

# DEMENTIA: THE GOOD, THE BAD, AND THE POSSIBLE

WILL I REMEMBER MY GRANDCHILDREN'S NAMES?

Barry Goldlist

November 23, 2018



# SAMMY & CHARLIE WITH STELLA





# DISCLOSURES

- No financial interests in any company involved in dementia research
- I have not accepted any money from pharmaceutical interests in the 21<sup>st</sup> century
- I have accepted industry money in the form of unrestricted educational grants



# OBJECTIVES

- Create joy by highlighting secular trends in dementia incidence and despair by highlighting medical advances in dementia treatment
- Discuss dementia in residential care and its impact
- Identify ‘evidence-based’ care initiatives that make a difference for persons with dementia in residential care
- Learn a bit about dementia, (particularly AD and vascular dementia) and some of the pitfalls in interpreting research



# WHAT IS DEMENTIA?

## Major Neurocognitive Disorder (DSM V)

1. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains — such as complex attention, executive function, learning, memory, language, perceptual-motor or social cognition.

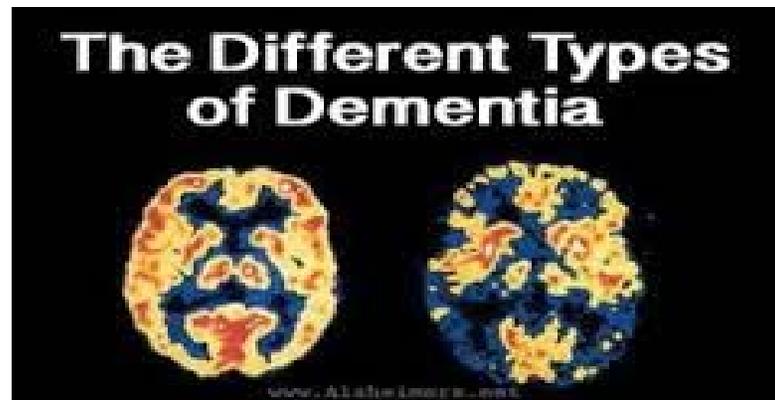
This evidence should consist of:

- Concern of the individual, a knowledgeable informant (such as a friend or family member), or the clinician that there's been a significant decline in cognitive function  
and
- A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing. Of if neuropsychological testing isn't available, another type of qualified assessment.



# WHAT IS DEMENTIA

2. The cognitive deficits interfere with independence in everyday activities (e.g., at a minimum, requiring assistance with complex instrumental activities of daily living, such as paying bills or managing medications).
3. The cognitive deficits don't occur exclusively in context of a delirium, and are not better explained by another mental disorder.



# CAUSES OF DEMENTIA: DSM V

- Alzheimers Disease
- Frontotemporal lobar degeneration
- Lewy body disease
- Vascular disease
- Traumatic brain injury
- Substance/medication use
- HIV infection
- Prion disease
- Parkinson's Disease
- Huntington's disease
- Another medical condition
- *Multiple etiologies*
- Unspecified



**FIRST THE GOOD NEWS**  
**Report from Framingham Study**  
**February 2016**



Medicine  
UNIVERSITY OF TORONTO

*Geriatrics*

**Table 2. Temporal Trends in the Incidence of Dementia.\***

Subtype	No. of Cases	Total No. of Observation Periods	5-Yr Cumulative Hazard Rate (95% CI) <sup>†</sup>				5-Yr Hazard Ratio (95% CI) <sup>‡</sup>				P Value for Trend
			Epoch 1	Epoch 2	Epoch 3	Epoch 4	Epoch 2	Epoch 3	Epoch 4	Trend <sup>§</sup>	
Overall dementia	371	9015	3.6 (2.9–4.4)	2.8 (2.2–3.5)	2.2 (1.8–2.8)	2.0 (1.5–2.6)	0.78 (0.59–1.04)	0.62 (0.47–0.83)	0.56 (0.41–0.77)	0.80 (0.72–0.90)	<0.001
Alzheimer's disease	264	9015	2.0 (1.5–2.6)	2.0 (1.5–2.6)	1.7 (1.3–2.3)	1.4 (1.0–1.9)	1.00 (0.70–1.43)	0.88 (0.62–1.25)	0.70 (0.48–1.03)	0.88 (0.77–1.00)	0.052
Vascular dementia	84	9014	0.8 (0.6–1.3)	0.8 (0.5–1.2)	0.4 (0.2–0.7)	0.4 (0.2–0.7)	0.89 (0.51–1.56)	0.46 (0.25–0.86)	0.45 (0.23–0.87)	0.71 (0.56–0.90)	0.004

\* The baseline examination period was between 1977 and 1983 for the first epoch, between 1986 and 1991 for the second epoch, between 1992 and 1998 for the third epoch, and between 2004 and 2008 for the fourth epoch.

<sup>†</sup> The 5-year cumulative hazard rates (the cumulative incidence of dementia per 100 persons over a period of 5 years) are adjusted for age and sex.

<sup>‡</sup> The 5-year hazard ratios (the incidence of dementia during each epoch relative to the incidence during the first epoch) are adjusted for age and sex.

<sup>§</sup> We estimated linear trends (the decline per decade in the 5-year incidence of dementia) using the elapsed mean time (in decades) between the first epoch and each consecutive epoch.



**Table 3. Temporal Trends in the Incidence of Dementia, Stratified by Age, Sex, Educational Level, and Apolipoprotein E ε4 Status.\***

Variable	No. of Cases of Dementia	Total No. of Observation Periods	P Value for Interaction	5-Yr Hazard Ratio (95% CI)†				P Value for Trend
				Epoch 2	Epoch 3	Epoch 4	Trend‡	
Age at entry (yr)			0.82					
60–69	42	4418		0.43 (0.18–1.00)	0.36 (0.15–0.89)	0.38 (0.15–0.93)	0.65 (0.47–0.89)	0.008
70–79	133	3229		0.91 (0.59–1.42)	0.67 (0.42–1.07)	0.64 (0.36–1.11)	0.83 (0.68–1.00)	0.047
≥80	196	1368		0.86 (0.56–1.33)	0.72 (0.48–1.09)	0.68 (0.44–1.06)	0.86 (0.74–1.01)	0.06
Sex			0.27					
Female	234	5173		0.70 (0.50–1.00)	0.52 (0.36–0.74)	0.53 (0.36–0.78)	0.77 (0.67–0.89)	<0.001
Male	137	3842		0.96 (0.59–1.57)	0.89 (0.55–1.43)	0.64 (0.38–1.08)	0.85 (0.71–1.02)	0.08
Educational level			0.031					
No high school diploma	130	1831		1.46 (0.94–2.26)	0.97 (0.58–1.61)	1.66 (0.87–3.15)	1.11 (0.89–1.39)	0.34
High school diploma	228	6948		0.54 (0.36–0.81)	0.55 (0.38–0.79)	0.46 (0.31–0.67)	0.77 (0.67–0.88)	<0.001
APOE ε4 status§			0.15					
Any genotypic information	246	6304			0.96 (0.70–1.30)	0.83 (0.60–1.16)	0.89 (0.74–1.08)	0.25
Negative for APOE ε4	169	5000			0.95 (0.65–1.37)	0.75 (0.50–1.13)	0.84 (0.66–1.06)	0.14
Positive for at least one APOE ε4 allele	77	1304			1.01 (0.58–1.75)	1.09 (0.61–1.93)	1.05 (0.75–1.47)	0.76

\* The baseline examination period was between 1977 and 1983 for the first epoch, between 1986 and 1991 for the second epoch, between 1992 and 1998 for the third epoch, and between 2004 and 2008 for the fourth epoch.

† The 5-year hazard ratios (the incidence of dementia during each epoch relative to the incidence during the first epoch) are adjusted for age and sex, except for those stratified by sex (which were adjusted only for age at entry) and those stratified by age (which were adjusted only for sex).

‡ We estimated linear trends (the decline per decade in the 5-year incidence of dementia) using the elapsed mean time (in decades) between the first epoch and each consecutive epoch.

§ Data were available for only a subgroup of participants with genotypic information. Data for APOE ε4 genotyping were limited during the first epoch; therefore, the hazard ratios for the third and fourth epochs were calculated relative to the data obtained during the second epoch.



**Table 4. Temporal Trends in the Incidence of Dementia, Adjusted for Educational Level, Vascular Risk Factors at Midlife, and Cardiovascular Disease.\***

Variable	No. of Cases of Dementia	Total No. of Observation Periods	5-Yr Hazard Ratio (95% CI) <sup>†</sup>				P Value for Trend
			Epoch 2	Epoch 3	Epoch 4	Trend <sup>‡</sup>	
High school diploma	358	8778	0.82 (0.61–1.10)	0.68 (0.50–0.91)	0.65 (0.47–0.91)	0.85 (0.75–0.95)	0.005
Increase in systolic blood pressure at midlife	361	8837	0.76 (0.56–1.01)	0.61 (0.46–0.81)	0.54 (0.40–0.75)	0.79 (0.71–0.89)	<0.001
Increase in body-mass index at midlife	352	8658	0.78 (0.59–1.05)	0.62 (0.47–0.83)	0.56 (0.41–0.76)	0.80 (0.71–0.89)	<0.001
Type 2 diabetes at midlife	284	7418	0.76 (0.55–1.06)	0.55 (0.39–0.76)	0.50 (0.35–0.71)	0.76 (0.67–0.86)	<0.001
Preexisting and incident stroke	371	9015	0.78 (0.59–1.04)	0.62 (0.47–0.82)	0.58 (0.42–0.78)	0.81 (0.72–0.90)	<0.001
Preexisting cardiovascular disease	371	9015	0.78 (0.59–1.04)	0.62 (0.47–0.82)	0.57 (0.41–0.77)	0.80 (0.72–0.90)	<0.001
Preexisting atrial fibrillation	371	9015	0.78 (0.59–1.04)	0.61 (0.46–0.81)	0.55 (0.40–0.75)	0.79 (0.71–0.89)	<0.001

\* The baseline examination period was between 1977 and 1983 for the first epoch, between 1986 and 1991 for the second epoch, between 1992 and 1998 for the third epoch, and between 2004 and 2008 for the fourth epoch.

<sup>†</sup> The hazard ratios in each row are adjusted for the variable shown in the first column of that row. In addition, the 5-year hazard ratios (the incidence of dementia during each epoch relative to the incidence during the first epoch) are adjusted for age and sex.

<sup>‡</sup> We estimated linear trends (the decline per decade in the 5-year incidence of dementia) using the elapsed mean time (in decades) between the first epoch and each consecutive epoch.



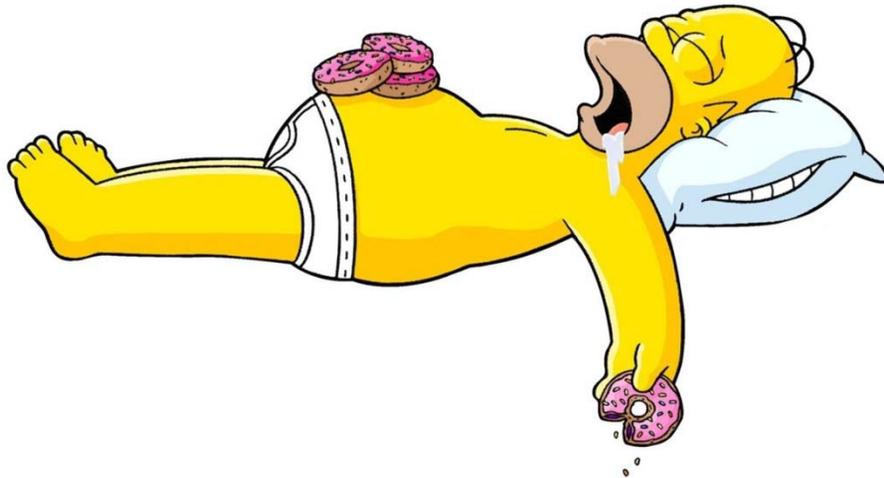
...the incidence of dementia is about ½ what it was 40 years ago, while the prevalence of dementia is also down at least 20%....

Salizabal CL et al, NEJM 2016;374:523-532;  
Langa KM, et al, [jamainternmed.2016.6807](#)



# WHY HAS THIS HAPPENED?

## WE DO NOT KNOW



Unlikely that this is the answer

It has happened despite:

- Increasing BMI
- Increasing prevalence of diabetes
- Overall aging of the population

This has been suggested in other studies as well. Possible factors:

- ↑ wealth
- ↑ education
- ↑ increased control of vascular risk factors (statins, BP medications, less smoking)



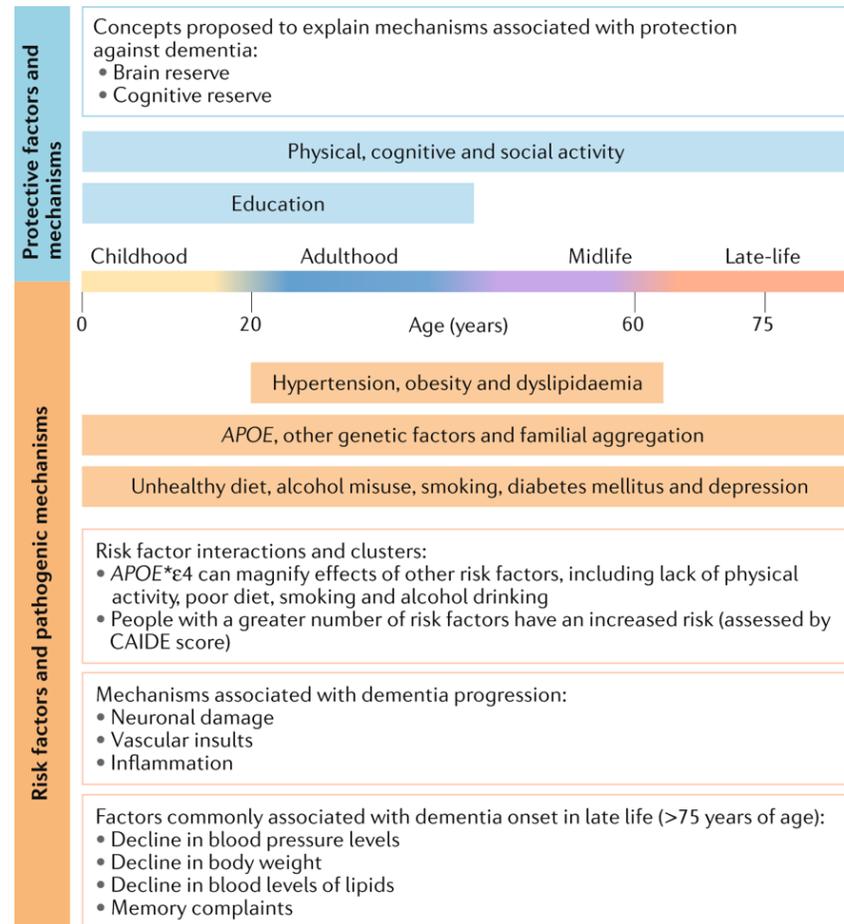
## **OTHER POSSIBILITIES** (per Chris Brymer)

- Increased exercise
- reducing hypoglycemia in NIDDM
- Reducing head injuries (helmets/seat belts)
- Drug reduction: postmenopausal estrogen, anticholinergics, and benzodiazepines over the last 40 years
- May decline further with dietary change (e.g. Mediterranean diet)



# LIFE COURSE AND DEMENTIA RISK FACTORS

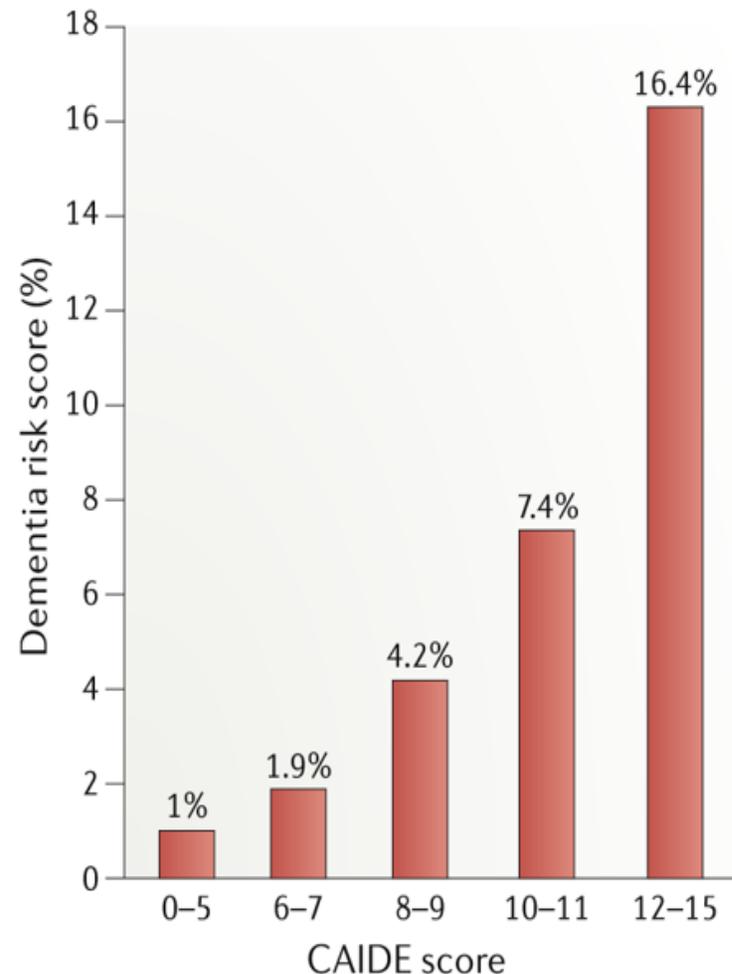
Nature Reviews Neurology November 2018



# CVS risk factors, Aging & Dementia (CAIDE) Risk Score Applied in Mid-Life (40-65)

## The CAIDE dementia risk score

Risk factor		Points
Age	<47 years	0
	47–53 years	3
	>53 years	4
Education	≥10 years	0
	7–9 years	2
	<7 years	3
Sex	Female	0
	Male	1
Blood pressure	≤140 mmHg	0
	>140 mmHg	2
BMI	≤30 kg/m <sup>2</sup>	0
	>30 kg/m <sup>2</sup>	2
Total cholesterol	≤6.5 mmol/l	0
	>6.5 mmol/l	2
Physical activity	Yes	0
	No	1



# CAN LIFESTYLE INTERVENTIONS PREVENT DEMENTIA?

- Not surprisingly, the single domain lifestyle interventions to prevent cognitive decline and dementia have been disappointing
- Nature Reviews Neurology highlights 9 multi-domain trials to prevent cognitive decline, some with encouraging results



## OTHER IMPROVEMENTS

- Incidence of injurious falls is decreasing
- Incidence of hip fractures is declining
- 80 year olds in the 21<sup>st</sup> century have fewer impairments in ADL's than their counterparts 30 years earlier

However the number of older people is increasing, so the ***absolute*** number of hip fractures, people with dementia, those needing LTC, etc. is increasing



# BE WARY WHEN INTERPRETING THE LITERATURE

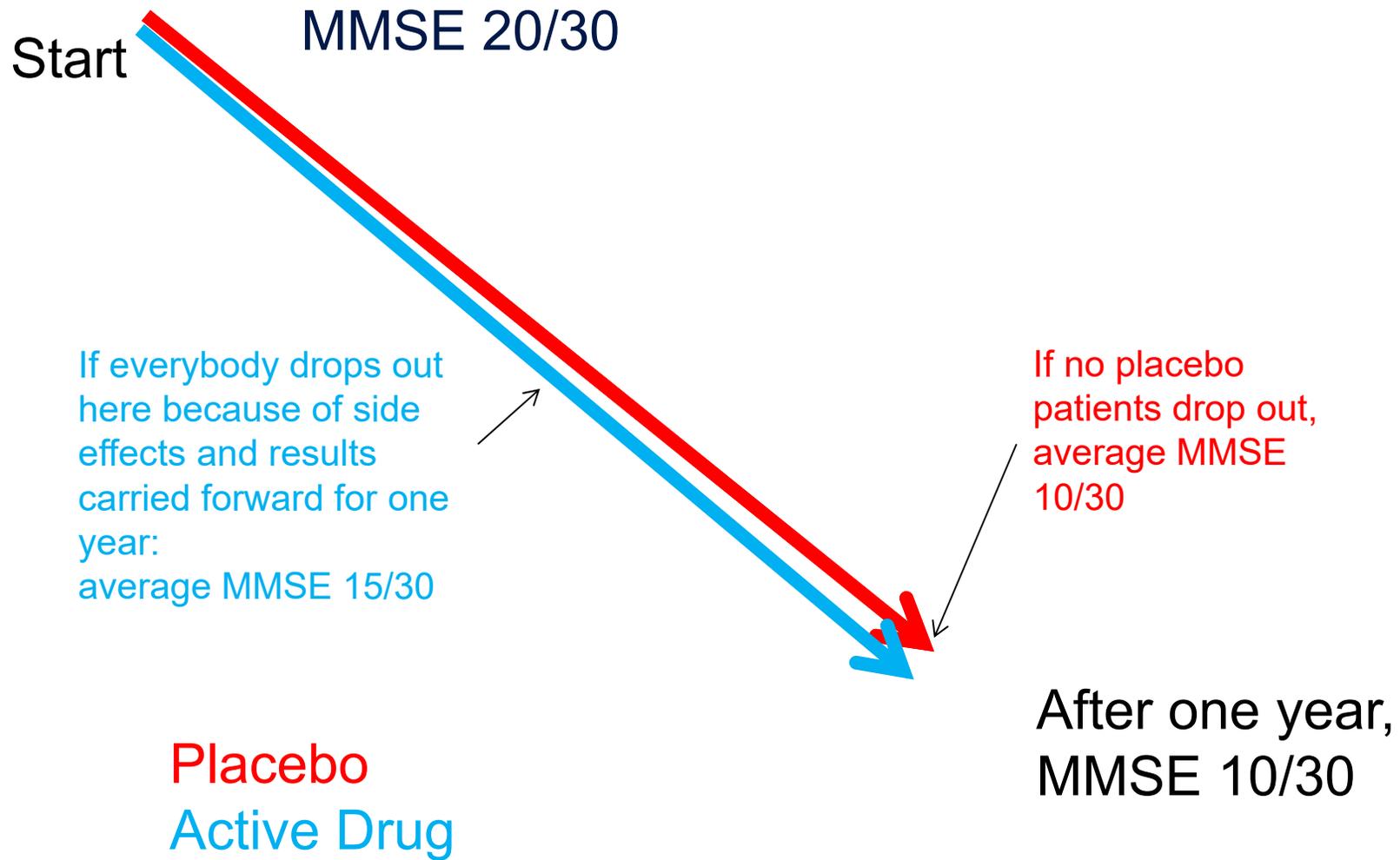
- It is well known that correlation does not imply causation (skin tags and colon cancer; ministers and rum)
- But correlations more common in old age. The old truck pictured has a bad bumper, no brakes, poor transmission etc., but it is time and usage that has caused all these independently



# INTENTION TO TREAT ANALYSIS

- Standard interpretation of clinical trials, but best used when disease is not invariably progressive (i.e. treatment modifies the disease)
- For symptomatic treatments in a progressive disease (e.g. cholinesterase inhibitors for AD), early drop out favors treatment group as last results are carried forward. If drop out from side effects are more common in treatment group, that makes treatment seem more effective.





# GENERAL PRINCIPLES OF DEMENTIA MANAGEMENT

- General medical care
  - Rule of halves
- support services
- caregiver support and education
- environmental modification
- Non-pharmacological management (music therapy, etc.)
- pharmacological agents



# RULE OF HALVES

From Larsen's studies (descriptive cohort) in Seattle at the University of Washington memory clinic

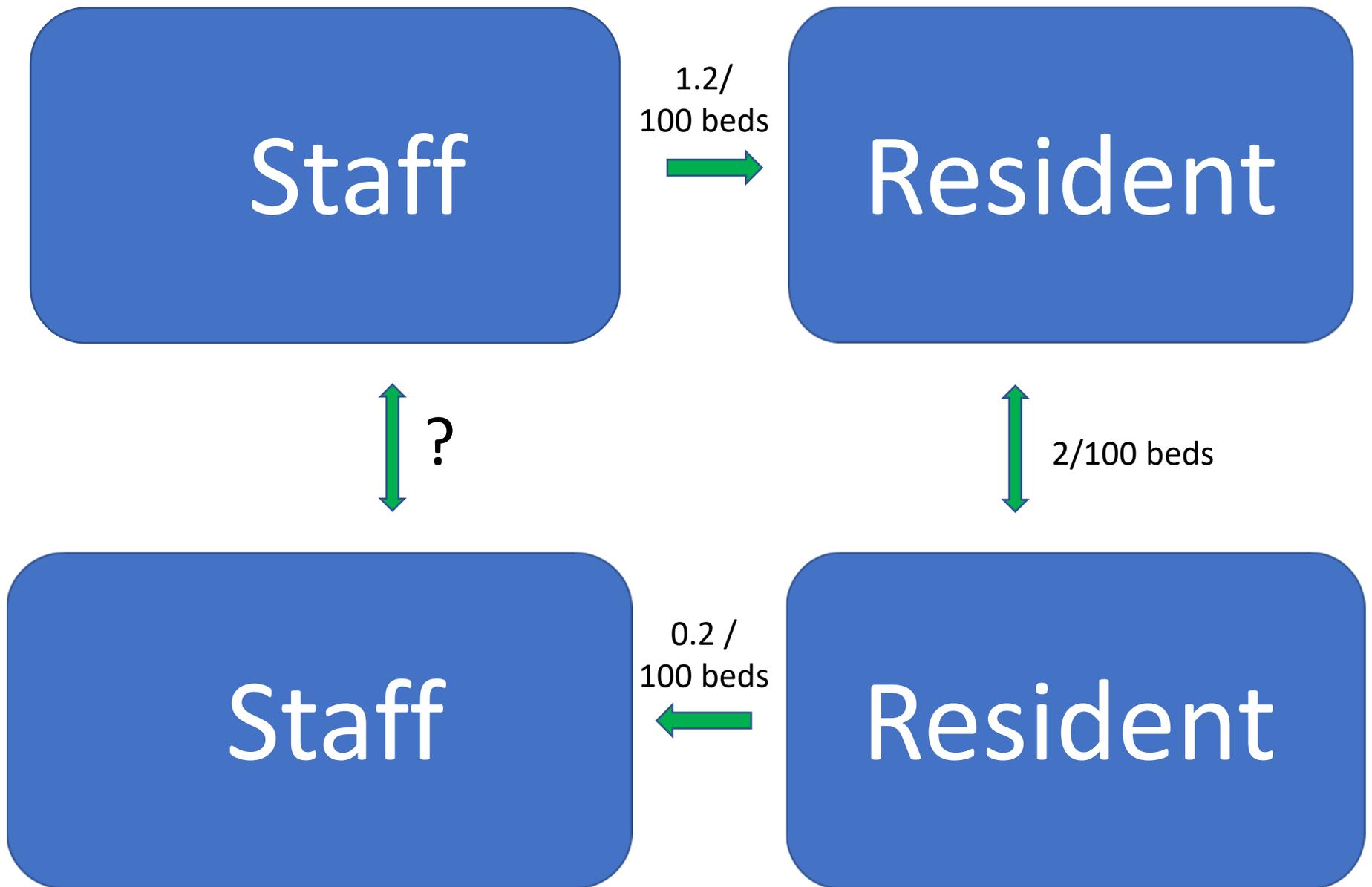
- patients were elderly with multi-morbidity
- $\frac{1}{2}$  the patients had imperfectly controlled medical issues
- $\frac{1}{2}$  of these ( $\frac{1}{4}$  of total) had cognitive improvement with optimal management
- $\frac{1}{2}$  of these ( $\frac{1}{8}$  of total) remained improved at one year (*better results than any drugs*)



# VIOLENCE IN LONG TERM CARE (LTC)

- The Chief Coroner of Ontario's Geriatric and Long Term Care Review Committee (GLTCRC) reviews difficult cases and those where police intervened
- Issues in BC probably similar
- Of note the initial legislation in Ontario was for Nursing Homes, and current name of LTC reflects the declining role of nurses
- Unfortunately, nurses are the most versatile health care providers for LTC (medical knowledge + prolonged intimate contact)





## RECENT CASE (09/18) FROM GLTCRC

- Mr. X an 86 year old man with AD, multiple co-morbidities but no behavioural issues
- Mr. Y an 80 year old man with dementia and aggressive behaviours successfully managed by re-direction and minimal meds
- One night Y was found nude in X's room assaulting him
- X developed a subdural and died despite neurosurgical intervention



## GLTCRC RECENT 5 YEAR EXPERIENCE IN LTC

- 33 homicides
- 17 from trauma/beating
- 15 from falls/push
- 1 from asphyxia/positional restraint

Not a huge number considering vastness of Ontario's LTC system, but impact on staff, family and other residents, is enormous.

Current investigation of 'Wetlaufer' case has added further anxiety.



# Dementia friendly health-care environments: anticipated outcomes and ways they might be achieved

Systematic Reviews 2015 (adapted from Royal College of Nursing 2013)

OUTCOMES	ACHIEVED THROUGH
Skilled staff with time to care	<ul style="list-style-type: none"><li>• Staff training focused on dementia awareness</li><li>• Support and reinforcement from leaders</li><li>• Identifying dementia champions</li><li>• <b><i>Attention to staffing levels and mix</i></b></li></ul>
Partnership working with carers	<ul style="list-style-type: none"><li>• Using tools that include carer knowledge and opinion</li><li>• Flexible visiting hours</li><li>• <b><i>Assessment of carer needs</i></b></li></ul>
Assessment and early identification	<ul style="list-style-type: none"><li>• Staff training (use of incentives)</li><li>• Screening and assessment tools</li><li>• <b><i>Protocols and pathways (a paper exercise at times)</i></b></li><li>• Medication reviews</li></ul>



## Dementia friendly health-care environments 2: anticipated outcomes and ways they might be achieved

OUTCOMES	ACHIEVED THROUGH
Individualized care (person-centred care)	<ul style="list-style-type: none"> <li>• Assessment and documentation that focuses on the person’s biography, preferences and priorities, <b>and retained abilities</b></li> <li>• Activities to support social engagement and inclusion in everyday activities</li> <li>• Access to dementia and palliative care specialists who can guide care</li> </ul>
Environments that are dementia friendly	<ul style="list-style-type: none"> <li>• Promote independence by being safe for walking and navigating</li> <li>• Not confusing (e.g. shiny floors can look like water)</li> <li>• Limiting moves in acute hospital stay</li> <li>• <b>Size</b> (my addition)</li> </ul>



# NY TIMES ARTICLE ON A DUTCH FACILITY

## August 2018



Images of Nature to calm a patient



Medicine  
UNIVERSITY OF TORONTO

*Geriatrics*  
11/28/2018

## Husband and Wife at a Tram Stop



## The Beach Room



## A Pub (based on an actual Amsterdam Pub)



## Rooms Reminiscent of Childhood



## SOUNDS GREAT, BUT ...

It is likely that the Canadian elderly population is more diverse than that in the Netherlands.

This does not negate the approach, but makes it even more difficult to accomplish.



# THE BUTTERFLY APPROACH

- Recently discussed in a Toronto Star series reviewing success in a LTC facility dementia ward
- The Butterfly Household Model of Care was founded by Dr David Sheard in 1995 where the model was extensively piloted over a 5-year period at a care home called Merevale House in the UK
- [www.dementiacarematters.com](http://www.dementiacarematters.com)



# Knowing feelings matter most is the start

Life is an emotional journey. We all crave real human connection. This applies even more to people living with a dementia. People learn to trust emotions and rely more on themselves as feeling beings rather than thinking beings.

The heart of care is all about emotional care. This requires a shift in care services from solely providing task based care. The shift from 'doing' it to achieving real emotional connection is at the heart of 'being' person centred.



## Accepting a person's reality makes sense

All of us live in our own reality. Joining someone in their reality, entering their bubble, is the only way to reach people. Trusting there is always a way to reach another person is at the centre of valuing people and life.

In positive focused dementia care this begins with seeing, hearing and feeling the lived experience of people on a minute by minute basis. Leaving the bubble of our busy work lives to enter the bubble of peoples lived experience is the beginning of good quality dementia care.



# Facing the truth requires real leadership

In dementia care, leadership involves facing different types of truth. It is not easy to take a mirror to oneself, and to outdated models of care. It involves facing the truth in what as a Manager and leader we are responsible for delivering now. Leadership is about creating services that hold up an exciting mirror image of what dementia care can look, sound and feel like.

Detached management has created institutionalised task based 'care' lacking real emotional connection. Attached leadership inspires people to be whole people at work. Real leadership is demonstrated through the heart and not just the hand.

Leadership, not management, is what being person centred is all about.



# Becoming a butterfly increases positive moments

We all live in the moment – moments matter. For everyone with or without a dementia all we have is now. We cannot yet fix dementia as a condition. We can fix our approach. Showing people living with a dementia that we know their feelings matter most can transform lives.

Dementia Care Matters has developed an approach using the metaphor of a butterfly. Staff who ‘get it’, know in their heart that quality of life matters. They learn how to look, sound and feel like butterflies at work. Being natural in dementia care involves flitting between people, being still, connecting, creating colour and changing moments.



# Being a Butterfly in dementia care works

Adults learn through reflecting on their experiences. Real learning requires expert facilitation. For too long dementia care has relied on teaching or awareness raising training. This may inspire some individuals but it does little to transform care practices.

Our innovative learning methods develop the capacity in people to become real stars in dementia care. Being a Star focuses on improving self awareness and emotional intelligence in people. This is the route to providing high quality emotional care. Being A Star transfers skills development into measurable action.



# Coaching skills leads to action

Coaching creates practice based evidence. Coaching is the way to transfer learning directly into practice.

Coaching involves imparting a mixture of inspiration and passion with new learning. Enabling staff to experience repeated practice and reflection on their learnt skills leads to improving people's daily quality of life. Coaching works when this is coupled with inspiring leaders committed to ensuring that measurable action is achieved.



# Supporting staff's emotions produces strength

Competencies and qualifications are no match for emotional intelligence. Feelings, spontaneity, being self aware, and flexibility are what counts in being person centred. However, being person centred is not easy as an individual. It involves a lot of giving. It involves a lot of emotional connection.

The emotional support of staff trying their very best has to be at the core of services aiming to be person centred.

The symbol of a gladioli represents being given a break, being sincere and having strength of character. Demonstration of these values requires a clear strategy on emotional labour. For staff to be person centred they also have to receive person centred care from their employers



# Developing dementia care is like magic

Service development in dementia care needs its own special form of magic. Transforming dementia care isn't rocket science. However, simple ideas can be difficult to implement in complicated organizations.

Creating magic can take phenomenal levels of creativity, endurance and dogged determination. Maintaining momentum matters in dementia care. Achieving sustainability is important for those who have already been working incredibly hard to improve people's quality of life.

The old culture is powerful and can so easily return when backs are turned. Sharing our consultancy expertise is the way to help other staff who have service development responsibility to produce their own magic in dementia care.



## Dr. Sheard's Article from 2013

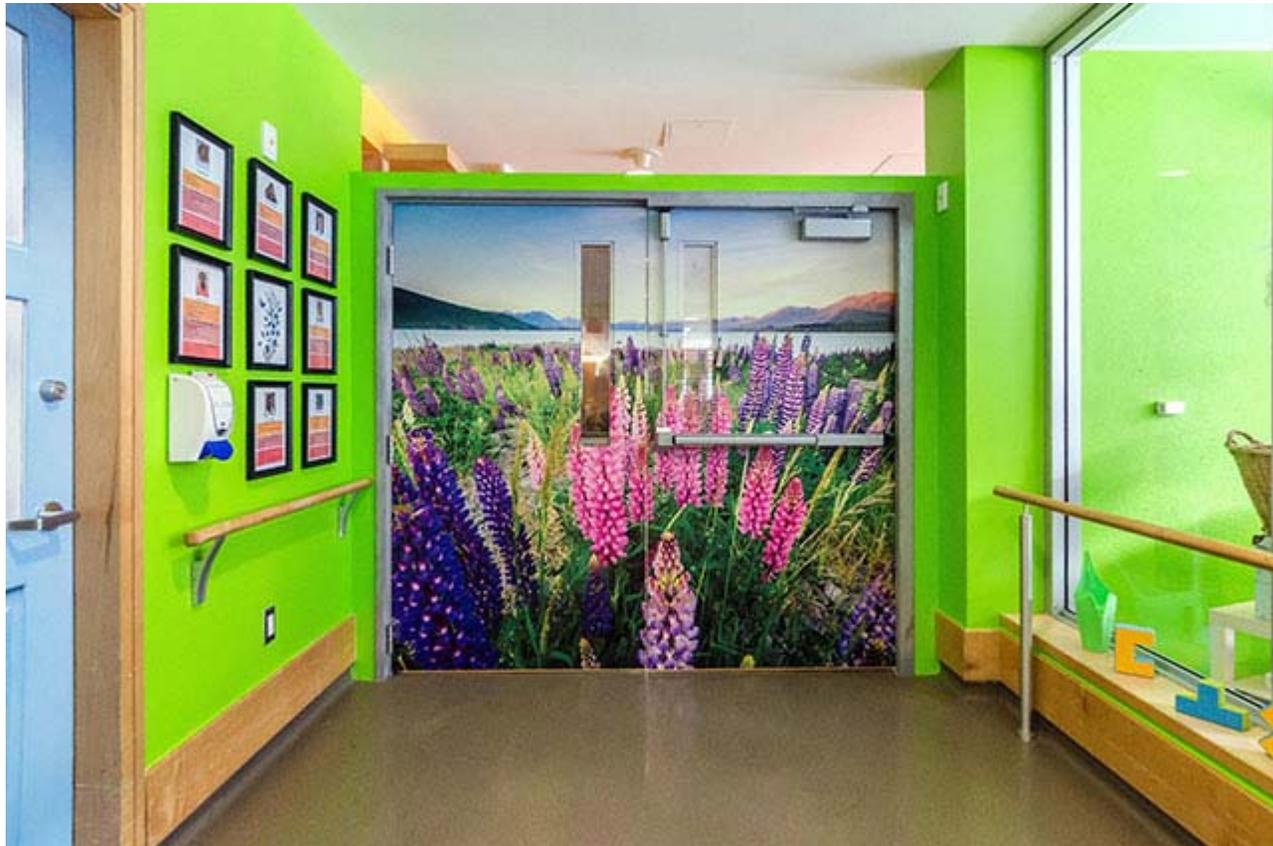
- Initial home had 36 people
  - *Will it work in larger homes?*
- Staffing levels not specified
  - *Are Canadian staffing levels sufficient? Does focusing on emotional care diminish need for physical care?*
- Evidence based outcomes
  - *Not easy to find on the website or his article*



# Corridor prior to adopting Butterfly Approach



# Redecorated Corridor



# Redecorated Lounge



# Playing Ball in Decorated Area



# MY THOUGHTS

- Design is important
- Smaller is better, but in areas of high land costs (hello Vancouver!) can larger buildings be designed with modules that create more home-like environments?
- Whatever 'system' of care is used, the key is knowing the person
- Dementia  $\neq$  Stupid; understanding retained abilities can be immensely helpful, but these change over time
- Current staffing levels and mix dictated by money available, not patient needs and outcomes
- 'upstream' improvements to diminish need for LTC





An Australian Government Initiative

## 12 top tips in caring for a person with dementia

### 1 Remember the person

- Their likes and dislikes
- Provide photos, pictures and mementos to help remember
- Talk about special occasions

### 2 Smile!

- The person will notice
- Your emotional state
  - Your body language
  - Tone of voice

### 3 Slow down

- Provide care in a relaxed manner
- It's ok for the person to do things for themselves
- Keep it simple

### 4 Help with orientation

- If they forget, remind them who you are
- Remind of daily routine
- Use cues – words, signs, pictures

### 5 Communicate clearly

- One point at a time
- Make sure glasses and hearing aides are clean and working
- Take time to understand

### 6 Step back

- When the person is angry
- Keep yourself safe – have a safety plan
  - Work out why the behaviour happened
  - Try again later

### 7 Keep it quiet

- Stop and listen
- Reduce conflicting noises – TV, radio, children
- Avoid overstimulation – crowds, shopping centres

### 8 Don't argue

- Go with the flow
- Acknowledge and respect what the person is saying and doing
- Telling them they are wrong may have a negative effect

### 9 Engage and encourage

- Get the person started with a meaningful activity
- Set activities up to succeed
- Thank them for assisting you and themselves

### 10 Distract

- Talk/yarn about their life
- Give them something to do
- Provide a relaxed environment

### 11 Talk with others

- Develop support network
- Talk about what has worked and what hasn't
- Record what you did – journal or diary

### 12 Be aware of sudden changes

- Look for a reason – pain, dehydration, infection, constipation
- See GP



# UPSTREAM IMPROVEMENTS

- Models of primary care (team based care, home based primary care)
- Better funding for home care
- More availability of supportive care homes that are less institutional and costly than LTC
  - Ability to achieve rapid transitions to LTC if necessary
- Availability of day centres (including at night)
- Better and more timely access to specialist services (geriatric psychiatry and medicine)
- Plus many more



# QUESTIONS?



# MULTI-MORBIDITY IN DEMENTIA

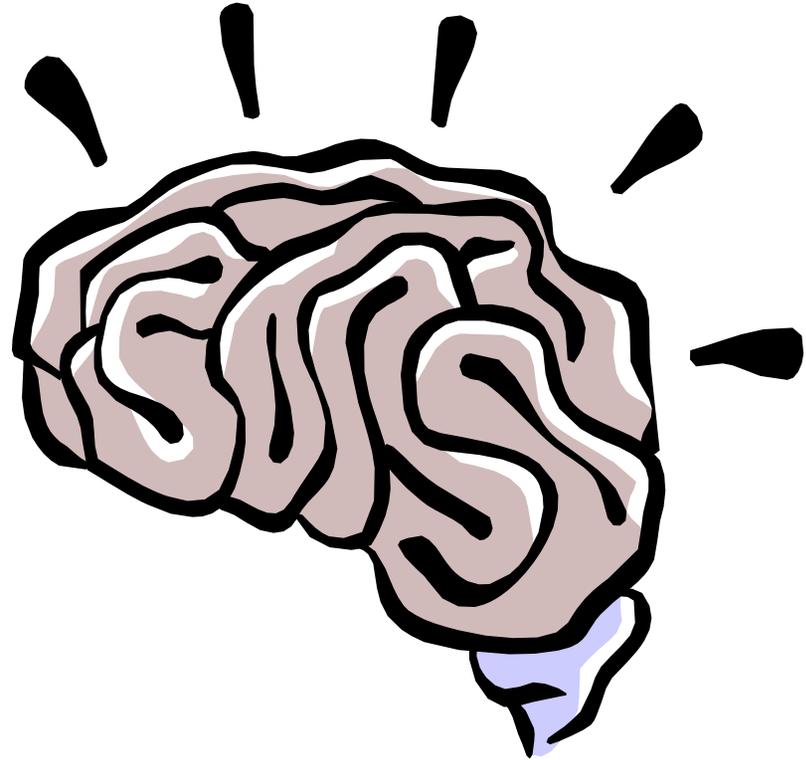
- Geriatric syndromes rarely have ‘one cause’, rather they are the results of numerous factors (age related, disease related, environment related).
- Older people usually have more than one diagnosis or issue
- Not surprising that multiple pathologies can contribute to dementia, so AD, vascular dementia etc. not as distinct as we once thought

*LR White et al, Neurology, March 2016*



# VASCULAR DEMENTIA

- An entity in a state of flux
- A stroke in the memory area clearly can cause dementia
- Role of 'small' strokes complex

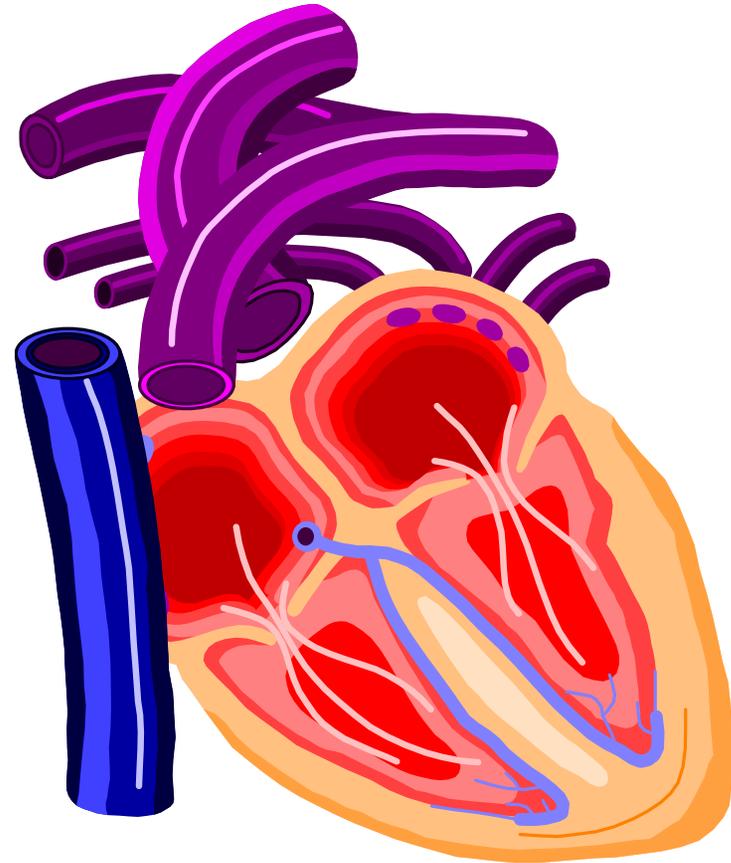


# PREVENTING 'VASCULAR' DEMENTIA

- Treat high blood pressure
- treat high cholesterol
- anticoagulants for atrial fibrillation
- Stop smoking
- Exercise
- Weight reduction (likely specific diets as well)

***Traditional risk factors more important in mid-life (?young age) than in old age. Also related to AD***

*(Gottesman et al, JAMA April 2017)*



# Risk factors for developing AD

<b>Definite Risk</b>	<b>Putative-Recent</b>	<b>Putative-Older</b>	<b>Protective</b>
age	Women <small>(confirmed in Sept 2018 CMAJ)</small>	depression	NSAIDS?
Apo E4	Low education	Head trauma	Estrogen? <small>(role of timing)</small>
Family history	Vascular factors	alcohol	Smoking?
MCI	Hyper-tension	Aluminum?	
	Smoking?		

## Relative Risk of AD in a patient with positive family history but no clear autosomal dominant inheritance

Number of 1 <sup>st</sup> degree relative affected	Age of Onset	Relative Risk	95% C. I.
1	60-69	5.3	2.8-10
1	70-79	2.3	1.4-4.6
1	80 and over	2.6	1.3-5.2
1	overall	3.5	2.6-4.6
2 or more	overall	7.5	3.3-8.7

From Table 2.1 Chapter 2. Atlas of Alzheimer Disease

# GENETICS OF ALZHEIMER'S

## Early onset

- chromosome 21: APP gene, age of onset 40-65
- chromosome 14: presenilin 1, onset 35-65
- chromosome 1: presenilin 2, onset 40-85, modified by other genes
- others?



# GENETICS OF ALZHEIMER'S

## Late onset:

- Chromosome 19: APO E4 allele, age of onset usually >65
- Chromosome 12
- Others, definitely



# NON-PHARMACOLOGICAL RECOMMENDATIONS

- The evidence at the present time is insufficient to conclude that organized cognitive intervention is beneficial to preventing progression in MCI or warrants prescription. (Recommendation Grade C, Evidence level I).  
(recent positive result in small study in African Americans JAMA Neurology 09/2018)
- There is fair evidence that physicians and therapists should promote engagement in cognitive activity as part of an overall "healthy lifestyle" formulation for elderly individuals with and without memory loss. (Recommendation Grade B, Evidence level I).
- There is fair evidence that physicians and therapists should promote physical activity at an intensity level that is adapted to the persons' overall physical capacities, as part of a "healthy lifestyle" for older individuals with and without memory loss. (Recommendation Grade B, evidence level II).
- Current evidence is insufficient to conclude that a specific program of physical training warrants prescription in MCI patients in order to prevent progression to dementia. (Recommendation Grade C, evidence level III).



# PREVENTING COGNITIVE DECLINE IN MCI

Jama Neurology published on-line Sept 10/18

- Black individuals with MCI
- Randomized clinical trial
- Intervention was behavioural activation to increase physical, cognitive, and social activity
- Less cognitive decline, less functional decline but more serious adverse events, mostly related to falls



# Weight loss to improve cognition if BMI>30?

- Horie NC, et al, J Clin Endocrinol Metab 2016;101;1104
- Randomized 80 persons (average BMI 35, average age 68) to weight loss counselling or routine care; weight loss (BMI down by 2 on average) improved verbal memory/fluency, executive function, and global cognition at 1 year.

The significance of these changes, and the likelihood of dementia prevention are unclear.



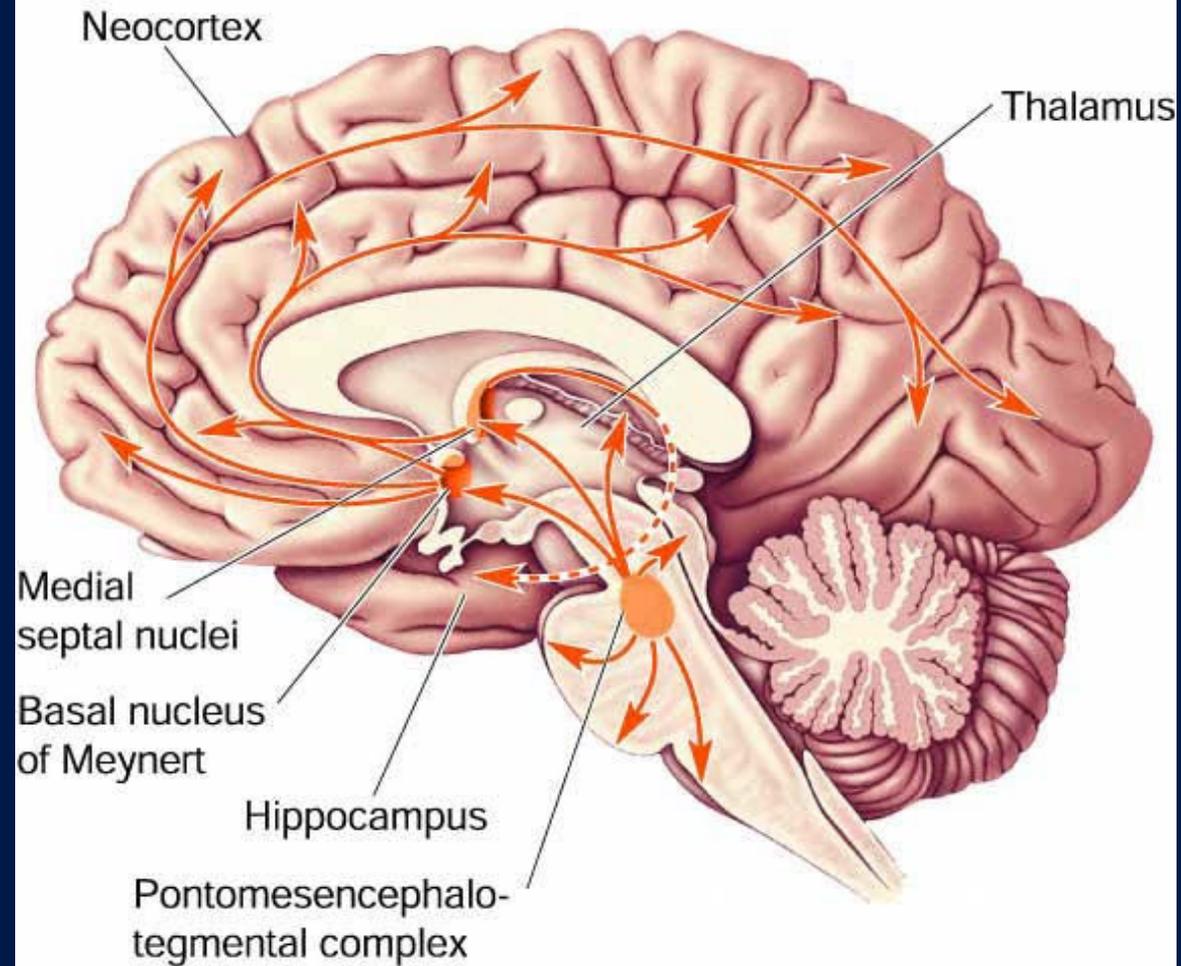
# B12 supplementation to at least 400 pmol/L

- B12 levels predict brain volume loss over time (Hooshmand B, et al, JAMA Psychiatry 2016;73:606)
- better hippocampal structure, learning ability /memory performance if B12 over 300 (Kobe T, et al, Am J Clin Nutr 2016;103:1045)

Once again, significance and relation to dementia are unclear.



## Acetylcholine system



# Available AChE inhibitors for AD

AChE inhibitor	Selectivity	T <sub>1/2</sub>	Starting dose	Minimal effective dose	Usual recommended dose (mg)
Donepezil	AChEI	Approx .70 h	5 Qam	5 Qam	5-10 mg/d
Galantamine	AChEI & Nicotinic modulator	7-10 h	4 bid	8 bid	8-12 bid
Rivastigmine	AChEI & BuChEI	1-2 h	1.5 bid	3 bid	3-6 bid



# Meta-analysis

SPECIAL ARTICLE

- Richie et al. Am J Geriatr Psychiatry 2004; 12:358–369
- All three drugs had similar cognitive efficacy, with donepezil and rivastigmine showing a dose effect across the dosing levels studied.
- Dropout rates were greater with galantamine and rivastigmine.

## Metaanalysis of Randomized Trials of the Efficacy and Safety of Donepezil, Galantamine, and Rivastigmine for the Treatment of Alzheimer Disease

Craig W. Ritchie, M.B., Ch.B., MRCPsych, M.Sc.  
David Ames, B.A., M.D., FRCPsych, FRANZCP  
Tim Clayton, M.Sc., Rosalind Lai, M.Lib.

The authors estimated the effects of each of the three commonly used drugs for Alzheimer disease (donepezil, galantamine, and rivastigmine) in terms of predefined clinical outcomes and trial completion rates, by dosing level, and described differences among them. Using both electronic and manual search strategies (January 1992 to July 2002), a metaanalysis examined the effect of the drugs on clinical outcomes and completion rates. Regression analyses compared the effect of dose on clinical outcomes and completion rates, using 10 donepezil, 6 galantamine, and 5 rivastigmine articles. All three drugs showed beneficial effects on cognitive tests, as compared with placebo. For donepezil and rivastigmine, larger doses were associated with larger effect. This was not the case with galantamine. The odds of clinical global improvement demonstrated superiority over placebo for each drug, with no dose effects noted. Dropout rates were greater with galantamine and rivastigmine. There was little difference in dropout rate for each drug at each dose level, except with high-dose donepezil. This was accounted for by the high dropout rate in two 52-week studies using larger doses. In summary, all three drugs had similar cognitive efficacy, with donepezil and rivastigmine showing a dose effect across the dosing levels studied. However, both galantamine and rivastigmine were associated with a greater risk of trial dropout than placebo, especially at higher dosing levels. (Am J Geriatr Psychiatry 2004; 12:358–369)

The pathological process of Alzheimer disease (AD) has a predilection for certain neurochemical pathways.<sup>1</sup> Although, toward the end of the illness, most neurotransmitter systems are affected, the cholinergic system is affected both early and more severely than other systems. This deficiency is impli-

Received December 19, 2002; revised September 9, October 2, 2003; accepted October 10, 2003. From the Metabolic and Clinical Trials Unit, Department of Psychiatry and Behavioural Science, Royal Free and University College Medical School, University College London (CWR), the Department of Psychiatry, University of Melbourne, Victoria, Australia (DA), the Medical Statistics Unit, London School of Hygiene & Tropical Medicine, London, UK (TC), and the Medical Library, Royal Free & University Medical School, London, UK (RL). Send correspondence to Dr Ritchie, Department of Psychiatry and Behavioural Science, Royal Free and University College Medical School, University College London, Royal Free Campus, Rowland Hill Street, London, UK NW3 2BF; e-mail: c.ritchie@ucl.ac.uk  
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# SYMPTOMATIC TREATMENT 1

## From Canadian Consensus Conference on Dementia

- All three CIs have demonstrated efficacy for mild to severe AD. We recommend a trial of a CI for most patients with AD. (Grade 1A)
- Combination therapy of a CI and memantine is rational (as the medications have different mechanisms of action) and appears to be safe, but there is insufficient evidence to recommend for or against this combination (Grade 2B) (NEJM review suggested that memantine = placebo)
- If symptoms of major depression present, recommend that a trial of an antidepressant could be considered (Grade 2A)



# SYMPTOMATIC TREATMENT 2

- recommend that valproate should not be used for agitation and aggression in AD (Grade 1A)
- There is no good evidence to recommend for or against the use of CIs and/or memantine for the treatment of neuropsychiatric symptoms as a primary indication (Grade 2B).
- recommend that risperidone, olanzapine and aripiprazole be used for severe agitation, aggression and psychosis associated with dementia where there is risk of harm to the patient and/or others. The potential benefit of all antipsychotics must be weighed against the significant risks such as cerebrovascular adverse events and mortality. (Grade 2A)
- There is insufficient evidence to recommend for or against the use of SSRIs or trazodone in the management of agitated patients. (Grade 2B)



# SYMPTOMATIC TREATMENT 3

- We recommend CIs as a treatment option for AD with cerebrovascular disease. (Grade 1B)
- We recommend CIs as a treatment option for dementia associated with Parkinson's disease. (Grade 1A)
- There is insufficient and inconsistent evidence on which to make a recommendation either for or against the use of the currently available CIs for the treatment of vascular dementia. (Grade 2B)
- Memantine of uncertain benefit. JAMA June 2014, showed no benefit in mild to moderate dementia, and a review article in NEJM suggested memantine=placebo (not covered in Ontario).



# MORE RECENT FAILURES

- Testosterone in older men
- Individual Cognitive Stimulation therapy
- Tai Chi—recent article positive effects on cognition of unknown significance, no data re dementia
- Music therapy helpful in for depression but not for agitation and aggression (Cochrane Review May 2017)
- More bad things: decreased smell, slowing of gait, decreased hearing, use of anticholinergic meds, possibly PPI's, seem related to incident dementia



# DISEASE-MODIFYING TREATMENTS

- **Ginkgo Biloba**
  - Mild efficacy, metanalysis in Neurology found it not useful
  - Non-regulated product
- **Estrogens**
  - Compelling epidemiological data
  - Disappointing intervention trials, timing is crucial (harmful in older women)
- **NSAID's/Prednisone**
  - Very mild efficacy—mostly epidemiological studies
  - Prohibitive side effect profile
- **Vitamin E**
  - One major RCT showed delayed progression of AD (death, institutionalization, deteriorating function and dementia) with high doses (1000 UI BID) (*Sano et al., NEJM 1997*). JAMA January 2014 article showed small improvement in ADL, none in cognition
  - Lots of controversy and May 2017 prevention randomized trial in JAMA Neurology found no effects of Vitamin E and selenium (both are anti-oxidants)



<b>TREATMENT</b>	<b>RESULT</b>
<b>Estrogen, combined Estrogen/Progesterone ERT</b>	<b>Negative</b>
<b>Anti-inflammatories, NSAIDs</b>	<b>Negative</b>
<b>Statins</b>	<b>Preliminary epidemiological positive (-ve in randomized trials)</b>
<b>Nootropics (Piracetam – pyrrolidine acetamide)</b>	<b>Negative</b>
<b>AMPA modulator (Ampakine CX516)</b>	<b>Negative</b>
<b>Anti-oxidants (e.g., Vitamin E)</b>	<b>last randomized trial negative</b>

Petersen RC et al. Arch Neurol, 2001;

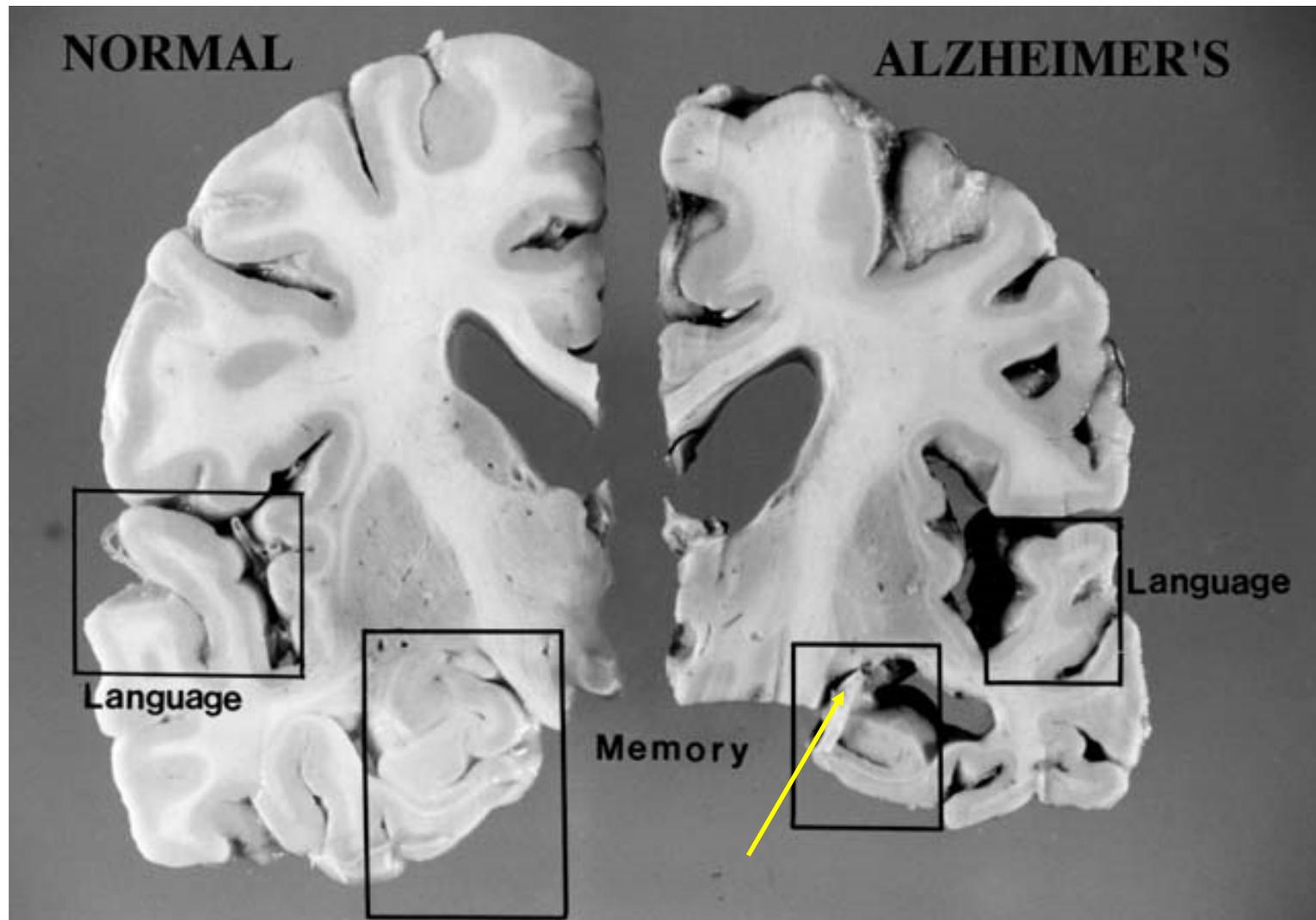
Almkvist O et al. J Neural Trans Suppl, 1998; Sramek JJ et al. Ann Pharmacother, 2000



**PERHAPS THE EARLIER THE BETTER**

11/28/2018

# Atrophy in Alzheimer's disease



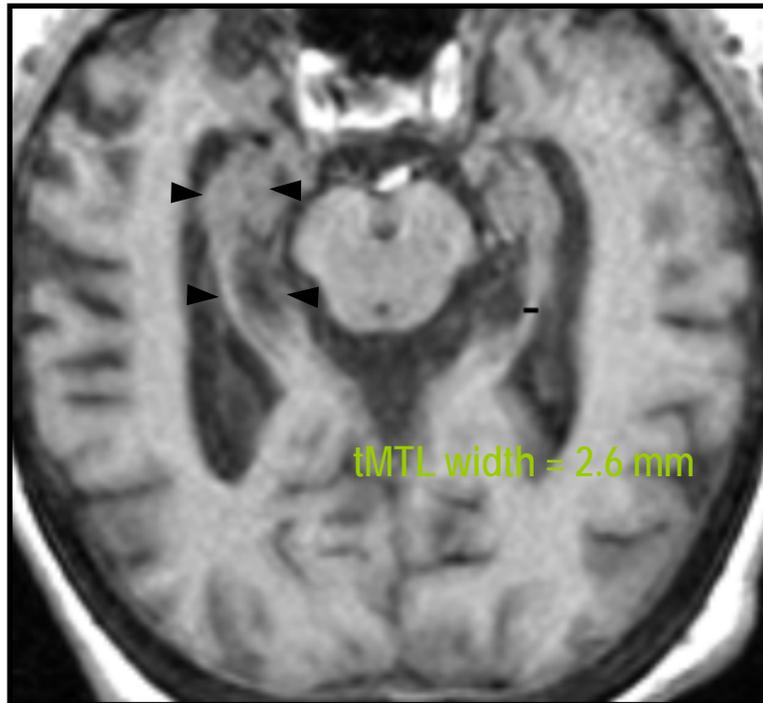
Atrophy of the brain in AD: Medial temporal lobes are affected first and most severely

Medicine  
UNIVERSITY OF TORONTO

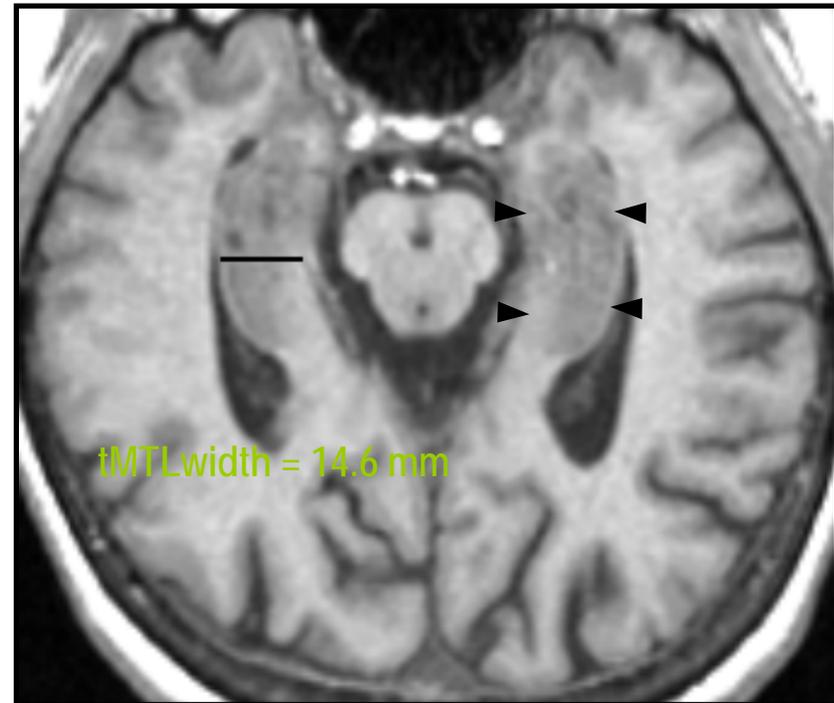
*Geriatrics*

# Hippocampal volume in Alzheimer's disease

AD



Normal



Dark lines cross the thinnest width of the hippocampus and arrowheads indicate hippocampal boundaries.

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# HOW TO GET 'EARLIER' PATIENTS

- Study familial early onset AD. This assumes that late onset AD will respond similarly (it looks the same under the microscope, that does not mean pathophysiology is the same)
- Get biomarkers for pre-symptomatic late onset AD (MRI, amyloid and tau levels in spinal fluid)



# Amyloid $\beta$ vaccination: reduced plaques and improved cognition

NATURE MEDICINE • VOLUME 7 • NUMBER 1 • JANUARY 2001



Tg2576 transgenic mice.

Vaccination with  $A\beta$  peptide prevents memory deficits in an animal model of Alzheimer's disease (*Morgan et al., 2001*)

$A\beta$  immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease (*Janus et al., 2001*)



# RECENT STUDIES

- Amyloid vaccine too toxic in humans (encephalitis)
- Monoclonal antibodies—ineffective
- Avagacestat—an oral  $\gamma$ -secretase inhibitor
  - Once again a negative trial

Are these ineffective drugs, or is the amyloid hypothesis wrong?



# REDUCING RISK OF DEMENTIA: NIA

## Lifestyle Habits

- **Increase physical activity.** Physical activity is a key factor for brain health. Regular exercise as simple as brisk walking for as little as 15 minutes a day protects brain structure and function.
- **Eat healthily.** A Mediterranean diet consisting of fish, olive oil, nonstarchy vegetables, and nuts has been related to lower risk of dementia.
- **Get a good night's sleep.** Adequate and uninterrupted sleep helps the brain repair itself. Good sleep hygiene improves the function of brain cells.
- **Do not smoke.** Smoking damages brain cells and vessels.

JAMA May 16, 2017



# REDUCING RISK OF DEMENTIA: NIA

## Medical Conditions

- **Treat heart problems.** Whatever is bad for the heart is bad for the brain. Heart attacks and heart failure have close links with dementia. Treating heart problems may protect the brain.
- **Control blood pressure and blood sugar levels.** High blood pressure and diabetes, especially in middle age, can damage the brain. Control of blood pressure and blood glucose (sugar) levels in midlife can improve brain health and may lower the risk of dementia in older age.
- **Protect the head.** Head injury increases the chance of developing memory and thinking problems. Wearing helmets and/or avoiding behaviors that increase the risk of head injury can decrease the risk of dementia.
- **Test hearing.** Hearing loss is linked to dementia.



# REDUCING RISK OF DEMENTIA: NIA

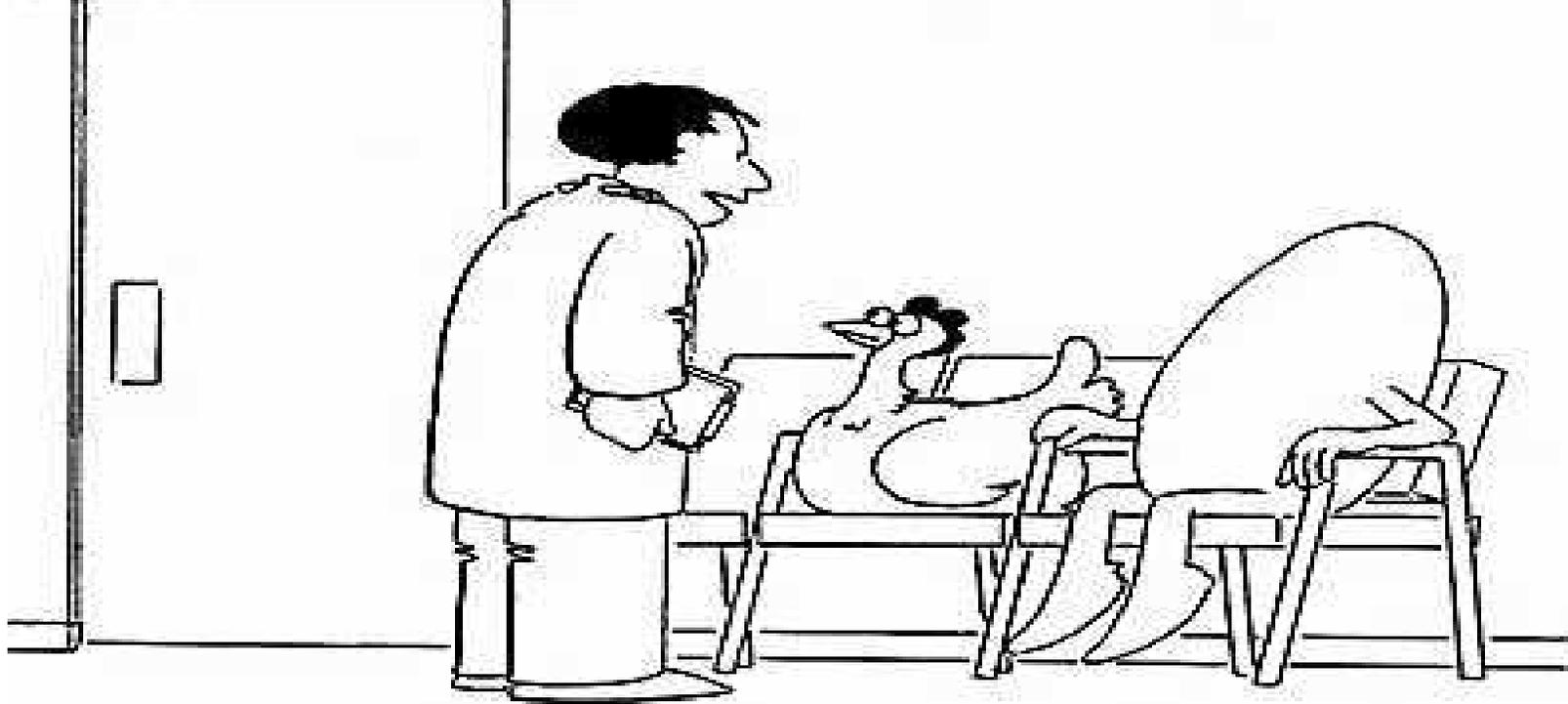
## Mental and Social Well-being

- **Stay involved, curious, interested, and willing to learn new things.** Being an active learner keeps the brain engaged and has beneficial effects on memory and information processing.
- **Stay socially engaged.** Engagement in social activities including sports, cultural programs, and support groups has a positive effect on brain structure and function and is associated with a lower risk of dementia.



# QUESTIONS

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"Who was first?"



# QUESTION ANSWERED

