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HEALTH PROMOTION PROGRAM ON PREVENTION OF LATE ONSET DEMENTIA

IAGG WORKSHOP: HEALTH PROMOTION PROGRAM ON PREVENTION OF LATE ONSET DEMENTIA

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IAGG, WHO, and SFGG organized a international workshop on "Health promotion programs on prevention of late on-set dementia. Thirty world specialists coming from Europe, North America, Asia, South America, Africa and Australia, shared their experience on methods and results of large epidemiological interventions to reduce incidents of dementia or delay its on-set. Chaired by Laura FRATIGLIONI, an expert in Epidemiological studies on dementia issues, the workshop gave opportunity for discussions and controversies about the state-of-the-art. Based on different national and international trials (ADAPT, MAPT, FINGER, GUDIAGE, GEM etc) the questions remained opened for different aspects of methodology, the choice of domain or multi domain intervention, the choice and the definition of the target populations, the best age of candidates, the issues related to the discrepancy between late effects, and interventions' duration.

We are please to publish in the Journal , the presentations presented to this workshop. These publications will complete previously task force published in the journal in the last two years on methodological issues for Alzheimer's trials including end point (1, 2) , biomarkers (3, 4) , and the experience of past therapeutic trials (5, 6).

THE GLOBAL BURDEN OF DEMENTIA WORLDWIDE, *P. Du (China)*

Population ageing and dementia

As the achievements of socioeconomic developments in the past decades, world population has been ageing rapidly, which poses a series of challenges to the existing health system as well as the development itself worldwide. With the growth of aged population and the ageing of the aged population, dementia has become one of the leading causes of death and an increasing burden for the society, family and the elderly themselves. This trend deserves more and more attention from the governments and public awareness worldwide.

In 2009, the number of older persons aged 60 and over surpassed 700 million globally, and it is projected to increase to 2 billion by 2050, implying that their number will triple over a span of 40 years. The older population will increasingly be concentrated in the less developed regions, currently 64 per cent of older persons are living in less developed countries. It is expected to increase from 473 million in 2009 to 1.6 billion in 2050, namely nearly 80 per cent of the world's older population is expected to live in developing countries by 2050 (United Nations, 2010). This scenario reminds both the developing

countries and developed countries' need to pay more attention to dementia and health cares for the elderly.

Dementia is a syndrome that can be caused by a number of progressive illnesses that affect memory, thinking, behavior and the ability to perform everyday activities. Dementia mainly affects older people, although there is a growing awareness of cases that start before the age of 65. After age 65, the likelihood of developing dementia roughly doubles every five years (ADI, 2010).

According to Alzheimer's Disease International's estimates in the World Alzheimer Report 2009, there are 35.6 million people living with dementia worldwide in 2010, it will increase to 65.7 million by 2030 and 115.4 million by 2050. Nearly two-thirds live in low and middle income countries, where the sharpest increases in numbers are set to occur (ADI, 2009). In the latest World Alzheimer Report 2010, Alzheimer's Disease International estimates the total worldwide costs of dementia are US$604 billion in 2010, about 70% of the costs occur in Western Europe and North America (ADI, 2010).

Global burden of dementia

Dementia is a health issue as well as societal issue; it affects not only the medical costs but also the community care, family care and the elderly persons' quality of life. Therefore, the burden of dementia includes economic costs for the medical treatment and institutional care, community services for the home care, and daily care burden as well as emotional burden on family members, relatives and friends.

It is important to notice that medical costs of dementia worldwide are only the minor part in the global burden, and the majority of dementia burden is on the informal and social care. According to ADI's estimate in 2010, costs of informal care (unpaid care provided by families and others) and the direct costs of social care (provided by community care professionals and in residential home settings) contribute similar proportions (42%) of total costs worldwide; while direct medical care costs are much lower (16%) (ADI, 2010). This estimate turns our focus on the burden of care, as the older persons with dementia usually need long term care and services.

The feminization of the older persons with dementia makes the situation even worse, usually the females take the daily responsibility to care the husband with dementia, especially in developing countries, with the increasing gap between genders on life expectancy and the higher prevalence rate of dementia for female elderly comparing to males, the older persons with dementia need more and more help from their children or community care, the care burden of dementia becomes more social and depends on the generational solidarity.

The global burden of dementia is uneven between developed countries and developing countries. Economically, the current estimated costs of dementia is mainly occurring in developed countries, however, with the growing numbers of older persons and increasing prevalence in developing countries, at least the societal and family burden of dementia can be expected to surpass the developed countries in the near future. At the same time, the medical costs in developing countries will certainly increase simultaneously with the better awareness and more health intervention programs develop. For example, as a developing country with the biggest population in the world, China has 6.35 million older persons with dementia by 2010, the average medical cost for each person is estimated at around 2,000 US dollars, and each year 300 thousand new cases are added.

Although the burden of dementia is well estimated worldwide from the perspectives of medical care, institutional care and community services, the burden on family members and others is still underestimated, especially in developing countries, many family members have to give up their job to take care of the older persons with dementia, devote a lot of time and efforts on daily care, experience stress and emotional difficulties, their contribution to the society and older persons is not well appreciated both economically and socially.

Generally, the global burden of dementia worldwide is enormous even measured by the current available estimates, it will be a more serious challenge when we consider the burden on family members and others and the quality of life on the older persons themselves. Dementia is a bitter process for the older persons and their family members, early diagnosis and treatment, good community services, better emotional support and family care are crucial to slow the process and improve the quality of life both for older persons with dementia and their family members. It is urgent to raise the awareness of government and the public worldwide, take further actions to make it a priority both in health prevention and care system, and eventually decrease relatively the burden of dementia worldwide.

Further actions needed

Dementia is a challenge worldwide, both in developed countries and developing countries; the global burden of dementia deserves more attention and actions from governments, the public and families. Active policies and health prevention programs will play an important role in promoting the early diagnosis and treatment, keeping the functions of the older persons with dementia as long as possible, and finally they will have positive economic and social impacts, helping to save medical resources and social/family costs of care.

At government level, governments should make dementia a health priority. It is also governmental responsibility to invest much more on research on dementia, aiming at early diagnosis, cost-effective treatment and better care. Based on the rapid developing trends of dementia, it is urgent for governments in developing countries to reform its existing health prevention strategy and formal/informal care systems. For example, more medical doctors to be trained for the purpose of early diagnosis of dementia, more institutional care for the older persons with dementia, more training on the specific skills for family care

givers.

At a societal level, public awareness of dementia needs to be raised. The majority of older persons with dementia in developing countries are not diagnosed; the symptoms of dementia are misunderstood as normal process of ageing. Therefore, public media and health professionals should make more efforts to disseminate the relevant knowledge of dementia, so that policy makers, service providers, family members can learn more about dementia and its possible impacts on the society, family and the older persons' quality of life, take more concrete actions to provide better treatment and care. Developing countries should make more efforts due to the rapid increase of older persons with dementia, changing living arrangements and the lack of social support system to the older persons with dementia and their family members.

At family level, family members need to be knowledgeable on the early symptoms of dementia of their older members, seek early diagnosis, provide more emotional support and daily living support, and improve the living environment for the older persons with dementia. Family care givers also need more professional guidance and social support to take the responsibility of long term care for these older persons. At global level, international collaborations led by WHO and Alzheimer's Disease International should be further enhanced, findings from monitoring report on dementia and good experiences on the diagnosis, treatment and care should be shared and promoted effectively worldwide. References: United Nations (2010) World Population Ageing 2009, ST/ESA/SER.A/295, New York. Alzheimer's Disease International (2010). World Alzheimer Report 2010. London: Alzheimer's Disease International. Alzheimer's Disease International (2009) World Alzheimer Report 2009. London: Alzheimer's Disease International.

LIFE-COURSE EPIDEMIOLOGY IN DEMENTIA - STATE OF THE ART,

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Dementia is defined as a clinical syndrome characterized by progressive deterioration in multiple cognitive domains that are severe enough to interfere with daily functioning. It was estimated that worldwide more than 25 million people were affected by dementia in 2005, with 5 million new cases occurring every year (1). Dementia is a principal cause of functional dependence, institutionalization, and death in older people. Since the 1980s, numerous community-based studies focusing on aging and health in elderly people have been launched in the world. These studies, joined by several long-term observational studies that were initially focused on cardiovascular disease of middle-aged people, have significantly contributed to the understanding of etiology of dementia and thus, pave the way for potential intervention.

Life-course perspective in dementia risk

Dementia is a multifactorial disorder. The risk of late-life dementia is determined by exposures experienced over the lifespan. The pathways of different risk factors leading to dementia are not fully understood, but several etiological hypotheses have been proposed such as vascular hypothesis, inflammatory hypothesis, oxidative-stress hypothesis, and toxic exposures (Fig 1) (2). These hypotheses highlight potential links of various risk factors to brain pathologies that may cause the dementia syndrome. For instance, both vascular and neurodegenerative pathways may play a part in the association of high homocysteine with brain aging and dementia; inflammatory markers are likely to reflect both peripheral and cerebrovascular mechanisms that may be linked to dementia. Furthermore, epidemiological research has also suggested that psychosocial and healthy lifestyle factors may postpone the onset of dementia, possibly by enhancing cognitive reserve. These factors include high education and socioeconomic status (SES) in early-life as well as rich social network, social engagement, mentally-stimulating activity, and regular physical exercise over adult-life. In addition, several follow-up studies have reported a decreased risk of dementia associated with healthy dietary patterns and nutritional factors such as high adherence to a Mediterranean diet as well as dietary or supplementary intake of antioxidants (e.g., vitamins E and C) and ω-3 polyunsaturated fatty acid.

Systematic reviews and meta-analyses have highlighted the relevance of a life-course perspective in studying the risk and protective factors for dementia because this approach has helped to demonstrate that age or specific time-windows of exposures as well as accumulative or combined exposures are critical in determining the risk of late-life dementia (2, 3). This life-course approach in dementia has been supported by numerous reports, such as:

1. Longitudinal studies often report a decreased incidence of dementia, and of Alzheimer's disease (AD) in particular, associated with high SES and educational achievement early in life.

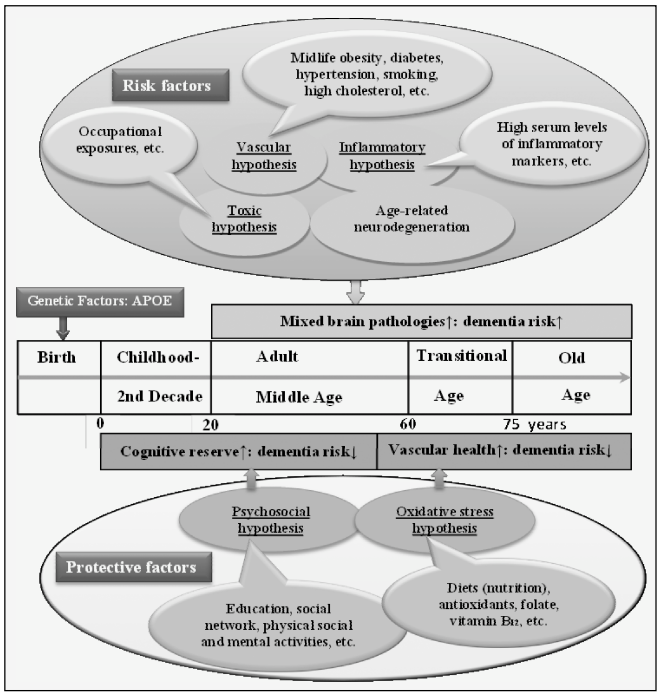
2. Long-term observational studies of the general population have consistently suggested that elevated blood pressure in midlife, especially when not controlled with antihypertensive agents, is associated with an increased risk of dementia in late-life.

3. Similarly, several studies also showed that possessing a few other vascular risk factors in midlife such as obesity and high total cholesterol was more consistently associated with an increased risk of late-life dementia. For example, the HARMONY study of dementia among Swedish twins suggested that being obese at midlife was associated with a nearly 4-fold increased odds ratio of dementia. However, epidemiological evidence supporting a risk effect of having these vascular risk factors in late-life (e.g., 75+ years) in dementia is less evident, indicating the relevance of the time at exposure in the dementing disorder.

4. Diabetes in association with dementia is supported by systematic reviews and meta-analyses of longitudinal studies, which show that diabetes is associated with an approximately 2-fold increased risk of dementia (3). Furthermore, in the Kungsholmen Project, borderline diabetes or impaired glucose

regulation was associated with an increased risk of dementia and AD independent of future development of diabetes, possibly by accelerating the progression of mild cognitive impairment to dementia (4). Borderline diabetes may also interact with severe systolic hypertension to synergistically increase the dementia risk. Long-term observational studies show that midlife-onset diabetes as compared to late-life diabetes is more strongly associated with an elevated risk of dementia, even when controlling for the duration of diabetes (5).

Figure 1
Etiological hypotheses for dementia from life-course perspective



In conclusion, the life-course model for dementia risk is now well recognized by the scientific community. This model has several implications. Most importantly, any preventive or therapeutic intervention programs targeting, for example, vascular risk factors are likely to be effective only if implemented from midlife. Other implications are discussed below.

Cumulative and combined exposures

The combined or cumulative effect of multiple risk factors on the risk of dementia has been investigated in several population studies. For example, the large-scale community-based Faenza Project in Italy detected a joint effect of age, stroke, and education on the odds of dementia, such that older people as compared to younger persons had a higher prevalence of dementia across various educational and stroke groups. Furthermore, stroke is a strong risk factor for dementia among younger-old and highly educated subjects; the onset of dementia might occur about 10 years earlier owing to stroke, possibly by accelerating progression from cognitive impairment no dementia to clinical dementia. Other explicative examples derive from the Swedish Kungsholmen Project, the Finnish CAIDE data, and a few other population-based studies, which consistently suggested a cumulative effect of aggregating vascular disorders on dementia risk such that an increasing burden of multiple vascular risk factors and disorders was associated with an increased risk of the dementing disorder.

The combined effect of genetic-environmental or environmental-environmental joint exposures may lead also to the attenuation of the dementia risk. For example, in the CAIDE study, more frequent leisure-time physical activity in midlife was associated with a reduced risk of dementia; such effect was particularly strong among carriers of the APOE ε4 allele, suggesting that physical activity may modify the effect of the ε4 allele on the risk of dementia. Furthermore, the Kungsholmen data also suggested that work complexity with data and people was related to a decreased risk of dementia and that the highest level of work complexity may modulate the increased dementia risk due to low education.

Increased dementia risk with advanced age

Both prevalence and incidence of dementia increase steeply with advancing age. Globally, the prevalence of dementia was estimated to be approximately 3.9% in people age 60+, with prevalence varying from 1.6% to 6.4% by regions across the world. In Europe, the pooling data of population surveys suggest that the age-standardized prevalence of dementia in people aged 65+ years is 6.4%. The prevalence of dementia doubles almost every 5 years from 65 years until very old ages; nearly half of the oldest-old people (90+ years) become demented. Thus, the overall prevalence and the burden of dementia depend largely on age structure of the population. Similar to prevalence, the incidence of dementia increases substantially with age. The pooling data of population-based incidence studies in Europe suggested that approximately 2 per 1000 person-years become demented in people aged 65-69 years, and the incidence increases to 70-80 per 1000 person-years for people 90+ years (6). Therefore, as population ages, the number of patients with dementia is projected to nearly double every 20 years (1).

Mixed dementia

The strong association of dementia with age leads to the fact that in the general population 70% of the dementia cases are over age 75 (6). At these advanced ages, more than 50% of people are affected by multimorbidity as defined by the presence of two or more chronic conditions (7). As comorbidity is a common feature among patients with dementia (8), it is plausible to hypothesise that different pathologies may affect

also the brain. Using current clinical criteria, we are used to state that AD and vascular dementia (VaD), the two main dementia subtypes, account for approximately 70% and 20%, respectively, of all dementia cases. In the Kungsholmen Project of 75+ years old people, over 50% of AD cases had vascular involvements, suggesting that patients with "pure" AD and "pure" VaD constitute only a minority of all dementia cases. These clinical observations are supported by neuropathological and neuroimaging data, which show that there is a spectrum of dementia-associated brain pathologies from relatively pure vascular pathologies on one end and relatively pure Alzheimer pathologies on the other end, and in-between the majority of dementia cases are likely owing to cerebrovascular and neurodegenerative pathologies (9). Therefore, in most cases, clinical dementia represents a mixture of neurodegenerative and cerebrovascular pathologies that may be impossible to untangle, especially among very old people. If these observations question the traditional classification scheme of AD and VaD, from the public health perspective, the ultimate purpose becomes to prevent the dementia syndrome as a whole.

Conclusions

In summary, dementia will reach an epidemic level in the coming decades as a result of population aging and the lack of effective intervention strategies. This will pose a serious threat to public health as well as to the social and economic development of the modern society. Research from multidisciplinary perspectives involving epidemiology, neuropathology, and neuroimaging has provided sufficient evidence that vascular risk factors significantly contribute to the expression and progression of cognitive aging including dementia, whereas active engagement in social, physical, and mentally-stimulating activities may delay the onset of the dementia syndrome. A promising strategy to deal with dementia is to implement intervention programs that take into account both the life-course perspective and the multifactorial nature of the disease. The multi-domain interventions should include strategies to enhance cognitive reserve as well as maintaining vascular health by adopting actively-integrated lifestyles and optimally controlling vascular disorders to reduce the burden of vascular lesions in the brain. These intervention studies need to have sufficient sample size and several branches to be able to further clarify which interventions can better help people to maintain their cognitive ability as long as possible or at least to delay the dementia onset.

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MULTI-DOMAIN PREVENTIVE INTERVENTIONS: EXPERIENCES FROM FINLAND,

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From cardiovascular-related conditions to dementia prevention

Cardiovascular conditions and dementia have more in common that it was previously thought (1). Dementia-related disorders (i.e. Alzheimer disease, AD) are often multifactorial, resulting from interactions between genetic and environmental factors (such as modifiable vascular or lifestyle-related factors). The traditional late-life perspective is presently being replaced by a life-course approach, with more focus on windows of opportunity for prevention.

The step towards the multi-domain Finnish Geriatric Intervention Study to prevent cognitive impairment and disability (FINGER) was taken on a research platform that has been developed in Finland over several decades. Some of the main components of this platform are:

1. The nearly 40 years long experience in countrywide risk factors monitoring and effective prevention of cardiovascular conditions, which started with the community-based North Karelia Project in the 1970s and the WHO-MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) Project in the 1980s (2). Such projects were extended over the years beyond the field of Cardiology, developing into the current FINRISK system (Finnish national system for monitoring of risk factors for chronic non-communicable diseases) (3). FINRISK is a large population survey carried out since 1972 every five years using independent, random and representative population samples from different parts of Finland. Work is at present ongoing to integrate dementia-related diseases into FINRISK. The FINRISK database is regularly linked to several national registers, such as the Population Register, Hospital Discharge Register, Drug Reimbursement Register, and Causes of Death Register. Because a large amount of information is already available on the survey participants, the decision was made to select the FINGER study participants from FINRISK.

2. The Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE) study, partly based on FINRISK, is one of the few studies in the world with a large and representative population-based cohort including both males and females,

long follow-up times (up to three decades), and measurements of several risk factors and health-related outcomes from several time points (midlife and late-life). Based on CAIDE results, the first tool was formulated for estimating dementia risk based on risk factor profiles (4). The CAIDE Dementia Risk Score includes modifiable risk factors such as hypertension, hypercholesterolemia, obesity, physical inactivity, and has been validated in a population from USA (Kaiser Permanente of Northern California). This tool is now being used to select participants in the FINGER study.

3. Two intervention studies in Finland have shown that trial participants can be motivated to make major changes in their lifestyle. The Diabetes Prevention Study (now completed) is a landmark randomized controlled trial (RCT) showing the effectiveness and feasibility of physical exercise and dietary interventions as preventive measures in general populations (5). The ongoing exercise and dietary 4-year intervention study Dose-Responses to Exercise Training (DRs EXTRA) had a drop-out rate of only 8% after two years, and its intervention protocol served as a model for FINGER.

The FINGER study

The Finnish Geriatric Intervention Study to prevent cognitive impairment and disability (FINGER) is a multicenter (6 sites) RCT currently ongoing in Finland. The main objective is to investigate to what extent a multi-domain intervention can reduce the risk of cognitive impairment and dementia in an elderly population at increased risk of cognitive decline. FINGER involves 1200 participants, aged 60-77 years, who previously participated in population-based non-intervention surveys (i.e. FINRISK). Participant selection is done according to the CAIDE Dementia Risk Score and CERAD cognitive test battery performance. Inclusion criteria are meant to select elderly who are at risk of cognitive decline/dementia, and who are most likely to benefit from the intervention. Persons with dementia/substantial cognitive decline are excluded. In the intervention group, each subject receives all four components: nutrition; physical activity; cognitive and social activity; monitoring/treatment of metabolic and vascular risk factors (Figure). Intervention programs follow a detailed and cautiously planned and monitored protocol, but are at the same time individually tailored according to participants' needs and health status. Subjects in the reference group are given general public health advice on lifestyle and vascular risk factors.

The four components of the 2-year multi-domain intervention are:

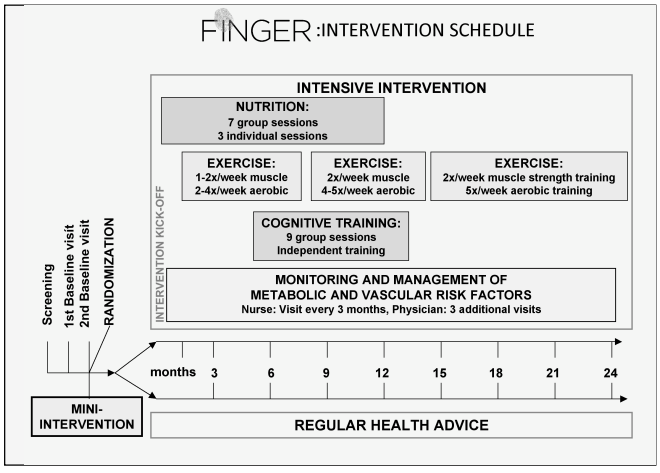
1) Dietary intervention, supervised by nutritionists, and formulated according to current guidelines for cardiovascular disease prevention, studies on diet and dementia risk, and Finnish nutrition recommendations. The dietary intervention is also adjusted to the needs of an elderly population. Nutrient intake in all participants is periodically assessed.

2) Exercise training program, supervised by physiotherapists, and based on international guidelines. Subjects participate in a supervised, individually prescribed strength training and aerobic exercise program. Compliance to training and physical performance is periodically evaluated by a validated questionnaire and standardized tests.

3) Cognitive training, supervised by psychologists, is organized into group sessions and individual training. Several cognitive domains are targeted by the intervention. Social activities are stimulated via group meetings of the other interventions within the treatment arm, and also arranged with local offices of the Finnish Alzheimer Association. Participation in social and cognitive activities is monitored during the study, and participants are asked to keep diaries.

4) Intensive monitoring and management of metabolic and vascular risk factors (i.e. hypertension, dyslipidemia, waist/hip ratio, impaired glucose tolerance). At baseline all participants are evaluated by the study physicians according to the latest evidence-based guidelines. The treatment group meets periodically the study physicians for evaluation of laboratory test results, anthropometric measures (height, weight, blood pressure, hip and waist circumference) and cardiovascular/metabolic morbidity. Participants in the intervention arm receive oral and written information on their laboratory analyses, on the risks associated with these values, on the importance of management of metabolic/vascular risk factors, and are motivated to adhere to adequate lifestyle changes and pharmacological treatment. If initiation/adjustment of pharmacological treatment is necessary, participants are strongly recommended to visit their own physician.

Figure



The primary outcome is cognitive impairment, diagnosed using accurate and validated neuropsychological tests (Neuropsychological Test Battery, Trail Making and Stroop Tests). Secondary outcomes are depressive symptoms, cardiovascular and cerebrovascular morbidity and mortality, quality of life, disability, and utilization of health resources, measured using validated scales selected according to recent

recommendations (e.g. European Medicines Agency). Brain MRI is performed in a sub-group of participants at baseline and at month 24 to evaluate vascular lesions and hippocampal and total brain atrophy. An extended 7 years follow-up is planned to fully analyse the effect of the intervention on dementia incidence and secondary outcomes.

Addressing current problems in cognitive impairment/dementia prevention trials: contributions of the FINGER study

Robust evidence on prevention of dementia/AD is missing, and many studies done so far are limited by methodological problems. Recent recommendations for AD research include use of a life-course approach, with combination of retrospective and prospective data, use of standardized and well-validated neuropsychological batteries, comprehensive approach in outcome assessment and biomarkers validation and implementation (6). The FINGER study follows these suggestions. This RCT targets risk/protective factors chosen based on the best available knowledge; focus is on simultaneously addressing several common modifiable risk factors to obtain an optimal prevention effect. The attention is on vascular and lifestyle-related risk factors shared by AD, vascular dementias and other major chronic diseases common in the elderly, with an integrative approach including several secondary outcomes and estimation for cost/effectiveness and total benefit.

Disappointing results of previous trials with single agents in elderly or already cognitively impaired persons pointed out some key issues, which have been taken into account in the FINGER study design:

1) Balancing the timing of the intervention and the selection of the target group: starting the intervention earlier may lead to better effects, but a healthy, too young target population would require long follow-up times, large sample sizes and considerable financial resources. FINGER inclusion criteria select thus a population at increased risk of cognitive decline, but without advanced cognitive impairment.

2) Representative target group: recruiting FINGER participants from FINRISK ensures a truly population-based sample.

3) Baseline data: the information on earlier lifestyle and vascular factors from FINRISK offers detailed baseline data for FINGER, which is very rare in RCTs.

4) Outcome measures: cognitive impairment may be a better outcome than just conversion to dementia.

5) Ethical issues: it is no longer possible to have a traditional placebo group where risk factors for cardio/cerebrovascular conditions are not treated.

6) Investigating potential mechanisms of action: collecting blood samples at baseline, month 12 and month 24 allows detailed biomarker measurements (i.e. inflammation, redox status, lipid and glucose metabolism, NMR metabonomics). In addition, MRI and PET measurements are planned for a subsample of the participants.

The lessons learned from this multi-domain intervention will help in planning and conducting future interventions and in the implementation of preventive measures for the whole population at risk in the future.

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MAPT STUDY: A 3-YEAR RANDOMIZED TRIAL OF MULTIDOMAIN INTERVENTION AND OMEGA-3 FOR THE PREVENTION OF COGNITIVE DECLINE IN FRAIL ELDERLY SUBJECTS,

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Abstract: *Prevention strategies for Alzheimer's disease (AD) are urgently needed due to its high and rising prevalence. Because of the multifactorial nature of AD, it now seems pertinent to propose a « multi-domain » intervention, combining interventions that target several factors associated with the onset of the disease, in order to examine their potential synergistic action in reducing risk. We have initiated the Multi-domain Alzheimer Preventive Trial (MAPT), a 3-year prospective prevention study involving frail elderly subjects. The primary objective is to determine the effect of treatment with omega-3 and/or multi-domain intervention (nutritional, physical and cognitive training) on cognitive decline. The MAPT Study is a randomized controlled trial conducted by hospital practitioners specializing in memory disorders in thirteen French cities. Ambulatory subjects aged 70 years and over who experienced at least one of the following criteria: subjective memory complaint spontaneously expressed to a general practitioner, limitation in one instrumental activity of daily living (IADL), and slow walking speed, were included. Subjects with dementia, incapacities for basic activities of daily living (ADL) and depression (GDS) were excluded. Enrolled participants undergo a bi-annual visit. A series of tests are administered each year to assess cognitive function and functional status. Imaging data are collected in subgroups at baseline (PET for imaging beta-amyloid pathology and metabolism, MRI) and 3 years of follow-up (MRI). A total of 2574 subjects were screened for participation, of which 1680 fulfilled the eligibility criteria and were entered into the study. Subjects were randomized into one of the following four*

groups: omega 3 alone, multi-domain intervention alone, omega 3 plus multi-domain intervention, or placebo. The primary outcome is a change in cognitive function at 3 years, as determined by a memory test. The MAPT Study is the first preventive trial involving multi-domain interventions. Final results should be available in 2014.

Key words: *Prevention, Alzheimer Disease, multidomain, omega 3, frailty.*

Introduction

The high prevalence and incidence of dementia make it one of the most common diseases of the elderly. Alzheimer's disease (AD) is the most frequent form of dementia. It is presently estimated that the number of elderly people living with AD will increase from 26.6 million to 106.2 million by 2050 (1). The development of dementia at an advanced age could be the consequence of accumulated exposure to various risk factors throughout life. The search for modifiable risk factors is one of the present challenges facing epidemiological research on the causes of AD. Observation studies carried out in recent years show that modifiable risk factors such as arterial hypertension, diabetes and lifestyle could be implicated in the mechanism leading to dementia, thus opening new perspectives for developing preventive strategies (2). Several prospective studies emphasize in particular the importance of diet in maintaining good cognitive health. For this reason, considerable attention has since recently been given to the potential protective role of long-chain polyunsaturated omega-3 fatty acids in preventing cognitive decline and dementia (3). Other potentially modifiable lifestyle factors, such as cognitive training, physical exercise and social activities have also been linked with decreased cognitive decline and decreased incidence of dementia suggesting that it is very important for the elderly to maintain an active and socially integrated lifestyle. In spite of these results, it seems difficult to propose specific recommendations on changes in lifestyle, particularly due to the lack of randomized controlled studies because of questions as to methodology (randomization of a large number of subjects, duration of interventions extending over several years) (4, 5). Recently, two randomized controlled studies presented encouraging results on the prevention of dementia in the elderly (6, 7). Based on the ACTIVE trial, it was shown that cognitive training in individuals aged more than 65 years over a 5-year period made it possible to reduce functional decline, assessed by self-reported evaluation of instrumental activities of daily life (6). More recently, the findings of the FABS trial suggested that regular practice of moderate-intensity physical activity by elderly subjects with objective and subjective cognitive deficits led to a modest improvement in their cognitive function (7). In both these studies, the benefits observed were maintained one or even two years after intervention completion. Because of the multi-factorial nature of AD, it now seems pertinent to propose a « multi-domain » intervention, combining interventions that target several factors associated with the onset of the disease, in order to examine their potential synergistic action in reducing risk.

The MAPT Study is a three-year prospective study of frail elderly subjects randomized to treatment (omega-3 and /or multi-domain intervention) or placebo. The primary objective of the study is to determine the effect of treatment with omega-3 and/or multi-domain intervention on cognitive decline. The principal outcome measure is the change in cognitive function at 3 years determined by a memory test. Secondary objectives include imaging (PET-scan, MRI), biological material collection (blood specimens, RNA, DNA genomic), assessments of the efficacy of intervention on functional decline and functional capacities, and compliance. We also set up collection of medico-economic data which should allow us to assess the differential costs of the interventional strategies tested. This sub-study should determine the value of one or several strategies, taking into account the effectiveness of the resources put to use in each of the strategies. We present in this paper the design of the MAPT study.

Methods

Study design

MAPT is a multicentre, randomized, placebo controlled study, using a 4-group design including 3 treatment groups (omega 3 alone, multi-domain intervention alone, omega 3 plus multi-domain intervention) and a placebo group. Visits are scheduled every 6 months to assess physical condition, diseases and corresponding treatments, adherence to and tolerance of omega 3 treatment, adherence to multi-domain intervention, and to deliver the supplement. Cognitive and functional assessments are conducted at baseline, six months, and annually at 1, 2 and 3 years by independent research staff not knowing the group where the subject is assigned. All the assessments are performed by hospital practitioners specializing in memory disorders and AD. The inclusion period began in May 2008 and was completed in February 2011. Participants were enrolled from various sources, including advertisement in the local media, conference, general practitioners, and memory clinics in 13 French cities. A total of 2574 subjects were screened for participation, of which 1680 fulfilled the eligibility criteria and were entered into the study (see Figure 1). The study is coordinated from the hospital reference centre in Toulouse. The MAPT study treatment period will end in February 2014. The protocol is registered on a public-access clinical trial database (www.clinicaltrials.gov).

Patients

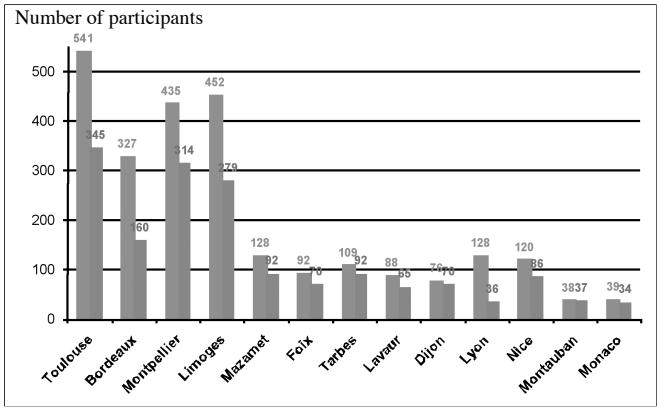
The recruitment goal for the MAPT trial is to enrol a sample of frail elderly people, aged 70 years and over, living independently in good functional and cognitive status. Definition of frailty is to date not consensual but we practically used three clinical components to identify frail persons based

on epidemiological evidence: spontaneous memory complaint expressed to the general practitioner, limitation in one instrumental activity of daily living (IADL) and slow walking speed. We exclude from the study demented subjects (DSMIV criteria), subjects who had incapacities for basic activities of daily living, and those who are severely depressed. In addition, other disorders that could interfere with the interpretation of the study are evaluated and patients with such disorders excluded.

Sample size. The sample size required for this trial is based on a 0.3-SD difference between the four trial arms (three treatment groups plus placebo group) according to a free recall score in the Grober and Buschke Test over the 3 years of the intervention. To detect a 0.3-SD difference between trial arms, with an alpha risk of 1% and a power of 80% power, 201 individuals are required per group. Anticipating a 30% dropout over 3 years of intervention, the total sample size required for the study is 1148 (287 per group). According to data collected during the first months of follow-up, the rate of drop out being higher than initially expected, we have had to recalculate the required sample size.

Figure 1

Number of screened (blue bars) and randomized (red bars) participants in the 13 French centers involved in the MAPT Study. The inclusion period began in May 2008 and was completed in February 2011. A total of 2573 subjects were screened for participation, of which 1680 fulfilled the eligibility criteria and were entered into the study. Approximately 700 participants were enrolled in the Midi-Pyrénées region



Interventions

Multi-domain intervention

The multi-domain intervention consists of collective training sessions and a yearly personalized preventive consultation which aims to detect dementia risk factors (sensory disturbances, difficulty in walking, nutritional disturbances, vascular risk factors) and to set up management in collaboration with the general practitioner.

Training sessions are conducted in small groups (6-8 participants) settings in twelve 120 minutes sessions over the first two months (two sessions a week for the first month and one session a week the second month). Each training session during these "intensive period" includes 60 minutes for the cognitive training, 45 minutes for the physical training and 15 minutes for nutritional advices (see Table 1). After the second month, sessions are planned monthly throughout the 3-year intervention period to reinforce the key messages of the program and increase the compliance. Participants are asked to use a diary to record their cognitive and physical activities each month. Booster training will be delivered in each multi-domain group one year and second year after their initial training sessions. Training sessions are delivered by qualified trainers. Compliance to the multi-domain intervention will be estimated from the number of sessions followed by each participant. Due to the nature of the intervention, participants are not blinded to group membership. Participants are explicitly asked at the beginning of the trial and at each subsequent assessment not to discuss information regarding the intervention with independent research staff conducting the cognitive assessment in order to limit subjective assessment and with other participant in order to limit contamination.

Omega 3 treatment duration and dose

The intervention arm will be asked to consume two soft capsules daily as a single dose, containing omega-3 fatty acids per day for 3 years. The placebo arm will be asked to consume two identical soft capsules per day for 3 years. Blinding is ensured by the identical appearance (size, colour and shape) of the placebo and active capsules. Unused study supplement is returned at each visit and compliance to supplement assessed by tablet count.

Ancillary neuroimaging studies

We performed neuroimaging exams (PET-scan and MRI) in sub-groups of participants:

1/ to explore the effects of interventions on cerebral atrophy (total brain volume and hippocampal volume) (MRI-MAPT ancillary study): MRI is performed within the two months following the inclusion visit (or the 6-month follow-up visit) and at 36 months. Currently, 486 subjects have undergone baseline MRI.

2/ to explore the effects of multi-domain intervention on cerebral metabolism (FDG-PET ancillary study): FDG-PET scans are performed at baseline, six months and one year in a sub-groups of participants followed in Toulouse centre. Sixty eight participants were included in the FDG-PET ancillary study and 45 have performed images at 6 months and 35 at one year.

And 3/ to evaluate brain amyloid deposits (Florbetapir-PET ancillary study). Florbetapir-PET imaging is proposed within the first year of follow-up. Currently, 139 participants were enrolled in the Midi-Pyrénées Region. This ancillary study will be extended to 4 additional centres (Montpellier, Bordeaux,

Table 1
Cognitive, physical and nutritional components proposed in the multi-domain intervention

Cognitive training	During the first two months, sessions 1 to 8 are focused on reasoning training and sessions 9 to 12 on memory training (mnemonic strategies: organization, visualization, association). One of the main objectives of the cognitive sessions is to teach to participants how to use these strategies to solving everyday problems (i.e. mnemonic strategies to remember a grocery list; reasoning strategies to understand the pattern in a bus schedule). The cognitive component of the multi-domain program was designed in collaboration with Sherry Willis from the University of Seattle, and Sylvie Belleville, Brigitte Gilbert and Francine Fontaine from the University of Montreal.
Physical training	The global aim of the physical intervention is to encourage participants to perform at least 150 minutes of moderate-intensity physical activity per week (Recommendations of the American College of Sports Medicine) [30]. The most frequently recommended type of activity is walking (30 minutes per day). However, participants could choose other forms of exercise to achieve the five 30-minutes sessions per week (e.i aerobic exercises, strength training activities….). The program includes a general advice component and a personalised home-based physical activity program designed with each participant during individual interviews planned every six months (6 interviews during the 3 years).
Nutritional advices	Nutritional advices are based on dietary guidelines established by the French National Nutrition and Health Program (PNNS) for elderly, which are now considered as the official reference in France. Eight key guidelines are proposed during the first two months. They offer specific recommendations to have a healthy diet.

Limoges and Nice).

Procedures for quality control and data acquisition were standardized. Analysis and interpretation of exams are centralized.

Ethics

The study is conducted according to the Declaration of Helsinki, Good Clinical Practices and pertinent legal and regulatory requirements. Written informed consent was obtained for each participant. The protocol was submitted to and approved by the Advisory Committee for the Protection of Persons participating in Biomedical Research of the Toulouse University Hospital.

Conclusion

In the absence of curative treatment, lifestyle factors (diet, social engagement, cognitive stimulation, physical exercise) seem the most reasonable candidates for prevention trials at the current time, in particular due to their safety. The MAPT study is one of the first trials involving a multidomain intervention on the prevention of cognitive decline. It has been designed to include a sufficient large series of subjects to evaluate the potential efficacy of two preventive measures (multidomain intervention and/or omega 3 supplement) in 1680 frail older people. The multidomain intervention consists of training sessions focused on physical, cognitive and nutritional areas, and preventive consultations for 3 years. It has been designed to be cost-effective and easily transferable to the population level in order to have a real public health impact if the MAPT study showed positive effects. Final results should be available in 2014.

Grant: This study was supported by grants from the Gerontopole of Toulouse, the French Ministry of Health (PHRC 2008; PHRC 2009), the Pierre Fabre Research Institute (manufacturer of the omega-3 supplement), Exonhit Therapeutics SA and Avid Radiopharmaceuticals, Inc. Promotion of the study is supported by the University Hospital Centre of Toulouse. Trial registration: clinicaltrials.gov identifier NCT00672685.

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PREVENTION OF LATE ONSET DEMENTIA: MOVING FROM RANDOMIZED TRIALS TO PUBLIC HEALTH INTERVENTION,

J.A. Luchsinger (USA)

Existing paradigms for translation of evidence to public health intervention

A common paradigm used to translate research knowledge into public health implementation is the following: findings in observational studies support or lead to hypotheses about risk factors for disease. The plausibility of these hypotheses may be supported by basic science. With data from observational studies and basic science interventions are designed. In the case

of drugs, these are tested in Phase I trials for preliminary data on safety and dosage, in Phase II trials for further data on safety, feasibility and efficacy, and Phase III trials for proof of efficacy. After phase III trials, public health interventions are implemented. However, randomized trials have important limitations (1). First, results of randomized trials are an average of effects for winers, losers, and those who are indifferent to the intervention. Few major winners could skew the mean effect and create the false appearance of a significant public health benefit. Secondly, clinical trials are difficult to replicate in real world settings. Randomized trials' interventions are usually highly structured and costly, and thus difficult to translate into real world settings. Clinical trial samples are highly selected, and their results may not be generalizable. The concepts of efficacy and effectiveness are important in this context. Efficacy refers to effect of an intervention under ideal conditions. Effectiveness refers to the effect of an intervention with proven efficacy in real world settings. These concepts are central to the field of comparative effectiveness research(CER) (2), which could be defined as the direct comparison of existing interventions to determine which work best for whom and which pose the greatest benefits and harms. An ideal paradigm to translate clinical trials to public health intervention is to obtain proof of efficacy, then obtain proof of effectiveness in real world settings, proceed to public health implementation, and then conduct surveillance of the effects of the public health implementation.

Challenges in implementation of dementia prevention

Proof of efficacy. The main challenge to dementia prevention is that evidence on efficacy is limited or absent. A recent consensus statement from the National Institutes of Health in the United States stated that "Currently, firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or Alzheimer's disease. …Evidence is insufficient to support the use of pharmaceutical agents or dietary supplements to prevent cognitive decline or Alzheimer's disease" (3). Most evidence suggestive of prevention comes from observational studies and basic science, and does not meet the criterion of proof of efficacy. Clinical trials testing strategies for the prevention of dementia need very large sample sizes and relatively long observation times, making them extremely expensive and difficult to conduct. There are several ways to overcome this. One is by using biomarkers as intermediate proxies of disease to decrease sample size and observation time, but this paradigm is controversial. Another strategy is adding cognitive measures as secondary outcomes to clinical trials, and this is an increasing practice. However, evidence of benefit for secondary outcomes has caveats, could be due to chance, and may need another trial with the cognitive outcome as a primary outcome to prove an initial finding.

Competition with other outcomes: a common axiom in cognitive impairment research these days is that "what is good for the heart is good for the brain", mainly based on observational studies. These studies have shown that cardiovascular risk factors such as hypertension, obesity, diabetes, insulin resistance, and dyslipidemia are associated with a higher risk of dementia. This has ethical and practical implications. If we know of effective interventions for the primary and secondary prevention of heart disease and stroke (which we do), is it ethical to test them for the primary and secondary prevention of cognitive impairment? If we know that interventions are good for heart disease and stroke risk independent of cognitive benefits, why test them at all? These considerations limit testing cardiovascular interventions for the primary and secondary prevention of cognitive impairment. However, many questions that are pertinent to cognitive impairment remain that need research. For example, it is not known if vigorous hypertension treatment in elderly persons may decrease brain perfusion and increase the risk of cognitive impairment. It seems reasonable to suggest that known interventions (e.g. for cardiovascular disease and cancer prevention) should be tested for cognitive benefits particularly when there is a concern for cognitive harm in susceptible populations.

Lifecourse challenges: Dementia and cognitive impairment in general have long and complex causal pathways. Putative risk factors for dementia such as hypertension, obesity, and dyslipidemia change over time, and could have a narrow "therapeutic window". In addition, brain physiology changes over time, and interventions may have different effects at different points in the lifecourse (e.g. hypertension treatment on brain perfusion). Aging is related to the addition of new sources of disability, conditions, and medications that can modify the effect of an intervention for the prevention of dementia. From a public health perspective, this complexity puts stresses on the health care system.

Case study: Prevention of diabetes as a strategy for the prevention of dementia

The observation that insulin resistance and type 2 diabetes are associated with a higher risk of dementia led to the hypothesis that decreasing insulin resistance and preventing type 2 diabetes could prevent dementia (4). On this basis, the Diabetes Prevention Program (DPP) Outcomes Study (DPPOS) (ClinicalTrials.gov Identifier: NCT00038727) added a neurocognitive battery as a secondary outcome in 2009. The DPPOS is the observational phase of a clinical trial of metformin, lifestyle intervention (diet and exercise) vs. placebo. The DPP showed that metformin and lifestyle interventions were effective in preventing type 2 diabetes (5). Relating the DPPOS interventions with cognitive outcomes could allow making inferences about treatment effects that have many caveats. The possible results for the cognitive outcomes in DPPOS are that there is no evidence of cognitive effect, that there is evidence of cognitive benefit, or that there is evidence of harm. Any result will be hampered by the fact that cognition

is a secondary outcome, and by the fact that the DPPOS is likely to be implemented using CER principles independent of its cognitive effects. However, the DPPOS will provide data to understand mechanism of effect, and to conduct post-hoc analyses that may shed light on who is more likely to benefit or harm from a cognitive standpoint, and what DPPOS processes are responsible for the benefits or harms. If cognitive outcomes are measured in studies of CER of DPPOS, we will further be able to identify winners, losers, and indifferent, and identify barriers and modifiers of the intervention from a cognitive standpoint. Finally, the finding of a cognitive benefit in addition to cardiovascular benefits could be a potent message that may sway public health officials and the public in implementing this kind of public health intervention.

Recommendations: Moving from Randomized Trial to Public Health Intervention

Given considerations described in this article, it seems reasonable to classify public health interventions for dementia prevention in 2 types: 1) General public health interventions (e.g. for cardiovascular disease or cancer) with possible or probable cognitive benefits; 2) public health interventions that are specific to dementia prevention. Examples of general public health interventions are dietary interventions, exercise, and interventions that seek to decrease cardiovascular disease in general. Examples of possible interventions that are specific to dementia prevention could be particular supplements or pharmacologic agents, mental exercise, and multidomain interventions specifically geared to improving brain health and preventing dementia.

It seems unlikely that there will be randomized trials of existing interventions with dementia prevention as a primary goal. It seems more likely that evidence supporting the use of existing interventions for dementia prevention will come from observational studies or clinical trials in which cognition is a secondary outcome. These general interventions with possible or probable cognitive benefit are likely to be implemented for other goals such as prevention of cancer or cardiovascular disease. It seems reasonable to suggest that public health entities conduct surveillance of cognitive outcomes (e.g. dementia diagnosis in administrative datasets) to further support the cognitive benefits of these interventions, to identify winners and losers, to identify barriers, key process components that are responsible for benefit, and modifiers of benefit or harm. This surveillance could also help estimate cost-effectiveness of these interventions taking into account the costs related to dementia in addition to their original target (e.g. cardiovascular disease). These revised estimates could help policy makers in prioritizing health care funds for interventions that improve health in several domains including cognition. This proposed surveillance is limited by inherent bias, confounding, and chance, and would require the refinement of existing epidemiological methods and perhaps development of new ones.

Interventions that are specifically geared towards dementia prevention should apply CER principles that lead to public health implementation. That is, once efficacy is established, winners, losers, indifferent, and doomed should be identified to refine the target population. Barriers, optimal doses, modifiers, and key components of interventions should also be identified. Then, effectiveness should be tested in real world settings. If effectiveness is proven, public health interventions should be implemented followed by surveillance. References: 1. Victora CG, Habicht JP, Bryce J. Evidence-based public health: moving beyond randomized trials. Am J Public Health 2004;94:400-5. 2. Sox HC, Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. Ann Intern Med 2009;151:203-5. 3. NIH Consensus Development Conference Statement on Preventing Alzheimer's Disease and Cognitive Decline. NIH Consensus and State-of-the-Art Statements 2010;27. 4. Luchsinger JA. Type 2 Diabetes and Related Conditions in Relation to Dementia: An Opportunity for Prevention? In: J Alzheimers Dis. 2010/04/24 ed. 5. Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009;374:1677-86.

IMPLEMENTATION RESEARCH AND INNOVATION IN PUBLIC HEALTH: PERSPECTIVES ON DEMENTIA, *D.R. Gustafson (Sweden)*

Dementia prevention strategies should echo those summarized by the Institute of Medicine in relation to obesity in 2005: 'For such complex challenges in implementation where evidence from randomized controlled trials may not exist or even be possible to collect, other sorts of evidence from quasi-experimental trials, to mixed-methods research, to expert panels may need to be used for making decisions with the best available evidence, not the best possible evidence.'

Implementation science, the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and to improve the quality and effectiveness of health services, is Public Health (1). Implementation science creates generalizable knowledge that is applied across contexts to answer central questions, and relies on multidisciplinary teams. Implementation science initiatives related to dementia are ongoing in France (the University-Hospital Aging Institute (IHU)); the U.S. (linkages between academic medicine, research and health care (1)); Sweden (lifestyle departments in primary health care clinics);(Läkartidningen, 2011); and other areas around the world (2).

Top ten implementation innovations in dementia prevention, will be discussed.

Innovation #1: Primary prevention of dementia includes reduction of overweight and obesity to at least age 70 years and promotion of physical activity always to improve metabolic and vascular health

Global epidemiology strongly suggests that vascular risk is important for cognitive health. Overweight and obesity, affecting over 50% of the world's population, are cornerstones of vascular risk. The World Health Organization reports that half of the Top 10 causes of death worldwide, accounting for 40.3% of all deaths, are related to obesity. These include:

ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, Type 2 diabetes, and hypertensive heart disease. Obesity and its sequelae are associated with cognitive impairments and dementia. 2 In addition to body mass index (BMI), waist circumference (combined with triglyceride levels), should be measured. Physical activity confers metabolic health irrespective of any measure of overweight or obesity.

Table 1
Innovations in Dementia Prevention

Innovation #1: Primary prevention of dementia includes reduction of overweight and obesity to at least age 70 years and promotion of physical activity always to improve metabolic and vascular health.
Innovation #2: Dementia intervention must be bottom-up and top-down.
Innovation #3: Dementia prevention begins in utero.
Innovation #4: Dementia prevention acknowledges lifetime critical periods of exposure.
Innovation #5: Risk phenotyping is based on consistent screening over time.
Innovation #6: Understanding absolute levels and trajectories of metabolic and cardiovascular risk factors over time is required to enhance successful aging.
Innovation #7: Prevention of dementia in susceptible populations is prioritized.
Innovation #8: Trials designed for vascular and metabolic risk modulation in elderly should be adequately powered for cognitive outcome measures and should include older participants at higher risk for cognitive impairments.
Innovation #9: Studies should focus on cognitive and biological marker-based dementia phenotypes as outcomes.
Innovation #10: A common health language that is used in multidisciplinary settings and across populations brings sustainable change.

Innovation #2: Dementia intervention must be bottom-up and top-down.

Globalization, the diaspora of people groups, and increasing genetic heterogeneity, lead to increasingly complex populations and environments. Systems level reformation allowing individual choice of healthy options, expedites societal health behavior change. Appropriate and nurturing systems facilitate community readiness, conscienceness and motivation for change. As not all risk factor-dementia associations are replicated, population-specific recommendations are timely. Combined collective support and individual responsibility for personal health brings the population to a lower level of common risk. 'The use of collective action to support personal responsibility is central to public health' (3).

How are overweight and obesity reduced and a physically active lifestyle that promotes healthy cognitive and physical aging encouraged at the systems level? The Robert Woods Johnson Foundation supports creation of Healthy Communities. In Sweden there are 'levande stadsdelar' or 'living neighborhoods'. Well-circumscribed communities that include food shops, pharmacies, primary care clinics, recreation centers across age groups, churches, schools and playgrounds, all within walking distance of where people live, promote physical, mental and social health and minimize stress. Often there is a purposeful mixing of ages - seniors living alongside younger families and multigenerational families. The built environment has the power to encourage or discourage physical activity.

Tobacco use prevention and control are examples of successful system-wide public health interventions resulting in behavior change and reduced mortality. Taxing cigarettes and limiting smoking to defined areas reduced cigarette smoking and lung cancer incidence. Related to obesity, there is a US initiative to tax beverages with added sugar or caloric sweeteners. The suggested tax is one penny per ounce, with revenue used for obesity prevention programs or healthy food subsidies. This tax is estimated to reduce consumption of sugar-sweetened beverages 23% and generate US$150 billion over 10 years.

While vascular risk may be the umbrella for dementia intervention over the life course, cross-national and cross-cultural comparisons show that understanding sociocultural and biological characteristics of communities when implementing interventions is essential. Sociocultural differences that guide health and competing risks for healthy behaviors, such as suicide, drug abuse and depression must be understood. In U.S. Native American communities, for example, elders are respected, and the today's youth are prioritized to ensure survival of communities and traditions. Biological risk related to neurodegeneration in dementia across populations is the focus of the Global Alzheimer's Disease Neuroimaging Initiative 2 (ADNI 2). Allelelic distribution differences in the APOE gene exemplify biological differences in genetic susceptibility for late onset dementia.

Innovation #3. Dementia prevention begins in utero (4)

Preferences for certain nutrients, metabolic regulation of energy expenditure, establishment of regulatory axes, stress responses, even brain size, are early developmental, in utero processes. The nutritional and physical activity health of pregnant women is key for health of offspring and forecasts future health of the central nervous system, lowering risk for dementia.

Innovation #4. Dementia prevention acknowledges lifetime critical periods of exposure

Risk periods are chronologically and biologically age-related (4). In relationship to dementia, critical periods overlap temporally in relation to neuropathology, vascular changes, and/or clinical manifestation of cognitive impairments and dementia. Vascular lesions are observed in utero. First amyloid plaques are observed in Downs' Syndrome in the 3rd decade of life. Understanding dementia susceptibility by age, preclinical phenotype, and position on the age by cognitive or metabolic trajectory is important for prevention. In children, periods of 'catch-up' growth, as well as puberty, set the stage for healthy aging. In women, age of menses onset, reproductive status, and menopausal age denote significant biological aging events. These events may interact with interventions beneficial for cognition. The Women's Health Initiative Memory Study I (WHIMS I) and now WIHMS II illustrate importance of timing of hormone replacement therapy in relation to cognition. Lifetime dementia risk should not be based solely on survivorship models. Population risk models for dementia based on continuous observation over time are not informative

(Gothenburg Birth Cohort Studies, unpublished data) due to competing risks for mortality. All best available evidence should be used for defining dementia prevention strategies and for prioritizing optimal aging.

Innovation #5. Risk phenotyping is based on consistent screening over time

The prevalence of undiagnosed hypertension, hyperlipidemia, obesity, and type 2 diabetes is high, especially among certain segments of the population. Guidelines for the frequency of blood pressure, blood lipid, and blood glucose monitoring hardly vary from age 18 years. Many hospitals and clinics have Electronic Medical Records, some of which include Health Risk Assessments (HRAs), however screening and evaluation tools must be used to be effective. Barriers to use are time in the clinic and perceived importance among practitioners.

Innovation #6. Understanding absolute levels and trajectories of metabolic and cardiovascular risk factors over time is required to enhance successful aging

Guidelines for absolute levels of cardiovascular risk indicators hardly vary from age 18 years, and need modification for persons over the age of 70 years. Among these survivors, higher levels of body mass index, blood cholesterol, and blood pressure, may not be as risky. However, this must be re-evaluated due to observed birth cohort differences in levels of cardiovascular risk indicators.

Innovation #7. Prevention of dementia in susceptible populations is prioritized

Susceptible populations include those with cardiovascular diseases such as hypertension, hyperlipidemias, type 2 diabetes mellitus (T2DM), and overt cardiovascular disease, as well metabolic syndromes or subclinical constellations of metabolic and vascular symptoms. Of high global importance is the HIV/AIDS epidemic affecting 33.3 million people. In the developing world and certain large cities in the Western world, there is imminent a sobering cluster of cardiovascular, cognitive, and infectious disease (ID) due to the globalization and co-occurrence of overnutrition and ID treatments related to metabolic syndrome development. Not only has highly active antiretroviral therapy (HAART) for HIV/AIDS reduced mortality to that of the uninfected population, but it is also effective in reducing community viral load (17th Conference on Retroviruses and Opportunistic Infections, February 2010). Priority intervention recommendations (World Health Organization and others, 2010), advocate earlier use of HAART in HIV (CD4+ count < 500 cells/mcl), and in children. The metabolic consequences of HAART therapy are disastrous for dementia risk, and include lipodystrophy, type 2 diabetes, and cardiovascular disease. Up to one third of children with HIV experience lipodystrophy in response to HAART. The consequences of HAART on metabolic cardiovascular complications among increasing numbers of HIV/AIDS survivors, and therefore dementia risk, is staggering.

Innovation #8. Trials designed to test vascular and metabolic risk modulation in elderly should be adequately powered for cognitive outcome measures and include older participants at higher risk for cognitive impairments.

Innovation #9. Studies should focus on cognitive and biological marker-based dementia phenotypes as outcomes (5)

While memory-based deficits and neurodegenerative and amyloid phenotyping approaches in dementia are ongoing (ADNI) and form the basis for some clinical trials (Lipididiet), other dementia phenotypes, for example vascular pathologies and white matter changes, also warrant attention.

Innovation #10. A common health language that is used in multidisciplinary settings and across populations brings sustainable change

Scientists, researchers, and medical professionals, must communicate a vision for building healthy systems and health messages to key opinion leaders, with dissemination to local gate keepers, physicians, other health professionals, educators, communities and clinics. Communities desiring action have a basic awareness of need and ask for assistance in ways they deem most appropriate based on knowledge. It is through a common health language, that system change becomes sustainable change. Dr. Gustafson receives research funding related to this summary from the EU FP7 project LipiDiDiet, Grant Agreement N° 211696; the Swedish Research Council; the National Institutes of Health/National Institute on Aging, National Institute of Allergy and Infectious Diseases and the Native American Research Centers for Health; the State University of New York Research Foundation; and the Hans-Gabriel och Alice Trolle-Wachtmeisters Foundation for Medical Research. In addition, a special thank you to Professor John Kral, SUNY-Downstate Medical Center, for his insightful edits. References: 1. Madon T, Hofman KJ, Kupfer L, Glass RI. Public health. Implementation science. Science. Dec 14 2007;318(5857):1728-1729. 2. Khachaturian ZS, Snyder PJ, Doody R, et al. A roadmap for the prevention of dementia II: Leon Thal Symposium 2008. Alzheimers Dement. Mar 2009;5(2):85-92. 3. Brownell KD, Kersh R, Ludwig DS, et al. Personal responsibility and obesity: a constructive approach to a controversial issue. Health Aff (Millwood). Mar-Apr 2010;29(3):379-387. 4. Gustafson D. A life course of adiposity and dementia. Eur J Pharmacol. May 6 2008;585(1):163-175. 5. Aisen PS, Andrieu S, Sampaio C, et al. Report of the task force on designing clinical trials in early (predementia) AD. Neurology. Dec 23, 2010.

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