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Title: Pre-Frailty sub-phenotype exploration by a multidimensional approach for an earlier integrative diagnosis

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Frailty, a geriatric syndrome of physical vulnerability, is characterized by multi-system dysfunctions and increased risks of disability and mortality. As it represents a transition phase between successful aging and negative health outcomes, it is of great important to specifically diagnose and target it. In early phases, we hypothesize that different subpopulations of pre-frail patients exist, and that multidimensional biomarkers can be used to distinguish and stratify them, to optimize clinical follow up. This project combines multidisciplinary approaches to decipher the complex interactions between the early phase of this aging syndrome and phenotypes. Its objectives are: (i) to better define and understand the pre-frailty status and its phenotypes, (ii) to identify and validate multidimensional signatures of pre-frailty sub-phenotypes. Untargeted metabolomics performed on serum samples within the NU-AGE project, revealed presence of sub-phenotypes of pre-frailty both at the gender level and depending on the pre-frailty progression and reversibility. Additionally, early markers, able to predict the evolution towards pre-frailty within one year, were identified for both genders; and some of these early biomarkers were found to be still relevant for classification of a 'light pre-frail' phenotype after its clinical appearance (Pujos-Guillot *et al.*). These first results open the door to the possibility of monitoring the disease progression over time at a very early stage. Actually, this syndrome progression is studied in larger and deeply phenotyped populations, using a longitudinal analysis of individual time trajectories over 4 years, to detect early deviations of health status that would indeed contribute to a better disease prevention.

Pujos-Guillot, E.; Pétéra, M.; Jacquemin, J.; Centeno, D.; Lyan, B.; Montoliu, I.; Madej, D.; Pietruszka, B.; Fabbri, C.; Santoro, A.; Brzozowska, A.; Franceschi, C.; Comte, B. *Front Physiol.* 2019, 9, 1903.