Review Article

Malnutrition and Fragility: From Children to Elderly with Probiotics

Margarita J Salvatella-Flores[1*] and Luis G Bermúdez-Humarán[2*]

[1]Pediatra, Neonatóloga, UNAM, Mexico

[2]Université Paris-Saclay, INRAE, AgroParisTech, Micalis Institute, Jouy-en-Josas, France

[*]**Corresponding Authors**: Margarita J Salvatella-Flores, Pediatra, Neonatóloga, UNAM, Mexico, Tel: 55 20653620; E-mail: doctorasalvatella@yahoo.com.mx

Luis G Bermúdez-Humarán, Université Paris-Saclay, INRAE, AgroParisTech, Micalis Institute, 78350, Jouy-en-Josas, France, Tel: +33 134652463; Fax: +33 134652462; E-mail: luis.bermudez@inrae.fr

Received: 26 October 2020; **Accepted:** 05 November 2020; **Published:** 20 November 2020

Citation: Margarita J Salvatella-Flores and Luis G Bermúdez-Humarán. Malnutrition and Fragility: From Children to Elderly with Probiotics. Archives of Clinical and Biomedical Research 4 (2020): 709-720.

Abstract

The great economic and social disparities, as well as the climatic changes which have caused natural disasters and migration in numerous parts of the planet, have greatly contributed to the increase in malnutrition around the world. Moreover, as if that were not enough, the Declaration of Alma Ata to the Millennium Declaration (in order to reduce poverty and related pathologies such as malnutrition) have not presented satisfactory results yet. Therefore, this review will resume the scientific papers about malnutrition. One of the most serious expression of malnutrition is emaciation or Kwashiorkor, which affects the vulnerability of the individuals from childhood, in most cases, until old age. The keyword global malnutrition, will be linked to the use of probiotics as a preventive way to reduce vulnerability (in children) and frailty (frailty syndrome in the elderly). In this type of patients, there are a susceptibility to other pathologies, especially contracting infections as a result of malnutrition. If an adequate gut microbiota (ecological communities of commensal, symbiotic and pathogenic microorganisms found in the gastrointestinal tract) has been established since childhood, the response to

medical treatments and recovery in the elderly stage would probably be better and therefore it would reduce the possible complications and disabling side-effects, of a timely manner. The risk of malnutrition coupled with the frailty syndrome, with a history of a poor microbiota during childhood, can make it difficult for the patient to recover and even lead to death. In contrast, the administration of probiotics can make the intervention timelier and avoid severe complications, even with a fatal outcome.

Keywords: Malnutrition; Elderly; Frailty; Kwashiorkor; Microbiota; Probiotics

1. Introduction

According to the World Health Organization (WHO), the United Nations General Assembly, in 2016, declared the “United Nations Decade of Action on Nutrition 2016-2025” (WHO, 2020), in which, the doors are opened to join efforts against any form of malnutrition, including malnutrition from childhood to that of the elderly in both genders [1-3]. In this review, we summarize the bibliography (made by reviewing international databases) about world malnutrition and probiotics use, which emphasizes fragility and malnutrition during the elderly and their prevention with probiotics from childhood. Forty-one articles with the words "malnutrition in the world and probiotics" were reviewed in the PubMed database. Five articles were discarded because they were not related to the topic. The search was supplemented, reviewing 60 articles in total. Malnutrition in childhood is briefly mentioned to explain why it should be prevented at this stage, depending on the intestinal microbiota, with a view to old age and the importance of the indication of the use of probiotics in a timely manner [1]. The great economic and social inequalities worldwide, as well as the climatic changes that have caused disasters and migrations in many places of the planet, have contributed to the increase in malnutrition throughout the world. From this perspective, this review will summarize malnutrition, with a particular emphasis to emaciation or Kwuashiorkor, the most serious expression of malnutrition. In malnourished patients, there is susceptibility to other diseases, especially to contracting infections and developing other non-infectious pathologies, derived from malnutrition, for which the intestinal microbiota plays an important role.

2. Epidemiology

2.1 Malnutrition in childhood

Malnutrition [4] is a situation in which there is an imbalance of energy, macro and micronutrients that affect the health of the individual, due to a poor intake of them or a deficit in their absorption, causing an inadequate energy metabolism. In addition, excess consumption of nutrients causes obesity, which is the other extreme of malnutrition, consequently generating disease [4]. The United Nations Children's Fund (UNICEF) [5], the World Health Organization (WHO) [5] and the World Bank (WB) [5], in 2017, reported: "155 million children under 5 years of age who were stunted in 2016 and 52 million were wasted, of which 17 million were severely wasted. "However, in the 2020 edition [6], the reports have a slight decrease in the previous figures, but now increasing one more range, that of obesity. The quote verbatim says [6]: "144 million children under 5 are stunted, 47.0 million children under 5 are wasted, of which 14.3 million are severely emaciated and 38.3 million are overweight "(UNICEF) [6]. In both

children and the elderly, malnutrition [7] is significantly related to low socioeconomic status [7]. Protein-caloric malnutrition, called Marasmus [8], is clinically characterized by loss of muscle mass and adipose tissue, with large-appearing eyes due to the thinness of the muscle and adipose tissue. Patients are listless, irritable, and their skin is flabby. In malnutrition characterized as Kwashiorkor [8], in addition to the loss of protein that is even more important than the general loss of calories present in marasmus, there is a state of hypoalbuminemia and hemodilution, which generates edema and may present anasarca. Several organs present atrophy, hepatic steatosis (fatty liver) and oral fissures, immunodeficiency and concomitant infections. Chronic malnutrition causes a state of chronic inflammation, alterations in neuronal maturity with specific involvement of the cognitive area and concomitant metabolic alterations [8].

Children under 5 years of age [9] suffer the worst and most serious forms of severe malnutrition, which includes malnutrition resulting from long-term poverty [10], including maternal and child malnutrition, due to poor hygiene conditions and sanitation, a shortage of nutrients, as well as exposure to infections and environmental aggressions. Environmental malnutrition in children leads them to a state of vulnerability, which can lead to death [9-10].

It is well known that from the birth of the human body, there is also bacterial colonization, which strengthens the immune response and allows the maturation of various organs and systems [11]. The role of the microbiota through its metabolites, against toxic agents through fermentation, constitutes an important defense for the host since childhood [11]. After birth, the intestinal microbiota acquires its more or less fixed constitution [12], in the host, after 3 years of age, if it does not suffer any alteration due to other causes [12]. This link between microorganisms and the gut microbiota is relevant for the maturation of many functions of their organs and systems [13], as well as for the behavior and maturation of the nervous system. Therefore, all these functions are bioadaptive in co-participation with nature through the intestinal microbiota, being reflected in old age [13].

Malnutrition manifested since childhood [14], has some determining factors to delay linear growth in children with severe to moderate diarrhea. From very early stages of life there is an opportunity to prevent linear growth retardation [14], since malnutrition can cause serious consequences such as the lack of immune defenses against a pathogen that causes diarrhea and that will probably trigger a delay in growth [14]. In Bangladesh, Sánchez et al. [15], publish domestic factors associated with the presence of Campylobacter. They found that Campylobacter is negatively associated with the growth of children between 12 and 21 months of age, as well as with the use of antibiotics and treated water [15]. According to the United Nations Children's Fund (UNICEF) [16] and the World Health Organization (WHO) [17], there is a “decrease in the prevalence of stunting.” In a study on the prevalence of stunting [18], it is mentioned that it decreased from 39.7% in 1990 to 22.2% in 2017. However, Asian and sub-Saharan African children presented [19], stunting in a third of all children [16-19].

The transformation of the planet has been seen with climate change and subsequent infections with various viruses [19, 20], HIV, Zicca, Ebola, etc. Also infestations by parasites, or by bacilli such as Tubercusosis [21], gastrointestinal infectious diseases [22-25] and more recently the Coronavirus, Sars-Cov 2, Covid 19 [19-26].

In general, Reiten and Bremer [19], raise multiple questions about malnutrition and decreased growth and wonder why some individuals have it and others do not, and about the role of inflammation, immunity and the intestinal microbiome.

2.2 Malnutrition and frailty in older adults

It is known that malnutrition [27] is widespread throughout the world, including elderly individuals, since the population of the elderly over 65 years now occupies 8.5% of the world population, but with the eve of double in 2050 [27]. On the other hand, in the elderly, malnutrition constitutes a great vulnerability, over a deteriorated immune system. The "frailty" in the elderly or Frailty Syndrome [28], is defined as a state of low organic reserve of the individual in the senile stage, due to aging, associated with the decrease in the functions of multiple organs and systems, therefore that the ability to respond to aggressive factors, internal and external, is also diminished [28]. Frailty denotes vulnerability generated by multiple diseases, among them, frequently as a basis, malnutrition and other disabilities due to age [28]. Both situations, malnutrition and frailty, cause a significant deterioration of vital functions for one's own health [29], susceptible to infection, which in most cases, has a fatal outcome [29].

An association of approximately 80% [30] has been found between protein-energy malnutrition and frailty in adults over 80 years of age. 15% of older adults in the United States [31] present fragility or vulnerability when falling ill, which in most cases triggers disability. Globally, the range is 3.5% to 27% [30, 31]. Malnutrition in the elderly [30, 32] occurs 15% in outpatients, 35%-65% in hospitalized patients, 24%-74% in institutionalized frail elderly [30, 32]. The prevalence differs in the different countries of the European Union [33], for example, in Spain it is 15.2%, but in Switzerland it is 37.7%, and it is associated with other factors but is highly variable between each country [33].

Furthermore, the “Frailty Syndrome” presents alterations in cognition and psychosocial deterioration [34]. Vulnerability in the elderly causes the loss of the functions of their organs and systems, which at the time of infection [35], are more susceptible to infection and have a higher risk of dying. However, the intervention of an adequate microbiota is correlated with a better immune response to influenza vaccination [34, 35]. It is important to know the main causes of vulnerability or "frailty" in older people, to control them and, if possible, prevent them [36]: "i) neurological control ii) mechanical performance iii) energy metabolism" [36].

Considering this situation and the global increase in malnutrition problems, as well as a much larger demographic explosion [36, 37], it is estimated that by the year 2050, the world population of adults over 60 years of age will increase from 900 million to 2000 million, that is, it will be 22% of the world's population. We must consider in the future what our

position should be regarding the prevention of these 3 factors that surround frailty due to malnutrition in old age [36, 37]. If we analyze these concepts in depth, from the neurological point of view, we know that there are diseases of the elderly, such as neurodegenerative diseases [38, 39], among them, Alzheimer's disease (AD) or Parkinson's disease (PD), which have a preclinical antecedent in the conformation of the intestinal microbiota, several years before manifesting in senescence. Up to 20 to 30 years before the onset of the clinical manifestations of neurodegeneration [38-40].

On the other hand, we have updated knowledge on the salutogenic effects of some bacteria of the intestinal microbiota [41], and of certain prevalent pathogens in it, which block normal physiological and metabolic pathways in the processing of some metabolites, giving rise to pathways erratic in protein formation and therefore in a defective accumulation of amyloid protein in specific areas of the brain, specifically in neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amniotrophic lateral sclerosis (ALS), which certainly involve serious motor disability problems, almost in all of them. In AD and PD [41], cognitive, sensory and non-sensory disabilities such as gastroparesis also occur. (Friedland and Chapman) [41].

There are 5 characteristic elements [42-44] of frailty in the elderly: i) weakness, slowness, exhaustion, low activity and weight loss; ii) fragility in mechanical performance, as a consequence of malnutrition and the series of concomitant degenerative pathologies during senescence, exacerbated in neurodegenerative problems; iii) the energy metabolism of the elderly is vulnerable, since both in malnutrition and in senescence, there are significant alterations in it, most of the time creating a state of inflammation [42], secondary to malnutrition and deterioration of the immunity, as well as atrophy. They also have a decrease in bone quality, secondary to osteoporosis [45], frequent at that age, so the fear of suffering repetitive falls causes fear to move, to avoid consequences and this in turn causes another series of complications [42-45].

2.3 Microbiota and intestinal inflammation

The human body [46] is the host of millions of microorganisms, among which are bacteria, viruses, fungi, archaea and protozoa, which constitute important ecological groups, where approximately 10^{13} to 10^{14} number of bacteria reside, of which approximately 1000 species, constitute the intestinal microbiota. Said microbiota generally remains stable; however, internal and external changes to the body, often secondary to a catastrophe such as malnutrition [46], or infectious processes, can lead to significant dysbiosis that in turn generate other types of pathologies [46]. Approximately [47], up to 30% of the energy from indigestible proteins and carbohydrates, upon reaching the colon, can be digested by anaerobic bacteria, due to the action of the enzymes that they release, so they can be metabolized and absorbed. In the state of malnutrition, where nutrient intake is low [47], are released, especially proteins, cytokines, tumor necrosis factor (TNF), IL-1 and IL-6. During stress [47], adipose tissue recruits immune cells, creating an inflammatory process that generates metabolic alterations [47].

Protein malnutrition generates [48]: hypoproteinemia, hypoalbuminemia, hypoglycemia, growth retardation and generalized edema. Furthermore, not only protein deficiency causes Kwuashiorkor, but also dysbiosis of the intestinal microbiota, which causes alterations in the lining of the intestinal epithelium [48]. By impairing immunity, the malnourished patient is easily infected, leading to acute inflammation, for example, persistent or rotavirus infections, salmonellosis, or parasitic infections, such as amebiasis, which in turn cause intestinal malabsorption [48].

2.4 Microbiota and childhood and its impact on senescence

Gopalakrishna [49], states that at birth, depending on the route of delivery (vaginal or cesarean section), Bacteroides and Lactobacillus, (vaginal) or Enterobacteriaceae, Enterococcacea (cesarean section) may prevail. Bacteroides and Firmicutes are part of the usual colonization of children 3 years and older, being necessary for the production of short chain fatty acids (SCFA). However, the microbiota can be modified by the type of diet, by the administration of antibiotics and multiple external factors of the environment [49]. The colonization of the intestine by the intestinal microbiota [50] establishes a communication in time with the immune system, which allows in other stages of life, such as senescence, a better defense against external factors that cause the disease, previously mentioned [50]. During senescence [50], immunity is influenced by T-cells, which recognize exogenous antigens such as lipopolysaccharides generated by Gram negative bacteria; IgE immunoglobulins produced by B cells, regulatory T cells, and TLR signaling [50]. Neurodegenerative diseases, to a large extent, have their origin precisely in the alterations of the intestinal microbiota during childhood [41].

2.5 Prevention

With the aforementioned, we can ask ourselves how to prevent dysfunctions secondary to malnutrition in childhood and the dysfunctions of old age, with adequate nutritional support during the first years of life. However, given the lack of it and with it the implantation of dysbiosis, the use of probiotics would facilitate the establishment of an adequate intestinal microbiota, in order to improve the type of microorganisms that can establish survival mechanisms in emerging situations such as malnutrition. It is a fact that there are great deficiencies in the world that have caused alarming numbers of malnutrition in childhood, the problem is that not everyone has the opportunity to regain their health with food and appropriate treatments to improve their functions. Therefore, given the deficiency and the significant damage caused by malnutrition, the administration of probiotics would greatly facilitate a timelier restoration of the intestinal microbiota and therefore the prevention of consequences and complications derived from the same situation, upon reaching the third Age.

Even the application of oral vaccine [51], may be less effective in inducing immunogenesis than the proper intestinal microbiota [51]. The intestinal microbiota administered through probiotics [52, 53], is capable of positively modulating the organic functions of the host and modulate its influence on health and disease [52, 53]. Bacteria with salutogenic effects [54], administered through probiotics, would prevail and benefit the host, preventing or reducing problems health problems that occur in old age, as a

consequence of the persistence of an altered intestinal microbiota, of little benefit, installed in the host since childhood [54]. Likewise, the prevalence of pathogenic microorganisms would be transformed, by microorganisms with beneficial effects, within the intestine. This is very important, since once malnutrition is installed, its integral recovery only with diet, would be much more difficult and it would take longer to recover, therefore it would not be effective to recover the decrease in muscle strength and all the Physiological processes to maintain health in balance [54]. This fact would justify the study and administration of probiotics, from infancy to old age, especially in the presence of malnutrition and Frailty Syndrome.

Among the strategies, on interventions to treat frailty syndrome [55], we can find those referring to the care of "frailty" in the elderly, which manifest in such a way that they can be fatal. However, in none of them, the prevention or reduction of the severity of neurodegeneration is mentioned, improving the intestinal microbiota. The use of probiotics is not the only prevention tool to improve the quality of life in adulthood, since there are more tools such as exercise [55], which is another important prevention factor. However, the use of probiotics is one of the most studied and easiest to administer strategies [55].

2.6 Gut dysbiosis-related diseases

Some diseases linked to dysbiosis [56] include several pathologies associated with old age, such as chronic autoimmune and inflammatory diseases, diabetes mellitus and cancer [56]. Some bacteria are able to produce bacteriocins (*eg. Lactobacillus salivarius*), which neutralize the action of pathogen microorganisms such as *Listeria monocytogenes* [57], with the use of antibiotics, during old age. On the other hand, bacteria such as *Enterococcus faecium* and *Kebsiella* create resistance [57], which is why they are immune to antibiotics, colonizing the intestinal lumen in patients with fragility. This pathogenic colonization, hematogenously invades other organs, causing sepsis and, on some occasions, leads to multiple organ failure and death [57].

2.7 Microbiome metabolites in the host

It is said that [58, 59], that approximately 10 million genes make up the gut microbiome. The way in which the intestinal microbiome protects the host is through its different metabolites [58-60], which have effects on it, modifying bile salts, preventing the erosion of the gastrointestinal epithelial barrier, also preventing damage to the DNA. The prevalence of pathogenic microorganisms acts in the opposite direction to the aforementioned forms of prevention. There are many more mechanisms of pathogenic action, in the absence of beneficial microorganisms, that counteract the pathogenic effects, however it will be analyzed in another context [58-60].

3. Discussion

Many questions remain to be resolved, especially in the host's response to the same gut microbiota, which should be strengthened with further studies. There has really been no preventive planning in the administration of probiotics in the elderly, despite the growing increase in this population, neither at the institutional level, nor in the general population, since there has been none since childhood, only in some institutions.

4. Conclusion

Malnutrition is increasing in the world. It is characterized by a state of vulnerability in childhood and in the elderly, it generates fragility or frailty syndrome to which many other diseases are added. Malnutrition in adults is closely related to the microbiota established during childhood. Therefore, it is much more efficient and effective to maintain an adequate microbiota from the first stages of life, in order to recover the damage caused by malnutrition in a timely manner, preventing morbidity and mortality at this stage of life. The older adult represents our living history, not the end of its history. As we know and understand more, the total importance of the individual throughout its life cycle, both human and microorganisms, we will understand more about the bioadaptive bond of life. Respect for nature, the environment, the human being and knowledge are essential to achieve a better evolution.

References

1. https://www.paho.org/hq/dmdocuments/2012/Alma-Ata-1978Declaracion.pdf.
2. https://www.onu.org.mx/agenda-2030/objetivos-de-desarrollo-del-milenio/.
3. https://www.who.int/es/news-room/fact-sheets/detail/malnutrition.
4. Siddiqui F, Salam RA, Lassi ZS, Das JK. The Intertwined Relationship between malnutrition and poverty 8 (2020): 453.
5. United Nations Children's Fund, World Health Organization and World Bank Group. Joint Child Malnutrition Estimates 2017. WHO; 2017.
6. https://www.who.int/news/item/31-03-2020-unicef-who-wb-jme-group-new-data
7. Flannery JE, Stagaman K, Burns AR, et al. Gut feelings begin in infancy - the gut metagenome correlates with early environment, care, and behavior. MBio 11 (2020): e02780-19.
8. Ibrahim MK, Zambruni M, Melby CL, Melby PC. Impacto de la desnutrición infantil en la defensa y la infección del huésped. Clin Microbiol Rev 30 (2017): 919-971.
9. Bhutta ZA, Berkley JA, Bandsma RHJ, Kerac M, Trehan I, Briend A. Severe child malnutrition. Primers Nat Rev Dis 3 (2017): 17067.
10. Flannery JE, Stagaman K, Burns AR, et al. Gut feelings begin in infancy - the gut metagenome correlates with early environment, care, and behavior. MBio 11 (2020): e02780-19.
11. Bulgart HR, Neczypor EW, Wold LE, Mackos AR. Microbial participation in the development and progression of Alzheimer's disease. Mol Neurodegener 15 (2020): 32.
12. Bermúdez H LG, Salinas E, Ortiz GG, Ramirez-Jirano LJ, Morales JA, Bitzer-Quintero OK. From probiotics to psychobiotics: live beneficial bacteria that act on the brain-gut axis. Nutrients 11 (2019): 890.
13. Leung K, Thuret s Gut microbiota: a modulator of brain plasticity and cognitive function in aging. Health (Basel) 3 (2015): 898-916.
14. Brander RL, Pavlinac PB, Walston JL et al. Determinants of linear growth retardation in children with moderate to severe diarrhea in

the Global Enteric Multicenter Study. BMC Med 17 (2019): 214.

15. Sánchez JJ, Alam A, Stride CB, et al. Campylobacter infection and household factors are associated with child growth in urban Bangladesh: an analysis of the MAL-ED study. PLoS Negl Trop Dis 14 (2020): e0008328.
16. UNICEF and WHO: World Bank Group Child Malnutrition Estimates: Levels and Trends (2019 Edition) [(cited 2019 Nov 15)]; Available online Prevalence and trends of stunting among preschool-age children, 1990-2020.
17. OMS / FAO. Healthy and nutritional properties of powdered milk with live lactic acid bacteria. Córdoba, Argentina: WHO / FAO; 2001
18. De Onis M, Blössner M, Borghi E. Public Health Nutr 15 (2012): 142-8.
19. Raiten DJ, Bremer AA. Exploring the nutritional ecology of stunting: new approaches to an old problem. Nutrients 12 (2020): 371.
20. UNICEF and WHO: World Bank Group Child Malnutrition Estimates: Levels and Trends (2019 Edition) [(cited 2019 Nov 15)]; Available online Prevalence and trends of stunting among preschool-age children, 1990-2020.
21. Omoni AO, Ntozini R, Evans C, Prendergast AJ, Moulton LH, Christian PS, Humphrey JH. Child growth according to maternal and child HIV status in Zimbabwe. Pediatric Infect Dis J 36 (2017): 869-876
22. Prendergast AJ, Humphrey JH. The stunting syndrome in developing countries.Paediatr Int Child Health 34 (2014): 250-65.
23. Tickell KD, Atlas HE, Walson JL. Environmental enteric dysfunction: review of possible mechanisms, consequences, and management strategies.BMC Med 17 (2019): 181.
24. Villapol S. Gastrointestinal Symptoms Associated With COVID-19: Impact on the Gut Microbiome. Transl Res August 20, 2020.
25. Crane RJ, Jones KD, Berkley JA.Environmental enteric dysfunction: an overview. Nutr Bull food. 36 (2015): S76-87.
26. Owino V, Ahmed T, Freemark M, Kelly P, Loy A, Manary M, Loechl C. Environmental enteric dysfunction and growth retardation in global child health. Pediatrics 138 (2016).
27. He W, Goodkind D, Kowal P. An Aging World: 2015. In: Bureau USC, editor. International Population Reports, P95 / 16-1. Washington, DC: US Government Publications Office; 2016
28. Xue QL. The frailty syndrome: definition and natural history.Clin Geriatr Med 27 (2011): 1-15
29. Dwyer JT, Gahche JJ, Weiler M, Arensberg MB. Detection of malnutrition and frailty in older adults living in the community: update and next steps. J Community Health 45 (2020): 640-660.
30. Verlaan S, Ligthart-Melis GC, Wijers JLJ, Cederholm T, Maier AB, de van der Schueren MAE. High prevalence of physical frailty among malnourished older adults

living in the community: a systematic review and meta-analysis. Journal of the American Association of Medical Directors 18 (2017): 374–382.

31. Bandeen-Roche K, Seplaki CL, Huang J, Buta B, Kalyani RR, Varadhan R, Xue QL, Walston JD, Kasper JD Fragility in Older Adults: A Nationally Representative Profile in the United States. J Gerontol A Biol Sci Med Sci 70 (2015): 1427-34.
32. Marco J, Barba R, Zapatero A, Matía P, Plaza S, Losa JE et al. Prevalence of the notification of malnutrition in the departments of internal medicine and its prognostic implications. Clin Nutr 30 (2011): 450–4.
33. Leij-Halfwerk S, Verwijs MH, van Houdt S, Borkent JW, Guaitoli PR, Pelgrim T, Heymans MW, Power L, Visser M, Corish CA, de van der Schueren MAE; MaNueL Consortium. Prevalence of protein-energy malnutrition risk in European older adults in community, residential and hospital settings, according to 22 malnutrition screening tools validated for use in adults ≥65 years: A systematic review and meta-analysis. Maturitas 126 (2019): 80-89.
34. Gordon SJ, Baker N, Kidd M, Maeder A, Grimmer KA. Pre-frailty factors in people aged 40 to 75 living in the community: opportunities for successful aging. BMC Geriatr 20 (2020): 96.
35. Bartley JM, Zhou X, Kuchel GA, Weinstock GM, Haynes L. Impact of age, caloric restriction, and influenza infection on the mouse gut microbiome: an exploratory study of the role of age-related microbiome changes in responses to influenza. Front Immunol 8 (2017): 1164.
36. Buchner DM, Wagner EH. Preventing frail health. Clin Geriatr Med 8 (1992): 1-17
37. https://www.who.int/features/factfiles/ageing/ageing_facts/en/
38. Peng B, Yang Q, Joshi R B, et al. Role of alcohol consumption in Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Int J Mol Sci 21 (2020): 2316.
39. Ma Q, Xing C, Long W, Wang HY, Liu Q, Wang RF. Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis. J Neuroinflammation 16 (2019): 53.
40. Nagpal R, Neth BJ, Wang S, Craft S, Yadav H. The modified Mediterranean ketogenic diet modulates the gut microbiome and short-chain fatty acids in association with markers of Alzheimer's disease in subjects with mild cognitive impairment. EBioMedicine 47 (2019): 529-542.
41. Friedland RP, Chapman MR. The role of microbial amyloid in neurodegeneration.Neurological deterioration in these elderly patients, linked to a chronic history of dysbiosis, in turn generates frailty syndrome. PLoS Pathog 13 (2017): e1006654.
42. Fried LP, Walston J. Frailty and Failure to Thrive. In: Hazzard WR, et al., Editors. Principles of Geriatric Medicine and Gerontology 4 (1998): 1387-1402.
43. Walston J, Buta B, Xue QL. Frailty Detection and Interventions: Considerations for Clinical Practice. Clin Geriatr Med 34 (2018): 25-38.

44. Kamada N, Seo SU, Chen GY, Núñez G. Role of the intestinal microbiota in immunity and inflammatory diseases. Nat Rev Immunol 13 (2013): 321-35.
45. Amarilla DF, Roncero MR, Lavado GJ, Toribio FR, Morán G J, López EF. Quality of life after hip fracture: a 12-month prospective study. Peer J 8 (2020): e9215.
46. Kim D, Zeng MY, Núñez G. The interaction between host immune cells and the intestinal microbiota in chronic inflammatory diseases. Exp Mol Med 49 (2017): e339.
47. Grant RW, Stephens JM. Fat in flames: influence of cytokines and pattern recognition receptors on adipocyte lipolysis. Am J Physiol Endocrinol Metab 309 (2015): E205-E213.
48. Vlasova AN, Paim FC, Kandasamy S, et al. Protein malnutrition modifies innate immunity and gene expression by intestinal epithelial cells and human rotavirus infection in neonatal gnotobiotic pigs.mSphere 2 (2017): e00046-17.
49. Gopalakrshna KP, Mano TW. Influence of breast milk on the neonatal gut microbiom. Nutrientes 12 (2020): 823.
50. Gensollen T, Iyer SS, Kasper DL, Blumberg RS. How colonization by microbiota in early life shapes the immune system. Science 352 (2016): 539-544.
51. Parker EP, Ramani S, Lopman BA, et al. Causes of impaired oral vaccine efficacy in developing countries. Future Microbiol 13 (2018): 97-118.
52. Nataraj BH, Ali SA, Behare PV, Yadav H. Postbiotics-parabiotics: los nuevos horizontes en bioterapia microbiana y alimentos funcionales. Hecho de células microbianas 19 (2020): 168.
53. Sánchez B, Delgado S, Blanco-Míguez A, Lourenço A, Gueimonde M, Margolles A. Mol Nutr Food Res 61 (2017).
54. Payette H, Boutier V, Coulombe C, Gray-Donald KJ Benefits of nutritional supplementation in malnourished, frail and free-living older people: a prospective randomized community trial Am Diet Assoc 102 (2002): 1088-95.
55. Walston J, Buta B, Xue QL. Frailty Detection and Interventions: Considerations for Clinical Practice. Clin Geriatr Med 34 (2018): 25-38.
56. Gómez A. Biomedica 39 (2019):617-621.
57. Keith JW, Pamer EG. Recruit commensal microbes to resist antibiotic resistant pathogens. J Exp Med 216 (2019): 10-19.
58. Glowacki RWP, Martens EC. In disease and health: Effects of intestinal microbial metabolites on human physiology. PLoS Pathog 16 (2020): e1008370.
59. Li J, Jia H, Cai X, Zhong H, Feng Q, Sunagawa S, et al. An integrated catalog of reference genes in the human gut microbiome. Nat Biotechnol 32 (2014): 834-41.
60. Pasolli E, Asnicar F, Manara S, Zolfo M, Karcher N, Armanini F, Beghini F, Manghi P, Tett A, Ghensi P, Collado MC, Rice BL, DuLong C, Morgan XC, Golden CD, Quince C, Huttenhower C , Segata N. Wide diversity of unexplored human microbiomes revealed by more than 150,000 metagenome genomes spanning age, geography, and lifestyle Cell 176 (2019): 649-662.e20.