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Challenges of Longevity in Developed Countries: Vascular Prevention of Dementia as an Immediate Clue to Tackle an Upcoming Medical, Social and Economic Stretch

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Aging societies · 80+ generation · Dementia · Vascular prevention · Translational research · Socioeconomic burden

Abstract
Aging of societies, with increasing life expectancies, results in surging health care expenditures, as older age is closely associated with an increasing number of chronic and often resource-consuming diseases. Among those, dementia has the greatest impact on an individual's quality of life, the level of burden on the family and expenditures to finance nursing. Currently, pharmacological dementia treatment is exclusively focused on neurotransmitter-modulating medicines. Unfortunately, their effectiveness is not interminable, and the effect size limited. Novel approaches such as vaccinations are currently under vigorous investigation, but still far from translation into clinical practice. Thus, the consequent exploitation of opportunities which are already known is pivotal. Dementia prevention can become effective without delay if the vascular components of dementia are aggressively targeted through life style modifications as well as the treatment of vascular risk factors (e.g. hypertension). Longevity will become a significant burden for developed countries already within the next 10–20 years. By 2020, the 80+ generation will increase by at least 30% and in 2030 by at least 50%, compared to 2010. If the associated dementia challenge is not adequately tackled, longevity may no longer remain desirable for aged societies.

Introduction

Aging populations in both developed and developing countries are essentially on the increase. From 2000 to 2050 – according to the medium variant projections of the United Nations Population forecast [1] – the global population will have increased by 50% from 6.1 billion to roughly 9.2 billion. The respective number of people aged 65 years and above will grow from 600 million to 2 billion (increase of 330%) and the 80+ generation will increase

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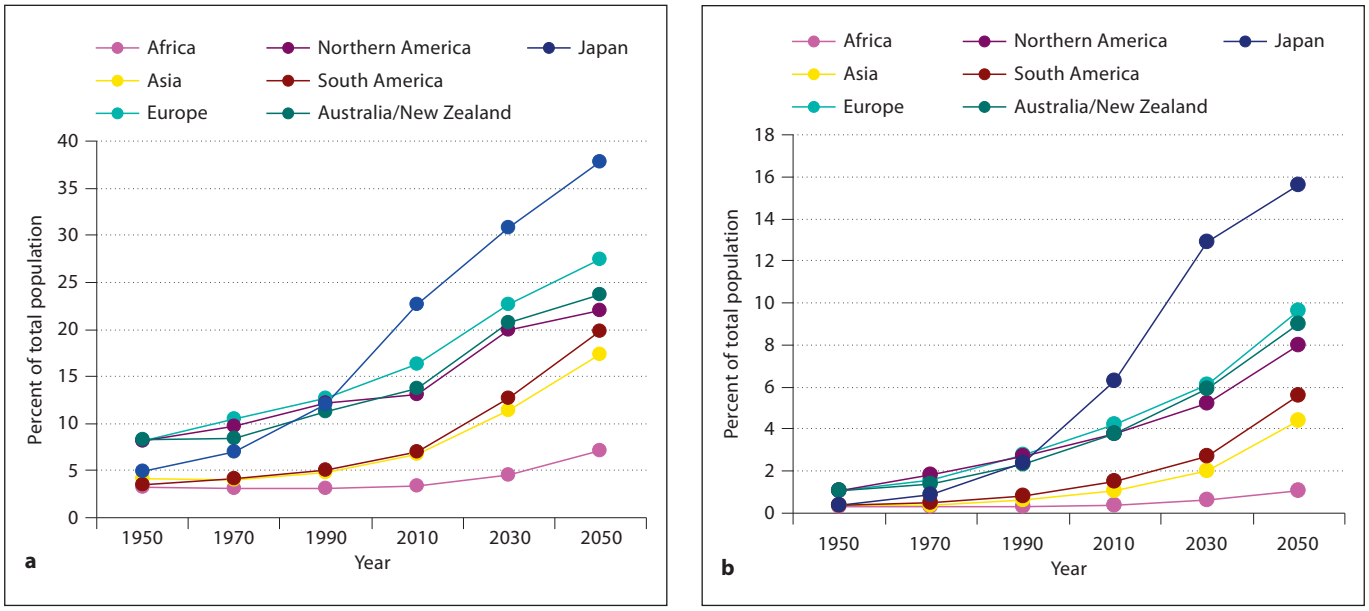

Fig. 1. Growth of the 65+ (**a**)- and 80+ (**b**)-year-old populations across the world (percentage of total population). Data from UN Population Division 2009 (medium variant) [1].

by more than 400% from 105 million to 400 million (see fig. 1 for a global overview).

The social security impact of aging populations will become significant. The elderly will increasingly and for prolonged times claim a disproportionately high share of health care and other public resources.

Much of the discussion surrounding this topic exclusively focuses on the associated challenges rather than on the opportunities that already exist today. They are exemplified in this paper for one of the most important drivers of strain in aging societies – dementia.

The increase in longevity gained momentum in the early 19th century due to socioeconomic progress arising from improvements, for example, in hygiene, nutrition, clean water, health care, and health literacy. This contrasts with a continuous decline in birth rates to beyond replacement levels. For example, in Germany, birth rates per woman have declined from around 2.5 in 1965 (slightly above replacement level) to 1.4 by the end of the 1970s, a level at which it has since remained. A similar pattern in terms of timing and magnitude can basically be drawn for all developed countries.

This aggravates the 'endogenous' socioeconomic challenges inherent within aging populations, as younger supporting and working populations tend to shrink inversely [2].

In this context, the exploding prevalence of dementia as the most proliferative age-related disease will become a 21st century challenge of unprecedented dimensions.

This viewpoint paper aims (a) to describe the evolving aging changes of the developed world (with particular focus on Europe) and highlight pending age-related disease patterns and prevalence; (b) to outline socioeconomic implications especially of dementia, and (c) to discuss interventions to help the aging societies to cope with dementia as one of the inevitable perspectives, in particular those for vascular prevention which are known, but presently underutilized.

Potentially frightening scenarios, therefore, must not be an inevitable fate of an aging society.

Aging Scenarios in the Developed World

There has been a steady increase in life expectancy in developed countries, which has been witnessed over the past centuries. If this pace continues through the 21st century, then most babies born since 2000 in the developed world will celebrate their 100th birthday [3]. This longevity is aggravated by a decline of the young age replacement cohorts and, thus, the total population will inevitably shrink. By 2050, the European population will

most likely have shrunk by 5–10%, depending on immigration and the forecast scenario, and the Japanese population will have shrunk by at least 30%. In this scenario, the US appears as a 'demographic exception', with high forecasted (near-replacement) birth rates and a robust inflow of immigrants (roughly half of them unauthorized, by US Census Bureau estimates). This country can expect to see continuing working-age population growth between now and the year 2030 [1].

Japan has led and still leads the global ranking of life expectancy both for women and men. In the period of 2005–2010, life expectancy at birth was 79.0 years for men and 86.2 years for women [1]. It is predicted to further increase until 2050 to 83.5 and 91.0 years, respectively. As shown in table 1 for Europe, the longest life expectancies can be found in France, Italy, Spain, Sweden, and Switzerland, while Eastern European countries currently have a shorter life expectancy by up to 10 years. The ongoing trend of increasing longevity will significantly alter the composition of the age-specific cohorts. For example, by 2030, people aged 80 years and above will represent 6–8% of the French, Spanish, British, German, and even 12% of the Japanese populations, compared to only 4–5% in 2010. In 2050, Germany and Italy will have the largest percentages of 80+ populations in Europe [1]. Even the number of 'very' senior citizens continues to 'explode' as demonstrated by the following example from Germany: in 2002, there were 334 persons aged 105 years and above, compared to only 54 in 1989 [4].

One does not need to be a prophet to predict that the dependency ratios (retired divided by working populations) will be significantly affected and will reach 50% and above in many European countries between 2030 and 2050 [1]. This change of societies in the developed world will have an unprecedented impact on their economic growth potential, social security transfer payments, tax revenues as the base of any state budgets and private and public consumption patterns.

Table 1. Life expectancies at birth in Europe in 1950, 2000, and 2050 (estimate, median variant)

	1950		2000		2050	
	male	female	male	female	male	female
Austria	63.6	68.8	75.8	81.6	82.8	87.2
Belgium	65.9	70.9	75.1	81.2	82.1	88.0
Bulgaria	62.2	66.1	68.7	75.6	76.5	82.5
Czech R.	64.5	69.5	72.1	78.7	79.1	84.9
Denmark	69.6	72.4	75.0	79.6	80.7	85.2
Finland	63.2	69.6	74.8	81.6	81.5	87.5
France	64.1	69.9	75.8	83.1	83.1	88.9
Germany	65.3	69.6	75.8	81.4	81.8	87.0
Greece	64.3	67.5	75.9	80.4	81.8	86.6
Hungary	61.5	65.8	68.3	76.6	76.3	82.8
Ireland	65.7	68.2	75.3	80.3	82.1	86.9
Italy	64.4	68.1	77.2	83.1	82.5	88.4
Lithuania	61.5	67.8	66.3	77.5	74.5	82.9
Netherlands	70.9	73.4	76.3	81.0	82.4	86.1
Norway	70.9	74.5	76.8	81.8	83.2	87.3
Poland	58.6	64.2	70.4	78.8	77.4	84.3
Portugal	56.9	61.9	74.1	80.8	80.2	86.2
Romania	59.4	62.8	67.8	75.1	76.2	82.2
Russia	60.5	67.3	58.5	71.8	70.5	79.0
Serbia	57.1	58.8	70.9	75.6	77.2	81.7
Slovenia	63.0	68.1	72.6	80.3	80.0	86.7
Spain	61.6	66.3	76.4	83.1	83.1	88.0
Sweden	70.4	73.3	77.8	82.3	83.5	87.0
Switzerland	67.0	71.6	78.0	83.3	84.4	88.5
UK	66.7	71.8	76.1	80.7	81.9	86.4
Ukraine	61.3	69.7	62.1	73.4	71.3	78.8
Japan	60.4	63.9	78.3	85.7	83.5	91
China	39.3	42.3	70.5	73.7	77.4	81.3
India	38.7	37.1	60.9	63.3	71.4	75.4
USA	66.1	72.0	75.8	80.6	80.8	85.8

Figures for Japan, China, India and the USA are given for comparison at the bottom.

Changing Morbidities in Aging Societies: Dementia as the Leading Example

Aging goes hand in hand with surging health care expenditures, as higher age is closely interrelated with an increasing number of chronic and often resource-consuming diseases. On average, males who are 80 years and above have 3.4 diagnoses and females 3.6 diagnoses, rising from 1.3 diagnoses between the ages of 20 and 39 [5]. Recently, the 'Institut für Gesundheits-System-Forschung Kiel' estimated the relative change in the prevalence of major diseases between 2007 and 2050 for Germany as follows [6]: acute pneumonia +198%, macula degeneration +169%, dementia +144% (fig. 2), hip fractures +125%, myocardial infarction +109%, stroke +94%, colon cancer +67%, lung cancer +66%, chronic obstructive pulmonary disease +47%, and diabetes mellitus +45%.

Dementia has the greatest impact on an individual's quality of life, as well as the level and duration of burden on the affected family, and, not to forget, expenditures to finance nursing. According to German data, its prevalence increases from 5% between the ages of 65–69 to 50%

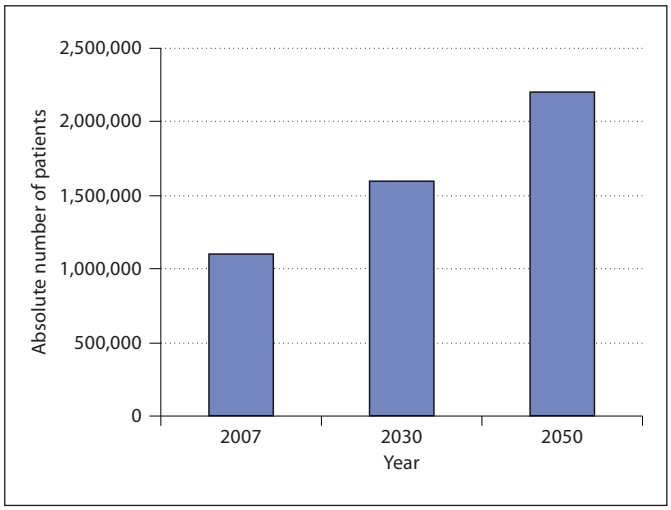

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Fig. 2. Estimates for absolute numbers of dementia patients in Germany. Data from Beske et al. [6].

at the age of 90 years and above [7]. Comparable figures are reported for Switzerland: its prevalence is 3% in the 65–69 age cohort and 36% in the group aged between 85 and 93 years [8]. Most likely, this relationship flattens beyond this age as genetic factors contributing to the onset of the disease earlier in life become less important or are even absent.

Switzerland, Germany, the US, and Japan may serve as illustrative examples for the developed countries. In 2007, there were 67,000 persons aged 80 and above with dementia in Switzerland (<1% of the population), and this figure is predicted to nearly triple to 161,000 by 2050. This represents 2.3% of the population and is a consequence of this age group increasing from 344,000 in 2008 to 874,000 in 2050 (forecast based on a constant population size of 7 million) [adapted from ref. 9]. In Germany, the 1.1 million dementia patients reported in 2007 will most likely at least double to 2.2 million (fig. 2) by 2050 [6].

In the US, the prevalence of patients with Alzheimer's disease will increase from about 5 million in 2010 to 8.5 million in 2030 (from 1.6 to 2.3% of the population). In Japan, the estimated number of dementia patients will increase from about 2 million at present to 4 million in 2040 (from 1.6 to 3.6% of the population) [10, 11].

To sum up: the forecasted prevalence of dementia, of up to 3.6% of a nation's population by 2050, will seriously challenge any social welfare system, any economical setting, as well as major ethical standards. The degree of this 'stress factor', however, will essentially depend on the efficacy of available coping mechanisms.

Socioeconomic Considerations

The broader socioeconomic impact of dementia is immense as it constitutes a major burden with an essential loss in quality of life, independence, freedom of mobility, and cognition. In Switzerland, it is assumed that the increase in nursing costs alone will range from CHF 1.6 to 7 billion between 2008 and 2050, depending on the severity of the disease and type of nursing service applied [adapted from ref. 9]. For the US, the 5.3 million patients with a dementia diagnosis in 2008 produced direct and indirect costs of USD 148 billion. Lost wages of patients and their families, plus the costs for non-nursing home patients add USD 94 billion to the bill, with annual costs totaling USD 244 billion [12].

The overall ethical impact of this development is tremendous. Societies will have to cope with the dilemma of the epidemic surge in dementia of their aging populations or face the accusation of being neglectful. Surprisingly, the UN Millennium Development Goals [13] do not even mention the problems of aging and dementia as one of the leading objectives for the third millennium of mankind.

Taken together, these considerations give ample reason for concern about the impact of demography on equal access to health care in the decades to come. Without a fundamental and far-reaching rethinking of the developed countries' current approaches to work and retirement, pension and health care policies, the great achievement of longevity may become progressively more difficult to maintain; or even worse, longevity may no longer remain desirable for aged societies.

Treatment Options for Dementia

In principle, 2 different treatment strategies for dementia need to be separated: (a) symptom-oriented treatment and/or (b) disease-modifying treatment. The latter should be subclassified into treatments for the manifest disease and preventive measures.

Current Treatment Strategies: Symptomatic

At present, pharmacological dementia treatment is exclusively symptomatic. Most therapies are focusing on neurotransmitter modulation, thereby, for example, increasing the concentration of acetylcholine in certain brain regions. Based on current knowledge, the most important neurotransmitter abnormalities are of cholinergic origin: (a) reduced activity of choline acetyltransferase (synthesis of acetylcholine) [14]; (b) reduced number

of cholinergic neurons in late Alzheimer's disease [15] (particularly in the basal forebrain), and (c) selective loss of nicotinic receptor subtypes in the hippocampus and cortex [14, 16].

Clinically, acetylcholinesterase inhibition in the central nervous system is the main mechanism of action for acetylcholine elevation. The main compounds currently available in clinical practice are donepezil, galantamine or rivastigmine. Acetylcholinesterase inhibitors may improve, maintain, or – at least – slow down the decline of cognitive, behavioral, and functional performance in patients with mild to moderate dementia. This treatment effect delays disease progression by a maximum of up to 1 year (relative to placebo treatment) with an effect size in controlled clinical trials for donepezil of 38 weeks [17], for rivastigmine of 38–42 weeks [18], and for galantamine of 52 weeks [19]. These rather limited time frames indicate that the burden of disease cannot be sustainably lowered if we continue to rely on the treatment options mentioned above; these medicines do not essentially influence the underlying process of neurodegeneration.

More severe dementia cases can be treated with the NMDA glutamate receptor blocker memantine as a dysfunction of glutamatergic neurotransmission is also thought to be involved in the etiology of dementia. The limitations in terms of treatment effectiveness of memantine are comparable to those of acetylcholine esterase inhibitors. Memantine received market approval in 2002; thus, this latest innovation for dementia treatment is already 8 years old.

The currently achievable treatment results indicate that the need for innovation in the dementia area is tremendous both in terms of effectiveness and importance for the society.

Future: Direct Impact on Neurodegeneration

Serious preclinical research efforts to target the disease pathology and attack neurodegeneration are presently under way involving numerous pharmaceutical companies as well as major academic centers. The NIH alone has spent an estimated USD 644 million on Alzheimer research in 2008 [20], and will probably reach the billion-dollar goal in the near future.

Many novel approaches for causal treatment of Alzheimer's dementia focus on β-amyloid. Evidence for its relative importance is derived from cases of early-onset Alzheimer's dementia, called familial Alzheimer's dementia. In familial Alzheimer's dementia, a number of different gene mutations on chromosomes 21, 14, and 1 cause the formation of abnormal proteins (for a review, see Williamson et al. [21]) including abnormal amyloid precursor protein and an increased amount of the β-amyloid protein. β-Amyloid is created from amyloid precursor protein by sequential cleavage of the amyloid precursor protein through α-, β-, and γ-secretases, which are being explored as potential new drug targets.

Another important target is tau aggregation, which causes cellular toxicity in conjunction with β-amyloid formation [22]. In addition, vaccination strategies against β-amyloid peptide are being developed [23]. Thus, novel approaches are focusing on tau aggregation and β-amyloid aggregation inhibition; RAGE inhibition and microtubule stabilization are further, largely unrelated targets.

At the time of this paper, no causal treatment principle has entered daily clinical practice. The pipelines of research-based pharmaceutical companies have partly reached the level of clinical development; however, the overall number of about 700 ongoing clinical trials to test new dementia medicines appears minuscule when compared to the 5,000 plus trials in the diabetes area [24].

This finding highlights that the translation of basic science into clinical benefits in the CNS/dementia research is still in its infancy, as predictive animal models and even a basic understanding of disease pathophysiology are still lacking.

Plaque formation as a marker for disease progression has also been questioned, for example, in the findings from the 'Nun Study' in which striking discrepancies between brain plaque volume and cognitive functions have been reported [25]. Thus, the translatability of plaque-reducing strategies into clinical care remains a challenge with risks for failure.

The hope for radical improvement of therapeutic options in dementia is considerable, but progress may be slower than desired – at least – in the near future.

The Old/New Paradigm: Coping by Preventive Measures

At present, the only appealing choices to alleviate this situation are preventive measures against dementia. Their compelling advantage is that they can be easily translated to clinical practice already today. Age-related dementia is not different from many other degenerative diseases, in that we tend to treat the symptomatic disease rather than preventing its occurrence by an earlier intervention. Examples are numerous and include diabetes mellitus type II, atherosclerosis-related cardiovascular disorders, heart failure, osteoporosis, some cancer types

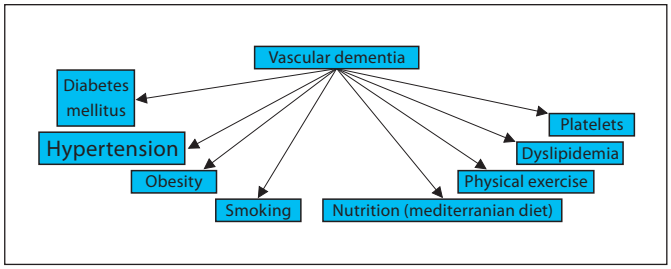

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Fig. 3. Preventive measures aim at the depicted vascular component of dementia, with hypertension treatment being the most important one.

(e.g. smoking-related cancers), and finally – dementia. Prevention is an efficient and cost-effective option to reduce morbidity and mortality including their share inherent in aging processes. Evidence-based preventive measures target, for example, cardiovascular risk factors such as hypertension, dyslipidemia, smoking, and diabetes mellitus; or osteoporosis through exercise, vitamin D and calcium, and certain types of cancer by smoking cessation. Existing and well-known medicines are available to implement this preventive approach and future new medicines will create additional, enormous windows of opportunity [26].

If we accept that the pathophysiological process leading to neurodegeneration in Alzheimer's disease cannot be fully tackled at present, one has to exploit other traits of modifiable contributors and thus etiologic conditions of dementia at large. Neurodegeneration could be primarily driven by unknown processes; however, another driver leading to secondary neurodegeneration has been neglected in this context – vascular incompetence. Various forms of vascular dementia are more important than generally presumed – including multiple strokes which ultimately lead to debilitation [27]. Recently, the considerable contribution of vascular biology to the etiology of dementia has been acknowledged. Therefore, and as of today, an essential overlap between vascular and Alzheimer's dementia is no longer seriously disputed [28]. In recent studies, Alzheimer's dementia is seen to constitute 60–80% of all dementias, but vascular dementia is rated at 20–70%, which is indicative of a considerable overlap between both etiologies of dementia of up to 50% [28–30]. Explicit studies to detect the so far underestimated coincidence of Alzheimer's and vascular dementia still need to be performed, yet assuming that a contribution of vascular disease, especially in the elderly population, provides a promising opportunity. We already know from epidemiological studies that hypertension and diabetes are significantly, but not massively, associated with an increased risk of dementia in patients with either condition [31]. By contrast, as hypertension and diabetes are very frequent conditions with a thoroughly high prevalence, this modest increase in risk translates into a significant attributable risk at the overall population level. In the Honolulu-Asia Aging Study [32], the population's attributable risk of dementia for untreated hypertension was estimated at approximately 40%.

In a recent meta-analysis on vascular dementia, the authors conclude that 'recent literature confirms that brain matter damage caused by long-standing hypertensive status is associated with cognitive impairment. Accordingly, strict BP control, including during sleep periods may have a neuroprotective effect on the brain and thereby prevent the incidence of dementia' [33]. This statement is based on other reviews: older studies showed a small but insignificant effect [Cochrane Review on SHEP, Syst-Eur, and SCOPE trials, risk reduction of dementia by 11% (odds ratio = 0.89; 95% CI = 0.69–1.16)] [34]. More recent studies demonstrate a larger, significant effect [results of the SHEP, Syst-Eur, PROGRESS, and HYVET trials, risk reduction of dementia by 13% (HR = 0.87; 95% CI = 0.76–1.00)] [35].

The pivotal implication of such data relates to the fact that arterial hypertension is amenable to effective pharmaceutical interventions. Though the effect size of hypertension treatment regarding dementia reduction seems small, it should be noted that a combined effort to treat all major cardiovascular risk factors should lead to a more appreciable larger effect though such data are still unavailable.

In the light of the dementia challenge, it is crucial to note that this opportunity is still largely underutilized in the developed world. DETECT, a huge primary care study in 55,000 patients from general practitioner offices in Germany, showed that only about 20% of hypertensive patients aged 60+ were treated to goal [36]. Undertreatment in other countries has principally the same dimension [37].

Underutilization of preventative measures for cardiovascular protection similarly also exists for the treatment of dyslipidemia, diabetes mellitus type II, obesity, and smoking cessation. Life style changes are difficult to implement, but would be very effective in terms of cardiovascular outcome as shown in the INTERHEART study [38].

As the main message of this viewpoint, it should be increasingly acknowledged that dementia prevention is

possible and effective if the vascular components of dementia are aggressively targeted through the treatment of vascular risk factors such as hypertension, diabetes, dyslipidemia, and life style modifications (e.g. smoking cessation, weight loss, exercise) (fig. 3). The contribution of vascular components to dementia is increasingly considered to be significant, even in the most prevalent etiology, Alzheimer's disease, and preventive cardiovascular measures bear a very appealing potential.

Implications and Conclusions

Demographic change will lead to a dramatic increase in the global aged population – by 2050 two billion people will be aged 65+. Dementia is a leading challenge as its prevalence exponentially rises with age. Today, this disease already causes vast socioeconomic challenges and expenditures, and unprecedented further increases are expected in the future.

Current treatment options are very limited in terms of their long-term effectiveness. Prevention will be essential to reduce the burden of this new epidemic of the 21st century; the good news is that these options are already available and have proven efficacy in relation to vascular dementia; however, prevention has to start decades before disease manifestation.

If both the existing options are not fully utilized and innovations are not rigorously pushed by society, the great achievement of longevity will generate dramatic social and economic drawbacks. The yet unbroken claim for even longer life expectancies may no longer be desirable in the light of those drawbacks. Ultimately, even the foundation of humanity could be questioned in that elderly patients with dementia may become such burdens to societies that in searching for solutions currently unthinkable means may be considered.

Coping with aging and, in particular, dementia has become a millennium goal and may be seen as a greater threat to humanity than climate change and energy shortages together.

Take Home Messages

(1) The dementia burden will overload all budgets in health care and even general public affairs; thus, it will cause a threat to societies and ethics of unprecedented vigor.

(2) Treatment options today are meager, just symptomatic and very limited; causal treatments for neurodegenerative disease are – despite exploding efforts – far from clinical translation.

(3) As the vascular component of dementia particularly in the aged population becomes increasingly recognized, its appreciation as a viable, endpoint-relevant preventive and therapeutic option could have immediate impact. Its underutilization is notorious, and utilization, thus, opens a large window of opportunity.

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