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Letter to the Editor

Expanding on Gut Microbiota Insights in Sarcopenia and Osteoporosis

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Dear Editor,

We read with great interest the comprehensive systematic review and meta-analysis by Lu et al. investigating disease-associated and shared gut microbes in sarcopenia (SP) and osteoporosis [1]. The study provides a valuable synthesis of current evidence, highlighting overlapping microbial signatures such as the enrichment of *Eggerthella*, a genus often linked to increased systemic inflammation and the production of pro-inflammatory metabolites that may accelerate tissue catabolism, and depletion of *Lachnospiraceae* and *Blautia*, and suggesting common metabolic disruptions in purine, pyrimidine, and cysteine/methionine metabolism as inferred from functional prediction tools. While the authors have made significant strides in consolidating this complex field, we believe several avenues warrant further exploration to fully harness the potential of gut microbiota research in these interconnected conditions.

Firstly, the concept of osteosarcopenia, the comorbidity of SP and OP, represents a distinct clinical challenge [2]. The current meta-analysis, by examining SP and OP separately before identifying shared features, infers mechanisms rather than directly characterizing the unique microbial landscape of osteosarcopenia. Future research designs would benefit from directly comparing four groups: healthy controls, isolated SP, isolated OP, and co-occurring osteosarcopenia. Such an approach could reveal specific microbial alterations or synergistic effects unique to the combined condition, potentially offering more targeted therapeutic strategies for this vulnerable patient population.

Secondly, the current findings, while robust in identifying differential abundance, primarily focus on the presence or absence of disease. A deeper understanding of the dose-response relationship between specific microbial taxa and the severity of musculoskeletal decline is crucial [3]. For instance, does the abundance of *Eggerthella*, a pro-inflammatory genus producing metabolites such as TUDCA [4], correlate with lower bone mineral density or muscle strength metrics? Investigating continuous associations between microbial profiles and quantifiable disease severity indices (e.g., grip strength, gait speed, femoral neck BMD T-scores) in future longitudinal studies or through individual participant data meta-analyses would provide more nuanced insights into disease progression and could establish microbial biomarkers for monitoring therapeutic efficacy.

Finally, the authors acknowledge the limitations of functional predictions based on 16S rRNA sequencing. While tools like PICRUSt and Tax4Fun offer valuable hypotheses, their accuracy is inherently constrained by the genus-level resolution of 16S rRNA data. This taxonomic limitation is particularly evident in the case of *Bacteroides vulgatus* (*B. vulgatus*). Although they identified *B. vulgatus* as enriched in OP, the biological impact of this

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species is highly strain-dependent and functionally Janus-faced. According to recent research, while some strains are associated with pro-inflammatory responses in colitis, others, such as *B. vulgatus* FTJS7K1, exert protective effects by secreting short-chain fatty acids (SCFAs) and modulating regulatory T cell (Treg) proportions to suppress systemic inflammation [5]. Such crucial functional nuances are entirely obscured by genus-level or even species-level data. To advance our understanding, future studies should prioritize species-level or even strain-level resolution, ideally coupled with shotgun metagenomics and untargeted metabolomics. Validating the predicted functional pathways with actual measured metabolites (e.g., specific amino acids, purines, pyrimidines) in biological samples would provide a more direct and reliable link between the gut microbiota and the host's physiological state in SP and OP.

In conclusion, the work by Lu et al. lays a strong foundation. By focusing on the unique profile of osteosarcopenia, exploring microbial dose-response relationships, and employing higher-resolution multi-omics approaches for functional validation, future research can unlock more precise mechanistic insights and pave the way for more effective, personalized interventions for sarcopenia and osteoporosis.

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