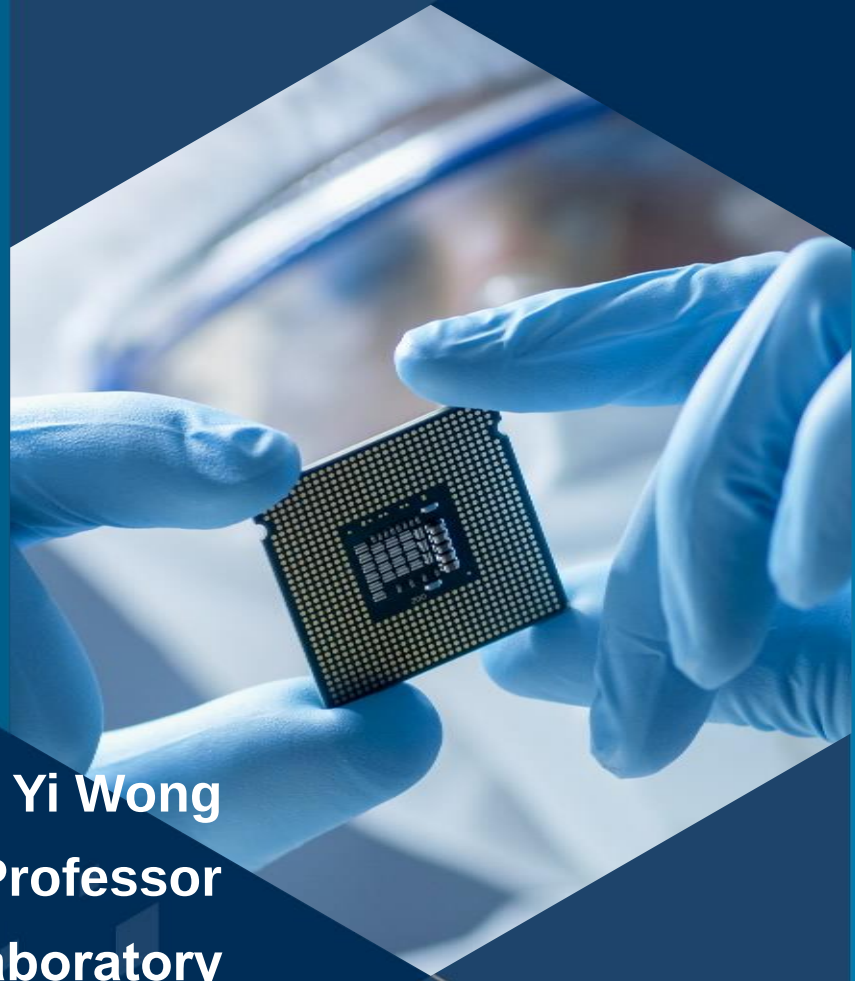
Regulation of microglial functions by IL-33/ST2 signaling: Finding therapeutic targets for Alzheimer's disease



Anna Hiu Yi Wong

Research Assistant Professor

Professor Nancy Ip's Laboratory

The Hong Kong University of Science and Technology

22nd Feb 2023

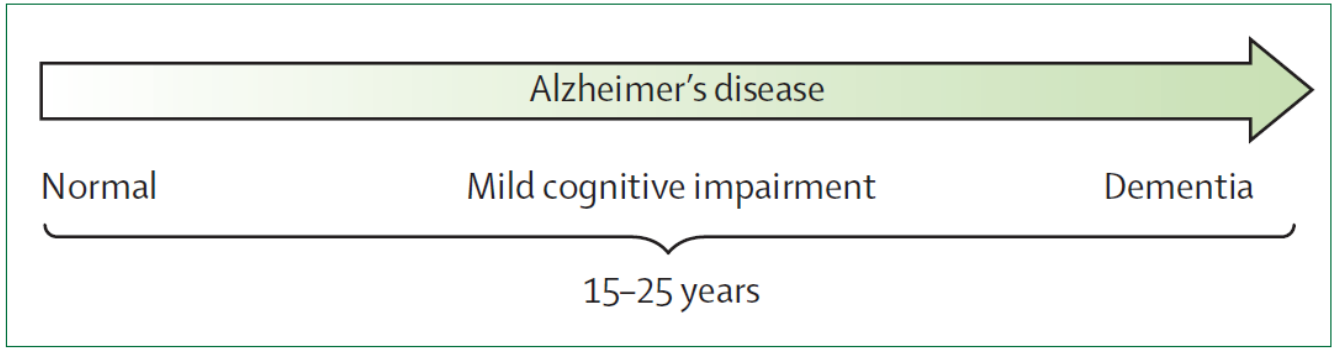
香港科技大學
THE HONG KONG UNIVERSITY OF SCIENCE AND TECHNOLOGY

Topics to be covered:

- Epidemiology, risk factors, clinical presentation, and current treatment modalities of Alzheimer's disease (AD)
- Local data on how patients with AD are managed in Hong Kong
- Pathophysiology of AD and role of microglia
- How IL-33/ST2L signaling regulates microglial function and amyloid pathology
- Recent findings demonstrating plasma soluble ST2 as a novel biomarker and therapeutic target of AD

Alzheimer's disease

- Commonest cause of dementia in the elderly
- One of the most common neurodegenerative diseases
- Characterized by progressive memory loss, cognitive impairment, and neuropsychiatric symptoms
- Early-onset AD vs. late-onset AD (i.e., age > 65 years)
- Gradual decline in cognition and impairment of daily activities (i.e., mild-to-moderate to severe stages of AD)
- AD is a continuum and can progress for as long as 25 years



Scheltens et al., Lancet. 2021.

Alzheimer's disease: Epidemiology

Estimated global prevalence in 2040: 82.1 million[1]

	WHO region	Dementia prevalence in people over 60 years old (%)	Number of people over 60 years old who have dementia (millions)		
			2000	2020	2040
Western Europe	EURO A	5·4	4·9	6·9	9·9
Eastern Europe low adult mortality	EURO B	3·8	1·0	1·6	2·8
Eastern Europe high adult mortality	EURO C	3·9	1·8	2·3	3·2
North America	AMRO A	6·4	3·4	5·1	9·2
Latin America	AMRO B/D	4·6	1·8	4·1	9·1
North Africa and middle eastern crescent	EMRO B/D	3·6	1·0	1·9	4·7
Developed western Pacific	WPRO A	4·3	1·5	2·9	4·3
China and the developing western Pacific	WPRO B/D	4·0	6·0	11·7	26·1
Indonesia, Thailand, and Sri Lanka	SEARO B	2·7	0·6	1·3	2·7
India and south Asia	SEARO D	1·9	1·8	3·6	7·5
Africa	AFRO D/E	1·6	0·5	0·9	1·6
Total		3·9	24·3	42·3	81·1

Reproduced from Ferri et al,[2] by permission of Elsevier.

***Table 1*: Estimates of dementia prevalence worldwide according to the Delphi consensus study in 2005**

- In China, more than 7 million were living with AD in 2018[2]
- Annual cost per person with AD: ~USD 20,000; total annual socioeconomic costs: ~USD 167 billion[3]

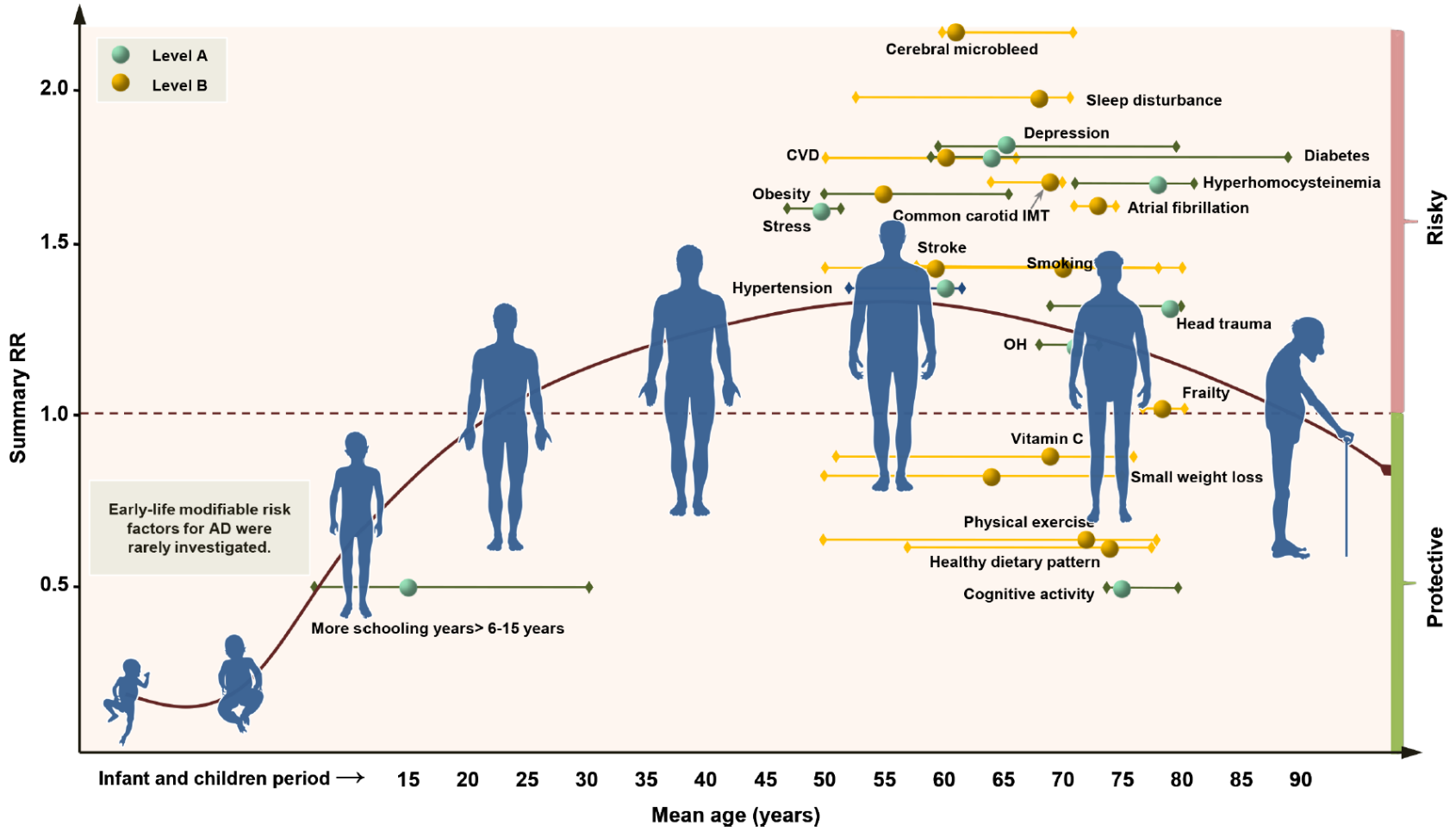
- In the United States, ~6.5 million people were living with AD in 2022[4]
- Annual cost per person with AD: ~USD 40,000[4]

- Prevalence and socioeconomic burden expected to increase with global population aging

[1]Ferri et al., Lancet. 2005; [2]Scheltens et al., Lancet. 2021; [3]Jia et al., Alzheimers Dement. 2018; [4] 2022 Alzheimer's disease facts and figures.

Alzheimer's disease: Associated risk and protective factors

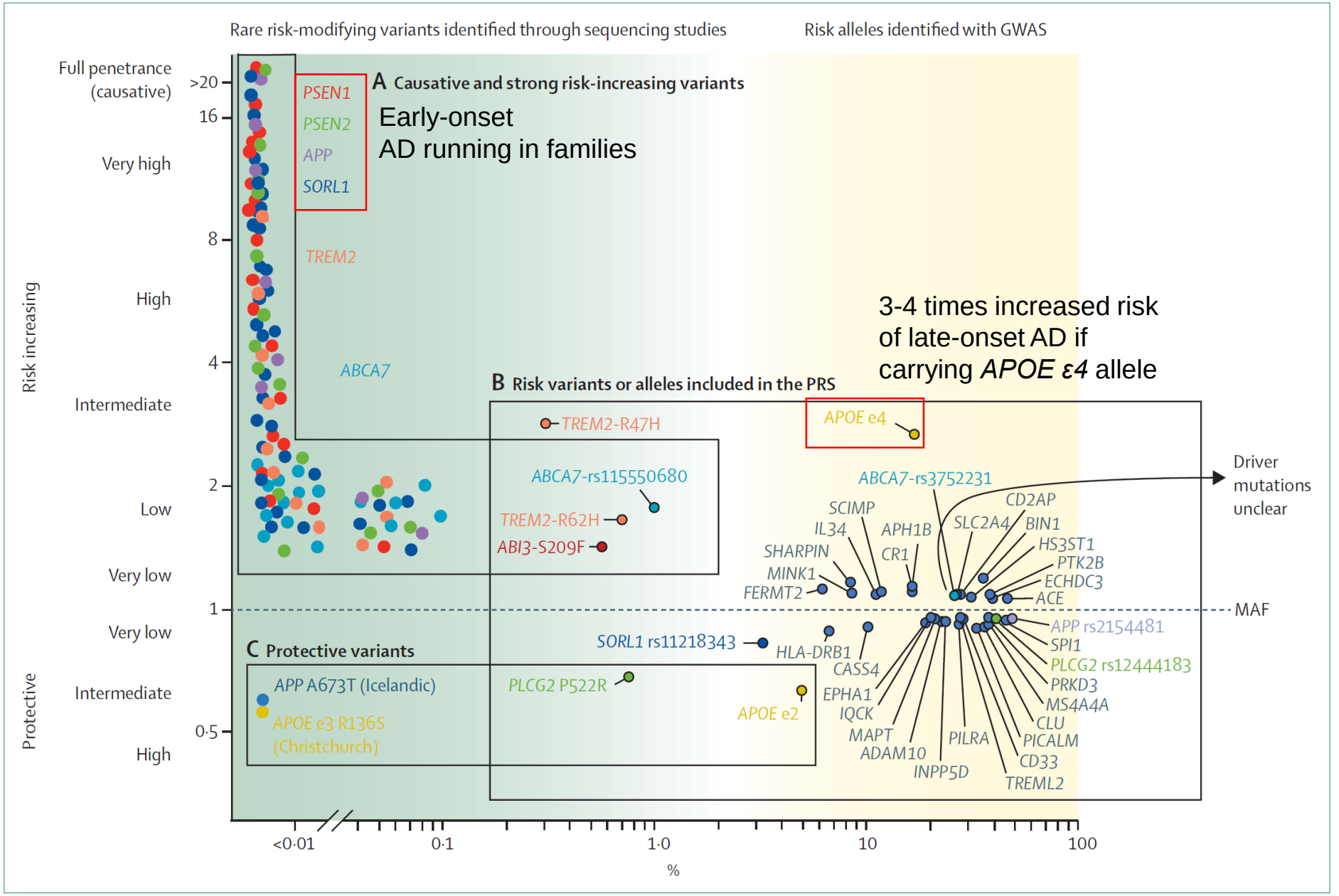
- Advanced age is strongest risk factor
- Female sex (vs. male)
- Lifestyle factors: smoking, obesity, physical inactivity, and alcohol intake
- Medical conditions: hypertension, diabetes, stroke, hypercholesterolemia, and vitamin B12 and folate deficiency



Yu et al., Cogn. Neurol. 2020.

Alzheimer's disease: Causative and risk genes

- Twin studies showing that AD risk is 60–80% dependent on heritable factors
- Genome-wide association studies (GWASs) identify risk and protective genes associated with AD
- AD is associated with genes that modulate amyloid metabolism, immune response, lipid dysfunction, endocytosis, and vascular factors



Scheltens et al., Lancet. 2021.

Alzheimer's disease: Clinical presentation

- **Episodic memory loss**
  - ✓ Forgetting recent events (immediate recall)
  - ✓ Misplacing personal items
  - ✓ Asking repetitive questions
  - ✓ Missing appointments

- **Cognitive impairment**
  - ✓ Visuospatial: navigational problems, problems recognizing faces and objects
  - ✓ Language: difficulty retrieving words, problems comprehending words
  - ✓ Executive functions: problems organizing and maintaining focus, difficulty reasoning, poor judgement
  - ✓ Other: problems with calculations, disoriented perception of time and space

- **Neuropsychiatric**
  - ✓ Mood disorders: depression, anxiety, agitation
  - ✓ Delusions and hallucinations
  - ✓ Changes in personality
  - ✓ Loss of apathy and poor hygiene

Rabinovici et al., Continuum. 2019.

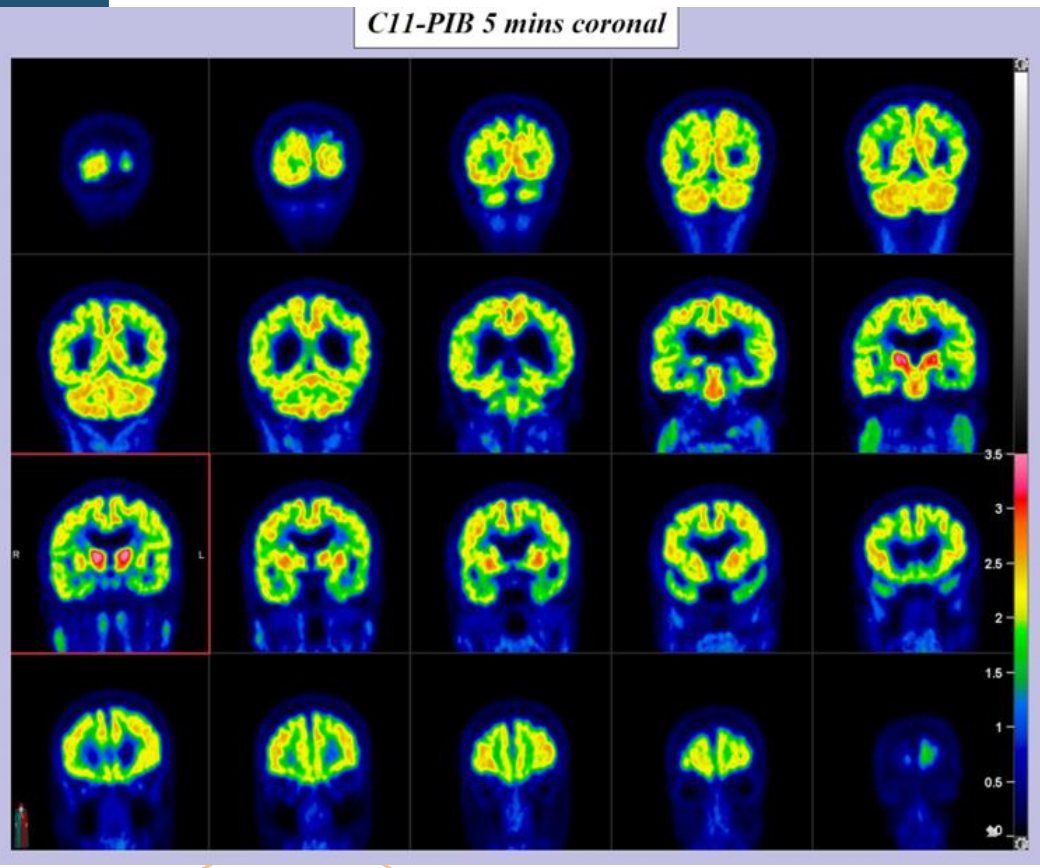
Alzheimer’s disease: Diagnostic criteria

- Definitive diagnosis can only be made postmortem by studying the pathological hallmarks of AD
- **NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association) criteria:**
  - Probable diagnosis based on clinical presentation (i.e., core diagnostic criteria)
  - Assessment of memory and cognitive domains by validated scoring systems
  - Exclusion of other reversible causes of dementia and other neurodegenerative diseases
  - Supportive radiological evidence from computed tomography (CT) and magnetic resonance imaging (MRI) to identify AD-related pathologies and brain volume loss
  - Supportive evidence from validated cerebrospinal fluid and blood biomarkers to reflect brain pathologies in AD

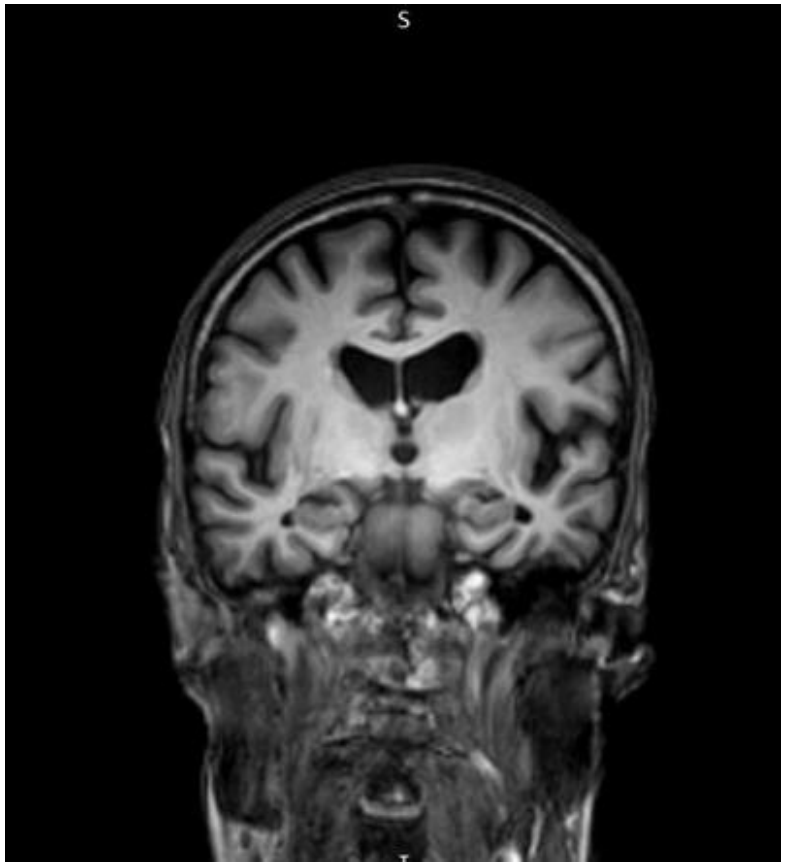
Dubois et al., Lancet Neurol. 2007.

Alzheimer’s disease: Diagnosis based on radiological findings

^{11}C-PiB PET scan

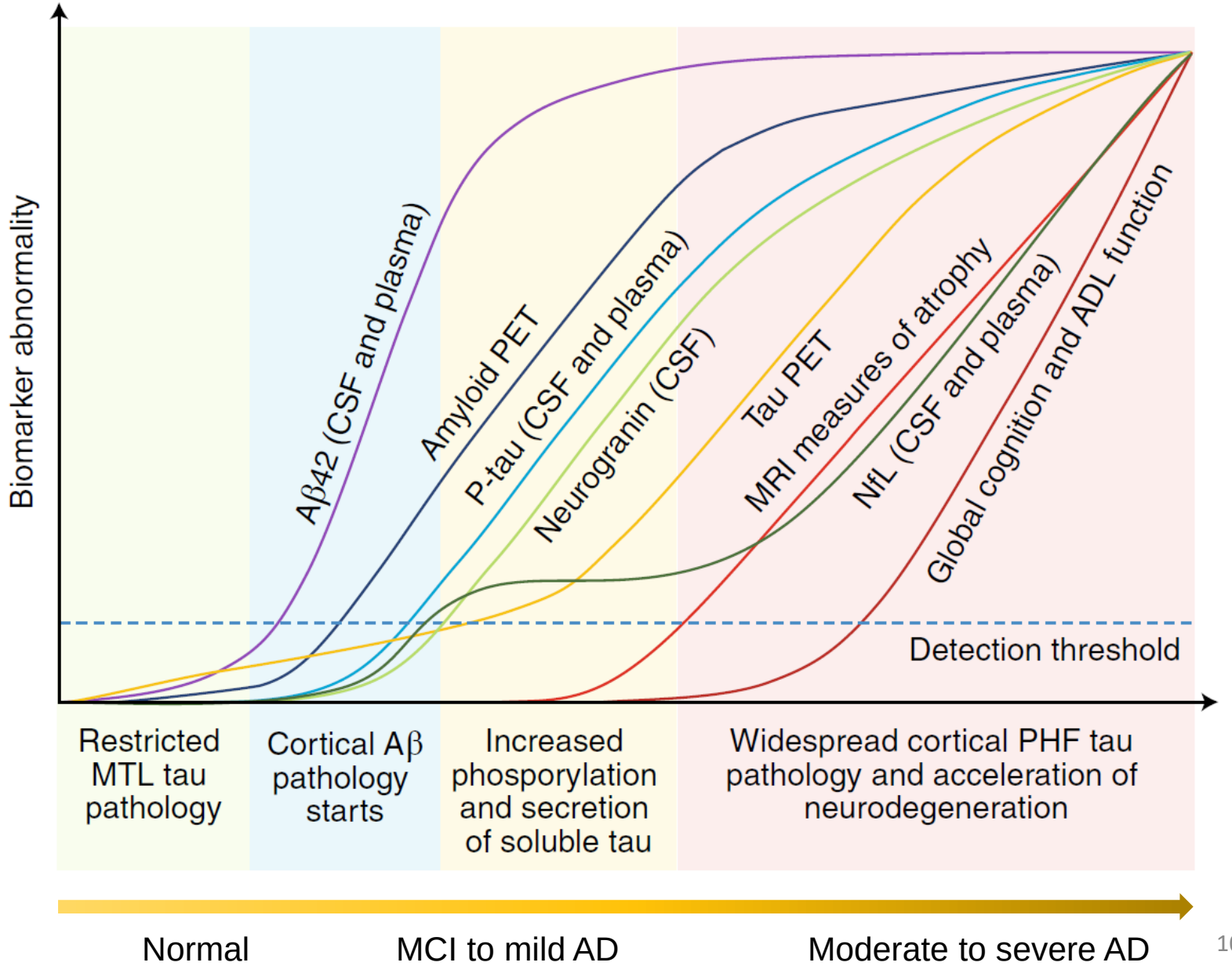


MRI brain



Alzheimer's disease: Diagnosis based on biomarkers

- Many biomarkers of AD pathologies and neurodegeneration can be detected in the cerebrospinal fluid and blood
- Biomarker levels change with disease progression



Hansson, Nat Medicine. 2021.

Alzheimer's disease: Treatment by medication

- **Symptomatic**

✓Cholinesterase inhibitors: donepezil, rivastigmine, galantamine

✓NMDA receptor antagonist: memantine

- **Neuropsychiatric symptoms**

✓Atypical antipsychotics

✓Antidepressants

✓Anticonvulsants

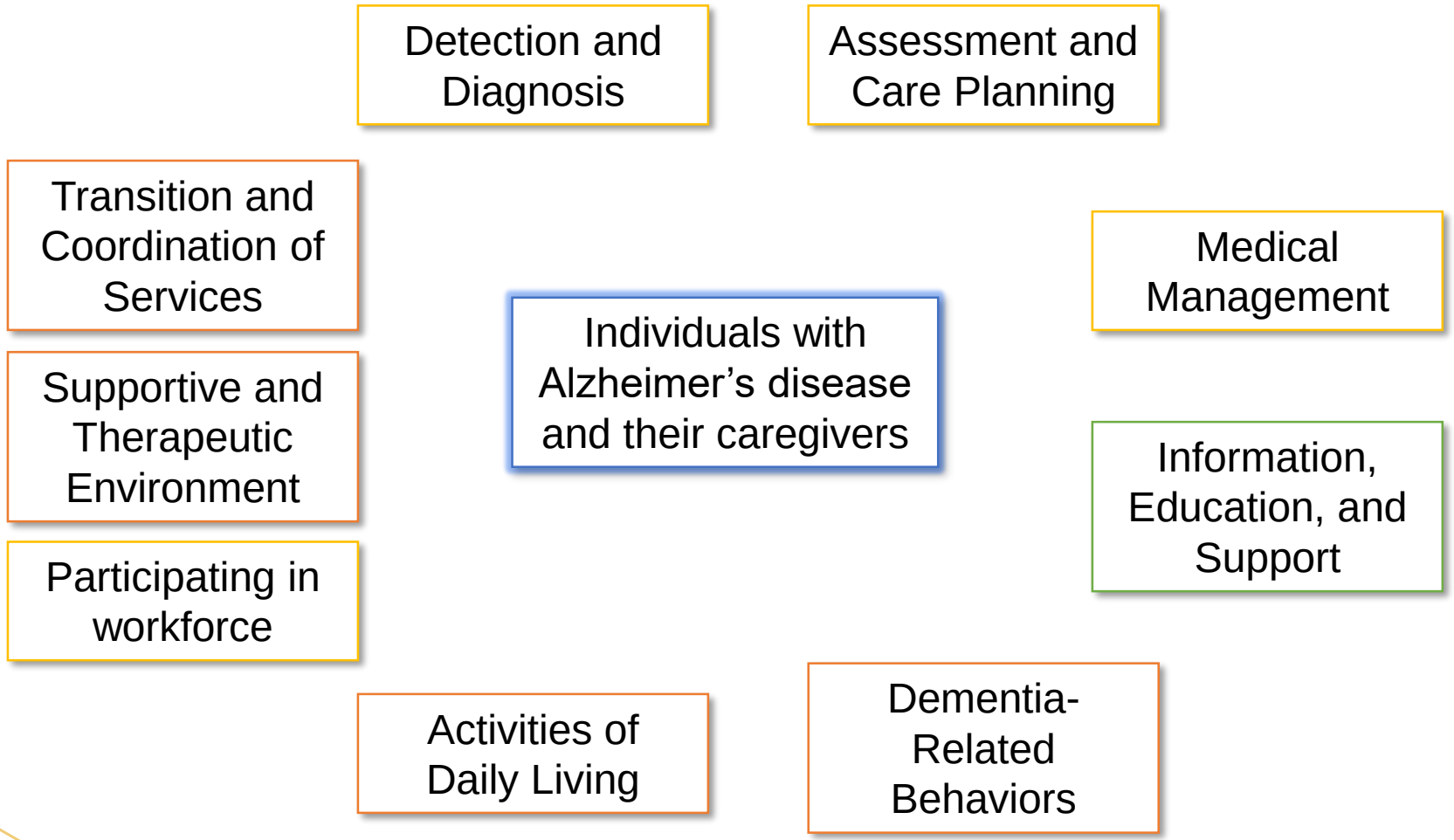
- **Disease-modifying treatments**

✓Passive immunotherapy: aducanumab

✓Active immunotherapy and amyloid/tau aggregators (still in clinical trials)

In Hong Kong and prescribed to patients by specialists (i.e., neurologists, geriatricians, and psychiatrists)

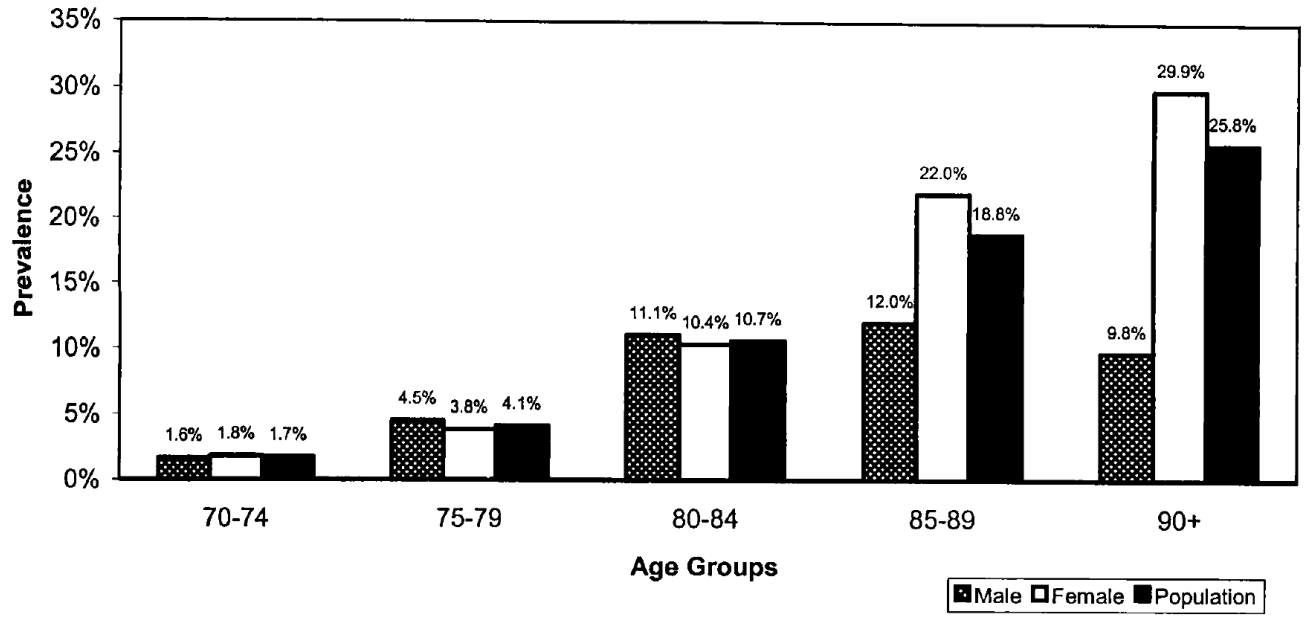
Alzheimer’s disease: Psychological, social, and family support



Adapted from Alzheimer's Association: Dementia Care Practice Recommendations.

Alzheimer’s disease in Hong Kong

Alzheimer's disease in Hong Kong: Local prevalence



- Estimated to affect 7.2% of the local population
- AD prevalence increases with age
- Female predominance
- AD risk increases with age, female sex, and cardiovascular risk factors

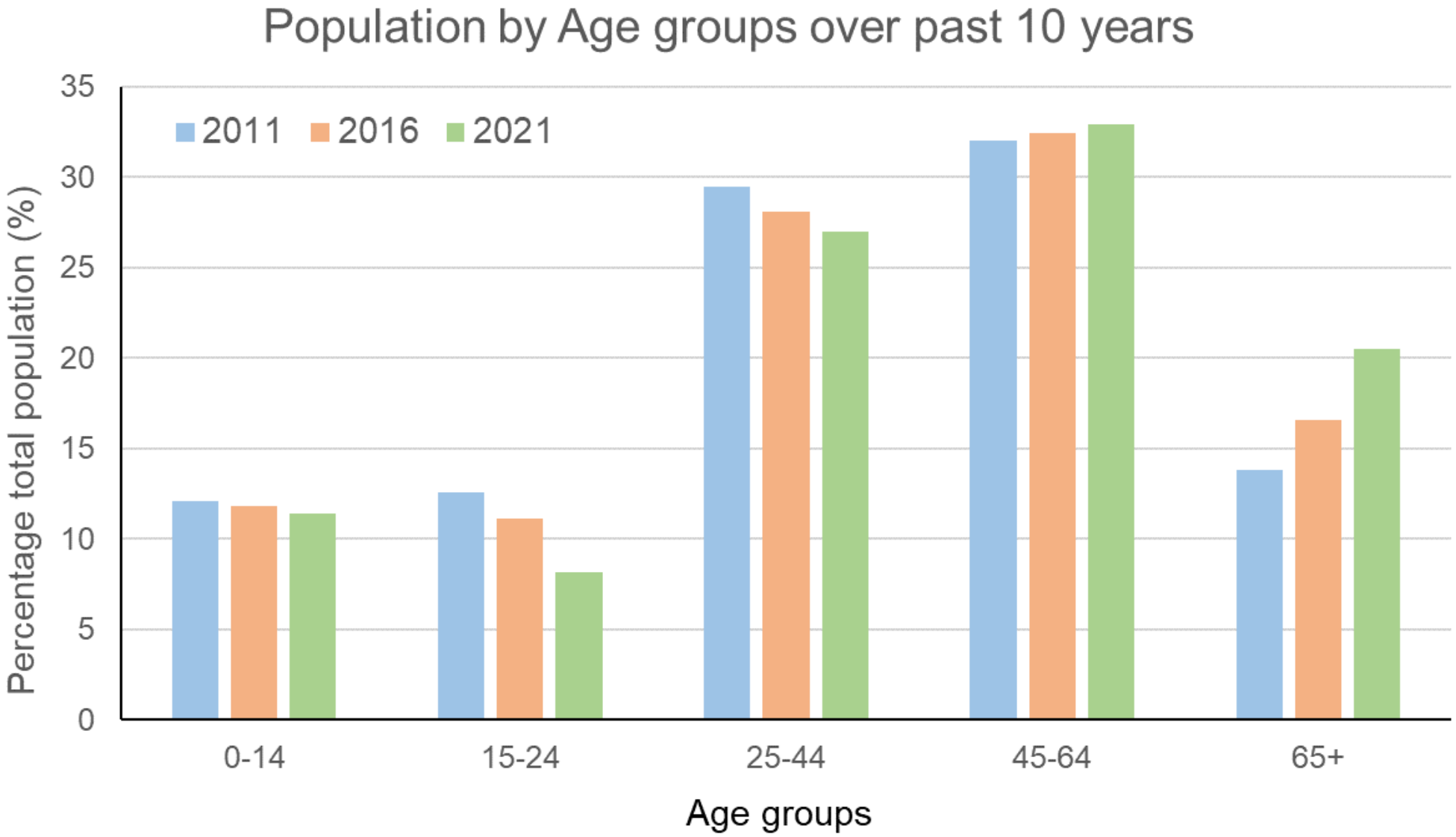
Table 4. Logistic regression analyses of demographic and physical health factors in differentiating subjects with normal cognition from very mild and mild dementia

	VERY MILD DEMENTIA	MILD DEMENTIA (CDR 1)
Age*†		
OR	1.13	1.16
95% CI	1.09–1.18	1.11–1.21
Sex		
OR	1.33	1.29
95% CI	0.75–2.35	0.72–2.33
Education*†		
OR	0.85	0.72
95% CI	0.79–0.91	0.65–0.80
Significant CVRFs		
OR	1.21	1.20
95% CI	0.97–1. 51	0.97–1.47
Exercise (SE)*		
OR	0.59	0.55
95% CI	0.33–1.09	0.30–1.0
Exercise (AE)*		
OR	0.34	0.23
95% CI	0.12–1.02	0.07–0.81
Exercise (MB)*†		
OR	0.23	0.34
95% CI	0.07–0.76	0.12–0.97

OR, odds ratio; CI, confidence interval; *significant risk factor differentiating subjects with CDR 0 from mild dementia; †significant risk factor differentiating subjects with CDR 0 from those with very mild dementia $p < 0.05$; exercise (with reference to no exercise), SE = stretching exercise, AE = aerobic exercise, MB = mind body exercise.

Chiu et al., Neurology. 1998; Lam et al., Int. Psychogeriatrics. 2008.

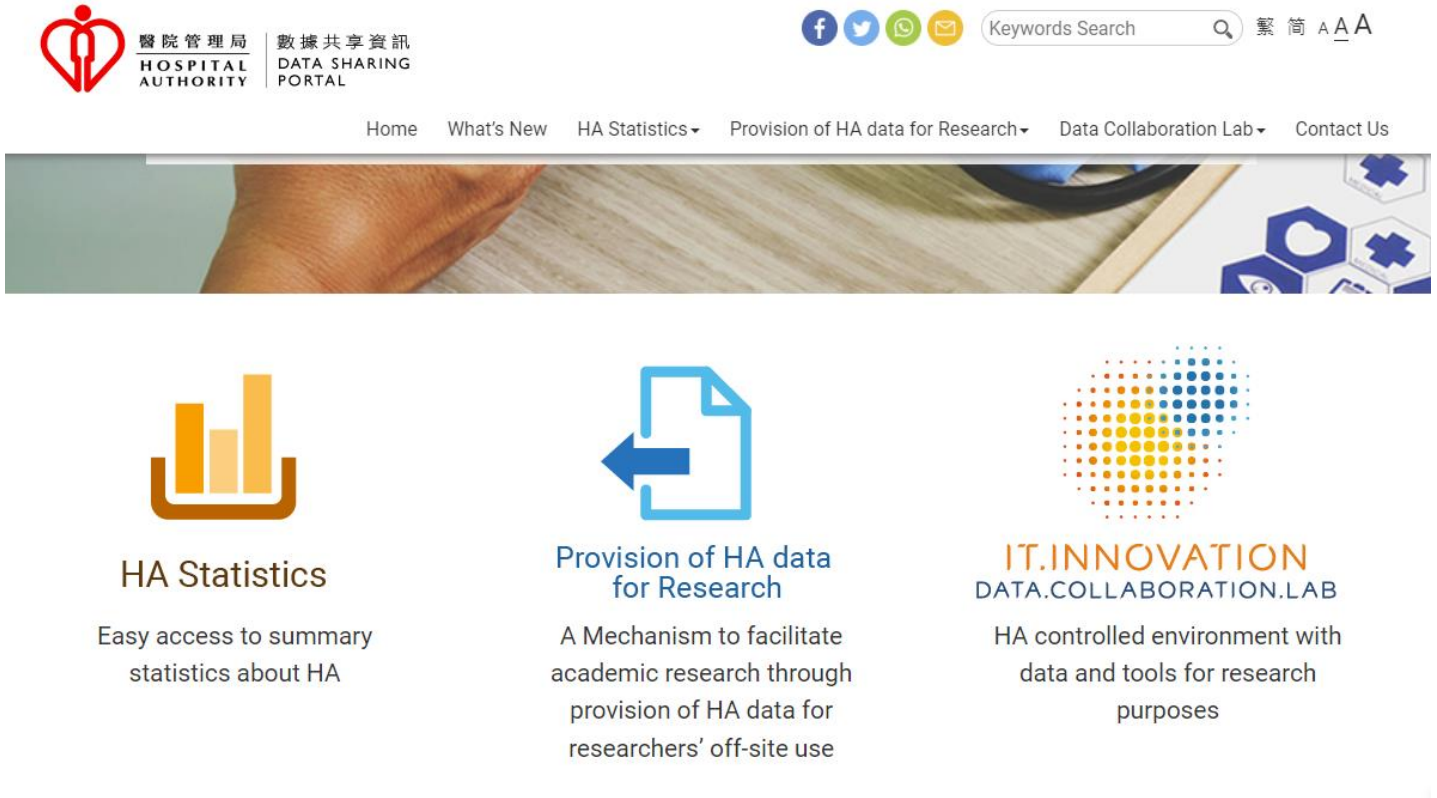
Alzheimer's disease in Hong Kong: Population aging



Population Census Summary Results 2021, Census and Statistics Department, Hong Kong Special Administrative Region.

Alzheimer's disease: Big data analysis

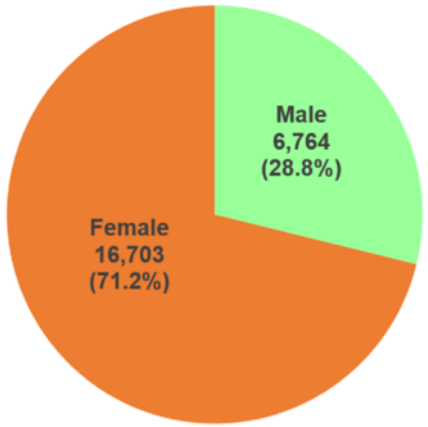
- Collaborative study with Data Collaboration Lab of the Hospital Authority
- Big Data Analytics Platform: Enables researchers to access demographic data, clinical records, diagnoses, investigations, and medication records of patients under the care of the Hospital Authority between January 1, 2007 and December 31, 2017



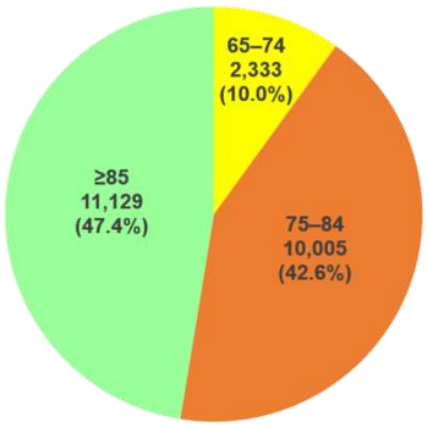
Wong et al., J. Alz. Dis. 2022; https://www3.ha.org.hk/data/Home/Index/

Alzheimer's disease in Hong Kong: Demographics

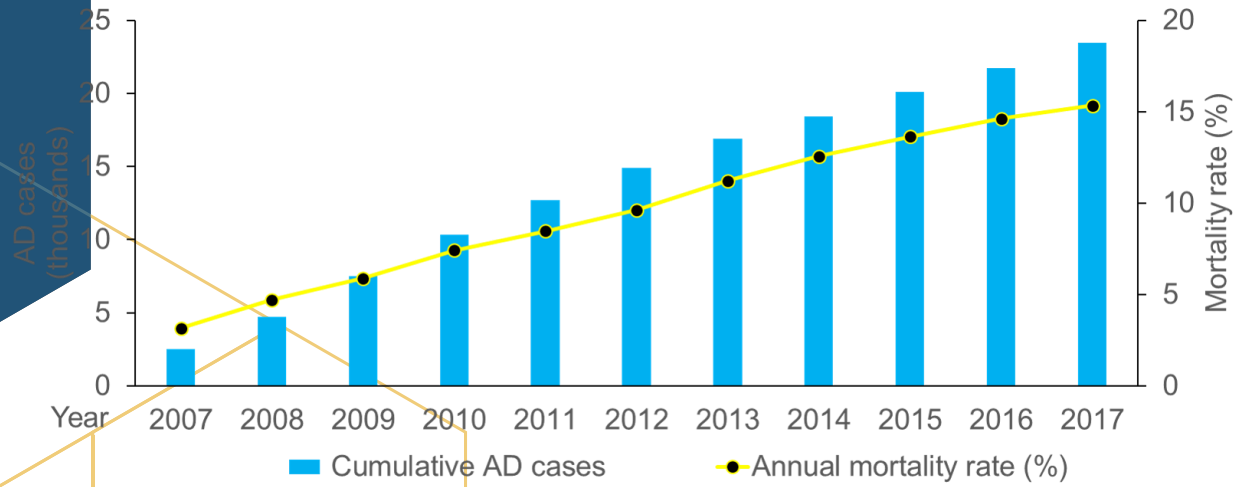
Identified 23,467 patients with AD (10-year period)



Sex distribution



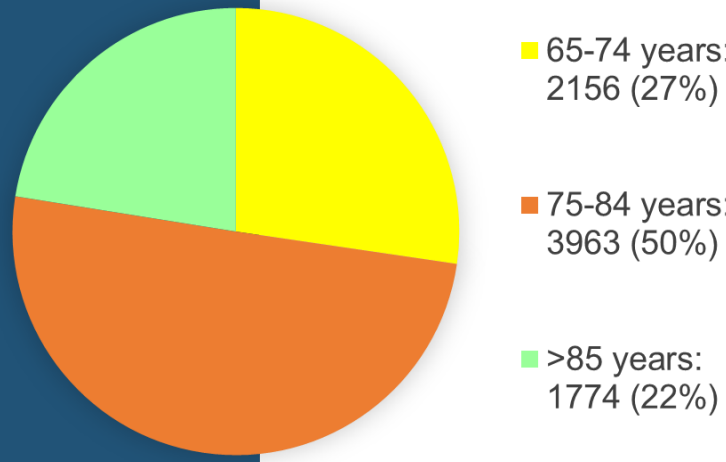
Age at AD onset



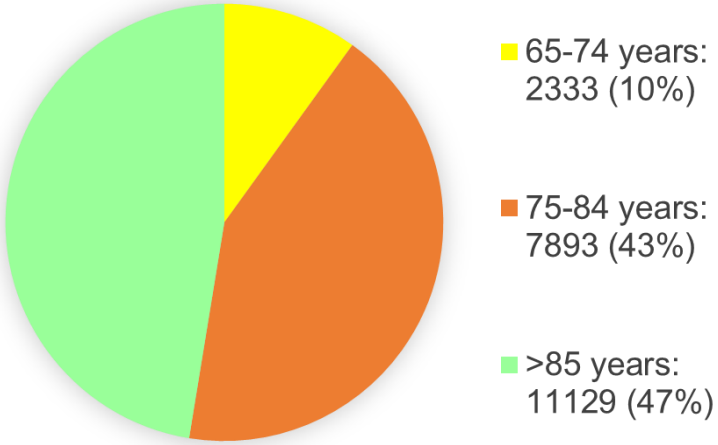
Cause of death (Top 10)	Number (%)
Pneumonia	1,954 (54.3)
Acute myocardial infarction	203 (5.6)
Cancers	192 (5.3)
Sepsis	125 (3.5)
Congestive heart failure	116 (3.2)
Cerebrovascular accident	112 (3.1)
Urinary tract infections	104 (2.9)
Renal failure	72 (2.0)
Infected bedsores	65 (1.8)
Gastrointestinal bleeding	55 (1.5)

Wong et al., J. Alz. Dis. 2022.

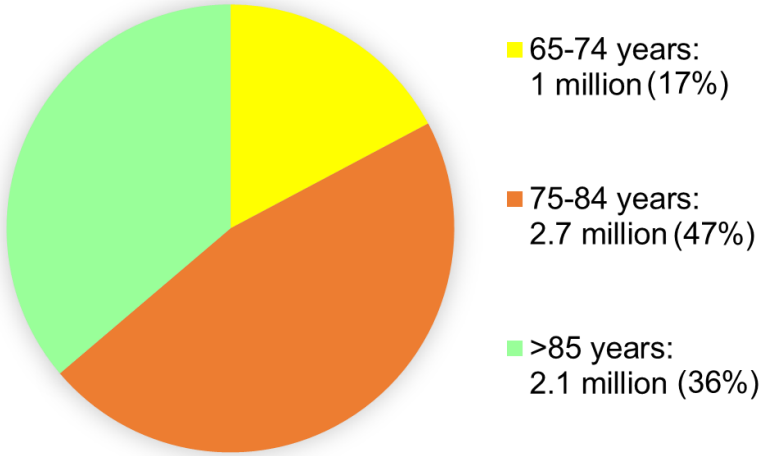
Alzheimer's disease in Hong Kong: Comparison with other cohorts



Taiwan (*n* = 7,893)



Hong Kong (*n* = 23,467)



*USA (*n* = 5.8 million)

Study	Our cohort	Leung et al.	Yang et al.	Jia et al.	Hung et al.	Sekita et al.	Imfeld et al.
City/Country	Hong Kong	Hong Kong	Hong Kong	China	Taiwan	Japan	UK
Year	2017	2013	2014	2014	2016	2010	2013
Female:Male Ratio	71%:19%	72%:18%	73%:17%	58%:42%	54%:46%	73%:17%	69%:31%
Patient group	AD	AD	AD	Dementia	AD	Dementia	AD

**2020 Alzheimer's disease facts and figures.*

Alzheimer's disease in Hong Kong: Medical conditions and medication use

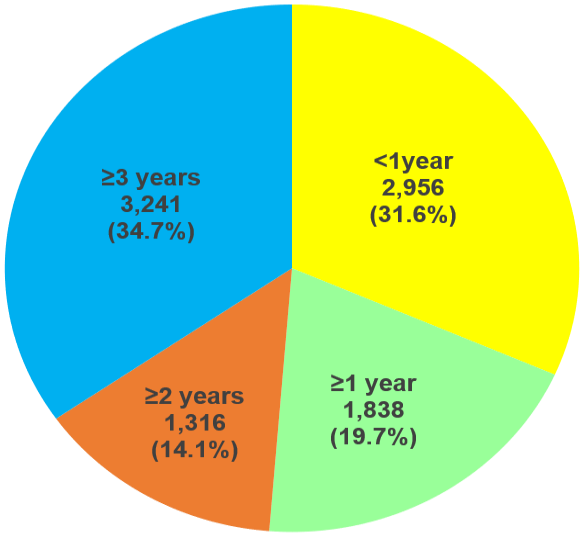
Comorbidities	*n* (%)
Hypertension	12,343 (52.6)
Diabetes mellitus	10,969 (46.7)
Hyperlipidemia	2,501 (10.7)
Cerebrovascular accident	4,148 (17.7)
Coronary heart diseases	2,833 (12.1)
Cancers	2,682 (11.4)
Chronic renal diseases	4,409 (18.8)
Chronic respiratory diseases	2,650 (11.3)
Chronic liver diseases	1,039 (4.4)

Medication	*n* (%)
Drugs for dementia	9,351 (39.9)
Drugs for hypertension	15,813 (67.4)
Drugs for diabetes	5,215 (22.2)
Lipid-regulating drugs	6,216 (26.5)
Antiplatelets	9.856 (42.0)
Antipsychotics	11,895 (50.7)
Antidepressants	9,457 (40.3)
Hypnotics	6,819 (29.1)

Wong et al., J. Alz. Dis. 2022.

Alzheimer's disease in Hong Kong: Medication use

- A total of 9,351 patients with AD had history of taking AD medication (39.9%)
- Comparison of the demographics and medication history of long-term AD medication users and nonusers:



Duration of AD medication intake

Long-term AD medication users: total duration of medication intake ≥ 1 year

	AD medication nonusers Number (%)	AD medication long-term users Number (%)	*p* values
Total	13,077	6,395	
Male	3,692 (28.2)	1,815 (28.4)	0.84
Female	9,385 (71.8)	4,580 (71.6)	
Median age at diagnosis	86	82	**<0.001**
Medication			
Drugs for hypertension	9,273 (70.9)	4,570 (71.5)	0.44
Calcium-channel blockers	7,098 (54.3)	3,678 (57.5)	**<0.001**
ACEI	3,748 (28.7)	1,873 (29.3)	0.37
Beta-adrenoceptor blocking drugs	3,307 (25.3)	1,566 (24.5)	0.23
Drugs for diabetes	2,863 (21.9)	1,633 (25.5)	**<0.001**
Oral hypoglycemic drugs	2,416 (18.5)	1,548 (24.2)	**<0.001**
Insulins	1,416 (10.8)	580 (9.1)	**<0.001**
Lipid regulating drugs	2,832 (21.7)	2,405 (37.6)	**<0.001**
Antiplatelets	5,763 (44.1)	2,865 (44.8)	0.34
Antipsychotics	7,366 (56.3)	3,133 (49.0)	**<0.001**
Antidepressants	5,375 (41.1)	2,886 (45.1)	**<0.001**
Hypnotics	4,113 (31.5)	1,938 (30.3)	0.11

Abbreviation: ACEI: angiotensin-converting enzyme inhibitors

Wong et al., J. Alz. Dis. 2022

Alzheimer's disease in Hong Kong: Medications for neuropsychiatric symptoms

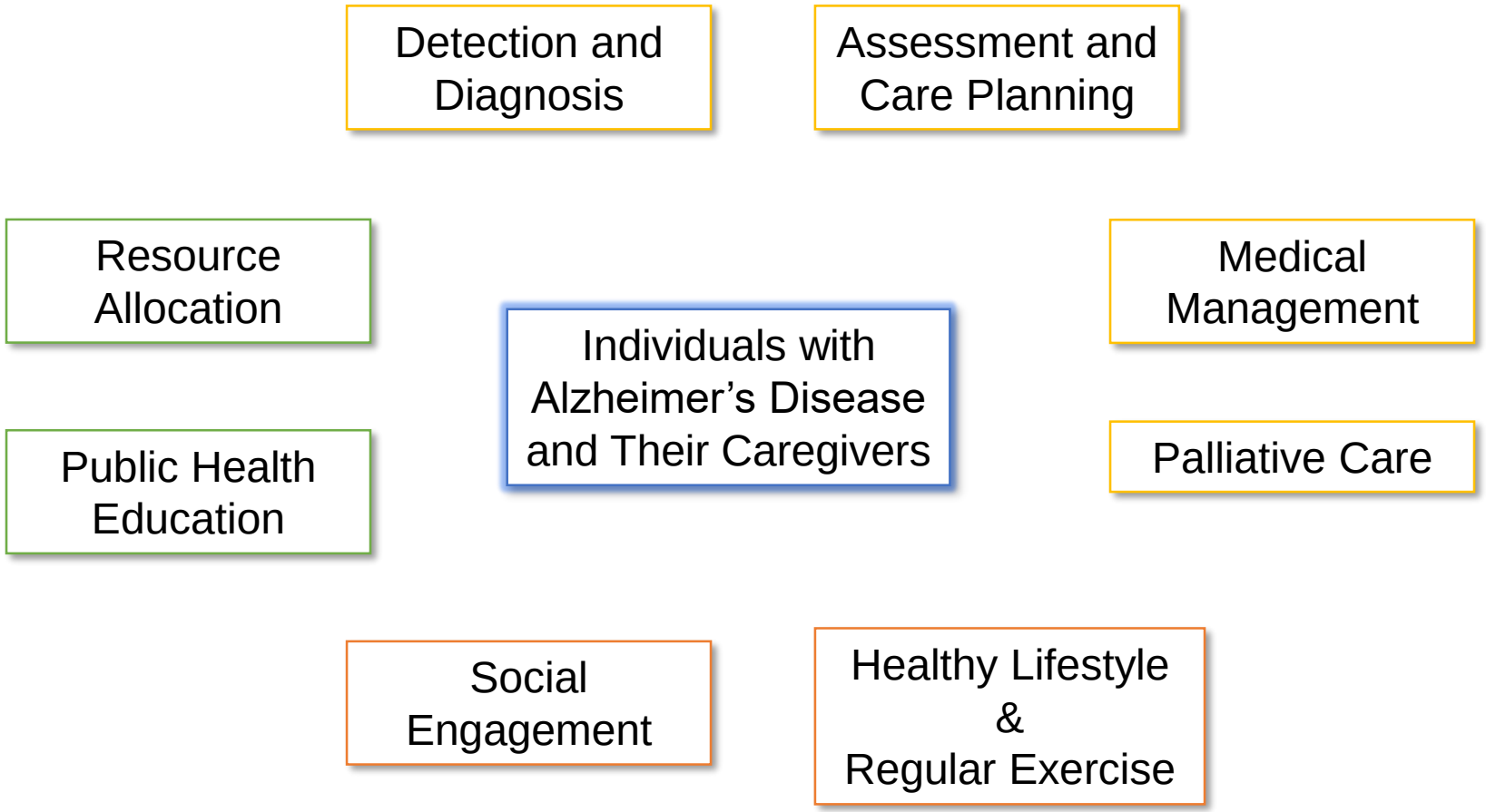
- Significantly higher demand for simultaneous antipsychotics and hypnotics in patients with AD who have not received AD medication
- Psychotropic medication use was negatively associated with acute medical care, especially emergency services[1]
- Psychosis, behavioral problems, and mood disturbance were strongly associated with caregiver stress[2]

	AD medication nonusers Number (%)	**AD medication long-term users Number (%)**	***p* values**
Total	13,077	6,395	
Medication combination			
Antipsychotics + Antidepressants	2,528 (19.3)	1,275 (19.9)	0.33
Antipsychotics + Hypnotics	2,481 (19.0)	1,040 (16.3)	**<0.001**
Antidepressants + Hypnotics	1,801 (13.8)	902 (14.1)	0.25
All three drugs	908 (6.9)	417 (6.5)	0.28

Wong et al., J. Alz. Dis. 2022; Leung et al., Aging Ment. Health. 2013; Cheng et al., Am. J. Geriatr. Psychiatry. 2013.

Alzheimer's disease in Hong Kong: Challenges and directions

- Ensuring wellbeing of patients with AD to reduce complication and mortalities
- Multidimensional geriatric care



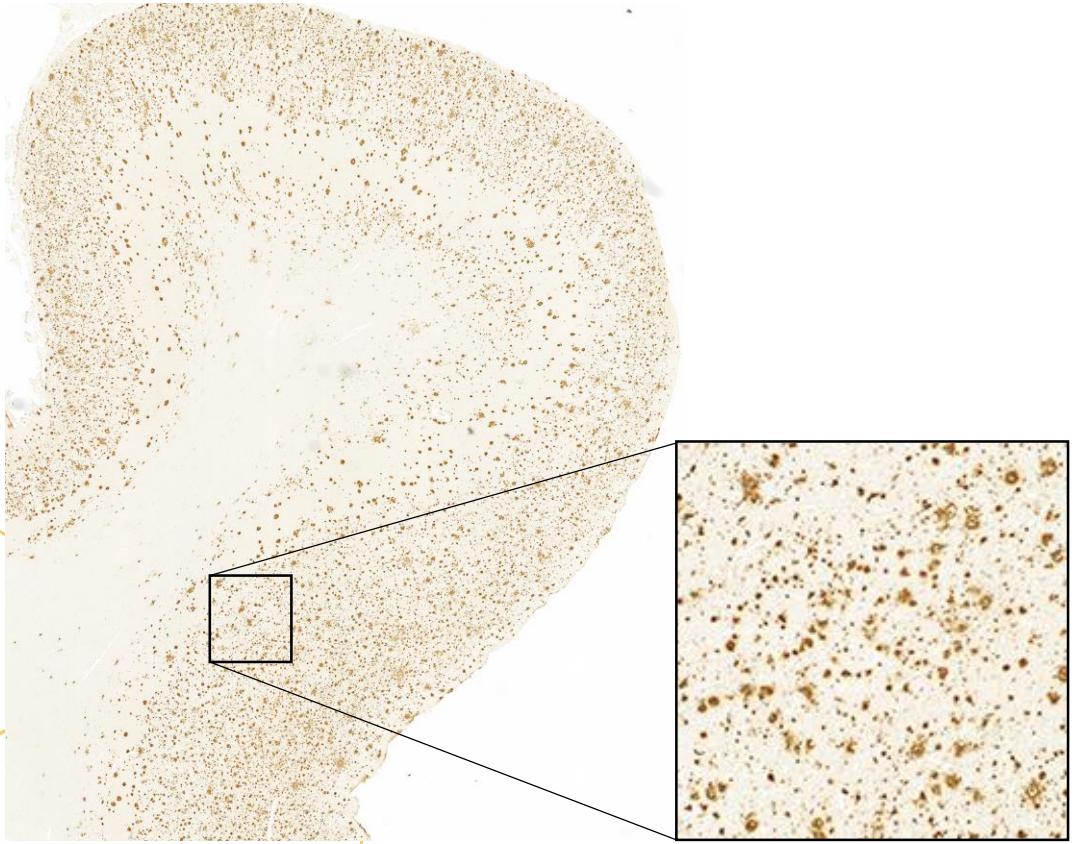
Adapted from Fang et al., Ageing Res. Rev. 2020.

Pathophysiology of Alzheimer’s disease and importance of IL-33/ST2L signaling

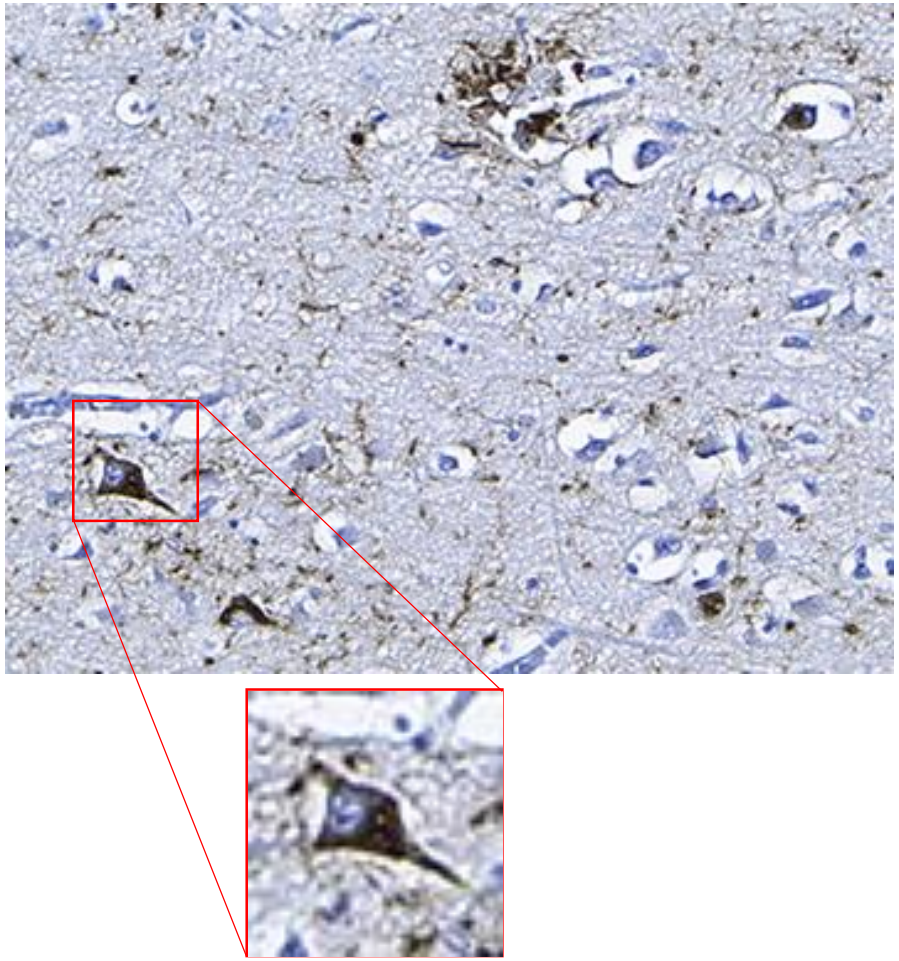
Alzheimer's disease: Pathophysiology

- Two pathological hallmarks: Deposition of beta-amyloid (Aβ) and neurofibrillary (NF) tangles of pathological tau protein → toxic to neurons → death of neurons and brain volume loss

Abnormal cleavage of amyloid precursor protein (APP) → toxic peptides → aggregate to form amyloid plaques

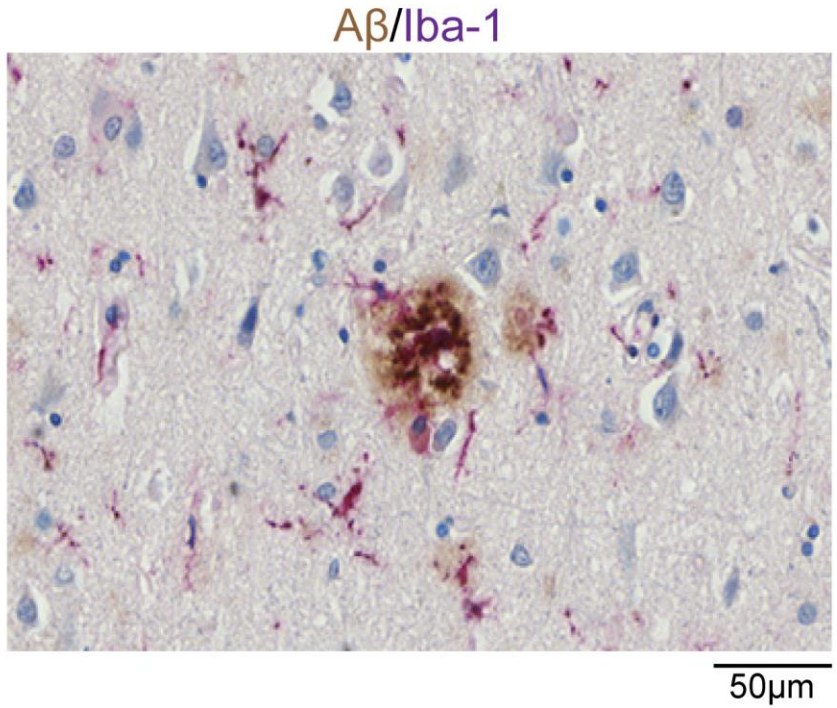


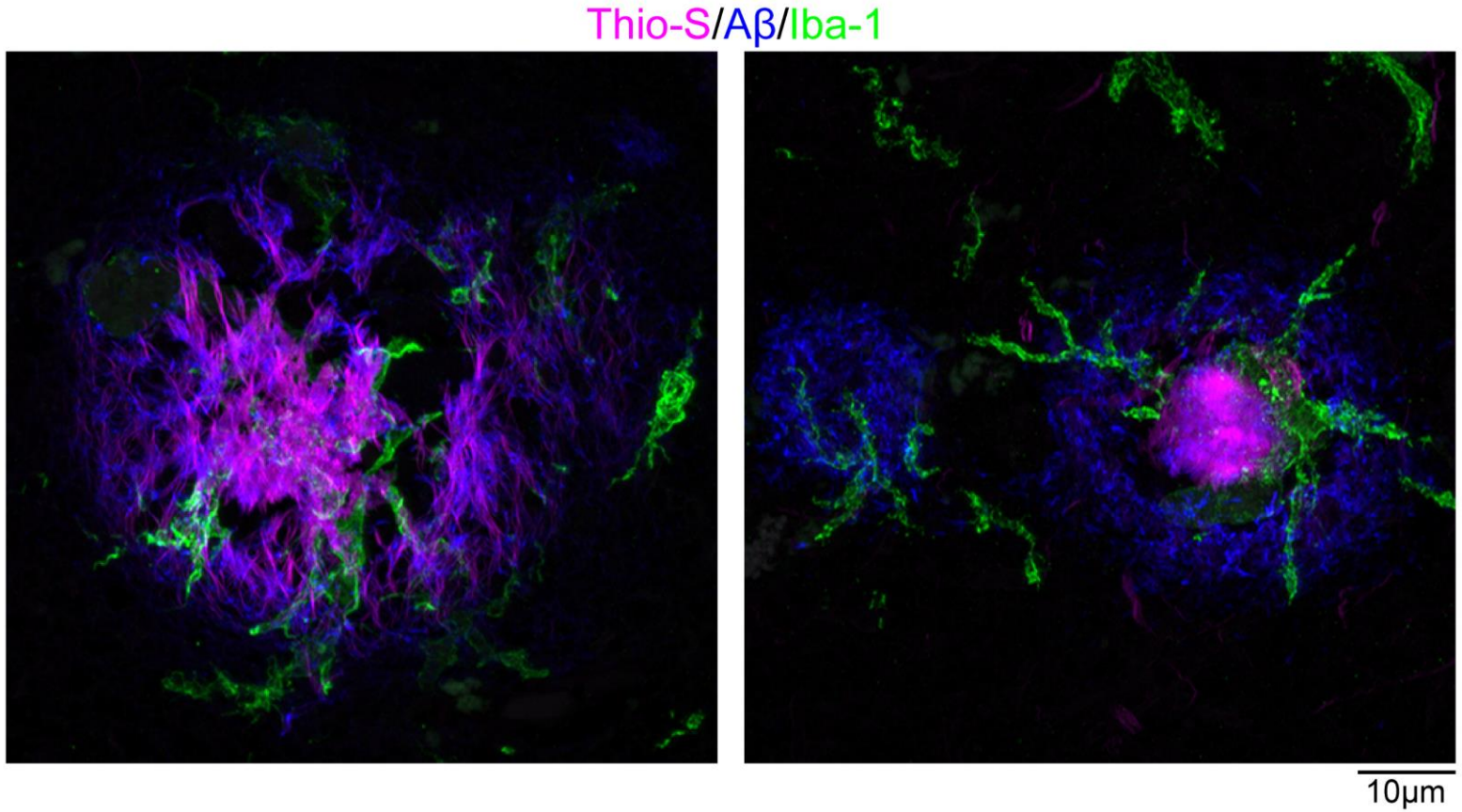
Phosphorylation of tau protein



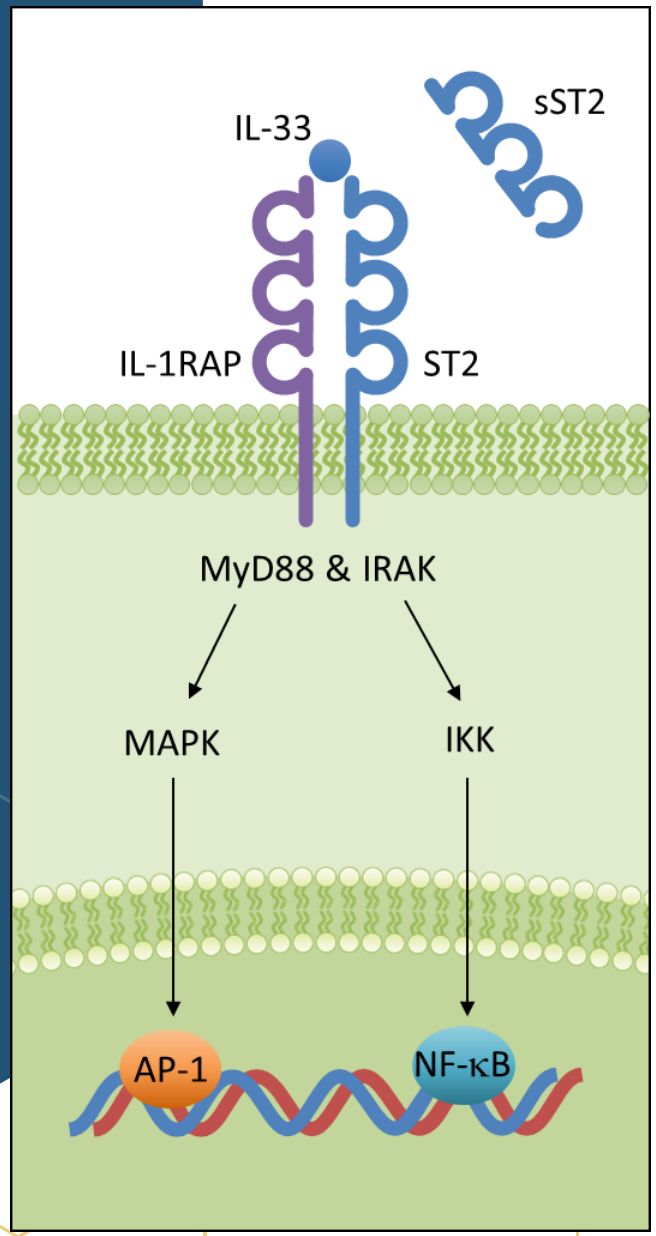
Alzheimer's disease: Role of microglia

- Resident macrophages (i.e., scavenger cells) in the brain uptake and clear Aβ peptides
- Release of inflammatory cytokines promotes microglial migration and activation
- Many AD-risk genes are associated with microglial activation and function

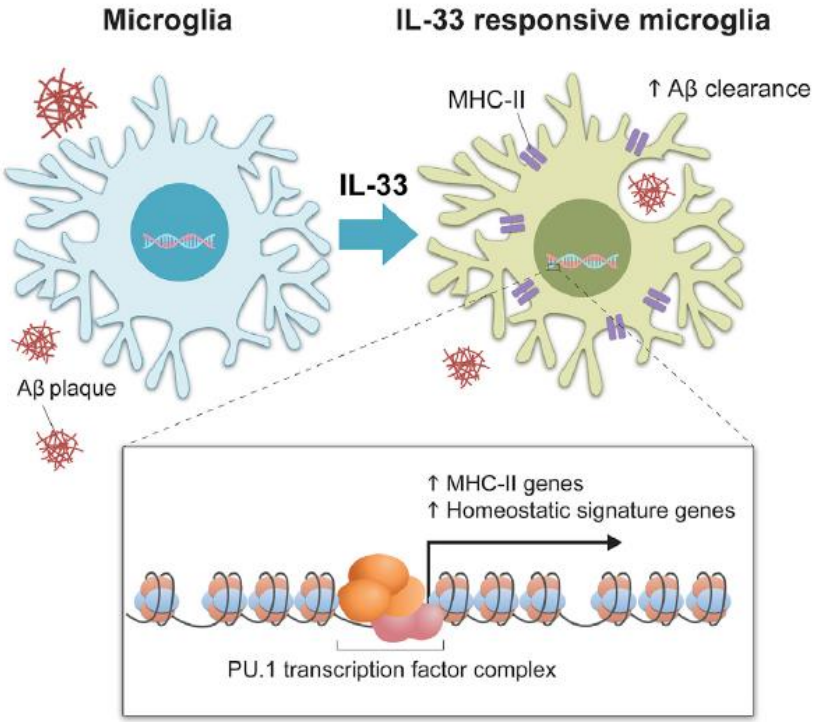


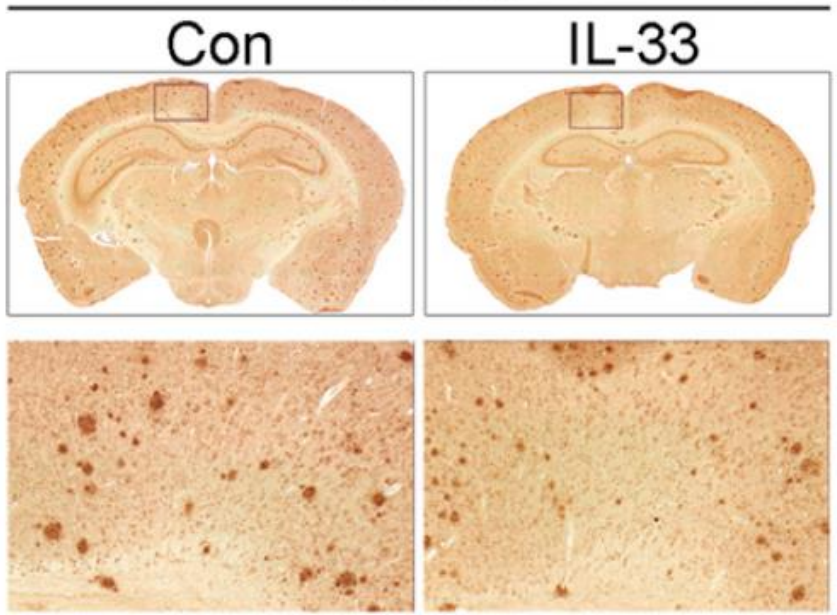


Alzheimer's disease: IL-33/ST2L signaling activates microglia



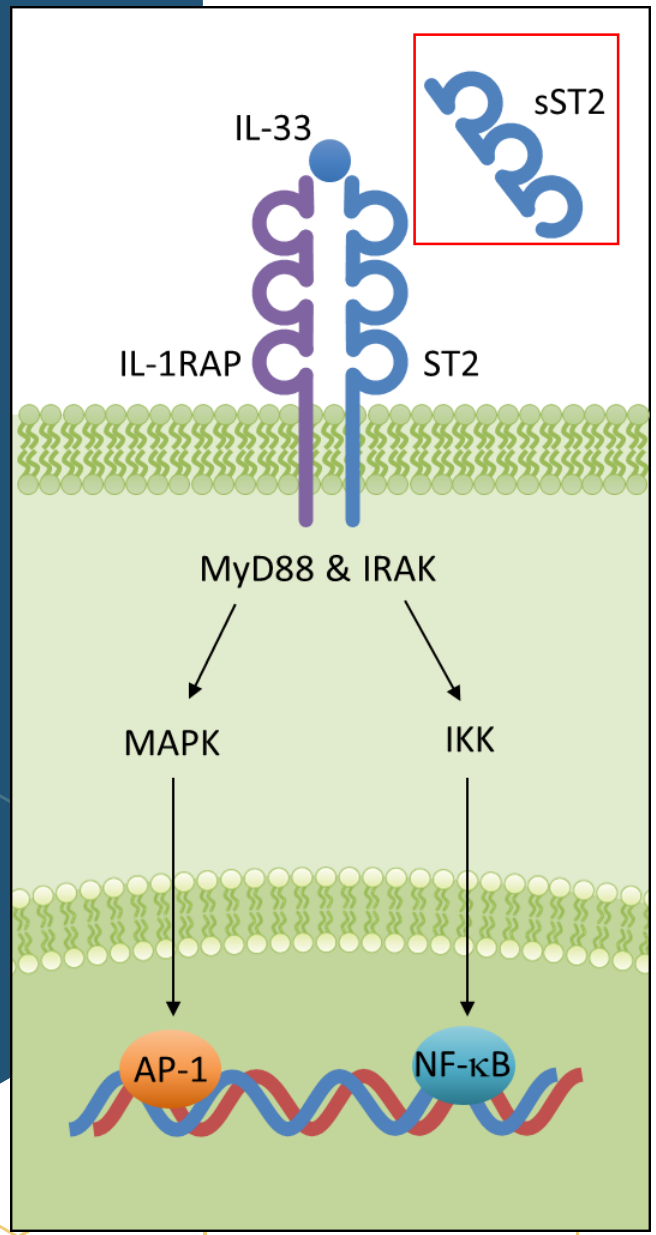
- IL-33 is a cytokine released upon tissue injury
- Interacts with receptor ST2 on microglia → activation of microglia
- IL-33–responsive microglia exhibit enhanced activation and uptake of Aβ peptides[1]
- IL-33/ST2L signaling → reduces amyloid plaque load and cognitive dysfunction in amyloidosis mice model[2]





[1]*Lau et al., Cell Reports. 2020;* [2]*Fu et al., PNAS. 2016.*

Alzheimer's disease: Soluble ST2 as a novel AD biomarker



- Soluble ST2 is a decoy receptor of IL-33
- Is the secreted isoform of full-length ST2 (i.e., ST2L)
- Binds to IL-33 and inhibits IL-33/ST2L signaling
- High blood levels of soluble ST2 found in various diseases

nature aging

ARTICLES

https://doi.org/10.1038/s43587-022-00241-9

Check for updates

OPEN

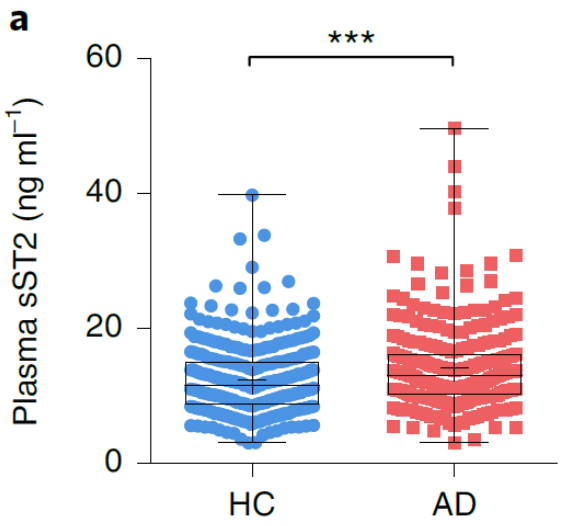
An *IL1RL1* genetic variant lowers soluble ST2 levels and the risk effects of *APOE*-ε4 in female patients with Alzheimer's disease

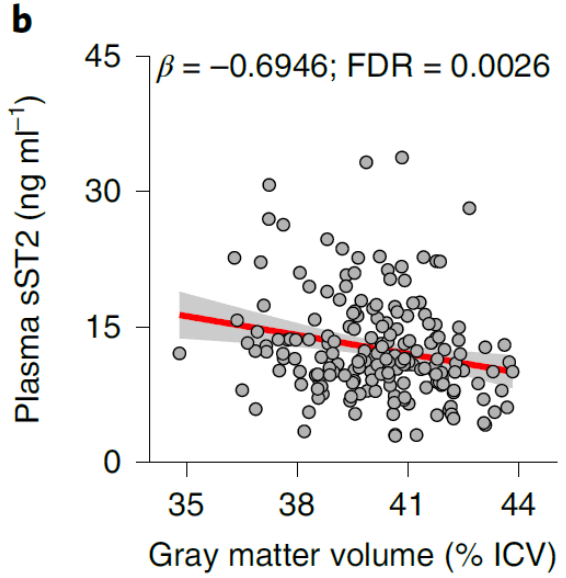
- First study of a local cohort of patients with AD in Hong Kong (Prince of Wales Hospital)
- Novel biomarker detected in the blood is associated with both amyloid pathology and clinical outcome
- Potential pathway to modulate microglial function

Jiang et al., Nat. Aging. 2022.

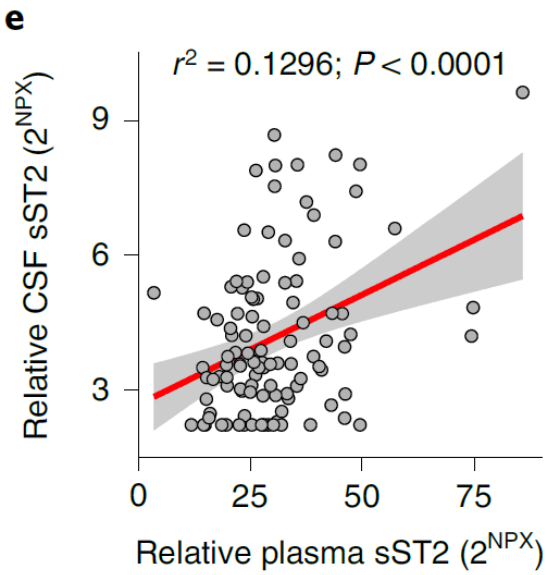
Alzheimer's disease: Blood levels of soluble ST2 in AD

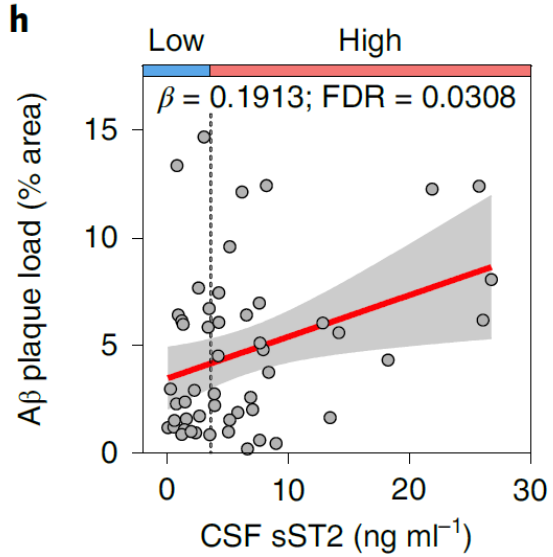
Blood levels of soluble ST2 are higher in patients with AD than in healthy controls (i.e., in a local Hong Kong cohort)





Blood levels of soluble ST2 reflect pathological changes in the brain (i.e., in postmortem brain tissues from European-descent cohorts)

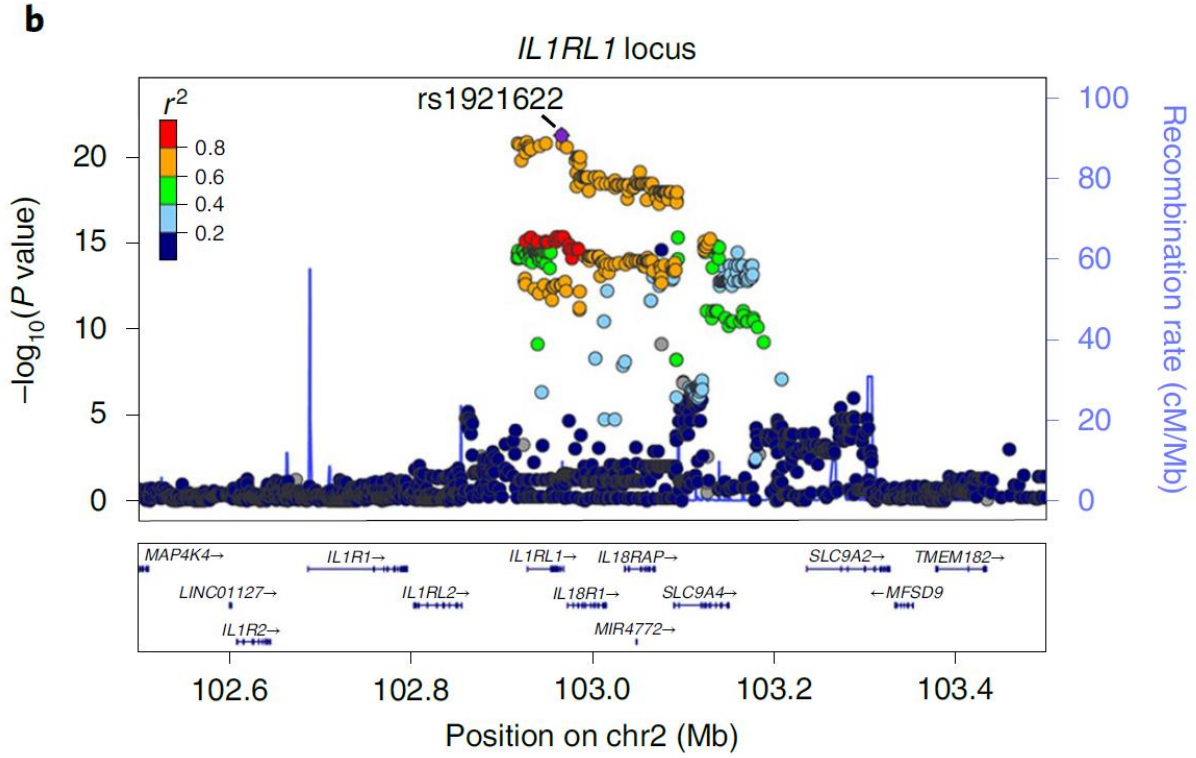


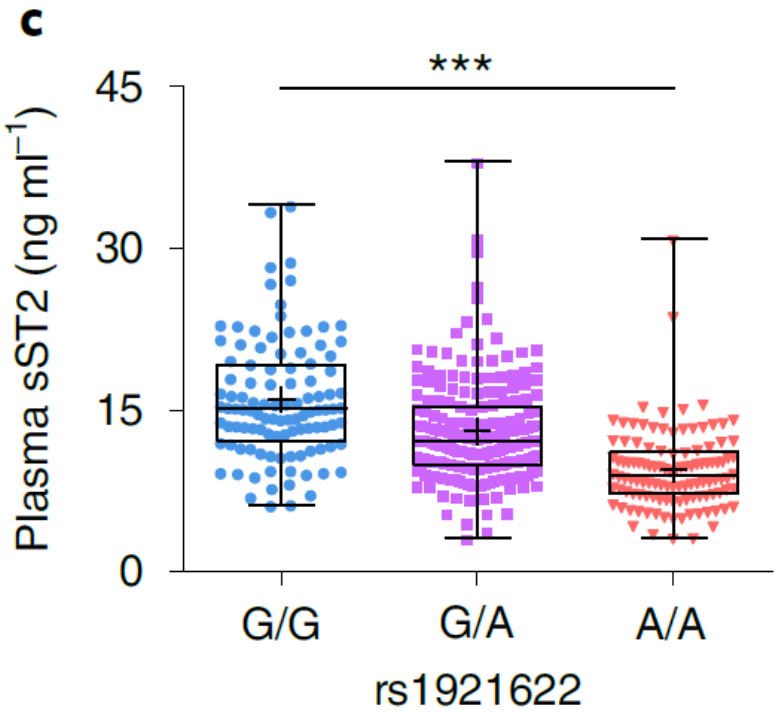


Jiang et al., Nat. Aging. 2022.

Alzheimer's disease: rs1921622 genetic variant on the *IL1RL1* locus

- The *IL1RL1* gene locus encodes ST2L
- The rs1921622 genetic mutation on the *IL1RL1* locus alters soluble ST2 secretion from endothelial cells to the blood
- Carriers of at least one A allele of rs1921622 have lower plasma soluble ST2 levels than noncarriers

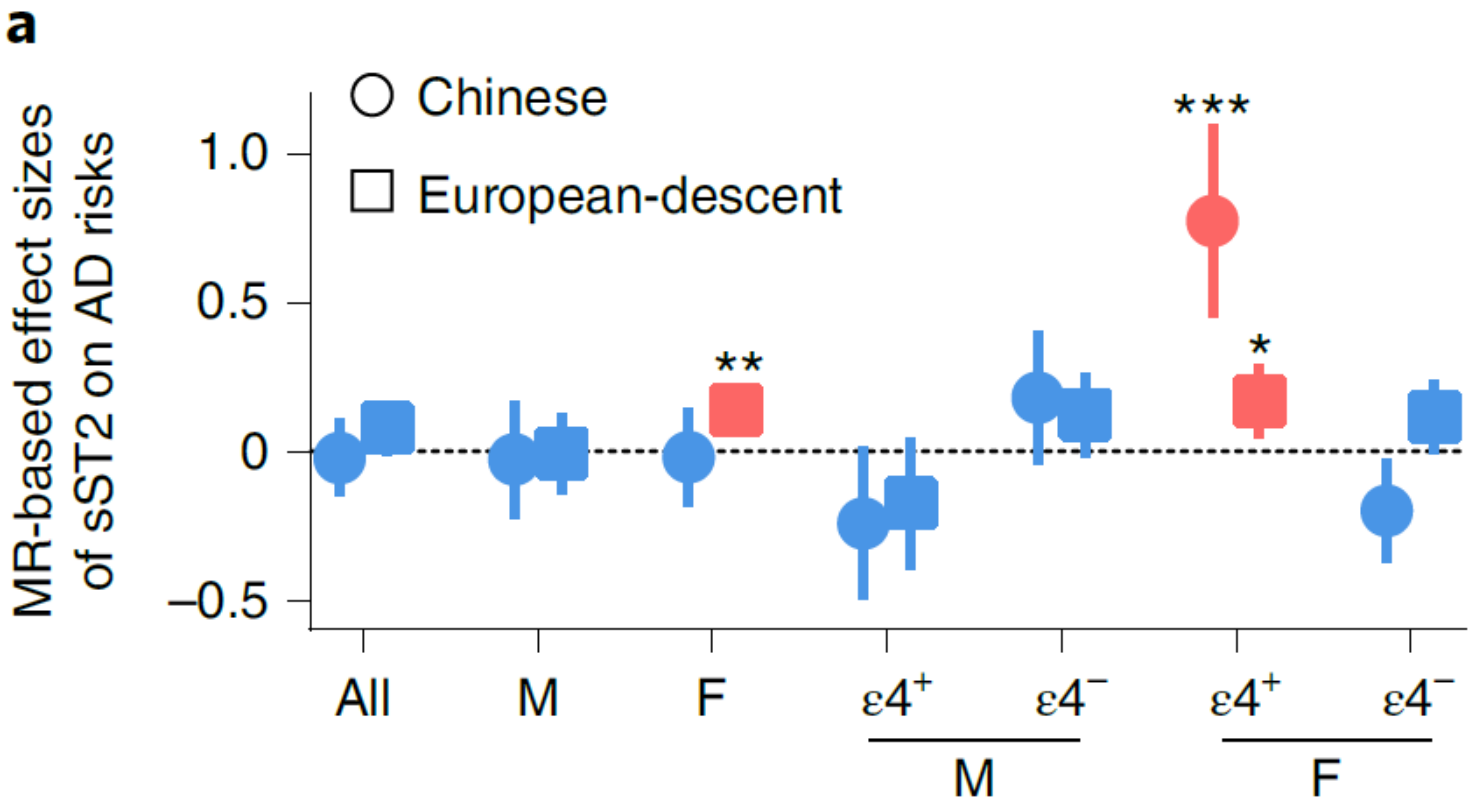




Jiang et al., Nat. Aging. 2022.

Alzheimer's disease: The rs1921622 A allele and AD risk

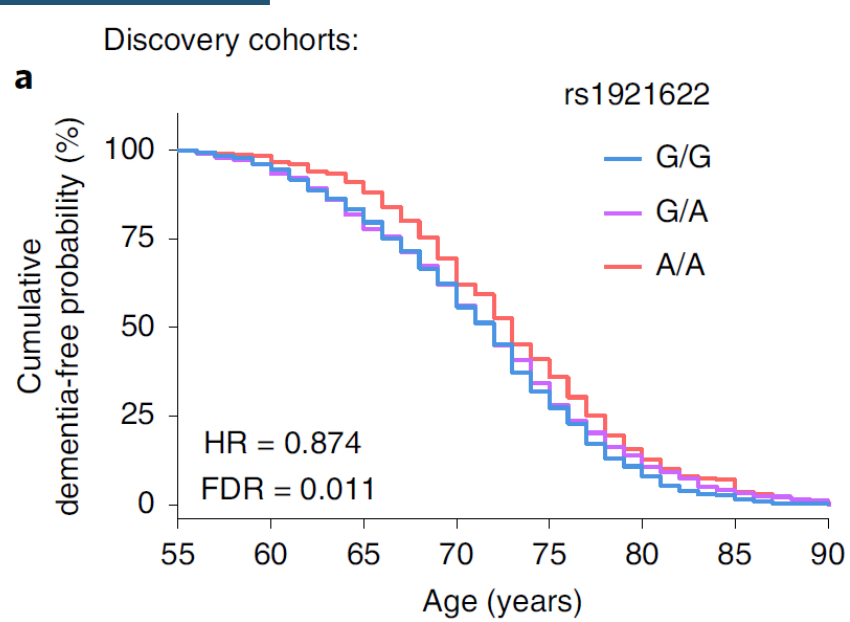
- Mendelian randomization analysis of both Chinese and European-descent AD populations
- Effect of rs1921622 A allele only seen in female patients carrying *APOE*-ε4 allele
- Female patients carrying *APOE*-ε4 allele had the highest risk of developing AD

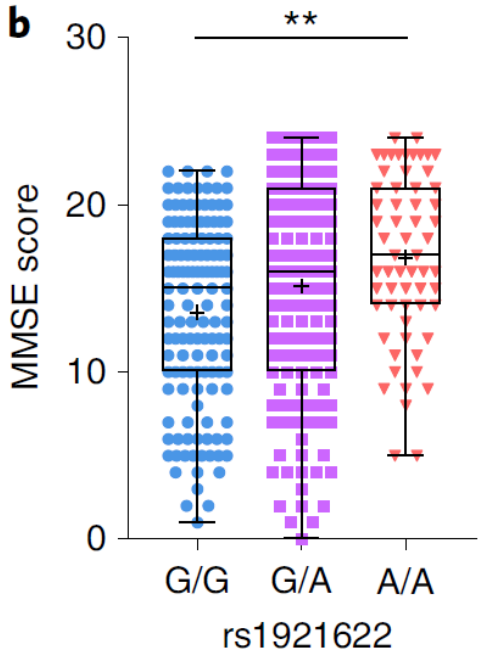


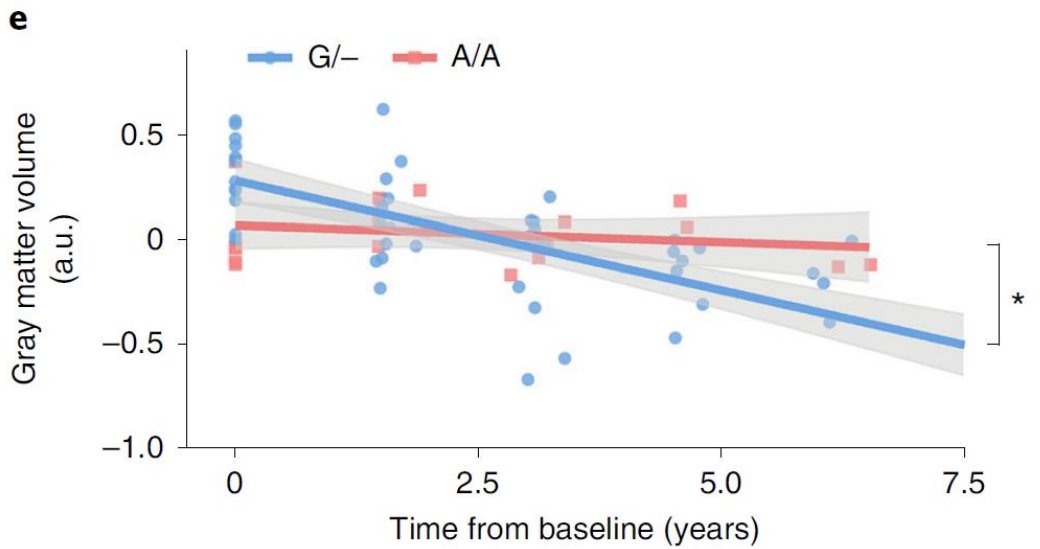
Jiang et al., Nat. Aging. 2022.

Alzheimer's disease: Protective effect of the rs1921622 A allele

- Presence of the rs1921622 A allele is associated with better clinical outcome (i.e., disease-free probability, cognitive scores, and brain volume loss) in female patients carrying *APOE*-ε4 allele
- Validated with data from overseas replication cohorts





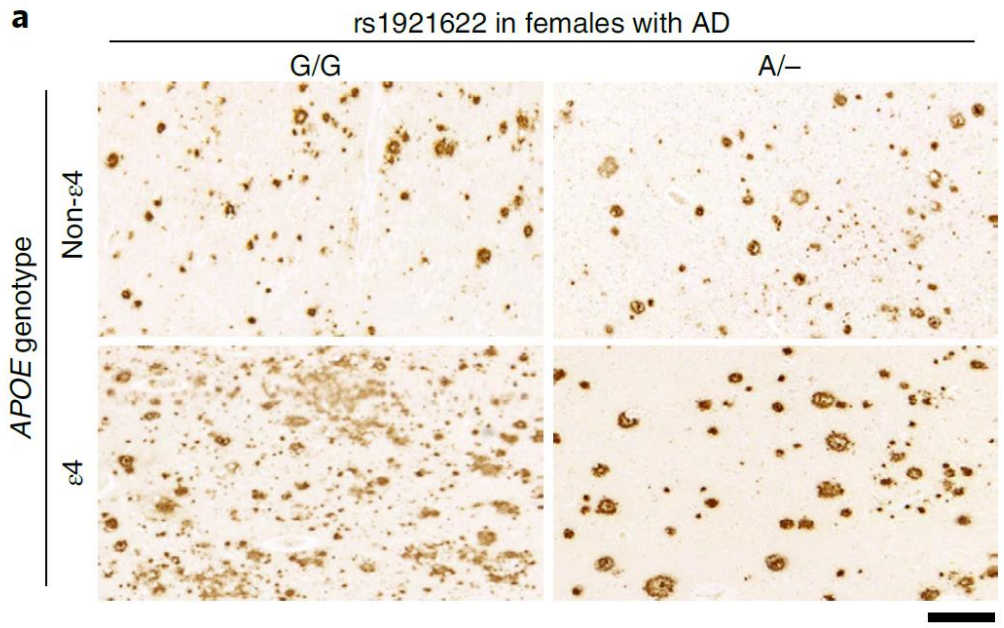


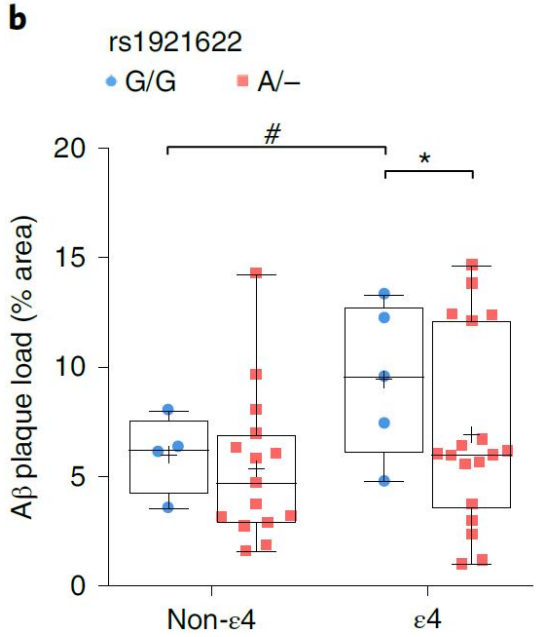
Jiang et al., Nat. Aging. 2022.

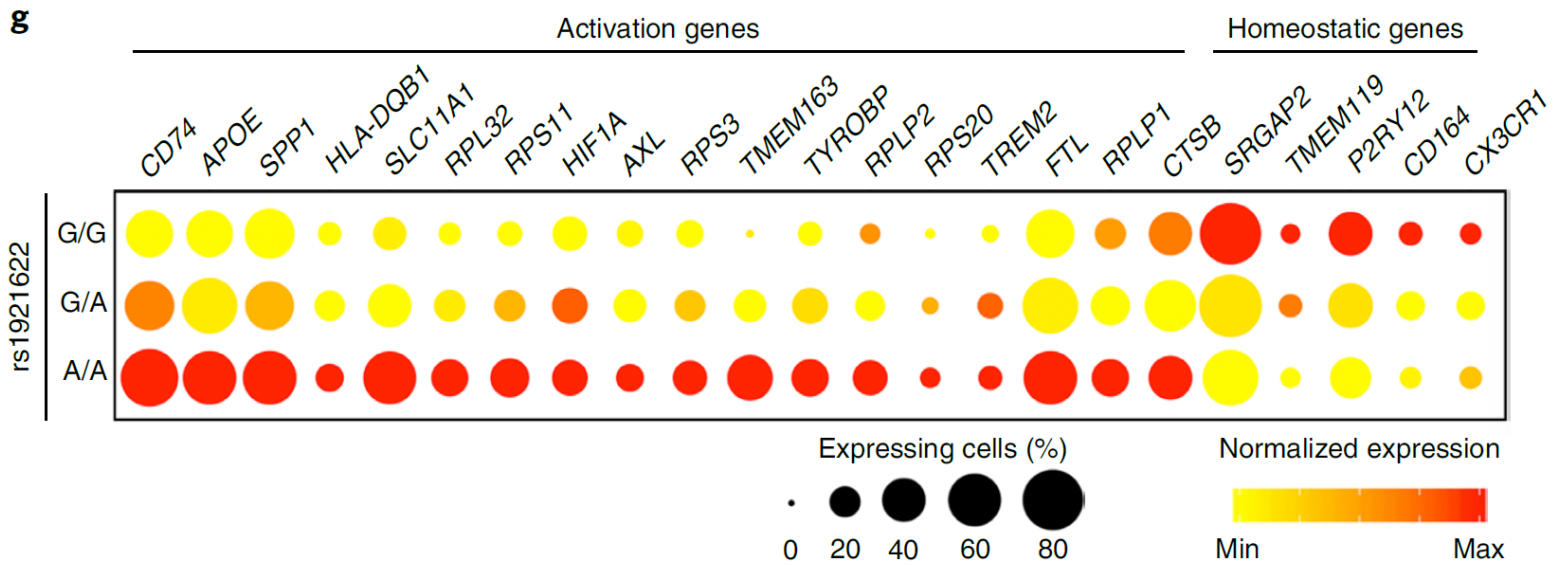
Alzheimer's disease: The rs1921622 A allele associates with enhanced microglial activation

Pathological evidence of reduced amyloid plaque load

Upregulation of microglial function and activation at the molecular level





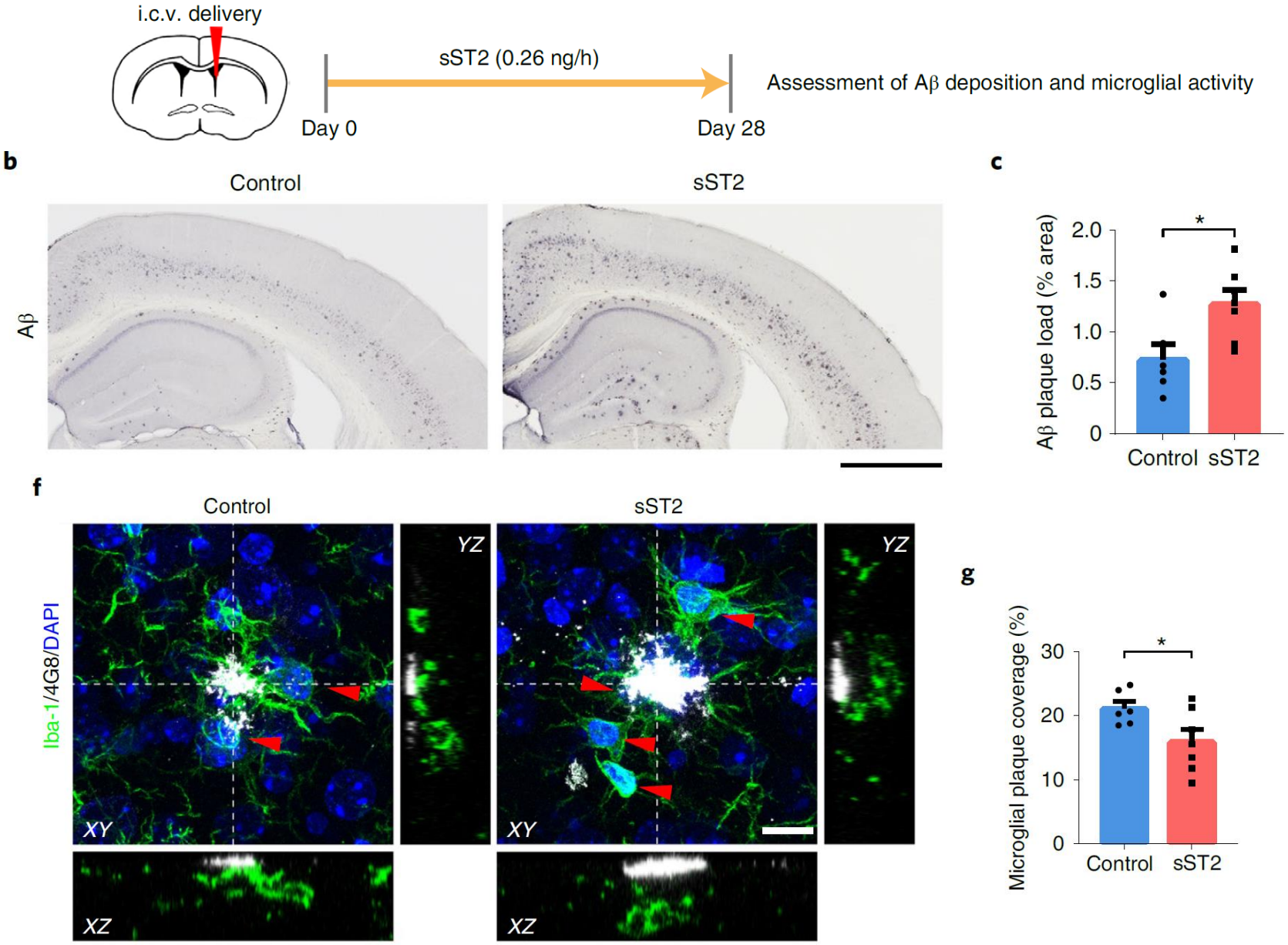


Jiang et al., Nat. Aging. 2022.

Alzheimer’s disease: Increased soluble ST2 levels worsen disease in mice

Increased amyloid plaque load after soluble ST2 (sST2) injection

Downregulation of microglial activation and interaction with amyloid plaque

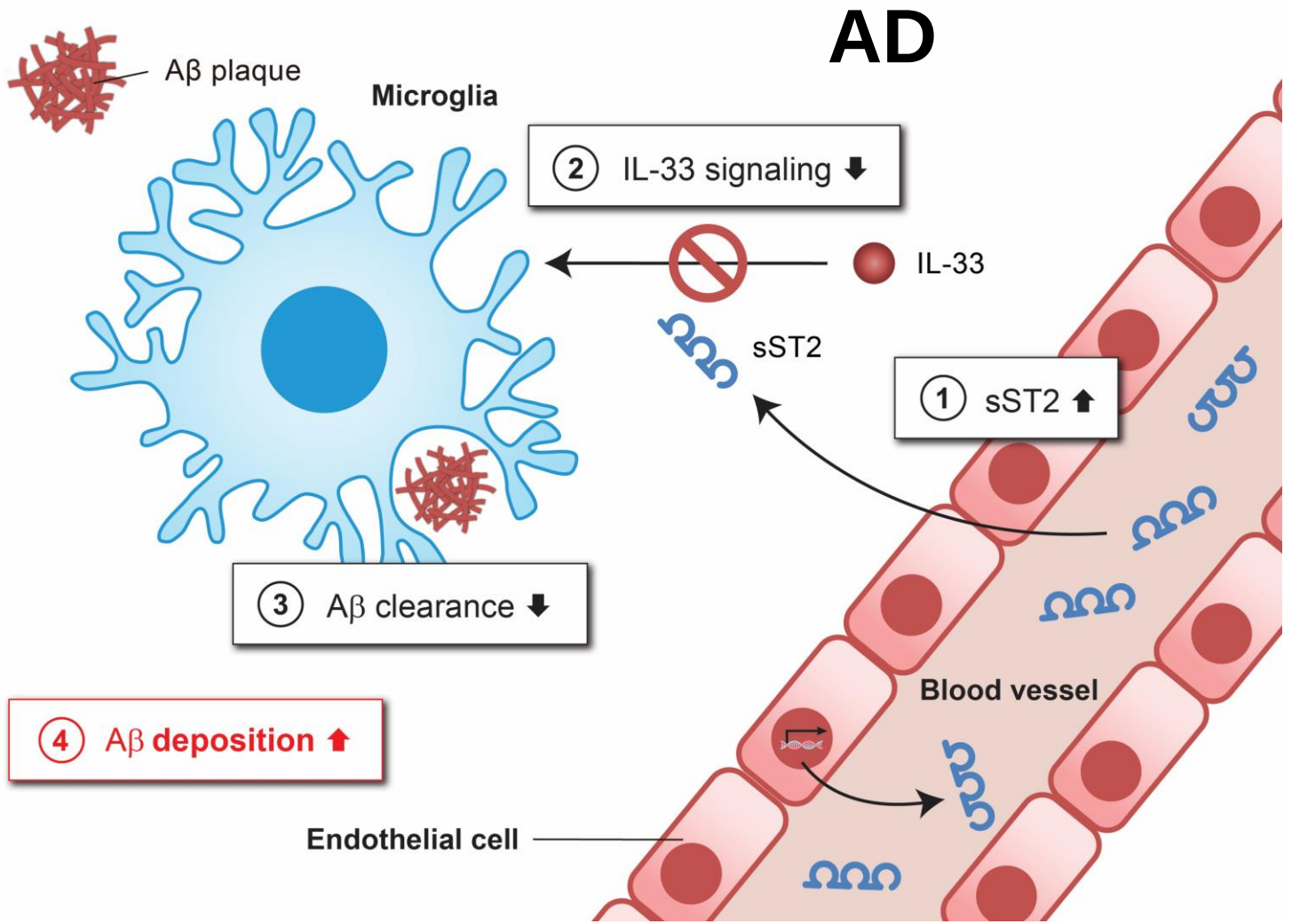


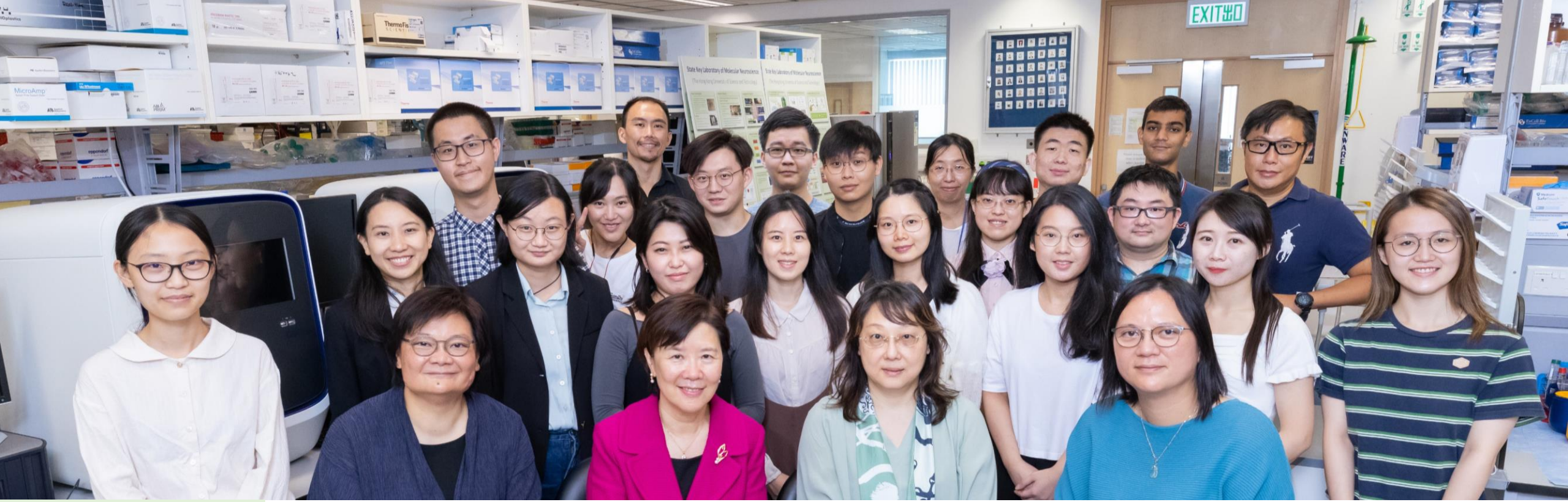
Jiang et al., Nat. Aging. 2022.

Alzheimer's disease: Soluble ST2 as a biomarker and therapeutic target

Future Directions:

- ✓ Stratify patients according to soluble ST2 levels and rs1921622 A allele
- ✓ Monitor disease progression according to soluble ST2 levels in the blood
- ✓ Investigate disease-modifying therapies to reduce soluble ST2 levels and enhance microglial clearance of Aβ





Yuanbing Jiang
Shun-Fat Lau
Xiaopu Zhou
Anna Wong
Joyce Ouyang
Wei Wu
Daniel Wong
Wing-Yu Fu
Fanny Ip
Amy Fu

John Hardy (UCL)
Kin Y. Mok (UCL)
Henrik Zetterberg (U of Gothenburg)
Tony Wyss-Coray (Stanford U)
Colin Masters (U of Melbourne)
Yu Chen (SIAT)
Tom H. Cheung (HKUST)

- Chinese cohorts
  - Qihao Guo (Shanghai Jiao Tong U)
  - Timothy Kwok (CUHK)
  - Vincent Mok (CUHK)
  - Baorong Zhang (Zhejiang U)
- Australian Imaging, Biomarkers and Lifestyle Study cohort (AIBL)
- MRC UK Brain Bank Network (Bristol)
- Alzheimer's Disease Neuroimaging Initiative cohort (ADNI)
- Late Onset Alzheimer's Disease Family Study (LOAD)
- NIA Alzheimer's Disease Centers cohort (ADC)
- Genotype-Tissue Expression project dataset (GTEx)

The State Key Laboratory of Molecular Neuroscience

The University Grants Committee of Hong Kong
The Research Grants Council of Hong Kong
Innovation Technology Commission of Hong Kong
Ministry of Science and Technology
National Natural Science Foundation of China

Thank you

Q&A