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K-I

Economic, Fiscal and Societal Consequences of Population Ageing – Looming Catastrophe or Fake News?

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Population ageing is often perceived negatively from an economic standpoint. Yet, taking a more balanced view, it becomes evident that an increasingly older population is not necessarily very costly to care for and that older people provide significant economic and societal benefits – particularly if they are healthy and active. In this brief article we consider key policy questions associated with population ageing, bringing together the latest evidence. We review what is known about the health and long-term care costs of older people, and consider many of the economic and societal benefits of healthy ageing. We also explore policy options within the health and long-term care sectors, as well as other areas beyond the care sector, which either minimize avoidable health and long-term care costs, support older people so that they can continue to contribute meaningfully to society, or otherwise contribute to the sustainability of care systems and the wider public sector in the context of changing age demographics.

Introduction

By 2050, nearly every country will experience an increase in the share of their population over age 60 due to reductions in fertility rates, coupled with declines in both infant mortality and premature deaths that have enabled longer life expectancies(1). High-income countries in particular are seeing sizeable increases in the oldest old, those people 80 years and older.

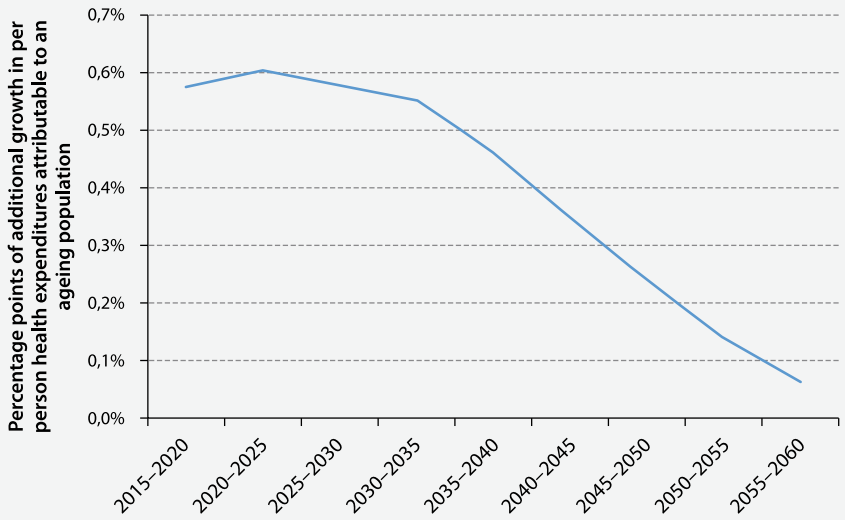
Such population ageing presents both challenges and opportunities for societies around the world (2, 3). As the share of the population at older ages increases, there are concerns over how to respond to greater health and long-term care needs and how to cope with the possible economic and fiscal implications of having a smaller share of people at traditional working ages. Many perceive that a changing population age-structure will have inevitable consequences for households, public finances and possibly even for economic growth and development.

However, evidence suggests that many of the commonly considered macro effects of population ageing are exaggerated and that there are a range of appropriate policy responses that can help avoid the worst outcomes commonly associated with population ageing. First, while ageing will bring higher needs for and costs of care, population ageing is not and will not become a primary driver of health expenditure patterns. The additional demands on the health system coming from a larger older population can in part be moderated with better choices and configurations in health and social care. Likewise, although population ageing will lead to changes in economic behaviours (and in turn the ability to generate public sector revenues through taxations), there are a number of strategies that can mitigate the effects on public finances. Lastly, the evidence suggests that while many older people leave the formal labour market, older people can provide significant economic and societal benefits – particularly if they are healthy and active –through both paid and unpaid work, including caring for other older people.

To manage the challenges and to take advantage of the opportunities afforded by population ageing, policy makers must act across a range of domains such as, on work and employment, on income security, on promoting healthier lifestyles and on developing new and more efficient models of care. This short article aims to provide a balanced summary of the evidence, drawing on some of the work from the European Observatory on Health Systems and Policies programme on the Economics of Healthy & Active Ageing.

What are the implications of population ageing for health and long-term care expenditures?

In general, on a per person basis, health and long-term care needs and expenditures increase with age. This contributes to concerns that an ageing population will rapidly accelerate health expenditure growth rates. It should be noted, however, that there are important differences across countries in how much is spent on health per person for older people. For example, according to health care spending by age data collected for countries in the European Union (EU) by the



Source: (5)

FIGURE 1. ADDITIONAL GROWTH IN PER PERSON HEALTH EXPENDITURE ATTRIBUTABLE TO POPULATION AGEING, EUROPEAN UNION AVERAGE, 2015–2060

Working Group on Ageing Populations and Sustainability (AWG) of the European Commission, in 2015, health care spending for the average 80-year-old in Hungary were almost 16 times higher than spending on the average 20-year-old in Hungary, but this difference was only 2.7-fold in Cyprus(4).

Despite this typical pattern of higher health care spending on older people, available data show that population ageing has in fact a relatively modest effect on health care expenditure trends compared to other important historical drivers of health expenditure growth, such as prices or technological innovation. Changes in population age structure alone are expected to add less than one additional percentage point to the average annual per person health care expenditure growth rates between 2010 and 2060 in the average EU country (Figure 1). Population ageing is simply too gradual a process to rapidly accelerate health care expenditure growth.

Additionally, much of the evidence suggests that calendar age itself is not the primary reason for higher health care spending associated with older ages anyways. Rather, related factors such as proximity to death and poor health are more important determinants of health spending (6–8). Poor health and disability are important drivers of health care expenditure trends at all ages, not just among older people. Likewise, although health care spending increases rapidly in the final months of life, there is research showing that beginning at some age, the older people are when they die, the lower their health spending is near to the end of their life(7) (9). This is likely due to lower use of resource-intensive interventions in older ages (although it may also reflect discriminatory practices and ageism). Therefore, as longevity increases, it is possible that the health care costs of older people relative to younger people will actually fall, especially if older people live in better health, thereby reducing the otherwise expected effects of population ageing on total health care expenditure growth in the future.

It is worth noting that the presence of a formal or informal long-term care system may be another reason behind declining health care expenditures among the oldest old, as costs are shifted outside of the traditional health care sector into other settings. Where formal long-term care is available, its costs are expected to increase rapidly as a result of population ageing. However, this growth in spending on long-term care is coming from a low baseline in most countries. The majority of Organisation for Economic Co-operation and Development (OECD) countries with data available currently spend less than 2% of gross domestic product (GDP) on long-term care, which means that even large increases in spending are unlikely to consume a large share of resources.

How will population ageing affect the ability to generate revenues for health and the public sector more broadly?

There is a common belief that older people are 'dependent' on the financial support of society, particularly younger people in paid employment who fund the public sector through their taxes. This misconception is reinforced by traditional metrics like the old-age support ratios, which assume that all people over a certain age threshold (usually age 65) depend on the support of all adults below it. However, not all people over 65 retire and/or are dependent and many people stop paid work below the age of 65. Alternative approaches to measuring support ratios attempt either to more properly account for changes in population health and disability (though few studies measure care or functional dependency states), or for changes in the

Source: (13)

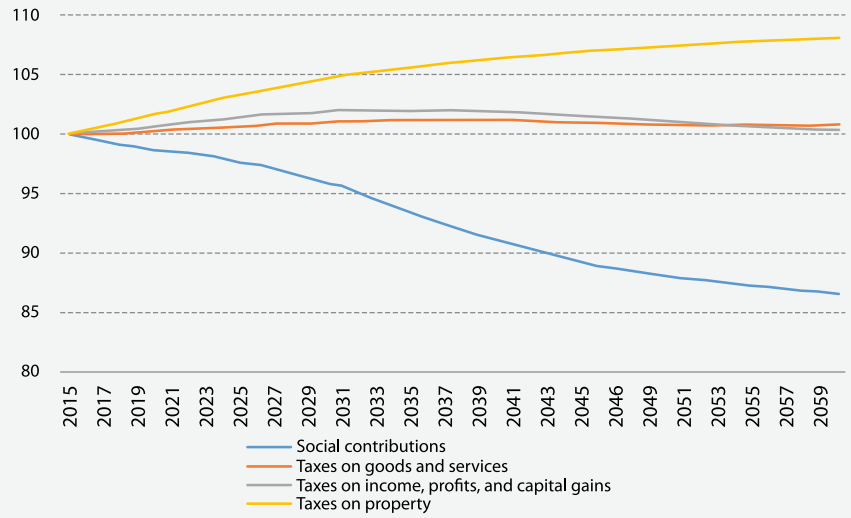


FIGURE 2. HOW WILL PER PERSON TAX AND SOCIAL CONTRIBUTIONS BE AFFECTED BY POPULATION AGEING? (JAPAN EXAMPLE, INDEX 2015 = 100)

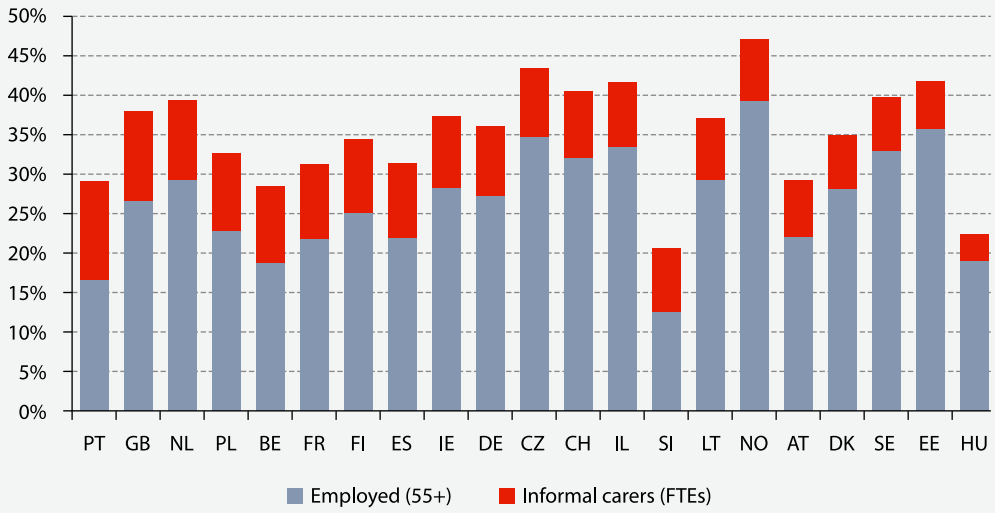
number of consumers and producers in the population(10) (11). These refined indicators suggest that population ageing will create significantly fewer dependency related challenges than anticipated. For example, estimates from the United Kingdom suggest that while the traditional old-age support ratio will increase from 27% (2005–10) to 41% (2045–50), the share of the adult population with disability will stay unchanged at 10% during the same period.

It is important to move even further beyond old-age support ratios to have a clearer sense of how population ageing affects the ability to generate public sector revenues. In European countries, the main sources of public sector revenues are income taxes, goods and services taxes, property taxes, and social contributions. As populations age, countries will likely experience changes in the ability to generate revenues from each of these sources. Older people on average contribute less to public-sector revenues than working-age people as they leave the formal labour market, although they do still contribute significant amounts through taxation. For example, older people who are not in paid work continue to pay goods and services taxes as well as taxes on non-labour income and assets (e.g. property). These may still be significant shares of public sector revenues: tax revenues generated from purely non-income sources (i.e. non-labour, but also capital gains which may be earned by older people) comprise around 30% to upwards of 50% of tax revenues in OECD countries (12).

Simulations allow us to quantify precisely how population ageing affects the ability to generate public sector revenues from different revenue sources. Using population data from Japan, where a large share of the population is already at older ages and increasingly exiting the formal labour market over time, estimates suggest that relying on social contributions primarily generated from the labour market to raise public sector revenues and pay for health and other services results in declining revenues per person over the coming decades (13). Other forms of taxation, such as taxes on goods and services or income taxes appear less susceptible to population ageing, while property taxes may even increase as the age-structure of the population shifts (Figure 2).

Possible policy options to address declines in labour-related social contributions due to population ageing include: increasing the number of contributors; increasing the contribution rate on social contributions; and diversifying the mix of financing sources. However, for countries that depend heavily on the labour market to finance health, none of these policy options on its own is likely to make up for the shortfall in revenues due to population ageing according to simulations. Declining social contribution revenues can be expected even if the revenue base were broadened or if contribution rates were raised equally across all age groups. Diversifying the mix of revenue sources in favour of sources that are less affected by ageing may be an appropriate solution. However, countries will likely still need to reprioritize their current public-sector budgets and allocate more resources to health, or increase tax rates on alternative revenue generation sources in order to maintain sufficient and stable revenues for health(13).

This type of analysis demonstrates that sustainable revenue generation is possible in the context of population ageing, but it underscores the importance of moving away from financing the health system and public sector more broadly through labour-related contributions and premiums and instead relying more on general non-earmarked taxation as the population ages.



Source: Author's calculation based on ESS, 2014 [31].
Notes: Sorted by size of workforce in informal caregiving.

FIGURE 3. PARTICIPATION IN PAID EMPLOYMENT AND FULL TIME EQUIVALENT (FTE) INFORMAL CAREGIVING AMONG THE 55+, SELECTED EUROPEAN COUNTRIES

What are the implications of population ageing for paid and unpaid work?

While population ageing will likely lead to changes in economic behaviours that have consequences for public sector revenues, as discussed above, there remains great scope for older people to contribute meaningfully to society and the economy through both paid and unpaid work, particularly if they are healthy and able to remain active. Although many people leave paid employment in their 60s, others do remain in paid work(14). Comparatively older workers have historically produced less economic output than younger workers, however this may reflect labour market realities that are no longer valid, such as requiring the capacity to carry out physically demanding work. There are important differences in how productivity changes over the life course by type of occupation; for example, jobs requiring less physical exertion may benefit from additional years of experience where skills continuously improve with age, and more experience often improves the quality of the work. Even if older workers are slightly less productive (which may be due to discriminatory practices and ageism, such as poorer access to training at older ages), they are still able to make a positive economic contribution compared to if they are not working at all. In fact, empirical evidence suggests that on average many people have considerable health capacity to continue to engage in the formal labour market at older ages (15, 16).

Many older people produce unrecognized economic and societal value through unpaid work. One of the most relevant forms of unpaid work is informal caregiving. If national statistics accounted for informal carers (adjusted for full-time equivalency (FTE)) it would have a substantial effect on measured employment rates of older people. For example, among the population aged 55+ in Portugal, including informal carers would have increased the employment rate by nearly 13 percentage points in 2014 (Figure 3). Methods to monetize the value of unpaid informal caregiving also demonstrate its considerable economic value, with one study in Spain suggesting the value of informal caregiving being in excess of 2% of GDP (17). However, informal care, especially if it is very demanding on those providing it is not without cost, and the availability of informal caregiving depends in part on the supports given to carers and the availability of complementary formal care.

Provision of informal care by older people also has knock-on effects on formal employment rates, for example, of adult children. If older people are able to provide informal care to dependent older people or care for grandchildren, adult children who would otherwise be providing care may be able to work in paid employment. This is an important channel through which older people contribute to the economy that remains invisible in national statistics.

The policy options: how can decision-makers respond to population ageing?

The health care and long-term care costs of older people, as well as the ability of older people to contribute meaningfully to society and the economy are de-

pendent on a number of factors, many of which are amenable to policy intervention. Undoubtedly, health and functional ability are of utmost importance. This is because of their intrinsic value as well as their indirect effects on the economy via their impacts on reducing care costs and promoting the ability of older people to contribute. Healthy older people require less intensive and expensive care; they are able to engage in paid or unpaid work if they choose to do so; and they accumulate greater asset wealth compared to unhealthy people. Policy-makers can employ a range of policies and strategies in order to control costs of care and enhance economic and societal contributions of older people, ensuring that population ageing does not lead to undue economic pressures. Examples of such interventions, both indirect (via improvements in health and functional ability) and direct, are summarized below.

Policies to promote healthy and active ageing

The types of interventions that support health and activity at older ages include those that delay the onset and progression of disease, as well as those that prevent or delay care dependency. Importantly, policies which encourage behavioural changes can have significant health effects even if those changes do not occur until older ages. For example, there is good evidence that those who quit smoking at age 65 live longer than those who continue to smoke. To prevent dependency, a key focus should be on preventing cognitive decline, where there is some evidence that taking a multidomain approach can improve or maintain functionality. Other interventions to prevent or reduce frailty, such as resistance training or promoting physical activity at older ages, can also be effective.

Policies to promote cost-effective health and long-term care interventions

Technological advancements, such as telemedicine, as well as assistive technologies, such as digital memory aids or automated medication dispensers, can be effective ways to provide care using relatively low resource levels. There has also been widespread interest in integration of health and long-term care and other models of care delivery to help control care costs, particularly given the complex care needs of older populations. There are many varied examples of delivering coordinated or integrated health and long-term care. There is also good evidence that supporting better treatment and care choices near the end of life can reduce the use of unnecessary treatments and tests, lower costs, improve the experiences of patients and carers and even, in some cases, contribute to longer survival.

Policies to support acceptable, equitable and efficient funding and income transfers

Given likely reductions in the share of the population in paid work as a result of population ageing, health and long-term care financing systems may need to diversify their sources of revenue if they are to continue to generate sufficient, stable resources. For example, health and long-term care financing systems that are heavily reliant on payroll contributions may need to be redesigned to fill the financing gap from general revenues or private sources.

Increasing the reliance on locally raised taxes or, conversely, centrally raised taxes is one focus of ongoing debate and reforms, with countries moving in different directions. The use of hypothecation (or earmarking) of payroll or 'sin' taxes has been seen by some as a potential source of funding. However, many argue that this introduces unwelcome budgetary controls and that spending is ultimately determined by revenue generated rather than based on changing needs and demand. Earmarked funding sources are also likely to be susceptible to economic fluctuations, resulting in unstable revenue streams. Similar arguments have been made against the introduction of mandatory long-term care insurance arrangements, such as those seen in Germany, Japan and Korea. Overall, acceptability of higher taxes and transfers varies between countries and can depend in part on the transparency of the process and the perceived fairness of the rules.

Policies to support paid and unpaid work

While there is widespread interest in keeping people in paid work for longer, raising pension ages alone may simply divert some older people into other state support for unemployed people or people with disabilities if they are not healthy enough to work productively. Health systems can usefully help to keep older people healthy and able to remain in the workforce. There is also growing recognition that workplace health promotion interventions, such as screening activities to identify potential health risks and lifestyle management activities to improve health and health behaviours, can keep older workers healthy and productive. Adapting work practices to accommodate older workers' needs and circumstances can also help older people to remain in work. Good evidence shows that flexible working practices, such as flexitime, part-time working, job-sharing and working from home, can help older people, particularly those with health issues or caring responsibilities, to remain in employment for longer and can result in healthier lives overall. Changes to the physical work environment can also support older workers to remain in employment, while contributing to improvements in productivity.

On the unpaid work side, strategies that support informal carers through training or by providing cash for care have been shown to reduce carers' stress and may also improve the quality of care. However, it is important to acknowledge that cash-for-care benefits can act as a disincentive to participating in formal employment. Much emphasis has been placed on implementing reforms to enable carers to combine unpaid care with paid employment, including the introduction of paid or unpaid leave and flexible working arrangements.

Conclusion

Policy-makers require high-quality information to make informed decisions and develop policies with respect to older people. This overview of evidence on some of the costs and benefits associated with population ageing suggests that older people are likely to be less costly to societies than often perceived, at least in terms of health and long-term care. Older people also provide benefits that are frequently not quantified, such as in the form of informal caregiving, while others remain in paid work at older ages, particularly if they are healthy enough and choose to do so.

There are many benefits from investing in the health of older people, not least for the sake of economic growth and sustainable public finances. Any questions regarding the costs of interventions to support the health and activity of older people should take into account the potential benefits not only from an economic perspective, but also in terms of improving quality of life and experiences in older age. As has been described above, these sorts of benefits are often not properly taken into account.

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K-II

Geroprotectors: Time to Change the Way We Take Care of Older People?

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Human life expectancy has been increasing steadily over the last century but this has resulted in an increasing incidence of age-related chronic diseases. Patients often present with more than one disease at the same time (multimorbidity) and develop frailty. Multimorbidity and frailty have complex medical needs and are strongly associated with disability and hospitalization. However, current treatments are suboptimal with problems of polypharmacy due to the fact that each disease is treated individually.

Geroprotectors target fundamental mechanisms of ageing common to multiple age-related diseases and shows promise in delaying the onset of multimorbidity in animal models. I will present preclinical data on a new geroprotector, Zoledronate (1), together with the recommendations from the European network MouseAGE and Healthy Lifespan Institute thinking on the steps required to ensure these new interventions are translated from the bench to the bedside

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K-III

Importance of Sleep for Healthy Ageing – Impact of Sleep-Disordered Breathing

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Abstract

Sleep Medicine is growing multidisciplinary field within the biomedicine and health. According to the International Classification of Sleep Disorders 3 (ICSD-3), there are about 80 sleep disorders, divided into 6 different clinical divisions: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep–wake disorders, parasomnia, sleep-related movement disorders, as well as "other sleep disorders". Some sleep disorders are strongly associated with specific age and they appear almost exclusively in childhood or in the elderly, but most sleep disorders may appear in all age groups. However, the prevalence is significantly positively associated with ageing. Also, there is a significant negative correlation of sleep duration and sleep quality with age, but the impact of poor sleep quality and sleep disorders on health, healthy ageing and quality of life is not recognized enough, and the public awareness is not at the satisfactory level. It is important to state that general statements about sleep architecture and sleep stages proportions in the total sleep time presented in the literature can only be made regarding sleep in the normal young adult without sleep complaints who is living on a conventional sleep-wake schedule. One of the most notable findings regarding sleep in the elderly is the profound increase in inter-individual variability, which thus precludes generalizations such as those made for young adults.

The most prevalent sleep disorders of today, such as insomnia or sleep-related breathing disorders are strongly positively associated with age and make one of the most important risk factors for diminished quality of life, as well as increased morbidity and mortality of the most prevalent diseases in general population, such as cardiovascular and glucose metabolism disorders, but also cancer, which has been published in many recent studies. Also, cognitive and psychomotor impairments are facilitated in the elderly in the presence of sleep disorders.

Increasing public awareness, improving and expanding diagnostic and treatment capacities for sleep disorders, as well as education of sleep medicine experts, which was recently developed in the Republic of Croatia according to European guidelines, are the primary goals of up-to-date sleep medicine, one of the most prosperous medical discipline, which is going to be even more important in the future due to increased longevity in general population and strong links of sleep medicine and ageing.

Sleep

There are many definitions of sleep. According to a simple behavioral definition, sleep is a reversible behavioral state of perceptual disengagement from and relative unresponsiveness to the environment. It is also true that sleep is a complex amalgam of physiologic and behavioral processes. Sleep is typically (but not necessarily) accompanied by postural recumbence, behavioral quiescence, closed eyes, and all the other indicators that one commonly associates with sleeping (Carskadon and Dement, 2011). We spend nearly one-third of our lives asleep, and many mammals, includ-

ing small laboratory rodents, spend half or more of their existence in this state.

The sleep-wake cycle is regulated by two separate biological mechanisms, which interact together and balance each other. This model is often referred to as the *two-process model* of sleep-wake regulation composed of the Process C that reflects the *circadian rhythm*, and the Process S that reflects the *sleep-wake homeostasis* (Borbély, 1982).

There are two distinct states of sleep, defined on the basis of several physiologic parameters. Rapid eye movement (REM) and non-REM (NREM) sleep exist in most mammals studied. These states are both different from wakefulness and distinct from one another (Dogas et al., 2014). However, differentiating sleep (or sleep stages) from quiet wakefulness is hardly possible at the behavioral level. NREM sleep, formerly subdivided into four stages according to standard Rechtschaffen & Kales (R&K) sleep scoring rules (Rechtschaffen and Kales, 1968), is currently distinguished into three stages according to the American Academy of Sleep Medicine (AASM) scoring rules (Iber *et al.*, 2007; Berry *et al.*, 2014). Those stages are mostly defined based on the electroencephalogram (EEG). The EEG pattern in NREM sleep is commonly described as synchronous, with characteristic waveforms such as sleep spindles, K-complexes, and high-voltage slow waves. NREM stages (stages 1, 2, 3, and 4 according to R&K, and stages 1, 2, 3 according to AASM, stage 3 according to AASM being composed of stages 3 and 4 according to R&K) represent a depth-of-sleep continuum, where the arousal threshold is generally lowest in stage 1 and highest in stage 3 (or 4) sleep. Classical studies showed that the sound intensity needed to awake a subject is positively correlated with the depth of sleep. That is, during deep sleep characterized by the slow wave activity as seen in the EEG (hence the name "*slow wave sleep*"), sound intensity had to be greatest to lead to awakening. In traditional perspective, NREM sleep was usually associated with reduced mental activity. However, recent studies showed it is not the case, as for instance there are strong associations between NREM sleep and memory consolidation processes.

Importantly, general statements about sleep stages proportions in the total sleep time presented in the literature can only be made regarding sleep in the normal young adult without sleep complaints who is living on a conventional sleep-wake schedule. One of the most notable findings regarding sleep in the elderly is the profound increase in inter-individual variability, which thus precludes generalizations such as those made for young adults (Carskadon and Dement, 2011).

Chronotypes and sleep

In humans, the most obvious variation in behavior organization, during the 24-hour day, can be seen in their preferred timing of sleep and wakefulness. Total amount and the timing of sleep are determined by several factors, including environmental factors, endogenous circadian rhythms and time awake. Human preferences in the timing of sleep and wake are called "chronotypes" and are at least partly based on genetics. Human chronotypes can be easily investigated using convenient self reported questionnaires, such as Horne-Ostberg morningness-eveningness questionnaire (Horne and Ostberg, 1976), and Munich Chrono Type Questionnaire, that differentiate timing of the daily activities during workdays versus free days (Roenneberg *et al.*, 2007). Chronotypes (morningness–eveningness) are one of the most common inter-individual differences in circadian rhythmicity. As such, chronotype represents a phenotypic aspect of the circadian rhythmicity. Morning-type and evening-type persons differ in endogenous circadian phase of their biological clocks (Roenneberg *et al.*, 2007). Moreover, it is well known that diurnal preferences (morningness–eveningness) are influenced by person's gender, showing a greater shift toward morningness in women than in men. They are driven by reproductive hormones and thus endogenously generated. Sex differences in human chronotypes disappear at approximately age of 50 (Roenneberg *et al.*, 2007).

Diurnal preferences are associated with age, as well. Although thought to be primarily a genetic trait, it is well established that chronotype is not constant throughout the adult lifespan. During the childhood, children are more morning-types, while during the adolescence change in chronotype occurs, shifting adolescents towards eveningness-types. Also, it has been found in cross-sectional studies that chronotype changes towards a morning-type orientation with advancing age (Monk and Buysse, 2014). The biological foundation of this has been confirmed by laboratory studies showing that older adults (seniors) have circadian rhythms, which phase at an earlier clock time (usually by 1–2 h) than those of younger adults (Monk and Buysse, 2014).

Sleep and age

Sleep is an important component for health and wellness across the lifespan. However, older adults do not sleep as well as younger adults. Why? What alterations in sleep quantity and quality occur as we age, and are there functional consequences? What are the underlying neural mechanisms that explain age-related sleep disruption? There are well-known changes in human sleep quantity and quality in cognitively nor-

mal older adults and the functional consequences of age-related sleep disruptions. However, there is a still-debated question: do older adults simply need less sleep, or rather, are they unable to generate the sleep that they still need? (Mander *et al*., 2017).

Sleep disturbances are a common presenting symptom of older-age adults to their physicians. There are normal changes in sleep pattern with ageing and primary sleep disorders in the elderly, but behavioral factors and primary psychiatric disorders affecting sleep in this population are numerous.

Normal age-related changes to sleep-wake physiology

Physicians addressing sleep complaints in older adults are commonly asked about how much sleep is enough. The National Sleep Foundation recommends 7–8 hours of sleep for adults aged 65 and older. This recommendation is supported by evidence that older adults sleeping anywhere from 6–9 hours have better cognition, mental and physical health, and quality of life compared to older adults with shorter or longer sleep durations. Thus, the need for sleep is not reduced in older adults, but the ability to get the required sleep may be decreased due to normal changes in sleep architecture through the lifespan. Age-related changes in sleep physiology have been well-documented using polysomnography. Most age-dependent changes in sleep parameters occur by age 60 years, with the exception of sleep efficiency. Sleep efficiency (percentage of time spent asleep while in bed), on the other hand, continues to show an age-dependent decline beyond age 90 years. Older adults also have a decline in total sleep time, with corresponding decreases in the percentage of time in slow wave sleep (SWS or N3) and rapid eye movement (REM) sleep. SWS and REM sleep are thought to promote metabolic and cognitive recovery, and to enhance learning and memory, respectively. Older adults also have an increase in time awake after sleep onset (WASO). While the number of arousals from sleep increase in healthy older adults, evidence suggests they do not have greater difficulty falling back to sleep. There is an increase in sleep latency (the time it takes to fall asleep) up to age 60, with no clear age effect beyond that point (Monk, 2005).

Circadian rhythm in elderly

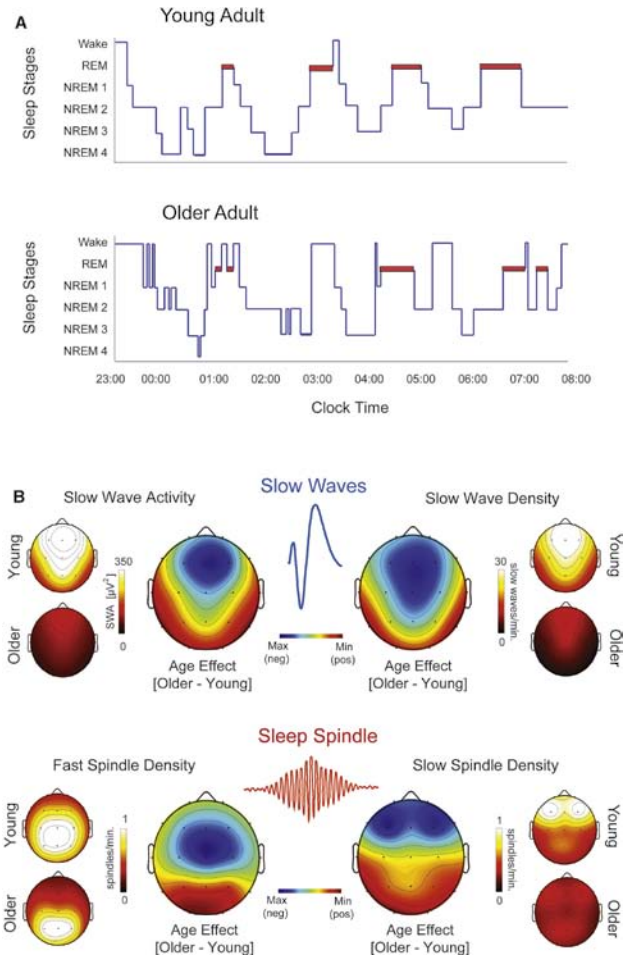
Circadian rhythms also change over the lifespan. These rhythms are 24-hour intrinsic physiological cycles that are involved in control of sleep-wake and many other physiologic processes (e.g. blood pressure, bone remodeling, release of certain hormones). Ageing is associated with a phase advance, resulting in an earlier onset of sleepiness in the evening and earlier morning awakening. Daytime wakefulness is affected by phase advance, with older adults being more alert in the morning and more somnolent in the evening. Studies conducted in different age groups revealed that adolescents and elderly population are two populations predominantly at the risk of circadian rhythms disorders. Adolescents go to bed considerably later in the evening. This is mostly pronounced during working days and associated with sleep rebound, characterized by extended time spent in bed on weekends. Changes in circadian rhythm associated with advanced age include a tendency to sleep earlier and shift toward morning type, with an increased number of naps during daytime (Park *et al*., 2002). While napping is common in older adults, results with regard to the benefit or harm of this practice are mixed. Some studies show beneficial and potentially protective effects of napping in later life, while others show it to be a risk factor for morbidity and mortality. There is some evidence to suggest that naps are protective for mortality if nighttime sleep duration is short, but are associated with increased mortality risk if nighttime sleep duration is longer than nine hours.

Changes in circadian rhythms are associated with a decline in sleep quality due to increased sleep latency and more pronounced sleep fragmentation during the night, emphasizing weakened and fragmented circadian rhythms during ageing (Huang *et al*., Bliwise *et al*., 2005).

Sleep, Ageing and Gender

Though reliable macro and micro sleep differences exist between younger and older adults, not all older adults suffer the same degree of sleep disruption. Instead, there is large inter-individual variability. This means that age per se is not the sole determinant of sleep disruption in later life. Rather, factors that interact with the aging process must confer vulnerability or resilience to age-associated declines in sleep quantity and quality.

In the context of older age, one such interacting factor is gender. Men experience far greater relative disruption and impairment in NREM sleep than women later in life. In a study comparing over 2,500 older adults between the ages of 37 and 92 (Redline *et al*., 2004), increasing age was reliably associated with the same features described above: decreased slow wave sleep time, reduced sleep efficiency, increased NREM stage 1 sleep time, increased number of arousals, and modest decreases in REM sleep time. However, when stratified by gender, differences emerged. Men over the age of 70 demonstrated a highly significant 50% reduction in slow wave sleep, relative to men under the age of 55, together with a concomitant increase in lighter NREM stages 1 and 2. In contrast, women showed no such significant decline in slow wave sleep or increase in lighter NREM sleep time relative to their younger



(A) Prototypical sleep stage architecture across a 9 hr sleep period in a younger adult (top) and an older adult (bottom), using classic sleep staging criteria (Rechtschaffen and Kales, 1968). Relative to younger adults, older adults demonstrate: longer sleep latency, a greater number of transitions to lighter stages of sleep and wakefulness, more time spent awake after sleep onset, more fragmented sleep, and less time in slow wave sleep, especially within the early sleep cycles.
(B) Upper: Representative topographical head plots of EEG-quantified differences between younger and older adults in slow wave activity (left upper) and density (right upper). A similar sleep spindle density for fast sleep spindles (13.5–15 Hz; bottom left) and slow sleep spindles (12–13.5 Hz; bottom right) is shown in the bottom image. The hotter colors represent higher values. The center rainbow topoplots in each image represent the subtracted difference between younger and older adults, with darker blue representing larger deficits in older relative to younger adults. For both slow waves and sleep spindles, older adults demonstrate the largest regional oscillation impairments over frontal EEG derivations (*From Mander et al., 2017; the data are adapted from previous reports Mander et al., 2013, 2014, 2015, 2016b).*

Figure 1. Schematic of Age-Related Changes in Sleep Architecture and NREM Sleep Oscillations

gender group. Compared between genders, men over the age of 70 had more than a 3-fold deficit in slow wave sleep amount compared with age-matched women. Meta-analyses have replicated this gender-specific difference in slow wave sleep in older age (Ohayon *et al.*, 2004). Interestingly, the moderate reduction in REM sleep time in the oldest participants (>70 years old) was common to both males and females, suggesting a gender-independent deterioration of this sleep stage.

Gender also impacts age-associated changes in slow wave sleep homeostasis. Older adult men demonstrate significantly less homeostatic slow wave sleep rebound during recovery sleep following sleep deprivation than equivalent-age older women. As with the comparison of basic sleep stages, both elderly men and women show similar homeostatic rebounds in REM sleep during post-deprivation recovery nights (Reynolds *et al.*, 1986). Therefore, gender-dependent and gender–independent effects emerge in older age, further suggesting a model in which some homeostatic mechanisms of sleep remain equivalent and somewhat intact in cognitively normal older adult men and women, such as REM sleep, while others show strong gender-dependent differences, such as slow wave sleep.

Despite gender-specific changes in NREM sleep quantity and quality being more severe in men, a paradoxical and, as yet unexplained, finding is that women are more likely to suffer subjective complaints of poor sleep as they get older, relative to older men (Ohayon *et al.*, 2004). Whether this is due to report bias on the basis of gender, or is explained by an underlying physiological mechanism, remains unclear.

Sleep medicine and ageing

Sleep Medicine is growing multidisciplinary field within the biomedicine and health. According to the International Classification of Sleep Disorders 3 (ICSD-3), there are about 80 sleep disorders, divided into 6 different clinical divisions: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep–wake disorders, parasomnia, sleep-related movement disorders, as well as "other sleep disorders". Some sleep disorders are strongly associated with specific age and they appear almost exclusively in childhood or in the elderly, but most sleep disorders may appear in all age groups. However, the prevalence is significantly positively associated with ageing. Also, there is a significant negative correlation of sleep duration and sleep quality with age, but the impact of poor sleep quality and sleep disorders on health, healthy ageing and quality of life is not recognized enough, and the public awareness is not at the satisfactory level.

Sleep disorders in elderly

The number of people in Croatia, as well as in the United States who are 65 years or older is steadily increasing. In Croatia, according to the State Department for Statistics and the Teaching Department for Public Health „Dr. Andrija Štampar", in 2011 there

were about 17,7% people at 65 years or older and this proportion increased in 2016 to 19,41%.

In the US, proportion of this population is expected to double over the next 25 years to about 72 million. By 2030, roughly 1 in 5 people in this country will be over the age of 65.

Sleep complaints are common among older adults, and as this segment of the population grows, the prevalence of sleep disturbances will also increase. However, sleep problems are not an inherent part of the ageing process (Miner and Kryger, 2017).

There are changes to sleep architecture over the lifespan that are not, in themselves, pathologic, but can be viewed as making older adults more vulnerable to sleep disturbances. It is the consequences of ageing, in the form of medical and psychiatric comorbidity, medication and substance use, psychosocial factors, and primary sleep disorders that put older adults at risk for sleep disturbance. The increasing prevalence of multimorbidity (i.e., having at least 2 concurrent diseases in the same individual) among older adults means that sleep disorders might arise from multiple different domains. Thus, sleep disturbance in this age group should be considered a multifactorial geriatric health condition (previously referred to as a geriatric syndrome), (Miner and Kryger, 2017) requiring consideration of multiple risk factors and a comprehensive treatment approach.

In general, changes to sleep architecture with normal ageing include decreases in total sleep time, sleep efficiency, slow wave sleep, and REM sleep, and an increase in wake after sleep onset. Although sleep disturbance is common with ageing, it is not an inherent part of the ageing process and medical, psychiatric, and psychosocial factors overshadow age as risk factors. There are numerous studies confirming that sleep disturbance in older adults is associated with increased morbidity and mortality and the evaluation and management of sleep disturbances in older adults is best approached as a multifactorial geriatric health condition, arising from impairments in multiple domains.

The most prevalent sleep disorders of today, such as insomnia or sleep-related breathing disorders, among which, Obstructive Sleep Apnea (OSA) is the most prevalent and important one, are strongly positively associated with age and make one of the most important risk factors for diminished quality of life, as well as increased morbidity and mortality of the most prevalent diseases in general population, such as cardiovascular and glucose metabolism disorders, but also cancer, which has been published in many recent studies. Also, cognitive and psychomotor impairments are facilitated in the elderly in the presence of sleep disorders.

Increasing public awareness, improving and expanding diagnostic and treatment capacities for sleep disorders, as well as education of sleep medicine experts, which was recently developed in the Republic of Croatia according to European guidelines, are the primary goals of up-to-date sleep medicine, one of the most prosperous medical discipline, which is going to be even more important in the future due to increased longevity in general population and strong links of sleep medicine and ageing.

Obstructive sleep apnea

Obstructive sleep apnea (OSA) increases with advancing age, with prevalence estimates differing depending on the definition used. Using a definition of 10 or more apneas and/or hypopneas per hour of sleep, OSA prevalence estimates in older adults may be as high as 70% in men and 56% in women. This is in contrast to prevalence estimates in the general adult population of 15% in men and 5% in women. While it is more common, this condition frequently goes undiagnosed because the phenotype of OSA can look very different in older adults. After the age of 60, the prevalence of OSA is equivalent in males and females, obesity is no longer a significant risk factor, and witnessed apneas and snoring are not as frequently reported. Older adults are also more likely to present with more sleep-related complaints, including daytime sleepiness and nocturia. Older adults are at risk for OSA for several reasons. With aging there is loss of tissue elasticity as well as sarcopenic muscle wasting. There are also structural changes to the upper airway, including lengthening of soft palate and upper airway fat pad deposition. These age-related changes increase the tendency for oropharyngeal collapse. In addition, ventilatory control instability may predispose older adults to apneic events. The negative consequences of OSA in older adults include excessive daytime sleepiness, decreased quality of life, neurocognitive impairment, nocturia, and worsening of cardiovascular disease, particularly hypertension, heart failure and stroke. Diabetes mellitus and depression have also been found to be more common in older adults with OSA. The impact of untreated OSA in older adults on mortality is not clear. However, older adults have similar adherence rates to treatment, so there is no clear reason not to treat older adults with OSA. Recently there was a report of estimated risk for OSA in the Croatian population published using the standardized international questionnaire named STOP (S-noring, T-iredness, O-bserved apneas, elevated blood P-ressure), which was validated in Croatian language and proved to have high sensitivity and a reasonable specificity for detecting people at risk for OSA (Dogas *et al.*, 2018). In this report, on a rather large sample of almost 11,000 respondents, there were high proportions of people at risk with strong and highly significant positive associ-

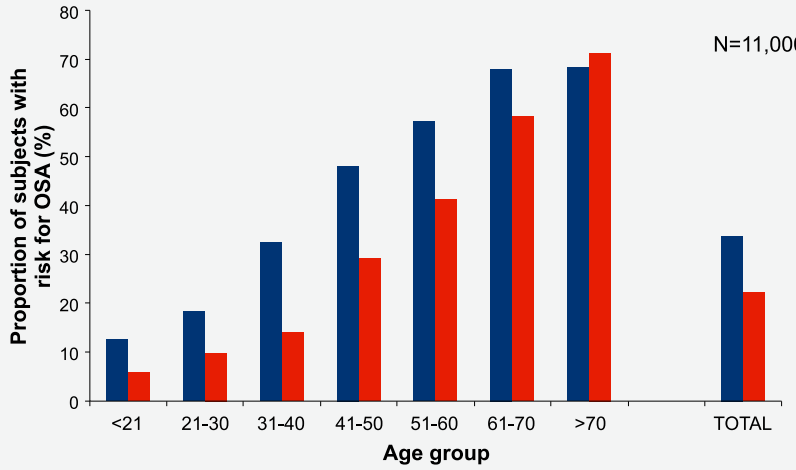


Figure 2. Obstructive sleep apnea risk according to STOP questionnaire in different age groups (blue columns – male, red columns – female) in the Croatian population (*Dogas et al., in prep*).

ation with age (Figure 2). Also, men were at significantly higher risk than women until elderly, were the numbers were similar.

Sleep and ageing during the COVID-19 pandemics

Poor sleep is a risk factor for mental health, well-being and susceptibility for infective diseases such as COVID-19 especially considering the crisis measures such as quarantine

Long-term home confinement due to an unprecedented global viral outbreak by COVID-19 of vague duration entails increased levels of stress and anxiety, disruption of established daytime and nighttime routines, as well as working schedules, causing deterioration of positive associations between home, relaxation and sleep (Altena *et al.*, 2020). Given the commonness of stress-related sleep problems with possible adverse health consequences and the well-known bidirectional relation between emotional and behavioral reactivity and sleep quality, sleep disturbances during quarantine may become an important issue for everyone. Furthermore, misalignment between behavioral and environmental cycles and environmental setting changes during isolation, including limited beneficial effects of natural daytime light exposure and artificial light suppression of the regular circadian rhythm, may impair circadian system organization and significantly influence sleep patterns, resulting together in an array of metabolic abnormalities (Altena *et al.*, 2020). The rising pervasiveness of circadian rhythm and sleep disruptions during home confinement with increasing evidence of detrimental effects on health, emphasizes the importance of circadian system function and addressing sleep disturbances.

Sleep has been well-recognized as a marker of mental health, especially in the elderly. Sleep problems were observed in most mental disorders and it has been proposed that sleep disturbances imply an arousal system imbalance likely representing a basic dimension of mental health, with polysomnographic findings possibly playing a key role in psychiatric comorbidity processes. Also, it has been well established even in non-clinical populations that sleep quality is associated with mental health problems such as depression, anxiety and stress. Considering that elderly population is at particular risk for sleep disorders and mental health problems, the proposed association is of specific relevance in this population. Association of sleep and mental health has been extensively reported in elderly females, even after controlling for risk factors common to both. In addition, mental health is associated with physical health issues including general health status, activity limitations, and chronic health conditions in elderly females. The clinical and epidemiologic evidence on the relationship between sleep and physical and mental outcomes highlight the relevance of screening sleep issues in the general population, and especially in vulnerable groups such as the elderly, those with multiple chronic diseases, sucha as sleep breathing disorders patients with cardiovascular and glucose metabolism comorbidities, but also students as a partucularly sensitive group due to their specific sleep habits and risky environment such as quarantine and ongoing online education process.

Vulnerable population groups in COVID-19 pandemics

Present data point to the fact that COVID-19 infection is particularly serious in some population groups. Thus far, there is an international consensus that vulnerable populations for COVID-19 may include anyone who is an older adult (65 years of age or older), anyone at risk due to an underlying medical condition

(such as cardiovascular disease, hypertension, diabetes, chronic respiratory diseases, cancer), anyone at risk due to a compromised immune system from a medical condition or treatment and anyone with severe obesity (BMI>40) (ECDC-Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK – eighth update; WHO-Coronavirus disease 2019 (COVID-19) Situation Report-51). At present, there is no data that sleep-disordered breathing (especially Obstructive Sleep Apnea, OSA) increases the risk for contracting or developing more severe forms and outcomes of COVID-19. However, OSA is a condition characterized by many comorbidities including cardiovascular diseases, metabolic diseases (especially diabetes mellitus type 2; see Table 1 and Figure 3 for illustration of this overlap in the Croatian population; Dogas *et al.*, 2018) and respiratory diseases (Bonsignore *et al.*, 2019), all of which put the individual at a higher risk of COVID-19. Although it is considered a sleep disorder, OSA is also included in the International Classification of Diseases list as a chronic respiratory disease (ICD-11, WHO). In OSA, the respiratory function is severely modified such that the episodes of partial or complete airway obstructions affect normal breathing patterns and gas exchange. Additionally, OSA is also more common in the older population (Young *et al.*, 2004), therefore it can be viewed as a superimposing factor to the initial risk stated for this specific population. Finally, another risk factor for COVID-19 is obesity and obese patients have been shown to have a higher incidence of OSA (Malhotra *et al.*, 2002; Young *et al.*, 2004), but are also more prone to developing other chronic diseases, especially the ones affecting the immune system. Having all of this in mind, this could make the individuals suffering from sleep-related breathing disorders more susceptible to viral pneumonia-like diseases, such as COVID-19. Considering the high prevalence of sleep-disordered breathing, which is estimated in recent studies to be up to 25–50% in the adult population, it is of major interest to assess the risk, prevalence and the outcomes of the COVID-19 disease caused by novel coronavirus SARS-CoV-2 in this population.

OSA patients as a vulnerable group particulary sensitive to COVID-19

So far there is no data that OSA by itself increases risk of infection. For most OSA patients, a reduction in their quality of life is due to symptoms such as poor sleep quality, excessive daytime somnolence, and fatigue with differences between gender, ages and nations. Also, because of the known comorbidities such as hypertension, diabetes and obesity OSA patients are at higher risk in all age groups, especially in elderly, but also in many cases where OSA was not recognized and diagnosed before the COVID-19 infection. Also OSA patients might be more likely to develop complications of COVID-19 than other individuals because of an already compromised upper airway system, repetitive episodes of hypoxia and hypercapnia during the night, and also immune system. Therefore we might speculate whether OSA promotes negative outcomes and more complications in patients diagnosed with COVID-19 especially if they have been diagnosed with comorbidities such as arterial hypertension, diabetes mellitus and obesity.

In patients who are diagnosed with moderate to severe OSA, a continuous positive airway pressure (CPAP) device is a gold standard therapy and should be used permanently during sleep because without treatment, exacerbation of the disease will also include further weakening of the immune system, which make them more susceptible for infection. Precaution should be advised for patients who are at home in quarantine and regularly use CPAP devices. Usage of CPAP could spread the virus through the exhalation port, which allows carbon dioxide to escape from the mask. This port also may release smaller virus-containing particles as an "aerosol," which can remain suspended in the air for a few hours. However, patients with severe OSA should continue using CPAP while sleeping alone in a separate bedroom. So far, there is no studies showing that using CPAP will cause more severe forms of

Table 1. Proportion of subjects with Diabetes Mellitus type 2 (DM2) in the groups of respondents with and with no risk for OSA according to STOP questionnaire in different age groups; Number of subjects and proportions in each subgroup (%) are shown.

Age group (years)	Total N=10196	No risk for OSA N=4794	With risk for OSA N=5402	χ^2	*P**
<21	48/2944 (0.6)	31/2675 (1.2)	17/269 (6.3)	40.59	<0.001
21–30	76/2628 (2.9)	52/2253 (2.3)	24/375 (6.4)	19.17	<0.001
31–40	59/1112 (5.3)	32/858 (3.7)	27/254 (10.6)	18.57	<0.001
41–50	75/1547 (4.9)	30/967 (3.1)	45/580 (7.8)	17.04	<0.001
51–60	157/1479 (10.6)	49/739 (6.6)	108/740 (14.6)	24.72	<0.001
61–70	131/589 (22.2)	35/217 (16.1)	96/372 (25.8)	7.42	0.006
>70	124/555 (22.3)	28/166 (16.9)	96/389 (24.7)	4.09	0.043
Total	670/10854 (6.2)	257/7875 (3.3)	413/2979 (13.9)	419.32	<0.001

*Chi-squared test

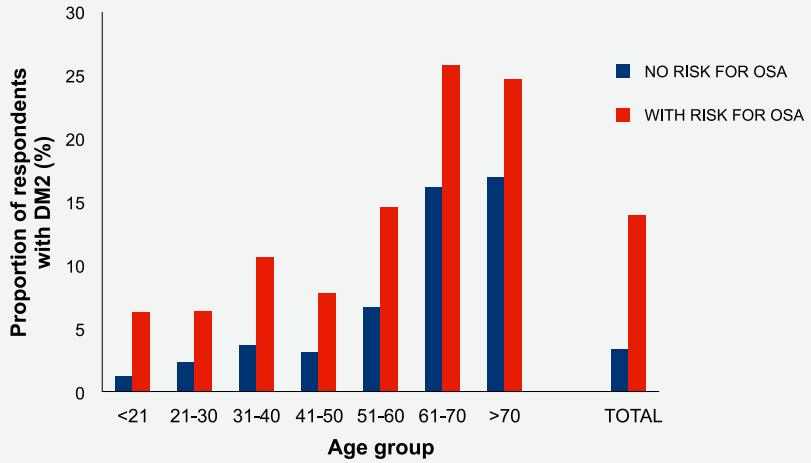


Figure 3. The proportions (%) of respondents with diabetes mellitus type 2 (DM2) among those with and with no risk for OSA according to the STOP questionnaire in the Croatian population.

COVID-19, but we need more scientific research to provide evidence.

It should be emphasized that due to the lack of evidence on COVID-19 infection severity and outcomes in OSA patients, both those treated at home or in a hospital settings with provided respiratory care (oxygen and/or mechanical ventilation), especially in the vulnerable elderly populations during quarantine, this research question provides an innovative scientific research interest.

Conclusions

Sleep Medicine is growing multidisciplinary field within the biomedicine and health. The most prevalent sleep disorders of today, such as insomnia or sleep-related breathing disorders are strongly positively associated with age and make one of the most important risk factors for diminished quality of life, as well as increased morbidity and mortality of the most prevalent diseases in general population, such as cardiovascular and glucose metabolism disorders, but also cancer, which has been published in many recent studies. Also, cognitive and psychomotor impairments are facilitated in the elderly in the presence of sleep disorders.

One of the most notable findings regarding sleep in the elderly is the profound increase in inter-individual variability, which thus precludes generalizations such as those made for young adults.

The latest global developments empasized the fact that poor sleep is a risk factor for mental health, well-being and susceptibility for infective diseases such as COVID-19 especially considering the crisis measures such as quarantine.

At present, there is no data that sleep-disordered breathing (especially OSA) increases the risk for contracting or developing more severe forms and outcomes of COVID-19. However, OSA is a condition characterized by many comorbidities including cardiovascular diseases, respiratory diseases, metabolic diseases (especially diabetes mellitus type 2) and obesity, all of which put the individual at a higher risk of COVID-19.

Increasing public awareness, improving and expanding diagnostic and treatment capacities for sleep disorders, as well as education of sleep medicine experts, which was recently developed in the Republic of Croatia according to European guidelines, are the primary goals of up-to-date sleep medicine, one of the most prosperous medical discipline, which is going to be even more important in the future due to increased longevity in general population and strong links of sleep medicine and ageing.

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K-IV

Confronting the Dementia Pandemic: A World Economic Forum and Global CEO Initiative on Alzheimer's Disease

Global Partnership to Speed Collaboration and Innovation

George Vradenburg

Convener, The Global CEO Initiative on Alzheimer's Disease

Introduction: The Urgent Need for Action

The world is confronting an emerging pandemic with absolutely no preparedness plan – one that threatens to be larger, longer, more devastating, and more costly than COVID-19. The emerging pandemic: the expensive and lengthy chronic diseases of aging, especially dementia. The COVID-19 outbreak illustrates the dire consequences if health systems don't prepare for dementia, which is already devastating older populations and impacting every aspect of society. It comes at a time when caregiving and working-age populations are shrinking, when national fiscal budgets needed to support aging healthcare costs are under stress, and when the monetary policy mechanisms to drive economic growth in the face of a declining global workforce are exhausted. While COVID-19 is the current public health priority, global leaders cannot afford to overlook dementia's immense impacts – today and in the long-term. Already, more than 2.4 million people die from dementia *every* year, and, in the U.S. alone, cumulative costs of care could exceed $20 trillion from 2015 to 2050.(1,2) As the next pandemic, dementia is both inexorable and foreseeable.

The world needs a global preparedness plan for dementia. On our current course, global dementia prevalence is projected to triple to 152 million families by 2050, or close to 500 million affected people. In Europe, the number of people 60+ with dementia will grow by roughly 60% to more than 14 million by 2040. (3,4) This surge in prevalence threatens to take an unsustainable toll – upending people's lives and communities, straining healthcare systems, generating immense costs, and draining workforces and economies.

We can change this trajectory. There is a growing consensus about the elements of a dementia preparedness plan: early and systematic testing and detection, a standing global, industrial- strength, trial-ready system for testing new therapies, public health intervention plans to reduce peak prevalence, and a healthcare system ready and able to get the right intervention to

the right patient at the right time in disease progression. Sound familiar? What we largely did not have in place to address COVID-19, we need to put in place to address dementia.

This plan will require overcoming a number of challenges, from basic science to healthcare and public health system preparedness. Researchers need a better understanding of the heterogeneity of the causal pathways of dementia. Differential pathways require biomarker systems that can identify the differential populations for testing differential interventions. Current sporadic clinical testing systems must be built into efficient global trial platforms. Healthcare systems need accessible and affordable diagnostics to identify those at-risk for dementia and deliver precision interventions to the right patient when they need them. Physicians need training, tools, and incentives to provide early, accurate diagnoses. And the public needs the hope and confidence that there is something that can be done to prevent or treat cognitive decline – now.

To address the challenge of developing a global preparedness plan for dementia, the World Economic Forum (WEF) and the Global CEO Initiative on Alzheimer's Disease (CEOi) launched a new, global effort in Davos in January 2020: The Davos Alzheimer's Collaborative (DAC). DAC is premised on the proposition that all nations and all sectors are in this together; that individual governments, as well as inter- governmental organizations, the pharmaceutical and biotech industries, leading researchers, and patient advocates, must come together to develop and execute a consensus preparedness plan.

DAC will link current dementia efforts, scale successful models, and create new initiatives – targeting four key areas:

- Build a targeted global cohort of populations with or at risk of Alzheimer's disease to drive discovery of precision intervention targets by focusing on research with populations that have genetic and genomic diversification.
- Build a clear, coordinated, and comprehensive precision biomarker development process to accompany the development of new precision targets.
- Create a global platform to support global clinical trials capable of bringing new drugs to market at a faster rate.
- Drive healthcare system preparedness to improve early detection and diagnosis, diagnostic and treatment delivery infrastructure, and patient affordability of treatments.

We believe these steps are essential to making faster progress toward the discovery, testing, and delivery of precision interventions for dementia – and we believe Europe can and should take the lead. On behalf of DAC's leadership and members, we look forward to discussing this urgent issue with European policymakers, exploring opportunities for collaboration, and deepening our shared commitment to speeding dementia innovation and preparedness.

Challenge: Global Population Aging and the Growing Impacts of Dementia

Rapid population aging presents a number of pressing challenges for every nation, for global economic growth, and for families around the world. Scientific and medical advances have brought us unprecedented longevity, raising average global life expectancy by more than 30 years in the past century.(5) There are now roughly one billion people over the age of 60 globally, and this number is projected to increase to 2 billion by mid-century.(6) Europe is at the forefront of this trend: there were more than 100 million people over the age of 65 in the EU-28 in 2018, or 20% of the population, and these numbers are projected to increase to 149 million older people, or 29% of the population, by 2050.(7)

While today's aging and longevity are a modern miracle, they will also dramatically increase the burden of age-related health conditions. We are not prepared for this emerging pandemic, and dementia is the epicenter of the looming crisis. More than 50 million people live with dementia globally; projected to increase to 152 million by 2050.(8) Europe is on the frontlines due its aging population. The number of people 60+ with dementia in the EU increased from 5.9 million in 2000 to 9.1 million in 2018, and, if current prevalence rates continue, this total is projected to grow by roughly 60% to 14.3 million in 2040.(9)

Without an urgent and coordinated response, this dramatic rise in prevalence will generate tremendous impacts on people, families, communities, and national healthcare systems, as well as on economic growth, workforce size and participation rates, and fiscal and monetary policy. Dementia is already the fifth leading cause of death worldwide, and, as of this paper, the only one of the top ten leading causes of death for which there is no truly effective treatment or cure.(10) The condition is responsible for roughly $1 trillion in annual costs, and this total is projected to double by 2030.(11) Dementia also takes an enormous toll on families, who often provide unpaid, informal care for years or decades.

Now is the time for leaders to join together, across sectors and national boundaries, to take immediate, sustained, innovative action to develop and execute a dementia preparedness plan. We must accelerate research progress to improve our understanding of dementia and develop precision therapies and accompanying biomarkers, while also drastically improving healthcare systems' preparedness to effectively differ-

entially diagnose dementia and deliver precision therapeutics as they become available.

Context: The State of Dementia Science and Policy

There is a growing consensus that meaningful therapeutic progress against dementia will require "shifting the science to the left" – understanding, detecting, diagnosing, and treating the condition in its earliest stages, including even before symptoms arise. This early intervention appears to be necessary for disease-modifying therapies to maximize their effects over a long period, as indicated by promising recent clinical trial results for aducanumab and BAN 2401.(12,13) Therefore, "shifting to the left" offers a potential breakthrough in an area where a new therapy has not been approved in the U.S. or Europe since 2003, and where more than 99% of clinical trials have not advanced to regulatory approval – the lowest for any therapeutic area.(14,15)

At the same time, there is also a growing scientific consensus that the causes and course of dementia varies from individual to individual based on individual genetic, biological, and phenotypical variability and heterogeneity. This means that more diverse cohorts of individuals must be investigated to identify the "clusters" of populations with sufficiently similar characteristics that can be treated with the same intervention. That variability, in turn, requires accompanying biomarkers or biomarker "clusters" to stratify populations for clinical research studies and for clinical diagnostics, so that the healthcare system can "match" precision medicines to different subpopulations with or at risk of dementia.

As effective therapies are developed, regulators and payers will need to develop innovative methods to approve and reimburse for treatments that may slow, but not stop, disease progression and that may not show health system cost savings for years or decades – challenging current regulatory and payment models. Healthcare systems will need to improve rates of early detection and diagnosis, better characterize patient populations and people at-risk, and ensure necessary infrastructure to diagnose and deliver treatments. Additionally, many dementia patients have one or more comorbid chronic conditions, further complicating efforts to understand the disease, characterize patient populations, provide appropriate therapies, and measure the economic and health benefits of treatment.

Despite these challenges, growing momentum among policymakers, the private sector, international organizations, and dementia advocacy organizations points a way forward – and Europe can play a leadership role in developing a transnational dementia pandemic preparedness plan. Europe has already led historic efforts to address dementia, including the first national dementia plan in France in 2001 and the United Kingdom's focus on dementia at the meeting of G8 Health Ministers in 2013.(16,17) Today, global leaders are stepping up their focus on dementia, as this topic was on center stage at the World Economic Forum in 2020 and spotlighted at the 2019 meeting of the G20 in Japan.(18)

These efforts provide hope, especially in light of recent positive clinical trial results, a promising pipeline of new therapies, and a number of innovative dementia initiatives in countries around the globe. Leading governments, companies, and international organizations are better positioned than ever before to change the trajectory of dementia and elevate dementia preparedness on the global agenda. We cannot leave the lessons of COVID-19 unlearned as we confront the slow-burn pandemic of dementia.

The Global Initiative: The Collaboration to Speed Alzheimer's Innovation

In January 2020, the World Economic Forum (WEF) and the Global CEO Initiative on Alzheimer's Disease (CEOi), launched the Davos Alzheimer's Collaborative (DAC), a multi-stakeholder, pre-competitive coalition designed to drive global scientific, business, policy, and financial coordination in dementia preparedness.

DAC will build a coordinated strategy to link, scale, or initiate actions to diversify, accelerate, and deepen dementia preparedness efforts. Our long-term vision is to create a highly prioritized, well-resourced global Alzheimer's research environment with an efficient path to market, supported by an engaged healthcare system.

DAC is uniquely positioned to achieve this vision because of members' recognized global leadership, deep expertise, significant resources, and long-standing commitment. Members include leading governments, the leading and largest biopharmaceutical companies working in the dementia space, top international organizations, and influential organizations from the philanthropic sector. In addition, DAC is conducting ongoing discussions with a number of national governments to lead the policy element of the collaboration – including the United States, the Netherlands, Japan, and Brazil – and we are eager to explore collaboration with other governments.

The leadership and members of DAC recognize that there are a wide range of important dementia efforts already underway around the globe. Therefore, DAC will embrace a "link, scale, create" approach – linking together relevant efforts to maximize their impact, identifying and scaling the best existing models, and creating new initiatives when no relevant efforts al-

ready exist. We believe this approach will enable greater efficiency and faster results.

Based on discussions with leaders and experts, DAC will target four key opportunities for innovation in dementia: global cohort development; biomarker development; global clinical trials; and healthcare system readiness. We believe these four pillars offer the greatest promise to solve existing challenges in the space and catalyze rapid progress that makes a meaningful difference for people living with or at risk for dementia.

1. Build a targeted global cohort of populations with or at risk of Alzheimer's disease to drive discovery of precision intervention targets by focusing on research with populations that have genetic and genomic diversification.

Progress against dementia requires a comprehensive, nuanced understanding of the condition. However, at the present time, researchers do not fully understand the disease's heterogeneity. This lack of understanding limits the ability to identify new targets for drug development, as well as to execute precision medicine approaches to dementia.

DAC aims to address this challenge by creating a large prospective cohort – ideally, including 1 million people or more – with standardized approaches to deep biotyping and phenotyping. This effort will include the creation of Centers of Excellence to serve as pilot sites and leaders on innovation. To create the cohort, DAC will explore how to link relevant efforts that are already underway.

2. Build a clear, coordinated, and comprehensive precision biomarker development process to accompany the development of new precision targets.

New targets for therapeutic interventions and precision medicine approaches require validated, standardized biomarkers and diagnostics to improve early detection and diagnosis, identify people for select treatment, and better measure the efficacy of new therapies. However, existing biomarker development efforts are largely siloed, and biomarker data is rarely reproducible. Further, there is no clear pathway for the private sector to validate or qualify biomarkers, and there are limited commercial incentives to invest in this area.

DAC aims to address this challenge by building a clear pre-competitive pathway for the identification, standardization, validation, and reproducibility for biomarker development. The platform will standardize data sharing for biomarkers and enable the sharing of biological samples, thereby speeding research and treatment delivery. The platform will also align stakeholders on high-value biomarkers and testing through current and future trials, further accelerating development.

3. Create a global platform to support global clinical trials capable of bringing new drugs to market at a faster rate.

Progress against dementia requires faster and less costly clinical trials, thereby accelerating the development of new therapies and attracting research investment. However, clinical trials are currently slow, laborious, and expensive, often requiring years of effort from researchers, trial participants, and care partners, as well as immense investments from biopharmaceutical companies.

DAC aims to address this challenge by creating a global clinical trial support infrastructure. This will include a standing, trial-ready platform and an integrated network of high-performing institutional and private trial sites. The effort will also develop the capacity for adaptive and combination trials. These initiatives, together, will accelerate the delivery of new, more diverse therapies to market at greater speed and lower cost.

4. Drive healthcare system preparedness to improve early detection and diagnosis, diagnostic and treatment delivery infrastructure, and patient affordability of treatments.

DAC will engage national healthcare systems to improve their preparedness for new Alzheimer's therapies, focusing on increasing testing and diagnosis, expanding the availability of healthcare infrastructure and capacity, and ensuring access when new treatments become available.

Progress against dementia requires dramatically **improving rates of early, accurate testing, detection, and diagnosis.** Currently, testing, detection, and diagnosis is often late, slow, or inaccurate, if it's made at all. Indeed, 50% of patients with any form of dementia are not formally diagnosed, and, when diagnosis is made, it's delayed by an average of 2–3 years after the onset of symptoms.(19,20) Further, 25% of patients clinically diagnosed with probable Alzheimer's disease during their lifetime are found not to have Alzheimer's pathology at autopsy – raising questions about the accuracy of diagnosis.(21) There are a number of causes for these diagnostic challenges: providers lack sufficient training; the public is not educated about brain health, and patients rarely raise symptoms with providers; and there is a lack of simple, effective, and inexpensive diagnostics.

DAC aims to address this challenge through efforts to train physicians, educate the public, and spur the creation of diagnostics. DAC will increase the number of healthcare providers who are trained to detect and diagnose dementia and Alzheimer's, as well as prioritize brain health and dementia prevention with the public and healthcare systems. DAC will also catalyze innovation in diagnostics and provide access to those diagnostics.

Progress against dementia requires **healthcare infrastructure** to effectively and efficiently test for the condition and provide appropriate treatment. However, healthcare systems currently lack critical infrastructure for imaging, fluid, and genetic testing, infusion sites for treatment, and sufficient training of the healthcare workforce. For example, genetic testing is not available in Germany, and Italy only provides reimbursement for infusion in a hospital by a specialist. (22) The introduction of new treatments will place greater pressure on these gaps.

DAC aims to address this challenge by improving access to existing infrastructure and creating additional system capacity. Working with national governments and healthcare systems, DAC may support the development of a "treatment-ready" population, drive access and acceptance of cerebrospinal fluid testing, and address access barriers for existing infrastructure.

Progress against dementia requires **sufficient access to treatment** for new therapies that enter the market. However, payers are concerned that new dementia therapies will require high upfront costs, but without clear evidence, available when they enter the market, about whether and when a treatment will reduce downstream costs, improve health outcomes, and provide value. These concerns are particularly pressing for therapies that will need to be administered in pre- symptomatic or early-stage patients for a number of years.

DAC aims to address this challenge by increasing patient access, while reducing the risk to payers. Specifically, DAC will support innovative payment models and catalyze a post-approval platform to capture data on costs and outcomes in heterogenous populations. DAC will also support reimbursement for diagnostic testing and the availability of approved fluid diagnostic tools.

The Path Forward: Building Cross-Sector Collaboration and Leadership for Dementia Innovation

Global leaders must prioritize dementia innovation, if we are to build a healthy, prosperous, and productive future. While past dementia efforts have delivered important results, there is a pressing need to dramatically accelerate the pace and scale of global cross-sector collaboration, leadership, and innovation. This is the only way to achieve the advances that can make a meaningful difference for communities, societies, and economies, as populations age in Europe and around the world.

DAC is eager to explore collaboration with European governments to achieve this vision. National governments will play a critical role as members of DAC by providing policy and financial support, co-convening stakeholders, and prioritizing and crafting innovative dementia preparedness systems within their countries.

Together, we can seize the most important opportunities for innovation and change the course of dementia in our aging world.

For more information and to join our effort:
Please contact Drew Holzapfel, Executive Director, The Global CEO Initiative on Alzheimer's Disease at dholzapfel@highlanterngroup.com or +1.703.599.9617.

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K-V

Dying Young, as Old as Possible: Public Health Challenges for Healthcare Systems in Ageing Societies

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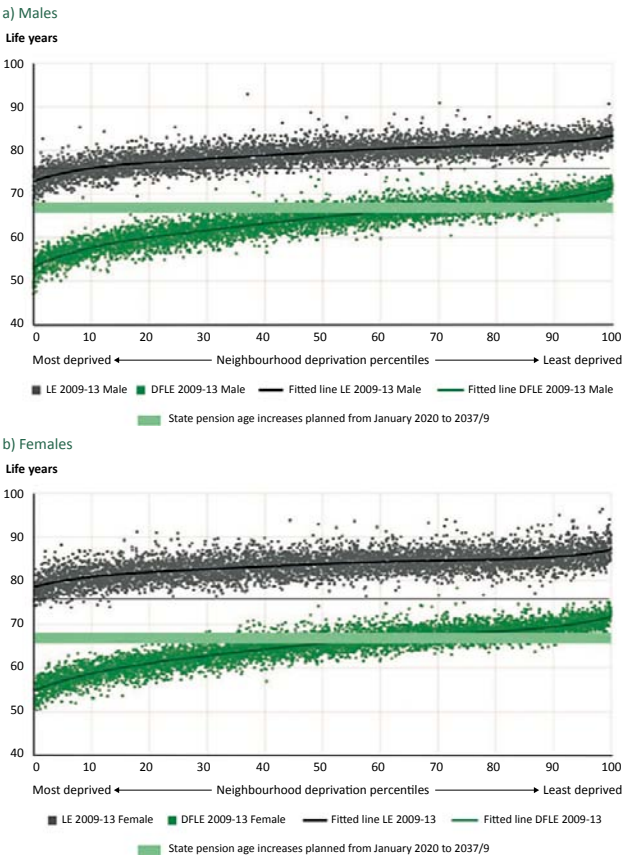
Immediate Past President, United Kingdom Faculty of Public Health Sir Richard Doll said he wanted 'to die young as old as possible'. In his vision, the chance for more people to live to the Biblical 70 years was made greater by his discovery of cigarette smoking killing people prematurely, from lung cancer and heart disease and the opportunity presented to prevent all these diseases, by education. There was a post Second World War and post antibiotic revolution chimera, that infectious disease had been conquered and now we would apply all our efforts to the epidemics of non-communicable disease. We would eradicate these too by rational investigation and removal of risks.

The reality in the United Kingdom, and perhaps for most countries is that this ideal is not being delivered. For many '70 maybe the new 50' but the benefits in improving life expectancy are not being experienced equally, within countries, or between countries and continents. Life expectancy may have been improving greatly in many countries. Healthy life expectancy is improving less, and inequalities in healthy life expectancy are widening. Sir Michael Marmot's graph of life expectancy and healthy life expectancy in over 200

Figure 1.



Source: Office for National Statistics (ONS) and Department for Work and Pensions (14) (15) (16)
Note: Each dot represents life expectancy (LE) or disability-free life expectancy (DFLE) of a neighbourhood (middle level super output area)

Figure 2. Life expectancy at birth by neighbourhood deprivation percentiles, 2009–13, England

neighbourhoods of England shows a gap of over 10 years in life expectancy, but a gap of over 20 years in healthy life expectancy. This gap represents the time a person will live with one or more long term conditions. (1)

I used to be Director of Public Health in Sandwell in the post-industrial West Midlands of England. There, a poor working-class man in West Bromwich may think it is normal to have chest pain at 45, or to be breathless climbing a flight of stairs. Many more will live with the daily diet and treatment rituals of obesity-induced type 2 diabetes. Obesity is the norm in the West Midlands, with over two thirds of the adult population obese or overweight. Lifetimes of poor and insecure employment, poor education opportunities and life without hope, leave people prone to the ravages of multinational companies peddling highly processed high-fat high-sugar foods, alcohol, tobacco and gambling. The multi-national companies employed the 'merchants of doubt' to question Sir Richard's rational evidence of tobacco as the cause of lung cancer. The 'Big' purveyors of non-communicable disease, Big Food, Big Tobacco, Big Alcohol, Big Gambling, Big Fossil fuel, have all adopted their merchants of doubt,

are still alive and thriving on human misery. Years of austerity since the 2008 financial crash, have seen a double assault on the health and livelihoods of people in the poorer areas of the United Kingdom. Health has been directly damaged, with the resultant diseases of despair- alcoholism, addictions, poor mental health and suicide, accidents and violence. Alongside this the services many have come to rely on to help them in these times of need, have been cruelly and cynically cut. I reviewed the extent of the damage to United Kingdom public health in my President's valedictory address to the members of the United Kingdom Faculty of Public Health in June 2019. (https://betterhealthforall.org/2019/07/30/past-presidents-end-of-term-report-part-2-the-health-of-the-public/) It has also been graphically set out by Marmot and colleagues this year. (1)

A public health approach to healthy ageing requires good data to describe the position of older people are living in and to propose solutions and evaluate interventions. It requires thorough knowledge of the major causes of ill health, dependency and inequality- in poor housing, inadequate income, environmental problems, poor and unrewarding work and poor chances for a fulfilling life and leisure, unsatisfactory family and social support networks. And it requires healthy public policy interventions to address these.

A public health approach requires improvement of environments in which older people live- involving town planners and engineers in moves towards 'dementia friendly cities', and 'accessible cities', and for communities which enable active travel and participation throughout life. Strong community involvement is required, and inter-generational activities. Citizen-led activities to promote healthier ageing are vital; a central tenet of health promotion is that health and care needs cannot be met solely through expert and professional provision- most care is delivered by family and community carers, so too must preventive interventions. Across the social divide, people live increasingly sedentary leading older people to become frail and dependent before their time. Resources developed by Sir Muir Gray in the United Kingdom seek to help people stay active, physically and mentally, as they get older, developing the concept of "optimal ageing' https://www.livelongerbetter.net. Individuals can be given the tools for personal support and for maintaining their own health- support from peers, self help groups, 'expert patients' can be important in helping people to maintain their independence and assert their personalities and their dignity and respect as human beings. Social prescribing has come into vogue- health professionals able to 'prescribe' a fitness class or a cooking class. This risk professionalising everyday activities, but it also enables prescriptions to be for more appropriate care. Many schemes recognise the need for housing repairs on prescription and welfare rights, rather than just 'lifestyle' prescriptions. Some of the tools for personal support are in the fields of new technology. Video conferencing has been propelled to routine and everyday by the current pandemic. Older people who may not have been computer literate are picking up the controls. Micro-technologies also enable more activities of daily living to be supported; the costs of mass production and modular production for aids and adaptations is coming down and enabling more people with disabilities, to not be handicapped, and so remain independent.

And we need health and social care services which are reoriented towards effective interventions, and which are responsive to personal needs. Within health systems, public health approaches are important – some of these can be considered the 'epidemiology of health care'. 'Value-based health' also as advocated by Muir Gray, and as presented in a European Union report last year (2), require all working in public health and health care to re-evaluate effective health service interventions and eliminate wasteful practices and the least effective clinical and care measures. The OECD report on "Wasteful Spending in Health" (2017) presented alarming data on inappropriate care and wasted resources with estimations ranging from a conservative 10% up to 34% of expenditures. Less wasteful care can reduce costs, but also reduce health harms, iatrogenic disease including side effects of medications, hospital acquired infections and blood clotting disorders, acute anxiety and disorientation, and so on. Appropriate care requires much more active involvement of individual patients and their carers. Less intervention may be better care. 'Adding life to years' becomes more important than merely 'adding years to life'. Quality of life becomes of paramount importance. But even where high technology and heroic intervention is justified, patients, carers and families, must be informed and be able to play an active part in the decision making, in what has come to be called 'the co-production of health'. Even in end of life care, a public health approach, as exemplified by the compassionate communities model, is important; as advocated by Professor Alan Kellahear, death cannot be professionalised and managed exclusively by health and care services; families and communities are the most affected and need to be given the tools and resources to be confident in talking about death and being supportive for people in the last period of life, and those around them.

All of these areas of intervention require a public health system and public health professionals to be inclusive and working in partnership, with health and care services, but also with many other agencies, communities and disciplines. The public health professional does not have exclusive and comprehensive knowledge of everything that can be done to protect and improve the health of the public. We need to under-

stand other languages- and speak them well enough- town planner, transport manager, housing specialist, economist, educationist, communications expert, community activist, public policy analyst and increasingly, we need to add climate scientist, ecologist, theologian, international lawyer and political scientist. All of these and more are vital to the health of the people and planet (3)

And we need to embrace law, ethics, rights and values. We need to reaffirm our values. We need to restate our belief in equality, in the rights of individuals to health and to access to health and social care which is universally available. We must value all individuals equally. We must avoid drifting into the uncaring sentiments, which do not value or recognise the rights and autonomy or even become a cynical expression of political philosophy, such some have expressed in the current COVID-19 pandemic. 'It's only killing the elderly', or, 'those with underlying conditions'; invoking herd immunity in which some will 'taking it one chin' for others to survive.

The COVID-19 pandemic has highlighted weaknesses in my country, of social care, which is run by private companies and individuals, which is unplanned, unresilient, and dependent on an army of over 1.5 million low paid care workers who are mainly from European Union countries and minority ethnic groups. Some English local health organisations have been reluctant to support privately run care homes with NHS expertise, in such crucial areas as infection control, medicines management, falls prevention and tissue viability and pressure sores prevention. There is a growing call for a national health and social care system in England. Other countries may face similar problems- while others, notably Scandinavian countries, have organised older persons care more securely.

There is clearly much to be done, in our respective countries, and internationally, to ensure we all have the maximum opportunity to live fulfilling lives, free of ill health for as long as possible, and protected by safety net coverage of health and care services when we need them. The COVID-19 pandemic has uncovered weaknesses in services in some countries and offered glimpses of how health might be improved for the future. Beyond COVID-19, we will need to redouble our efforts to prevent climate breakdown, address major health damaging trade problems, curb the obscene powers of multinational corporations which damage our health and address global problems of intolerance, epidemic resort to violence and organised armed conflict.

There is an emergency planning cliché, that *'we should hope for the best and plan for the worst'*. The best we should hope for, is to die young as old as possible, in a peaceful , more equal world, but we should plan for the worst- develop our health and care systems and our preventive services, to make our hope a reality.

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K-VI

Biomedical Engineering, Artificial Intelligence and Internet of Things for Healthy Ageing

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In 2014, the World Health Organization (WHO) stated that more '*trained and qualified biomedical engineering professionals are required to design, evaluate, regulate, maintain and manage Medical Devices, and train on their safe use in health systems around the world*'. In 2015, the European Institutions engaged in a wide discussion with the European (i.e., European Alliance for Medical and Biological Engineering and Science, EAMBES) and the global (i.e., The International Federation of Medical and Biological Engineering, IFMBE) community of biomedical engineering (BME) practitioners and scholars. The results of this discussion resulted in a report published in the European Journal in April 2015 (2015/C 291/07) stating that '*Biomedical Engineering is not simply a subset of modern medicine. Modern medicine predominantly secures important advances through the use of the products of biomedical engineering*'. In 2018, the European Commission included for the first time "Biomedical Engineering" in the European Skills, Competences, Qualifications and Occupations (ESCO) database.

This growing attention is probably due to the dizzying growth of the main *product of biomedical engineering*: medical devices. In fact, Europe is leading the growth of the medical device sector, accounting for the 30% of the global market, employing about 1 million

of workers in this area and leading by large the innovation in this field (e.g., number of papers, patents and research grants in this area). The market of medical devices will probably become one of the main drivers of the EU economy over the next years. A proxy for this forecast is the number of patent applications submitted per year. In fact, while the yearly number of patent applications per pharma and biotechnologies is still doing very well (about 6,000 novel patent applications per year), the number of patents for medical technologies is doing twice better, with over 12,000 novel patent applications in 2016 (1).

The fast evolution and diffusion of available and affordable medical devices is contributing to shape the future of medicine focus and practice. In fact, medicine is going to be more focused towards the wellbeing (not just health) of citizens, focusing more and more on primary prevention and lifestyle management. After hundreds of years, medical practice is expanding the remit of medical care from hospitals towards the monitoring and correction of citizens' health trajectories in real-life.

The fast development of artificial intelligence (AI), internet of things (IoT), telecommunications (e.g., 5G) and the convergence of these technologies into the medical device domain is offering novel and unprecedented opportunities to collect and use huge amount of data (a.k.a., big-data) for advancing medical knowledge and improving patient management, especially in later life.

In this fascinating scenario, this talk will illustrate how AI, IoT and big-data are going to be used in the forthcoming years in order to make healthcare interventions more affordable, sustainable, effective and safe.

This talk will present a series of pilot studies in which these innovative technologies are used for fostering active and healthy ageing and to improve the prevention, diagnosis, treatment and management of chronic conditions.

Finally, this keynote will rise the attention on current gaps, which are hindering the adoption of these promising technologies in everyday clinical practice and citizen life, and what policy-makers can do, in order to foster this unprecedented opportunity to improve the quality of life and the independency of senior citizens. Among other challenges, policy-makers will have to drive the change towards the adoption of novel assessment and reimbursement strategies for technologies improving primary prevention.

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