Understanding Alzheimer's Disease and the Dementias: What We Know, What We Can Do

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Q & A

- I will welcome questions.
- However, for legal and many other reasons, I cannot offer specific advice, even about ‘close personal friends.’

Handout available

- A pdf version of this presentation (except for material from outside sources, and late changes) is available through the chatbox.

For Your Education Only!

- The matters I am going to discuss are vast, complex, incompletely understood, and often hotly debated. My presentation is not intended to be comprehensive, nor could it possibly be.
- None of what I am going to say (or what you may think I say) should be interpreted as specific medical advice. It is only intended to better inform about these topics and issues.

Dementia prevalence*

- Age 65-75: ~ 5%
- Age 85 up: ~ 30%+ or more

- * These numbers are very approximate; definitions and estimates vary considerably

Dementia

- Is the person's condition, not a specific disease
- (In medical terms, a "syndrome," not a "specific diagnosis")
- The dementia condition is what is wrong with their behavior, not necessarily what is causing their behavior to be wrong

Dementia

Many definitions. The one I'll use:

- Decline from prior status in
- Two or more 'different' mental functions ('different' brain regions)
- "Severe" in some fashion
- Has lasted at least 6 months

Two or more “different” mental functions

- “Different” : produced by different brain regions (more than one)
- E.g.:
  - memory and speech production
  - judgment
  - personality

Mental Functions: Anything coming from the brain

- Memory
- Speech (e.g., word-finding)
- Vision, spatial awareness
- Judgment
  - Including self-awareness of one's own abilities/disabilities
- Personality – Exaggeration, Change
- …[everything else, positive and negative]…….....

Mental Functions affected

- Most commonly
  - Memory
    - Forgetting recent events (“short-term”), but not older (“long-term”)
  - Speech (e.g., word-finding)
  - judgment (e.g., not being aware of their own problems)
- But that’s because these are the ones most commonly affected by the most common underlying diseases, e.g., Alzheimer’s disease
- Other diseases causing dementia may have different early manifestations (e.g., Frontotemporal dementias → profound speech impairments, personality changes)

‘Different’ Mental functions (other examples)

- Vision – e.g., recognizing your own car, hotel room
- Judgment (e.g., with telemarketers)
- Reasoning ability
- Everyday skills (e.g., driving)
- Personality
- Manual skills (e.g., using the remote control, tools)
- Delusions, hallucinations, paranoia

“Severe” in some fashion

- Different definitions (and some descriptive names attached to ranges of scores in the MiniMental and the MoCA
- In general:
  - For things people don’t usually forget
  - Frequent
  - Can’t be cued or reminded

“Severe”?

- “Normal” memory and mental functions can have the same kinds of problems, to some extent
  - Forgetting that a boiling pot is on the stove
  - Where you parked your car
  - “bad days” of moodiness, irritability
- Difference is in degree x frequency x repairability (cued or reminded)

Has lasted at least 6 months

- Some relatively temporary conditions can depress and impair mental functions, e.g.
  - Operations, anesthesia
  - Illnesses (e.g., UTIs)
  - Sedative drugs, sleeping pills, other medications. alcohol
  - Depression (“pseudo-dementia”)
    - But can also be a precursor of true dementia

Onset and progression

- Onset is usually gradual (months to years) and often imperceptible
  - But can seem to appear suddenly (e.g., after an illness or operation, or change in circumstances such as a move)
- There is typically progression (worsening) over time
  - typically from year-to-year, at least at onset

Mild Cognitive Impairment (MCI)

- Definition (varied, somewhat imprecise):
  - Subjective complaints
  - Some evidence of memory or other problems
  - But problems not severe enough to interfere with everyday life
  - Last >= 3 months

Mild Cognitive Impairment (MCI)

- At risk for developing dementia, but not necessarily do so
- Some people diagnosed with MCI get better (no longer qualify for diagnosis) after 1 year

Specific (single, on their own) conditions causing dementia

Individual Causes of dementia

- Alzheimer's disease
- LATE syndrome
- Vascular dementia
- Frontotemporal dementias
- Lewy Body Dementia/Parkinson's dementia
- …[many others]...

Alzheimer's Disease

- "typical" or "textbook" example
- Imperceptible onset
- Initially, progresses gradually over several years
- Typically, memory, thinking (e.g., comprehension), and self-awareness

What is wrong in the brain

- Loss of nerve cells
- Amyloid plaques
- Neurofibrillary tangles

Basic cause(s)?

- Far from certain, but popular hypothesis: build up of toxic protein fragments (A*B*42)
- Current attempts to remove these fragments using antibodies
  - **Lecanemab** (brand name **Leqembi**), **Donanemab** (brand name **Kisunla**)
  - Some success, but also appreciable toxicity in some
- Some have argued for different basis or bases (e.g., tau protein)

Individual Causes of dementia

- Alzheimer's disease
- LATE syndrome
- Vascular dementia
- Frontotemporal dementias
- Lewy Body Dementia/Parkinson's dementia
- …[many others]...

LATE syndrome

- Limbic-predominant age-related TDP-43 encephalopathy
- Perhaps as many as 1/5 of those who had been thought to have Alzheimer's disease (AD)
- Typically slower and milder than typical AD (when it occurs by itself)

Individual Causes of dementia

- Alzheimer's disease
- LATE syndrome
- Vascular dementia
- Frontotemporal dementias
- Lewy Body Dementia/Parkinson's dementia
- ….

Vascular dementia

- Diseases in the blood vessels can damage the brain directly, and also indirectly reduce its essential supplies of oxygen and glucose (fuel)
  - Multiple large strokes
  - Multiple small strokes (lacunes)

Individual Causes of dementia

- Frontotemporal dementias (FTD)
- Lewy Body Dementia/Parkinson's dementia
  - Synnucleopathy
- Normal Pressure Hydrocephalus
- Crueutzfeld-Jacob disease and variants
  - Prion disease
- *…. Dozens of others….*

Initial symptoms and signs may be different than classical Alzheimer's disease, e.g.:

- Marked fluctuations
- Personality changes
- Motor signs (masked looks, tremor, slowness of motion)

But Alzheimer's disease…

- Can also present and behave atypically, e.g.
  - with pronounced speech problems ("Progressive aphasia")
  - With pronounced visual problems ("cortical blindness")
  - Etc.

Furthermore…

- Any of these conditions can occur at the same time
- In older individuals, it is common for more than one dementia-causing disease to be present (multiple diagnosis)
  - (cause for hope – I'll explain!)

What can the medical diagnostic process look like?

- Reasonable suspicion of dementia
- History
  - Very important
  - What were the first signs?
  - What has happened since?

Mental status exam (part of the physical exam)

- Brief (10-15 minutes)
  - Abbreviated memory tests
  - MiniMental State Examination (MMSE) (Folstein et al., 1975)
  - Montreal Cognitive Assessment (MoCA) (https://mocacognition.com/)
- Full neuropsychologic testing (2 hours and up)

Clinical diagnosis (cont'd)

- Physical exam to look for e.g., bradycardia, congestive heart failure, orthostatic hypotension, etc.
- Neurologic exam to look for evidence of stroke, Parkinson's disease
- Lab tests to rule out other conditions (thyroid disease, renal disease, B12 deficiency, etc.)

Clinical diagnosis (cont'd)

- CT/MRI brain – to look for other problems
- Blood test(s)
  - *Lumipulse* (**Lumipulse G pTau217/β-Amyloid 1-42 Plasma Ratio**) – for positive diagnosis
  - *Elecsys*® pTau181 – more to rule out Alzheimer's
  - Both are intended for symptomatic adults (>=55)
- Amyloid PET scan – reference standard
  - But >20% of individuals can have positive scans, without clinical evidence of Alzheimer's disease

End result(s)

- Make diagnosis of Alzheimer's Disease more or less likely
- Make other diagnoses more or less likely
- Rule out conditions that could be contributing to mental (cognitive and behavioral) impairments
- Basis for a rational treatment plan

POSSIBLE TREATMENTS

- Reduce if possible other contributing factors
- Current drug treatment(s)
  - **Lecanemab** (brand name **Leqembi**), **Donanemab** (brand name **Kisunla**)
- Behavioral and lifestyle changes
- (Implications for family members – genetic, others)

So, in theory beneficial for someone to be medically evaluated for dementia

- If other individuals think something is wrong, chances that something is truly wrong are high
- What is wrong may not be a dementia *per se*
  - *E.g., depression, sedative drug effects, alcohol, etc.*
- Beneficial to detect problems early, as still might be reversible, or modifiable

But….

- Still risky to suggest that there is a problem and that a person should get a professional evaluation:
  - Ordinary situations often don't unambiguously expose mild dementia, even for professionals
    - May not strain critical mental abilities
    - People cover up deficits
    - Deficits can have other very plausible explanations
    - Social poise and skills often maintained
- Raising possibility socially awkward (at the very least)

…In part as a result

- In AD, average time from suspicion to diagnosis: 3 years
  - Note: some interval may be necessary to confirm progression
- Many individuals with dementia not brought to medical attention for a considerable time, if ever (and if they are brought to attention, often because of some significant event (e.g., getting lost)

Prevention?

- If you're not currently demented, what might you do to decrease your chances?
- Some old and some recent findings suggest there are some possibilities.

Facts or possibilities that might be exploited

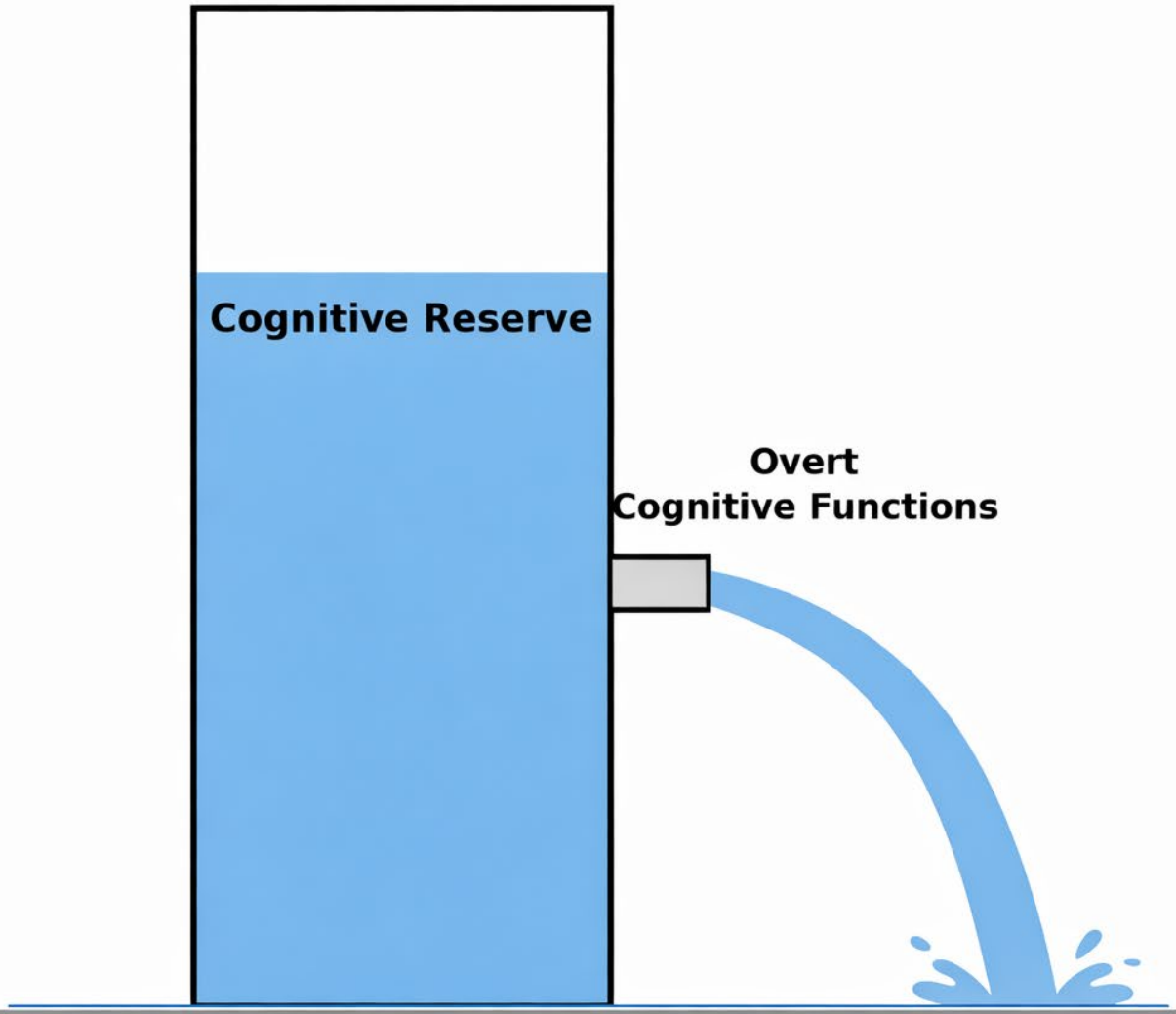
- Dementing diseases gradually worsening 10-20 years before overt dementia
- Many (20-40%?) overt dementias are due to the presence of two or more brain diseases
  - Particularly true for dementia occurring in those 85+ (“oldest old”)

Facts or possibilities that might be exploited

- Some of brain diseases might be mitigated by our actions
  - Small blood vessel disease (short of vascular dementia)
    - Accelerated by hypertension, diabetes, hypercholesterolemia, etc.
  - “cellular health” (“mitochondrial health”)?
    - Exercise might boost this in the brain, as well as in the muscles
  - Others (e.g., microglial function)

Facts or possibilities that might be exploited (cont'd)

- There might be a "cognitive reserve" (excess capacity) for brain functioning



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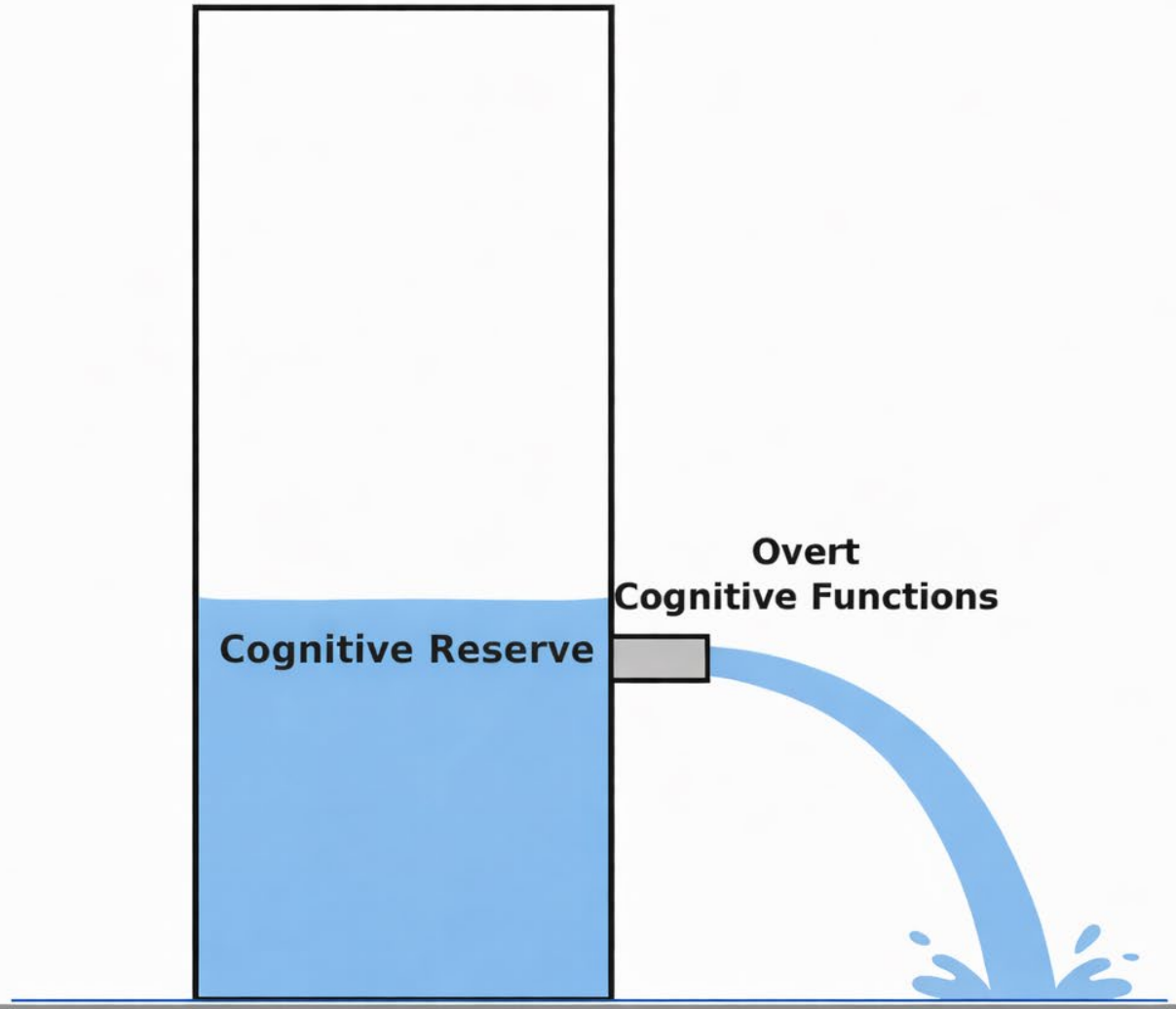
Facts or possibilities that might be exploited (cont'd)

- There might be a "cognitive reserve" (excess capacity) for brain functioning
  - True for kidney functioning, liver functioning
  - Suspected but not yet proven for the brain

Facts or possibilities that might be exploited (cont'd)

- Therefore, if a modifiable condition can be mitigated enough, a person might be able to prevent his/her cognitive abilities from falling below a threshold (becoming overtly demented).



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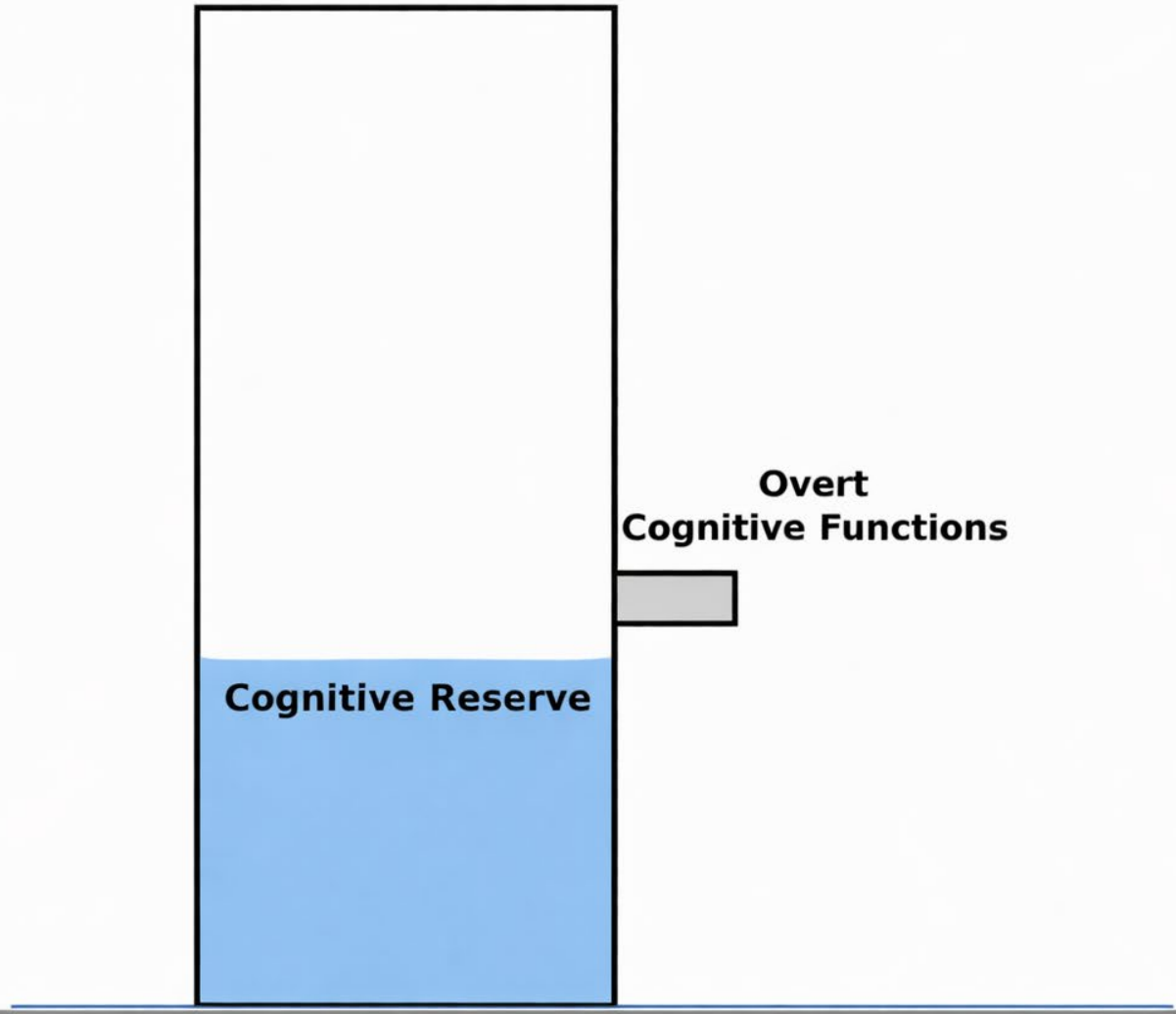

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Someone getting older, and concerned for the future

The action plan:

- Are you getting demented?
- What is your risk?
- Reducing your risk
  - Addressing your own specific risks, if any
  - Addressing general risk factors

Are you getting demented?

- Self-observations
- Observations by others (e.g., spouse, family members, co-workers)
- More objective testing
  - Mental status testing

Self-observations

- “Normal” memory is generally far from perfect
- The vast majority of times, subjective memory complaints and apparent problems are within the range of ‘normal,’ e.g.
  - Forgetting why you went to the refrigerator
  - Having a hard time with names (Proper nouns << nouns << verbs: “Mr. Baker” vs “baker” vs “bake”)

“Normally” imperfect mentation

- Often, even valid memory problems are the result of depression, sleep disturbance, change in situations, etc.
- There are many other reasons for “temporary” (< 6 month) changes in mentation (e.g., an operation)

Self-observation?

- Remembering you've forgotten requires memory and self-awareness
- Self-awareness is often impaired in the most common dementias
- So self-observation often unreliable

Online self-assessment

- E.g., Self Administered Gerocognitive Examination (SAGE) - Douglas W. Scharre, M.D. https://wexnermedical.osu.edu/brain-spine-neuro/memory-disorders/sage

What are your risks?

- Unalterable factors influencing risk
  - **Age**
  - **APOE-ε4 (ApoE4) status (genetic)**
  - **Family history**
  - Education
  - Gender
  - Ethnicity
- Potentially modifiable factors influencing risk
  - Specific medical conditions

APOE status

- APOE gene – each of us has 2 copies of the gene
- Gene comes in 3 different varieties: APOE-ε2, APOE-ε3, APOE-ε4 (aka ApoE4)
- In Caucasians:
  - One APOE-ε4: 3 x higher risk of AD
  - APOE-ε4+APOE-ε4: 8-12x higher risk of AD
- In African-Americans and other ethnic groups, risks unclear (data sparse)

Family history

- Specific to specific diseases:
  - Alzheimer's Disease
    - If a 1st degree relative (parent, sib, child) has had it, chances ~ 3 X increased
    - Seems to be independent of ApoE4 status
  - Parkinson's disease/Lewy Body Dementia
    - Some increase in risk
  - Frontotemporal dementias – genetics complex, but definite

Educational and vocational achievements

- Surrogate marker for how much cognitive reserve may be present

- So far, factors influencing your risk that you can’t change
- Factors that you may be able to change:

Reducing your risk

- Reduce the big factors specific to you (e.g., hypertension)
- Improve the general factors that are currently thought to be important (e.g., aerobic fitness)

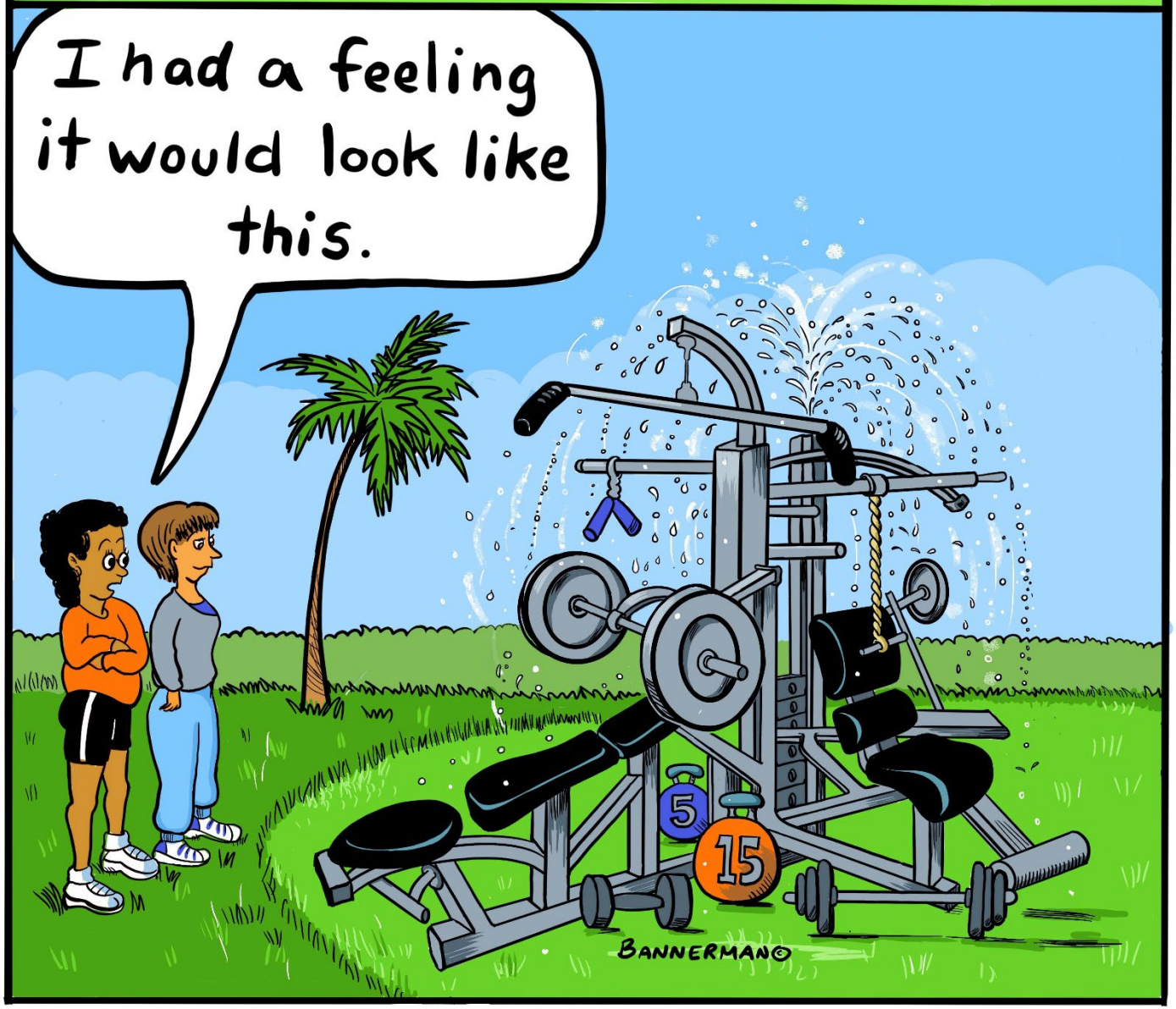
Reducing your risks as much as possible

- Hypertension
- Diabetes (? prediabetes ?)
- Hypercholesterolemia/hypertriglyceridemia, other cardiovascular risk factors
- Insufficient sleep
- Sleep apnea
- Smoking
- (excessive?) alcohol
- Hearing loss (deafness)
- Getting vaccinated (shingles)
- Your medications? (e.g., sedative drugs)
- Others? (e.g., visual impairment)

Improve what you can improve

- Aerobic fitness
- Intra-abdominal fat (metabolic syndrome)
- Strength training?
- (social engagement/mental engagement)
- (+/- mental training)
- Diet (e.g., the Mediterranean diet)
- Multivitamin supplements (see reference list)

The Fountain of Youth:



Aerobic fitness

- Prevents or helps reduce cardiovascular disease and its attendant risks to the brain
- Has definite direct effects on the brain (mechanisms poorly understood, but seem to be even at the genetic level)
- (Reduced risks of heart attack, other vascular diseases)

Improve what you can improve

- Aerobic fitness
- Intra-abdominal fat (metabolic syndrome)
- Strength training?
- (social engagement/mental engagement)
- (+/- mental training)
- Diet (e.g., the Mediterranean diet)
- Multivitamin supplements (see reference list)

Improve what you can improve

- Ideally, treating specific risk factors, and improving general risk factors, should start in mid-life (if not before)
- However, the possibility that there is a threshold of brain dysfunction before dementia becomes overt, opens the possibility that even late and relatively small efforts could be beneficial

Critical step

- Modifying one's habits to make such life-style changes possible
  - See scholarly references at end
  - E.g., James Clear, *Atomic Habits*, 2018

Accessible further reading

- Alzheimer's Disease Association: www.alz.org
- Lewy Body Disease Association: www.lbda.org
- Some informative articles in the popular press:
- 5 surprisingly hopeful things we learned about Alzheimer's this year - The Washington Post
- What's my Alzheimer's risk, and can I really do anything to change it_ New Scientist
- 8 things you can do to boost cognition and reduce dementia risk - The Washington Post
- Alzheimer's Is One Form of Dementia. Here's What to Know About the Others. - The New York Times
- A Different Type of Dementia is Changing What's Known About Cognitive Decline - The New York Times [LATE disease]

Accessible further reading (cont'd)

- Why people can have Alzheimer's-related brain damage but no symptoms – New Scientist, 30 January 2026
- A new mitochondrial theory of Alzheimer's deserves serious attention – New Scientist, 8 March 2023

- Note: the reference citations that follow may be available via Open Access, or through other servers that Google Scholar may suggest

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- My water tank graphics of the possible threshold effect were produced using ChatGPT 5.2

Questions? (maybe answers)

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