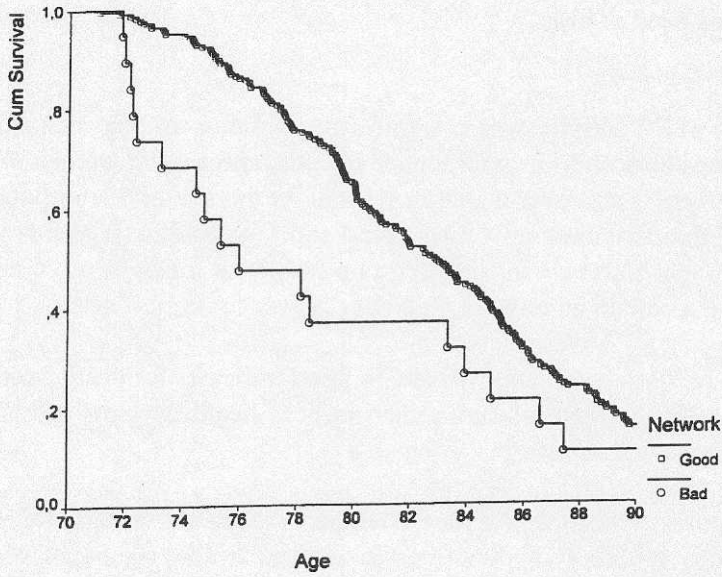


Figure 9. The importance of quality of networks as a predictor for survival among healthy men.

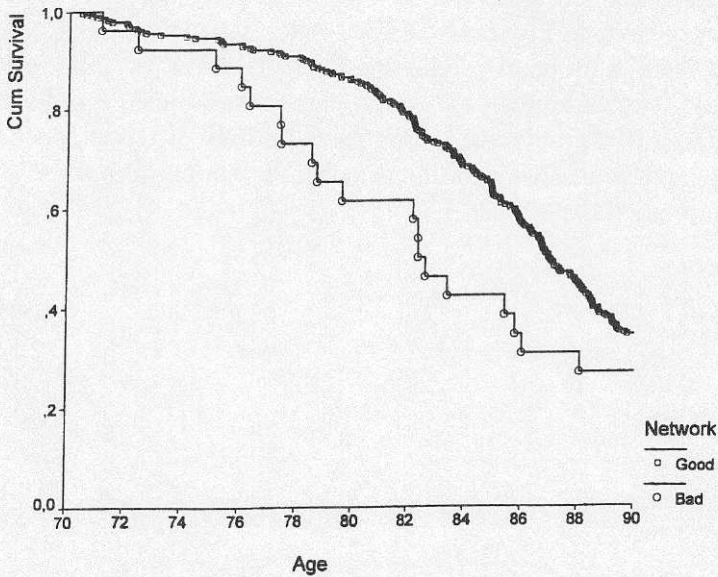


Figure 10. The importance of quality of networks as a predictor for survival among healthy women.

Study I and Study II combined

The results from the first two studies were very much in agreement; a synthesis is given in Tables 3-5. Table 3 shows results from the whole sample of men and women, respectively. In Table 4 results from the healthy subgroups are presented, and Table 5 contains results from the subgroups of less healthy individuals.

Study I and Study II showed that

- the choice of predictors of survival basically is dependent on health status, and
- the predictive power in factors changes with age, which has rarely been discussed in the literature previously (23)

Table 3. Significant predictors of survival for males (M) and females (F) at different ages and over short and longer intervals, based on results from Study I and Study II.

Interval From-To	Socio- economic	Networks	Health	Bio- markers	Cognition	Life style	Need of help
70-75	F	M	M,F	M,F	F	M,F	M,F
75-80	F	M	M,F	M,F	M,F	M,F	M,F
80-85	F		M,F	M	M,F	M	M,F
70-90	F		M,F	M,F		M	M,F
75-90	F	F	M,F	M,F	M,F	F	
80-90	F	F	M,F	M,F	F	M,F	M,F

Table 4. Significant predictors of survival for healthy males (M) and females (F) at different ages and over short and longer intervals, based on results from Study I and Study II.

Interval From-To	Socio-economic	Networks	Health	Bio-markers	Cognition	Life style	Need of help
70-75	F	M	M	F		M	M
75-80			M,F	M,F	M	F	M
80-85	M			M,F			
70-90	F		M	M,F	M		
75-90	F				M,F	F	
80-90				F			F

Results from the analyses in Studies I and II on healthy elderly can, for example, be explicitly expressed as follows:

The 70-year old man with good physical health, but still an increased risk to die within five years, has some of the following characteristics: His network is bad, he has no or little contact with his children, his self-rated health is bad, his mobility is reduced, he needs help with the household chores, and he has no hobbies.

The 70-year old woman with good physical health, but still an increased risk to die within five years, has the following characteristics: Her lung capacity is reduced, and her income is low.

Table 5. Significant predictors of survival for not healthy males (M) and females (F) at different ages and over short and longer intervals, based on results from Study I and Study II.

Interval From-To	Socio- economic	Networks	Health	Bio- markers	Cogni- tion	Life style	Need of help
70-75				M,F	F	M	M,F
75-80		M	M	M,F	F	F	
80-85				M	M	M	
70-90		M				M	F
75-90				M,F	F		
80-90	F			F		F	F

Results from the analyses in Studies I and II on less healthy elderly can, for example, be explicitly expressed as follows:

The 70-year-old man with bad physical health but still a good chance to survive another fifteen to twenty years, has some of the following characteristics:

His network is good, he has contact with his children, and he reads books and magazines or performs other kinds of hobby activities.

The 70-year-old women with bad physical health but still a good chance to survive another fifteen or twenty years, has the following characteristics: Her mobility is good, and she gets help with her household chores.

Study III

By multivariate logistic regression analyses in Study III, a number of risk factors belonging to different domains were selected as predictors of survival over a period of 10 years.

When the analyses in Study III were repeated on a second birth cohort born five years later, the selection of the most significant predictors for survival differed somewhat from the results based on the first birth cohort. The most presumable explanation of this divergence is randomness rather than any real differences between the two birth cohorts. To verify this hypothesis, the variables identified in the logistic regression model of the second birth cohort were entered in a new analysis in the first birth cohort. The probabilities of death, computed for each individual on basis of the two regression models, were then compared. There were no statistically significant differences in the mean values of these probabilities, neither among the survivors (0.38 in both models) nor among the non-survivors (0.62 in the first model and 0.65 in the second model). The individual changes in estimated probability of death from the first model to the second model was also calculated.

The distribution of differences proved to be somewhat skewed to the right for survivors and to the left for the non-survivors, indicating that there was a small tendency to overestimate the risk of death for survivors and underestimate the risk of death for non-survivors when risk factors from the second birth cohort were used in the first birth cohort.

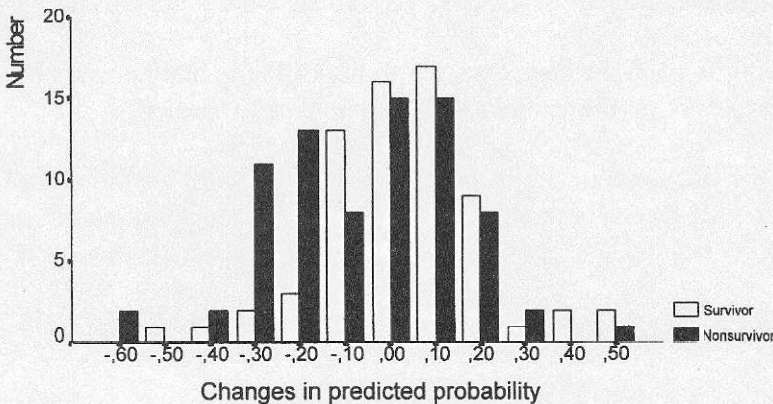


Figure 11. Distribution of changes in estimated probability of death for men in the first birth cohort, obtained when variables found to be predictors of survival in a second birth cohort were used in the first birth cohort instead of the predictors originally selected in the regression model.

The variables were classified into seven domains. As an alternative to consider single variables for estimation of the probability of survival the number of risk domains was used as a predictor of survival. The number of domains, containing significant risk factors, was counted for each person. Survival functions were estimated for groups of persons based on the number of their risk domains. A log rank test showed an overall significant difference in the survival functions. Figures 12 and 13 show the survival functions for men and women, respectively, for groups of individuals with different numbers of domains containing variables identified as significant predictors of survival.

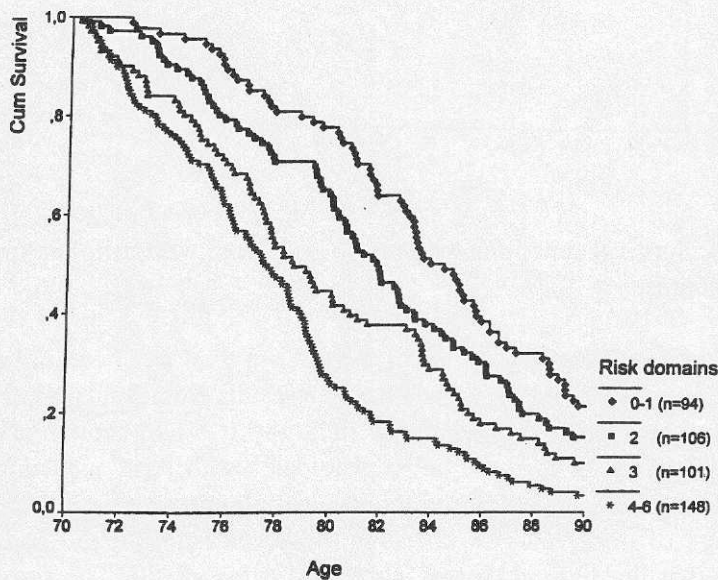


Figure 12. Survival functions for groups of men with different numbers of risk domains.

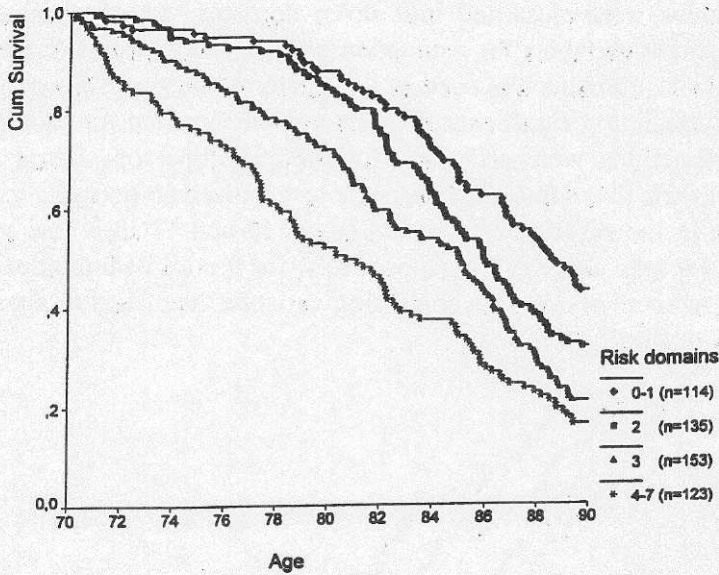


Figure 13. Survival functions for groups of women with different numbers of risk domains.

The method using domains as predictors of survival has been utilised on data from Study I to investigate whether the results from Study III could be replicated. Six domains were defined in Study I: Socio-economic status, networks, life style, need of help, physical health, and mental health. Survival functions were estimated for men and women, respectively, based on numbers of observed risk domains at the entrance in the study and providing that the individual was alive at the age of 70. The results are presented in Figures 14 and 15. As can be seen from the Figures, number of domains were a good predictor of survival also in Study I.

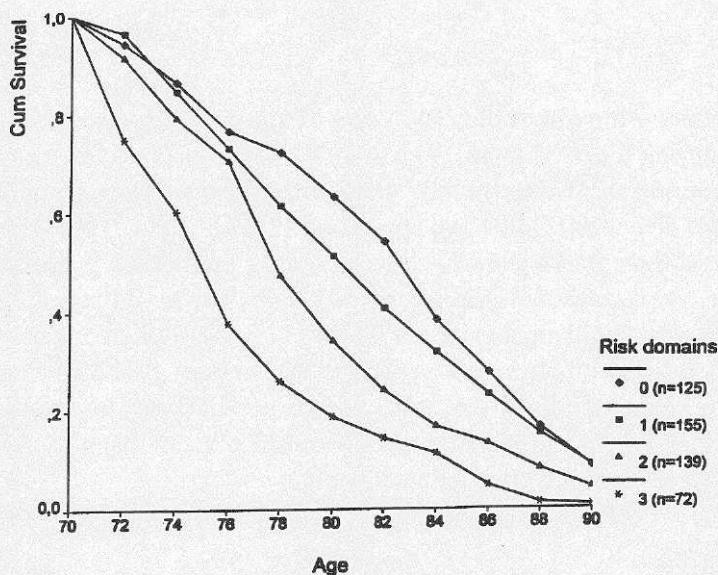


Figure 14. Survival functions for groups of men with different numbers of risk domains at the entrance into Study I.

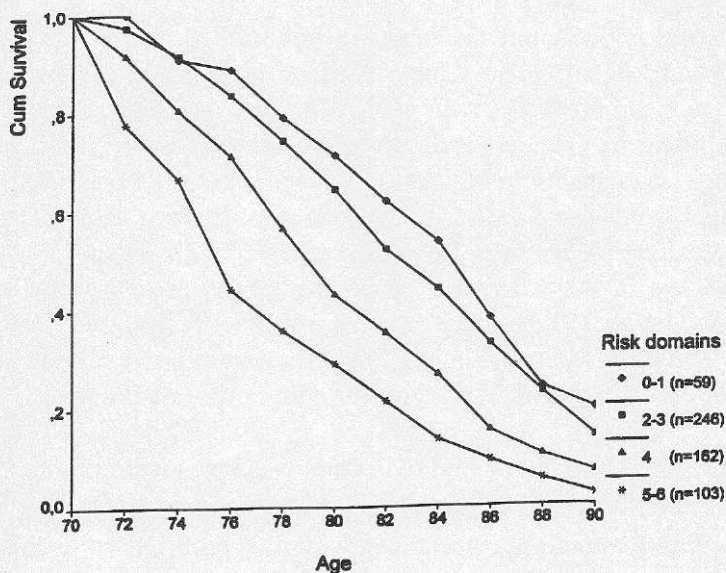


Figure 15. Survival functions for groups of women with different numbers of risk domains at the entrance into Study I.

Study IV

Mortality among the oldest old, 100 years of age or older, was observed in Study IV during a period from 1911 to 1970. The mortality rate proved to be higher during the winter months than during the summer months. The period was also split into two parts, 1911-1947 and 1948-1970, to investigate if there had been any changes during the period. It was shown that there were seasonal variations in both parts, however greater variations were found in the period from 1911 to 1947. No statistically significant gender differences were found. A seasonal effect in mortality can also be detected in the general Swedish population. However, when compared to the general population, it could be seen that the seasonal variations were higher among the centenarians.

Study V

The effect of genetic factors on longevity was studied using data from the Swedish Twin Registry. The sample used in this study comprised 3,656 MZ twin pairs and 6,849 DZ twin pairs. Mortality rates were calculated in groups defined by gender and zygosity. As the study was mainly concentrated on mortality in old ages, differences between zygosity groups were studied using those who had survived until the age of 65. The only significant difference between MZ twins and DZ twins was found among men at the age of 80, where the proportion of deceased MZ twins was significantly lower (53,4%) than the proportion of deceased DZ twins (57,5%). The survival curves, however, showed no overall significant differences between MZ and DZ twins for either men or women.

The similarity in longevity within twin pairs was investigated by intraclass correlation coefficients. As there still are many survivors left in the twin registry ordinary intraclass correlations were inappropriate to use. Instead the rank intraclass correlation coefficient of the Spearman type was used. Among twins reared together, the intraclass correlation coefficient was

calculated to 0.36 and 0.14 for male MZ and DZ twins, respectively and to 0.32 and 0.15 for female MZ and DZ twins, respectively. These values indicate that part of the variance in longevity is accounted for by genetic factors. Cox proportional hazards analyses with time-dependent covariates were used to explore the effect of a twin's death on the remaining survival time for the co-twin. These analyses also showed dependency within twin pairs. There was a significant increased mortality risk for a twin with a deceased co-twin relative that of a twin with the co-twin alive, and the increase was significantly higher among MZ twins than among DZ twins. The gender differences were small. Among female twins reared apart there were similar but less significant findings. Among male twin pairs reared apart no differences were found between MZ twins and DZ twins.

Deaths among young people are often caused by accidents, and among the oldest survivors, deaths are likely to occur more randomly. A hypothesis to be tested was thus whether the intraclass correlations for age at death are lower among twins that die in young ages or in old ages. This hypothesis was verified in the analyses.

In the oldest birth cohorts, 1886 to 1900, only a few complete twin pairs were alive. These were excluded and product moment intraclass correlation coefficients were computed on the remaining observations. The results were in accordance with the results from the rank intraclass correlation analyses. Model fitting analyses, using the LISREL method, showed that most of the variation in survival capacity was due to environmental effects (62% among men and 68% among women) and primarily due to environmental effects defined as nonshared environmental effects (58% among men and 66% among women). In the best fitting models the genetic effect was interpreted as additive among women and dominant among men.

DISCUSSION

A number of studies of aging include estimation of the predictive power of variables considered as presumable indicators of death or survival. Several different techniques have been used for these analyses, among them multivariate survival models. The variations in results are, however, noticeable. It clearly shows that there are no simple answers to the question of how to find the best predictors of survival. This, however, does not mean that there are no answers to be found. It just emphasises how important it is to be careful in the choice of design and analyses methods (19, 118, 29). The presumptions of the study must be cautiously controlled and conclusions drawn from a certain study must not be generalised without caution.

There are many possible reasons for the divergent results reported in the literature. Sample sizes and sampling techniques are important for the accuracy in estimates (101). The inclusion criteria must be carefully declared to clarify what population the sample represents. There are many questions to be answered. Does the sample include individuals living in institutions? How are the tests performed on demented persons or on persons who for some reason are unable to answer any questions by themselves? Are proxies used or are these individuals excluded from the study? In case of a proxy, how well suited is she or he to answer on behalf of the true respondent? Sometimes the sample has comprised quite a specific group of individuals, not representative for any community.

The data used in all five studies in this thesis are of good quality. The Swedish National Register guaranties that all persons can be reached and followed till their deaths and that correct dates for deaths are recorded.

An advantage of the H70-investigation, used in Study II and III, is that it consists of individuals of the same age at registration. Dropout from the study has not been substantial so the changes in variables under study between different ages are mainly dependent on changes within individuals, and on the fact that some individuals have been deceased since the previous observation point. It is a true random sample of the

population in Göteborg as it includes not only those who live in their homes but also those who are institutionalised. The sample used in Study I comprises only persons still living in their homes, but they are all followed until their deaths.

Age at observation has proven to be of great importance when estimating the predicting power of a covariate, and thus age must be controlled for which is often not done. When subjects are included in a study at old ages, the impact of risk factors earlier in life have been reduced. The remainders belong to a group of survivors with less mortality risks. The effect of age can be studied easily with a longitudinal design if the dropout is small, as is shown in Study II. Most studies are, like Study I, based on samples including individuals from a range of birth cohorts which makes it difficult to interpret the outcome from an analysis. One aspect to consider is the definition of time. The effort to survive one year at the age of 70 cannot be compared on equal terms to the effort to survive one year at the age of 90. Time measured in calendar years is thus not an appropriate variable to study; it should be converted into a variable measured in a unit that makes it comparable over age and birth cohorts.

It is essential to control not only for age at observation but also for birth cohorts. Great progress has been made in the last decades within many areas. The social situation has changed in many aspects; the number of years in the obligatory school have increased and a greater proportion of the population has some higher education. The developments in medicine, technology, and other disciplines have been huge. The living conditions for a "young" old birth cohort is thus not comparable to that in the birth cohorts born only one or two decades earlier.

The length of the observation period is another factor of great importance for the power of a covariate. One aspect of this is that, with a long predictive period, the situation for the respondent may have changed considerably from date of observation until the end of the study. Another aspect is that a covariate can be an extremely strong indicator of mortality over a short period of time but this effect can completely vanish if the prediction period is prolonged. One explanation to this can be that the covariate causes a large proportion of deaths during a short first period and leaves only few observations with a risk value for the remaining period.

An inappropriate method for the analysis can fail to discover this effect over a long observation period (89). It is an intricate task to identify a covariate to be a predictor of death over a long period unless the effect is reasonably equally distributed over the whole period, and this is not always the situation. In a sample comprising individuals in "young" old ages the situation is often drastically changed when studied over a long period by reasons like illnesses, deaths of spouses, and general loss of vigour. In a sample comprising individuals in "high" old ages, on the contrary, a long predictive period means that a high percentage of the individuals will be deceased and the number of survivors will be too few for any statistically significant conclusions to be drawn on predictors for survival.

Terminal drop is another aspect to be considered. There have been different definitions of terminal drop. A usually accepted definition is given by Palmore and Cleveland (78) who suggested that terminal drop should be used for "a curvilinear or accelerated decline before death." Terminal drop is, by this definition, a short-time effect closely related to death. Therefore, in identifying predictors of survival over a short period, the terminal drop effect cannot be neglected. To separate terminal drop effects from normal aging changes is, however, another intricate task. A review of terminal drop studies is given by Siegler (102) and a review of research that relates behaviour to terminal drop is given by Berg (6).

As mentioned above the choice of methods of analyses is also crucial for the result (8). Multivariate step-wise regression analyses are often used for selection of predictors for survival. In case of a binary dependent variable, that is the dependent variable is a status - dead or alive- at some age, logistic regression analyses can be used, and in case of censored observations, with the exact age at death or at censoring as the dependent variable, Cox hazard proportion regression analyses can be used. The benefit of using a proportional hazards model, is limited when the follow-up period is short (30). Several covariates are time-dependent in a way that is not quite obvious without close investigation. Many regression analyses are performed without considering this fact and the results may be deceiving.

Another aspect to consider, when a multivariate method is used, is the number of covariates entered in a model in relation to the number of observations. Moreover, as most covariates are correlated, multicollinearity must be avoided and the relative importance of involved covariates has to be explored. There are techniques to handle these problems (98). Simple univariate analyses, easily interpreted, are often good complements to more sophisticated analyses. The choice of methods is of course ultimately dependent on the aim of the study.

In his book, *Biology of Aging*, Arking warns of placing too much weight on correlations between a covariate and chronological age as there always are great variations among studies, which suggests one or more sources of variation that are not under control (3).

The results in this thesis show that both gender, age at observation, health status, and length of the predictive period are of great importance for the selection of predictors of survival and for the predictive strength of variables. The results are mostly in accordance to but in some cases at variance with those of many other studies. The most important findings are discussed below.

Occupational class has been shown, in some studies, to be associated with mortality and health (62). Swedish studies on mortality and social class among younger individuals (35-69 years) show a higher mortality among manual workers (115) and suggest a trend for this difference to increase. In Study I and II, social class and income were of some importance for survival among women but not among men. There is a strong correlation between health status and social class, and this can imply that social class also has an effect on longevity at higher ages, but mainly indirectly by supporting good health.

Marital status had little significance for survival among both men and women. Among men the never-married ones had a poorer prognosis for survival and a hypothesis is that they might belong to a particularly frail group among Swedish men (75). Among women the situation seems to be the opposite.

Social networks was of less importance in our studies than what has been reported from many other studies (31, 116). Most studies in which social networks was highly correlated to mortality, comprised individuals younger than those in our studies. The results pointed to interesting differences between gender for the importance of social networks. Among women, it was of importance over long predictive periods, 10-15 years, and then mainly among the oldest agegroups and among unmarried ones. For men, social networks was of greatest importance over a short period and in the 70-year-olds. Mortality risk was, in Study I, highest for those men who were married or lived with one or more persons, which can imply that social support permits people with illness to stay in their homes and survive into old age. A similar pattern was not found among women. Another unexpected gender difference was the importance of having children and contacts with them that prolonged the life for men but not for women.

The main finding was a dominant importance of health and activity factors which has previously been confirmed in many other survival studies. Lung functioning was the overall best predictor of survival for both sexes, for all ages, for healthy as well as less healthy groups and over short and longer intervals of prediction. This is in agreement with other studies. The importance of forced vital capacity was pointed out in the Framingham study by Kannel and Hubert (45) as "one of the strongest predictors of mortality; second only to age itself... It appears to be a measure of vigour, general musculoskeletal functional capacity and overall health; truly a measure of living capacity." Lung functioning is apparently a measure that reflects the influences of several other factors, like good health, high functional capacity, physical activity, and non-smoking habits.

Self-rated health has in a number of studies proved to be a strong indicator of survival among elderly, quite in parity with other objective measures of health, and sometimes even better (39, 48, 40, 46, 71, 119). This was also verified in our studies (I, II, III). Study II, however, showed a strong gender influence as the association between mortality and self-rated health was significant at all ages and over most prediction periods among men but only at higher ages among women. A gender difference has been reported in most other studies, as well, but it is not quite so pronounced as that found in Study II. There is no explanation for this gender difference in

the literature, but our suggestion is that the higher average age at death among women compared to men makes the average distance to death for 70-year-old women too long to be predicted by perceived health status.

The oldest old, those who are centenarians and above, have a minimum of reserve capacity left, and exhausted organs and decreased resistance capacity is a liable explanation to most of the seasonal variations found in mortality in those agegroups. Similar results have been reported from many other countries (4, 82, 49).

There are divergent results regarding correlation between cognitive functioning and mortality. In some studies a relation is found (79, 6). The New Haven EAC community study, for example, found an increased risk of mortality for both sexes over a nine-year follow-up period among those with decline in Mini-Mental State Examination (MMSE) score (61). In other studies, no such relationships are found (117). A reason for those different findings can be that cognitive impairment often is seen together with physical illness and controlling for this illness may reduce the power of cognitive functioning as a predictor of mortality to become non-significant. In Study II, however, cognitive functioning, measured as inductive reasoning according to Thurstone's Primary Mental Abilities, was found to be a strong significant predictor of mortality for both sexes, and in groups with good physical health as well as in the groups of sick individuals over short and long observation periods.

Consistent with other studies, Activities of Daily Living (ADL) proved to be correlated with mortality over a predictive period of short or medium length (81, 64). It could be argued that reduced mobility and possibilities to live an independent life often, but not necessarily, are reflecting an underlying bad physical health. Other variables like need of help, amount of daily chores, mobility and outdoor stays, which are related to ADL, were shown in Studies I and II to be strong predictors of mortality over a short period of time both among physically healthy and sick persons.

The heritability of human longevity was investigated in Study V. Association in age at death between offspring and parents has been reported in a number of other studies (29, 112, 83, 67), but just a few twin studies have been performed on this subject previously (41, 38). The

studies most comparable with ours have used data from the Danish Twin Registry (69, 113). Their results are, in essential parts, in close agreement with our studies on the Swedish Twin Registry. From a study on the Danish Twin Registry (121) was thus reported that about 50% of the variability in individual frailty among both men and women, survived to age 30, was determined by nonshared effects which is close to the findings in Study V. Also a greater similarity in age at death within MZ twin pairs than within DZ twin pairs was found in both twin registries. There were, however, also some dissimilar results. The DZ twin pairs in the Danish Registry were not found to be significantly more similar in age at death than two randomly selected like-sexed individuals. In the Swedish Twin Registry we found that there was a significant similarity in age at death also between the two twins in DZ twin pairs, but not as high as among MZ pairs.

Among female twins reared apart there were similar but less significant differences in similarity in age at death between MZ and DZ twins. Among male twins reared apart no differences were found between MZ and DZ twins. This result is not definitive for a genetic interpretation, however. It is possible, for example, that this difference in risk is attributable to more similar environmental circumstances of MZ than of DZ pairs, rather than to their differences in genetic similarity. Another possible interpretation is that the impact of bereavement is greater for the surviving twin when the deceased is genetically identical.

In both twin registries, environmental factors accounted for most of the variance in longevity, mainly nonshared environmental effects. In another twin sample comprising male U.S. veterans, Hrubec and Neel reported an estimated heritability of liability of death (h^2) that was approximately 0.50 between the ages of 20 to 60 years (38). This figure does not significantly differ from the results in Study V. The age intervals are, however, not comparable, and among the twin pairs in the Swedish Twin Registry in which both twins died in early old ages (before their 70th birthday), the twin similarity in age at death was not significantly higher for MZ twin pairs than for DZ twin pairs. This would indicate a less genetic influence in the younger agegroups.

The results from the five studies demonstrate that there are several variables that predict survival but there is not one set of "best predictors". Variables that are strongly correlated can be exchanged without much loss of power. This can be seen as an explanation to the lack of consistency among many survival studies. In Study III, domains have been utilised as an alternative to the use of individual variables. For both sexes, the risk of death increases with the number of domains containing risk factors. An individual with frailty in several areas has an increased risk of death, but deficits in one domain can be compensated by great capacities in other domains. There are, thus, no overall most important factors for a long life to be found. Rather, there are combinations of factors which together produce a stable and secure situation of life, and this overall status can be seen and understood as an indicator of survival. As McClearn (68) says in his discussion on biomarkers of aging, "There is good agreement, however, that aging is a complex process or set of processes... It is apparent that a comprehensive view of aging will require representation of biological and functional age in terms of a complex nexus of interrelated variables constituting a system... no one marker can characterize a system; searching for a marker for all purposes is futile and misguided."

CONCLUSIONS

The main conclusions from these studies are:

- The length of the predictive period is crucial when searching for predictors of survival. Some factors are good predictors of survival over a short period and those factors often reflect diseases. Other factors are good predictors of survival over a long period and those factors have a more general preventive or deteriorating long-term effect on the individual.
- Age at observation must be controlled. Chronological time is not an appropriate measure of survival capacity in a study that comprises individuals belonging to different birth cohorts. The efforts to survive one calendar year are not comparable among individuals of different ages and with different cohort experiences. A superior alternative to chronological time is the endured integrated mortality risk.
- Multivariate analyses ought to be performed with carefulness. Interactions between covariates must be considered. Time-dependent covariates, effects of unobserved age-related factors, extreme distribution of deaths, and a large proportion of censored observations can give unreliable results.
- Correlated variables can be exchanged in a set of selected predictors of survival without any statistically significant loss of power.
- Related variables can be systematised into higher level domains. A domain containing one or more variables, which are identified as univariate significant predictors of death, can be defined as a risk domain. As an alternative to the use of a set of specific variables for predicting survival/death, the number of risk domains can be used.

- A good predictor of survival reflects the effects of a complex network of markers. A measure of lung capacity proved to be the single best variable to predict survival among all those variables which were used in these studies. This variable was a good predictor of survival independent of age at observation, length of predictive period, and physical health status. This can be understood in the light of the previous points. Lung capacity, in these studies classified as a biomarker of aging, is a measure that reflects the influence of markers from various domains like health, mobility, lifestyle, smoking habits, activity pattern, social networks, etc.
- Twin studies show that most of the variance in longevity can be explained by environmental effects and then mainly by nonshared environmental influence.

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Appendix

Variable	Study	No risk	male/female %	Risk	male/female %	p-value ^{a)} male/female
Socio-economic status						
Marital status	I	Married	60/90	Widow(er),div, single	40/67	NS/NS
	III	Married/div/ widow(er)	93/82	Never married	7/18	NS/NS
Social class	I	Higher	30/30	Lowest	70/70	NS/*
Children	I	Yes	81/75	No	19/25	NS/NS
	III	Yes	75/69	No	25/31	NS/NS
Education	II-70	Above oblig school	41/30	Obligatory school	59/70	NS/NS
	III	Above oblig school	41/30	Obligatory school	59/70	**/NS
Income	II-70	≥8000 Skr/year taxed income	82/70	<8000Skr/year taxed income	18/30	*/***
	III	≥8000 Skr/year taxed income	82/70	<8000Skr/year taxed income	18/30	NS/***
Life style						
Outdoor stays	I	At least 3 times/week	87/67	Less than 3 times/week	13/33	***/***
Physical activity	III	Often- sometimes	82/77	Seldom-never	18/23	NS/NS
Read newspapers	I	Yes	92/87	No	8/13	NS/*
Read books	III	At least one book/month	52/62	Seldom or never	48/38	NS/NS
Read newspapers or magazines	III	Daily reading	97/98	Not regularly reading	3/2	*/NS
Hobby activities incl reading books	II-70	At least each month	80/79	Seldom or never	20/21	***/*
Read newspapers or magazines	II-75	At least each month	56/68	Seldom or never	44/32	***/***
Hobby activities incl reading books	II-79	At least each month	59/56	Seldom or never	41/44	***/*
	III	At least each month	80/79	Seldom or never	20/21	**/*
Daily chores	I	Heavy-easy	45/84	None	55/16	*/***
Gainful work	I	Part time-Full time	30/6	None	70/94	**/NS
Attitude to religion	III	Positive	66/88	Negative or indifferent	34/12	NS/NS
Read religious books	I	Yes	8/20	No	92/80	NS/NS

Variable	Study	No risk	male/female %	Risk	male/female %	p-value ^{a)} male/female
Listening to radio mass	I	Every sunday	50/57	Sometimes-never	50/43	NS/NS
Attend mass in church	I	At least once a month	18/30	Sometimes-never	82/70	*/**
Alcoholic abuse	III	No	83/99	Reg in temperance board	77/1	*/*
Smoking	III	Moderate or not	59/83	Heavy, at least 15 cig/day	41/17	NS/*
Social networks						
Household size	I	Live together with others	81/66	Live alone	19/34	NS/NS
	III	Live together with others	80/48	Live alone	20/52	NS/NS
Distance to children	I	In the neighbourhood	60/56	Far away-have no children	40/44	NS/NS
Contacts with children	I	At least once a week	43/43	Less often-have no children	57/57	*/NS
	III	At least every month	62/60	Less often-have no children	38/40	*/NS
Enough contacts with children	III	Enough/too much	64/56	Too little	36/44	*/NS
Visit friends/children	III	At least once a month	68/75	never-less than once a month	32/25	NS/*
Contacts relatives/friends	I	At least once a week	58/45	Less than once a week	42/55	NS/NS
Contacts children/relatives/friends	II-70	At least once a week	90/92	Less than once a week	10/8	**/**
	II-75	At least once a week	87/93	Less than once a week	13/7	NS/NS
	II-79	At least once a week	84/86	Less than once a week	16/14	NS/**
Contacts relatives/friends	III	Daily	85/85	Not daily	15/15	**/NS
Feel lonely	I	No	92/85	Yes	8/15	NS/NS
	II-70	Never-seldom	88/75	Often-sometimes	12/25	*/NS
	II-75	Never-seldom	86/74	Often-sometimes	14/26	NS/**
	II-79	Never-seldom	80/67	Often-sometimes	20/33	NS/NS
Feel bored	III	Never-seldom	88/85	Often-sometimes	12/15	NS/NS
				Often-sometimes		

Variable	Study	No risk	male/female %	Risk	male/female %	p-value ^{a)} male/female
Household	III	Live together with spouse	77/44	Live alone	23/56	*NS
Club activity	I	Sometimes-often	23/22	Seldom-never	77/78	NS/***
	III	Yes	39/54	No	61/46	*NS
Need of help						
Living conditions	III	Own house/flat	92/95	Collective	8/5	*/*
Help with personal hygien	III	No	97/94	Yes	3/6	*/***
Help with household	III	No	83/77	Yes	17/23	***/**
Independent living without help	II-70	Yes	82/77	No	18/23	***/**
	II-75	Yes	72/59	No	28/41	**/**
	II-79	Yes	63/50	No	37/50	***/**
Social support	I	Enough	90/86	Desire for more society	10/14	NS/NS
Help from whom	III	Private	9/8		91/92	NS/NS
Nursing load score	III	No nursing requirements	94/91	Some to heavy requirements	6/9	***/**
ADL	III	No mobility	95/92	Mobility	5/8	**/**
Mobility Score		restrictments		restrictments		
Mobility	I	Good	57/44	Less good-bad	43/56	***/**
Biomarkers of aging						
Weight	III	62-90 kg	77/62	<62 kg/>90 kg	23/38	**/**
BMI	II-70	23-29	58/59	<23/>29	42/41	NS/NS
	II-79	23-29	56/55	<23/>29	44/45	NS/NS
	III	22-27	49/48	<22/>27	51/52	NS/NS
Blood pressure systolic	III	135-190 mmHg	89/85	<135/>190 mmHg	11/15	NS/NS
Blood pressure diastolic	III	85-100 mm Hg	80/79	<85/>100 mmHg	20/21	*/*
Lung capacity/ peak flow measure	II-70	≥260 l/min(M)/ ≥230 l/min (F)	78/73	<260 l/min (M) <230 l/min(F)	22/27	***/**
	II-75	≥280 l/min(M)/ ≥220 l/min (F)	81/85	<280 l/min (M) <220 l/min(F)	19/15	***/**
	II-79	≥280 l/min(M)/ ≥220 l/min (F)	86/84	<280 l/min (M) <220 l/min(F)	14/16	***/**
	III	≥260 l/min(M)/ ≥230 l/min (F)	78/73	<260 l/min (M) <230 l/min(F)	22/27	***/**

Variable	Study	No risk	male/female %	Risk	male/female %	p-value ^{a)} male/female
Physical health						
Visit doctors	III	Less than 4 times/year	78/69	At least 4 times/year	22/31	***
Self-rated health	I	Good	50/37	Less good-bad	50/63	***/**
	II-70	Good	67/64	Less good-bad	33/36	***/NS
	II-75	Good	65/65	Less good-bad	35/35	***/*
	II-79	Good	78/71	Less good-bad	22/29	*/NS
	III	Good	67/64	Less good-bad	33/36	***/**
Feel tired	III	No	82/75	Yes	18/25	***/**
Number of prescribed drugs	III	Three or less	79/70	Four or more	21/30	***/**
Number of defined diseases	II-70	Two or less	76/84	Three or more	24/16	***/**
	II-75	Two or less	67/81	Three or more	33/19	***/**
	II-79	Two or less	53/77	Three or more	47/23	***/**
	III	Two or less	76/84	Three or more	24/16	***/**
Rated health	I	Good	71/59	Less good-bad	29/41	***/**
Cognition/ Mental health						
Verbal meaning	III	≥12 points (max 30 points)	79/77	≤11 points	21/23	NS/NS
Inductive reasoning	II-70	≥ 8 points (max 30 points)	82/73	≤7 points	18/27	**/*
	II-75	≥ 8 points	83/79	≤7 points	17/21	**/**
Inductive reasoning	II-79	≥ 8 points	80/83	≤7 points	20/17	*/NS
Rated mental health	III	≥ 8 points	82/73	≤ 7 points	18/27	**/**
	I	Good	82/77	Less good-bad	18/23	***/**
Dementia	II-70	No	97/98	Yes	3/2	NS/NS
	II-75	No	93/96	Yes	7/4	*/NS
	II-79	No	85/91	Yes	15/9	***/**

a) Prediction of survival until death (I) or until present date (II) or until the age of 80 (III).

* p<0.05; ** p<0.001; *** p<0.001.

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