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Hot topic in geriatric medicine

Healthy ageing: Evidence that improvement is possible at every age



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ABSTRACT

Fighting against risk factors for disability and dependency throughout the whole life process and – more specifically relevant to this paper – during the second part of life, needs to become a core focus of adult public health actions. In order to engage positive actions towards this goal, it is important to identify and target modifiable risk factors. One would imagine that it is always possible to positively modify “intermediate” risk factors, such as health habits (sedentary lifestyle and diet), health behaviours (alcohol consumption, smoking or other addictions...), as well as living and working conditions, and access to healthcare. However, the simplest interventions of all could target “proximal” risk factors that closely relate to disease and disability, such as hypertension, metabolic disorders (malnutrition and diabetes), mood and cognitive impairments, musculoskeletal disorders, inappropriate drug prescriptions and frailty. A careful review of the world literature allows to identify the most effective and efficient medical interventions allowing to prevent or delay these disabling clinical conditions and allow to reach the WHO goal of “healthy ageing”, which is developing and maintaining the functional ability that enables well-being in older age.

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“Prevention is not well understood, probably because its challenges are not well understood”

Jean-François Mattei

1. Introduction

One of the main challenges facing medicine in these early years of 21st century is the foreseen ageing of the world population [1], and more specifically, the increase in the number of years spent in disability [2]. These assertions are consolidated by the 1st World Health Organisation (WHO) global report devoted to ageing (2015), which defines healthy ageing as a “process of developing and maintaining the functional ability that enables well-being in older age” [3]. As stated by WHO general director Margaret Chan in the preface of the report, “healthy ageing is more than just the absence of disease; the maintenance of functional ability has the highest importance” [3].

The “healthy ageing” pathway corresponds to a lifelong process. After conception, the first and second parts of life appear to have the greatest influence on a person’s functional trajectory, which

has the potential at any time to become more or less positive. Building and maintaining intrinsic capacity, and living in functional independence within our own surroundings until the end of life is the most favourable outcome [3].

Fighting against risk factors for disability and dependency throughout the whole life process and – more specifically relevant to this paper – during the second part of life, needs to become a core focus of adult public health actions. In order to engage positive actions towards this goal, it is important to identify and target modifiable risk factors. Indeed, it is not yet possible to modify “non-controllable” risk factors, such as genetics, gender, ethnicity, intellectual quotient or family background [4]. It is also difficult (albeit not impossible) to hope to change “distal” risk factors, such as economic background, socio-cultural determinants, education, air pollution, or exposure to noise or the sun. One would imagine that it is always possible to positively modify “intermediate” risk factors, such as health habits (sedentary lifestyle and diet), health behaviours (alcohol consumption, smoking or other addictions...), as well as living and working conditions, and access to healthcare. However, the simplest interventions of all could target “proximal” risk factors that closely relate to disease and disability, such as hypertension, metabolic disorders (malnutrition and diabetes), mood and cognitive impairments, musculoskeletal disorders, inappropriate drug prescriptions and frailty [4].

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Given the functional focus of the 2015 WHO global report on ageing, it would appear essential to demonstrate that interventions focusing on lifelong health habits and behaviours, as well as on “proximal” risk factors during the second part of life could improve functional capacity or delay disability in old age.

2. Interventions focused on health habits and health behaviours

Interventions focussing on health habits and health behaviours are based on “health promotion”. This is a lifelong process that gives people the means to control and promote their own health. It is never too late to adopt new life habits, as shown below.

2.1. Advantages of physical exercises and sport activities during the second part of life

Self-reported walking difficulty, not linked to disability, was found to increase the risk of overall (HR = 1.74 [95% CI 1.71–1.74]) and cardiovascular mortality at 10 years (1.98 [95% CI 1.95–2.02]) in a Finnish cohort of male Second World War veterans [5]. A study of physical activity in US adults showed that exercisers performed consistently better on the long distance corridor walk over 8 years, and had greater aerobic fitness compared to inactive or lifestyle active participants [6]. Similarly, an English observational study of 3454 adults aged 63.7 ± 8.9 years at inclusion with 8 years follow-up, reported that taking up physical activities, even at an older age, has positive physical, functional and mental repercussions (*P* values ranging from > 0.005 to 0.001), compared to participants who remained sedentary [7].

Clearly, regular, reasoned and reasonable physical exercise and sport activities throughout one's life, even those started at midlife, have multiple positive benefits and minimal disadvantages in the fight against the “sedentary death syndrome” [8].

2.2. An adapted diet at midlife greatly modifies health

It is now well established that a Mediterranean diet has significant beneficial effects on 10-year incidence of metabolic syndrome, diabetes, hypertension and inflammatory markers [9]. The Predimed randomized trial, which included 7447 volunteers aged 55 to 80 years at high cardiovascular risk, demonstrated that a Mediterranean diet supplemented with extra-virgin olive oil or nuts significantly reduced major cardiovascular events after a median follow-up of 4.8 years [10]. In a separate analysis from the same study, compared to a low-fat control diet, a Mediterranean diet supplemented in extra-virgin olive oil or mixed nuts significantly slowed cognitive decline, as assessed by the MMSE and clock drawing tests [11].

In summary, involuntary weight loss at midlife is a risk factor for mortality, while obesity at the same time period increases cardiovascular risk. This latter risk could be controlled by physical exercise and a Mediterranean diet supplemented in virgin olive oil or nuts, leading to a reduction or mitigation of clinical conditions causing disability.

2.3. Non-smoking adults have a greater chance of living longer, healthier lives

At the world level, between 1965 and 2014, passive and active smoking caused more than 20 million premature deaths (10 million from metabolic, cardio-, neuro- and reno-vascular events and 6.9 million from respiratory diseases) [12]. Moreover, it was recently shown that mid-life and late-life smokers had a significantly greater risk than lifelong non-smokers of developing

all-cause dementia (adjusted hazard ratio (aHR) = 2.28 [95% CI 1.49–3.49]), vascular dementia (aHR = 2.88 [95% CI 1.34–6.20]) and Alzheimer's disease (aHR = 1.98 [95% CI 1.09–3.61]) [13]. Indeed, many diseases caused by tobacco smoking have a negative impact on daily functioning.

To fight against this scourge, the WHO has proposed to prohibit tobacco advertising, to protect non-smokers, promote education and help to increase the numbers of those who quit smoking. The World Bank has also reported that increasing the price of tobacco by 10% resulted in a 4% decrease in global tobacco sales, and an 8% decrease among the youngest smokers [14].

Without doubt, abstaining from smoking is the single lifestyle habit that offers the greatest protection against cardiovascular, neurological and renal vascular events, as well as respiratory diseases, and consequently, against their negative functional repercussions in daily life.

2.4. Light or moderate alcohol consumption does not make you live longer

Studies focused on life course trajectories of alcohol consumption are scarce. However, an analysis of 9 English studies demonstrated that 2 peaks of alcohol consumption exist, namely young, and pre-retired adults [15]. In France, 37% of adults aged 18 to 74 years are considered to have an at-risk level of alcohol intake [16]. The possible positive effect of light to moderate alcohol consumption on longevity was completely rejected by the Pianoro study. This 6-year follow-up of 5256 community-dwelling adults aged > 65 years from Northern Italy (2318 abstainers and 2309 light to moderate drinkers at ≤ 2 alcoholic drinks per day) showed that when adjusted for physical activity and self-reported health, light to moderate alcohol consumption had no direct protective effect on mortality [17]. On the contrary, harmful effects of moderate to heavy alcohol consumption appear at midlife, mainly in the form of acute cardiovascular and neurological events [18].

It is therefore essential to recall that a long-term or midlife sedentary lifestyle, malnutrition, tobacco smoking and moderate alcohol consumption are all avoidable health scourges that negatively affect health and functional capacity, and precipitate death. The key new message is that randomized controlled studies have shown that it is never too late to reap the positive benefits of controlling these deleterious life habits.

3. Interventions focused on diseases that increase both disability and mortality

Two main groups of chronic diseases that can increase both disability and mortality deserve to be targeted. The first group is composed of diseases that not only increase mortality, but in case of survival, will also be the cause of disability. The second group comprises classical geriatric diseases that do not directly bring on death, but do increase disability. A third and often-neglected issue, namely adverse effects of drugs and inappropriate prescriptions, also need to be addressed.

3.1. Life course vaccination program

The 2013 WHO report stated that currently, worldwide, vaccines annually prevent more than 2.3 million deaths from communicable diseases [19], which perfectly explains the decrease observed in worldwide communicable diseases, from 33% of all deaths in 1990 to 25% in 2010 [20]. However, there is a striking imbalance between the burden of preventable infectious diseases in US older adults compared to US children [21], reflecting the

erroneous beliefs and attitudes in the general population towards vaccination programs, as well as the resurgence and changing patterns of common vaccine-preventable diseases across the different age strata [22,23]. By stimulating immune memory responses, vaccines administered early in life can usually provide long-term, if not lifelong immunity against many vaccine-preventable diseases [24]. In addition, in 2006, the American Heart Association and American College of Cardiology recommended influenza vaccine as part of secondary prevention in persons with coronary and other atherosclerotic diseases [25]. It has been shown that influenza vaccination within-season was associated with a 24% decrease in stroke risk [26]. Herpes zoster vaccine in young adults appeared to cause varicella zoster vasculopathy explaining myocardial infarction, stroke and transient ischemic attack appearing up to 6 months after the clinical features of the disease [27,28]. Herpes zoster vaccine could probably prevent the viral multiplication into the arterial walls and reduce the dramatic consequences of the disease.

In old adults, the expected benefits of vaccine are enormous, with decreased mortality and disability linked to preventable infectious diseases, reduced complications and hospitalizations, reduced antibiotic use and antibiotic resistance, while at the same time, being cost effective [29].

3.2. Midlife interventions on cardiovascular, neurological and renal disease

In case of long-term survival after any acute events, cardiovascular, neurological and renal diseases can be the cause of restrictions on activity and engagement in society for the individual. For each of these medical conditions, it is important to target midlife or potentially reversible risk factors and demonstrate that prevention is active and useful, even late in life.

Cardiovascular and neurological diseases, which are highly prevalent in people aged over 70, are the primary cause of morbidity and mortality. Among the modifiable risk factors for these diseases are a sedentary lifestyle, smoking, high-salt diet [30], overweight, hypertension, diabetes [31], kidney failure [32], hypercholesterolemia and also depression and sleep apnoea [33,34], and even non-steroidal anti-inflammatory drugs (NSAIDs) [35]. Controlling these main risk factors is essential, as demonstrated by the Whitehall study, a 38-year longitudinal study including 19,019 male civil servants aged between 40 and 69 at their first examination on inclusion in the study between 1967 and 1970 [36]. In this study, it was shown that an adult of 50 years who smokes and is both hypertensive and hypercholesterolemic has a reduction of 10 years in life expectancy. If at the same time this patient is obese and diabetic, the life expectancy will be reduced by 15 years [36]. Arterial hypertension is also a major risk factor [37]. The Three-City (3C) study demonstrated in 7612 adults over 65 years of age presenting with no cardiovascular disease at inclusion that after 5.2 years of follow-up, metabolic syndrome was associated with significant risks of fatal (HR: 2.40; 95% CI 1.41–4.09) and non-fatal coronary heart disease events (HR: 1.64; 95% CI 1.24–2.17) [38].

On the positive side, a randomized controlled trial testing the effectiveness of dietary guidelines among 162 non-smoking men and women aged 40 to 70 years showed that compared to controls ($n = 80$), after only 12 weeks, the group with strict application of dietary guidelines ($n = 82$) had a significant decrease in body weight (-1.9 kg, $P < 0.001$), daytime systolic blood pressure (-42 mmHg, $P < 0.001$), the total/HDL cholesterol ratio (-0.13 , $P = 0.044$) and high sensitivity C-reactive protein (-36% , $P = 0.17$) [39]. In a Canadian study, a health educator-led heart-health intervention to help family members of patients with coronary artery disease to better understand cardiovascular risk factors, and

set dietary and life habit goals, appeared to significantly favour a healthier diet and the level of physical activity [40]. Even in very old age, control of arterial blood pressure reduces both mortality and morbidity, as shown by the Hyvet study in adults with a mean age of 83 years. In this population, active treatment was associated with a reduced rate of neurological and cardiovascular death ($P = 0.05$ and $P = 0.06$, respectively), and a 64% reduction in the rate of heart failure (95% CI, 42–78; $P < 0.001$) [41].

Therefore, even in mid- to late-life, interventions focusing on cardiovascular, neurological and renal risk factors remain possible, and have been proven beneficial in terms of the duration and quality of survival.

3.3. Midlife prevention of diabetes

Diabetes is a silent disease. Indeed, one in five diabetic patients between the ages of 18 and 70 is not diagnosed. The peak prevalence of diabetes is beyond the age of 74, reaching 15% in women and 20% in men. Risk factors for diabetes are well established, and include low socio-economic status, sedentary lifestyle, overweight, high waist circumference, hypertension and depression. It was shown in a group of 290 hyperglycemic patients that compared to controls, an intervention in midlife targeting life habits (i.e. a 5% decrease in bodyweight among overweight patients, and an increase in physical activity) significantly delayed the appearance of diabetes, whose annual incidence was 5.1 per 100 participants in the control group, vs. 2.3 per 100 participants in the intervention group ($P < 0.04$) [42]. Unfortunately, a US study of an intensive lifestyle intervention promoting weight loss and increased physical activity had to be interrupted after a median follow-up of 9.6 years for futility. Overall, at the study end, the lifestyle intervention produced greater weight loss, reduced glycated haemoglobin, and greater initial improvements in fitness and all cardiovascular risk factors, but without reaching statistical significance [43].

Diet and lifestyle interventions, even later in life, have been shown to be effective in delaying progression of diabetes. However, poor compliance may explain the disappointing long-term results obtained with such programmes.

3.4. Prevention of chronic respiratory diseases

Asthma often occurs along the life cycle starting from early childhood [44], and affecting 30 million children and adults under the age of 45 years in Europe [45]. Chronic Obstructive Pulmonary Disease has an estimated annual death rate of over 3 million people globally [44,46]. There is an urgent need to understand, prevent, detect and manage these diseases across the life cycle [47], particularly in older people, and their socio-economic impact at the global level also deserves to be investigated.

In Finland between 1994 and 2004, a structured national asthma program including earlier diagnosis and active treatment, implementation of simple guidelines, organization of collaboration between primary care and specialists, development of local asthma physician, nurse and pharmacist networks and patient-centered asthma education and empowerment (guided self-management) resulted in significant reductions in asthma morbidity, hospital admissions, disability pensions and costs [48]. Other successful results of national asthma programs have been published from around the world [49].

The AIRWAYS ICPs initiative (Integrated care pathways for airway diseases) [50] has been approved by the European Innovation Partnership on Active and Healthy Ageing as the model of chronic diseases of the B3 Action Plan. It is a GARD (Global Alliance against Chronic Respiratory Diseases, WHO) Research Demonstration Project with a specific focus on old age adults in AIRWAYS ICPs.

4. Interventions focused on chronic diseases and conditions that most increase disability

4.1. Midlife prevention of cognitive decline and dementia

Four out of five women over the age of 85 suffer from dementia. Apart from ageing, the modifiable risk factors for dementia are well known, namely low educational attainment (HR: 1.59 [95% CI 1.35–1.86]), less than 30 minutes of physical activity per week (HR: 1.82 [1.19–2.78]) and at midlife, smoking (HR: 1.59 [1.15–2.20]), hypertension (HR: 1.61 [1.16–2.24]), obesity (BMI > 30 kg/m²) and diabetes (HR: 1.46 [1.20–1.77]) [51].

The impact of these different risk factors on cognitive decline has been widely investigated. A longitudinal study by the Mayo clinic investigating the interaction between basic education and professional responsibility among 1995 ApoE4-negative adults aged 50 to 65 years, showed that cognitive decline was significantly greater in participants with low education and without professional responsibility [52]. A meta-analysis of 15 prospective studies including 33,816 adults aged > 65 years who were cognitively intact at inclusion, showed that after a mean follow-up of 5 years, intense or moderate physical activity significantly reduced cognitive decline, testifying that physical activity is an excellent means to prevent or delay dementia [53]. The multi-domain randomized “Finger” trial combining better diet, physical activity and control of cardiovascular risk factors in 1260 adults aged 60 to 77 years demonstrated a reduction in cognitive decline in the intervention group, although the participants had more muscular side effects (7%) [54]. Similarly, the longitudinal community-based Framingham Heart study performed between 1948 and 2014 on participants of the first cohort (*n* = 5209), their children (*n* = 5214) and grandchildren (*n* = 4201) showed that stroke multiplies the incidence of dementia by 2. Moreover, it was reported that 12% of participants without any clinical features or suspicious stroke event had vascular lesions on MRI, which could also lead to cognitive decline or dementia [55].

The constant enhancement of cognitive reserve and the prevention of cardiovascular risk factors, notably through physical exercise, are keys to delaying cognitive decline and onset of dementia.

4.2. Midlife prevention of musculoskeletal diseases

4.2.1. Osteoporosis

Age-related osteoporotic clinical expression in women depends greatly on post-puberty level of peak bone mass, which is in turn related to genetics, but also diet (calcium intake), exposure to the sun (vitamin D), and physical activity during the first period of life [56]. Later in life, menopause provokes a considerable decrease in bone mass, which is aggravated by numerous factors, such as low weight, anorexia, a voluntarily restrictive diet, a sedentary lifestyle, a deficit in calcium or vitamin D, smoking, alcohol consumption as well as potential diseases and their specific treatments (e.g. corticosteroids). The accumulation of these risk factors compounds the decline in bone mass, exceeding the fracture threshold. Indeed, the control of modifiable risk factors is essential in order to reduce their negative repercussions on bone and fall risks [57].

A meta-analysis of 10 studies focusing on the effect of physical activities on fracture risk in elderly patients showed promising evidence of a positive effect (relative risk for fractures in the physically active group = 0.49, 95% CI [0.31–0.76]), although the possibility of publication bias could not be ruled out [58]. In addition to exercise, a diet including whole milk, whole dietary products, water enriched in calcium and fat fish, and supplemented in calcium (1200 mg/day) and vitamin D (800 to 1200 IU/day), is the

best method of preventing osteoporosis. Numerous drugs with proven beneficial effects can also be used to the same end [59].

Secondary prevention after a first fracture, based on a personalized management program and including increased physical activity, adapted diet and anti-osteoporotic medications, has also been shown to be useful in preventing new trauma lesions [60].

4.2.2. Osteoarthritis

Osteoarthritis mainly affects women. By the age of 65 years, 65% suffer from osteoarthritis, and this rate rises to 80% by the age of 80 years. Osteoarthritis is as complex disease that simultaneously affects the cartilage, chondral bone and synovium, and includes a local or systemic inflammatory process [61]. The modifiable risk factors of osteoarthritis include metabolic disorders (mainly obesity) and excess pressure and constraints (overweight, bearing heavy loads, excessively intense physical or sport activities). Secondary osteoarthritis can occur in relation with anatomic abnormalities (e.g. dysplasia, varus, valgus), post-traumatic lesions (e.g. fractures, sprains, dislocation), surgery (specifically meniscectomy), or in association with numerous diseases, such as osteonecrosis, chondrocalcinosis, hemochromatosis, or rheumatoid arthritis [59].

Prevention is mainly based on weight loss in case of obesity, as well as regular, moderate and progressive physical activity (outside of acute inflammatory flares), and avoiding heavy lifting.

On the medical side, custom-made shoe inserts, other orthotic devices or technical walking aids, as well as adaptation of the patient's surroundings are useful. Articular rest (outside of the inflammatory flares), physical rehabilitation, manual therapy and possibly thermal bath therapy can also be proposed. Surgery is usually required in case of anatomic abnormality. Long-term medical therapy remains the subject of considerable debate [62], although a single multicentre study reported that sulfate chondroitin could reduce articular pain and control inter-articular damage [63].

4.2.3. Sarcopenia

The European Working Group on Sarcopenia in Older People (EWGSOP) defines age-related sarcopenia as “a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death” [64]. The EWGSOP also proposed diagnosing sarcopenia using the criteria of low muscle mass and low muscle function (either low strength and/or low physical performance) [64]. It was also determined that sarcopenia could be either primary (age-related) or secondary (precipitated by a sedentary lifestyle, under-nutrition, or disease-related) [64].

The International Sarcopenia Initiative analyzed all published papers concerning interventions devoted to reversing sarcopenia [65]. Among them, different resistance training programs appeared to increase muscle strength more than muscle mass, and surprisingly, the benefit was more pronounced in older compared to younger adults. Combining resistance training and nutritional supplements yielded even more positive results by increasing muscle strength, facilitating activities of daily living, and decreasing bone mineral loss [65]. Dietary protein interventions using various combinations and various durations were shown to favour muscle mass and strength recovery as well as activities of daily living. However, results suggested an additive effect of exercise and nutrition interventions that remain to be further explored [65].

4.3. Midlife prevention of age-related sensory deficiencies

4.3.1. Vision

With increasing age, eyesight spontaneously deteriorates, with an ensuing reduction of visual acuity and field of vision, and diseases, such as cataracts, macular degeneration, glaucoma and

diabetic or hypertensive retinopathy become more common. The Health, Aging and Body composition study included 1862 participants aged 70 to 79 years, with no mobility limitation at baseline, despite visual impairment (7.4% had impaired visual acuity, 27.2% had impaired contrast sensitivity, and 29.2% had impaired stereoacuity). At follow-up, visual impairment was associated with walking limitations (HR = 2.0 [95% CI 1.6–2.5]) and stair climbing limitation (HR = 2.1 [95% CI 1.6–2.8]) [66]. Without appropriate care and correction, age-related visual impairments can lead to a deterioration in posture, gait and balance, and thereby increase the fall risk [67–69]. Addressing visual impairment can help to limit negative repercussions on functional capacity.

4.3.2. Vestibular function

Visuospatial and vestibular skills are closely linked, as demonstrated by a specific cross sectional analysis performed within the Baltimore Longitudinal Study of Aging among 183 community-dwelling adults with a mean age of 72 years [range 26–91]. Vestibular-evoked myogenic potentials and various visuospatial cognitive tests were correlated to executive, memory and attention tests, and showed that vestibular loss could be part of the first signs of dementia and Alzheimer's disease [70].

4.3.3. Hearing

Age-related hearing impairments (tonal, sounds, vocal, word repetition) contribute to isolation and cognitive decline [71]. The Epidemiology of Hearing Loss Study, a 15-year longitudinal population-based cohort study involving 1925 individuals aged between 43 and 84 years, reported that the 15-year cumulative incidence of hearing impairment (over 25 decibels in either ear) reached 56.8%. Adjusted for age and gender, the most important risk factors were waist circumference (HR: 1.08 per 10 cm), current smoking (HR = 1.31) and poorly controlled diabetes (HR = 2.03). These findings underline that targeting these risk factors may help prevent or delay the onset of hearing impairment [72].

4.3.4. Age-related olfaction impairment

Dysosmia, hyposmia or anosmia are not frequently investigated in clinical practice, but it is now recognized these impairments are markers of cognitive decline [71].

Apart from non-controllable risk factors, modifiable risk factors for sensory impairments are numerous and accumulate during the life course, such as excessively intense exposure to the sun or to noise, too rich a diet, a sedentary lifestyle, smoking, alcohol, air-conditioning as well as hypertension, diabetes and certain drugs (e.g. corticosteroids, antidepressants).

All these age-related functional abnormalities can contribute to disturbed posture, balance and gait, and thus negatively impact both on daily life and survival. Evidence from the MRC National Survey of Health and Development in England, Scotland, and Wales, involving 1411 women and 1355 men clearly illustrated this point [73]. Participants in this study underwent assessment of physical capability at age 53 (in 1999) using three objective measures, namely grip strength, chair rise time, and standing balance time, and all-cause mortality was recorded up to age 66 (2012). After adjustment for anthropometric measurements, lifestyle and health status, the authors found that subjects in the lowest quintile (worst performance) had lower socio-economic status, more diabetes, cardiovascular and respiratory diseases, and those who could not perform any of the tests had significantly increased rates of death compared with those who were able to perform all three tests (HR 8.40, 95%CI 4.35–16.23) [73].

Taken together, all these findings highlight the interaction between sensory connections and ageing, and the importance of mid-life assessment of vision, hearing and olfaction, to identify risk factors and slow age-related changes [57,68,69].

4.4. Medications and their possible negative impact on age-related dependency

Two contradictory aspects need to be taken into consideration when considering the use of medications, and their possible negative effects [74]. In real life, treatment compliance is insufficient for many diseases for which effective treatments exist (40 to 70% for hypertension, 60% for diabetes, 50% for hypercholesterolemia). On the other hand, polypharmacy (defined as use of more than four different drugs per day) appears to be very common in aged persons. Four different community-based surveys with one to seven years of follow-up demonstrated that polypharmacy favors functional decline and dependency ($P < 0.001$) [75], while prescription of benzodiazepines or anticholinergic drugs negatively impacts on activities of daily living ($P < 0.001$) [75]. Similarly, numerous drugs are known to provoke muscular lesions, such as statins (which may be harmful when given in association fibrates, clofibrate or amiodarone), anti-rheumatic drugs, NSAIDs, or antipsychotics [76].

Another major danger of medications in ageing or aged adults is the potential for kidney failure. NSAIDs have been reported to be responsible for acute kidney failure (adjusted rate ratio 2.30, 95% CI [1.60–3.32]) [77]. Iodinated contrast agents induce asymptomatic kidney failure in 0.1 to 13% of patients within 72 hours after any radiological examination with injection. In most cases, this renal insufficiency resolves spontaneously, however the abnormality could also lead to the need for renal dialysis [78]. In a study of 8357 patients undergoing percutaneous coronary intervention, Mehran et al. established a risk score for contrast-induced nephropathy [79]. A score > 16 points was associated with 57.3% risk of contrast-induced nephropathy and 12.8% risk of dialysis [79]. These data prove the need for careful clinical and biological assessment before radiological examination using contrast medium in ageing and aged patients, in order to avoid kidney failure and the dependency inherent to requirements for constraining and expensive care. Two preventive actions are essential to prevent contrast-induced nephropathy in ageing adults undergoing radiological examinations with contrast injection, namely rehydration and careful choice of the contrast agent by the radiologist.

5. Interventions to delay or prevent the frailty process

Frailty is an age- or disease-related state of increased vulnerability to poor resolution of homeostasis following a stress, which increases the risk of adverse outcomes, including impaired balance, falls, trauma, infection, increased drug use, hospitalization, disability and mortality [80]. Preceded by a totally silent intermediate phase (termed pre-frail), a frailty phenotype was operationalized, and includes unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed and weak grip strength [81].

5.1. The potential “spontaneous” reversibility of the frailty pathway

An adapted version of Fried's criteria for physical frailty [81] was used by the SHARE study (Survey of Health, Aging and Retirement in Europe), the largest observational survey to date performed in Europe, including more than 85,000 individuals aged 65 or over from 19 countries across Europe and Israel [82]. In this study, the prevalence of frailty reached 17%, varying from 5.8% in Switzerland to 27.3% in Spain and the prevalence of pre-frailty was considerably higher, ranging from 34.6% in Germany to 50.9% in Spain [83]. The comparison of naturally occurring transitions between the 2nd (2006) and the 4th (2011) waves of SHARE,

including 15,776 European adults [84], confirmed that the non-frail or robust state deteriorates over time, as do the pre-frail and frail states. Surprisingly, however, without known intervention, pre-frail and frail states were reversible in more than one third of the older adults studied, with transition towards the non-frail or pre-frail states [84]. The spontaneous possible reversibility of frailty was confirmed by the Precipitating Events Project in the USA involving 754 non-ADL-disabled community-living persons aged 70 years or older, followed from 18 to 54 months. Transitions to lesser frailty (rates up to 23.0%) exist, even though they are less frequent than transitions to greater frailty (rates up to 43.3%) [85].

5.2. Risks and protective factors associated with transitions in frailty status

A two-year longitudinal study of 3018 Chinese community-dwelling adults identified risk factors for transition between frailty states in both genders. Older age, previous stroke or cancer, osteoarthritis, lower cognition, chronic lung diseases and hospitalizations were all shown to be risk factors for decline. Conversely, factors favouring improvement away from pre-frail or frail states were lower age, higher MMSE and absence of stroke in men, and lower age, higher economic status, absence of diabetes and no hospitalization in women [86].

5.3. Results of randomized control trials to reverse the frailty pathway

The number of randomized controlled trials performed to reverse the frailty process has escalated in recent years [87]. Published data testify to the fact that protein-energy supplementation alone [88–90] is less effective than physical exercise alone [91–93], and each of these measures individually is less effective than the combination of the two together [94]. The most promising results in terms of frailty reversibility were obtained by randomized controlled trials based on multidisciplinary interventions targeting individual frailty components. However, it appears that the use of classical outcome measures (Short Physical Performance Battery test, Barthel's index, or health related quality of life) is less demonstrative [95] than more targeted and personalized outcome evaluations (Goal attainment scale, life space assessment or self-report measures of activity) [96]. Currently, a number of trials focusing on multifactorial interventions are ongoing [97–99], and their results will be a welcome addition to the body of literature on this topic.

6. Concluding messages

To close this long review of interventions focused on medical conditions that can cause functional disabilities, it is essential to stress again that ageing is a lifelong process. Indeed, lifestyles and behaviours across the life course (physical exercise, adequate nutrition, low alcohol consumption and non-smoking) are fundamental in order to foster functionally independent ageing. In parallel, prevention of diseases that increase disability is necessary and possible at any age. Findings from a number of randomized controlled trials prove that interventions are truly effective in preventing cardiovascular, neurological and renal disease, diabetes, cognitive decline, osteoporosis and sarcopenia, as well as sensory impairments. Targeting populations at-risk, particularly during the second part of life, could help to delay or prevent frailty and its major complications, and specifically disability, which is the most important WHO target on ageing.

Disclosure of interest

The authors declare that they have no competing interest.

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