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Letter to the Editor

In reply to "Small, however significant differences in the definition of physical frailty and sarcopenia"

We thank Dr. Yilmaz and colleagues [1] for their comment that allows us to further clarify a major strength of the BIOSPHERE study [2]. Many operational definitions of frailty exist, each of them describing specific aspects of the condition and capturing different risk profiles. The two constructs mentioned by the authors (i.e., the phenotype proposed by Fried et al. [3] and the FRAIL criteria designed by Morley [4]) are not gold standards for the assessment of physical frailty, simply because no reference tool is recognized in this field. Furthermore, these instruments (as many other operational definitions of frailty) are unsuitable for use in clinical trials, especially those investigating biomarkers and/or testing pharmacological interventions. In fact, the wide and heterogeneous spectrum of confounders potentially biasing their results may affect the correct interpretation of an intervention effect or the identification of reliable biormakers. It is also noteworthy that the "traditional" models of frailty were not designed to focus on a specific "target organ" towards which drugs and biomarkers may be developed. For example, the frailty phenotype and/or the FRAIL scale include criteria measuring mood (i.e., fatigue), behavior (i.e., sedentariness), heterogeneous signs (i.e., weight loss), or nosological conditions (i.e., illnesses), which are only indirectly related with the skeletal muscle. It follow that, although designed to assess the physical domain of frailty, their defining criteria inevitably capture a syndromic and multidimensional entity.

The construct of Physical Frailty and Sarcopenia (PF&S) was specifically operationalized to overcome these limitations [5]. More in detail, PF&S was conceptualized in response to a call by the Innovative Medicines Initiative - Joint Undertaking (IMI-JU) [6], a pan-European public/private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associates (https://www.imi.europa.eu/). Indeed, the IMI-JU identified in the vagueness of existing frailty definitions the major obstacle for the development of novel therapeutic interventions tackling the age-related muscle decline, a major cause of disability in older persons and relevant burden for public health systems. To address this issue, the "Sarcopenia and Physical Frailty in Older People: Multi-component Treatment Strategies" (SPRINTT) consortium was established in order to develop an operational definition of PF&S meeting the stringent requirements of regulatory agencies, including the need of being agreed upon by relevant stakeholders (i.e., academia, industry, policy-makers, healthcare professionals, and older patients' representatives) and isolating the target organ at the basis of a clear and straightforward pathophysiological mechanism (i.e., skeletal muscle decline).

The PF&S concept, designed in SPRINTT and adopted in BIOSPHERE, finds its biological substratum in the skeletal muscle, which is objectively quantified by DXA [5]. The clinical manifestation of the condition of interest (i.e., the muscle impairment) is captured by means of the Short Physical Performance Battery (SPPB) [5], a well-established instrument for the assessment of lower extremity function (and a strong predictor of negative health-related outcomes in older persons) [7].

Although the SPPB is commonly neglected as a measure of frailty (probably because its development is antecedent the publication of the first formal operationalizations of this condition), it allows the detection of individuals with 1) reduced homeostatic reserves, 2) increased vulnerability to stressors, and 3) higher risk of incident negative outcomes; thus, it perfectly captures the very essence of frailty [8]. We strongly believe that SPPB represents a way to optimally measure the individual's physical frailty, even in a more objective way than traditional tools may do. In fact, it cannot be overlooked the fact that the SPPB is based on the quantification of standardized physical tests, whereas the constructs mentioned by Yilmaz and colleagues [1] largely rely on self-reported answers/questionnaires.

Finally, we point out that the robustness of our model is reflected by the methodological endorsement the PF&S definition has received by the European Medicines Agency, which has recognized the SPPB as an ideal marker for clinical trials on physical frailty [9]. Therefore, we are confident that the BIOSPHERE study is embracing a definition of physical frailty able to objectively capture the sarcopenia phenomenon in both its clinical and biological features [10]. The clarity of our model may support advancements in the study of sarcopenia pathophysiology and pave the way for future initiatives for tackling this burdensome age-related condition.

Competing interests statement

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