Dunedin Multidisciplinary Health & Development Study

Concept Paper Form

Provisional Paper Title: *"Development and validation of a screening tool for middle-aged adults to predict the risk of sarcopenia."*
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Objective of the study:

The aim of this current study is to develop and validate a prognostic screening tool to identify middle-aged adults at risk for developing sarcopenia.

One of the most common musculoskeletal conditions associated with advanced age is sarcopenia. Sarcopenia is a geriatric syndrome, described as a progressive and generalised loss of skeletal muscle mass and strength from the age 65 years onwards with risk of adverse outcomes (1). The burden of this condition is extensive and increasing because of the growing aging population (2). Skeletal muscle mass reaches its peak around age 30 and then starts a slow decline of between 1 to 2% per year resulting in a loss of about 40% of muscle mass at the age of 80 (3). Despite the loss of skeletal muscle mass starting in early middle-age, sarcopenia is considered a geriatric disorder, which raises the question of whether sarcopenia begins in early middle age as "pro-dromal" sarcopenia (4). Although there is some evidence that abnormal body composition can be present in middle-age (5, 6), the majority of sarcopenia research continues to be focused on older adults (65+). This could have important public health implications as older people with sarcopenia are consistently reported to have lower physical function, overall health and survival compared to people with normal body composition (7, 8).

Data analysis methods:

The data for this study has reached a formal approval in our previous concept paper ("Pro-dromal markers of low appendicular lean muscle mass in a middle-aged birth cohort", accepted on April 17th, 2020.). Due to the novelty of this research, this first step of the analysis has led to a separate manuscript. The analysis proposed in the current concept paper is a secondary analyses to develop, internally and externally validate a screening tool based on risk factors identified in the previous concept paper.

The previous approved concept paper included variables at age 26, 32, 38. These three phases were chosen as they best represent our primary aim which is to determine a set of variables measured in early middle-age that best predict those people who will develop sarcopenia. It is possible that there are factors that occur before age 26 that might negatively impact the attainment of peak muscle mass, but that is not the aim of the current proposal. Although, that is an interesting research question, unfortunately body composition measurements that were collected before the age of 26, are not adequate to answer this question.

Variable selection

Significant predictors from univariate models developed as proposed in our previous, accepted, concept paper: "Pro-dromal markers of low appendicular lean muscle mass in a middle-aged birth cohort" will be included in the analysis proposed in this concept paper. A multivariate logistic regression analysis will be used with low or normal appendicular lean muscle index (ALMI) as the dependent variable, with an automated backward elimination procedure and using $P<0.05$ as selection criterion. Due to the sex-specific nature of many of the predictors sex-specific models will be created. Lastly, the probability of a participant having low muscle mass will be predicted by the regression equation, predicting the log odds using the estimated β coefficients multiplied by the corresponding predictor. This will lead to a risk score prediction of low ALMI = $1/(1+e^{riskscore})$ with a risk-score between 1 and 0.

Multiple strategies will be used simultaneously to reduce or eliminate the risk for confounding and to optimize the model fit during the variable selection process. Variable selection will be done using an automated backward elimination procedure (9). All variables will be checked for multicollinearity and shared variance between the main outcome and possible predictors. To minimize fit noise and systematic effect, the original cohort data will be split into two groups to estimate its performance (10). We will use a recommended 80/20 split and use the first 80% as a training set to determine the significant predictors. The next 20% will be used as a validation set.

To externally validate the screening-tool we will use baseline data collected for an intervention study of males and females aged 40 to 50 years. Participants for this study were recruited through flyers, community webpage postings, electronic bulletin boards and local newspapers. Interested people were directed to complete an online screening questionnaire. Participants were pre-screened for exclusion criteria, exercise safety and their weekly amount of physical activity. Participants were deemed eligible to attend a screening appointment, if they did not meet the minimum weekly current exercise recommendations and if they did not meet any of the exclusion criteria. Ethical approval for the study has been obtained from The University of Otago Human Ethics Committee (H18/131).

Validation and testing

Different statistical methods will be used to validate the final model in the internal validation sample. Nagelkerke R2 and the Brier score will be used to estimate the overall performance, calibration of both models will be measured with the Hosmer-Lemeshow test and discrimination of the models will be tested by using a Receiver Operator Characteristic Curve analysis as well as with measures of sensitivity and specificity. After the internal validation, both final models will also be validated in the separate external validation sample by calculating their discriminatory

capacity, using the AUC, sensitivity and specificity. 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:

This analysis is a secondary analysis of the variables that were included in our previous, accepted, concept paper: "Pro-dromal markers of low appendicular lean muscle mass in a middle-aged birth cohort", accepted on April 17th, 2020. We will therefore not require any additional variables. For the list of variables and rationale for choosing them, please see our previous concept paper.

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

Although there are several screening tools available to assess sarcopenia in older adults (11) there are currently none developed to assess the risk of developing sarcopenia in younger people once they have reached peak skeletal muscle mass which usually occurs around age 30yr. With a growing ageing population and the predicted increase in people with sarcopenia, from almost 11 million in 2016 to almost 20 million in 2045 (a 72.4% increase) in Europe (12), it is important to identify those at risk for developing sarcopenia in middle-age. By developing and validating a screening tool to identify these individuals in middle-age will then allow interventions to be developed and tested that prevent or slow the progression of sarcopenia.

References:

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