A Unified Concept on Dementia and Cognitive Impairment towards Management

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15/1/2017

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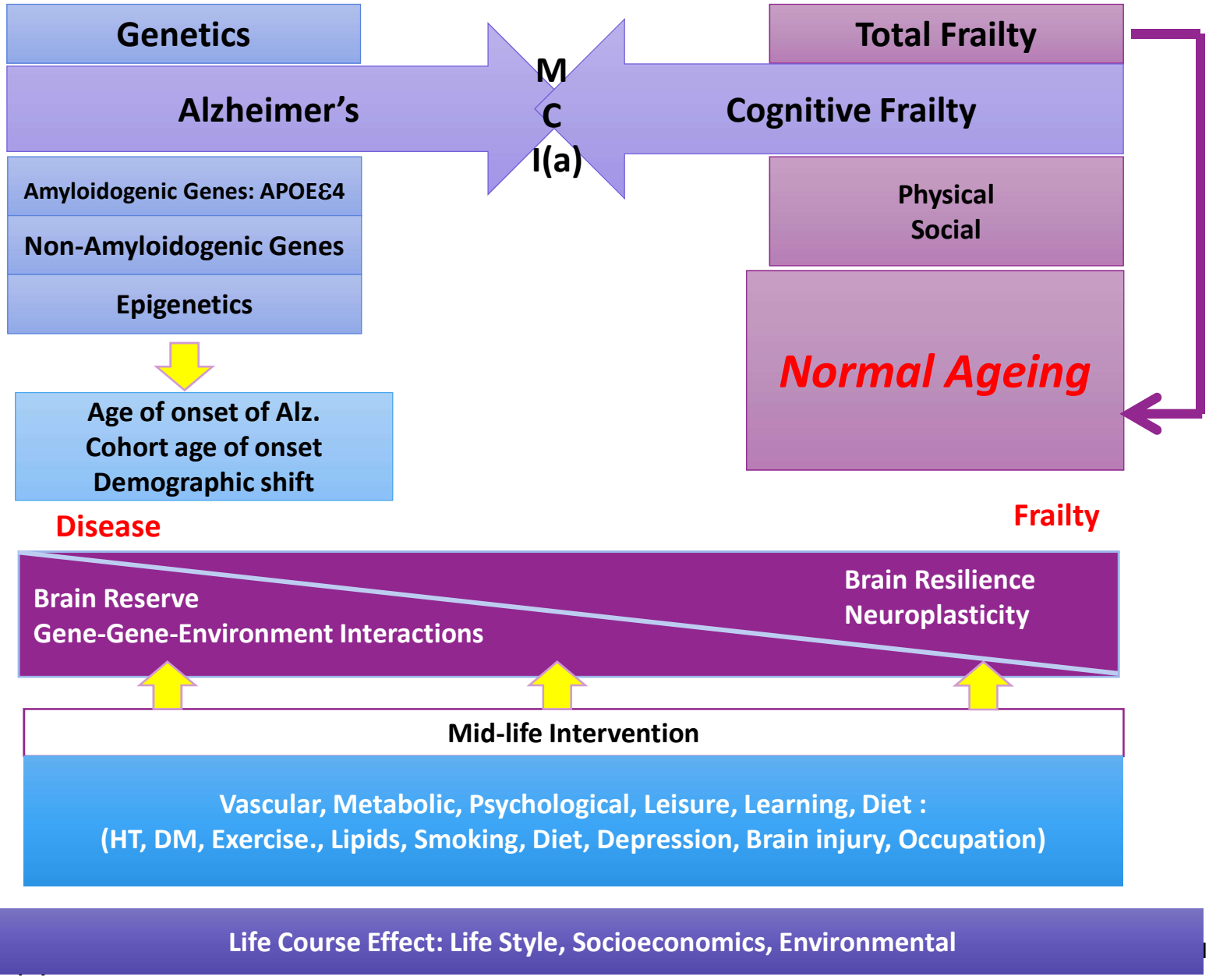
Unifying Concept of Alzheimer's & Cognitive Frailty 2017



Age-related

Changes in *Cognition*

- Slower reactions
- Slower central processing time
- Picture completion, picture arrangement, object assembly, block design affected
- Accumulated knowledge and experience
- Vocabulary, arithmetic, comprehension, knowledge and digital span resistant to change
- Crystallized intelligence and wisdom
- 95% >65 yrs show no mental impairment

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Ageing and Mental Growth

- Wisdom
- Sharp wittedness
- Ability to deliberate
- Ability to reason
- Ability to comprehend the whole
- Better verbal command
- Better control of life
- Stronger commitment to work
- More faithful to employer
- Less absence from work
- Higher motivation to learn

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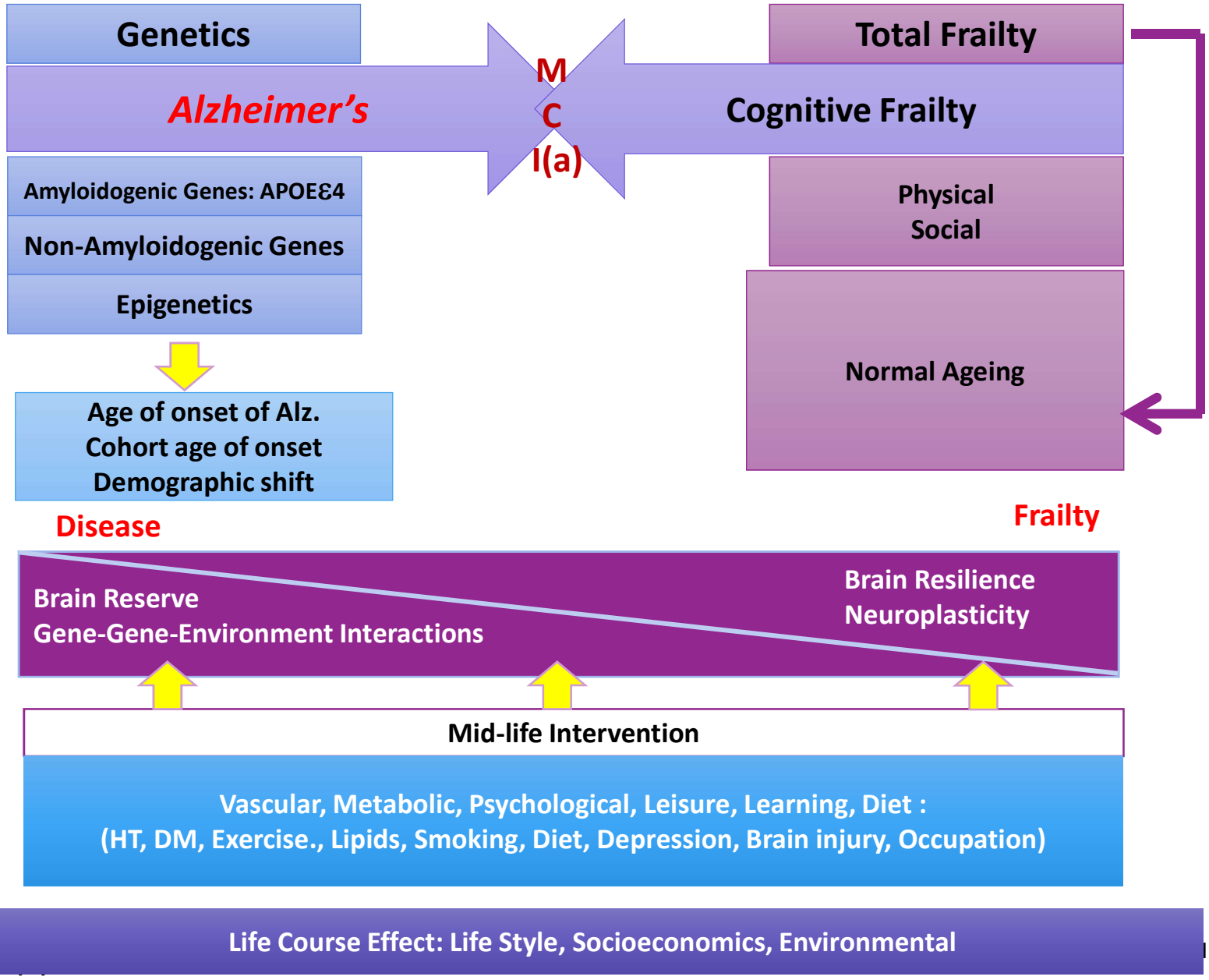

Alzheimer's Disease

1907

"An unusual condition of the cerebral cortex"

痴呆症

腦退化

認知障礙

Prevalence of dementia in community (2006)

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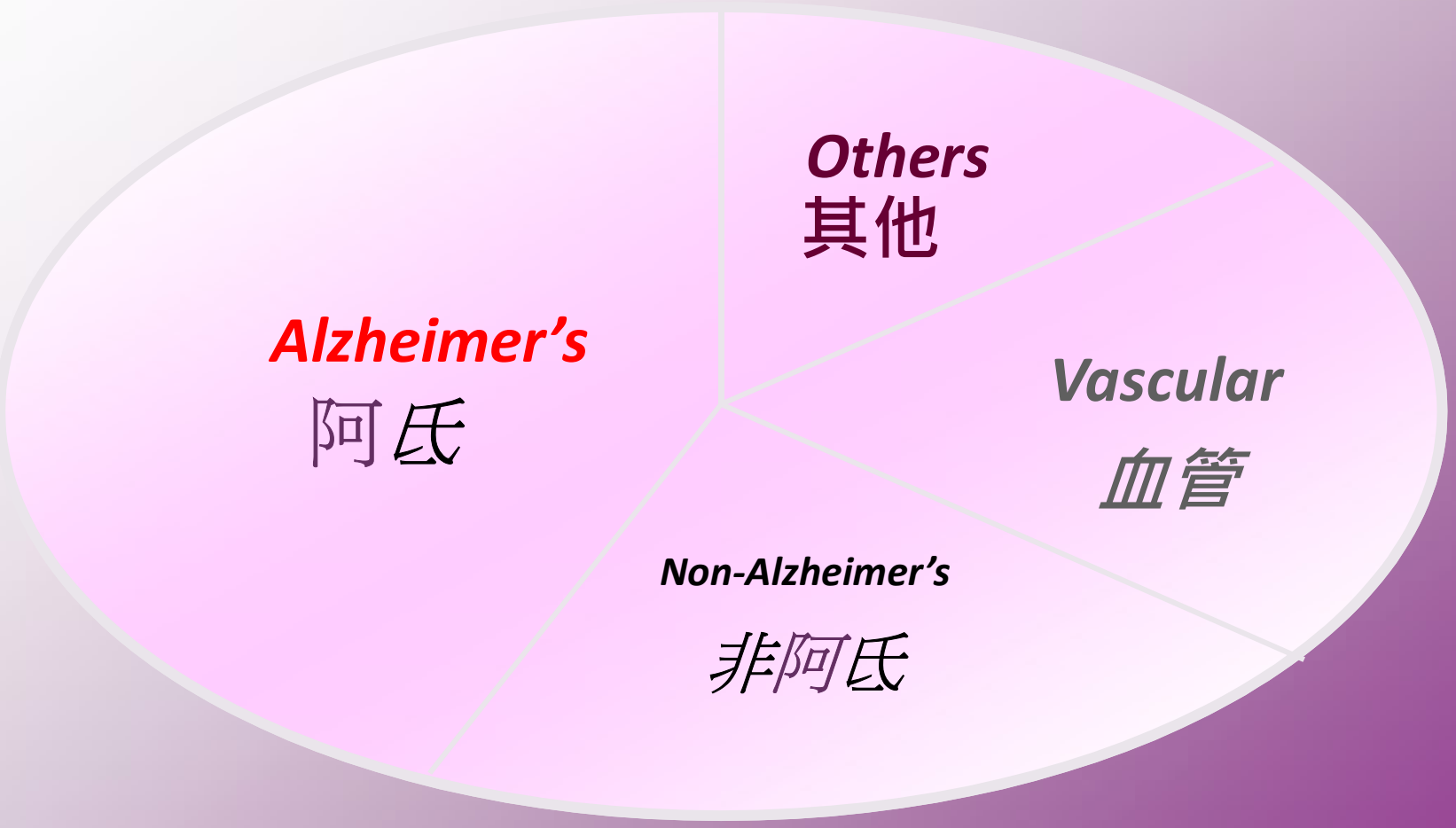
Age	60-64	65-69	70-74	75-79	80-84	85 and above
Total	1.2%	2.5%	3.5%	9.9%	19%	32.1%
Female	0.4%	3.2%	5.3%	11.4%	24%	32%
Male	1.9%	1.9%	1.6%	8.3%	12.3%	33.1%

Total estimated number 70-80 thousands



Types of Dementia: Heterogenous

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Non-Alzheimer Degenerative Dementia

(Curr Opin Neurol 1998, 11:417 - 427)

Frontotemporal(behavioral, semantic, PPA)

Progressive Supranuclear Palsy(Occular, bulbar)

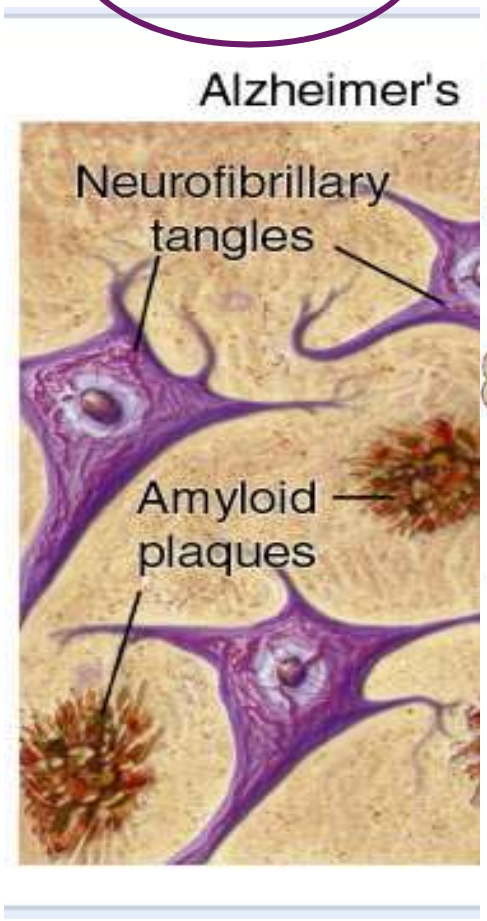
Corticobasal Degeneration(Apraxia)

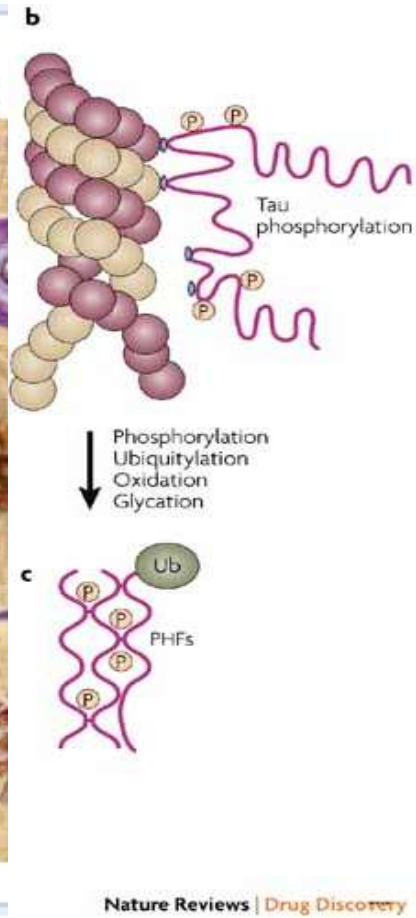
Cerebral Lewy Body Disease(CVH)

Amyloid

Tau

Synuclein





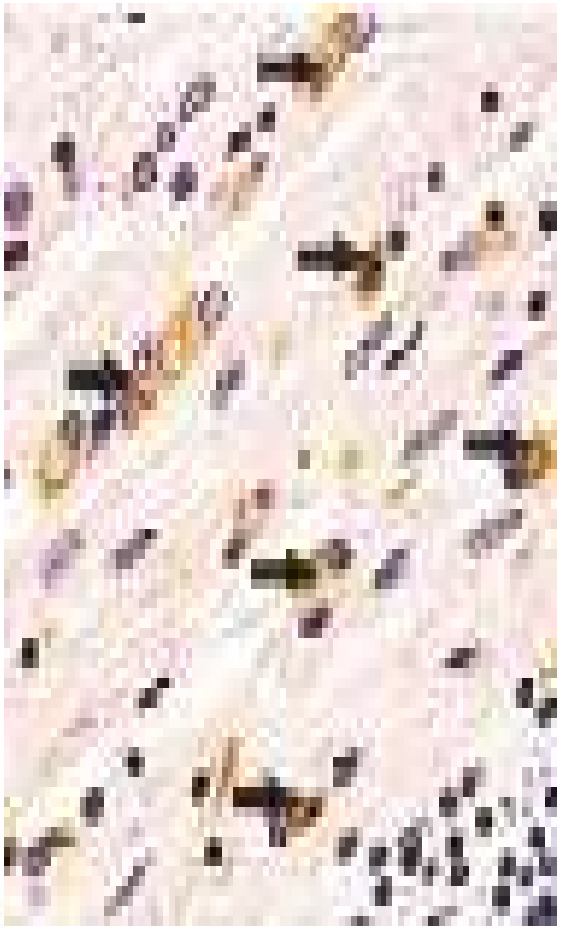


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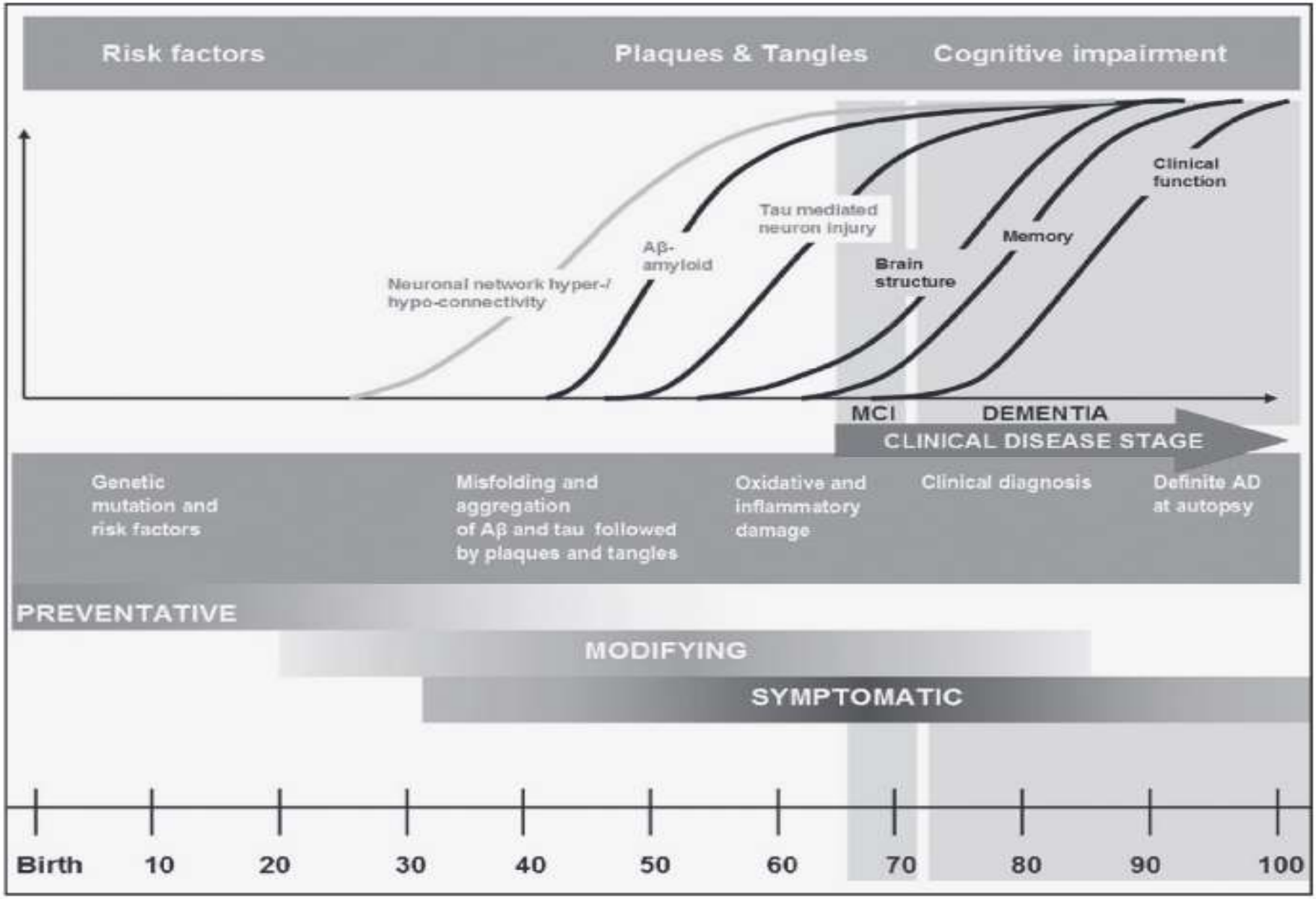
Figure 1



J Nutr Health Aging 2015;19(2): 154-163

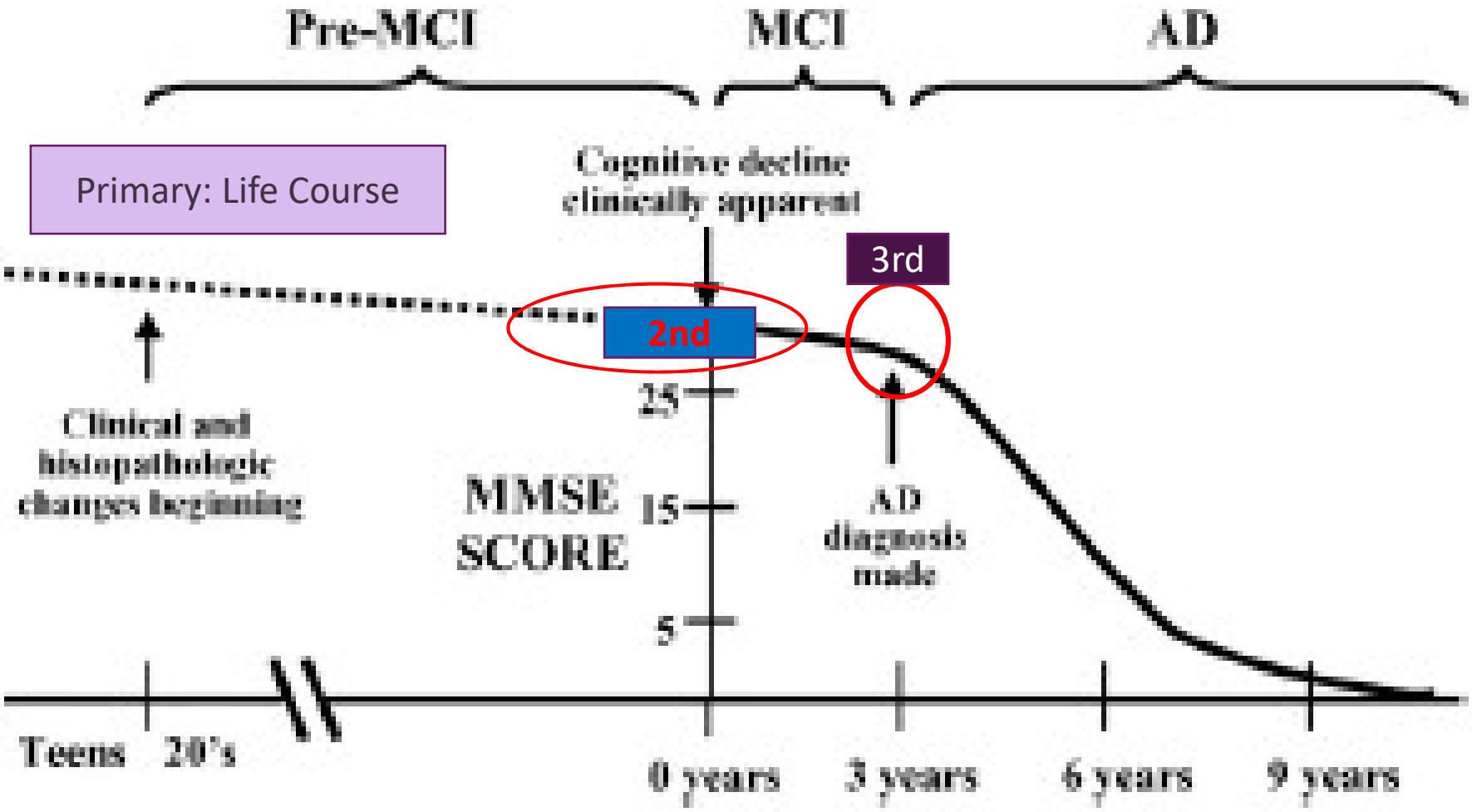


Fig. 3. Cognitive decline in Alzheimer's disease follows a trajectory that appears to include most of adulthood. AD, Alzheimer's disease; MCI, mild cognitive impairment; MMSE, mini mental state exam.

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Neurobiology of Aging 2007:28

Prevention

- ***Primary:*** Life course and life style modification

- ***Secondary:*** Risk modification, mid life intervention and anti-amyloid treatment

- ***Tertiary:*** Early diagnosis, interventions (medical and social) and reduce complications and disability

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NATURE | VOL 537 | 1 SEPTEMBER 2016

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

Alzheimer's disease (AD) is characterized by deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, accompanied by synaptic dysfunction and neurodegeneration. Antibody-based immunotherapy against Aβ to trigger its clearance or mitigate its neurotoxicity has so far been unsuccessful. Here we report the generation of aducanumab, a human monoclonal antibody that selectively targets aggregated Aβ. In a transgenic mouse model of AD, aducanumab is shown to enter the brain, bind parenchymal Aβ, and reduce soluble and insoluble Aβ in a dose-dependent manner. In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain Aβ in a dose- and time-dependent manner. This is accompanied by a slowing of clinical decline measured by Clinical Dementia Rating—Sum of Boxes and Mini Mental State Examination scores. The main safety and tolerability findings are amyloid-related imaging abnormalities. These results justify further development of aducanumab for the treatment of AD. Should the slowing of clinical decline be confirmed in ongoing phase 3 clinical trials, it would provide compelling support for the amyloid hypothesis.

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ALZHEIMER'S DISEASE

Testing the Right Target and Right Drug at the Right Stage

Reisa A. Sperling,[1*] Clifford R. Jack Jr.,[2] Paul S. Aisen[3]

www.ScienceTranslationalMedicine.org 30 November 2011

- Amyloid accumulation starts many years before the onset of symptoms, and initiation of anti-amyloid treatment only after dementia develops may be too late to affect the clinical course of the disease.

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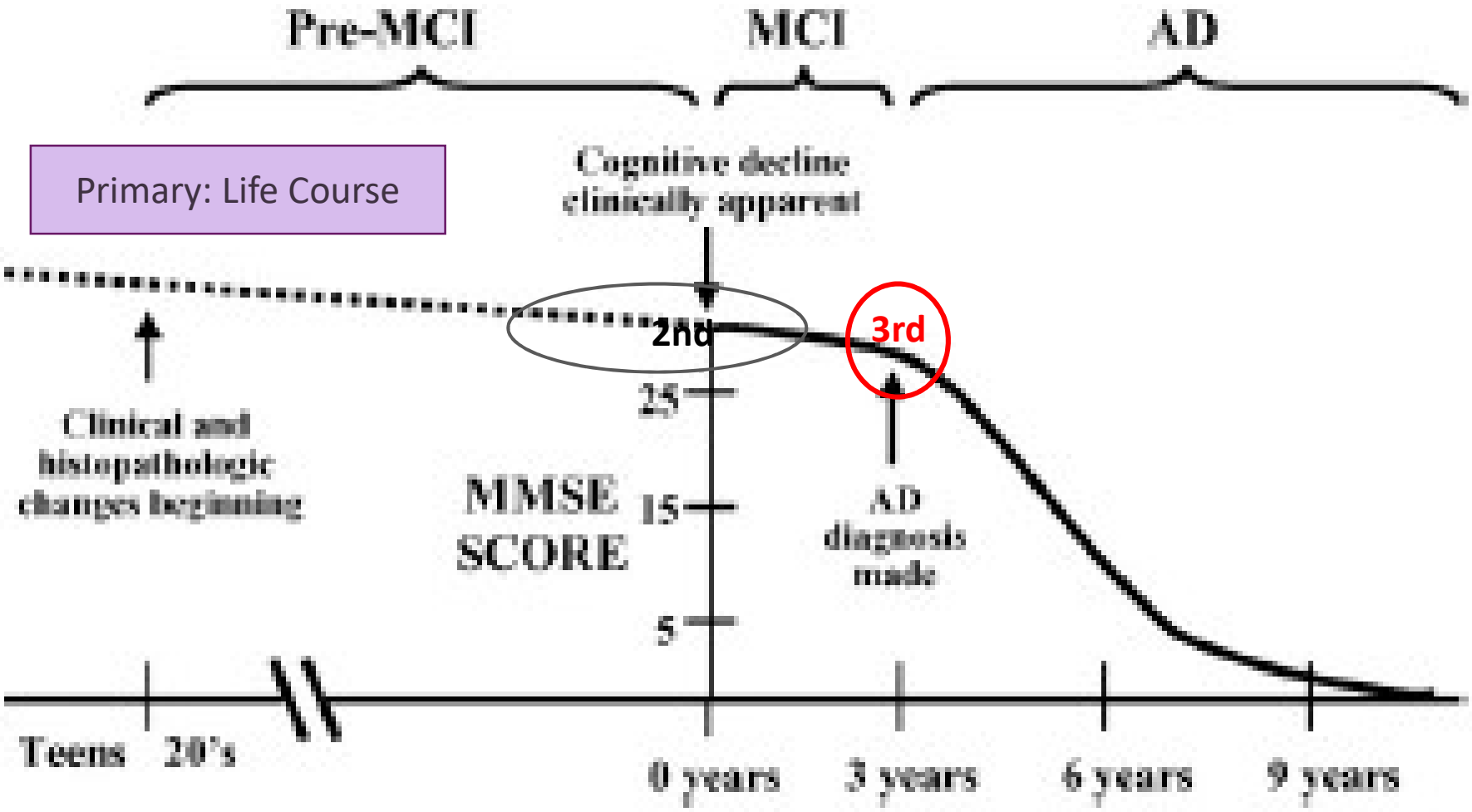

Fig. 3. Cognitive decline in Alzheimer's disease follows a trajectory that appears to include most of adulthood. AD, Alzheimer's disease; MCI, mild cognitive impairment; MMSE, mini mental state exam.

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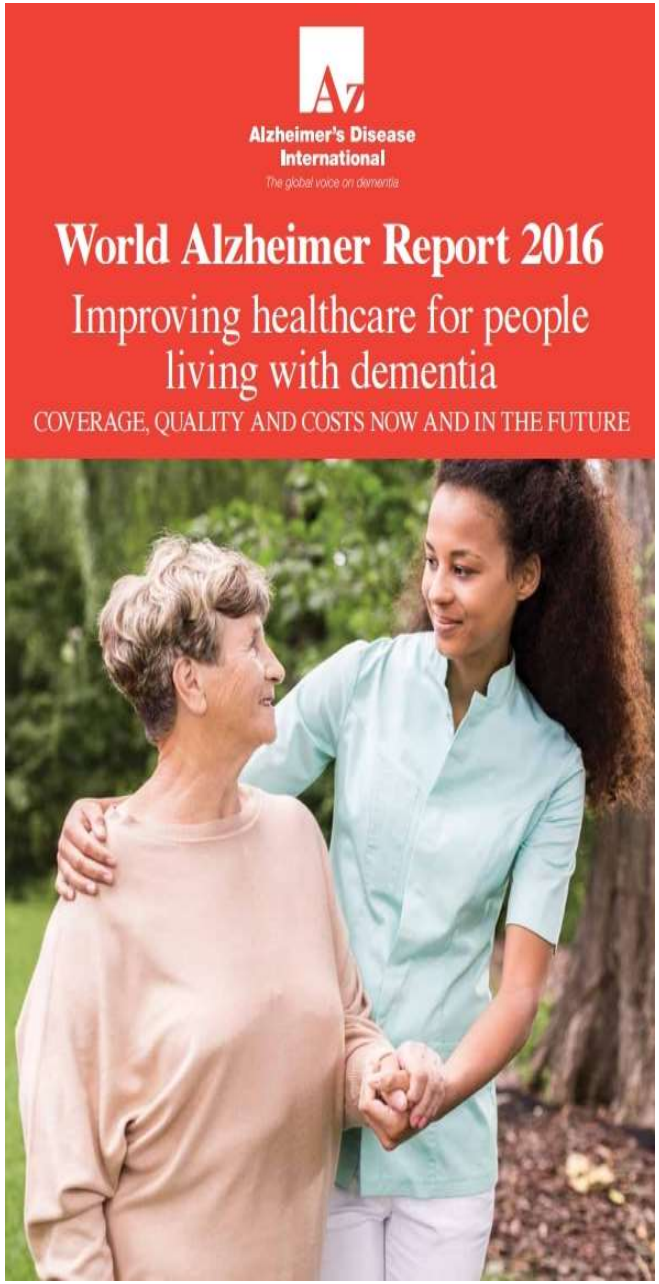
Neurobiology of Aging 2007:28

Importance of engagement of Family Physician in Dementia Care

- **Dementia care is over-specialised**
  - Current specialist models of dementia care (where geriatricians, neurologists and psychiatrists provide dementia care) are unlikely to be able to scale up to provide sufficient coverage for the growing number of people affected by dementia
  - Primary care physicians take responsibility for dementia care they can attain similar outcomes to specialists.

(World Alzheimer Report 2016, ADI)



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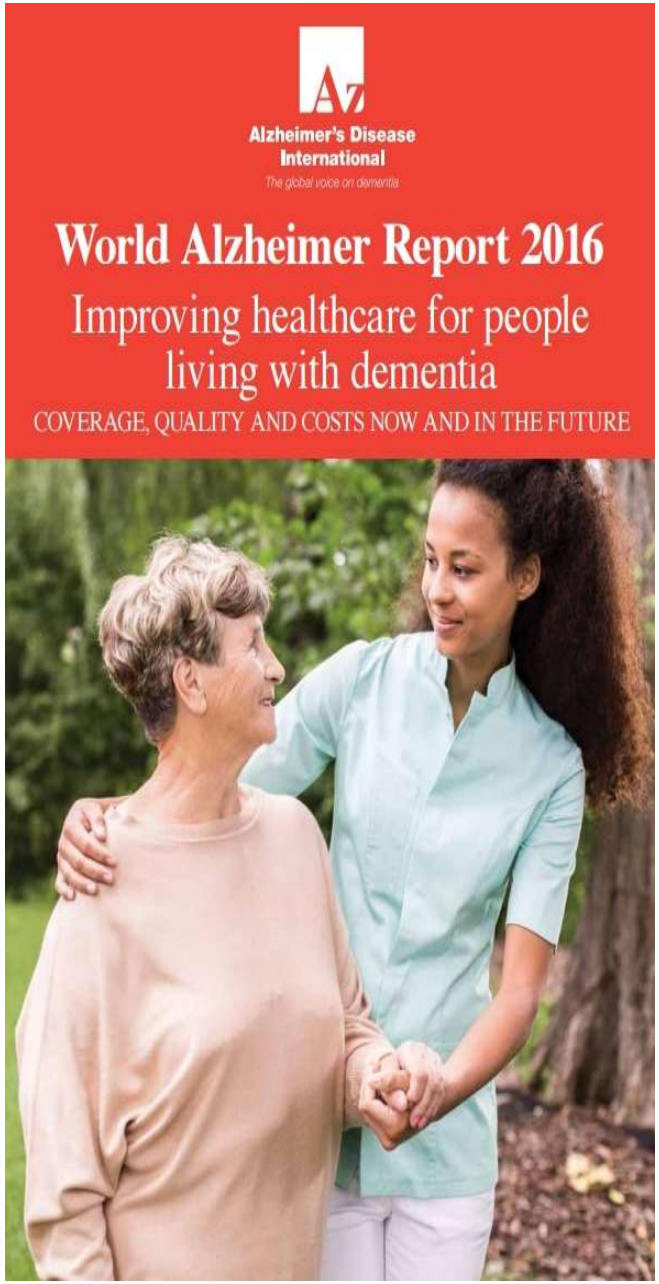
Importance of engagement of Family Physician in Dementia Care

- **Task-shifting and task-sharing with primary care services will be a core strategy for improving the coverage of diagnosis and continuing care**
  - Increasing the role of primary care services can unlock capacity within the system for diagnosis and continuing care, and may be up to 40% cheaper than specialist care in high income countries,e.g. from a neurologist to a primary care physician
  - Training, mentoring and support by specialists are essential.

(World Alzheimer Report 2016, ADI)



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<table>
<tr><td>Advocacy and Policy</td><td colspan="4">1. Primary Care Model For Early Dementia
2. Early Detection → Early Diagnosis → Early Intervention
3. Capacity Building (Medical and Social)
4. Medical and Social Collaboration → Task Shifting and Sharing
5. District based collaboration</td></tr>
<tr><td>Research</td><td colspan="3">1. Efficacy of FM in Diagnosis of Early Dementia (mainly Alzheimer’s Disease)
2. Primary Care Model - Medical-Social Collaboration (MSC)
3. Shorten waiting time to diagnosis and intervention
4. Primary Symptoms of Early Dementia in Community Sample
5. Carer Satisfaction</td><td>Training Manual for HKCOG
- Guidelines
- 100 Cases of Community Subjects with Early Dementia</td></tr>
<tr><td rowspan="2">Practice Model</td><td>FM Training</td><td>Early Diagnosis & Medical Intervention</td><td>- Feedback By Specialist Panel
- Follow Up</td><td>- Case Conference and Feedback</td><td rowspan="2">HKCOG</td></tr>
<tr><td>EDS</td><td>Certified Dementia Care Planner (CDCP)</td><td>Follow through patients</td><td>Day Centre Programme</td></tr>
</table>

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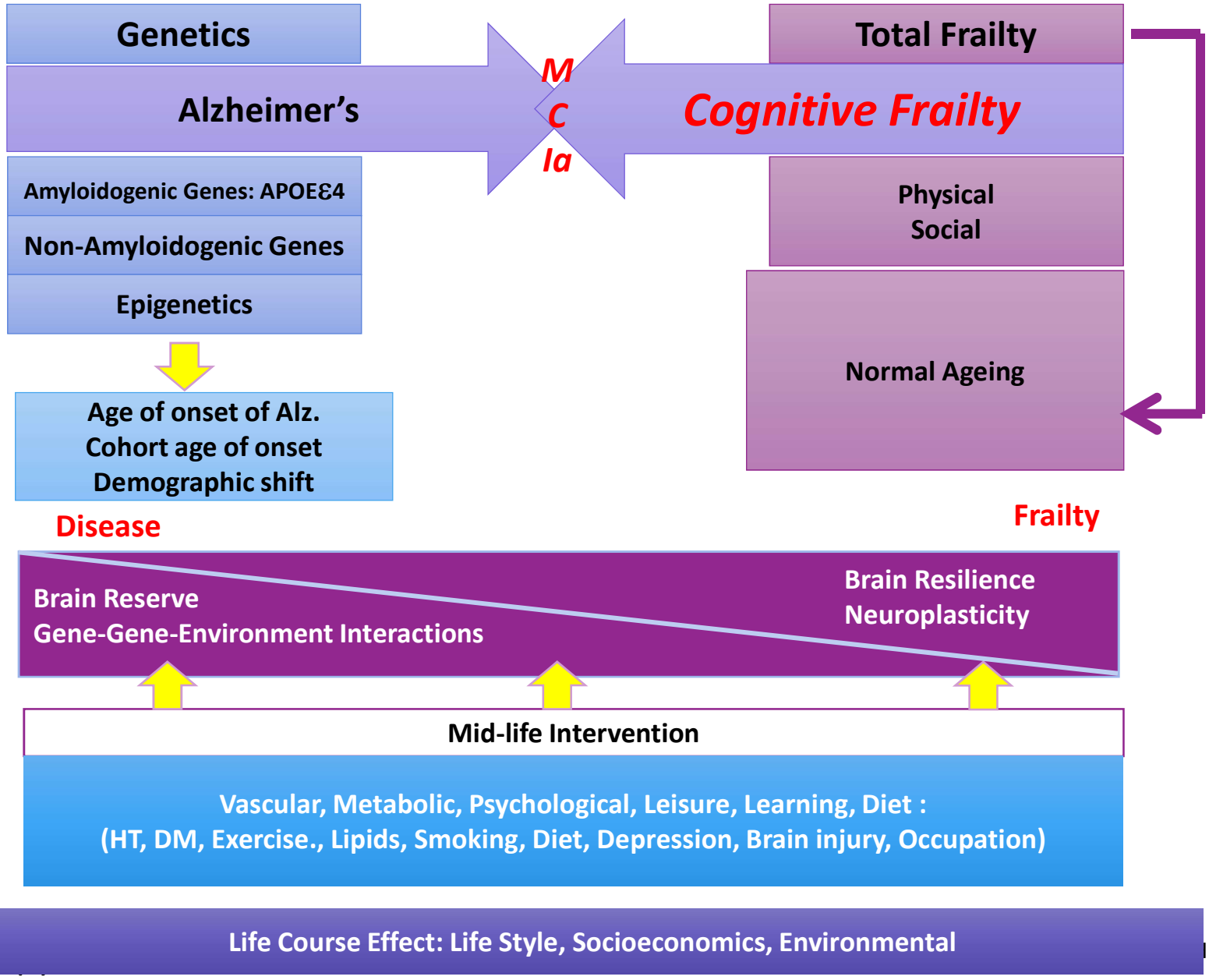
Unifying Concept of Alzheimer's & Cognitive Frailty 2017



Amnestic MCI (Petersen, 2001)

- Memory complaint, preferably corroborated by a informant
- Objective memory impairment for age and education
- Essentially preserved general cognition
- Preserved activities of daily living
- Not demented

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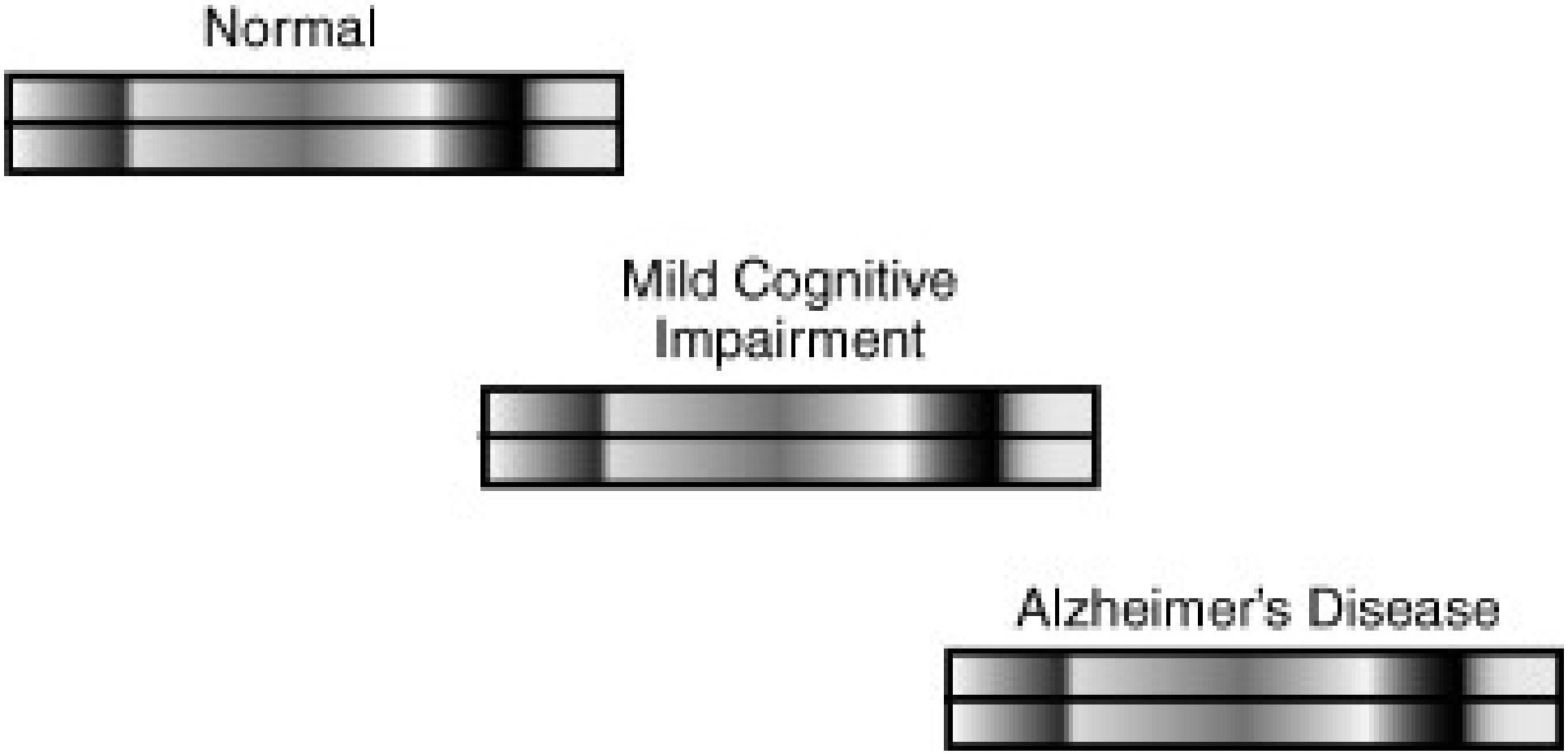

Fig 2. Cognitive continuum showing the overlap in the boundary between normal Ageing and mild cognitive impairment and Alzheimer's disease (adapted with Permission from Ref [link-RIDb1111]

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J Intern Med 2004; **256:** 183–194.

- Heterogeneity
- Uncertainty
- Ambiguity
- Poor conceptualisation

(Editorial, Lon S Schneider
Am J Geriatr Psy 2005; 138: 629-632)

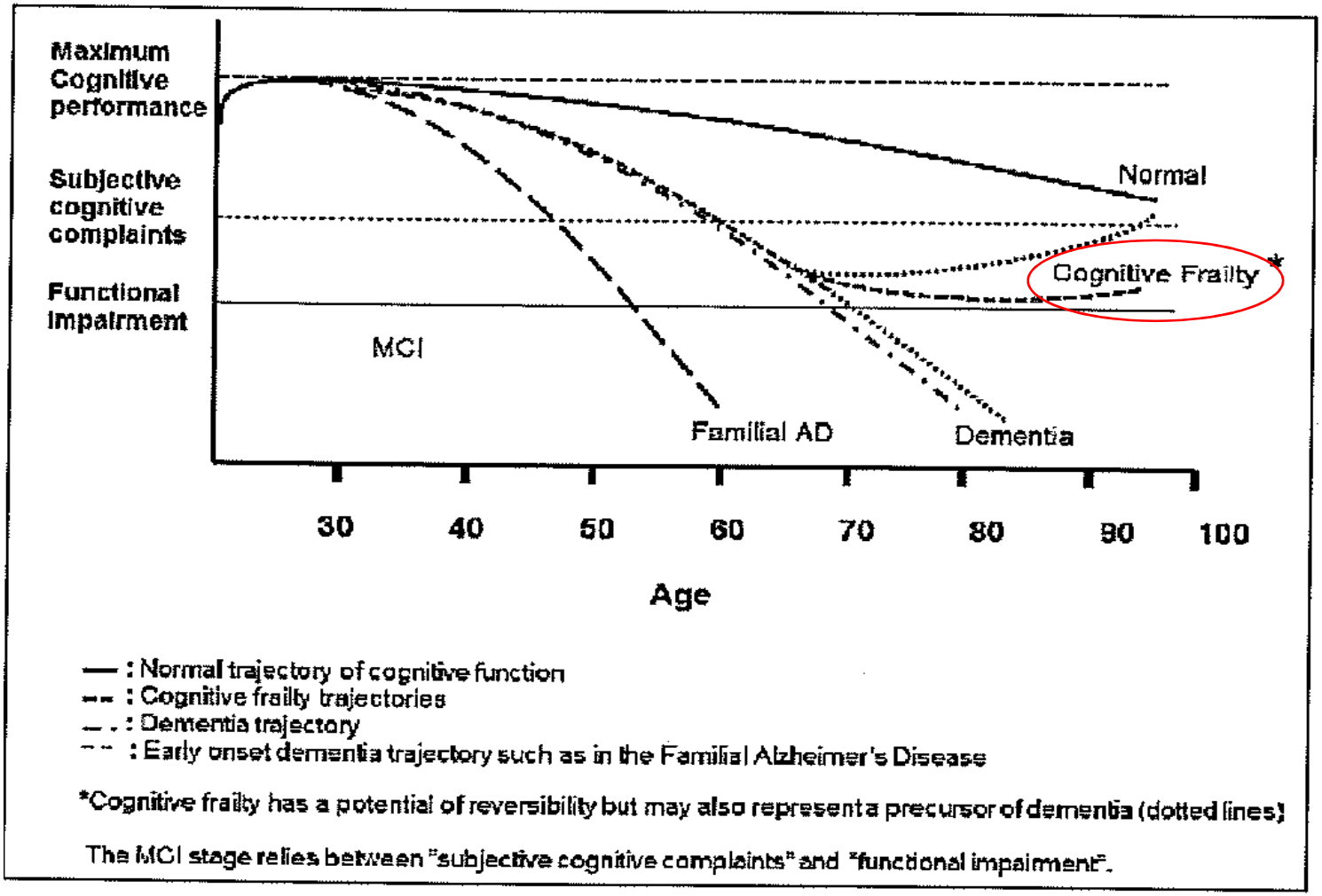
Table 1. Diagnostic criteria for mild cognitive impairment.

Definitions	Terminology for MCI	Requirements
Mayo Clinic	MCI	Subjective memory complaint either from the patient or reliable informant Normal cognitive function Objective memory impairment Preserved activities of daily living No dementia
Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders	Mild neurocognitive disorder	Noticeable cognitive decline from a previous level of performance in one or more cognitive domains) raised by the patient or an informant or observations made by a clinician Cognitive impairment doesn't interfere with independence or activities of daily living Cognitive symptoms are not due to delirium No dementia
International Working Group Criteria	Prodromal AD	Amnestic syndrome of the hippocampal type (Free and Cued Selective Reminding Test) specifically recommended). One or more positive *in vivo* evidence of Alzheimer's pathology in either cerebrospinal fluid (decreased $A\beta_{1-42}$) together with increased T-tau or P-tau or in PET with increased tracer retention on amyloid Absence of dementia
National Institute on Aging-Alzheimer's Association Workgroup	MCI MCI due to AD	Concern regarding cognitive a change in cognition (individual, informant who knows them well or clinician) Cognitive impairment in one or more domains Preservation of independence in functional abilities No dementia Positive or negative on biomarkers reflecting neuropathology (Aβ protein) and/or neuronal injury High likelihood: positive Aβ protein and neuronal injury biomarker. Intermediate likelihood: positive Aβ protein biomarker (neuronal injury biomarker not tested) OR positive biomarker of neuronal injury (Aβ biomarkers not tested) Unlikely: negative biomarkers for both Aβ and neuronal injury

$A\beta_{1-42}$: Amyloid β_{1-42}; AD: Alzheimer's Disease; MCI: Mild cognitive impairment.

Figure 2

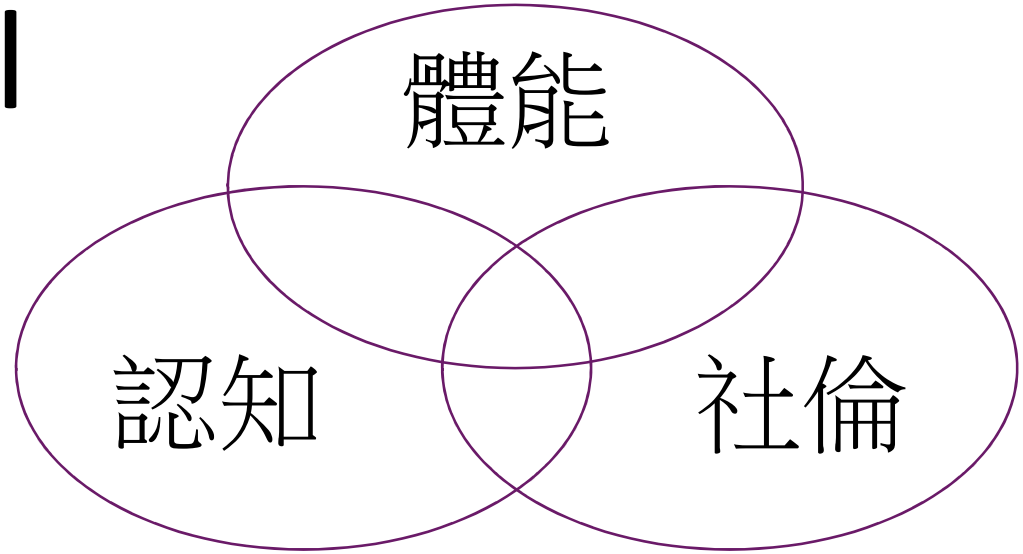
Different trajectories of cognitive function according to specific conditions



The J Nutrition, Health & Aging 2013; 17(9): 726-734

Total FRAILTY

- Physical
- Cognitive
- Psychosocial



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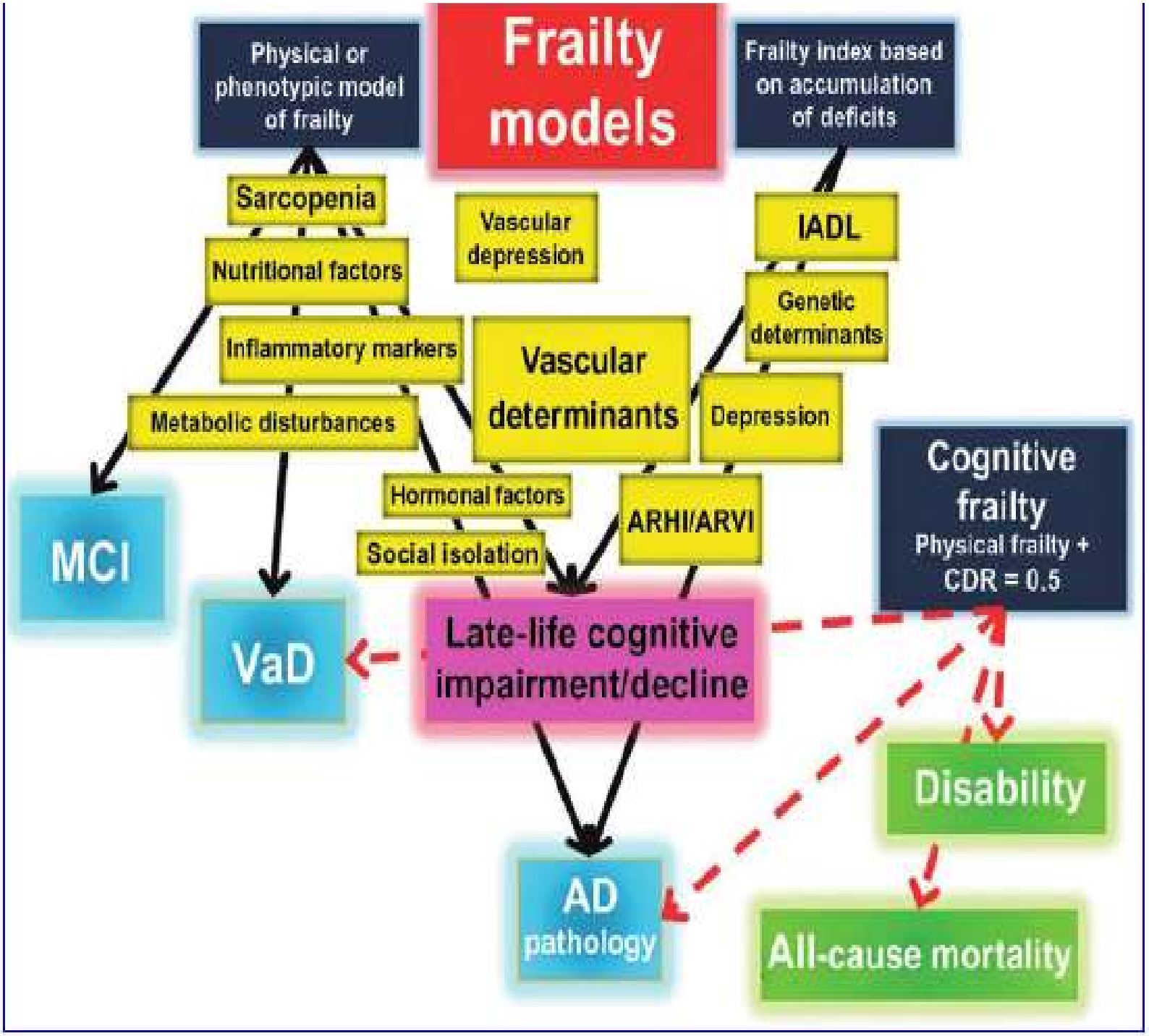
Frailty models
Physical or phenotypic model of frailty
Frailty index based on accumulation of deficits
Sarcopenia
Nutritional factors
Inflammatory markers
Metabolic disturbances
Vascular depression
Vascular determinants
Hormonal factors
Social isolation
IADL
Genetic determinants
Depression
ARHI/ARVI
MCI
VaD
Late-life cognitive impairment/decline
Cognitive frailty
Physical frailty + CDR = 0.5
Disability
AD pathology
All-cause mortality

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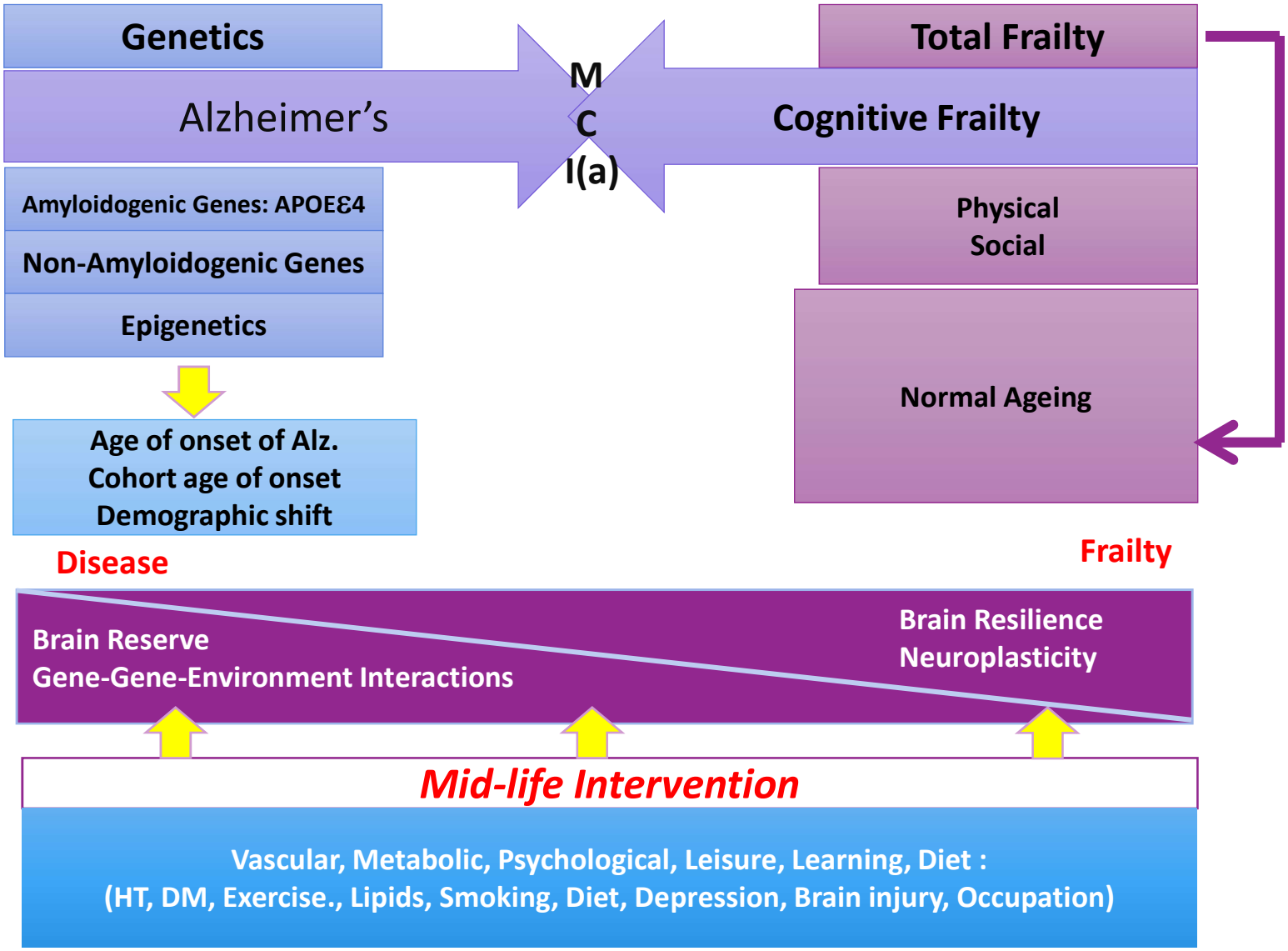


ELSEVIER

Alzheimer's & Dementia: Translational Research & Clinical Interventions 1 (2015) 122-130

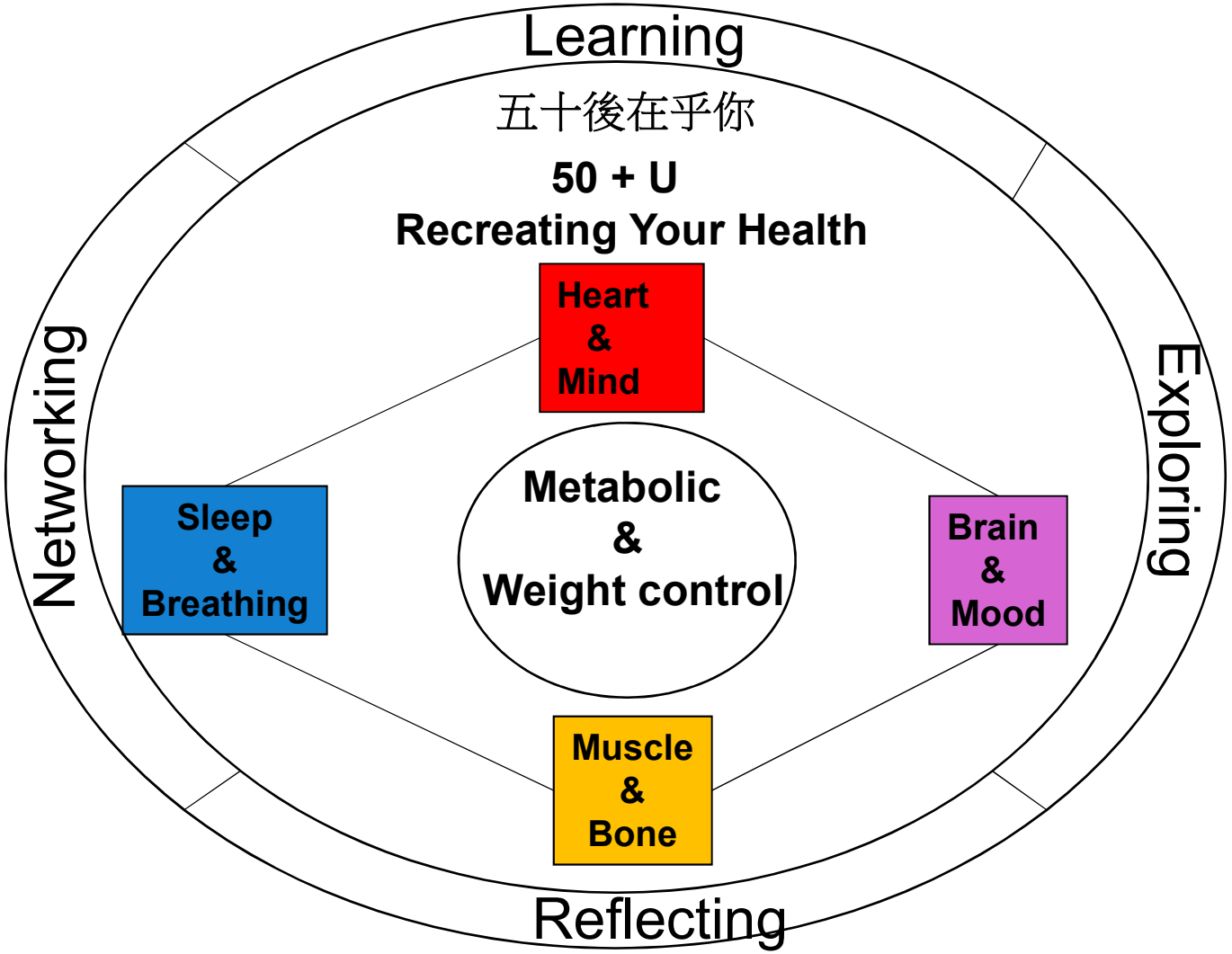
Alzheimer's & Dementia

Review Article

Is late-onset Alzheimer's disease really a disease of midlife?

Karen Ritchie[a,b,*,1], Craig W. Ritchie[c,d,1], Kristine Yaffe[e], Ingmar Skoog[f], Nikolaos Scarmeas[g,h]

[a]*Institut National de la Santé et de la Recherche Médicale, U1061 Neuropsychiatry, Montpellier, France*
[b]*Faculty of Medicine, University of Montpellier, France*
[c]*Faculty of Medicine, Imperial College London, UK*
[d]*Department of Psychiatry, University of Edinburgh, UK*
[e]*University of California at San Francisco, USA*
[f]*Centre for Health and Ageing (AgeCap), Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Sweden*
[g]*Department of Social Medicine, Psychiatry and Neurology, National and Kapodistrian University of Athens, Greece*
[h]*Taub Institute for Research in Alzheimer's Disease and the Aging Brain, the Gertrude H. Sergievsky Center, Department of Neurology, Columbia University, New York, NY, USA*



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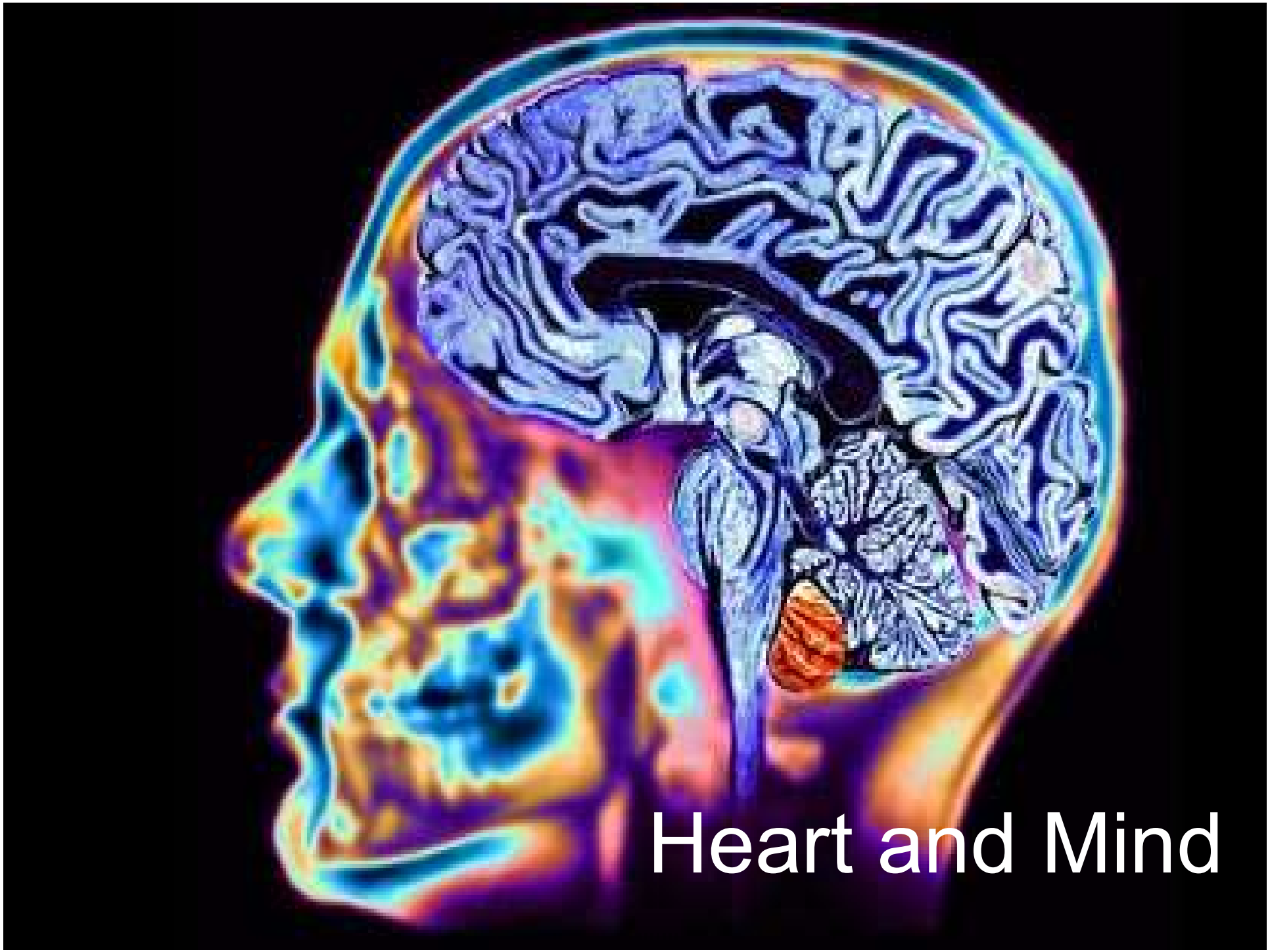
Heart and Mind

Heart and Mind

(J Int Med 2015, 277; 426-428)

- Sporadic AD: multiple genetic, epigenetic, environmental, lifestyle, behavioral factors against a background of senescence-related diseases and functional/cognitive declines

- **Brain hypoperfusion:**

hypertension, hypotension,

arterial stiffness, atherosclerosis, myocardial infarction, valvulopathies, arrhythmias, cardiomyopathies

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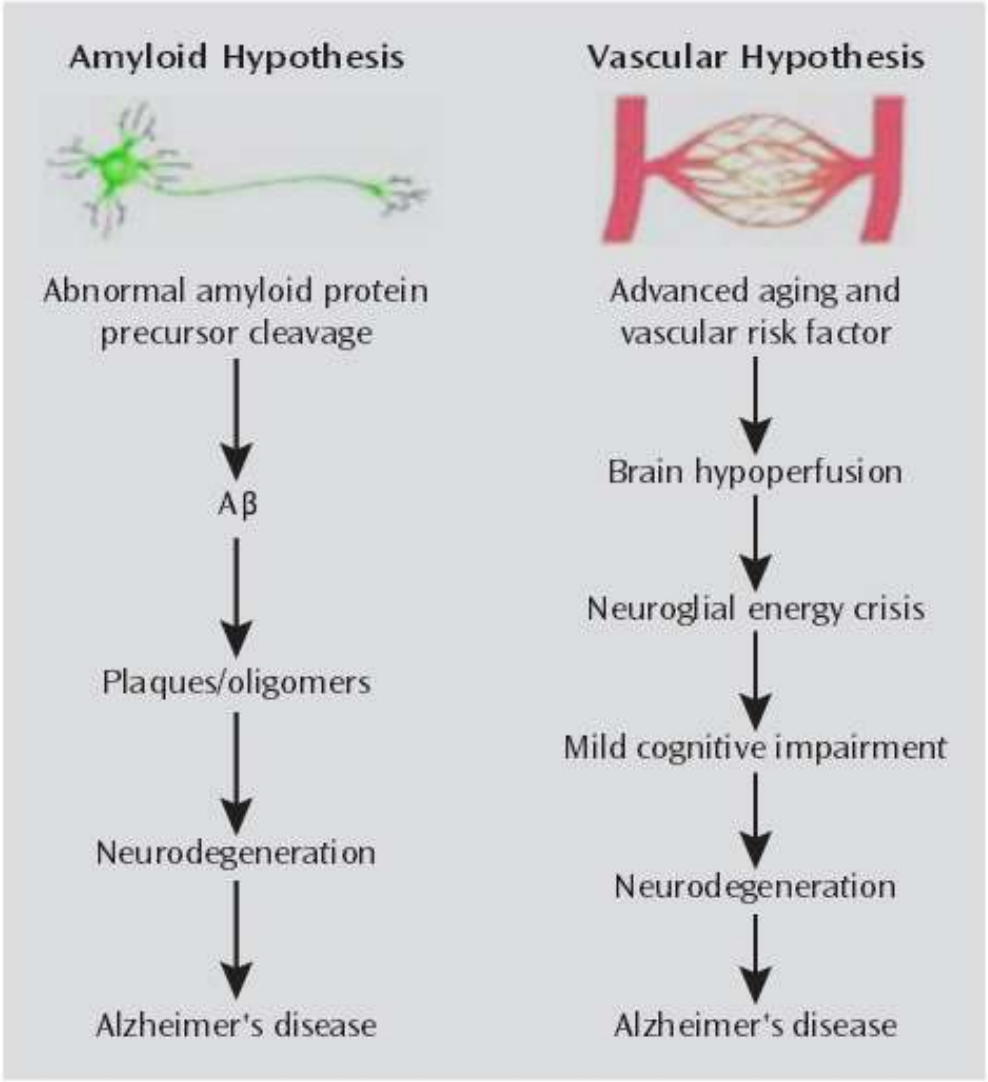
Figure 1. Two Theories of Alzheimer's Disease[a]



[a] The original amyloid hypothesis has been modified to implicate soluble oligomers (rather than plaques) as the neurotoxic trigger. The vascular hypothesis posits that amyloidogenesis is a consequence of hypoperfusion. Some evidence suggests that the two insults may be synergistic, highlighting the need to better integrate both theories. (Figure adapted/modified with permission from de la Torre JC, "Is Alzheimer's Disease a Neurodegenerative or a Vascular Disorder? Data, Dogma, and Dialectics" [Lancet Neurol 2004; 3:184–190]. Copyright © Elsevier 2004).

Can we save the brain from the ravages of midlife CVDRFs

(Neurology 1999, 52(6): 1114-1115)

Currently, we should double our efforts to detect and control modifiable cardiovascular risk factors that decrease the brain volume

(Gorelick, Editorial)

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DM, Cognitive and Dementia

(Int J Environ Res PH 2015, 12, 8281-8294)

- Hyperglycemia
- Hyperinsulinaemia
- Comorbid vascular risk (hypertension, obesity)
- Dislipidemia (high TGs, Low HDL, dense LDL)
- Cerebrovascular dysregulation (endothelial dysfunction, microinfarcts, WMD)
- Amyloid-B metabolism (generation and clearance)
- inflammation

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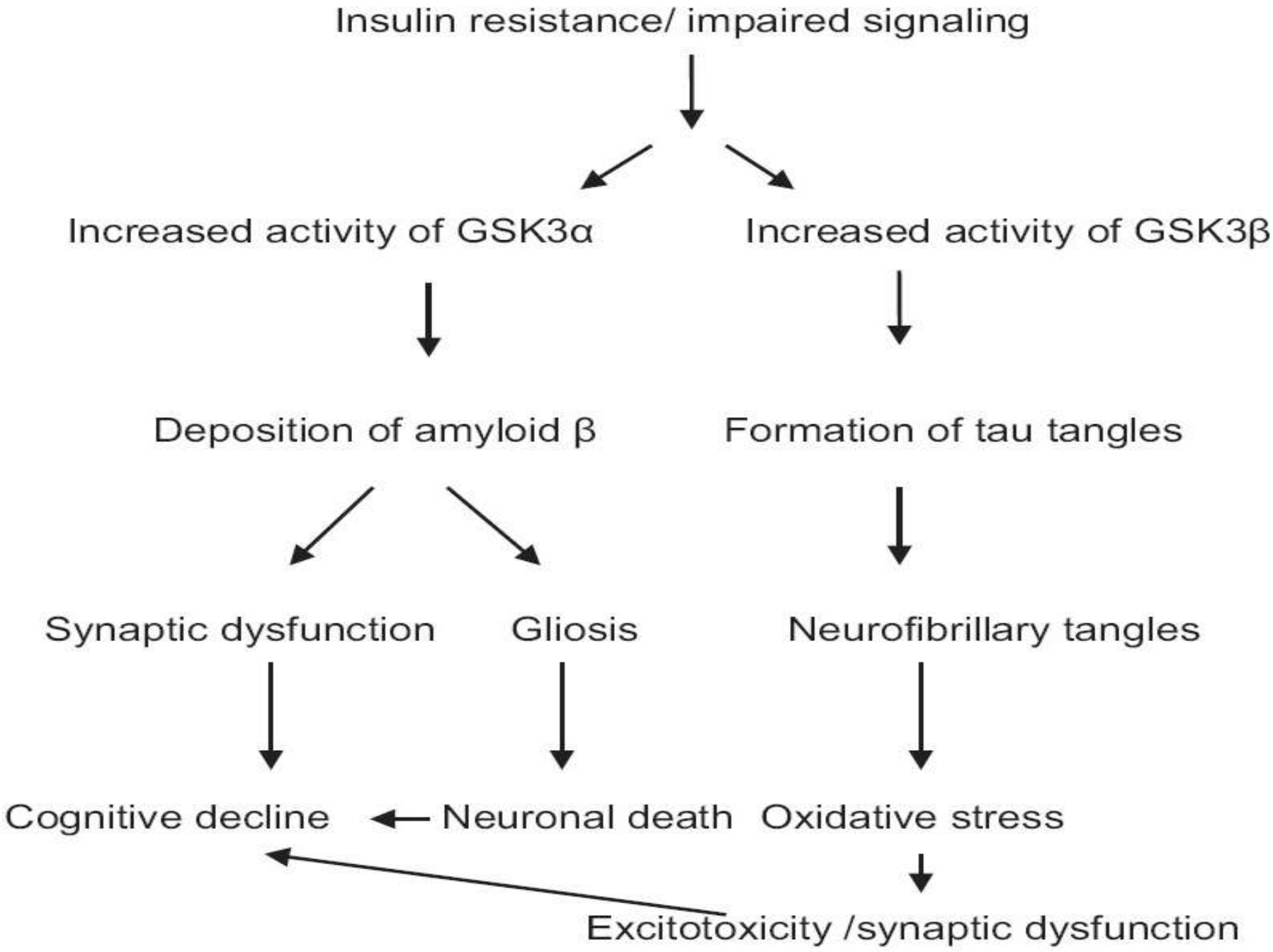


Link between insulin defects and the formation of major pathological hallmarks in AD

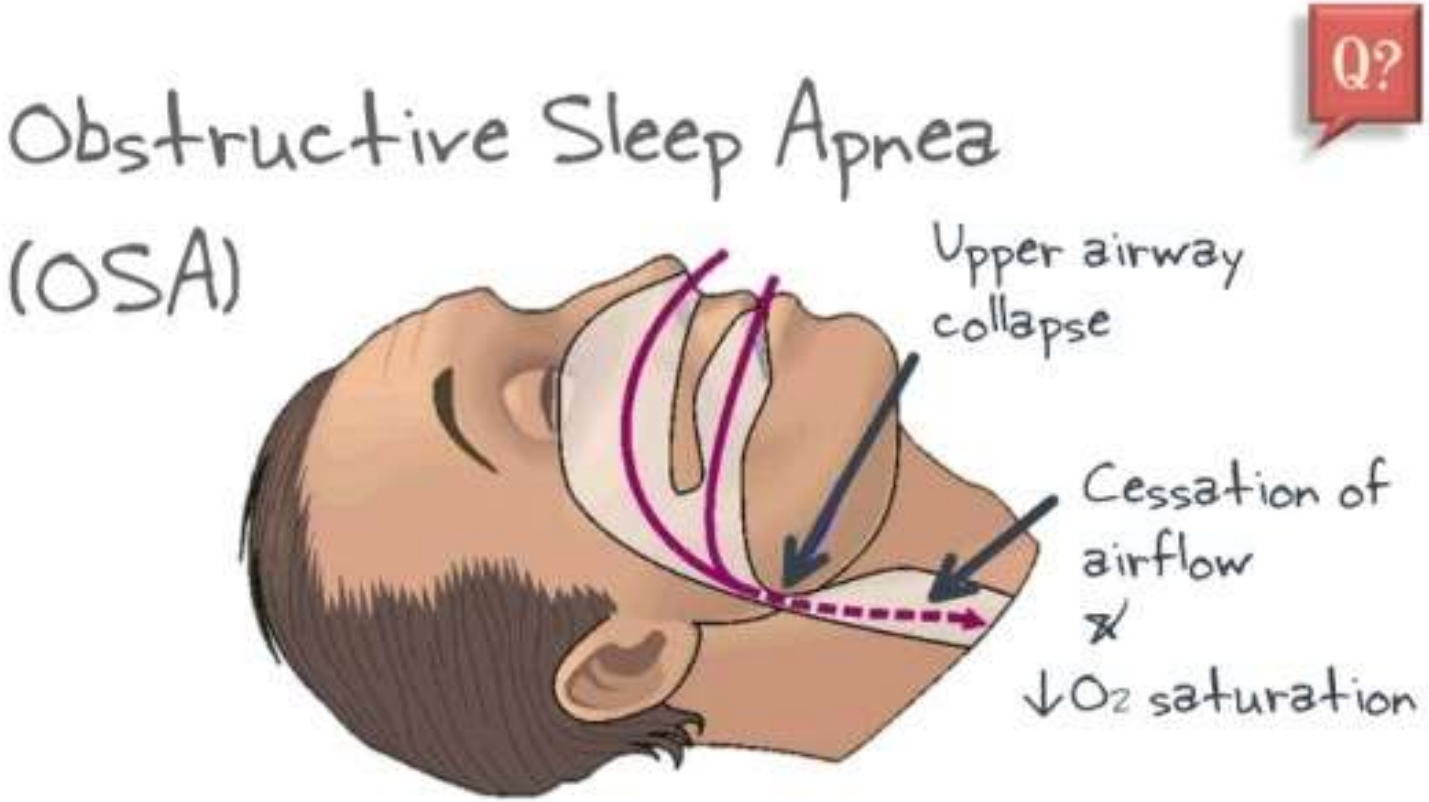
Indian J Pharm Sci. 2015 Sep-Oct; 77(5): 511–514

Cerebral(Type III) Diabetes

(Indian j Pharm Sci 2015; 77(5):5111-514)

- Hyperinsulinemia induced insulin resistance activated glycogen synthase kinase 3B, key in cognitive decline
- Hippocampus and amygdala atrophied in DM, reducing cognitive reserve
- DM confer a RR of 1.46 for AD
- Chronic hypoglycemia lead to brain damage
- DM promote neurodegeneration independent of AD, via tau phosphorylation (Neurology 2015; 85:1123-1130)

Sleep and breathing



Watch the diagram above for a visual depiction of sleep apnea

Diagnosis | Definitions | Treatment | Summary

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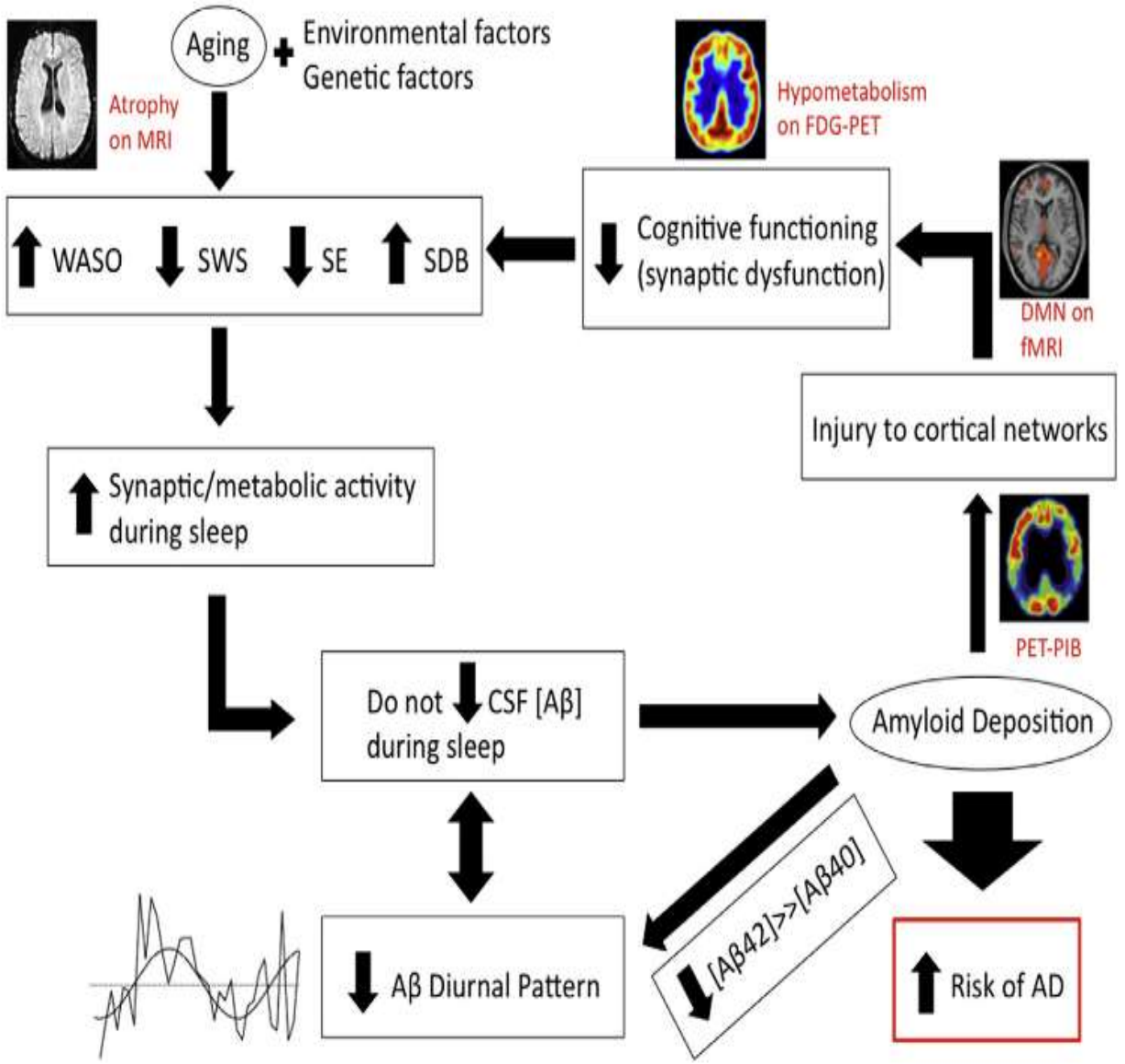
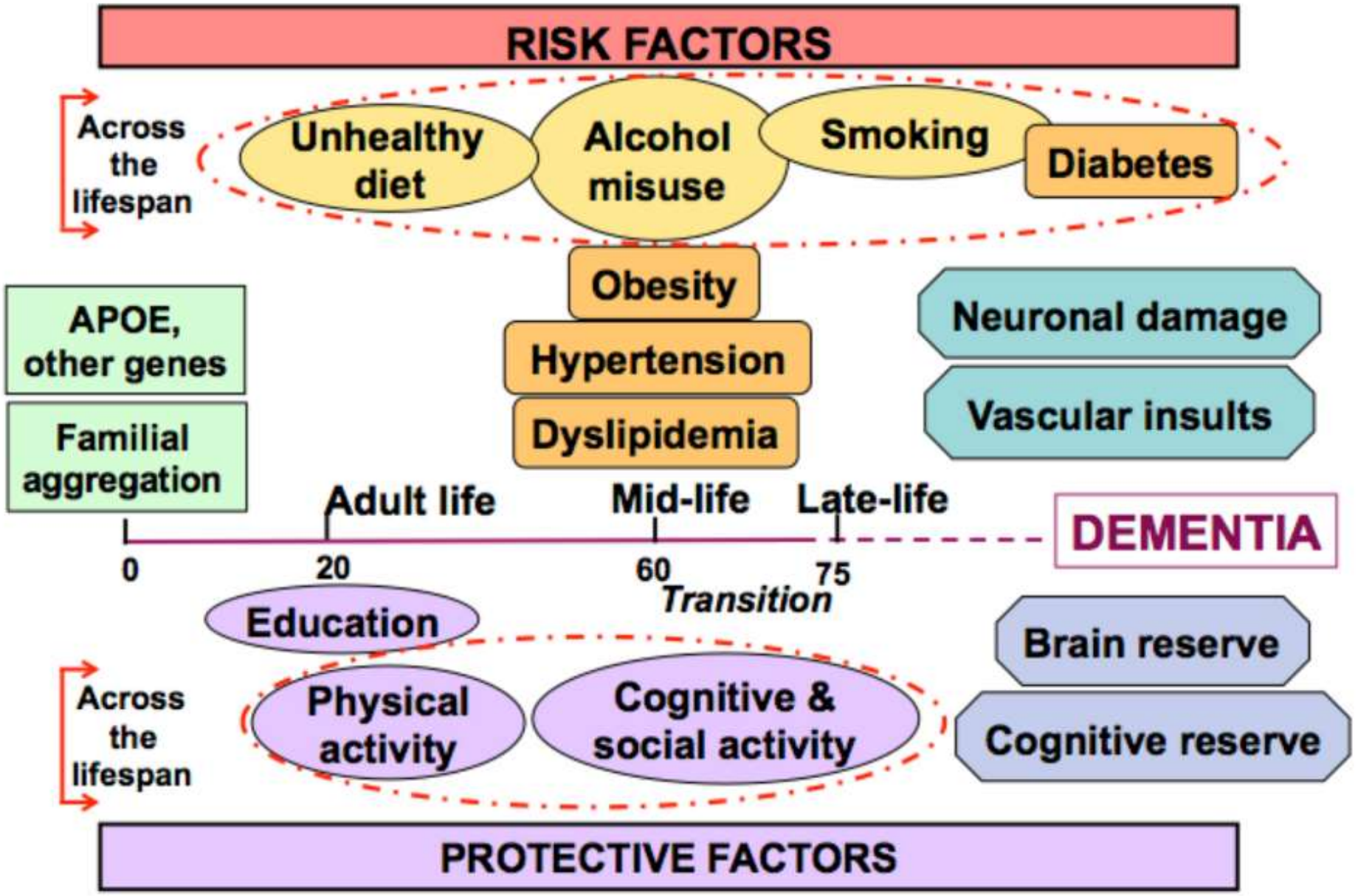


Fig. 2. Hypothetical model for the role of sleep in Alzheimer's disease pathogenesis. Abbreviations: Aβ, amyloid-beta; CSF, cerebrospinal fluid; DMN, default mode network; FDG, fluorodeoxyglucose; fMRI, functional MRI; MRI, magnetic resonance imaging; PET, positron emission tomography; PIB, Pittsburgh compound B; SE, sleep efficiency; SWS, slow wave sleep; SDB, sleep disordered breathing; WASO, wake after sleep onset.

Neurobiology of Aging 2014;35:S29-S34

Figure 1. Risk factors for dementia and Alzheimer's disease across the lifespan (Figure modified from [51])



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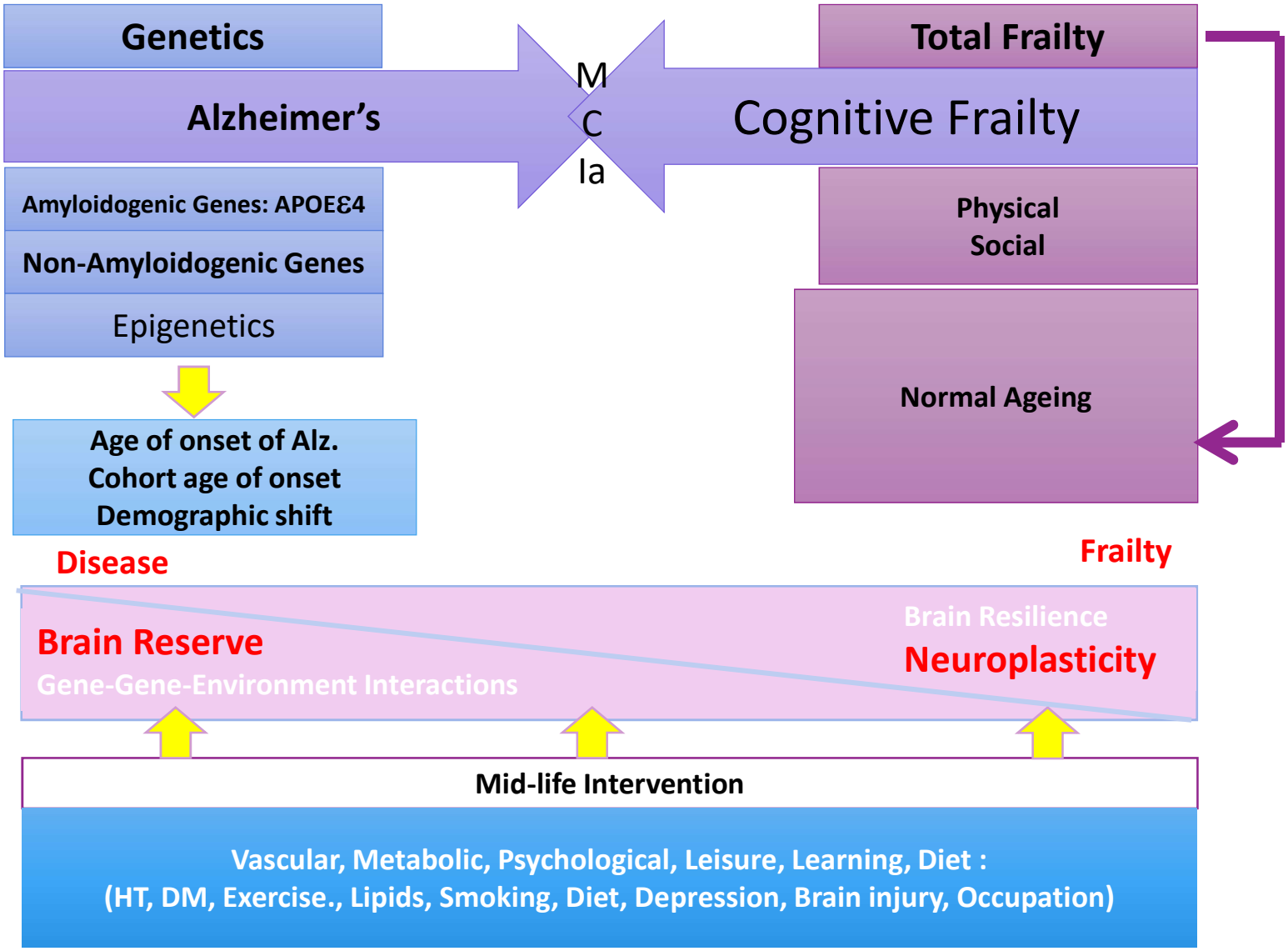
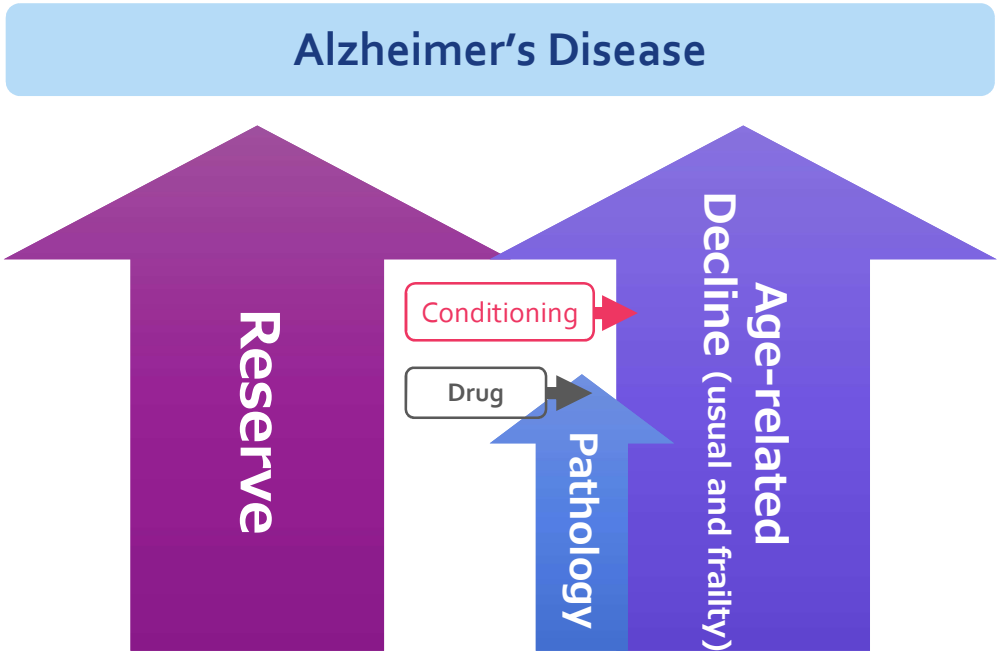


The Concept of Reserve

Leveraging on Brain & Cognitive Plasticity

- Mature adult brain to sustain the effect of disease or injury sufficient to cause clinical dementia in an individual possessing less cognitive reserve
- No direct relationship between degree of brain pathology/damage & clinical manifestation



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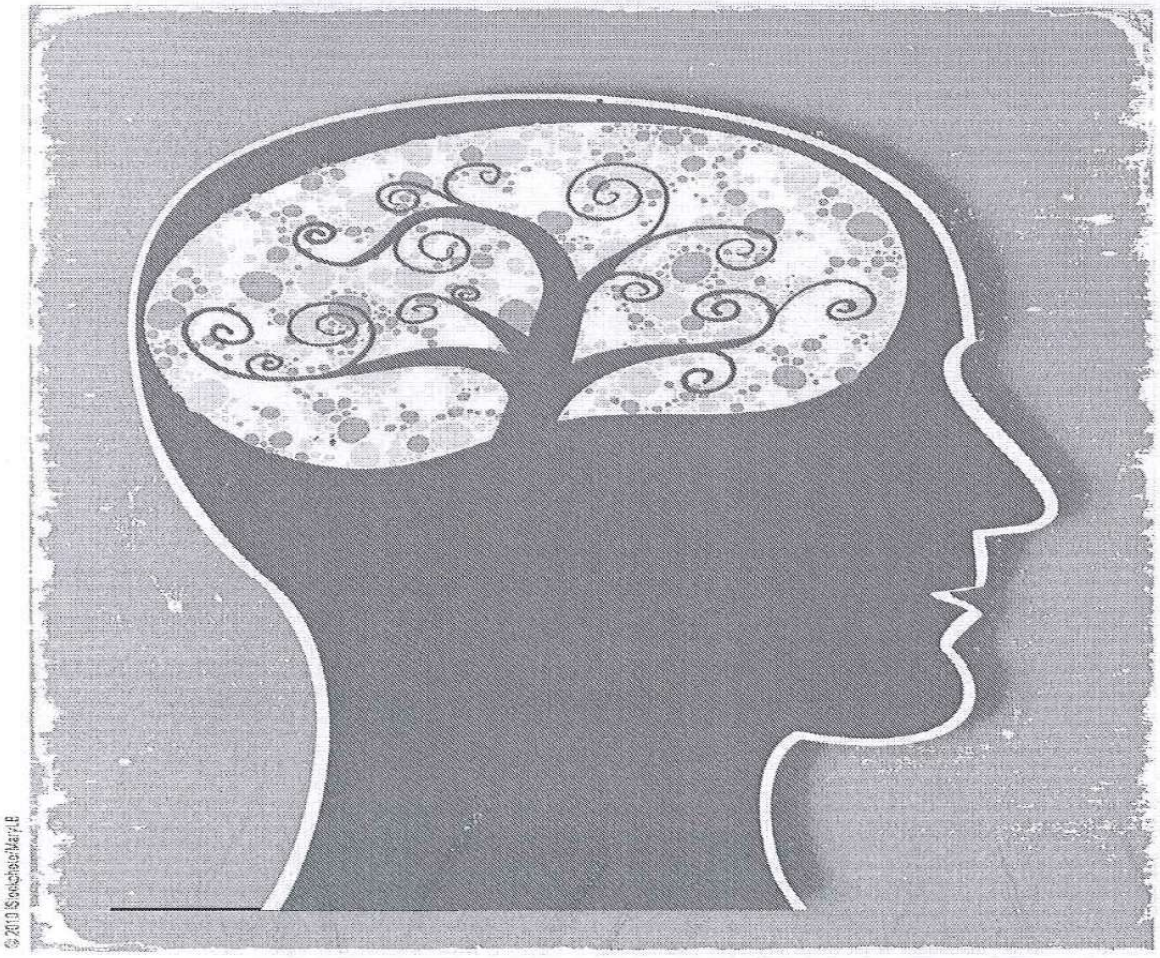
J Psychosocial Nursing 2010 (48);4:23-30

Earn 4.0 Contact Hours

How Neuroplasticity and Cognitive Reserve

Protect Cognitive Functioning



ABSTRACT

Overall cognitive status can vary across an individual's life span in response to factors that promote either positive or negative neuroplasticity. *Positive neuroplasticity* refers to the physiological ability of the brain to form and strengthen dendritic connections, produce beneficial morphological changes, and increase cognitive reserve. *Negative neuroplasticity* refers to the same physiological ability of the brain to atrophy and weaken dendritic connections, produce detrimental morphological changes, and decrease cognitive reserve. Factors that promote positive neuroplasticity include physical activity, education, social interaction, intellectual pursuits, and cognitive remediation. Factors that promote negative neuroplasticity include poor health, poor sleep hygiene, poor nutrition, substance abuse, and depression and anxiety. Implications for promoting positive neuroplasticity and avoiding negative neuroplasticity across the life span are emphasized to facilitate optimal cognitive health and ensure successful cognitive aging.

David E. Vance, PhD, MGS; Anthony J. Roberson, PhD, PMHNP-BC;

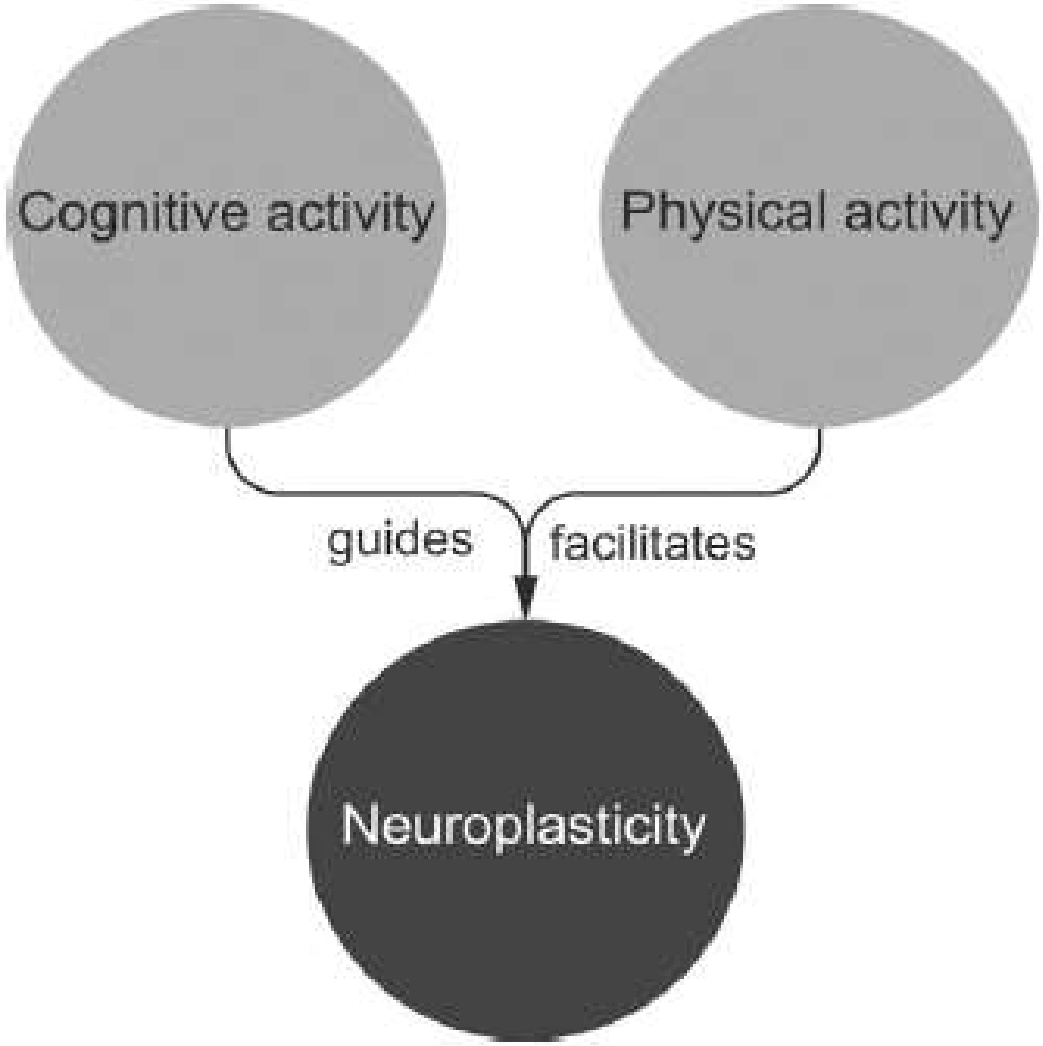


Fig. 1. Guided plasticity facilitation framework.
Figure is adapted from Fissler et al. (2013).

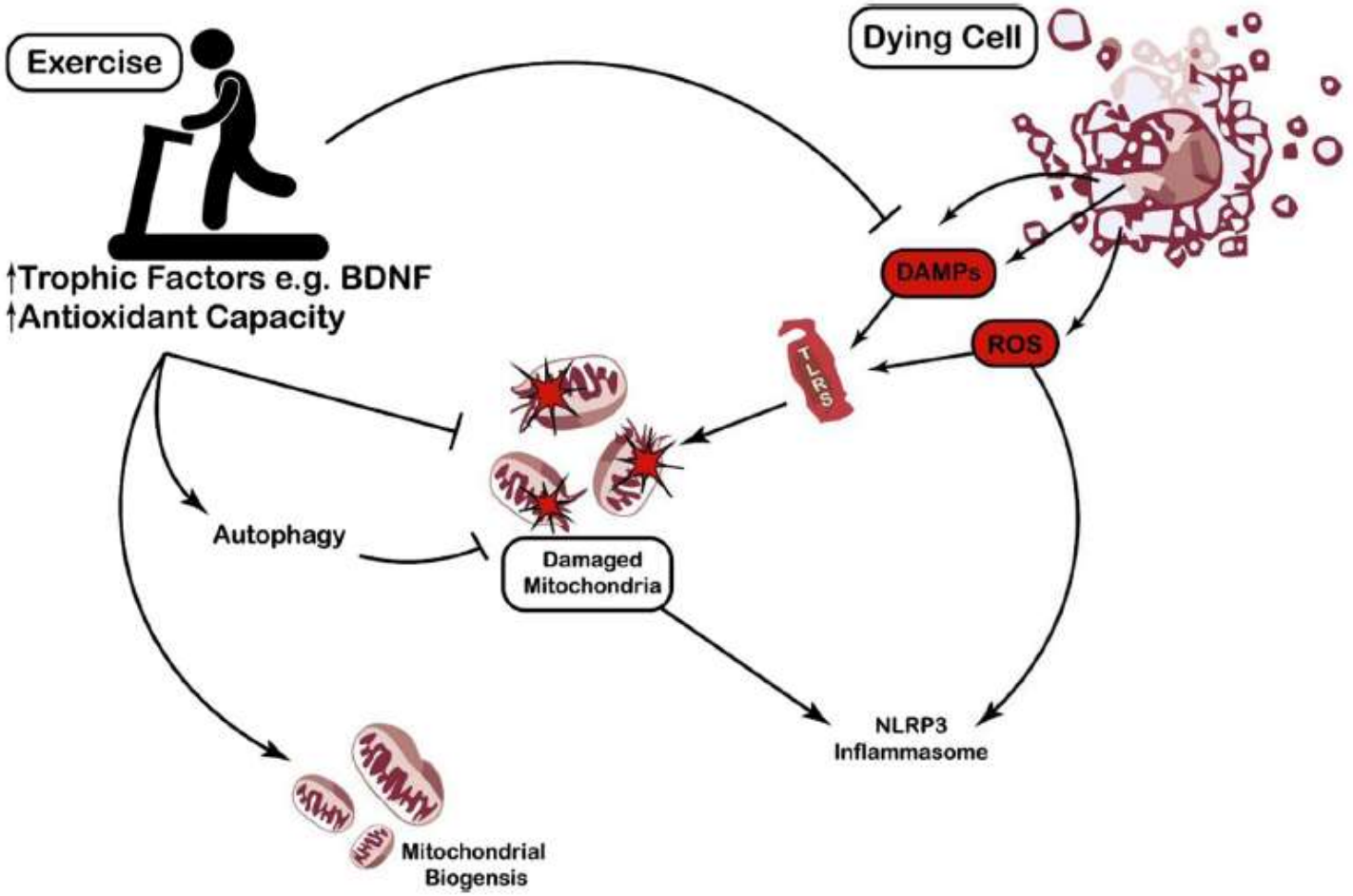


Fig. 1. A hypothetical role of exercise in controlling of mitochondrial ROS-induced inflammasome formation through increasing trophic factors (e.g. BDNF) that promote autophagy activation, mitochondrial biogenesis and antioxidant capacity.

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Low-Intensity Daily Walking Activity is Associated With Hippocampal Volume in Older Adults

Vijay R. Varma,[1,2*] Yi-Fang Chuang,[3,4] Gregory C. Harris,[1,2] Erwin J. Tan,[5] and Michelle C. Carlson[1,2*]

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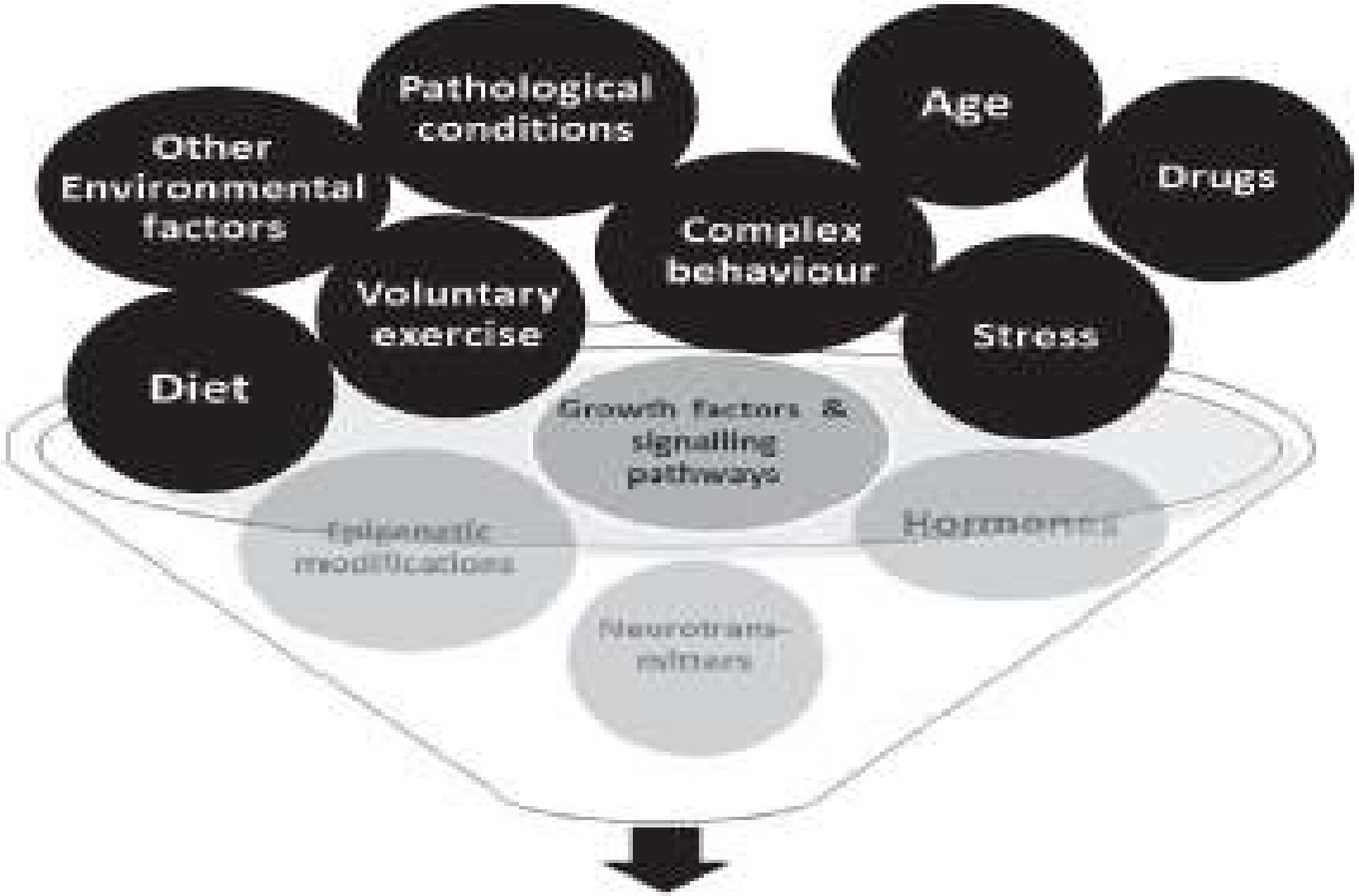

Fig. 1. Interplay between several extrinsic and intrinsic factors shapes adult hippocampal neurogenesis.

Leisure

"It seems prudent to encourage persons of **all ages, not just older persons**, to engage in an active lifestyle that includes frequent participation in a wide range of **cognitively, physically,and socially challenging activities**, but to turn the TV off."

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(Neurology 2006: 66: 794-795)

Multidimensional Activities

Building Cognitive Reserve

Participatory art improves cognitive functioning, communication, self-esteem, pleasure, enjoyment of life & memory in old age:

- Music (singing & playing musical instruments)
- Drama
- Visual arts
- Storytelling
- Mixed art forms

Also increases levels of general daily activity, improved breathing, joint mobility, and CV health

UK Mental Health Foundation 2011
(Review of 31 studies in 2,040 elders from western countries: UK, US, Australia, Canada, Spain & Sweden)

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Rowe and Kahn 1997

Selective Neuronal Vulnerability & Neuroplasticity

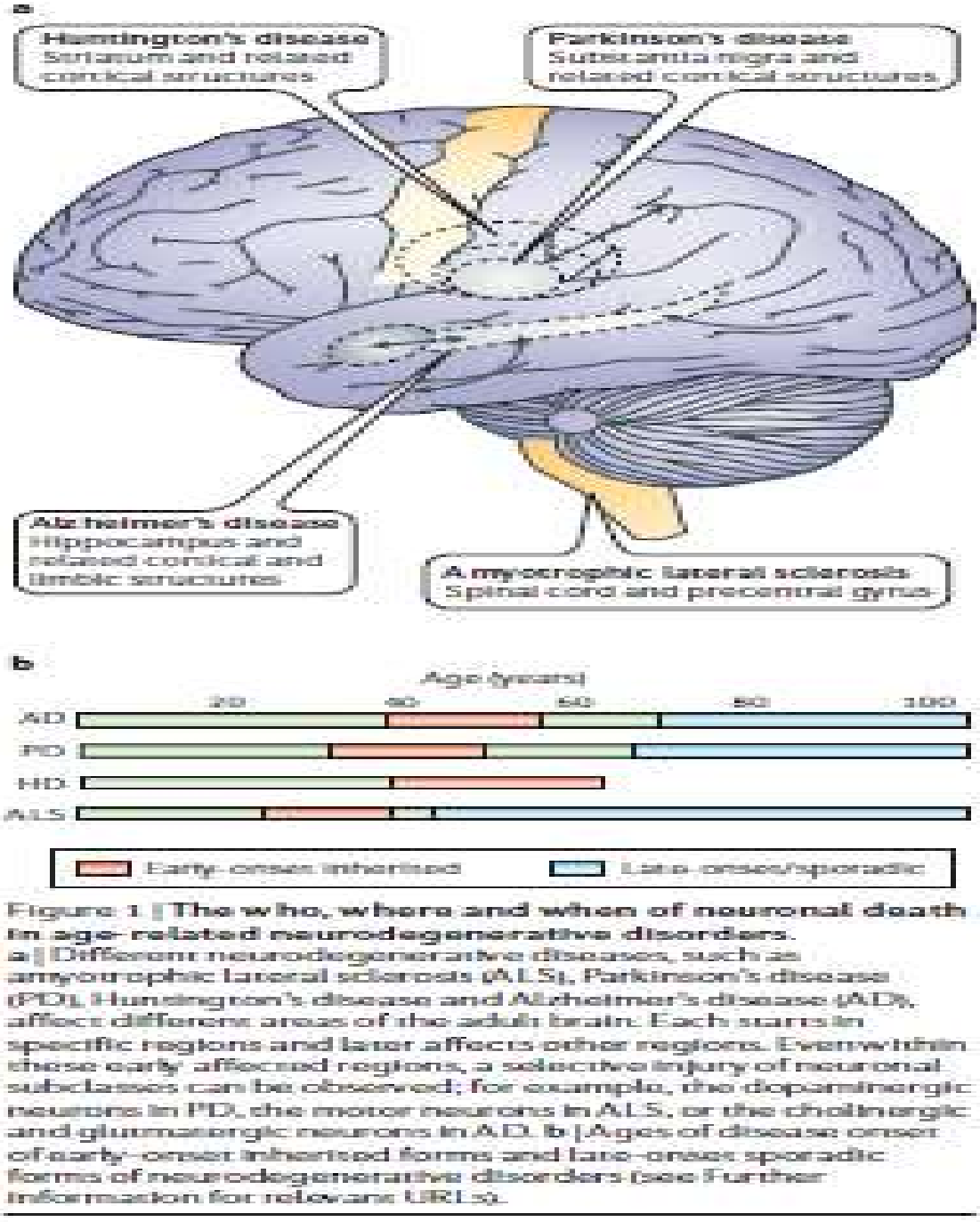

Figure 1 | **The who, where and when of neuronal death in age-related neurodegenerative disorders.** a | Different neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Huntington's disease and Alzheimer's disease (AD), affect different areas of the adult brain. Each starts in specific regions and later affects other regions. Even within these early affected regions, a selective injury of neuronal subclasses can be observed; for example, the dopaminergic neurons in PD, the motor neurons in ALS, or the cholinergic and glutamatergic neurons in AD. b | Ages of disease onset of early-onset inherited forms and late-onset sporadic forms of neurodegenerative disorders (see Further information for relevant URLs).

Selective neuronal vulnerability

(Prog Neurobiol 2014 June;117:20-40)

- Neuroplasticity
- Medial temporal lobes and other parts of DMN in learning and memory, with high demands for life-long plasticity
- Neuroplasticity higher in limbic system; MTL in learning and memory
- Activity-dependent amyloid accumulation
- Cognitively active persons develop more efficient ways of performing tasks and produce less Aß

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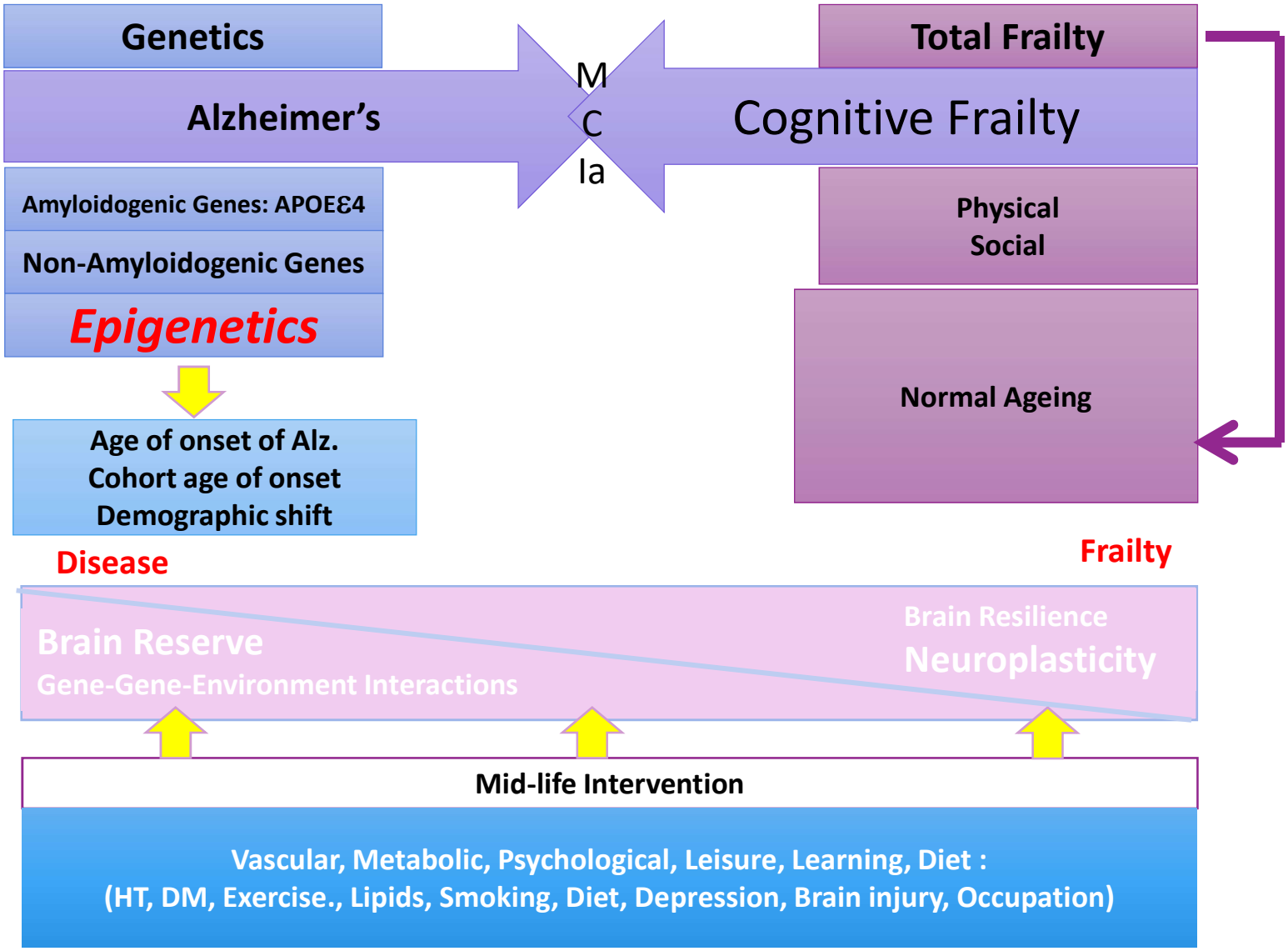
Unifying Concept of Alzheimer's & Cognitive Frailty 2017



Epigenetics

(Exp Geron 2015,68: 81-12; JAMA Neurol 2013 ; 70(6): 711-718)

- Different biological traits that are responsible for regulation of gene expression through the interaction with the DNA sequence of a gene, without altering the DNA sequence
- Many different environmental factors (nutrients, pollutants, chemicals, physical activity, lifestyle, physical and mental stress)
- Genetic influences on longevity account for 25 % of the variance and environmental and lifestyle factors govern the remaining 75%

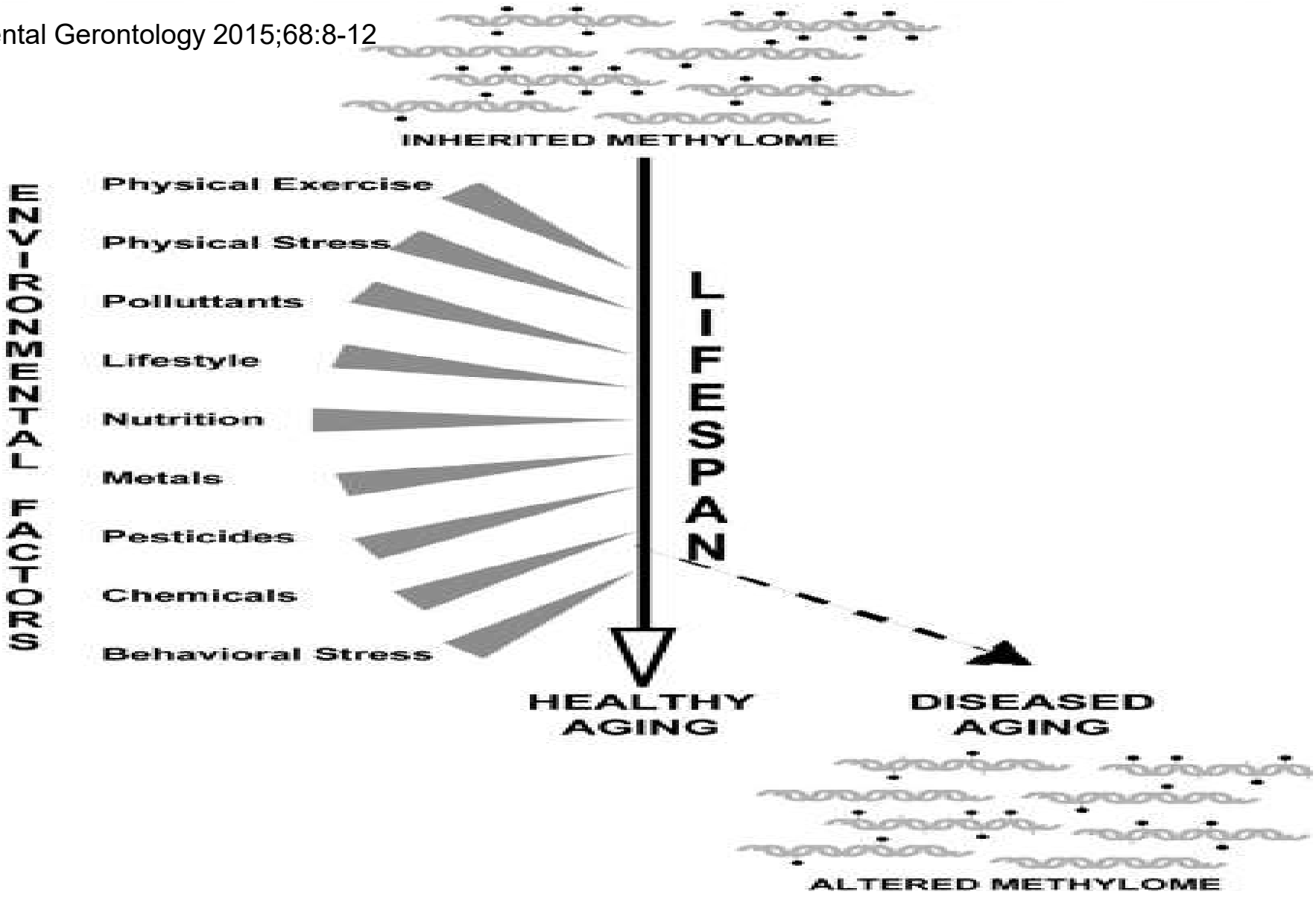


Fig. 1. Environmental factors modify aging through epigenetics. Several environmen factors can affect the metabolism of an individual by inducing epigenetic modificatio The figure depicts the inherited DNA methylation pattern which can be modified at lo and sequence-specific levels by different (even mild) stressors. The modification of t inherited methylome (or of the epigenome, in general) can be responsible for t alteration of the expression of specific (aging-associated) genes, leading to conditions diseased aging.

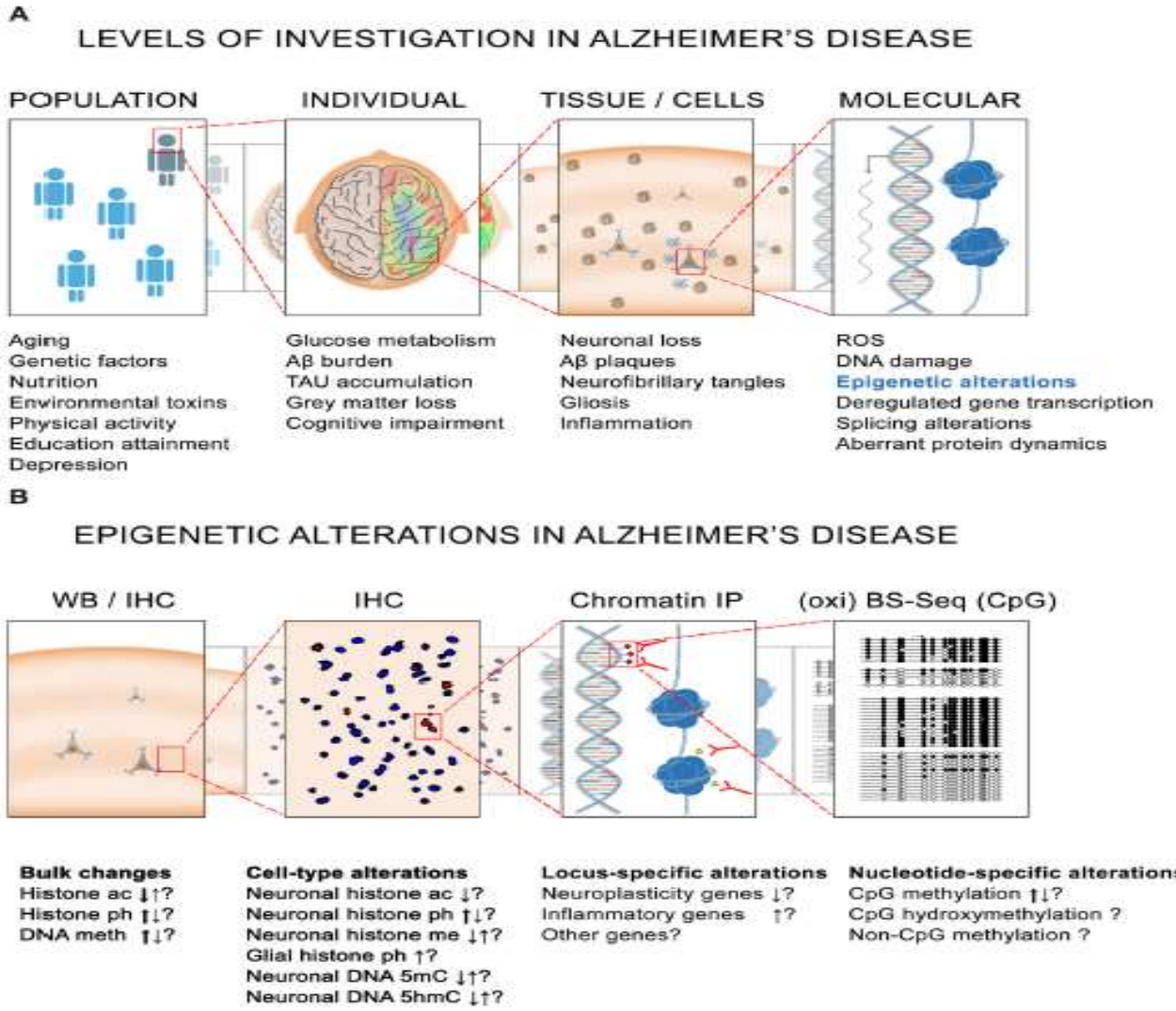


FIGURE 1 | Epigenetics in Alzheimer's disease (AD). (A) Different levels of investigation in AD pathology. At the population level, several genetic and non-genetic factors contribute to the risk for developing the disease. At the level of the individual, several pathophysiological characteristics such as altered glucose metabolism are observed in the brain of cognitively impaired AD patients. Associated with these alterations are – at the tissue and cellular level – yet other pathological hallmarks such as the presence of amyloid plaques and neurofibrillary tangles. Finally, at the intracellular level, higher levels of reactive oxygen species (ROS) and DNA damage, together with dysregulated gene transcription, splicing alterations and aberrant protein dynamics are also believed to be implicated in the onset and development of the pathology. **(B)** Similarly, epigenetic alterations have been reported in AD at different levels. Bulk histone acetylation (ac), phosphorylation (ph), and methylation (me) changes as well as DNA methylation (5mC) and hydroxymethylation (5hmC) alterations have been reported in AD tissues by IHC and WB. Major tendencies for these changes (as observed by several studies) are indicated by thick arrows. Locus-specific alterations mainly causing a repression of neuroplasticity genes and an activation of inflammatory genes have also been observed by ChIP using antibodies against histone modifications. Greater resolution is also possible for DNA methylation analysis in which nucleotide-specific alterations can be detected by oxi- and BS-sequencing. BS, bisulfite sequencing; ChIP, chromatin immunoprecipitation; CpG, cytosine-guanine dinucleotide; IHC, immunohistochemistry; IP, immunoprecipitation; WB, western blotting.

Adaptative Response Hypothesis

Strategies to improve response to stress:

- Caloric restriction
- Exercise
- Environmental enrichment
- Neonatal handling
- Supplementation in antioxidants

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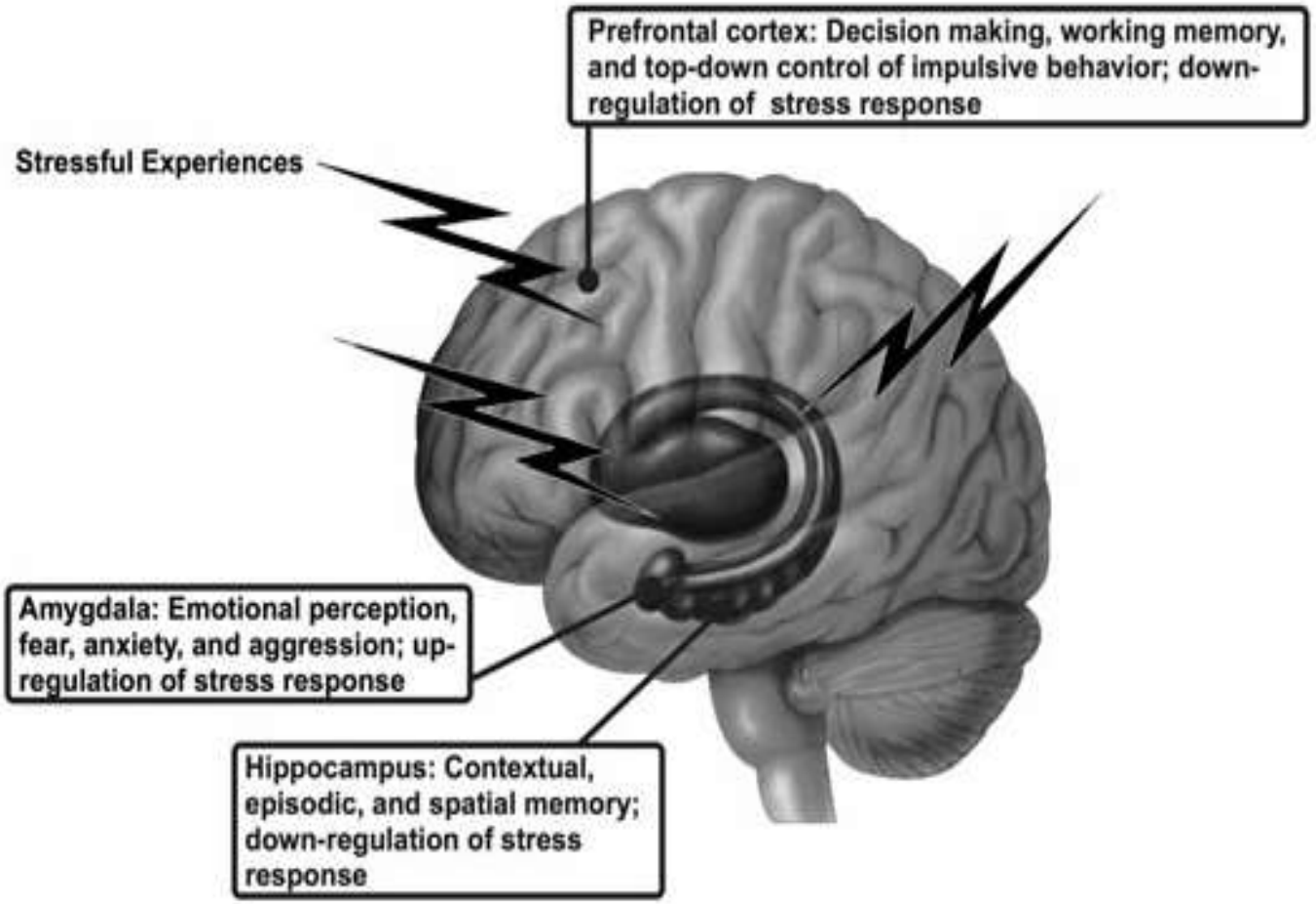

Figure 1. Schematic illustration of the location and key functions of limbic brain areas that play an integrated role in cognitive, emotional, and visceral control processes important for allostasis, allostatic load, and stress responding. Each of the three brain areas is discussed in detail in the text in relation to both animal model studies that focus on what happens at the cellular and molecular levels and studies on the human brain using functional and structural imaging and neuropsychological and neuroendocrine assessments.

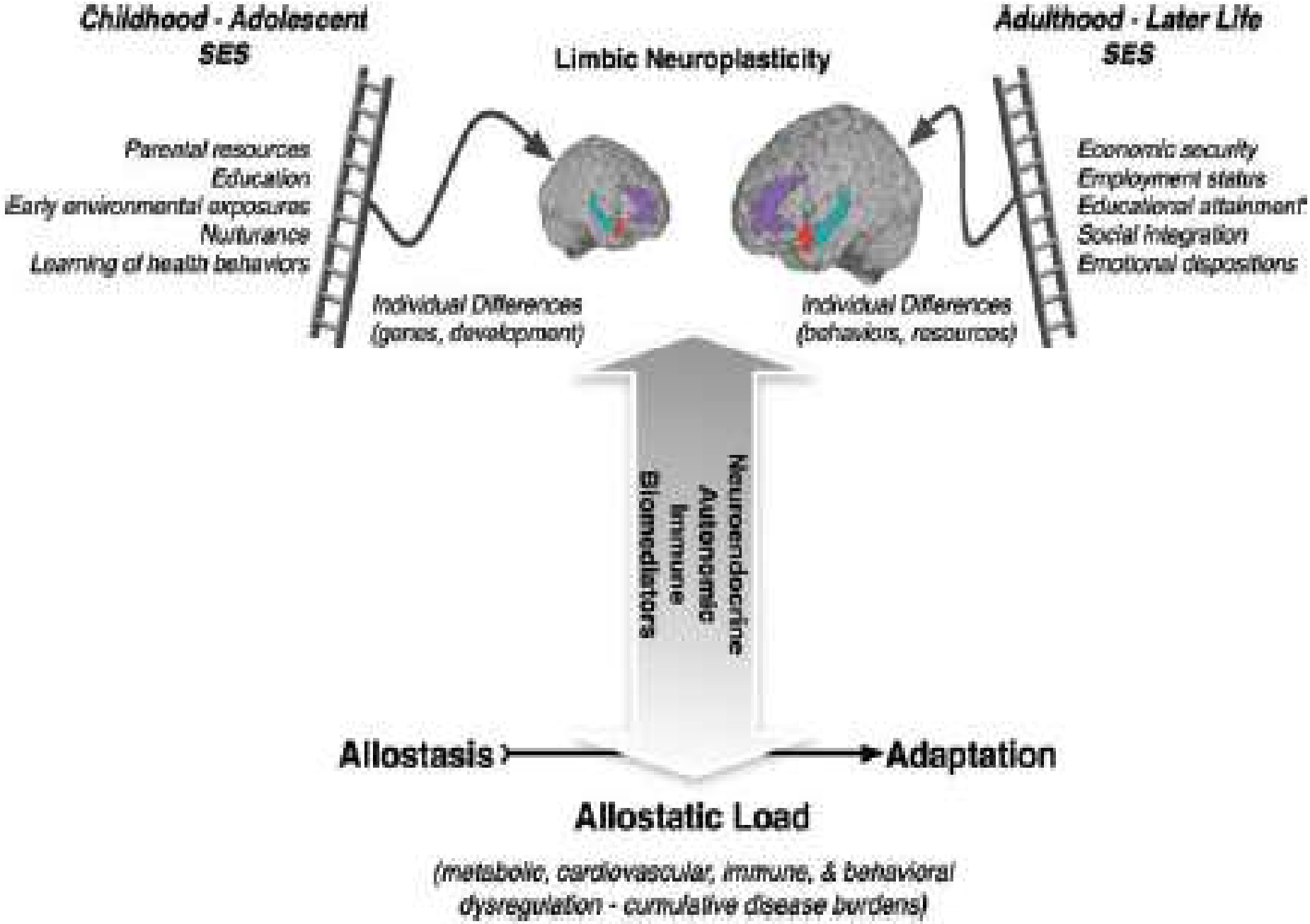

Figure 2. Neurobiological pathways of SES and allostatic load. A heuristic schematic illustrating the potential neuro-

Socioeconomic Status
(Ann NY Acad Sci 2010; 1186: 190-222)

- Top down strategies to alter brain function that will improve allostasis and allostatic load.
- Instill optimism, a sense of control and self-esteem, finding meaning and purpose in life

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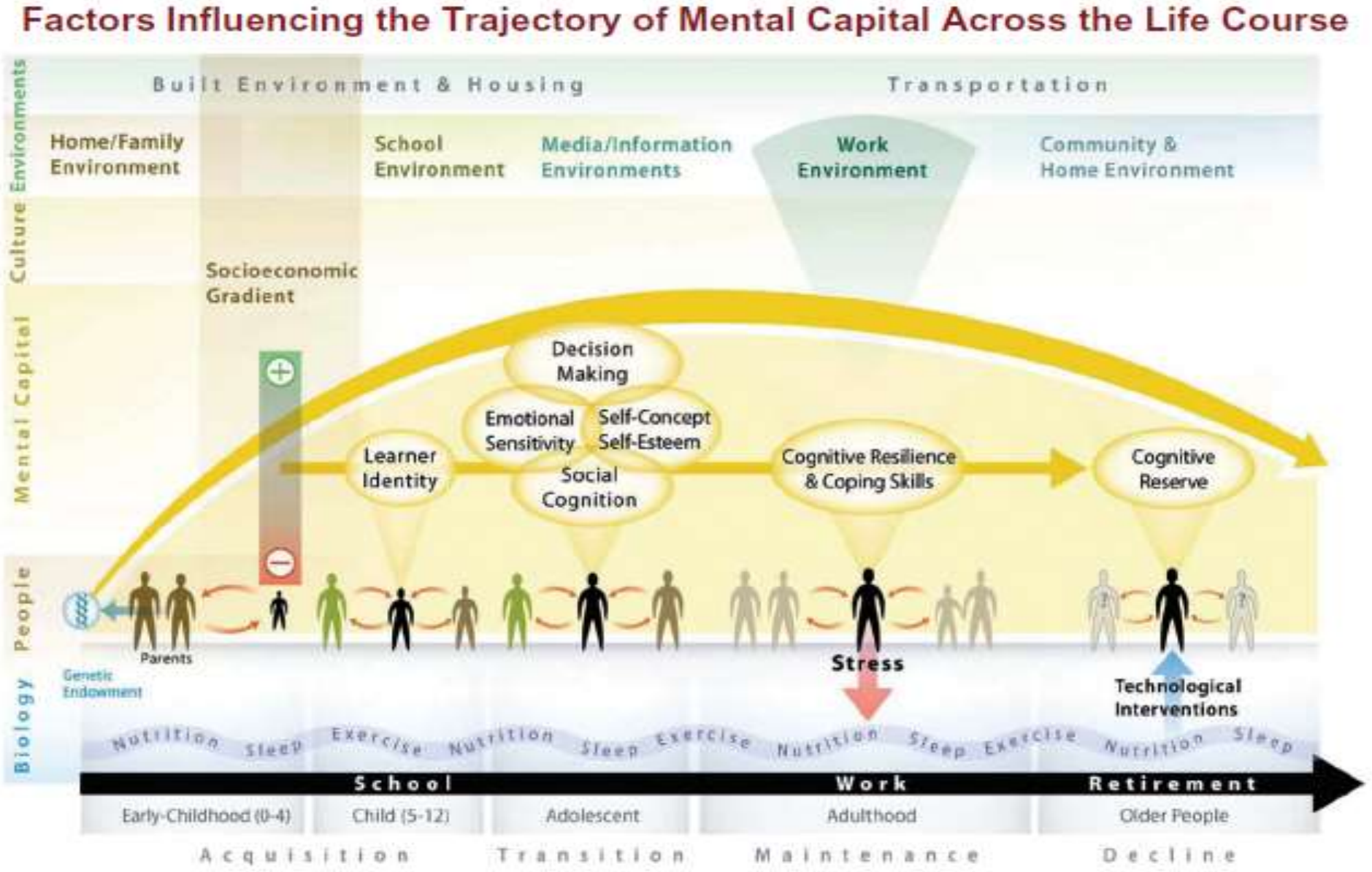

Figure 1 **Schematic representation of the multiple factors influencing the trajectory of mental capital across the life course. Adapted from [19] and [20].**

Nutrition Reviews Vol 68(Suppl 2):S65-S69