Summary

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Chapter 1. Aging is associated with a progressive decline in muscle mass (sarcopenia) and muscle strength, which contribute to the onset and progression of disability with advancing age. The process of sarcopenia and loss of muscle strength is believed to be multifactorial, occurring over a prolonged time period. Known determinants include physical activity and other life style variables, chronic diseases and genetic factors. This thesis focuses on concentrations of inflammatory markers and sex hormones as possible determinants of sarcopenia and decline in physical functioning. It 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 in both older men and women. Data from two large population-based cohort studies are used: a well-functioning sample of older persons living in the United States (Health Aging and Body Composition (Health ABC)), and a representative sample of the Dutch older population, including frail and poorly functioning persons (Longitudinal Aging Study Amsterdam (LASA)). Both prospective studies include objective, repeated measures of skeletal 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 potential confounding.

Inflammation and sarcopenia

Chapter 2 describes the associations of higher concentrations of the inflammatory markers Interleukin-6 (IL-6), C-reactive protein (CRP) and α1-antichymotrypsin (ACT) with 3-year loss of muscle mass (sarcopenia) and muscle strength, using data from the LASA study. Higher concentrations of IL-6 were associated with greater decline in muscle strength. High concentrations of IL-6 (>5 pg/ml) and high concentrations of CRP (>6.1 μg/ml) were associated with a two to three-fold higher risk of losing more than 40% muscle strength compared to low concentrations of IL-6 and CRP. Persons with high concentrations of ACT (>181% of the normal human pooled plasma) were 40% less likely to experience loss of muscle strength and tended to have a smaller decline in muscle mass compared to those in the lowest quartile of ACT. No consistent associations of IL-6 and CRP with sarcopenia were found.

Chapter 3 describes the associations of higher concentrations of inflammatory markers (IL-6, tumor necrosis factor-alpha (TNF-α) and CRP) and soluble receptors 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. Higher concentrations of inflammatory markers were generally associated with greater five-year decline in thigh muscle area. Most associations, with the exception of soluble receptors, were attenuated by adjustment for five-year change in weight. Higher TNF-α and IL-6 soluble receptor concentrations remained associated with greater decline in grip strength in men. Analyses in a subgroup of weight-stable persons showed that higher concentrations of TNF-α, and its soluble receptors, were associated with five-year decline in thigh muscle area and with decline in grip strength. TNF-α and its soluble receptors showed the most consistent associations with decline in muscle mass and strength. The results suggest a weight-associated pathway for inflammation in sarcopenia.

Sex hormones and sarcopenia

In Chapter 4 we investigated the cross-sectional association between concentrations of testosterone and estradiol with self reported and performance-based mobility function, grip strength and the incidence of falls, using data from the LASA study. Men in the highest quartile of the estradiol/sex hormone-binding globulin (SHBG) ratio had significantly better physical performance scores than men in the lowest quartile. Moreover, in men, concentrations of testosterone were positively associated with muscle strength and calculated bioavailable testosterone concentrations were positively associated with physical performance and grip strength. No associations between estradiol and mobility or grip strength were found in women. Concentrations of estradiol and testosterone were not associated with falls. These results suggest that low concentrations of testosterone are associated with impaired mobility and low muscle strength in men, but not in women. Concentrations of sex hormones were not associated with the incidence of falls.

Chapter 5 we examined the associations between low testosterone concentrations and three-year decline in physical performance and muscle strength in older men, using data from LASA and Health ABC. Low concentrations of total testosterone were not associated with three-year decline in physical performance or with decline in muscle strength in both cohorts. Similar results were found for free testosterone concentrations.

Chapter 6 describes the associations between low testosterone concentrations and three year change in physical performance and muscle strength in a large sample of older women from the Health ABC study. Lower concentrations of total and free testosterone were not associated with baseline physical performance. However, lower concentrations of

total testosterone were associated with a two times greater three-year decline in physical performance score in women with total testosterone concentrations ≤ 20 ng/dl, compared to women with concentrations ≥ 34.7 ng/dl. Lower concentrations of total and free testosterone were associated with lower baseline grip strength and with greater three-year decline in grip strength in women 73 years or older, but not in younger women. These data suggest an association between low testosterone concentrations and greater decline in physical performance and grip strength in older women.

Chapter 7 shows the associations between testosterone concentrations and all cause and cardiovascular mortality, using data from older men included in the LASA study. There were 373 deaths during the average 10.9 years of follow-up including 83 deaths from cardiovascular causes. There was no association between low concentrations of total and free testosterone and all cause or cardiovascular mortality after adjusting for age, physical and lifestyle factors.

Chapter 8 summarizes and discusses the main findings of this thesis. Furthermore, methodological issues related to the studies are explored, implications of the findings for public health are discussed and recommendations for future research are made. The findings described in this thesis show that higher concentrations of inflammatory markers are associated with increased decline in muscle mass and muscle strength in older persons, supporting the evidence that inflammation is associated with decline in physical functioning through the effects of higher inflammatory marker concentrations on muscle. Also, change in weight should be considered as an important factor in the mechanism behind sarcopenia and loss of muscle strength and therefore future studies should further explore the effects of weight change on these associations. Low testosterone concentrations were not associated with decline in muscle strength, physical performance and mortality in men, but showed significant associations with decline in muscle strength and physical performance in women. More research is needed to elucidate the exact role of testosterone in women and to explore these sex differences. As the population grows older, becomes more obese and less active, more people will experience sarcopenia and a decline in physical functioning. Insight into the mechanisms underlying sarcopenia and loss of muscle strength is important to prevent disability.