Time-Ordered Metabolic vs Nutritional Pathways to Sarcopenia: Longitudinal Analysis with MFR-Based Classification

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Introduction: Sarcopenia is the pathological decline of skeletal muscle mass related to aging, in terms of quality and strength. This condition is attributed to fat infiltration into the muscles of the body leading to decreased body control and physical function. Patients with sarcopenia display increased risk of falling and difficulty executing routine tasks. Sarcopenic Obesity (SO) is a related condition, which is a coexistence of sarcopenia, low muscle mass, and obesity; it differs from sarcopenia alone. The metabaging cycle is a vicious positive feedback loop of inflammation/insulin resistance (IR) and metabolic dysregulation of fat and skeletal muscle and can lead to myosteatosis, sarcopenia, and SO. Fat accumulation in the muscles, known as myosteatosis, accelerates muscle degeneration. This condition contributes to comorbid metabolic abnormalities and IR. Data analysis suggests that the pathways that sarcopenia will develop are different between males and females. Females display a stable amount of fat-free mass with a redistribution of fat mass to their trunk with age, while males depict a fat accumulation with age. The aim of this study is to investigate the underlying patterns of sarcopenia by analyzing physical and environmental factors as well as comparing the differences in muscle and fat distributions. Simultaneously, the quality and quantity of the muscle and fat mass will be examined to observe whether the atrophy or fat pathway will progress first. In the end both pathways will converge into Advanced Sarcopenia, and determining the origin could allow for detailed planning for muscle atrophy prevention. This evaluation of the BMI and the MFR (skeletal muscle to fat ratio) is useful for discovering high risk patients and providing them with early intervention opportunities.

Methods: Clinical data was collected from 503,317 participants from the UK Biobank including 231,098 males and 272,219 females. The information included age, sex, height, BMI, fat percentage and mass, and fat-free masses from the trunk and extremities. Volunteers between the ages of 40-69, at baseline, were observed based on their lifestyle habits, physical measurements, imaging, and past medical records. Segmental bioimpedance outputs were height-squared normalized to Muscle Index ($MI=FFM/height^2$) and Fat Index ($FI=FM/height^2$). Agreement with legacy outcomes was confirmed by linear correlations ($r^2=0.166$ for SO; $r^2=0.45$ for sarcopenia). New case definitions: sarcopenia = $MI\_z \leq -1$; SO = whole-body $FI\_z > 0.193$ & $MI\_z \leq -1$. Incident (newly developed) cases of Sarcopenia and SO were classified among participants who were negative at the previous visit. Additionally, blood markers were observed to determine changes in the metabaging cycle. Correlation graphs were created to compare the changes in fat and fat free masses from the prospective repeated measures cohort. The data was observed using longitudinal associations and analyzed using linear regression models. Variables were standardized by sex×age bands. Systematic mediation (sequential regression/SEM): Along the directed graphs (A: Lipid→ IR/Inflammation→ Fat Score →AnCat→ Muscle→ Grip→ SO; B: Malnutrition → Muscle → Grip→ Sarcopenia), continuous nodes used linear models (standardized β per 1-SD), binary nodes logistic models (OR per 1-SD). Controlled direct effects (CDE) included downstream mediators; indirect effects and mediated proportions were obtained by bootstrap. MFR analysis: MFR=MI/FI (Leg-MFR, Trunk-MFR) was evaluated via 1-SD logistic models**.** MFR scores were calculated separately for the limbs and trunk and used as an objective variable for the regression analysis. The MFR was then converted into z standardized scores. The participants were divided into cutoff categories based on the Youden Index with 1. Normal, 2. Sarcopenia (FIz<-1), 3. Pre-SO (FIz>0.193), 4. SO (FIz≤ 0.193), and an additional red-flag if the MFR was especially low (FIz≤ −1).

Results: Fat mass was predicted to be higher in all categories for females, and the fat free mass was expected to be higher in all areas for males. The data displayed the cross-sectional findings at a single time point, the prevalence showed that 58% were normal, 16% had sarcopenia, 15% displayed Pre-SO, and 11% had SO. Cross-sectional (per 1-SD): Path A (Sarcopenia) Lipid→ IR/Inflammation β=0.33; IR/Inflammation→ FatScore β=0.26; Fat Score→AnCat β=0.21; AnCat→ Muscle β=−0.29; Muscle→Grip β=0.35; SO ← Grip OR=0.40. Chained indirect effect 0.007–0.008 (p≈0.001). Path B (SO) Malnutrition→Muscle β=−0.24; Muscle→Grip β=0.35; Sarcopenia ← Grip OR=0.42. Indirect effect −0.084 to −0.091 (p≈0.001). The Longitudinal findings suggest that achieving the $\Delta MI\_z \geq +0.20$ reduced next visit SO risk 0.18% vs 0.43% → ARR 0.25%, RR 0.42, NNT ≈ 399; and sarcopenia 0.00% vs 5.94% → ARR 5.93%, NNT ≈ 17. MFR-based classification indicated that the $\Delta Trunk\text{-}MFR\_z \geq +0.20$—SO 12.6% vs 18.7%, OR 0.158, AUC 0.834, ARR 6.1% (2.0–9.8), RR 0.67, NNT 16(n=492,044). $\Delta Leg\text{-}MFR\_z \geq +0.20$—Sarcopenia 9.8% vs 15.3%, OR 0.117, AUC 0.845, ARR 5.5% (1.6–9.1), RR 0.64, NNT 18(n=491,953). As a ratio metric, MFR sharpened phenotyping for Trunk-MFR, best tracked SO, whereas Leg-MFR aligned well with sarcopenia.

Discussion: The results suggest that MFR is a more accurate tool for measuring the divergent pathophysiology of sarcopenia and SO, which provided for a strong causal inference more than basic cohort analysis. Validating MFR cutoffs for diverse populations in a clinical setting could benefit future studies in understanding fat distribution to muscle decline. Pathway limitations can be seen as the data is based on mediation models. The ARR/RR/NNT values represent associations, not randomized interventions, so the data is based on observation rather than a controlled environment. The data was also provided by the UKB so there are limitations to the way that the data was collected.

Significance/Clinical Relevance: The data analysis depicts that females have a higher fat concentration in their legs and trunk when they are younger and as they age there is a stable fat free mass suggesting that there is an age-related redistribution of fat; Males begin lean and progressively gain fat with age, particularly in the trunk area suggesting that there is an increased risk of sarcopenia related mobility decline. This will provide insight for preventative care measures regarding patients displaying sarcopenia and SO, by increasing muscle mass while decreasing fat volume.

References: 1. Chun-Wei L+. Journal of the Cachexia Sarcopenia Muscle. 2022

	40-44	45-49	50-54	55-59	60-64	65-69
F/Fat/Arm	0.9971±0.6300	1.0314±0.6323	1.0719±0.6210	1.0822±0.6123	1.0869±0.5755	1.0819±0.5444
F/FF/Arm	1.6694±0.3302	1.6976±0.2969	1.7064±0.2967	1.7079±0.30184	1.7123±0.3054	1.706±0.3320
F/Fat/Leg	3.6207±1.4633	3.7531±1.4612	3.9011±1.4592	3.9788±1.4598	4.0578±1.4194	4.0558±1.3759
F/FF/Leg	5.6084±1.0420	5.6585±0.9205	5.6322±0.9251	5.5758±0.9486	5.5410±0.9635	5.4960±1.0147
F/Fat/Trunk	4.6573±2.1523	4.8128±2.0905	5.0569±2.0816	5.1582±2.0345	5.2297±1.9742	5.2491±1.9165
F/FF/Trunk	9.3161±1.6087	9.4174±1.3819	9.3934±1.3792	9.3449±1.4220	9.3278±1.4676	9.2679±1.5589
M/Fat/Arm	0.6825±0.3203	0.6979±0.3308	0.7154±0.3500	0.7155±0.3432	0.7108±0.3242	0.7025±0.3089
M/FF/Arm	2.4115±0.4085	2.3995±0.4143	2.3781±0.4286	2.3385±0.4373	2.2954±0.4444	2.2321±0.4584
M/Fat/Leg	1.8703±0.8352	1.9341±0.8648	1.9986±0.8914	2.0118±0.8747	2.0548±0.8728	2.0216±0.8279
M/FF/Leg	7.0563±1.0800	7.0023±1.1032	6.9333±1.1613	6.8048±1.2073	6.6780±1.2453	6.5173±1.2969
M/Fat/Trunk	3.9540 ±1.5800	4.1374±1.6329	4.3393±1.7041	4.4599±1.7315	4.5677±1.7304	4.6615±1.7259
M/FF/Trunk	11.1900±1.5772	11.2260±1.5822	11.2263±1.6406	11.1749±1.7222	11.1204±1.8072	11.0063±1.9435

Figure 1: Fat and Fat-Free Mass for Male and Female all Ages

Female (F), Male (M), Fat-Free (FF)