SPONSOR FEATURE

Nutrition throughout life: innovation for healthy ageing

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The demographic of global populations is changing more rapidly than ever in the 21st century. Improved health and longevity have altered demographic trends dramatically, reflecting advances in reducing disease and mortality and leading to a real extension of life expectancy[1]. The World Health Organization estimated that there were 650 million senior citizens in 2007 and the figure is predicted to triple in the next 50 years with about 80% of the elderly population living in developing countries.

These demographic changes have had unprecedented effects on individuals, economies and cultures and will have a major impact on nutrition and healthcare in the future. As the ageing population increases, there is a growing awareness of the importance of "healthy ageing" and "quality of life." Longevity is influenced by multiple factors throughout the lifespan, including genetic makeup, metabolism and physiology, social and environmental factors and lifestyle habits, which evolve from foetal development to adult and senior years (during which the risk of disease and frailty increases).

Nestlé Research seeks to understand and develop nutritional strategies that provide clear benefits for ageing, with an emphasis on attenuating the decline of physiological function and on maintaining quality of life.

Four main aspects of ageing-related research at Nestlé include musculoskeletal health, immune defence, metabolic health and cognitive function. These have been discussed at a recent symposium on *Nutrition and the Biology of Human Ageing* at the Nestlé Research Center in Lausanne, Switzerland.

Determinants of physiological ageing

On the physiological level, several principles are emerging that modulate longevity at the level of the cell or organism. Telomere function, autophagy, epigenetics and caloric restriction are under particular investigation for the critical role they play in determination of lifespan.

Telomeres, the ends of eukaryotic chromosomes, represent DNA fragments, which in somatic cells shorten with each mitotic cell division owing to the *end replication problem*. Telomere length, in particular the relative abundance of short telomeres, is considered a biomarker for physiological life expectancy. Determination of telomere length and its comparison with age-matched controls has the potential to provide a diagnostic marker for physiological age and to help assess the risk of frailty and disease. Remarkably, in a gene therapy approach, treating adult and old mice with a virus for the expression of telomerase reverse transcriptase (TERT) resulted in 24% extension of longevity without increasing the risk of cancer[2].

Another hint towards the mechanistic and physiological manifestation of lifespan has been observed in nematodes and in plants through transgenerational epigenetic inheritance of longevity. The concept of transgenerational epigenetic inheritance was established more than a decade ago in *Linaria vulgaris*, in which a phenotype switch in plants from bilateral to a radial mutant symmetry is associated with a massive change of methylation of the *Lcyc* gene. This is hypothesized to be involved in the control of dorsoventral asymmetry[3]. Other incidences of transgenerational epigenetic inheritance have been found since then. Yet, it was still a surprise in 2011 when the phenomenon was also observed for longevity. The laboratory of Anne Brunet at Stanford University identified a mechanism of chromatin modification, where perturbation of the H3K4me3 regulatory complex (ASH-2, WDR-5 and SET-2) in the parental generation extends the lifespan of descendants in subsequent generations in *C. elegans*[4].

On the organismal level cellular processes of apoptosis and autophagy contribute to controlling and modulating physiological longevity. Upon exposure to stress conditions a cell can enter either an apoptotic

or autophagic pathway[5]. As a tightly regulated lysosomal process, autophagy leads to clearance and degradation of cell products and organelles, which are either damaged or no longer necessary. While catabolic in nature, autophagy does however contribute to longevity. An intriguing observation was made by the Kroemer and Madeo laboratories where autophagy was induced through food-based supplementation with the natural polyamine spermidine in yeast and in Drosophila fruitflies. Under experimental conditions, processes associated with ageing were reduced and longevity was extended[6].

Autophagy also seems to be one of the principle processes behind extension of the lifespan attributed to caloric restriction[7]. Extrapolating from model organisms to humans, it still remains unclear to what extent epigenetics, autophagy and caloric restriction contribute to a longer lifespan. Whereas two recent studies on primates provide controversial results regarding the effect of caloric restriction on longevity, both studies show that fewer calories ingested are associated with less disease and a healthier life[8, 9].

Nestlé's interest in nutrition and ageing

***Nestlé Research for musculoskeletal ageing, mobility and quality of life*:**
Good physical function and mobility is a core indicator of health in the ageing population. Musculoskeletal ageing is characterized by decreasing bone and muscle mass and strength, joint pain and stiffness, reduced mobility, and increased risk of falls and fractures.

Age-related loss of bone mass and strength is a significant risk factor for developing osteoporosis, predisposing an individual to an increased risk of fractures associated with morbidity and mortality. Nutrition plays an important role in contributing to peak bone mass acquisition during childhood and in attenuation of bone loss with age. Many studies focus on calcium and vitamin D, however a multitude of further nutrients have been identified with effects on bone, individually and in combination[10].

Nestlé Research recently investigated the effect of the citrus flavanone hesperidin (hesperetin-7-O-rhamnoglucoside) on attenuation of postmenopausal bone loss. In this first placebo-controlled, randomized, double-blind clinical trial testing the effect of dietary supplementation with hesperidin (500 mg daily for 2 years), it was found that women consuming hesperidin presented a better balance in bone metabolism as reflected by the bone turnover index. However, there was no significant change in bone mineral density (BMD), possibly since this could require the combination of hesperidin with sufficient levels of calcium and vitamin D.

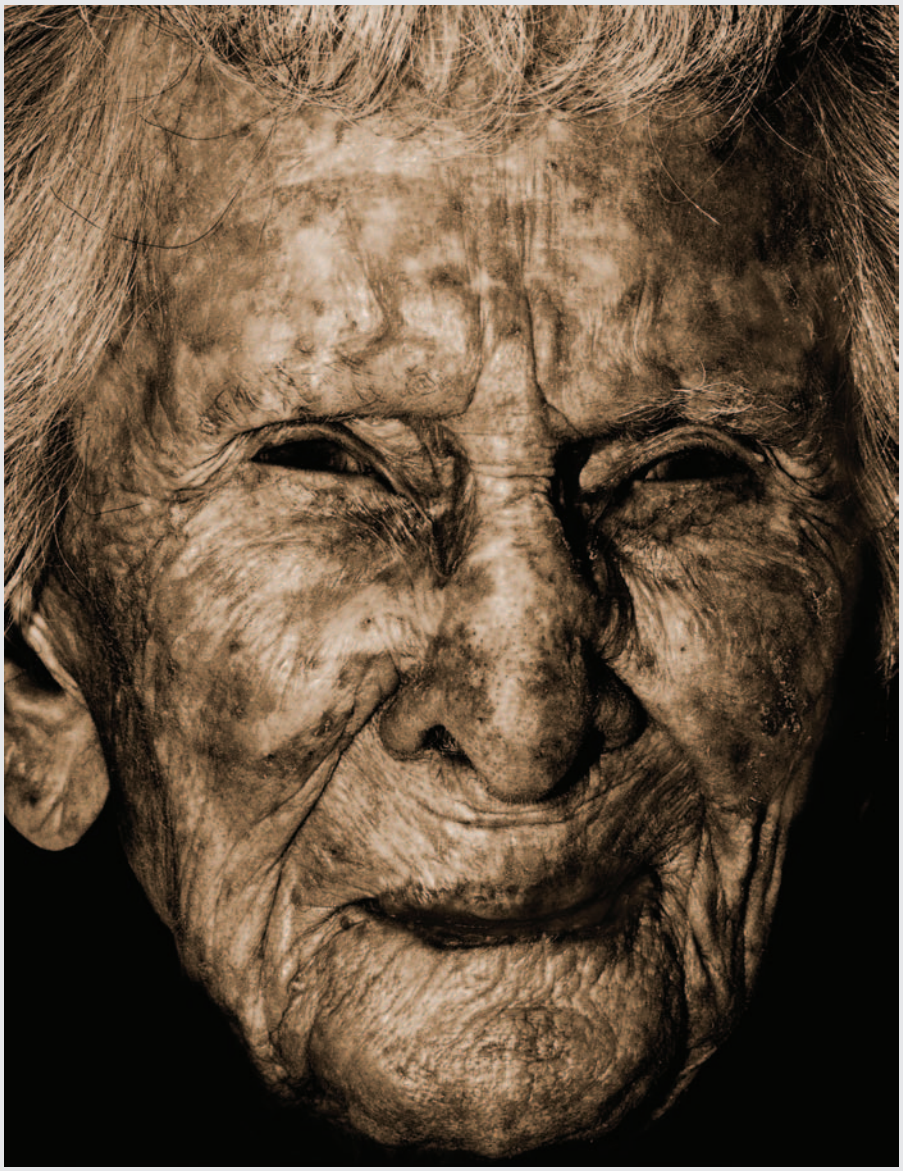

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Figure 1 | A 109-year-old American woman of Irish and English descent. Her husband, to whom she was married for 80 years, lived to 100 after which she lived alone until 105. She stopped bowling at 107 and The Guinness Book of World Records lists her as the oldest person to ride in a hot air balloon at 109.

Age-related loss of muscle mass, strength and function, widely termed as sarcopenia[11] is exacerbated by reduced physical activity or immobilization due to illness (*i.e.* disuse of major muscle groups), which contributes to functional limitations and disability in the elderly. Healthy older adults who maintain higher levels of physical activity are more likely to maintain mobility later in life. Ageing muscle appears to be "anabolically" resistant to nutrients compared to young and healthy muscle. However, this "anabolic resistance" may be overcome by exercise, and further enhanced by the co-ingestion of dietary amino acids, for example from whey protein[12]. Whey protein is rapidly digested and leads to greater protein gains compared with casein protein, particularly in the elderly[13]. Nestlé Research focuses on attenuating the decline in physical mobility related to ageing, including monitoring the appropriate parameters combined with nutrition and possibly exercise, to provide an effective way to improve mobility and quality of life.

***Nestlé Research for immune response*:**
Ageing is accompanied by a deterioraration of the immune system (immunosenescence) and a low-grade chronic inflammatory status (inflammageing). Elderly people are more susceptible to infectious agents, have an increased risk of disease and often show poor recovery. Nestlé Research is interested in

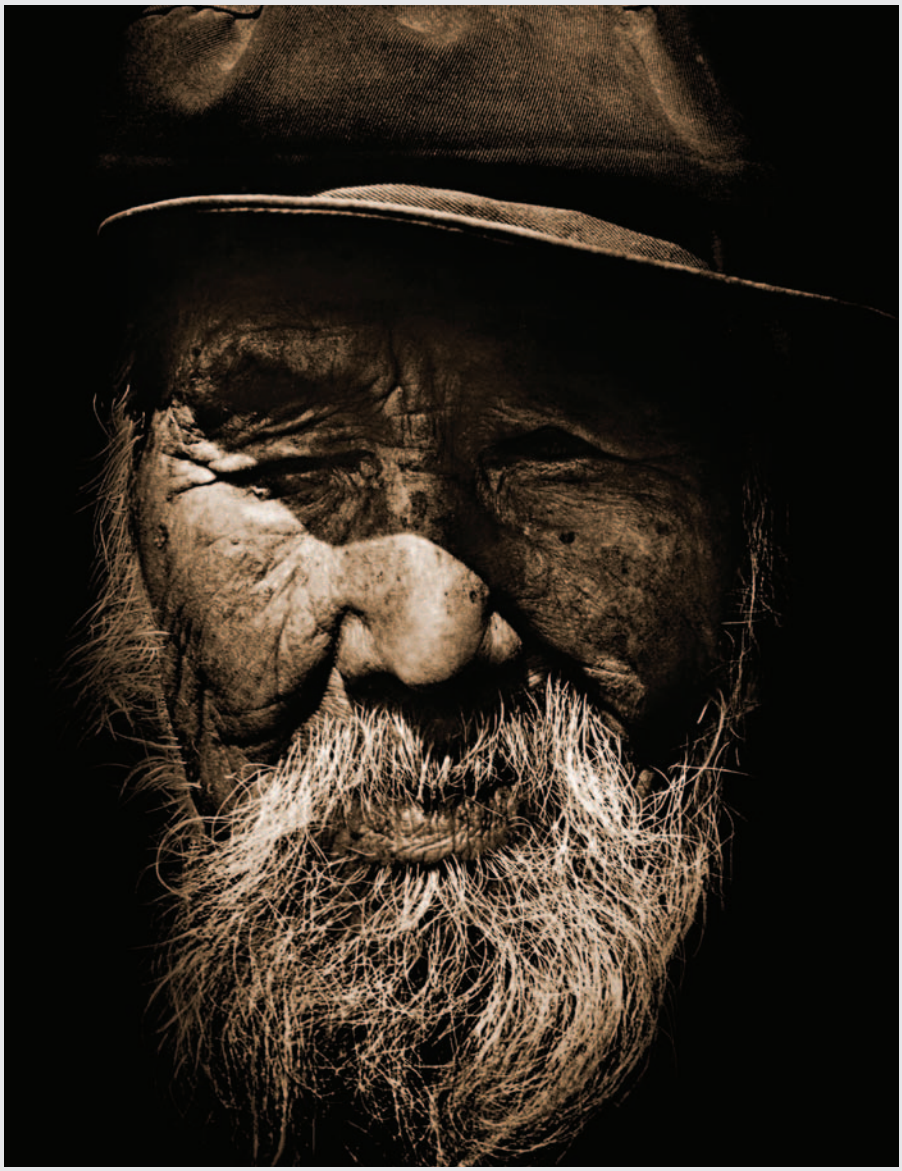

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Figure 2 | This 102-year-old Chinese man made bamboo bird cages for 92 years and could imitate the calls of twenty different birds.

developing nutritional strategies to reinforce the immune system, and to help protect against infections, with the overall goal of delaying frailty and maintaining autonomy and independence for the elderly.

Influenza is the infection with the highest population-related mortality in people over 65 years of age, and thus the WHO recommends vaccination. However, elderly people exhibit poor vaccine response compared with that in younger adults. Therefore, nutritional strategies to improve the vaccine response include trace elements, prebiotics and probiotics, as well as traditional medicinal ingredients.

Recently, Nestlé Research carried out a randomized, double-blind, placebo-controlled trial in 150 healthy community-dwelling Chinese elderly people. The trial was investigating the immune response to influenza vaccine after three months supplementation with a special milk-based formulation of the Chinese fruit wolfberry (*Lycium barbarum*)[14]. The subjects receiving this milk-based formulation, Lacto-Wolfberry, had significantly higher post vaccination serum influenza-specific immunoglobulin G levels and seroconversion rates, compared with the placebo group. These results indicated an enhanced capacity to respond to antigenic challenge, an important factor for this population to fight infections.

Evidence is emerging on the correlation between diet, health and frailty status in the elderly[15]. The inflammageing process is linked to the fine balance of gut microbiota and its interaction with the gut-associated immune system. Therefore, any changes in intestinal microbial structure and composition are hypothesized to have an impact on immune response. Nestlé Research is working on understanding the effects of diet on gut microbiota composition and homeostasis and the effects of probiotics in modulating gut microbiota as a means to improve immune defence.

***Nestlé Research for metabolic health and food intake*:**

The quantity and quality of calories ingested throughout life is a determinant of susceptibility to metabolic diseases. Trials have shown that diet has a strong influence on the prevention and delay of metabolic changes occuring during aging such as as glucose intolerance and elevation of plasma cholesterol levels, especially when combined with regular physical activity and maintenance of a healthy body weight. A balanced, healthful diet helps in the prevention of developing non-communicable diseases such as cardiovascular disease (CVD) and type 2 diabetes.

Nestlé Research seeks to develop food and nutrition solutions for weight management and improved metabolic health. This includes development of food or use of ingredients which promote satiety, activate energy metabolism and improve blood glucose management in healthy and at-risk populations across the lifespan.

A recent study in healthy men and women confirmed the greater thermic response of a protein-rich meal compared to a carbohydrate-rich meal. Thermic response varied when the protein composition of the diet was altered[16]. Indeed, the increase in energy expenditure was greater following ingestion of a whey protein-rich meal compared to casein or soy-rich meals, showing that food composition can impact physiological responses and deliver certain metabolic advantages. Ultimately, a combination of nutritional and lifestyle interventions will be required to provide solutions for weight management for people of all ages.

Besides the increased risk of developing metabolic syndrome and CVD that is linked to positive energy balance and excess adiposity, there is another threat to healthy ageing – the gradual decrease in energy and nutrient intake. Prolonged insufficient energy and nutrient intake may exacerbate the development of disabilities. Indeed, decreased food intake seems to be linked to a loss of appetite or enjoyment of food, frequently reported by the elderly[17]. One hypothesis to explain reduced food intake is linked to a reduction in olfactory capacity.

Preclinical studies demonstrate that in mice of different age groups, no marked change in taste preference is observed for a broad range of tastants including salty, sour, sweet, bitter and umami taste[18]. For olfaction however, it is likely that a reduced sense of smell and the perception of food related aromas has an impact on the motivational aspect of food intake.

***Nestlé Research for cognitive function*:**
Most people fear a decline in cognitive ability and will indeed experience mild cognitive decline, the severity of which often increases with age. The degree of age-related decline is influenced by the evolution of cognitive function throughout the lifespan, from development during childhood through optimal functioning in adult years, and then declining with age. Factors such as education, lifestyle and occupation are thought to contribute to the rate and magnitude of cognitive ageing. Given the impact of age-related cognitive problems, particularly for maintaining autonomy, the need to understand the role of nutrition in preserving and promoting cognitive performance is critical.

One area of interest is the clinical dietary management of the metabolic processes associated with mild cognitive impairment and early Alzheimer's disease (AD). Clinical trials in elderly subjects with mild to moderate AD showed cognitive improvement following daily supplementation for 90 days with a ketogenic agent based on medium-chain triglycerides[19]. Treatment effects were notably significant among patients who were not carriers of the apolipoprotein E4 allele (APOE4), a genetic risk factor associated with a higher probability of developing AD. Approximately 50% of individuals diagnosed with probable AD are estimated to be APOE4 negative. Such results open interesting biomedical opportunities for the management of cognitive decline in the elderly.

Nestlé Research is interested in the role of nutrition and diet on cognitive function throughout the lifespan and in attenuating age-related cognitive decline. A particular area of study for Nestlé is the effect of coffee consumption on age-related cognitive decline. One approach is to establish whether habitual coffee intake may acutely alleviate cognitive decline or have a preventive effect. The acute effects of caffeine intake on cognition have been extensively investigated, with the most consistent results showing improvement of reaction time, sustained attention and attenuation of fatigue-induced performance deficit. Specifically, acute studies conducted with the elderly suggest an effect of 200-250mg of caffeine on age-related cognitive impairment when there was a proneness to fatigue. Evidence for longer-term cognitive benefits of coffee is less clear, due in part to multiple factors from the diet and the environment which may influence cognitive outcomes.

More recently, Nestlé Research has investigated the effects on cognition of chlorogenic acid, a polyphenol which is abundant in coffee. In a pilot study examining decaffeinated coffees with different levels of chlorogenic acid content and their acute effects on mood and cognitive performance in older adults, it was shown that regular caffeinated coffee enhanced mood and attention compared to the placebo and regular decaffeinated coffee. The decaffeinated coffee with high chlorogenic acid content increased alertness, reduced feelings of mental fatigue, and decreased the number of reported headaches, relative to the placebo and regular decaffeinated coffee[20]. Although further research is needed, these preliminary results show an interesting potential for coffee compounds on cognition and mood in an older population.

Research into the complexities of nutrition and ageing is of great significance because of the worldwide demographic trend of increased longevity and the ongoing quest for increased quality of life at any age. The aspiration is not only to "live longer" but to "live better," and to maintain optimal quality of life during the later stages of life. With this in mind, Nestlé Research will accelerate science-driven nutritional solutions and consumer-centric food and nutrition products, systems and services which promote and support healthy ageing.

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