Muscles growing older

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Chapter 1

General introduction

General introduction

Aging society

In 2009, almost 2.5 million persons (15%) living in the Netherlands were aged 65 years and over and 26% of these older persons was aged 80 years and over. The population in the Netherlands will continue to grow older; in 2050 it is expected that 25% of the population will be aged 65 years and over. Life expectancy at birth is also expected to continue to increase in the next 40 years to 81.5 years for men and 84.2 years for women.[1] Therefore, an increasing number of people will grow old and they will become relatively older in the next 40 years. Parallel with increased life expectancy, healthy life expectancy (expected years in good health) has increased in both men and women, although not as much in women as compared to men. As women live longer, they will live more years in suboptimal health compared to men. In the year 2008, of all Dutch persons aged 65 years and over, 18.8% was limited in one or more ADL-activities (activities of daily living, e.g. bathing, dressing) and more than 50% had one or more chronic diseases. For the aging individuals this means he or she is likely to be confronted with health decline.[1]

Age-associated loss of muscle mass (sarcopenia) and muscle strength

Aging is associated with a progressive decline of muscle mass.[2,3] This age-associated change in muscle mass is observed in healthy, active adults who are 50 years and older.[4] Rosenberg first coined the term sarcopenia, from the Greek, which literally means poverty of flesh, to describe age-associated loss of skeletal muscle mass.[5] There is a decrease in muscle cross-sectional area, a loss of muscle fibers, and fiber atrophy. The age-associated decline in muscle mass is accompanied by other body composition changes: visceral fat and intramuscular fat tend to increase (Figure 1), while subcutaneous fat in other regions of the body declines.[6-9] In the literature, various definitions of sarcopenia exist, based on low muscle mass, loss of muscle mass, low muscle strength and loss of muscle strength.[10-14] The prevalence of sarcopenia varies between 6% to 24%, depending on the definition used.[10,15,16] and increases with age. It is important to note that sarcopenia occurs even in successfully aging adults.[17] Existing evidence suggests that the age-associated changes in body composition and decline in muscle strength contribute to the onset and progression of disability with advancing age.[18] The role of muscle mass and strength is supported by numerous studies that have shown a strong association between low muscle mass and/or strength and decreased physical perfor-

mance and mobility limitations in older persons.[19-22] In the United States, the direct costs of sarcopenia in 2000 has been estimated at $ 18.5 billion,[23] representing about 1.5% of total healthcare expenditures, which is higher than the costs associated with osteoporosis ($ 16 billion). The proportion of age-associated disability that could theoretically be prevented if sarcopenia were eliminated has been calculated as the population-attributable-risk (PAR). The PAR for disability in older men due to sarcopenia was 85.6% and the PAR in older women was 26.0%. This suggests that, if sarcopenia were completely eliminated, 85.6% of the disability cases in men and 26.0% of the disability cases in women would be prevented. Thus, understanding the underlying mechanisms leading to age-associated muscle mass and muscle strength loss has a high public health priority.

The process of sarcopenia and loss of muscle strength is believed to be multifactorial, occurring over a prolonged time period. Determinants include physical activity levels, other life style variables, chronic diseases, genetic variables, increased concentrations of inflammatory markers and hormonal changes. This thesis will focus on two (possibly modifiable) determinants: concentrations of inflammatory markers and sex hormones. Because sarcopenia (in this thesis defined as loss of muscle mass) and loss of muscle strength are significant risk factors for decline in physical functioning with aging, investigating possible determinants of sarcopenia is important to identify persons who are at risk of developing sarcopenia and for preventive treatment.

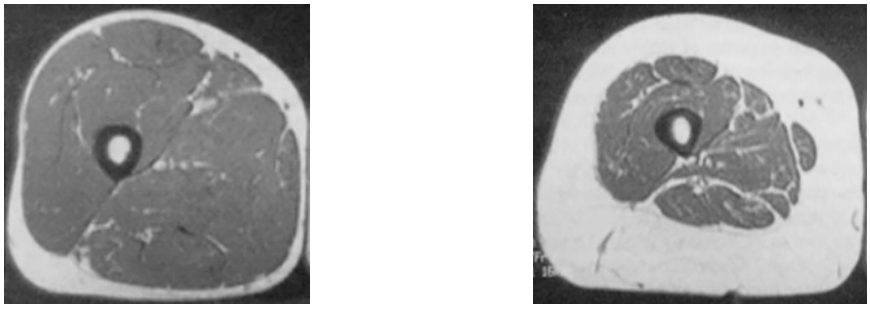

Figure 1

Computed tomography scan of mid thigh skeletal muscle in a 47-year old man (left) and 70-year old man (right), demonstrating muscle (gray), adipose tissue (white) and bone (black).

Inflammatory markers

Inflammation is the body's integrated reaction and defense against disturbances of homeostasis, particularly infections and injuries. This response is initially characterized by a local release of cytokines, specifically tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-6 and interferons.[24] Cytokines are responsible for the progression of the reaction to a more systemic involvement, encompassing a wide range of organ systems.[25] Cytokines stimulate the hepatic production of acute phase proteins, such as C-reactive protein (CRP) and other acute phase proteins.[26] In situations of acute illness, inflammation is an important part of the host defense system.

Aging is associated with an increase in concentrations of inflammatory markers such as IL-6 and TNF-α.[27, 28] Inflammatory marker concentrations in aged persons are much lower compared to the concentrations seen during acute illness or infection. Therefore, age-associated inflammation is often called chronic low-grade inflammation. There is strong evidence that increased concentrations of inflammatory markers, including IL-6 and CRP, are associated with chronic diseases such as cognitive decline,[29] diabetes mellitus,[30] atherosclerosis,[31, 32] and cardiovascular disease[33-35] in older persons. However, low-grade inflammation is also observed in apparently healthy persons without any (chronic) disease.[36] Furthermore, high concentrations of inflammatory markers are associated with increased mortality.[37] Higher concentrations of inflammatory markers have been hypothesized to play a role in the functional decline of older persons. Both cross-sectional and longitudinal studies have shown associations of high IL-6 and/or CRP with low physical performance and disability.[39-44] The causal pathway leading from inflammation to disability has not been fully explained, but it has been suggested that inflammatory markers may cause a decline in physical functioning through the catabolic effects of inflammatory markers on muscle.[45] Muscle protein degradation occurs through various mechanisms, of which the adenosine triphosphate dependent ubiquitin-proteasome pathway is suggested to be the most important.[46, 47] Inflammatory markers can activate nuclear factor kappa B (NF-κB), which in turn upregulates the adenosine triphosphate dependent ubiquitin-proteasome pathway in case of disease and perhaps also with (healthy) aging.[48] Studies in animal models of sarcopenia have suggested that increased activity of NF-κB may contribute to age-associated muscle loss[49] (Figure 3). Experimental studies have shown that administration of IL-6 or TNF-α in rats causes muscle breakdown.[50,51] Importantly, increased concentrations of TNF-α mRNA and protein have been observed in aged human skeletal muscle.[52] There is evidence that higher concentrations of soluble receptors may represent a more prolonged or severe underlying inflammatory state[53, 54] and might be more reliable markers of chronic inflammation.[55] Therefore, it is

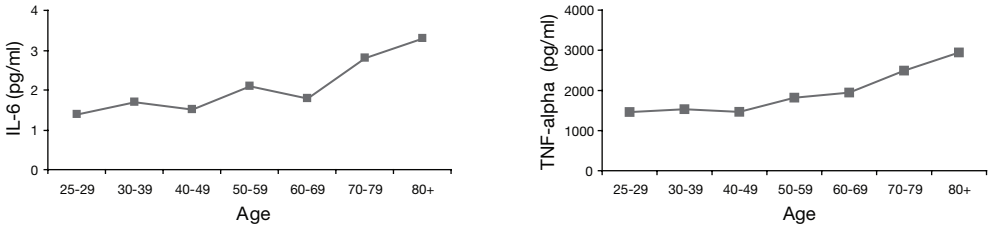

Figure 2

Plasma concentrations of IL-6 and TNF-α as a function of age in a population-based sample living in Texas City. [Adapted from Stowe, RP. et al.][38]

important to not only study inflammatory markers, but also their soluble receptors in the association with sarcopenia and decline in physical functioning.

Only few observational studies on the associations of inflammatory markers with muscle mass and strength in humans have been conducted. A cross-sectional study showed an association of high concentrations of IL-6 and TNF-α with low muscle mass and strength.[56] In the only one longitudinal study, high baseline concentrations of CRP were not predictive of 7-year decline in grip strength.[41]

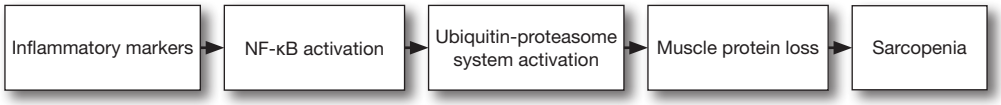

Figure 3

Suggested pathway leading from inflammation to sarcopenia

Sex hormones

Aging results in a highly significant decline of testosterone and estradiol concentrations in both men and women. Unlike the steep estradiol decline in women at menopause, the decline in estradiol concentrations in men and testosterone concentrations in both sexes is gradual[57-59] (Figure 4). The rate of age-related decline is affected by co-morbid diseases, medications, and adiposity.[60, 61] Thus, individuals with chronic diseases such as diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, and chronic kidney disease are likely to experience a more accelerated decline in testosterone and estradiol concentrations than healthy individuals.[61]

In aging men, a decrease in testosterone concentrations results from a decline in testicular production of testosterone, as well as from reduced hypothalamic secretion of gonadotropin-releasing hormone. The number of Leydig cells in the testes may decline with aging.[62] 60% of testosterone in premenopausal women originates from ovarian sources, whereas 40% is derived from adrenal precursors. This distribution changes little with menopause, with about 50% of testosterone concentrations continuing to be derived from ovarian sources.[63] Postmenopausal women have lower testosterone concentrations than premenopausal women, but the age-associated decline is gradual and likely results from declining ovarian and adrenal function with aging.[64]

In men, up to 80% of estradiol originates from aromatization of testosterone and androstenedione, mainly in fat tissue and striated muscle, and 20% of estradiol is secreted by the testes. The age-associated decline in estradiol concentrations is a result of a decline in testosterone and androstenedione and by an increase in sex hormone-binding globulin (SHBG). In women, estradiol concentrations decline predominantly due to a decrease in ovarian estradiol production. In both men and women, sex hormone concentrations can be affected by changes in body composition, smoking, alcohol use, presence of chronic diseases, use of some medications (e.g. glucocorticoids)[65, 66] and bilateral oophorectomy in women.[67]

Both testosterone and estradiol concentrations exert direct and indirect effects on skeletal muscle.[68] Skeletal muscle has estrogen receptors (ERs) on the cell membrane, in the cytoplasm, and on the nuclear membrane. It is believed that estrogen exerts direct effects on skeletal muscle through ERα, but there is a possibility that estrogen influences the maintenance and well being of skeletal muscle using other pathways. Recently, a second ER type was discovered in skeletal muscle (ERβ), but its function is largely unknown, particularly in humans.[68]

Testosterone increases muscle mass by multiple mechanisms; it promotes muscle protein anabolism[69-72] and the differentiation of pluripotent stem cells toward the myogenic lineage and inhibits adipogenic differentiation.[73] Motor neurons also contain androgen receptors and animal studies have shown that motor neurons increase in size in response to testosterone administration.[74] Testosterone effects on myogenic differentiation are mediated through an androgen receptor-dependent pathway;[73, 75] androgen receptor-independent pathways mediating anabolic effects of androgens on the muscle have not been clearly demonstrated. Given the effects of sex hormones on muscle, it can be hypothesized that lower concentrations of sex hormones in older men and women are associated with a decline in muscle mass and muscle strength. Serum testosterone and estradiol are mainly bound to SHBG and albumin. The fraction available to the tissues (also called bioavailable testosterone) is believed to be

the free (unbound) fraction plus the albumin-bound testosterone and estradiol.[77] Because SHBG concentrations increase with aging, free and bioavailable testosterone and estradiol concentrations decline at a greater rate than total testosterone and estradiol concentrations.[57, 61, 78, 79] It remains to be established whether total, bioavailable or free sex hormone concentrations are the best representation of the bioactive concentrations.

Few studies examining the association between endogenous androgen levels and muscle mass in elderly men are available. In a study of middle aged and elderly community-dwelling men,[80] no association was found between testosterone or free testosterone levels and lean muscle mass. Similar negative findings were reported in another cross-sectional study.[79] Another study in men aged 20–90 yr old, showed no association between testosterone levels and muscle mass, but did show a positive association of free testosterone levels with muscle strength.[81] In institutionalized healthy elderly men, an association was observed between testosterone levels and ADL limitations.[82] In another study, a positive association of free testosterone with muscle mass, but not with muscle strength was found.[83] In summary, the literature shows that data on associations of testosterone concentrations with muscle mass and strength are limited and not consistent.

Recently, an association between low testosterone levels and mortality was proposed, but results from studies among older men are inconsistent.[84-87] The biological mechanism linking low testosterone to increased mortality remains elusive, but some suggestions have

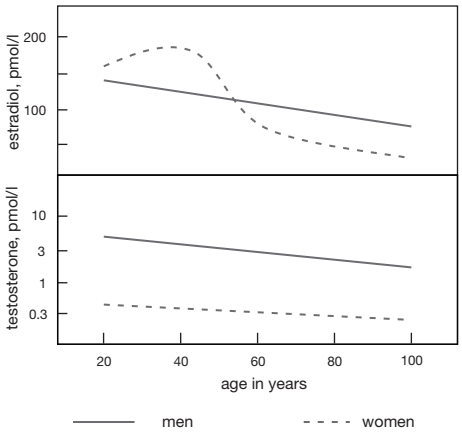

Figure 4

Serum total testosterone and serum total estradiol level as a function of age among an age-stratified sample of Rochester men (solid lines) and women (dashed lines). [Adapted from Khosla, S. et al. J Clin Endocrinol Metab 1998;83:2266-2274][76]

been made. Low testosterone might lead to a decline in muscle mass and bone strength, and thereby to more fractures, complications of which could lead to deaths. Another possible link between low testosterone and cardiovascular mortality is metabolic risk factors. Epidemiological studies have shown that low testosterone concentrations precede the development of central obesity, metabolic syndrome, and diabetes mellitus.[88-90] In one study, low testosterone was associated with central obesity and higher glucose and insulin concentrations.[90]

Cohort studies

For this thesis, data from two large ongoing cohort studies were used: the Longitudinal Aging Study Amsterdam (LASA) and the Health, Aging, and Body Composition (Health ABC) Study.

LASA is an ongoing multidisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional and social functioning in older people in the Netherlands.[91-93] The design of LASA is presented in Figure 5. A random sample of persons aged 55-85 years, stratified by age and sex and expected five-year mortality, was drawn from population registers of eleven municipalities in the West, South and Northeast of the Netherlands. In total, 3107 respondents were enrolled in the baseline examination (1992/1993) who were representative of the Dutch older population. Follow-up measurements were done every three years, consisting of a face-to-face main interview, a face-to-face medical interview and a self-administered questionnaire. Both face-to-face interviews were carried out at the subject's home by specially trained interviewers. Appendicular skeletal muscle mass was measured by dual-energy x-ray absorptiometry (DXA) in the second wave (1995/1996) and three years later in a subgroup of the study (persons living in the western part of the Netherlands). Muscle strength was measured as grip strength and the level of physical functioning was measured both objectively with physical performance tests[94] and subjectively as self reported functional limitations. Blood samples were collected during the second wave in persons who participated in the medical interview. The Medical Ethics Committee of the VU University Medical Center approved the study and informed consent was obtained from all respondents.

The Health ABC Study is an ongoing cohort study on the interrelationship of changes in body composition and health conditions and their effects on physiological and functional changes in older persons. The design of this study is presented in Figure 6. The study sample includes 3075 black and white men and women, aged 70-79 years at baseline (1997/1998).

Whites were recruited from a random sample of Medicare Beneficiaries residing in zip codes from the metropolitan areas surrounding Pittsburgh, PA, and Memphis, TN. Blacks were recruited from all age-eligible residents in these geographical areas. Eligibility criteria included age 70-79 years in the recruitment period from March 1997 to July 1998; self-report of no difficulty in walking one quarter of a mile or climbing ten steps without resting; no difficulty performing basic activities of daily living; no reported use of a cane, walker, crutches or other special equipment to get around; no history of active treatment for cancer in the

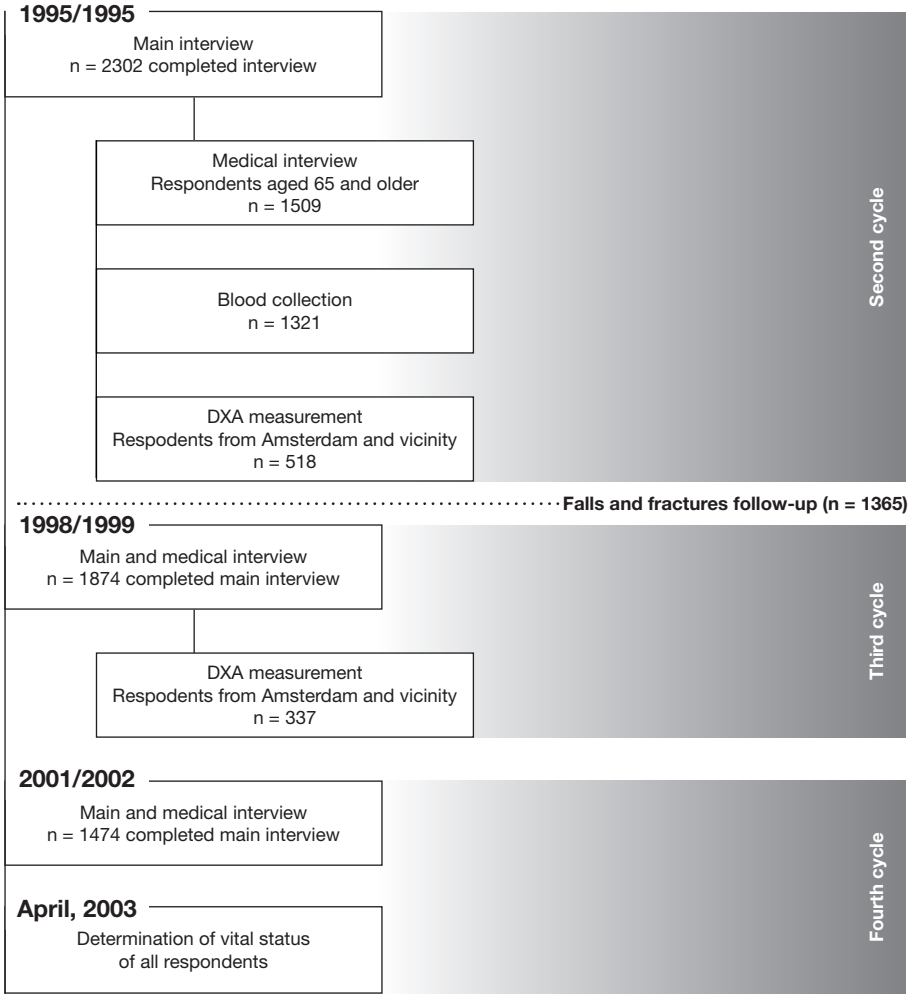

Figure 5

LASA study design

prior three years; and no plan to move out of the area in the next three years. Appendicular skeletal muscle mass was measured with DXA and computed tomography (CT). Muscle strength was measured as grip strength and knee extensor strength. Physical functioning was measured using physical performance tests.[94] Blood samples were collected at the clinic in the morning following an overnight fast of at least 8 hours. The study was approved by the Institutional Review Boards at the University of Tennessee and the University of Pittsburgh. All respondents provided informed consent before participating in the study.

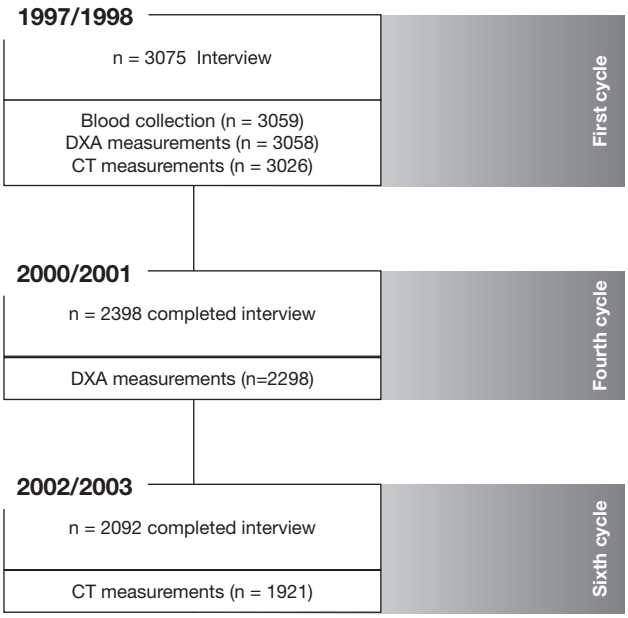

Figure 6

Health ABC study design

Objectives and outline of this thesis

This thesis focuses on determinants of sarcopenia, loss of muscle strength and decline in physical performance in older persons. The main determinants of interest are serum concentrations of inflammatory markers and sex hormones. This thesis aims to contribute to a better understanding of the mechanisms underlying sarcopenia, loss of muscle strength and decline in physical performance, using longitudinal data collected from both older men and women. Data from two large population-based cohort studies are used: a well-functioning sample of older persons (Health ABC), and a representative sample of the Dutch older population, including frail and poorly functioning persons (LASA). Both studies include data

on objective measures of muscle mass, muscle strength and physical functioning and a large variety of other behavioral and health associated measures, which makes it possible to carefully adjust for confounding. Most of the associations described in this thesis are studied longitudinally, limiting the potential risks of reverse causation. Studies investigating determinants of change in muscle mass, strength and functioning are scarce at present.

Figure 7 shows the research model of this thesis in which the numbers refer to the different chapters of this thesis. Chapter 2 describes the association between high serum concentrations of inflammatory markers (IL-6, CRP and ACT) with loss of muscle mass and loss of muscle strength during three years of follow-up in the LASA study.

Chapter 3 describes the association between concentrations of inflammatory markers (IL-6, TNF-α and CRP) with five-year decline in muscle mass and muscle strength in men and women from the Health ABC study. In addition, the role of weight change was explored.

Chapter 4 describes the cross-sectional association between concentrations of testosterone and estradiol with self reported and performance based impaired mobility, low grip strength and the incidence of falls in the LASA study.

Chapter 5 examines the association between low serum testosterone concentrations with three-year decline in physical performance and muscle strength in older men, using data from both the LASA study and the Health ABC Study. Besides data on grip strength, isoki-

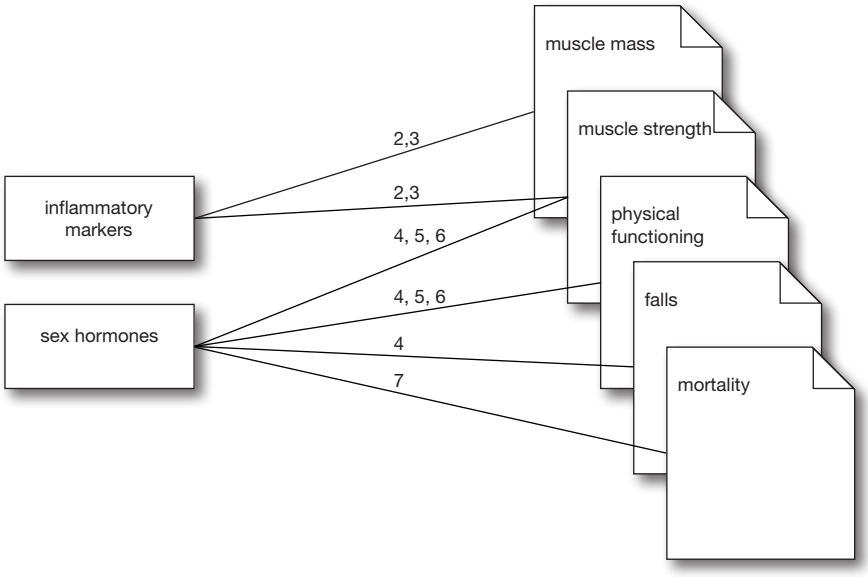

Figure 7

Research model of this thesis. Numbers indicate the chapters of this thesis.

netic strength of the knee extensors, measured within the Health ABC Study, was also included as an outcome measure.

Chapter 6 examines the relationship between low serum testosterone concentrations with three-year decline in physical performance and muscle strength in older women, using data from the Health ABC Study.

Chapter 7 describes the association between low testosterone concentrations with age and mortality in men from the LASA study.

Chapter 8 summarizes the main findings of this thesis, discusses the methodology that was used, and provides recommendations for further research.

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