Comment on: "What is aging-related disease? An epidemiological perspective" by Le Couteur and Thillainadesan

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Dear Editor,

We have perused with great interest the article by Le Couteur and Thillainadesan (1) who studied relationships between diseases and age from an epidemiological perspective. As Group A they identified diseases with an exponential increase with age -- such as major non-communicable diseases including ischemic heart disease -- and suggested them to be labelled as 'aging-related diseases'. In contrast to 'age-related disease', 'aging-related disease' implies that hallmarks of aging (i.e., genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication) are instrumental in the pathogenesis (2). Consequently, the occurrence of aging-related diseases should be universal and take place in all individuals who gain sufficiently life years.

However, we would argue that many non-communicable diseases are 'age-related' conditions in which risk factors rather than aging are driving the pathophysiology. Chronological age is routinely considered as the most powerful risk factor for non-communicable diseases like ischemic heart disease. While this may superficially be true, it is important to realize that the development of non-communicable diseases, where atherosclerosis is a frequent pathophysiological factor, is typically decades-long and chronological age may simply reflect the time of exposure to risk factors like hypertension and hypercholesterolemia. If these factors were prevented, disease incidence would not necessarily increase with age.

Proof for this concept may be driven from studies in traditionally living populations (3). One example is Tsimane, a population of forager-horticulturalists in Bolivian Amazon. In contrast to Westerners, they have minimal age-related increase of blood pressure (4) and in their natural environment have very low lifetime levels of low-density lipoprotein (LDL) cholesterol, low glucose, healthy body mass index, no smoking, and plenty of physical activity (5). Concomitantly, atherosclerosis and risk of cardiovascular disease, like ischemic heart disease, does not increase with age among Tsimane people (5).

For risk factors of non-communicable diseases to cause clinical condition, it is not only 'how high or low' but also 'how long' (6). This is reflected in genetically driven hypercholesterolemia (familial hypercholesterolemia, FH) and hypocholesterolemia (nonsense mutations in the proprotein convertase subtilisin/kexin type 9 serine protease [PCSK9] gene) starting in early life, and respectively high or low risk of ischemic heart disease. For FH, early correction of hypercholesterolemia prevents age-related risk of

ischemic heart disease (7) and with PCSK9 mutations long-term ischemic heart disease risk may be reduced as much as 88% (8).

We agree that biological aging *per se* (e.g. telomere attrition) could also contribute to vascular disease, especially in very old age (9). Further biological studies are needed as stated by Le Couteur and Thillainadesan. In general, however, we would argue that many non-communicable diseases are 'age-related' rather than 'aging-related' conditions. An important practical consequence is that while clinicians do not have proven 'anti-aging' drugs, they do have efficient, safe and currently also inexpensive options to treat risk factors, prevent or postpone many non-communicable diseases, with potential contribution to compression of morbidity (10).

Conflict of Interest: Dr Strandberg: Educational, consultative, and research collaboration with several companies (incl. Amgen, Novartis, NovoNordisk, OrionPharma, Sankyo, Sanofi) marketing cardiovascular drugs; a member in several boards preparing national treatment guidelines (Hypertension, Dyslipidemia, Memory disorders). Dr Kivimäki: No conflicts of interest.

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