Physiology of Ageing

2

William Browne and Balakrishnan Kichu R. Nair

Key Points

- Physiological ageing is a complex process of progressive reduction in function that occurs in all organ systems. This process may be summarized in the expression "homeostenosis".
- Processes influencing ageing include gene variations and differences in expression and environmental factors. The interplay between these elements is not well understood.
- Pathological processes have a major impact on the rate and character of organ changes with age that may not be readily distinguished from "physiological ageing".
- Tissues in all organ systems undergo changes with age including alterations in connective tissue makeup, cell numbers and neurohormonal signalling manifesting as reduced function.
- Understanding the typical physiological changes of ageing improves a clinician's ability to provide care to older patients.

Case Study

Jack, a 92-year-old man, presents to his primary care provider following a brief hospitalization. Jack is a retired soldier and enjoyed an active life until recent years. He lives alone in a two storey home which he previously shared with his late wife. Jack has two adult children. His daughter lives locally with her family

W. Browne, M.B.B.S., F.R.A.C.P.
Eastern Health, Melbourne, VIC, Australia
e-mail: brownew@me.com

B.K.R. Nair, AM, MBBS, MD (Newcastle) (✉)
School of Medicine and Public Health, Newcastle, NSW, Australia
e-mail: kichu.nair@newcastle.edu.au

B.K.R. Nair (ed.), *Geriatric Medicine*, DOI 10.1007/978-981-10-3253-0_2

and his son lives overseas. Today he walks slowly from the waiting room with the aid of a cane. He reports having had an unprovoked fall during the night, following which he presented by ambulance to the local emergency department for care. After several hours he was discharged home with advice to attend your clinic for follow-up. There is a superficial skin tear on his forearm that has been dressed with butterfly closures. He also has a hematoma over his left hip and an abrasion to his ankle. The discharge letter written by the emergency physician describes Jack as being vague during his presentation.

Jack's past health problems include hypertension, type II diabetes mellitus which has been managed by diet and constipation. His current medications include metformin, perindopril, amlodipine and aspirin.

On assessment today he is orientated to place and person, but was unsure of the date or day of the week. He was unable to recall three items at 5 min. His gait is slow but steady and he uses a single point stick for balance. Jack has difficulty getting in and out of your office chair and looks unsteady when turning. Jack's blood sugar was 14 on the clinic glucometer.

Jack's primary care provider was concerned about both the risk of further falls and by what seemed to be a decline in both mobility and cognition.

2.1 Ageing as a Process

Age and disease are closely associated phenomena—in many places the greater proportion of patients seeking the care of a physician are older people. Consequently in both outpatient and inpatient settings, patients resembling Jack are extremely common. Because older people have predictable and progressive changes in diverse physiological processes, understanding these changes is valuable as a means to improve both patient care and outcomes. Such an understanding is invaluable when seeking to ensure safe care. Geriatric medicine refers to the medical care of people in whom the parameters of typical organ function are likely to be different and the ability to compensate for disturbances reduced, when they are compared with those usually seen in the young. Predicting the challenges ahead for the care of a patient like Jack can guide interventions, such as fall reduction, screening, vaccination and prescribing (Fig. 2.1).

2.1.1 Ageing Versus Disease

When discussing the notion of "normal ageing" or "physiological ageing", one generally refers to the process of change that reflects alteration of organ structure and function with time alone and in the absence of supervening disease processes. This is referred to by some authors as primary ageing. Secondary ageing then refers to those aspects of the aged state that are attributable to disease. Disease-free individuals with the purely ageing-related changes suggested by the concept of primary ageing do not, and effectively cannot, in practice exist. Further, many changes in organs with ageing are arbitrarily defined as a disease when they progress to a point where they are recognizable clinically. Distinguishing between the

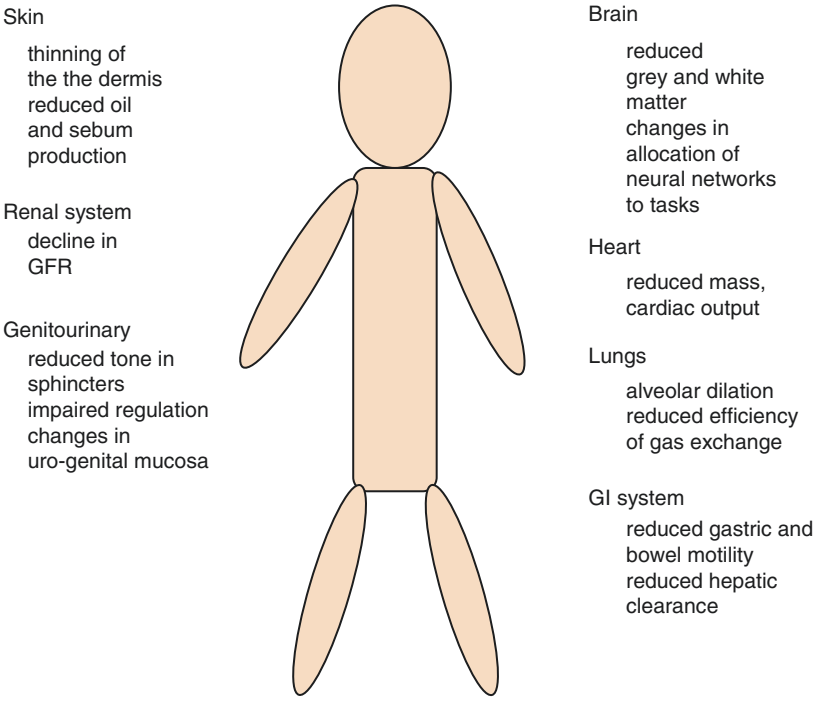

Fig. 2.1 Summary of ageing changes in selected systems

effects of one of these degenerative diseases and "physiological ageing/primary ageing" becomes one of the preferred definitions in many cases.

2.1.2 The Impact of Ageing on Medical Care

Changes in the susceptibility of individuals to disease, as well as alterations in the way older people cope with metabolic disturbance, pathology and surgical or pharmacologic treatments have led to the discipline of geriatric medicine. Changes in physiology with age therefore will be built upon throughout the entirety of this text.

The distinct physiology of ageing can be summarized in the word "homeostenosis". Coined by Walter Cannon, the influential American physiologist, this refers to a progressive loss of physiological reserve [1].

2.1.3 Why Do We Age?

Ageing represents cumulative changes in multiple organ systems. Rather than being a single process, the term is best thought of a reference to the net effects of accumulated degeneration in cells and tissues. A search for mechanisms that underlie ageing has been a focus of some interest in recent decades, and aspects of the biochemical and cellular processes which drive ageing have become somewhat better understood.

While there is no doubt all people experience ageing, there is a marked variability in the apparent pace of this process. This variability contributes to the wide range of lifespans observed across populations and suggests that at least some aspects of the physiological changes of ageing are influenced by an individual's environmental exposures and peculiar genetic makeup.

2.1.3.1 Caloric Restriction and Other Interventions Known to Influence Ageing

Early insights into the potential for certain environmental factors to influence ageing derived from the effects of caloric restriction in rodents and other species in the laboratory [2]. In such studies, animals fed lower calorie diets compared to animals allowed to feed "ad libitum" exhibited longer total lifespans.

Calorie restriction is certainly associated with physiological adaptations including an altered metabolic rate. Sirtuin gene expression is influenced by caloric restriction and may in part be responsible for some aspects of altered physiological activity identified in calorie-restricted animals. While efforts have been made to replicate the effects of caloric restriction observed in the laboratory in humans, the long lifespan of our species and the difficulty of maintaining dietary interventions over long periods remain formidable obstacles to such clinical studies. At best surrogate markers of the effects of ageing are employed.

While the benefits and risks of caloric restriction in humans are unknown, there is compelling evidence for the adverse effects of malnutrition, which remains a major clinical concern worldwide and is prevalent even in developed countries among older people.

2.1.4 Cellular Processes and Ageing

2.1.4.1 Genetic Elements

Genes influence both lifespan and ageing. There is intriguing evidence that certain genes influence cellular senescence, a component of ageing, in many organisms and presumably in humans.

Rare genetic disorders described in humans suggest a prematurely aged state can be caused by mutations of specific genes, a group of disorders referred to as progeroid syndromes. Werner's syndrome and Hutchinson-Gilford syndrome represent two examples of this unusual group of disorders. While these conditions are intriguing, whether they truly represent an acceleration of physiological ageing or merely resemble it remains unclear.

A number of mutations are associated with extended lifespans in laboratory models. Among the most studied of such genes are the previously mentioned sirtuins [3]. Originally identified in brewer's yeast, these genes are now thought relevant to the process of ageing in many species. Sirtuins have been linked to ageing-related changes in the cardiovascular system [3]. Induction of sirtuin gene expression in response to environmental stressors seems to trigger metabolic and cell division changes in cells that are associated with longer usual lifespans in some species.

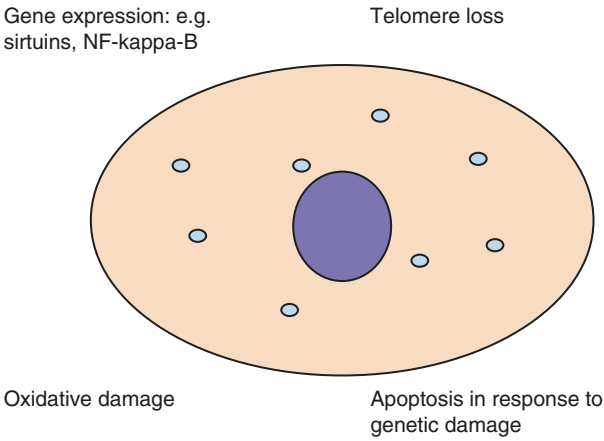

Fig. 2.2 Cellular processes influencing ageing

NF-kappa B influences gene expression both in inflammation and during ageing [4]. This gene may therefore be included among the "ageing" genes, and its expression presumably regulates some aspects of ageing physiology.

The complex relationship between an individual's genetic code and the development of aged characteristics is clearly extremely complicated. To add to the complexity, it has recently been observed that epigenetic factors—that is, changes in the way DNA is regulated which are either somatotopically acquired or transgenerationally inherited and do not rely on DNA sequence—have been suggested to influence some aspects of the physiology of ageing [5].

2.1.4.2 Telomeres and Senescence

Cellular senescence refers to a response by dividing cells to stress. Activation of this state permanently prevents further cellular division and can be triggered by several different assaults on the cell, including telomere shortening and DNA damage [6].

The term telomere refers to sequences of DNA at the ends of chromosomes that progressively shorten with somatic cell division. Eventually this process prevents further divisions by inducing cellular senescence, creating a limit to the number of times somatic cells can divide—the Hayflick limit. This limit is presumed to be a component of ageing, though it is clearly only one factor of many [7] (Fig. 2.2).

2.2 Ageing in Individual Systems

2.2.1 Cardiovascular System

Ageing represents the most important risk factor for diseases of the cardiovascular system. Changes in the cardiovascular system contribute to reductions in exercise tolerance and greater susceptibility to disease. Measurement of "normal function" across the lifespan, as in other aspects of ageing physiology, is hard to distinguish from the effects of clinical and subclinical disease.

Changes may be grouped in the following general categories: structural disease, disorders of function and the presence of disease more prevalent with ageing [8].

With ageing, there is an increase in the size of cardiac myocytes and, due to this, an increase in the relative cardiac wall thickness [9]. At the same time, the loss of numbers of cardiac myocytes results in reduced heart mass. Cardiac hypertrophy is therefore not an invariable result of physiological ageing [10]. As discussed earlier in this chapter, the effects of ageing on the heart and vascular system are influenced to some degree by the effect of sirtuin gene expression.

2.2.2 Respiratory System

Thoracic structural changes with ageing are associated with reductions in lung function. This includes changes in the ribs, spine and musculature. Wall compliance declines progressively in later life, presumably related to calcification of chondral rib insertion and changes in vertebral height. Kyphosis with ageing-related osteoporosis can cause reductions in FVC and FEV1 and an associated increase in AP diameter which effectively weakens the diaphragm.

Reduced gas exchange and increased stiffness of the lung both impact respiratory reserve, which declines progressively as an individual ages. Such changes may be readily demonstrated by use of serial spirometry. Changes in advanced age in the pulmonary parenchyma include alveolar dilatation which reflects changes in connective tissue composition [11].

There is a predictable reduction in lung elasticity with ageing which has consequences for lung function. The alteration seems to relate more to cross-links between collagen and elastin rather than the loss of such tissue from the lungs. The change in connective tissue arrangement produces dilation of the alveoli and the ducts producing a state that resembles emphysema and which is sometimes referred to by clinicians as "senile emphysema". The production and function of surfactant do not seem to alter greatly with age [11].

Ageing-related changes in the properties of skeletal muscle cells, altering myosin production, patterns of fibre type and myocyte numbers all potentially contribute to reduced respiratory function which manifests as reductions in the strength of diaphragmatic contractions.

Disturbance of respiratory function during sleep is a particular problem and often is associated with pathological consequences.

2.2.3 Renal and Urological Systems

The urological system undergoes changes in structure and function with ageing that are expanded in the incontinence chapter of this text.

There is a reduction in the size of the kidney and number of glomeruli with ageing. As in other organs, the changes of physiological ageing are hard to distinguish from those of disease. Hypertension and even elevation of blood pressure in the

normal range are associated with a greater rate of reduction in renal function [12]. Whether a fall in GFR is the normal physiological outcome of ageing or not remains a matter of debate. Renal blood flow in response to renal vasodilatation is reduced with healthy ageing [13]. Because loss of renal function is to some extent predictable by chronological age, this measure is usually incorporated into calculations estimating the glomerular filtration rate, such as the Cockroft-Gault and MDRD formulae.

Voiding difficulty is a common concern among older patients. Advancing age is associated with diminution of bladder capacity. There is an increase in the frequency of detrusor contractions. Despite this the effective expulsion urine falls with age so that the post-void residual increases. Urine flow rate decreases progressively with ageing. There is a detectable increase in neurotransmitter sensitivity in the bladder, accounting for the relatively high rate of adverse effects on bladder function observed with the use of medications acting on neurotransmitter pathways such as cholinergic drugs. There is a reduction in urethral pressure. Bladder ischemia may be an important factor in detrusor function change in some older people. There is fibrosis of the bladder wall which may be a consequence of ischemia. The bladder wall becomes thinner and the amount of muscle it contains diminishes.

The internal and external urethral sphincters are important for maintaining urinary continence. These structures are innervated by the sympathetic and parasympathetic nervous systems in the case of the internal sphincter and predominantly by spinal motor neurones in the external sphincter. Damage or deterioration of these control mechanisms in an older person is one factor resulting in greater risk of incontinence.

In men change in the size of the prostate with ageing frequently results in dysfunction of the lower urinary tract. Most men experience a benign increase in the size of the prostate with ageing which often results in symptoms of urinary retention and incontinence.

Antidiuretic hormone (ADH) is important in regulating fluid balance, and its secretion in the supine position changes with ageing in important ways with respect to the common problem of orthostatic hypotension.

2.2.4 Nervous System

No system is of greater importance to the diseases of ageing than the nervous system. Alterations in neurological function contribute to almost all the major physiologic alterations described in this chapter. Dysfunction of the nervous system is a component of all major geriatric syndromes (delirium, incontinence, falls and frailty). The effect of dysfunction of the brain in particular is a major reason for loss of independence and has a large and increasing effect on society as a whole.

2.2.4.1 Brain

Brain weight and the number of neurons and synapses decline progressively with ageing. This is observable as thinning of the cortical grey matter. Additionally there

are changes in white matter tracts. In physiological ageing this loss of neurone density is in some measure compensated for by the development of new neuronal connections. The brain and other neurological tissues contain stem cells and are able to replace neuronal tissues throughout life. The failure of this compensatory mechanism results in the progressive changes described.

Functional MRI has been able to identify changes in recruitment of brain networks with ageing which are presumed to reflect compensatory adaptations to neuronal loss and impaired function [14].

Some aspects of cognitive function remain preserved with ageing in the absence of disease. Semantic memory, "world knowledge" and emotional regulatory skills would be among these relatively preserved domains [14]. Short-term recall and the learning of new material are thought to be less reliable than in youth.

Alzheimer's disease and Parkinson's disease are important diseases causing degeneration of brain function in multiple domains and will be discussed elsewhere in this text.

2.2.4.2 Spinal Cord

While less is known regarding changes of ageing in the spinal cord, one known issue is the reduced capacity for remyelination with ageing which affects the central nervous system tissues [15]. This loss of ability to repair and replace the myelin sheath is of significance in diseases of the spinal cord and elsewhere, such as multiple sclerosis. Clinically, there are important changes in the function of the autonomic nervous system with ageing which may account in part to the tendency of older people to experience serious autonomic dysfunction.

2.2.4.3 Peripheral Nerves

The reduction in peripheral sensory sensitivity in ageing is widely observed by clinicians. Not surprisingly then, the ageing peripheral nervous system displays changes at multiple levels. These changes were reviewed by Wickremaratchi [16]. There is a reduction in the number of myelinated nerves in the spinal roots. The density of afferent fibres in the fasciculus gracilis is consistent with observed decline in peripheral sensory information appreciated by the patient.

2.2.5 Muscular and Skeletal Systems

Muscle weakness is an important limiting factor for quality of life in older people with a large number of older people at risk of loss of the ability to complete self-care activities due to weakness.

Ageing is associated with a progressive decline in gait velocity [17]. In large measure this reflects degenerative change in the joints (such as arthritis) and muscle weakness (due to sarcopenia and the effects of disuse). Generally these and other changes, such as the development of Parkinsonism, that result in reductions in gait speed can be attributed to diagnosable diseases of the structures in question.

Changes in bone density with ageing are associated with increased risk of fractures and as such contribute to morbidity and mortality in older people. The extent of bone loss varies and is influenced by physiological processes such as hormone changes after menopause and the effect of environmental exposures and disease.

The loss of muscle mass occurs progressively with ageing though the rate and extent are significantly influenced by exercise habits. Sarcopenia refers to the loss of muscle mass that is attributed to the effects of ageing. Likely contributing factors include reduction in the ability of damaged muscle fibres to be replaced, a process that involves recruitment of support cells to replace damaged fibres.

2.2.6 Endocrine Systems

The hypothalamus may influence the general processes of systemic ageing [18], and additionally there are changes in the production of pituitary hormones with ageing which are clinically relevant.

In the later part of middle age, important and predictable changes in the production of sex hormone secretion have important effects on many aspects of metabolic function.

Menopause in woman represents an important physiological ageing process of the endocrine system and has important effects of diverse systems including bone density and urogenital function. The transition to menopause is marked by reduced circulating levels of oestradiol and progesterone.

In men, testosterone levels decline through later life and will occasionally cause symptoms such as fatigue, irritability and loss of libido, and this change likely also contributes to loss of skeletal muscle.

Changes in glucose tolerance are frequent with ageing and have an important impact on the development of disorders of glucose regulation—in particular type II diabetes mellitus. β-Cell function declines as ageing occurs and contributes to this association [19]. In people without diabetes, insulin release in response to glucose declines progressively [19].

Thyroid function changes with ageing include an elevation in TSH levels which may be due to changes in the set point for T4 production and to changes in the sensitivity to TSH [20].

2.2.7 The Ageing Skin

While the changes observed in the skin with ageing are often overlooked by physicians, they are frequently a preoccupation for patients, for whom they represent an important cosmetic alteration and a visual reminder of the progress of the ageing process. Practical concerns consequent on skin ageing include reduced barrier function, the predisposition to malignancies, incontinence and greater risks of infection.

The skin of older people is thinner and drier than in the young. There are changes in the thickness of the dermis, and the ratios of connective tissue. In particular, changes in the extracellular matrix have important implications for skin elasticity and barrier function [21]. Reductions in the numbers of sebum-producing cells may result in dryness.

2.2.8 The Gastrointestinal Tract

The function of some aspects of gastrointestinal tract function declines with ageing.

The number of taste buds declines during later life and is thought to contribute to reduced sense of taste and enjoyment of food in older people [22].

These changes include decreases in bowel motility and gastric emptying which in frail people greatly increase the difficulty of meeting nutritional requirements.

The liver undergoes morphological changes during ageing—in particular a reduction in size that is likely due in part to alterations in its perfusion [23]. The cellular characteristics are relatively well preserved during ageing, perhaps reflecting the considerable regenerative powers of hepatocytes.

Changes in hepatic perfusion, in endothelial cell function, in the extent of drug binding to serum proteins and in the induction of liver enzymes can all potentially reduce hepatic clearance in older people [24] though the extent of reduction in function is quite variable.

2.3 Frailty

Frailty may be considered an end result of the physiological changes of advanced ageing. In practical terms the development of frailty is often influenced by associated pathologies, and this interaction is the subject of the other chapters of this text. In many respects frailty provides a more reliable index of the likely extent of homeostenotic reductions in physiological reserve than chronological age. The impact of the frail state is of such importance that it will be developed in detail in the next chapter of this text.

2.3.1 What Happened to Jack?

You ask Jack's permission to contact his daughter who was unaware of last night's fall. She arranges to stay with Jack in his home for several weeks, and you recommend dietary supplements, reorientation and supervision of mobility. Jack's progress was complicated by a fluctuating delirium which seemed to last several weeks after his fall. His laceration became infected and was treated with a week of oral flucloxacillin with improvement. Jack's blood sugars improved over the week, and a local physiotherapist is arranged to provide a supervised exercise programme.

After several weeks Jack's gait and cognition seemed to have returned to baseline, and he has resumed living independently with daily visits by his family. He and his family are looking at options to relocate him to a single storey dwelling or to come and live with them. He consumes regular nutritional supplements and exercises daily.

2.4 Summary Points

1. Physiological ageing is a complex process of progressive reduction in function that occurs in all organ systems. This process may be summarized in the expression "homeostenosis".
2. Processes influencing ageing include gene variations and differences in expression and environmental factors. The interplay between these elements is not well understood.
3. Pathological processes have a major impact on the rate and character of organ changes with age that may not be readily distinguished from "physiological ageing".
4. The cardiovascular system alters with ageing with reductions in the cardiac size and in the ability of the heart to sustain cardiac output.
5. Respiratory function declines with reduced FVC and FEV1, changes in alveolar size and in lung elasticity resulting in reduced respiratory reserve.
6. Renal function declines resulting in a predictable reduction in GFR.
7. The ageing brain undergoes a reduction in size, and there are modest changes in cognitive function. The peripheral nervous system has many changes, and these are clinically represented by dysautonomia, reduced peripheral sensation and impairment of postural reflexes.
8. The skin and mucosal surfaces are less effective barriers to the environment and tend to be thinner, drier and less elastic.
9. Gastrointestinal changes include loss of taste, reduced gastric motility and reduced bowel motility. Changes in hepatic function have effects of drug metabolism.
10. Understanding the typical physiological changes of ageing improves a clinician's ability to provide care to older patients.

References

1. Taffett GE. Physiology of aging. In: Cassel CK, Leipzig R, Cohen HJ, Larson EB, Meier DE, editors. Geriatric medicine: an evidence-based approach. 4th ed. New York: Springer; 2003. http://link.springer.com/content/pdf/10.1007/b97639.pdf#page=50.
2. Mair W, Goymer P, Pletcher SD, Partridge L. Demography of dietary restriction and death in Drosophila. Science. 2003;301(5640):1731–3. sciencemag.org
3. Cencioni C, Spallotta F, Mai A, Martelli F, Farsetti A, Zeiher AM, Gaetano C. Sirtuin function in aging heart and vessels. J Mol Cell Cardiol. 2015;83(June):55–61. researchgate.net

4. Adler AS, SaurabhSinha TLAK, Zhang JY, Segal E, Chang HY. Motif module map reveals enforcement of aging by continual NF-κB activity. Genes Dev. 2007;21(24):3244–57. genesdevcshlporg
5. Cencioni C, Spallotta F, Martelli F, Valente S, Mai A, Zeiher AM, Gaetano C. Oxidative stress and epigenetic regulation in ageing and age-related diseases. Int J Mol Sci. 2013;14(9): 17643–63.
6. Collado M, Blasco MA, Serrano M. Cellular senescence in cancer and aging. Cell. 2007;130(2):223–33. Elsevier
7. Shay JW, Wright WE. Hayflick, his limit, and cellular ageing. Nat Rev Mol Cell Biol. 2000;1(1):72–6. nature.com
8. Strait JB, Lakatta EG. Aging-associated cardiovascular changes and their relationship to heart failure. Heart Fail Clin. 2012;8(1):143–64.
9. Olivetti G, Melissari M, Capasso JM, Anversa P. Cardiomyopathy of the aging human heart. Myocyte loss and reactive cellular hypertrophy. Circ Res. 1991;68(6):1560–8.
10. Lieb W, Xanthakis V, Sullivan LM, JayashriAragam MJP, Larson MG, Benjamin EJ, Vasan RS. Longitudinal tracking of left ventricular mass over the adult life course: clinical correlates of short- and long-term change in the Framingham Offspring Study. Circulation. 2009;119(24):3085–92.
11. Janssens JP, Pache JC, Nicod LP. Physiological changes in respiratory function associated with ageing. Eur Resp J. 1999;13(1):197–205. Wiley Online Library
12. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. J Am Geriatr Soc. 1985;33(4):278–85. Wiley Online Library
13. Fuiano G, Sund S, Mazza G, Rosa M, Caglioti A, Gallo G, Natale G, et al. Renal hemodynamic response to maximal vasodilating stimulus in healthy older subjects. Kidney Int. 2001;59(3):1052–8. naturecom
14. Grady C. The cognitive neuroscience of ageing. Nat Rev Neurosci. 2012;13(7):491–505. nature.com
15. Ruckh JM, Zhao J-W, Shadrach JL, van Wijngaarden P, Nageswara Rao T, Wagers AJ, Franklin RJM. Rejuvenation of regeneration in the aging central nervous system. Cell Stem Cell. 2012;10(1):96–103. Elsevier
16. Wickremaratchi MM, Llewelyn JG. Effects of ageing on touch. Postgrad Med J. 2006; 82(967):301–4.
17. Patterson KK, Nadkarni NK, Black SE, McIlroy WE. Gait symmetry and velocity differ in their relationship to age. Gait Posture. 2012;35(4):590–4. Elsevier
18. Gabuzda D, Yankner BA. Physiology: inflammation links ageing to the brain. Nature. 2013;497(7448):197–8. nature.com
19. Szoke E, Shrayyef MZ, Messing S, Woerle HJ, Haeften TW v, Meyer C, AsiminaMitrakou WP, Gerich JE. Effect of Aging on glucose homeostasis: accelerated deterioration of β-cell function in individuals with impaired glucose tolerance. Diabetes Care. 2008;31(3):539–43.
20. Bremner AP, Feddema P, Leedman PJ, Brown SJ, Beilby JP, Lim EM, Wilson SG, O'Leary PC, Walsh JP. Age-related changes in thyroid function: a longitudinal study of a community-based cohort. J Clin Endocrinol Metab. 2012;97(5):1554–62. press.endocrine.org
21. Röck K, Tigges J, Sass S, Schütze A, Florea A-M, Fender AC, Theis FJ, et al. miR-23a-3p causes cellular senescence by targeting Hyaluronan synthase 2: possible implication for skin aging. J Invest Dermatol. 2015;135(2):369–77. naturecom
22. Toffanello ED, Inelmen EM, Imoscopi A, Perissinotto E, Coin A, Miotto F, Donini LM, et al. Taste loss in hospitalized multimorbid elderly subjects. Clin Interv Aging. 2013; 8(February):167–74. ncbi.nlm.nih.gov
23. Anantharaju A, Feller A, Chedid A. Aging liver. A review. Gerontology. 2002;48(6):343–53. karger.com
24. McLachlan AJ, Pont LG. Drug metabolism in older people—a key consideration in achieving optimal outcomes with medicines. J Gerontol A Biol Sci Med Sci. 2012;67A(2):175–80. biomedgerontology.oxfordjournals