

**Promotion of Dementia Prevention
for Healthy and Active Aging**

**Hidenori Arai
National Center for Geriatrics and
Gerontology**

National Medical Research Centers in Japan



By Briet, French preacher, 1650

National Center for Geriatrics and Gerontology: NCGG

We promote the physical and mental independence of older people

Target: Dementia and Frailty



NCGG Dementia Research

2010 2011 2012 2013 2014 2015 2016 2017 2018 2019

New Drug/
Biomarker

CAMD

Lead compound
Anti Aβ (patent)
Anti Tau (patent)

New alternative biomarker of
Amyloid imaging



Lead compound

FDG PET
Tau PET

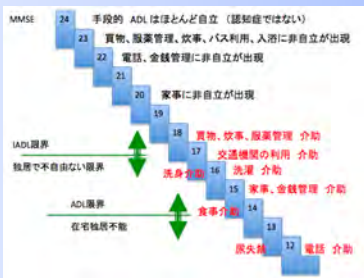
Clinical Mode

Comprehensive Research
1200 new patients/year

Dementia- ADL
relationship by large data

DNA database (6700)
Medical Genomic Center

Data base



Nationwide Preclinical
MCI Dementia Registry

Clinical trial

Clinical Trial
Management



Cohort

NILS-LSA
Aging research

Successful
Exercise Intervention

NCGG-SGS (large cohort on dementia and frailty)

Education

Systematic GP Education
(1000人/year)



Propose New Orange Plan

Making Policy

Proposal of Community based
Medical service

Leader of the Committee of
Promotion For Dementia Care



Host Dementia G7 Summit

High performance plasma amyloid- β biomarkers for Alzheimer's disease

Akinori Nakamura¹, Naoki Kaneko², Victor L. Villemagne^{3,4}, Takashi Kato^{1,5}, James Doecke⁶, Vincent Doré^{3,6}, Chris Fowler⁴, Qiao-Xin Li⁴, Ralph Martins⁷, Christopher Rowe^{3,4}, Taisuke Tomita⁸, Katsumi Matsuzaki⁹, Kenji Ishii¹⁰, Kazunari Ishii¹¹, Yutaka Arahata⁵, Shinichi Iwamoto², Kengo Ito^{1,5}, Koichi Tanaka², Colin L. Masters⁴ & Katsuhiko Yanagisawa¹

アルツハイマー病原因物質 血液から高精度検出 長寿研と島津製作所

2018年2月1日 3:00 [有料会員限定]

国立長寿医療研究センターと島津製作所は、アルツハイマー病の原因となる物質を血液中から90%程度の精度で検出する技術を確認した。島津製作所の田中耕一シニアフェローがノーベル賞を受賞した質量分析技術で調べる。脳内に原因物質が異常に蓄積されているか否かが早い段階で分かり、治療薬や予防薬開発につながる。英科学誌「ネイチャー（電子版）」に1日掲載される。

65歳以上の認知症患者数は462万人（2012年）で、6~7割がアルツハイマー病とみられている。原因物質の一つに、アミロイドベータ（ β ）と呼ぶたんぱく質がある。発症する20年以上前から脳内にたまり始めるとされるが、簡単に検出する方法がなかった。

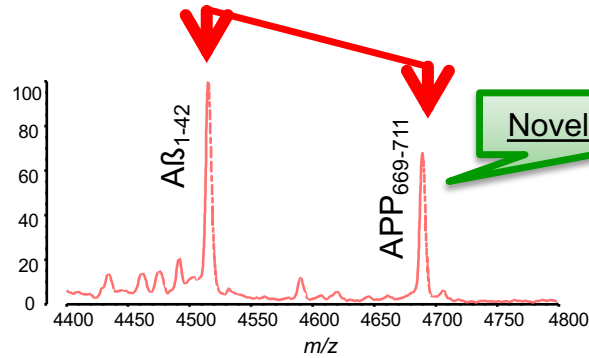
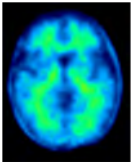
新手法は採血後の血液から、質量がわずかに違う複数のアミロイド β 関連のペプチド（たんぱく断片）を調べる。それぞれの割合からアミロイド β が脳内に異常に蓄積しているかが分かる。

日本とオーストラリアの患者などで分析した。陽電子放射断層撮影装置（PET）で脳内を調べた場合と比べ、新手法の検出精度は90%程度と高かった。アルツハイマー病の根本的な治療薬や予防薬はまだ開発されていない。田中シニアフェローは「治療薬や予防薬の臨床試験をする際、分析サービスを提供できれば」と話している。

2014

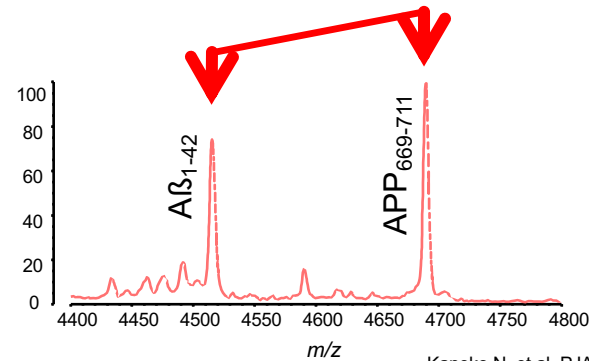
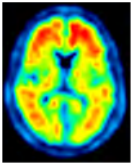
Discovery of serum biomarker ($APP_{669-711} / A\beta_{1-42}$)

Amyloid negative
(Normal)



Ration of $A\beta_{1-42}$ and
 $APP_{669-711}$

Amyloid positive
(AD)



Novel Biomarker
 $APP_{669-711} / A\beta_{1-42}$

Kaneko N. et al. PJAB (2014)より変更して引用

$A\beta_{1-40}$

$A\beta_{1-42}$

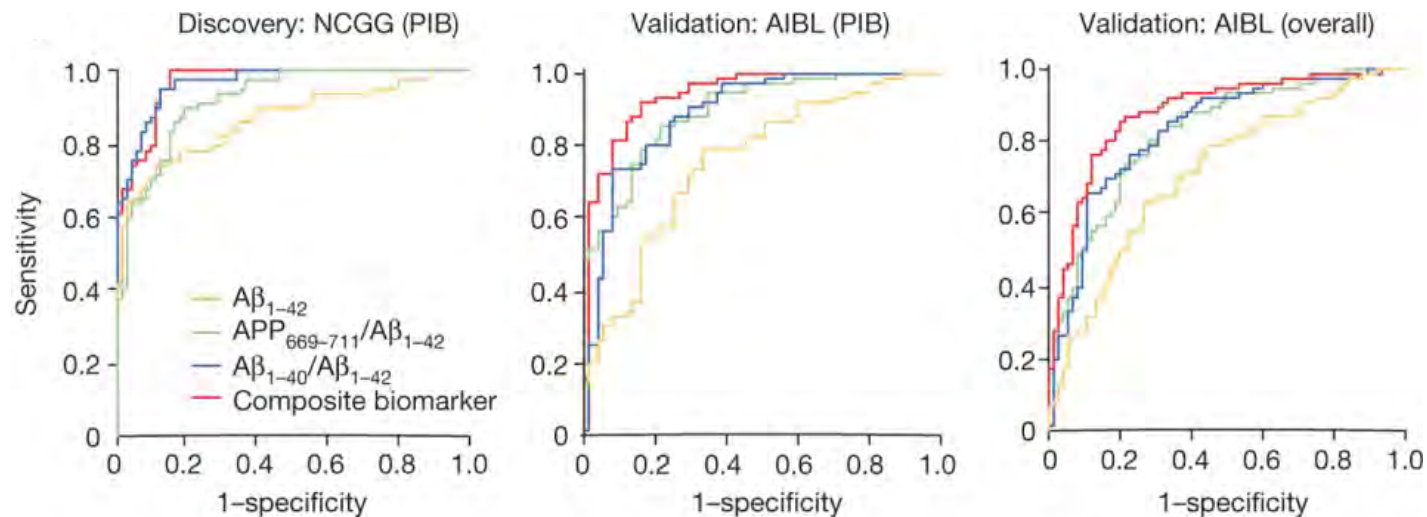
$APP_{669-711}$

DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV

DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA

VKM DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV

High specificity and sensitivity of the novel biomarker to detect amyloid deposition in the brain



LETTER

doi:10.1038/nature25456

High performance plasma amyloid- β biomarkers for Alzheimer's disease

Akinori Nakamura¹, Naoki Kaneko², Victor L. Villemagne^{3,4}, Takashi Kato^{1,5}, James Doecke⁶, Vincent Doré^{3,6}, Chris Fowler⁴, Qiao-Xin Li⁴, Ralph Martins⁷, Christopher Rowe^{3,4}, Taisuke Tomita⁸, Katsumi Matsuzaki⁹, Kenji Ishii¹⁰, Kazunari Ishii¹¹, Yutaka Arahata⁵, Shinichi Iwamoto², Kengo Ito^{1,5}, Koichi Tanaka², Colin L. Masters⁴ & Katsuhiko Yanagisawa¹

Multi-sector Approaches to Dementia in Japan

Organized **R**egistration for the
Assessment of dementia on **N**ation-
wide **G**eneral consortium toward
Effective treatment in Japan

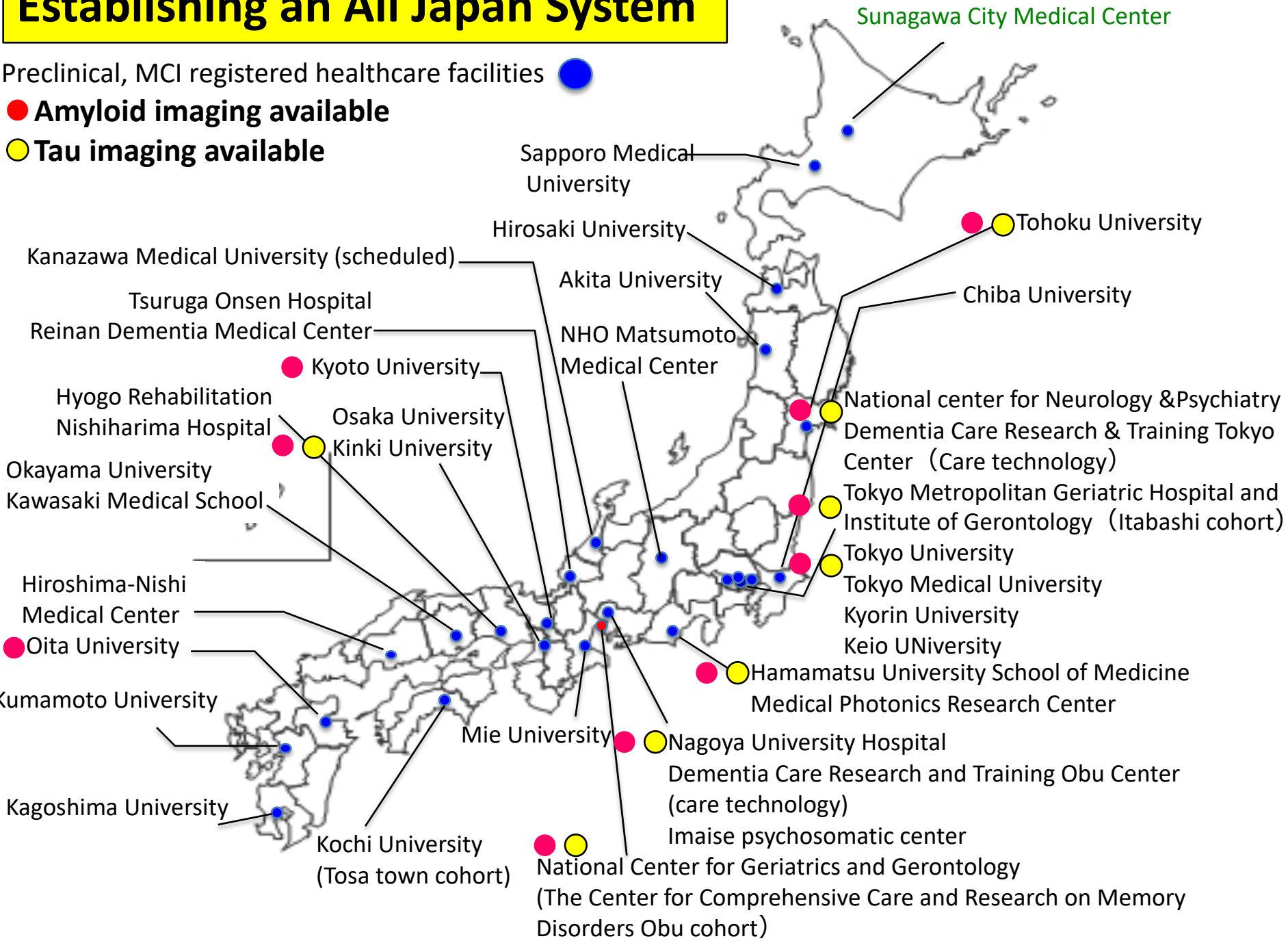
ORANGE Platform

Establishing an All Japan System

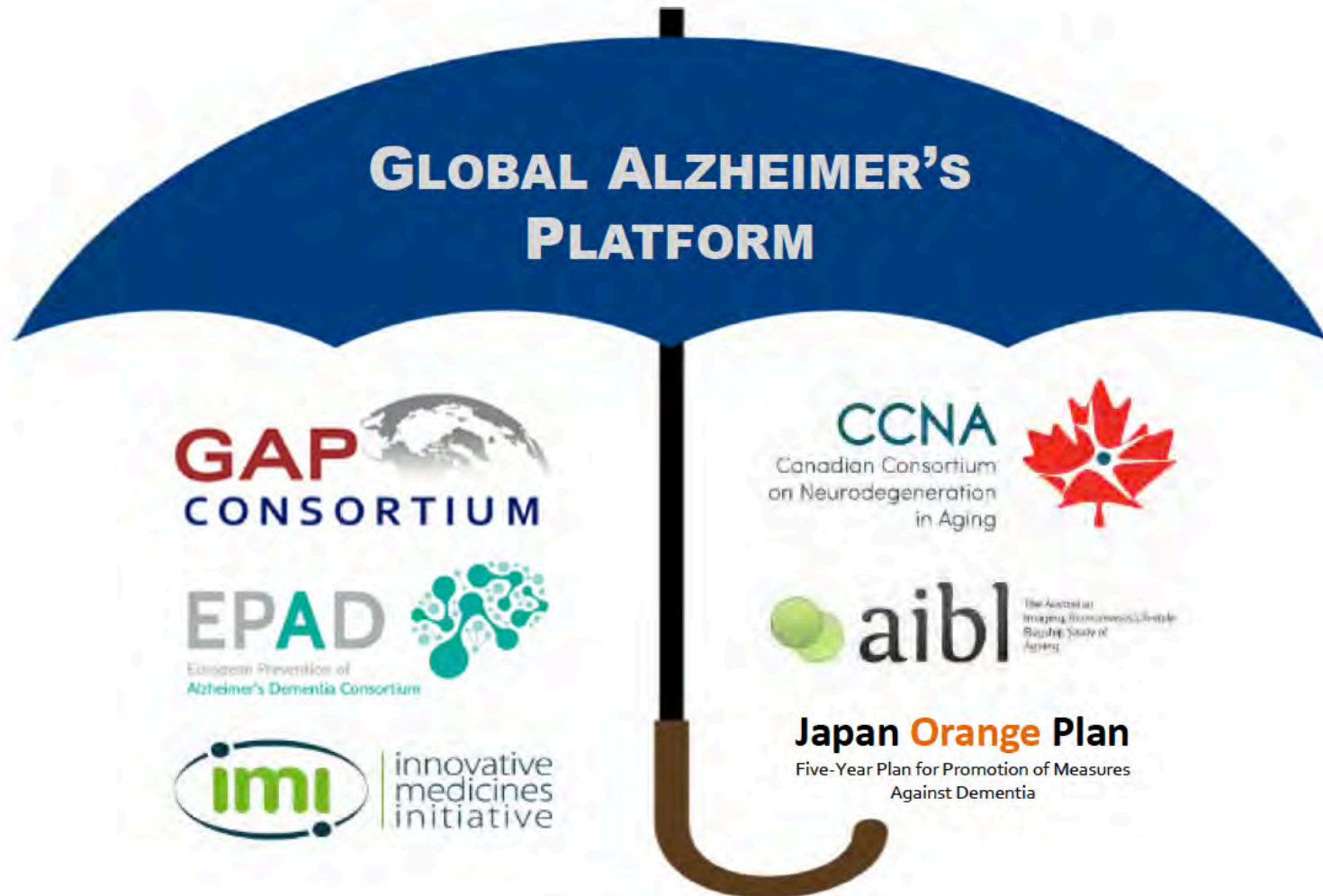
Preclinical, MCI registered healthcare facilities ●

● Amyloid imaging available

● Tau imaging available



An integrated global approach accelerates path to treatment and prevention

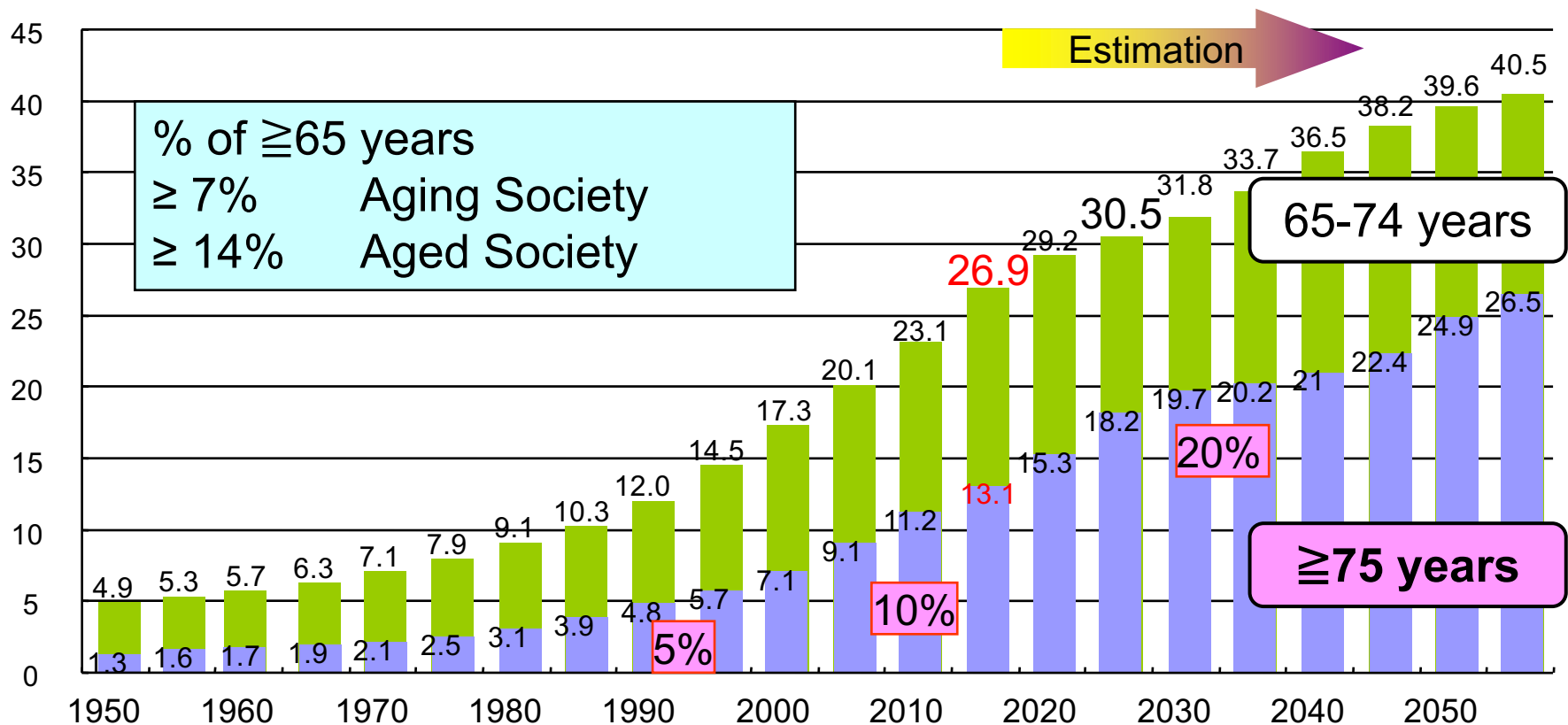


Aging Tsunami in Japan

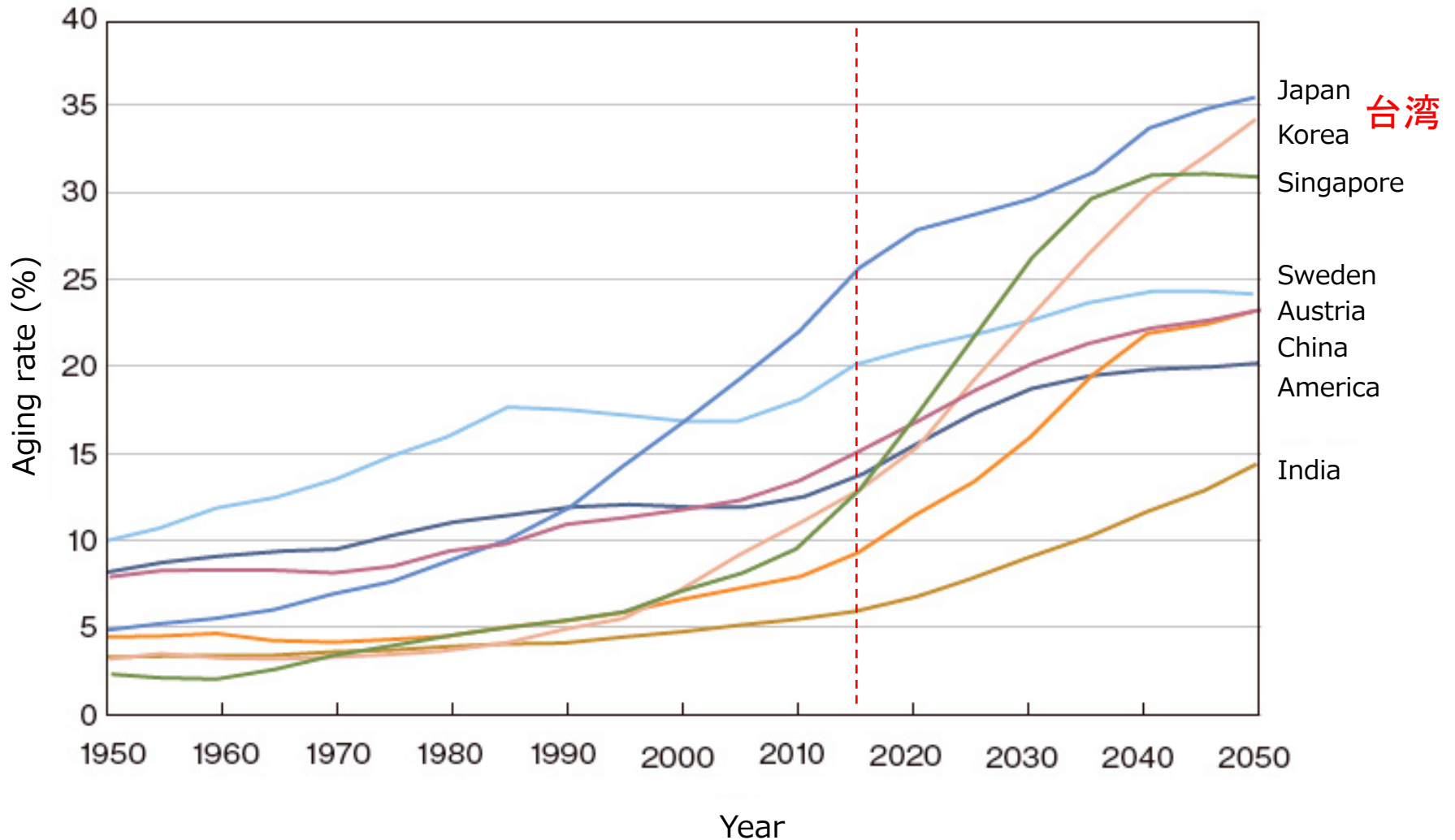
Rapid Increase of Older Population

Japan's 2025 problem

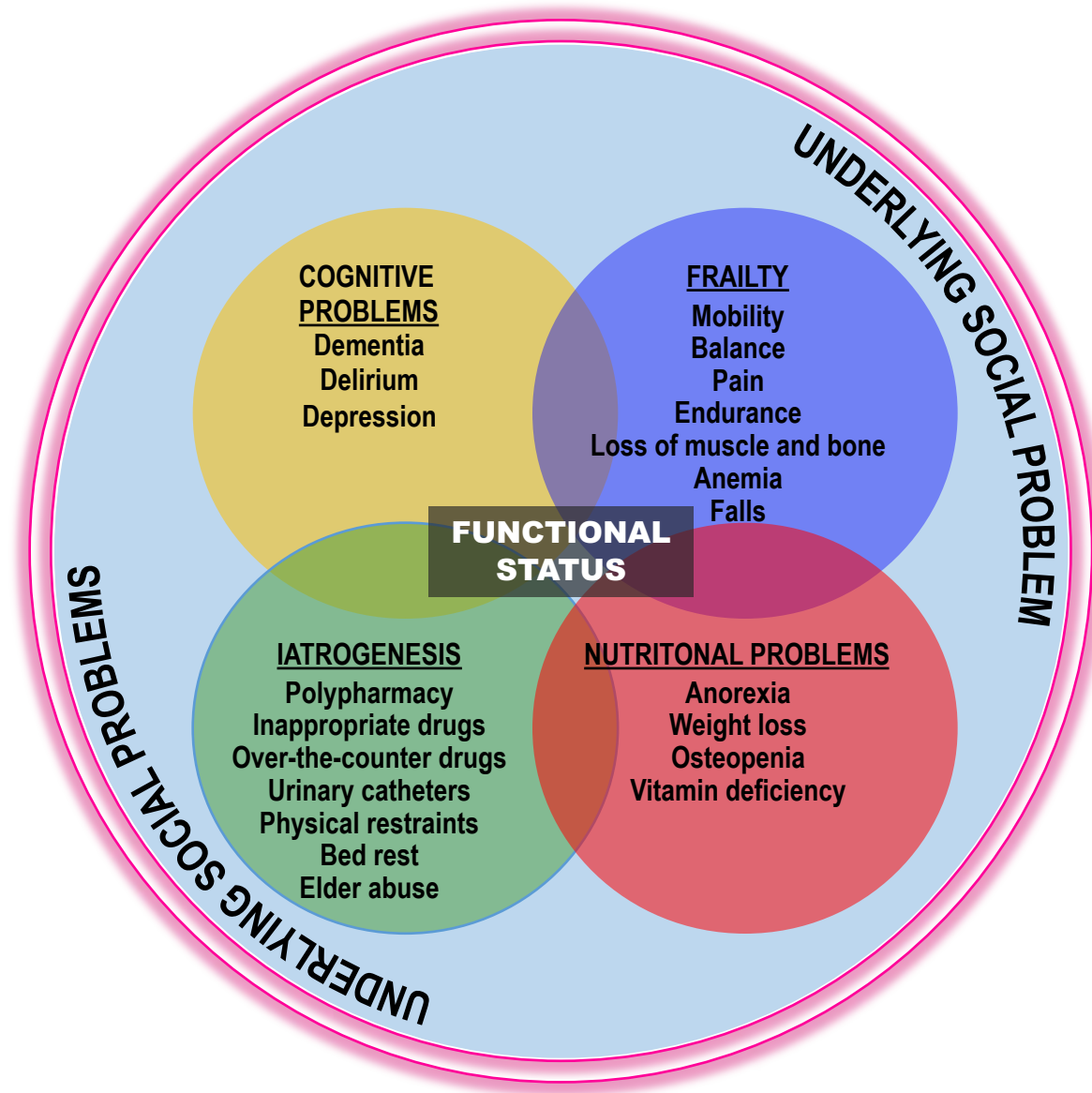
*Baby boomer generation becomes over 75 years at 2025.
Estimated number of old-old population (≥ 75 years) is about 20 million (18.2%) at 2025.*



Changes in aging rate



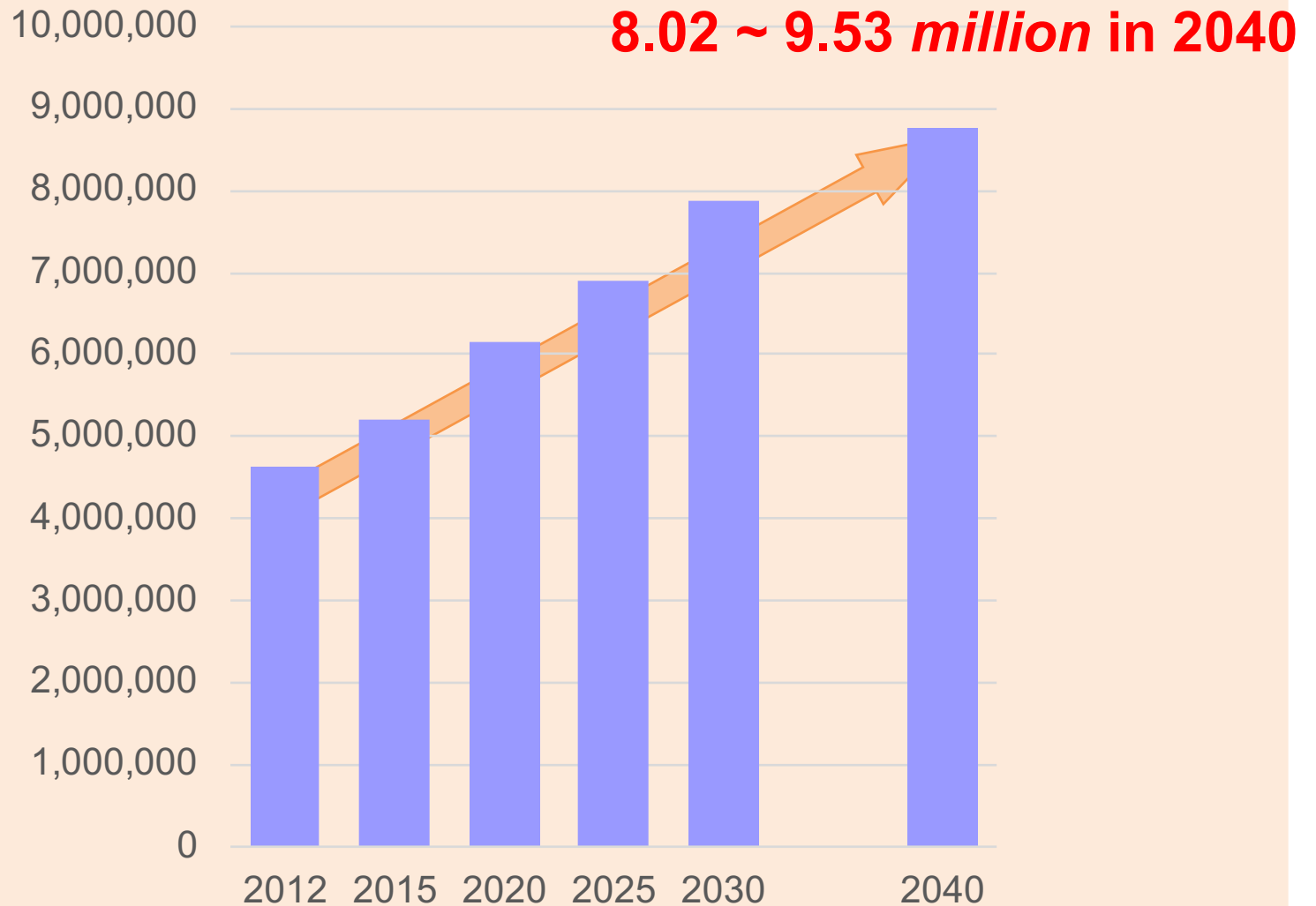
Taking care of older people



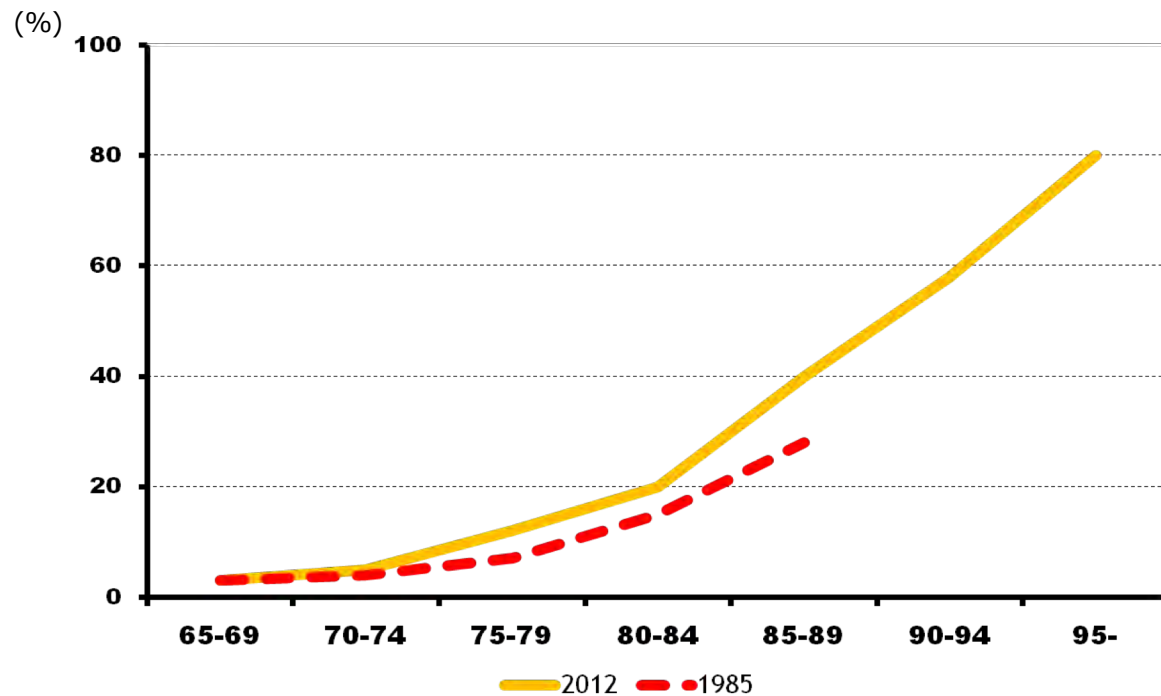
Other problems in older patients

- **Disease-oriented**
- **Lack of EBM**
- **Fragmented care**
- **No preventive care (lack of awareness of frailty and cognitive impairment)**
- **Insufficient social support**

Estimation of people with dementia in Japan



Age-dependent increase of dementia



厚労省版研究による有病率を国立社会保障・人口問題研究所による高齢者人口(12年)に当てはめて推計

Current issues for dementia care in Japan

- **Symptomatic worsening due to the delay of early medical examination/response**
- **Prolonged hospitalization of dementia patients in mental hospitals**
- **The admission of people with dementia to general hospitals is sometimes refused due to the shortage of staffs who can handle the illness**
- **The circumstances for people with dementia to continue to live in home are poor in terms of quality and quantity**
- **An inadequate community support service for people with dementia and their families**
- **A lack of service coordination by healthcare and social care professionals in dementia care**

What can we do to live well with dementia in Japan?

- **Prevention of dementia**
 - **Prevention and management of diabetes, hypertension, dyslipidemia**
- **Early detection for dementia**
- **Lifestyle modification of dementia patients**
- **Establishment of Dementia-friendly society**

History of Dementia Policy in Japan

- 1984 Launch of Dementia Care Training Program
- 1987 “MHLW Headquarters for the Promotion of Dementia Elderly Measures” Report
- 1989 Establishment of Medical Center for Dementia
- 1992 Establishment of Day-Service Center for Dementia
- 1997 Establishment of Group Home for Dementia
- 2000 Enactment of Long-Term Care Insurance Act
- 2005 Launch of **Training Program for Dementia Support Doctors**
 - Launch of Nationwide Program to Train One Million Dementia Supporters
- 2006 Launch of Training Program for Primary Care Doctors to upskill Dementia Practice
- 2012 Formulation of Five-Year Plan for promotion of Dementia Measures (“**Orange Plan**”)

New Orange Plan (2015-2017)

1. Inclusion of People of Dementia and their Family Caregivers

2. Educational Program for better Understanding and Awareness to Dementia

3. Timely Medical and Health Care Services adequate for the Stages of Dementia

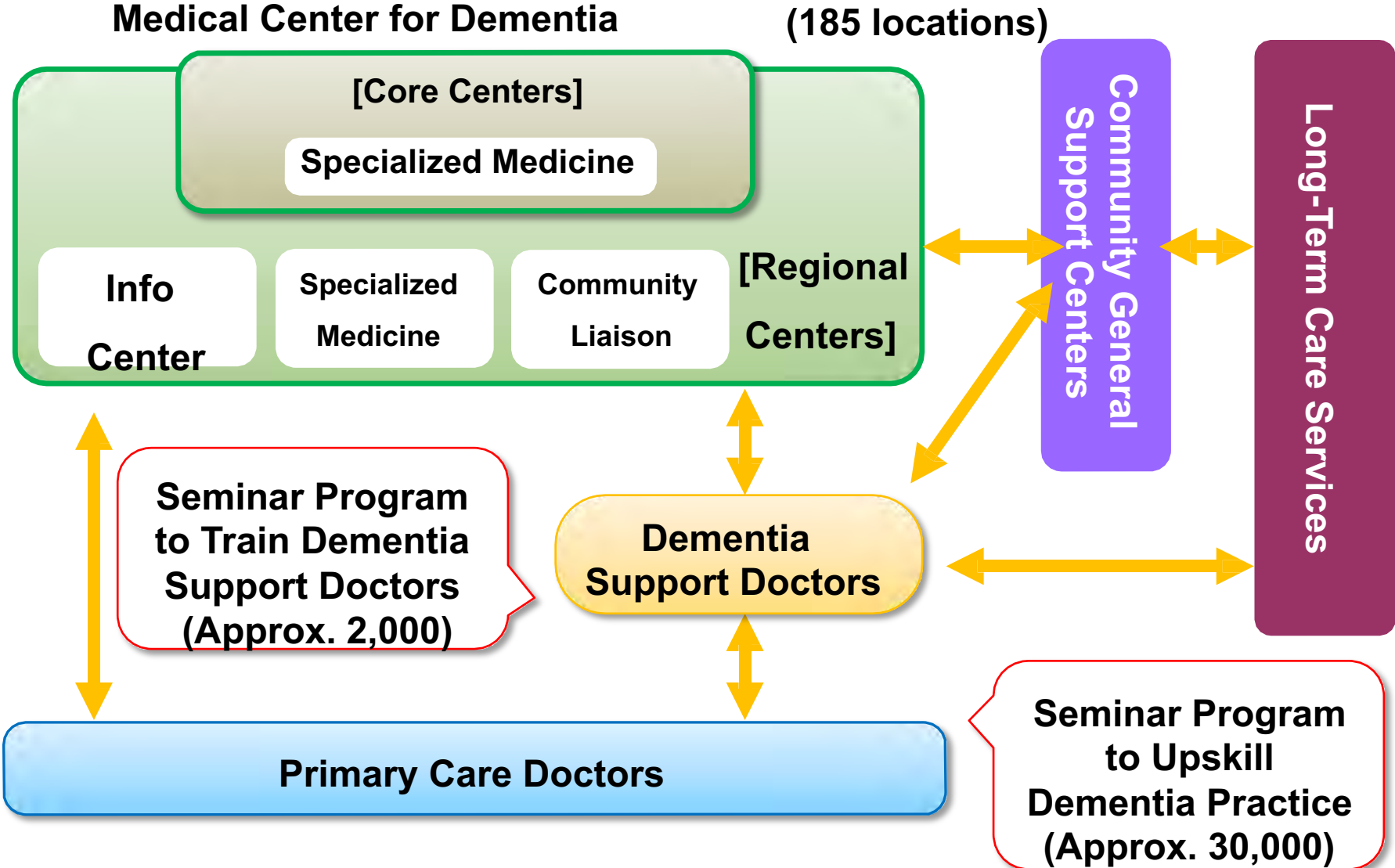
4. Promotion of Dementia-friendly Community

5. Better Support for Family Caregivers

6. Driving Research of Prevention, New Drug, Rehabilitation & Care for Dementia

7. Reinforcement of Measures for Younger Onset Dementia

Medical Care System and Training Program



Dementia Supporters from 2005

Over 3 million Dementia Supporters are trained nationwide.

Who are Dementia Supporters?

- With good knowledge and understanding of dementia, they support the elderly with dementia and their families at regional/professional levels, to the extent possible

Dementia Supporter Training Programme (90 min)

3,363,024 attendees as of 30 June, 2012

Training for "Caravan Mates",
or lecturers who teach in Supporter Training
Program (6 h)



73,824 participants as of 30 June, 2012

4. Promotion of Dementia-friendly Community

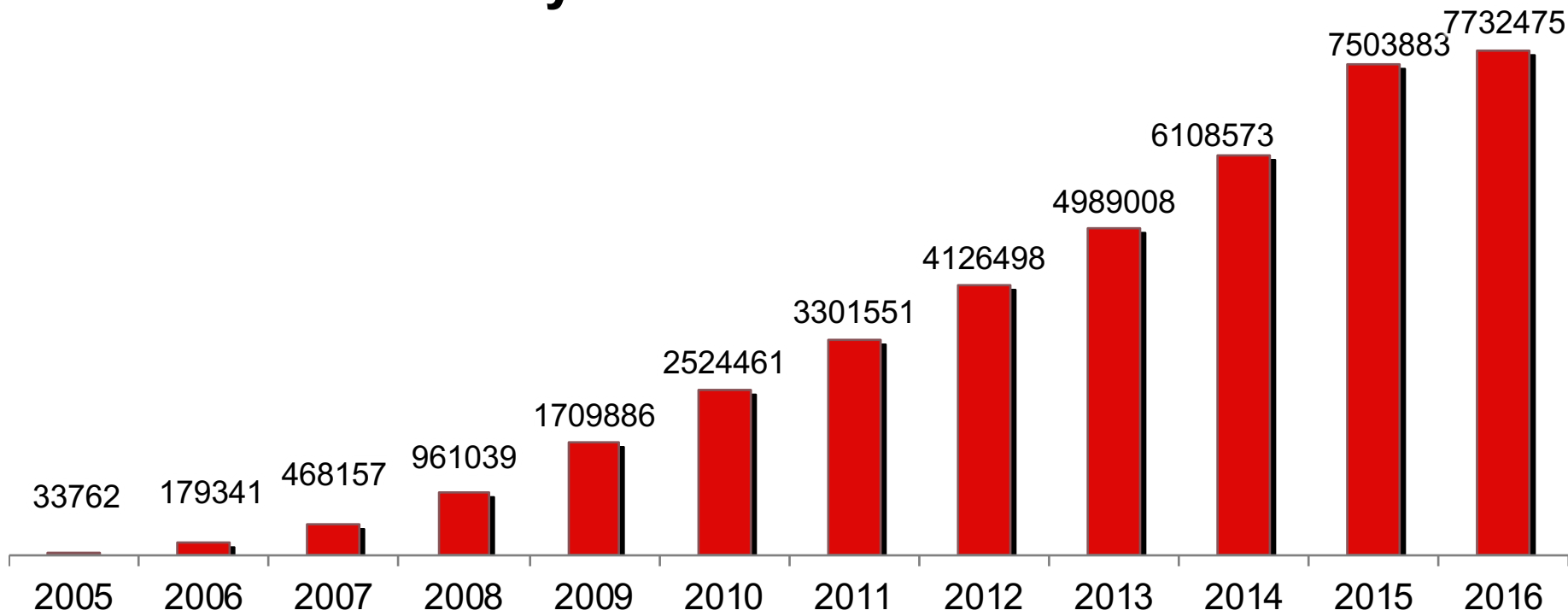
From 2005, N of Supporter 8 million (Dec 2016)

Teacher (Caravan mate) 126400

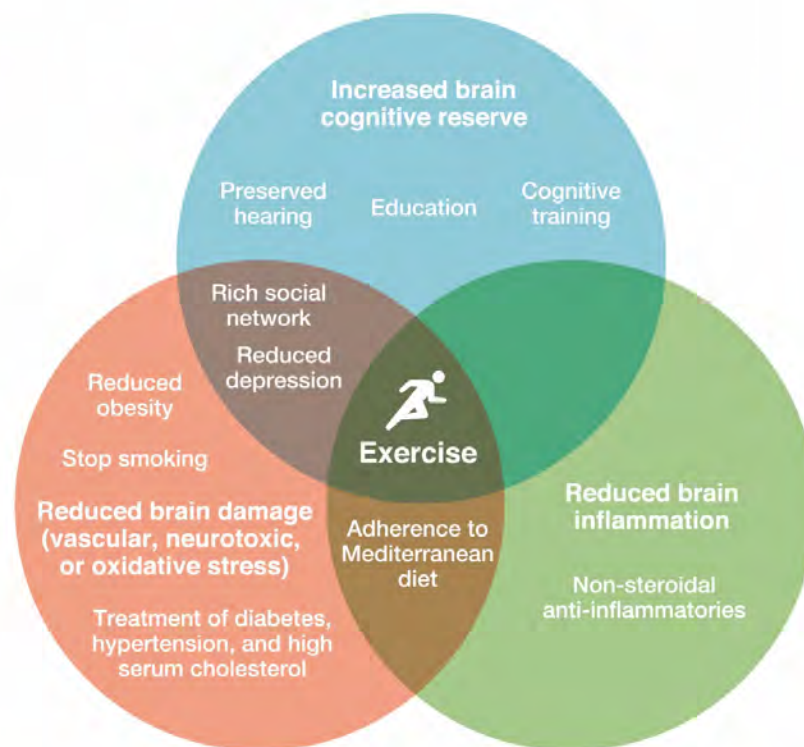
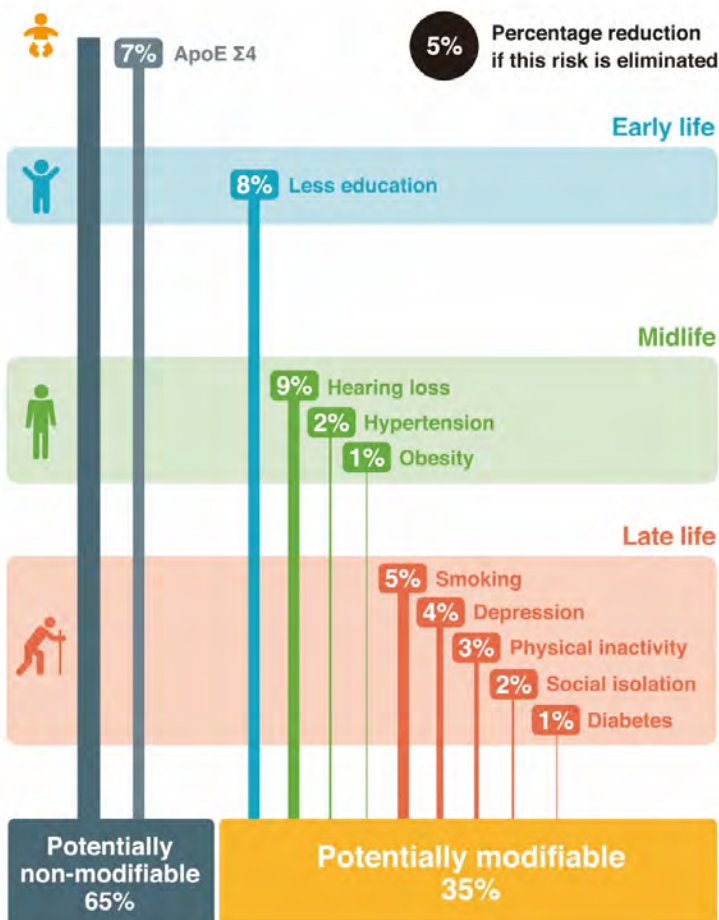
What is Dementia

You Can be Friendly to Persons with Dementia

Role of Community



Life-course model of contribution of modifiable risk factors to dementia

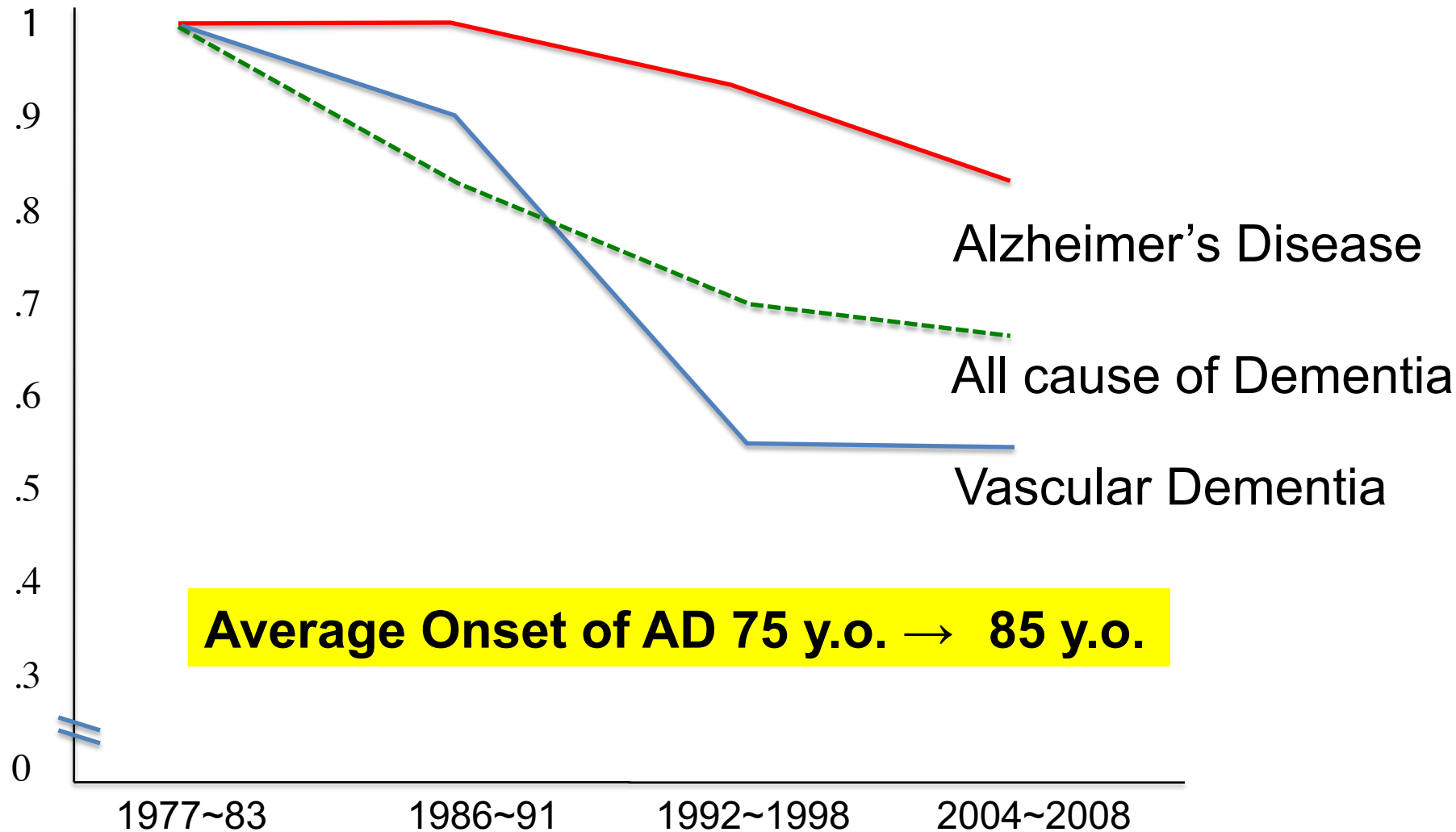


How much AD can be attributed to environmental factors?

- **2%** Diabetes
- **2%** Obesity at middle age
- **5%** Hypertension at middle age
- **10%** Depression
- **13%** Inactivity
- **14%** Smoking
- **19%** Lack of intellectual stimulation and Short education period

Incidence of Dementia over Three Decades in the Framingham Heart Study

Claudia L Satizabal et al. *New Engl. J Med* FEB 11, 523~532, 2016



A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012

Kenneth M. Langa, MD, PhD^{1,2,3,4}; Eric B. Larson, MD, MPH⁵; Eileen M. Crimmins, PhD⁶; [et al](#)

» [Author Affiliations](#)

JAMA Intern Med. Published online November 21, 2016. doi:10.1001/jamainternmed.2016.6807



Editorial
Comment



Author
Interview



Multimedia

11.6% → 8.8% (for 12 years)

Key Points

Question Has the prevalence of dementia among older adults in the United States changed between 2000 and 2012?

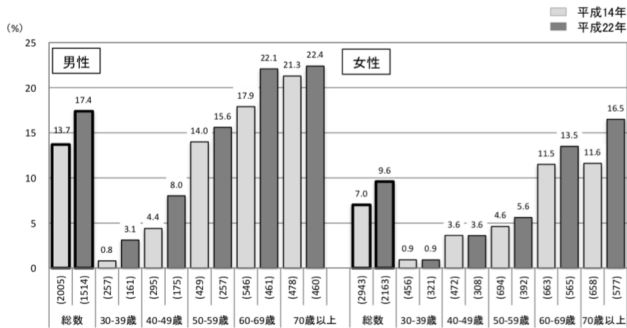
Findings In this observational cohort study of more than 21 000 US adults 65 years or older from the nationally representative Health and Retirement Study, dementia prevalence declined significantly, from 11.6% in 2000 to 8.8% in 2012.

Change of risk factors for dementia in Japan

認知症リスクの近年の変化

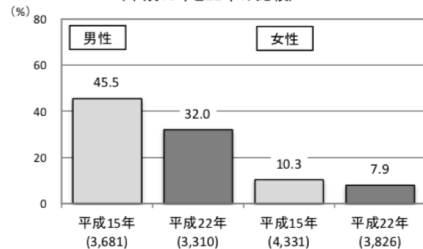
1) 糖尿病 (寄与率2%) 悪化

図6 糖尿病が強く疑われる者の割合 (30歳以上) (平成14年*と22年の比較)



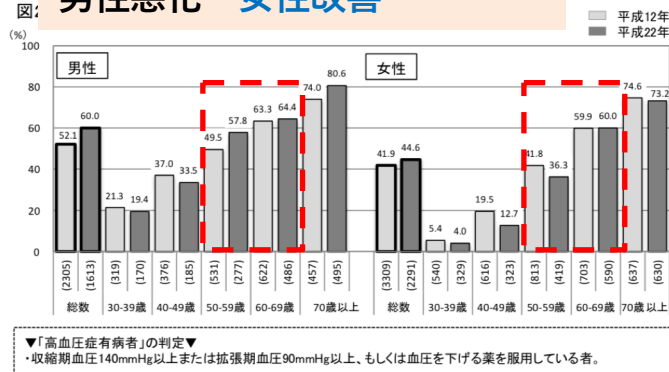
4) 喫煙 (寄与率14%) 改善

図13-1 喫煙者*の割合 (30歳以上) (平成15年と22年の比較)



*喫煙者: 現在習慣的に喫煙している者 (24ページ参照)

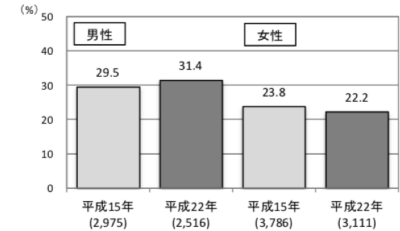
2) 中年期高血圧 (5%) 男性悪化 女性改善



▼「高血圧症有病者」の判定▼
 ・収縮期血圧140mmHg以上または拡張期血圧90mmHg以上、もしくは血圧を下げる薬を服用している者。

3) 中年期肥満 (寄与率2%) 男性悪化、女性改善

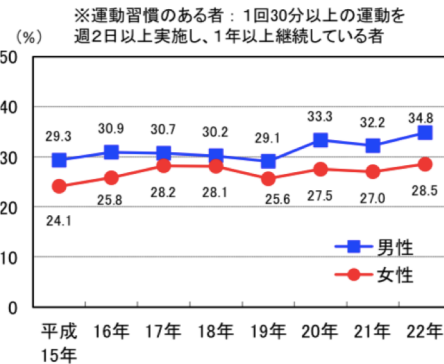
図13-3 肥満者*の割合 (30歳以上) (平成15年と22年の比較)



*肥満者: BMI≥25の者 (12ページ参照)

5) 運動習慣 (寄与率13%) 改善

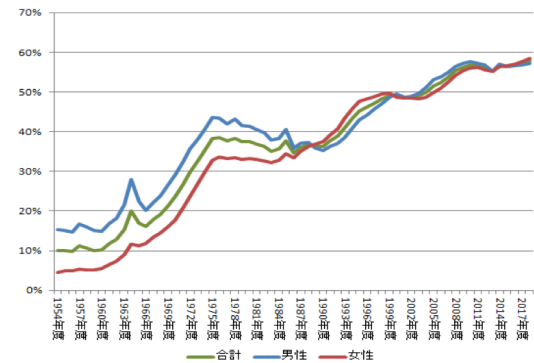
図24-1 運動習慣のある者の割合の年次推移 (20歳以上) (平成15年~22年)



※運動習慣のある者: 1回30分以上の運動を週2日以上実施し、1年以上継続している者

6) 教育年数 (寄与率19%) 増加 老年期の知的刺激は不明

大学・短期大学への進学率 (過年度高卒者などを含む)



1) ~ 5) 平成22年 国民健康・栄養調査結果の概要

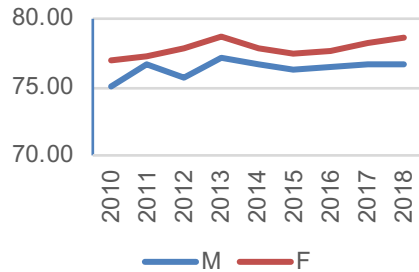
6) ガバージニューズ - 2018/08/23

Character change of new patients to memory clinic

国立長寿もの忘れセンター(9年間)

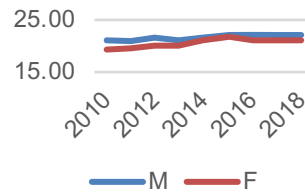
初診年齢

9年間で男女共1.5歳以上
高齢に



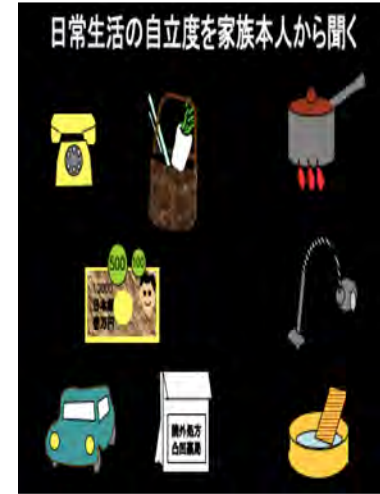
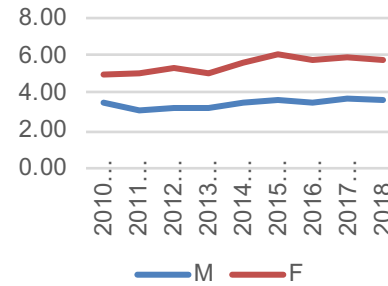
MMSE

9年間で男女共
0.7点増加
(より軽度)

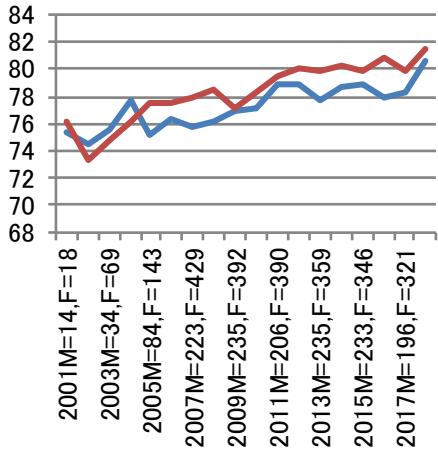


IADL (独居機能)

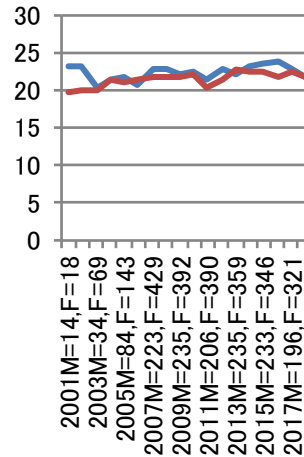
女性8点満点
男性5点満点
9年間で改善見られている



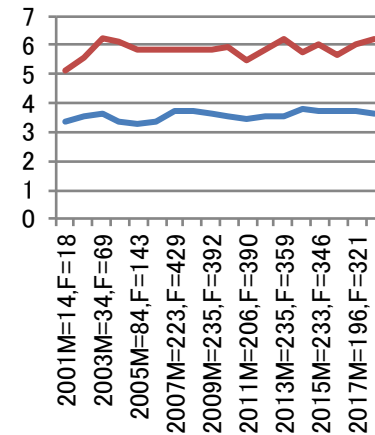
杏林大学もの忘れセンター(18年間)



— 男性
年齢
— 女性
年齢



— 男性MMSE
— 女性MMSE



— 男性IADL
— 女性IADL

Flow of preventing dementia and disability

1 Health screening and test for older person



Cognitive function test
Cognitive Assessment Tool
NCGG-FAT




Cognitive Assessments



Questionnaire

Physical Assessments

Blood test

Risk classification & Improve motivation

2 High-risk approach

Group activities



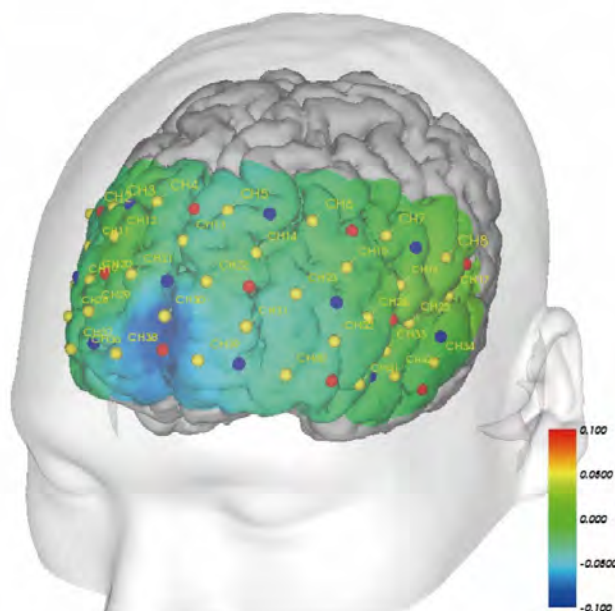
3 Population approach

Education Classes and self-monitoring

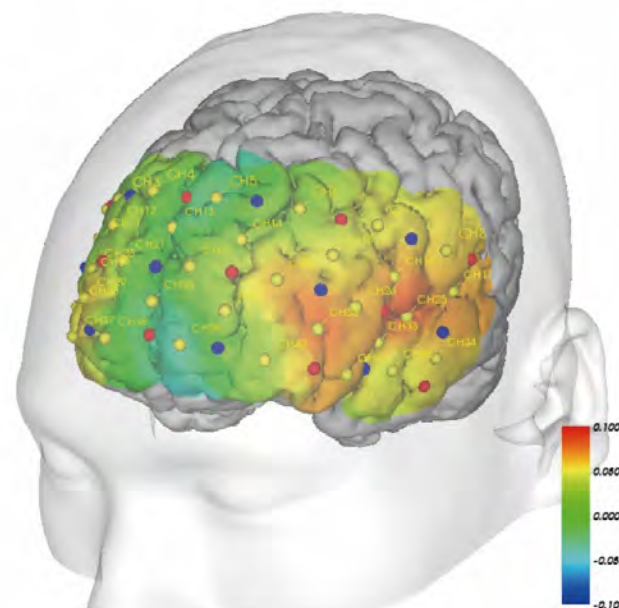


New exercise program for improving cognitive performances

Aerobic Exercise



COGNICISE

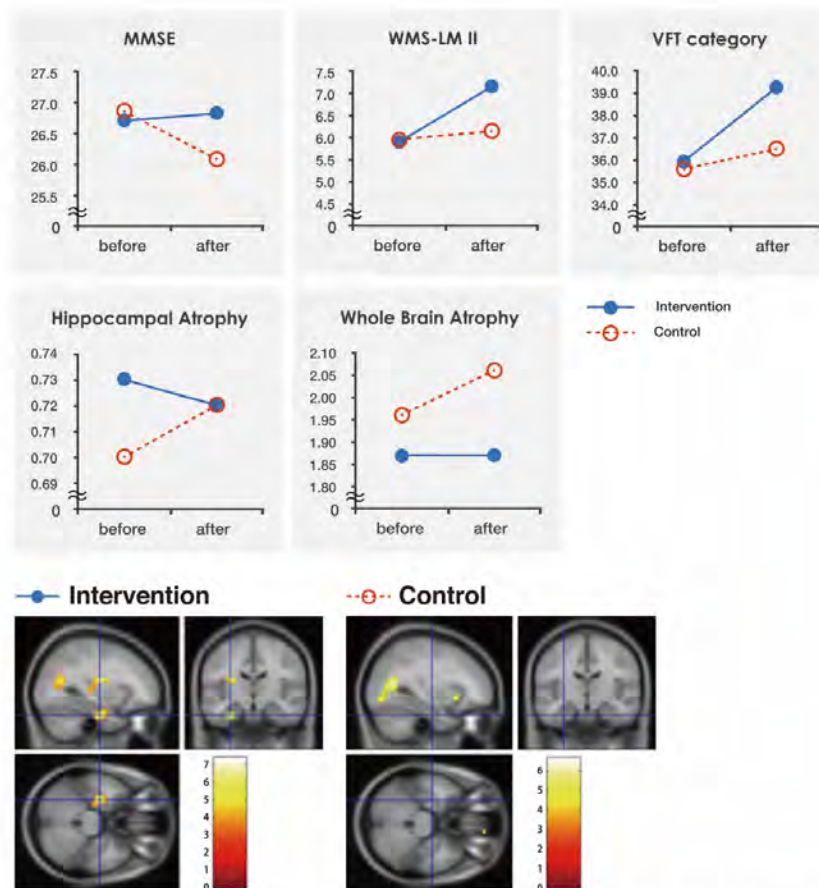


Effects of COGNICISE on cognitive performances

Subjects: 308 older adults with MCI
 Design: RCT
 Setting: Community
 Intervention:
 Multicomponent exercise program
 10 months, weekly, 90 min/session

RESULTS

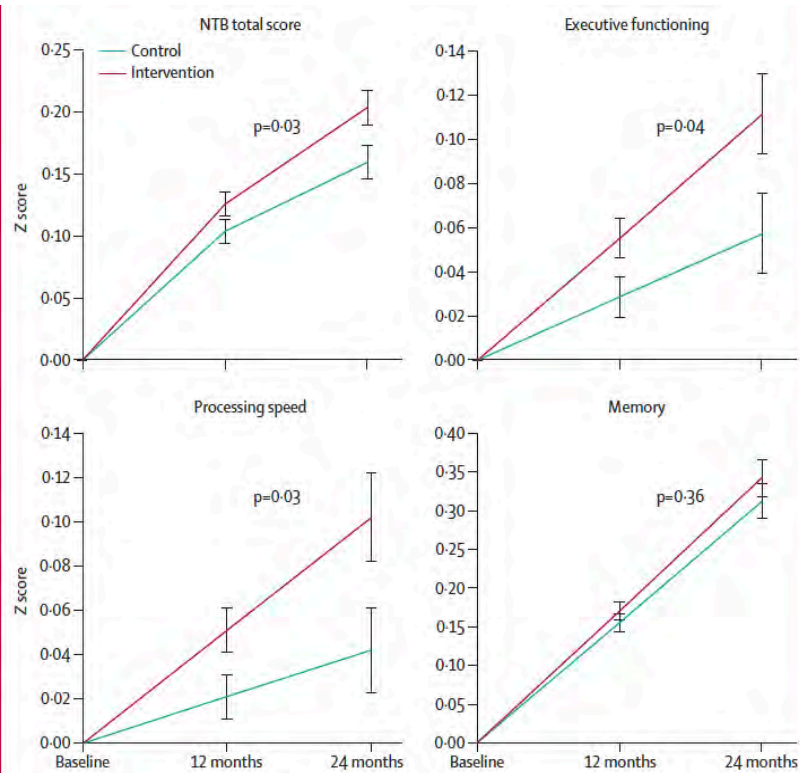
- 1 Mini-mental state examination, $p < .01$
- 2 Wechsler Memory Scale-logical memory II, $p < .01$
- 3 Verbal Fluency Test, $p < .01$
- 4 Hippocampal atrophy, $p < .05$
- 5 Whole brain atrophy, $p < .01$



A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

Tiia Ngandu, Jenni Lehtisalo, Alina Solomon, Esko Levälähti, Satu Ahtiluoto, Riitta Antikainen, Lars Bäckman, Tuomo Hänninen, Antti Jula, Tiina Laatikainen, Jaana Lindström, Francesca Mangialasche, Teemu Paajanen, Satu Pajala, Markku Peltonen, Rainer Rauramaa, Anna Stigsdotter-Neely, Timo Strandberg, Jaakko Tuomilehto, Hilikka Soininen, Miia Kivipelto

Lancet march 12, 2015



	Odds ratio (95% CI)		p value
	Intervention (n=554)	Control (n=565)	
Overall cognitive decline			
NTB total score	1 (reference)	1.31 (1.01-1.71)	0.04
Cognitive decline per domain			
NTB memory score	1 (reference)	1.23 (0.95-1.60)	0.12
NTB executive functioning score	1 (reference)	1.29 (1.02-1.64)	0.04
NTB processing speed score	1 (reference)	1.35 (1.06-1.71)	0.01



**Japan-multimodal
intervention Trial for
prevention of dementia
(J-MINT)**

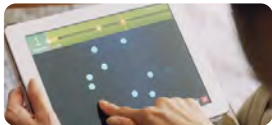
認知症予防を目指した多
因子介入による
ランダム化比較試験

Aim

To clarify the **effectiveness of multimodal dementia prevention programs**, and to make an **applicable program to future social implementation**.



Intensive and face to face support is necessary for the older adults with cognitive impairment.



Collaborative research with private enterprises for future social implementation.



To clarify the mechanism of cognitive change by using advanced technologies (serum biomarkers, omics analysis, brain imaging).

J-MINT Overview

🌿 Multicenter, Open-label RCT

🌿 Inclusion criteria: aged **65-85** years, with **mild cognitive impairment**

age-adjusted decline at least 1.5 SD below the reference threshold in any cognitive domains; NCGG-FAT

Exclusion criteria: MMSE<24, dependency

🌿 Sample size: **440** (intervention 220, control 220)

🌿 Intervention for **18 months**

Management of Lifestyle related disease, Exercise, Nutritional guidance, & Cognitive training

🌿 Primary outcome:

Change in **composite score of cognitive tests**

NCGG-FAT



Recall (word list, story), TMT, Digit symbol substitution, digit span

J-MINT structure

Supported by the Japan Agency for Medical Research and Development (AMED)

National Center for Geriatrics and Gerontology
PI: Dr. Hidenori Arai

NCGG, Nagoya U, Nagoya-City U, Fujita Health U, TMIG <Registration>

NCGG, Nagoya U, Nagoya-City U, Fujita Health U, TMIG

**Medical check of
Lifestyle-related disease**

Control group (N=220)

SOMPO HD

<Supervision of conducting intervention>

**Nutritional
guidance**

SOMPO
Health
Support

**Physical
exercise**

KONAMI
Sports Club

**Cognitive
training**












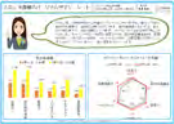
Nestle Japan

Intensive intervention group (N=220)

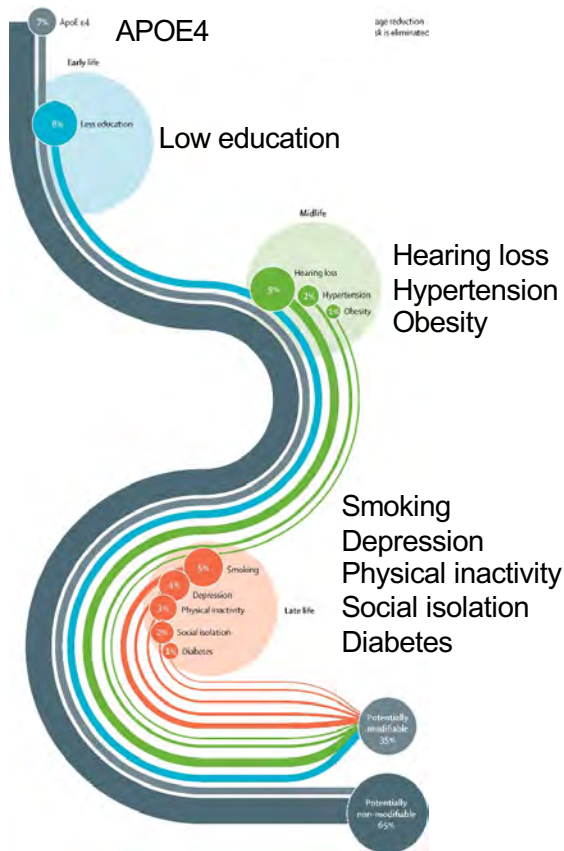
*Advisory Services Agreement
with Professor Kivipelto*



J-MINT Multimodal Intervention

Contents	Provider	Summary	
Medical check of Lifestyle disease	NCGG Nagoya U Nagoya City U Fujita Health U TMIG	Management of vascular risks and provide advice for oral health   	Length: 18 mo. Frequency: at the time of regular medical examination
Physical exercise	KONAMI Sports Club	Multicomponent exercise program (stretch, muscle strength, aerobic, exercise with dual task and behavior modification)   	Length: 18 mo. Frequency: Once a week 90minutes for each
Nutritional guidance	SOMPO Health Support	Support for taking meals regularly and well-balanced food including dementia preventive food   	Length: 18 mo. Frequency: 3 times meetings 12 times telephone calls
Cognitive training	Nestle Japan	Cognitive training by iPad-based computer program   	Length: 3 mo × 3 times 30 minutes a day 4 times a week

Assessments of risk factors for dementia



Lancet. 2017;390(10113):2673-2734.

Factors	Measurements
Low education	Self-reported questionnaire
Physical frailty	CHS criteria
Medications	Polypharmacy, Risky medications
Comorbidities	Hypertension, Diabetes, Cardiac disease, Atrial fibrillation, Dyslipidemia, Obesity, Low BMI, Oral frailty
Lifestyle	Smoking, Alcohol, Physical activity, Cognitive activity, Social activity, Hobby
Subjective cognitive complaints	Self-reported questionnaire
Poor sleep	PSQI
Depressive symptoms	GDS-15
Social isolation	LSNS-6
Hearing impairment	HHEI
Nutritional status/Appetite	MNA-SF/SNAQ
Genome	Whole genome analysis

Physical exercise program

➤ Menu (each time)

- before** • Medical check
- 10 minutes** • Warm-up exercises
- 20 minutes** • *Cognicise* (Aerobic exercise + dual tasks)
- 25 minutes** • Exercise for strengthening muscles
- 30 minutes** • Group meeting
- 5 minutes** • Warming down exercises

“Cognicise” and exercise for strengthening muscles by qualified trainers



- **Dementia preventive physical exercise**
- **Program to improve physical strength by increasing the load incrementally**

Various elements in order to motivate participants to change their behavior



- **Support exercises at home**
- **Set the goal for each participant and make records by using pedometer and special notebook**



- **Hold group meetings after exercises**

Multicomponent Exercise Program



Task 1

Stretch and muscle strength



Task 3

Exercise with learning-task



Task 2

Aerobic exercise



Task 4

Behavior modification technique

Nutritional counseling program

➤ Menu (for 18 months)



Support for taking meals regularly and well-balanced food including dementia preventive food by qualified counselors*



- Check the timing and times of taking meals and appetite
- Assess metabolic syndrome and frailty and set the goal for each participant
- Guide based on “Dietary Reference Intakes for Japanese”
- Take dementia preventive food such as nuts, fish, vegetable, and dairy product

Check and monitor the goal achievement status by using special notebook

実践記録表

決めた行動計画を実践しながらこの記録表をつけてみましょう。

月/日	4/1	4/2	4/3	4/4	4/5	4/6
曜日	月	火	水	木	金	土
標準項目						
体重 (kg)	-42.0			42.5		
腹囲 (cm)	60.0			60.5		
歩数 (歩)	4500	4550	4600	4650	4750	4800
体脂肪率 (%)	19.0			19.5		
血圧上 (mmHg)			138		136	
血圧下 (mmHg)			82		78	
行動計画						
決まった時間に食事をとる	×	×	○	×	○	○
野菜を摂取する	○	×	×	○	○	○
1日に1杯の牛乳を摂取する	×	○	○	○	×	○
ナッツ類、魚を摂取する	○	×	○	○	○	○



- Check and monitor the goal achievement status by using special notebook
- Motivate the participants to continue and change the goal, if necessary

*1 Qualified counselors consist of National registered nutritionists, Public health nurses and Nurses.

Cognitive training program

➤ Menu (for 18 months)

- Explanation on how to use *Brain HQ*
- Start 1st round
- Feedback
- Start 2nd round
- Feedback on 2nd round
- Start 3rd round
- Feedback on 3rd round



Provide cognitive training game by using iPad named “Brain HQ”*

- ✓ conducted for 30 minutes a time, 4 days a week
- ✓ set the program according to each participant’s level

*Training program for improving;



Memory and attentiveness



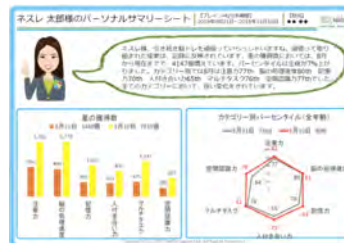
Speed of visual processing



Supported by Nestle Japan’s support system



- Operation is thoroughly explained



- Feedback by personalized summary sheet



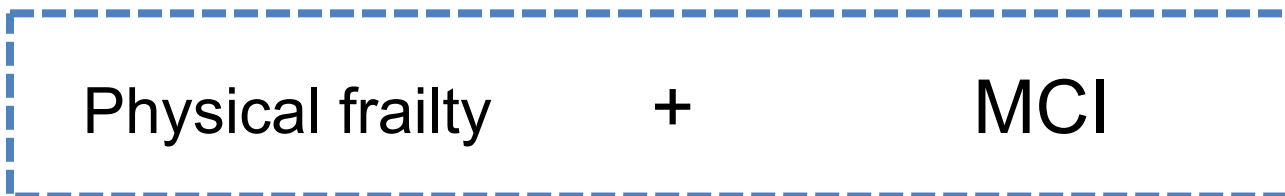
- Telephone support system by trained operator

Each set will be provided by reflecting the level of the previous round’s result.

Cognitive Frailty

Cognitive frailty is characterized by the simultaneous presence of both physical frailty and cognitive impairment.

- Presence of physical frailty and cognitive impairment (CDR = 0.5).
- Exclusion of concurrent AD dementia or other dementia.
- ✘ Reversibility also characterize cognitive frailty.
- ✘ Cognitive impairment is related to physical causes



Cognitive frailty by IANA and IAGG

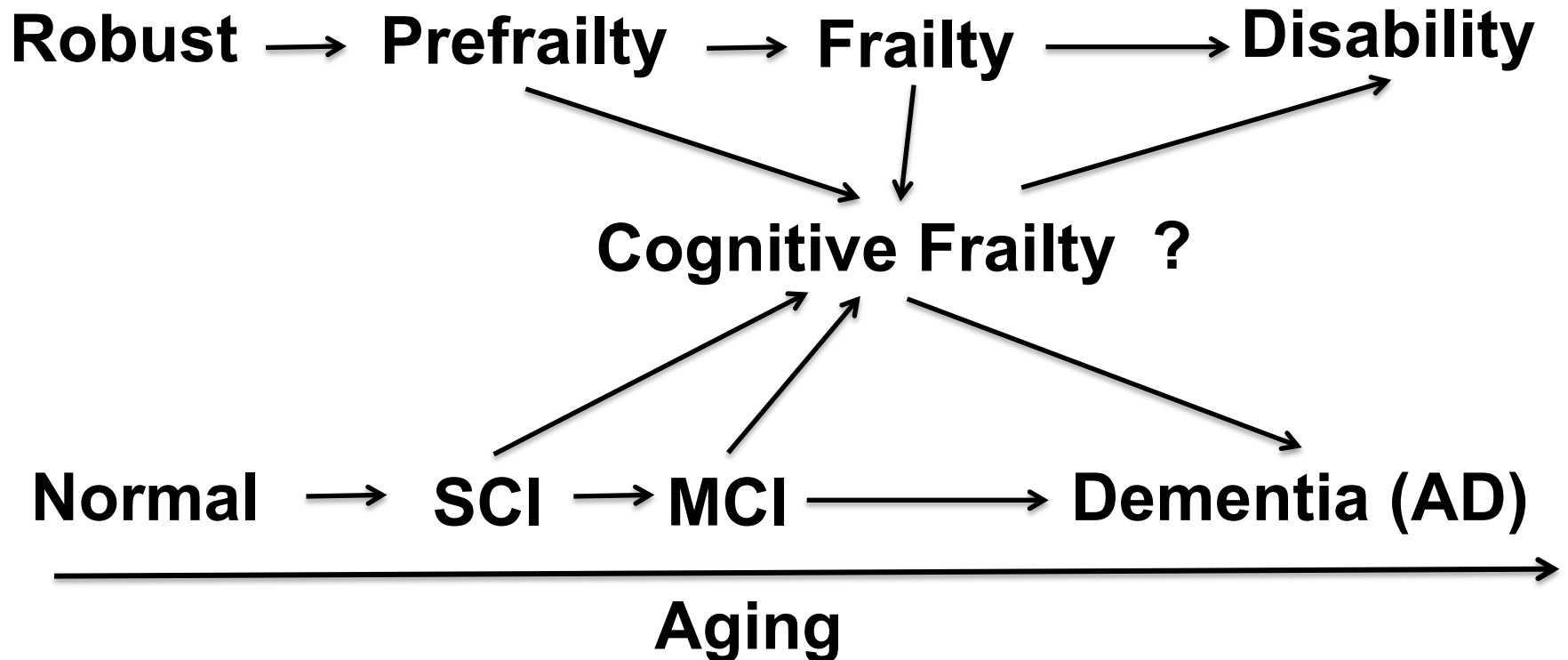
How to define cognitive frailty?

IANA/IAGG Operational definition of cognitive frailty 2013

Physical frailty + MCI

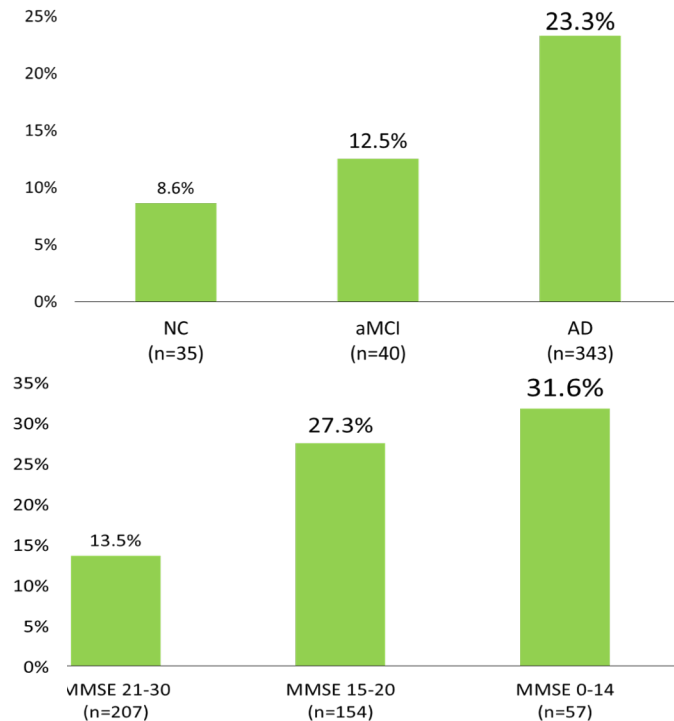
Solfrizzi, V et al. 2017

Physical frailty + pre-MCI-SCD (excluded concurrent MCI, AD, or other dementia)

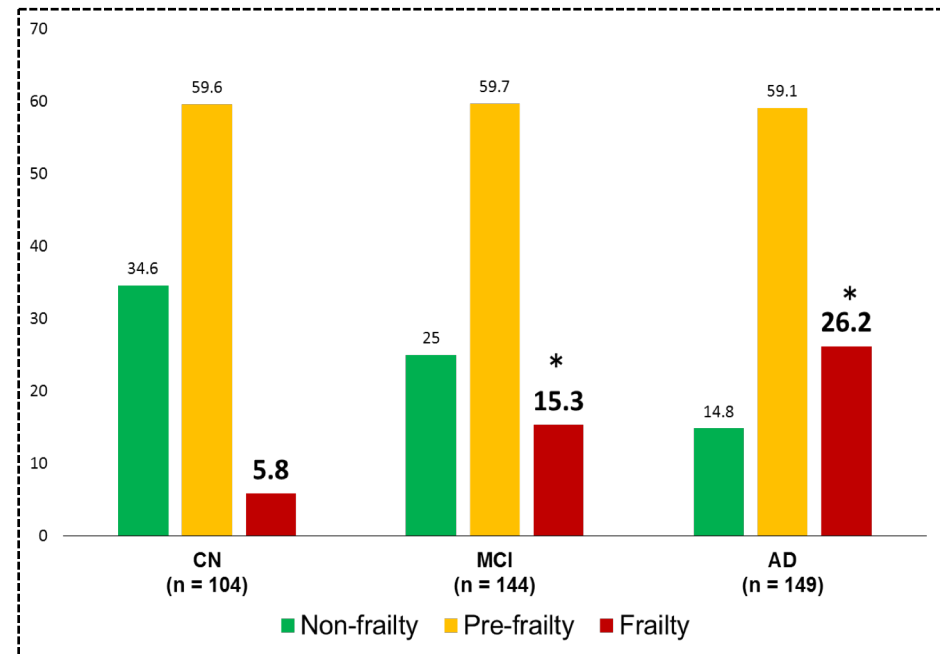


Prevalence of sarcopenia and frailty in people with cognitive impairment

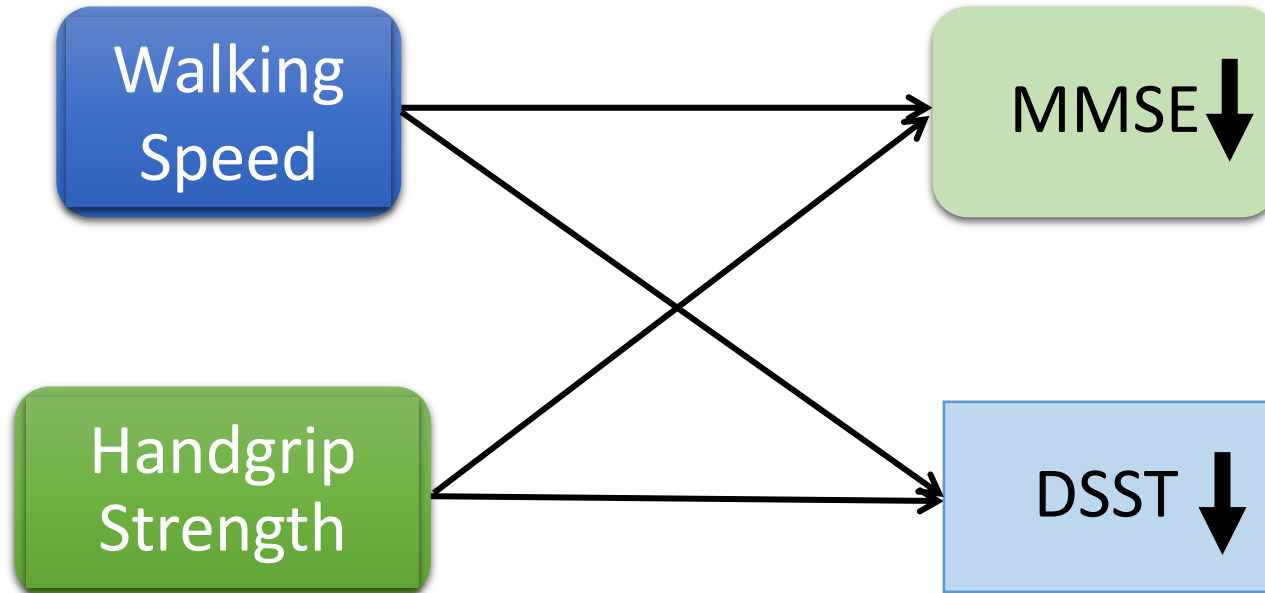
Sarcopenia



Frailty (CHS)

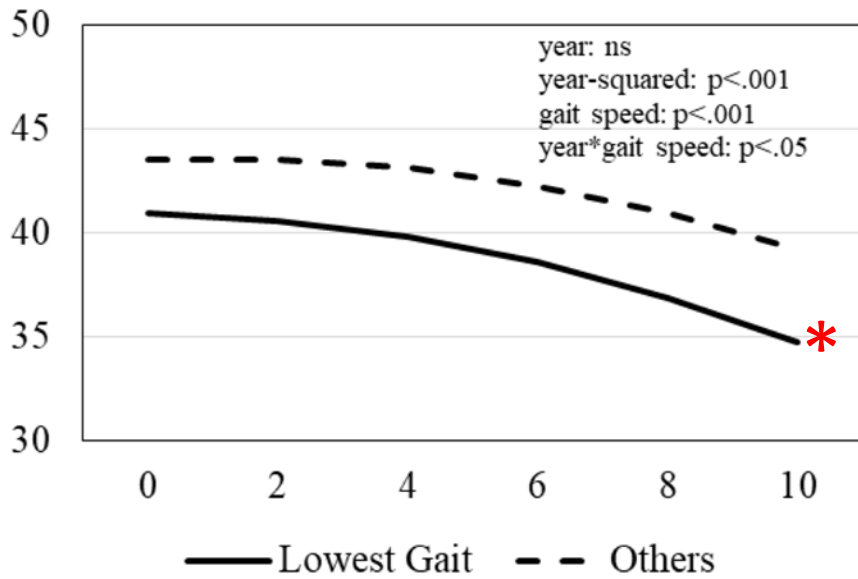


In this study

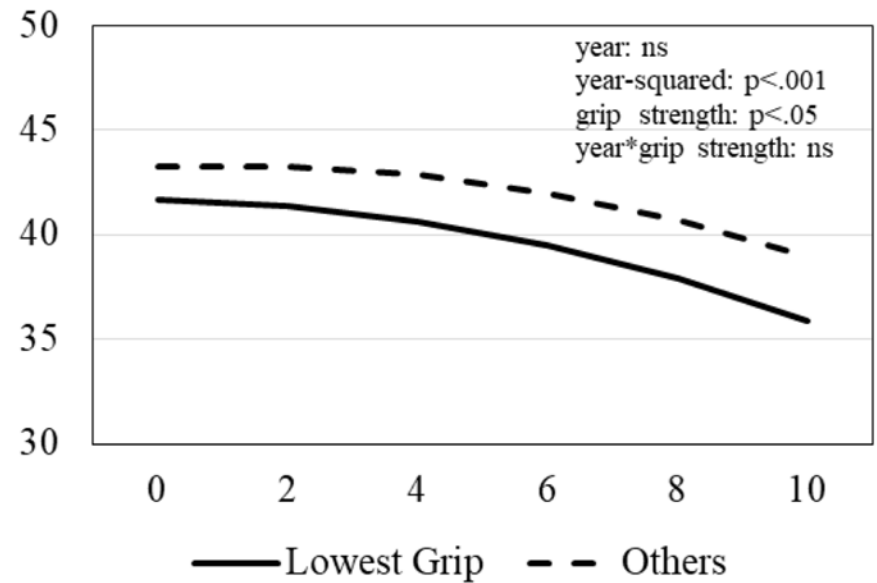


the main aim of this study was to evaluate the effects of **gait speed** and **handgrip strength** on **10-year cognitive changes** by using the **DSST** in addition to the **MMSE** among community-dwelling older people.

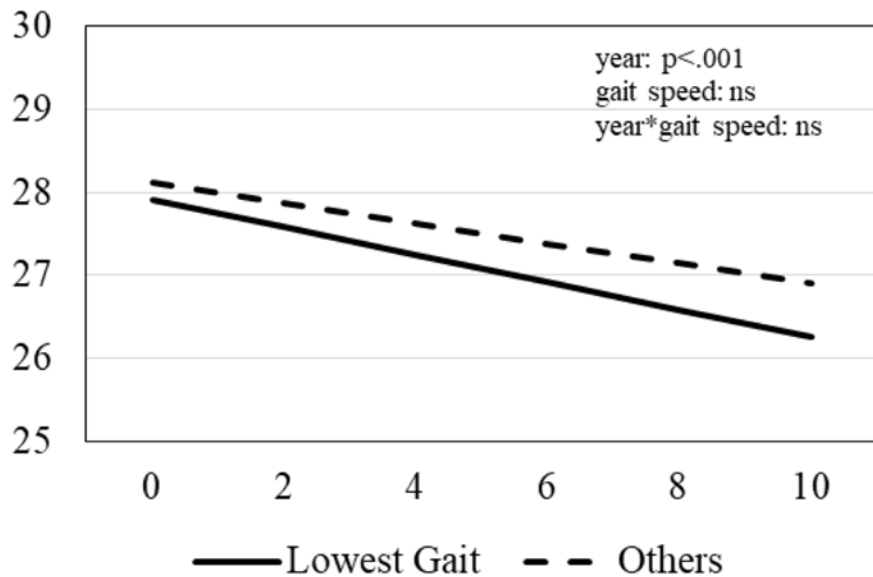
DSST



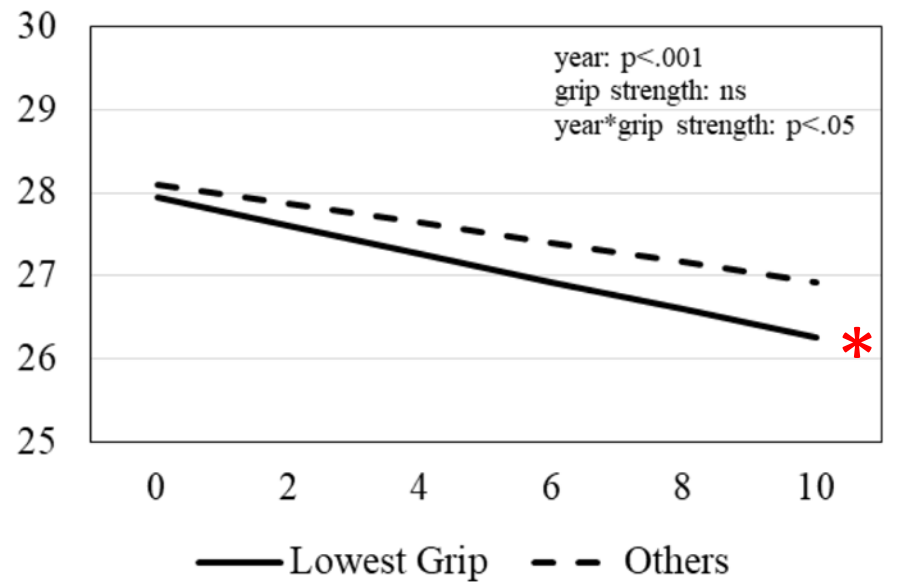
DSST



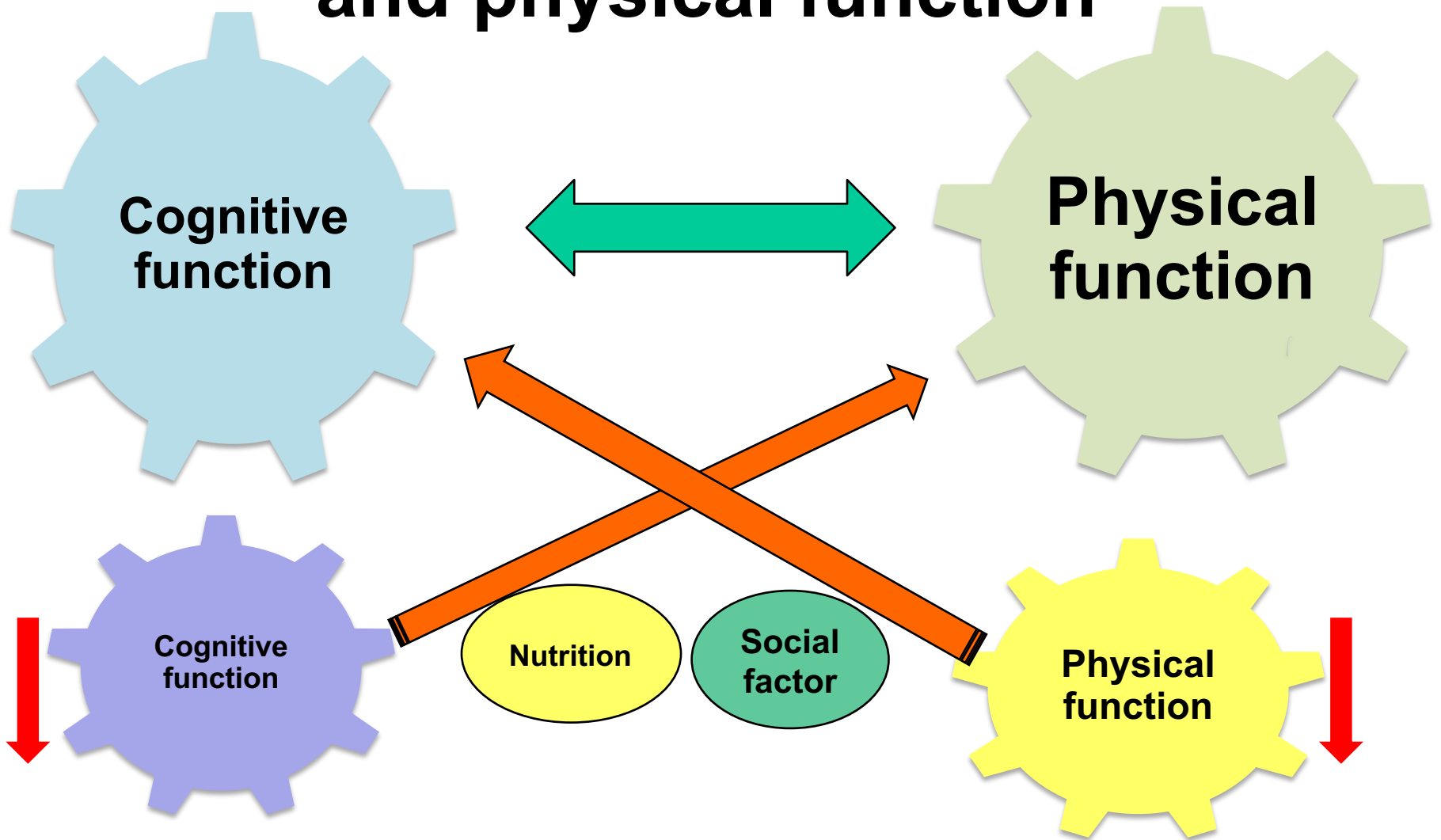
MMSE



MMSE



Interaction between cognitive and physical function



Results

【Physical frailty type】

Physical frailty group (Non-frail group; Pre-frail group; Frail group)

【The components of physical frailty】

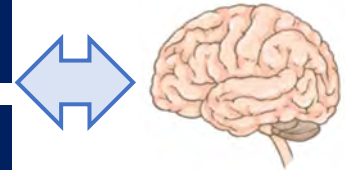
Weight loss: body weight loss $\geq 5\%$ in the prior 2 years

Weakness: grip strength < 26 kg in men and < 18 kg in women

Slowness: walking speed < 1.0 m/sec

Low physical activity: the lowest 20% of leisure-time physical activity

Exhaustion: CES-D questionnaire Q7 or Q20

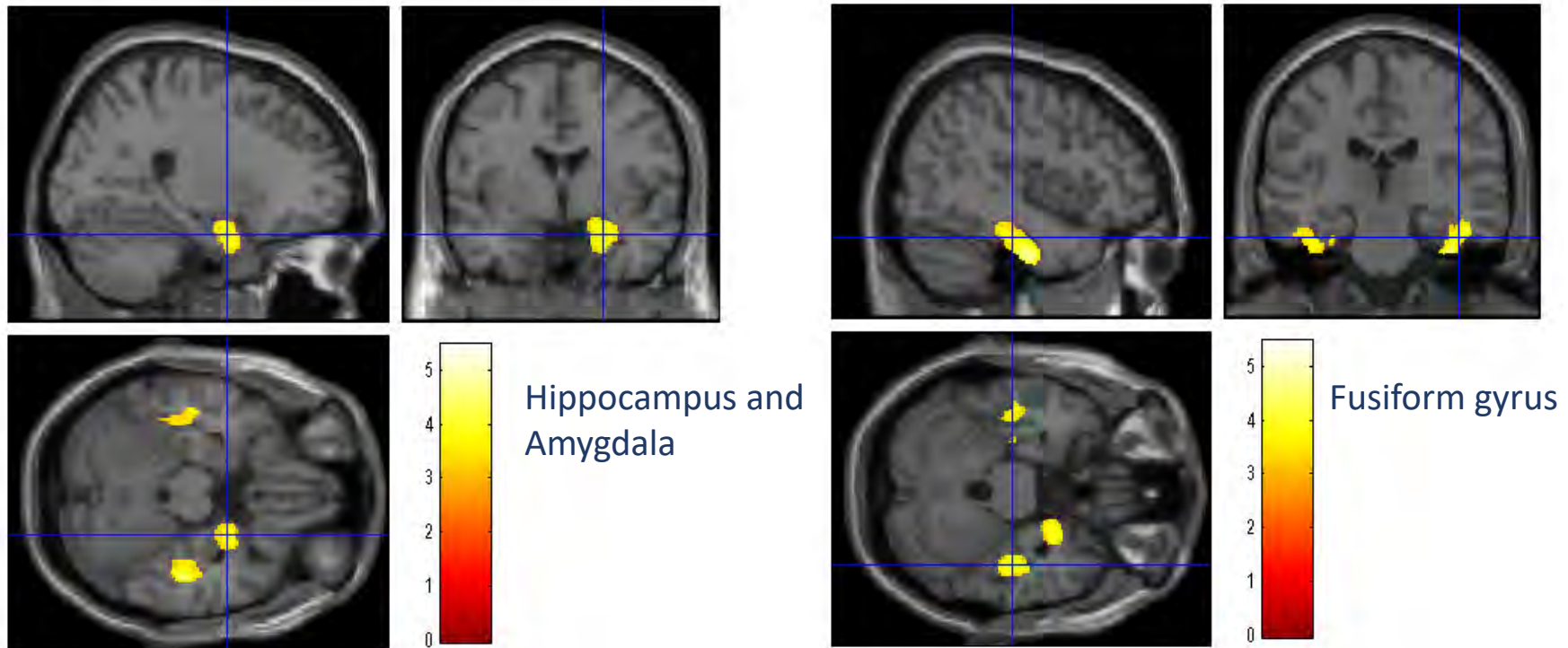


Results



Relationships between **weakness** and regional gray matter volume N=835 age:65-89

Definition of weakness: grip strength <26 kg in men and <18 kg in women



SPM adjusted for age, sex, and education

FWE corrected cluster $p < 0.05$, at height $p = 0.001$

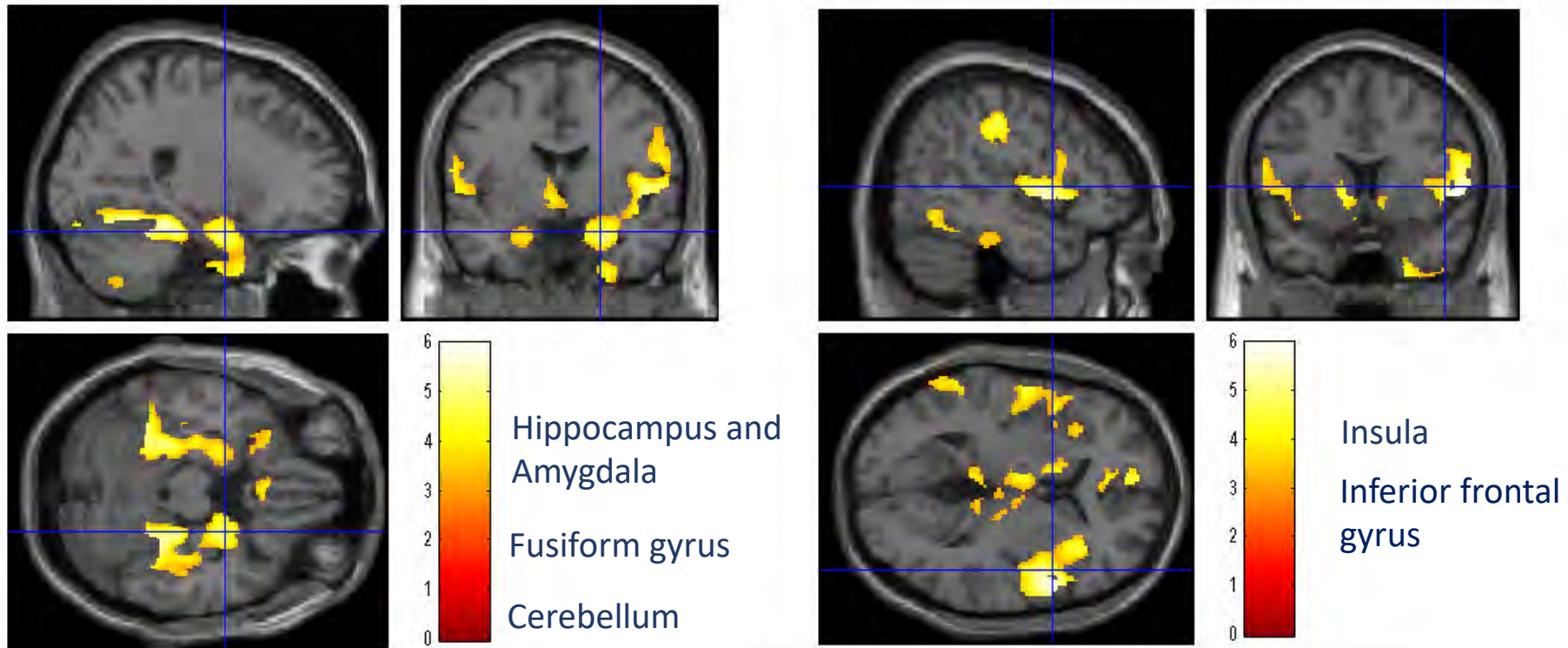
Nishita et al., *JAMDA*, in press

Results



Relationships between **slowness** and regional gray matter volume N=835 age:65-89

Definition of slowness: walking speed < 1.0 m/sec



SPM adjusted for age, sex, and education

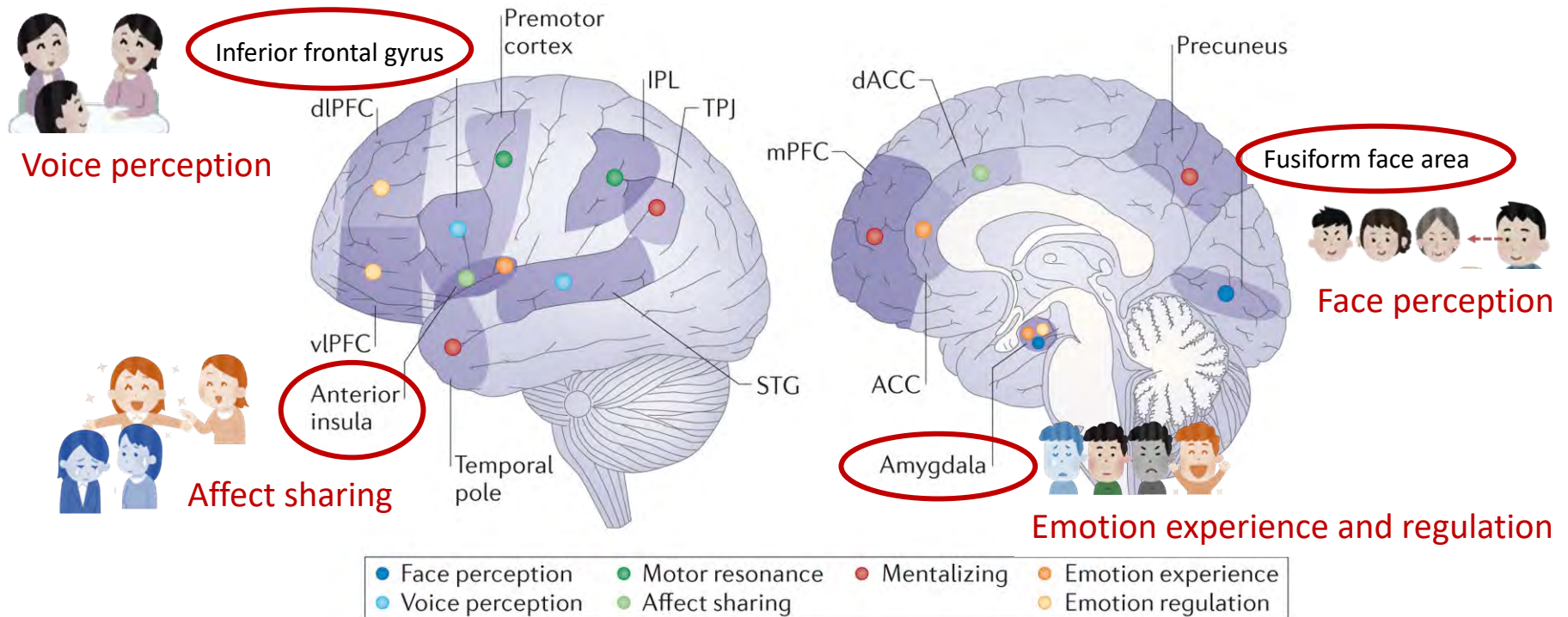
FWE corrected cluster $p < 0.05$, at height $p = 0.001$

Nishita et al., JAMDA, in press

Discussion

Which regions of the brain are closely related to physical frailty?

- Physical frailty, especially weakness and slowness, was associated with the smaller gray matter volumes in the *hippocampus*, *amygdala*, *fusiform gyrus*, *inferior frontal gyrus* and *insula*.



Brain regions associated with social processes. Green et al., Nature reviews, 2015

- Physical frailty is likely to link with brain regions associated with social processes involving *social frailty*.

Conclusions

- **The progression of physical frailty, such as low grip strength and slow gait speed, are associated with a decrease of regional brain volumes related to cognition and social processes.**
- **Further longitudinal studies are needed to clarify the details mechanisms of causal relationships.**