

## セッション-2

### 認知症予防とケアの科学的側面

(13:00～15:00)

スカイスタジオ

従来、経験に多くを依存していた認知症の予防やケアの分野において、客観性を確保するための取組みが進められている。認知症の予防やケアに関し、各地で進められている実証的研究から、科学的な根拠に関する現在の知見を共有し、今後の施策への活用の可能性や、今後進むべき研究の方向についての示唆を得る。

【座長】鈴木 隆雄(独立行政法人国立長寿医療研究センター)

【座長】Martin Prince (キングス・カレッジ・ロンドン,英)

Vladimir Hachinski (ウェスタンオンタリオ大学,加)

Piu Chan (北京首都医科大学)

柳澤 勝彦(独立行政法人国立長寿医療研究センター)

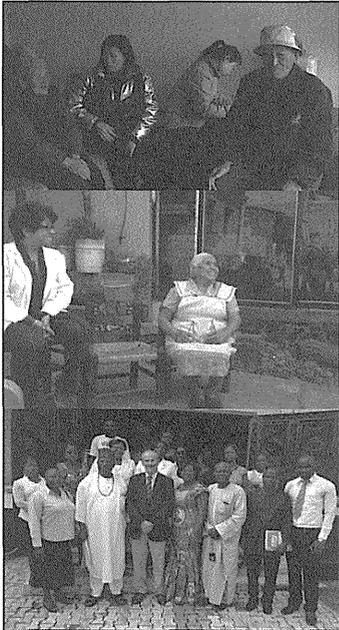
Liang-Kung Chen (台北退役軍人病院老年医学センター,台湾)

島田 裕之(独立行政法人国立長寿医療研究センター)

Dawn Brooker (ウースター大学,英)

Graham Stokes (Bupa)

数井 裕光(大阪大学)



# Global prevalence of dementia and prevention strategy

Martin Prince

Centre for Global Mental Health  
King's College London  
1066drg@iop.kcl.ac.uk



**Alzheimer's Disease  
International**  
*The global voice on dementia*

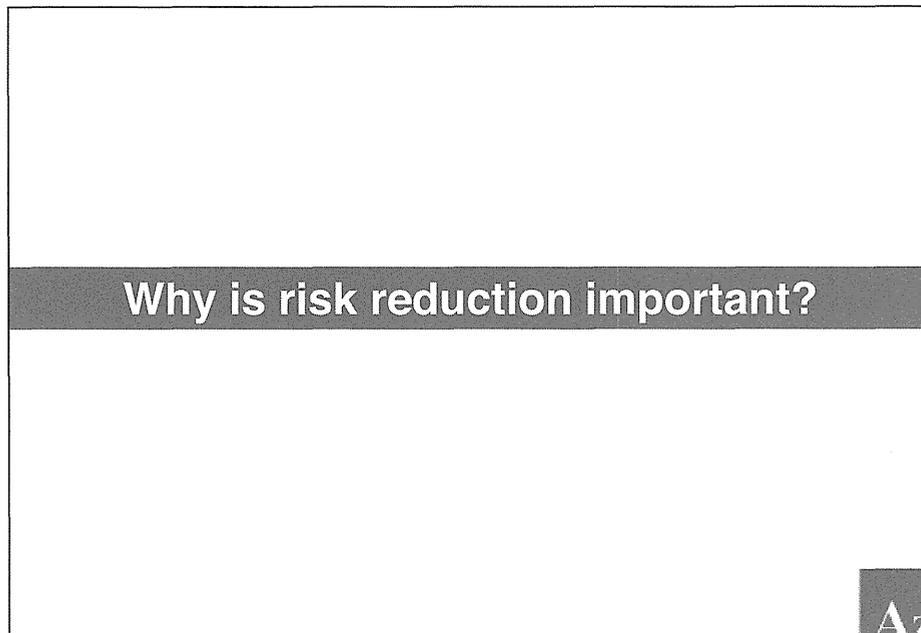
# World Alzheimer Report 2014

## Dementia and Risk Reduction

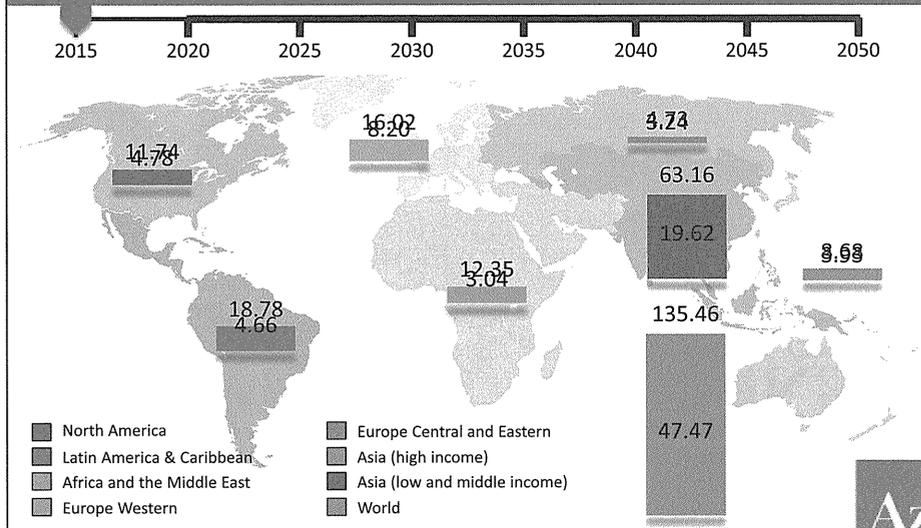
AN ANALYSIS OF PROTECTIVE AND MODIFIABLE FACTORS

Martin Prince  
Global Observatory for  
Ageing and Dementia Care

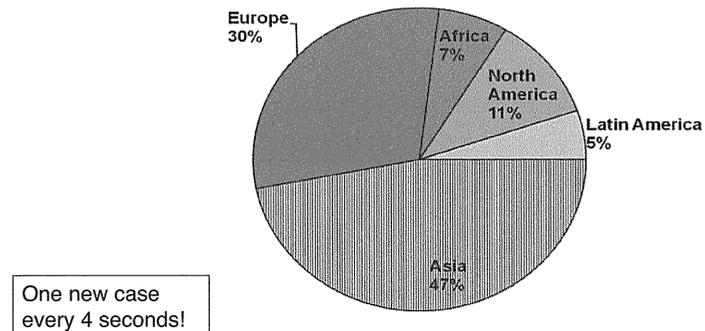
Martin Prince  
Emiliano Albanese  
Maelenn Guerchet  
Matthew Prina



## Numbers of people with dementia by world region (2015-2050)



## Global Distribution of Incident Dementia (7.7 million new cases per year)



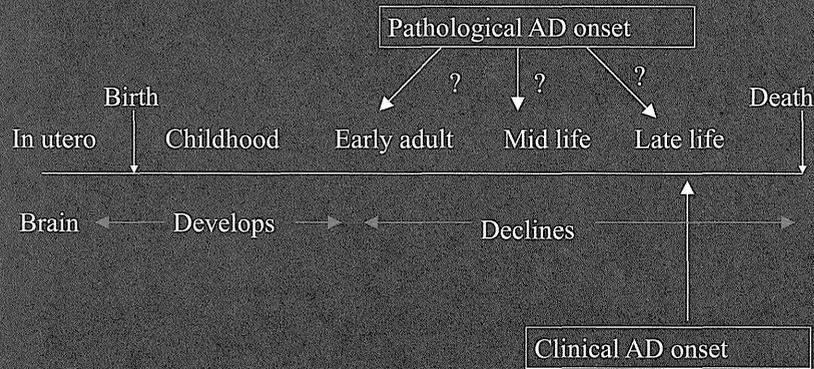
WHO Report 2012 – Dementia a Public Health Priority

## Background – concept and methods

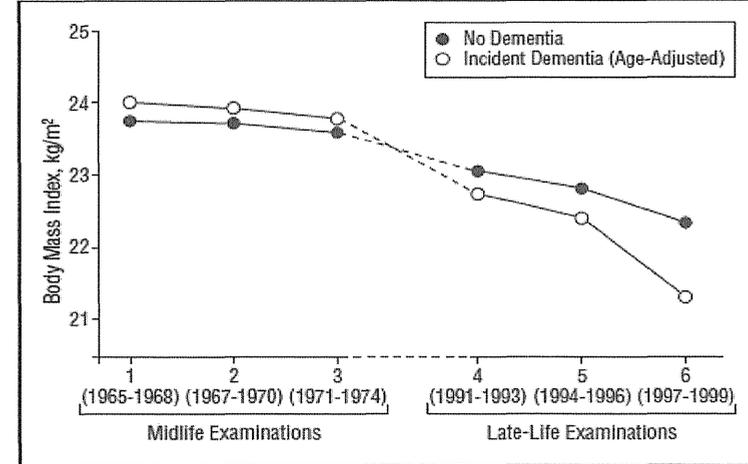
## Risk factors and causes

- If A is associated with B, this does not demonstrate that A causes B
  - Chance
  - Bias
  - Confounding
  - Reverse causality
- Sources of evidence
  - Longitudinal cohort studies (bias and reverse causality)
  - Randomised controlled trials (confounding)
  - Systematic reviews and meta-analyses (consistency)
  - Biological studies (mechanisms)

## A lifecourse perspective



## Changes in body mass index from mid to late-life for those with and without late-life dementia onset



Stewart et al. *Arch Neurol.* 2005

## What did we do?

- Determined the scope
- Appointed review groups
- Identified reviews
- Read all the papers
- Updated the search
- Critically appraised the evidence
- Considered need for new systematic review/ meta-analysis
- Summarised the evidence – consistency/ strength

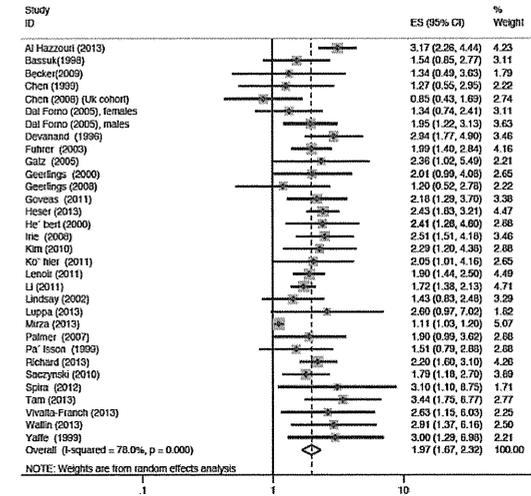
## Domains (lifecourse)

- Developmental and early-life factors
- Psychological factors
- Lifestyle
- Cardiovascular risk factors

## Key findings



Figure 3.1  
Meta analysis for the unadjusted effect of depression on the risk of incident dementia



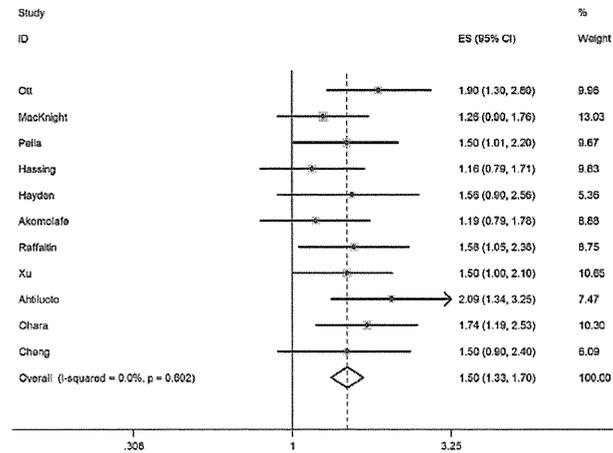
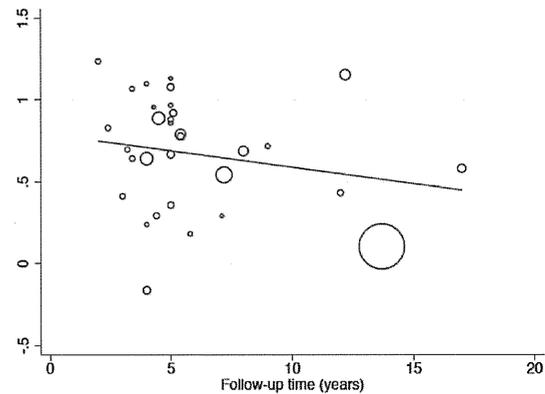
RR 1.97 (1.67-2.32)  
Heterogeneity 78%



## Reverse causality?

(Bigger effect of depression with shorter follow-up periods)

Figure 3.2  
Meta regression exploring the effect of length of follow-up on the risk of incident dementia



RR 1.50 (1.33-1.70)  
Heterogeneity 0%

Figure 5.1  
Forest plot for the association of diabetes in late-life with the incidence of any dementia (AnyDem)



## Robust findings

Exposure	Period
Education	Early life
Hypertension	Midlife
Diabetes	Mid- to late-life
Smoking	Mid- to late-life

Az

## Mechanisms

- Cognitive/ brain reserve (education)
- Vascular disease (hypertension, smoking, diabetes)
  - Additive effect in combination with AD pathology?
  - Interactive effect promoting AD pathology?
  - Other (non-vascular) effects on AD pathology?

Az

## What have we achieved?

- We started with a long list of potential risk factors
- We have reduced these to just four where the evidence is strongest
- This does not mean that other factors may not also be modifiable risk factors
  - Less consistent evidence
  - Insufficiently studied
  - No/ few long-term cohort studies (reverse causality)
  - Confounding or bias likely explanations
  - Need for RCTs where feasible

Az

## Future Research

- Dementia as an outcome
- Systematic reviews and meta-analyses
  - More collaboration using primary data
  - Standardisation (harmonisation)
  - Quality control (!)
  - Open source documentation
- RCTs in late-life
  - Diabetes (glycemic) control
  - Physical activity
  - Cognitive stimulation
  - Micronutrient deficiency
  - Complex interventions for at risk groups ([www.edpi.org](http://www.edpi.org))
- Monitoring the course of the epidemic

Az

A black and white photograph of a large, Gothic-style building with a prominent spire, likely a university building. The building is surrounded by trees and a paved area. The text is overlaid on the right side of the image.

UNIVERSITY OF  
WESTERN ONTARIO  
LONDON, ONTARIO

# PREVENTING DEMENTIA: CAN WE DO BETTER?

Vladimir Hachinski, CM, MD, FRCPC, DSc  
Department of Clinical Neurological Sciences  
University of Western Ontario, London, Ontario

## PREVENTING DEMENTIA: CAN WE DO BETTER?

- I ACKNOWLEDGING REALITY
- II FOCUSING ON THE TREATABLE,  
VASCULAR COMPONENT
- III TRYING NEW, MULTIMODAL  
INTEGRATED APPROACHES

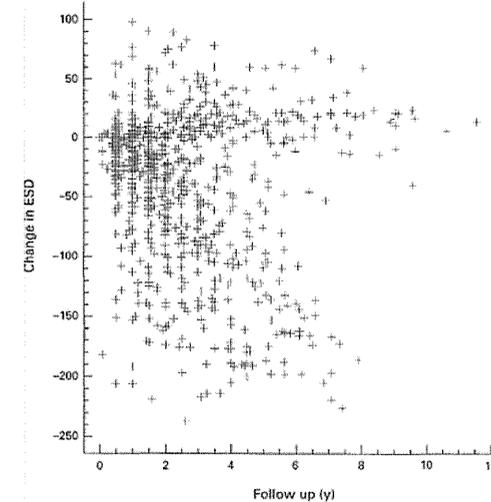
*The greatest obstacle to discovery is  
not ignorance – it is the illusion of  
knowledge*

Daniel J. Boorstin

# THE EFFECT OF DIFFERENT DIAGNOSTIC CRITERIA ON THE PREVALENCE OF DEMENTIA

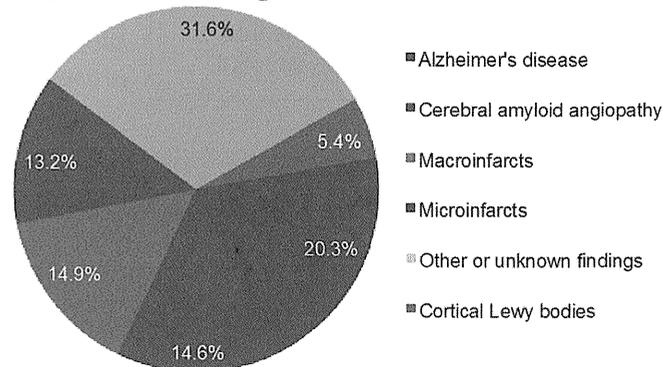
Canadian Study of Health and Ageing (n=1879)	
DSM-111	29.1%
DSM-III-R	17.3%
DSM-IV	13.7%
ICD-9	5.0%
ICD-10	3.1%

Erkinjuntti T et al. N Engl J Med 1997;337:1667-74



Follow-up of patients initially diagnosed as having Alzheimer disease clinically, but neuropsychological testing and brain imaging

## Percent Population Attributable Risk of Dementia of Vascular and Non-Vascular Pathological Findings



Hachinski & Sposato (unpublished)

## Original Contributions

### National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards

Vladimir Hachinski, MD, DSc; Costantino Iadecola, MD;  
 Ron C. Petersen, MD, PhD; Monique M. Breteler, MD, PhD;  
 David L Nyenhuis, PhD; Sandra E. Black, MD; William J. Powers, MD;  
 Charles DeCarli, MD; Jose G. Merino, MD; Raj N. Kalaria, PhD, FRCP;  
 Harry V. Vinters, MD; David M. Holtzman, MD; Gary A. Rosenberg, MD;  
 Martin Dichgans, MD; John R. Marler, MD; Gabrielle G. Leblanc, PhD

**Background and Purpose**—One in 3 individuals will experience a stroke, dementia or both. Moreover, twice as many individuals will have cognitive impairment short of dementia as either stroke or dementia. The commonly used stroke scales do not measure cognition, while dementia criteria focus on the late stages of cognitive impairment, and are heavily biased toward the diagnosis of Alzheimer disease. No commonly agreed standards exist for identifying and describing individuals with cognitive impairment, particularly in the early stages, and especially with cognitive impairment related to vascular factors, or vascular cognitive impairment.

Stroke. 2006;37:2220-2241

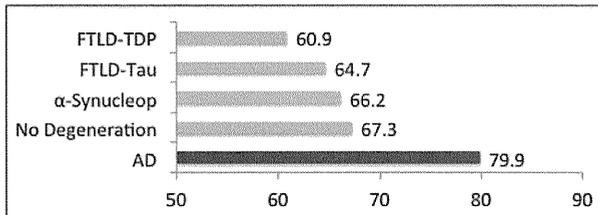
## Contribution of Cerebrovascular Disease in Autopsy Confirmed Neurodegenerative Disease Cases

### Cases

National Alzheimer's Coordinating Centre Database 6 205 autopsy cases

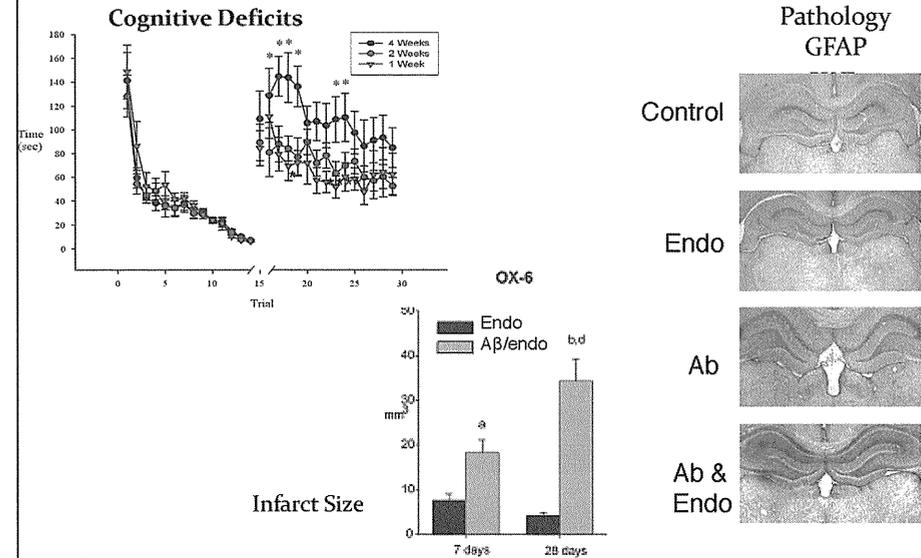
Prevalence of Vascular Pathology (%)

Vascular findings reaching or not a threshold sufficient enough to contribute to clinical status



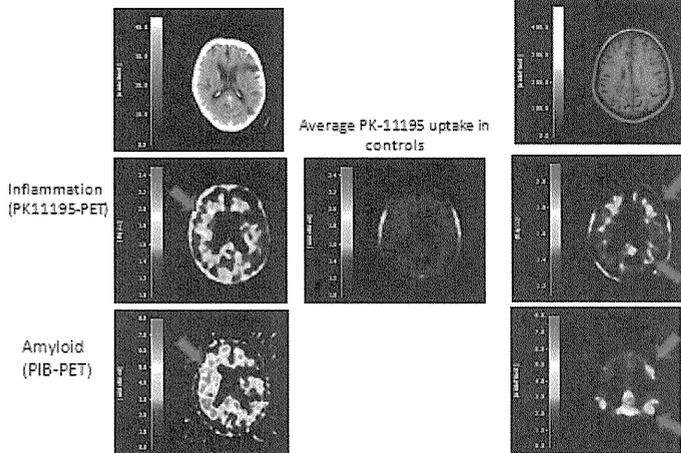
Toledo JB, Arnold SE, et al. Brain 2013;135:2697-2706

## Preliminary Data and Survivability



Patient 1 (left cortical stroke)

Patient 2 (right cortical stroke)



Two patients with cortical strokes, demonstrating widespread increased neuroinflammation (middle row) and corresponding amyloid deposits (lower row) 3 months after the stroke. Both patients exhibited lasting post-stroke cognitive impairment.

Thiel A. et al. 2013 (unpublished)

## PREVENTING DEMENTIA: CAN WE DO BETTER?

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## Main Proposed Risk & Protective Factors Common for Stroke & Dementia

Non-modifiable	Modifiable	
Risk Factors	Risk Factors	Protective Factors
Advanced age	Cerebrovascular disease/stroke	High education
Genetic factors (Apo E4)	Cardiovascular diseases	Physical activity
Family history	Hypertension	Active lifestyle
	Hypercholesterolemia	Alcohol consumption
	Obesity	Antioxidants
	Diabetes	Fish oils
	Smoking	Antihypertensives
	Homocysteine	Statins
	Pyschosocial stress/depression	
	Atrial fibrillation <b>(added)</b>	Anticoagulation <b>(added)</b>

Kivipelto and Solomon. Eur Neurol 2008

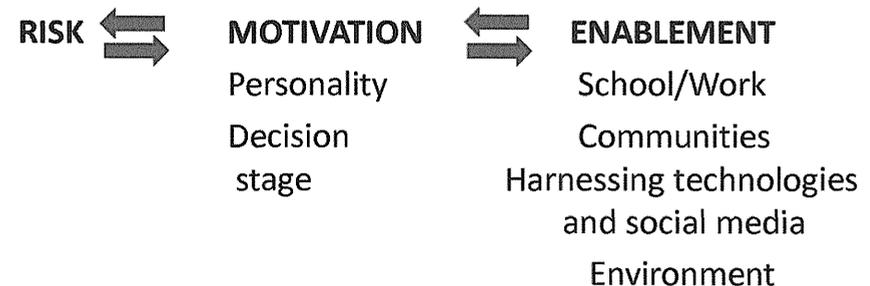
....no RCT's that investigated overall blood pressure control, weight reduction, smoking cessation or other interventions related to reduction of vascular risk factors that may.....reduce cognitive decline

Naqvi R. et al. CMAJ 2013;185:881-885

## PREVENTING DEMENTIA: CAN WE DO BETTER?

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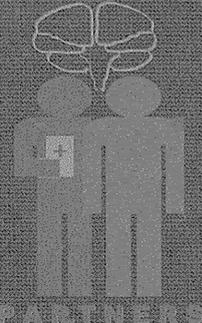
## 3 STEPS IN PREVENTION





# PARTNERS

A Canadian Multi-Center, Randomized, Controlled, Open-Labeled, Blinded Adjudication Clinical Trial



**CLIP-IRSC**  
Canadian Lung Initiative for Research in Smoking Cessation

**UNIVERSITY OF TORONTO**  
SCHOOL OF KENNEDY INSTITUTE OF HEALTH POLICY STUDIES

**LAWSON**  
HEALTH RESEARCH INSTITUTE

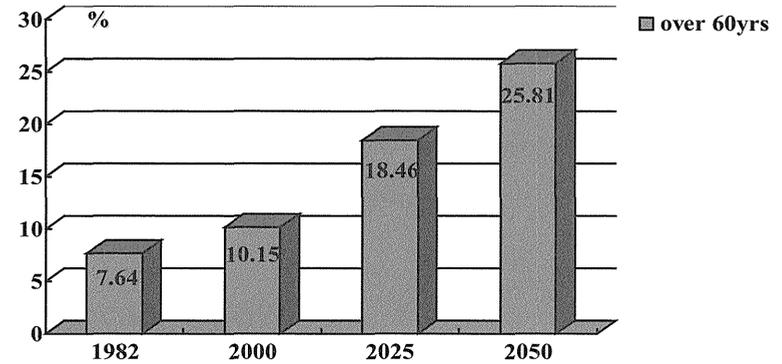
**ICI**

**PARTNERS**

# Current Status of Dementia and Challenges in China

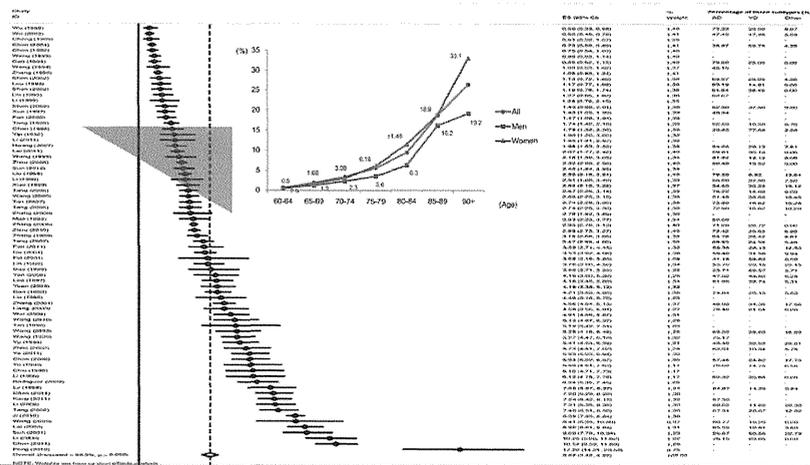
Piu Chan, MD PhD  
 Xuanwu Hospital  
 Capital Medical University  
 Beijing, China

## Population Ageing in China: past, present and future



The Fifth National Population Survey, 2002

## Dementia Prevalence in Chinese



PLOS One, 2013. 8(6)

## The JAMA Network

From: Dementia Subtypes in China: Prevalence in Beijing, Xian, Shanghai, and Chengdu

Arch Neurol. 2005;62(3):447-453. doi:10.1001/archneur.62.3.447

3.5% (3.0%-3.9%) or  
 4.8% (after post hoc  
 correction for  
 negative screening  
 errors) for older than  
 65

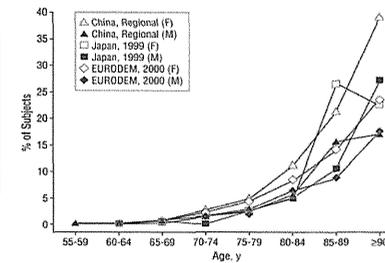


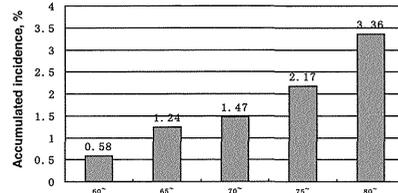
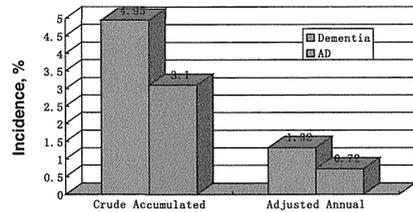
Figure Legend:

Age- and sex-specific prevalence of Alzheimer disease in China (present study) compared with east Asian (Japan, 1999) and Western (European Community Concerted Action on the Epidemiology and Prevention of Dementia Group [EURODEM], 2000) studies.

Date of download: 9/23/2012

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## Incidence of Dementia and Alzheimer's Disease (1997-2000)



Beijing Longitudinal Study on Aging I (BLSA-I)

## Estimated Number of Dementia Patients

Table 2. Estimated number of people with dementia in mainland China, Hong Kong and Taiwan (Based on DSM-IV).

Area	Total population (million)	Elderly population * (60+ in mainland China; 65+ in Hong Kong and Taiwan, million)	Number of people with dementia (million)	Prevalence % (95% CI)
Mainland China (age 60+)*	North	563.8	73.4	3.76
	Central	492.4	73.3	3.22
	South	276.6	30.9	1.20
	Total	1332.6	177.6	8.18
Hong Kong (age 65+)*	6.9	0.9	0.06	6.9 (3.4, 9.3)
Taiwan (age 65+)*	23.2	2.5	0.15	5.7 (3.2, 8.2)
<b>Total</b>	<b>1362.92</b>	<b>181</b>	<b>8.39</b>	<b>4.6 (3.4, 5.8)</b>

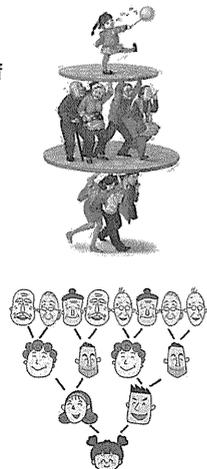
Table 3. Projected number of people with dementia from 2012 to 2060 in mainland China, Hong Kong and Taiwan (Based on DSM-IV, unit: million).

	Current	2020	2030	2040	2050	2060
Mainland China (age 60+)	8.18	13.5	20.3	29.59	40.63	48.68
Hong Kong (age 65+)	0.06	0.09	0.13	0.20	0.29	0.32
Taiwan (age 65+)	0.15	0.21	0.32	0.49	0.66	0.71

PLOS One, 2013. 8(6)

## Challenges China is Facing

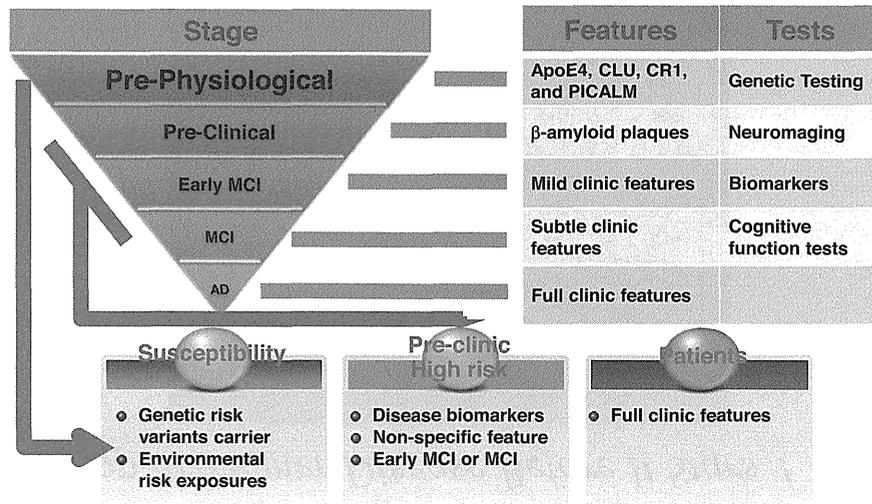
- China is facing a new epidemic of unprecedented increase of population ageing and burden associated with dementia
- Societal costs will rise inexorably, driven by the increasing need for long term care
- Limited number of specialized dementia clinics
- Limited number of family doctors and GPs, & lack of specialized training on caring dementia patients
- Limited beds and nursing homes and experienced care takers
- Lack of specialized dementia nursing homes
- Change of family structure with 4:2:1 and even 8:4:2:1 families



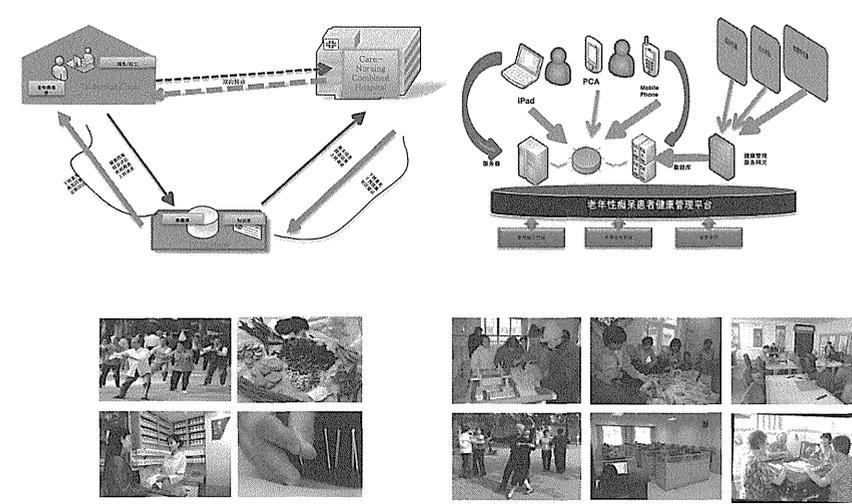
## Time for Action

- Clinical care
  - ✓ Promoting awareness of dementia in the community
  - ✓ Establishing more dementia clinics & guideline
  - ✓ Increased coverage of drugs & included in special schemes of insurance
  - ✓ Building more specialized dementia nursing homes
  - ✓ Establishing the integrated "Care and Nursing Combined Community Hospitals"
  - ✓ Programs to train more GPs and care takers
- Social policy
  - ✓ National Day on Dementia
  - ✓ Enforcing laws on responsibility of caring elderly
  - ✓ Promoting commercial insurance and increased investment on research and care
- Prevention
  - ✓ Promoting research for early diagnosis and intervention
  - ✓ Comprehensive programs including community health and rehab centers, and community activities

## Screening Programs and Dementia Clinic



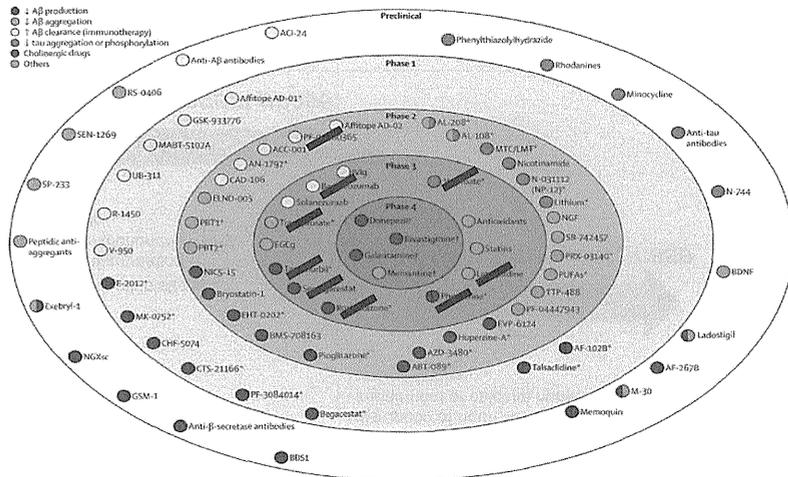
## Building Integrated Model for Care & Prevention



# Thanks!



- 1 Aβ production
- 1 Aβ aggregation
- 1 Aβ clearance (immunotherapy)
- 1 tau aggregation or phosphorylation
- Cholinergic drugs
- Others



Mangialasche et al., *Lancet Neurology*, 9:702-716, 2010

### A tangled web of targets

Drugs in development for Alzheimer's disease take aim at a variety of neural mechanisms. But despite a wealth of possibilities, there have been few successes.

Lauren Gravitz

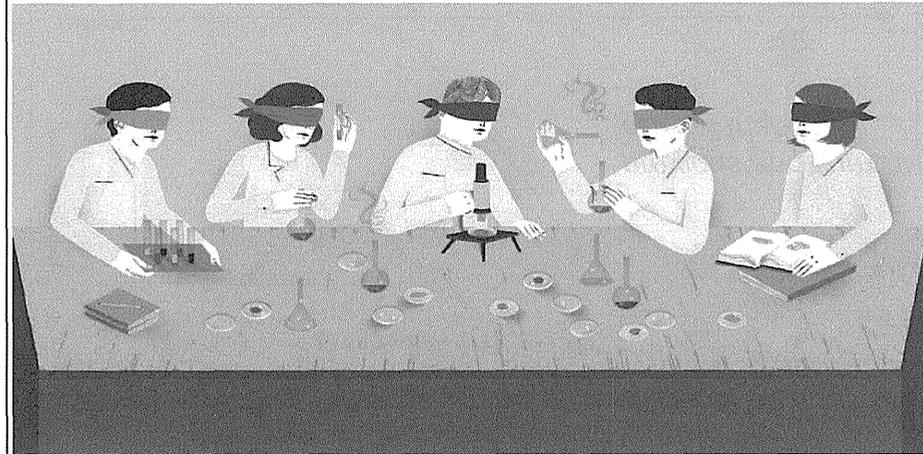
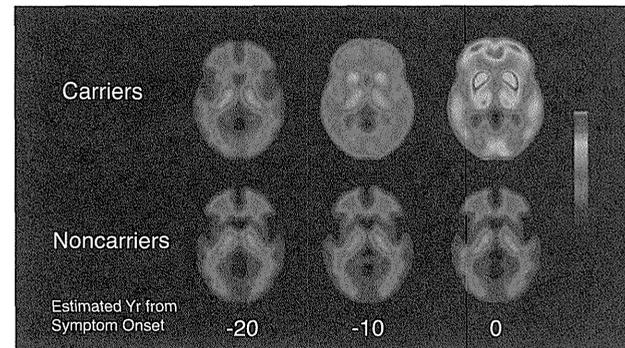


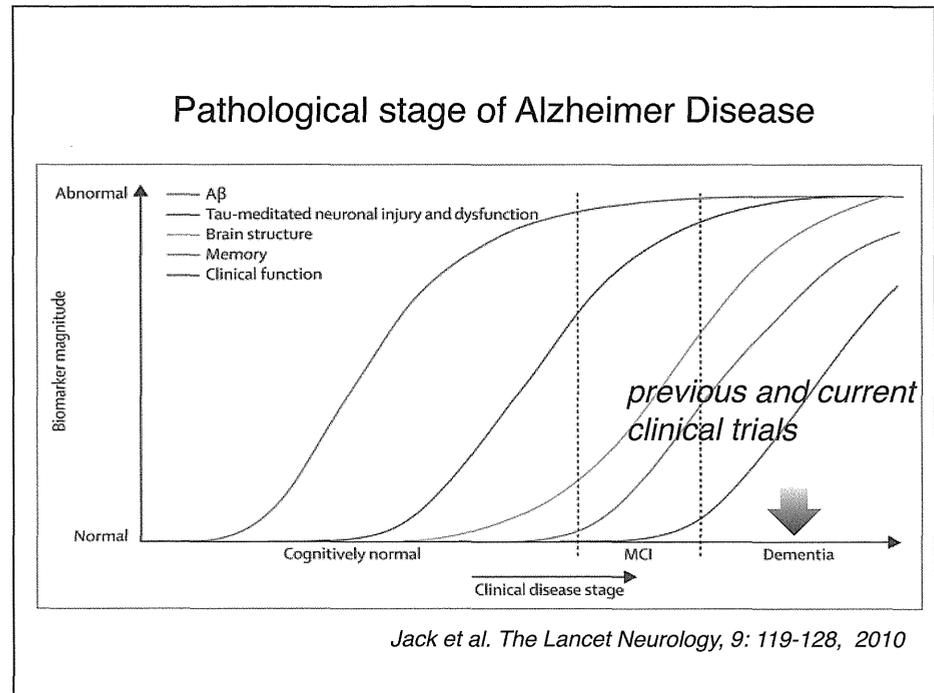
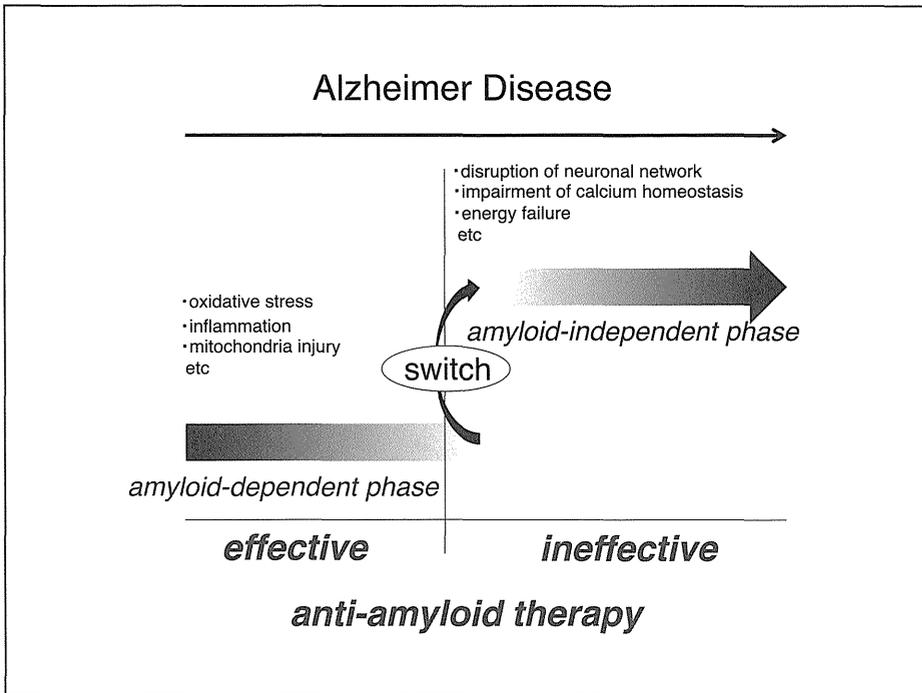
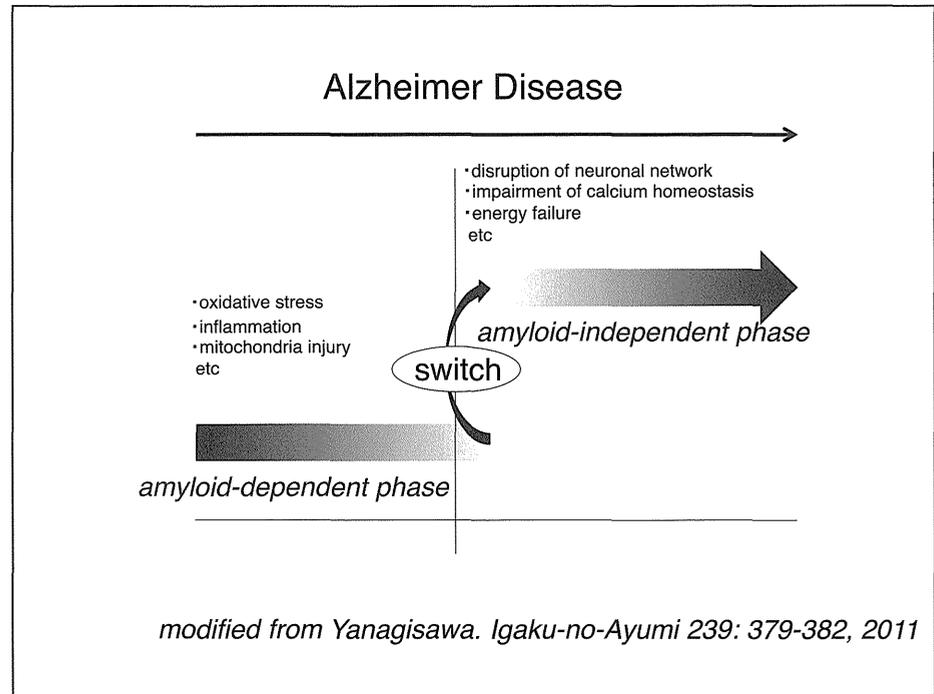
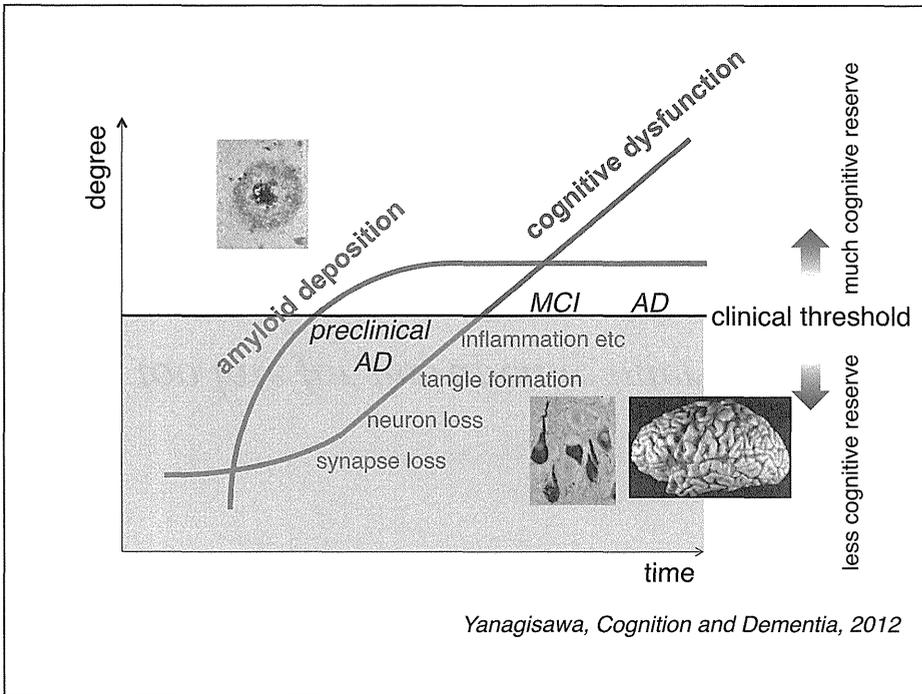
Illustration by Gracia Lam *Nature* 475, S9, 2011

*too late for therapeutic intervention*

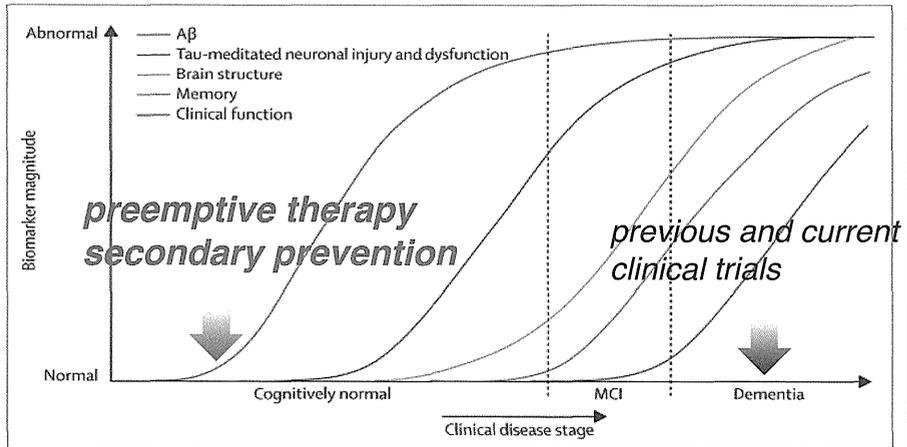
### PiB-amyloid imaging on PET - Study on familial Alzheimer disease -



Bateman et al, *New Engl J Med*, 367: 795-804, 2012



## Pathological stage of Alzheimer Disease



Jack et al. *The Lancet Neurology*, 2010

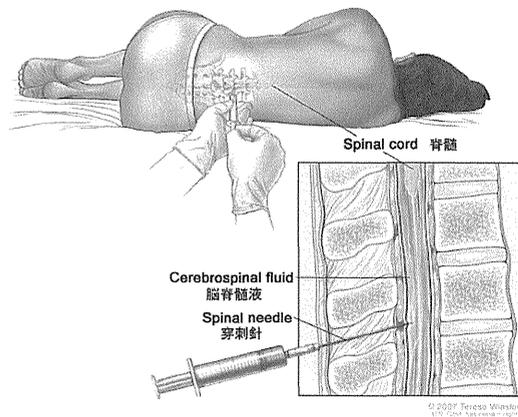


*Alzheimer*

*Alzheimer Disease*

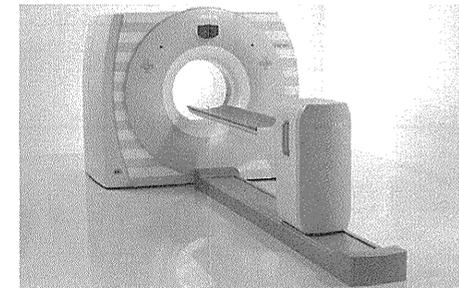
*How should you know the pathological change before clinical onset?*

## Cerebrospinal fluid examination

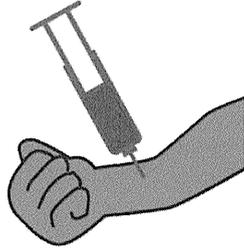


(Yahoo Japanより取得)

## Amyloid imaging on PET



# Plasma!

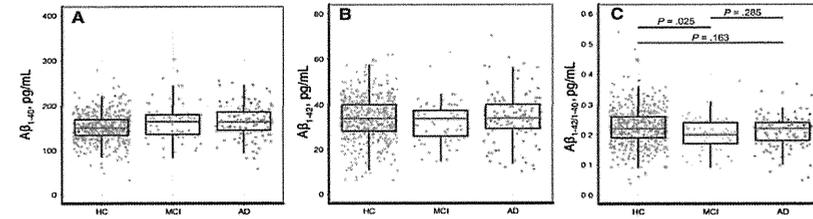


obtained from Yahoo Japan

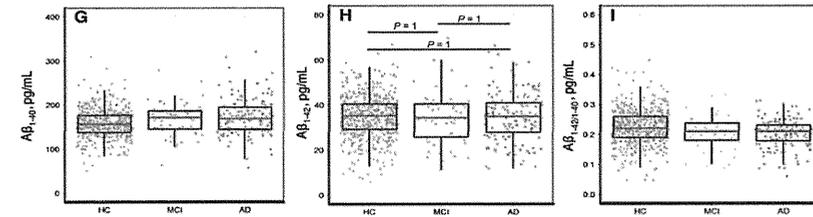
Novel procedure to detect A $\beta$  from plasma using mass spectrometry

## Plasma amyloid $\beta$ -proteins

Baseline

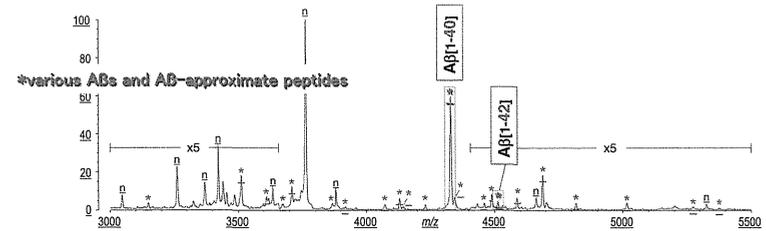


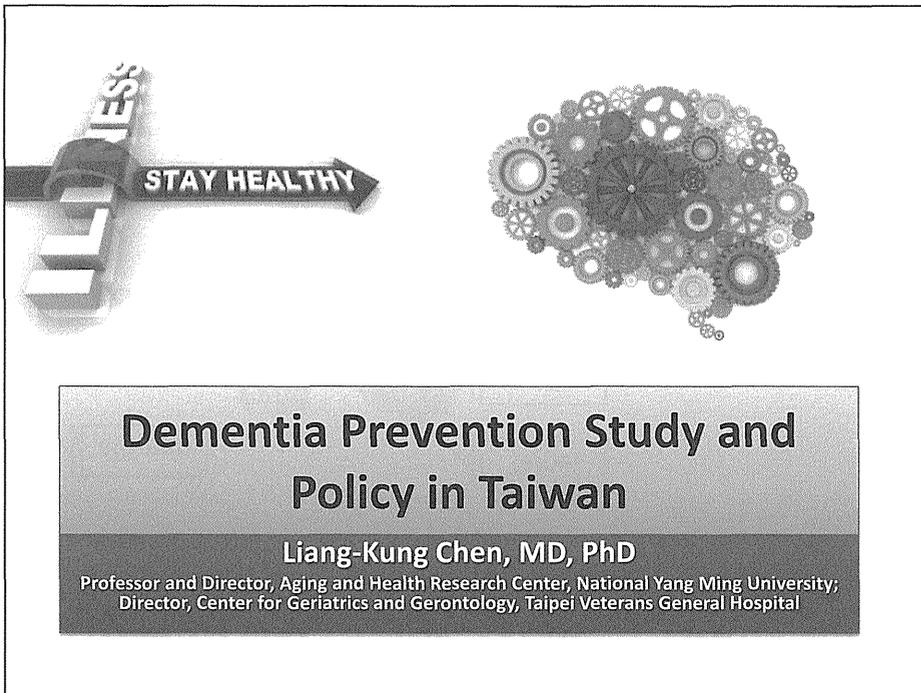
18-months later



Rembach A et al., *Alzheimer's and Dementia*, 10: 53-61, 2014

Novel procedure to detect A $\beta$  from plasma using mass spectrometry





## Dementia Prevention Study and Policy in Taiwan

**Liang-Kung Chen, MD, PhD**  
 Professor and Director, Aging and Health Research Center, National Yang Ming University;  
 Director, Center for Geriatrics and Gerontology, Taipei Veterans General Hospital

### Identifying residents at greater risk for cognitive decline by Minimum Data Set in long-term care settings

Liang-Yu Chen, MD<sup>a, b, c</sup>, Li-Kuo Liu, MD<sup>a, c, d</sup>, Li-Ning Peng, MD<sup>a, b, c</sup>,  
 Ming-Hsien Lin, MD<sup>a, c</sup>, Liang-Kung Chen, MD, PhD<sup>a, b, c, \*</sup>, Chung-Fu Lan, MD, PhD<sup>e</sup>,  
 Po-Lun Chang, MD, PhD<sup>d</sup>

<sup>a</sup> Aging and Health Research Center, National Yang-Ming University, Taipei, Taiwan  
<sup>b</sup> Institute of Public Health, National Yang-Ming University, Taipei, Taiwan  
<sup>c</sup> Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan  
<sup>d</sup> Institute of Biomedical Informatics, National Yang-Ming University, Taipei, Taiwan  
<sup>e</sup> Institute of Health and Welfare Policy, National Yang-Ming University, Taipei, Taiwan

**Table 2**  
 Factors associated with cognitive decline by multivariate analysis.<sup>a, b</sup>

Variables	Decliner		
	Odds ratio	95% confidence interval	p
Age (y)	1.061	1.008–1.115	0.023*
Cancer	1.613	0.304–8.547	0.574
Chronic lung disease	1.018	0.448–2.309	0.966
RUG-III ADL	1.111	1.008–1.225	0.034*
RAP trigger for cognitive loss/dementia	3.774	1.825–7.813	<0.001*
Sum of RAP triggers	1.188	1.046–1.349	0.008*

**Physical function is a good predictor for cognitive decline**

*Chen LY, et al., J Clin Gerontol Geriatr (in press)*

### LATE-LIFE METABOLIC SYNDROME PREVENTS COGNITIVE DECLINE AMONG OLDER MEN AGED 75 YEARS AND OVER: ONE-YEAR PROSPECTIVE COHORT STUDY

C.-L. LIU<sup>1,2</sup>, M.-H. LIN<sup>1,2</sup>, L.-N. PENG<sup>1,2</sup>, L.-K. CHEN<sup>1,2</sup>, C.-T. SU<sup>3,4</sup>, L.-K. LIU<sup>1,2</sup>, L.-Y. CHEN<sup>1,2</sup>

1. Aging and Health Research Center, National Yang Ming University, Taipei, Taiwan; 2. Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan;  
 3. Department of Family Medicine, Taipei Medical University Hospital; 4. School of Public Health, College of Public Health and Nutrition, Taipei Medical University, Taipei, Taiwan.  
 Corresponding author: Dr. Liang-Kung Chen, Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan 11217.  
 TEL: +886-2-28757830, FAX: +886-2-28757711, Email: lkchen2@vghtpe.gov.tw

**Table 2**  
 Comparisons of cardiometabolic risk factors between subjects with and without cognitive decline (Cog-D)<sup>1</sup>

	Cog-D (+) (N=43)	Cog-D (-) (N=186)	P-value
Age (yr)	83.8±4.2	82.1±4.2	0.020*
Current smoking (%)	10(23.3)	49(26.3)	0.330
Hypertension (%)	30(69.8)	107(57.5)	0.168
Diabetes mellitus (%)	12(27.9)	40(21.5)	0.419
ATP III-defined Metabolic syndrome (%)	7(16.3)	44(23.7)	0.299
IDF-defined Metabolic syndrome (%)	7(16.3)	34(18.3)	0.775
Body mass index (kg/m <sup>2</sup> )	23.6±3.2	23.8±3.3	0.673
Waist circumference (cm)	86.9±7.9	85.6±9.3	0.430
Systolic blood pressure (mmHg)	135.8±20.8	138.4±22.1	0.479
Diastolic blood pressure (mmHg)	66.7±12.7	71.5±13.9	0.040*
Fasting plasma glucose (mg/dL)	110.1±29.4	105.8±34.5	0.446
Serum total cholesterol (mg/dL)	167.6±29.2	182.8±36.5	0.011*
Serum triglyceride (mg/dL)	114.7±59.0	128.6±67.2	0.215
Serum HDL-C (mg/dL)	55.5±13.2	60.0±15.0	0.072



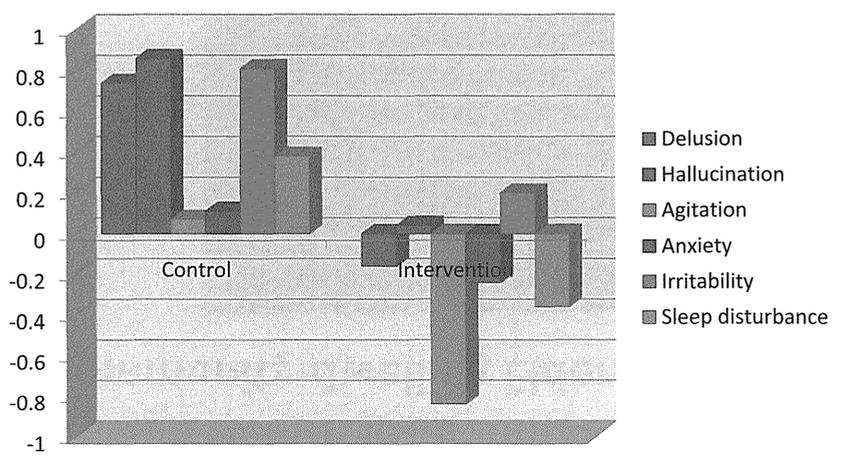
**Good nutrition is protective**

*Liu CL, et al., J Nutr Health Aging 2013;17:523-6*

### Non-pharmacological treatment reducing not only behavioral symptoms, but also psychotic symptoms of older adults with dementia: A prospective cohort study in Taiwan

Rue-Chuan Chen,<sup>1,2</sup> Chien-Liang Liu,<sup>3</sup> Ming-Hsien Lin,<sup>1,3</sup> Li-Ning Peng,<sup>1,3</sup> Liang-Yu Chen,<sup>1,3</sup> Li-Kuo Liu<sup>1,3</sup> and Liang-Kung Chen<sup>1,3</sup>

<sup>1</sup>Aging and Health Research Center, National Yang Ming University, <sup>2</sup>Department of Family Medicine, Taipei City Hospital Zhongshiao Branch, and <sup>3</sup>Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan



Symptom	Control	Intervention
Delusion	0.8	0.1
Hallucination	0.9	0.2
Agitation	0.8	0.4
Anxiety	0.1	0.1
Irritability	0.2	0.2
Sleep disturbance	-0.8	-0.2

*Chen RC., Geriatr Gerontol Int 2014;14:440-6*