Concept Paper Template

Provisional Paper Title: Abdominal visceral fat reference values associated with increased risk of cardiometabolic disease

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

Objective of the study:

The aim of this study is to develop reference values for VAT mass (g) and volume (cm³) in a large sample of men and women of varying age, sex and BMI using the GE Healthcare Lunar Prodigy instrument along with the dedicated CoreScan application. Additionally, we aim to assess the association between DXA-VAT and traditional cardiometabolic risk factors, and estimate VAT thresholds that are associated with elevated cardiometabolic risk

Data analysis methods:

Age-related reference intervals will be derived by modelling the mean and standard deviation (SD) for VAT (g) and (cm³) as a function of age (if the age range is varied enough) by sex and BMI category. Estimated 1st, 2.5th, 97.5th and 99th centiles, providing 95 and 98% reference intervals will be computed. Confidence intervals (90%) for these centiles across the age range will be derived from the obtained standard errors. The presence of two or more risk factors defined according to the Harmonized Metabolic Syndrome (11) thresholds [elevated waist circumference ≥88 cm in women and ≥102 cm in men, systolic blood pressure ≥130 or diastolic blood pressure ≥85 mmHg or reported hypertension, fasting glucose ≥5.6 mmol/L or reported diabetes, triglycerides ≥1.7 mmol/L, HDL-cholesterol ≤1.0 mmol/L (men) or ≤1.3 mmol/L (women)] will be used to define elevated cardiometabolic risk. Logistic regression will be used to assess the association between DXA VAT and elevated cardiometabolic risk. Receiver Operating Characteristic (ROC) curves will be used to select VAT thresholds that identify individuals with two or more risk factors. Since the area under the curve (AUC) is considered a measure of utility and represents the trade-off between the correct identification of high-risk individuals (sensitivity) and of low-risk individuals (specificity), the VAT threshold will be estimated from the nearest to (0,1) method, finding the cut-point for VAT that is closest to perfect sensitivity and specificity. While we will be using a wide range of ages in this analysis, the majority of the sample will be mid-40s, which means that estimates for those ages will be more precise.

Variables needed at which ages:

The sample will be selected using data from six studies that have been conducted between 2009 and 2019. These six studies, the sample size and the variables included are listed below:

Study	N	Age range	BMI	WC	BP	TC	HDL	LDL	TG	glucose
HIIT	142	40-50	✓	✓	✓	✓	✓	✓	✓	
Power	221	19-66	✓	✓	✓	✓	✓	✓	✓	✓
Snack	100	18-64	✓	✓	✓	✓	✓	✓	✓	
Ice Tea	114	19-55	✓	✓	✓	✓	✓	✓	✓	
Swift	222	20-73	✓	✓	✓	✓	✓	✓	✓	
Dunedin Study Phase 45	**904**	**45-46**	✓	✓	✓	✓	✓	✓	✓	✓

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

Although a high level of body fat is a known risk factor for metabolic disease, the distribution of fat may be more important for cardiometabolic risk than excess adiposity per se. Advances in technology have identified that two distinct types of fat exist in the abdominal region, namely the visceral component (VAT) and the subcutaneous component. VAT, due to its proximity to the liver and more pathogenic cytokine profile, has been implicated in insulin resistance as well as a number of other related cardiovascular and metabolic conditions including type 2 diabetes [1]. In many studies, the association between VAT and disease remains significant even after statistical adjustments for other measures of obesity and regional adiposity such as body mass index (BMI) and waist circumference [2, 3].
Currently, the two most commonly used imaging techniques for measuring VAT are abdominal X-ray computed tomography (CT) and magnetic resonance imaging (MRI). However, although both techniques are well validated, neither option is a viable screening tool for VAT because of radiation dose (CT), and/or the need for access to heavily utilized clinical equipment. Dual-energy X-ray absorptiometry (DXA) is an established technique for the measurement of body composition in both research and clinical practice and it is often used in investigations of the effects of interventions on body composition [4]. Although traditional DXA estimates did not discriminate between VAT and subcutaneous fat a new algorithm commercialized under the brand CoreScan (GE Healthcare, Madison, WI) to estimate VAT has been shown to be highly correlated (r = 0.95) with actual CT measures [5]. In this study, only a small average difference in VAT (60 g from a mean of 1029g) was observed between the two methods.

However, the ability to derive meaningful interpretations of the results from DXA derived visceral fat estimates obtained with a GE-Healthcare system has been challenging as representative reference values have not been available. To-date, there has been three studies that have published VAT reference values in adults. DXA-derived reference values for total body fat mass variables in adults were derived from the 1999–2004 NHANES dataset, which used measurements directly obtained from the Hologic QDR 4500A system. However, it is well known that measurements between DXA manufacturers cannot be compared. Using percentiles in 421 healthy Polish adults aged 20-30 years Imboden et al (2017) developed VAT reference values generated directly from measurements of %BF, FMI, trunk/limb and trunk/leg ratio obtained using the GE-Healthcare DXA system but the age range was narrow (20-30 years) and the majority of participants were normal weight. More recently age and sex-specific reference intervals have been published in a large sample of adults 18-83 years using a GE iDXA system, however in this study clinical thresholds associated with the presence of cardiovascular risk factors were not identified. As the GE Lunar Prodigy is one of the most commonly used DXA systems and has a large install base in over 120 countries, reference standards are needed to define visceral obesity and to evaluate the cardiometabolic risks associated with excess VAT quantified by this instrument.

References:

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2. Canoy D, Boekholdt SM, Wareham N, Luben R, Welch A, Bingham S, Khaw K-T, Body Fat Distribution and Risk of Coronary Heart Disease in Men and Women in the European Prospective Investigation Into Cancer and Nutrition in Norfolk Cohort: A Population-Based Prospective Study. *Circulation* 2007;116(25): p. 2933-2943.
3. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu C-Y, O'donnell CJ, Abdominal Visceral and Subcutaneous Adipose Tissue Compartments: Association With Metabolic Risk Factors in the Framingham Heart Study. *Circulation* 2007;116(1): p. 39-48.
4. Kendler DL, Borges JLC, Fielding RA, Itabashi A, Krueger D, Mulligan K, Shepherd J, The Official Positions of the International Society for Clinical Densitometry: Indications of Use and Reporting of DXA for Body Composition. *Journal of Clinical Densitometry* 2013;16(4): p. 496-507.
5. Kaul S, Rothney MP, Peters DM, Wacker WK, Davis CE, Shapiro MD,Ergun DL, Dual-energy X-ray absorptiometry for quantification of visceral fat. *Obesity (Silver Spring, Md.)* 2012;20(6): p. 1313-8.