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on Demographic Issues

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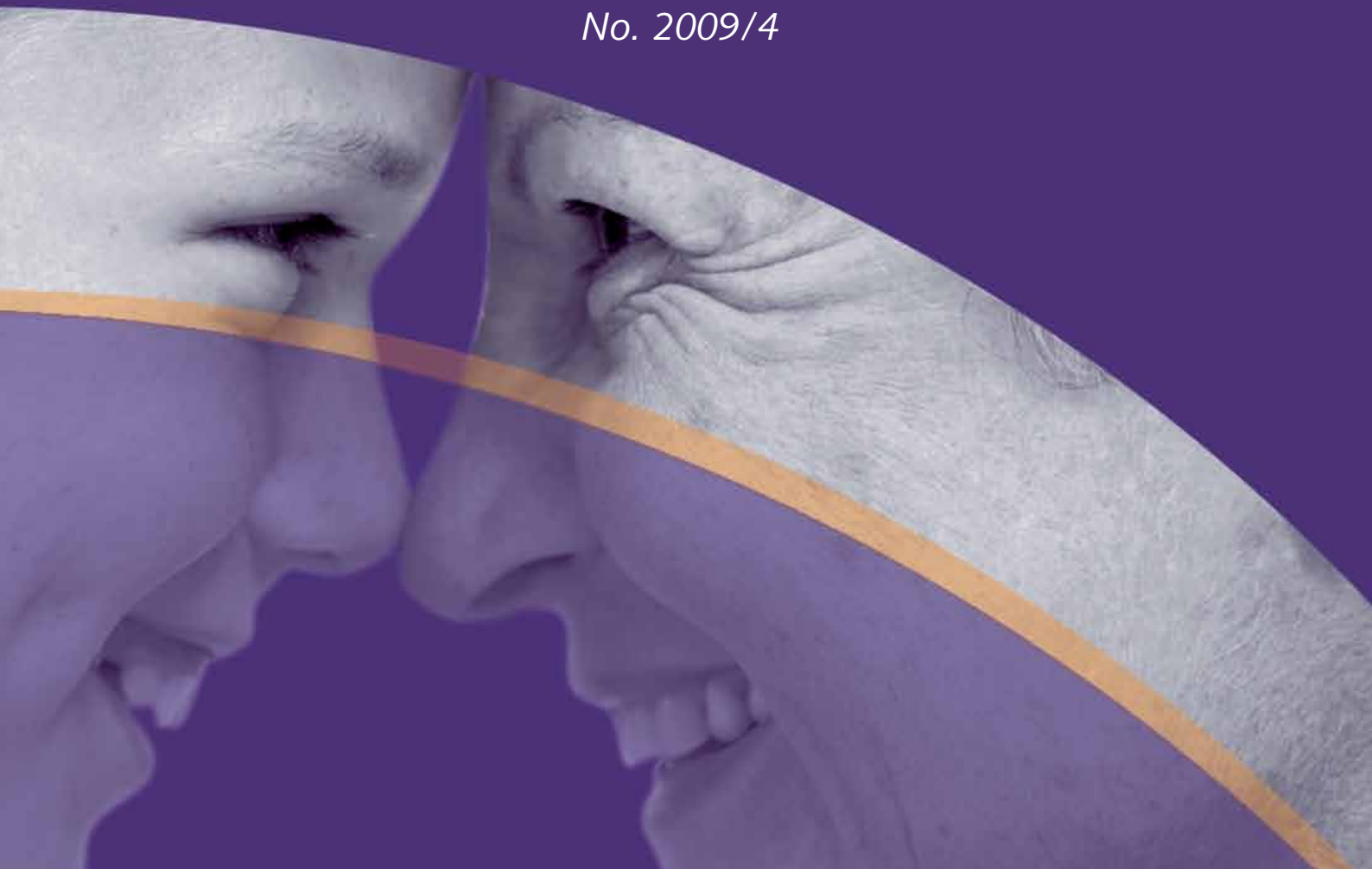
No. 2009/4



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FUTURE DEMOGRAPHIC CHALLENGES IN EUROPE: THE URGENCY TO IMPROVE THE MANAGEMENT OF DEMENTIA

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Abstract

Demographic change and ageing is silently and steadily occurring across the developed and developing world. It is evident, that ageing goes hand in hand with surging healthcare expenditures, as older age is closely interrelated with an increasing number of chronic diseases. Among these age-related diseases, dementia is the one, which has the greatest impact on an individual's quality of life, the level of burden on the family, financing either through private or public sources, and the ethical/humane standards that need to be maintained. The situation becomes even more complicated due to the emerging shortage of caregivers and other services related to caring for dementia patients.

Needless to say, innovations and progress in developing medicines for the prevention and cure of dementia are critical components of the strategy to face this growing global challenge. At present, pharmacological dementia treatment is focused on neurotransmitter-modulating medicines of mainly cholinesterase inhibitors, such as rivastigmin, galantamine or donezepil, the effectiveness of which, are not interminable; more severe cases are treated with the NMDA glutamate receptor blocker, memantine. Novel approaches include Tau aggregation inhibition, amyloid beta aggregation inhibition, RAGE inhibition, microtubule stabilization, gamma-secretase modulation, just to name a few of the targets currently under investigation. However, translating these approaches into practical medicine still seems far away from realization. Nevertheless, even at present, prevention is possible and effective if, at least, 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 and physical exercise).

If the growing dementia challenge is not tackled, extended longevity may no longer remain desirable for any given society and could thus generate a source for a new type of community conflict and a tenuous situation.

Key words:

Ageing society, dementia, treatment options, translational research, socio-economic burden.

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Introduction

Ageing populations in both developed and developing countries are substantially 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. This is a smaller, but still very relevant increase compared to the period 1950 to 2000 when the population increased by 144% from 2.5 to 6.1 billion. Furthermore, the respective numbers for people aged 65 and above will grow from 600 million to 2 billion, which is an increase of 330% compared to an increase of only 220% between 1950 and 2000.

The economic impact of ageing populations appears to be a tantalizing perspective. The elderly will increasingly claim a disproportionate share of healthcare and other public resources. Well-established social security systems in the developed world will have to adapt, while the developing world will, first of all, need to provide basic care for its rapidly ageing societies.

Clearly, these demographic changes require comprehensive responses. However, much of the discussion surrounding this subject exclusively focuses on the associated challenges rather than on the opportunities. Some nations – such as Japan and, before long, also certain European countries – are predisposed to become showcases for the management of ageing populations having hopefully updated societal governance systems, high ethical standards as well as an innovative spirit. Potentially negative scenarios, therefore, must not be an inevitable fate. On the contrary, even a significant benefit could be drawn from an ageing world, but this would require engagement and the implementation of smart policies.

If this endeavour is successfully executed, a quote from the French actor and chansonnier Maurice Auguste Chevalier (1888-1972) is very fitting here: “Ageing is not as bad if one thinks of the alternatives.” (Cited from[2]).

The continuous increase in longevity gained momentum already in the early 19th century

due to socio-economic progress arising from improvements, for example, in hygiene, nutrition, the water supply, healthcare, and health literacy. This contrasts to a continuous decline in birth rates to beyond replacement levels - the reasons for which are manifold. If we take Germany as a case in point for Europe as a whole, 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. This aggravates the socio-economic challenges inherent within a growing elderly population, as the younger supporting and working populations shrink both absolutely and relatively.[3] Thus, the homework that needs to be done is significant.

While on the one hand, it can be said that the ongoing demographic revolution with its uninterrupted increasing life expectancy since the middle of the 19th century is a wonderful achievement, on the other hand, the exploding prevalence of dementia as the most proliferative age-related disease will become a challenge of unprecedented dimensions.

This review aims to:
(1) describe the evolving demographic changes in Europe and Japan until 2050
(2) highlight pending age-related disease patterns and prevalences
(3) outline socio-economic implications
(4 discuss current and potential future interventions to help the ageing society to cope with this inevitable perspective of age and disease.

As a consequence, this paper seeks to initiate a broad public discussion to both reflect on and respond to the urgent challenge, which we face. As a first step, everybody is then encouraged to ask his or herself the serious question: What will happen if nothing is done?

Demographic Scenarios in Europe and Japan

Europe and Japan share patterns concerning the ongoing demographic change in many aspects. Both have a below replacement fertility, a shrinking population in the productive

age cohort (15-65 years) and an ongoing increase in life expectancy. If the pace of increasing life expectancy in developed countries that has occurred over the past centuries continues through the 21st century, then most babies born since 2000 in Europe, the USA, Japan and many other developed countries with long life expectancies will celebrate their 100th birthday.[4] The only striking difference between Europe and Japan relates to the predicted scenarios regarding their population size. Whereas the European population will – albeit immigration and depending on the forecast scenario - most likely shrink by 5-10%, the Japanese population will shrink by at least 30% until 2050. The countries that are driving population decline in Europe are primarily Germany and Eastern European countries including Russia. The main explanation for Japan's significant population decline is the practical absence of any migration to compensate for low birth rates.

This, however, is not the only difference: for many decades, Japan has led and still leads the global ranking of life expectancy both for women and men. In the period 2005-2010, life expectancy in Japan at birth was 79.0 years for men and 86.2 years for women,[1] and it is predicted to further increase until 2050 to 83.5 and 91.0 years respectively.

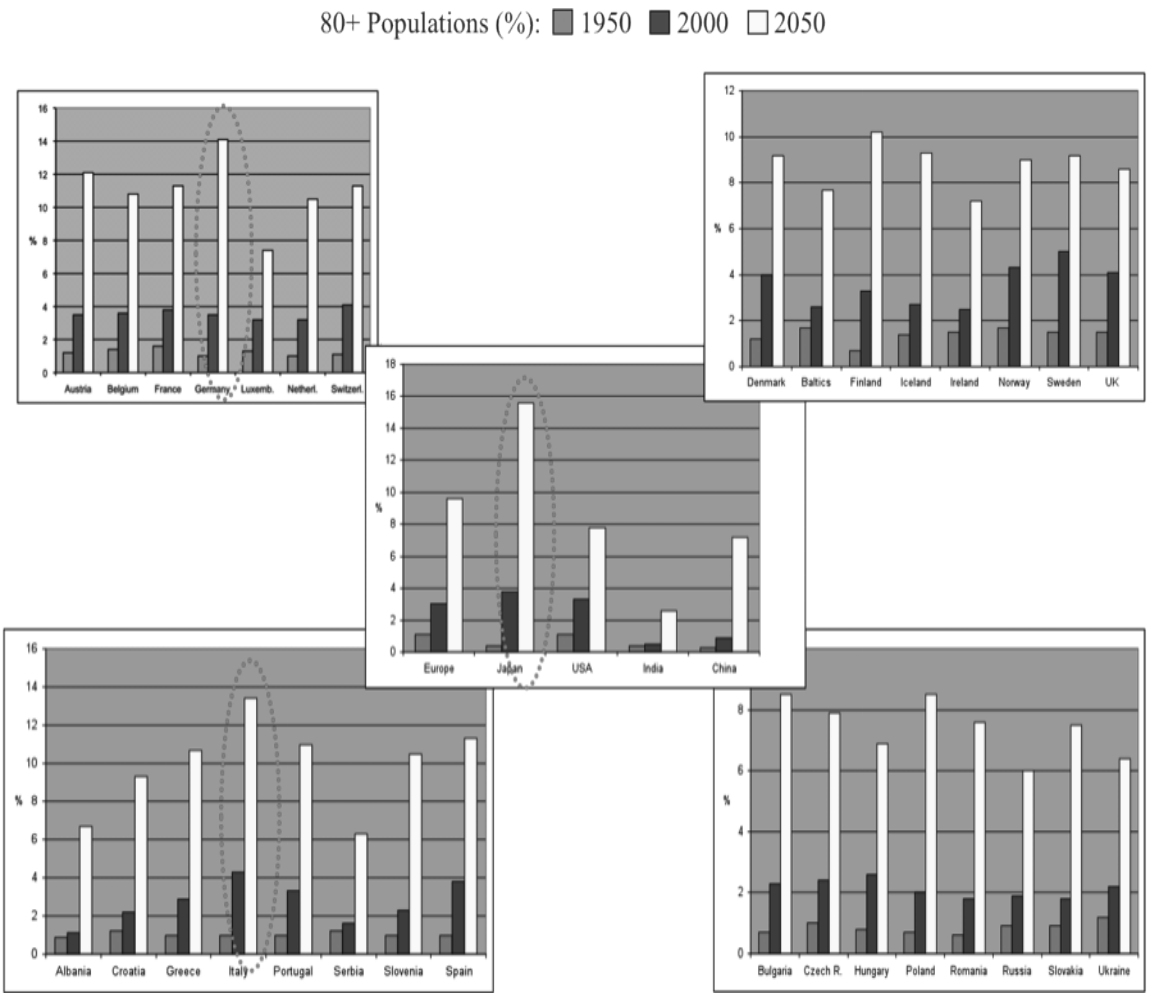
Life expectancy in Europe shows considerable variation, but "best practice" countries do exist. As depicted in Table 1, the longest life expectancies can be found in France, Italy, Spain, Sweden and Switzerland while Eastern European countries have up to a 10-year lower life expectancy. This ongoing 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.

Table 1: Life Expectancy at Birth

	1950		2000		2050	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**
Albania	54.4	56.1	72.6	79.0	78.7	84.3
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
Croatia	59.0	63.2	71.4	78.4	78.8	84.5
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
Estonia	61.7	68.3	65.6	76.9	76.0	83.6
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
Iceland	70.0	74.1	79.3	82.7	84.5	87.7
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
Latvia	62.5	69.0	65.3	76.2	75.3	82.7
Lithuania	61.5	67.8	66.3	77.5	74.5	82.9
Luxembourg	63.1	68.9	75.1	81.3	82.4	86.8
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
Slovakia	62.4	66.2	69.8	77.8	77.1	83.5
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
Europe	63	68	69.6	78	78.5	84.5

Life expectancies at birth in different European countries in 1950, 2000 and 2050 (estimate, median variant).[1] At the bottom of the table, figures for Japan, China and India are provided for comparison. It is worth mentioning that the speed of ageing in the coming 50 years will progress more quickly in the developing countries compared to the developed countries where life expectancies have already started to expand in the 19th century.

Figure 1



European demographic change compared to other selected geographic regions and Japan: relative population size for people aged 80 and above (%).[1] Values for 1950, 2000 and estimates for 2050 (median variant) are given. The centre graph compares some different regions of the world and clearly shows that by 2050 Japan will have the largest proportion of the 80+ population. The four outer graphs depict central European (upper left), Northern European (upper right), Southern European (lower left) and Eastern European (lower right) populations. In 2050, Germany and Italy (red circles) will have the largest percentages of 80+ populations in Europe.

Figure 1 provides an illustrative overview of the evolution of the 80+ cohort over the 100-year time period between 1950 and 2050 and demonstrates that the increasing momentum will triple in the 21st century. 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.[5]

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 Japan and many European countries between 2030 and 2050.[1]

Changing morbidities: future priorities and demands

It can be deemed obvious, that ageing goes hand in hand with surging healthcare expenditures, as higher age is closely interrelated with an increasing number of chronic diseases. On average, males who are 80 years and above have 3.4 diagnoses and females 3.6 diagnoses, rising from 1.3 diagnoses respectively between the ages of 20-39.[6] Patients with multimorbidity are likely to receive multiple drug treatments (polypharmacy). Kaufmann et al.[7] demonstrate that patients aged 65 and above take >5 drugs in 44% (male) and 57% (female) of cases and >10 drugs in 12% of cases. Polypharmacy is associated with adverse drug events leading to 2.1 million hospital admissions and 100,000 drug-related deaths in the US (population 265 million at the time of study).[8] In this study, the economic impact of this particular aspect (adverse drug reactions) of multimorbidity/polypharmacy alone is associated with expenditure estimates between USD 1.5 and 4 billion. This multi-morbidity phenomenon is, therefore, one of the major reasons for an almost exponential increase in health expenditures over an individual's lifetime.

The prevalence of almost all chronic or degenerative diseases increase with age; with the exception of Alzheimer's dementia, most are amenable to preventive measures. The major chronic disorders, which are particularly age-related and increasingly shape a given country's healthcare bill, are:

- Dementia and depression
- Chronic musculoskeletal disorders/falls
- Chronic arthrosis/arthritis
- Cardiovascular diseases
- Cancer (colon, prostatic, lung, etc., not breast cancer)

As these diseases are age-related, their prevalence will sharply rise with a growth in the elderly population. In a recent report from the 'Institut für Gesundheits-System-Forschung, Kiel', the following estimates for the relative change in prevalence between 2007 and 2050 were predicted for Germany.[9]

Acute pneumonia	+198%
Macula degeneration	+169%
Dementia	+144%
Hip fracture	+125 %
Myocardial infarction	+109%
Stroke	+ 94%
Colon cancer	+ 67%
Lung cancer	+ 66%
COPD	+ 47%
Diabetes m.	+ 45%

Among these age-related diseases, dementia is the one with the greatest impact on an individual's quality of life, as well as the level and duration of burden on the affected family, and financing from either private or public sources. Its prevalence is strictly age-related and, according to German data, increases from 5% between the ages of 65-69 to 50% at the age of 90 years and above.[10] Comparable figures are reported for Switzerland: its prevalence is 3% in the 65-69 age group and 36% in the group aged between 85 and 93 years.[11] Whether or not the age-related prevalence of Alzheimer's dementia is rising further beyond 90 years and above is unclear. 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.

The ongoing ageing, which is evident in societies will inevitably lead to the growing prevalence of dementia. Japan – the most advanced nation in terms of ageing – will be leading and followed by the developed countries. Earlier or later, even developing countries will be exposed to this challenge.[12] To understand the dimension involved in the Western world, Switzerland, Germany, the US and Japan may serve as illustrative

examples. 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 rise to 161,000 in 2050. This translates into 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[13]]. In Germany, the 1.1 million dementia patients existing in 2007 will most likely compare to 2.2 million in 2050.[9]

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 or from 1.6% to 2.3% of all people living in the US. In Japan, where an even more pronounced ageing society is already evident today, the estimated number of dementia patients will increase from about 2 million at present to 4 million in 2040. While currently, 1.6% of the population are affected, this proportion will more than double to 3.6% in the coming 30 years.[12,14] Furthermore, whereas the dementia prevalence was between 3.8% and 8.5 % in older studies,[15-19] it appears to have risen: in the rural island town of Ama-cho,[20] it was recently reported to be at 11% due mainly to the migration of younger people from rural into urban areas.

Dementia

It is extremely apparent that this highly prominent age-related disease will result in a serious stress on any social welfare system, a nation's economy and ethical standards. The degree of this stress, however, will essentially depend on the efficacy and safety of the future **preventive** and therapeutic intervention options available.

In this context, it is important to note that two different strategies need to be separated: symptom-oriented treatment and disease-modifying treatment. The latter should be grouped into treatments for the manifest disease and preventive measures.

Current treatment options

At present, pharmacological dementia treatment is symptom-oriented. Most therapies are focused on neurotransmitter modulation, thereby, for example, increasing acetylcholine in certain brain regions. The most prominent neurotransmitter abnormalities are of

cholinergic origin: a reduced activity of choline acetyltransferase (synthesis of acetylcholine);[21] a reduced number of cholinergic neurons in late Alzheimer's disease[22] (particularly in the basal forebrain); and a selective loss of nicotinic receptor subtypes in the hippocampus and cortex[21,23] have been found.

Clinically, acetylcholine elevation is mainly achieved by central nervous acetyl cholinesterase inhibition. Only a few compounds are currently available and in clinical practice; namely rivastigmine, galantamine and donezepil being the most important ones.

Acetyl cholinesterase inhibitors may improve, maintain, or slow down the decline of cognitive, behavioural, and functional performance in patients with mild-to-moderate Alzheimer's dementia. They have demonstrated consistent efficacy and safety in maintaining cognitive function in patients with mild-to-moderate Alzheimer's dementia by up to one year (relative to placebo treatment). Acetyl cholinesterase inhibitors may delay nursing home placement by 20 months and potentially for a longer period if started early. On the other hand, a delay in treatment leads to a loss of the potential benefits.

The retardation of dementia progression in terms of symptom deterioration delay has been demonstrated for the compounds mentioned in mild to moderate dementia cases:

donepezil	38 weeks[24]
rivastigmine	38-42 weeks[25]
galantamine	52 weeks[26]

These numbers indicate that, as a result of using these drugs, dementia progression is retarded on average by only 6-12 months; this means that the burden of disease cannot be sustainably lowered in an aging population utilising current treatment options. Thus, it is also fair to assume that these drugs do not essentially influence the underlying disease, which leads to neurodegeneration.

The more severe cases are treated with the NMDA glutamate receptor blocker memantine. This compound blocks the toxic effects associated with excess glutamate

and regulates glutamate activation; a dysfunction of glutamatergic neurotransmission is thought to be involved in the etiology of Alzheimer's disease. The limitations in the treatment effectiveness of memantine are comparable to those of acetylcholine esterase inhibitors.

With memantine having received market approval in 2002 (cholinesterase inhibitors were approved from 1996 onwards), the last significant innovation on the market today is already seven years old. This demonstrates an urgent need for progress in this area.

Future treatment options based on new mechanisms of action

As the benefits of the currently available medicines are not long lasting and only postpone the symptomatic progress of the disease by just 6-12 months, serious preclinical research efforts to target the disease pathology at a more basic stage are presently being undertaken by numerous pharmaceutical companies as well as by major academic centres. The NIH alone has spent an estimated USD 644 million on Alzheimer research in 2008,[27] and will probably approach the billion-dollar goal in the near future.

Many novel approaches for causal treatment of Alzheimer's dementia aggregate around Beta-amyloid. Evidence for its relative importance is genetically derived. Some cases of early-onset Alzheimer's dementia, called Familial Alzheimer's Dementia (FAD), are inherited. FAD is caused by a number of different gene mutations on *chromosomes 21, 14*, and *1*, and each of these mutations causes the formation of *abnormal proteins* [for review see[28]]. Mutations on *chromosome 21* cause the creation of abnormal amyloid precursor protein (APP). Each of these mutations causes the formation of an increased amount of the *beta-amyloid protein*. *Beta-amyloid*, is created from APP. Aβ is formed after sequential cleavage of the amyloid precursor protein, a transmembrane glycoprotein of undetermined function. APP can be processed by α-, β- and *γ-secretases*; Aβ protein is generated by successive action of the *β and γ secretases.*

Another important target is TAU aggregation, which seems to be involved in Alzheimer's disease and causes cellular toxicity in conjunction with Aß formation.[29] Thus, novel

development approaches are clustering around Tau aggregation and amyloid beta aggregation inhibition; RAGE inhibition, microtubule stabilization, and gamma-secretase modulation are further, largely unrelated targets, and are a few of the targets currently under investigation. These approaches include novel vaccination strategies against β-amyloid peptide.[30]

Although there is a wealth of potential targets for Alzheimer treatment, no causal treatment principle has entered the daily clinical practise until the time of writing this review. The pipelines of drug companies are rich in compounds in this regard, and many have reached the level of clinical development. Nevertheless, there are only about 690 ongoing clinical trials to test new dementia drugs, a figure which appears minuscule when compared to the 5,000 plus trials, which are currently ongoing in the diabetes area [www.clinicaltrial.gov, Basic Keyword Search, all studies (recruiting, completed, active not recruiting), 23 September 2009].[31]

This finding highlights that the translation of basic science into clinical benefits in the CNS/dementia research is still far away from being at a level, which can be classified as broadly successful when compared to other more intensive research fields such as pain or diabetes (as referred to above). Currently, few new drugs are being tested against dementia; clinical translation appears to be more difficult than in other areas such as diabetes, for example, as appropriate animal models and even a basic understanding of disease pathophysiology is still lacking. The critical importance of plaque formation for disease progression has been questioned as, for example, in the findings from the 'Nun Study' in which appalling discrepancies between brain plaque volume and cognitive function have been reported.[32] Thus, the translatability of plaque-reducing strategies into clinical care remains a challenge.

In light of these considerations, it seems fair to say that hope for radical improvement of therapeutic options is considerable, but success may be limited - at least - in the near future. On the other hand, innovation in this area is still the only causal cure for the dementia catastrophe and, related activities with a particular emphasis on translatability

aspects, still need to be intensified.

Socio-economic considerations

The broader socio-economic impact of the dementia problem is immense. Dementia not only affects a large number of patients in the rapidly growing elderly cohort, but constitutes a major burden of disease with an essential loss in life quality, independence, freedom of mobility, and cognition.

In Switzerland, it is assumed that the increase in nursing costs for this condition alone will be in the range of CHF 1.6 and 7 billion between 2008 and 2050 depending on the severity of the disease: homecare patients are assumed to cost CHF 16,000 per case p.a., nursing home patients CHF 73,000 per case p.a. [adapted from[13]].

For the US, 5.3 million dementia patients produce direct and indirect costs of USD 148 billion. Most patients live at home and are cared for by family and friends. Lost wages of patients and their families, plus the costs for non-nursing home patients add USD 94 billion to the bill, so that we are looking at total annual costs of USD 244 billion.[33]

Today, there is already a shortage in the supply of key services evident in the US involving caregivers for dementia patients; home support is only available to 44% of patients, day care to 42% and residential/nursing home care to 34%.[34]

This problem is especially aggravated by the future shortage of caregivers: a recent study estimated that between 120,000 and 190,000 new persons will need to be recruited by 2030 in Switzerland to replace the retired care givers (two-thirds) or compensate for the increased demand due to the ageing population.[35]

The overall ethical impact of this development is tremendous. Societies will have to cope with the dilemma of the epidemic surge in dementia in their ageing populations or face the accusation of being neglectful. It is an appalling and possibly symptomatic fact, that the UN Millenium Development Goals[36] does not mention the problems of ageing and

dementia as one of the leading objectives for the third millennium of mankind.

Coping by preventive measures

At present, the only immediate way to alleviate this situation appears to lie in utilizing preventative measures to reduce the incidence of dementia. The reasons for the attractiveness of this option are very practical: it can be easily translated to clinical practise today and without any delay.

As such, dementia in the elderly is not different from many other chronic or degenerative diseases, which occur in the elderly with increasing incidence. Currently, we tend to treat the manifest disease although an earlier intervention could have prevented its occurrence: we neglect prevention and are finally urged to treat the disease. Many such examples can be given, including diabetes mellitus type II, atherosclerosis and related cardiovascular disorders, heart failure, osteoporosis, cancer (e.g. smoking-related cancers), even hair loss, and finally – dementia. Prevention is rather effective and also cost effective in terms of reducing morbidity and mortality. For example, the ageing process can be counteracted by treating cardiovascular risk factors associated with hypertension, dyslipidemia and smoking; preventing diabetes by exercising and weight loss; osteoporosis through exercise, vitamin D and calcium; and certain types of cancer by smoking cessation.

Existing and well known drugs are very useful in implementing this preventative approach and there is an enormous window of opportunity for new drugs.[37]

As mentioned above, there is no causal therapy for dementia available at present. Due to not being able to rely on the magic bullet to reverse neurodegeneration or at least stop its progression in the near future, all means to prevent the occurrence of dementia must be utilized; if they are not yet available, they should be developed for clinical use.

If we accept that the primary process leading to Alzheimer's disease cannot be tackled at present, we need to look into the broad etiology of dementia at large. Literature seems to convey the impression that Alzheimer's dementia is the absolutely dominant entity in this regard and other etiologies are far less important. It is apparent that this view needs to be re-visited if opportunities for successful interventions are not to be missed.

Vascular dementias are more important than generally presumed as all are debilitating - also, subsequent, multiple strokes belong to this group.[38] Furthermore, there is increasing awareness of the fact that dementia exposes a considerable contribution of vascular biology to all etiologies with increasingly acknowledged overlap between vascular and Alzheimer‘s type dementia.[39] In newer 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.[39-41] Although exact figures are lacking and clear studies to detect the important coincidence of Alzheimer’s and vascular dementia need to be performed, assuming a contribution of vascular disease, especially in the elderly population, provides a promising opportunity.

In epidemiological studies, elevated blood pressure or diabetes do not massively increase the risk of dementia in individual patients with either condition (relative risk).[42] By contrast, as hypertension and diabetes are frequent conditions with a relatively high prevalence, this modest increase in risk translates into an elevated attributable risk at the population level. Based on results from the Honolulu-Asia Aging Study[43] the population attributable risk of dementia for untreated hypertension can be estimated at approximately 40%. The critical point here is that arterial hypertension is amenable to effective interventions by modern drugs; however, this opportunity is still under-utilized in the Western world. The huge primary care study, DETECT, showed that in 55,000 patients from GP offices in Germany, only about 20% of hypertensive patients aged 60+ were treated to goal.[44] Figures in other countries are not essentially better.[45]

Similar problems arising from the under-utilization of preventative measures for cardiovascular protection exist 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.[46]

Even at present, 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). As the contribution of vascular components to dementia is increasingly considered to be significant, even in the most prevalent etiology - Alzheimer's disease, preventative cardiovascular measures appear to be a very appealing option. However, the prevention and treatment of neurodegenerative processes in Alzheimer's disease remain as unmet medical needs of the highest priority. Thus, all means to increase preclinical/clinical research, clinical guidelines and, especially translational efforts, need to be intensified and reach new standards of excellence (see Figure 2).

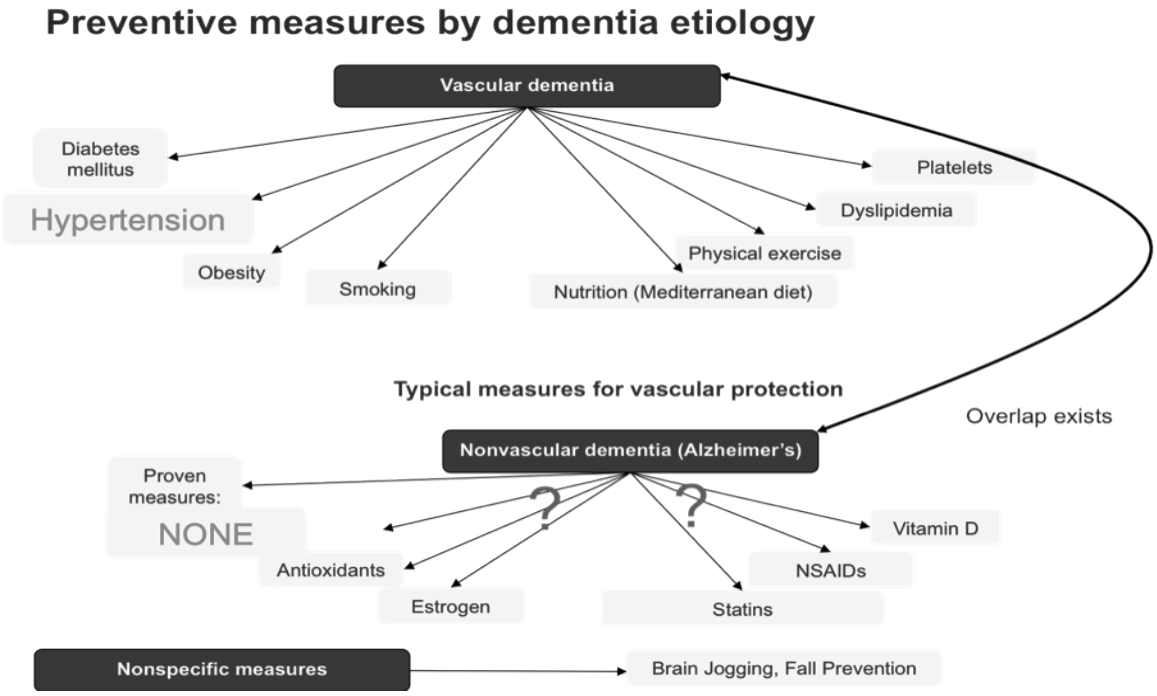


Figure 2

Currently, there are three basic principles of dementia treatment: (1) Vascular dementia: treatable and preventable; (2) Nonvascular dementia: no sustainable treatment of causal relevance known; (3) Nonspecific measures apply to all etiologies. Given these scenarios, the necessity to tackle vascular dementia is a call for immediate action.

Conclusion

Demographic change will lead to a dramatic increase in the global aged population – by 2050 two billion people will be aged 65+; in Europe this will be between one-quarter and one-third of the population. Dementia is a leading challenge as it is an age-related disease and its prevalence sharply rises with age. Today, this disease already causes vast socio-economic challenges and expenditures, and dramatic increases are expected in the future.

At present, treatment options are very limited in terms of their effectiveness. Effective prevention will be the clue to reduce the burden of disease and the good news is that it is already available and effective for vascular dementia. Nevertheless, the crucial point is that it has to start decades before disease manifestation. Prevention together with the treatment of nonvascular (Alzheimer‘s) dementia is an urgent challenge for biomedical innovation. However, new principles (e.g. vaccination, anti-plaque drugs) are still relatively far from successful translation into medical practice.

If the existing options are not utilized and innovations are not rigorously pushed by society, the ageing society will face dramatic social and economic drawbacks. Thus, increasing longevity may no longer be as desirable. Coping with ageing and, in particular, dementia has become a millennium goal, however the related change in people’s mindsets has just begun and still needs to be strengthened, structured and adapted by official public health strategies both on a national and a global scale. As the burden of ageing varies between different regions, those countries most affected by this socioeconomic threat should become leaders in the development of coping strategies. Thus, Japan has a special responsibility in terms of coping with the demographic revolution and the related dementia burden, which can be seen both as an opportunity and a challenge.

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