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Prevalence and Impact of Chronic Diseases and Multimorbidity in the Aging Population:

A Clinical and Epidemiological Approach

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To the memory of my grandparents
Marcella & Giacomo
and
Ninì & Tonino
for making me love elderly people

ABSTRACT English

Due to the aging of the population, the absolute number of subjects affected by age-related diseases is expected to increase as well as their coexistence – known as multimorbidity. The aims of this thesis were to evaluate the prevalence, distribution and patterns of chronic multimorbidity in the elderly population, and its impact on disability, functional decline and mortality. The data were gathered from the Kungsholmen Project (Study I, II, and III) and from an Italian database on the hospitalized elderly (Study IV). The Kungsholmen Project is a longitudinal population-based study on 75+ year-old people, living in Stockholm, Sweden, who were clinically re-examined every three years. The Italian database includes clinical data from 923 patients, 65+ year-old, admitted to an acute geriatric ward in the Spedali Civili Hospital, Brescia, Italy.

Study I. Cardiovascular and mental diseases emerged as the most common chronic disorders in both men and women. However, cardiovascular diseases reached a plateau after 75 years (55%), whereas mental disorders continued to rise with increasing age from 18% in the 77-84 year-old to 36% in 85+ year-old subjects. The prevalence of multimorbidity was 55%. Older age, female gender, and lower education were independently associated with a more than 50% higher occurrence of multimorbidity.

Study II. Heart failure and visual impairments were the diseases with the highest comorbidity (mean: 2.9 and 2.6 co-occurring conditions, respectively) while dementia had the lowest (mean: 1.4 comorbidities). Further, heart failure very rarely occurred without any comorbidity (0.4%). The observed prevalence of comorbid pairs of conditions exceeded the expected one for many circulatory diseases, and also for dementia and depression, which were further correlated to hip fracture and cerebrovascular diseases. The cluster analysis showed five clusters, three of which grouped circulatory, cardiopulmonary, and mental diseases. The last two clusters included only one disease (diabetes and malignancy) together with their consequences.

Study III. During a 3-year follow-up, of 1099 old persons, 363 died and 85 showed functional decline. The number of chronic conditions incrementally increased the risk of functional decline. The Relative Risk (RR) increased from 1.5 in subjects with one disease to 8.0 in persons with 5+ diseases. However, this was not the case for mortality. Baseline disability had the highest impact on survival, independently of the number of diseases (RR= 7.8; 95% Confidence Interval (CI) = 4.6-13.4 in subjects with one disease; RR= 6.9;95% CI=4.2-11.3 in those with 2+ diseases) and amplified the effect of multimorbidity on further functional decline (RR= 11.6;95% CI= 4.1-32.9 for persons with both multimorbidity and disability).

Study IV. In a cohort of geriatric patients, older age, poor cognitive status, and depression were associated with functional disability at hospital discharge in all age groups, whereas multimorbidity was independently correlated with disability only in the older patients (75+ yrs) (OR=1.5;95%CI=1.2-2.0), in particular among those who were cognitively impaired (OR=4.0;95%CI=2.0-8.1). Cognitive impairment and depression showed an additive effect on disability especially in the younger patients (65-74 yrs).

In **conclusion**, multimorbidity is the most common clinical situation in the aging population, affecting mostly the very-old and women. Poor education is associated with an increased risk of multimorbidity, suggesting that risk behaviors learnt in early life may still affect the health status of old persons. Disability and functional decline increase with increasing number of chronic conditions. Moreover, the impact of multimorbidity on disability differs depending on age and could be severer in the cognitively impaired elderly. Finally, disability seems to have greater impact on survival than multimorbidity. Assessing multimorbidity, disability and depression leads to the identification of groups of old persons particularly at risk of functional decline who should be a target for clinical and preventative intervention.

Key words: chronic diseases, multimorbidity, comorbidity, education, occupation, disability, mortality.

SAMMANFATTNING Svenska

Befolkningen blir allt äldre och det absoluta antalet personer som påverkas av åldersrelaterade sjukdomar förväntas öka, såväl som förekomsten av flera sjukdomar samtidigt, sk multisjuklighet. Syftet med denna avhandling var att studera förekomst, fördelning och eventuella mönster av kronisk multisjuklighet i den äldre befolkningen, samt dess betydelse för fysisk och mental funktionsnedsättning och mortalitet. Data hämtades från Kungsholmsprojektet (Studie I, II och III) och från ett italienskt slutenvårdsregister (Studie IV). Kungsholmsprojektet är en longitudinell befolkningsstudie där deltagarna, 75+ år och boende i Stockholm, undersöktes vart tredje år. Den italienska databasen innehöll kliniska data från 923 patienter som var 65+ år och inskrivna på en akutgeriatrisk avdelning vid Spedali Civili Hospital i Brescia, Italien.

Studie 1. Kardiovaskulära och mentala sjukdomar var de vanligaste kroniska sjukdomarna bland både män och kvinnor. Förekomsten av kardiovaskulära sjukdomar nådde en platå efter 75-års ålder (55%), medan de mentala sjukdomarna fortsatte att öka med stigande ålder, från 18% bland de yngre-äldre till 36% bland de som var 85+ år. Prevalensen för multisjuklighet var 55%. Faktorer som hög ålder, låg utbildning och att vara kvinna var oberoende av varandra relaterade till mer än 50% av en ökad förekomst av multisjuklighet.

Studie II. Hjärtsvikt och synnedsättning var de sjukdomar som hade högst samsjuklighet (medelvärde: 2,9 respektive 2,6 samtidigt förekommande tillstånd) medan demens hade lägst samsjuklighet (1,4). Hjärtsvikt förekom dessutom mycket sällan utan någon annan samtidig sjukdom (0,4%). Den observerade prevalensen av samsjuklighet översteg den förväntade för många cirkulationssjukdomar, men även för demens och depression som ofta förekom tillsammans med höftfraktur och cerebrovaskulära sjukdomar. Vid klusteranalys framkom fem kluster varav de tre första kunde tolkas som cirkulatoriska, kardiopulmonära och mentala kluster. De övriga två klustren innefattade diabetes och dess konsekvenser samt malignitet och anemi.

Studie III. Under en treårs uppföljning av 1099 äldre personer, avled 363 och 85 fick försämrad funktion. Antalet kroniska tillstånd ökade risken för funktionsnedsättning. Den relativa risken ökade från 1,5 för personer med en sjukdom till 8,0 för de som hade fler än 5 sjukdomar. Detsamma gällde inte för mortalitet. Fysisk funktionsnedsättning vid baseline hade störst betydelse för överlevnad, oberoende av antal sjukdomar (RR=7,8; 95% KI 4,6-13,4 för personer med 1 sjukdom och RR=6,9; 95% KI 4,2-11,3 för dem med 2 eller fler sjukdomar). Nedsättningen förstärkte dessutom effekten av multisjuklighet och bidrog till ytterligare funktionsnedsättning (RR=11,6; 95% KI 4,1-32,9).

Studie IV. I en kohort geriatriska patienter var hög ålder, nedsatt kognition och depression kopplat till fysisk funktionsnedsättning vid utskrivningen i samtliga åldersgrupper. Multisjuklighet däremot var oberoende korrelerad med fysisk funktionsnedsättning enbart hos de allra äldsta (OR=1,5; 95% KI 1,2-2,0), framför allt hos de med kognitiv nedsättning (OR=4,0; 95% KI 2,0-8,1). Kognitiv nedsättning och depressiva symptom uppvisade en additiv effekt på fysisk funktionsnedsättning, speciellt bland de yngre-äldre patienterna.

Slutsatser. Multisjuklighet utgör den vanligaste kliniska bilden i en åldrande befolkning, vilket påverkar de allra äldsta och kvinnorna mest. Låg utbildning har samband med en ökad risk för multisjuklighet, vilket antyder att riskbeteenden som lärts in tidigt i livet fortfarande kan påverka hälsan när man blir äldre. Fysisk och mental funktionsnedsättning ökar med antalet kroniska tillstånd. Dessutom skiljer sig multisjuklighetens betydelse för funktionsförmågan beroende på ålder och kan bli allvarligare för dem som är kognitivt nedsatta. Slutligen tycks fysisk funktionsnedsättning ha en större betydelse för överlevnaden än multisjuklighet. Att mäta multisjuklighet, fysisk funktionsförmåga och depression underlättar identifikation av de äldre som är i riskzonen för funktionsnedsättning och som därmed bör utgöra en målgrupp för kliniska och preventiva interventioner.

Nyckelord: kroniska sjukdomar, multisjuklighet, samsjuklighet, utbildning, yrke, fysisk funktionsnedsättning, mortalitet.

RIASSUNTO Italiano

A causa dell'invecchiamento della popolazione, il numero di persone affette da malattie croniche e da multimorbilità è destinato ad aumentare. Lo scopo di questa tesi è la valutazione della prevalenza e distribuzione della multimorbilità cronica nella popolazione geriatrica, e il suo impatto sulla disabilità, sul declino funzionale e sulla mortalità. I dati sono tratti dal Kungsholmen Project (Studio I, II e III) e da un database su anziani italiani ospedalizzati (Studio IV). Il Kungsholmen Project è uno studio longitudinale su anziani di 75+ anni residenti a Stoccolma, Svezia, mentre il database italiano include dati clinici di pazienti di 65+ anni ricoverati presso la divisione di Geriatria degli Spedali Civili di Brescia, Italia.

Studio I. Le malattie cardiovascolari e mentali sono risultate le più frequenti sia negli uomini che nelle donne. Tuttavia, le malattie cardiovascolari raggiungevano un plateau dopo i 75 anni di età (55%), mentre le malattie mentali continuavano ad aumentare con l'età (dal 18% negli anziani al di sotto degli 84 anni al 36% negli ultraottantacinquenni). La prevalenza di multimorbilità era del 55%. L'età avanzata, il sesso femminile, e una bassa scolarità risultavano indipendentemente associati alla multimorbilità.

Studio II. Lo scompenso cardiaco e i disturbi della vista erano le malattie con la più elevata comorbilità (media: 2.9 e 2.6 condizioni coesistenti, rispettivamente) mentre la demenza con la più bassa (media: 1.4 comorbilità). Inoltre, lo scompenso cardiaco molto raramente non risultava associato a nessuna comorbilità (0.4%). La prevalenza osservata delle combinazioni di 2 malattie è risultata maggiore di quella attesa per molte malattie circolatorie, ma anche per demenza e depressione che risultavano correlate anche alla frattura di femore e alle malattie cerebrovascolari. L'analisi di cluster ha rivelato 5 clusters, tre dei quali raggruppavano malattie circolatorie, cardiopolmonari e mentali. Gli altri due clusters includevano solo una malattia (diabete e neoplasie) con le rispettive conseguenze.

Studio III. Durante i 3 anni di follow-up, dei 1099 partecipanti, 363 sono morti e 85 hanno peggiorato lo stato funzionale. Il numero di malattie croniche incrementava proporzionalmente il rischio di declino funzionale. Il Rischio Relativo (RR) aumentava da 1.5 in soggetti con una malattia a 8.0 in quelli con 5+ malattie. La disabilità al baseline aveva l'effetto maggiore sulla mortalità, indipendentemente dal numero di malattie (RR= 7.8;95% Intervalli di Confidenza (CI)=4.6-13.4 in soggetti con una malattia; RR= 6.9;95%CI=4.2-11.3 in quelli con 2+ malattie) e amplificava l'effetto della multimorbilità sul peggioramento funzionale (RR=11.6;95% CI= 4.1-32.9 per persone con multimorbilità e disabilità).

Studio IV. In pazienti anziani, l'età avanzata, il decadimento cognitivo, e la depressione risultavano associati con la disabilità alla dimissione ospedaliera in ogni gruppo di età, mentre la multimorbilità era indipendentemente correlata con la disabilità solo nei pazienti più anziani (75+ anni) (OR=1.5;95%CI=1.2-2.0), in particolare in chi aveva decadimento cognitivo (OR=4.0;95%CI=2.0-8.1). Il decadimento cognitivo e la depressione avevano un effetto additivo sulla disabilità specialmente nei pazienti più giovani (65-74 anni).

In **conclusione**, la multimorbilità è il quadro clinico più frequente nella popolazione geriatrica, e colpisce prevalentemente le persone più anziane e le donne. Una bassa educazione si associa con una probabilità maggiore di multimorbilità, suggerendo che comportamenti a rischio acquisiti in giovane età possano compromettere lo stato di salute degli anziani. La disabilità e il declino funzionale aumentano con il numero di malattie croniche. Inoltre, l'impatto della multimorbilità sulla disabilità è diverso in funzione dell'età e potrebbe essere maggiore in persone con decadimento cognitivo. Infine, la disabilità ha un impatto maggiore sulla sopravvivenza della multimorbilità. La valutazione della multimorbilità, della disabilità e della depressione permette l'identificazione di gruppi di anziani particolarmente a rischio di declino funzionale che dovrebbero rappresentare un target di intervento clinico e preventivo.

Parole chiave: malattie croniche, multimorbilità, comorbilità, educazione, attività lavorativa, disabilità, mortalità.

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living scale
BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Intervals
CIRS	Cumulative Illness Rating Scale
COPD	Chronic Obstructive Pulmonary Diseases
CVD	Cerebrovascular Diseases
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
GIC	Geriatric Index of Comorbidity
GDS	Geriatric Depression Scale
IADL	Instrumental Activities of Daily Living
ICD-9	International Classification of Diseases, 9th revision
ICED	Index of Co-existent Disease
ICF	International Classification of Functioning, Disability and Health
IDS	Index of Disease Severity
ILSA	Italian Longitudinal Study on Aging
MMSE	Mini-Mental State Examination
OR	Odds Ratio
RR	Relative Risk
SES	Socio-Economic Status
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

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

I. **Marengoni A,** Winblad B, Karp A, Fratiglioni L. Prevalence of chronic diseases and multimorbidity in the old population: differential distribution by age, gender and socio-economic status.
Am J Public Health, in press.

II. **Marengoni A**, Rizzuto D, Wang H-X, Winblad B, Fratiglioni L. Patterns of comorbidity and multimorbidity in the aging population.
Submitted.

III. **Marengoni A,** von Strauss E, Rizzuto D, Winblad B, Fratiglioni L. The impact of chronic multimorbidity and disability on functional decline and survival in old persons. A community-based, longitudinal study.
Submitted.

IV. **Marengoni A**, Agüero-Torres H, Cossi S, Ghisla MK, De Martinis M, Leonardi R, Fratiglioni L. Poor mental and physical health differentially contributes to disability in hospitalized geriatric patients of different ages.
Int J Geriatr Psichiatry 2004;19:27-34.

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'The aging of the population is one of the major public health challenges of the 21st century…the prevention of diseases and injuries is one of the few tools available to reduce the expected growth of health care and long-term care costs.'

Julie Louise Gerberding

Director of the Centres for Disease Control and Prevention, 2007

'The term multimorbidity helps geriatricians to see the whole forest.'

Wayne C. McCormick and Peter A. Boling, 2005

1 INTRODUCTION

1.1 THE AGING SOCIETY

Thousands of persons turn 65 years of age every day (Cohen, 2003; Kinsella and Velkoff, 2001a) (Figure 1). Life expectancy has already exceeded age 75 in 45 countries (World Health Organization, WHO, 2006), and it is expected to continue to rise (Oeppen and Vaupel, 2002). Because life expectancy has increased by 2.5 years per decade for a century and a half, one reasonable scenario would be that this trend will continue in coming decades. If so, record life expectancy will reach 100 in about six decades (Oeppen and Vaupel, 2002). In the world, the proportion of 60+ year-old people has gradually increased from 8.1% in 1960 to 10% in 2000. By 2050, there will be 3.2 people aged 60+ years old for every 0-4 year-old child (Cohen, 2003). This reversal in the numerical proportions of the old and young reflects improved survival and reduced fertility. Improved survival results from the intricate interplay of advances in income, salubrity, nutrition, education, sanitation and medicine. Population aging has already become a well-known phenomenon in the industrialized nations of Europe and North America, but developing countries are aging as well, often at a much faster rate than in the developed world. The current growth rate of the elderly population in developing countries is more than double that in developed countries (Kinsella and Velkoff, 2001a).

Figure 1. Average annual population growth rate at ages 60 or over, 65 or over and 80 or over: world, 1950-2030 (modified by United Nations. Department of Economic and Social affairs, population division, 2007)

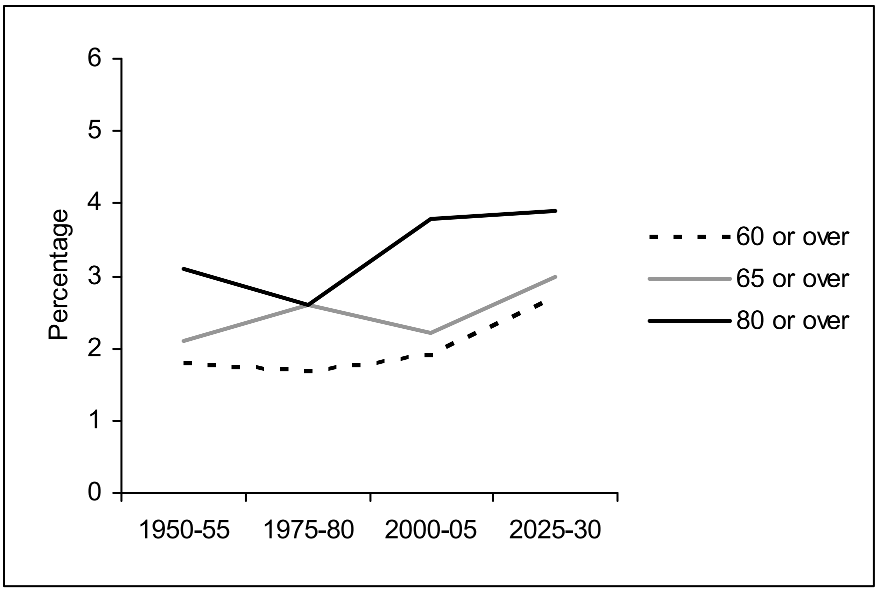
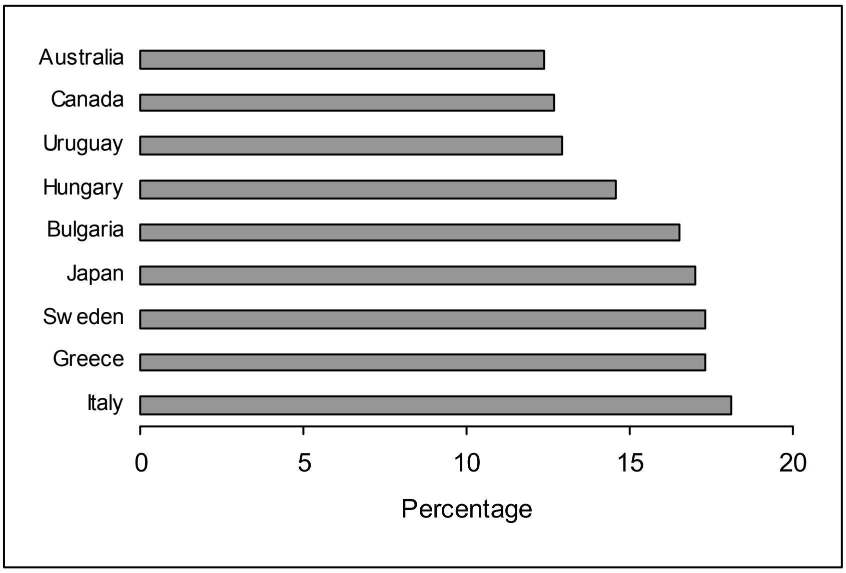
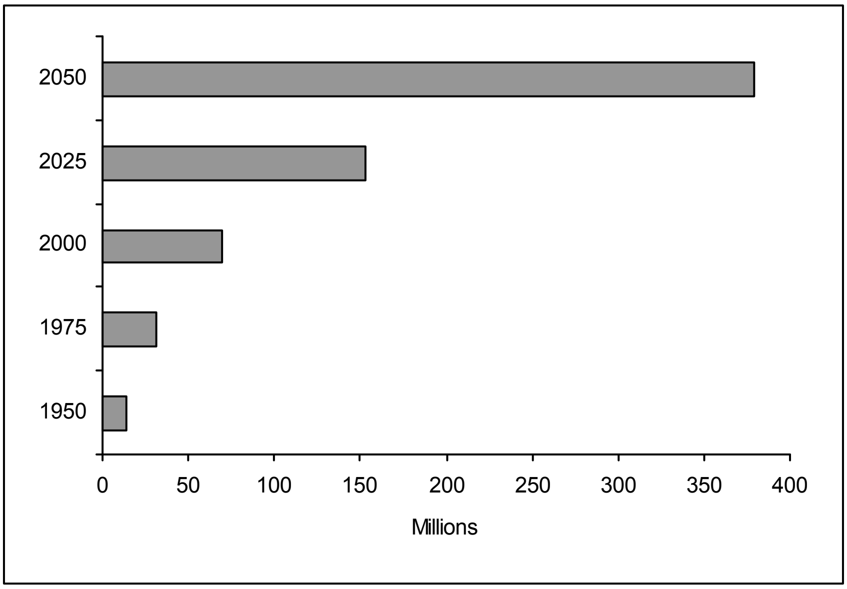


Figure 2. Proportion per 100 of 65+ year population. The US Census Bureau, 2001 (Kinsella and Velkoff, 2001a)



However, Europe is still the "oldest" world region and Italy and Sweden are at the top of the world's oldest countries list (Figure 2). These European countries will experience the progressive aging of the elderly population itself, with the oldest old being the fastest-growing proportion of the population (Figure 3). In 2030, nearly 12% of all Europeans are projected to be over the age of 74, and 7% over the age of 79 (Kinsella and Velkoff, 2001a).

Figure 3. Population aged 80 or over: world, 1950-2050. (modified by United Nations. Department of Economic and Social affairs, population division, 2007)



In Sweden, 80+ years old persons constituted approximately 22% of the elderly population in 1992; by the year 2025 they are expected to increase to 32% (Statistics Sweden, 2005). The Italian population will follow a similar pattern, as in 2025 one in every 14 Italians will be over 80 (Walker, 2002).

1.2 HEALTH OF AGING POPULATIONS

In recent years, several theories regarding trends in the health of the elderly have been debated. The 'compression of morbidity' theory is based on the assumptions that mortality at older ages will reach a limit beyond which there can be no further decline, and that there is an ongoing increase in the age of disability onset. Under these conditions, there would be a compression of morbidity into a smaller number of years at the end of life (Fries, 1980). The 'expansion of morbidity' theory and the 'age of delayed degenerative diseases' theory imply that the extension of life for persons with chronic and disabling conditions, due to medical progress, without a reduction in the incidence of these conditions, will lead to a deterioration in the health of the population (Gruenberg, 1977; Olshansky and Ault, 1986; Olshansky *et al*., 1991). Manton, 1982, proposed a position between the two outlined above. His hypothesis, termed 'dynamic equilibrium', is that alongside the reduction in mortality there will also be a reduction in the rate of deterioration of the body's vital organ systems. This could result in more diseases in the population, but the diseases will be at a lower level of severity. Finally, other authors wondered whether opposite trends could correspond to different phases of the same transition or they could differ by population strata (e.g., poorly or well educated persons) (Robin and Michel, 2004; Crimmins and Saito, 2001). Recently, Robin and Michel, 2004, reviewed the main theories on population aging, and concluded that future trend scenarios (expansion or compression of morbidity and disability) depend on four factors: 1) increase in the survival rates of sick persons; 2) control of the progression of chronic diseases; 3) improvement of the health status and health behaviors of new cohorts of elderly people; and 4) emergence of very old frail populations.

Increasing life expectancy does not necessarily mean improving the population's health. If longer life occurs because the incidence of diseases declines, then the health of the population will improve. On the other hand, if longer life occurs because sick persons are surviving longer in their disabled status, then the health of the population will not improve (Crimmins, 1996). However, the contemporary phenomenon of population aging falls outside the boundaries of theories and models, as the health status of older populations across the globe is experiencing a complex mixture of increased frailty accompanied by reductions in some measures of disability (Olshansky and Ault, 1986; Parker and Thorslund, 2007).

In the Nineties, some researchers reported data showing an improvement in the health of the elderly population, such as a decline in the prevalence of some chronic conditions and an increase in disability-free life expectancy (Manton *et al*, 1995; Robin *et al*, 1998). On the contrary, other authors found a decrease in the number of old persons with no disease and an increase in the proportion of people with multiple conditions (Crimmins and Saito, 2000). Yet, the evidence is not unequivocal. Studies of health trends have provided inconsistent results, due to the fact that not all aspects of health, such as diseases, impairments, and disabilities, have changed in the same direction at the same time (Crimmins, 2004). Moreover, changes in health do not have to be consistent across all segments of the population. Improvements in the health of persons in their 60s can be linked to the eventual deterioration in the health of those in their 80s. Thus, when thinking about the future, it is important to avoid considering the elderly as an homogeneous group (Gee, 2002). The most likely future will contain periods of both improving and deteriorating health in the population. What is certain is that the inevitable growth of the old population will have a profound influence on the organization of health care and social services in the coming decades.

1.3 CHRONICITY

Since the beginning of the last century, chronic health problems have replaced infectious diseases as the dominant health care burden. This ‘epidemiological transition’ and the rapid changes in disease patterns have posed serious problems for health care systems still rooted in episodic and acute care. Nevertheless, the importance and consequences of chronic illnesses have been underestimated for a long time. A major effort to understand and predict the effect of epidemiological change is the Global Burden of Disease Study undertaken jointly by the WHO, Harvard University, and the World Bank. The study was implemented to stimulate the inclusion of non-fatal health outcomes when quantifying the burden of diseases in worldwide health policy debates. And in fact the Global Burden of Disease Study showed that a chronic disorder (depression) was the fourth leading worldwide cause of disease burden in 1990. The study also estimated that by 2020 the burden attributable to non-communicable diseases would rise sharply, with ischemic heart diseases and depression at the top of the leading causes (Murray and Lopez, 1996). Other authors have shown similar pessimistic projections (Anderson, 2003).

In response to the worldwide aging phenomenon, many health care planners and governments have promoted further research regarding age-related pathologies. In fact, the cost of health care is highly related to the number of persons treated or monitored for various diseases (Crimmins and Saito, 2000). However, the majority of the studies have focused on specific illnesses. Dementia, for instance, has been investigated extensively enough to allow the estimation of worldwide occurrence (Ferri *et al*, 2005). Several other studies have concentrated on a relatively small number of diseases, such as cardiovascular diseases, diabetes, cancer, and chronic obstructive pulmonary diseases (Fillenbaum *et al*, 2000; Menotti *et al*, 2001), rather than the whole range of chronic morbidity.

1.4 THE DIMENSION OF MULTIMORBIDITY IN THE ELDERLY POPULATION

As stated by the National Institute on Aging Task Force on Comorbidity, the use of the terms ‘comorbidity’ or ‘multimorbidity’ needs clarification (Yancik *et al*, 2007). The term comorbidity was introduced in 1970 by Feinstein and refers to the combination of additional diseases beyond an index disorder. This definition implies that the main interest is on the index condition and the possible effects of the other disorders, for instance, on its prognosis. In contrast, multimorbidity is defined as any co-occurrence of diseases in the same person indicating a shift of interest from a given index condition to individuals who suffer from multiple disorders (Batstra *et al*, 2002). However, as the term multimorbidity addresses a wide range of health problems and conditions, the measurement of multimorbidity is particularly complicated (Yancik *et al*, 2007). This is one of the reasons why a consistent amount of data is available on comorbidity, but few studies have analysed the distribution of multimorbidity in the elderly population

(Gijsen *et al*, 2001). Given the complexity and heterogeneity of chronicity in the elderly, no single definition or operational criteria will serve all research and clinical purposes effectively.

The available data on multimorbidity derive mostly from American and Dutch cohorts, based on general practitioner records or Medicare registers. A total of 83 percent of Medicare beneficiaries have at least one chronic condition, and the 23 percent of beneficiaries with five or more chronic conditions account for 68 percent of the program's spending (Anderson, 2005). van den Akker and colleagues, 1998, have reported a multimorbidity prevalence in 80+ year-old persons of 74% in men and 80% in women, using a broad definition of multimorbidity including permanent, chronic, and recurrent health problems. Consistently across studies, older persons are more likely to be affected by multimorbidity: in the Italian Longitudinal Study on Aging (ILSA), about 25% of the 65-69 years old subjects, and more than 50% of persons aged 80-84 years were affected by 2 or more chronic conditions (Amaducci *et al*, 1996) (Figure 4). Table 1 reports the prevalence of multimorbidity from population-based studies. The prevalence figures vary widely according to the number of conditions evaluated and the age structure of the study populations.

Figure 4. Age-specific prevalence of old persons affected by no disease, 1-2 diseases, and 3+ diseases. The Italian Longitudinal Study on Aging (Amaducci *et al*, 1996)

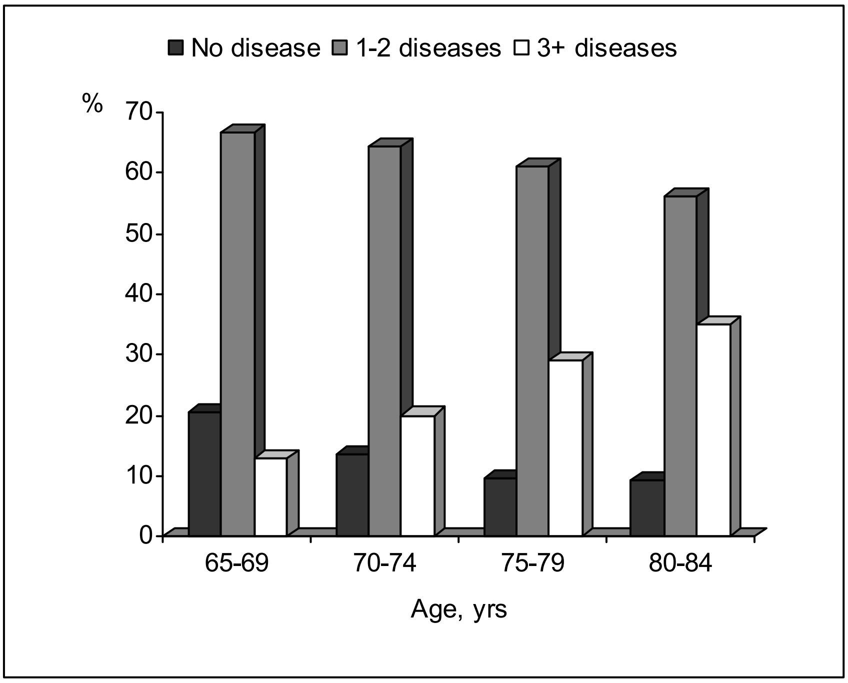


Table 1. Main population-based studies evaluating the prevalence of multimorbidity among elderly persons

Author, y	Project & Study Population	Age, yrs	Ascertainment of chronic diseases	Multimorbidity definition	Prevalence of multimorbidity
Guralnik *et al*, 1989	The National Health Interview Survey (NHIS), Supplement on Aging (SOA) N=13807 community US residents	60+	Self-report of 9 chronic conditions	2+ diseases among hypertension, cataract, heart disease, varicose veins, diabetes, arthritis, cancer, hip fracture, stroke	49%
Seeman *et al*, 1989	The Alameda County Study N=4174 community US residents	38+	Self-report of 22 chronic conditions and symptoms	2+ diseases among a list of 22	56% (60+ yrs old)
Verbrugge *et al*, 1989	The National Health Interview Survey (NHIS), Supplement on Aging (SOA) N=16.148 community US residents	55+	Self-report of 13 chronic conditions	2+ diseases among arthritis, hypertension, deafness, anomaliae visus, circulatory diseases, diabetes, atherosclerosis, cancer, cerebrovascular diseases, osteoporosis, hip fracture	63%
Dunn *et al*, 1992	Longitudinal Study on Aging N=4270 community US residents	70+	Self-report of 11 chronic conditions	3+ diseases among osteoporosis/hip fracture, arthritis, hypertension, heart diseases, stroke, vascular disease, diabetes, cancer, visual and hearing deficit, thinness	50%
Knottnerus *et al*, 1992	The Registration Network Family Practices of the University of Limburg N=25357 community residents in the Netherlands	All ages	General practitioners registers	1+ diseases among 11144	70-80% (75+ yrs old)
Shellevis *et al*, 1993	N=25534 community residents in the Netherlands	All ages	General practitioners registers (5 chronic conditions)	2+ diseases among hypertension, diabetes, coronary heart diseases, lung disease, arthritis	4% (65+ yrs old)
Ettinger *et al*, 1994	The Cardiovascular Health Study N=5201 community US residents	65+	Self-report of 11 chronic conditions and clinical tests for some diseases	3+ diseases among coronary heart disease, stroke, hypertension, diabetes, lung disease, arthritis, cancer, kidney, nervous disease, hearing and vision problems	40%
Seeman *et al*, 1994	The MacArthur Successful Aging Study N=1192 community US residents	70-79	Self-report of 7 chronic conditions	2+ diseases among heart infarction, stroke, cancer, diabetes, hypertension, fractures	33%

Hoffman *et al*, 1996	National Medical Expenditure Survey N=34459 community US residents	All ages	Self-report of chronic conditions	2+ diseases (no number specified)	69% (65+ yrs old)
van Weel *et al*, 1996	The Continuous Morbidity Registration N=12000 community residents in the Netherlands	All ages	General practitioners registers (10 chronic conditions)	2+ diseases among hypertension, obesity, heart disease, arthritis, lung disease, eczema, diabetes, hay fever, hyperlipidaemia, psoriasis	39% (65+ yrs)
Amaducci *et al*, 1996	The Italian Longitudinal Study on Aging (ILSA) N=5632 community residents Italian	65+	Self-report and some clinical tests (11 chronic conditions)	2+ diseases among dementia, parkinsonism, stroke, peripheral neuropathy, coronary artery disease, heart failure, arrhythmias, peripheral atherosclerosis, hypertension, diabetes, thyroid dysfunctions	from 25% (60-64 yrs old) to 55% (80-84 yrs old)
Mendes de Leon *et al*, 1997	The EPESE study N=2812 in New Haven and N=4162 in North Carolina, community-US residents	65+	Self-report of 6 chronic conditions	2+ diseases among myocardial infarction, hypertension, stroke, cancer, diabetes, hip fracture	from 22% in whites to 32% in blacks
Kriegsman *et al*, 1997	The Longitudinal Aging Study Amsterdam (LASA) N=2830 community residents in The Netherlands	55-85	Self-report of 7 chronic conditions	2+ diseases among lung, cardiac diseases, diabetes, stroke, arthritis, malignancies, atherosclerosis, others	40.5%
Chapleski *et al*, 1997	The Long-term care and Social Support Study: American Indian project N=309 community residents American Indians	55+	Self-report of 21 chronic conditions in the past 12 months	3+ diseases among 21 non specified	68%
Fuchs *et al*, 1998	The CALAS study N=1487 community residents Israeli Jewish	75-94	Self-report of 14 chronic conditions	2+ diseases among arthritis, hypertension, gastrointestinal, heart, urinary, lung, circulatory diseases, Parkinson, hip fracture, diabetes, osteoporosis, stroke, heart attack, anemia	64.5 %
van den Akker *et al*, 1998	The Registration Network Family Practice N=60857 community residents in The Netherlands	All ages	General practitioners registers	2+ diseases among 355 diagnoses	78% (80+ yrs old)
Fried *et al*, 1998	The Cardiovascular Health Study N=5201 community US residents	65+	Self report of 15 diseases with examinations only for some diseases	2+ diseases among myocardial infarction, angina, heart failure, hypertension, stroke, transient ischemic attack, asthma, emphysema, diabetes, claudication, renal, hearing and visual disease, arthritis and cancer	61%

Fried *et al*, 1999	The Women's Health and Aging Study N=3841 women community US residents	65+	Self report of 14 chronic conditions	2+ diseases among myocardial infarction, angina, heart failure, other heart diseases, hypertension, diabetes, arthritis, stroke, cancer, lung disease, visual and hearing problems, Parkinson and hip fracture	81%
Fillenbaum *et al*, 2000	The EPESE study N=4126 community US residents	65-100	Self-report of 5 chronic conditions	2+ diseases among hypertension, heart and cerebrovascular disease, cancer, diabetes	29%
von Strauss *et al*, 2000	The Kungsholmen Project N=502 living in community and institutions Sweden	90+	Clinical examination	2+ diseases among cardiac, cerbrovascular, hematological, endocrine, gastrointestinal, infectious, neurological psychiatric, respiratory diseases and malignancy	29.5%
Menotti *et al*, 2001	The Fine Study N=2285 rural men community residents in Finland, The Netherlands, Italy	65-84	Clinical examination and interviews of 9 chronic conditions	2+ diseases among angina, myocardial infarction, heart failure, stroke, transient ischemic attack, intermittent claudication, chronic pulmonary disease, diabetes, cancer	From 13% to 23% in different cohorts
Valderrama-Gama *et al*, 2002	N=772 community residents in Spain	65+	Self-report of 14 chronic conditions	2+ diseases among arthritis, chronic bronchitis, hip fracture, heart diseases, cataracts, diabetes, cerebrovascular diseases, hypertension, depression, prostate disease, deafness, cancer, vein insufficiency, vision problems	80%
Wolff *et al*, 2002	Medicare beneficiaries N=1217103 community US residents	65+	Administrative data on 24 main organ systems	2+ diseases among those affecting the 24 organ systems	65%
John *et al*, 2003	N=1.039 rural community residents American Indian	60+	Self-report of 11 chronic conditions	2+ diseases among arthritis, visual, hearing, eating problems, tuberculosis, stroke, hypertension, heart diseases, diabetes, urinary diseases, depression	74%
von Strauss *et al*, 2003	The Kungsholmen Project among with the St. Göran population N= 1424 living in community and institutions in Sweden	77+	Clinical examination	2+ diseases among cardiac, cerbrovascular, hematological, endocrine, gastrointestinal, infectious, neurological psychiatric, respiratory diseases and malignancy	29.5%

Yu *et al*, 2004	Veterans affair database N=1596789	65+	Electronic medical records on 29 common chronic conditions	2+ diseases among a list of 29	64%
Bisschop *et al*, 2004	The Longitudinal Aging Study Amsterdam N=2288 community residents in The Netherlands	55-85	Self-report of 7 chronic conditions	2+ diseases among cardiac disease, peripheral atherosclerosis, stroke, diabetes, lung disease, cancer, arthritis	20.5%
Kriegsman *et al*, 2004	The Longitudinal Aging Study Amsterdam N=2497 living in community and institutions in The Netherlands	55-85	Self-reported of 7 chronic conditions	2+ diseases among lung disease, cardiac disease, peripheral atherosclerosis, stroke, diabetes, arthritis, malignancy	21%
Fortin *et al*, 2005	N=980 community residents in Canada	18+	General practitioners registers	2+ diseases (no number specified)	98% (65+ yrs old)
Di Bari *et al*, 2006	The ICARe Dicomano Study N=688 rural community residents in Italy	65+	Questionnaires, physical examination, lab tests to identify 14 chronic conditions	3+ diseases among hypertension, musculoskeletal, peripheral vascular, heart, gastrointestinal, respiratory, hepatobiliary, cerebrovascular diseases, diabetes, cancer, anemia, parkinsonism, renal disease	78%
Patel *et al*, 2006	The MHAS and the EPESE studies N=4872 Mexican and N=3050 Mexican American community residents	65+	Self-report of 7 chronic conditions	2+ diseases among diabetes, cancer, heart attack, stroke, arthritis, bone fractures, respiratory diseases	19% in MHAS and 30% in EPESE
Tas *et al*, 2007a	The Rotterdam Study N= 7368 community residents in the Netherlands	55+	Self-report of 8 chronic conditions	2+ diseases among depression, Parkinson's disease, diabetes, hypertension, myocardial infarction, stroke, pulmonary diseases, arthritis.	21%
Schoenberg *et al*, 2007	The Health and Retirement Study N=8180 community US residents	73.8 mean	Self-report of 8 chronic conditions	2+ diseases among hypertension, diabetes, cancer, lung and heart diseases, stroke, arthritis, psychiatric problems	58%

1.5 SOCIO-ECONOMIC STATUS AND MULTIMORBIDITY

The last decade a life-course perspective has been adopted with a growing interest to the study of adult health outcomes. If early-life factors affect future health, then socioeconomic differences in childhood and throughout life are likely to play an intrinsic role (Kinsella and Velkoff, 2001b). Socio-economic status (SES) is a 'composite measure that typically incorporates economic status, measured by income; social status measured by education; and work status measured by occupation' (Dutton and Levine, 1989). The present thesis will focus on two aspects of SES: education and occupation.

1.5.1 Education

Education has been often used in epidemiological studies as a measure of SES for several reasons: it is often available for all the individuals, has high reliability and validity, is easily reported and can be collected as continuous variable (Winkleby *et al*, 1992). While occupation status may change during the person's lifetime, education is, in most cases, acquired in childhood and young adulthood. For that reason, it may represent a proxy for socio-economic or environmental influences in childhood (Hall *et al*, 2000). Indeed, education is a good indicator of the social backgrounds of children as well as their level of knowledge and skills (Marmot, 2003). Winkleby and colleagues, 1992, compared the relationship between different health-related behaviors and three status indicators – education, income, and occupation - and showed that education was the indicator most consistently correlated with such behaviors. Persons with a low level of education may have less knowledge concerning healthy behaviors, worse self-management of chronic diseases, and lower use of preventive services. Education, as measured by schooling, is an important predictor of mortality (Pappas *et al*, 1993) and has been reported to be associated with a higher risk of poorer physical and mental health in the general population (Wolf *et al*, 2005).

1.5.2 Occupation

Occupation is one of the most predominant aspects of adult life. As well as being a principal prerequisite of income and forming personal growth and identity, and providing a criterion for social stratification, occupational settings produce the most pervasive and continuous demands during life (Marmot *et al*, 1999). Specific occupations have been explored in studies on selective conditions, such as neurodegenerative and cardiovascular diseases (Schulte *et al*, 1996). However, few studies have evaluated the influence of education, occupation or other indicators of SES on the distribution of chronic conditions and multimorbidity specifically in old persons. House and colleagues, 1990, found that the prevalence of self-reported chronic conditions in middle-aged and young-old Americans was higher in the lowest SES. In addition, they found a considerable postponement of morbidity in the highest socio-economic group. Finally, Chandola and colleagues, 2007, have detected clear social inequalities in the trajectories of age-related physical decline. In a cohort of British civil servants, they found a more rapid age-related deterioration in physical health among subjects with the lowest than with the highest occupational grade.

All these findings concerning the correlation of education and occupation with health and survival suggest that both early life and middle-age SES may be still relevant for the health in the old age. This effect may be due to exposure to risk factors during childhood, as well as to a longer period of exposure during the life course; e.g., adolescents who start smoking very early and continue throughout their life course. In particular, three hypotheses concerning the relationship between SES and health have been debated. The neomaterial interpretation states that gains in health result from steps up in the income ladder which add neomaterial benefits, and health inequalities result from the differential accumulation of exposures and experiences (Lynch *et al*, 2000). The health behaviors hypothesis explains the association between SES and morbidity or mortality through a higher prevalence of health-risk behaviors among persons with lower SES (van de Mheen *et al*, 1998). The third hypothesis regards psychological and stress-related factors. Low control, insecurity, and loss of self-esteem and work stress can mediate between health and SES (Wilkinson, 1997). Moreover, lower SES groups may have fewer social resources to cope with health-related problems (Adler *et al*, 1994).

1.6 THE EVALUATION OF DIFFERENT PATTERNS OF COMORBIDITY AND MULTIMORBIDITY

Despite the increasing prevalence of chronic conditions with aging, knowledge concerning how diseases distribute or co-occur in the same individual is still limited. Our knowledge is incomplete because few studies have attempted to describe the overall pattern of diseases within a given population, and most of them have used different approaches to address this issue (Gijsen *et al*, 2001). One of the first problems in evaluating the combinations of clinical conditions is the lack of consensus regarding the definition of multimorbidity. In this thesis, following the suggestion of van den Akker and colleagues, 1996, we defined multimorbidity as the presence of two or more health problems in the same individual, whether coincidental or not, and comorbidity as the presence of additional conditions given an index disease.

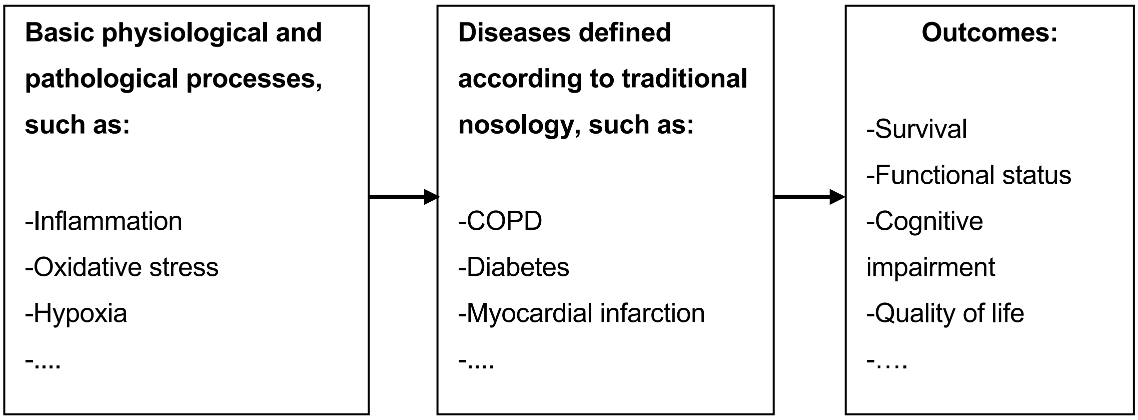
A second problem is the use of different methods to explore the co-occurrence of diseases (Guralnik, 1996). One possible basic method is the conditional count. The conditional count is the number of chronic diseases given that the patient has a particular index disease. This approach is useful when studying one particular condition, e.g. arthritis, and its comorbid conditions (Verbrugge *et al*, 1989). The results strongly depend on the number of conditions evaluated in the study. A second method, which has been extensively employed, is the use of indices including both the number and the severity of the individual conditions (Guralnik, 1996), such as the Charlson Comorbidity Index (Charlson *et al*, 1987), the Index of Co-existent Disease (ICED) (Greenfield *et al,* 1993), and the Cumulative Illness Rating Scale (CIRS) (Linn *et al*, 1968). Major limitations of these indices are due to the fact that they usually do not cover the overall conditions affecting the population, and often require medical records or skilled researchers. A third approach is to assess the proportion of people who have pairs of comorbid diseases. Fried and colleagues, 1999, used this approach in the Women Health and Aging Study and found that the most common comorbid pair was arthritis and visual impairments, with 44% of elderly participants reporting both conditions. Verbrugge and colleagues, 1989, used the same approach in community-resident individuals aged 55 years and older, and found that arthritis and high blood pressure was the most common comorbid pair (21.1%). This approach, as well as the estimation of the odds ratios, is useful in assessing the degree to which comorbid diseases occurrence exceed a level of expected frequency due to chance (Verbrugge *et* *al*, 1989). In fact, conditions that co-occur may have a non-causal statistical association or can share a common patho-physiological cause (van den Akker *et al,* 1998). Finally, the cluster analysis is a descriptive technique that considers how variables tend to occur in conjunction with each other. With this method it is possible to go beyond simple comorbid pairs to obtain a general overall picture of how and which diseases are associated in a particular population and where particular diseases of interest appear in the pattern. John and colleagues, 2003, used cluster analysis to describe the distribution of diseases in a sample of old American Indians. They found that diseases aggregated in two major clusters; the cardiopulmonary and the sensory-motor one.

1.7 MULTIMORBIDITY AND DISABILITY

Disability is defined as difficulty or dependency in carrying out activities essential to everyday life, including tasks needed for self-care and living without help at home (Fried *at al,* 2004). Recent conceptualizations have considered the development of diseases as the initial change from functional independence to disability (Crimmins, 2004), but also as the intermediate factors between various patho-physiological processes and final health outcomes (e.g., functional status) (Yancik *et al*, 2007). Indeed, a number of conditions typical of older persons, such as chronic inflammation, oxidative stress and hypoxia, can represent the basic physiological and pathological processes leading to disability through co-occurring diseases (Yancik *et al*, 2007) (Figure 5). The understanding of these two processes (from biological dysfunctions to diseases and from diseases to adverse outcomes) has emerged as one of the crucial issues in the field of aging research (Karlamangla *et al*, 2007; Fortin *et al*, 2007). Physical disability could be considered as the final outcome of aging-related patho-physiological alterations and diseases (Fried *et al*, 2004).

However, it is becoming clear that disability is often an interaction between features of the person (diseases) and features of the context in which the person lives (environment). The International Classification of Functioning, Disability and Health (ICF) offers a classification of health-related domains based on what a person with a health condition can do in a standard environment (capacity) as well as what they do in their usual environment (performance) (WHO, 2001).

Figure 5. Multimorbidity as an interface between basic pathology and health-related outcomes (modified from Yancik *et al*, 2007)



1.7.1 Population-based studies

Early studies carried out at the end of the '80s reported that disability rises almost exponentially with an increase in the number of chronic diseases (Verbrugge *et al*, 1989). In the last two decades a large number of cross-sectional studies have confirmed the association between multimorbidity and disability in old age (Table 2). Moreover, Fried and colleagues, 1999, reported that specific diseases pairs (e.g. arthritis and visual impairments) were synergistically associated with different types of disability in old women. Longitudinal observations on multimorbidity and functional decline are numerous, but the findings are difficult to compare due to different outcomes and measurement tools (Table 3). The most consistently reported findings showed a stepwise increasing risk of mobility loss and incident functional dependency linked to the number of chronic diseases (Guralnik *et al*, 1993; Wolff *et al*, 2005; Kriegsman *et al*, 2004). The majority of studies have used self-reports in direct interview or self-administered questionnaires to ascertain diseases. Only a few studies have assessed health status by means of a medical examination.

In spite of the numerous studies (Table 2 and 3), a systematic review graduating levels of evidence of prognostic factors for disability in old persons can only muster limited proof supporting an association between chronic diseases and disability (Tas *et al*, 2007b). Tas and colleagues, 2007b, suggested the interesting hypothesis that chronic diseases may play a role in the development of disability, whereas the course of disability is not much altered by their presence at baseline.

Table 2. Major cross-sectional studies evaluating the association between multimorbidity and disability in the old population

Author, y	Sample	Study description	Ascertainment and n° of diseases	Ascertainment of disability	Covariates	Results
Guralnik *et al*, 1989	N=13807 community US residents 60+ yrs old	The National Health Interview Survey (NHIS), Supplement on Aging (SOA), 1984	Self-report of 9 chronic conditions	Self-report of difficulty in ADLs	Age	Disability rose with number of chronic conditions in men and women
Verbrugge *et al*, 1989	N=16.148 community US residents 55+ yrs old	The National Health Interview Survey (NHIS), Supplement on Aging (SOA), 1984	Self-report of 13 chronic conditions	Self-report of difficulty in 10 physical functions, 5 personal care, and 5 household tasks	Age, gender, race	Disability rose with number of chronic conditions
Ettinger *et al*, 1994	N=5201 community US residents 65+ yrs old	The Cardiovascular Health Study, 1989-90	Self-report of 11 chronic conditions	Self-report of difficulty in 17 tasks of daily life	-	Prevalence of disability in persons with 3+ conditions was 59% and in those with <3 conditions 32% (p<0.01).
Chapleski *et al*, 1997	N=309 community residents American Indians 55+ yrs old	The Long-term care and Social Support Study: American Indian Aged project, 1994	Self-report of 21 chronic conditions in the past 12 months	Self-report of difficulty in ADLs and IADLs	Age, gender, education, marital status, urban and health risk behaviors	Number of diseases was significantly associated with disability
Fuchs *et al*, 1998	N=1487 community residents Israeli Jewish 75-94 yrs old	The CALAS study, 1989-92	Self-report of 14 chronic conditions	Self-report of difficulty in ADLs and IADLs	Age, sex, origin	Only persons affected by 3+ diseases had increased risk of disability
Fried *et al*, 1999	N=3841 women community US residents 65+ yrs old	The Women's Health and Aging Study, 1992-1995	Self-report of 14 chronic conditions	Self-report of difficulty in 15 tasks of daily life (mobility, upper-extremity, higher functions, and basic self-care tasks)	Age, race, education, MMSE	Almost all the diseases were associated with different types of disability

von Strauss *et al*, 2000	N= 502 living in community and institutions in Sweden 90+ yrs old	The Kungsholmen Project, 1993	Clinical examination	ADLs scored by a nurse asking and testing the subjects	Age, education, all chronic diseases	In a logistic regression model testing differences between gender having 1+ disease was associated with disability in women OR=2.2;95%CI=1.1-4.3
John *et al*, 2003	N=1039 rural community residents American Indian 60+ yrs old	Survey research on American Indian	Self-report of 11 chronic conditions	Self-report of difficulty in ADLs	Age, gender	The number of diseases was weakly associated with disability
Cesari *et al*, 2006	N=364 community residents in Italy 65+ yrs old	The ilSIRENTE study, 2003	Self-report and clinical records of13 chronic conditions	The Short Physical Performance Battery: 4-meter walking, balance, and chair-stand tests and ADLs, IADLs	Age, gender, smoking, cognition, and physical activity level	Having 3+ diseases was associated with lower SPPB score and more IADL impairment
Patel *et al*, 2006	N=4872 Mexican and N=3050 Mexican American community residents 65+ yrs old	The Mexican Health and Aging Study (MHAS), 2001, and the Hispanic Established Population for Epidemiologic Studies of the Elderly (EPESE), 1993/4	Self-report of 7 chronic conditions	Modified Katz's ADL scale: self-report inability to perform one of the follow items: walk across a room, bathe, eat, get into or out of a bed, use the toilet	Age, gender, education	Having 2+ diseases had an association with disability. OR=4.7 (95%CI=3.7-6.0) in MHAS and OR=3.6 (95%CI=2.5-6.0) in EPESE
Cigolle *et al*, 2007	N=11093 living in community and institutions in US 65+ yrs old	The Health and Retirement Study survey, 2000	Self-report of 7 active or severe conditions	Self-report of difficulty in ADLs (excluded continence)	Age, gender, race, marital status, education, income, and geriatric conditions	Increasing number of chronic diseases increased the risk ratios for disability (from 1.9 for 1 disease to 4.0 for 3+ diseases)

Table 3. Major studies evaluating the longitudinal association between multimorbidity and disability in the old population

Author, y	Sample	Study description	Ascertainment of chronic diseases	Ascertainment of functional status	Covariates	Outcomes	Results
Harris *et al*, 1989	N=1791 community US residents 80+ yrs old	The Longitudinal Study on Aging Baseline in 1984	Self-report of 7 chronic conditions	Interviews on ability in walking ¼ miles, in stooping, kneeling, lifting 10 pounds, walking up to 10 steps without resting	No specified	2-year change in functioning (walking or climbing)	Multiple and cardiovascular diseases were related to functional change
Kaplan *et al*, 1993a	N=356 living in community and institutions in US 65+ yrs old	The Alameda County Study Baseline in 1983-4	Self-report of 6 chronic conditions developed during follow-up	18-item self-report scale, including 7 basic activities, 3 instrumental activities, 2 mobility measures, 5 Nagi physical performance items	Age and baseline function	6-year change in functioning	Presence of 1+ diseases was significantly associated with functional change
Guralnik *et al*, 1993	N=6981 community US residents 65+ yrs old	The EPESE Baseline in 1981/3	Baseline self-report of 10 chronic conditions and annual self-report of new diseases out of 5	Annual self-report of ability to walk and climb stairs	No specified	4-year mobility loss in persons with baseline intact mobility	The risk of mobility loss increased with increasing number of diseases
Seeman *et al*, 1994	N=1192 community US residents 70-79 yrs old	The MacArthur Successful Aging Study Baseline in 1988-9	Self-reported of 7 chronic conditions at baseline and during follow-up	Several tests of physical performance (hand, trunk, lower extremity, balance, gait)	Socio-demographic characteristics	3-year change in physical performance	The number of incident diseases was related with physical decline
Mor *et al*, 1994	N=7527 community US residents 70+ yrs old	The Longitudinal Study on Aging Baseline in 1984	Self-report of 13 chronic conditions	Self-report of difficulties in ADLs and IADLs	Age, gender, disability, self-rated health	6-year change in functional status mortality, institutionalization	N° of diseases was associated with different types of new disability

Boult *et al*, 1994	N=6862 community US residents 70+ yrs old	The Longitudinal Study on Aging Baseline in 1984	Self-report of 8 chronic conditions	Self-report of difficulties in 7 tasks: eating, transferring, using a toilet, dressing, bathing, preparing meals, light cleaning	Age, gender, race, education, income, marital status	4-year onset of functional limitation	The risk of being disable was more than 4 times greater in subjects with four diseases (vs. no diseases)
Mendes de Leon *et al*, 1997	N=2812 in New Haven and N=4162 in North Carolina, community US residents 65+ yrs old	The EPESE study : the New Haven (baseline 1982) and the North Carolina (baseline 1986) populations	Self-report of 6 chronic conditions	Self-report of ability to bathe, dress, use the toilet, walk across a room, transfer from bed to chair	Age, education, race, income, BMI, cognition	Risk of develop disability (9-year of follow-up for the NH and 7 for the NC population)	Having chronic diseases increased the odds to develop disability OR=1.4 95%CI=1.3-1.6
Ho *et al*, 1997	N=1483 Community residents in Hong Kong 70+ yrs old	The Hong Kong Old-old study Baseline in 1991	Self-reported of 15 chronic conditions confirmed by physicians	Barthel Activities of Daily Living Scale assessed at baseline by interview at home and by telephone at follow-up	Age and gender	18-month mobility decline (lost of the ability to walk 50 meters and /or going up and downstairs on their own)	Having 2+ chronic diseases was related to 2.3 times increased risk of mobility decline
Hèbert *et al*, 1999	N=504 community residents in Canada 75+ yrs old	Baseline in 1991	Self-report of 15 chronic conditions	The Functional Autonomy Measurement System scale (interviewing and testing by nurses)	Unadjusted	2-year change in physical functioning (improve and decline)	The number of diseases was not significantly associated with decline in functioning
Béland *et al*, 1999	N=1273 community residents in Madrid 65+ yrs old	The Ageing in Leganès study Baseline in 1993	Self-reported of 13 chronic conditions	Self-report of difficulties in performing upper and lower limb movements, IADLs, and ADLs	Age, gender, education, baseline function, cognition, depression	2-year predictors of functional status, mortality and institutionalisation	Having 4+ diseases increased the risk of functional limitations and ADL disability

Kriegsman *et al*, 2004	N=2497 living in community and institutions in The Netherlands 55-85 yrs old	The Longitudinal Aging Study Amsterdam Baseline in 1992/3	Self-report of 7 chronic conditions	Self-report of difficulty in performing daily activities: climb stairs, getting dresses, rising, cutting nails, walking 400 meters and using own or public transportation	Age, gender, education, institutionalisa-tion, baseline function, depression, cognition	3-year change in physical functioning (both decline and improvement)	Having 2 diseases was associated with change in functioning OR=1.96;95%CI=1.4-2.7
Wolff *et al*, 2005	N= 4968 community US residents 65+ yrs old	The Medicare Current Beneficiary Survey Baseline in 1997/8	Self-report of 14 chronic conditions at baseline and developed during follow-up	Self-report of difficulty in performing ADLs	Age, sex, education, baseline conditions	12-24-36 months dependency onset in disability-free persons at baseline	The number of both baseline and incident diseases increased the risk to develop dependency
Di Bari *et al*, 2006	N=688 rural community residents in Italy 65+ yrs old	The ICARe Dicomano Study Baseline in 1995	Physical examination, questionnaires and lab data of 14 chronic conditions	Guralnik's lower extremity physical performance battery and ADLs	Age, sex, marital status, baseline disability	4-year incident ADL disability	Having 6+ diseases increased the risk of incident disability
Tas *et al*, 2007a	N=4258 Community residents in the Netherlands 55+ yrs old	The Rotterdam Study Baseline in 1990	Self-report of 8 chronic conditions	The Standford Health Assessment Questionnaire	Age, gender, smoking, BMI, self-rated health, medication use	6-year incidence of disability in disability- free persons at baseline	Having 2+ diseases increased the risk of new mild dependency in men OR=2.2;95%CI=1.4-3.5

1.7.2 Clinical studies

In most cases, hospitalized old persons are affected not only by the acute disease leading to hospitalization, but also by one or more chronic conditions which make it difficult for them to cope with acute stressors. Moreover, cognitive impairment and depressive symptoms often coexist with poor health status and can worsen functional abilities (Inouye *et al*, 1993; Covinsky *et al*, 1997; Wu *et al*, 2000; Pouget *et al*, 2000; McCusker *et al*, 2002). In fact, a higher prevalence of functional disability is usually found in hospitalized-based studies (29% to 61%) than in community-based studies (5% to 35%) (Incalzi *et al,* 1997; Inouye *et al*, 1998; Winblad, 1993; Guralnik, 1991). The natural history of functional status during hospitalization is a progressive and significant deterioration with a slow, delayed recovery (Hirsch *et al,* 1990). Functional abilities rather than diagnoses and indices of disease burden are the strongest predictors of hospitalization outcomes, such as further functional decline, length of stay and institutionalization. Moreover, functional measurements are important predictors of early and late mortality after hospitalization in old persons (Inouye *et al*, 1993). Although the influence of physical health, cognition, and depression on functional dependency at hospital discharge has been evaluated (Covinsky *et al,* 1997), a possible synergistic effect of these three conditions has seldom been studied.

1.8 MULTIMORBIDITY AND MORTALITY

The evaluation of the impact of several co-occurring diseases on survival is a critical and complex issue. Chronic diseases can be widely different in terms of severity and effect on survival. Indeed, the hypothesis explored in this thesis is that an increasing number of chronic conditions do not necessarily have a major impact on survival. Few studies have attempted to examine the effect of multimorbidity on mortality risk in the old population (Table 4). One of the first reports goes back to the end of the Eighties, when Seeman and colleagues, 1989, showed that having three or more of 22 self-reported chronic conditions or symptoms was associated with an increased risk of 17-year mortality in 60+ year old persons. More recently, results from the 'Finland, Italy, and the Netherlands Elderly (FINE) study' and the 'Established Populations for Epidemiologic Studies of the Elderly (EPESE) study' showed that two or more chronic conditions were significantly associated with higher risk of mortality in the elderly, but only 9 and 5 chronic conditions detected by interviewers were taken into account respectively (Menotti *et al*, 2001; Fillenbaum *et al*, 2000). Fried and colleagues, 1998, found an association between chronic diseases and 5-year mortality in a large American population, but only cardiovascular diseases were evaluated. These studies provide useful information concerning the impact on survival of some chronic diseases in old age, but they do not cover the total burden of chronicity within a population.

Table 4. Major studies examining the association between multimorbidity and mortality in the old population

Author, y	Sample	Study description	Ascertainment and n° of chronic diseases	Covariates	Outcomes	Results
Seeman *et al*, 1989	N=4174 community US residents 38+ yrs old (21%, 65+yrs)	The Alameda County Study: Baseline in 1965	Self-report of 22 chronic conditions and symptoms	Age	17-year mortality risk	The presence of 3+ diseases was associated with an increased risk of mortality RH=1.24;95%CI=1.03-1.49 for subjects aged 60+yrs
Ferrucci *et al*, 1991	N=967 community-residents in Italy 60+ yrs old	Longitudinal survey in Florence Baseline in 1980	Self-report of chronic conditions from a predefined list of 7 diseases	Age, sex, disability, number of drugs, contacts with physicians and days in hospital	7-year mortality risk	The number of disabling and non disabling diseases was associated with higher mortality risk
Ho, 1991	N=1054 community residents in China 70+ yrs old	Baseline in 1985	Self-report of 25 chronic conditions experienced in the previous 12 months	Age and sex	2-year mortality risk	An increased number of diseases did not increase mortality risk
Mor *et al*, 1994	N=7527 community US residents 70+ yrs old	The Longitudinal Study on Aging Baseline in 1984	Self-report of 13 chronic conditions	Age, gender, baseline disability, self-rated health	6-year change in functional status, mortality, and institutionalization	N° of diseases was associated with mortality OR = 1.3; 95%CI=1.2-1.3 per disease
Mendes de Leon *et al*, 1997	N=2812 (New Haven) and N=4162 (North Carolina) community US residents 65+ yrs old	The EPESE study : the New Haven (baseline 1982) and the North Carolina (baseline 1986) populations	Self-report of 6 chronic conditions	Age, education, race, income, BMI, cognition	Mortality risk (9-year risk for the New Haven and 7 for the North Carolina cohort)	N° of diseases was not significantly associated with higher odds of mortality
Fillenbaum *et al*, 2000	N=4126 community US residents 65+ yrs old	The EPESE study Baseline in 1986-7	Self-report of 5 chronic conditions	Age, gender, education, race, type of conditions	6-year mortality risk	The presence of 2+ diseases was associated with an increasing risk of mortality RR=1.28, 95%CI=1.04-1.59

Menotti *et al*, 2001	N=2285 men rural community in Finland, Italy, and the Netherlands 65-84 yrs old	The FINE Study Baseline in 1984-5	Clinical examination and reports of 9 chronic conditions (only 7 included in the definition of multimorbidity)	Age, cohort, smoking habits, and heart rate	10-year mortality risk	Having 2 or 3+ diseases significantly increased the mortality risk in all cohorts
Di Bari *et al*, 2006	N=688 rural community residents in Italy 65+ yrs old	The ICARe Dicomano Study Baseline in 1995	Physical examination, questionnaires and lab data of 14 chronic conditions	Age, sex, MMSE, and baseline function	9-year mortality risk	The presence of 3+ diseases was associated with an increased risk of mortality HR=1.6, 95%CI=1.0-2.5
Tas *et al*, 2007a	N=4258 Community residents in the Netherlands 55+ yrs old	The Rotterdam Study Baseline in 1990	Self-report of 8 chronic conditions	Age, gender, smoking, alcohol use, BMI, self-rated health	6-year mortality risk	The presence of 2+ diseases was not associated with an increasing risk of mortality

1.9 METHODOLOGICAL ISSUES

The selection of different assessment tools for the measurement of health status is critical in determining the outcome of interest. Current methods include interviews, self-reports, medical record reviews, administrative databases, and clinical examinations (Yancik *et al*, 2007). Analyses of surveys containing both self-report and objective measurements of health status have documented systematic biases in self-reports according to age, sex and SES (Sadana, 2000). It has been shown that older age is associated with less accurate self-reports of diseases, independently of cognitive status (Kriegsman *et al*, 1996), and that having multiple diseases decreased the agreement between self-reports and medical records in older women (Simpson *et al*, 2004). The Italian Longitudinal Study on Aging showed substantial under- and over-reporting for several chronic diseases by elderly persons (ILSA working group, 1997). To avoid misreporting and recall biases, we used different sources of medical diagnoses, limiting potential errors which often affect the accuracy of the assessment of multimorbidity in the elderly population. A multiple informants approach is considered one of the best choices in addressing multimorbidity in epidemiological studies. Moreover, this method assures independence of comorbid diseases scoring from other study variables.

One of the methods available for quantitative evaluation of the health status of the elderly is the number of chronic conditions (multimorbidity) they are affected by. However, this tool is not without methodological problems, and it has both advantages and disadvantages (Lash *et al*, 2007). A chief advantage of this procedure is conceptual simplicity and parsimony, especially when a high number of diseases are evaluated. Second, the resulting composite expresses multimorbidity in an additive form, and it conveniently differentiates people at each level of morbidity. Finally, using the count variable approach, the contribution of x disease, expressed in the multimorbidity term, can be estimated, avoiding problems of insufficient statistical power, especially if rare diseases are evaluated (Ferraro and Wilmoth, 2000). On the other hand, one of the most widely reported disadvantages is that all diseases are scored equally, regardless of their severity. Secondly, a substantial number of people suffer from less prevalent diseases. The prevalence of multimorbidity largely depends on the number of diseases included in the different studies and the diagnostic criteria used. Generally, the higher the number of diseases studied, the higher the occurrence of multimorbidity.

Restrictions regarding age groups or care settings can also have a large impact on study results. Third, the summer score ignores potentially important relationships between diseases that might differ from their simple sum (Lash *et al*, 2007).

When studying multimorbidity from a qualitative perspective, it is important to take into account that disorders may co-occur due to coincidence or biases in the study. Coincidental comorbidity is the proportion of comorbidity to be expected due to their prevalence (van den Akker *et al*, 1996). If disorders are completely independent of one another, they can be expected to co-occur at a rate which equals the product of the prevalence of the separate conditions. For some pairs of conditions, the rate of co-occurrence could be higher than expected. There are a number of possible explanations for the increase in observed versus expected co-prevalence for conditions not generally recognized as associated (Guralnik *et al*, 1989). Detection bias could influence the results, as persons affected by one condition may have more contacts with the medical care system and greater likelihood of being diagnosed with a second condition. Examples of bias are the over-reporting of comorbidity associated with certain conditions like depression (Neeleman *et al*, 2001), or the concentration of comorbid cases among hospitalized patients. However, there could be an underlying biological basis: genetic, environmental, and psychosocial factors may increase a general susceptibility to disease, resulting in the co-occurrence of diseases in late life. When the prevalence of comorbidity exceeds the expected (coincidental) level and biases can be excluded, there must be substantive associations between diseases. This proportion of comorbidity has been referred to as causal-comorbidity, where there is a proven patho-physiological correlation between co-occurring conditions (van den Akker *et al*, 1998, Batstra *et al,* 2002). Finally, there is a descriptive method named cluster analysis that makes it possible to go beyond comorbid pairs of conditions and considers how diseases tend to occur in conjunction to each other. With the use of this technique, it is possible to obtain an overall picture of how diseases are associated in a particular population. The distribution of diseases seen in the cluster should be significantly different from random distribution (John *et al*, 2003).

2 AIMS

2.1 GENERAL AIMS

The general aim of this thesis was to evaluate the health status of elderly persons to detect its impact on disability and mortality.

2.2 SPECIFIC AIMS

1. To assess the prevalence of chronic diseases and multimorbidity in the elderly population under the hypothesis of differential distribution by age, gender, and socio-economic status (*Study I*).
2. To analyse patterns of comorbidity and multimorbidity in the elderly population with different approaches and to compare the results (*Study II*).
3. To evaluate the impact of chronic multimorbidity and disability on 3-year functional decline and mortality in the elderly population (*Study III*).
4. To evaluate the association of somatic and mental health with functional disability in geriatric patients at hospital discharge (*Study IV*).

3 METHODS

The data in this thesis are gathered from two different sources: the Kungsholmen Project and an Italian database of hospitalized elderly.

3.1 THE KUNGSHOLMEN PROJECT (Study I, II, and III)

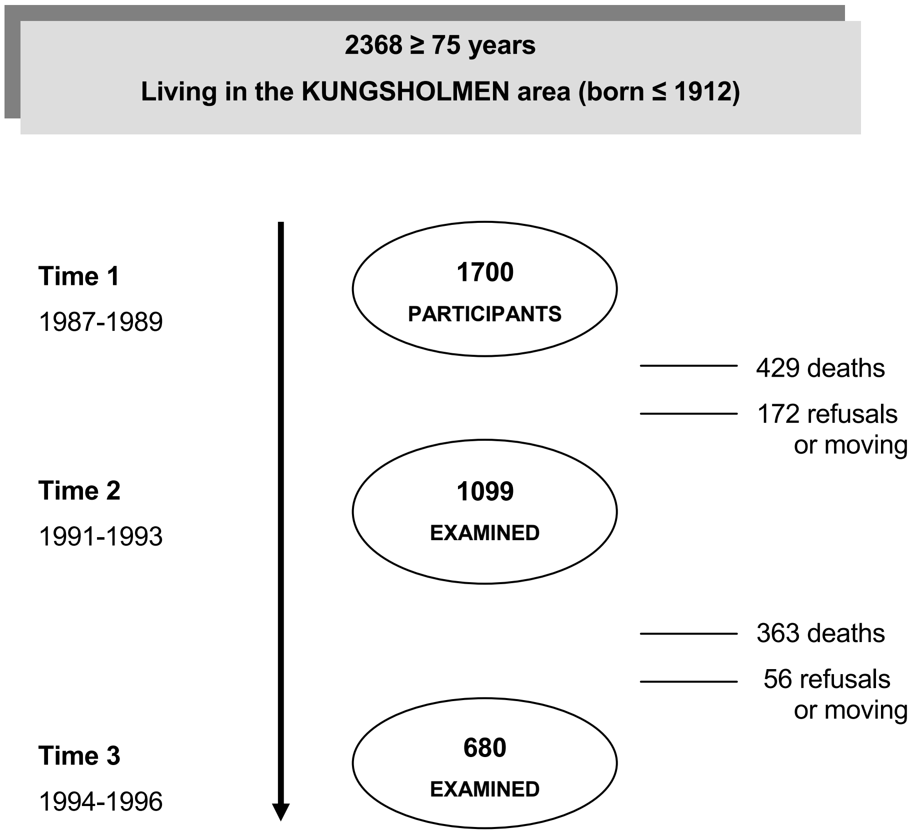
3.1.1 Study population

The Kungsholmen Project is a longitudinal, population-based study on aging and dementia in which all persons born before 1913 living in the Kungsholmen district of Stockholm on October 1st, 1987 were invited to participate (a total of 2368 persons including both community-dwelling and institutionalized persons) (Fratiglioni *et al*, 1992). The baseline phase and four follow-up examinations (every three years) have been completed in the summer 2000. The design of the Kungsholmen Project and its participants are described in Figure 6. In the studies included in this thesis, the baseline population consisted of participants in the first follow-up (n=1099), when all persons underwent an extensive clinical examination performed by physicians.

3.1.2 Data collection

All participants were examined following a standardized protocol, including a social interview, a neuropsychological battery, and a medical examination, lasting about three hours. The nurses measured blood pressure, height, and weight, collected blood samples, and assessed cognitive status with brief cognitive tasks, as well as assessed and tested physical functioning. The subjects and their next-of-kin were also interviewed on living conditions and social status. Living situations included living at home, in sheltered accommodation (service building) or in an institution. The clinical examination was similar to the comprehensive somatic, neurological, and psychiatric examination usually performed in clinical practice, but was structured and defined according to various scoring criteria. The examination included: family medical history with a structured family interview of all first-degree relatives; personal clinical history (previous diseases, hospitalization, and drug use); cognitive assessment (memory, orientation, social behavior, personality); and clinical examination (physical, neurological, and psychiatric examination). At the end, the examiner made diagnoses of current diseases according to standardized criteria.

Figure 6. Study design of the Kungsholmen Project



Assessment of chronic diseases and multimorbidity. A disease was classified as chronic if one or more of the following characteristics were present: 1. being permanent, 2. caused by non-reversible pathological alteration, 3. requiring rehabilitation, or 4 requiring a long period of care (Timmreck *et al*, 1987). A subject was classified as affected by a chronic disorder when diagnosed by the examining physician, or detected in the computerized Stockholm Inpatient Register, as described below. Diagnoses were made by physicians based on the clinical examination, medical history, laboratory data, and current drug use. The participants were asked by physicians to show prescription forms and/or drug containers for the drugs used. The names and dosages of the drugs were registered according to the Anatomical Therapeutic Chemical (ATC) classification system (WHO, 1990). The International Classification of Diseases –

– Ninth Revision (ICD-9) (WHO, 1987) was used for all diagnoses, except for the following disorders: 1) Sensory function: deafness was defined as being unable to hear the interviewer's voice and visual impairment was defined as being blind or almost blind; 2) Diagnosis of major depression was made by a psychiatrist according to DSM-IV criteria (American Psychiatric Association, 1994), using data from the Comprehensive Psychopathological Rating Scale (Åsberg *et al*, 1978); 3) The DSM-III-R diagnostic criteria were used for the clinical diagnosis of dementia and different dementia types (American Psychiatric Association, 1987); and 4) Anemia was defined as haemoglobin <13 g/dL in males and <12 g/dL in females according to the WHO definition (WHO, 1968). Further information on health status for all participants was derived from the computerized Stockholm Inpatient Register System, which encompasses all hospitals in the Stockholm area since 1969, and records up to six diagnoses at discharge. Diseases reported in the Stockholm Inpatient Register are also coded with the ICD-9 system. We limited our review to clinical records during the examination period (1991-1993). Eighty-seven undiagnosed diseases were detected from this source.

Multimorbidity was defined as any co-occurrence of two or more chronic conditions in the same individual, whether coincidental or not (van den Akker *et al*, 1996). Every single disease (n=30) was included.

Assessment of socio-economic status (SES). SES was evaluated using two different variables: education (years of schooling) and occupation. Information on the highest educational level achieved was assessed at baseline directly from the subject or from an informant. Data on educational background were missing for seven subjects, who were excluded from all the analyses. Education was divided into three main categories: primary (six years of primary school and, in some cases, one year of practical vocational training), secondary (8-12 years), and university level (13+ years). All analyses were performed using the three educational levels; however, as results in the last two groups were comparable, we reported only findings related to primary *versus* secondary/university levels. The occupation-based socio-economic status was assessed at first follow-up by trained nurses who interviewed a relative or another significant person about the lifetime work history of each subject. The interview questionnaire was developed by an expert in occupational medicine and explored lifetime work activities with regard to employer, job title, time period, and tasks for all jobs lasting at least six months. In a subgroup of 770 subjects, SES was estimated. For women who had been housewives for most of their lives, the second longest-held job was used. Eleven subjects, who had been housewives their whole life, were included in the high occupation-based SES category (Karp *et al*, 2004). All occupational periods were grouped according to the Swedish socioeconomic classification system (SEI) developed by Statistics Sweden (1982). The subject's longest-held job was considered the main occupation, and on this basis participants were classified as blue-collar workers (low occupation-based SES), white-collar employees (intermediate occupation-based SES), and self-employed and academic professionals (high occupation-based SES). Due to similar results in all analyses, the last two groups were merged.

Assessment of functional status. Functional status was measured by the Katz index of ADL (Katz *et al*, 1963), which is a hierarchical scale comprising dependency in the following six activities: bathing, dressing, going to the toilet, transferring, continence, and feeding. This scale has previously been reported to provide good reliability and construct validity when administered by nurses (Brorsson and Asberg, 1984). Functional independence was defined as no need for assistance or need for assistance in one activity, partial disability was defined as need for assistance in two to four activities, and total disability was defined as need for assistance in five or six activities. Data on functional status were collected by a nurse by questioning and observing the subjects. Functional decline was defined as a change in functional status from being independent or partially dependent to become partially or totally dependent during the follow-up period. Because of the small number (N=3), older persons who functionally improved during follow-up in all the analyses were included in the group of persons with no change in functioning. In order to be more confident in using this categorization, we cross-checked the entire analysis defining no disability as having no basic function lost and decline in functioning as any basic function lost during the follow-up, obtaining similar results. Seventeen subjects had missing data on functional status at baseline, and nine persons at follow-up.

Mortality data. Mortality data for all participants were derived monthly from the Swedish National Death Register.

3.2 THE ITALIAN STUDY
(Study IV)

3.2.1 General description

The Italian study is a cross-sectional study on hospitalized old persons. From February 1998 to December 2000, 923 patients 65 years of age and older were consecutively admitted into the acute care Geriatric Ward of the Spedali Civili Hospital, Brescia, Italy. The Spedali Civili Hospital is the main hospital of the city, evaluating about 250 persons per day in the Emergency Room.

3.2.2 Data collection

Information on socio-demographic characteristics such as age, gender, years of education, and marital status was collected at hospital admission. Each patient underwent a routine comprehensive medical, functional, and neuropsychological assessment at times of both admission (the day of admission or the day after) and discharge. The comprehensive assessment was performed by junior physicians trained by the same senior physician.

Functional status was investigated using the basic Activities of Daily Living scale (ADL) (Katz *et al*, 1963) to assess the individual's ability to manage activities such as bathing, dressing, going to the toilet, continence, feeding, and transferring. ADL is a 6-point scale that ranges from 0 (independent in all activities) to 6 (totally dependent). Disability was defined as needing physical assistance in at least 1 of 6 basic ADL functions. ADL disability at discharge was included as dependent variable in all the analyses. As the correlation between ADL at admission and at discharge was very high (Pearson coefficient= 0.86), the admission ADL score was not included as a covariate in the multivariate analysis.

Multimorbidity. We collected information on diseases in accordance with the International Classification of Diseases, 9th revision (ICD-9) (WHO, 1987). The most prevalent diseases were grouped into 11 categories according to the classification used by Greenfield and colleagues, 1993 (Table 5). Hypertension, malignancy, diabetes and anemia were categories *per se*.

Multi-morbidity was measured by the Geriatric Index of Comorbidity (GIC) (Rozzini *et al*, 2002) which takes into account both the number and the severity of diseases as assessed by the Greenfield Index of Disease Severity (IDS) (Greenfield *et al*, 1993). The IDS grades each disease on a 0-4 scale on the basis of the following general framework: 0 = absence of the disease; 1 = asymptomatic, controlled disease; 2 = symptomatic disease, controlled by the treatment; 3 = uncontrolled disease; 4 = life-threatening disease or greatest severity of the disease. The GIC is a four-point scale that classifies individual diseases into four classes of comorbidity (Table 6). The IDS and the GIC scores were assessed during hospitalization, and the acute diseases leading to admission were included. The Geriatric Index of Comorbidity was developed and validated in an Italian population; the advantage of this index is that functional status and cognition are not included in the calculation, and can therefore be used as independent predictors. The GIC was included in the statistical models both as a continuous and as a dichotomous variable, using 2/3 as a cut-off point. This cut-off point was chosen on the basis of the findings of Rozzini and colleagues, 2002.

Table 5. Most prevalent diseases grouped according to the classification of Greenfield *et al*, 1993

Heart diseases	**Cerebro-vascular diseases**	**Gastro-hepatic diseases**	**Lung diseases**	**Peripheral vascular diseases**	**Renal diseases**	**Musculo-skeletal diseases**
- Coronary heart disease - Heart failure - Arrhythmias	- Stroke - Transient ischemic attack	- Gastritis - Peptic ulcers - Pancreatico-biliar disorders - Intestinal obstruction - Hepatitis - Cirrhosis	- Chronic obstructive pulmonary diseases - Recurrent pneumonia	- Arterial thrombosis - Venous thrombosis - Pulmonary embolism	- Acute renal failure - Chronic renal failure	- Arthritis - Fractures

Table 6. The Geriatric Index of Comorbidity (GIC) based on the Greenfield Index of Disease Severity (IDS). IDS: 0 = absence of the disease; 1 = asymptomatic, controlled disease; 2 = symptomatic disease, controlled by the treatment; 3 = uncontrolled disease; 4 = life-threatening disease or greatest severity of the disease

GIC score			
Class I	1+ conditions with IDS=1 or lower	**Class III**	1 condition with IDS=3 and the others with IDS<3
Class II	1+ conditions with IDS=2	**Class IV**	2+ conditions with IDS=3 or 1+ conditions with IDS=4

Cognitive status. The Mini-Mental State Examination (MMSE) (Folstein *et al*, 1975) assessed cognitive status. The MMSE score was adjusted by age and education using the weights suggested by Magni and collaborators, 1996, which validated this test in a 65+ year-old population in Northern Italy. The MMSE was entered in the models as both continuous and dichotomous variable using 23/24 as cut-off point. This cut-off is the one most commonly used for the MMSE as indicator of possible dementia (Grut *et al*, 1993; Fratiglioni *et al*, 1991). The DSM-IV criteria were used for dementia diagnosis (American Psychiatric Association, 1994).

Depressive symptoms. Depressive symptoms were assessed with the Geriatric Depression Scale (GDS), which is a 30-point depression-screening scale (Yesavage *et al*, 1983). Increasing score indicates increasing depressive symptoms: a score lower than 11 indicates the absence of depression, whereas a score higher than 20 indicates severe depression. The GDS was administered only in persons with a MMSE score >16. A cut-off point between 10 and 11 was used to identify subjects with mild and severe depression in the analyses.

3.3 STATISTICAL ANALYSIS

Statistical tests. Chi-square and independent Students' t tests were used for assessing proportion and mean differences between groups. Logistic regression models were employed to test bivariate associations. Relative risks of functional decline or death were estimated using Cox proportional hazard models. Table 7 summarizes the statistical analysis, the outcome, and the independent variables that were considered in the four studies.

Specific analyses for each study.

Study I: the prevalence of each chronic disease, morbidity (1 chronic disease) and multimorbidity (2+ chronic diseases) was calculated by age, gender, education, and occupation-based SES. Ninety-five percent confidence intervals (95% CI) for prevalence figures were based on the binomial distribution. Logistic regression models were used to study the association of multimorbidity with age, gender, education, and occupation-based SES.

Study II: for each chronic disease we estimated the prevalence per 100 and 95% CI of the disease independently of comorbidity, and the mean number and standard deviation of co-occurring conditions. The expected prevalence of diseases pairs was computed as (prevalence of disease A) X (prevalence of disease B), and compared with the observed co-prevalence. Several logistic regression models were run to analyze the crude and adjusted bivariate association between each pair of co-occurring diseases. The adjustment included age, gender, education, and all the other diseases. In order to analyze different patterns of associative comorbidity, a cluster analysis was performed using the Yule's Q measure of association and average linkage as combination method. To further analyze the distribution of diseases, a cluster analysis was run after stratification by age (77-84 and 85+ year-old subjects) and gender.

Study III: the cross-sectional association between chronic multimorbidity and disability was tested using prevalence figures and logistic regression models. Cox regression analysis was employed to analyze the association between increasing number of diseases and functional decline and mortality during the 3-year follow-up. Apart from disability at baseline, the models included age, gender, and education as covariates. Persons with total disability were excluded from all models testing functional decline. Finally, to confirm the reliability of the previous analyses, multinomial logistic regression models having either functional decline or death as dependent variables were created.

Study IV: logistic regression models were employed to study factors associated with disability. Several logistic regression models were constructed for both age strata (65–74 and 75+ years), including sociodemographic factors, length of hospitalization, cognitive status, affective status, and the Comorbidity index. As the GDS scale was administered only in persons with MMSE score>16, we created two models. In model 1, all patients were included, while in model 2 only those with MMSE>16 points were included. Additional multivariate models were created including MMSE, GDS, and GIC as dichotomous variables, using 23/24 as cut-off point for the MMSE score, 10/11 as cut-off point for the GDS score, and 2/3 as cut-off point for GIC, and adjusting for age, gender, education, and length of hospitalization. To study the combined effect of multimorbidity, cognition and depression, stratification was used and interaction terms were introduced into the models.

Table 7. Statistical models, dependent and independent variables used in the four studies included in this thesis

Study	Models	Dependent variables	Independent variables	Comments
Study I	*Logistic regression*	Multimorbidity (2+ *vs*. 0 diseases)	Age continuous or dichotomised (85+ *vs*. 77-84 yrs) Gender: female *vs*. male Education: ≤ 7 *vs.* ≥ 8 years of schooling Occupation-based SES: low *vs*. high	First model: age, gender and education Second model: occupation-based SES was added Interaction between age and gender, age and education, and gender and education were tested by adding specific terms to the models
Study II	*Logistic regression*	Bivariate association between pairs of diseases	Chronic diseases with prevalence >3% Age, gender, education, and other chronic diseases as possible confounders	First model: only the disease pairs was included Second model: age, gender, education, and all the other diseases were added
	Cluster analysis	-	-	A correlation matrix was computed among all the conditions, using the Yule's Q measure of association and average linkage as the combination method Cluster analysis was repeated for different age groups (77-84 and 85+ yrs) and gender
Study III	*Logistic regression*	Functional disability at baseline (ADL=2+ lost function)	N° of chronic diseases analyzed as continuous and categorized variable. No disease as reference group Age, gender, and education as possible confounders	The analyses were run in the whole population and in men and women separately All models: persons with total disability were excluded from testing functional decline Last model: the population was stratified into five groups according to presence or absence of disability and number of chronic diseases. Having no disability and no disease was the reference group
	Cox regression *Multinomial logistic regression model*	Functional decline and mortality during 3-year of follow-up	N° of chronic diseases analyzed as continuous and categorized variable. No disease as reference group Functional disability at baseline: defined as either partial or total disability Age, gender, education as possible confounders	
Study IV	*Logistic regression*	Functional disability (ADL=1+ *vs*. 0 lost functions) at hospital discharge	MMSE at admission: continuous and dichotomized at 23/24 GIC: continuous and dichotomized at 2/3 GDS: continuous and dichotomized at 10/11 Age, gender, education, and length of hospitalization as possible confounders	All models were carried out separately for the two age groups (65-74 and 75+ yrs) First model: all patients included Second model: only persons with a MMSE >16 included Third model: the combined effect of cognition /depression and cognition/multimorbidity was tested

4 ETHICAL ISSUES

4.1 THE KUNGSHOLMEN PROJECT

The studies included in this thesis covered the data collected at phase III and IV of the Kungsholmen Project as well as the data from the death certificates, and the inpatient register database. Approval from the Ethics Committee of the Karolinska Institutet was obtained for each phase and differential data acquisition:
Phase III (i.e., the first follow-up examination): Dnr. 90:251;
Phase IV (i.e., the second follow-up examination): Dnr.94:122;
Death Certificates and the Stockholm Inpatient Register data: Dnr.99:025; Dnr. 01:020.

4.2 THE ITALIAN DATABASE

The Ethics Committee of the Spedali Civili Hospital authorized Dr. Alessandra Marengoni to use data (socio-demographic characteristics, cognitive and functional status, and clinical data) collected during hospitalization in patients admitted to the Geriatric Ward of the Spedali Civili Hospital for research purpose (2003-05-14). The Ethical Committee of the Karolinska Institutet further approved the project (Dnr. 327/03).

5 RESULTS

5.1 THE KUNGSHOLMEN PROJECT

Study I, II, and III

5.1.1 Characteristics of the study population

The study population consisted of 1099 subjects; the majority were women (77%). The youngest participants were 77 years old, and the oldest were 100 years old. Nearly half of the population had higher education and worked in white-collar occupations. Most people (81.4%) lived at home, while some lived in service-houses (7.3%), institutions (10.6%), and psychiatric hospitals (0.6%). Women were older (84.8 ± 4.6 vs. 83.8 ± 4.2 years, $p<0.01$) and less well educated (55 vs. 39.2% with 2-7 years of education, $p<0.001$) than men. Older persons (85+ year-old) were more likely to be female (81.2 *vs.* 73.9%, $p<0.01$) and less well educated (57.3 *vs.* 46.3% with 2-7 years of education, $p<0.001$) than younger participants (77-84 year-old).

5.1.2 Prevalence of chronic diseases (Study I)

Hypertension, dementia, and heart failure were the most common disorders with a prevalence of 38, 21, and 18 per cent, respectively. Coronary heart disease, anemia and visual impairments showed prevalence ranging from 11 to 15%, while all the other disorders were less frequent (≤10%) (Table 8). Chronic diseases were grouped following the ICD-9 classification (Table 9).

The prevalence of cardiovascular diseases did not differ by age or gender, whereas a higher proportion of mental disorders were found among very-old (85+ years) than among old persons (77-84 years), and among women than men. Malignancy and respiratory diseases were more common in men than in women, whereas musculoskeletal and endocrine diseases were more common in women (Figure 7a and 7b).

Table 8. Chronic diseases detected in the study population grouped according to prevalence range (per 100)
Single disorders are listed in ascending order of prevalence

Prevalence per 100					
0.1-3%	**4-5 %**	**6-10%**	**11-15%**	**16-20%**	**21-40%**
Rheumatoid arthritis	Hip fracture	COPD	Anaemia	Heart failure	Dementia
Arthritis	Malignancy	Diabetes	Visual impairments		Hypertension
Rheumatic polymialgia		Deafness	CHD		
Parkinson disease		Thyroid dysfunction			
Intestinal diverticula		CVD			
Prostate hypertrophy		Major depression			
Migraine		Atrial fibrillation			
Epilepsy					
Renal lithiasis					
Peripheral neuritis					
Valvular heart diseases					
Cholelithiasis					
Renal failure					
Schizophrenia					
Inflammatory bowel diseases					

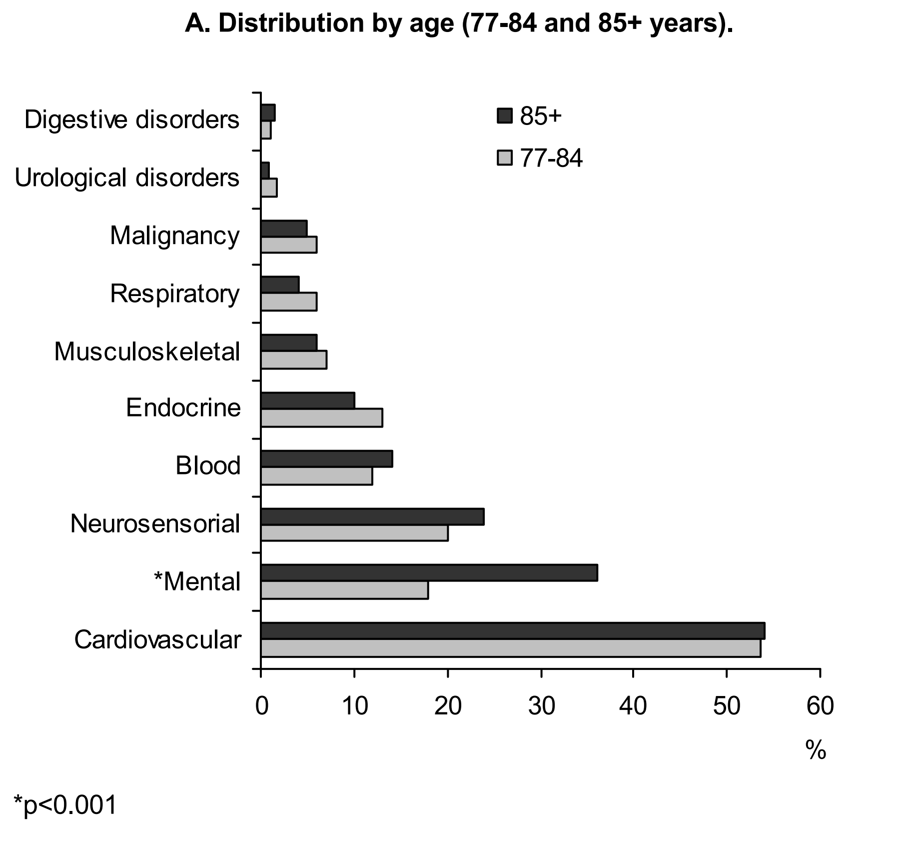
CHD=coronary heart disease
CVD=cerebrovascular disease
COPD=chronic obstructive pulmonary diseases

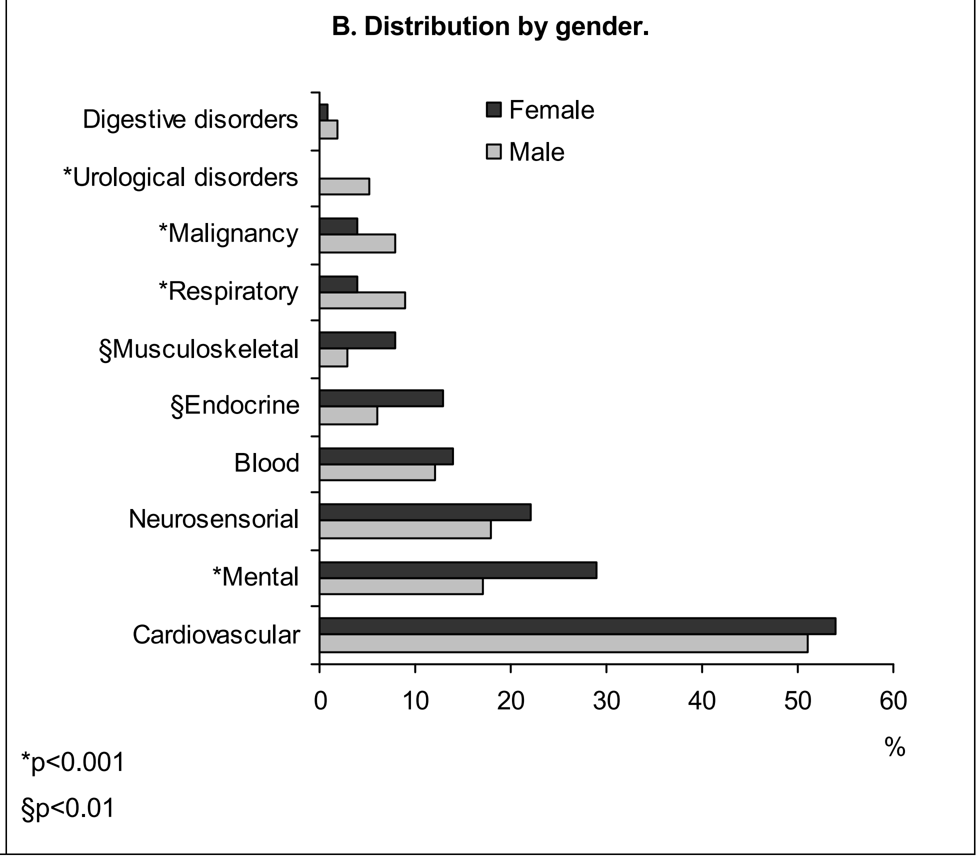
Table 9. Chronic diseases grouped following the ICD-9 classification

Cardiovascular (or circulatory) diseases	**Mental diseases**	**Neurosensorial diseases**	**Musculoskeletal diseases**	**Respiratory diseases**
Hypertension	Dementia	Migraine	Arthritis	Chronic bronchitis
CHD	Depression	Peripheral neuropathies	Osteoporosis	Emphysema
Atrial fibrillation	Schizophrenia	Epilepsy	Hip fracture	Asthma
Heart failure		Visual impairments		
CVD		Deafness		

Endocrine diseases	**Digestive disorders**	**Urological disorders**	**Malignancy**
Diabetes	Intestinal diverticula	Renal failure	Blood
Thyroid dysfunction	Chron disease	Renal calculosis	Solid
	Ulcerous colitis	Prostate hypertrophy	
	Liver cirrhosis		
	Cholelithiasis		

Figure 7. Prevalence per 100 of chronic disorders grouped according to the ICD-9 classification



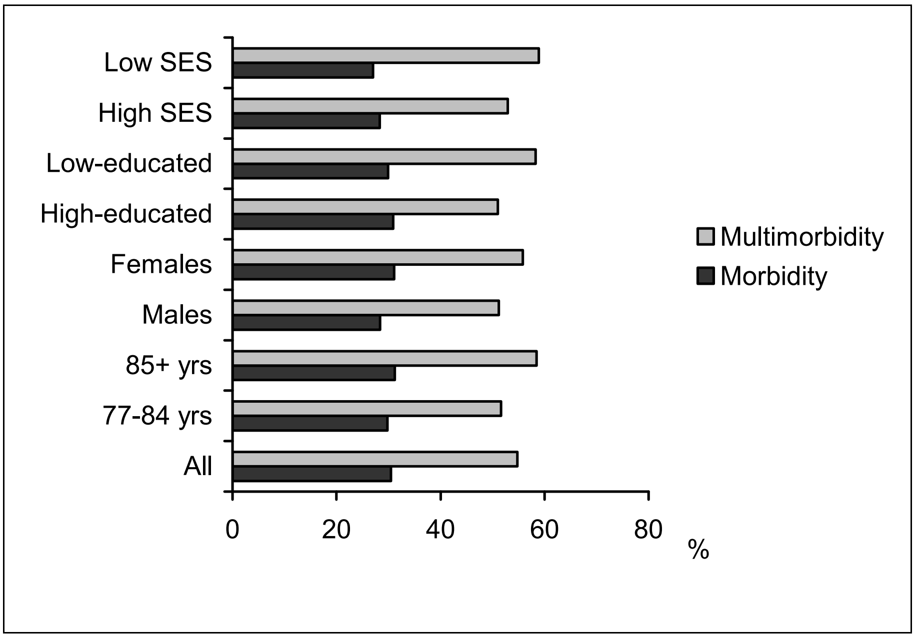


The prevalence of cardiovascular diseases did not differ by education level, but persons with low occupation-based SES had a higher proportion of cardiovascular diseases than those with high occupation-based SES, although the difference was not significant (57.1 *vs.* 52.3%). Poorly educated subjects had a higher proportion of mental diseases than better educated subjects (31.4 *vs.* 20.5%, $p<0.001$), but no difference was found by occupation-based SES. The prevalence of the other chronic diseases did not significantly differ by education or occupation-based SES.

5.1.3 Prevalence of multimorbidity and associated factors (Study I)

About one third of the population had only one disease, while 55% of them were affected by multimorbidity (2+ co-occurring diseases). The prevalence of multimorbidity was higher in the 85+ year-old persons ($p<0.05$), women, and persons with low levels of education ($p<0.01$) and low occupation-based SES, whereas there were no differences in the prevalence of one chronic condition by age, gender, education or occupation-based SES (Figure 8). The proportion of multimorbidity among subjects with disease was 64%.

Figure 8. Prevalence (P) per 100 of persons affected by one chronic disease (morbidity) and by 2+ chronic diseases (multimorbidity) by age, gender, education, and occupation-based SES



A multivariate logistic regression analysis was carried out to test the effect of age, gender, and education on multimorbidity. All three sociodemographic variables were independently associated with multimorbidity. When age was entered as a continuous variable in the model, a one-year increase in age was associated with a 10% increase in odds for multimorbidity. The interaction terms among age and gender, age and education, and gender and education did not show any synergistic effect. Occupation-based SES showed a crude association with multimorbidity (OR=1.5;95%CI=1.0-2.3), but not when adjusted for the other sociodemographic variables. Due to the high correlation between education and SES, we verified the possible combined effect by classifying education and occupation-based SES into four groups. The population with a high level of education and high occupation-based SES was the reference group. A low level of education showed a strong association with multimorbidity independently of high or low occupation-based SES (Table 10).

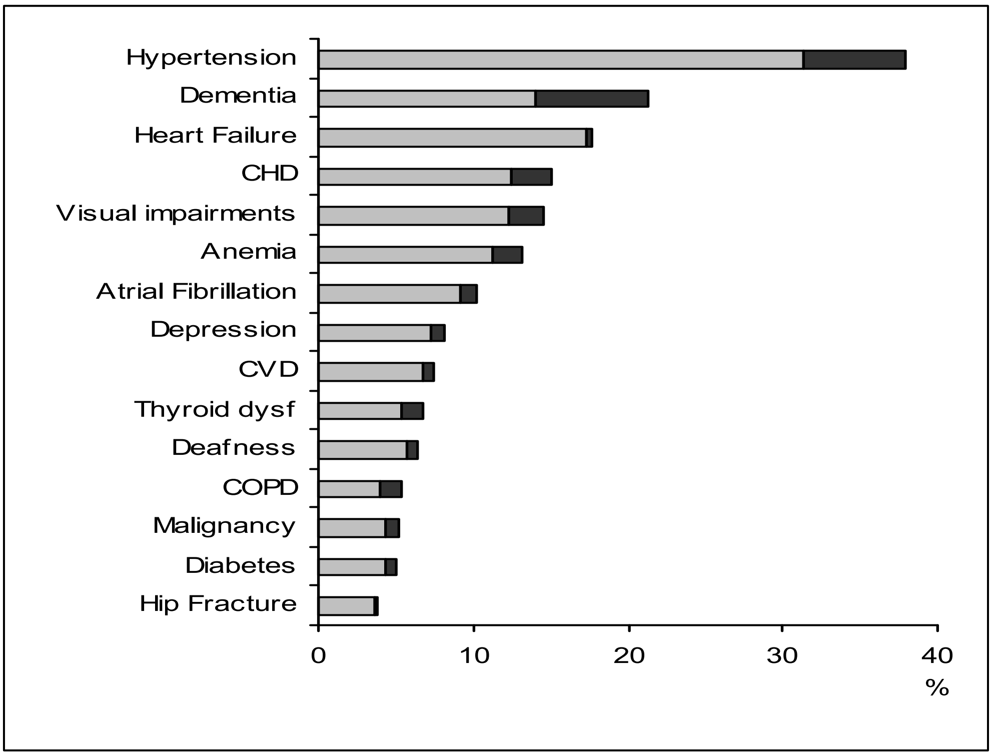
Table 10. Age and gender adjusted-odds ratio (OR) and 95% confidence intervals (95% CI) of multimorbidity (2+ diseases *vs.* 0 disease) due to the combined effect of education and occupation-based SES

Education	Occupation-based SES	All N	Subjects with multimorbidity N	OR	95%CI
High	High	345	167	1	
High	Low	52	28	1.8	0.7 – 4.5
Low	High	141	89	1.9	1.1 – 3.3
Low	Low	229	138	1.7	1.03 – 2.7

5.1.4 Patterns of comorbidity and multimorbidity (Study II)

The prevalence figures of each chronic disease with and without comorbidity are shown in Figure 9. Dementia and hypertension, although frequently associated with other diseases, had the highest prevalence when cases with comorbidity were excluded: 7.2% and 6.5%, respectively. Hip fracture and heart failure were the diseases occurring most rarely without any comorbidity (0.2 and 0.4%, respectively). All the other chronic conditions occurred without any comorbidity at a prevalence ranging from 0.6 to 2.5% (Figure 9). The number of comorbid conditions ranged from an average of 1.4 to 2.9. Visual impairments and heart failure had the highest comorbidity in terms of number of co-occurring chronic conditions, whereas dementia had the lowest. In fact, 33.8% of all cases of dementia occurred in the absence of other chronic conditions.

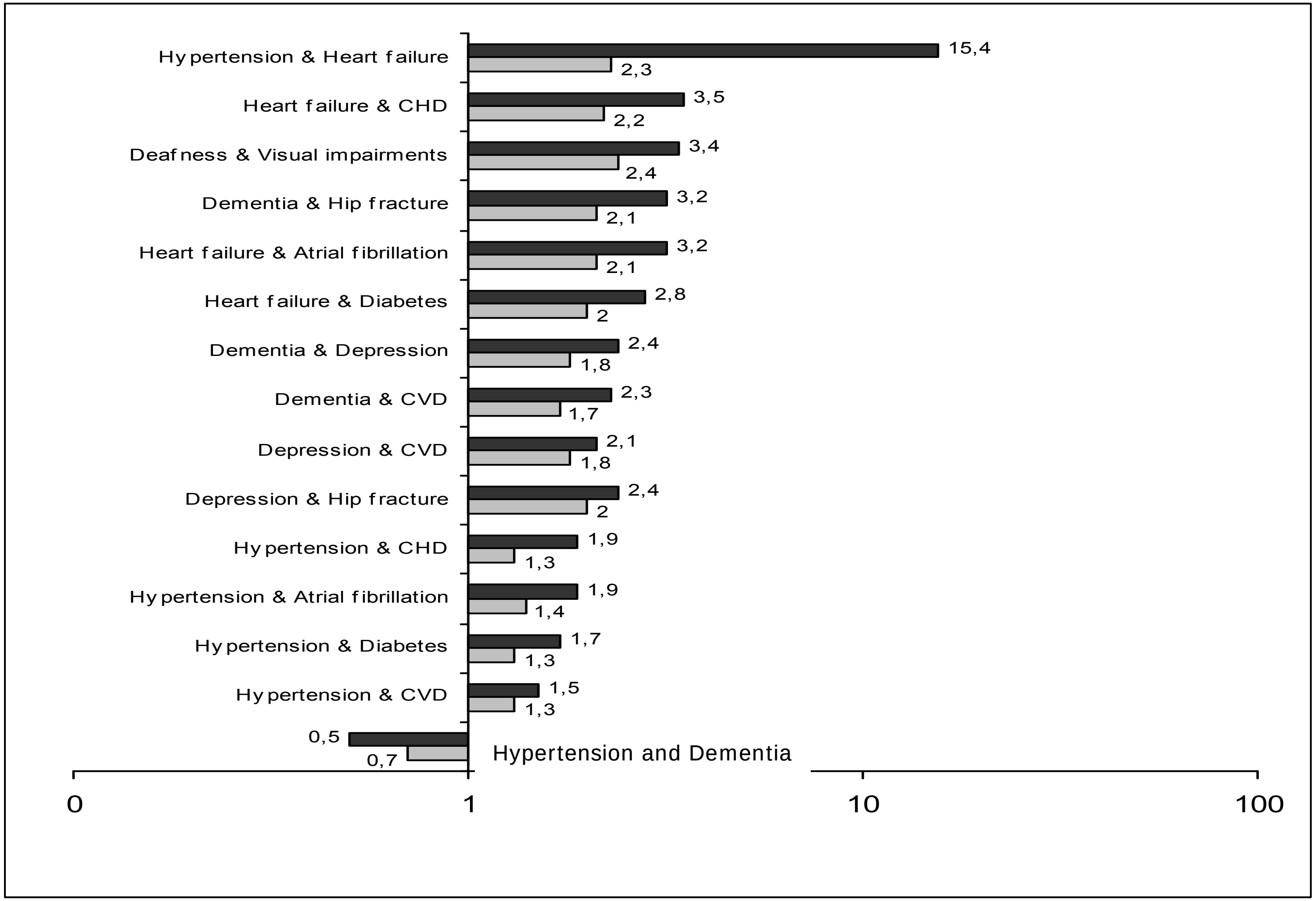
Figure 9. Prevalence per 100 of most frequent chronic diseases when occurring independently of comorbidity (grey+black) or without any comorbidity (black)



The ratio of the observed and expected prevalence of the most frequently co-occurring pairs of conditions as well as odds ratios testing their association are described in Figure 10. Circulatory disorders often occurred in pairs, mostly associated to heart failure and hypertension. Among the other pairs of disorders, the association of dementia with depression, hip fracture, or CVD was higher than expected, as was the prevalence of visual impairments and deafness. On the other hand, the expected prevalence of dementia and hypertension was higher than that observed.

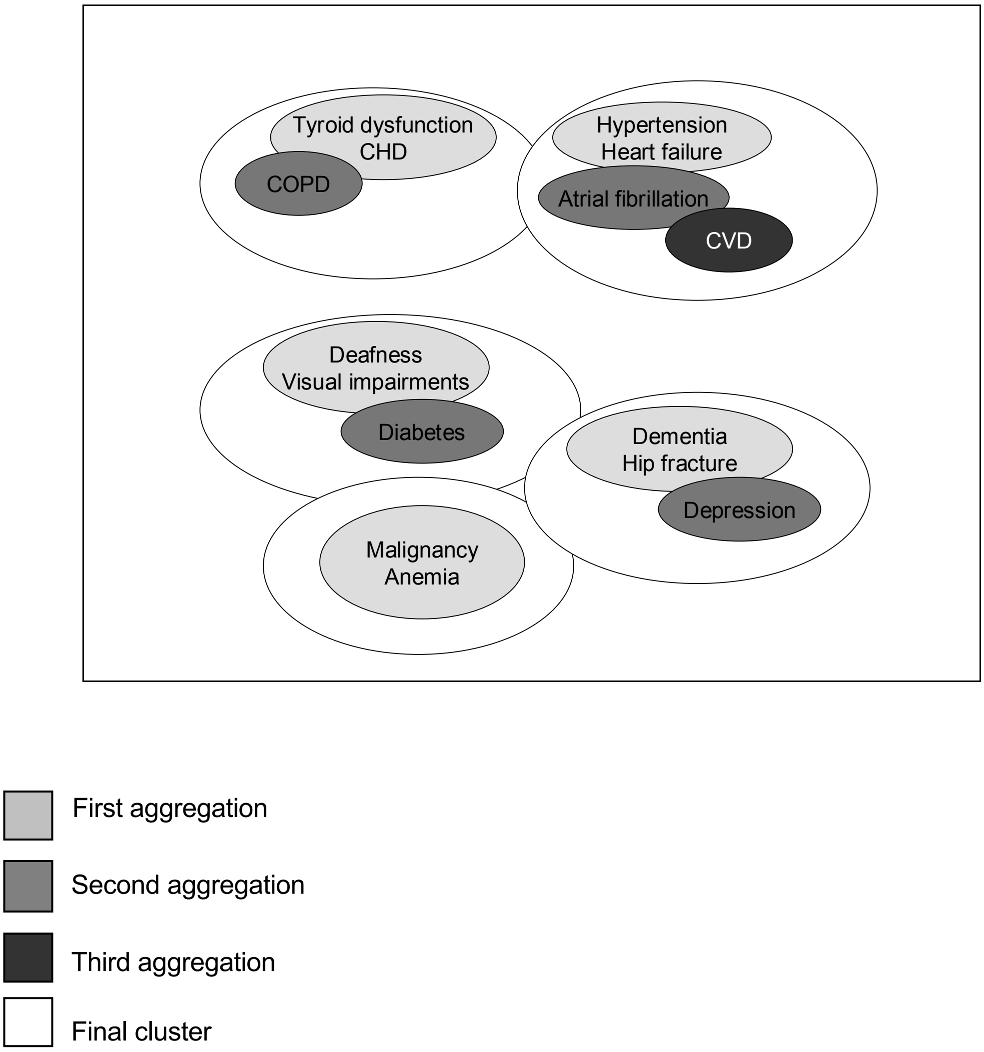
These findings were confirmed by logistic regression analysis. Only significant odds ratios are graphed in Figure 10. Hypertension and heart failure emerged as by far the most strongly associated pair of diseases. Apart from circulatory conditions, dementia and depression were both significantly correlated not only to each other but also to other diseases such as hip fracture and CVD. Two sensorial disorders, visual impairments and deafness, were also significantly correlated. Dementia and hypertension were the only inversely correlated pair of conditions. Most associations remained significant after adjustment for age, gender, education, and all the other chronic conditions.

Figure 10. Log ratio of observed and expected prevalence (grey) of most frequently co-occurring pairs of chronic conditions, as well as log odds ratios (black) testing the association between pairs of chronic conditions



A five-cluster structure was derived from the cluster analysis (Figure 11). One cluster consisted of four conditions: hypertension, heart failure, chronic atrial fibrillation, and CVD. Three clusters consisted of three chronic conditions. The first included thyroid dysfunction, CHD, and COPD. The second included diabetes, visual impairments and deafness. The third comprised dementia, hip fracture, and depression. The last cluster consisted of only two diseases: malignancy and anemia. The structures of the clusters for men and women were very similar. They differed in the distribution of depression, which clustered with malignancy in women and with hip fracture in men. There was also a difference between older- and younger-old persons, as CVD clustered with depression among the younger-old persons (77-84 yrs), but with dementia among the older subjects (85+ yrs).

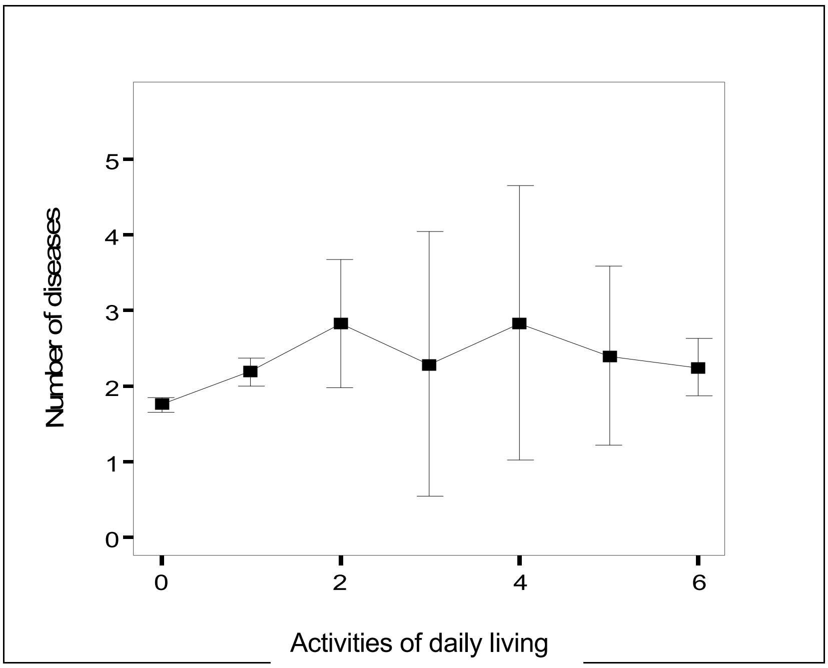
Figure 11. Cluster analysis testing the distribution of chronic diseases



5.1.5 Multimorbidity and concurrent functional status (Study III)

At baseline, 86.5% of the subjects were functionally independent in the basic activities of daily living according to our definition (see methods). Older persons (85+ years old) were more likely to be either partially or totally disabled (p<0.01), whereas no gender differences were detected. Less well educated subjects were more likely to be partially dependent (p<0.001), and the prevalence of disability (either partial or total) increased with an increase in the number of chronic conditions, from 13.7% in subjects with one chronic disease to 19.6% in persons with 5+ conditions (p for trend <0.001). After adjusting for socio-demographic characteristics, the logistic regression analysis showed odds ratios (OR) for disability similar among persons with one (10.3;95%CI=2.5-42.9), two (10.1;95%CI=2.4-42.8) or three (10.4;95%CI=2.4-44.5) diseases, but they increased to 12.6 (95%CI=2.8-56.7) in subjects with four chronic conditions, and to 14.1 (95%CI=3.0-66.3) in subjects with 5+ diseases. In women the association between disability and morbidity was stable irrespective of the number of diseases (adjusted OR ranging from 16.7 to 16.9), whereas in men the difference in odds ratios with an increasing number of diseases was more marked (adjusted OR ranging from 3.8 to 20.3). The mean number of diseases was very similar among subjects with an increasing number of impaired baseline functions (Figure 12).

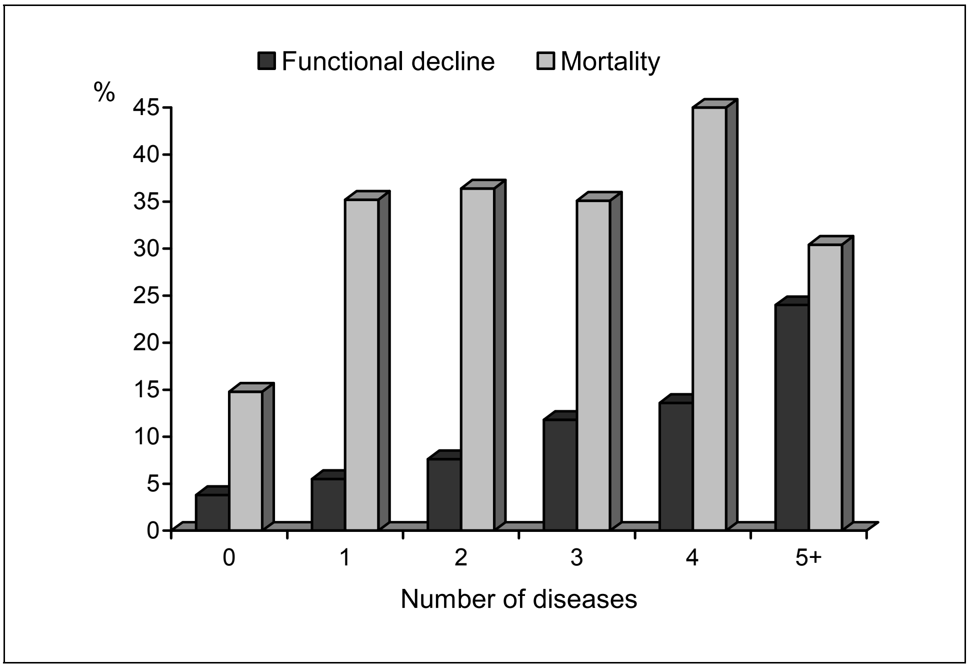
Figure 12. Mean number of diseases by number of impaired functions and 95% CI



5.1.6 Multimorbidity, functional decline, and mortality (Study III)

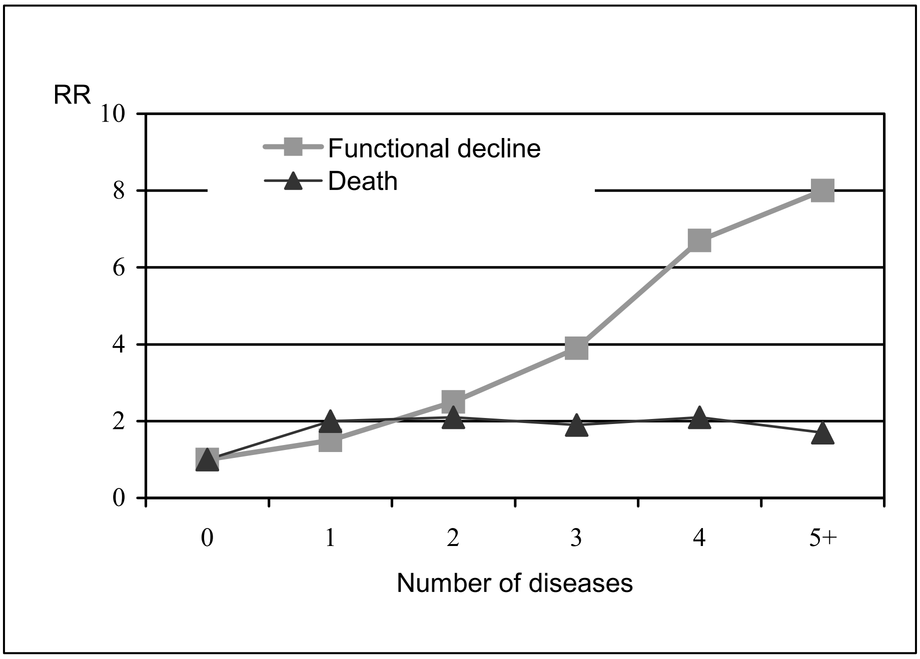
During the three years of follow-up (average 2.8 ± 1.1 yrs), 363 (33%) persons died and 85 persons worsened in functional status (56 were lost at follow-up due to either moving or refusal). The proportion of subjects with functional decline at follow-up was higher in older and less well educated subjects, and increased with an increase in the number of chronic conditions ($p<0.001$) (Figure 13). Among older persons with no disease, fifteen percent died during follow-up; 25.5 % of men and 9.9% of women ($p<0.01$), and the proportion of diseased participants who died during follow-up was independent of the number of conditions affecting the subjects at baseline (Figure 13). Only one third of persons with no disability at baseline died during follow-up in comparison to 80% of persons with any degree of disability.

Figure 13. Percent proportion of subjects who died or experienced functional decline during follow-up by number of diseases at baseline



After adjusting for socio-demographic characteristics and baseline disability, the Cox regression model showed that the number of diseases incrementally increased the risk of functional decline, but not mortality. When the number of diseases was included as a linear variable, each additional condition increased the risk of functional decline by fifty percent (RR=1.5; 95%CI=1.3-1.8), with no differences between men and women. Figure 14 contrasts the relative risks of functional decline and death due to each additional chronic condition, showing a clear divergence in the association pattern of multimorbidity with functional decline (Chi square for trend=22.1, p<0.001) and mortality (Chi square for trend=4.2, p=ns), respectively.

Figure 14. Relative Risk (RR) for functional decline and death during follow-up due to increasing number of coexisting diseases *versus* none disease Adjusted for age, gender, education, and disability at baseline



These results were confirmed in a multinomial logistic regression model, which showed a gradual increase in the odds of functional decline for persons with an increasing number of chronic conditions (OR ranging from 1.7 for persons with one disease to 8.5 for those with 5+ diseases) and a similar risk for death (OR ranging from 2.0 for persons with one disease to 1.0 for those with 5+ conditions).

When examining the combined effect of chronic diseases and baseline disability, the subgroup of persons with disability had a much higher risk of dying independently of the number of diseases, and the presence of disability increased the risk of functional decline due to multimorbidity (Figure 15). Older age was associated with both functional decline and death (RR=2.4;95%CI=1.5-3.9; RR=1.8;95%CI=1.5-2.3, respectively); females had a lower mortality risk (RR=0.6;95%CI=0.5-0.8) whereas poorly educated persons had a higher mortality risk (RR=1.4;95%CI=1.1-1.7).

Figure 15. Relative Risk (RR) for functional decline and mortality during follow-up due to morbidity (1 disease) or multimorbidity (2+ diseases) and presence of disability at baseline. RR adjusted for age, gender, and education

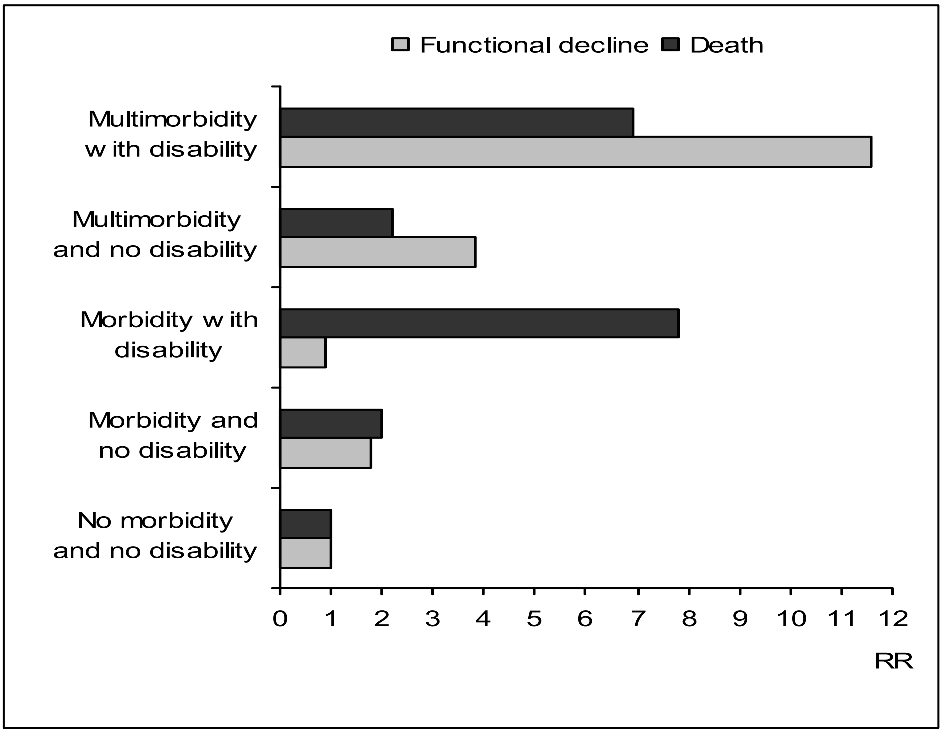
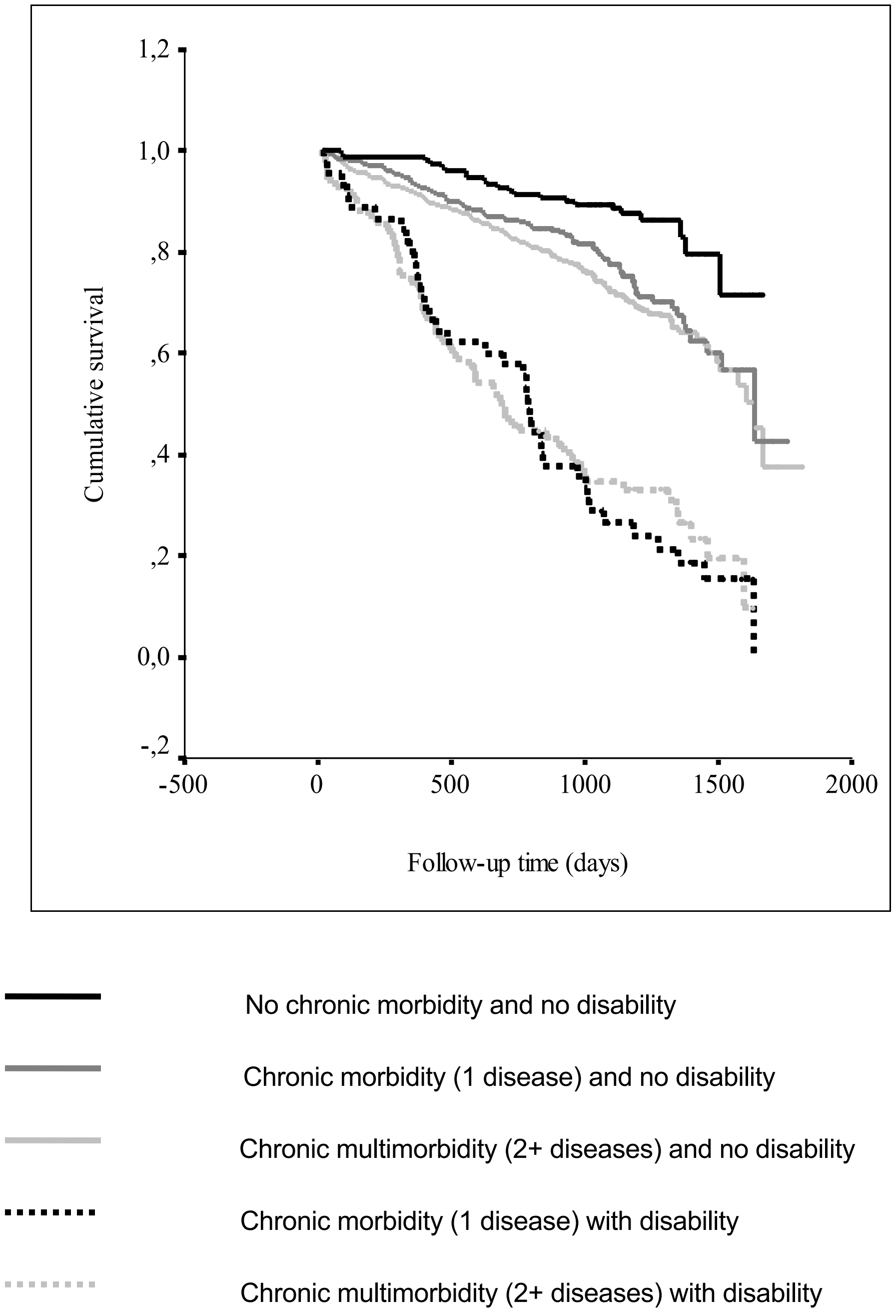


Figure 16 describes survival curves for old persons with no chronic diseases and no disability, and for those affected by morbidity (1 disease) or multimorbidity (2+ diseases) with or without disability.

Figure 16. Survival curves for subjects affected by different numbers of chronic diseases with or without disability



5.2 THE ITALIAN STUDY

Study IV

Among the eligible 923 patients, 29 subjects did not have complete information on functional assessment, and 64 individuals died during hospitalization and were not included in the study. Patients who died were significantly older, more cognitively impaired and affected by higher comorbidity than those who were included in the analysis.

5.2.1 Socio-demographic characteristics of the participants

Our study sample consisted of 830 old persons (65+ year old). The mean age was 78.7 ± 7.2 years and 50.5% were female. Combining males and females, 65–74 year-old patients constituted 33% of the sample and those 75+ accounted for 67%. Education was significantly lower in the oldest old than in the younger old: 5.4±2.8 and 6.2±3.2 years of schooling respectively ($p<0.001$).

5.2.2 Clinical characteristics

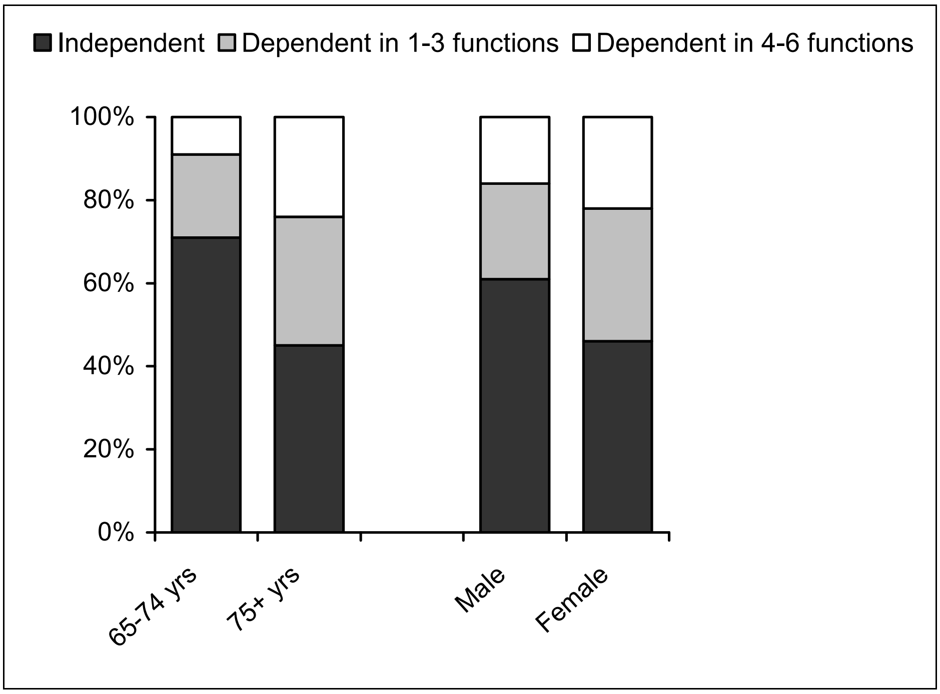
The most frequent causes of hospital admission from the Emergency Room were cardiovascular diseases (43%), cerebrovascular diseases (19%), dementia (14%), lung diseases (9%), and anemia (6%). The most prevalent diseases detected during hospitalization were cardiovascular diseases (61%), hypertension (55%) and cerebrovascular (31%), gastro-hepatic (50%), and lung diseases (34%) in both age groups. The majority of the patients had a high comorbidity index score (2.8 ± 0.8), without differences across ages, indicative of multiple and severe coexisting diseases.

5.2.3 Functional and cognitive status

Almost half of the population was disable in the basic activities of daily living. Figure 17 shows functional status at hospital discharge according to the number of impaired

ADL functions by age groups (65-74 and 75+ yrs) and gender. In the youngest age group 29% were functionally dependent in comparison to 55% in the oldest age group ($p<0.001$). Women had higher disability prevalence than men (54 *vs*. 39%, $p<0.001$). Eighty-eight percent of the population had the same ADL score at admission and discharge, 0.8% improved their ADL score after hospitalization and 11.2% had a worse ADL score at discharge. About one third of the sample had a MMSE score indicative of cognitive impairment (MMSE<24). Older patients were more likely to be cognitively impaired (46 *vs*. 25%, $p<0.001$), and had a higher mean number of depressive symptoms (10 ± 6.2 *vs*. 8.9 ± 5.9, $p<0.05$).

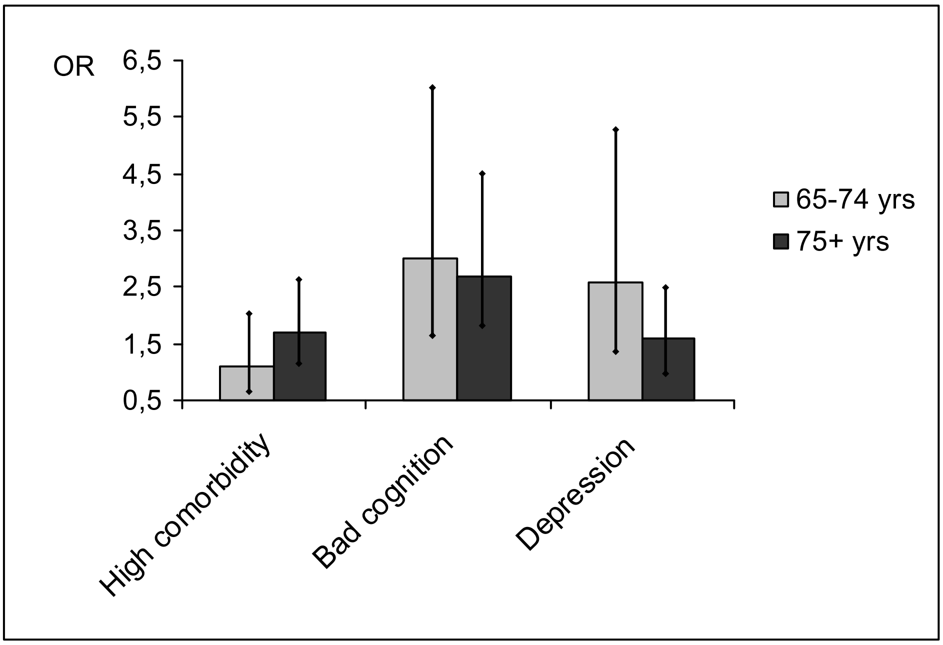
Figure 17. Functional status at hospital discharge according to the number of ADL functions lost by age groups (65-74 and 75+ yrs) and gender



5.2.4 Factors associated with disability at hospital discharge

In both age groups older age, length of hospitalization, and poor cognitive status were independently associated with functional dependence at discharge. However, in the oldest age group but not in the younger, poor health status (= a high comorbidity score) was also associated with disability. When the same analyses were carried out in persons with MMSE>16 points, having more depressive symptoms was also related to disability in both age groups (data not shown). Additional multivariate models were created including MMSE, GDS, and GIC as dichotomous variables as described in the methods. In the younger age group, low MMSE (<24 points) and high GDS (>10 points) were still associated with disability, whereas in the oldest old, low MMSE, high GDS, and high GIC were associated with functional impairment (Figure 18). Correlations between cognitive status and depression, and between comorbidity and depression, were estimated in both age groups. MMSE and GDS were inversely correlated only in the older patients (Pearson correlation = - 0.195, p<0.001), and GIC was positively correlated with GDS only in the younger age group (Pearson correlation =0.136, p<0.05). The mean GDS score by age group in relation to cognitive and health status was calculated. Younger patients with low MMSE score had more depressive symptoms if they had high comorbidity, whereas very old subjects with low MMSE score had more depressive symptoms independently of comorbidity.

Figure 18. Odds ratios (OR) and 95%CI for functional dependence at discharge due to high comorbidity (GIC>2), bad cognition (MMSE<24), and depression (GDS>10) in two age groups (65-74 and 75+ yrs). Adjusted for age, gender, education, and length of stay



Finally, the combined effect of multimorbidity and cognition and cognition and depression on functional disability was evaluated (Table 11). The results showed that multimorbidity played a role in worsening functional status only in the oldest old, in particularly among those who were cognitively impaired, but cognitive impairment was the major determinant of disability in both age groups. Additionally, MMSE and GDS showed an additive effect on disability, especially in the younger elderly.

Table 11. The combined effect of cognitive status (MMSE), depressive symptoms (GDS) and comorbidity (GIC) on disability (ADL) by age groups (65-74 and 75+ years) derived from logistic regression models. OR= odds ratio. 95% CI= 95% confidence intervals

	65-74 years (N=245)	75+ years (N=399)
	OR (95%CI)	OR (95%CI)
*Model 1**		
Low multimorbidity and good cognition	1	1
Low multimorbidity and bad cognition	8.2 (2.5-27.5)	2.4 (1.2-5.0)
High multimorbidity and good cognition	1.8 (0.7-4.3)	1.7 (0.9-2.9)
High multimorbidity and bad cognition	3.6 (1.2-11.2)	4.0 (2.0-8.1)
*Model 2***		
Good cognition without depression	1	1
Bad cognition without depression	4.8 (1.7-13.2)	2.5 (1.4-4.7)
Good cognition with depression	3.3 (1.5-7.5)	1.6 (0.9-2.9)
Bad cognition with depression	8.3 (2.7-25.8)	4.3 (2.2-8.5)

* Adjusted for age, gender, education, length of stay, and comorbidity.
** Adjusted for age, gender, education, length of stay and depression.

6 DISCUSSION

6.1 SUMMARY OF MAIN FINDINGS

This thesis investigated the prevalence, distribution, and impact of multiple chronic diseases in the elderly population, in both community-dwelling and hospitalized old persons. The main findings can be summarized as follows:

6.1.1 Prevalence and distribution of chronic diseases and multimorbidity:

- Cardiovascular and mental diseases emerged as the most common chronic disorders in both men and women. While cardiovascular diseases reached a plateau after 75 years of age, the prevalence of mental disorders rose with increasing age.
- Multimorbidity, defined as 2+ co-occurring diseases, affected more than 50% of the population. Older age, female gender, and lower levels of education were independently associated with multimorbidity.
- Heart failure and visual impairments were the diseases with the highest associated comorbidity, and dementia with the lowest. The most common co-occurring pairs of conditions were mainly circulatory diseases, some of which exceeded the expected prevalence and had a statistically significant association (e.g., hypertension and heart failure).
- Chronic diseases affecting the population aggregated in five major clusters, with few differences between men and women and age groups.

6.1.2 Impact of chronic diseases and multimorbidity on functioning and survival:

- In the community-dwelling elderly, prevalence of disability increased with an increase in the number of chronic conditions. Multimorbidity incrementally increased the relative risk of functional decline, but not mortality.

- The subgroups of persons with disability showed a much higher mortality risk independently of multimorbidity.
- In hospitalized geriatric patients a poorer health status measured by means of a comorbidity index was associated with functional disability only in older age (75+ years), especially among persons with cognitive impairment, whereas cognitive impairment and depression were strongly associated with disability at hospital discharge in all age groups.

6.2 INTERNAL VALIDITY

Some general aspects of the design of the studies need to be discussed. The Kungsholmen Project is a population-based study that evaluates both community-living and institutionalized subjects. The major strengths of the study are the longitudinal design with follow-up every 3 years and the extensive evaluation of the participants in several health-related aspects (medical, psychological, and social). One limitation is the generalisability, which is limited to relatively highly- educated subjects living in urban areas. Indeed, only two persons who had been farmers were included among the participants.

The Italian Study has the advantage of having a well-defined study population, but is based only on one hospital. Moreoever, the cross-sectional design limits the interpretation of the results.

Possible selection biases, misclassification of both outcomes and exposures, and potential confounders are further discussed below.

6.2.1 Selection bias

Selection biases might have been introduced by the drop-outs, as non-participation can have influenced our results in the following way:

In the Kungsholmen Project, the dropout rate in the screening phase (phase I) was 23.6% (558/2368), mainly due to death (32%), refusal (52%), and moving (15%) (Fratiglioni *et al*, 1992). Of the 1700 elderly who agreed to participate in the first examination (1987-1989), 429 died and 172 moved or refused the first follow-up

(1991-3). Thus, 1099 subjects participated in the first follow-up. Between the first and second follow-ups, 363 persons died and 56 either refused to participate or moved. The participants at the second follow-up numbered 680 (Figure 6). We do not have any information on the health status of the non-participants at the first follow-up. The only available information on diseases could be obtained from the inpatient register, which however underestimates the prevalence of morbidities. Thus we can not compare the health status of participants and non-participants. Moreover, old persons with a high number of chronic diseases may have refused to participate because of their poor health status. This could have led to an underestimation of the prevalence of multimorbidity.

In the Italian database almost all the patients admitted to the geriatric ward of the Spedali Civili Hospital were evaluated. The dropout rate was 10%, mainly due to in-hospital deaths (N=64) and refusals of functional status tests (N=29). Patients who died were significantly older, more cognitively and functionally impaired and affected by higher comorbidity than those who were included in the analysis.

The choice of a special population such as hospitalized patients can cause selection bias. Hospital admissions are often selective on the basis of personal characteristics, severity of disease, associated medical conditions, and admissions policies that vary from hospital to hospital. Moreover, hospitals do not have often a well defined catchment area. In Study IV we collected data from only one ward, and different comparisons were made within the same population. In addition, in emergencies, in Brescia, old persons go to the closest of the three main hospitals available in the city, and thus subjects admitted to the Spedali Civili Hospital may be considered representative of the ill elderly population living in the surrounding area.

6.2.2 Misclassification

Misclassification bias in disease ascertainment is common, often due to recall bias. Data from the Italian Longitudinal Study on Aging showed that there is a substantial underreporting as well as overreporting of chronic disease diagnoses by old persons (ILSA working group, 1997). Detection bias may also affect the results, as patients with chronic diseases have more contacts with health care professionals, and consequently there is a higher possibility that other comorbid diseases will also be detected.

Moreover, old persons with one or more diseases could be more alert in recognizing and/or presenting other diseases themselves. In order to minimize misclassification biases, in the Kungsholmen Project we used different sources of information regarding the health status of the participants, and overall every subject was clinically examined by a physician.

In the Italian Study, misclassification of diseases was also unlikely due to the diagnostic procedure typical of a geriatric department, in which no disease affecting the patient should ever be overlooked. In our department each patient is examined every day by a senior physician, clinical history and drug use are collected at admission, and a large spread of laboratory tests is performed during the hospitalization. However, several problems arise when using hospital data for research purposes. Hospital records are not designed for research but rather for patient care. The diagnostic quality of hospital records may vary between hospitals, physicians, and clinical services.

As with disease diagnosis, other variables may be biased by misclassification.
Imprecision is implicit in the assessment of risk factors from surrogate informants as for example in the case of occupational exposure in Study I. Furthermore, although the Swedish system for classification of SES from occupation is a well-established scheme (Statistical Co-ordination, SCB, 1982), interpretation is always necessary when occupation is coded into different SES categories. The estimation of SES from occupation was particularly difficult for subjects whose longest period of occupation was as housewives. However, it is likely that the misclassification of SES generated by our approximations were non-differential. For the purpose of this thesis, only broad categories, giving more information about general social class than specific work activity, were taken into account.

6.2.3 Potential confounders

Major confounders potentially associated with both outcome and determinant variables were assessed. Their effects were addressed simultaneously by multivariate regression models and controlled for by stratified analyses.
Briefly, in **Study I** the independent effect of the two socio-economic variables was evaluated creating subgroups of persons according to high/low level of education and high/low occupation-based SES. In **Study II** the analysis testing the association

between each pair of co-occurring conditions was adjusted for age, gender, education, and all the chronic diseases as possible confounders. The distribution of diseases was studied with cluster analysis in the whole population and after stratification by age (77-84 and 85+ yrs) and gender. In **Study III** age, gender, education, and baseline disability were identified as possible confounders of the association of multimorbidity with functional decline and mortality and included in the multivariate analysis. Moreover, the effect of baseline disability and multimorbidity was explored by creating different subgroups according to presence/absence of disability and number of chronic conditions. In **Study IV** age, gender, education, and length of hospitalization were included as covariates in all the models testing factors associated with disability at discharge. Each logistic regression model was run after stratification by age groups (65-74 and 75+ yrs).

6.3 INTERPRETATION OF THE FINDINGS AND EXTERNAL VALIDITY

6.3.1 Prevalence of chronic diseases

Research into the health status and the impact of chronic disease in the elderly population is a relatively young scientific field. In fact, despite the fact that advancing age is associated with increased vulnerability to chronic health problems, empirical data on the health status of elderly people from around the world are lacking (Harwood, 2003).

We found that cardiovascular disorders were the most prevalent chronic conditions independently of age. Although ischemic heart diseases are still the largest cause of death worldwide (Lopez *et al*, 2006), the proportion of people surviving with these conditions has increased over the past 20 years due to the introduction of new therapeutic measures (Hann *et al*, 1996). This pattern may explain the high prevalence of cardiovascular disease even in the very old. The prevalence was similar in men and women, in contrast with middle-age, when men are more likely to be affected by heart disease than women (Lerner and Kannel, 1986).

Mental conditions were the second most frequent chronic disorders. Their prevalence increased with increasing age, mostly due to the high number of very old (85+ yrs) women affected by dementia, in agreement with the age-related distribution of prevalence and incidence figures reported by other studies (Lobo *et al*, 2000; Fratiglioni *et al*, 2000). A large proportion of participants were also affected by neurosensorial disorders, especially among the very old elderly. The overall prevalence of mental and neurosensorial diseases as a whole was 34% in the old and 53% in the very old.

The prevalence of chronic diseases was in line with the figures reported by other authors in old populations (Salive *et al,* 1992; Viegi *et al*, 2001), except for musculoskeletal diseases. The prevalence of musculoskeletal diseases was definitely underestimated in our study mainly due to the fact that the Kungsholmen Project started in the late ‘80s, when diagnoses of arthritis and osteoporosis were often underreported by both patients and physicians. In particular, the use of osteoporosis diagnosis to describe the condition has been disseminated only in the last years.

6.3.2 Prevalence of multimorbidity

In our study, multimorbidity affected more than half of the participants. The prevalence of multimorbidity in old age reported in the literature varies from 13 to 98% (Table 1). This variation is largely due to the number of diseases included in different studies and the diagnostic criteria used. Fillenbaum and colleagues, 2000, considering only five chronic health conditions, reported that the proportion of 65+ year old subjects affected by more than one disease was 29%, whereas Fried and colleagues, 1999, who included fourteen chronic conditions, found a prevalence of 81%. Another problem in measuring the prevalence of multimorbidity is the selection of the most severe chronic conditions. In agreement with van den Akker *et al*, 2001, we included all chronic diseases regardless of severity.

The prevalence of multimorbidity was higher in the very old persons. Despite methodological differences, this pattern has also been reported by others: a prevalence of multimorbidity ranging from 54% in 65-69 year-old to 73% in 85 year-old persons has been estimated (Wolff *et al*, 2002). Yet, in line with previous studies (van den Akker *et al*, 1998; Wolff *et al*, 2002), we found that female gender was related to multimorbidity, and the association was not explained by age or education. Due to a limited number of male survivors in the Kungsholmen Project, especially after age 85 (n=95), the estimation of the prevalence of multimorbidity in men could lack precision.

However, it is possible that the few men who survive to old ages are healthier, and thus at lower risk of developing chronic diseases than women.

6.3.3 Patterns and distribution of chronic diseases

In **Study II** we examined multimorbidity from the qualitative perspective of characterizing the co-occurrence of diseases by using different approaches. Similar findings were detected from the different methods. All chronic diseases were more likely to occur with comorbid conditions than alone, confirming previous reports that most elderly people are affected by 2+ conditions (Wolff *et al*, 2002; van den Akker *et al*, 1998). Hypertension and dementia were the most frequent disorders occurring both with and without a comorbid condition, whereas very few cases of heart failure and hip fracture occurred without any comorbidity. Indeed, heart failure among with visual impairments was associated with the highest number of comorbid diseases. Further, the most common co-occurring pairs of conditions were mainly circulatory diseases, several of which exceeded the expected prevalence and had a high odds ratio. The strongest association was found between hypertension and heart failure, and, in line with these findings, the cluster analysis identified two groups related to vascular diseases. First, there was a ‘circulatory cluster’ that was one of the main aggregations, and included the majority of cardiovascular diseases. The circulatory cluster divided into a subgroup of cardiovascular chronic conditions such as hypertension and heart failure, and a second group of arrhythmias and its consequences (atrial fibrillation and CVD). Second, there was a ‘cardiopulmonary cluster’ that included CHD and COPD, and interestingly linked these two conditions with thyroid dysfunction (Sin and Man, 2003; Singh *et al*, 2007). Apart from circulatory diseases, dementia and depression were both significantly correlated not only to each other but also to other diseases such as hip fracture and CVD, and grouped by the cluster analysis in a ‘mental cluster’ including also hip fracture. Finally, diabetes and malignancy emerged as relevant disorders grouped in two clusters together with their major consequences.

Due to the high comorbidity and the use of several medications, the subgroup of elderly affected by heart failure may represent an at risk group for an increased occurrence of drug-drug and drug-disease interactions. Indeed, persons affected by heart failure *per se* often use several medications especially in the advanced stages of the disease, and this number may increase due to the comorbid conditions. In addition, heart failure is a very common condition in this age group, representing a major public health burden, as well dementia (Marengoni *et al*, 2008). The finding that dementia had the lowest comorbidity is not surprising. In fact, the health status of persons affected by dementia is still a debated issue. Previous studies have shown controversial results concerning the prevalence of comorbidities in old people with dementia (Sanderson *et al*, 2002; Lyketsos *et al*, 2005). We are more prone to interpret these findings as an underestimation of comorbidity, due to either under-reporting of symptoms or difficulties in performing diagnostic procedures, than as a genuine lower level of comorbidity in persons affected by dementia. Dementia clustered with depression and hip fracture, which confirmed the public health relevance of this disorder. The association between dementia and depression is well-known, although the pathophysiological mechanisms are still not well clarified (Berger *et al*, 1999). Hip fracture can be easily interpreted as a consequence of dementia because of the link between osteoporosis, decreased mobility, and increased risk of fall due to unbalance in demented persons (Sheridan and Hausdorff, 2007). However, an alternative mechanism to explain the association between hip fracture and dementia may be based on common pathophysiological mechanisms such as estrogen deficiency, leading to both dementia and osteoporosis (Xu *et al*, 2006).

Dementia and hypertension emerged as the only inversely correlated diseases pair. This finding could be explained by the well-known reduction of blood pressure levels in preclinical and clinical stages of dementia (Guo *et al*, 1999). A second explanation could lie in a possible protective effect of antihypertensive medications on the development of dementia, as has been demonstrated by Qiu and colleagues, 2003.

Stratifying the population by age groups and gender did not macroscopically change the results of the cluster analysis run in the whole sample. However, some interesting differences were found. For example, in younger persons CVD was in the same cluster as depression, whereas in the older group it clustered with dementia. These findings could suggest that cerebrovascular pathology may lead to the development of depressive syndromes in relatively young elderly, whereas in very old persons it is more often correlated with cognitive impairment. On the other hand, depression was in the same cluster as malignancy in women, whereas in men it occurred in the hip fracture cluster, suggesting that different diseases can have a different impact on the affective status of men and women.

6.3.4 Education and occupation were differently related to chronic diseases and multimorbidity

Although different dimensions of SES are interrelated, it has been proposed that each reflects somewhat different associated with health and disease (Winkleby *et al*, 1992). When we analyzed the distribution of chronic diseases by SES, we found that mental conditions were more prevalent in poorly educated subjects, while cardiovascular diseases were slightly more prevalent in low occupation-based SES. The association of education and mental disorders, such as dementia, has been extensively demonstrated (De Ronchi *et al*, 1998; Karp *et al*, 2004), whereas both low educational level and low social and occupational class have been reported to be associated with cardiovascular diseases and related risk behaviours (Davey Smith *et al*, 1998; Kaplan and Keil, 1993b). Lower education was independently associated with multimorbidity, but not occupation-based SES. Indeed, even high occupation-based SES in poorly educated subjects could not compensate for the increased risk of multimorbidity due to education. There are several different mechanisms through which education may influence health. Culture in general and education in particular can improve health-related knowledge, problem-solving abilities, access to preventive health service and affect lifestyles such as drinking, smoking and exercise. Low educational level could also be an indicator of low family SES. Those elderly persons who had access to only a few years of education probably grew up in low income families, which affected their first years of life. Unfortunately, we do not have data to verify this hypothesis. Moreover, we have to be cautious in drawing conclusions about a lack of association between occupation-based SES and multimorbidity, because we could not gather the occupation-based SES variable for all participants. However, these results are in line with a report by Winkleby and colleagues, 1992, who found that higher education was the SES indicator most consistently correlated with healthy behaviors.

6.3.5 The correlation of multimorbidity with disability and functional decline

In the last few decades, the assessment of disability has become an essential part of the comprehensive evaluation of the health status of the elderly. Disability is defined according to the WHO criteria, 1980, as any restriction or lack of the ability (resulting from a psychological, physiological, or anatomical structure or function impairment) to perform an activity in the manner or within the range considered normal for the human being. An estimated 12% of community-dwelling old persons report at least one limitation in IADLs and 18% in ADLs, and the frequency of disability rises with age (Lubitz *et al*, 2003). Although there is some evidence of a decline in the prevalence of different types of disability in old age in the last two decades (Manton *et al*, 1995; Freedman *et al*, 2002), the most likely current scenario is a fluctuation rather than a clear trend in disability prevalence. Describing the functional status of elderly persons has added a very important dimension to the traditional approach to medical care. Disability helps to identify the vulnerable subset of the old population, among with multimorbidity and frailty (Fried *et al,* 2004). These terms have often been considered interchangeable, but recent research supports geriatricians' perceptions that these are distinct clinical entities, although interrelated (Fried *et al*, 2004). The complex relationship among these conditions is not yet properly elucidated.

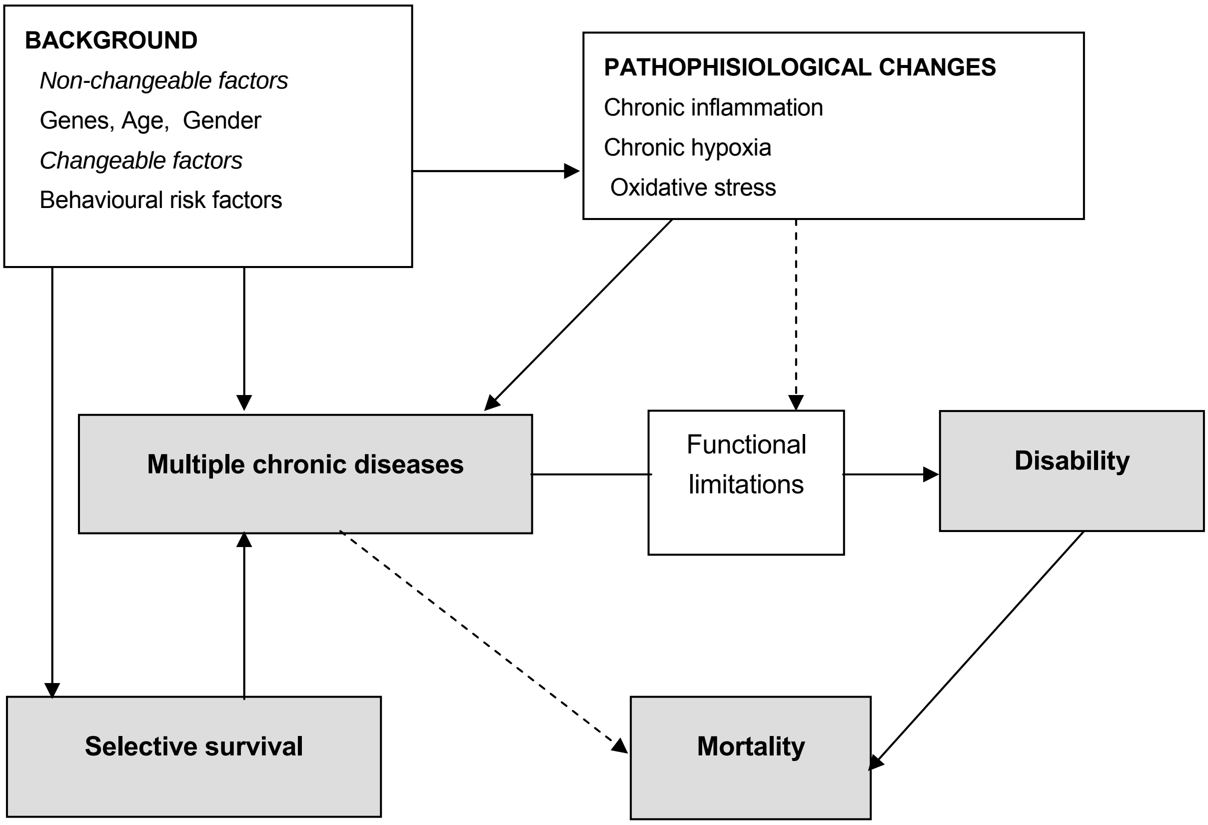
In the Cardiovascular Health Study, of the 2762 participants, 2131 were affected by 2+ chronic conditions, but did not have either disability or frailty (Fried *et al*, 2004). In line with this finding, in the Kungsholmen population the majority of persons with multimorbidity were still functionally independent, although the prevalence of disability rose with the number of chronic conditions (**Study III**). On the contrary, the majority of persons with disability were affected by multimorbidity (66%). A report from Guralnik and colleagues, 1989, showed an age-related graded increase in disability among old persons in line with an increase in the number of chronic conditions, with no major differences between men and women. In our study, the association between disability and number of chronic diseases was more pronounced in women than in men, as in women a very high odds ratio for disability was already detected in the presence of only one chronic disease, suggesting a more favourable survival rate in women than men in the presence of chronic diseases (Mongella, 1995).

Moreover, although only 8% of the baseline population showed a decline in functioning during follow-up, the number of diseases was a good indicator of functional decline. Not only did previously independent persons with multimorbidity develop dependency, but those with partial disability further declined (28% of persons with 2+ diseases *vs*. 4% of those with 0-1 disease). This is in contrast to previous hypotheses that chronic disorders are relevant for determining new disability, but do not worsen functional status (Tas *et al,* 2007b). In addition, the effect of disability on functional decline was amplified by multimorbidity, as people with both multimorbidity and disability had the highest relative risk of further decline in functioning.

In **Study IV**, factors associated with functional disability at hospital discharge differed according to age. The burden of physical illness played a more important role in functional disability among very old patients (75+ yrs) than among younger subjects (65-74 yrs). This can be explained by the higher frequency of cardiovascular, musculoskeletal diseases, and dementia usually associated with greater disability in the oldest old (Boult *et al*, 1994; Agüero-Torres *et al*, 1998). Moreover, we found an additive effect of poor health and poor cognition on disability only in the oldest age group. In agreement with our findings, a population-based study investigating very old subjects found a similar additive effect on disability (Aguero-Torres *et al*, 2002). In relatively young elderly, poor cognition and depressive symptoms had an independent effect on disability and their combined effect was additive, suggesting that these two conditions are two independent problems in this age group. In very old subjects, depressive symptoms and cognitive impairment were highly correlated, but having depressive symptoms and good cognition did not increase disability, suggesting that in this age group, these two conditions might be the expression of the same disease. This hypothesis is also supported by the fact that the correlation between cognitive impairment and depression was significant only in the oldest age group. Cognitive problems may be more manifest as depressive symptoms in very old people than in younger elderly. Another explanation of this finding could be the emerging concept of vascular depression (Thomas *et al,* 2001), which suggests that in the oldest old, cerebrovascular diseases may be the underlying cause of depression (Kumar *et al*, 2002). The vascular depression hypothesis is supported by clinical and laboratory data regarding vascular diseases associated with the presence or the development of depression (Alexopoulos *et al,* 1999; Lyness *et al*, 2000). As vascular cognitive impairment is also a recognized problem in old persons (Qiu *et al*, 2002), we can speculate that these two conditions, which share the same etiology, could be parts of the same disease.

All these findings taken together show that the number of chronic conditions only partially explain disability and functional decline in aging. The role of chronic conditions in causing functional limitation is intuitively important, but we still lack consensus on the pathway from disease to disability, mechanisms whereby diseases cause disability, and the degree to which this occurs (Guralnik, 1994). One of the best known models on this issue proposed by Nagi, 1991, hypothesized that pathology (presence of disease) leads to impairments (anatomic and structural abnormalities) which lead to functional limitations (restrictions in physical and mental actions) which in turn lead to disability (difficulties in performing the activities of daily living). This model was very important in revealing that the progression from disease to disability passes through the development of functional limitation, which is in turn a risk factor for ADL disability (Guralnik and Ferrucci, 2003). This could explain why some people are affected by several chronic diseases but not yet by disability. Another model proposed by Verbrugge and Jette, 1994, extends this concept by including the evaluation of several other factors, such as intra-individual and extra-individual factors that speed up or slow the ‘disablement process’. Contextual factors include housing standards, assistive technology, public transportation as well as social changes (Parker and Thorslund, 2007). Finally, a recent theory suggests that diseases are an interface between basic pathophysiological processes (such as inflammation, oxidative stress, apoptosis, etc.) and final health outcomes (e.g., functional disability) (Yancik *et al*, 2007). Figure 19 summarizes our findings in accordance with a hypothetical model explaining the interrelationship among multimorbidity, disability, and mortality (Figure 19). However, beyond chronic diseases, age, body composition, physical activity, health risks behaviours, social activities, and geriatric conditions were all found to be significantly associated with disability in the old population (Stuck *et al*, 1999; Tas *et a*l, 2007b; Cigolle *et al*, 2007).

Figure 19. A hypothetical model for the interrelationship among multimorbidity, disability, and mortality



6.3.6 The weak correlation between multimorbidity and mortality

Previous research on multimorbidity and mortality in the elderly has reported controversial results (Ferrucci *et al,* 1991; Ho, 1991; Di Bari *et al*, 2006; Mendes de Leon *et al*, 1997). In this population, having an increasing number of chronic diseases did not affect survival. We can reasonably hypothesize that disease severity, disease duration and interactions between acute and chronic conditions are probably much more important than the mere count of chronic morbidities in increasing mortality risk. A potential limit of using the sum of diseases as ordinal scale without taking into account severity is that a participant moving from zero to one disease could realize the majority of the multimorbidity effect, with additional disease having a minor impact (Lash *et al,* 2007). On the other hand, baseline disability emerged as a strong risk factor for mortality independently of the number of diseases. In agreement with previous findings (Strawbridge *et al*, 1992; Ferrucci *et al*, 1996), the large majority of old persons with partial or total dependence did not survive, supporting the hypothesis that disability in basic activities of daily living is a good indicator of disease severity.

Older age was also strongly correlated with death. In fact, mortality was high even in subjects with no disease and no disability, showing that there is a proportion of old old persons who are still healthy and independent and die from an acute disease. A slow progression from good health to disability and mortality is not the only possibility. Many old persons die suddenly with essentially no disability beforehand. In our population, these persons were more likely to be males. The relationship between gender and mortality is not yet well-elucidated. Previous studies have shown that although women are more disable than men in advanced age, they have lower mortality (Guralnik *et al*, 1997; Nybo *et al,* 2001), which can be explained by the higher prevalence of some chronic non-fatal but disabling conditions, such as dementia and arthritis in women than in men (von Strauss *et al*, 2000; Ferrucci *et al,* 2003).

7 CONCLUSIONS

I: Cardiovascular and mental diseases emerged as the most common chronic disorders in both men and women. While cardiovascular diseases reached a plateau after 75 years, the prevalence of mental disorders rose with increasing age. Multimorbidity affected more than 50% of the population. Older age, female gender, and a lower level of education were independently associated with a higher prevalence of multimorbidity.

II: The most common co-occurring pairs of conditions were mainly circulatory diseases, some of which exceeded the expected prevalence and had a statistical association (e.g., hypertension and heart failure). Chronic diseases affecting the population aggregated in five major clusters, with few differences by age and gender.

III: Over a three-year period, old persons with chronic multimorbidity experienced functional decline with a fifty percent increase in risk for each additional disease. However, multimorbidity did not affect survival, whereas baseline disability increased the risk of dying at least six fold, independently of the number of diseases. Moreover, baseline disability amplified the effect of multimorbidity on further functional decline.

IV: Poor health status, measured by means of a comorbidity index, was correlated with disability at hospital discharge only in older patients (75+ yrs), especially among those who were cognitively impaired. Cognitive impairment and depressive symptoms had an additive effect on disability, especially in younger patients (65-74 yrs).

7.1 GENERALIZABILITY

No study population can ever be fully representative of all other populations. The Kungsholmen Project cohort consisted of very old individuals (75+ years), living in a geographically defined central area of Stockholm. The special features of this population are that there were a high proportion of women, the mean educational level was high, and most of the persons had an office-related occupation (very few farmers or industrial workers). Findings from studies carried out in this population may be generalized to old urban populations in Western countries, but some caution is needed when generalizing the findings to younger persons or residents in rural areas.

The Italian study was conducted in an acute hospital ward. Hospitalized patients have peculiar characteristics which are different from those of the geriatric population as a whole. They are usually more ill, functionally impaired, and frail. This limits the generalizability of our results to the frail part of the old population.

7.2 RELEVANCE AND IMPLICATIONS

Knowing the distribution and patterns of diseases in a given population can be particularly important for several purposes. First, for research aims; in fact, as we have shown, several research hypotheses can be formulated from our findings. Second, for daily clinical practice; multimorbidity requires special attention, knowledge, and skills on the part of clinicians, nurses and families. Finally, multimorbidity has also important implications for preventative actions in health care programs. Knowledge of the types of relationships among co-occurring diseases may help when developing strategies to improve clinical practice and selecting specific target and at risk groups.

7.2.1 Clinical relevance

The co-occurrence of chronic conditions may lead to faster disease progression, problems in diagnosing new conditions, and complex therapy and care. However, evidence-based medical treatment has usually been directed toward single diseases.
Ignoring concomitant diseases while applying single-disease guidelines may lead to harm, i.e. most guidelines do not consider drug-drug and drug-disease interactions (Boyd *et al*, 2005). In fact, the data available do not reflect the broader physical, cognitive, and psychological effects of multimorbidity and polytherapy on the old person (Tinetti *et al*, 2004). Moreover, it has been shown that unrelated disorders tend to be relatively neglected in patients with chronic diseases (Redelmeier *et al*, 1998).

Multimorbidity and disability each imply specific care for old patients, and prognosis differs for each condition. The evidence that disability has a greater effect than multimorbidity on survival is important for guiding clinical processes. In fact, in caring for old persons, the traditional medical model should shift from a disease-centred view to a functioning-centred perspective. Furthermore, the identification of factors, such as depression, which are strongly related to disability in the elderly, may help physicians in targeting subjects at high risk of physical dependency and in implementing preventative strategies.

7.2.2 Public health relevance

Prevention of chronic diseases and disability is the major goal of public health professionals and clinicians. In terms of disability prevention, primary prevention should avert the onset of diseases and secondary prevention should focus on the early detection and treatment of those conditions. Finally, tertiary prevention aims to reduce the impacts of disability, such as institutionalisation and death. Nowadays, all the three stages are fundamental, but often cannot be applied. If we think for example of dementia, the most disabling chronic disease among old persons (Agüero-Torres *et al*, 1998), we can easily realize that both primary and secondary prevention are still limited, although possible, and require extra investment from the public health system. On the other hand, other chronic diseases which often occur with dementia and increment its effect on disability, such as depression and hip fracture, could be more easily prevented or treated early even in very advanced aged. However, we have shown that chronic diseases only partially explained disability and functional decline in the old population. Thus, in preventing disability the research effort should focus not only on etiopathological factors related to disease, but also on all the possible factors which affect the severity of disease and consequently the disablement process.

Recent research showed that a person with no functional limitation at 70 years of age has a life expectancy of about 14 years, whereas a person of the same age with a limitation in at least one basic activity of daily living has a life expectancy of 11.6 years but has similar cumulative health care expenditure until death (Lubitz *et al,* 2003). These findings support the current view that medical spending in the old population is related to disability more than to longevity (Cutler, 2003) and confined to the last years of life.

8 FUTURE DIRECTIONS

Future research on multimorbidity needs to focus more on aetiology and pathogenetic mechanisms (Gijsen *et al*, 2001). Attention should be paid to genetic and biological factors and lifestyles, as well as social determinants of multimorbidity. Moreover, risk factors that involve pathological problems of importance for multiple diseases (e.g. chronic inflammation, oxidative stress and obesity) should be investigated with particular attention.

Clinical trials and treatment guidelines should allow appropriately for persons with multimorbidity; otherwise they fail to address the needs of a majority of older individuals. Yet most research and clinical practice is still based on a single disease paradigm, which may not be appropriate for patients with complex and overlapping health problems (Fortin *et al*, 2007). Moreover, patients with several coexisting conditions are treated with a combination of medications prescribed in compliance with disease-specific guidelines. The long-term benefits and harm of this polytherapy are still not clear (Tinetti *et al*, 2004). Optimistic findings have been reported on the relationship between quality of care and number of chronic conditions in the overall population (Higashi *et al*, 2007), but the investigation of the care process should be specifically deepened with reference to old persons.

Other areas of potential investigation of multimorbidity include the development of new tools and analytic strategies for the investigation of multimorbidity and its consequences. However, given the complexity and heterogeneity intrinsic to multimorbidity, no single measure would effectively serve all research lines and clinical purposes. What has already been suggested is that different methods could be appropriate for different outcomes of interest (Yancik *et al*, 2007).

Further investigation into the cumulative or multiplicative effect of multimorbidity, not merely alone but also with other factors, such as social backup, economic status and environment, on adverse outcomes (e.g., functional decline and mortality) in the aging population is needed.

'So far, research on multimorbidity is in its infancy'

Martin Fortin, 2007

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11 APPENDIX

List of dissertations from Stockholm Gerontology Research Center and Aging Research Center 1991-2007

1991
Herlitz Agneta. Remembering in Alzheimer´s disease. Utilization of cognitive support. (Umeå University and Karolinska Institutet).

1992
Borell Lena. The activity life of persons with a dementia disease.

1993
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