CONCEPT PAPER DUNEDIN STUDY

Provisional Paper Title: *"Development and validation of a screening tool to predict the risk of developing osteosarcopenia in middle aged adults."*

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Date: 10-04-2018

Topic and significance

Topic

Two of the most common musculoskeletal conditions associated with aging are sarcopenia and osteopenia/ osteoporosis. Sarcopenia is a syndrome, described as a progressive and generalised loss of skeletal muscle mass and strength with risk of adverse outcomes.[1] The burden of this condition is extensive and increasing because of the growing aging population.[2] The European Working Group reported that up to 33.0% of community-dwelling elderly are sarcopenic, with even higher estimates in long-term and acute care settings. [1] Sarcopenia is also associated with other chronic health conditions including dementia, [3] obesity,[4] type 2 diabetes,[5] and osteoporosis.[6] Age-related osteopenia/osteoporosis is a characterised by deterioration of bone microarchitecture and decreasing bone mineral density (BMD), thus increasing bone fragility and the risk of fractures. Because bone and muscle are metabolically interconnected and alterations in stem cell differentiation common are both conditions, there is increasing evidence that sarcopenia and osteoporosis are closely linked.[7] Therefore, the term "osteosarcopenia" has been proposed to describe individuals suffering from both conditions, which contributes to an increased fracture risk, disability and a loss of independence for these individuals.[7]

Peak bone mass is reached around age 30, after which time, it starts to decline. Between the third and seventh decades of life there is an estimated loss of around 30% in peak bone mass. [8] In contrast to bone, muscle mass reaches its peak slightly earlier around age 25 and remains relatively stable until the age of about 50.[9] After that, the estimated annual loss of muscle mass is between 1 to 2% per year resulting in a loss of about 40% of muscle mass at the age of 80.[9] The progressive decrease in skeletal muscle mass and bone from early middle age leads to the question of whether these conditions exist much earlier in life as "pro-dromal" conditions.[10] Although there is some evidence that abnormal body composition is apparent before age 50yrs,[11, 12] the majority of sarcopenia and osteoporosis research continues to be

focused on older adults, rather than earlier in the life course. This could have important public health implications as older people with sarcopenia and osteoporosis are consistently reported to have lower physical function, overall health and survival compared to people with normal bone density and body composition.[13, 14]

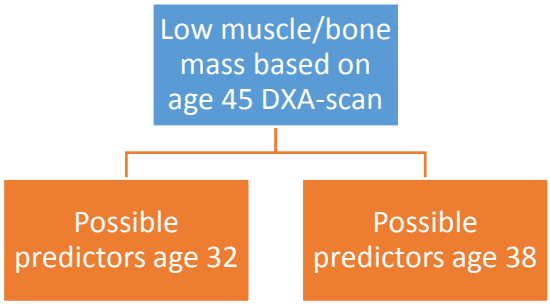
As osteosarcopenia is a recent terminology there are relatively few studies assessing its epidemiology and the prevalence of sarcopenia differs depending on the methods used. Our preliminary analyses on the age 38 Dunedin Study cohort, using bioelectrical impedance and appendicular skeletal muscle mass (ASMI) cut-offs developed by Prado,[12] suggested that 45% of the cohort had low skeletal muscle mass. Of those assessed to-date at the age 45 assessment using DXA (Lunar Prodigy), almost 22% of the cohort was identified as having low bone mass at the hip (T-score <-1.0) and almost 15% have a combination of low muscle mass and low bone density (ie: osteosarcopenic).

Significance

Although there are several screening tools available to assess sarcopenia in older adults [15] there are currently none developed for a younger cohort and none that screen for osteosarcopenia. There is also a distinct need for a robust sarcopenia and osteosarcopenic screening tool that uses biomarkers to screen for these conditions. With a growing ageing population and the predicted increase in people with osteosarcopenia, from almost 11 million in 2016 to almost 20 million in 2045 (a 72.4% increase) in Europe,[16] it is more important than ever to identify those at risk for developing osteosarcopenia earlier in the lifecourse. Identifying individuals at risk for these conditions earlier in the lifespan may also inform interventions developed to prevent or slow down the progression, rather than treat osteosarcopenia. **Therefore, the aim of this current study is to develop and validate a prognostic screening tool to identify middle aged adults at risk for developing a combination of sarcopenia and osteopenia (ie: osteosarcopenia).**

Analysis

For this data-analyses we will identify participants with low muscle mass and low bone density, based on the DXA measurements performed at the age 45 time point, using muscle mass cut-scores as described by Prado et al [12] and low bone density (total hip or neck T-scores <-1.0). After identifying participants we will examine the association between demographics, comorbid conditions and health behaviours, using two separate models at age 32 and 38, with these bone and body composition phenotypes. These characteristics will be developed into a screening tool to identify individuals at risk for pro-dromal sarcopenia and osteosarcopenia in the general population.



Variable selection

To investigate the relationship between a possible predictor and the measure of low muscle mass and/or low bone mass, multivariate logistic regression analysis will be used at two different time-points; age 32 and age 38, independently. Two subsets of predictors will be included in both models to examine the predictive power of each predictor at each age (e.g. 32 and 38). Subset 1 will include biomarkers and subset 2 will include physical function

measures and other health related measures. To lessen the complexity of the final model, sex will be entered as step one of a multivariate logistic regression analysis. In the second step, each potential prognostic predictor of the subsets will be added stepwise to the model by using an automated backward selection procedure. Significance level will be set at $p<0.15$ to select variables that remain in the model.

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.[17] All variables will be checked for multicollinearity and shared variance between the main outcome and possible predictors. As multivariate logistic modelling tends to over-fit a model, we will use bootstrapping sampling with replacement to estimate the prediction model and the model fit will be assessed using the C-statistics as proposed by Harrell.[18] To minimize fit noise and systematic effect, the original cohort data will be split into groups to estimate its performance.[19] We will use a typical 60/20/20 split and use the first 60% as a training set to determine the significant predictors. The next 20% will be used as a validation set and the last 20% will be used as a test set.

Performance
To measure the performance of each full algorithm, consisting of the values of each included significant predictor and its regression coefficient. We will measure both the calibration of each model and the discrimination of each model. The calibration will be measured by using calibration slopes and calibration intercepts by plotting the observed and predicted outcomes. By using discrimination slopes and calculating risk-stratified likelihood ratios, we will measure the discrimination.

Validation and testing
Every prognostic model will be tested in the validation sample. The best performing model will be evaluated using the test set, which will only be done once. To estimate the overall performance both Nagelkerke R^2 and a Brier score will be calculated on every prognostic model. Discrimination of the models will be tested with the area under the curve (AUC) as well as with likelihood ratios and discrimination slopes. Calibration plots and Hosmer-Lemeshow tests will be used to calibrate every model. To calculate the predicted versus the observed risk, validation plots will be produced.

Variables
The initial set of possible predictors was selected from those measured in the cohort at phase 32 and phase 38. These two phases were chosen as they best represent our primary aim which is to determine a set of variables measured in early middle-age which best predict those adults who will develop osteosarcopenia. Furthermore, as bone and lean mass peak around the 3rd decade these two phases encompass that period. Finally, from a clinical point of view detecting and understanding the cause of age-related loss of muscle and bone in early in middle-age is important because of the potential gain in health associated with successful prevention. The table below includes the variables to be included in the model and their respective assessment phase.

Variable	**Assessment phase**	**Subset**
Date of birth, sex	Birth	-
Smoking	32, 38	2

Alcohol Cannabis Hard drugs		
Reproductive	32, 38	2
Sleep quality Pain Impact Short Questionnaire Fatigue Impact Short Form Physical exercise/activity	38 38 38 32, 38	2
Glucocorticoid and thyroid medications	32, 39	2
Injuries (falls and fracture)	32, 38	2
Anthropometry Cardio-respiratory Fitness (VO^2max)	32, 38 32, 38	2
Grip strength Balance (eyes closed) Sit to stand GaitRITE (normal speed, max speed and while doing mental task)	38, 45	2
Physical activity	32, 38	2
Blood pressure Heart rate Height Weight Waist circumference Hip circumference	32, 38	2
Adiposity Anthropometrics Body Mass (total and regional) Bone Density (total and regional) Lean Mass (total and regional) Fat Mass (total and regional)	45	2
Cholesterol (HDL, LDL, TC, Triglycerides) Glyc haemoglobin Serotonin Tryptophan Haemoglobin Platelets Creatine CRP Testosterone Oestradiol Apolipoprotein Lipoprotein Serum cortisol Sex hormone binding	32, 38	1
SF-36 health survey	38	2
Self-related health	32, 38	2

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Data Security Agreement

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Proposing authors	Dr. Kim Meredith-Jones, Assoc Prof Debra Waters, Lara Vlietstra, Ari Samaranayaka
Today's date	10th April, 2018

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KMJ, LV, DW, AS	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
KMJ, LV, DW, AS	My project is covered by Duke or Otago ethics committee OR I have /will obtain ethical approval from my home institution.
KMJ, LV, DW, AS	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) b) password-protected d) has an antivirus client installed as well as being patched regularly.
KMJ, LV, DW, AS	I will not "sync" the data to a mobile device.
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KMJ, LV, DW, AS	I will not post data online or submit the data file to a journal for them to post. *Some journals are now requesting the data file as part of the manuscript submission process. The Dunedin Study Members have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Terrie or Avshalom for strategies for achieving compliance with data-sharing policies of journals.*
KMJ, LV, DW, AS	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. The data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

Signature: 

CONCEPT PAPER RESPONSE FORM

A

Development and validation of a screening tool to predict the risk of developing osteosarcopenia in middle aged adults	
Proposing Authors: Dr. Kim Meredith-Jones, Assoc Prof Debra Waters, Lara Vlietstra, Ari Samaranayaka	
Other Contributors: **we have not contacted anyone formally yet, but we have had informal discussions with Dave Baxter and Ram Mani. We are also planning on contacting Bob Hancox to discuss the physical activity data and other variables he may be responsible for. We will contact the PI's responsible for all of the other data included in the model.	
Potential Journals:	
Intended Submission Date: Aug 2018	

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B. To be completed by potential co-authors:

	Approved
	Not Approved
	Let's discuss, I have concerns

Comments: gaitrite and sit to stand are new at 45. I would prefer we work with them first, to learn about them, before others use them. Temi

Please check your contribution(s) for authorship:

TEM	Conceptualizing and designing the longitudinal study
KMJ, DW, TEM	Conceptualizing and collecting one or more variables
KMJ, TEM	Data collection
KMJ, LV, DW	Conceptualizing and designing this specific paper project
LV, AS	Statistical analyses
KMJ, LV, DW	Writing
KMJ, LV, DW	Reviewing manuscript drafts
KMJ, LV, DW, TEM	Final approval before submission for publication
	Acknowledgment only, I will not be a co-author

Signature: Temi