Pathophysiological Mechanisms Explaining the Association Between Low Skeletal Muscle Mass and Cognitive Function, Susanne Janette Oudbier, et al., The Gerontological Society of America, May 18, 2022.

The central premise of this review is that low skeletal muscle mass is associated with cognitive impairment and dementia in older adults.

It proposes these underlying mechanisms, the central driving force in the overall pathophysiology being dysfunctional myokine secretion due to minimal physical activity.

1. **Systemic inflammation** - Normally, these myokines are released by physically active muscle and cross the blood-brain barrier. These myokines, now in the brain, cause expression of a factor (BDNF) that exerts anti-inflammatory effects that may provide protection in the brain.
2. **Insulin Metabolism** - This altered myokine secretion also leads to additional inflammation and impairs muscle glucose metabolism, which may affect insulin transport into the brain as well as overall hyperinsulinemia (too much insulin in the bloodstream) which may contribute to Alzheimer's Disease
3. **Protein Metabolism** - A negative systemic protein balance, commonly observed in older adults, contributes to low skeletal muscle mass and may also affect protein metabolism in brain tissues. The age-related decrease in protein synthesis comprises changes in protein folding, maintenance and breakdown throughout the body (and brain) which is common in several types of dementia.
4. **Mitochondrial function** - Dysfunctional mitochondria (the organelles that provide energy for muscle contractions) in skeletal muscle and the brain result in the excessive production of reactive oxygen species, which drives tissue oxidative stress and causes additional dysfunction in the mitochondria. Both oxidative stress and accumulation of mitochondrial DNA mutations due to aging drive cellular senescence (the ability of cells to divide and grow).

Although these mechanisms are described as separate entities, there is interplay between them. The authors hypothesize that altered myokine release from skeletal muscle is the key modulator of the four physiological hallmarks that accompany cognitive decline. Myokines cross-talk with other molecular players in the brain to exert positive effects on neurogenesis (the growth and development of nervous tissue), the nervous system development as a whole and neuroprotection - in response to exercise.

The key takeaway from this review is that the described mechanisms may lead to a negative spiral, in which cognitive impairment may further exacerbate (make the problem worse) the loss in muscle mass, and vice versa, and therefore, reverse causation cannot be excluded.

Physical inactivity is a major risk factor for sarcopenia (loss of muscle mass) and cognitive impairment, and most studies highlight the positive effects of physical activity on dementia and cognitive impairment.