Independent Ageing in Very Old Swedish Men

KRISTIN FRANZON
Predictors for survival have been investigated thoroughly, but less is known about how to reach high age with preserved physical and cognitive function. These functions are crucial to stay independent in daily life, which is highly valued by the oldest old.

This thesis was based on data from the Uppsala Longitudinal Study in Adult Men. In 1970, all men born in 1920-24 and living in Uppsala were invited to the study, and 82% (n=2,322) participated in the first investigation. In this thesis, data are used from the investigations cycles at the ages of 50, 71, 87 and 92 years. Independent ageing was defined as follows: having independency in personal care and the ability to walk outdoors alone, being community-dwelling, having a Mini-Mental State Examination score of 25 points or greater, and having no diagnosed dementia.

Thirty-seven percent of the original cohort survived to the age of 85. At a mean age of 87, 74% of the participants were independently aged, while at a mean age of 92 the prevalence of independent ageing was 64%. In Paper I, non-smoking and normal weight at a mean age of 50 were associated with independent ageing at a mean age of 87 years. In Paper II, never smoking, not being obese, and a high adherence to a Mediterranean-like diet at a mean age of 71 were associated with independent ageing at a mean age of 87. In both Papers I and II, high leisure time physical activity was associated with survival, but not with independent ageing. In Paper III, higher gait speed and hand grip strength and a faster chair stand test were cross-sectionally associated with independent ageing at a mean age of 87. Higher gait speed was also longitudinally associated with independent ageing five years. However, muscle mass and sarcopenia were not associated with the outcome. In Paper IV, a history of stroke, osteoarthritis, hip fracture and chronic obstructive pulmonary disease were associated with loss of independent ageing at a mean age of 92.

Smoking, weight and diet are all modifiable risk factors associated with independent ageing. If decreased smoking and a normalised weight in the population could diminish stroke, hip fracture, chronic obstructive pulmonary disease and osteoarthritis, the prevalence of independent ageing could rise, even in nonagenarians. Additionally, a Mediterranean-like diet may contribute to both survival and independent ageing.

Keywords: Independent ageing, survival, sarcopenia, comorbidity, body mass index, smoking, dietary pattern, dietary biomarkers, longitudinal, octogenarians, nonagenarians

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To my family
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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Abbreviations

AD Alzheimer’s disease
ADL Activities of daily living
BIA Bioelectrical impedance analysis
BMI Body mass index
BP Blood pressure
CHS Cardiovascular Health Study
CI Confidence interval
COPD Chronic obstructive pulmonary disease
CST Chair stand test
CVD Cardiovascular disease
DSM Diagnostic and Statistical Manual of Mental Disorders
DXA Dual energy X-ray absorptiometry
EWGSOP European Working Group on Sarcopenia in Older People
FAs Fatty acids
GS Gait speed
HDL High-density lipoprotein
HGS Hand grip strength
HHP Honolulu Heart Program
HIMS Health in Men Study
HOMA-IR Homeostasis Model of Assessment-Insulin Resistance
HR Hazard ratio
IADL Instrumental activities of daily living
ICD International Statistical Classification of Diseases and Related Health Problems
LDL Low-density lipoprotein
MDS Mediterranean Diet Score
MELSHA Melbourne Longitudinal Studies on Healthy Ageing
MMSE Mini Mental State Examination
MUFA Monounsaturated fatty acid
OR Odds ratio
PADL Personal activities of daily living
PA Physical activity
PHS Physicians’ Health Study
PUFA Polyunsaturated fatty acid
SFA Saturated fatty acid
SMI Skeletal muscle index
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>TG</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>TLSA</td>
<td>Taiwan Longitudinal Survey on Ageing</td>
</tr>
<tr>
<td>ULSAM</td>
<td>Uppsala Longitudinal Study of Adult Men</td>
</tr>
<tr>
<td>UPA</td>
<td>University of Pennsylvania Alumni</td>
</tr>
<tr>
<td>WC</td>
<td>Waist circumference</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
Introduction

Life expectancy is increasing worldwide and the number of persons aged 80 years or older is expected to triple by 2050.[1] However, there is no consensus on whether this increased life expectancy is associated with compression or expansion of morbidity or disability. To what extent can the ageing trajectory be influenced by modifiable lifestyle factors? Factors predicting survival have been investigated thoroughly, but less is known about how to age with preserved health and independence. And how do we define health in the oldest old, i.e. those aged 85 years or older?[2] In a Dutch study of health valuations, the oldest old preferred functional independence while the younger olds preferred less morbidity.[3] Furthermore, in 2013, one researcher suggested that health is “a state of complete or adequate physical and mental independence in activities of daily living”.[4]

The aim of this thesis was to increase the understanding of how people can age with preserved physical and cognitive functioning. All studies in the thesis are based on data from the Uppsala Longitudinal Study of Adult Men (ULSAM). This prospective cohort study started in 1970 and is still ongoing. At baseline, all men born in 1920-24 and living in Uppsala were invited to participate, and in 2020, the oldest participants who are still alive will become centenarians.

Population ageing

Population ageing is a consequence of increasing life expectancy and decreasing fertility rates.[5] Increasing life expectancy in low-income countries is a result of increased survival at younger ages, which was also the reason in high-income countries at the beginning of the 20th century. However, today the increasing life expectancy in high-income countries is the result of increased survival at higher ages. Life expectancy at birth is a measure often used in population statistics, and it means the average number of years a new-born would live if current age-specific mortality rates were to continue.[6] In 2016, life expectancy at birth globally was 70 years for men and 74 years for women.[7] Furthermore, the number of persons aged 80 years or older globally is projected to increase from 137 million in 2017 to 425 million in 2050.[1] In Sweden, the
number of those aged 80 years or older is projected to increase from 0.5 million in 2015 to 1.05 million in 2050.[8] Not only is the proportion of older people increasing, but also the pace of this increase. While Sweden had 100 years to adapt to an increase from 10 to 20% of the population being aged 60 years or older, China will have 20 years.[5] Population ageing places great demands on societies worldwide.

Health and ageing according to the WHO

The World Health Organization (WHO) was established in 1948, and since then it has defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". [9]

In 2002, the WHO introduced the concept of ‘active ageing’ and defined it as “the process of optimising opportunities for health, participation and security in order to enhance quality of life as people age”. [10] However, active ageing has been replaced by the concept of ‘healthy ageing’, which is now the focus of the work of the WHO on ageing for 2015-30.[11] First, the WHO states that being free of disease is not a requirement for healthy ageing, as the presence of disease says nothing about the impact the disease will have on life.[5] Healthy ageing is instead defined as “the process of developing and maintaining the functional ability that enables well-being in older age”.[5] Functional ability is determined by the interaction between the individual’s intrinsic capacity (physical and mental) and the environment at home and in the society. The WHO also emphasises the life-course perspective in healthy ageing by concluding that healthy ageing starts at birth with the genetic inheritance and continues with the effect of socioeconomic position during childhood and adult life, before reaching mid- and late life.

Healthy ageing and related terms

Over the years, different theories concerning good life in old age have been discussed. The focus of the more scientific theories has often reflected the academic background of the researchers in either socio-psychological or biomedical disciplines. One of the first to introduce the concept of successful ageing in the 1960s was Havighurst, representing the socio-psychological field of science.[12] In his view, successful ageing was about life satisfaction and happiness on the individual level. In 1990, Baltes defined successful ageing as reaching individual goals and minimising losses and maximising gains.[13] The theory, selective optimisation with compensation, focuses on how to adapt to the losses during life.

In the field of biomedical science, Rowe and Kahn made a distinction between “usual” and “successful” ageing in 1987.[14] Both usual and successful ageing include the absence of disease, but in the case of usual ageing there are
risk factors for disease, which are not found in successful ageing. Ten years later Rowe and Kahn defined successful ageing as including three components: low probability of disease and disease-related disability, high cognitive and physical functional capacity and active engagement with life.[15]

Although the paper by Rowe and Kahn was published over two decades ago, there is still no consensus on the definition of successful ageing or even on the name of the concept. One review in 2006 identified 28 studies with 29 different definitions of successful ageing and related terms, such as ‘healthy ageing’, ‘optimal ageing’ and ‘ageing well’. [16] In this review, 26 out of 29 definitions included the absence of disability or maintained physical functioning, while 13 included well-preserved cognitive functioning. A review in 2007 reported that biomedical models primarily emphasise physical and mental functioning, while socio-psychological models emphasise social functioning, life satisfaction and psychological resources as components of successful ageing.[17] Another review in 2013, found as many as 84 studies with 105 operational definitions of successful ageing.[18] Of the 105 definitions, 92% included physical constructs, 50% engagement constructs, 49% well-being constructs, 26% personal resources and 6% extrinsic factors such as financial resources. Not only did the type of construct vary, but also the number of constructs included, and as a consequence of this the proportion of successful agers varied widely between studies.[16, 18]

The definition by Rowe and Kahn has been criticised over the years.[19] One criticism concerns the name of the concept. Another name would perhaps be less of a value judgement, as ‘successful’ implies that there is a competition, with winners and losers.[20, 21] Another criticism is that Rowe and Kahn’s model, like many of the other biomedical definitions, makes a static assessment instead of seeing successful ageing as a process in a life-course perspective.[22] Furthermore, the role of social structures is not considered in the Rowe and Kahn definition.[23] Finally, some researchers highlight the need to incorporate a lay perspective and subjective criteria derived from older adults themselves to ensure that the concept has social relevance.[17, 24]

The lay perspective on healthy ageing

In a British survey of people aged 50-94 years, the most frequently mentioned components associated with successful ageing were functioning and health, followed by psychological factors, social roles and activities.[25] In those aged under 65, compared to those aged 65+, finances were mentioned more often, while the older group mentioned social activities more often.

The participants in the Finnish Vitality 90+ Study were asked to give their opinion about what constitutes a good old age.[26] Physical, cognitive, social and psychological themes were mentioned, as in other studies. Additional important themes were life circumstances and independence, and one shared example of both these themes was the desire to live in one’s own home as long
as possible, and to die there. Furthermore, the participants did not address absence of disease as a part of a good old age.

Australian community-dwelling participants aged 65 years or older were asked about their main fear for the future, and the most common answer was their own future physical health, and after that loss of independency and nursing home admission.[27] The fear of loss of independency was associated with higher age in men. This is in line with a Dutch study where the oldest old preferred functional independency.[3] This was in contrast to the 65-year-old Dutch who emphasised less morbidity.

A subsample of the ULSAM cohort participated in a qualitative interview-based survey at the age of 85-90 years, exploring their perspectives on a “good old age” and successful ageing.[28] Four themes were commonly important to a good ageing, well-being and life satisfaction.[28] The first theme was adaptation, which meant the participants’ ability to adapt to ageing and subsequent limitations. Not only physical and cognitive health, but also financial resources were important for the second theme; sustaining independence. The third theme was belongingness, representing close relationships and especially the role of a spouse. The fourth theme was the perspective of time, which emphasises past life experiences and their contribution to life satisfaction at high age.

A review of layperson perspectives on successful ageing revealed that psychosocial factors were the most frequently mentioned component of successful ageing, especially social engagement.[29] Lay views are often broader than theoretical models,[25, 30] while longevity is seldom mentioned as important for successful ageing in lay definitions.[29-31] Certain domains of healthy ageing are valued differently across cultures. In a review, "family" was perceived as a more important domain among older people in Asia, than in people in North America or Europe. On the other hand, mental function was not mentioned in Asian, but in North American and European studies. However, where was a cross-cultural consensus of the importance of preserved physical functioning.[30] Finally, older people define themselves as successfully aged more often than researchers’ definitions do.[21, 32]

**Operational definition of ‘Independent Ageing’**

In the light of the literature review and our clinical experience of geriatric medicine, we chose to base our definition on preserved physical and cognitive function, which are crucial for independency in daily life. In order not to add another definition to the concept of healthy ageing, we chose to name this state of preserved physical and cognitive functioning as ‘Independent Ageing’. However, physical and cognitive functions are the most common elements in definitions of healthy age[16, 18].

In epidemiology, physical function is commonly measured as ‘functional limitations’ or ‘disability’.[33] Functional limitations are usually assessed by
tests of physical performance in a standardised way. Gait speed (GS) as a single assessment, or as a part of the Short Physical Performance Battery,[34] is an objective way to measure functional limitations. Assessment of disability reveals what individuals really can do in their own environment. Disability can be measured objectively by an observer, or subjectively by self-reported data. Personal activities of daily living (PADL) include bathing, dressing, toileting, transferring, continence and feeding[35] while instrumental activities of daily living (IADL) includes ability to use the telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medication and ability to handle finances.[36] Also, disability in mobility may be used, like walking inside the home, climbing a flight of stairs or walking outside the home. Gill et al. emphasise the importance of distinguishing between being dependent, on equipment or another person, or just having difficulty with a task.[33] In our definition, we use self-reported data on dependence in PADL and the ability to walk outdoors without assistance from another person as measurements of physical functioning.

Cognitive function can be measured in several ways. However, Mini-Mental State Examination (MMSE) is one of the most used screening tests, both in clinical settings and research.[37] It includes tests of orientation, calculation, language, figure drawing, registration and recall, with a high score (maximum 30 points) representing preserved cognitive function. MMSE is a valuable tool for identifying possible cognitive impairment, as well as for monitoring decline in global cognitive functioning. However, it is well known that increasing age, as well as lower education, is associated with lower scores on MMSE.[38] In a study from the US, the median MMSE score in participants aged 85 years or older was 24 points for those with five to eight years of education and 28 points for those with at least college experience.[38] Based on data from the 90+ study a suggested cut-off for MMSE in participants aged 90-93 years is ≤25 points for dementia screening.[39] A Swedish study, using data from the Elderly in Linköping Screening Assessment, suggested MMSE 26 to be a reasonable cut-off for detection of possible cognitive impairment in individuals aged 85 to 93 years.[40] We chose the cut-off ≥25 points for the present definition of independent ageing.

Third, our definition of independent ageing requires the absence of diagnosed dementia, which in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-4) was defined as a significant impairment in memory and at least one other cognitive domain.[41] The impairments should cause significant difficulties in social function and/or activities of daily living (ADL) and should represent a marked deterioration from a previous level of functioning.

Finally, our definition of independent ageing included living at home.
In summary, independent ageing was operationalised as:

- independency in personal care/PADL
- ability to walk outdoors alone, with assistive devices allowed
- MMSE score ≥25 points out of possible 30
- absence of diagnosed dementia
- community-dwelling

Healthy ageing in the oldest old in published studies

Longitudinal studies that include both physical and cognitive function in the definition of the outcome are rare. We have identified 11 longitudinal studies with physical function (ADL and/or mobility) in the outcome. These have at least 10 years of follow-up and the outcome is measured beyond the age of 80 years (Table 1).[42-53] Three of these studies also include cognitive function in the outcome: the Cardiovascular Health Study (CHS),[45] the Health in Men Study (HIMS)[47] and the Taiwan Longitudinal Survey on Ageing (TLSA)[50]. Furthermore, three of the reports, two based on the Honolulu Heart Program (HHP) and one based on CHS, require absence of common age-related diseases in addition to conserved physical and cognitive function.[48, 52, 53] Finally, some of the studies also call for good self-rated health,[42, 49] community-dwelling[49] or absence of depressive symptoms[47, 50] to be defined as successful or healthy ageing. These studies use different names for the concept, for example ‘healthy ageing’, ‘successful ageing’, ‘ageing well’ and ‘healthy octogenarian’. However, healthy ageing is the most common name and all these concepts will henceforth mainly be referred to as ‘healthy ageing’.
Table 1. Longitudinal studies with ≥10 years of follow-up and the outcome measured at age ≥80 years.

<table>
<thead>
<tr>
<th>Study subjects</th>
<th>Baseline age (years)</th>
<th>Follow-up time (years)</th>
<th>Preserved physical function</th>
<th>Preserved cognitive function</th>
<th>Other criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENECA[42]</td>
<td>70-75</td>
<td>10</td>
<td>PADL</td>
<td></td>
<td>Self-rated health</td>
</tr>
<tr>
<td>Physicians’ Health Study (PHS)[43]</td>
<td>Mean age 72</td>
<td>16</td>
<td>PADL, mobility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jerusalem Longitudinal Cohort Study[44]</td>
<td>70</td>
<td>18</td>
<td>ADL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Health Study (CHS)[45]</td>
<td>≥65 years (median age at follow-up 85)</td>
<td>13</td>
<td>PADL</td>
<td>3MS[54] ≥80/100</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Health Study (CHS)[53]</td>
<td>Mean age 74</td>
<td>22</td>
<td>PADL</td>
<td>3MS[54] ≥80/100</td>
<td>No CVD, cancer, COPD, severe kidney disease</td>
</tr>
<tr>
<td>University of Pennsylvania Alumni (UPA)[46]</td>
<td>Mean age 68</td>
<td>16</td>
<td>ADL, mobility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health in Men Study (HIMS)[47]</td>
<td>65-83</td>
<td>10-13</td>
<td>PADL, IADL</td>
<td>TICS[55] &gt;27</td>
<td>No depressive symptoms</td>
</tr>
<tr>
<td>Honolulu Heart Program (HHP)[52]</td>
<td>Mean age 54</td>
<td>40</td>
<td>No difficulty walking half a mile</td>
<td>CASI[56] ≥74</td>
<td>No CVD, cancer, COPD, Parkinson, diabetes</td>
</tr>
<tr>
<td>Honolulu Heart Program (HHP)[48]</td>
<td>Mean age 76</td>
<td>21</td>
<td>No difficulty walking half a mile</td>
<td>CASI[56] ≥74</td>
<td>No CVD, cancer, COPD, Parkinson, diabetes</td>
</tr>
<tr>
<td>Melbourne Longitudinal Studies on Healthy Ageing (MELSHA)[49]</td>
<td>Mean age 73</td>
<td>12</td>
<td>IADL</td>
<td></td>
<td>Community-dwelling Psychological well-being Self-rated health</td>
</tr>
<tr>
<td>Taiwan Longitudinal Survey on Ageing (TLSA)[50]</td>
<td>62-69</td>
<td>14-18</td>
<td>PADL</td>
<td>SPMSQ[57] cut-off dependent on educational level</td>
<td>Able to provide social support No depressive symptoms</td>
</tr>
</tbody>
</table>

PADL=personal activities of daily living, ADL=activities of daily living, IADL=instrumental activities of daily living, 3MS=Modified Mini-Mental State Examination, TICS=Telephone Interview for Cognitive Status, CASI=Cognitive Abilities Screening instrument, SPMSQ=Short Portable Mental Status Questionnaire, CVD=cardiovascular disease, COPD=chronic obstructive pulmonary disease
Midlife and late life predictors of healthy ageing

**Cardiovascular risk factors**

In the TLSA, hypertension was associated with reduced odds for staying independent in ADL and with preserved cognition 18 years later.[50] In the CHS, hypertension in late life was not associated with physical and cognitive impairment as a combined outcome.[45]

Diabetes was associated with loss of independence in ADL and cognitive impairment in the TLSA.[50] This association was also found in the University of Pennsylvania Alumni study (UPA), where the outcome was defined by ADL and mobility, but not cognition.[46]

Cardiovascular risk factors were investigated in the HHP,[48, 52] but as these studies required absence of diseases, such as diabetes or cardiovascular disease (CVD), it was not possible to determine if there were independent associations between cardiovascular risk factors and functioning or not.

**Lifestyle factors**

In CHS, TLSA and HHP higher education was associated with healthy ageing,[45, 48, 50, 52] while the other studies listed in Table 1 did not take educational level into account.

There was no association between marital status in midlife or late life and healthy survival in the HHP[48, 52], while in the TLSA, being separated or never married (vs. married) were associated with less chance of ageing well.[50]

Never smoking (vs. current) was associated with preserved ADL and cognitive function in the TLSA.[50] Non-smoking was also associated with independence in ADL in the Physicians’ Health Study (PHS)[43], the UPA[46] and the Melbourne Longitudinal Studies on Healthy Ageing (MELSHA).[49] In contrast, no association with smoking status was seen in the CHS.[45] Ever smoking in midlife was associated with unhealthy survival in HHP.[52] Current smoking (vs. never) was associated with unhealthy survival in the age-adjusted model in HHP but not included in the final stepwise model.[48] However, one meta-analysis showed consistent evidence from longitudinal studies of the association between a non-smoking status and healthy ageing.[58]

Normal weight (body mass index (BMI) 18.5-24.9 kg/m²)[59] at the age of around 70 was associated with preserved independence in ADL 16 years later in two studies.[43, 46] In the CHS, higher body weight in late life was associated with combined impairment in physical and cognitive functions.[45] In the HHP, requiring absence of diseases in the definition, there was a direct association between BMI <25 kg/m² and the outcome both in midlife and late life.[48, 52] In MELSHA, underweight (vs. normal) was associated with not ageing well for men and women together, but not for men only.[49] None of the aforementioned studies investigated the relationship between waist circumference (WC) and healthy ageing, but in the Whitehall II study with baseline at a mean age of 51, a large WC (men: ≥94 cm, women: ≥80 cm) was
associated with reduced odds for successful ageing 16 years later.\textsuperscript{[60]} In this study successful ageing was defined as no chronic disease at age >60 years and not in the worst quintile of cognitive, physical, respiratory, cardiovascular and mental health.

Physical activity (PA) can be defined as any bodily movement produced by skeletal muscles that results in energy expenditure.\textsuperscript{[61]} The Global Recommendations on Physical Health from the WHO says that adults should do at least 150 minutes of moderate-intensity PA or 75 minutes of vigorous-intensity per week.\textsuperscript{[62]} Moderate-intensity activity noticeably accelerates the heart rate and is exemplified by brisk walking and gardening. A vigorous-intensity activity requires a large amount of effort and causes a substantially increased heart rate. Examples of activities in this category are running, fast cycling and aerobics. In the HIMS \geq 150 minutes of vigorous PA every week was associated with the combination of preserved independence in ADL and cognitive functioning more than 10 years later.\textsuperscript{[63]} However, in the CHS high PA was not associated with this combined outcome.\textsuperscript{[45]} In the Jerusalem Longitudinal Cohort Study, PA at the age of 70 was directly associated with preserved independence in ADL at the age of 85.\textsuperscript{[44]} Furthermore, initiating higher PA in old age was associated with better performance in ADL in this study. In the PHS, compared to exercise \leq 1 time every week, exercise 2-4 times was associated with better physical function, while exercise \geq 5 times per week was not significantly associated.\textsuperscript{[43]} In the UPA, vigorous PA that works up a sweat was not associated with better performance in ADL.\textsuperscript{[46]} Higher PA in midlife or late life was not associated with the outcome in HHP.\textsuperscript{[48]} In those studies, PA was measured as metabolic work in a typical 24-hour day. A meta-analysis states that there is consistent evidence from longitudinal studies that PA is positively associated with healthy ageing, regardless of the type of measurement.\textsuperscript{[64]}

Diet

Biomarkers of dietary intake

Circulating antioxidants and fatty acids (FAs) can be used as biomarkers of the dietary intake of different antioxidants and fats. The following studies are all based on dietary biomarkers and not on records of the dietary intake.

A FA consists of a carbon chain of variable length with a carboxyl group at one end and a methyl group at the other end. The different groups of FAs have different dietary sources.\textsuperscript{[65]} Saturated FAs (SFAs) have no double bonds and are mainly found in animal products, e.g. meat and dairy products, but also have some vegetable sources like palm and coconut oil. Monounsaturated FAs (MUFAs) have one double bond and are found in olive and canola oil, nuts and seeds, but also in animal products. Polyunsaturated FAs (PUFAs) have several double bonds and are divided into subgroups, depending on the position of the first double bond. The main sources of n-3 PUFAs are seafood and linseed oil, while n-6 FAs are found in corn oil, sunflower oil and soy bean oil. FAs in cholesterol esters reflect the dietary intake of the
recent weeks.[66, 67] PUFAs are a better biomarker than SFAs, which in turn are better than MUFAs.[67, 68] In the CHS, a high level of circulating n-3 FAs at a mean age of 74 years was associated with functional ageing, defined as preserved physical and cognitive function, 22 years later.[53] In this study, n-3 FAs was also associated with healthy ageing, additionally requiring the absence of CVD, cancer or chronic obstructive pulmonary disease (COPD). To the knowledge of the author, this is the only investigation of the relationship between circulating FAs and healthy ageing.

Antioxidants are substances involved in the defence against oxidative stress.[65] Carotenoids are mainly found in yellow or orange vegetables and fruits, and beta-carotene is established as a biomarker of fruit and vegetable intake.[69] Vitamin E is found in vegetable oils, nuts and seeds. There are different forms of vitamin E, but most studies use circulating alpha-tocopherol as a biomarker of the intake of vitamin E. Selenium is found in fish, green lentils, Brazil nuts, milk and cheese. No study of the association between circulating antioxidants and subsequent healthy ageing has been found.

Dietary patterns

In contrast to investigate specified nutrients, the use of dietary patterns considers the synergistic effect of foods and nutrients consumed together. In a review from 2015, most studies reported a positive association between a healthier diet and successful ageing, and the majority of the studies assessed adherence to the Mediterranean diet.[70] This pattern is characterized by a high intake of olive oil, fruits, vegetables, legumes, cereals and fish, a low intake of meat, meat products, milk and dairy products and a moderate intake of alcohol.[71]

In the French SU.VI.MAX study, a Literature-Based Adherence Score to the Mediterranean diet (LAMD) [72] was associated with healthy ageing 13 years later in a cohort of both men and women aged 45-60 years at baseline.[73] When considering each component of the index, a high intake of fruits and vegetables was associated with the outcome. In the Nurses’ Health Study, greater adherence to the Alternate Mediterranean Diet[74] was associated with healthy ageing after 15 years of follow-up.[75] The median age at baseline was 59 years and the cohort consisted of women only. In an Australian study, a dietary pattern in midlife including plenty of fruit, but a limited amount of meat and fried foods, was associated with successful ageing almost 12 years later.[76] Also, in another Australian study investigating the association between adherence to national dietary guidelines in participants ≥49 years and successful ageing, a high intake of fruit as well as high adherence to the complete guidelines was associated with a favourable outcome.[77] All the four studies included physical and cognitive function in the definition of the outcome, but also absence of specified diseases such as CVD and diabetes.[73, 75-77] No study with both physical and cognitive function in the outcome and participants older than 80 years at follow-up was found. However,
in the European SENECA study, including men and women aged 70-75 years at baseline, there was no association between adherence to a Mediterranean diet and independency in ADL 10 years later.[42]

The impact of sarcopenia on healthy ageing

Preserved physical and cognitive function are dependent on preserved function of the neuromuscular system. With this in mind, sarcopenia can be a threat to independent ageing and is therefore of interest in this research field. The Greek roots of sarcopenia are sarx for flesh and penia for deficiency, and the phenomenon of sarcopenia was named by Rosenberg in 1989.[78] The term was introduced to describe the age-related loss of lean mass and was initially defined as low muscle mass only. There is now general agreement that low muscle mass must be combined with low muscle function to define sarcopenia, but different definitions exist in parallel.[79-83] The definitions differ in how they measure muscle mass and muscle function. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) presented their definition of sarcopenia after a review of tools that can be used to measure muscle mass and muscle function.[79] The EWGSOP suggested an algorithm based on measurement of gait speed (GS) with a cut-off point of ≤0.8 m/s. If below this cut-off, muscle mass should be measured. Low GS and/or low hand grip strength (HGS) together with low muscle mass would confirm the sarcopenia diagnosis. However, in 2018 an update of the definition was published, EWGSOP2.[80] This definition further emphasises muscle strength, measured by HGS or the chair stand test (CST). If muscle strength is low (denoting probable sarcopenia), muscle mass or quality should be measured to confirm the sarcopenia diagnosis. Finally, in this algorithm, tests of physical performance (e.g. GS) assess the severity of the sarcopenia.

The prevalence of sarcopenia is of course dependent on the definition criteria, but also differs with age and gender.[84] In a review in 2014, the prevalence was 1-29% in community-dwelling populations, 14-33% in long-term care populations and 10% in acute hospital care populations aged ≥50 years.[85] The prevalence in octogenarians was 12.5% in a Belgian study and 21% in a British study, both using the EWGSOP1 definition.[86, 87] So far, only two studies using the updated EWGSOP2 definition have been published.[88, 89] The mean ages of the participants in these studies were 74 and 76 years, respectively, and the prevalence was below 10%.

Meta-analyses and reviews have shown that sarcopenia is associated with unfavourable outcomes such as mortality,[90, 91] functional decline[90], cognitive impairment[92] and hospitalisation.[90, 93] One study from the USA by Tolea et al. investigated the cross-sectional relationship between sarcopenia and impairment in cognitive and physical function in participants aged 40 years or older.[94] Those with sarcopenia had a three-fold increased risk of
the combined impairment. No other study on the relationship between sarcopenia and an outcome similar to healthy ageing at any age was found.

According to muscle mass, the aforementioned study from the USA measured this by bioelectrical impedance analysis (BIA) but found no cross-sectional association with combined physical and cognitive impairment.[94] In contrast, in the MEDIS study there was a cross-sectional association between skeletal muscle index (SMI) which was equation-based and not measured, and successful ageing in the participants aged between 65 and 100 years.[95] The successful index combined 10 components including education, PA and BMI. No longitudinal study with healthy ageing, or a similar outcome, was found.

According to muscle function, GS, but not HGS, was cross-sectionally associated with active and healthy ageing in octogenarians in the Helsinki Business Men Study.[96] The definition of active and healthy ageing included absence of diseases and of functional and cognitive impairment but also “feeling happy”. In the study by Tolea et al., low HGS was cross-sectionally associated with an increased risk of a combined impairment in physical and cognitive functions, while the role of GS was not investigated.[94] In the HHP study, there was no association between HGS or GS at a mean age of 76 and healthy ageing nine years later (see Table 1).[48] To the best of our knowledge, there are no previous studies on the association between CST and healthy ageing or studies with a similar outcome.

The impact of somatic morbidity on healthy ageing

A number of disorders may have a negative impact on cognitive and physical function, but if the disorders are preventable, the loss of independence might be postponed. This is one reason to investigate the associations between common disorders and these functions. Community-living nonagenarians were investigated in the NonaSantfeliu study in Spain.[97] Hearing or visual impairment and a previous stroke were more common in the group with worse outcome in ADL and cognitive function, while there was no difference in the prevalence of diabetes, hypertension, ischaemic heart disease, heart failure or COPD. A study from Singapore, also investigating community-dwelling nonagenarians, consistently found an association between a previous stroke/TIA and MMSE <21 points, together with dependency in ADL and mobility.[98] There was no difference in the prevalence of other comorbidities such as diabetes, hypertension, atrial fibrillation or ischaemic heart disease. The association with stroke in both these studies is not surprising, since stroke can affect both physical and cognitive functions. Other conditions potentially having a negative impact on dependency are hip fracture, Parkinson’s disease, osteoarthritis and cancer. However, these disorders were not included in the aforementioned two studies and no other study was found exploring the association between disorders and a similar combined outcome in nonagenarians.
Some of the studies on healthy ageing require the absence of common diseases in their definition of the concept. However, at a very high age, the absence of disease is unusual.[99, 100] All nonagenarians in Tampere, Finland, were invited to the Vitality 90+ study and 91% participated.[99] In this population, only 0.2% had no recorded diagnoses that had required hospitalisation at any time since 1972.[99] In a Swedish study all inhabitants aged ≥90 years, living at Kungsholmen, were invited and 88% participated.[100] In this study, 17.3% of the women and 25.9% of the men had no current disease at the physical examination.

Midlife and late life predictors of survival

As there are numerous studies on predictors for survival, the following review only represents a selection based on studies with a baseline in midlife (~50 years old) or late life (~70 years old) and follow-up of survival beyond the age of 80 years. Some of the studies in Table 1 are included as they have survival, as well as healthy ageing, as an outcome.[43, 44, 46-48, 52] Additionally, results from the Framingham Heart Study,[101] Whitehall II study[102] and the study of men in Gothenburg born 1913[103] are discussed. These three studies have baseline in midlife and follow-up of survival at the age of 85[101, 102] and 90.[103] Furthermore, previous studies on mortality from the ULSAM are considered.[104-106]

Cardiovascular risk factors

Hypertension,[52, 101] high cholesterol[101, 103] and hyperglycemia[52]/glucose intolerance[101, 102] in midlife are all well-known risk factors for total mortality at high age. In the PHS study with baseline at a mean age of 72, hypertension and diabetes, but not hypercholesterolemia, were associated with increased mortality.[43] In the HHP study with baseline at a mean age of 76, diastolic blood pressure (BP) >90 mm Hg and systolic BP >160 or < 120 mm Hg were associated with mortality at the age of 85 in the age-adjusted analyses.[48] However, the associations with systolic BP were not included in the final stepwise logistic regression. There were no associations between high-density lipoprotein (HDL) cholesterol or glucose and mortality in this study.

Lifestyle factors

Socioeconomic position (SEP) can be measured by for example occupational class, wealth and income.[107] In many studies educational level is also used as an indicator of SEP. High educational level was associated with survival in advanced age in the Framingham Heart Study,[101] but not in the HHP study.[48, 52] In the Whitehall Study those with a clerical job (vs. professional or executive work) had a higher mortality, while in the Gothenburg study
those with higher household costs had lower mortality.[102, 103] One study in a Swedish and German population showed that education, income and occupational class were independently associated with all-cause mortality, but out of the three, income was the strongest predictor.[108]

Being married in midlife[52, 102] or late life[48] was associated with survival in the HHP and the Whitehall Study.

Smoking in midlife[52, 101-103] and late life[43, 46, 48] is well known to reduce survival in longitudinal studies.[109] A meta-analysis showed benefits for survival of smoking cessation in all age groups, including octogenarians.[109]

BMI is an inconsistent predictor of survival in late life. In the HHP study, BMI $\geq 25$ kg/m$^2$ (vs. $<25$ kg/m$^2$) in midlife[52] and a BMI $<19$ kg/m$^2$ (vs. $\geq 19$ kg/m$^2$) in late life[48] was associated with mortality.[52] In the PHS study with baseline in late life, BMI $\geq 30$ kg/m$^2$ (vs. $<25$ kg/m$^2$), but not 25-29.9 kg/m$^2$, was associated with mortality.[43] Furthermore, in the Whitehall II Study BMI $>25$ or $<18.5$ kg/m$^2$ (vs. normal) was not associated with mortality. A meta-analysis found overweight to be associated with less mortality than normal weight in all ages[110]. In participants 65 years or older no association was seen between higher BMI levels and mortality, while with all ages together an association was seen between BMI $\geq 30$ kg/m$^2$ (vs. normal weight) and mortality. A high WC at a mean age of 51 and in those aged $\geq 65$ years was associated with higher mortality more than 10 years later in different studies.[60, 111, 112] This is in line with a meta-analysis in 65- to 74-year-olds which showed an increased mortality with ‘healthy’ weight (BMI 20-24.9 kg/m$^2$), overweight and obesity in those having a high WC (vs. low).[113]

A physical activity index measured as the metabolic work performed in a typical 24-hour period using a structured questionnaire.[114] was used in the Framingham Heart Study[101] and the HHP[48, 52]. In the studies with baseline in midlife the physical activity index was not selected in the final stepwise model,[52, 101] while in the HHP study with baseline at a mean age of 76 a higher level of PA was associated with survival.[48] Also, in other studies with baseline in late life a higher PA was associated with survival.[42-44, 47] For example, in the HIMS $\geq 150$ minutes per week of vigorous PA was associated with increased survival 11 years later.[47] A meta-analysis including studies with participants older than 60 years found that even a lower dose of moderate-to-vigorous PA, compared to being inactive, reduced mortality.[115] A high level of physical activity at work was associated with total mortality 19 years later in men, but not in women, in the Copenhagen City Heart Study[116]. However, irrespective of the level of PA at work, high leisure time PA was associated with increased survival 22 years later in the same cohort[117].
Diet

Biomarkers of dietary intake

Studies of the association between dietary biomarkers for FA intake and mortality are scarce.

There are previous reports from the ULSAM cohort with baseline at the age of 50,[104] as well as from the CHS with circulating FAs measured at a median age of 74 years.[118-120] In both the studies, high 16:0 FAs was associated with increased mortality,[104, 118] while in the CHS, high 18:0, 22:0 and 24:0 FAs was associated with decreased mortality.[118] In ULSAM, there was no association between 18:0 FAs and mortality, and the more long-chained SFAs were not measured.[104] Furthermore, in ULSAM no association was found between n-3 FAs and mortality,[104] while in the CHS, a high level of n-3 FAs was associated with lower total mortality.[120] In both the ULSAM cohort and the CHS, higher linoleic acid (18:2 n-6) was associated with lower mortality.[104, 119] None of the studies reported an association between the other n-6 FAs and mortality.

Concerning the antioxidants, a previous report from the ULSAM found no independent association between alpha-tocopherol, beta-carotene or selenium in midlife and mortality 25 years later.[105] However a Finnish study of male smokers with a mean age of 57 years found an association between high circulating alpha-tocopherol and lower mortality 19 years later,[121] but in studies with baseline in late life there was no such association.[122-124] Furthermore, in a meta-analysis from 2018, higher alpha-tocopherol was associated with lower mortality but after exclusion of the aforementioned Finnish study,[121] which was much bigger than the other studies, the association became non-significant.[125]

Concerning beta-carotene, the results are divergent,[105, 123, 124, 126] but a meta-analysis showed an association between high levels and lower mortality.[125]

In previous reports,[105, 123, 127, 128] including a meta-analysis,[125] higher selenium was associated with lower mortality. However, caution should be exercised as one American study showed a decrease in mortality for medium levels, but a modest increase in mortality for higher levels of selenium.[129]

Dietary pattern

The so-called Mediterranean diet is one of the most commonly used dietary patterns in research studies. The Mediterranean Diet Score (MDS) was introduced by Trichopoulou et al. and was first used in a Greek population.[71] They found a reduction in mortality with a higher adherence to the MDS. A meta-analysis of 30 studies including all ages confirmed this association.[130] Concerning octogenarians, a high adherence to a Mediterranean-like dietary pattern at a mean age of 71 was associated with lower total mortality 10 years later in a previous report from the ULSAM.[106] One meta-analysis included
only longitudinal studies with participants aged ≥65 years at baseline and found that a one-point increase in the MDS was associated with 5% lower risk of all-cause death.[131]
Aims

The overall aim of this thesis was to investigate predictors of independent ageing in very old Swedish men.

The specific aims are described below for each manuscript.

**Paper I**: To examine the relationships between cardiovascular risk factors, lifestyle and dietary biomarkers at the age of 50 and independent ageing 37 years later. A secondary aim was to investigate the relationship between the same midlife factors and survival to the age of 85.

**Paper II**: To investigate the relationships between cardiovascular risk factors, lifestyle and dietary pattern at a mean age of 71 and independent ageing 16 years later. A secondary aim was to investigate the relationship between the same factors and survival to the age of 85.

**Paper III**: To explore the prevalence of sarcopenia and its components (muscle function and muscle mass), at a mean age of 87, and also the associations between these factors and independent ageing in cross-sectional analyses, as well as with five years of follow-up.

**Paper IV**: The objective of this study was to describe the associations between some common somatic disorders and independent ageing at a mean age of 92.
Methods

Subjects
The Uppsala Longitudinal Study of Adult Men
In 1970-73 all men born between 1920 and 1924 and living in Uppsala were invited to participate in the ULSAM.[132] The primary focus of the study was at that time risk factors for CVD. It was then believed that women had a much lower risk for CVD and therefore only men were invited to participate. Of the 2,841 men invited, 2,322 (82%) participated in the first investigation at the age of 50 years. The ULSAM population have since been reinvestigated six times, and in this thesis data are used from the investigations at the ages of 50, 71, 87 and 92 years.

All studies in this thesis are based on the ULSAM population.

![Figure 1. Overview of the participants in the investigations at a mean age of 50, 71, 87 and 92 years in the ULSAM.](image-url)
Study populations

**Paper I.** The study population in Paper I was based on the 50-year-old men with whom it was possible to follow up for survival at the age of 85 years (n=2,293). Eleven men had emigrated or had their personal number miscoded and were therefore lost to follow-up. Another 18 men died within two years from baseline and were excluded to limit the potential influence of reverse causation. At a mean age of 87, 472 out of 2,293 men were re-examined and could be classified as independently ageing or not.

**Paper II.** The baseline for this study was the third investigation cycle at a mean age of 71 years. Participants with complete information on educational level, smoking habits and dietary pattern were included in the analyses of survival (n=1,104). Of these participants, 369 men were re-examined at a mean age of 87 years and categorised as independently ageing or not.

**Paper III:** The baseline for the third study was the sixth investigation cycle at mean age 87 (n = 472). Of these participants, it was possible to define 287 men with regard to both independent ageing and sarcopenia. Out of the 287 participants, 49 did not fulfil the criteria for independent ageing at baseline and 87 men had died before follow-up five years later. Thus, 105 participants were re-examined at mean age 92. Another 46 men declined to participate but it was possible to re-evaluate 22 of these concerning dementia, living conditions and ADL after a review of their medical records. Thus, 127 participants were categorised as independently aged or not at follow-up.

**Paper IV.** This study was based on data from the seventh investigation cycle at a mean age of 92 years. Of 245 available men, 148 men were re-examined, while 97 men declined to participate in the policlinic re-examination. Of these 97 men, five had previously not consented to a review of the medical records. However, it was possible to evaluate 75 concerning dementia, living conditions and ADL after a review of their medical records until January 1, 2015. Thus, overall 223 men were categorised as independently ageing or not at a mean age of 92 years.

Exposures

A detailed description of all analyses in the investigation cycles can be found on the ULSAM home page (www.pubcare.uu.se/ulsam).[132]
Exposures at a mean age of 50

**Cardiovascular risk factors**

BP was measured in the supine position in the right arm to the nearest 5 mm Hg after 10 minutes' rest.

Fasting blood glucose was measured by spectrophotometry using the glucose oxidase method. An intravenous glucose tolerance test was performed in a subgroup of men and in these men, fasting serum insulin was determined. Insulin resistance was estimated using the Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR) and was calculated using the international formula (fasting insulin x fasting glucose/22.5).[133]

Determinations of serum cholesterol and triglyceride (TG) concentrations were performed on a Technicon Auto Analyzer type II. HDL cholesterol was assayed and low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula: LDL cholesterol = serum HDL cholesterol -(0.42 x serum TG).[134]

**Lifestyle factors**

BMI was calculated as the ratio of the weight to the height squared (kg/m²).[59] Height (without shoes) was measured to the nearest centimetre and weight (in undershorts) to the nearest kilogram.

Educational level was characterised using a self-administered questionnaire into lower; <8 years of formal education, medium; 8-13 years and higher levels; >13 years, and this data was used in all the papers.

Marital status was obtained from a questionnaire and was dichotomised into married or living alone.

PA at leisure time was categorised, after validated questions[135, 136], into four groups: sedentary (mainly reading, watching television or movies), moderate (walking or cycling during the week or at the weekends), regularly (sports or strenuous gardening at least three hours per week) and athletic (regular strenuous physical training and competition). Work-time PA was categorised into four groups: chiefly sedentary, mostly standing or walking, heavy lifting (>10 kg) or physically demanding work.

Smoking among the participants was categorised as never, former, or current after an interview with a physician.

**Dietary biomarkers**

The proportions of FAs, i.e. from 14:0 to 22:6 n-3, in serum cholesterol esters are presented group wise (SFAs, MUFAs, n-3 FAs and n-6 FAs) as the percentages of the total amount of FAs. Thin layer chromatography was used for separation of the serum cholesterol esters and the percentage composition of methylated FAs14:0 to 22:6 was determined by gas chromatography as previously described.[137]

Alpha-tocopherol and beta-carotene were determined by high-performance liquid chromatography. The serum tocopherol concentrations reported were
corrected for the sum of serum cholesterol and serum triglycerides (tocopherol/(cholesterol+triglyceride)).[138] Selenium was determined in serum using the graphite-furnace atomic absorption spectrometric method.[139]

Exposures at a mean age of 71

**Cardiovascular risk factors**

BP was measured to the nearest 2 mm Hg twice in the right arm with the subject in the supine position after resting for 10 minutes. The mean of the two values was used.

Fasting plasma glucose was measured by the glucose dehydrogenase method (Gluc-DH, Merck, Darmstadt, Germany) and plasma insulin was assayed using an enzymatic-immunological assay (Enzymmun, Boehringer Mannheim, Germany) performed in an ES300 automatic analyser (Boehringer Mannheim), and was given in mU/l. HOMA-IR index was calculated as described for the investigation at the age of 50.[133]

Cholesterol and triglyceride concentrations in serum were analysed by enzymatic techniques (Instrumentation Laboratories) in a Monarch 2000 centrifugal analyser. HDL cholesterol was assessed and LDL cholesterol was calculated using Friedewald's formula.[134]

**Lifestyle factors**

BMI was calculated (kg/m²).[59] Height was measured to the nearest centimetre and weight to the nearest 0.1 kilogram. The participants were divided into BMI categories according to the definition by the WHO (underweight BMI <18.5 kg/m², normal weight BMI 18.5-24.9 kg/m², overweight BMI 25-29.9 kg/m² and adiposity BMI ≥30 kg/m²).[59]

WC was measured in the supine position midway between the lowest rib and the iliac crest.

Leisure time PA was classified using the same validated questionnaire[135, 136] as at the mean age of 50, and the participants were again categorised into the following four groups: sedentary, moderate, regularly and athletic.

Living situation was dichotomised as living with someone (spouse/cohabitant, children/grandchildren or other relatives) or not. This data came from the questionnaire.

Smoking was categorised as never, former or current smokers after an interview.

The Charlson Comorbidity Index (Supplementary Table 1) was calculated using data from the National Patient Registry, which provided information on in-patient care before baseline for the third investigation cycle. [140, 141] The unweighted score ranged from 0 to 17, depending on the presence of 17 different diseases.
Dietary pattern
Dietary habits were determined from a validated seven-day food record.[142] Participants with extreme values for reported energy intake were excluded (>4200 or <800 kcal/day). The MDS is based on the traditional Mediterranean diet, [71] but in this study it was modified according to corresponding food groups more often consumed in Sweden (mMDS).[106] When estimating fat quality, MUFAs were replaced by PUFAs because MUFAs and SFAs acids have similar food origins and therefore correlate in the Swedish diet. In addition, the intake of olive oil was very low in the present population. Nuts and seeds were excluded due to a low intake. Potatoes were added to cereals, as potatoes were the predominant source for carbohydrates. In summary, the mMDS took into account the intake of PUFAs/SFAs, vegetables and legumes, fruit, cereals and potatoes, fish, meat, dairy and alcohol (Supplementary Table 2). The medians for the intake of energy-adjusted food components in the current population were used as cut-offs for scoring. An intake on the favourable side of the median gave 1 point, an intake on the opposite side gave 0 points and the score range was 0-8 p. The adherence to mMDS was classified as low (≤2 p), medium (3-5 p) or high (≥6 p).

Exposures at a mean age of 87
Lifestyle factors
BMI was calculated (kg/m²) from weight and height measured by a research nurse.[59]

Leisure time PA was categorised as sedentary, moderate, regular or athletic using the same valid questionnaire as in previous investigation cycles.[135, 136]

Living situation was obtained from a questionnaire and categorised as living with someone (spouse/cohabitant, other relatives) or not.

Smokers included those who smoked at a mean age of 87, but also those who smoked at the fifth investigation cycle at a mean age of 82.

The Charlson Comorbidity Index (Supplementary Table 1) was calculated using data from the National Patient Registry, which provided information on in-patient care before baseline for the third investigation cycle.[140, 141] The unweighted score ranged from 0 to 17, depending on the presence of 17 different diseases.

Sarcopenia
Sarcopenia was defined using both the old and the updated definitions recommended by the EWGSOP.[79, 80] According to the old definition (EWGSOP1), sarcopenia was defined as SMI <7.26 kg/m² and GS ≤0.8 m/s and/or HGS <30 kg.[79] In the updated definition (EWGSOP2), probable sarcopenia was defined by low muscle strength, i.e. HGS <27 kg and/or CST > 15 seconds.[80] Low muscle strength together with
SMI <7.0 kg/m² confirmed the sarcopenia diagnosis, and severe sarcopenia was present if GS ≤0.8 m/s. Body composition, including total fat mass, was measured by dual energy X-ray absorptiometry (DXA) using a DPX Prodigy, Lunar corp., Madison, WI, USA. SMI was calculated by dividing the sum of the lean mass in the arms and legs by height squared (kg/m²). GS was assessed in 284 men using a 10-metre course. Participants were instructed to walk at a comfortable speed, and GS was derived from the middle 6 m. If needed, an assistive device was allowed. HGS was measured in 285 men using a Baseline® hydraulic hand dynamometer. Both hands were measured three times and the highest value was used. CST was assessed in 244 men. The participants were asked to rise five times from a seated position with arms folded across the chest, and the amount of time needed was measured.

Exposures at a mean age of 92

Lifestyle factors
Leisure time PA: sedentary, moderate, regular and athletic, was obtained by the same valid questionnaire as in previous investigation cycles.[135, 136]

Living status was obtained from a questionnaire and categorised as living with someone (spouse/cohabitant, other relatives) or not.

Concomitant common somatic disorders
The Uppsala University Hospital, the Primary Health Care Centres and nursing homes (including dementia nursing homes) in Uppsala County use the same electronic medical record system, in which information from all contacts with health care providers is stored. All data available in these records until January 1, 2015 were reviewed in order to identify the following selected disorders: stroke, atrial fibrillation (paroxysmal or persistent), myocardial infarction, congestive heart failure (as diagnosed by echocardiography), diabetes mellitus (treated with oral antidiabetic drugs or insulin), COPD (diagnosed by spirometry and/or treated with anticholinergic drugs), all cancer (excluding non-metastatic skin cancer), osteoarthritis in the hip or knee (diagnosed by radiology or treated by surgery) and hip fracture. The National Patient Registry provided information on in-patient care from 1964 until December 31, 2014 and contributed additional information in some of the cases. The International Statistical Classification of Diseases and Related Health Problems (ICD)[143] was used, after 1997 the tenth revision (ICD-10), and prior to that corresponding codes in the seventh to ninth revisions. Diagnoses recorded were the following: stroke (ICD-10 codes: I60-63), atrial fibrillation (ICD-10 codes: I48), myocardial infarction (ICD-10 codes: I21), congestive heart failure (ICD-10 codes), diabetes mellitus (ICD-10 codes: E10-11), COPD (ICD-10 codes: J44), cancer (ICD-10 codes: C00-C41, C45-75 and C81-96), osteoarthritis in the knee/hip (ICD-10 codes: M16-17) and hip fracture (ICD-10 codes: S72). The information from this registry was also used to calculate the
Charlson Comorbidity Index (Supplementary Table 1).[140, 141] The weighted score ranged from 0 to 33, depending on the presence of 17 different diseases with assigned values. Data were also obtained from the Swedish Prescribed Drug Registry with coding according to the Anatomical Therapeutic Chemical (ATC)[144] classification. Apart from the aforementioned sources, diabetes and COPD were considered present when antidiabetic drugs (ATC code A10) and anticholinergic drugs for COPD (ATC code R03BB) were prescribed. Information on present hearing and vision was recorded in the questionnaires at a mean age of 92. Moderately to severe impairment was categorised as impairment.

Outcomes

Survival at the age of 85
The National Swedish Death Registry provided survival data at the age of 85.

Independent ageing at a mean age of 87
A questionnaire including questions on living conditions, ADL (bathing, dressing, toileting) and the ability to walk outdoors (assistive device allowed) was used. A subgroup of men only participated in a telephone interview with a physician, where they were asked the most relevant questions from the questionnaire. The number of men who only answered the questionnaire or participated in a telephone interview was 119. Twelve participants did not consent to chart review, but for the others the medical records from Uppsala University Hospital, primary care and nursing homes in Uppsala County were reviewed for consistency with the self-reported information. The MMSE[37] was administered to 353 men by an experienced research nurse. Two experienced geriatricians independently using all available data in the medical records until April 1, 2009 assigned the diagnoses of dementia. In the case of disagreement, a third geriatrician reviewed the case and the majority decision determined the diagnosis. In brief, different dementia types were diagnosed according to specified criteria[41, 145-148]. When data was insufficient, cases were classified as unspecified dementia.

Independent ageing at a mean age of 92
A questionnaire including questions on ADL (bathing, dressing, toileting) and ability to walk outdoors (assistive device allowed) was answered by 142 men. The medical records from Uppsala University Hospital, primary care and nursing homes in Uppsala County were reviewed for consistency with the self-reported information and provided supplemental information on participants who had not answered the questionnaire. The Swedish Population Register
provided data on institutionalisation. An experienced research nurse adminis-
tered the MMSE to 119 men. Two geriatricians independently determined de-
mentia status according to best practice and pre-specified criteria using all data
available in the aforementioned medical records until January 1, 2015.[41,
145-148] The medical records of non-participants at follow-up, except for five
who did not previously consent to chart review, were also reviewed and this
made it possible to classify another 75 men, except in regard to performance
on the MMSE.

Statistical analyses
Continuous variables are presented as means and standard deviations and cat-
egorical variables as the number of individuals and percentages. In all four
studies, odds ratios (ORs) for independent versus not independent ageing were
analysed using logistic regression. In study I also survival versus non-survival
were analysed using logistic regression, while in study II Cox proportional
hazard was used to calculate hazard ratios (HRs). In Cox proportional hazard,
survival was censored at death or the date of the 85th anniversary. The propor-
tionality of the hazards was verified by examining log-log plots. Both ORs
and HRs are presented with 95 % confidence intervals (CIs). The results are
shown as ORs/HRs per one standard deviation in continuous variables. In or-
dinal variables, the results are shown per category compared with the other
categories in Paper I, and per category compared with a reference level in Pa-
pers II-IV.

The statistical software package JMP 10-14 for PC (SAS Corporation,
Cary, NC, USA) was used in the analyses.

Specific analyses
Paper I
In study I, the participants were dichotomised with respect to degree of PA.
High leisure time PA included regular and athletic PA, and low work-time PA
included sedentary and moderate PA. Variables included in the multivariable
model were chosen from the statistically significant relationships observed in
the univariable analyses with independent ageing as the outcome (BMI, smok-
ing status, educational level and work-time PA), and also including age at
baseline. In the multivariable analyses, never and former smokers were
grouped together, as well as men with medium and high educational level.

As smoking status had a strong association with independent ageing, sepa-
rate multivariable analyses were conducted for smokers and non-smokers.

From the 144 men still alive in Uppsala on April 1, 2009, not participating
in ULSAM-6 but consenting to a chart review, another 112 men could be cat-
egorised as independently aged or not after a review of their medical files.
These men were included in the extended population (n=584), together with the participants in ULSAM-6. The extended population was used to check for external validity in the analyses of independent ageing. Absence of data recorded in the medical files reflected that no hospitalisations or other medical care contacts had occurred, and it was assumed that this was more likely to indicate independent ageing than not independent ageing. Therefore, men who lacked data recorded in medical files (n=32) were considered and included as independently ageing in the extended population (n=616 after imputation).

**Paper II**

In study II we used the directed acyclic graph approach[149] to select suitable covariates for the multivariable model, and the adjusted model included age at baseline, education level, smoking status and dietary pattern (mMDS).

Analyses were performed that were stratified according to smoking (current, former, never) and BMI (normal, overweight, obesity) to further evaluate their confounding effects. Of the 108 men still alive in Uppsala April 1, 2009, not participating in the re-investigation but consenting to a chart review, it was possible to classify another 79 men as independently aged or not after a review of their medical files. The extended population (n=448), included these men and the participants, and was used to check for external validity. The analyses of survival were conducted also after exclusion of men who died within two years from baseline (n=18) to check for reverse causation.

**Paper III**

The covariates included in the multivariable model were age, smoking status, Charlson Comorbidity Index and total fat mass.

**Paper IV**

Separate analyses were conducted for participants with conditions diagnosed before January 1, 2005, between January 1, 2005 and January 1, 2015 and before January 1, 2015. Regarding stroke, myocardial infarction, osteoarthritis and hip fracture, more than one event was possible, but only the date of the first event was used in the analyses. In the logistic regressions, dementia was excluded from the Charlson Comorbidity Index, as dementia was one of the components of independent ageing. The analyses were adjusted for age and education. Sensitivity analyses were conducted in the subgroup (n=148) who participated in person in the re-investigation.

**Ethics**

The ULSAM has been ongoing since 1970 and there has been a development in the approach to dealing with research ethics during these almost 50 years, but all investigation cycles were conducted in accordance with the Declaration
of Helsinki.[150] All individuals who participated gave informed consent, but a small number of the participants did not consent to a chart review. The ethics committees at the medical faculties in Sweden were established during the 1970s, but application for an approval was not mandatory at first. At the third investigation cycle, the ULSAM was approved by the Ethics Committee of the medical faculty at Uppsala University (Dnr 251/90). Later, in 2004, the Swedish Act concerning the Ethical Review of Research Involving Humans went into effect. The later investigation cycles in the ULSAM were approved by the Regional Ethics Review Board at Uppsala University (Dnr 2007/338 and Dnr 2013/350).

In the ULSAM, participation may be seen as a benefit for the participants as treatment and follow-up was offered for cardiovascular risk factors; obesity, hypertension, diabetes mellitus, and hyperlipidemia at the policlinical department of Geriatrics over the whole period of the study. Furthermore, when tests indicated cognitive impairment, the participants were offered a visit to the Memory Clinic at Uppsala University Hospital for further assessment. Other types of diseases identified were referred to primary or specialist care as needed.
Results

Population characteristics

The baseline characteristics of the total ULSAM cohort (n=2,322) at baseline are described in Table 2. At that point, 51% of the cohort were smoking and 47% were overweight or obese. Forty-nine percent were physically active, engaging for at least three hours per week in sports or strenuous gardening.

<table>
<thead>
<tr>
<th>Participants in ULSAM-1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n=2,322</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>49.6 (0.6)</td>
</tr>
<tr>
<td>Educational level, n (%)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1,456 (63)</td>
</tr>
<tr>
<td>Medium</td>
<td>613 (26)</td>
</tr>
<tr>
<td>High</td>
<td>248 (11)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>585 (25)</td>
</tr>
<tr>
<td>Former</td>
<td>552 (24)</td>
</tr>
<tr>
<td>Current</td>
<td>1,185 (51)</td>
</tr>
<tr>
<td>Leisure-time physical activity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>325 (15)</td>
</tr>
<tr>
<td>Moderate</td>
<td>802 (36)</td>
</tr>
<tr>
<td>Regular</td>
<td>967 (44)</td>
</tr>
<tr>
<td>Athletic</td>
<td>111 (5)</td>
</tr>
<tr>
<td>Work-time physical activity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>782 (35)</td>
</tr>
<tr>
<td>Standing or walking</td>
<td>681 (31)</td>
</tr>
<tr>
<td>Heavy lifting</td>
<td>402 (18)</td>
</tr>
<tr>
<td>Hard</td>
<td>344 (16)</td>
</tr>
<tr>
<td>Married or living with someone, n (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,895 (85)</td>
</tr>
<tr>
<td>Body mass index classification, n (%)</td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt;18.5 kg/m²)</td>
<td>16 (0.7)</td>
</tr>
<tr>
<td>Normal weight (18.5-24.9 kg/m²)</td>
<td>1,213 (52)</td>
</tr>
<tr>
<td>Overweight (25-29.9 kg/m²)</td>
<td>939 (40)</td>
</tr>
<tr>
<td>Obesity (≥30 kg/m²)</td>
<td>154 (7)</td>
</tr>
</tbody>
</table>

SD = standard deviation
Table 3 presents the prevalence of the indicators of independent ageing in UL-SAM-6 and ULSAM-7. At a mean age of 87, 94% of the participants had no dementia, while at a mean age of 92 90% had no diagnosis of dementia.

<table>
<thead>
<tr>
<th>Participant in ULSAM-6 (mean age 87)</th>
<th>Participants in ULSAM-7 (mean age 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=472</td>
<td>n=148</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Independent Ageing</td>
<td>348 (74)</td>
</tr>
<tr>
<td>Community-dwelling</td>
<td>458 (97)</td>
</tr>
<tr>
<td>No assistance with personal carea</td>
<td>403/467 (86)</td>
</tr>
<tr>
<td>No assistance with outdoor walking</td>
<td>420/465 (90)</td>
</tr>
<tr>
<td>MMSE score ≥25 p</td>
<td>289/353 (82)</td>
</tr>
<tr>
<td>No dementia</td>
<td>444 (94)</td>
</tr>
<tr>
<td></td>
<td>94 (64)</td>
</tr>
<tr>
<td></td>
<td>131 (89)</td>
</tr>
<tr>
<td></td>
<td>117 (79)</td>
</tr>
<tr>
<td></td>
<td>119 (80)</td>
</tr>
<tr>
<td></td>
<td>97/119 (82)</td>
</tr>
<tr>
<td></td>
<td>133 (90)</td>
</tr>
</tbody>
</table>

Paper I. Predictors at a mean age of 50

Of the original cohort of 50-year-old men, 37% survived to the age of 85. Among the participants in ULSAM-6, 74% met the definition of independent ageing (Table 3).

Independent ageing

Non-smoking status in midlife predicted subsequent independent ageing. Normal weight was associated with the highest OR for the outcome with decreasing odds with increasing BMI category. In the subgroup of non-smokers, BMI was inversely related to independent ageing (OR =0.74, 95% CI 0.56-0.98) while the OR in the smoking group was 0.90 (95% CI 0.65-1.24). High education level, but not marital status or leisure time PA, was associated with independent ageing. Furthermore, low work-time PA was associated with preserved independency, although the association was attenuated after adjustment for education. No significant association was found between conventional cardiovascular risk factors and the outcome. High beta-carotene was associated with independent ageing, but the association was attenuated in the extended population. After adjustments in the multivariable analyses the associations with BMI and smoking status stayed robust while the associations with education level and work-time PA were attenuated.
Survival
Non-smoking at the age of 50 was associated with survival to the age of 85. The odds for survival were highest within the normal weight group and decreased with increasing BMI. Marriage and high education were associated with survival, while traditional cardiovascular risk factors were associated with mortality. High leisure time PA was associated with survival, also after adjustment for education, while the association with low work-time PA was attenuated. SFAs and MUFAs in serum cholesterol esters were inversely related to survival, while n-6 FAs and antioxidants were directly associated with the outcome. No association was found between n-3 FAs and survival. The associations with BMI, smoking and education remained after adjustments in the multivariable analyses.

Paper II. Predictors at a mean age of 71
Of the men who participated in ULSAM-3 at a mean age of 71 and included in this study, 57% survived to the age of 85. Of these, 369 men participated in ULSAM-6 at a mean age of 87, and 75% met the criteria for independent ageing.

Independent ageing
In the crude analyses, overweight or normal weight vs. obesity, as well as lower WC (vs. >102 cm), were associated with subsequent independent ageing. Also never smoking (vs. current) was associated with independent ageing. Within the group of cardiovascular risk factors, high HDL cholesterol and low glucose, insulin and HOMA-IR were associated with independent ageing. Increasing adherence to mMDS was associated with increasing odds for independent ageing. All these associations remained after adjustment for age, education, smoking status and dietary pattern. There was no relation between the outcome and living status, Charlson Comorbidity Index or leisure time PA. The results remained mainly unchanged in the extended population.

Within the group of smoking participants there was an association between MDS and independent ageing, which was not seen among former or never smokers.

Survival
Normal weight and overweight (vs. obesity) were associated with survival to the age of 85, as was WC <94 cm or 94-102 cm (vs. >102 cm). Furthermore, never or former smoking (vs. current) was associated with survival.
As expected, there were inverse associations between systolic BP, glucose, insulin, HOMA-IR and survival, while HDL cholesterol was directly associated with survival. High educational level, high level of leisure time PA and living with someone were also associated with survival, as well as high adherence to MDS and a low score on the Charlson Comorbidity Index. The associations with obesity, WC and education were attenuated after adjustments for age, educational level, smoking status and dietary pattern, while the other associations remained.

Separate analyses for the different BMI categories were conducted. Never smoking was associated with survival in all groups. High HDL cholesterol and leisure time PA were associated with survival within the overweight group only. In the subgroup of current smokers, but not former or never smokers, high adherence to MDS (vs. low) was directly associated with survival. The exclusion of participants who died within two years from baseline did not change the associations.

Paper III. Sarcopenia and independent ageing

In ULSAM-6, at a mean age of 87, it was possible to define 287 of the participants as sarcopenic or not. In this group, 21% had sarcopenia according to the EWGSOP1 definition.[79] With the updated EWGSOP2 definition, the prevalence of probable sarcopenia was 73%, while 20% had confirmed sarcopenia and 2% had severe sarcopenia.[80] Six percent displayed GS ≤0.8 m/s and 61% performed the CST in >15 s. Close to half (46%) had HGS below 30 kg and 28% below 27 kg. The prevalence of independent ageing was 83% at mean age 87 and 67% five years later.

In the cross-sectional analyses, severe sarcopenia was associated with loss of independent ageing and needing assistance with outdoor walking. No other sarcopenia category or SMI were associated with independent ageing or its single components. Higher GS and HGS were associated with independent ageing and no need of assistance with outdoor walking. Faster GS was also associated with MMSE ≥25 p and independency in personal care. Furthermore, higher CST was inversely associated with independent ageing.

In the longitudinal analyses, no associations were found between the different sarcopenia categories or SMI, and independent ageing or its single components. Faster GS was associated with maintained independent ageing and no need of assistance with personal care five years later, while higher HGS was associated with still being community-dwelling at a mean age of 92. Finally, no associations were found between CST and independent ageing or its single components.
Paper IV. Somatic disorders and independent ageing

At a mean age of 92 years, the prevalence of independent ageing was 53% in the main study population. The most common disorders were atrial fibrillation (34%) and hip and/or knee osteoarthritis (25%) (Table 4). In those responding to the questionnaire, 13% reported visual impairment and 35% hearing impairment.

Table 4. Prevalence of common disorders in the study population at mean age 92

<table>
<thead>
<tr>
<th>Disorder</th>
<th>n=223</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer, n (%)</td>
<td>26 (12)</td>
</tr>
<tr>
<td>Other cancer, n (%)</td>
<td>33 (15)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>38 (17)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>76 (34)</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>51 (23)</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>39 (17)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>26 (12)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n (%)</td>
<td>13 (6)</td>
</tr>
<tr>
<td>Osteoarthritis, n (%)</td>
<td>56 (25)</td>
</tr>
<tr>
<td>Hip fracture, n (%)</td>
<td>28 (13)</td>
</tr>
<tr>
<td>Visual impairment, self-reported, n (%)</td>
<td>19/145 (13)</td>
</tr>
<tr>
<td>Hearing impairment, self-reported, n (%)</td>
<td>50/144 (35)</td>
</tr>
</tbody>
</table>

Stroke was associated with a low OR for independent ageing, no matter when the stroke occurred. Hip fracture was also associated with loss of independency, but with wide CIs if the hip fracture took place more than 10 years before the classification of independent ageing. COPD was associated with non-independent ageing when all COPD patients diagnosed before January 1, 2015 were considered. Osteoarthritis diagnosed before 2005 was associated with not being independently aged. In contrast, a history of myocardial infarction was associated with independent ageing, but with wide CIs. There were no associations between atrial fibrillation, congestive heart failure or diabetes and the outcome, while a higher score on the Charlson Comorbidity Index was associated with non-independent ageing. Visual, but not hearing, impairment was associated with not being independently aged in the subgroup who answered the questionnaire.
General discussion

Independent ageing

The definition

Most operational definitions of healthy ageing and related terms include high physical and cognitive function,[16, 18] and these are functions that are strongly related to preserved independence in daily life. Loss of independence is associated with lower quality of life and increased need for care. Hence, from both a societal and an individual perspective a definition focusing on physical and cognitive function is appropriate.

The most well-known definition of the concept of successful ageing, introduced by Rowe and Kahn, required high physical and cognitive functioning, along with a low probability of disease and disease-related disability.[15] However, with increasing age the presence of disease is rather the norm than the exception,[99, 100] and it is therefore questionable to require absence of disease when defining healthy ageing in the oldest old. Furthermore, Tinetti et al. argued for “the end of the disease era”.[151] Their opinion was that clinical decisions should be based on the goals of each individual patient and treatment of modifiable risk factors, rather than the prevention, diagnosis and treatment of individual diseases. Moreover, how should the concept of ‘disease’ be defined? Twaddle defined disease as “physiological malfunction independent of subjective experience and social conventions”, while illness is a “subjectively interpreted undesirable state of health”.[152] Examples of diseases, usually not considered as illnesses by patients are hypertension, hyperlipidemia and diabetes since they not affect the individuals’ subjective experience of health if they are properly treated. In the WHO report on Ageing and Health it was highlighted that the presence of a disease says nothing about the impact it may have on the daily life.[5] Therefore, according to the WHO, absence of disease should not be used in the definition of healthy ageing. Furthermore, some researchers postulate that healthy ageing can be achieved, regardless of illness, as long as compensations are made for physiological deficits and limitations.[153] This strengthened our choice not to include absence of disease, other than dementia, in our definition of independent ageing. Rowe and Kahn also included engagement in life in their definition.[15] The need of subjective criteria has also been highlighted by researchers,[24] but neither
this nor engagement in life are included in our definition of independent ageing. Both these criteria are difficult to measure and evaluate, especially in individuals with cognitive impairment or dementia.

One of the conclusions of a review of lay person perspectives on successful ageing, was that it is necessary to incorporate criteria reflecting what older people themselves consider most important for their quality of life.[17] We believe our definition does that, at least partly. In a Dutch study of health values, the 85-year-old persons claimed that functional independence was preferred, rather than less morbidity.[3] Being able to live in one’s own home as long as possible was important for the nonagenarians in the Vitality 90+ study, and they did not mention absence of disease.[26]

Prevalence of independent ageing

In the ULSAM, the prevalence of independent ageing was 74% at a mean age of 87 and 64% at a mean age of 92, in those participating in the investigation cycles (Table 3). In two reviews, not only the type of construct vary, but also the number of constructs included, and because of this, the proportion of healthy agers varied widely between studies, from <1% to >90%.[16, 18]

In the TLSA (Table 1), all survivors were reinvestigated at the age of 80-83 years.[50] In this study, 56% had no depressive symptoms or impairment in physical and cognitive function. Adding the social support criteria in the TLSA only marginally reduced the prevalence of healthy ageing to 52%. In the CHS, 74% of the eligible subjects were reinvestigated at the mean age of 85.[45] Fifty-three percent of these participants displayed healthy ageing. The definition used was, in concordance with the ULSAM, based on cognitive tests and self-reported independency in ADL (Table 1). However, both these studies included men and women, in contrast to the ULSAM. In the HHP, which included men only, 27 percent of those surviving from midlife to the age of 85 were exceptional survivors.[52] However, the HHP study required the absence of some specific common diseases for the fulfilment of their definition, which might explain the lower figure compared to the ULSAM and the other aforementioned studies.

In the Finnish Vitality 90+ study, different definitions of healthy ageing were tested.[154] The definition most similar to the definition of independent ageing included independency in five activities (ADL and mobility), no dementia, and good vision and hearing. With this definition the prevalence of healthy ageing was 25% in men. In this study, all inhabitants aged 90 years or older and living in Tampere were invited, and the response rate was 79%. In the NonaSantfeliu study in Spain, all inhabitants aged 90 years or older in the specified region were contacted and 61% with a mean age of 93 years replied.[97] However, institutionalised individuals were excluded, and then 32% of the men fulfilled the definition of healthy ageing consisting of cognition, ADL and mobility.
In the Vitality 90+ study, all data, including dementia diagnosis, was self-reported.[154] In the other studies, cognitive function was measured, while ADL and mobility were self-reported.[45, 50, 52, 97]

Predictors of independent ageing

Among the most important findings of Paper I and II are the associations between smoking status and BMI earlier in life and subsequent independent ageing. Another important finding is the association between high adherence to a Mediterranean-like diet in late life and preserved independence 16 years later. Smoking, weight and diet are all well-known modifiable factors.

When comparing the present results with previous research we mainly refer to the studies presented in Table 1, including 11 longitudinal studies with ≥10 years of follow-up; an outcome measured beyond the age of 80 years, and with at least physical function included in the definition of the outcome.[42-50] Never or former smoking in midlife and never smoking in late life were associated with independent ageing in the present study and with similar positive outcomes in those of the aforementioned studies investigating this relationship.[42, 43, 46, 49, 50] These findings are in line with a recently published meta-analysis.[58]

In the ULSAM, as well as in the HHP study,[52] normal weight in midlife was associated with preserved physical and cognitive function, but the HHP study also required the absence of specified chronic diseases for the fulfilment of their definition of exceptional survival. No other study with baseline in midlife, and a similar outcome and follow-up when becoming an octogenarian was found. None of the studies with only physical and cognitive function included in the outcome analysed the association between BMI and their outcome.[45, 47, 50] However, in the CHS, higher weight was associated with a combined impairment in physical and cognitive functions.[45] In the present study, normal weight and overweight at a mean age of 71 did not differ in their association with independent ageing, while obesity was associated with loss of independence. Furthermore, a WC >102 cm was also associated with non-independent ageing but none of the other studies measured WC. In the Whitehall II study, men with WC ≥94 cm had a reduced chance of successful ageing 16 years later.[60] However, the study’s definition required the absence of disease and the participants had a mean age of 51 years at baseline. One explanation for the association might be that high BMI and WC are both associated with osteoarthritis, which may lead to physical impairment.[155] Another explanation is the association between obesity and ischaemic stroke, since stroke can affect both physical and cognitive functions.[156] Furthermore, this explanation is in line with the association between a previous stroke and loss of independency shown in Paper IV. The present results suggest that 70-year-old men should predominantly be advised to lose weight only if they have abdominal obesity, although more studies are needed to fully support this advice.
The conventional cardiovascular risk factors in midlife were not associated with our outcome in Paper I, which might be explained by the treatment of identified risk factors during the whole study period. In the HHP study with baseline at the age of 54 years, hypertension, high triglycerides and glucose were associated with usual survival (vs. exceptional).[52] However, as this study required the absence of diabetes and cardiovascular disease, it was not possible to determine if there were independent associations between these risk factors and functioning or not. In Paper II, low HOMA-IR, which reflects preserved insulin sensitivity, and high HDL cholesterol were both associated with independent ageing. One probable explanation of this association is the reduced risk for stroke. In the CHS study, hypertension was not associated with increased risk for combined cognitive and physical impairment,[45] while in the TLSA both hypertension and diabetes were associated with this combined impairment.[50]

There was no association between high leisure time PA defined as ≥180 minutes per week of sports or strenuous gardening and independent ageing in Papers I or II. On the other hand, low work-time PA was associated with subsequent independence, also after adjusting for education. Heavy lifting and physically demanding work in midlife may result in osteoarthritis in the knee and/or hip, which in turn can lead to impaired physical function. In the HHP study there was no association between physical activity, measured as metabolic work performed in a typical 24-hour day, and exceptional survival.[52] One explanation of the null-finding in the HHP study and in the ULSAM, may be that the positive effect of midlife PA diminishes during the very long follow-up. Physical activity was associated with a positive outcome in some of the previous studies with baseline in late life,[43, 44, 47, 50] but not all.[46, 48, 49] In the HIMS, ≥150 minutes per week of vigorous PA was associated with absence of depression, preserved cognition and ADLs 10-13 years later.[47] In the CHS, high PA was not associated with the combined impairment in cognitive and physical function.[45] Different ways to measure PA or the chosen reference categories may explain the divergent results. However, a meta-analysis identified 23 longitudinal studies examining the association between PA and healthy ageing.[64] Data pooled from the studies showed a positive association between PA and the different outcomes, regardless of definition and measurement.

Dietary biomarkers of FAs and antioxidants were measured in midlife in Paper I. Beta-carotene, but not alpha-tocopherol or selenium, was associated with independent ageing in the crude analysis. No other study of the effect of circulating antioxidants on a similar combined outcome has been found. Concerning cognitive function, a previous report from the ULSAM found no association between alpha-tocopherol and future risk of Alzheimer’s disease or all-type dementia.[157] In line with this finding, a review on nutrition and cognitive impairment found that most observational studies have reported no benefit for vitamin E or beta-carotene on cognitive function and that studies on the effect of selenium are rare.[158]
No association was found between circulating FAs and subsequent independent ageing in the ULSAM, while the CHS study found an association between the highest quintile level of circulating n-3 FAs (vs. the lowest quintile) at a mean age of 74 and functional ageing 23 years later.[53] Functional ageing was defined as preserved ability in ADL and cognition. The dietary habits were also determined from a food frequency questionnaire and the participants in the highest group of circulating n-3 FAs consumed 2.3 servings of fish per week, compared with 1.3 servings in the lowest group. Previous studies in the ULSAM found no association between n-3 FAs and stroke and dementia, respectively, and one explanation of the consistent null-findings in the ULSAM can be that there were only minor differences in fish intake between Swedish individuals at baseline.[159, 160]

The European SENECA study measured adherence to MDS but found no association between a high adherence at the age of 70-75 years and preserved independence in ADL 10 years later.[42] However, in the ULSAM a high adherence to mMDS at a mean age of 71 was associated with independent ageing. Furthermore, the beneficial effect was most pronounced in current smokers, suggesting that this dietary pattern may counteract some of the negative effects of smoking. There are other studies with shorter follow-ups or younger participants showing a positive relationship between Mediterranean-like diets and successful ageing.[73, 75] These studies include the absence of specified diseases in the definitions of the outcomes, which makes it difficult to compare with the present study. In a previous study in the ULSAM cohort there was no association between adherence to a Mediterranean-like diet at a mean age of 71 and Alzheimer’s disease or all-type dementia 12 years later.[161] However, the results indicated a protective effect of the Mediterranean-like diet on the risk of all-type cognitive impairment (dementia, MMSE <25 points or ≥3 points decline in MMSE during follow-up). In a review from 2016, six out of nine studies found an association between adherence to a Mediterranean-like diet and dementia.[162] One recently published meta-analysis showed an association between high adherence to a Mediterranean-like diet and a lower risk of stroke,[163] which is another possible explanation of the association between this dietary pattern and independent ageing in the present study. However, it should be noted that the dietary pattern in old Swedish men in the 1990s deviated from the original Mediterranean diet.[71, 131] As the cut-offs (see Supplementary Table 2) are based on the intake in the present population, high adherence to a Mediterranean-like diet in our population may be equivalent to a low adherence in another population, having a more Mediterranean-like dietary pattern.

Different pathophysiological mechanisms can at least partly explain the positive effect of high adherence to the Mediterranean-like diet. One review suggested that the lipid-lowering effect and protection against oxidative stress and inflammation were some of the explanations of the positive effect.[164]
This diet is rich in antioxidants from fruits, vegetables and nuts, thereby protecting against oxidative stress, which is involved in the pathogenesis of CVD and dementia. The diet also has an anti-inflammatory effect from olive oil and fatty fish, which are rich in n-3 FAs.

The influence of sarcopenia
In the ULSAM, severe sarcopenia according to EWGSOP2, but not probable or confirmed, was cross-sectionally associated with loss of independent ageing and needing assistance with outdoor walking.[80] However, severe sarcopenia was only present in 2% of the participants. Sarcopenia, as defined by the EWGSOP1 definition,[79] was not associated with independent ageing, or any of its single components. Only one study of the association between sarcopenia and an outcome similar to independent ageing was found. In this study, Tolea et al. showed a cross-sectional relationship between sarcopenia and a combined impairment in physical and cognitive functions.[94] However, their study population consisted of both genders and included younger participants, i.e. 40 years or older, which makes further comparison difficult.

In Taiwanese men with a mean age of 83, sarcopenia was cross-sectionally associated with MMSE <24 points,[165] while there was no association between sarcopenia and cognitive impairment in French women with a mean age of 81 years.[166] Furthermore, in a meta-analysis of cross-sectional studies, sarcopenia was associated with cognitive impairment.[92] No longitudinal study in octogenarians was found. However, in two studies, both with mean age 77 years, sarcopenia was associated with disability in ADL five years later,[167, 168] and this association was confirmed in a meta-analysis.[90] There was also an association with institutionalisation seven years later in one of the aforementioned studies.[168]

With the EWGSOP1 definition,[79] the prevalence of sarcopenia at mean age 87 was 21%, which actually is the same as in men within the Newcastle 85+ Study.[87] In Italian octogenarian men the prevalence was 17%,[169] while 13% of Belgian octogenarian men had sarcopenia.[86] These three studies also used the EWGSOP1 definition,[79] but measured muscle mass with BIA, and not DXA. With the EWGSOP2 definition,[80] the prevalence of confirmed sarcopenia was 20% in the ULSAM. To the knowledge of the authors, only two studies using the EWGSOP2 definition have, so far, been published.[88, 89] In both these studies the prevalence was below 10%, which is probably explained by the lower mean age in these populations.

SMI was not associated with independent ageing, or any of its components, in the present study. Tolea et al. measured muscle mass by BIA and did not find any cross-sectional association with combined physical and cognitive impairment.[94] In contrast, the MEDIS study reported that higher SMI was cross-sectionally associated with successful ageing in their cohort including both genders aged 65-100 years.[95] Furthermore, in this study the SMI was
equation-based and the successful index added together 10 components including education, PA and BMI. The heterogeneity regarding population, exposures and outcomes makes it difficult to compare the results. No longitudinal study with healthy ageing, or a similar outcome, was found. Previous studies with mean age ≥75 years have not shown any associations with cognitive impairment,[170] dementia[171] or mobility.[172] However, in the aforementioned Australian study, in men with a mean age of 77 years, low muscle mass was associated with ADL disability five years later and institutionalisation seven years later.[168]

Higher GS and HGS and less time to perform CST were cross-sectionally associated with independent ageing in the present study. Furthermore, GS was associated with the outcome also in the longitudinal analysis. Concerning GS and HGS, this is not surprising since they are well known markers of biological ageing.[173-175] However, studies on the oldest old with outcomes similar to ours are scarce.[48, 96] In the cross-sectional analysis of the Helsinki Business Men Study, GS, but not HGS, was independently associated with active and healthy ageing at a mean age of 83 years.[96] The criteria of the outcome were self-reported and included the absence of disease, functional and cognitive impairment, but also “feeling happy”. In the HHP, there was no significant association between GS and HGS at a mean age of 76 and healthy ageing at age 85 (see Table 1 for the definition of healthy ageing).[48] CST is one of three components measured in the Short Physical Performance Battery,[34] but studies on CST as an independent exposure are less common than studies on GS and HGS. To the best of our knowledge, there have so far been no studies exploring the relationship between CST and healthy ageing.

In the ULSAM, high GS was associated with MMSE ≥25 points at baseline, but not five years later. The cross-sectional finding is in line with previous reports,[166, 176, 177] but other reports have also shown longitudinal associations between higher GS and a lower risk of subsequent cognitive decline[175, 176] and dementia.[171][175] The null-finding in the ULSAM may be explained by loss to follow-up, i.e. men with incident cognitive impairment at baseline declined to repeat the MMSE at follow-up. HGS was not associated with cognitive function in the present study. Two different cross-sectional studies in old women showed opposite results concerning HGS and cognition.[166, 178] In the Leiden 85-plus Study, low HGS was cross-sectionally associated with lower MMSE score, and also predicted an accelerated decline in this score four years later.[179] This later finding is in line with a review of longitudinal studies.[174] In the 90+ Study, slower CST was cross-sectionally associated with dementia,[180] while no association was found between CST at baseline and dementia 2.6 years later.[181] Walking, but also chair rising, are complex actions that do more than just indicate strength, and are therefore more sensitive to cognitive impairment, but may also be negatively influenced by skeletomuscular disorders.
Not surprising, high GS was correlated with independency in walking outdoors at baseline. High GS was also associated with independency in ADL, both at baseline and five years later. This is in line with other longitudinal studies\[182, 183\] and one review\[184\]. Although previous reports\[179, 183, 184\] have also shown an association between high HGS and preserved ability in ADL, the present study did not support this. High HGS was associated with lower risk for institutionalisation five years later in the ULSAM cohort. This supports findings in an American population with six years of follow-up from a baseline mean age of 78 years\[183\]. However, in the American study, high GS was also associated with a lower risk of institutionalisation. One explanation of the null-finding concerning GS in our cohort may be the high mean GS (1.4 m/s) compared to other octogenarian populations. In one meta-analysis, normal GS for men aged 80-99 years was 0.97 m/s, when the acceleration and deceleration phase were excluded\[185\].

With ageing, muscle strength is lost more rapidly than muscle mass\[186\], and this can be one explanation for the association seen between muscle function, but not muscle mass, and independent ageing. In the present studies, muscle quantity is measured, but increased attention is now aimed at the role of muscle quality in sarcopenia\[80, 186\]. However, measuring muscle quality requires other techniques than DXA or BIA. For example, MRI or CT can assess fat infiltration in the muscle, i.e. the muscle architecture\[80\]. So far, these techniques are expensive, not easily accessible, and time-consuming.

The influence of somatic disorders

Based on our clinical experience in geriatric medicine, we hypothesised that some common age-related disorders, besides dementia, would be associated with loss of independent ageing. As expected, a previous stroke was associated with non-independent ageing, no matter when the stroke occurred. Stroke can affect both physical and cognitive functioning and may lead to institutionalisation. This finding is in line with the only two studies found, in nonagenarians, having a similar outcome\[97, 98\]. The prevalence of stroke was lower in the group with successful ageing (vs. unsuccessful) in a Singaporean study on community-dwelling nonagenarians\[98\]. Their definition of successful ageing included MMSE ≥21 points and preserved independence in ADL and mobility. Also in the NonaSantfeliu study on community-dwelling nonagenarians, stroke was more common in the group with unsuccessful ageing\[97\]. Their definition of successful ageing was also based on physical (ADL) and cognitive function. In none of these studies, was there any difference in the prevalence of diabetes, hypertension, hyperlipidemia or ischaemic heart disease between those with and without successful ageing. The study from Singapore also investigated the prevalence of atrial fibrillation, while the Spanish study investigated COPD and heart failure, but no differences in prevalence were found between successful and unsuccessful ageing. None of these studies
investigated the influence of hip fracture, cancer or osteoarthritis on successful ageing.

However, previous studies on nonagenarians have shown an association between hip fracture and subsequent impairment in ADL and mobility, respectively.[187, 188] In addition, a review of studies with at least three months of follow-up concluded that hip fracture is associated with immobility, dependency in ADL and higher risk of institutionalisation.[189] Our study adds the knowledge that the association between hip fracture and loss of independency was only significant for hip fractures occurring in the last 10 years, when stratifying for the time frame. This reflects the fact that hip fractures in the oldest old also are markers of frailty and sarcopenia.

Osteoarthritis diagnosed before 2005 was associated with a lower chance of being independently aged, while later diagnoses had an OR over one, although with wide CIs. One explanation may be the slow development of arthritis over decades.[190] Although the subject is in pain, ADL or mobility do not need to be seriously affected at earlier stages of the disease.

The positive trend between a previous myocardial infarction and independent ageing is somewhat unexpected. Possible explanations could be that the assessment and treatment of the cardiovascular risk factors after the infarction reduce the risk for future stroke. A myocardial infarction may also be a strong incentive to change lifestyle, in order to reduce the risk of new events. The same pattern was found for congestive heart failure diagnosed before 2005, and the same explanations as for myocardial infarction are possible.

Congestive heart failure [191-193] and COPD [192, 193] were less prevalent in ULSAM than in other studies in nonagenarians. One explanation might be our requirement for a heart failure diagnosis to be verified by echocardiography, and possible underdiagnoses of COPD in Sweden when compared to Spain and the USA.[192-194] The prevalence of stroke was lower in the CHS than in the ULSAM, the Vitality 90+ and the NonaSantfeliu study.[191-193] The prevalence of dementia were similar in the ULSAM (17%) and in men in the Vitality 90+ Study (18%).[191] In the later study, data was based exclusively on information from medical journals, and 91% of all nonagenarians in Tampere were traced. There are some other studies reporting higher prevalence of dementia in nonagenarian men, which most likely can be explained by the higher frequency of clinical examination, including MMSE, in these studies. [100, 195]

In Papers I and II, we showed that smoking, as well as overweight in midlife and obesity in late life were associated with loss of independency at a mean age of 87. These risk factors are also risk factors for the disorders that were associated with non-independent ageing, i.e. stroke, hip fracture, osteoarthritis and COPD. One exception is osteoarthritis, as some studies have indicated a protective role of smoking, at least for osteoarthritis in the knee.[196] This was confirmed in a meta-analysis of 38 observational studies.[197] One
speculation is that nicotine may have anti-inflammatory effects on chondrocytes.[198] However, overweight and obesity are associated with osteoarthritis in the knee,[155, 199] but the relationship with osteoarthritis in the hip is weaker.[155] A second exception is the decreased risk of hip fracture associated with a high BMI, where instead underweight is associated with an increased risk.[200] However, smoking increases the risk for hip fracture.[201] Furthermore, overweight, obesity and smoking are all associated with ischaemic stroke.[156, 202] Finally, smoking is a well-known risk factor for COPD.[203] However, the prevalence of smoking and obesity has undergone a major change during the last 40 years. At baseline, 51% of the participants in the ULSAM were current smokers and 7% had obesity (Table 2). In 2010, 13% of Swedish men in their fifties were current smokers while 13% had obesity.[8] Furthermore, in Paper II, we showed an association between high adherence to a Mediterranean-like diet and subsequent independent ageing. High adherence to a modified MDS was associated with lower risk of hip fracture in a previous study in Swedish men and women,[204] and this is supported by a meta-analysis.[205] Furthermore, a recent meta-analysis showed an association between adherence to a Mediterranean-like diet and a lower risk of both ischaemic and haemorrhagic stroke, and in both Mediterranean and non-Mediterranean populations.[163] No study of the longitudinal association between adherence to a Mediterranean dietary pattern and osteoarthritis or COPD has been found.

If decreased smoking, a normalised weight and high adherence to a Mediterranean-like diet could reduce the occurrence of these disorders, the prevalence of independent ageing could rise, even in nonagenarians.

Predictors of survival

Normal weight in midlife was associated with survival in Paper I, in line with the results from the HHP study.[52] This finding is also confirmed by a meta-analysis.[206] However, in Paper II, as well as in the PHS, there was no difference in survival between normal weight and overweight participants at later ages.[43] In a meta-analysis from 2013, the lowest mortality was found for overweight (vs. normal weight) at all ages.[110] A more recently published meta-analysis found the same relationship, but after analysing a subgroup of never smokers with no chronic disease and at least five years of follow-up the lowest mortality was within the BMI span of 20-24.9 kg/m².[206] There is a well-established J-shaped relationship between BMI and mortality, with higher mortality for both underweight and higher BMI, but the nadir of the curve shifts with age. In the aforementioned meta-analysis, the lowest mortality in participants aged 50-69 years was found for BMI 23 kg/m², while the nadir was at BMI 24 kg/m² for those aged 70-89 years in the restricted analysis.[206] In agreement with the J-shaped curve, obesity was associated with
mortality in the PHS,[43] and also in the crude model in ULSAM. In the meta-
alysis, obesity was also associated with mortality but the HRs were higher
at younger ages than older ages.[206] Furthermore, BMI <19 kg/m² was asso-
ciated with mortality in the HHP,[48] and also in ULSAM (>18.5 kg/m²) but
with wide CIs due to the small number. A WC of < 94 cm (vs. >102 cm) in
late life was associated with survival in our analyses. In a meta-analysis in 65-
to 74-year-olds the mortality was increased with higher WC, even across BMI
categories.[113] One explanation of this is the harmful effect of abdominal
adiposity.[111, 207]

Smoking was associated with mortality in the ULSAM, in line with other
longitudinal studies.[42, 43, 46, 48, 52, 101-103] One meta-analysis with par-
ticipants ≥60 years concludes that smoking remains a strong risk factor for
mortality also at high age, and that smoking cessation is beneficial at all
ages.[109]

Higher education was associated with survival in the ULSAM, and also in
the Framingham Heart Study.[101] However, in the HHP, education <12 years
(vs. ≥12 years) was not included in the final stepwise model.[48, 52] Educa-
tion can be used as a marker of the childhood social environment and thereby
adds a life-course perspective to the study. Work-time PA is another indicator
of socioeconomic position. We observed that only two men, out of all 246
participants with high education, had a high work-time PA at baseline. Low
work-time PA was associated with survival in the crude analysis, but the as-
sociation was lost after adjusting for education. In the Copenhagen City Heart
Study, high occupational PA was associated with mortality in men.[116] In
contrast, in the same cohort, high leisure time PA was associated with sur-

As expected, the ULSAM results in Paper I confirm the well-established
relationships between cardiovascular risk factors in midlife and mortality. Ex-
amples of other studies with baseline in midlife and a similar length of follow-
up are the Framingham Heart Study and the HHP.[52, 101] Also at a mean
age of 71, low systolic BP, high HDL cholesterol, low fasting glucose and low
HOMA-IR were associated with survival (Paper II). However, there were no
longer any associations observed between diastolic BP, total cholesterol or
triglycerides and survival. This may be due to the treatment of risk factors in
affected participants, but also different effects of risk factors at different ages
as shown in other longitudinal studies in this age group.[43, 48, 208] One previous report from the ULSAM showed that the impact of traditional risk factors on incident CVD generally declined with ageing.[209] As CVD is the leading cause of death worldwide, it is likely that the impact of the risk factors on mortality also declines in the same way.

In the crude analyses, high n-6 FAs in the serum cholesterol esters was associated with survival, while SFAs and MUFAs were inversely associated with survival. This has been shown previously in the ULSAM cohort, although with shorter follow-up.[104] This is also in line with other studies of the association between n-6 FAs and SFAs, respectively, and survival.[119, 210] The inverse association between MUFAs and survival needs to be further discussed. Olive oil, traditionally a major source of oleic oil which is the most important MUFA, is well known to reduce total mortality.[211] Until recently, the intake of olive oil in Sweden has been very low. In the seventies and thereafter MUFAs mainly came from animal sources, i.e. the same sources as for SFAs, which are well known to increase mortality. In line with this, a study from the US showed that a high intake of MUFAs from animal sources was associated with a higher mortality, while a high intake of plant-derived MUFAs was associated with lower mortality.[212] Also the null-finding concerning n-3 FAs contrasts with other studies showing n-3 FAs to be associated with survival.[120, 210] One explanation of the null-finding in the ULSAM, may be that fish intake was more evenly distributed among different groups in the Swedish population 50 years ago than today.

Alpha-tocopherol, beta-carotene and selenium were associated with survival in the crude analysis in Paper I. Concerning selenium, other reports,[121, 123, 127, 128] including a meta-analysis,[125] supports this finding. For beta-carotene, some studies find an association while others do not. One meta-analysis including nine studies concluded that a higher level of beta-carotene was associated with lower mortality.[125] One large study in Finnish smoking men found an association between high circulating alpha-tocopherol and lower mortality, but this was not reported in other studies.[121-124] The aforementioned meta-analysis reported an association between high alpha-tocopherol and survival, but after exclusion of the Finnish study the association was attenuated.[125] One plausible explanation of the association between high circulating levels of antioxidants and survival is the protective effect of antioxidants against oxidative stress. CVD is the most common cause of death worldwide, and oxidative stress is involved in the development of atherosclerosis, leading to CVD.[213]

One important finding in Paper II was that high adherence (6-8 vs. 0-2 points) to a Mediterranean-like diet at a mean age of 71 increased the HR for survival to the age of 85 by 38%. This has been shown before in ULSAM, but after a shorter follow-up.[106] In a European study, high adherence (≥4 vs <4 points) to the Mediterranean diet in a population aged 70-90 years was associated with lower mortality 10 years later.[214] Meta-analyses, one including
all ages and one only those aged ≥65 years, have confirmed this association.[130, 131] The meta-analysis including all ages also investigated the relationship between the different components of the Mediterranean diet and mortality.[130] A moderate alcohol consumption and an intake above the median of fruits and vegetables were associated with decreased mortality, while an intake of meat above the median increased mortality. The pathophysiological mechanisms of the Mediterranean-like diet discussed in relation to independent ageing are applicable to survival as well.

Epidemiological aspects

Two main issues in epidemiological studies are to what extent the effects detected are truly associated with the exposure in the population under study (internal validity), and whether the findings can be generalized in other populations (external validity).

Biases and confounding are two threats against the internal validity in all studies. One explanation of the relatively low prevalence of for example dementia and COPD in the ULSAM cohort may be selection bias; i.e. the skewing of the study population towards a healthier population than the background population. This is in line with that participants in health surveys, in general, are healthier than non-participants, which most likely is the case also for the ULSAM. Survivors to this high age are a selected group, and those showing up for participation in person are even more selected. To deal with this, a chart review was conducted concerning the non-participants who had consented to this. At a mean age of 87 and 92 years, it was possible to characterise 78% and 77%, respectively, of those not participating in the investigation cycles as independently aged or not. Only 9% and 32%, respectively, were independently aged in these groups. However, this type of selection bias might lead to underestimation, rather than overestimation, of the associations observed. In addition, reporting bias of exposures might have been introduced since PA, smoking and the dietary intake in the seven-day food record were self-reported. However, the seven-day food record provides information that is more detailed compared with a food frequency questionnaire. In Paper I, biomarkers of the dietary intake of FAs and antioxidants were measured, which excludes the risk for reporting bias concerning diet. There might be a possibility of misclassification at follow-up since some of the criteria for independent ageing were self-reported. An attempt was made to minimise this bias in all four studies by reviewing the medical records for consistency with the self-reported information. Furthermore, participants who lacked information on MMSE might have been wrongly classified as independently aged.

Concerning confounding, all the studies included in this thesis were adjusted for age, although the age range among participants was narrow. Educational level, which we adjusted for in Paper I, II and IV, was used as a proxy
for SEP. In Paper I, some of the other variables included in the multivariable analyses might be seen as intermediates and not confounders, and these adjustments might thereby have introduced bias leading to underestimation of the associations. To further analyse the confounding effect of BMI and smoking, stratified analyses were performed according to smoking in Paper I, and both smoking and BMI in Paper II. Finally, although the associations were adjusted in different ways, residual confounding may still occur.

Regarding external validity, all the ULSAM participants were offered treatment of cardiovascular risk factors over the whole time period of the study. Non-beneficial associations might therefore be weaker in participants than in the general population. Finally, this cohort consisted of men of similar age and ethnic background, and it is therefore possible to exclude age, gender and ethnicity as confounders, but of course, the results may be inferred as possibly less relevant for females, other age groups or ethnicities.

Strengths and limitations

The major strength of the studies included in this thesis is the use of the well characterised population-based cohort of men followed since 1970, i.e. for almost 50 years. The follow-up periods in Papers I and II are 37 and 16 years, respectively, which reduces the risk of reverse causation. This risk was further reduced by the exclusion of participants who died within two years from baseline in Papers I and II. Concerning survival data, only 0.5% of the original cohort was lost to follow-up, which is another strength.

In Papers I and II, we could not define independent ageing at baseline using the same criteria as those used at follow-up. Thus, men with non-independent ageing already at baseline might therefore have been included in the analyses of independent ageing. Longitudinal data on smoking, PA, BMI and diet were not used during the long follow-up in Papers I and II and this is another potential limitation of these studies. A further issue is that chance associations may not be fully excluded because of the many analyses performed in Papers I and II.

One major strength of Paper IV is the use of information from both medical records and the nationwide registries to track the occurrence of the different disorders. This has been shown to be more reliable than using self-reported information on morbidity in the oldest old.[215] However, the prevalence of some of the disorders, including dementia, might have been higher if we had clinically examined all the participants. Our criteria may have been too strict, such as the requirement for spirometry to diagnose COPD. According to our clinical experience, this investigation is not very often conducted in the frailest old. Another strength of Paper IV is that we were able to stratify for time since diagnosis, which adds information about the long- and short-term effects of different disorders.
Future perspectives

Several research questions remain to be penetrated concerning independent ageing in the ULSAM. Smoking and high BMI at a mean age of 50 and 71 years were longitudinally associated with loss of independent ageing at a mean age of 87 years. However, changes in these risk factors during the long follow-up were not taken into consideration in the present studies. Doing this would further increase understanding of the role of smoking and BMI in ageing.

Paper IV showed associations between loss of independent ageing and both a previous hip fracture and stroke. In total, 13% of the men who were followed up at a mean age of 92 years had a history of hip fracture, but only 14% of these men had ever been on anti-resorptive treatment for osteoporosis. From our clinical experience, we believe this is due to underdiagnoses of osteoporosis, but further review of the medical records is needed to confirm this hypothesis. Furthermore, 14% had a history of ischaemic stroke when reaching a mean age of 92, and 63% of these men had atrial fibrillation in their medical history. Whether anticoagulants were used in a proper way in this group was outside the scope of this study to investigate. In a previous Swedish study, the benefits of secondary prevention with anticoagulants were not offset by haemorrhagic complications, not even in nonagenarians, so it would be interesting to study this further in the ULSAM.[216] Data from the Swedish Stroke Register shows that the incidence of stroke is decreasing, and one explanation is the increasing proportion of patients receiving secondary prevention with oral anticoagulants after both TIA and stroke, especially in patients 80 years or older.[217] In 2017, almost two thirds of those being prescribed oral anticoagulants at discharge got the novel anticoagulants.

Finally, on March 1, 2019, 79 of the participants in the ULSAM were still alive. In 2020, the oldest and still living participants will become centenarians and we plan for a new investigation cycle then. It remains to be seen how many of the participants will still be alive and with independent ageing.
Conclusions

- Non-smoking in midlife (at a mean age of 50 years) and never smoking in late life (at a mean age of 71 years) were associated with independent ageing at a mean age of 87 years.

- Normal weight in midlife and not being obese in late life were associated with independent ageing at a mean age of 87.

- A high adherence to a Mediterranean-like diet in late life was associated with independent ageing 16 years later.

- High leisure time physical activity in midlife and late life was associated with survival, but not with independent ageing.

- Higher gait speed and handgrip strength and a faster chair stand test at a mean age of 87 were cross-sectionally associated with independent ageing. Higher gait speed was also associated with independent ageing five years later. However, muscle mass and sarcopenia were not associated with the outcome.

- A history of stroke, osteoarthritis, hip fracture and chronic obstructive pulmonary disease were associated with loss of independent ageing at a mean age of 92, while no associations were seen between heart disease, diabetes or cancer and the outcome.

Smoking, weight and diet are all modifiable lifestyle factors. The prevalence of smoking and obesity has undergone a major change during the last 40 years, with a decreased prevalence of smoking and increased prevalence of obesity. Smoking and obesity are associated to different degrees with diseases, such as stroke and hip fracture, which in turn are associated with loss of independency and mortality. Reducing the obesity epidemic in midlife will not only increase survival, but may also increase the prevalence of independent ageing, an important goal for the ageing population. Additionally, a Mediterranean-like diet consisting of a high intake of fruits and vegetables, fish, cereals and polyunsaturated fatty acids may contribute to both survival and independent ageing.
Andelen äldre i befolkningen ökar över hela världen, och antalet personer som är 80 år eller äldre förväntas ha tredubblats år 2050. Prediktorer för överlevnad är välkända, men mindre är känt om hur man når hög ålder med bevarad fysisk och kognitiv funktion. Dessa funktioner är dock avgörande för att man ska kunna vara oberoende i det dagliga livet, vilket värderas högt av de allra äldsta enligt tidigare studier.

Det övergripande syftet med den här avhandlingen var att undersöka faktorer som kan påverka möjligheten att åldras med bevarad självständighet, vilket definierades som oberoende vid toalettbesök, påklädning och dusch, förmåga att promenera utomhus på egen hand, eget boende, god kognitiv förmåga enligt testning samt avsaknad av demensdiagnos.


Trettiosju procent av den ursprungliga kohorten överlevde till 85 års ålder. Vid en medelålder av 87 år var 74 procent av deltagarna åldrade med bevarad självständighet, medan 64 procent var det vid uppföljningen fem år senare.

I det första delarbetet var rökfrihet och normalvikt vid 50 års ålder associerat med bevarad självständighet vid 87 års ålder. I delarbete två såg vi att aldrig ha rökt, att inte lida av fetma samt hög följsamhet till ett medelhavsliknande kostmönster vid 71 års ålder var associerat med åldrande med bevarad självständighet vid 87 års ålder. Det medelhavsliknande kostmönstret karakteriseras av ett stort intag av fleromättat fett, fisk, frukt, grönsaker, spannmål och potatis och mindre kött och mejeriprodukter. I båda dessa studier var hög fysisk aktivitet på fritiden associerat med överlevnad, men inte med åldrande med bevarad självständighet.

I det tredje delarbetet undersökte vi sambandet mellan sarkopeni och åldrande med bevarad självständighet. Med sarkopeni menas den åldersrelaterade förlusten av muskels massa och muskelfunktion, vilken i tidigare studier är kopplad till bland annat ökad risk för fall, sjukhusvård och högre mortalitet. I

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Mum and Dad, I have never felt any demands from you, only support, and I thank you for that!

Svante, Edvin and Ida, you are my everything! Now I᾽m back! ♥
Supplementary Table 1. *Charlson Comorbidity Index*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Unweighted score</th>
<th>Weighted score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dementia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes without chronic complications</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes with chronic complications</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hemiplegia or paraplegia</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Any malignancy except skin</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Metastatic solid tumor</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>AIDS/HIV</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td><strong>0-17</strong></td>
<td><strong>0-33</strong></td>
</tr>
</tbody>
</table>
Supplementary Table 2. *Composition of the modified Mediterranean Diet Score*

<table>
<thead>
<tr>
<th>Cut-offs</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUFAs:SFAs ratio</td>
<td>&gt;Median</td>
</tr>
<tr>
<td>Vegetables and legumes</td>
<td>&gt;Median</td>
</tr>
<tr>
<td>Fruits</td>
<td>&gt;Median</td>
</tr>
<tr>
<td>Cereals and potatoes</td>
<td>&gt;Median</td>
</tr>
<tr>
<td>Fish</td>
<td>&gt;Median</td>
</tr>
<tr>
<td>Meat and meat products</td>
<td>&lt;Median</td>
</tr>
<tr>
<td>Milk and dairy products</td>
<td>&lt;Median</td>
</tr>
<tr>
<td>Alcohol</td>
<td>10-50 g/day and AST/ALT &lt;2</td>
</tr>
</tbody>
</table>

**Range** 0-8

PUFA = polyunsaturated fatty acids, SFA = saturated fatty acids, AST = aspartate aminotransferase, ALT = alanine aminotransferase
References


60. Singh-Manoux A, Sabia S, Bouillon K et al: Association of body mass index and waist circumference with successful aging. Obesity (Silver Spring) 2013.


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