Age, modifiable risk factors, and mortality.

A 42 years prospective follow-up study in a general population.

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Contents

Norsk sammendrag

Risikoforebygging er en viktig del av alt helsearbeid, men det meste av evidens med hensyn på forebyggende helsearbeid er fremkommet ved studier utført på middelaldrende befolkningsgrupper med ulik ekstern validitet, med variabel oppfølgingstid, og med overvekt av menn. Modifiserbare risikofaktorer har potensielt ulik innvirkning i ulike aldersgrupper, i ulike faser av en lengre oppfølgingstid og med hensyn på forskjellige endepunkter (dødelighet: total og årsaksspesifikk).

Målsetning: å studere forskjeller og likheter i effekten av livsstilsrelaterte risikofaktorer (særlig kroppsmasseindeks, fysisk aktivitet og lungefunksjon) på total dødelighet og årsaksspesifikk dødelighet som følge av hjerneslag og koronar hjertesykdom i ulike aldersgrupper av menn og kvinner i en generell norsk befolkning med 42 års oppfølgingstid.

Materiale og metode: 6811 tilfeldig utvalgte menn og kvinner i alderen 20-79 og bosatt i Bergen i 1964 ble invitert til en utvidet helseundersøkelse etter Blodtrykksundersøkelsene. 5653 personer møtte frem til undersøkelsen der 208 kliniske og selvrapporterte variabler ble registrert. Datamaterialet ble koblet mot Levekårsundersøkelsene i 1970-80-90 og 2000, Dødsårsaksregisteret (2005) og Folkeregisteret (2007). Cox-regresjon ble brukt for å studere sammenhengen mellom utvalgte variabler og dødelighet.

Resultater: Kroppsmasseindeks er assosiert til overdødelighet i yngre aldersgrupper, men er tilsynelatende inverst assosiert til dødelighet i eldre aldersgrupper, selv etter justering for multiple variabler og i subgruppeanalyser av de friskeste i utvalget. Fysisk aktivitet er minst like sterkt assosiert til overlevelse blant de eldre som i de yngre aldersgruppene, i motsetning til de fleste andre kjente risikofaktorer som har avtakende styrke i sin assosiasjon til død med økende alder. Lungefunksjon er inverst assosiert til risiko for dødelig hjerneslag. Validiteten av hjerneslag og koronar hjertesykdom registret som tilgrunnliggende dødsårsak i Dødsårsaksregisteret i perioden 1965-2005 er tilfredsstillende for bruk i epidemiologisk forskningsarbeid.

Konklusjon: Livsstil har implikasjoner for overlevelse i alle aldersgrupper. Fysisk aktivitet, kroppsmasseindeks og lungefunksjon er viktige livsstilsrelaterte prediktorer for god helse og økt overlevelse også blant gamle.

Abbreviations

ADL	activities of daily living
BCBPS	Bergen Clinical Blood Pressure Survey
BMI	body mass index
BP	blood pressure
BTPS	body temperature and pressure saturated conditions
CHD	coronary heart disease
CI	confidence interval
Cig/day	number of cigarettes consumed per day
COPD:	chronic obstructive pulmonary disease (defined as $FEV_1/FVC<0.7$)
CVD	cardiovascular disease
Eurocodes	65 different groups of ICD-codes on causes of death which are used in the European official mortality statistics
FEV_1	Forced expiratory volume in one second (L)
FEV_1%	Forced expiratory volume in one second as % of a predicted value
FVC	Forced vital capacity (L)
FVC%	Forced vital capacity as a percentage of a predicted value
HR	(Cox proportional) hazard ratio
ICD	International Classification of Diseases
IHD	Ischemic heart disease
LML plot	log minus log plot
LPA	leisure-time physical activity
M-code	morphological code
mmHg	millimeters of mercury
N	number of cases
OPA	occupational physical activity
OR	odds ratio
PA	physical activity
PAF	population attributable fraction
PPV	positive predictive value
RR	relative risk
SD	standard deviation
SNOMED	Systematic Nomenclature of Medicine (pathology-coding system)
SPSS	Statistical Package of Social Science
T-code	topographical code
WHO	world health organization
WC	waist circumference
WHR	waist/hip ratio

List of Papers

1. Gulsvik AK, Gulsvik A, Svendsen E et al. Diagnostic Validity of Fatal Cerebral Strokes and Coronary Deaths in Mortality Statistics: An Autopsy Study. Eur J Epidemiol 2011;26:221-8.
2. Gulsvik AK, Thelle DS, Mowe M, et al. Increased mortality in the slim elderly. A 42 year follow-up study in a general population. Eur J Epidemiol 2009;24:683-90.
3. Gulsvik AK, Myrstad M, Skovlund E, Thelle DS, Mowè M, Wyller TB; Ageing, physical activity and mortality – a 42 year follow-up study. In Press, Int J Epidemiol 2011.
4. Gulsvik AK, Gulsvik A, Thelle DS, Mowe,M, Humerfelt,S, Samuelsen s.o., Wyller TB; The association between lung function and fatal stroke in a community followed for four decades. Submitted to J Epidemiol Community Health, June 2011.

1 Introduction

1.1 Successful ageing

Resiliency and longevity are the opposites of frailty and mortality. When searching the literature for the word "ageing" these two more favorable words is much less used than their unfavorable counterparts. Ageing is a process of age-related cumulative declines across multiple physiologic systems, eventually leading to frailty with impaired homeostatic reserve and a reduced capacity of the organism to resist stress and functional decline. Biological age can be assessed using a profile of physical measurements and FEV_1 has been suggested as an important biomarker of ageing [11;23]. Frailty is a clinical syndrome associated with ageing and it includes unintentional weight loss and low physical performance and activity [56;213]. Interventions to try to delay the ageing processes imply that we can assess the individuals at risk. Studies assessing risk factors of functional decline define the outcome as a threshold decrease in activities of daily living (ADL), an evolving need for institutionalization or as mortality (definitively not functioning at all) [116]. The risk factors, causes and cofactors form a complex array and hence frail individuals at risk of functional decline benefit from the interdisciplinary management and treatment in geriatric units when hospitalized [16;157].

1.2 Modifiable risk factors of mortality

Risk factors or predictors of premature mortality may be fixed or modifiable. Prevention strategies focus mainly on modifiable factors but fixed predictors such as age and sex may be useful in guidance about whom and when to treat. Under the common (but rarely tested) assumption that the relative benefits of intervention are the same for different patients groups, greater absolute benefits may be expected for patients with higher underlying risk of disease. The balance of benefits and side effects may thus depend on the level of fixed risk factors. Risk evaluation strategies have so far mostly been based on data obtained from middle-aged populations, and aiming to prevent ischemic heart disease. As an example The British Regional Heart Study have reported that modifiable lifestyles (smoking, physical activity and BMI) in middle aged men play an important role in long-term survival free of

ischemic heart disease, stroke and diabetes[200]. Modifiable risk factors also play an important role in the life expectancy in the elderly[19]. The relative importance of the different risk factors may, however, vary between age strata, and most traditional risk factors have declining effect with increasing age[19;129;186]. In a public health aspect, with growing numbers of elderly and very old inhabitants, primary prevention strategies tailored for the elderly are increasingly important.

It has been suggested that 90 % of all health issues are due to general living conditions and individual life-style[2]. Risk factors associated with an unhealthy life-style are potentially modifiable without pharmacological intervention and a healthy life-style has to my knowledge no unwanted side-effects or interactions in any age-range or subgroups of the population. The long-term effects of life-style interventions are nevertheless difficult if not impossible to study in randomized controlled trials and the evidence is largely based on prospective cohort studies. Routinely interventions in people at risk are considered less applicable and are still uncommon compared to pharmaceutical therapies – especially in the elderly.

1.2.1 Body mass

Worldwide, obesity and overweight are steadily increasing in all age segments. The World Health Organization (WHO) categorizes body mass index (BMI; the body weight in kilograms divided by body height in meters squared) in four main categories: underweight (BMI<18.5 kg/m^2), normal weight (BMI 18.5-25 kg/m^2), overweight (BMI 25-30 kg/m^2) and obesity (BMI 30+ kg/m^2) [209]. The current knowledge of the relationship between BMI and mortality began with the life insurance studies in USA developing from the 1950es [87;205]. In Norway some of the first international publications on this topic were due to Westlund et al in 1972[203] and Waaler et al in 1984[196]. The influence of BMI upon total mortality is significant and well documented in the obese segment of the population for all age groups [117]. Overweight has also been found to be a considerable risk factor in young adult men in a recent publication [127]. In the younger age groups, a low BMI is usually associated with an increased survival after adjusting for smoking habits, but a few studies report an increased mortality among thin individuals even in the lower part of the acceptable BMI-range (20-25 kg/m^2) [146]. Below the BMI-range 22.5-25 kg/m^2, the overall inverse association with BMI is predominantly due to strong inverse associations for smoking-

related respiratory disease (including cancer), but the excess mortality in the lower BMI-range is not fully explained [142].

In the older age segments, the association between body mass and mortality is even less conclusive [37;77;184;214]. The relative risk of death associated with a high BMI seems to diminish with increasing age [178], and in the older age groups the highest mortality has sometimes been reported in the lower BMI segments [36;39]. Longitudinal studies are not free of bias. Preclinical disease as well as other factors affecting both body mass and mortality prior to base-line examination may confound the associations. Unrecognized preclinical disease causing underweight is one likely reason for this observation, as the leanest elderly have a high fatality rate in the hospital wards [124;125]. Another plausible contributory factor is a survival bias in cohort studies, implying that obese individuals that do not die young carry an extraordinary degree of biological robustness. The possible inverse relationship between BMI and mortality in the elderly remains unexplained. An overview of the literature on the association between body mass index in different age-ranges and mortality from all causes, published in the past 20 years, is presented in Table L-1 (Nordic countries) and Table L-2 (non-Nordic countries) in the Literature tables section. As we can see from Table L-1 and L-2 the study populations, follow-up period, categorization of the independent variable, adjustments, and conclusions varies between the different studies.

1.2.2 Physical activity

When centenarians and other long-lived individuals are studied, their longevity is often attributed to a healthy lifestyle. Three characteristic behaviors are routinely reported; these include exercising regularly, maintaining a social network, and maintaining a positive mental attitude. Regular physical activity seems to be the only lifestyle behavior identified to date, other than perhaps caloric restriction, which can favorably influence a broad range of physiological systems and chronic disease risk factors, and an active lifestyle may delay onset of dementia [54]. Despite large differences in genetic background among those of a given age cohort, it seems that physical activity may be a lifestyle factor that discriminates between individuals who have and have not experienced successful aging [30].

Sedentary living [135] has assumed epidemic proportions in the industrialized world and physical activity (PA) is one of the most important modifiable factors that determine the risk of chronic morbidity and high mortality in the population in general. The beneficial effect of PA on longevity and the disease-specific risks such as ischemic heart disease (IHD), stroke

and cancer has been studied since the 1950s in the adult and middle-aged segments of the population, and to a lesser extent in the old [21;98;123;132]. For older adults, evidence indicates that being physically active is associated with increased longevity, higher levels of functional health, a lower risk of falling, better cognitive functioning, and increased social integration [30]. Men have been studied more extensively than women, younger age-ranges more than older ones, and external validity, follow-up time and response rates vary greatly in earlier research work [25;134]. We are only aware of one previous population-based study which includes all adult age groups of both genders and with a follow-up period of more than 20 years [93]. A major question regarding this amendable risk factor is to what extent PA has an effect on longevity above and beyond the recognized mediators of blood pressure, blood lipids and body mass, and whether this effect is valid for both genders and all age groups.

The inverse association between physical activity and all-cause mortality has previously been reported to be similar in magnitude to the effect of hypertension, hypercholesterolemia and smoking alone [141;174], but the relative importance of the different risk factors may, however, vary between the age strata [19;129;186]. An overview of the literature on the association between physical activity in different age-ranges and mortality from all causes, published in the past 20 years, is presented in Table L-3 (Nordic countries) and Table L-4 (non-Nordic countries) in the Literature tables section. As we can see from Table L-3 and L-4 the study populations, follow-up period, assessment and categorization of physical activity, adjustments, and conclusions varies between the different studies.

1.2.3 Lung function

Lower lung function is one of many predictors of frailty and mortality. The associations between lower lung function, respiratory symptoms, and stroke are still under discussion [32;57]. The relationship between lower lung function and risk of stroke has previously been reported for both stroke incidence and stroke mortality [73;198], and the association is independent of other risk factors including smoking [83]. Asthma has been related to stroke and macrovascular disease. [130;159] Some of the previous studies in this field were not population based and included men only [180;198]. The largest population based study reported a response rate of 78% [82]. None of the studies published so far have been able to study the robustness of the association after more than 20 years of follow up, and all previous studies on this inverse relationship are based on one baseline measure of lung function only [40;170].

The robust inverse relationship between lung function and vascular events may be due to a common, unrecognized, offending factor (fetal or lifetime exposure) that affect both FEV_1 and the vascular system, or it may be due to a causally linked process [170]. If the risk of stroke were more strongly related to the rate of declining lung function than with the baseline lung function levels, this would suggest that the responsible mechanisms are mainly operating in adult life [40]. An overview of the literature on the association between lung function and cerebral stroke published in the past 20 years is presented in Table L-5 in the Literature tables section. As we can see from Table L-5 the study populations, handling of the independent variable (FEV), adjustments, validity of the endpoint (stroke), and conclusions varies between the different studies.

1.3 Mortality and cause of death

The specific cause of death reported in mortality statistics is a common endpoint in epidemiological studies and it is generally used as a surrogate marker of morbidity of diseases with serious outcome. Different causes of death may have different associations to the risk factors of interest. Ischemic heart disease and cerebral stroke are two major causes of death in the industrialized parts of world (including Norway) according to mortality statistics [210;211]. Both the disability and mortality attributable to vascular disease in ageing populations highlight the need to identify factors related to etiology and prevention.
Despite the decreasing autopsy rates, post mortem examination is still regarded as the most accurate means of determining the cause of death [143;151].
Previous studies on the validity of cerebrovascular mortality rates (based on death certificates issued by physicians) against autopsy findings have concluded, contradictorily, both that validity are unacceptable [176] and that the overall validity is largely reliable [192]. During the last two decades, as diagnostic technology and procedures have continued to improve, only a limited number of studies have been published validating mortality statistics on stroke or ischemic heart disease against autopsy findings [104;153;172]. These studies were based on cohorts selected for post-mortem examinations, and thus not able to address external validity. In Norway, the official department known as Statistics Norway compiles information on time and cause of death for all deceased inhabitants. The mortality statistics regarding stroke and ischemic heart disease in Norway have not been validated against autopsy findings since 1977 [192]. An overview of the limited available literature regarding the

correlation between diagnoses on death certificates or mortality statistics and autopsy data is presented in Table L-6 in the Literature tables section.

2 Aim of the study

We wanted to study the associations between markers of ageing and mortality and the modifying effect of age upon some of these associations. We did this by:

1. Validating the cause of death recorded as fatal stroke or coronary death in the official Norwegian mortality statistics by comparing them to autopsy records.
2. Exploring the association between BMI and all-cause mortality in different age-segments, while minimizing possible confounding from known clinical risk factors, smoking or bias from sub clinical disease ("reverse causation").
3. Exploring the association between physical activity and all-cause mortality, fatal stroke and coronary death in different age-segments and compare it to other established risk factors.
4. Studying the independent association between baseline lung function and the risk of fatal stroke as well as that of longitudinal changes in lung function upon the risk of fatal stroke in a general Norwegian adult population.

3 Material

The source population of this study was all men and women living within the old city borders of Bergen, Norway by Januray 1 1964, and who were born between January 1 1894 and December 31 1943. The total population in this age-range was 77694 residents.

3.1 Bergen Clinical Blood Pressure Survey

The number three was drawn from a hat defining a sample of the target population born on the 3rd, 13th or 23rd of each month, and invited to an extensive clinical investigation. 6811 individuals were invited (3104 men and 3708 women) and they were followed until 2005-7. The cohort and the original study protocol have been described in detail previously [68].

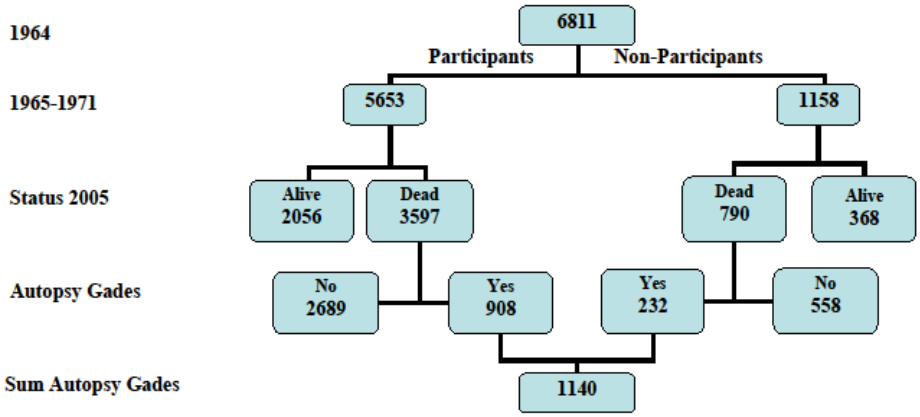

Figure 1. Flow chart of a random sample of the 6811 subjects from the population of Bergen, Norway, invited to the Bergen Clinical Blood Pressure Survey.

Of these, 67 were excluded because they had died, and six were excluded because they had emigrated before the screening had taken place, leaving 6738 eligible subjects. Of these, 5653 (84%) participated in the study. The start of follow-up for the non-participants was set to the median date of the examination of the participants, December 7, 1966. We grouped the participants into young adults, aged <45 years at baseline, middle aged, 45-64 years, and

older participants aged 65+ years. An extensive array of 208 variables was recorded for each participant at baseline, and it included personal and family medical history, age, sex, anthropometric measures (height, body weight, skin fold thickness in both the sub scapular and triceps region (mm), and triceps circumference (cm)), blood pressure, blood-lipids, blood glucose, history of diabetes, heart disease, or pulmonary disease, smoking habits, socioeconomic data, nutritional factors, physical findings, urine samples, pulmonary function (forced expiratory volume after one second - FEV_1), and an electrocardiogram (ECG). Procedures for ascertaining the data have been described elsewhere [64-68].

3.2 Follow-up 1988-90

The male survivors initially aged 22-54 years and who still lived in the study area (n=1154) were invited to a follow-up examination in 1988-90. 1032 (89%) of these men performed spirometric maneuvers with valid FEV_1-measurements. 953 of these also had valid FEV_1 data from the baseline examination.

3.3 Death surveillance

Information regarding cause of death was collected from two different sources namely the official Norwegian mortality statistics at Statistics Norway and autopsy records at the Gade Institute in Bergen for those of the deceased participants who had a post mortem examination.

Table 1. Deaths recorded at Norwegian mortality statistics during the cause-specific follow-up from 1965-2005 among the 6811 subjects invited to the study.

	Men N(%)	Women N(%)	Combined N(%)
Individuals at risk	3104 (45)	3707(55)	6811 (100)
All deaths (1965-2005)	2149 (69)	2238 (60)	4387 (64)
Deaths from ischemic heart disease[a]	623 (29)	498 (22)	1121 (26)
Deaths from cerebrovascular disease[b]	218 (10)	330 (15)	548 (12)

a: Eurocode 34; b: Eurocode 36 (both defined in Table 3)

During the cause-specific follow-up time 4387 persons died and 998 causes of death were recorded to be based on autopsy findings according to the official Norwegian mortality statistics. The local pathology department at Haukeland sykehus, Bergen (The Gade Institute) had records on 1140 post mortem verified causes of death from the same population. 742 causes of death were recorded to be autopsy-verified in both mortality statistics and the local autopsy records, 398 had autopsy reports at the Gade Institute which had failed to be forwarded or recorded at Statistics Norway, and 256 did not have an autopsy report at the Gade Institute but where still reported to have an autopsy-based cause of death at Statistics Norway (Figure 2). This may be due to death and post-mortem examination outside Bergen, tick-off errors in the death certificates or errors in the recording procedures at Statistics Norway.

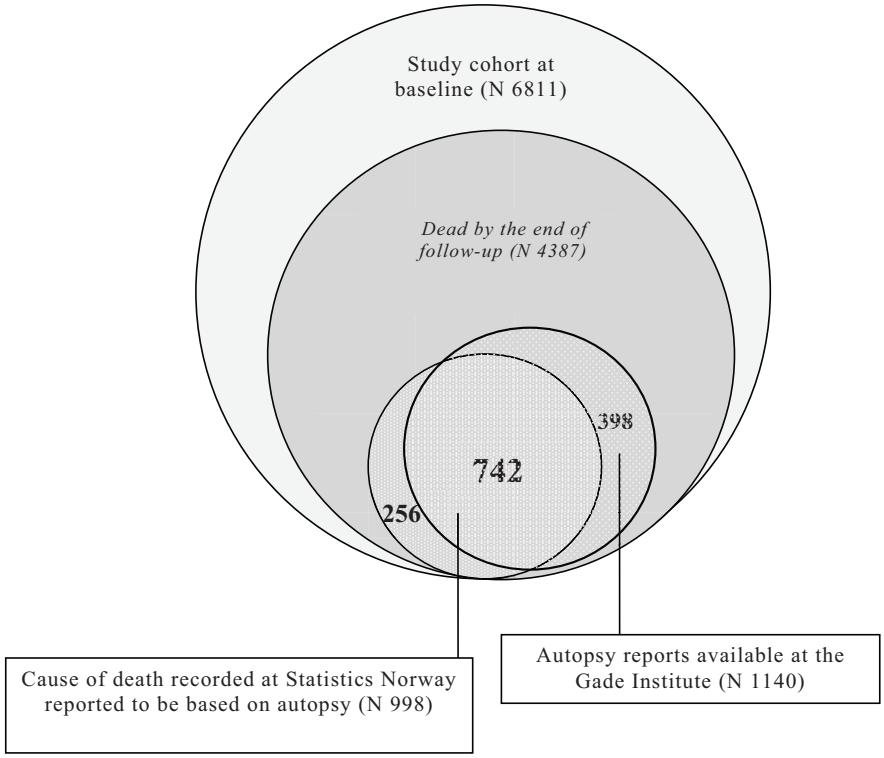

Figure 2. Recordings of deaths and post mortem examinations among all the 6811 invited subjects

4 Methods

4.1 Body Mass Index

Medical technicians measured height to the nearest centimeter and weight to the nearest half kilogram, without outer garments or shoes. All measurements on height and weight were made on the same height and weight scale. BMI was calculated as the body weight (kg) divided by the square of the body height (m) and was classified in four ranges: <22.0 kg/m^2, 22.0-24.9 kg/m^2, 25.0-27.9 kg/m^2, ≥28.0 kg/m^2 due to convenience. The lower and upper cut-off points where close to the limits of the respective quintiles of BMI and comparable to cut-off points used in previous studies [45;77;100]. The medial cut-off point of 25 kg/m^2 corresponds to the WHO´s definition of overweight. The WHO ranges of BMI (<18.5, 18.5-24.9, 25-29.9 and 30+) cut-off on extremes on the lower and upper end of the scale that apply to few people in Norway. In the interim analysis quintiles of the other anthropometric measures mentioned above were tested for their association to death.

4.2 Physical activity assessment

Physical activity (PA) was assessed using a standardized interview performed by trained nurses and including 6 questions with dichotomous (yes/no) answers, regarding involvement in different physical activities during the past 5 years. The respondents who reported "yes" to more than one PA-question were categorized according to their highest reported level of activity. The respondents answering "no" to all of the 6 questions were assigned to level 7. After the preliminary univariate Cox analyses stratified to age the 7 levels of PA were merged into 3 and 2 levels as described in paper 3. The 3 levels were largely comparable to the 4 level questions originally developed by Saltin & Grimsby during the 1960s [156]. Their questions regarding PA have previously been found to correlate positively with aerobic capacity [110] and their convergent validity has been studied by correlation with anthropometric markers and serum lipids [4;188].

Table 2. Levels of physical activity (PA) derived from the questionnaire (reported as the average during the 5 years preceding the baseline survey).

The initial seven PA-questions/levels	N	Collapse into 3 PA-levels (N)	Collapse into 2 PA-levels (N)
Performing competing sports	76	High (720)	Any activity (4349)
Taking regular exercise/gym	644		
Walking at least 2 km or bicycling at least 5 km at least 3 times a week	1003	Moderate (3629)	
Walking/bicycling to work for more than 10 minutes daily	988		
Strolling or gardening	1638		
Performing other kinds of exercise	80	No/Low (1304)	No/low activity (1304)
None of the above	1224		

4.3 Lung function measurements

The forced expiration maneuvers were measured using a dry-wedge bellow spirometers (Vitalograph) both at baseline in 1965-71 (P-model) and at follow-up in 1988-90 (S-model) [41;86]. The highest values of FEV_1 and forced vital capacity (FVC) were recorded by trained technicians from at least two acceptable attempts. All values used in the analyses were corrected to body temperature and pressure saturated conditions (BTPS) [86]. Level of FEV_1 and FVC at baseline was expressed in liters (L) whereas the longitudinal change in FEV_1 and FVC between baseline and follow-up was expressed as milliliters decline per year (mL/year). The predicted values of FEV_1 and FVC were calculated due to the prediction equations recently derived and published from the same geographic area [91]. As a supplement we performed standard adjustments for FEV_1 and FVC by expressing these variables as percentages of their respective predicted values (FEV_1% and FVC% respectively) and dichotomized these into a lower and upper median. Chronic obstructive pulmonary disease (COPD) was defined from the spirometric measurements as persons with $FEV_1/FVC<0.7$.

4.4 Variables for adjustment

Blood pressure (BP) was measured using a Mercury Sphygmomanometer, model Mark3, designed by Rose, Holland and Crowley [148]. Hypertension was defined as a systolic blood pressure of 140 mmHg or more, or a diastolic blood pressure above 90 mmHg or more.
In the 1960s and the 1970s, blood cholesterol and glucose were measured using a colorimetric three-channel auto analyser (Technicon AutoAnalyser II). Diabetes was defined as either known from an individual's medical history, or indicated by an incidental blood glucose level above 11.0 mmol/l.
The questionnaires used to assess possible angina pectoris and other chronic disorders were based on a combination of the chest pain questionnaire developed by G Rose and used by the WHO [149] and forms used by Statistics Norway supplemented with a few questions specific to this survey alone. Diagnoses of cardiovascular disease were based on a combination of self-reported cardiovascular disease and the interviewing medical officers' conclusions after interviewing the respondents regarding history and symptoms of intermittent claudicating, angina pectoris and myocardial infarction.
Information regarding bronchitis and asthma was obtained from self reports to a questionnaire used in standardized interviews. Bronchitis and/or asthma only present before 15 years of age was defined as childhood asthma/bronchitis (yes/no) and asthma and/or bronchitis present after 15 years of age was defined as adult asthma/bronchitis (yes/no). Breathlessness was recorded on a scale from 0=no respiratory difficulties to 7= constant breathlessness, based on physician-interview-conclusion. We dichotomized the breathlessness-information into no (0) and any kind of breathlessness (1).
Socioeconomic status was categorized into 5 groups according to profession and dichotomized into Social class C+D or Blue collar I+II and Social class A+B or White collar I+II and 'others' (students, housewives, etc). The social status were defined according to the standard for grouping of occupations in Norwegian health statistics [99].
Smoking habits were categorized into 5 groups: never-smokers, former-smokers, smoking of pipe/cigars, smoking 1-9 cigarettes per day and smoking ten cigarettes or more per day. Smoking was defined as consuming at least one cigarette per day for at least a year. Former smokers were defined as those who had stopped smoking at least one month before the baseline examination. Smoking of cigars was defined as at least one cigar used per week. Smoking of pipe was defined as at least 10 grams of pipe-tobacco used per week.

4.5 Mortality Statistics

Since 1964 all residents of Norway have been assigned a unique 11-digit identification number which includes their date of birth. Name, address and identification number are registered by the Central Population Register of Statistics Norway, which by law must be kept up-to-date regarding deaths and emigration. When a registered Norwegian dies inside Norwegian borders, a death certificate is issued by a physician, and sent to Statistics Norway. A death registered on the basis of a medical death certificate is matched with the corresponding identification number in the Central Population Register. The registered underlying cause of death is the disease that initiates the series of events that eventually leads to death [212]. Statistics Norway used the 7th, 8th, 9th and 10th revision of the International Classification of Diseases (ICD) during the study period from 1964 to 2005 (Table 3).

Table 3. ICD codes (and corresponding ICD versions) used in Norway during the study period covered by the variables Fatal stroke and Coronary death.

Year of death	ICD-version in use	Fatal stroke (Eurocode 36)	Coronary death (Eurocode 34)
1964-68	6/7	330-334	420, 422
1969-85/86-95	8/9	430-438	410-414
1996-2005	10	I60-I69	I20-I25

The causes of death were grouped into the 65 causes in the "European shortlist"(Eurocodes) which are used in the European official mortality statistics [48]. The analyses were based on mortality from ischemic heart disease (Eurocode 34, ICD10 I20-I25) and cerebrovascular disease (Eurocode 36, ICD10 I60-69), having been given as the underlying cause of death. Statistics Norway has linked information on emigration, time and the underlying cause of death from September 1965 until December 2005 (cause specific deaths) and September 2007 (mortality from any cause) to the database using the National Identity Numbers of all the invited subjects.

4.6 Post mortem examination

The autopsy assessments of the causes of death in this cohort have previously been published [75]. Necropsy findings were recorded by means of SNOMED codes. The Norwegian SNOMED has been prepared by the Norwegian Pathology Association Code and Nomenclature Committee in cooperation with the Competence Center for IT in the health and social sector, and is based on the Systematized Nomenclature of Medicine[34].

4.7 Statistics

4.7.1 Basic statistical terms and Kappa statistics

In the paper regarding validity of stroke and ischemic heart disease in mortality statistics the autopsy-verified cause of death was considered as the “gold standard”. The causes of death

recorded in the mortality statistics and at autopsy were compared and tabulated according to the following categories:

1. True positive: a correct match with the diagnosis from the mortality statistics and at autopsy.
2. Over-diagnosed (false positive): case diagnosed in the mortality statistics but not at autopsy. Over-diagnosed (%) is the proportion of false positives divided by all the positives according to the mortality statistics (test).
3. Under-diagnosed (false negative): case diagnosed at autopsy but not in the mortality statistics. Under-diagnosed (%) is the proportion of false negative cases divided by all the positives according to the autopsy records (truth).
4. Sensitivity of the diagnosis in mortality statistics was calculated as the proportion of true positives divided by all the positives according to autopsy records.
5. Positive predictive value (PPV) was calculated as the number of true positives divided by all the positives according to the mortality statistics.
6. Overall agreement between the mortality statistics and the autopsy results was assessed by Cohen's kappa and its 95% confidence interval [34].

Kappa can be interpreted as the proportion of agreement beyond chance, and Cohen's kappa is the most commonly used kappa-type statistic in epidemiological studies [33]. We adopted the Landis and Koch classification [190], classifying kappa between 0.00 and 0.20 as poor agreement; 0.21-0.40 fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80 substantial agreement, and 0.81-1.00 almost perfect agreement.

4.7.2 Descriptive statistical tests

The descriptive statistics used in the unadjusted, initial, and descriptive analyses (comparing groups) are presented below (Table 4).

Table 4. Statistical tests used for descriptive and initial analyses (not controlling for confounding)

Outcome variable	Exposure variable	
	Two independent groups (ex. gender)	**Three or more independent groups** (ex. age-range, PA-levels, BMI-range)
Dichotomous (ex. autopsy, participation)	chi-square or Fisher's exact test	chi-square or Fisher's exact test
Ordered categorical (ex. BMI-range or smoking habits)	Wilcoxon-Mann-Whitney (WMW) test	Kruskal-Wallis analysis of variance (ANOVA)
Continuous (normally distributed) (ex. s-cholesterol, follow-up time*)	independent sample T test	one-way ANOVA
Censored: time to event (ex. survival)	log-rank test (Kaplan Meier)	log-rank test (Kaplan Meier)

* including the deceased only

Chi-square tests and T-tests tests were used when appropriate. We used one-way ANOVA to test for both linear and quadratic trends in the association between follow-up time and BMI-range for the three different age-ranges. Kaplan Meier plots and log-rank tests were performed for upper/lower median of lung function, and for categories of BMI and levels of physical activity.

4.7.3 Logistic regression

Logistic regression was used in the paper regarding validity of cerebral stroke and ischemic heart disease in mortality statistics. This statistical method predicts the probability of a binary outcome (ex. referral for post mortem examination (yes/no)) in relation to several prognostic variables. The logistic regression model expresses the outcome as a combination of the explanatory variables (predictors) that may be either numerical or categorical. p is the probability of the binary outcomes being equal to one. The logit-transform $\log(p/(1-p))$ is expressed by: $b_0 + b_1x_1 + b_2x_2 + ...b_kx_k$ where b_0 is the intercept, and the other b's are the regression coefficients and k is the number of variables in the model. Odds ratio for each variable can be calculated from the regression coefficients [8].

4.7.4 Survival analyses and proportional hazard assumption

In contrast to logistic regression survival analyses handle censored data vs events. Censoring occurs when a person is still alive when he/she is lost-to-follow-up or when the study ends. In both cases the time followed until censoring will contribute to the results of the calculations. The survival analyses used in this thesis were based on survival tables, Kaplan-Meier plots, log-rank tests and Cox proportional hazard models with years of follow up as the underlying time axis. Survival models relate the time that passes before some event occurs to one or more covariates that may be associated with that outcome of interest (ex. death). Cox proportional hazard regression method is useful in discriminating between several simultaneous effects of different risk factors (explanatory covariates) over time. The Cox model consists of: the underlying hazard function, often denoted $H_0(t)$, describing how the hazard (risk) changes over time at baseline levels of covariates; and the effect parameters, describing how the hazard varies in response to explanatory covariates. The hazard function for the Cox proportional hazard model is expressed as:

$H(t \mid X) = H_0(t) \cdot \exp(\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 \ldots \beta_k x_k)$

A strong assumption is made that effects of the different variables on survival are constant over time and log-linear (additive). For categorical explanatory covariates like BMI-ranges or PA-levels, the assumption of proportional hazards was evaluated by visualizing log(-log) plots (or log minus log; LML) [166]. We can do this in SPSS by putting the covariate that we want to test in the Cox model as stratum variable, not as covariate (one at a time.) Tick LML plot in the Plot sub-dialog. The lines should be parallel if the assumption of proportional hazards is met.

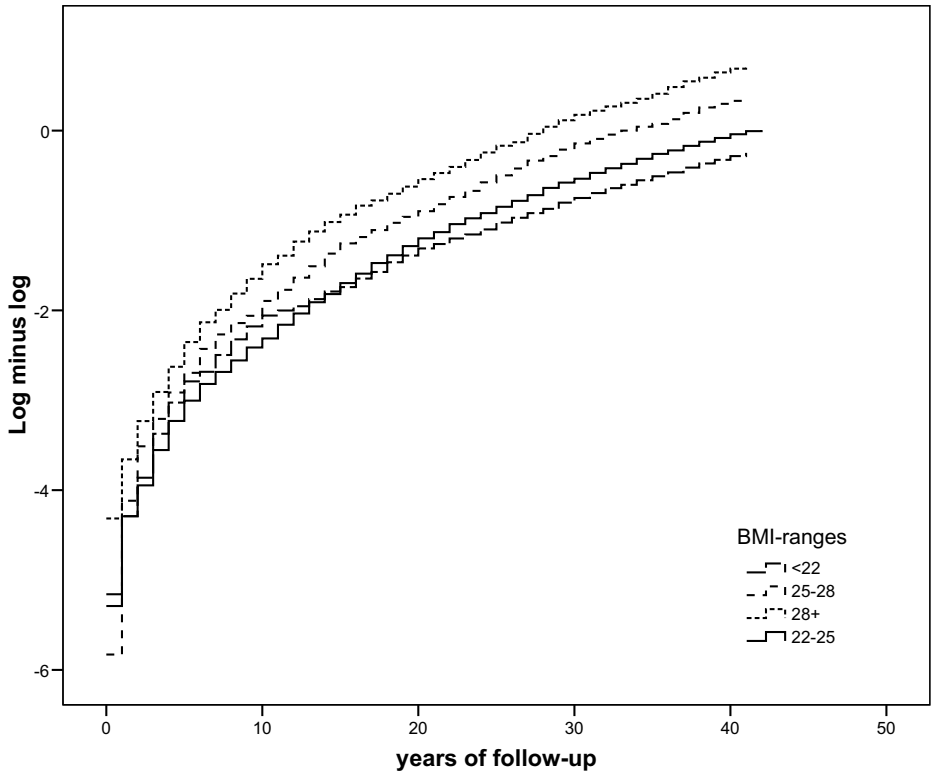

Figure 3. LML plot of strata for BMI (all age-ranges combined) against time of follow-up

As we can see in Figure 3 the line representing the lowest BMI-range (<22) crosses the line of the reference-range (22-25), but the lines are tolerably parallel before 10 years of follow up and beyond 20 years of follow-up. We also eliminated the participants who died within the first 72, 100 and 200 months of the follow-up time and it did not change the size or direction of the effect estimate (hazard ratio) associated with the lower BMI-range. As we can see the lines in Figure 4 are parallel over time for the different levels of physical activity.

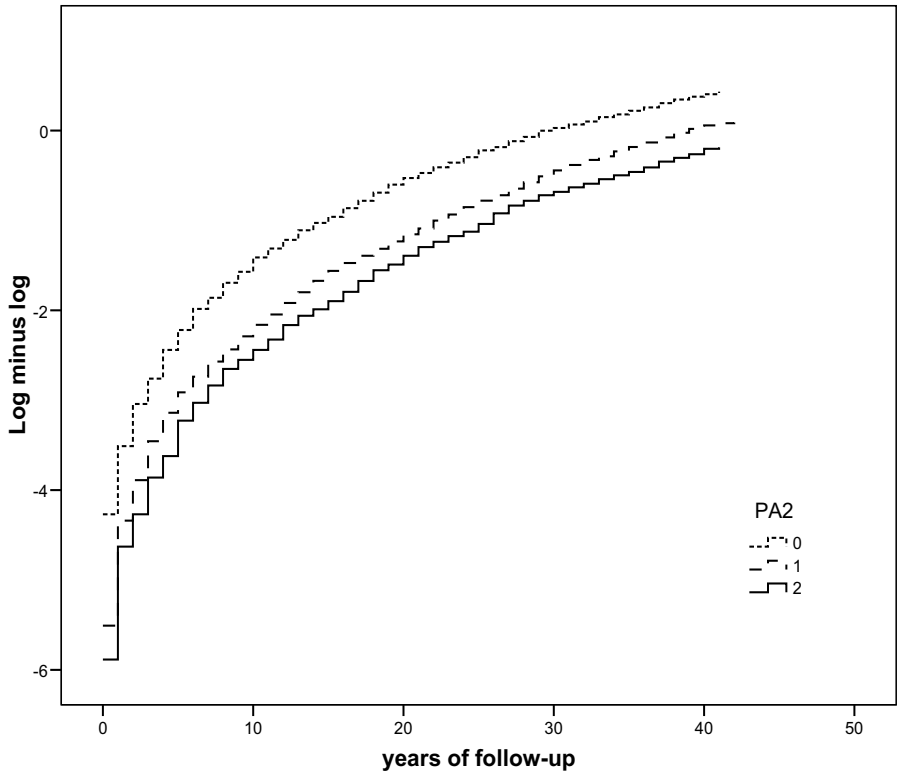

Figure 4. LML plot of strata for 3 levels of LPA (PA2) against time of follow-up

For continous explanatory variables (like FEV_1) the assumption of proportional hazards was evaluated by plotting Schoenfeld residuals [162] (Partial Residuals) against time. We can do this by ticking them in the Save sub-dialog when we are conducting a Cox analysis. A residual variable will be created for each covariate. Then we plot each residual variable against time and there should be no trend if the assumption holds (Figure 5). These residuals are computed only for cases with event (i.e., non-censored).

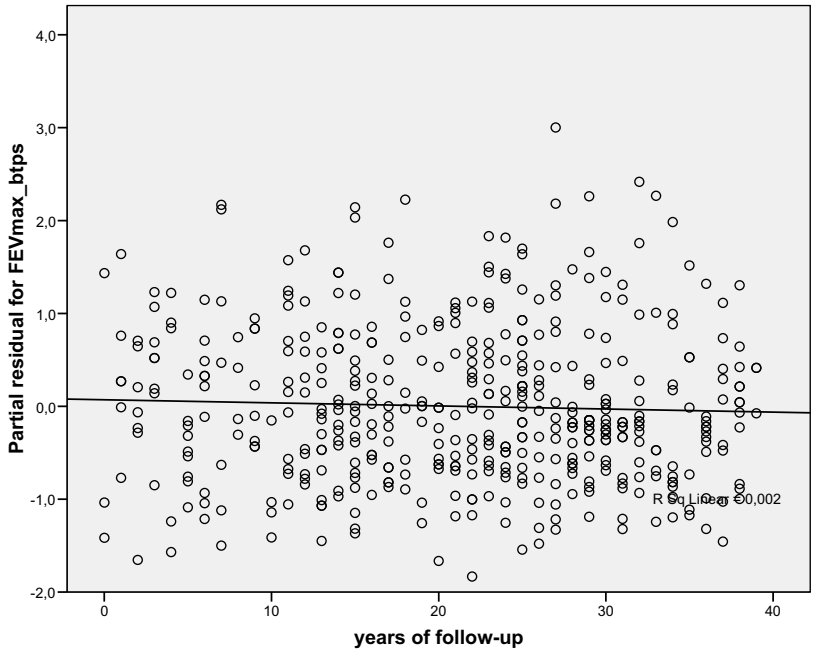

Figure 5. Plot of partial residuals for FEV_1 against time of follow-up for cases of death due to cerebral stroke.

As we can see from Figure 5 there is no trend over the follow-up time.

We explored associations to possible confounders and intermediate variables, and effect modification by both stratified analyses, use of interaction terms and bivariate/multivariate adjustments. Variables that changed the effect estimate of interest with more than 10% were included in the model.[150]

In the paper regarding age, physical activity and mortality, the population attributable fraction (PAF) was calculated for each of the risk factors included in the multivariate

analysis for the three different age ranges (20-44, 45-64, 65+) separately. PAF expresses the reduction in events when a risk factor is removed from a population. In contrast to a relative risk (RR), the PAF also involves the prevalence (p) of a risk factor in the population: PAF=p(RR-1)/(1+p(RR-1)). In survival analyses, when the outcome is not only RR, but a function of time (HR), the PAF expresses that part of mortality attributable to a risk factor in a given time-interval δt, but it might be easier to think of PAF as 'attributable shortening of longevity'. 95% confidence intervals of the PAFs were computed according to a bootstrapping approach [158].

In the paper regarding the association between lung function and risk of stroke the model fit of the two different measures of lung function (FEV1 at baseline and FEV1 decrease over time) were compared using likelihood ratio test (part of the output from a Cox algorithm in SPSS). Likelihood ratio test compares the fit of two models, one of which (the null model) is a special case of the other (the alternative model). A greater log-likelihood means a better model fit [204].

4.7.5 Bias reduction

To assess possible bias from under-nutrition, inactivity or poor lung function due to a pre-existing illness at baseline (reverse causation), the deaths that occurred in the initial six years (72 months) of the follow-up period were excluded from the preliminary analyses [66]. All analyses were performed using SPSS software, version 15.0 and Microsoft Office Excel 2007.

4.8 Ethical considerations

These data are anonymous, unidentifiable and confidential; their use in this study is by permission granted by The Data Inspectorate and the Norwegian Directorate of Health and Social Sciences. The participants volunteered to attend the survey examinations after having received a written, informational letter. At baseline in 1965-71 they gave informed, oral consent to have their data recorded for observational research (Sulheim O., personal communication, 2010).

5 Results

We tested BMI, PA, and FEV_1 as markers of ageing in different ways and we also explored predictors of autopsy. As an overview these key variables are presented in Table 1 as an introduction to the following sections. We have parted the population into those study subjects dying before reaching the age of 80 years and those surviving until 80 years or above for illustrative means. 80 years was the 75 percentile of age at death for men, whereas 85 years was the 75 percentile for women.

Table 5. Characteristics in 5040 participants of the Bergen Clinical Blood Pressure Survey followed until 2005-7 with valid data for all the explanatory variables explored in this thesis (BMI, PA and FEV_1), and with death before the age of 80 years or survival until 80 years or beyond.

Characteristics		Attained age at the end of follow-up		p-value
		< 80 years N (%)	≥ 80 years N (%)	
Sex	Male	1659 (71)	681 (29)	<0.001
	Female	1273 (47)	1427 (53)	
Autopsy	Yes	930 (83)	184 (17)	<0.001
BMI	<22 kg/m^2	522 (62)	325 (38)	
	22-24.9 kg/m^2	777 (54)	651 (46)	0.001
	25-27.9 kg/m^2	623 (55)	520 (45)	
	28+ kg/m^2	438 (57)	329 (43)	
PA	No	622 (62)	387 (38)	<0.001
	Yes (any)	1741 (54)	1501 (46)	
FEV_1%	Lower median	1462 (62)	909 (38)	<0.001
	Upper median	875 (47)	972 (53)	

Abbreviations: BMI: Body Mass Index; PA: Physical Activity (defined as regular engagement in any of 6 listed activities); FEV_1%: Forced Expiratory Volume after one second as a percentage of a predicted value, divided by the median=107.

5.1 Synopsis of papers

5.1.1 Paper 1: Endpoint ascertainment

Title: "Diagnostic Validity of Fatal Cerebral Strokes and Coronary Deaths in Mortality Statistics: An Autopsy Study"

1,140 (26%) of those invited to the study and who died during follow-up were examined by autopsy at the Gade Institute. The ratio of autopsies to the number of deaths decreased from 40% in the period 1964-75 to 11% in the period 1995-2005.

Only 742 (65%) of the autopsy-reports were forwarded and/or recorded in the mortality statistics

The validity of fatal cerebral strokes and coronary deaths reported as the underlying cause of death in mortality statistics for this cohort had a Cohen's kappa coefficient of 0.79 and 0.80, sensitivity of 0.75 and 0.88, and a positive predictive value of 0.87 and 0.86 respectively when compared with autopsy findings. These findings show substantial agreement between cause of death from autopsy findings and mortality statistics.

The kappa coefficients for the fatal stroke diagnoses calculated for the 4 different quartiles of the follow-up period (before 1978, 1978-1986, 1987-1995, 1996-2005) were 0.83, 0.77, 0.70, and 0.85 respectively, showing no trend of increasing diagnostic validity over time. For coronary deaths the corresponding kappa coefficients were 0.81, 0.79, 0.81, and 0.83, respectively.

Death from cerebral stroke was a negative predictor of referral for autopsy, whereas death from coronary heart disease was not, both adjusted for sex, period of death and age at death. Female sex was also a negative predictor of autopsy.

5.1.2 Paper 2: Body mass and all-cause mortality in different age-ranges

Title: "Increased mortality in the slim elderly. A 42 year follow-up study in a general population"

In all, only 3.2 % of the elderly participants (2.9 % of the women and 3.6 % of the men) had a BMI below 18.5 kg/m^2. 17 % (15% of the women and 19% of the men) had a BMI less than 22.0 kg/m^2.

The 20 years cumulative risk of death related to baseline BMI was U-shaped in the elderly (aged 65–75 years), whereas the pattern was more linear in the youngest age group (20–44 years). The hazard ratio of death during the follow-up was calculated for three age ranges. Adjustments were made to age and sex (Model 1) and multiple variables (Model 2). The calculations were also made stratified to sex. In contrast to the younger age groups, the highest mortality in the elderly was in the lower BMI range (<22.0 kg/m^2) (adjusted Cox proportional Hazard Ratio 1.39, 95% Confidence Interval 1.10, 1.75) compared to the BMI reference group (22.0–24.9 kg/m^2).

To address reverse causation bias we calculated the hazard ratio of death for the oldest age category (65+) with a BMI less than 22.0 kg/m^2 by selectively including participants who had survived a stepwise increasing number of months of early follow up. The crude hazard ratio of death related to the lowest BMI-group in the elderly, compared to the BMI-reference range (22.0-24.9), declined from a HR of 1.41 95% CI [1.13, 1.75] when all cases were included to 1.36 [1.06, 1.74] when we included only events for subjects who had survived more than 72 months of follow up. With further elimination of follow-up years the effect estimate remained in the same order of magnitude, but the confidence interval broadened due to decreasing sample size. For example, by eliminating 100 and 200 months of early follow up events, the HR became 1.30 [0.99, 1.69] and 1.45 [0.99, 2.12] respectively.

The predictive power of BMI was compared to the other anthropometric measure and the hazard ratios associated with the three upper quartiles (reference lowest quartile) of the other available anthropometric measures (skin fold thickness and triceps circumference) were smaller than the hazards associated with quartiles of BMI (HR BMI quartiles 2-4 relative to 1: 1.15, 1.61, 2.28, with quartiles of skinfold thickness subscapular region:1.24,1.51, 2.23, with quartiles of skinfold thickness triceps: 0.87, 0.84, 1.05 n.s., and with quartiles of triceps circumference: 1.15, 1.30, 1.48). The model also fitted slightly better with the BMI measurement (-2 log likelihood test [166]). Smoking and preexisting disease is assumed to be of the most important confounders in the association between a low BMI and the higher risk of death. The HR did not change significantly in any of the age segments after adjusting for smoking or in any of the subgroup-analyses performed (never-smokers, survivors of more than 72 months of follow up, and those without recognized obstructive lung disease or cardiovascular disease).

5.1.3 Paper 3: Physical activity and mortality in different age-ranges.

Title: "Ageing, physical activity and mortality – a 42-year follow-up study"

Men reported higher levels of physical activity than women did, and we found a positive trend towards higher levels of physical activity in men among all age groups. The number of participants reporting no engagement in any of the listed activities were 305 (39%), 579 (23%), and 402 (18%) in the old, middle-aged and younger adults respectively. 1754 participants reported that their activity level had decreased the last five years. Out of these 349 (20%) reported that the cause of change was disease. The majority (80%) reported it to be lack of interest or lack of time because of workload or children.

The HR(95%CI) associated with the highest level of physical activity was 0.63(0.56-0.71), 0.66(0.52-0.83) and 0.66(0.47-0.93) for mortality from all-causes, ischemic heart disease and stroke respectively compared to the group reporting no/low activity and adjusted for age and gender. For the moderately active participants the corresponding HRs were 0.75(0.69-0.81), 0.77(0.66-0.90) and 0.83(0.67-1.03) respectively.

Stratified analyses were successively carried out for all subgroups of the following variables for adjustment: gender, hypertension, cholesterol>median (yes/no), diabetes (yes/no), smoking status, BMI-range, socioeconomic status (poor = Blue collar)/good = White collar/others), pre-existing IHD, FEV_1%<median (yes/no). The analyses demonstrated a favorable effect of high physical activity compared to low physical activity in all strata of all these variables.

For the multivariate assessment, we amalgamated the PA measure into a dichotomous variable. Each of the selected modifiable risk factors was examined for their association to all-cause mortality adjusting for age and gender only. The inverse association between PA and all-cause mortality persisted after the elimination of deaths occurring in the first 72 months of the follow-up period (HR 0.67(0.56-0.79), p<0.001, 0.74(0.68-0.83), p <0.001 and 0.80(0.69-0.95), p 0.009, in the young, middle-aged and old respectively, all, adjusted for age and gender). We observed the same trend in a subgroup of participants without hypertension, diabetes, and ischemic heart disease (HR 0.64(0.54-0.77), p<0.001, 0.77(0.67-0.88), p<0.001 and 0.66(0.48-0.92, p0.013, in the young, middle-aged and old respectively, all adjusted for age and gender). The findings also seemed unaffected by exclusion of the participants who reported that they had changed their activity level due to disease in the 5 years preceding the baseline examination (HR 0.69(0.58-0.81), p<0.001, 0.77(0.70-0.85), p<0.001 and 0.79(0.68-0.93), p 0.004, in the young, middle-aged and old respectively, all

adjusted for age and gender). The final multivariate analysis was carried out to compare the effect of PA to other known risk factors of death. PA was associated with a 22-24 per cent lower risk of death in all three age-ranges compared to those who reported no participation in the listed activities. The association between physical activity and mortality was stable across the age ranges whereas the risks associated with smoking, diabetes, hypertension, and possibly overweight seemed to be less prominent in the old compared to younger age-groups. A low total cholesterol level and underweight were associated with increased mortality in the old in contrast to the younger age ranges.

Finally, the population attributable fraction (PAF) adjusted to age and gender was calculated for each of the risk factors for the three different age ranges separately. Multiadjusted calculations were also performed, but did not change the results. The leading risk factors contributing to PAF of mortality from all causes for the older subgroup were hypertension (18.9%), lack of participation in any of the listed activities (9.1%) and a low BMI (<22 kg/m^2) or a high BMI (≥28 kg/m^2) (5.8 and 6.0 % respectively). For the middle aged, the leading risk factors were hypertension (16.2%), smoking (10.0%), and lack of participation in any of the listed activities (7.7%). In the younger adult age-segment the leading risk factors were smoking (19.9%), s-cholesterol above the median (6.69 mmol/l) (11.5%), and lack of participation in any of the listed activities (7.3%).

5.1.4 Paper 4: Lung function and mortality from stroke

Title: The association between lung function and fatal stroke in a community followed for four decades."

The inverse association between stroke and level of FEV_1 was calculated separately for men and women using Cox proportional hazard regression models with progressive adjustments for age, sex, body height and different potential confounders [65]. Age, body height and sex are the variables included in the standard prediction models of both FEV_1 and FVC [91] and their influences on the association between FEV_1 and risk of fatal stroke was HR(95%CI): 2.6(2.3-2.9), unadjusted; 3.3(2.9-3.8), height-adjusted only; 1.1(1.0-1.3), age-adjusted only; 3.5(3.1-3.9), sex-adjusted only. These variables were included for adjustments due to common practice despite the minor influence from body height. After adjustments to these 3 variables the other confounding variables changed the FEV_1-related hazard ratio for a fatal stroke less than 10 percent and thus were not included in the main analyses. Since the age-adjustment resulted in a marked drop in the HR for FEV_1, we also studied the lung-stroke

association in different strata of age at baseline (tertiles). The overlapping 95% confidence intervals of these analyses indicated non-significant differences in the association between FEV_1 and the risk of stroke with increasing age (HR(95%CI) of fatal stroke associated with FEV_1 was 2.41(1.18-4.91) in age-range <40 years, and 1.41(1.14-1.77) in age-range 56+ years at baseline, adjusted for sex, age and height. The hazard ratios of the FEV_1*age and FEV_1*sex interaction terms tested separately in the main model were 1.00(0.99-1.01) and 1.02(0.78-1.33) respectively.

Previous studies have shown that the impact of risk factors may differ between successive time periods [72]. We calculated the hazard related to the early (0-19) years and the late (20-40) years of the follow-up period and found that these were comparable.

The calculations of the main model (adjustments for sex, age, height) were also carried out in a subgroup of lifetime non-smokers (n=2317), in order to eliminate potentially unrecognized residual confounding from smoking, resulting in a HR(95%CI) of 1.88(1.39-2.55) per liter lower level in FEV_1. When we did subgroup analyses of the main model in participants without breathlessness (n=4366) the HR(95%CI) was 1.47(1.16-1.86) per liter lower level in FEV_1. This was done in order to investigate whether the lung-function measurement would add information to stroke risk assessment in subjects free from respiratory symptoms. Finally we did subgroup analyses of the main model in participants without diabetes, hypertension and a medical history suggesting atherosclerotic symptoms (angina pectoris, intermittent claudicating or myocardial infarction) at baseline (n=3507), HR(95%CI) 1.43(1.07-1.90). This was done in order to assess whether the relationship between poor lung function and the risk of stroke precedes the presence of atherosclerotic disease. The hazard ratios associated with FEV_1 remained remarkably stable irrespective of the subgroups studied.

A multiple regression analysis was finally carried out to illustrate that none of the confounding factors reported in other research could explain the association of interest.

To minimize any bias from pre-clinical disease prior to baseline that could possibly lead to both reduced lung function and increased mortality from stroke, we performed a sensitivity (robustness) analysis where events from the first 5 years of the follow-up period were excluded. This changed the hazard ratio(95% CI), associated with one litre lower level in FEV_1 across baseline data, from 1.38(1.11-1.71) to 1.30(1.02-1.66) and from 1.62(1.22-2.15) to 1.61(1.20-2.15) for men and women respectively, indicating that this type of bias has not affected the results.

Previous studies have shown that the impact of risk factors may differ between successive time periods. [72] We calculated the hazard related to the early (0-19 years) and the late (20-40 years) of the follow-up period and found that these were comparable.

Finally we explored the association between FEV_1 and stroke-risk, after adjustments for changes in lung function during adult life. The final analyses were performed on a subgroup of 953 men who had recordings on FEV_1 at both baseline and the follow-up examination in 1988-90. The mean FEV_1(SD) at baseline in this subgroup was 4.42 (0.83) litres. The mean decline in lung function per year between the baseline examination and the follow-up examination in 1988-90 was 53 (19) ml/year. Of the 953 men who had complete sets of data on FEV_1 both at baseline and in 1988-90, 23 fatal strokes were recorded in the mortality statistics in the follow-up period running from the second FEV_1 measurement (1988-90) until end of follow-up (2005). The association between the two different lung function measures and fatal stroke was explored using four different models. Model 1: unadjusted, Model 2: including only baseline FEV_1, age, and body height, Model 3: including only change in FEV_1 per year between baseline and the follow-up survey in 1988-90, age, and body height, and Model 4: including both baseline FEV_1, change in FEV_1 per year between baseline and the follow-up survey in 1988-90, age, and body height. We found a better model fit with the baseline level of lung function than with the change in FEV_1 (-2 log likelihood test).

6 Discussion

6.1 Methodological considerations

6.1.1 Study design

A major asset of prospective studies is that the exposure of interest is measured and recorded before the outcome [1]. Strengths of this study are the very long follow-up period, the high participation rate, and inclusion of both sex from a general population and the access to an extensive array of possible confounders for each of the study participants. A possible weakness is the observational character of the study (in contrast to a randomized controlled trial) and that it was not initially designed to study elderly people specifically.

6.1.2 Bias

The sampling and attendance rate of a study are possible sources of selection bias [1;8]. Our cohort was randomly selected from a general adult population of both sexes, without any selection due to occupation, and with an extraordinarily high participation (84%). Some of the previously reported studies on this topic have been made on health personnel [5;13;113], assumed to be more concerned about health issues than the general population. Participation in previously reported population based studies in this field has varied from 46% to 72% [195]. The baseline characteristics of non-participants versus participants were compared. The proportion of participants was slightly higher in the middle-aged female category. The mortality was higher among the non-participating men compared to the participating men during the follow up period (Odds ratio (OR) 2.10, 95% Confidence Interval (CI):1.56, 2.83, adjusted for age at baseline). For women there was no statistically significant difference regarding mortality related to participation (OR 1.27, 95% CI 0.94, 1.71). Non-participants died at younger age for both sexes. The mean number of years lost for non-participants compared to participants was 4.7 for men and 2.7 for women. (P<0.001, Fisher exact test). Despite the high attendance rate at the initial survey in 1965-71 (84%), all the participants had to be capable of attending the clinic in person. Frail and ill members of the target population are therefore likely to be underrepresented. This selection is, however, more

likely to minimize than exaggerate the inverse association between BMI, level of physical activity, lung function and the fatal outcomes ("healthy participant effect").
A higher body mass, physical activity and a better lung function is more feasible in the absence of disease, and bias from reverse causation (pre-terminal illness as the cause of underweight, inactivity and poor lung function) may explain some of the findings. We limited bias from reverse causation by excluding the initial 72 months of early follow-up deaths in the preliminary analyses, but this did not change the finding.
Self-reporting is a common means of collecting data in other studies [178], and recall bias regarding body mass has been shown to increase with increasing body weight and age [152;179]. We have objective measurements of BMI and FEV_1 in contrast to self-report on height/weight and respiratory symptoms used in many other studies. The questions regarding physical activity during the past 5 years before baseline are based on validated questionnaires and used in other studies, but the records may still be biased. We do not know if there for instance is over-reporting of physical activity among the participants in the upper body mass ranges due to bad conscience.

6.1.3 Confounding

Confounding variables are associated with both the exposure and the outcome and can affect the strength of the effect estimates in the calculations [1]. Confounding is explored in the following way: 1) Biological plausibility: We include variables which seem reasonable to influence the association between an exposure variable of interest and the outcome. 2) Mechanical/statistical approach: We include variables on a threshold level of effect (for instance 10%) on the association of interest. A combination of these approaches seems justifiable. Unrecorded socioeconomic factors like education, diet, alcohol consumption, intensity/duration of physical activity might have influenced our results slightly, but information on these variables were not available to us.
The study population was less exposed to pharmaceutical and medical intervention strategies (due to changes in medical standards in the 1960s) than the population is today. For instance only 78(1.5%) of our cohort used antihypertensive drugs at baseline. Systematic guidelines for antihypertensive therapy was introduced after 1978 [197]and statins were introduced after 1994 [155]. This may have contributed to reduce the presence of bias and confounding in the association between physical activity and mortality.

6.1.4 Reliability

-describes the accuracy and precision of a test or measurement and its capacity to produce the same results when applied repeatedly under the same conditions.

The most important tools used in this thesis are the measurements of blood pressure, spirometric measurements, blood-sample analyses, body height and weight, and the questionnaire. These methods have been used in numerous previous studies referred to in the respective papers of this thesis.
The physical activity measure used in paper 3 is crude. There is a possibility of measurement error or misclassification to activity levels. The 6 questions regarding physical activity can miss some types of activity. For instance are household-activities not mentioned in the questionnaire. The participants may have interpreted the various terms differently, for instance "regular exercise". The intensity and duration of the activities is unknown and may have varied extensively between individuals assigned to the same PA-level. It is possible that these errors may be differential by gender as well as by age-range and socioeconomic group. Misclassification will rather minimize than exaggerate the findings of a beneficial association between PA and survival.

6.1.5 Validity

A measurement with high validity collects findings/interpretation of such which are close to the truth.

Internal validity is the ability to control for variables other than the dependent one. When the researcher may confidently rule out other explanations and attribute the observed changes or differences in the dependent variable to the independent variable, then his causal inference is said to be internally valid. Unrecognized confounding, systematic errors, biases and the reliability of the measurements used could distort the internal validity. The validity of the fatal endpoints has been investigated in a previous publication, and found to be in marked agreement with autopsy findings [64].

External validity refers to the generalizability of the study – to what extent the results of the study are applicable to people not in it. Internal validity is necessary for external validity. The representativity of the study sample for the reference population is also necessary for

external validity. When findings are consistent across different populations it supports external validity.

Patient populations selected from clinical settings are quite different from samples drawn from the general population [128]. Patients seeking medical supervision are likely to have more symptoms and comorbidities than subjects not seeking medical care.

Of the 6,738 eligible subjects for the clinical survey, 2,534 (83%) men and 3,119 (84%) women participated in the study. The clinical characteristics of the study population generally resembles those found in the county services in the 1970-ties [22].

Our findings could also be valid in 2011 taking into account the following: a) Differences due to treatment-effect. The study population used a limited number of drugs (only 10%, 18% and 23% of the young, middle-aged and elderly respectively used one or more drugs) so the influence of medical treatment upon the effect-estimates is assumed to be limited compared to studies conducted today. b) A possible effect-modification due to weight-gain after smoking cession (which is less harmful than continuing smoking and staying slim) and the fact that there are less smoking men and more smoking women today. c) The beneficial effect of increased physical activity may be superior to the possible adverse effects of overweight. However, considering our analyses of the non-responders, the validity of the methods used, the exploration for reverse causality and the knowledge that the human physiology has stayed remarkably unchanged over many years, we believe we have enough evidence to say that our major conclusions hold also external validity for individuals at age 20-79 years of today, living in Norway.

6.1.6 Causality

Our findings are observational. It is still tempting to address the Bradford Hill arguments of causation [80] and suggest that there is a causal link between body mass, physical activity, lung function, and mortality. The strength of the associations, consistency, temporality, coherence and biologic plausibility enable us to draw such a conclusion.

6.1.7 Long term-follow up and time-dependent covariates

The presence of all modifiable risk factors may change over time and physical activity is no exception [78;181]. Long-term follow-up and the influence of time dependent covariates have been discussed in previous publications [93]. Previous evidence suggests that the lack of

repeated measures of PA during follow up may result in under-estimating the strength of its association with mortality up to 60 % [9]. Our findings represent therefore a conservative estimate of the association between PA and mortality.

6.1.8 Stroke incidence vs. stroke mortality

Previous studies have compared risk factors for stroke incidence and stroke mortality [71;73]. These have concluded that studies with information on stroke mortality are likely to give results applicable to stroke incidence. Stroke mortality is however a more severe event than stroke incidence. Concomitant co-morbidities may be one explanation for incidence versus mortality of stroke.

6.1.9 Summary

The study was conducted in a random general population sample. Standardized methods, validated tools, and analytic techniques controlling for confounding were used. The external validity of the findings was further strengthened by the age span and by the comparable clinical characteristics of other cohorts from the same time period in Norway [22].

6.2 Discussion of the main results

6.2.1 Validity of fatal stroke and coronary deaths in mortality statistics

Our study indicates that the validity of fatal cerebral stroke as well as that of coronary death in the Norwegian mortality statistics for the city of Bergen seems to be satisfactory. The kappa coefficients, sensitivity and positive predictive values range between 0.71 and 0.92. Our findings are largely supported by the limited number of previous studies in this area [143;153;172]. Forty years ago a Norwegian study based on autopsy records [192] also concluded that the over-all figures for stroke deaths are generally reliable in the mortality statistics. The kappa coefficient of both the diagnoses fatal stroke and ischemic heart disease in the mortality statistics did not change significantly during the study period or across the different ICD versions in use (results not shown). This is somewhat surprising, as we have experienced an increased access to more advanced diagnostic procedures over the last

decades, improving the accuracy of both diagnoses in general. The fatal strokes may be clinically more obvious than the non-fatal strokes and the diagnostic accuracy of these cases may thereby be less influenced by the increasing access to advanced technology. While the disagreement between autopsy results and clinical diagnoses remains fairly stable [61], the number of post mortem examinations decreases. This may well result in an increase in diagnostic errors in the future, as this quality control is lost for the clinical work of physicians.

We found limited differences in the accuracy of the mortality statistics according to whether the diagnoses were autopsy-based or not. The value of an autopsy is only adequately exploited if the results are correctly incorporated into mortality statistics. In previous studies up to 40% of autopsied cases were not properly reported in mortality statistics [44;53].

Fatal stroke, increasing age and female sex are negative predictors of post mortem examination, whereas coronary deaths are not, which agrees with the findings of a Finnish study [104]. It has previously been shown that the location where death takes place also contributes to the demand for autopsy (hospital deaths are examined much more often than nursing home deaths and death in surgical wards more often than deaths in medical wards). Furthermore, more uncertain clinical diagnoses tend to be selected for autopsy and the pathologists tend to favor the more unusual diagnostic groups [75;95].

6.2.2 BMI and mortality

This study shows that in elderly people (65+) a BMI less than 22 kg/m^2 are an appreciable independent predictor of death. For a general population, BMI tends to increase during the first period of adulthood and decrease after the age of 65 [145;207]. Despite the large sample sizes of previous studies, the trends of association between BMI and all-cause mortality remain uncertain for the older age-segments [13;27;45;49;113]. In our study, the trend turned from almost linear in the younger age group, through J-shaped in the middle aged to U-shaped in the elderly. The shapes of the curves are comparable for the two sexes, especially in the elderly group, indicating minor risk of effect modification due to sex. The upper BMI-values seemed to be associated with an increased risk of death in all age ranges, but in the elderly the lower BMI-range, i.e. <22.0 kg/m^2 was more hazardous than belonging to those above 28.0 kg/m^2.

Moreover, the association could not be explained by preclinical disease at baseline or confounding factors, especially not former or current smoking, indicating that low BMI is

an independent risk factor among subjects aged 65 or older. The methods used to minimize bias from underweight caused by preclinical disease (reverse causation) vary between different research groups. Exclusion of early mortality is one approach, but there is no consensus as to how many years of follow up should be excluded [38;77]. Some investigators eliminate no deaths; some have suggested eliminating the first four years of death while others have recommended eliminating all individuals with any kind of weight loss before baseline. Effects from obesity, including hypertension, glucose intolerance and hypercholesterolemia, are considered as links in the causal pathway by which obesity influences mortality risk. It has been reported that the "independent" or residual effect of obesity on mortality is clinically non-relevant [112]. The causal pathway may not be that obvious with regard to the association between the lower BMI-segment and risk of death, except from confounding from smoking and bias from sub clinical disease. Restricting the analyses to never-smokers and eliminating the first 72 months of follow up showed only a limited effect from these two potential sources of bias. The crude HR was reduced from 1.41 to 1.34 in the elderly with BMI less than 22 kg/m^2. Hence it seems reasonable that the higher risk associated with low BMI in the elderly is due to causes other than bias from reverse causation. The effect persisted throughout the follow-up period; at its end, all of the elderly participants had died.

In the elderly, an increased risk of osteoporosis and lack of nutritional reserves to survive acute illness has been highlighted as contributory mechanisms for the increased risk of death in the lower BMI-ranges [12;140]. As senescence and degenerative diseases cause loss of weight, a higher weight may extend life by offering increased reserves. Studies have shown that subjects with low BMI have increased risk of falling [191], fracture [62], cardiovascular complications after hip fracture repair [14], and they suffer more severe outcomes of various chronic disease, like chronic obstructive lung diseases [163] and stroke [114]. These all are mechanisms that might help explain the association between thinness and increased mortality in the elderly.

It is often assumed that any associations between BMI and mortality are due to the accumulation of adipose tissue, whether overall adiposity or site-specific adiposity [50]. Body composition changes with increasing age towards an increasing fat/muscle mass ratio. In the upper BMI-ranges the fat/muscle ratio might potentially confound the association towards a higher risk in the sarcopenic obesity [199]. The percentage of body fat and BMI is quite well correlated in major parts of the BMI-range, but excess body fat storage (body fat %) trails

off with increasing BMI [102]. In our study 92% of the participants had a BMI less than 30 kg/m^2 leaving obesity of any kind a minor issue. Therefore in our study BMI might capture both sarcopenia and central obesity, unhealthy conditions in which the other anthropometric measures may be in the normal range. This may be why BMI showed the single most robust association to all-cause mortality.

6.2.3 Physical activity and mortality

This study demonstrates a long-lasting inverse association between physical activity and mortality from all causes, fatal strokes and coronary deaths in a general population. Stratified analyses indicated beneficial inverse associations in all subgroups of the study cohort and robustness to comprehensive adjustments. The results are comparable to findings in most other studies both nationally and internationally [15;20;106;134]. In contrast to others, we have also found that the associations persisted throughout the entire 42-year follow-up period, thus indicating the strength of this predictor.

Our results also indicate that the association between physical activity and mortality is consistent across all age-groups, and independent of age at baseline, which is in contrast to the findings for most of the other risk factors. The mortality-sparing effect of leisure-time physical activity has previously been reported to be especially visible among the old[18]. The apparent inverse association between total cholesterol and all-cause mortality in the old compared to younger individuals has been discussed in previous publications. A possible explanation may be that chronic or terminal illness (more prevalent in the old age-segment) is associated with a low total-cholesterol, especially in elderly not treated with statins as in this cohort[137].

In the younger age range (20-44 yrs), there was a positive 'dose-response' association between level of physical activity and survival. In another early cohort including middle-aged men only, health outcomes was associated with vigorous physical activity, but not with total activity [29]. This may be due to a more limited follow-up time or to methodological differences. In the oldest (65+) group in our material, the survival difference associated with the highest level of PA was between the levels of no exercise at all and that of any kind of activity. This may be due to limited statistical power for the upper PA-level or it could indicate that there exists a threshold for the beneficial effect of physical activity in the old. A previous study reported that the small differences found between moderate and highly active individuals could be related to the wording of the questionnaire [10].

A more recent Finnish study of men and women aged 35-63 found a higher participation in vigorous (high) levels of non-occupational PA than we found in our study [70]. This might be due to a lager load of physical activity at work in the past (and thus less time/energy to be physically active beside work), but it may also be due to time-trends, differences in the definitions and grouping of PA, selection bias (exclusion of 35% in the Finnish cohort), and national differences. Unfortunately, we can neither address time-trends nor compare our findings with the findings from other countries (like Finland).

6.2.4 Lung function and mortality

We found a robust and long-lasting association between lung function and fatal stroke in both men and women. Our study adds further information on this issue because of the very long and complete follow-up period, high response rate, adjustments for a wide range of possible confounding factors, the minimization of bias from ill-health, and the subgroup analyses that show robust, persistent, associations also in lifetime non-smokers, in participants reporting no respiratory difficulties and in those who had no signs of atherosclerosis at baseline.

Our analyses shed light on some possible explanations for the association between lung function and the risk of vascular events. The results weigh against a hypothesis that reduced FEV_1 may serve as an epiphenomenon for a common environmental offending factor that affects both the pulmonary and the vascular systems, as adjustments for the available, possible confounding factors and ill-health bias resulted only in minor changes on the risk estimates associated with FEV_1.

Another possible explanation for the association is that an inflammatory link exists between lung processes and cardiovascular disease. Inducing airway inflammation in rabbits can incite and propagate systemic inflammation, which in turn may contribute to the progression of atherosclerosis [183]. Low-grade systemic inflammation is a major risk factor for plaque genesis, progression and rupture[206] and might be a target for the possible pleiotropic effects of statins[136]. FEV_1 is known to be associated with carotid artery intimae-medial thickness [43] and is possibly a marker for smooth muscle hyperplasia. Chronic obstructive pulmonary disease (COPD) is associated with a systemic inflammatory response, with elevated white blood cell (WBC) count and levels of c-reactive protein, fibrinogen, and cytokines, which have the potential to activate the vascular endothelium[58;170]. The prevalence of COPD

defined as $FEV_1/FVC<0.7$ in our population was, however, too low to explain the findings, and the results persisted after elimination of all participants who reported any complaints of breathlessness. Thus this explanation is likely only if a systemic inflammatory response is initiated from a minor airway obstruction not recognized by the individual suffering from it and not included in the definition of COPD ($FEV_1/FVC<0.7$).

Interestingly, there seemed to be a sex difference in the association between FEV_1 and early and late follow-up strokes, but the FEV_1*sex interaction term failed to reach statistical significance. Such a difference, if real, might reflect a survivor effect and could hypothetically explain the increased overall stroke rate in females compared to males. A stronger association between FEV_1 and stroke in females may be partly explained by sex differences in lung growth, and structure, and hormonal determinants of airway behavior[17]. For example, women are more susceptible to the effects of smoking than men[28].

The apparent lung-stroke association may be due to an unrecognized common offending factor which influences both stroke risk and lung function. In that case adjustments for longitudinal changes in lung function would minimize the stroke hazard associated with the baseline lung function. In the subgroup analysis performed in the male survivors in average 23 years after baseline, the risk of fatal stroke was associated both with changes in lung function over time and with the baseline level. The adjusted effect estimate (HR) of 1.95 ($p<0.05$) associated with one liter reduction in FEV_1 across baseline data, indicated a possible strong and independent association between baseline FEV_1 and the risk of fatal stroke (though not formally statistically significant, probably due to lack of power).

The association between baseline lung function and fatal stroke persisted after adjustments for decline in lung function during adult life, which suggests that the lung-stroke association could not be solely explained by confounding mechanisms acting during adulthood.

To our knowledge this is the first study that reports on the association between lung function measurements and the risk of fatal stroke with a follow-up period longer than 20 years and it is the only study with adjustments for individual FEV_1-changes over time. The cohort was randomly selected from a general population of both sexes with an extraordinarily high participation rate (84%). The clinical characteristics of the study population generally resemble those found in the county services in the 1970's. [22] The study recorded an extensive number of clinical variables for each of the participants that were used to adjust for potential confounding factors. Our results support those from other recently published population-based studies including both sexes [83;194], but in contrast to these we have used

the unadjusted FEV_1 measure. Traditionally FEV_1 is adjusted for age and body height to express FEV_1 as a percentage of a predicted value. This adjustment hides the independent association between these three variables and stroke and therefore we examined the FEV_1 stroke association with progressive adjustments for age, height and other variables. [40]

Despite the very high attendance rate at the initial survey in 1965-71 (84%), all the participants had to be capable of attending the clinic in person, so frail and ill members of the target population are potentially underrepresented. This selection is, however, more likely to deflate than to exaggerate the association between level of lung function and excess risk of fatal stroke.

Information on previous strokes or transient ischemic attacks was not available from the data records. The generated variable "atherosclerosis" was therefore a surrogate variable based on ischemic symptoms from the heart and legs only.

There might be some residual confounding due to imprecise measurements of lifetime exposure to tobacco, but our analyses support the view that the association between lung function and stroke is independent of smoking. [83;194] Air pollution might represent further confounding [185], but the degree of atmospheric pollution in Bergen at this time was very low. [121] Occupational exposure to gas and dust was not measured, but socioeconomic status (which is related to occupational exposure) did not influence the association. Residual confounding from undiagnosed diabetes at baseline may be possible, but it seems less probable as the effect estimate (HR) of the lung-stroke association was the same in strata of diabetic and non-diabetic participants respectively. Obstructive sleep apnoea is increasingly described as an independent risk factor for stroke and might also confound the association. [42] 75% of the participants who smoked 10+ cigarettes per day were men and 77% were in the lower two tertiles of age at baseline (<56 years). The change in the association between smoking and fatal stroke from the univariate analyses to the multiple regression model is due to the fact that those smoking 10+ cigarettes per day died from other causes and at younger ages than those who died from stroke (competing risks). As an example the HR of death from ischemic heart disease (Eurocode 34) among the smokers of 10+ cig/day schemic heart disease was 1.39 [1.16-1.68], unadjusted compared to never smokers. It is conceivable that FEV_1 reductions may be due to childhood bronchiolitis, broncho-pulmonary dysplasia (although uncommon) or lung growth problems related to intra-uterine insults including maternal smoking. Information on these variables were not available from the baseline of our population study.

Finally, our outcome measure is based on fatal stroke diagnoses from the death certificates and not on measures of total-strokes. Previous studies have compared risk factors for stroke incidence and stroke mortality. [71;73] These have concluded that studies with information on stroke mortality are likely to give results applicable to stroke incidence.

We conclude that lung function is consistently, independently, and persistently associated with the risk of fatal stroke for both men and women. The mechanism of the association is still unknown, it might be neither causal nor reversible, but the findings indicate that the association is apparent also prior to changes in FEV_1 during adult life. FEV_1 as a percentage of a predicted value might therefore be useful in identifying individuals at particular risk of future fatal strokes.

7 Conclusion

1. We have shown substantial validity of fatal cerebral strokes and coronary deaths in Norwegian mortality statistics compared with autopsy data.
2. Our study confirms that a BMI below 22 kg/m^2 is an independent predictive factor of long-term mortality in elderly persons. Clinical and nutritional management should be applied to elderly persons in this BMI-range in a more careful manner. A BMI up to 28 kg/m^2 may not be associated with an increased risk of death in this age group, and elderly in this weight range should probably not be advised to reduce. The cut-off limits for BMI given by the WHO of ≥18.5 kg/m^2 and ≥25.0 kg/m^2 for normal weight and overweight, respectively, seem to have limited clinical applicability at least in geriatric medical practice in Norway.
3. Mortality attributable to inactivity is substantial in all age ranges. Motivating elderly people and supporting them in the pursuit of physical activity should be given as much attention as the traditional risk intervention measures.
4. Lung function is consistently, independently, and persistently associated with the risk of fatal stroke for both men and women. The mechanism of the association is still unknown, it might be neither causal nor reversible, but the findings indicate that the association is apparent also prior to changes in FEV_1 during adult life. FEV_1 as a percentage of a predicted value might therefore be useful in identifying individuals at particular risk of future fatal strokes.

8 Suggestions for further research

1. Later follow-up of the cohort to increase the power of our study regarding cause-specific mortality.
2. Study the risks of cerebral hemorrhage versus infarction by using autopsy findings.
3. Study of a dose-respond relationship between PA and mortality has not yet been established in the older age-ranges.
4. Studies of the association between other cause-specific mortalities (ischemic heart disease, lung cancer and chronic respiratory diseases) and lung function, BMI and physical activity.
5. Studies of how systemic inflammation markers in the elderly affect cause specific mortality.
6. Studies on early life event (in utero or childhood) and associations with cause specific deaths in the elderly
7. Studies on the efficiency of educational interventions on healthy life-style including physical activity, optimal body-weight and lung function achievement.

9 References

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10 Papers

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CARDIOVASCULAR DISEASE

Diagnostic validity of fatal cerebral strokes and coronary deaths in mortality statistics: an autopsy study

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Abstract Mortality statistics represent important endpoints in epidemiological studies. The diagnostic validity of cerebral stroke and ischemic heart disease recorded as the underlying cause of death in Norwegian mortality statistics was assessed by using mortality data of participants in the Bergen Clinical Blood Pressure Study in Norway and autopsy records from the Gade Institute in Bergen. In the 41 years of the study (1965–2005) 4,387 subjects had died and 1,140 (26%) had undergone a post mortem examination; 548 (12%) died from cerebral stroke and 1,120 (24%) from ischemic heart disease according to the mortality statistics, compared to 113 (10%) strokes and 323 (28%) coronary events registered in the autopsy records. The sensitivity and positive predictive value of fatal cerebral strokes in the mortality statistics were 0.75, 95% confidence interval (CI) [0.66, 0.83] and 0.86 [0.77, 0.92], respectively, whereas those of coronary deaths were 0.87 [0.84, 0.91] and 0.85 [0.81, 0.89] respectively. Cohen's Kappa coefficients were 0.78 [0.72, 0.84] for stroke and 0.80 [0.76, 0.84] for coronary deaths. In addition to female gender and increasing age at death, cerebral stroke was a negative predictor of an autopsy being carried out (odds ratio (OR) 0.69, 95% CI [0.54, 0.87]), whereas death from coronary heart disease was not (OR 1.14, 95% CI [0.97, 1,33]), both adjusted for gender and age at death. There was substantial agreement between mortality statistics and autopsy findings for both fatal strokes and coronary deaths. Selection for post mortem examinations was associated with age, gender and cause of death.

Keywords Autopsy · Stroke · Ischemic heart disease · Death certification · Validity · Mortality statistics

Abbreviations

ICD	International Classification of Diseases
PPV	Positive predictive value
CI	Confidence interval
N	Number of cases
OR	Odds ratio
SPSS	Statistical Package of Social Science
SNOMED	Systematic Nomenclature of Medicine (pathology-coding system)
T code	Topographical code
M code	Morphological code
Eurocodes	65 Different groups of ICD-codes on causes of death which are used in the European official mortality statistics

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Introduction

The specific cause of death reported in mortality statistics is a common endpoint in epidemiological studies and it is generally used as a surrogate marker of morbidity. Ischemic heart disease and cerebral stroke are the two leading causes of death in the industrialized parts of world according to mortality statistics [1 265/id]. Both the disability and mortality attributable to vascular disease in ageing populations highlight the need to identify factors related to aetiology and prevention.

Despite the decreasing autopsy rates, post mortem examination is still regarded as the most accurate means of determining the cause of death [2 299/id, 3 285/id].

Previous studies on the validity of cerebrovascular mortality rates against autopsy findings have concluded, contradictorily, both that the numbers are unacceptable [4 288/id] and that the overall numbers are largely reliable [5 239/id]. During the last two decades, as diagnostic technology and procedures have continued to improve, only a limited number of studies have been published validating mortality statistics on stroke or ischemic heart disease against autopsy findings [6 304/id, 7 276/id, 8 282/id]. These studies were based on cohorts selected for post-mortem examinations, and thus not able to address external validity. In Norway, the official department known as Statistics Norway compiles information on time and cause of death for all deceased inhabitants. The mortality statistics regarding stroke and ischemic heart disease in Norway have not been validated against autopsy findings since 1977 [5 239/id].

The aims of this study were to compare the accuracy of the diagnoses given in the mortality statistics between stroke and ischemic heart disease against autopsy findings, and to identify predictors of a general post mortem examination being carried out.

Methods

Study population

A random, population-based sample of 6,811 subjects aged 20–75 in 1964 was invited to the Bergen Clinical Blood Pressure Survey (1965–1971). Information from their medical history and from a standardized clinical examination was recorded for each of the participants. The study details have been extensively described elsewhere [9 266/id, 10 154/id]. Registration of mortality began on 1 January 1964 and ended on the date of death, date of emigration or on 31 December 2005, whichever occurred first.

Mortality statistics

Since 1964 all residents of Norway have been assigned a unique 11-digit identification number which includes their date of birth. Name, address and identification number are registered by the Central Population Register of Statistics Norway, which by law must be kept up-to-date regarding deaths and emigration. When a registered Norwegian dies inside Norwegian borders, a death certificate is issued by a physician, and sent to Statistics Norway. A death registered on the basis of a medical death certificate is matched with the corresponding identification number in the Central Population Register. The registered underlying cause of death is the disease (or injury) that initiates the series of events that eventually leads to death [11 305/id]. Notification of time, place and cause of death were obtained from Statistics Norway and linked to our data file on the basis of the identification numbers, with permission granted by the Data Inspectorate, the Norwegian Directorate of Health and Social Services, and the Regional Committee for Ethics in Medical Research. Statistics Norway used the 7th, 8th, 9th and 10th revision of the International Classification of Diseases (ICD) during the study period from 1964 to 2005 (Table 1). The causes of death were grouped into the 65 causes in the "European shortlist" (Eurocodes) which are used in the European official mortality statistics [12 307/id]. The analyses were based on mortality from ischemic heart disease (Eurocode 34, ICD10 I20–I25) and cerebrovascular disease (Eurocode 36, ICD10 I60–69), having been given as the underlying cause of death.

Autopsy records

The autopsy assessments of the causes of death in this cohort have previously been published [13 290/id].

Necropsy findings were recorded by means of SNOMED codes. The Norwegian SNOMED has been prepared by the Norwegian Pathology Association Code and Nomenclature Committee in cooperation with the Competence Center for IT in the health and social sector, and is based on the Systematized Nomenclature of Medicine [14 291/id]. The selection of SNOMED codes which identifies autopsy-verified fatal

Table 1 ICD codes (and corresponding ICD versions) used in Norway during the study period covered by the variables fatal stroke and coronary death [22 292/id]

Year of death	ICD-version in use	Fatal stroke (Eurocode 36)	Coronary death (Eurocode 34)
1964–1968	6/7	330–334	420, 422
1969–1985/ 1986–1995	8/9	430–438	410–414
1996–2005	10	I60–I69	I20–I25

strokes and coronary deaths is given in Table 5 in the "Appendix".

Statistical analyses

The causes of death recorded in the mortality statistics and at autopsy from the Gade Institute Department of Pathology were compared and tabulated according to the following categories:

True positive: a correct match with the diagnosis from the mortality statistics and at autopsy.

Over-diagnosed (false positive): case diagnosed in the mortality statistics but not at autopsy. Over-diagnosed (%) is the proportion of false positives divided by all the positives according to the mortality statistics (test).

Under-diagnosed (false negative): case diagnosed at autopsy but not in the mortality statistics. Under-diagnosed (%) is the proportion of false negative cases divided by all the positives according to the autopsy records (truth).

Sensitivity of the diagnosis in mortality statistics was calculated as the proportion of true positives divided by all the positives according to autopsy records.

Positive predictive value (PPV) was calculated as the number of true positives divided by all the positives according to the mortality statistics.

Overall agreement between the mortality statistics and the autopsy results was assessed by Cohen's kappa and its 95% confidence interval [15 297/id]. Kappa can be interpreted as the proportion of agreement beyond chance, and Cohen's kappa is the most commonly used kappa-type statistic in epidemiological studies [16 296/id]. We adopted the Landis and Koch classification [17 295/id], classifying kappa between 0.00 and 0.20 as poor agreement; 0.21–0.40 fair agreement; 0.41–0.60 moderate agreement; 0.61–0.80 substantial agreement, and 0.81–1.00 almost perfect agreement. Cox proportional hazard regression was used to test the influence of hypertension upon stroke mortality or death from ischemic heart disease defined by mortality statistics (Eurocode 36 or 34) and autopsy records, respectively, in order to assess whether the results were comparable. Binary logistic regression was used to explore potential predictors of autopsy. Analyses were performed using SPSS software, version 15.0.

Results

Study population

By the end of 41 years of the study, 4,387 persons (64% of the cohort) had died and 1,140 of these (26%) were examined by autopsy at the Gade Institute. The ratio of autopsies to the number of deaths decreased from 40% in the period 1964–1975 to 11% in the period 1995–2005. The autopsy ratio for the upper quartile of age at death (i.e. 84–103 years) fell from 25 to 4%. In participants dying from stroke (according to mortality statistics), the autopsy ratio decreased from 41 to 4%, whereas in those dying from coronary heart disease it decreased from 38 to 14%.

Of the 1,140 subjects examined by autopsy at the Gade Institute in Bergen only 742 (65%) of the autopsy-reports were forwarded and/or recorded in the mortality statistics (Fig. 1).

Of the specific causes of death recorded in mortality statistics, 3,389 (77%) were not based on autopsy findings. The 256 cases of death recorded at Statistics Norway as having been examined by autopsy, but with no autopsy record at the Gade Institute, were evenly distributed over the entire period of the study ("Appendix" Fig. 2). Until 1996 Statistics Norway recorded that the registered cause of death was based on an autopsy if the physician issuing the Death Certificate had indicated that an autopsy had been planned, but in many of these instances a post mortem examination never took place. The 398 individuals with autopsy records available at the Gade Institute, but with cause of death "not based on autopsy" in the mortality statistics died mainly in the period before 1987 when physicians ordering the post mortem examination were still responsible for forwarding the results of the autopsy to Statistics Norway. From 1987 the pathology departments were responsible for forwarding the autopsy reports and from 1996 Statistics Norway implemented systematic procedures to adjust the registered cause of death according to the findings of the autopsy ("Appendix" Fig. 3).

Validity of the diagnosis of fatal strokes in Norwegian mortality statistics

The validity of the diagnosis of fatal stroke in the mortality statistics was assessed by comparing the mortality statistics for which diagnosis had been based on autopsy results with those for which it had not (Table 2). The prevalence of fatal strokes in the mortality statistics was the same in the two groups (34/398 = 8.5 vs. 64/742 = 8.6%).

Of the 28 under-diagnosed (false negative) fatal strokes in the mortality statistics, the registered causes of death were diseases of the circulatory system (Eurocode 33) in 12 cases (including ischemic heart disease (Eurocode 34) in 9 cases), pneumonia (Eurocode 39) in 5 cases, malignant neoplasm (Eurocode 07) in 4 cases and other Eurocodes in 7 cases.

Of the 13 over-diagnosed (false positive) fatal strokes reported in the mortality statistics, the autopsy had identified diseases of the circulatory system in 9 cases (including ischemic heart disease in 5 cases), diseases of the lungs/airways in 2 cases, malignant neoplasm in 1 case and 1 other case.

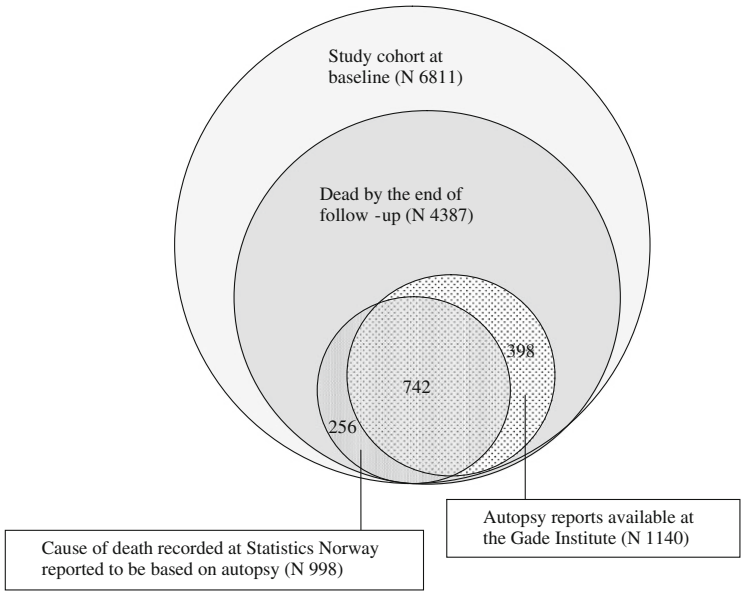

Fig. 1 Mortality and autopsy data for the 6,811 survey participants

Table 2 Validity of fatal strokes (Eurocode 36) recorded in Norwegian mortality statistics for 1,140 post mortem examinations, according to whether the autopsy results were available or not

Eurocode 36	Sensitivity [95% CI]	Positive predictive value [95% CI]	Over-diagnosed [95% CI]	Under-diagnosed [95% CI]	Kappa [95% CI]
Autopsy reported available	60/83 = 0.72	60/64 = 0.94	4/64 = 0.06	23/83 = 0.28	0.80
	[0.63, 0.82]	[0.88, 1.00]	[0.003, 0.12]	[0.18, 0.37]	[0.72,0.87]
Autopsy reported unavailable	25/30 = 0.83	25/34 = 0.74	9/34 = 0.29	5/30 = 0.17	0.76
	[0.70, 0.97]	[0.59, 0.88]	[0.12, 0.41]	[0.03, 0.30]	[0.64,0.88]
Total	85/113 = 0.75	85/98 = 0.87	13/98 = 0.14	28/113 = 0.25	0.79
	[0.67, 0.83]	[0.80, 0.93]	[0.07, 0.20]	[0.17, 0.33]	[0.73,0.85]

CI confidence interval

For fatal strokes the kappa coefficient indicated "substantial" agreement irrespective of whether autopsy results were available to inform the mortality statistics or not (Table 2). The positive predictive value of fatal stroke in mortality statistics was slightly improved when autopsy results were available, but the change of sensitivity was not statistically significant (based on the overlapping of confidence intervals).

The kappa coefficients calculated for the 4 different quartiles of the follow-up period (before 1978, 1978–1986, 1987–1995, 1996–2005) were 0.83, 0.77, 0.70, and 0.85 respectively, showing no trend of increasing diagnostic validity over time.

As hypertension is the most established risk factor for cerebral stroke, we tested whether hypertension had predicted fatal stroke according to the mortality statistics differently from fatal stroke according to the autopsy records. We used Cox proportional hazard regression, adjusted for age at the baseline examination (when the blood pressure was measured) and for gender. With fatal stroke from mortality statistics as the outcome the hazard ratio was 1.71, 95% CI [1.4, 2.08] and as the outcome from autopsy records the hazard ratio was 1.70, 95% CI [1.07, 2.68].

Validity of the diagnosis of coronary deaths in Norwegian mortality statistics

As for stroke, the recorded coronary deaths in the mortality statistics were divided into subgroups according to whether the diagnoses were based on autopsy results or not, and the validity of the mortality statistics was assessed (Table 3).

Table 3 Validity of coronary deaths (Eurocode 34) recorded in Norwegian mortality statistics for 1,140 post mortem examinations, according to whether the autopsy results were available or not

Eurocode 34	Sensitivity [95% CI]	Positive predictive value [95% CI]	Over-diagnosed [95% CI]	Under-diagnosed [95% CI]	Kappa [95% CI]
Autopsy reported available	219/237 = 0.92	219/253 = 0.87	34/253 = 0.13	18/237 = 0.08	0.84
	[0.89, 0.96]	[0.82, 0.91]	[0.09, 0.18]	[0.04, 0.11]	[0.79,0.88]
Autopsy reported unavailable	65/87 = 0.75	65/79 = 0.82	14/79 = 0.17	23/87 = 0.25	0.73
	[0.66, 0.84]	[0.74, 0.91]	[0.09, 0.26]	[0.17, 0.36]	[0.64,0.81]
Total	284/324 = 0.88	284/332 = 0.86	48/332 = 0.15	40/324 = 0.12	0.80
	[0.84, 0.91]	[0.82, 0.89]	[0.11, 0.18]	[0.09, 0.16]	[0.76, 0.84]

CI confidence interval

The prevalence of coronary deaths in the mortality statistics was 79/399 (20%) in the subgroup where autopsy results had been reported as unavailable, whereas it was 253/742 (34%) in the subgroup where autopsy results had been reported as available.

Of the 40 under-diagnosed (false negative) coronary deaths in the mortality statistics, the registered causes of death were diseases of the circulatory system (Eurocode 33) in 20 cases (of which stroke (Eurocode 36) in 5 cases), respiratory diseases (Eurocode 37) in 7 cases, malignant neoplasm (Eurocode 07) in 7 cases and others in 6 cases. Of the 48 over-diagnosed (false positive) coronary death reports in the mortality statistics, the autopsy reports concluded on diseases of the circulatory system in 20 cases (of which stroke in 9 cases), diseases of the lungs/airways in 11 cases and malignant neoplasm in 2 cases, and others in 15 cases.

For coronary deaths the kappa coefficient increased from "substantial" to "almost perfect" agreement when the autopsy results were available to the mortality statistics. The sensitivity of ischemic heart disease in the mortality statistics was slightly improved when the autopsy results were available, but for the positive predictive value the difference was not statistically significant (based on the overlapping confidence intervals).

In the 4 quartiles of the study period the combined kappa coefficients were 0.81, 0.79, 0.81, and 0.83, respectively.

With coronary death (Eurocode 34) from the mortality statistics as the outcome the Cox proportional hazard ratio associated with hypertension was 1.58, 95% CI [1.38, 1.82]. With coronary death verified from the autopsy record as the outcome the hazard ratio was 1.52 95% CI [1.17, 1.99], both adjusted for age at baseline and gender.

Predictors of post mortem examination and the association to fatal stroke

The selection of deaths for autopsy in a general population is not random. We tested the following potential predictors for effect upon the odds of undergoing post mortem examination: age at death (quartiles), period of death (before 1987 vs. 1987 or later), gender, and cause of death (cerebral stroke or coronary disease). The independent variables were explored in bivariate and multivariate analyses. Bivariate logistic regression included only the predictor of interest and the outcome (autopsy). Multivariate logistic regression included gender, age at death and period of death. Cause of death was compared to all other deaths (Table 4).

As can be seen from Table 4, death from cerebral stroke was a negative predictor of referral for autopsy, whereas death from coronary heart disease was not, both adjusted for gender, period of death and age at death. Female gender was also a negative predictor of autopsy. There was no statistically significant interaction between the categorical variables included in these analyses.

Discussion

Our study indicates that the validity of fatal cerebral stroke as well as that of coronary death in the Norwegian mortality statistics for the city of Bergen seems to be satisfactory. The kappa coefficients, sensitivity and positive predictive values range between 0.71 and 0.92. Our findings are largely supported by the limited number of previous studies in this area [7 276/id, 3 285/id, 6 304/id]. Forty years ago a Norwegian study based on autopsy records [5 239/id] also concluded that the over-all figures for stroke deaths are generally reliable in the mortality statistics.

The kappa coefficient of both the diagnoses fatal stroke and ischemic heart disease in the mortality statistics did not change significantly during the study period or across the different ICD versions in use (results not shown). This is somewhat surprising, as we have experienced an increased access to more advanced diagnostic procedures over the last decades, improving the accuracy of both diagnoses in general. The fatal strokes may be clinically more obvious

Table 4 Predictors of autopsy for 4,387 subjects who died during follow-up

	Autopsy		OR bivariate (95% CI)	OR multivariate (95% CI)
	Yes (n = 1,140)	No (n = 3,247)		
Gender				
Male	688 (59)	1,416 (45)	1	1
Female	475 (41)	1,763 (55)	0.57 (0.50, 0.66)	0.73 (0.63, 0.84)
Age at death				
<68	410 (35)	651 (20)	1	1
68–75	366 (32)	690 (21)	0.84 (0.71, 1.01)	0.91 (0.76, 1.09)
76–83	258 (22)	900 (28)	0.46 (0.38, 0.55)	0.56 (0.46, 0.68)
84+	129 (11)	983 (31)	0.21 (0.17, 0.26)	0.32 (0.25, 0.41)
Year of death				
1964–1986	747 (64)	1,316 (41)	1	1
1987–2005	416 (36)	1,908 (59)	0.38 (0.33, 0.44)	0.55 (0.47, 0.63)
Fatal stroke	100 (9)	448 (14)	0.58 (0.46, 0.72)	0.66 (0.52, 0.84)
Coronary death	336 (29)	785 (24)	1.25 (1.07, 1.45)	1.09 (0.93, 1.27)

OR Odds ratio, *CI* confidence interval, *n* number of cases

than the non-fatal strokes and the diagnostic accuracy of these cases may thereby be less influenced by the increasing access to advanced technology. While the disagreement between autopsy results and clinical diagnoses remains fairly stable [18 303/id], the number of post mortem examinations decreases. This may well result in an increase in diagnostic errors in the future.

We found limited differences in the accuracy of the mortality statistics according to whether the diagnoses were autopsy-based or not. The value of an autopsy is only adequately exploited if the results are correctly incorporated into mortality statistics. In previous studies up to 40% of autopsied cases were not properly reported in mortality statistics [19 300/id, 20 301/id]. The results from 421 (36%) autopsies conducted at the Gade Institute were not taken into account by Statistics Norway (Fig. 1). These autopsy results, which were mostly from the period before 1987, may not have been forwarded by the physician ordering the post mortem examination. Some of the 256 cases without autopsy records at the Gade Institute, but which had been reported as having autopsy results in the mortality statistics, may have died and undergone autopsy outside the city of Bergen. The routines regarding reception and implementation of these data at Statistics Norway may thus be in need of improvement. The proportion of non-recorded autopsy results has decreased during the study period but there might still be a potential for improvement.

Finally, we found that fatal stroke, increasing age and female gender are negative predictors of post mortem examination, whereas coronary deaths are not, which agrees with the findings of a Finnish study [8 282/id]. It has previously been shown that the location where death takes place also contributes to the demand for autopsy (hospital deaths are examined much more often than nursing home deaths and death in surgical wards more often than deaths in medical wards). Furthermore, more uncertain clinical diagnoses tend to be selected for autopsy and the pathologists tend to favor the more unusual diagnostic groups [13 290/id, 21 302/id]. Lack of interest in autopsy may also reflect lack of clinical involvement or therapeutic frustration. Thus the selection for post mortem examination is not random.

Limitations to this study are the limited sample size and that the necropsy findings are collected from a closed cohort, whereas the official mortality statistics record information on deaths in the entire (open) population. Thus incidence rates may not be comparable across the autopsy group and mortality statistics in general. Participation in the Bergen Clinical Blood Pressure Survey was not a predictor of selection towards autopsy (results not shown), so our findings are roughly applicable to an age-matched selection of subjects recorded in mortality statistics between 1965–2005. We found under-representation of the elderly, of females and of fatal strokes among the autopsy-investigated deaths. This means that younger males, who were not assumed to be dead from stroke (atypical strokes?) tended to be examined post mortem. This skewness would rather deflate than exaggerate the correlation between mortality statistics and autopsy findings. The false positive and false negative rates in this cohort ranged from 5 to 29%. Approximately half of the mismatches remained inside the circulatory system, whereas the others were more or less randomly distributed over the entire spectrum of diseases, which reduces the risk of systematic errors.

Epidemiological research using endpoints defined as fatal stroke or ischemic heart disease from mortality statistics is unlikely to be markedly biased and that the validity regarding the fatal strokes is acceptable for this age-range. Our findings may also be applicable to international mortality statistics based on similar sources of data.

Conclusion

We have shown substantial validity of fatal cerebral strokes and coronary deaths in Norwegian mortality statistics, though there is still some potential for improvement.

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Conflict of interest None of the authors has any proprietary interest in the results nor is there any financial conflict of interest.

Appendix

See Table 5; Figs. 2, 3.

Table 5 Topographical and morphological SNOMED codes representing the underlying (alternatively immediate) cause of death from autopsy records regarding fatal strokes and coronary deaths

Localisation	T-code
Heart including pericardium	31000, 32000, 32600, 32910, 33010, 33030, 35000, 38000, 39000, 39900, 43000, 43100
Brain	45510, X1110, X1120, X2000, X2070, X7000
Morphological finding	**M-code**
Infarct	54700, 54705, 54720, 54750, 54790, 52000, 52110, 52200, 35100, 35101, 35190, 35300, 36050
Haemorrhage	37000, 37001, 37003, 37004, 38000 (also 58000, 32400, 324401, 32431, 32470, 32471 (if T-code represents brain))
	32400, 324401, 32431, 32470, 32471

SNOMED Systematic Nomenclature of Medicine (pathology-coding system), *T-code* topographical code, *M-code*, morphological code

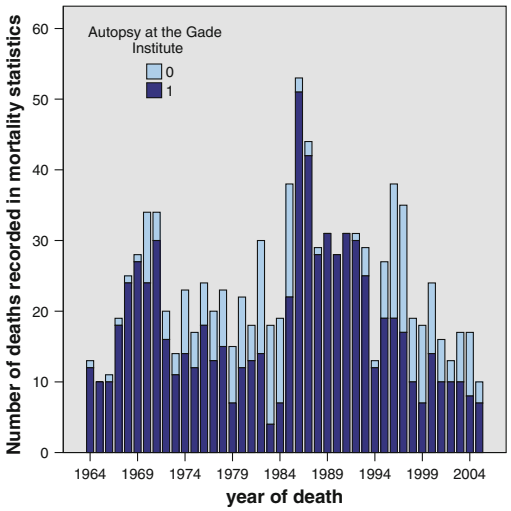

Fig. 2 Autopsy-based causes of death recorded in mortality statistics and the respective availability of autopsy data at the Gade Institute. ["*light grey*" (N = 256 cases) denotes autopsies recorded in the mortality statistics, though autopsy data were not registered at Gade.]

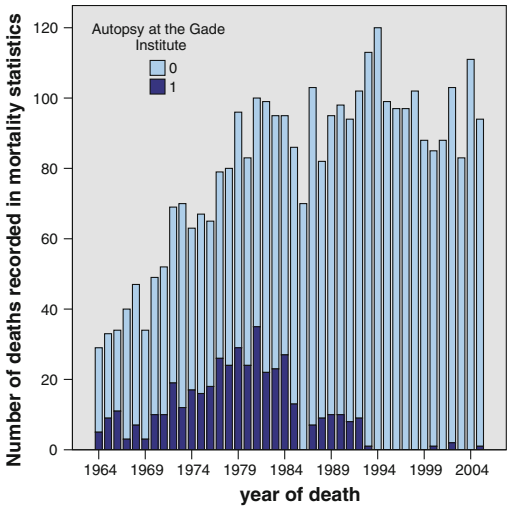

Fig. 3 Causes of death recorded without autopsy in mortality statistics and the respective availability of autopsy data at the Gade Institute. ["*dark grey*" (N = 398 cases) denotes autopsies at the Gade Institute, which were not registered in the mortality statistics.]

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Title:

The association between lung function and fatal stroke in a community followed for four decades

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Key words: Cerebrovascular disease, epidemiology, long-term studies, lung function, risk factors

Abbreviations:

BTPS: body temperature and pressure saturated conditions

CI: confidence interval

Cig/day: number of cigarettes consumed per day

COPD: chronic obstructive pulmonary disease (defined in this paper as $FEV_1/FVC<0.7$)

FEV_1: Forced expiratory volume in one second (L)

FVC: Forced vital capacity

HR: Cox proportional hazard ratio

ICD: International Classifications of Diseases

mmHg: millimetres of mercury

SD: standard deviation

SPSS: Statistical package of Social Sciences

KEY MESSAGES

What is already known?

An inverse association between lung function and the risk of fatal stroke has been suggested.

What this study adds?

The association cannot be explained by confounding from smoking, hypertension, diabetes, atherosclerosis, socioeconomic status, obstructive lung disease, physical inactivity, serum cholesterol, or body mass index. The association also persists in a subgroup of never-smokers, in a subgroup without respiratory symptoms and in survivors of the first 20 years of follow-up.

The association between baseline lung function and fatal stroke persists after adjustments for the changes in lung function during 23 years of adult life, which suggests that the lung-stroke association may be due to a common offending factors acting during foetal or childhood life or a possible causal mechanism.

Abstract

Background Previous studies, all of less than 20 years of follow-up, have suggested an association between lung function and the risk of fatal stroke. This study investigates the stability of this association in a cohort followed for four decades.

Methods The Bergen Clinical Blood Pressure Survey was conducted in Norway in 1964-71. The risk of fatal stroke associated with forced expiratory volume after one second (FEV_1) was calculated with Cox proportional hazards regression, making progressive adjustment for potential confounders.

Results Of 5,617 (84%) participants with recorded baseline FEV_1, 462 died from stroke over 152,786 subsequent person years of follow up according to mortality statistics of 2005; mean(SD) follow-up was 27(12) years. An association between baseline FEV_1 (L) and fatal stroke was observed; HR 1.38 (95% confidence interval (CI):1.11, 1.71) and HR 1.62 (95% CI: 1.22, 2.15) for men and women, respectively (adjusted for age and height). The findings were not explained by smoking, hypertension, diabetes, atherosclerosis, socioeconomic status, obstructive lung disease, physical inactivity, cholesterol, or body mass index, and persisted in subgroups of never-smokers, subgroups without respiratory symptoms, and survivors of the first 20 years of follow-up. For male survivors with a valid FEV_1 at follow-up (1988-90) (n=953), baseline FEV_1 (L) indicated a possible strong and independent association to the risk of fatal stroke after adjustments for individual changes in FEV_1 (mL/year) (HR 1.95 (95% CI: 0.98, 3.86)).

Conclusion There is a consistent, independent, and long-lasting association between lung function and fatal stroke, probably irrespectively of changes during adult life.

Introduction

Cerebral stroke is the second most frequent cause of death in the industrialized world, as it is in Norway, [1,2] and it is the leading cause of acquired and permanent disabilities. Adequate risk assessment for stroke and prophylactic interventions are essential to reduce the incidence and mortality of this devastating condition.

The associations between lung function, respiratory symptoms, and stroke are still under discussion. [3,4] The relationship between lower lung function and risk of stroke has previously been reported for both stroke incidence and stroke mortality [5,6], and the association is independent of other risk factors including smoking. [7] Asthma has been related to stroke and macrovascular disease. [8,9] Some of the previous studies in this field were not population based and included men only. [5,10] The largest population based study reported a response rate of 73.6%. None of the studies published so far have been able to study the robustness of the association after more than 20 years of follow up, and all previous studies on this relationship are based on one baseline measure of lung function only. [11,12] The robust relationship between lung function and vascular events may be due to a common, unrecognized, offending factor (foetal or lifetime exposure) that affects both FEV_1 and the vascular system, or it may be due to a causally linked process. [11] If the risk of stroke were more strongly related to the rate of declining lung function than with the baseline lung function levels, this would suggest that the responsible mechanisms are mainly operating in adult life. [12]

Thus, the aims of the present study are, in a general Norwegian population with both sexes represented, a long-term follow-up and a high response rate, to assess the independent association between baseline lung function as well as that of longitudinal changes in lung function and the risk of fatal stroke.

Methods

Study population

The study cohort and methods have been extensively described elsewhere. [13,14] A random, population-based sample of 6,811 subjects aged 22-75 years was invited to the Bergen Clinical Blood Pressure Survey in 1965-71. Sixty-seven persons were excluded because they had died, and six were excluded because they had emigrated before the screening took place, leaving 6,738 eligible subjects. The study participants and non-participants have been compared in a previous publication. [14] 3119 (85%) women and 2534 (83%) men participated (p 0.04). The mean age was 47.0 and 47.5 years in the participants and nonparticipants respectively (p 0.26), but non-participants died at younger age for both genders. The mean number of years lost for non-participants compared to participants was 4.7 for men and 2.7 for women. (P<0.001, T-test, Fisher exact test). In 1988-90 the survivors of men initially aged 22-54 years and who still lived in Bergen (n=1154) were invited to participate in a follow-up survey. [15] The cohort is assumed to consist exclusively of Caucasians. The aim of the baseline survey was to examine the prevalence of smoking and cardiovascular risk factors in a general population and the long-term effects from these. The study has been approved by the local committee of medical ethics and the institutional review board.

Independent variables

Lung function

Details of the forced expiration manoeuvres have been described elsewhere. [15] Briefly, dry-wedge bellow spirometers (Vitalograph) were used both at baseline (P-model)[16] in 1965-71 and at follow-up in 1988-90 (S-model). Trained technicians recorded the highest values of FEV_1 and forced vital capacity (FVC) from at least two acceptable attempts. All values used in the analyses were corrected to body temperature and pressure saturated conditions (BTPS). [15] Baseline levels of FEV_1 and FVC were expressed in litres (L) whereas the (longitudinal) changes in FEV_1 and FVC between baseline and follow-up in 1988-90 were expressed as millilitres per year (mL/year). The predicted values of FEV_1 and FVC were calculated due to the prediction equations recently derived and published from the same geographic area. [17] As a supplement we performed standard adjustments for

FEV_1 and FVC by expressing these variables as percentages of their respective predicted values (FEV1% and FVC% respectively) and dichotomized these into a lower and upper median. Information regarding bronchitis and asthma was obtained from self-reports. Chronic obstructive pulmonary disease (COPD) was defined from the spirometric measurements as $FEV_1/FVC<0.7\%$.

Variables for adjustment

An extensive array of variables was recorded for each participant at baseline. We first tested the association between lung function and stroke for confounding from the following baseline variables: sex, age, body height, hypertension, diabetes, pre-existing atherosclerosis, self reported bronchitis and/or asthma, self reported dyspnoea, smoking habits, socioeconomic status, physical inactivity, body mass index and cholesterol. Information on exposure to passive smoking in childhood or "in uterus" was not available.

Blood pressure (BP) was measured using a Mercury Sphygmomanometer, model Mark3, designed by Rose, Holland and Crowley. [18] Hypertension was defined as a systolic blood pressure of 140 mmHg or more, or a diastolic blood pressure of 90 mmHg or more.

The diagnosis of atherosclerosis was based on a combination of the interviewing medical officer's conclusions (after interviewing the respondents regarding their medical history and symptoms of intermittent claudication, angina pectoris and myocardial infarction) and information from the questionnaires. Information on previous transient ischemic attacks was not available.

Current smoking was defined as the consumption of at least one cigarette per day, 10 grams of pipe-tobacco per week or 1 cigar per week for at least one year. A smoker who had stopped smoking more than one month before the baseline examination was regarded as a former smoker. The smoking habits were divided into five groups: lifetime non-smokers, former smokers, current smokers of pipe/cigars, current smokers of 1-9 cigarettes per day, and current smokers of 10 or more cigarettes per day. [19]

Socioeconomic status was categorized according to the British Registrar General's classification of occupations [20] ; white collar 1 and 2 (upper), blue collar 1 and 2 (lower) and "others" (including students, housewives, retired etc). Physical activity was dichotomized into active or inactive in which inactivity was defined as physical activity less

than Sunday strolls or gardening. Bronchitis and/or asthma only present before 15 years of age was defined as childhood asthma/bronchitis (yes/no) and asthma and/or bronchitis present after 15 years of age was defined as adult asthma/bronchitis (yes/no). Dyspnoea was recorded on a scale from 0=no respiratory difficulties to 7= constant dyspnoea, based on self report and physician-interview-conclusion. We dichotomized the dyspnoea-information into no (0) and any kind of dyspnoea (1).

Serum (s) glucose and cholesterol was measured according to the Lipid Research Clinics Program, using a colorimetric three-channel auto analyser (Technicon Auto Analyzer II). [21] Diabetes was defined as either being known from an individual's medical history, or being indicated by an incidental blood glucose level above 11.0 mmol/l.

Ascertainment of outcome

The outcome of interest was fatal stroke reported as the underlying cause of death from the death certificates. When a registered Norwegian dies inside Norwegian borders, a death certificate is issued by a physician, and sent to Statistics Norway. The registered underlying cause of death is the disease (or injury) that initiates the series of events that eventually leads to death. [22] The physician issuing the death certificate uses available information from hospital records, clinical post mortem examination or other sources to complete the form. Statistics Norway (the country's compiler and keeper of all national statistics) has linked information on emigration, time and the underlying cause of death from September 1965 until December 2005 to the data-file using the National Identity Numbers for all the invited subjects. The causes of death were grouped into the 65 causes in the "European shortlist" (Eurocodes) which are used in the European official mortality statistics. [23] Eurocode 36 denotes fatal stroke and includes all stroke sub-types. The codes from International Classifications of Diseases (ICD-codes) used to identify fatal strokes are listed in Table 1.

Table 1. The ICD-codes Used to Identify Fatal Cerebral Stroke (Eurocode 36) in the Cause of Death Register in the Period 1965-2005.

Year of death	**ICD-version**	ICD-code
1964-68	6/7	330-334
1969-85	8	430-438
1986-95	9	430-438
1996-2005	10	I60-I69

ABBREVIATIONS: ICD: International Classifications of Diseases

The validity of fatal cerebral strokes reported as the underlying cause of death in mortality statistics for this cohort had a Cohen's kappa coefficient of 0.79, sensitivity of 0.75, and a positive predictive value of 0.87 by comparison to autopsy findings. [24] Data on non-fatal strokes were not available.

Statistical analyses

The strength of the association between lung function and fatal cerebral stroke was assessed using Cox proportional hazards models. Firstly we used quartiles of baseline FEV_1 and secondly we used quartiles of change in FEV_1 (longitudinal) in univariate analyses. Both these analyses showed an approximately linear trend in the association between lung function measurement and fatal stoke, enabling us to investigate the FEV_1-measures further on as continuous variables on an inverse scale (the hazard ratios calculated are per litre lower level in FEV_1 for baseline data, and per ml/year decrease in FEV_1 across longitudinal data).

The Cox assumption of proportional hazards over time was assessed by plotting partial residuals from the Cox analysis of the FEV_1-stroke association against time of follow-up. The association was also studied in the first and second halves of the follow-up time separately.

Interactions between FEV_1 and other explanatory variables were included one by one and excluded from the model if not statistically significant at the 5 % level.

We then performed univariate analyses of multiple variables potentially affecting the association between lung function and fatal stroke, and additionally univariate analyses of FEV_1% (cut point of median), FVC% (cut point of median), and $FEV_1/FVC<0.70$ (yes/no), with chi-square tests and T-tests used when appropriate.

Age, body height and sex are the variables included in the standard prediction models of both FEV_1 and FVC. [17] These variables were therefore chosen to be included in the adjusted Cox proportional hazard model. The assessment of confounding beyond age, body height and sex was accomplished by comparing the effect estimate obtained from calculations including just FEV_1, sex, age and height with the estimate obtained after the additional inclusion of each of the selected potential confounders. [25] Variables that were significant on a 5% level and that changed the estimate of the effect of FEV_1 with more than 10% were included in the model.

Subgroup analyses were also performed in lifetime non-smokers (never/ever), in a subgroup of participants reporting no subjective dyspnoea (yes/no), and in a subgroup without diabetes, hypertension or history of atherosclerosis (neither/any), adjusting for sex, age, and body height only (the main model).

A multiple regression model was finally carried out to illustrate the effect of further adjustments, including FEV_1, sex, age at baseline, body height, smoking habits (5 categories), hypertension (yes/no), diabetes (yes/no), serum cholesterol (cut point of median), presence of atherosclerosis (yes/no), and physical inactivity (yes/no).

Finally we studied the subgroup of participants with recorded measurements of FEV_1 both at baseline and in 1988-90. This enabled us to compare the strength of the association for baseline data and for longitudinal data respectively, and the effect of corresponding adjustments. Score tests were used to assess model fit for baseline data compared to change over time. Analyses were computed with SPSS (version 15.0) software.

Results

Of the 6,738 eligible subjects, 2,534 (83%) men and 3,119 (84%) women participated in the study. The proportion of fatal stroke was (467/3597) 13.0% among the study participants and (81/790) 10.3% in the non-participants who had died during follow-up. The odds of death from fatal stroke was 1.31 95%CI [1.02-1.69], p 0.03, in the participants compared to non-participants (logistic regression, adjusted for age at baseline and sex), but the OR was 1.14 and non-significant when adjusted for age at death instead of age at baseline. The participants reached a higher age at death causing the prevalence of fatal stroke to be higher (competing risks).

Among the participants, the percentage of cases with recorded data on FEV_1, FVC, sex, age, body height, blood pressure, s-cholesterol, smoking habits, self-reported breathlessness, atherosclerosis, socioeconomic status, history of bronchitis and asthma, diabetes, and physical inactivity varied between 96 and 100 %. Blood glucose measurements were done for 3,509 participants (62%). Of the male survivors initially aged 22-54 years (n=1316), altogether 162 men had moved out of the study area by follow-up in 1988-90. Therefore, 1154 men were invited at follow-up and 1032 (89%) participated and 953 (83%) obtained valid spirometric measurements at both baseline and follow-up.

The total follow-up time for the cohort with recorded data on FEV_1 was 152,786 person years and the mean±SD follow-up time was 25±12 and 29±11 years for men and women, respectively. By the end of 2005, 1714 (68%) men and 1850 (60%) women had died. From these, 186 (10.9%) men and 276 (14.9%) women had died from a stroke (Eurocode 36). [23] The characteristics of the study cohort are presented in Table 2.

Table 2. Characteristics of 5617 Participants with Valid Lung Function Measurements at Baseline in 1965-71.

Baseline examination 1965-71:	**Men n=2525**	**Women n=3092**	***p***
FEV_1(L), mean(SD)	3.9(1.0)	2.8(0.7)	<0.05
FEV_1 % (lower median), n(%)	1171(46)	1637(53)	<0.05
FVC (L), mean(SD)	4.9(1.1)	3.4(0.8)	<0.05
FVC% (lower median), n(%)	1131(45)	1671(54)	<0.05
Self reported childhood bronchitis or asthma, n(%)	208(8.3)	273(8.8)	0.33
Self reported adult bronchitis or asthma, n(%)	244(9.7)	311(10.1)	0.33
COPD, FEV_1/FVC<0.70, n(%)	318(13)	134(4.3)	<0.05
Dyspnoea (scale 1-7), n(%)	344(14)	758(25)	<0.05
Age (yrs), mean(SD)	47(14)	48(14)	<0.05
Body height (m), mean(SD)	1.75(7)	1.61(6)	<0.05
BMI (kg/m^2), mean(SD)	24.1(3.0)	24.2(4.4)	<0.05
Smoking habits			
Lifetime non-smoker, n(%)	392(16)	1925(63)	<0.05
Former smoker, n(%)	461(18)	144(5)	
Smoking of pipe or cigars, n(%)	240 (10)	2(0)	
Smoking 1-9 cig/day, n(%)	741(29)	783(25)	
Smoking 10+ cig/day, n(%)	688(27)	236(8)	
Systolic blood pressure (mmHg), mean(SD)	132(22)	135(28)	<0.05
Diastolic blood pressure (mmHg), mean(SD)	74(13)	74(13)	0.453
Hypertension, n(%)	780(31)	1157(37)	<0.05
s-cholesterol (mmol/l), mean(SD)	6.6(1.4)	7.0(1.6)	<0.05
s-glucose (mmol/l), mean(SD)	5.6(1.6)	5.4(1.3)	<0.05
Diabetes, n(%)	64(2.5)	47(1.5)	<0.05
Atherosclerotic disease, n(%)	160(6.3)	137(4.4)	<0.05
Lowest category of socioeconomic status, n(%)	1450(57)	932(30)	<0.05
Physical inactivity, n(%)	417(17)	781(25)	<0.05
Follow-up until Dec 2005:			
Deaths, n(%)	1714(68)	1850(60)	<0.05
Fatal strokes, n(%)	186(10.9)	276(14.9)	<0.05

ABBREVATIONS: SD: standard deviation; FEV_1: Forced expiratory volume in one second; FEV1%: Forced expiratory volume in one second as percentage of the predicted value; FVC: Forced Vital Capacity, FVC%: Forced Vital Capacity as percentage of the predicted value; mmHg: millimetres of mercury; cig/day: number of cigarettes consumed per day. COPD: Chronic Obstructive Pulmonary Disease.

Since FEV_1 showed a closer association with fatal stroke than FVC in the preliminary univariate analyses, we chose to continue the calculations with FEV_1 only (Table 3). The association between stroke and level of FEV_1 was initially calculated separately for men and women using Cox proportional hazard regression models with progressive adjustments for age, body height and different potential confounders. Age, body height and sex are the variables used in the prediction models for FEV_1. [17] In the association between lung function and risk of fatal stroke the unadjusted HR[95%CI] was 2.6[2.3-2.9], the height-adjusted HR[95%CI] was 3.3[2.9-3.8], the age-adjusted HR[95%CI] was 1.1[1.0-1.3], and the sex-adjusted HR[95%CI] was 3.5[3.1-3.9]. Since the age-adjustment resulted in a marked drop in the HR for FEV_1, we also studied the lung-stroke association in different strata of age at baseline (tertiles). The overlapping 95% confidence intervals of these analyses indicated non-significant differences in the association between FEV_1 and the risk of stroke with increasing age (HR of fatal stroke associated with FEV_1 was 2.41, 95% CI [1.18-4.91] in age-range <40 years, and 1.41 [1.14-1.77] in age-range 56+ years at baseline, adjusted for sex, age and height). The hazard ratios of the FEV_1*age and FEV_1*sex interaction terms tested separately in the main model were 1.00 [0.99-1.01] and 1.02 [0.78-1.33] respectively. We adjusted for sex instead of carrying out sex-stratified analyses in order to maintain power. After adjustments for sex, age and body height the other confounding variables changed the FEV_1-related hazard ratio for a fatal stroke less than 10 percent and thus were not included in the main model.

Table 3. The Association Between Lung Function and Fatal Cerebral Stroke Calculated With Different multiple regression models for adjustment in 2,525 Men and 3,092 Women Examined in 1965-71.

	Hazard Ratio [95% CI] of Fatal Stroke[a]		
	Univariate analyses	**Main model** (Including baseline FEV_1, sex, age, and body height)	**Multiple regression** (Main model with further adjustments)[b]
FEV_1(L)	2.63 [2.34-2.95]	1.50 [1.27-1.78]	1.41 [1.19-1.69]
FEV_1% (lower median)	1.69 [1.41-2.03]	-	-
FVC (L)	2.05 [1.86-2.26]	-	-
FVC% (lower median)	1.34 [1.12-1.61]	-	-
COPD (FEV_1/FVC<70)	2.48 [1.82-3.38]	-	-
Childhood bronchitis or asthma (yes/no)	0.67 [0.47-0.97]	-	-
Adult bronchitis or asthma (yes/no)	1.41 [1.06-1.87]	-	-
Dyspnoea (yes/no)	2.69 [2.19-3.31]	-	-
Sex (Female)	1.10 [0.92-1.30]	0.51 [0.38-0.69]	0.61 [0.44-0.85]
Age (yrs)	1.14 [1.13-1.15]	1.13[1.11-1.14]	1.12 [1.10-1.13]
Body height (m)	0.96 [0.95-0.97]	1.00 [0.99-1.02]	1.00 [0.98-1.02]
Smoking 10+cig/d	0.68 [0.51-0.92]	-	1.45 [1.03-2.04]
Hypertension (yes/no)	5.04 [4.18-6.08]	-	1.81 [1.47-2.23]
Diabetes (yes/no)	4.31 [2.78-6.69]	-	2.53 [1.62-3.95]
s-cholesterol ≥6.69 mmol/l	2.16 [1.79-2.61]	-	0.99[0.81-1.20]
Atherosclerosis (yes/no)	5.47 [3.94-7.59]	-	1.69 [1.20-2.38]
Physical activity (inactivity/activity)	1.64 [1.33-2.01]	-	1.16 [0.93-1.44]
BMI (kg/m^2)	1.10 [1.08-1.13]	-	-
Socioeconomic status (low/high)	1.17 [0.94-1.47]	-	-

ABBREVIATIONS: FEV_1: Forced expiratory volume in one second; FEV1%: Forced expiratory volume in one second as percentage of the predicted value; FVC: Forced Vital Capacity, FVC%: Forced Vital Capacity as percentage of the predicted value; mmHg: millimetres of mercury; cig/day: number of cigarettes consumed per day. COPD: Chronic Obstructive Pulmonary Disease; BMI: body mass index; HR: Cox proportional hazard ratio; CI: confidence interval;

[a] The hazard ratios express the risk associated with one litre lower level in FEV_1 across baseline data.

[b] including FEV_1, sex, age, body height (Main model) and additionally including smoking habits, hypertension, diabetes, cholesterol (median), symptoms of atherosclerosis, and physical inactivity.

The calculations of the main model were also carried out in a subgroup of lifetime non-smokers (n=2317), in order to eliminate potentially unrecognized residual confounding from smoking, resulting in a HR of 1.88, 95%CI [1.39, 2.55] per litre lower level in FEV_1. When we did subgroup analyses of the main model in participants without dyspnoea (n=4366) the HR was 1.47, 95% CI [1.16, 1.86] per litre lower level in FEV_1. This was done in order to investigate whether the lung-function measurement would add information to stroke risk assessment in subjects free from respiratory symptoms. Finally we did subgroup analyses of the main model in participants without diabetes, hypertension and a medical history suggesting atherosclerotic symptoms (angina pectoris, intermittent claudication or myocardial infarction) at baseline (n=3507), HR 1.43, 95% CI [1.07, 1.90]. This was done in order to assess whether the relationship between poor lung function and the risk of stroke precedes the presence of atherosclerosis. The hazard ratios associated with FEV_1 remained remarkably stable irrespective of the subgroups studied.

A multiple regression analysis was finally carried out to illustrate that none of the confounding factors reported in other research could explain the association of interest.

To minimize any bias from pre-clinical disease prior to baseline that could possibly lead to both reduced lung function and increased mortality from stroke, we performed a sensitivity (robustness) analysis where events from the first 5 years of the follow-up period were excluded. This changed the hazard ratio, associated with one litre lower level in FEV_1 across baseline data, from 1.38 95% CI [1.11-1.71] to 1.30 [1.02-1.66] and from 1.62 [1.22-2.15] to 1.61 [1.20-2.15] for men and women respectively, indicating that this type of bias has not affected the results.

Previous studies have shown that the impact of risk factors may differ between successive time periods. [26] We calculated the hazard related to the early (0-19 years) and the late (20-40 years) of the follow-up period and found that these were comparable (Table 4). (The corresponding results for the entire follow-up period are given in Table 3, Main model)

Table 4. The Association Between Baseline Level of FEV_1 and Fatal Cerebral Stroke During Early and Late Follow-up for 2,525 Men and 3,092 Women Examined in 1965-71, Adjusted for Age and Body-Height[a]

	Early follow-up strokes 0-19 years			Late follow-up strokes 20-40 years		
	N (strokes)	HR	95 % CI	N (strokes)	HR	95 % CI
Men	2,525 (102)	1.54*	1.18-2.10	1,666 (84)	1.13	0.78-1.64
Women	3,080 (86)	1.60	0.98-2.60	2,363 (190)	1.62*	1.15-2.29
Combined (adjusted for sex)	5617 (188)	1.56*	1.23-1.97	4029 (274)	1.37*	1.07-1.76

ABBREVIATIONS: CI: confidence interval; FEV_1: Forced expiratory volume in one second; HR: Hazard ratio; N: number of fatal strokes. $P<0.05$

[a] The hazard ratios express the risk associated with one litre lower level in FEV_1 across baseline data.

Finally we explored the association between FEV_1 and stroke-risk, after adjustments for changes in lung function during adult life. The final analyses were performed on a subgroup of 953 men who had recordings on FEV_1 at both baseline and the follow-up examination in 1988-90. The mean FEV_1(SD) at baseline in this subgroup was 4.42 (0.83) litres. The mean decline in lung function per year between the baseline examination and the follow-up examination in 1988-90 was 53 (19) ml/year. Of the 953 men who had complete sets of data on FEV_1 both at baseline and in 1988-90, 23 fatal strokes were recorded in the mortality statistics in the follow-up period running from the second FEV_1 measurement (1988-90) until end of follow-up (2005). The association between the two different lung function measures and fatal stroke was explored using four different models. Model 1: unadjusted, Model 2: including only baseline FEV_1, age, and body height, Model 3: including only change in FEV_1 per year between baseline and the follow-up survey in 1988-90, age, and body height, and Model 4: including both baseline FEV_1, change in FEV_1 per year between baseline and the follow-up survey in 1988-90, age, and body height (Table 5). We found a better model fit with the baseline level of lung function than with the change in FEV_1 (-2 log likelihood test).

Table 5. The Association Between Baseline FEV_1, the Change in FEV_1 During Adulthood (FEV_1 change/year), and the Risk of Fatal Stroke (N=23) in 953 Men Examined both at Baseline (1965-71) and in 1988-90.

	Cox proportional hazard ratio of fatal stroke (HR)[a] [95% CI]			
	Model 1 (univariate analyses)	**Model 2** (including only baseline FEV_1, age, and body height)	**Model 3** (including only FEV_1 change/year, age, and body height)	**Model 4** (including both baseline FEV_1, ΔFEV_1/year, age, and body height)
Baseline FEV_1 (L)	2.36 [1.45-3.84]	1.48 [0.79-2.77]	-	1.95 [0.98-3.86]
FEV_1 change/year[b] (mL/year)	1.02 [1.00-1.04]	-	1.02 [1.00-1.04]	1.03 [1.00-1.05]
Age[c] (yrs)	1.19 [1.11-1.28]	1.18 [1.10-1.28]	1.20 [1.11-1.30]	1.17 [1.08-1.27]
Body height[d] (m)	0.99 [0.93-1.06]	1.05 [0.97-1.12]	1.00 [0.94-1.07]	1.03 [0.96-1.11]

ABBREVIATIONS: FEV_1 change/year: mean change in FEV_1 per year between baseline and 1988-90, CI: confidence interval; FEV_1: Forced expiratory volume in one second; HR: hazard ratio; N: number; ml/yr: millilitres per year; SD: standard deviation;

[a] The hazard ratios express the risk associated with one litre lower level in FEV_1 across baseline data or/and one ml/year decrease in FEV_1 across longitudinal data.

[b] Calculated as the difference in FEV_1 between baseline and at the follow-up survey in 1988-90, divided by the number of years between the two examinations.

[c] age at baseline examination.

[d] height at baseline

Discussion

We found a robust and long-lasting association between lung function and fatal stroke in both men and women. Our study adds further information on this issue because of the very long and complete follow-up period, high response rate, adjustments for a wide range of possible confounding factors, the minimization of bias from ill-health, and the subgroup analyses that show robust, persistent, associations in lifetime non-smokers, in participants reporting no respiratory difficulties and in those who had no signs of atherosclerosis at baseline.

Our analyses shed light on some possible explanations for the association between lung function and the risk of vascular events. The results weigh against a hypothesis that reduced FEV_1 may serve as an epiphenomenon for a common environmental offending factor that affects both the pulmonary and the vascular systems, as adjustments for the available, possible confounding factors and ill-health bias resulted only in minor changes on the risk estimates associated with FEV_1.

Another possible explanation for the association is that an inflammatory link exists between lung processes and cardiovascular disease. Inducing airway inflammation in rabbits can incite and propagate systemic inflammation, which in turn may contribute to the progression of atherosclerosis. [27] Low-grade systemic inflammation is a major risk factor for plaque genesis, progression and rupture. [28] FEV_1 is known to be associated with carotid artery intimae-medial thickness [29] and is possibly a marker for smooth muscle hyperplasia. Chronic obstructive pulmonary disease (COPD) is associated with a systemic inflammatory response, with elevated white blood cell (WBC) count and levels of c-reactive protein, fibrinogen, and cytokines, which have the potential to activate the vascular endothelium. [11,30] The prevalence of COPD ($FEV_1/FVC<0.7$) in our population was, however, too low to explain the findings, and the results were robust in a subgroup of participants who did not report any complaints of dyspnoe. Thus this explanation is likely only if a systemic inflammatory response is initiated from a minor airway obstruction not even recognized by the individual suffering from it.

Interestingly, there seemed to be a sex difference in the association between FEV_1 and early and late follow-up strokes, but the FEV_1*sex interaction term failed to reach statistical significance. Such a difference, if real, might reflect a survivor effect and could

hypothetically explain the increased overall stroke rate in females compared to males. A stronger association between FEV_1 and stroke in females may be partly explained by sex differences in lung growth, and structure, and hormonal determinants of airway behaviour. [31] For example, women are more susceptible to the effects of smoking than men. [32]

The apparent lung-stroke association may be due to an unrecognized common offending factor which influences both stroke risk and lung function. In that case adjustments for longitudinal changes in lung function would minimize the stroke hazard associated with the baseline lung function. In the subgroup analysis performed in the male survivors in average 23 years after baseline, the risk of fatal stroke was associated both with changes in lung function over time and with the baseline level. The adjusted effect estimate (HR) of 1.95 (p 0.05) associated with one litre reduction in FEV_1 across baseline data, indicated a possible strong and independent association between baseline FEV_1 and the risk of fatal stroke (though not formally statistically significant, probably due to lack of power).

The association between baseline lung function and fatal stroke persisted after adjustments for decline in lung function during adult life, which suggests that the lung-stroke association could not be solely explained by confounding mechanisms acting during adulthood.

Strengths and limitations

A major strength of this study is the very long follow-up period and the access to longitudinal data on individual FEV_1-changes over time. To our knowledge this is the first study that reports on the association between lung function measurements and the risk of fatal stroke with a follow-up period longer than 20 years and it is the only study with adjustments for individual FEV_1-changes over time. The cohort was randomly selected from a general population of both sexes with an extraordinarily high participation rate (84%). The clinical characteristics of the study population generally resemble those found in the county services in the 1970's. [33] The study recorded an extensive number of clinical variables for each of the participants that were used to adjust for potential confounding factors. Our results support those from other recently published population-based studies including both sexes [7,34], but in contrast to these we have used the unadjusted FEV_1 measure. Traditionally FEV_1 is adjusted for age and body height to express FEV_1 as a percentage of a predicted value. This adjustment hides the independent association between these three

variables and stroke and therefore we examined the FEV_1 stroke association with progressive adjustments for age, height and other variables. [12]

Despite the very high attendance rate at the initial survey in 1965-71 (84%), all the participants had to be capable of attending the clinic in person, so frail and ill members of the target population are potentially underrepresented. This selection is, however, more likely to deflate than to exaggerate the association between level of lung function and excess risk of fatal stroke.

Information on previous strokes or transient ischemic attacks was not available from the data records. The generated variable "atherosclerosis" was therefore a surrogate variable based on ischemic symptoms from the heart and legs only.

There might be some residual confounding due to imprecise measurements of lifetime exposure to tobacco, but our analyses support the view that the association between lung function and stroke is independent of smoking. [7,34] Air pollution might represent further confounding [35], but the degree of atmospheric pollution in Bergen at this time was very low. [36] Occupational exposure to gas and dust was not measured, but socioeconomic status (which is related to occupational exposure) did not influence the association. Residual confounding from undiagnosed diabetes at baseline may be possible, but it seems less probable as the effect estimate (HR) of the lung-stroke association was the same in strata of diabetic and non-diabetic participants respectively (results not shown). Obstructive sleep apnoea is increasingly described as an independent risk factor for stroke and might also confound the association. [37] 75% of the participants who smoked 10+ cigarettes per day were men and 77% were in the lower two tertiles of age at baseline (<56 years). The change in the association between smoking and fatal stroke from the univariate analyses to the multiple regression model is due to the fact that those smoking 10+ cigarettes per day died from other causes and at younger ages than those who died from stroke (competing risks). As an example the HR of death from ischemic heart disease (Eurocode 34) among the smokers of 10+ cig/day schemic heart disease was 1.39 [1.16-1.68], unadjusted compared to never smokers. It is conceivable that FEV_1 reductions may be due to childhood bronchiolitis, broncho-pulmonary dysplasia (although uncommon) or lung growth problems related to intra-uterine insults including maternal smoking. Unfortunately, information on these variables were not available.

Finally, our outcome measure is based on fatal stroke diagnoses from the death certificates and not on measures of total-strokes. Previous studies have compared risk factors for stroke incidence and stroke mortality. [6,38] These have concluded that studies with information on stroke mortality are likely to give results applicable to stroke incidence.

We conclude that lung function is consistently, independently, and persistently associated with the risk of fatal stroke for both men and women. The mechanism of the association is still unknown, it might be neither causal nor reversible, but the findings indicate that the association is apparent also prior to changes in FEV_1 during adult life. FEV_1 as a percentage of a predicted value might therefore be useful in identifying individuals at particular risk of future fatal strokes.

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11 Literature tables

Table L-1. Studies on the association between Body Mass Index (BMI) and mortality in different age-segments, conducted in the Nordic countries and published in the past 20 years.

(Search performed in MEDLINE and EMBASE (limits: English language, 1991-current date, full-text available) and by scrutinizing lists of references in selected papers.)

Author Publ. year	Study name	N Population Age-range	Follow-up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Kvamme J M et al [101] 2011	The Tromsø and HUNT studies	16711 Norway both sexes age ≥65	9.3	BMI (intervals of 2.5 kg/m^2, 25-27.5 as reference) and waist circumference	Mortality from all-causes and cause-specific	BMI optimum 25-29.9 and 25-32.4 (men and women). U-shaped association for both BMI and WC	Age, smoking, marital status, study site and educational level	40% of mortality in lower BMI-range was due to respiratory diseases. WC and BMI performed app. Equally in identifying individuals in the higher weight-categories at higher risk of death.
Mørkedal B et al 2010 [122]	The HUNT Study	71348 Norway both sexes, age<65 or ≥65, SBP<160 or ≥160 ≥20	21	BMI (WHO-classification)	Mortality from IHD	RR 5.8 in lean , hypertensive middle-aged, RR 2.4 and 1.6 in overweight and obese compared to normotensive lean subjects	Age, sex, diabetes, smoke,	The effect of blood pressure on IHD is modified by BMI in middle age, and is much stronger in lean than overweight/obese.
Thinggaard M et al 2010 [189]	The Longitudinal Study of Ageing of Danish Twins (LSADT) and the Danish 1905 Cohort Survey.	6515 Denmark both sexes, age-ranges (70-74, 75-70, 70-89, 90-94) 70-95	10	BMI (6 equal groups).	Mortality from all-causes	HR and age-adjusted mortality rates showed significant decrease in the association with a low BMI with advancing age in both sexes (p 0.03)!!	Eliminated BMI <15 or >45.	Self reports in elderly - reports their maximal attained height and to report with error. Did not control for initial health. Twins are a selective group with low birth weight.

Table L-1 cont.

Author Publ. year	Study name	N Population Age-range	Follow-up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Wilsgaard T et al 2009 [208]	The Tromsø Study	9932 Norway both sexes 35-70	11	Weight loss	Mortality from CVD, non-CVD and all-causes	HR 2.09[1.56-2.81] for weight loss 2 kg/m2 compared to weight-gain 1 kg/m2 over 10 years in men	BMI, age, smoke, intention to loose weight. Exclusion of poor health, diabetes, HT, high alcohol	HR associated with weight loss was evident in MEN (all subgroups of baseline BMI, smoke and intention to loose) and in women (subgroup of unintentional weight loss), for CVD 2.41 and for non-CVD 1.89 in men.
Ringbäck G Weitoft et al 2008 [144]	ULF (Swedish survey of living conditions)	23814 Sweden both sexes 16-74	12	BMI (WHO-classification)	Mortality from CVD and all-causes	RR underweight men 2.4[1.6-3.6], women 2.0[1.5-2.7], but PARs were small 1.2-2.7%	Age, illness, smoke, education., cohort. Eliminated first 3 years.	Not addressing the elderly specifically.
Lindquist P et al 2006 [108]	Population Study of Women in Gothenburg	1462 Sweden women, age (38-40, 50-60) 38-60	24	BMI and waist/hip ratio (WHR)	Mortality from all-causes	HR older: BMI negative linear relation, younger: BMI-mortality U-shape. For all WHR was related to increased risk of death.	Age, smoke, PA, s-TG	For older women the highest survival was observed for those with the lowest WHR and highest BMI.
Hjartåker A et al 2005 [81]	The Women's lifestyle and health cohort study	102446 Norway and Sweden women, premenopausal, postmenopausal 30-50	9,1	BMI (WHO-classification)	Mortality from all-causes	HR (Model 1) in postmenopausal BMI 18.5 vs 18.5-24.5: 2.05[1.35-3.13]. NB only 23 deaths.	Model 1: age, Model 2: age, smoking, education, phys act. Elimination of smokers, early death (1 year) and disease at baseline	Risk associated with underweight depends on menopausal status (PRE/POST). Self-reports - misclassification - underestimation of the true effects of obesity. WH-ratio preferably. Elim. of early events depends on whether the primary interest is to find the overall true effect of obesity or the "independent" effect after elim.

Table L-1 cont.

Author Publ. year	Study name	N Population Age-range	Follow-up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Hu G 2005 [85]	"Finland"	47212 Finland both sexes, age-range 25-64	17,7	BMI (WHO-classification)	Mortality from CVD, cancer and all-causes	HR for mortality increased for both men and women in all Models 1-3 at BMI<18.5	Model 1: age, study year, Model 2: age, study year, smoking, education, phys act, Model 3: age, study year, smoking, education, phys act, SBP, cholesterol, diabetes. Elimination of smokers, early death (1 year) and disease at baselin	Higher HR associated with BMI<18.5 in age-range 50-64, than 25-49, especially in men. Mortality attributable to leannes is less than 0.3% in this cohort.
Engeland A et al 2003 [45]	The Norwegian National Health Screening Service	1977953 Norway both sexes, age-ranges 20-29, 30-39, 40-49, 50-59, 60-69, 70-74. 20-74	22	BMI 15 categories	Mortality from all-causes	Quadratic relationship (non-linear) confirmed for both men and women, when BMI continous. Nadir 22.5-24.9, BMI below 17.5 had HR 1.74 and 1.96 in men and women respectively.	Age, sex, area, observation in the period 5-15 years after baseline did not change pattern. Subanalyses on those who had answered on smoking habits (622308 participants)	J-shape in men U-shape in women. Lack of information on nearly all potential confounders (smoke, phys act, prevalent disease etc.). NB recruited from a general population with high attendance rate, measured height and weight instead of self-reports. Leanness in elderly may to a larger extent be of unhealthy etiology then leanness in the younger.

Table L-1 cont.

Author Publ. year	Study name	N Population Age-range	Follow-up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Lahmann PH et al 2002 [103]	Malmø Diet and Cancer Study	27716 Sweden both sexes, age-range (46-59, 60-73) 45-73	5,7	BMI (<25, 25-29, 30+) & BMI-quintiles, body fat%, lean body mass, WH-ratio	Mortality from all-causes	In 60+ group: HR <1.00 for all 4 upper quintiles of BMI compared lo lower quintile (exept upper in men), but all but one p>0.05 (low power).	Age, sex, smoke, phys.akt, disease. Eliminated smokers, early death & cancer/CVD at baseline	Sex and age differences for the effect of adiposity and WHR. No effect found for BMI, but indicates that short follow-up (<5) and/or small samples have been proposed as explanaitions of failure to detect ass between BMI/mortality. Participation 40% (selection bias). Short follow-up.
Meyer H E et al 2002 [119]	The Cardiovascular screening study (Finnmark, Sogn og Fjordane and Oppland)	22304 Norway men, PA, smoke 25-49	16,3	BMI (WHO-classification)	Mortality from CVD and all-causes	Obese smokers: HR 4.55 compared to normal-weight ever-smokers. The U-shape seemed to disappear by increasing levels of PA though n.s.	Age, smoke, body height, education, marital	Effect of elimination of early deaths is limited
Dey D K et al 2001 [38]	"Göteborg"	2628 Sweden both sexes ≥70	15	BMI quintiles	Mortality from all-causes	RR 1.2 and 1.49 (lowest quintile, men and women respectively). Non-smokers, and/or elim first 5 years showed no excess risk in men. BMI nadir ca 27 in non-smokers. Weight-loss >10% significantly excess risk.	Weight-loss (between 70-75 years). Elim. of the first 5 years and cancer. Never-smokers. The 3 five-year intervals of the follow-up-time were analysed separately.	Indicate sex differences - low BMI indicate short term mortality in men - long term in women. Fatness- lean mass discussion.

Table L-1 cont.

Author Publ. year	Study name	N Population Age-range	Follow-up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Flodin et al 2000 [52]	"Huddinge Hospital"	337 Sweden hospitalized geriatric patients ≥65	1	BMI ≤20, 21-25, >25	Mortality from all-causes	Multivariate logistic regression: BMI<20 turned out to be the strongest predicting factor of 1-year mortality: r 0.12	Sex, Katz (A-E), age, diagnoses	Dietary supplements are recommended to reduce mortality in the malnourished elderly geriatric patients.
Heitman n 2000 [79]	The Gothenburg 1913 birth cohort Study	787 Sweden men 60	22	BMI quintiles	Mortality from all-causes	RR 1.3 n.s. in quintile 1 compared to quintile 3, RR 1.5 in quintile 5. Analyses on fat mass% and fatfree%-mass showed a linear association to mortality		The U-shape may be a result of compound risk functions from body fat and fat free mass
Mikkelse n KL et al 1999 [120]	The Copenhagen City Heart Study and The Glostrup Population Studies (incl MONICA I)	15113 Denmark both sexes, smoke 20-93	10	BMI (cutoff: 22, 24, 26, 28), BMI-changes	Mortality from all-causes	HR <22 vs 22-24 increased risk in borth men and women.	Smoke. Elimination of the first 4 years of follow-up	Both weight-change (dynamic effect) and weight level (static effect) had independent effect on total mortality (U-shaped)
Mattila K 1996[115]	"Finland"	674 Finland both sexes ≥85	5	BMI	Mortality from all causes	BMI <20 highest mortality and BMI ≥30 lowest.	Age, sex	No sense in worrying very old people to reduce weight to increase lifespan

Table L-1 cont.

Author Publ. year	Study name	N Population Age-range	Follow-up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Selmer R et al 1995 [165]	Bergen Blood Pressure Survey	51475 Norway both sexes, age-ranges 30-79	27	BMI quintiles and 5 unit increments	Mortality from CVD, stroke, CHD and all-causes	HR and age-adjusted 27 year mortality rate	Age (strata of HT, sex, follow-up time)	Parabolic relationship between BMI and mortality for both sexes at all levels of blood pressure and for CVD in women (estrogen effect from fat?). In the elderly the thinnest hypertensive had the highest CVD-risk - postulates that lean hypertension is caused by excess alcohol and smoking.
Rissanen A et al 1991 [147]	"Finnish Social Insurance Institution Study"	17159 Finland Women, age-ranges (25-44, 45-54, 55-64) 25-79	12	BMI quintiles	Mortality from CVD, cancer, other causes and all-causes	RR 1.5 (quintile 1 and 5 vs 2)	Age, region	BMI-mortality association may change as the follow-up time increases. BMI-mortality from all-causes only evident in non-smokers. Older women had increased risk of cancer with thinness. BMI is no important predictor of mortality in old women.

Table L-2. Studies on the association between Body Mass Index (BMI) and all-cause mortality in different age-segments, conducted in non-Nordic countries and published in the past 20 years.

(Search performed in MEDLINE and EMBASE (limits: English language, 1991-current date, full-text available) and by scrutinizing lists of references in selected papers.)

Author Publ. year	Study name	N Population Age-range	Follow -up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Flicker L 2010 [51]	The Health in Men Study and the Australian Longitudinal Study of Women's Health	9240 Australia both sexes 70-75	10	BMI (WHO categories), physical activity	Mortality from CVD, cancer, respiratory death, and all-causes	Overweight HR 0.87. Sedentary women HR 2.08, men HR 1.28.	Education, marital, alcohol, exercise, Healthy: not reporting diabetes, heart disease, stroke, HT, COPD, smoke. Removed 1-2-3 early years events.	WHO-classification of BMI thresholds for overweight and obese are overly restrictive for older people. Being sedentary was associated with greater risk in women than in men. Other comment comparable to other studies.
Hastie C E et al 2009 [76]	Scottish Coronary Revascularisation Register Study	4880 Scottland both sexes, PCI-patients all	5	BMI <20, 20-25, 25-27.5, 27.5-30, ≥30	Mortality from all-causes	HR overweight II (27.5-30): 0.59. Underweight HR 2.12-1.69, but non-significant (N=54)	Age, sex, smoke, diabetes, left ventr.impairment, MI, sosec quintile, number of arteries stenosed, HT. Elimination of first 30 days of follow-up.	Obesity paradox in patients undergoing PCI. Causality is plausible: The adverse effect of excess adipose tissue may be offset by beneficial vasoactive properties as adipose tissue is now recognized as a major endocrine organ: associated with elevated s-LDL (anti-inflammatory) and soluble tissue necrosis factor receptors. Recommends WH-ratio.

Table L-2 cont.

Author Publ. year	Study name	N Population Age-range	Follow-up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Myrskylä M et al 2009 [126]	Health and Retirement Study	13104 USA weight-change categories 50-70	9,7	BMI change (5 categories)	Mortality from all-causes	Weight loss increases risk of mortality in all initial BMI levels below 32. Increased risk for larges losses and lower initial BMI. Weight gain only mortal among the initilally obese.	2-year weight-change, age, sex, cohort, race, education, income, LPA, smoke, subgroup analyses according to self-rated health	Self reports, cause of death is missing (previously found that weightloss is associated with increased CVD- and cancer mortality, but with decreased diabetes-mortality. Intentional/unintentional weightloss?
Stessman J et al 2009 [177]	"Western Jerusalem"	2403 Israel both sexes, age-group 70, 78, and 85 70	18 10 and 3	BMI continuous and categories(WHO)	Mortality from all-causes	higher BMI was associated with lower mortality from age 70-88	Elimination of the first 1/3 of follow-up mortality, smoke, LPA, ADL-dependency, sex, age, education, diabetes, self rated health, IHD, cancer, economy	Fat cells are biologically active secreting numerous hormones and cytokines, which may be related to atherosclerosis (pluripotent stem cells and control of mesenteric arterial tone by inducing vasorelaxation by adiponectin.
Batsis J A et al 2008 [14]	The Rochester Epidemiology Project	1195 USA Hip-fracture-patients ≥65	1	BMI (WHO-classification)	MI, AP, Congestive heart failure, arrhythmia	OR (underweight vs normal) MI: 1.44, arrhythmia: 1.59, multivariate - any-type-cardiac event: 1.56. Overweight and obese had no excess risk.	Age, sex, years of surgery, beta blockers, the Revised Cardiac Risk Index.	Hip-fracture pt, evidence of the "obesity paradox", sarcopenia/bone-mineral-density, serum lipids, anti-inflammation, survival-advantage of obese pt surviving into old age. BMI versus body-fat correlation is poor in the elderly leading to underestimation of the effect of obesity.

Table L-2 cont.

Author Publ. year	Study name	N Population Age-range	Follow -up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Janssen I et al 2008 [90]	The Framingham Study	3239 USA both sexes ≥70	10	BMI (WHO) midlife(50ties) and old age (70ties), BMI-change	Mortality from all-causes	HR 1.56 for obese(50)/nonobese (70), 1.47 for obese/obese, compared to nonobese/nonobese (ref)	Age, sex, smoke, alcohol	Midlife BMI was a better predictor for mortality than current BMI in older participants. Current BMI provided more useful info when put into context of their BMI at midlife.
Pischon T et al 2008 [139]	EPIC (prospective, 10 countries)	359387 Europe Sexes, age-range, etc. 25-70	9,7	BMI (9 categories)	Mortality from all-causes	HR 1.28-1.40 ($p<0.05$) at BM<21 in subjects aged 65+	Waist circumference (WC) , WH-ratio, education, smoke, alcohol, leisure time PA, height	WC and BMI correlation of 85%, WC improved the ability of BMI to predict vascular and all-cause mortality, but waist-to-hip ratio inferior predictor.
Snih S A 2007 [6]	Established Populations for Epidemiologic Studies of the Elderly	8359 USA non-disabled ≥65	7	BMI (WHO-classification)	Mortality from all-causes and disability	Overweight 25-30 had lowest risk of mortality. BMI 24 - lowest risk of disability.	Medical condition, Activities of daily living, demographic info, race, sex, age, education	Assessment of obesity effects on the health on the older Americans should account for mortality AND incidence of disability as disability-free life-expectancy is greatest among subjects with BMI 25-30
Takata Y et al 2007 [184]	"Japan"	697 (54.4%) Japan both sexes, weight-change-category 80	4	BMI (WHO-classification)	Mortality from CVD, cancer, pneumonia and all-causes	HR overweight vs under/normal: 0.22. CVD HR 4.64 in under vs over, Cancer HR 0.12 in under vs over. Pneumonia indifferent between weight groups	Sex, smoke, weightloss, current outpatient, SBP, phys act, functional status, marital, chol, gluc, preexisting disease, residence	Failure to adjust for socioeconomy, residual confounding from preexisting disease?

Table L-2 cont.

Author Publ. year	Study name	N Population Age-range	Follow-up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Weiss a et al 2007 [202]	"Israel patients"	470 Israel inpatients patients 81.5 (≥60)	4	BMI-quartiles, <22, 22-25, 25.02-28, 28+	Mortality from all-causes	age adjusted mortality rate/100 patient years and HR decreased with increasing BMI	Sex, age, renal failure, diabetes. Elim of first 6 months of follow-up.	Selective survival due to genetic predisposition + energy stores to protect the overweight elderly from catabolic processes. Lack of autopsy increased risk of misclassification on cause of death. Cohort of patients was originally studied for orthostatic hypotension - limits generalizability of findings. No test on effect of elim. of unhealty pt.
Corrada M M et al 2006 [37]	Leisure World Cohort Study	13451 USA both sexes, residents in Leisure World Laguna Hills retirement Community, smoke ≥65 (73)	23	BMI (WHO-classification)	Mortality from all-causes	RR 1.51 (underweight), 1.25 (obese) in later life, weightloss between age 21 and study entry had increased mortality regardless of initial BMI.	Age, sex, weight-loss, smoke, phys act, medical history. Eliminated first 5 years of follow-up events.	U-shape. Compares effect of obesity and underweight between younger and older study-participants - emphasizing different profiles according to age-range. weight-changes reported since 21 years age (recall bias?), but no info on recent weightloss, unintentional weightloss, weight cycling,
Freedman D M et al 2006 [55]	US radiologic technologists (USRT) study	83744 USA both sexes, radiation technologists, age-range: <55, ≥55 (5 categories) adults	14,7	BMI (WHO-classification) and 8 categories	mortality from all-causes	Older (>55 yrs) never smokers (after elim 5 years) HR began to rise at BMI above 25 for women and above 30 for men. (In the younger at 21 and 23)	Age, sex, race, education, residence (geography), smoke, alcohol. Separate analysis of never smokers and elimination of first 5 years of follow-up events	Linear association at age below 55, J-shape above 55. WH-ratio preferable according to 5 cited papers. Skinfold thickness or muscle volume? Lack of info on LPA, muscle-strength, diet, illness-related weightloss,

Table L-2 cont.

Author Publ. year	Study name	N Population Age-range	Follow-up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Gu D et al 2006 [63]	"China"	154736 China both sexes, age range (<65, ≥65), healthy/high-risk ≥40	10	BMI	mortality from CVD, cancer, etc and all-causes	HR and age-standardized mortality-rates, U-shape: nadir 23-24.9	Age, sex, smoke, alcohol, LPA, education, geographic region, urbanization, elimination of smokers, heavy drinkers, preexisting disease, deaths first 3 years.	U-shape. Recommend one single common recommendation for defining overweight and obesity among all racial and ethnic groups.
Breeze E et al 2005 [24]	The Whitehall Study	4862 USA men (former civil servants) 70-96	5	BMI-quartiles (<22.7, 22.7-24.4, 24.4-26.1, ≥26.1)	mortality from CVD, respiratory disease, cancer and all-causes	HR raised at BMI >22.7 also in apparently healthy elderly	Marital status, employment grade at time of leaving civil service, smoke, alcohol, physical functioning (SF36), ADL, present CVD, weight change at resurvey. Subgroup of never smokers, early (2 yrs) and late follow-up analysed separately	U-shape. Pattern differed between the different causes of death. Weight change of 10 kg or more over 30 years was a stronger predictor of CVD-mortality in old age than BMI in middle or old age. Weightloss and low BMI was strongly associated with respiratory mortality irrespectively of smoke. Steep increase in mortality after 2 years indicates some health selection in the cohort. Sequence of events (weightloss-disease-weightloss) was not directly measured, but, reverse causation seems less likely as association persisted 3-5 year of follow-up. Only 4% of cohort was obese (power). Weightloss due to loss of lean muscle mass may be reason for increased CVD-mortality in the lean.

Table L-2 cont.

Author Publ. year	Study name	N Population Age-range	Follow-up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Flegal KM et al 2005 [49]	NHANES I, II & III (National health and nutrition examination survey)	388622 USA both sexes, race, treatment, site, age-range 25-70+	7 (3-22)	BMI (WHO-classification)	mortality from CHD, CVD, cancer and all-causes	HR 1.69 in BMI<18.5 in age 70+, HR 2.30 in age 60-69	Sex, smoking, race, alcohol	Impact of obesity on mortality has decreased over time, probably because of improvements in public health and medical care.
Janssen I et al 2005 [89]	Cardiovascular Health Study	5200 USA both sexes, age-range (65-74, 75+), healthy at baseline 65+	9	BMI and WC (continuous, 1 SD increase)	mortality from all-causes	HR (BMI) 0.88, when adjusted for WC: 0.81. HR (WC) 0.94, adjusted for BMI: 1.12	Age, sex, race, smoke, PA, socioeconomy, disease.	.
Sergi G et al 2005 [167]	Italian Longitudinal Study of Aging (ILSA)	3110 Italy both sexes 65-84	3,5	BMI deciles	mortality from all-causes	PPV of death increases steeply below BMI 20	Age, sex, education, smoke, disability, disease status, Subgroup exclusion of participants with recent weight loss (5 kg during last yr), excluding first 6 and 12 months of deaths.	Low BMI is associated with higher mortality risks in men than in women. Threshold for "high risk" underweight should be set to BMI 20 in the elderly, but BMI 20-22 should be considered as "at risk" - possibly receptive of early intervention. Comparable results for recent vs stable underweight state - confirming that being underweight is an independent risk factor of mortality (and frailty?)

Table L-2 cont.

Author Publ. year	Study name	N Population Age-range	Follow-up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Ajani U A et al 2004 [5]	Physician Health Study	85078 USA men (physicians), age-ranges (40-54, 55-69, 70-84) 40-84	5	BMI (<20, 20-22.4, 22.5-24.9, 25-27.4, 27.5-29.9, 30+)	mortality from CVD and all-causes	BMI>30 increases risk of mortality and CVD mortality by 70% in all age-ranges	Age, alcohol, LPA Elimination of first 2 years, subgroup of never smokers	Linear association, no increased mortality in leaner men after adjustments, effect modification of physical activity on the BMI-mortality-association. Questions self-reports, early eliminations, lack of information on weight-change over time avd WH-ratio, physicians - health worker effect
Grabowski D C et al 2001 [60]	Longitudinal study of Aging (LSOA)	7527 USA community-dwelling elderly ≥70	8	BMI lower 10% <19.4 (thin), upper 15% >28.5 (obese), remaining 19.4-28.5 (normal)	mortality from all-causes	Model 1-2-3-4-5: HR obese 0.86, HR thin 1.46	Demographic, health service utilization, funct.status, race, age, sex etc. Sensitivity analyses income, mortality first 2 years, comorbidity did not alter conclusions.	No control for cigarette smoking.
Taylor D H et al 2001 [187]	National Long Term Care Survey (NLTCS)	4791 USA both sexes ≥65	1	BMI (WHO)	mortality from all-causes	BMI NADIR 30-34. for both elderly men and women	Smoke, alcohol, LPA, cognition, education, race, BMI at 1 year earlier and at age 50. Eliminationg smokers and unhealthy.	Effect of weightloss short-term/long-term (past year and past 15 years). Large group of participants (1200) aged 85+. Control for smoke/alcohol/LPA. Was weightloss intentional or not? Lack of information on functional status and body composition.

Table L-2 cont.

Author Publ. year	Study name	N Population Age-range	Follow-up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Calle EE et al 1999 [27]	Cancer prevention study II	1046454 USA both sexes, age-range, race 30-75+	14	BMI 12 categories	mortality from CVD, cancer, etc and all-causes	Model 1-5. HR increased for BMI<20.5 (compared to 23.5-24.9) in all whites and increasing with age. obesity risk white>black, men>women, young>old	Education, LPA, alcohol, age, marital, aspirin, fat/vegetables, estrogens (women). Eliminated smokers and presence of disease.	U-shape. Optimal weight for longevity increases with **age** and varies with race; BMI optimum 23.5-24.9 in men and 22-23.4 in women. The risk associated with a high BMI is greater for whites than blacks. Understanding of the risk associated with leanness is of scientific interest - but in terms of public health excess risk associated with obesity is of greater concern. WH-ratio would have been preferable in the elderly.
Singh pn 1999 [171]	California Seventh Day Adventist Study	16946 USA women (white, never smokers), age-range (30-54, 55-74) 30-74	26	BMI <21, 21-26.9, >27, weigh-change.	mortality from CVD, respiratory diseases, cancer etc. and all-causes	HR of respiratory death 0.6 in overweight (BMI>27) in age-range 55-74, but increased risk of all other disease categories. BMI<21 increased risk HR 1.4.	Weight-change over 17 years (1960-1976). Elimination of the first 15 years!	Age modifies the effect of the obesity-mortality association. Obesity increases risk, but apparently health, never-smoking women has increased risk of CVD and respiratory deaths due to lower BMI.
Stevens J 1998 [178]	American Cancer Society's Cancer Prevention Study	324135 USA both sexes, age-ranges 30-44, 45-54, 55-64, 65-74, 75-84, 85+) ≥30	12	BMI	mortality from CVD and all-causes	Higher BMI was associated with increased risk of mortality and CVD-mortality up to 75 years age, but the relative risk decreases with age after that (?)	No history of disease, smoke, recent unintentional weight-loss	Age modifies the effect of the obesity-mortality association

Table L-2 cont.

Author Publ. year	Study name	N Population Age-range	Follow -up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Allison D B et al 1997 [7]	The Longitudinal Study of Aging (LSOA)	7260 USA both sexes, race ≥70	6	BMI deciles and continuous	mortality from all-causes	Optimal hazard at BMI 31.7 for women, 28.8 for men	Age, sex, education, eating-difficulties, worry of health, perceived declining health, retiring due to ill health. Weighted analyses, excluding subjects in apparent ill health and exclusion of BMI <16 or >40	U-shape. The shape of the curve in older pt may be due to other influences on mortality overshadowing or "washing out" the effect of BMI among the elderly OR alternatively higher BMIs being protective against disease. **No effect of race.** No control for smoking, self-reports (8 studies show correlation of self rep and measured BMI ≥0.88), only one BMI-measurement (static vs dynamic effect of BMI), residual confounding despite elim early mortality. Body composition in old age - vs use of BMI.
Lindsted K D 1997 [109]	California Seventh Day Adventist Study	12576 USA women, age (30-54, 55-74), white, never-smokers, follow-up-range (year 1-8, 9-14, 15-26) 30-74	26	BMI quintiles	mortality from all-causes	Overweight was a risk factor for fatal disease throughout adulthood. Lean, healthy, middle-aged	age, alcohol, education, marital, diet	Age modifies the effect of the obesity-mortality association. BMI-mortality association may change as the follow-up time increases.
Manson JoAnn E et al 1995 [113]	Nurses Health Study	115195 USA women (nurses) 30-55	16	BMI categories <19 (ref), 19-21.9, 22-24.9, 25-26.9, 27-28.9, 29-31.9, 32+)	mortality from all-causes	HR increased in all BMI-categories above the reference. Lean women had no excess risk.	smoking, weight gain of 10+ kg since age 18 was associated with increased risk, alcohol, LPA, dietary fat, exclusion of 4 years of follow-up	J-shape. In never smokers no increased risk in the lower BMI-range. Nurses - health worker effect. No age-modifying effect on the obesity-mortality association was observed. Effect of elimination of early deaths is limited. The lowest mortality was in women who weighed at least 15% less than the US average for that age and who had a stable weight.

Table L-3. Studies on the association between non-occupational physical activity (PA) and all-cause mortality in different age-segments, conducted in the Nordic countries and published in the past 20 years.

(Search performed in MEDLINE and EMBASE, limits: English language, 1991-current date, full-text available) and by scrutinizing lists of references in selected papers.)

Author Publ. year	Study name	N Population Age-range	Follow-up (years)	Exposure	Outcome	Effect estimate	Adjustments	Comments
Byberg L et al [25] 2009	ULSAM (The Uppsala Longitudinal Study of Adult Men)	2205 Sweden Men only 49-51	35	PA (questionnaire) and change in PA during adult life	Mortality from all-causes	Absolute mortality rate 27-24-18/1000 py, relative rate reduction 32-22% in high-medium, increasing PA will (after 10 years) reduce mortality to the same level as unchanged high-level and comparable to smoking cessation	Age, weight, height, BMI, No(%) obese, SBP, DBP, antihypertensiva, cholesterol, self-rated health, smoking, OPA	Strenght in re-examination PA-level at age 60, 70 and 77. Weakness in the crude PA-measure, including men only and possibly for adjusting for intermediates.
Schnohr P 2007 [161]	Copenhagen City Heart Study	7308 Denmark both sexes 20-93	12	PA (questionnaire), walking duration (4 levels) and intensity (3 levels)	Mortality from all-causes	Longest duration HR 0.89 (men), 0.80 (women), both n.s. Highest intensity: 0.43 and 0.48 respectively.	Age, number of sports activities, BMI, SBP, antihypertensive med, cholesterol, HDL, smoke, education, income, alcohol, diabetes.	PA intensity concluded to be more important than duration.

Table L-3 cont.

Author Publ. year	Study name	N Population Age-range	Follow-up (years)	Exposure	Outcome	Effect estimate	Adjustments	Comments
Schnohr P et al 2006 [160]	Copenhagen City Heart Study	4894 Denmark both sexes 20-79	19	PA (unchanged between 1976-83), (3 levels)	Mortality from IHD, stroke, respiratory disease, cancer and all-causes.	HR all-cause mortality: 0.77 (moderate) and 0.75 (high), IHD 0.71 and 0.56. Respiratory disease and stroke did not reach statistical significance.	Age, sex, smoke, cholesterol, SBP, DM, alcohol, BMI, education, income, FEV%	Saltin & Grimsby questionnaire! The data show a clear tendency towards higher risk factor burden for both men and women in the low PA group. Kaplan-Meier plots to calculate gained years of expected lifetime, (difference in median survival between a 50-year-old person in the low, moderate and high PA group). (Men/women (high) 6.8/6.4 yrs, (moderate) 4.9/5.5 yrs). FEV% is a strong predictor of mortality and also a limiting factor for PA.
Hu G et al 2005 [85]	Finnish Cohort random sample (Baseline formed by 6 indep. cross sectional studies)	47212 Finland both sexes, 25-64	18	PA (3 levels), BMI (strata of smoke and age) and PA (strata of BMI)	Mortality from CVD, cancer and all-causes	HR (multivariate) PA vs. Mortality: 1.00-0.64-0.53(men) and 1.00-0.69-0.52(women). Low BMI indicated higher mortality, but attributed only 0.3% of deaths, whereas in 5.5% of men and 17.7% of women deaths were attributed to obesity.	Age, study year, smoke, SBP, chol, BMI, diabetes, education. Elim first 2 years. (also elim of cancer/CVD-pt at baseline). Studied effect in different time-periods of the follow-up.	Most studies have found that the protective effect of PA is found in different population groups and is usually stronger in women than in men. OPA should be included. Self reports are crude and imprecise, only baseline measurements. Changes in exposure status during follow-up time/misclassification of the exposure, but this leads to underestimation of the association between PA and outcome. Alcohol information lacking.

Table L-3 cont.

Author Publ. year	Study name	N Population Age-range	Follow-up (years)	Exposure	Outcome	Effect estimate	Adjustments	Comments
Sundquist K et al 2004 [182]	Swedish Annual Level-of-Living Survey (SALLS)	3206 Sweden both sexes, age: 65-69, 70-74, 75-79, 80-89, 90+), com. living ≥65	12	PA (5 levels)	Mortality from all-cause	HR in PA-level 2-5 compared to 1 (multivariate): 0.72, 0.60, 0.50, 0.60	Age, education, LPA, smoke, BMI, DM, HT, self-rated health	Adjusting for self-rated health at baseline to evaluate physical inactivity that is not a result of disease processes. Tables on covariates and their association to mortality!
Schroll M 2003 [164]	Review of The Glostrup Population Studies, The Copenhagen City Heart Study, and The Copenhagen Male Study	976 and 30000 (baseline) Denmark both sexes 50-85	35 (and 14.5)	OPA, LPA	Changes in PA over time (with longitudinal ageing), MI, hip-fracture, functional ability mortality from all-cause	A stable PA level was inversely associated with mortality, hip fractures, MI and functional ability.	div.	Saltin & Grimsby questionnaire! Extended questionnaire for elderly (including ADL) which can be compared to the original. Decreased risk of hip fracture in 50 years olds who are PA (after multiple adjustments and exclusion of chronically ill and early 5 year events) ref Sex differences disappeared when domestic activities were taken into account - questionnaires not taking ADL into account will underestimate the activities of women/elderly.

Table L-3 cont.

Author Publ. year	Study name	N Population Age-range	Follow-up (years)	Exposure	Outcome	Effect estimate	Adjustments	Comments
Andersen L B et al 2000 [10]	Copenhagen City Heart Study and The Glostrup Population Studies	13375 women and 17265 men Denmark both sexes 20-93	14,5	PA during work leisure-time, cycling to work and sports participation (quartiles)	Mortality from all-causes	mortality rates (age- and sex adjusted): 0.68, 0.61, and 0.53 PA-groups 2-4 compared to sedentary. Sports participants had half the mortality of non-participants (within the moderately- and highly active).	Age, sex, education, blood-lipids, BP, smoke, BMI	Refers to all previous Scandinavian studies in women and PA which show significant protective effect from high levels of PA, RR inactive vs most active: 1.9-2.4-1.6 (studier published in 86, 88, 96): Tendency of increased benefit with higher age (in women). lower mortality levels with higher activity in the elderly. Framingham RR 0.24 in PA women 75+, but not in men.
Johansson S E et al 1999 92	The Swedish Annual Level-of-loving Survey	3843 Sweden both sexes 25-74	7	LPA, combined PA+BMI+smoke, LPA-changes over 8 years	Mortality from all-causes (1988-95), poor health status (second survey (1988-89)	HR mortality PA no-no 1.87, yes-no 1.73, no-yes 1.39 (PA yes both surveys ref 1.00)	Age, sex, marital, education, smoke, BMI, HT	Refer to the Longitudinal study from Alameda County on predictors of successful ageing form men and women 65-95: walking for exercise was prospectively associated with successful ageing. PA is one of four a 'cornerstone' approaches in securing cardiac health in community preventing trials.

Table L-3 cont.

Author Publ. year	Study name	N Population Age-range	Follow-up (years)	Exposure	Outcome	Effect estimate	Adjustments	Comments
Agnarsson U et al 1999 3	The Reykjavik Study	4484 (249 strokes) Iceland men 45-80	10,6	Leisure-time PA (yes/no in different age-ranges, ≥or<6h/w, typea or B) and FEV1 and FVC	Stroke (ischemic, hemorrhagic from hospital records and death certificates)	RR (multivariate) 0.69 n.s. for stroke, 0.62 for ischemic stroke for the PA. RR 1.9 for stroke for the lowest vs highest quintile of FEV or FVC.	Age, fasting blood glucose, smoke, HT, FEV1, PA after age 40	Lowest risk seemed to be associated with the low-intensity sports like walking/swimming (no dose-respond in contrast to Sacco rl et al, The northern Manhattan stroke study 1998). No association found for hemorrhagic stroke (in contrast to Abbott rd The Honolulu heart program 1994): Important finding is that the protective effect seems to be regular PA maintained into ages at which the risk for stroke increases. Retrospective nature of the inquiry of the former levels of phys act in the elderly. Stroke misclassifications.
Eriksen G et al 1998 [47]	Norwegian population	2014 Norway men (apperantly healthy) 40-60	22	Physical fitness PF (4 quartiles), change in fitness over 7 years (bicycle work capacity)	Fitness-change, mortality from CVD and all-causes	Multivariate: age, SBP, P, chol, TG, BMI, amount of physical activity, exercise ECG-results and smoke. Only smoke, heartrate, SBP and VC appeared as confounders of the predictive power of physical fitness.	Inverse relation between all-cause mortality and fitness: HR 3 upper quartiles: 0.63, 0.37, 0.31 (age-adjusted). Correlation between PF1 and PF2 good: *r=0.74*	Not only fitness, but also the magnitude and direction of changes in fitness over 7 years give information on risk of death during the following 15 years.
Håheim L L et al 1993 [71]	The Oslo Study	14403 Norway men 40-49	12	LPA and OPA	Stroke, mortality from all-causes	RR 0.36 highest level of PA, unadjusted, Multivariate RR 0.70 per unit (PA level 1-4).	Age, chol, DBP, smoke	LPA, but not OPA was a risk factor for stroke, but not for stroke-mortality. [Small (N) numbers of fatal stroke (7+17+2)].

Table L-4. Studies on the association between physical activity (PA) and all-cause mortality in different age-segments, conducted in non-Nordic countries and published in the past 20 years.

(Search performed in MEDLINE and EMBASE, limits: English language, 1991-current date, full-text available) and by scrutinizing lists of references in selected papers.)

Author Publ. year	Study name	N Population Age-range Subgroups	Follow-up	Exposure	Outcome	Effectestimate	Adjustments	Comments
Wen C P et al 2011 [26]	MJ Health Management Institution Pragramme	416175 Taiwan both sexes private screen 20+	13	PA 15 minutes per day	Mortality from all causes, and cause-specific	HR 0.86, 3 year longer life expectancy. Additional 15 minutes PA per day reduced mortality by 4% per 15 minutes per day.	Sex, age, education, OPA, smoke, drink, BMI, SBP, glucose, cholesterol, metabolic syndrome, kidney disease,	Taiwanese population, health/high socioeconomic group. Effect in all agegroups, sexes, and those with cardio disease risk.
Lantz P M 2010 [105]	Americans' Changing Lives (ACL) longitudinal study	3617 USA ≥25 age-range: <55, 55+, non-institutionalized (68% response rate)	19	PA (quintiles)	mortality from all-causes	HR (multivariate) lowest quintile of PA (highest quintile ref): 2.22-1.58, for age-range 55+: 2.65-1.88 (model 2-3). HR to underweight and to obesity persists after adjustments to PA in the age-range 55+.	Model 1: age, sex, ethnicity, education, residence, income. Model 2: +smoke, alcohol, BMI. Model 3: +PHYSICAL IMPAIRMENT and SELF-RATED HEALTH.	The extended follow-up allowed stratified analyses by age which revealed some differences in determinants of mortality. In addition, confirming that key results from prior works holds over much longer follow-up periods provides more evidence of the scientific reliability and thus the policy relevance of these findings.

Table L-4 cont.

Author Publ. year	Study name	N Population Age-range Subgroups	Follow-up	Exposure	Outcome	Effectestimate	Adjustments	Comments
Chow C K et al 2010 [31]	The Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)	18809 World (41 countries) 67 (mean) Patients with acute coronary syndrome, country, smoking	0,5	PA, diet, smoke adherence to recommendation at day 30	mortality from CVD (MI, stroke, CVD-mortality) and all-causes	OR MI 0.52, stroke 0.46, death 0.45,	Age, sex, region, HT, diabetes, prior MI, BMI, krea, PCI/CABG before 30 days, beta-blocker, statins, antiplatelets, ACE-drugs at 30 days	Patients who smoked, and did not adhere to recommendations regarding PA nor diet at day 3+ had an increased OR 3.77 of repeated MI/stroke/death. LIFESTYLE risk factors are important already in a short period of time!
Stamatakis E et al 2009 [174]	The Health Survey for England (HSE) and The Scottish Health Survey (SHS)	20177 Great Britain ≥35 both sexes, medicated (CVD-drug: N=3116) vs unmedicated	6, 6	PA	mortality from all-causes	HR unmedicated 0.58 all-cause, 0.65 CVD; medicated 0.54, 0.46.	Multivariate: age, sex, OPA, BMI, Soc.ec, ethnicity, chronic illness, marital, smoke, parental cause of death, alcohol, self-reported health, diabetes, HT.	Drugs for primary prevention are often prescribed with little attention to lifestyle modification
Stamatakis E et al 2009 [173]	The Scottish Health Survey	13726 Scotland ≥35 both sexes, CVD-free-respondents	8, 4	Intense domestic physical activity (IDPA)	mortality from CVD (fatal and non-fatal combined) and all-causes	RR all-causes: 0.68 (men), 0.70 (women). None effect found on CVD.	Age, semi-adjusted (age, social class, marital) fully-adjusted (all co variables incl. Adjustment for other activity groups)	.

Table L-4 cont.

Author Publ. year	Study name	N Population Age-range Subgroups	Follow-up	Exposure	Outcome	Effectestimate	Adjustments	Comments
Bembom o et al 2009 18	The Study of Physical Performance and Age-Related Changes in Sonomans.	2092 USA (better educated and health conscious) ≥54 age range ≤75, >75, CHD +/-, exercise+/-	2	PA 22 activities, times per week last yr - MET	mortality from all-causes	(MSM pooled over 4 time points) Estimated excess risk: ≥75 yrs, -CHD, +PA: -10.2%, <75: -0.7%	Confounders: sex, environmental smoke, weight, height, chronic diseases (incl depression), smoke, living arrangements. Effect modifiers? Cardiac disease (self reported), past levels of activity	Mortality-sparing-effect of PA seems more evident in the oldest subgroup. Non significant effect modification by present CHD. Mortality-sparing benefits of PA are achieved quickly and are nor dependent on past levels of activity (Benetos). Few deaths in <75 yrs. Grouping of levels of activity. Measurement errors.
Besson H et al 2008 [20]	The European Prospective Investigation Into Cancer (EPIC) Study	14903 England 45-79 working/non-working	7	PA (validated EPAQ2 questionnaire)	mortality from CHD, cancer, and all-causes	RR (multi) 0.77 (mort) and inversely ass to CHD-mortality (p trend 0.007). No ass. to cancer mortality.	Age, sex, soc class, alcohol, smoke, history of diabetes, cancer, CHD, or stroke. Elim those with cancer, CHD, stroke and those who died first 2 yrs	PA at home and during exercise is inv ass to mortality, but neither occupational nor transportation-related activities. Reducing platelet aggregation, increased fibrinolytic activity, improving insulin sensitivity, improving cardiac function/cardiorespiratory fitness and lowering resting HR.
Manini T M et al 2006 [111]	The Health, Ageing, and Body Composition (ABD) Study	302 USA 70-82 both sexes	6,15	Free-living energy expenditure over 2 weeks (doubly labeled water) in tertiles	PA	HR 0.68 in highest compared to lowest tertile.	Age, sex, race, study site, weight, height, %body fat, sleep duration	Those with more energy expenditure were more likely to work for pay and climb stairs, but not more high intensity exercise, walking, volunteering or care giving (did not differ across EE-tertiles). Self reports on PA may underest. the benefits of higher levels of PA in older adults. Investig. of modifiable risk factors in older adults is important (growing segment, contributes disproportionally to health care costs.)

Table L-4 cont.

Author Publ. year	Study name	N Population Age-range Subgroups	Follow-up	Exposure	Outcome	Effectestimate	Adjustments	Comments
Benetos A et al 2005 19	Centre d'Investigations Préventives et Cliniques (IPC Centre)	7467 France 60-70 both sexes, IPC Center examinants in Paris area	18	PA (questionnaire) (BP, tot-chol, glycemia, smoking, ECG-LVH, BMI, TG, HR)	mortality from all-causes before 80 (men) and 85 (women), compared to survivors	OR (survival) PA 1.52 PP (10mmHg) 0.89, glycemia (1mmol/l) 0.96, HR(>80 bpm) 0.77	Age, sex, history of disease, FEV. Elim first 2 yrs.	PA, PP, HR<80, glycemia were those modifiable risk factors significantly related to odds of reaching a very advanced age and the changes in impact of certain risk factors in elderly. Suggests that increased longevity in PA is not due to reverse causation because of adjustments and elim 2 yrs. Observational study cannot draw conclusions on the benefits of "correcting" the risk factors.
Hu F B et al 2004 84	Nurses Health Study	116564 USA 30-55 women (nurses), smoke, free of CVD+cancer	24	PA (<1, 1-3,4 and 3,5+ hours exercise per week), BMI	mortality from CVD, cancer and all-causes	RR multivariat of death in lean (BMI<25)/sedentary women was 1.55, in obese/active 1.91, and obese/inactive 2.42 compared to lean/active.	Age, smoke, alcohol, menopausal status, use of hormone replacement, family history of MI before age 60.	All weight gain during adulthood was associated with higher risk. Excess weight (BMI 25+) and inactivity account for 31% of all premature deaths, 59% of CVD deaths and 21% of cancer deaths among nonsmoking women.

Table L-4 cont.

Author Publ. year	Study name	N Population Age-range Subgroups	Follow-up	Exposure	Outcome	Effectestimate	Adjustments	Comments
Wannamethee S G 2000 201	The British Regional Heart Study	963 Great Britain 63 (mean) men wit established IHD (<65, 65+)	5	PA (4 levels)	mortality from all-causes	HR 0.42 (light), 0.47 (moderate), 0.63 (mod-vigorous). Change from sedentary to light activity HR 0.58 (p 0.06)	Smoke, social class, obesity, disability, diabetes, stroke, breathlessness, chest pain, calf pain on walking.	Non-sporting activities were more important than sporting activities.
Wannamethee 1998 200	British regional heart study	4311 England 40-59 men	3	Physical activity change over 12-14 years (questionnaires)	mortality? from CHD	Risk 0.62 becoming active (vs remaining sedentary), 0.49 maintenance of physical activity		Increasing or maintenance of activity reduces risk of CHD
Bijinen F C H et al 1998 [21]	The Zutphen Elderly Study	802 Netherlands 64-84 men	10	PA (validated questionnaire) tertiles	mortality from CVD, CHD, stroke and all-causes	RR CVD 0.70 and all-cause 0.77 in highest vs lowest tertile of PA	Age, chronic disease, smoke, alcohol	Time spent in more intense activities was more strongly associated. Recommended walk/cycling at least 3/week for 20 minutes RR 0.69 and 0.71 (CHD and all-cause)
Kaplan G A et al 1996 [94]	The Alameda County Study, California	6131 USA 16-94 both sexes	28	LPA (quartiles)	mortality from CVD and all-causes	HR: 0.72-0.90 for all-cause, 0.67-0.85 for CVD (PA inter quartile-range)	Model 1: age, sex, ethnicity, education, Model 2: + health conditions, Model 3: +health behaviors and social isolation. Fixed PA and Time-dependent PA.	Despite the adjustments for baseline health status it may still be possible to some extent that the results reflect the impact of health status on PA (not the opposite!), but the effect of eliminating early deaths was trivial.

Table L-4 cont.

Author Publ. year	Study name	N Population Age-range Subgroups	Follow-up	Exposure	Outcome	Effectestimate	Adjustments	Comments
Sherman S E et al 1994 168	The Framingham Heart Study	285 USA 75+ both sexes	10	PA (quartiles)	mortality from all-causes	Women in PA quartile 3 had a RR (adjusted) 0.24). In men the findings were n.s.	Free of CVD. Cardiac risk factors COPD, cancer	Benefit seemed to be attenuated in the most active group.
Simonsick E M et al 1993 169	Established Populations for Epidemiologic Studies on Elderly	1815 USA 65+ both sexes, unimpaired elderly	6	PA	mortality from MI, stroke, diabetes, angina, and all-causes, functional decline	div	div	Frequent walking reduces likelihood of mortality over both 3 and 6 years in PA. Moderate to high activity appears to reduce the risk of functional decline over 3 years. Inactive have more depressive symptoms. Inactivity may be due to disease, but due to the sizable proportion of physically inactive younger adults (despite low rates of chronic diseases) the majority of inactivity is due to habit and not because of poor health!
Paffenbarger R S et al 1993 133	Harvard Alumni Study	10269 USA 45-84 men (Harvard alumni, response rate 71%)	9	PA (kcal below2000/week) and change in PA over 8 years.	mortality from all-causes and IHD	RR IHD and all-cause: 0.77 in beginning moderately vigorous sports activity compared to staying inactive largely independent of age.	HT, smoke, extremes or gains in body weight, or early parental death	.

Table L-5. Studies on the association between lung function and stroke published in the past 20 years.

(Search performed in MEDLINE and EMBASE (limits: English language, 1991-current date, full-text available) and by scrutinizing lists of references in selected papers.)

Author Publ. year	Study name	N Population Age-range	Follow -up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Sabia S et al 2010 [154]	Whitehall Study	4817 UK both sexes, civil servants (white collar) 35-55	6, 4	FEV1/height^2 (tertiles)	mortality from all-cause, cardiovascular (n=35), and cancer (n=68)	HR (CVD) n.s. 1.90 (0.94-3.85) for FEV1/height^2 (adjusted)	age, sex, smoke, inflammatory markers, CHD, stroke, diabetes, alcohol, diet PA, BMI, sosec, CVD-risk factors (Model 1-8)	Several subgroup analyses. Soc. Ec. Limitation due to white-collar population. Subgroup analyses: smoke, self-reported asthma, FEV/FVC-ratio<0.70, lowest tertile of fat-free-mass (sarcopenia?), BMI<30, BMI30+, elim first 2 years , elim crp>10
Iwamoto H et al 2009 [88]	Case (smokers with airflow limitations FEV/FVC<0.7) control (smokers and non-smokers) study	305 Japan healthy men 45-60	.	FEV1%, plaque	Carotid-intimal-media thickness, crp		age, pack-years, BMI, peripheral mean arterial pressure, HR, glucose, LDL chol.	Smokers with airflow-limitations had exaggerated subclinical atherosclerosis which indicates that atherosclerotic change starts early in the disease process of COPD.
Onufrak S J et al 2008 [131]	The ARIC Study	14567 USA both sexes 45-64	des.13	asthma (self-report)	Stroke incidental and fatal	HR (multivariate) 2.08 for stroke in women with adult onset asthma compared to no asthma history. In never smokers only HR 2.05.	smoke, diabetes, LDL, HDL, HT, education, asthma medication, FEV, FVC (sex specific quartiles)	? Estrogen modulated alterations in inflammatory cytokine and leukotriene regulations? Subgroup analyses: asthma subtypes, smoke

Table L-5 cont.

Author Publ. year	Study name	N Population Age-range	Follow -up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Chowdhuri S et al 2007 [32]	review (4 studies on stroke, and 8 on cardiac disease)	N not reported USA, UK and Denmark 40-84	14.8-16.6	FEV1 (1-SD decrease), FEV1-tertiles, FEV1% (1-10% decline)	Stroke and Cardiac disease	OR/RR 1.88-1.4 tertiles, 1.30 (lowest vs highest?)	div	Early studies showed no association probably due to a limited number of strokes (short follow-up): Framingham, Gothenburg Study, and Seven Countries Study. Later studies with larger number of strokes showed inverse association between lung function and stroke: Whitehall, British regional Heart Study, and Copenhagen Study. Pathway suggested: hypoxemia-small vessel-ischemia, hypoxia-hematocrit-blood-viscosity-ischemia, inflammation
Guo Xinxin et al 2006 [69]	Gothenburg Study	379 Sweden 70-92	20 (long) and cross-sect.	FEV1 and FVC (1-SD decrease)	white matter lesions (WML) and lacunar Infarcts	OR FVC(1-SD)1.49 (WML) and 1.95 (lacunar infarcts), FEV(1-SD) 1.46 and 1.42. PEF not associated.	multivariate	Both longitudinal association (lung function measures in 1980) and cross sectional (lung functional measures in 2000) confirmed the inverse relation between lung function and stroke. Suggested pathways: hypoxia-ischemia, inflammation, disturbances in the blood-brain barrier
Hozawa A et al 2006 83	Atherosclerosis Risk in Communities (ARIC) study	USA both sexes, 45-64	13	FEV%, FVC%, quartiles	ischemic stroke incidence	HR 1,59 FEV% quart 1 vs 4, HR 1.56 FVC% quart 1 vs 4.	multivariate	Residual confounding from smoking? Inflammatory pathway (WBC adjustments), symptoms subgroup analysis. Subgroup analyses: race, -symptoms, -smoke.

Table L-5 cont.

Author Publ. year	Study name	N Population Age-range	Follow -up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Sin D D et al 2005 [170]	National Health and Nutrition Examination Survey (NHANES) and literature review	1861 USA both sexes 40-60	18	FEV1% (quintile)	CVD-mortality, CVD-hospitalization, IHD-mortality, IHD. Hospitalization.	HR of CVD mortality (quint1 vs 5) all/non-smokers: 3.36/2.68, CVD-hospitalization: 1.69/1.71, IHD-mortality 5.65/3.98, IHD-hospitalization: 1.52/1.61. Metaanalysis: RR 1.75/1.67 (CVD-mortality)	age, BMI, sex, race, BP, chol, antihypertensive medication, Framingham risk score, smoke	Potential explanations: 1. Common offending factor (FEV as an epiphenomenon of such), 2. Confounding, 3. causal link (rabbit-models: airway-obstruction leads to systemic inflammation leads to atherosclerosis)
Stavem K et al 2005 [175]	Occupational Oslo Study	1623 Norway men, workers 40-59	26,0	FEV1 (10% reduction)	CVD-mortality, mortality from all-causes	RR 1.07 (adjusted) for CVD-mortality	smoke, physical fitness, age, SBP, BMI, chol	FEV1% was not associated with mortality among never-smokers. Subgroup analyses: smoking
Hart Carole L et al 2000 [73]	Renfrew/Paisley Study	15406 Scotland both sexes 45-64	20	FEV1 % quintiles and 1-SD.	Incidental stroke and stroke mortality	RR 1.23 and 1.22 respectively for incidental stroke	age	Fatal stroke and incidental stroke holds the same risk factors with comparable magnitude. Subgroup analyses: intervals of follow-up time
Engstrøm G et al 2001 [46]	Men Born in 1914, Malmø	639 Sweden men	28	FEV1 height adjusted (2 groups by median)	stroke, cardiac events, all-cause mortality	Stroke rates were 13.4 vs 5.8/1000, cardiac events 27.1 vs 12.8/1000 and all-cause mortality 52.5 vs 28.8/1000 py in lower FEV-median of hypertensive men.	smoking, tobacco consumption, antihypertensive treatment, PA, preexisting disease. Subgroup analyses: HT	Synergistic interaction between hypertension and lower lung function. In normotensive men stroke and cardiac events did not reach statistical significance.

Table L-5 cont.

Author Publ. year	Study name	N Population Age-range	Follow -up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Truelsen T et al 2001 [194]	Copenhagen Heart Study	12878 Denmark both sexes, free of stroke 45-84	15	FEV1	stroke, incidental stroke	RR first stroke 1.05 (p 0.03) for each 10% decrease in FEV1%. RR fatal stroke 1.11		30% higher risk in group with lower lung function compared to group with highest lung function.
Agnarsson U et al 1999 [3]	The Reykjavik Study	4484 Iceland men 45-80	10, 6	FEV1% (quintiles), FVC% (quintiles)	stroke (total=fatal+incidental), ischemic strokes	RR 1,80 in FVC quintiles 1 vs 5. FEV/FVC-ratio had no predictive power.	Age, smoke	FEV and FVC are composite indicators: genetic and environmental influences. No trend in stroke-risk for obstructive vs restrictive lung function.
Hart C L et al 1999 74	Renfrew/Paisley Study	15406 Scotland both sexes 45-64	20	FEV1 % quintiles	Fatal stroke	RR 1.27 and 1.24 in men and women respectively for fatal stroke	Age	FEV1 not much studied in other stroke-studies. Subgroup analyses: intervals of follow-up time
Knuiman M W et al 1999 [97]	Busselton Health Study	4277 Australia both sexes 25-79	20-26	FEV1%	mortality from all-cause, CHD, stroke, cancer and resp. Disease	HR stroke 1.120 (multivariate) for women, n.s. for men.	Age, smoke, resp.symptoms, CHD, CVD-risk factors. Subgroup analyses: smoke, sex	Lung function is associated with mortality from many diseases independent of smoking and respiratory symptoms. For stroke the association was significant only in women. If lung function is not a risk factor, but a concomitant indicator of disease and health status, then it should show a strong association with mortality and a weak association with the incidence of disease
Liao D et al 1999 [107]	ARIC	1917 multicenter both sexes 55-72	cross sectional	FEV1 (1-SD decrease)	cerebral subclinical abnormalities on MRI	OR 1.63 for infarction, 1.35 for white matter lesions (WMLs) in non-smokers. Similar in smokers and when using FVC.	Ethnicity, age, sex, height, height squared, smoking, education.	Results not changed by additional adjustments for cardiovascular disease or cognitive function. Subgroup analyses: race, non-smokers. In the lowest quartile 15% had CI and WMLs, 6% in the upper quart.

Table L-5 cont.

Author Publ. year	Study name	N Population Age-range	Follow -up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Hole D J et al 1996 [82]	Renfrew/Paisley Study	15411 Scotland, both sexes 45-64	15	FEV1 % quintiles.	Fatal stroke	HR/RR 1,66-1,65 quintile 5 vs 1	Age, smoke, DBP, s-chol, BMI, soc. Class	Commentary by Strachan. Subgroup analyses: intervals of follow-up time
Wannamethee S G et al 1995 [198]	Britisk Regional Heart Study	7735 England men 40-59	14, 8	FEV1 (>3.65 vs < 3.10	Incidental stroke	RR 1.40. Similar results for FVC. Association was noted only in subjects with preexisting IHD)	Age, smoke, social class, PA, alcohol, SBP, BP-treatment, diabetes, preexisting IHD, and interaction for smoking.	Weakness: women not included. Recall bias. Subgroup analysis: preexisting IHD
Cook N R et al 1994 [35]	Established populations for epidemiological studies of the elderly poject	3040 USA Elderly, without history of stroke or MI.		height (quintiles), PEF (peek expiratory flow rate)	cardiovascular death, stroke	Body height major predictor	Age, BMI, smoke, sbp, antihypertensive treatment, alcohol, education, resp symptoms,	association between quintiles of height and mortality could not be explained by lung function
Menotti A et al 1993 [118]	Seven countries Study	1709 Italian subpopulation, men, free from CVD-events 40-59	25	FEV, VC	Stroke (fatal and non-fatal)	OR (FEV1) 0.84 (youngest), OR (VC) 0.94 and 0.91 other age-ranges.	Multivariate	Association only evident in fatal strokes. No women.

Table L-5 cont.

Author Publ. year	Study name	N Population Age-range	Follow -up	Exposure	Outcome	Effect estimate	Adjustments	Comments
Strachan DP 1992 180	Whitehall Study	18403 England men, civil servants 40-64	18.jan	FEV1 (≥3.5 L compared to <3 L)	Fatal stroke	RR 1.88	Age, height, smoke, employment status, BP, weight, chol, gluc, ECG abnormalities, history of chest pains	Weakness: women not included.

Table L-6. Studies validating fatal stroke and ischemic heart disease in death certificates or mortality statistics against autopsy **findings, published in the past 30 years.**

(Search performed in MEDLINE and EMBASE and by scrutinizing lists of references in selected papers.)

Author Publ. year	N	Population	Subgroup	Autopsy rate	Outcome	Effect estimate	Comments
Carvalho F L P et al 2008 [138]	100	Brazil (Hospitalized patients)	Emergency or not emergency room	11.4%	VASCULAR DISEASE (Cause of death: 21-17 ICD groups)	Circulatory system: agreement 71%, disagreement 29%, Overall underlying cause of death kappa 0.38 (fair agreement). Agreement rate 64%	Disagreement between clinical and pathological diagnosis on cause of death did not differ according to length of hospital stay (Emergency room death etc.)
Saad R et al 2007 [153]	406	Brazil (Cardiac hospitalized patients)	Age-range, sex, hospital ward (ED or not)	23.6%-22.4%	VASCULAR DISEASE (Cause of death: 21 ICD groups)	Agreement circulatory 67.3%, neuro 33.4%	Lower autopsy-rates in the older, but equal in the sexes. Age, diagnosis, hospital ward may influence on the discrepancy and the low autopsy rate is a problem.
Ravakhah K 2006 [143]	223	USA (Hospitalized patients).	medical/surgical ward	14 %	Myocardial infarction (Diagnostic groups incl. IHD and cerebral haemorrhage.)	False negative MI: 48%, False positive MI: 25%	With careful selection and aggregation of the data obtained from autopsies, better generalizations could be made.
Grade M H C et al 2004 [61]	4828	Brazil	none	78 %	Cause of death (17 ICD groups of 1975) in 1990-95 compared to 1978-80	Circulatory: sens 0.75, ppv 0.85, false pos 0.15, false neg 0.25 (1990-95):	Discrete improvement tendency of correlation between clinical and post-mortem data, but discrepancies remained high and therefor autopsy continues to be an essential instrument.

Table L-6 cont.

Author Publ. year	N	Population	Subgroup	Autopsy rate	Outcome	Effect estimate	Comments
Sington J D et al 2002 [172]	440	UK (Hospitalized patients).	.	21 %	6 diagnostic groups incl. Cardiovascular and neurological (infarct+haemorrhage) diseases	Neurological system: Sensitivity 0.90, ppv 0.61, false pos 0.39; Cardiovascular system: Sensitivity 0.28(!!), ppv 0.65, false pos 0.35	"The relevance of these discrepancies at a population level is that they may also significantly alter mortality data, with subsequent inaccuracies in epidemiological statistics hiding potential associations between risk exposure and possible outcome". Bias: more difficult clinical cases are chosen for autopsy.
Karwinski B & Hartveit F 1989 [95]	742 + 833	Norway (Necropsies conducted in Gade in 1975 + 1984).	Age-range, sex, hospital department of death, Cause of death (WHO 17 main diagnostic groups)	75-81%	VASCULAR DISEASE (17 WHO-diagnostic groups)	1975-84: 81-88% agreement between autopsy and clinical diagnosis (n.s. increase). In the disagreement-cases (19-12%) Disagreement 14% vascular diseases.	Male dominance. The sex-distribution was equal. CVD (group VII) agreement was unchanged 86%. Increasing representation of neoplasia from 1975-1984. Reports of certainty about cause of death increased (42-64%) from 1975-84, but was not confirmed by autopsy. Errors are substantial even when the diagnoses are considered certain.
Kircher T et al 1985 [96]	272	USA		14 %	Cause of death (17 ICD groups)	Circulatory sens 0.82, ppv 0.75, false pos 0.25, false neg 0.18	Deaths most commonly overdiagnosed were circulatory disorders.
Goldman L et al 1983 [59]	100 +100 +100	USA (Hospitalized patients in 1960-70 and 80)	none	75-71-38%	Cause of death (cardiovascular incl. MI) ++	MI overall sens 0.75 (decline: 0.85-0.79-0.68)	NOT ADDRESSING STROKE - ONLY MI. Overall: 10% disconcordance that would have lead to increased survival both in 1960 and 1980, but decreasing autopsy-rate and probably different selections for autopsy in 1960 than 1980.
Torvik A et al 1981 [192]	ca 30000	Norway	year of death, M:F ratio, age-range (40-69, 70+)	79-86-72%	Stroke: cerebral hemorrhage, cerebral infarction etc.	Fatal stroke (%) 16-14 (autopsy data, age-group 40+)	Stable overall-mortality rate, hospital deaths, autopsy rate and admission policy during the 20 years of study, thus the figures from autopsy records are believed to indicate a true decline in stroke frequency (particularly for brain hemorrhage in younger individuals)

12 Appendix: The original questionnaire

THE BERGEN BLOD PRESSURE SURVEY IN 1965-71

Identification number: _____ 2

Date: _____ Time: _____ Physician: Interwiewer: Investig. 3

Other examination situation: 4

Surname: First name: Sex: male ❒ female ❒ 5

Address: Past surname: 6

Occupation: Own Shift work: Yes ❒ No ❒ 7

Occupation: Husband, supporter:

Past occupations (years):

Married ❒ Unmarried ❒ Widow(er) ❒ Divorced/Separated ❒ 8

Private physician(s), years:

Hospital admissions:

Hospital name	Year:	Diagnosis

Parents: Both alive ❒ Farther dead ❒ Mother dead ❒ Both dead ❒ 9

Don't know: Farther ❒ Mother ❒

If one or both are dead:

	Cause of death:	Don't know:	Age, aprox.:	Don't know:
Father		❒		❒
Mother		❒		❒

Siblings: Numbers: (including possible deceased) 10

Is any of your siblings dead? Yes ❒ How many:..... No❒ Don't know ❒

If Yes: Name	Cause of death:	Don't know:	Age, aprox.:	Don't know:
		❒		❒
		❒		❒

Children: Numbers: (including possible deceased) 11

Is any of your children dead? Yes ❒ How many:..... No❒ Don't know ❒

If Yes: Name	Cause of death:	Don't know:	Age, aprox.:	Don't know:
		❒		❒
		❒		❒
		❒		❒

Is any of these diseases existing in your nearest relatives (parents, siblings, children)?	Yes	No	Don't know	Age at onset	12
High blood pressure	☐	☐	☐		
Renal disease	☐	☐	☐		
Cystitis/Pyelonephritis	☐	☐	☐		
Diabetes	☐	☐	☐		
Cerebro-vascular accidents	☐	☐	☐		
Sudden death without known cause☐	☐	☐			

Has your blood pressure been measured previously (prior to the mass screening in 1963)?	☐	☐	☐	13
If Yes: By whom:	When:			
At what level was the blood pressure:	Normal ☐	Elev.☐	☐	
Have you taken medication to lower the pressure?	Yes ☐	No ☐	☐	
If yes; Which medication? Dose? Time?				
Do you use such medication at the moment?	☐	☐	☐	14

Do you have, or have you ever had:	Yes	When:	No	Don't know		15
Cystitis, dysuria or frequency?		☐		☐	☐	
Pyelonephritis?		☐		☐	☐	
Proteinuria?		☐		☐	☐	
Renal stone?		☐		☐	☐	
Other renal disease?		☐		☐	☐	
Diabetes?		☐		☐	☐	
Pulmonary disease?						
Prior to your 15. birthday 1☐		Twice or more after 15. birthday 3☐				
Once after 15. birthday 2☐		Pleuritis, any age			4☐	
Bronchitis?		☐		☐	☐	
Heart disease?		☐		☐	☐	
Rheumatic fever?		☐		☐	☐	
Paralysis, difficulty moving arm/leg, convulsive fit?☐				☐	☐	

For men:	Yes	No	16
Have you or have you had difficulty urinating? (frequent, slow or hesitant micturition)	☐	☐	For how long?
For women:	Yes	No	17
Have you been pregnant?	☐	☐	
The year of birth of your children:			
Have you had any abortion?	☐	☐	
If yes, when?			

Did you in any of your pregnancies suffer the following?	Yes	No	Don't know
Protein in the urine?	❒	❒	❒
Swelling of the legs?	❒	❒	❒
High blood pressure?	❒	❒	❒
Convulsions, visual difficulties?	❒	❒	❒
Cystitis?	❒	❒	❒
Pyelonephritis?	❒	❒	❒
Did these symptoms disappear after the delivery?	❒	❒	❒

Angina pectoris	Yes	No	Don't know 18
1. Have you ever had pain or discomfort in the chest?	❒	❒	❒
If No:			
2. Have you ever had pressure or heavyness in the chest?	❒	❒	❒
3. Do you notice this if you walk uphill or if you walk quickly on level ground? ❒	❒	❒	
Never walk quickly or uphill ❒			
4. Do you notice this if walking in ordinary pace on level ground?	❒	❒	❒
5. Do you notice this during other forms for activity?	❒	❒	❒
If Yes to 3 og 4:			
6. What do you do to relieve this during activity? Stop or reduce the pace? (Mark Yes if the subject continues after taking glyseryl trinitrate etc.)	❒	❒	❒
7. Does the pain (discomfort) disappear when you stop?	❒	❒	❒
8. If yes to 7: Within 10 minutes or less?	❒	❒	❒
Would you show me where you feel the pain (discomfort):			
9. Sternum, upper or middle part?	❒	❒	❒
10. Sternum, lower part?	❒	❒	❒
11. Left front of chest?	❒	❒	❒
12. Left arm?	❒	❒	❒
13. Other parts? Where:	❒	❒	❒
14. How long time is it since you first noticed these symptoms?			
15. Do you notice this when you sit still or lie down? (mark Yes if 4 times or more last month)	❒	❒	❒
If Yes to 15:			
16. Do you notice same during excitement or emotion?	❒	❒	❒

Angina pectoris continue	Yes	No	Don't know
17. Do you use glyseryl trinitrate?	❒	❒	❒
If Yes, how many per day , on average:			
18. How quickly is the pain relieved when you use glyseryl trinitrate?	0-5 ❒	6-10 ❒	⩾10 ❒
	No relief ❒		

Physician's interview:

Past own physician/Hospital

Past ECG

Conclusion: Ordinary interview
Physician interview
Past investigations

Infarction	Yes	No	Don't know 19
Have you ever had severe pain lasting 30 minutes or more localised to the front of the chest?	❒	❒	❒
How many such attacks have you had?			
First attack: When? The duration of the pain?			
Last attack: When? The duration of the pain?			
Have these attacks been associated with: Syncopy?	❒	❒	❒
Cold swets?	❒	❒	❒
Peculiar dissiness?	❒	❒	❒
Have you been bedridden due to such attacks?	❒	❒	❒
Have you contacted a physician due to these attacks?	❒	❒	❒
Have you been admitted to hospital due to such attacks?	❒	❒	❒
Possible doctor/hospital. When?			
Have you been treated with anticoagulants?	❒	❒	❒
Has an ECG been taken in connection to any of these attacks?	❒	❒	❒
If yes: of whom/which hospital? When?			
Physician's interview			
Supplemental information collected:	❒	❒	❒

Conclusion: Ordinary interview
Physician interview

Intermittent claudication	Yes	No	Don't know 20
1. Do you notice pain in you legs when walking?	❒	❒	❒
2. Does this pain start when you are standing still or while seated?	❒	❒	❒
3. Where in your legs do you feel the pain? Localized to the leg(s)	❒	❒	❒
Localized to other parts: Where?			
4. Do you notice this if you walk uphill or if you walk quickly on level ground?	❒	❒	❒
Never walk quickly or uphill: ❒			
5. Do you notice this if walking in ordinary pace on level ground?	❒	❒	❒
If Yes to 4 or 5:			
6. Does the pain disappear when you continue to walk? ❒		❒	❒
7. What do you do when you notice the pain while walking? Stop or reduce the pace?	❒	❒	❒
8. Does the pain disappear when you stop?	❒	❒	❒
9. If Yes to 8: Within 10 minutes or less?	❒	❒	❒
10. Have you had surgery to improve the blood circulation to your legs?	❒	❒	❒
Possible type of operation?			
11. Have you consulted a physician or admitted to hospital due to these symptoms?	❒	❒	❒

Supplemental information:

Conclusion: Ordinary interview
Physician interview

Dyspnea: (Present or past). If the subject due to other disabilities is unable to walk as usual, mark here: ❒ and go to question 4. 21	Yes	No	Don't know
1. Are you breathless when you walk quickly on level ground or uphill?	❒	❒	❒
2. Are you breathless when you walk together with others in ordinary pace on level ground?	❒	❒	❒
3. Do you have to stop due to breathless when you walk in ordinary pace on level ground?	❒	❒	❒
4. Do you get breathless when you wash yourself or during dressing?	❒	❒	❒
5. Are you breathless also at rest?	❒	❒	❒

6. Have you had attacks of breathless during the night? ❒ ❒ ❒

Physician's interview:

Cough	Yes	No	Don't know	22
1. Do you cough just after getting up in the morning? ("Clearing the voice" or one simple cough doesn't count)	❒	❒	❒	
2. Do you cough otherwise during the day or night? (Random cough doesn't count)	❒	❒	❒	
If Yes to 1 or 2:				
3. Do you cough more or less daily during a period as long as 3 months each year?	❒	❒	❒	

Phlegm				
4. Do you cough up phlegm just after getting up in the morning?	❒	❒	❒	
5. Do you cough up phlegm otherwice during the day or night? (Mark Yes if twice or more)	❒	❒	❒	
6. Do you have phlegm more or less daily during a period as long as 3 months each year?	❒	❒	❒	

Cough and phlegm (If Yes on any of the quastions 1, 2, 3, 4, 5.)				23
7. Have you had cough and phlegm in more than 3 years?	❒	❒	❒	
8. During the last 3 years have you had any period with increased cough and phlegm lasting in 3 weeks or more?	❒	❒	❒	
9. How many times have you had such a period?	❒	❒	❒	

Physician's interview:

Smoking habits				24
1. Do you smoke? (Mark Yes if daily smoking until 1 month ago)	❒	❒		
2. If No: Have you ever smoked previously? (Mark Yes if smoked as much as one cigarette per day for one year)	❒	❒	❒	

3. How much do you smoke (smoked)	Yes to 1	Yes to 2	
Cigarettes per day, with filter	.....	.....	❒
Cigarettes per day, without filter	.....	.....	❒
Gram tobacco per week, hand rolled	.....	.....	❒
Gram tobacco per week, in the pipe	.....	.....	❒
Cigars per week	.....	.....	❒

4. Do you inhale? ❒ ❒ ❒
5. At what age did you start to smoke regularly? ❒
6. If Yes to 2: At what age did you stop to smoke regularly? ❒
   What was the reason for stopping smoking? ❒

Physical activity: 25

1. How many hours per week do you work?
   (Including extra work and overtime)
2. Do you work during evenings? Yes No Don't know
   never or seldom ❒ Often ❒ Permanent ❒
3. Is most of your work in sitting position? ❒ ❒ ❒
4. Is most of your work in standing position? ❒ ❒ ❒
5. Do you perform much walking or lifting at your work? ❒ ❒ ❒
6. Do you walk to and from your place of work? ❒ ❒ ❒
   Number og km: .....
7. Do you bicycle to and from your place of work? ❒ ❒ ❒
   Number og km: .....
8. Do you have a car? ❒ ❒ ❒

Exercise outside work the last 5 years: 26

1. Do you participate in competitive sport? ❒ ❒ ❒
2. Do you do regular fysical training, gymnastics etc.? ❒ ❒ ❒
3. Do you walk (at least 2 km) or bicycle (at least 5 km)
   at least 3 times per week? ❒ ❒ ❒
4. Sunday walking or bicycle? Garden work? ❒ ❒ ❒
5. Other forms of exercise? What kind?
6. No physical activity: ❒
7. Change the last 5 years: No: ❒ Increased: ❒ Reduced: ❒

Sleep: Do you usually sleep less than 6 hours per 24 hours? ❒ ❒ ❒ 27

Diet: Are you using a diet at the moment? Possible which type? 28

Slimming diet? How long? ❒ ❒ ❒
Low salt diet? How long? ❒ ❒ ❒
Do you spread extra salt on the food? ❒ ❒ ❒

Medication: Do you currently use digitalis? ❒ ❒ ❒ 29
Do you currently use quinidine? ❒ ❒ ❒

Do you use medication against swellings in the body ? ❒ ❒ ❒
Do you use medication against cystitis,
urinary tract infection? ❒ ❒ ❒
Other medication? (Sulpha-prep., antibiotics, hormon therapy)
Possible type/dosage:

Information on medication comes from: Own estimate: ❒ Verified: ❒
Obtained information: ❒
Do you disagree that we ask for informations on results from previous investigations
from your physician(s) or from hospital: No: ❒ Ja: ❒

Appearance: 30
Behaviour: Quiet, natural, relaxed: ❒ Nervous, worried, tense, unease: ❒
Angry, irritating, agressive: ❒ Suppl.:
Puls: Regular: ❒ Irregular: 31
Pupils: Senile arcus: Ja: ❒ No: ❒ 32
Xanthelasms: No: ❒ Yes: ❒ Xanthelomata: No: ❒ Yes: ❒ 33
Goitre: No: ❒ Yes:: ❒
Venous congestion of neck: Sitting No: ❒ Yes: ❒
Thorax: 34
Lungs: 35

Heart: Ictus: Not palpable: ❒ Uncertain: ❒ Loc. .....cm I.C. Raised: Yes: ❒ No: ❒ 36
Systolic murmur: 37
Diastoloc murmur: 38
A2 acc.: Yes: ❒ No: ❒ P2 acc.: Yes: ❒No: ❒ A2 P2 39
Other ausc. signs: Gallop: ❒ Rub: ❒ Extracard: ❒
Abdomen:Liver 40
Kidneys Ausc.
Other signs:
Oedema:
Conclusion: Heartfailure, grade 41
Hearts disease, etiol class.

Foot arteries: 42

	Right side			Left side		
	Normal	Weakend	Not present	Normal	Weakend	Not present
A. Tibialis post.	❒	❒	❒	❒	❒	❒
A. Dorsalis pedis	❒	❒	❒	❒	❒	❒
A. Poplitea	❒	❒	❒	❒	❒	❒
A. Femoralis	❒	❒	❒	❒	❒	❒

Oscillometry: Yes: ❒ No: ❒

Ophtalmology: Right Left 43

Media

Optic cup.

Arteries

Veins

A-V phenomena:

haemorrhages:

Exudates:

Degeneration:

Other signs:

Unsuccessful

Received supplemental information 67

Doctor's report sent

Reffered to radiography

Referred to admitance into hospital

Refrerred treatment to usual doctor

Therapy started here

Supplemental investigations: 44

Body height cm Not satisfactory due to: 45

Body weight kg Not satisfactory due to: 46

Circumference upper arm cm 47

Skinfold thickness: Triceps 1: 2: Sum: M: Log: 48
Subscap. 1: 2: Sum: M: Log:
Sum: M: Log:

Vitalograph: FEV1 1: l. % FVC: 49
FEV1 2: l. % FVC:
Sum:
Mean value:

Haemoglobin:: % Cholesterol: mg% Uric acid in blood: mg% 50-52

Blood pressure.Pulse: Systolic Diastolic IV Diastolic V Pulse

Sitting 53
Lying down, before rest 54
Lying down, after rest 55
Sitting 56
Lying 57
Standing 58

Urine: Mid-stream ❒ Ordinary fresh ❒ "Old" ❒ Menstruation: Yes❒ No❒ 59
Albustix: Protein reaction: Blood:
Test-Tape: Benedict:
Orthostatic test:: Specific weight: Protein reaction:
Microscopy: Erythrocytes: Leucocytes: Cylinders Bacteria: 60

Bacteriological investigation of urine: 61
Type of bacteria: Bacteria count: 62
63
64
ECG: 65
Blood sugar: mg%. Time since last meal: 66

“Theory without fact is fantasy, but fact without theory is chaos.”

C. W. Whitman, 1894

“As persons, we are incomparable, unclassifiable, uncountable, and irreplaceable.”

W. H. Auden, 1967