DUNEDIN STUDY CONCEPT PAPER FORM

Provisional Paper Title: Pro-dromal markers of low appendicular lean muscle mass in a middle-aged birth cohort.

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Today's Date: 29-01-2020

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

The aim of the current study will be to identify middle-age adults with low appendicular skeletal muscle mass at age 45 and to identify pro-dromal markers of low muscle mass at age 38, to better understand if pro-dromal markers exist.

Data analysis methods:

Means and standard deviations will be calculated to describe the continuous variables, two-way tables and marginal distributions will be used to describe categorical variables. The main outcome variable will be pre-sarcopenia at age 45. Appendicular lean muscle mass (ALM) was measured by DXA and sex-specific cut-scores based on 1SD below the mean will be used to define low appendicular lean muscle mass (ALM). Age and sex appropriate cut-scores will be used to define low grip strength. Pre-sarcopenia will be defined as low ALMI and low grip strength. Logistic regressions will be used to describe the relationship between low ALM at age 45 and a possible pro-dromal marker measured at age 38. Significant predictors at age 38, will also be tested for significance at age 32 and 26, to determine how early in the life

course each significant predictor can be identified. Possible predictors before the age of 26 might negatively impact one's ability to reach peak muscle mass, but that goes beyond the question raised for this paper and therefore won't be included.

Analyses will be stratified for sex, except for female reproductive variables. A sensitivity analysis to adjust the stratified analysis for BMI and socio-economic status will be conducted. Relative risk ratios with 95%CI will be reported. Data analyses will be carried out using STATA version 15.1 (StataCorp. 2017. Stata Statistical Software: V15. College Station, TX: StataCorp LLC).

Variables needed at which ages:

Age 45
Arms, Legs, Trunk and Total Lean Mass
App Lean Muscle and the Index

Age 26, 32 & 38

Chronic disease markers; lipid profile, glycated haemoglobin, sensitive CRP, cortisol, blood pressure.

Muscle catabolism; haemoglobin, creatinine,

Sex hormones; testosterone, oestradiol

Anthropometrics; Body Mass Index, height, circumference, birth weight

Bone turnover; year of primigravida, total number of pregnancies, age at menarche.

Functional measurements; grip strength, one-legged balance, VO2Max,

Lifestyle factors; perceived fitness level, SF36 physical functioning, cigarettes a day, Cumulative Cigarette Pack Years To Age, drinking year, glasses of alcohol a week, socio-economic status

Physical activity; The following variables will be used to create 2 variables

1) METS per week of activity; household activity (METS /week), occupation activity (METS /week), sport/leisure activity (METS /week)
2) Hours per week of activity; moderate occupational activity (hours/week), moderate household activity (hours/week), moderate leisure/sport activity (hours/week), hard occupational activity (hours/week), hard household activity (hours/week), hard leisure/sport activity (hours/week), very hard occupational activity (hours/week), very hard household activity (hours/week), very hard

leisure/sport activity (hours/week)

The list of variables has been carefully chosen and based on previously published literature reporting the relationship of the possible predictor and sarcopenia in diverse populations, including different clinical populations as well as different age ranges. Sarcopenia is associated, as previously reported, with chronic diseases such as hyperlipidaemia, diabetes and hypertension (1-3), we therefore would like to test these relationships in middle-aged adults by looking for an association with lipid profile, glycated haemoglobin, sensitive CRP and blood pressure. Furthermore, the following biomarkers have been previously reported to be associated with sarcopenia; creatinine (4), testosterone (5), estradiol (6) and cortisol (7). Clinical markers: height (8), BMI (9) and waist- and hip-circumference (10), birth weight (11), grip strength (12), balance (13) and VO2 (14). Lifestyle markers of smoking (15), alcohol consumption (16), physical activity; intensity (METS) and volume (17), self-reported fitness (18) and quality of life (19). The following possible predictors are related to the age-related loss of bone mass and may also be related to the age-related loss of muscle mass; year of primigravida, total number of pregnancies and age at menarche (20).

Significance of the Study (for theory, research methods or clinical practice):

Sarcopenia, the age-related progressive loss of skeletal muscle mass and physical function, is well described in older adults (11). The majority of sarcopenia research continues to be focused on older adults, despite the evidence that abnormal body composition is apparent before the age of 50 (21). Pre-sarcopenia is the early stage of sarcopenia in which muscle mass deteriorates, but muscle strength is still intact (12) and is prevalent in up to 20.8% of middle-aged (≤59 years) men and 15.6% of middle-aged women, depending on the diagnostic criteria used (21). This shows that abnormal body composition is already prevalent earlier in life than from age 65 years.

In clinical medicine, a prodrome refers to early symptoms and signs of illness that precede the characteristic manifestations of the fully developed illness (22). In the case of sarcopenia, pro-dromal markers have been described as subtle changes in function that occur in middle age which precede changes in muscle mass (23). Although a life course approach to understanding sarcopenia, focusing on factors operating earlier in life including developmental influences, has previously been described by Sayer et al (11), only Kobayashi and colleagues have conducted a small cohort study in older adults, to specifically identify risk factors for the early stages of sarcopenia (24). They suggested that BMI, grip strength, bone mineral density, back muscle strength, and osteoporosis deteriorated more over 5 years in the pre-sarcopenic group compared with the control group. However, this study was in older adults (≥60 years) and they acknowledged that further studies were needed to identify other factors related to sarcopenia in order to prevent and treat this disease (24).

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