

**UNIVERSITI TEKNOLOGI MARA**

**GUT MICROBIOTA AND  
INTESTINAL PERMEABILITY IN  
OLDER ADULTS AND THEIR  
ROLES IN COGNITIVE FRAILITY**

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## ABSTRACT

The rapid growth of the global ageing population has led to a surge in age-associated syndromes including cognitive frailty (CF). CF is characterised by the coexistence of physical frailty and mild cognitive impairment (MCI) without dementia, which poses major risks for mortality, hospitalisation, and reduced quality of life. Ageing is often accompanied by gut frailty, marked by low-grade inflammation and reduced gut microbiota diversity and composition (dysbiosis), which may impair brain function and increase susceptibility to CF. To date, there remains very limited integrative research in this area. The present study aimed at exploring the changes in gut microbiota as well as intestinal permeability and inflammatory markers in older adults through a multi-tiered research approach, which included systematic review and meta-analysis as well as comprehensive microbiome sequencing and statistical analyses. The present systematic review and meta-analysis found that previous studies on intestinal permeability in older adults ( $n = 10$ ) focused predominantly on faecal calprotectin (an intestinal inflammatory marker). Although elevated faecal calprotectin was consistently observed in cases (diseases) versus controls, findings on intestinal permeability markers such as alpha-1-antitrypsin and zonulin remain limited, inconsistent, and largely underexplored in the context of ageing. These findings highlight the urgent need for robust validation of faecal markers as surrogate tools for monitoring intestinal health in clinical practice. Building on these insights, a cross-sectional study of 231 community-dwelling older adults ( $\geq 60$  years), were stratified into young-old, middle-old, and oldest-old groups, which examined gut microbiota composition and diversity among age groups for identification of specific gut microbial taxa that mediate the relationships between age and parameters including intestinal permeability and inflammatory markers, as well as physical, psychosocial, and cognitive parameters in older adults. The present results indicated increased beneficial short-chain fatty acid (SCFA)-producing taxa (the phylum Bacillota and the genera *Megamonas*, *Bifidobacterium* and *Agathobacter*) in the young-old age group. Conversely, potentially pathogenic taxa, including CAG-352 (Ruminococcaceae Family) and species like *Bacteroides stercoris* and *Bacteroides thetaiotaomicron*, were enriched in the oldest-old group. Subsequent mediation analysis identified the phylum Bacillota as a mediator that linked age with LDL cholesterol and mobility decline, with its abundance further modulated by thyroid disease and thyroid therapy. Additionally, the genus *Collinsella* and its species *Collinsella aerofaciens* mediated associations between age and LDL cholesterol, influenced by lipid-modifying agents. While 16S rRNA gene sequencing offers insights into microbial composition, shotgun metagenomic analysis enabled a more comprehensive comparison between CF-related and robust older adults. Given the limited sample size of CF, individuals with CF and frailty alone were grouped under the term “CF-related”. Shotgun metagenomic analysis demonstrated that the CF-related group was enriched in genus *Faecalimonas*, whereas the robust group was presented with higher prevalent of the order composed of the genus *Taraxisvirus*. Predicted functional profiling showed the CF-related group to be associated with upregulated biofilm formation and redox regulation whereas the robust group to be associated with higher carbon and pyruvate metabolism. The CF-related group exhibited features displayed of stress-adaptive metabolism whereas the robust group retained pathways associated with efficient energy utilisation. Altogether, this study revealed distinct microbial and functional profiles in older adults of different age groups and between those who are robust and CF.

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# CHAPTER 1

## INTRODUCTION

### 1.1 Research Background

The global population is ageing rapidly, with the number of people aged 60 years and older projected to increase from 1 billion in 2020 to 1.4 billion by 2030 and thereafter double to 2.1 billion by 2050 (World Health Organization, 2024). The continuous growth of the ageing population is characterised by multimorbidity, as well as deteriorating physical and mental functions, raises concerns over the increased risks of age-associated syndrome especially cognitive frailty (CF), which poses challenges to the healthcare systems worldwide (Ansari *et al.*, 2022; Khan *et al.*, 2024). CF is defined as the coexistence of physical frailty and mild cognitive impairment (MCI) in the absence of dementia, based on the consensus of the International Academy of Nutrition and Ageing (IANA) and the International Association of Gerontology and Geriatrics (IAGG). Individuals with CF are particularly vulnerable to adverse health outcomes, including increased risk of hospitalisation, institutionalisation, long-term care dependency, and mortality (Bu *et al.*, 2021; Miri *et al.*, 2024; Rivan *et al.*, 2021; Tang *et al.*, 2023; Yarnall *et al.*, 2017).

As one ages, the intestinal barriers, which is made up of adhesive mucous layer, immunoglobulin A, antibacterial peptides, intercellular tight junctions and several barrier components (Neurath *et al.*, 2025; Suzuki, 2020), become more vulnerable, leading to increased intestinal permeability, also known as the "leaky gut" (Di Vincenzo *et al.*, 2023; Walrath *et al.*, 2021). In fact, the ageing process is associated with a diminished mucus layer in the gut, exposing the intestinal epithelium to a barrage of microorganism responses (Branca *et al.*, 2019). The increased intestinal permeability can be caused by both endogenous factors, such as psychological stress and intestinal inflammation, and exogenous factors, including diet and alcohol intake (Vanuytsel *et al.*, 2021). More specifically, inflammation, which is one of the seven evolutionarily conserved hallmarks of ageing and a common feature of age-related disorders (Franceschi *et al.*, 2018; Li *et al.*, 2023), increases intestinal permeability by promoting the migration of leukocytes to the mucosal layer, leading to their leakage into the intestinal lumen (Schwiertz *et al.*, 2018).