Duke

BIODEMOGRAPHY OF AGING RESEARCH UNIT (BARU)
CENTER FOR POPULATION HEALTH & AGING
SOCIAL SCIENCE RESEARCH INSTITUTE

THE PROGRESS IN UNDERSTANDING ALZHEIMER'S DISEASE

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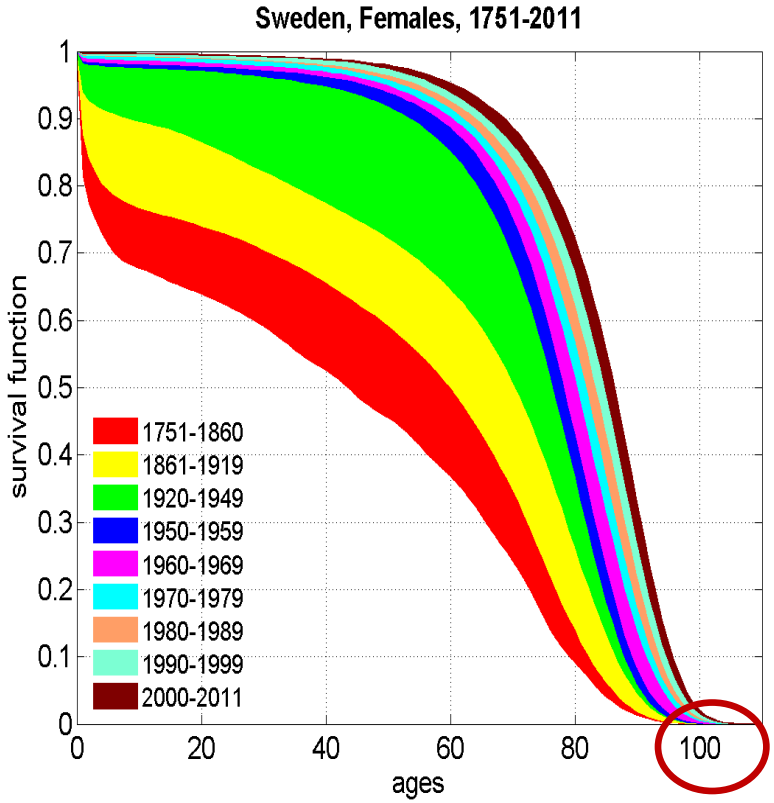
OUTLINE

- Biodemography of Aging Research Unit (BARU) at Duke University
- Alzheimer's disease and other dementias
- Why studying Alzheimer's disease?
- Alzheimer's disease in the United States
- Two types of Alzheimer's disease
- Causes of Alzheimer's disease
- Hypotheses
- Alzheimer's disease hallmarks: beta amyloid and tau protein
- Four main research areas on Alzheimer's disease
- The results of GWAS of Alzheimer's disease (AD)
- APOE, TOMM40, NECTIN2 (PVRL2), APOC1 and other genes
- New AD hallmarks
- Stress and Alzheimer's disease
- Cellular stress
- Cellular stress response: its role in AD and other chronic conditions
- Genetic heterogeneity in AD
- New ideas about uncovering hidden heterogeneity in AD
- Conclusions

SURVIVAL OUTCOMES RESULT FROM THE INTERGRATION OF THE EFFECTS OF MANY GENETIC AND NON-GENETIC FACTORS

PATTERNS OF SURVIVAL IMPROVEMENT IN SWEDEN



Insights:

- human mortality rate keeps improving
- this improvement is induced by changes in external and living conditions
- these changes are likely to influence mortality rates by cause
- changes in these conditions may
- modify activity of certain genes
- polymorphisms in activated genes may influence variability of aging, health, and longevity related traits

Yashin et al. (2016) How the Effects of Aging and Stresses of Life Are Integrated in Mortality Rates: Insight for Genetic Studies of Human Health and Longevity, 17(1), 89-107

WHAT IS ALZHEIMER'S DISEASE?

- Alzheimer's disease is a progressive neurological disease that, over time, results in the brain's inability to function correctly.
- Alzheimer's disease causes changes in memory, communication, judgment, personality, and overall cognitive functioning.
- Alzheimer's was first identified by Alois Alzheimer in 1906 in Germany and is the most common type of dementia, a general term for impaired brain functioning.

ALZHEIMER'S DISEASE

- It is a chronic neurodegenerative disease that usually starts slowly and worsens over time.
- It is the cause of 60% to 70% of cases of dementia.
- The most common early symptom is difficulty in remembering recent events (short-term memory loss).
- As the disease advances, symptoms can include problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, not managing self care, and behavioral issues.
- As a person's condition declines, they often withdraw from family and society.
- Gradually, bodily functions are lost, ultimately leading to death. Although the speed of progression can vary, the average life expectancy following diagnosis is three to nine years.

ALZHEIMER'S DISEASE

- The cause of Alzheimer's disease (AD) is poorly understood.
- About 70% of the risk is believed to be genetic with many genes usually involved.
- Other risk factors include a history of head injuries, depression, or hypertension.
- The disease process is associated with plaques and tangles in the brain.
- A probable diagnosis is based on the history of the illness and cognitive testing with medical imaging and blood tests to rule out other possible causes.
- Examination of brain tissue is needed for a definite diagnosis.
- Mental and physical exercise, and avoiding obesity may decrease the risk of AD; however, evidence to support these recommendations is not strong.
- There are no medications or supplements that decrease risk of AD.

ALZHEIMER'S DISEASE

- No treatments stop or reverse AD progression, though some may temporarily improve symptoms.
- Affected people increasingly rely on others for assistance, often placing a burden on the caregiver; the pressures can include social, psychological, physical, and economic elements.
- Exercises may be beneficial with respect to activities of daily living and can potentially improve outcomes.
- Treatment of behavioral problems or psychosis due to dementia with antipsychotics is common, but not usually recommended, as there is little benefit with an increased risk of early death.
- It most often begins in people over 65 years of age, although 4% to 5% of cases are early-onset Alzheimer's which begin before this. It affects about 6% of people 65 years and older.
- In developed countries, AD is one of the most financially costly diseases.

IS THERE A CURE FOR ALZHEIMER'S DISEASE?

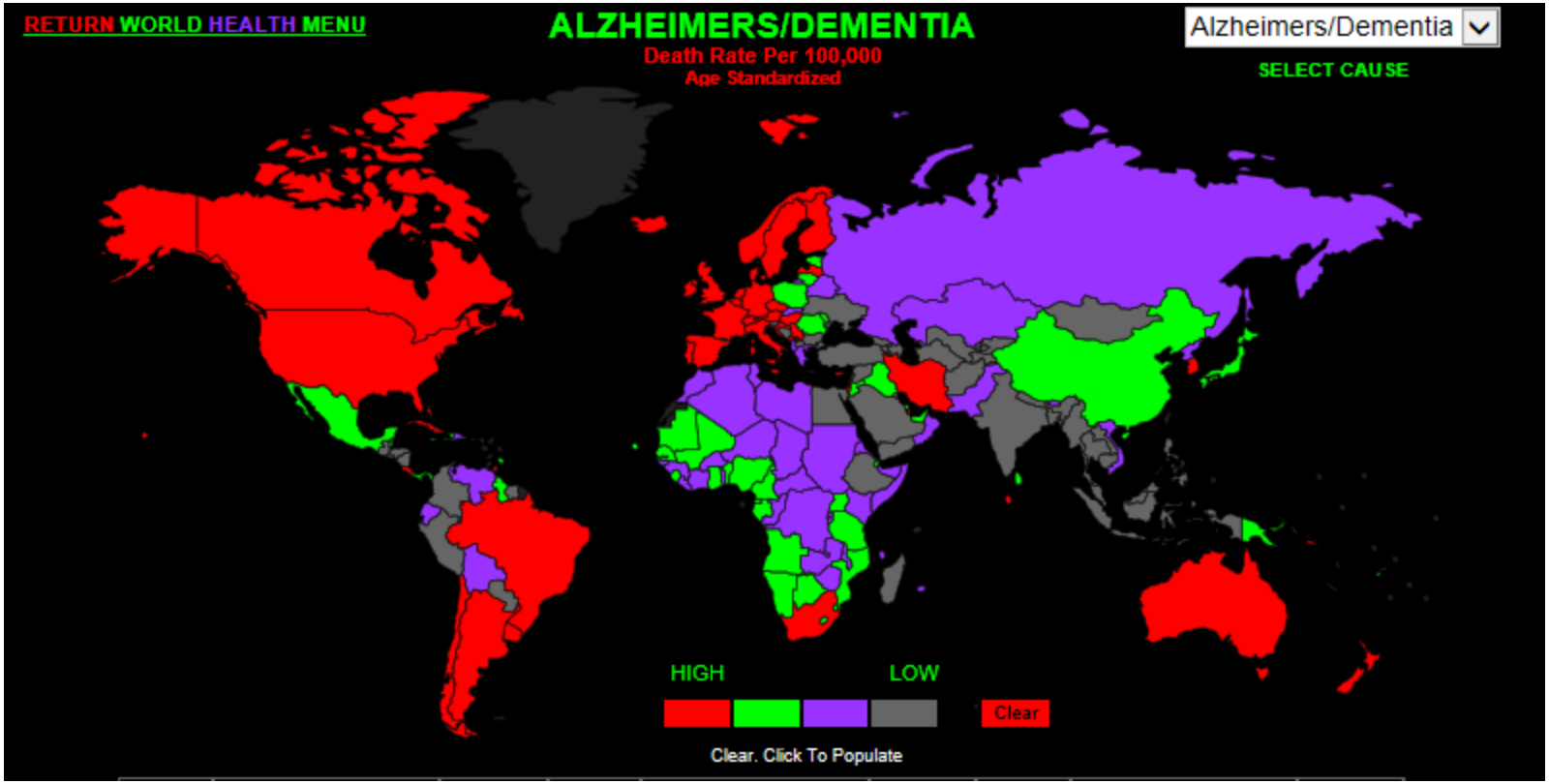
- There is currently no cure for Alzheimer's disease.
- However, there are a handful of FDA-approved medications to manage the symptoms of Alzheimer' disease.
- While these medications do not cure Alzheimer's, they may delay the progression of symptoms in some people for a limited amount of time.
- There is also no medication or other therapy that can prevent the onset of Alzheimer's disease at this time, but researchers continue to work toward this goal.

WHAT IS THE AVERAGE LIFE EXPECTANCY FOR A PERSON WITH ALZHEIMER'S DISEASE?

- According to the Alzheimer's Association, the average life expectancy for a person age 65 years or older diagnosed with Alzheimer's disease is about four to eight years after a diagnosis is made.

SITUATION WITH DEMENTIA IN THE WORLD

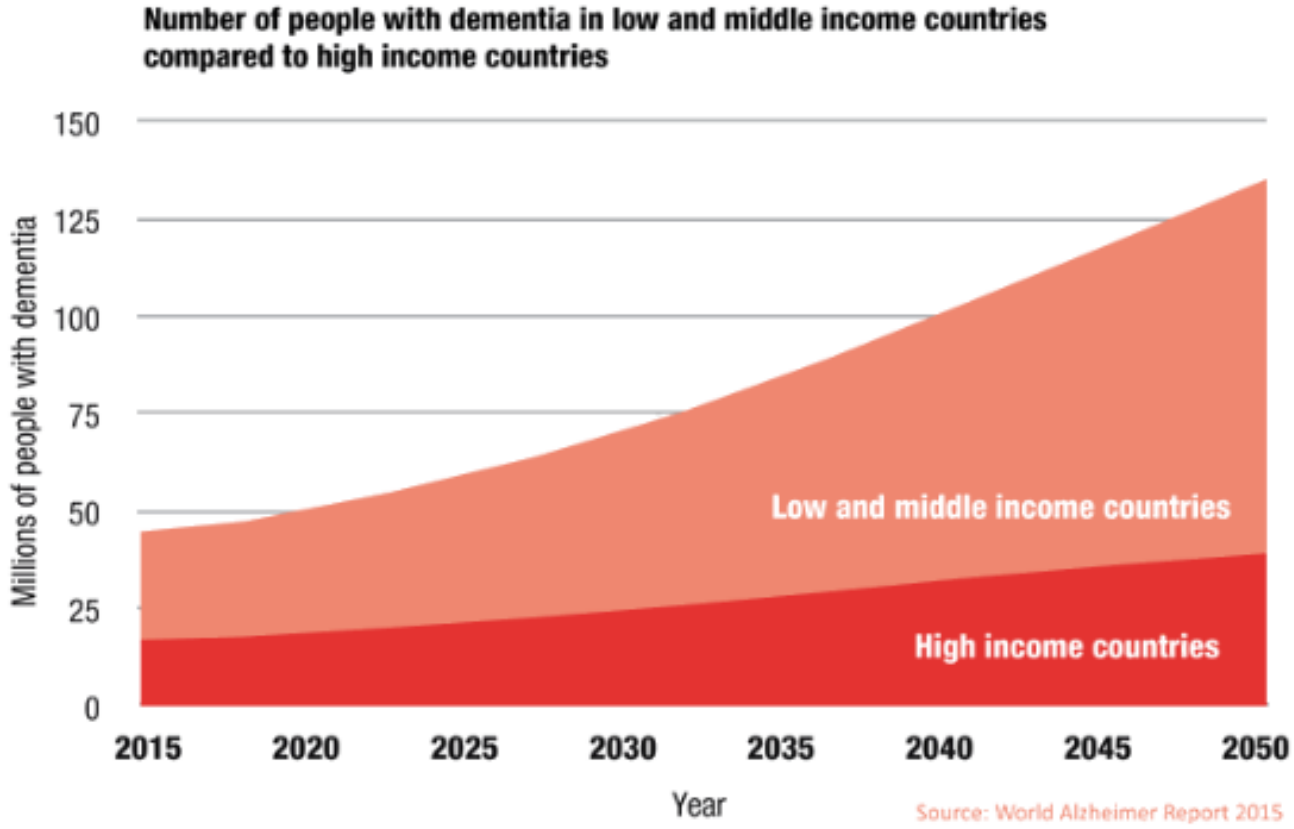
- Today, 47 million people live with dementia worldwide, more than the population of Spain.
- This number is projected to increase to more than 131 million by 2050, as populations age.
- Dementia also has a huge economic impact. The total estimated worldwide cost of dementia is US$818 billion, and it will become a trillion dollar disease by the end of 2018.
- The huge majority of people with dementia have not received a diagnosis, and so are unable to access care and treatment.
- Even when dementia is diagnosed, the care provided is too often fragmented, uncoordinated, and unresponsive to the needs of people living with dementia, their carers and families.


RETURN WORLD HEALTH MENU
ALZHEIMERS/DEMENTIA
Death Rate Per 100,000
Age Standardized
Alzheimers/Dementia
SELECT CAUSE
HIGH
LOW
Clear
Clear. Click To Populate

Age Adjusted Death Rates Per 100,000 Population: Alzheimer/Dementia
Data Source: Published By WHO 2014 Age Standardized Estimate

Rank	Country	Rate	Rank	Country	Rate	Rank	Country	Rate
1	FINLAND	53.77	59	DJIBOUTI	4.23	117	NORTH KOREA	2.20
2	UNITED STATES	45.58	60	GABON	4.20	118	VENEZUELA	2.20
3	CANADA	35.50	61	ESTONIA	4.05	119	ZAMBIA	2.19
4	ICELAND	34.08	62	GUYANA	4.02	120	RUSSIA	2.17
5	SWEDEN	32.41	63	SENEGAL	3.93	121	BURUNDI	2.12
6	SWITZERLAND	32.25	64	JORDAN	3.90	122	ERITREA	1.98
7	NORWAY	30.24	65	MALI	3.88	123	CENTRAL AFRICA	1.92
8	DENMARK	29.53	66	NAMIBIA	3.84	124	DR CONGO	1.87
9	NETHERLANDS	29.32	67	ROMANIA	3.82	125	SOMALIA	1.84
10	BELGIUM	27.23	68	MOLDOVA	3.73	126	PAKISTAN	1.78
11	SPAIN	26.90	69	BAHRAIN	3.72	127	BOLIVIA	1.77
12	AUSTRALIA	25.91	70	PANAMA	3.69	128	TUNISIA	1.77
13	FRANCE	25.62	71	GHANA	3.56	129	BHUTAN	1.70
14	UNITED KINGDOM	24.35	72	MEXICO	3.48	130	SYRIA	1.66
15	CUBA	22.38	73	SIERRA LEONE	3.47	131	TURKEY	1.65
16	CHILE	21.03	74	MAURITANIA	3.43	132	NICARAGUA	1.63
17	URUGUAY	20.74	75	TANZANIA	3.38	133	EGYPT	1.59
18	ISRAEL	19.90	76	SRI LANKA	3.36	134	MADAGASCAR	1.58
19	NEW ZEALAND	19.02	77	POLAND	3.36	135	BOSNIA/HERZEG.	1.53
20	IRELAND	17.70	78	BENIN	3.31	136	LEBANON	1.50
21	ITALY	16.96	79	MOZAMBIQUE	3.30	137	ETHIOPIA	1.48
22	HUNGARY	15.23	80	BELIZE	3.30	138	NEPAL	1.36

- Someone in the world develops dementia every 3 seconds.
- Currently about 50 million people worldwide live with dementia.
- This number will almost double every 20 years, reaching 75 million in 2030 and 131.5 million in 2050.
- Much of the increase will be in developing countries. Already 58% of people with dementia live in low and middle income countries, but by 2050 this will rise to 68%.
- The fastest growth in the elderly population is taking place in China, India, and their south Asian and western Pacific neighbours



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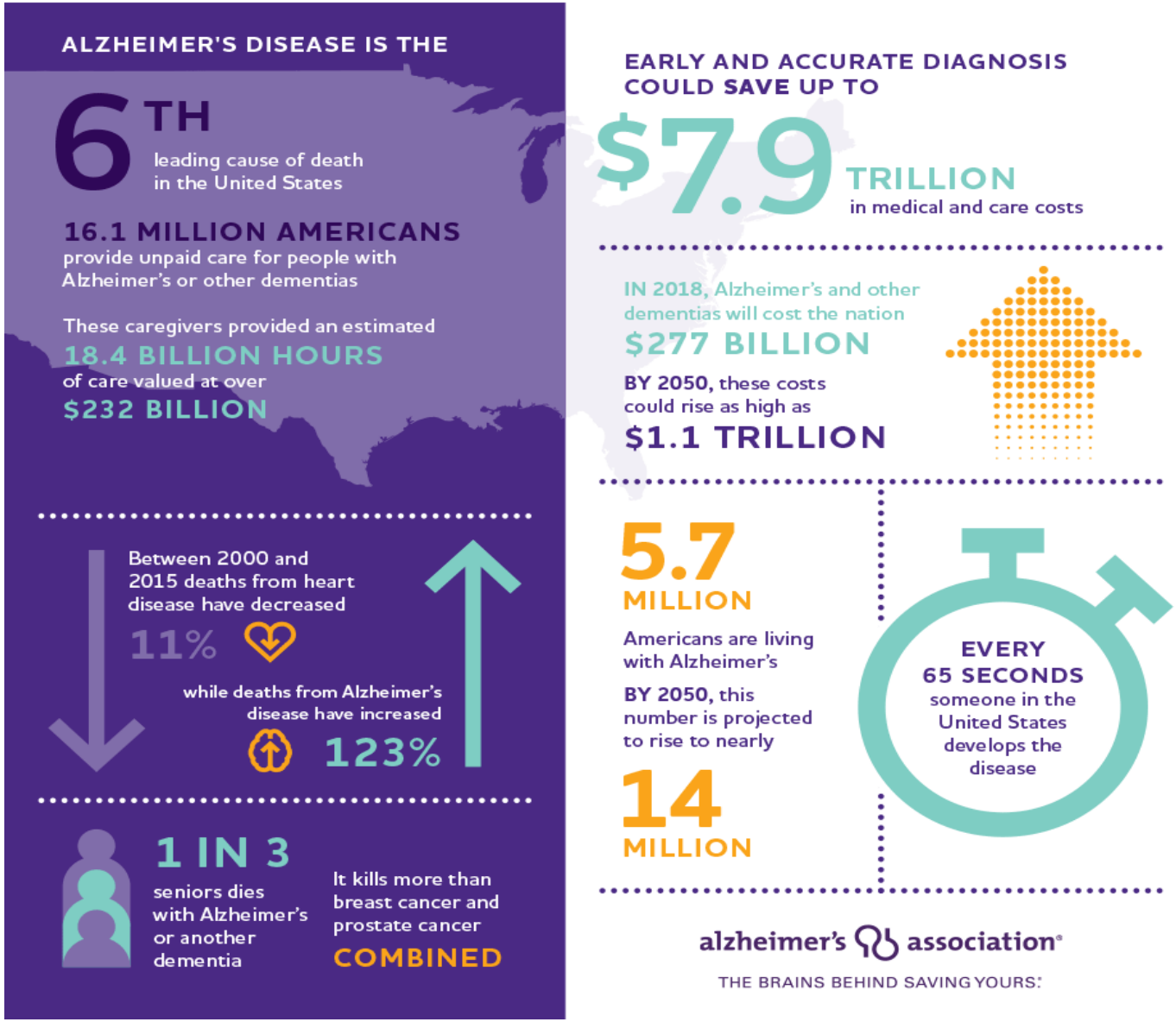
DIAGNOSTICS

- Research shows that most people currently living with dementia have not received a formal diagnosis.
- In high income countries, only 20-50% of dementia cases are recognized and documented in primary care.
- This ‘treatment gap’ is certainly much greater in low and middle income countries, with one study in India suggesting 90% remain undiagnosed.
- If these statistics are extrapolated to other countries worldwide, it suggests that approximately **three quarters of people with dementia have not received a diagnosis**, and therefore do not have access to treatment, care and organized support that getting a formal diagnosis can provide

ALZHEIMER'S DISEASE IN THE UNITED STATES



PREVALENCE

The number of Americans living with Alzheimer's is growing — and growing fast. An estimated 5.7 million Americans of all ages have Alzheimer's.

An estimated 5.7 million Americans of all ages are living with Alzheimer's dementia in 2018. This number includes an estimated 5.5 million people age 65 and older and approximately 200,000 individuals under age 65 who have younger-onset Alzheimer's.

- One in 10 people age 65 and older (10 percent) has Alzheimer's dementia.
- Almost two-thirds of Americans with Alzheimer's are women.
- Older African-Americans are about twice as likely to have Alzheimer's or other dementias as older whites.
- Hispanics are about one and one-half times as likely to have Alzheimer's or other dementias as older whites.

As the number of older Americans grows rapidly, so too will the numbers of new and existing cases of Alzheimer's. Today, someone in the United States develops Alzheimer's every 65 seconds. By mid-century, someone in the United States will develop the disease every 33 seconds.

Source: Alzheimer's Association

MORTALITY

Alzheimer's disease is the only top 10 cause of death in the United States that cannot be prevented, cured or even slowed.

- Alzheimer's disease is the sixth-leading cause of death in the United States, and the fifth-leading cause of death among those age 65 and older. It also is a leading cause of disability and poor health.
- Although deaths from other major causes have decreased significantly, official records indicate that deaths from Alzheimer's disease have increased significantly. Between 2000 and 2015, deaths from Alzheimer's disease as recorded on death certificates increased 123 percent, while deaths from the number one cause of death (heart disease) decreased 11 percent.
- Among people age 70, 61 percent of those with Alzheimer's are expected to die before the age of 80 compared with 30 percent of people without Alzheimer's — a rate twice as high.

Source: Alzheimer's Association

CAREGIVERS

Eighty-three percent of the help provided to older adults in the United States comes from family members, friends or other unpaid caregivers. Nearly half of all caregivers who provide help to older adults do so for someone with Alzheimer's or another dementia.

Who are the caregivers?

- About one in three caregivers (34 percent) is age 65 or older.
- Approximately two-thirds of caregivers are women; more specifically, over one-third of dementia caregivers are daughters.
- Approximately one-quarter of dementia caregivers are "sandwich generation" caregivers — meaning that they care not only for an aging parent, but also for children under age 18.

Alzheimer's takes a devastating toll on caregivers. Compared with caregivers of people without dementia, twice as many caregivers of those with dementia indicate substantial emotional, financial and physical difficulties.

Of the total lifetime cost of caring for someone with dementia, 70 percent is borne by families — either through out-of-pocket health and long-term care expenses or from the value of unpaid care.

Source: Alzheimer's Association

COST TO NATION

Alzheimer's places a huge burden on the health care system, with annual costs exceeding a quarter of a trillion dollars.

In 2018, the direct costs to American society of caring for those with Alzheimer's will total an estimated $277 billion, including $186 billion in Medicare and Medicaid payments. Unless something is done, in 2050, Alzheimer's is projected to cost more than $1.1 trillion (in 2018 dollars). This dramatic rise includes more than four-fold increases both in government spending under Medicare and Medicaid and in out-of-pocket spending.

The costs of health care and long-term care for individuals with Alzheimer's or other dementias are substantial. Dementia is one of the costliest conditions to society.

- People with Alzheimer's or other dementias have twice as many hospital stays per year as other older people.
- Medicare beneficiaries with Alzheimer's or other dementias are more likely than those without dementia to have other chronic conditions.
- People with Alzheimer's or other dementias make up a large proportion of all elderly people who receive adult day services and nursing home care.

Source: Alzheimer’s Association

THE TWO TYPES OF ALZHEIMER'S DISEASE

- The causes of disease seems to be different for the two types of AIzheimer's disease:

  - (i) the early onset AD (EAD, EOAD, FAD, or eFAD) and
  - (ii) the late onset of AD (LOAD), or sporadic AD (SAD)

THE EARLY ONSET ALZHEIMER'S DISEASE

- The genetic heritability of Alzheimer's disease (and memory components thereof), based on reviews of twin and family studies, ranges from 49% to 79%. Around 0.1% of the cases are familial forms of autosomal (not sexlinked) dominant inheritance, which have an onset before age 65.
- This form of the disease is known as early onset familial Alzheimer's disease. Most of autosomal dominant familial AD can be attributed to mutations in one of three genes: those encoding amyloid precursor protein (APP) and presenilins 1 and 2 (PS1 and PS2).
- Of these, PS1 mutations account for most eFAD, while APP and PS2 are more rare.
- Most mutations in the APP and presenilin genes increase the production of a small protein called Aβ42, which is the main component of senile plaques. Some of the mutations merely alter the ratio between Aβ42 and the other major forms—particularly Aβ40.

LATE ONSET ALZHEIMER'S DISEASE

- The causes of late onset Alzheimer's disease are less clear. Environmental and genetic differences may act as risk factors.
- The best known genetic risk factor is the inheritance of the ε4 allele of the apolipoprotein E (APOE). Between 40 and 80% of people with AD possess at least one APOEε4 allele.
- The APOEε4 allele increases the risk of the disease by three times in heterozygotes and by 15 times in homozygotes. Like many human diseases, environmental effects and genetic modifiers result in incomplete penetrance.
- More recent genome-wide association studies (GWAS) have found more genes that appear to affect the risk.

AD PATHOLOGICAL HALLMARKS

- **Extracellular senile plaques of beta amyloid protein** Aβ
- **Intracellular neurofibrillary tangles (NFT) of tau protein**
- **Oxidative stress**
- **Mitochondrial dysfunction**
- **Synaptic dysfunction**
- **Neuroinflammation**
- **Death of neurons**

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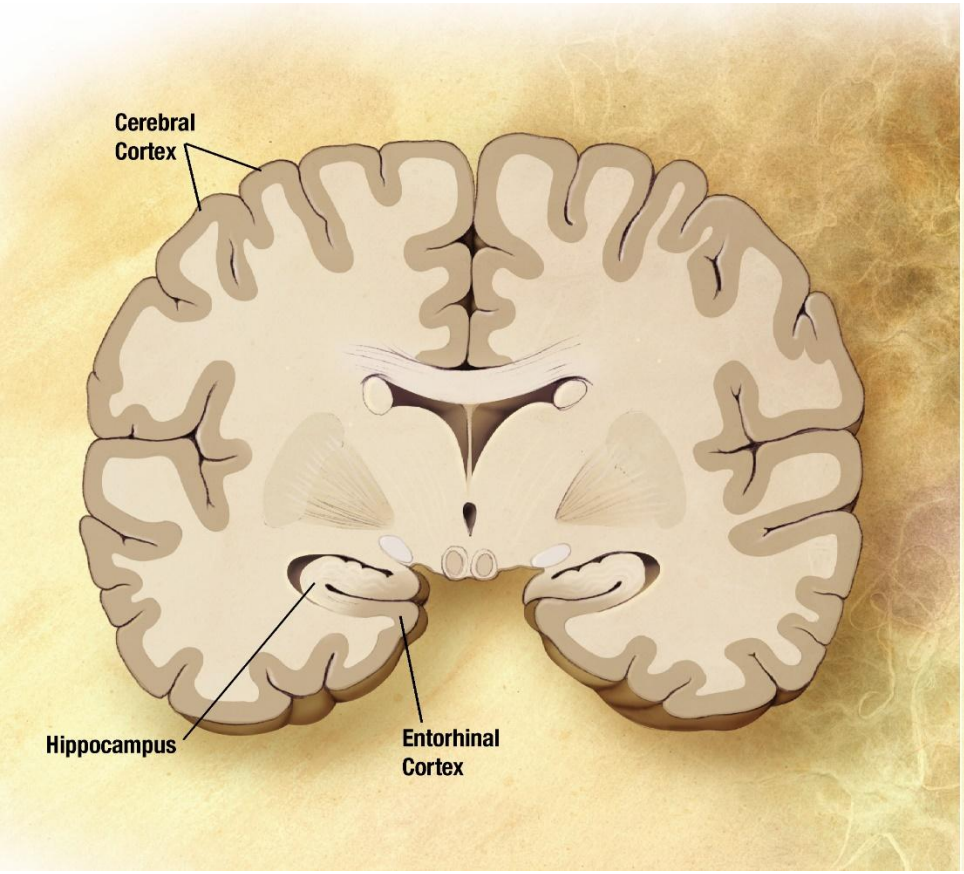
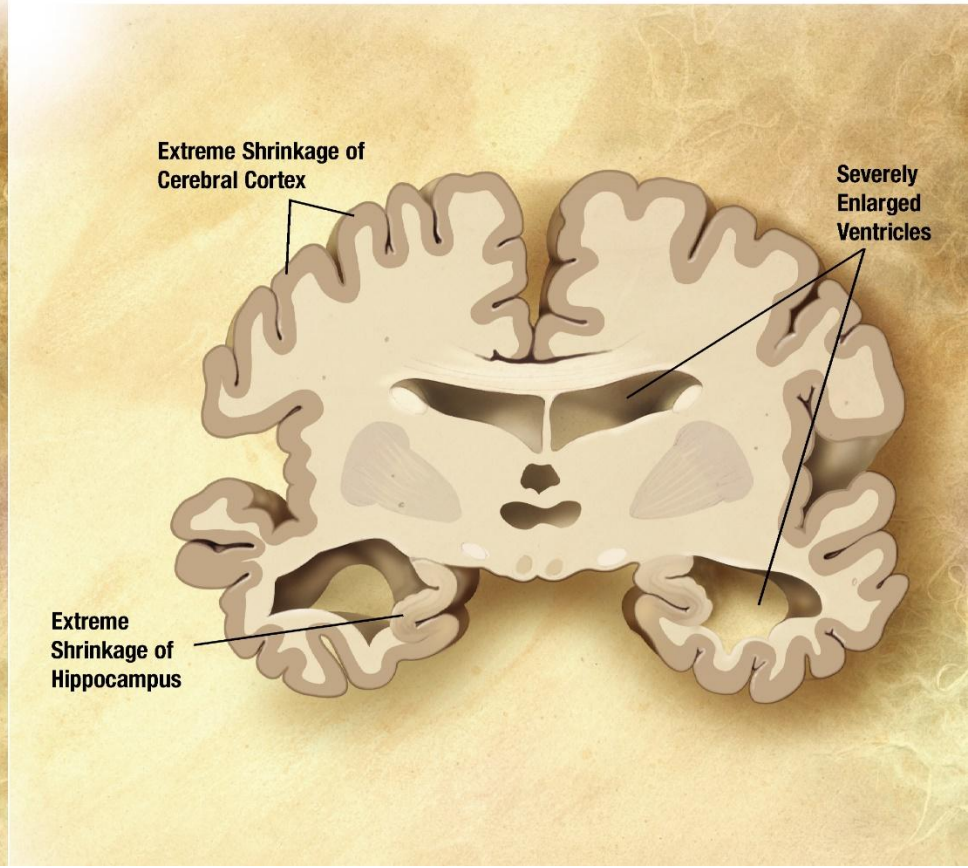
AMYLOID HYPOTHESIS

- In 1991, the *amyloid hypothesis* postulated that extracellular amyloid beta (A_β) deposits are the fundamental cause of AD.
- Support for this postulate comes from the location of the gene for the amyloid precursor protein (APP) on chromosome 21, together with the fact that people with trisomy 21 (Down Syndrome) who have an extra gene copy almost universally exhibit at least the earliest symptoms of AD by 40 years of age.
- Also, a specific isoform of apolipoprotein, APOE (APOE e4), is a major genetic risk factor for AD. While apolipoproteins enhance the breakdown of beta amyloid, some isoforms are not very effective at this task (such as APOE e4), leading to excess amyloid buildup in the brain.
- Further evidence comes from the finding that transgenic mice that express a mutant form of the human APP gene develop fibrillar amyloid plaques and Alzheimer's-like brain pathology.



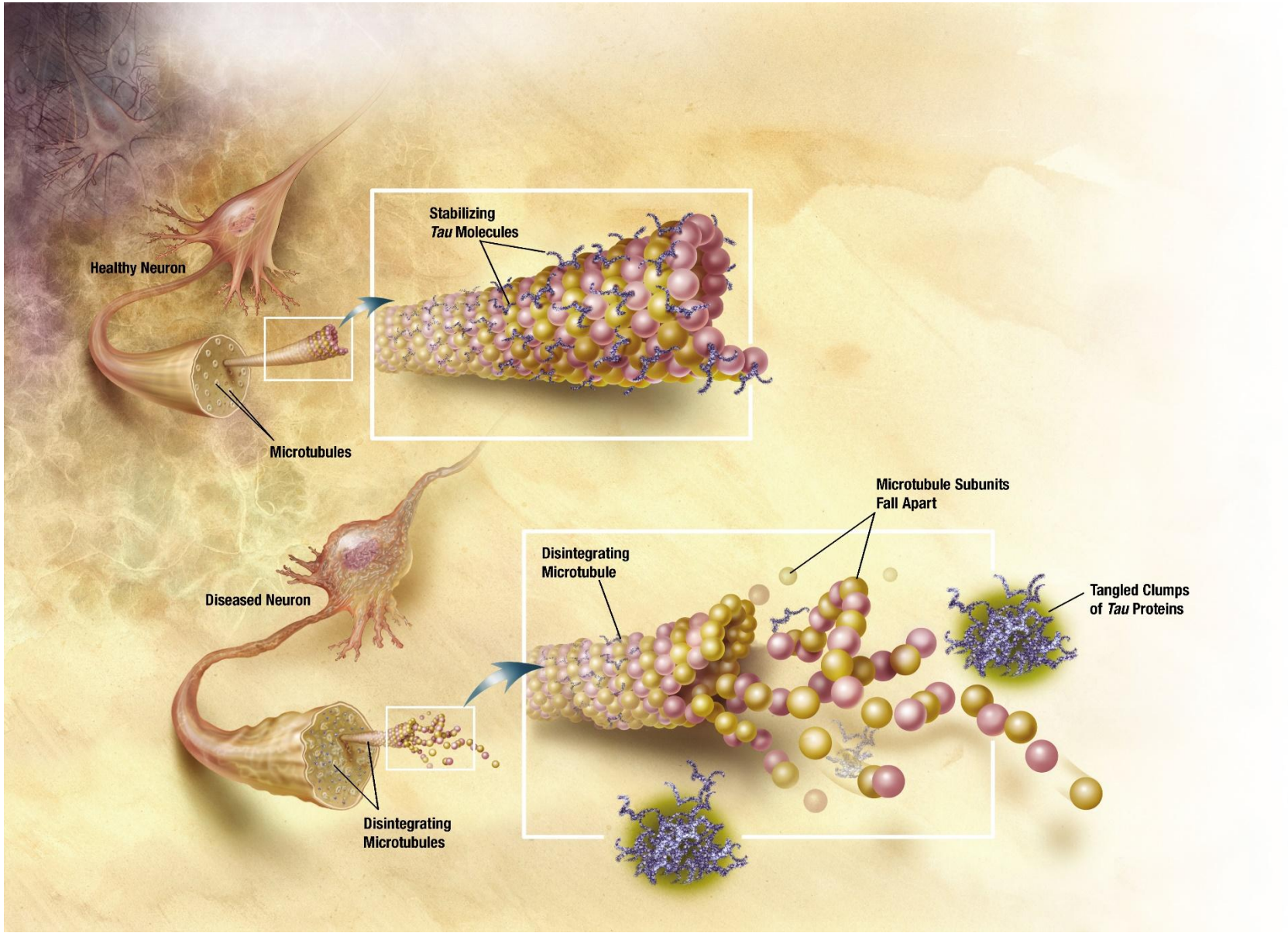


Comparison of a normal aged brain (left) and the brain of a person with Alzheimer's (right). Characteristics that separate the two are pointed out.

Source: National Institute of Aging, Alzheimer’s Association

TAU-HYPOTHESIS

- The *tau hypothesis* proposes that tau protein abnormalities initiate the disease cascade.
- In this model, hyperphosphorylated tau begins to pair with other threads of tau.
- Eventually, they form neurofibrillary tangles inside nerve cell bodies.
- When this occurs, the microtubules disintegrate, destroying the structure of the cell's cytoskeleton which collapses the neuron's transport system.
- This may result first in malfunctions in biochemical communication between neurons and later in the death of the cells.



In Alzheimer's disease, changes in tau protein lead to the disintegration of microtubules in brain cells.

Source: National Institute of Aging, Alzheimer's Association

CHOLINERGIC HYPOTHESIS

- The oldest, on which most currently available drug therapies are based, is the *cholinergic hypothesis,* which proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine.
- The cholinergic hypothesis has not maintained widespread support, largely because medications intended to treat acetylcholine deficiency have not been very effective.
- Other cholinergic effects have also been proposed, for example, initiation of large-scale aggregation of amyloid, leading to generalized neuroinflammation.

OTHER HYPOTHESES (I)

- A neurovascular hypothesis has been proposed which states that poor functioning of the blood–brain barrier may be involved.
- The cellular homeostasis of biometals such as ionic copper, iron, and zinc is disrupted in AD, though it remains unclear whether this is produced by or causes the changes in proteins.
- These ions affect and are affected by tau, APP, and APOE, and their dysregulation may cause oxidative stress that may contribute to the pathology.
- Smoking is a significant AD risk factor.
- Systemic markers of the innate immune system are risk factors for late-onset AD.
- There is tentative evidence that exposure to air pollution may be a contributing factor to the development of Alzheimer's disease.

OTHER HYPOTHESES (II)

- An infection with Spirochetes (a bacterium) in gum disease may cause dementia and may be involved in the pathogenesis of Alzheimer's disease.
- A fungal and viral infections may also be a factor.
- One hypothesis posits that dysfunction of oligodendrocytes and their associated myelin during aging contributes to axon damage, which then causes amyloid production and tau hyper-phosphorylation as a side effect.
- Retrogenesis hypothesis claims that as the fetus goes through a process of neurodevelopment beginning with neurulation and ending with myelination, the brains of people with AD go through a reverse neurodegeneration process starting with demyelination and death of axons.

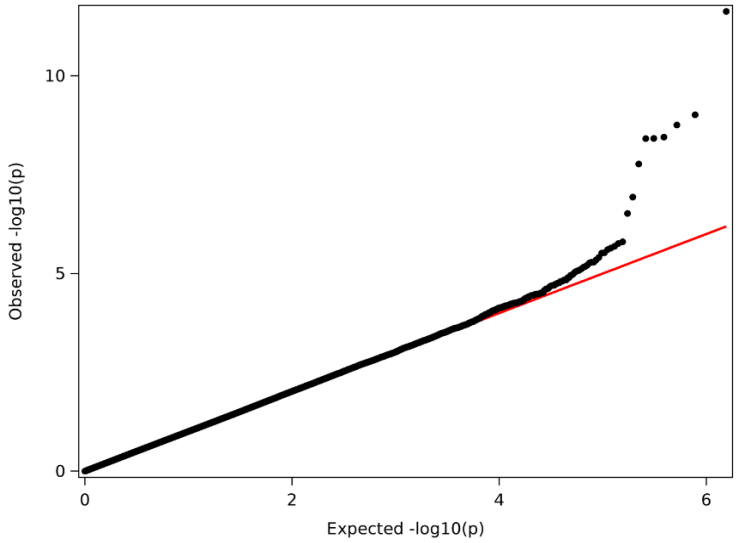
RISK FACTORS FOR ALZHEIMER'S DISEASE

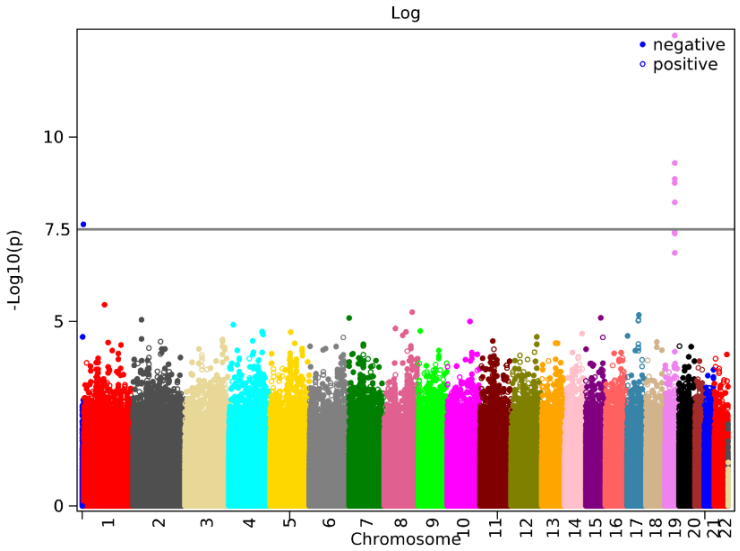
- Vascular risk factors including hypertension, high cholesterol, diabetes, and atherosclerosis are well known in the literature to increase risk of AD, with estimated effects ranging from 1.2 to 4 times, depending on the risk factor in question.
- Obesity, usually indicated by a body mass index (BMI) >= 30 or some anthropomorphic indicators such as waist circumference, has been associated with a 2- to 5-fold increase in risk of AD.

FOUR MAIN RESEARCH AREAS FOR STUDYING ALZHEIMER'S DISEASE

- Clinical trials (e.g., drug testing)
- Experimental studies with laboratory animals (e.g., transgenic animals)
- Molecular biological studies (e.g., human microglia cell lines)
- Population genetic association studies (e.g., genome wide association studies (GWAS).

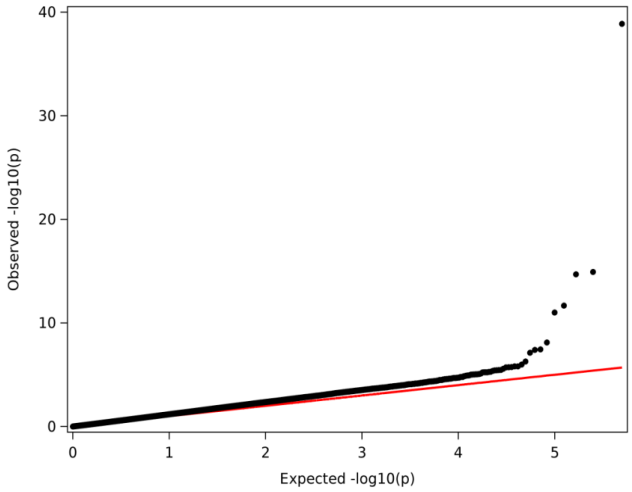
GENOME WIDE ASSOCIATION STUDIES OF ALZHEIMER'S DISEASE

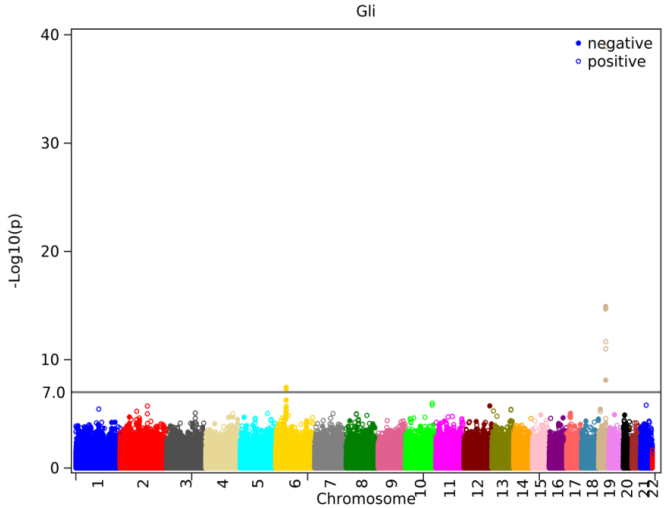




Left panel. QQ-plot of the results of GWAS of Alzheimer's disease obtained in the analyses of HRS data on females using logistic regression model. **Right panel.** Manhattan plot of the results of GWAS of Alzheimer's disease obtained in the analyses of HRS data on females using logistic regression model.

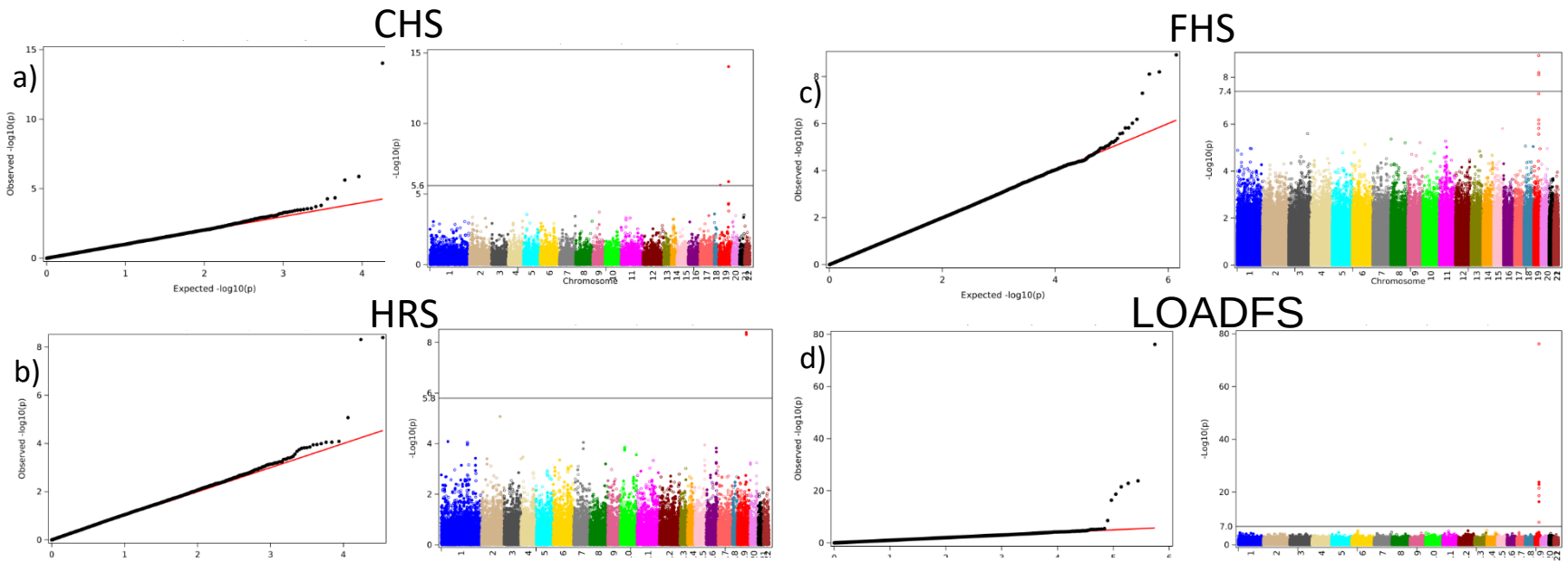
(Yashin et al., 2017, Experimental Gerontology)





Left panel. QQ-plot of the results of GWAS of Alzheimer's disease obtained in the analyses of LOADFS data on males and females combined using GLIMMIX. **Right panel.** Manhattan plot of the results of GWAS of Alzheimer's disease obtained in the analyses of LOADFS data on males and females combined using GLIMMIX.

(Yashin et al., 2017, Experimental Gerontology)



The QQ-plots and Manhattan plots of the results of GWAS of Alzheimer's disease obtained in the analyses using logistic regression (GMMAT in LOADFS) for males and females combined. **a)**. CHS (case: 286; control: 4732); **b)**. FHS data on males and females combined using Cox regression (case: 308; control: 3,343); **c**). HRS (case: 992; control: 8039); **d)**. LOADFS (case: 2319; control: 2242).

(Yashin et al., 2017, Experimental Gerontology)

SNP	pCox	pLog	HR	OR	fdr_log	Chr	Ref	Alt	MAF	Gene	Location
rs769449	**2.34E-12**	1.76E-13	2.0	2.1	2.74E-07	19	A	G	0.08	APOE	intr. var.
rs2075650	**9.67E-10**	5.05E-10	1.7	1.8	0.000393	19	G	A	0.13	TOMM40	intr. var.
rs157582	**1.76E-09**	1.36E-09	1.7	1.7	0.00068	19	T	C	0.28	TOMM40	intr. var.
rs115881343	**3.54E-09**	3.71E-08	2.5	2.9	0.008025	19	T	C	0.02	TOMM40	intr. var.
rs71352238	**3.81E-09**	1.75E-09	1.7	1.8	0.00068	19	C	T	0.10	TOMM40	intr. var.
rs76366838	**3.87E-09**	4.13E-08	3.3	3	0.008025	19	A	G	0.02	TOMM40	intr. var.
rs283815	**1.70E-08**	5.86E-09	1.7	1.7	0.001825	19	G	A	0.28	PVRL2	intr. var.
rs483082	**1.16E-07**	2.32E-08	1.7	1.6	0.006027	19	T	G	0.26	APOE	downstr. var
rs483082	**1.167E-07**	2.32E-08	1.7	1.6	0.006027	19	T	G	0.26	APOC1	upstr. var.
rs34095326	**3.027E-07**	1.37E-07	1.7	1.8	0.023783	19	A	G	0.04	TOMM40	intr. var.

Table 1. SNPs from TOMM40, APOC1, PVRL2, and APOE genes that showed most significant associations in GWAS of Alzheimer's disease using Cox regression and logistic regression models applied to **HRS** data on females. The column notations: SNP name, p-value in Cox model, p-value in logistic regression model, Hazard Ratio, Odds Ratio, false discovery rate, chromosome number, reference allele, alternative allele, minor allele frequency, gene, location.

(Yashin et al., 2017, Experimental Gerontology)

SNP	p-value	OR	Chr	Ref	Alt	Gene	Location
rs2075650	1.33E-39	0.3	19	A	G	TOMM40	intron variant
rs8106922	1.19E-15	1.9	19	A	G	TOMM40	intron variant
rs157580	2.04E-15	1.9	19	G	A	TOMM40	intron variant
rs6859	9.88E-12	0.6	19	A	G	PVRL2	intron variant
rs439401	7.70E-09	1.6	19	T	C	APOC1	upstr gene var
rs439401	7.70E-09	1.6	19	T	C	APOE	Downstr. gene var

Table 2. SNPs from TOMM40, APOC1, PVRL2, and APOE genes that showed most significant associations in GWAS of Alzheimer's disease using logistic regression model applied to **LOADFS** data on males and females combined. The column notations: SNP name, p-value in logistic regression, Odds Ratio, reference allele, alternative allele, gene, location.

(Yashin et al., 2017, Experimental Gerontology)

BRIEF HISTORY:
THE AMYLOID CASCADE HYPOTHSIS STARTED FROM STUDIES OF THE EARLY ONSET AD

- Connection between Aβ and Alzheimer's disease was initially detected in studies of early onset AD (EAD).
- Mutations in APP, PS1, PS2 genes are responsible for production of toxic versions of beta amyloid peptide (Aβ). The amyloid cascade hypothesis of AD was based on the results of these analyses.
- This hypothesis served as dominating conceptual framework for more than two decades in the studies of the late onset AD.
- Intensive GWAS of late onset AD have been performed to find genes other than APP, PS1, PS2.
- These most significant genetic variants associated with AD are from the APOE, TOMM40, PVRL2 (NECTIN2) genes.

TAKE-HOME MESSAGE:

THE "AMYLOID CASCADE HYPOTHESIS" IS THE PRODUCT OF SUCCESSFUL GENETIC STUDIES OF THE EARLIER ONSET ALZHEIMER'S DISEASE WHERE THE TOXIC Aβ RESULTED FROM MUTATIONS IN APP, PSEN1, AND PSEN2 GENES

MORE THAN TWO DECADES OF STUDIES OF LATE ONSET AD WITH THE FOCUS ON BETA AMYLOID PRODUCED MANY IMPORTANT RESULTS BUT DID NOT SOLVE THE MAIN PROBLEM

THE GENETICS OF LATE ONSET AD (LOAD) INVOLVES MORE GENES MANY WITH SMALL EFFECTS. ABOUT TWO DOZENS OF GENES HIGHLY ASSOCIATED WITH AD ARE DETECTED IN DIFFERENT GWAS

APOE, TOMM40, AND PVRL2 (NECTIN2) GENES SHOWED MOST SIGNIFICANT CONNECTIONS WITH AD IN STUDIES OF LOAD

- **APOE** codes for most abundant class of apolipoproteins in the brain produced most notably astroglia and microglia. Neurons preferentially express the receptors for **APOE**

- **TOMM40** codes for a protein that is the channel-forming subunit of a translocase of the mitochondrial outer membrane (TOM) that is essential for protein transport into mitochondria

- **PVRL2 (NRCTIN2) - poliovirus receptor-related 2** (formerly **herpesvirus entry mediator B**, **HVEB**), is a human plasma membrane glycoprotein that serves as one of the plasma membrane components of adherent junctions. It is involved in entry of mutant strains of herpes simplex virus and in cell to cell spreading of these viruses.

APOE AND AMYLOID-β (Aβ)

- While transporting cholesterol is a primary function, apoE regulates Aβ metabolism, aggregation, and deposition.
- It has been proposed that differential physical interactions of *apoE* isoforms with soluble Aβ in brain fluids influence the metabolism of Aβ, providing a major mechanism to account for how APOE influences Alzheimer's disease risk.
- Their results suggest that apoE isoforms influence Aβ metabolism by competing for the same clearance pathways within the brain through APOE receptors.

TOMM40 AND ALZHEIMER'S DISEASE

- The translocase of the outer mitochondrial membrane 40 (TOMM40) gene plays a role in the transport of proteins from the cytoplasm to the mitochondria.
- Clinical studies showed that individuals bearing a polymorphic poly-T variant rs10524523 in this gene have a higher risk to develop late onset AD.
- Disturbances in the TOMM40-dependent trafficking of essential protein may possibly induce oxidative stress and bioenergetic deficits, leading to cell death by apoptosis.
- Placing mitochondria in the center of the degenerative mechanisms is the basis of the ‘‘Alzheimer's disease mitochondrial cascade hypothesis’’.

PVRL2 (NECTIN2) AND MICROBIAL ORIGIN HYPOTHESIS

SPECIFIC MICROBES DETECTED IN THE BRAINS OF AD PATIENTS:

- **HERPES SIMPLEX VIRUS TYPE 1 (HSV1)**
- ***CHLAMYDIA PNEUMONIAE***
- ***SPIROHETE***
- **FUNGAL INFECTION**

THE PRESENCE OF MICROBES IN THE BRAIN INDUCES THE NEUROINFLAMMATION

MORE AD HALLMARKS and MORE GENES

More genes are added
Now they include:

APOE,
TOMM40,
PVRL2
and about two dozens of other highly significant genes

More hallmarks of AD are added
Now they include:

Beta amyloid (Aβ) plague
Tangles of hyperphosporilated tau protein
Dysfunction of mitochondria
Oxidative stress
Neuroinflammation
Synaptic dysfunction
Death of neurons

TAKE-HOME MESSAGE:

THE NEW CONCEPTUAL FRAMEWORK DOES NOT CONSIDER BETA AMYLOID AS MAIN FOCUS OF THE RESEARCH IN LATE ONSET OF AD BUT TAKES ALL DETETED LINKS INTO ACCOUNT

THE EXTENDED LIST OF AD HALLMARKS INCLUDES:

- **EXTRACELLULAR PLAGUE OF BETA AMYLOID PEPTIDE**
- **TANGLES OF HYPERPHOSPHORILATED TAU PROTEIN**
- **OXIDATIVE STRESS**
- **MITOCHONDRIAL DYSFUCTION**
- **SYNAPTIC DYSFUNCTION**
- **NEUROINFLAMMATION**
- **NEURONAL DEATH**

APOE, TOMM40, AND PVRL2 AND OTHER GENES MAY CLARIFY POSSIBLE MECHANISMS OF CONNECTIONS BETWEEN HALLMARKS AND AD

AGING, STRESS AND ALZHEIMER'S DISEASE

FROM GENETIC STUDIES TO ANALYZING GxE

FROM GxE TO ENVIRONMENTAL STRESS

FROM ENVIRONMENTAL STRESS TO CELLULAR STRESS

AND CELLULAR STRESS RESPONSE

FROM CELLULAR STRESS RESPONSE TO ALZHEIMER'S DISEASE

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AGING CONTRIBUTES TO THE DECLINE IN STRESS RESISTANCE, THEREBY INCREASING VULNERABILITY TO DISEASES AND DEATH

HOW DO RISK FACTORS INFLUENCE HEALTH AND SURVIVAL OUTCOMES?

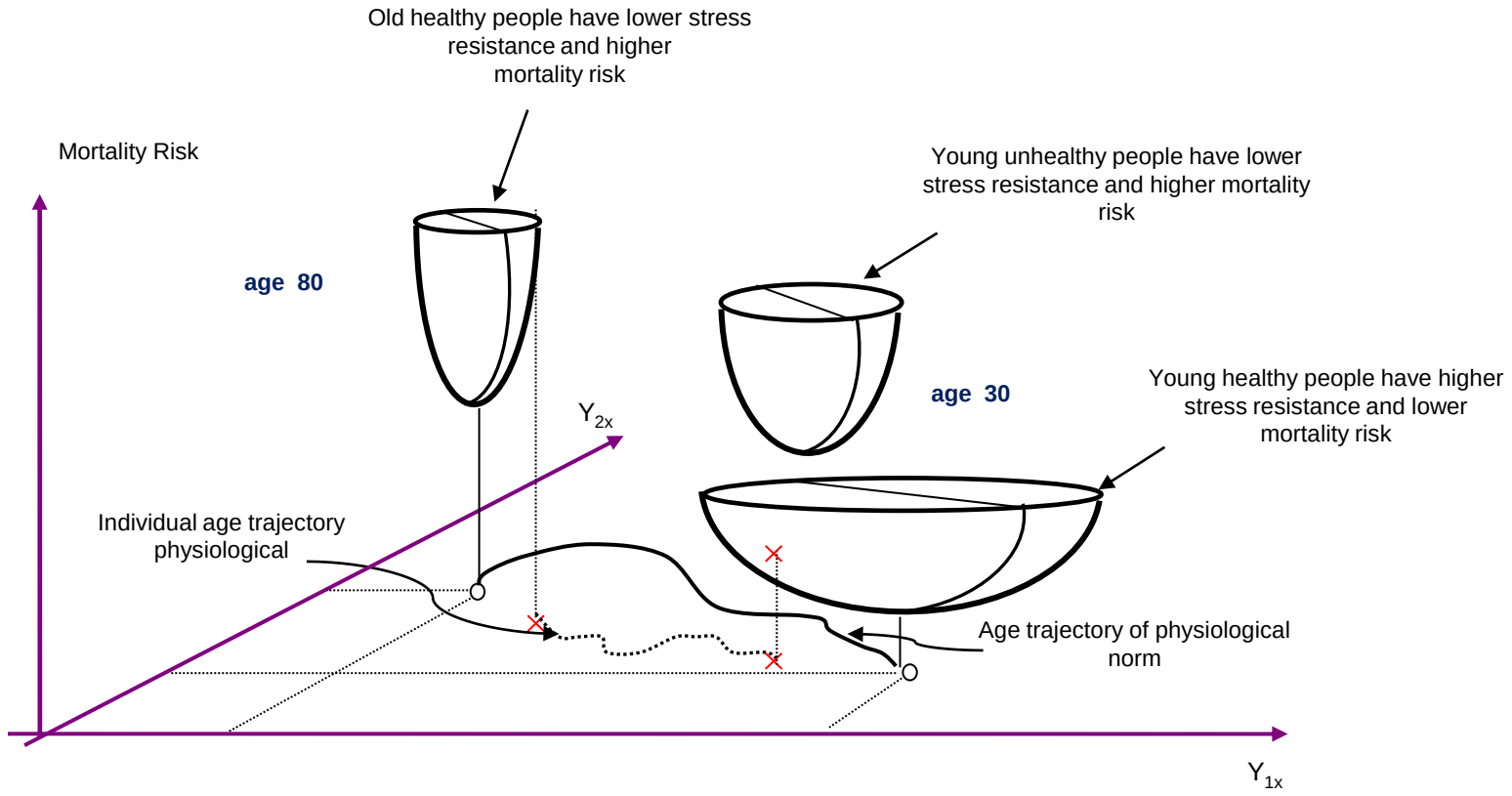


Illustration of hypothetical two-dimensional U-shaped mortality risks (quadratic hazards) considered as a function of two risk factors Y_{1x} and Y_{2x} (e.g., physiological variables) for the 30 and 80 years old individuals. The width of each paraboloid characterizes resistance to stresses for the healthy young, healthy old and unhealthy young individuals. The coordinates of the minimal values of each paraboloid correspond to physiological norms. The model assumes that the normal values can be different at different ages. Individual's physiological state can also change with increasing age.

CELLULAR STRESS AND ALZHEIMER'S DISEASE

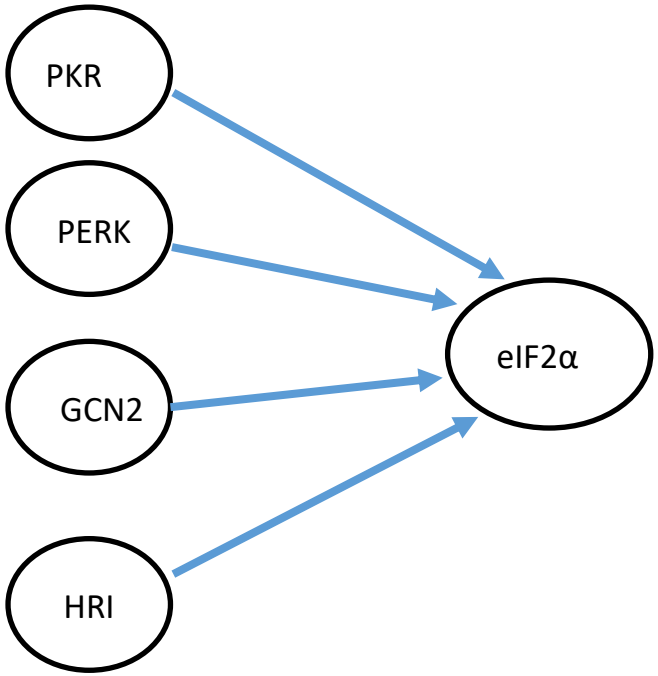
Types of cellular stressors:

- Infections
- Hypoxia
- Amino acid starvation
- Unfolded proteins accumulation
- UV radiation
- Oxidative stress
- Toxic materials
- Others

FOUR KINASES – FOUR SENSORS OF CELLULAR STRESS

- **PKR --** interferon-induced, double-stranded RNA-activated protein kinase
- **PERK --** protein kinase R (PKR)-like endoplasmic reticulum kinase
- **GCN2 --** general control nonderepressible 2 kinase
- **HRI –** heme regulated inhibitor

INTEGRATED STRESS RESPONSE



Four kinases serve as sensors of stress signals. In response to stress they can phosphorylate eukaryotic initiation translation factor eIF2α:

One is called PKR – double stranded RNA-dependent protein kinase.

The second in PERK –PKR-like Endoplasmic Reticulum protein kinase.

The third is GCN2 – general control nonderepressible kinase.

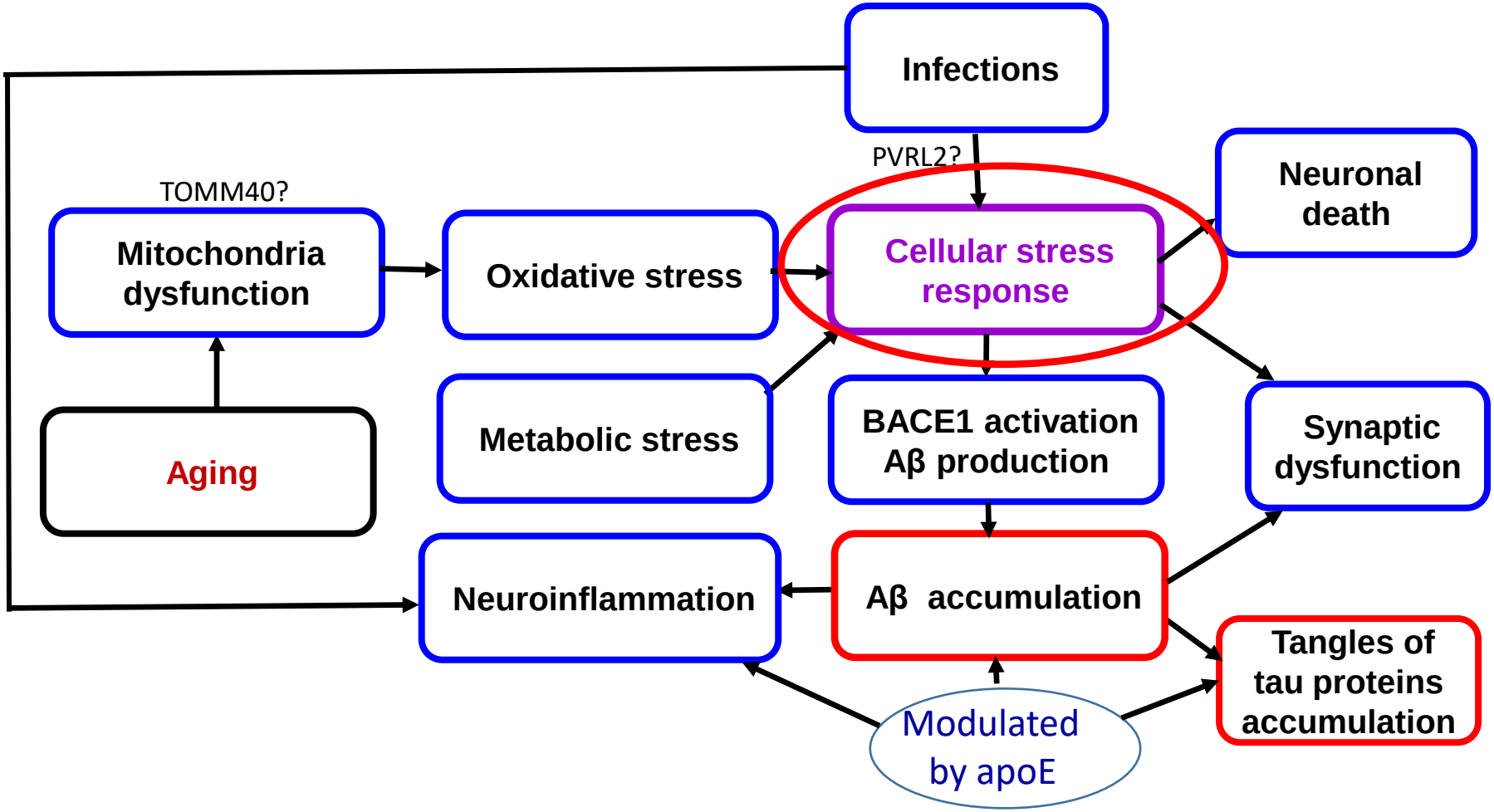
The fourth, HRI, is heme-regulated inhibitor kinase.

Figure 2. Four eukaryotic initiation factors 2 alpha (EIG2A) kinases: PKR (EIF2AK2), PERK (EIF2AK3); GCN2 (EIF2A4) and HRI (EIF2AK1)

GENETIC VARIANTS FROM CORRESPONDING GENES ARE DETECTED IN GWAS OF AD WITH NOMINAL LEVELS OF STATISTICAL SIGNIFICANCE

CONNECTIONS AMONG AGING, AD HALLMARKS, AND ALZHEIMER'S DISEASE

CONNECTIONS AMONG AGING, AD HALLMARKS, AND ALZHEIMER'S DISEASE



INTEGRATED STRESS RESPONSE

- Cellular integrated stress response could be the unifying systemic conceptual framework for studying Alzheimer's disease in its connection with other aging related health disorders
- SNPs from genes involved in cellular stress response show nominally significant associations with ad in genome wide associations studies

SYSTEMIC PREVENTION OF ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

- There is a strong evidence from a population-based perspective, that regular physical activity and management of cardiovascular risk factors (especially diabetes, obesity, smoking and hypertension) reduce the risk of cognitive decline.
- A healthy diet and lifelong learning/cognitive training may reduce the risk of cognitive decline.

WHIS DIET IS THE "HEALTHY DIET"? EXAMPLES

- The accumulating evidence shows that the diets that are best for your brain health include the Mediterranean diet and diets that are moderate in calories and include optimal amounts of protein and vitamins.
- In fact, certain protein deficiencies and some vitamin deficiencies are linked with increased chances of having a stroke.
- Seafood had been shown to reduce stroke risk, while a vegetarian diet has its pros and cons in terms of stroke risk.
- Wine and other alcoholic beverages also have an impact on stroke risk.
- The chocolate has been shown in some research studies to lower stroke risk.

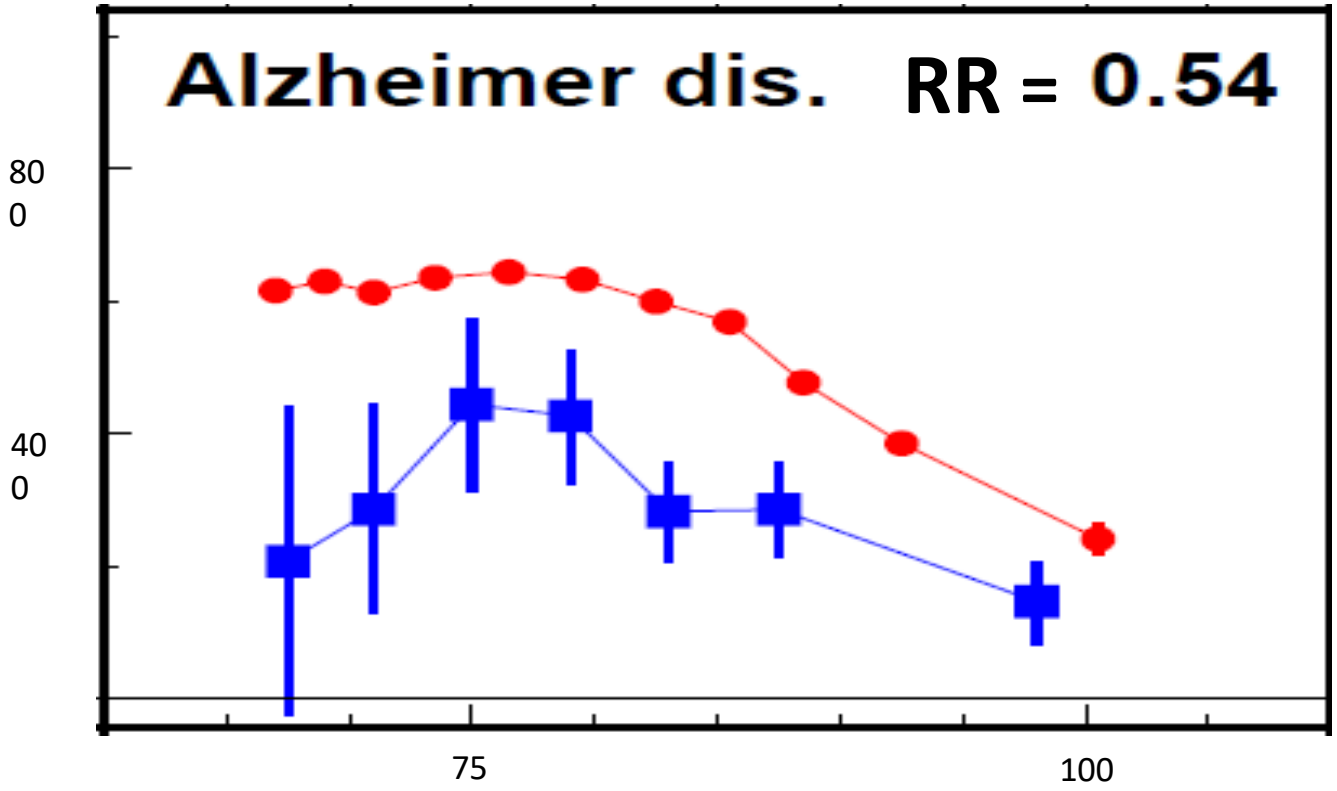
SYSTEMIC DEALING WITH STRESS OVERLOAD

- In 1949, Swiss physiologist Walter Hess, PhD, was awarded the Nobel Prize in Medicine and Physiology for his description of two centers in the hypothalamus of the cat.
- One of the points, which he called the ergotrophic center, when stimulated electrically, produced the typical physiological features of the sympathetic stress response: rise in blood pressure, increase in pulse, faster respiratory rate, and an increase in oxygen consumption.
- He broke new ground when he demonstrated an additional point in the hypothalamus that, when stimulated, caused the exact opposite of the stress response.
- He called it the trophotrophic center, which was associated with parasympathetic activation, relaxation, sleepiness, and withdrawal from activities.
- The trophotrophic system protects against stress overload and allows for recovery and regeneration.
- This dichotomy suggests that there exists an innate, natural way to reduce the deleterious effects of stress.

TRADEOFF BETWEEN AD AND CANCER

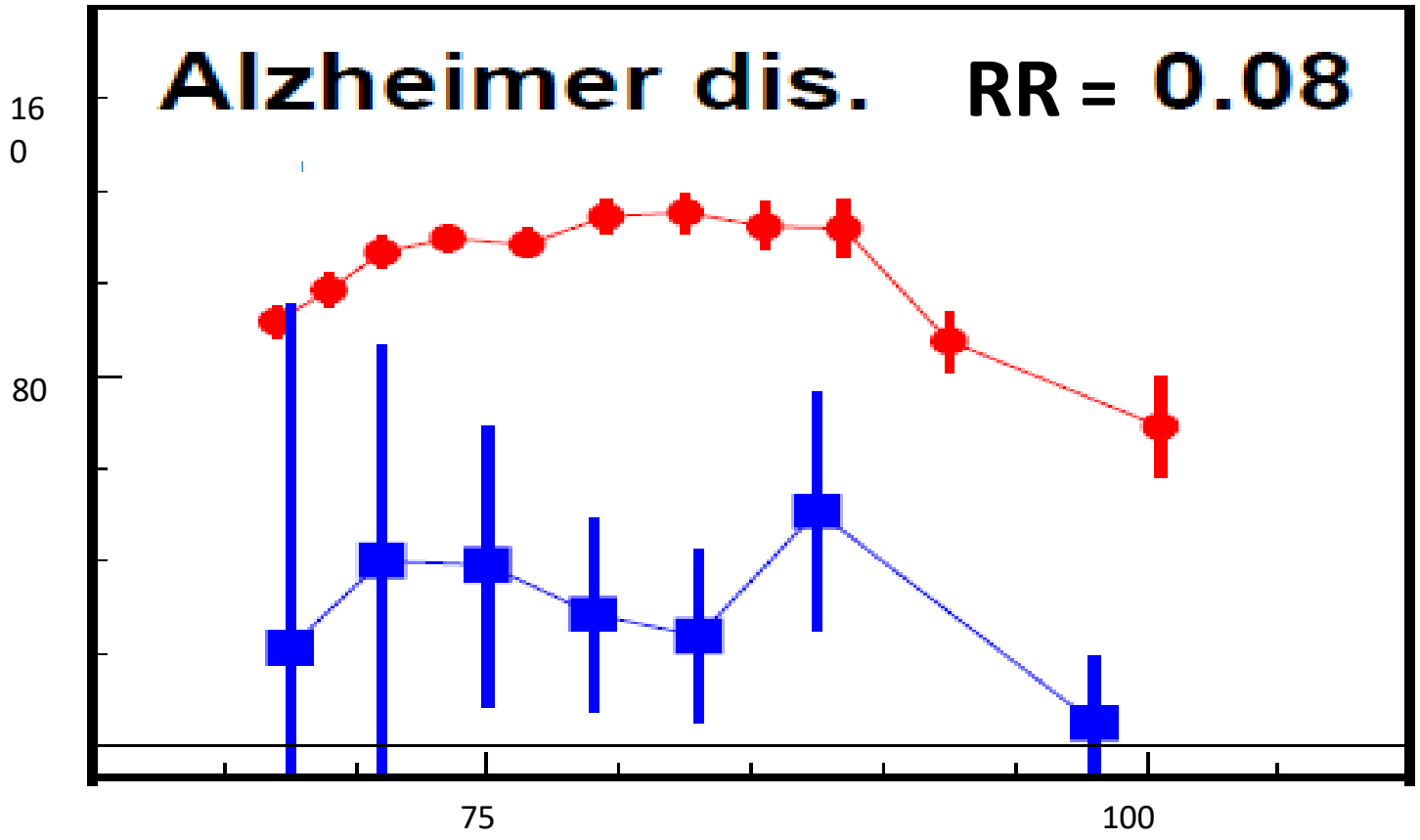
- **EPIDEMIOLOGIC STUDIES SHOWED AN INVERSE ASSOCIATION BETWEEN AD AND CANCER**
- **PRO-APOPTOTIC MUTATIONS PROMOTE AD AND PROTECT FROM CANCER**
- **ANTI-APOPTOTIC MUTATIONS PROMOTE CANCER AND PROTECT AGAINST AD**

INCIDENCE OF BREAST CANCER AMONG PEOPLE WITH AD (BLUE) AND IN THE US POPULATION (RED). SEER-M DATA



Akushevich et al., 2013

INCIDENCE OF MELANOMA AMONG PEOPLE WITH AD (BLUE) AND IN THE US POPULATION (RED). SEER-M DATA



Akushevich et al., 2013

AD AND TYPE 2 DIABETES

RECENT STUDIES PROVIDE EVIDENCE THAT AD AND T2D ARE TWO PARTS OF THE SAME METABOLIC DISORDER

IN SOME STUDIES AD IS CALLED TYPE 3 DIABETES.

CONCLUSIONS (I)

1. The results of our GWAS of AD using four independent datasets confirm:

   (i) strong associations of the APOE, TOMM40, and PVRL2 genes with AD
   (ii) potential role of genes involved in cellular stress response in AD

2. Mutations in these genes may influence AD through:

   (i) dysregulation of the mechanisms of Aβ removal from the brain (APOE),
   (ii) dysfunction of mitochondria (TOMM40),
   (iii) compromising defense against infection agents (PVRL2),
   (iv) neuroinflammation induced by the integrated stress response,
   (v) dysregulation of cellular stress response

3. These results indicate that AD is highly heterogeneous systemic health disorder.

CONCLUSIONS (II)

4. Studies of AD will benefit from joint analyses of cancer, T2D, and other AD related health disorders

5. Molecular biological mechanisms involved in cellular stress response can be a common basis for these analyses

6. Integrative analyses of the results of GWAS of AD and related diseases, together with research findings obtained in clinical, experimental, and molecular biological studies is needed to better understand heterogeneous nature of Alzheimer’s disease

WHY IS THE PROGRESS IN REDUCING AD BURDEN SO SLOW?

- It looks that intervention methods that address the AD problems focusing on specific AD hallmarks, used so far, are not successful.
- The most likely reason is the systemic nature of this health disorder initiated by stressful events affecting many processes, organs and systems during the life course.
- This means that the systemic approaches of dealing with Alzheimer's disease, as well as with other aging related health disorders are needed.
- Developing such approaches is a challenging research proplem.
- Is there any hope?

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