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## Role of Muscle and Fat in Physical Function and Survival

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## Summary

The central topic of the studies in this thesis is (changes in) body composition in relation to healthy aging. We investigated 1) different patterns of BMI in relation to change in lean mass and physical function, 2) which fat depots and the density of those specific fat depots are associated with physical function, 3) which thigh-muscle composition is associated with physical function and survival, and finally 4) whether polyunsaturated fatty acids are associated with thigh-muscle composition or physical function. This summary provides an overview of the study results described in this thesis.

*Trajectories of BMI in old age and the associations with concomitant change in lean mass and physical function*

Previous research has shown that obesity in old age is associated with greater risk of functional decline compared to normal weight or overweight. However, it is unclear whether different trajectories of BMI relate to changes in body composition or physical function. In **Chapter 2** we were interested in trajectories of BMI, and the contemporaneous changes in appendicular lean mass (determined by dual-energy X-ray absorptiometry) and physical function per specific BMI trajectory. We investigated this question among 998 black and white participants with a mean age of 73.1 years of the Health ABC Study. There was no interaction between race and BMI, and therefore results were presented for blacks and whites together. In both men and women, four distinctive trajectories with significantly different BMI at baseline were detected. All trajectories showed a modest decline in BMI over a time span of 9 years. The rate of decline was different between trajectory groups for women, but not for men. Based on solely the BMI trajectories, it is unclear whether this decline (weight loss) represents loss in fat mass and/or lean mass. We showed that women in the highest trajectory (mean BMI at baseline 34.9 kg/m<sup>2</sup>) lost relatively more lean mass in the arms than those in the lowest trajectory (mean BMI at baseline 20.5 kg/m<sup>2</sup>). There was no difference in body composition across trajectories among older men. In addition to changes in lean mass, changes in strength (grip strength and leg strength) and physical function (gait speed) were assessed. We observed that men in the highest trajectory (mean BMI at baseline 33.9 kg/m<sup>2</sup>) had a greater decrease in gait speed and lost more leg strength than those in the lowest trajectory (mean BMI at baseline 22.9 kg/m<sup>2</sup>). No differences in physical function across trajectories were observed for women. Our different results for men and women may be explained by duration and type of activity. I.e. older men are overall less sedentary and report more often greater-intensity activity compared to older women. An important conclusion of our results is that BMI changes modestly over time, and that, compared to older adults with a healthy weight, women with the highest weight at old age lose relatively more lean mass in the arms, and older men with the highest weight have

relatively greater decreases in gait speed and leg strength. This indicated the importance of healthy weight during life.

#### *Type and location of fat depots with physical function*

Obesity is associated with increased risk for physical dysfunction and mortality. However, limited research has been performed investigating specific fat depots in relation to mobility limitation and physical performance. In **Chapter 3** we examined the association of BMI and areas and densities of several fat depots (determined by computed tomography) with incident self-reported mobility disability and poor performance (gait speed < 1.0m/s). The results based on data of 3011 participants of the Health ABC Study suggest that even in old age, higher BMI, greater visceral adipose tissue, greater abdominal subcutaneous adipose tissue, greater thigh subcutaneous adipose tissue, and greater thigh intermuscular adipose tissue (IMAT) were associated with increased risk of mobility disability or poor performance in a basic model. However, adjustment for e.g. physical activity and midlife weight attenuated the associations for some areas, but BMI and thigh IMAT area remained robustly associated with risk of mobility limitation and poor performance into late life. Higher densities of different fat depots were also associated with an increased risk of incident mobility disability and poor performance, although risk relations were less convincing than for fat area and generally not independent of BMI. These results suggest that interventions aiming at lowering IMAT in addition to the promotion of healthy body weight are necessary.

#### *Muscle composition, strength and physical function*

Limited studies have examined the association between muscle composition (muscle mass and muscle fat infiltration) in relation to subjective and objective indicators of physical function. **Chapter 4** describes which thigh muscle composition (determined by computed tomography) were related to incident mobility disability and change in gait speed, using data from the AGES-Reykjavik Study. Among 2725 men and women, mean age 74.8 years, greater thigh muscle strength and thigh muscle mass (cross-sectional muscle area) were associated with decreased risk of mobility disability and a slower decline in gait speed. Muscle fat infiltration was not associated with either mobility disability or decline in gait speed. The contradictory results regarding IMAT in comparison to other studies requires additional studies to clarify the potential role of muscle fat infiltration in physical function. In view of clinical practice, it may be advised to determine leg strength in geriatric care since leg strength and thigh muscle mass (which only can be determined using advanced techniques) show comparable results. Using that data, cut-off values could be determined, which in turn could be used to identify older adults with an increased risk of functional

decline. These individuals could benefit from additional care, such as nutritional or physical support, to prevent further functional decline.

### *Muscle composition, strength and all-cause mortality*

Previous studies investigating muscle composition with mortality risk mainly used bioelectrical impedance or dual-energy X-ray absorptiometry to determine muscle composition, and show inconsistent results. Computed tomography imaging gives more precise measures of muscle composition. In **Chapter 5** we determined mortality risk after 8.8 years of follow-up for different thigh muscle composition measures assessed by CT imaging, and leg strength. Results show that greater thigh muscle mass (cross-sectional muscle area), greater strength, and higher muscle quality (strength per area) were associated with lower mortality risk among 4824 men and women with a mean age of 76.4 years from the AGES-Reykjavik Study. In contrast, more muscle fat infiltration (both fat between and within the muscle) was associated with higher mortality risk. These results emphasize the importance of greater thigh muscle strength and thigh muscle mass, and lesser muscle fat infiltration to reduce the risk of premature death.

### *Polyunsaturated fatty acids in relation to muscle composition and strength*

Previous studies in cancer patients have shown that supplementation of n-3 polyunsaturated fatty acids (PUFAs) may result in better maintenance of muscle mass during chemotherapy. It is possible that PUFAs are associated with improved muscle composition due to the incorporation of PUFAs in muscle membranes and thereby improve function. However, large, population-based longitudinal data in older adults who are at risk of functional decline are lacking. In **Chapter 6** we examined the association between plasma PUFAs with thigh muscle mass, muscle fat infiltration (both determined by computed tomography) and grip and knee extension strength. Cross-sectional associations were determined among 836 participants and longitudinal associations (after a median of 5.2 years) were determined among 459 participants from the AGES-Reykjavik Study. Cross-sectional results show that higher concentrations of total PUFAs were associated with larger thigh muscle mass and with greater knee extension strength. Higher concentrations of arachidonic acid were associated with lower muscle mass. Higher linoleic acid concentrations were associated with less muscle fat infiltration. In contrast, higher concentrations of eicosapentaenoic acid were associated with more intermuscular adipose. Longitudinal analyses only showed positive associations for alpha-linolenic acid concentrations with increased knee extension strength. In addition to plasma PUFAs and muscle composition, we also determined whether fish oil consumption was associated with muscle composition, however, no independent associations were observed. Our

results show inconsistent relationships of PUFAs with thigh muscle mass, muscle fat infiltration and strength, and little evidence of their role in change in muscle composition.

#### *Polyunsaturated fatty acids in relation to physical function*

Previous cross-sectional studies have shown positive associations between concentrations of PUFAs with physical function, however, longitudinal studies using data on circulating PUFAs are limited. **Chapter 7** describes the associations between plasma phospholipid n-3 and n-6 PUFAs with risk of incident self-reported mobility disability (having much difficulty, or being unable to walk 500 meters, or climb up 10 steps) and objectively measured gait speed decline after  $5.2 \pm 0.2$  years. Data from the AGES-Reykjavik Study were used and included 556 men and women with a mean age of 75.1 years. Higher concentrations of total n-3 PUFAs and docosahexaenoic acid were associated with lower mobility disability risk among women only. No associations with gait speed were observed. We also investigated the association between fish oil consumption and physical function. Our results do not support a major role for fish oil consumption in preventing mobility disability or decline in gait speed. We cannot explain why associations were observed among women and subjective measures of physical function only.

### **CONCLUSION**

In this thesis we examined various measures of body composition, fat depots and muscle composition, in relation to physical function and survival. Our results provide further evidence that a better body composition in old age, defined as greater muscle mass, higher muscle strength and lower muscle fat infiltration, is associated with better physical function and lower mortality risk. We recommend that intervention programs for obese older adults focus on weight loss by caloric restriction and resistance training in order to improve body composition and thereby lower the risk of functional impairments and premature death. Regarding normal weight older adults, resistance training alone should be recommended to improve body composition.

We also examined associations between polyunsaturated fatty acids with muscle composition and physical function. We did not observe strong associations for polyunsaturated fatty acids in relation to muscle composition and physical function, however, this might be due to our single measurement of polyunsaturated fatty acids or our population with relatively high fish intake. Therefore, more studies investigating changes in polyunsaturated fatty acids in different study populations are required to determine the potential role of polyunsaturated fatty acids on muscle composition and physical function.