# *A systems-based model of cognitive decline*

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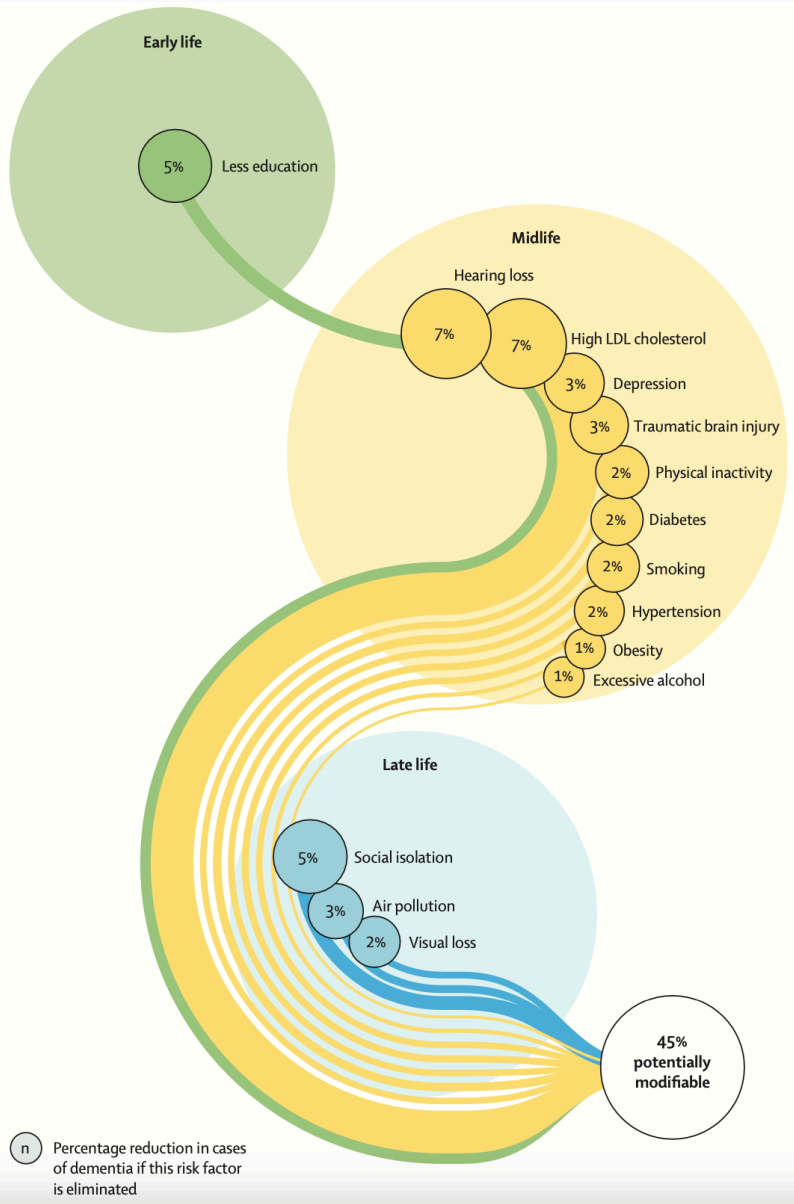
ALZHEIMER'S PREVENTION: NEW FRONTIERS


Livingston *et al.*, Lancet 2020

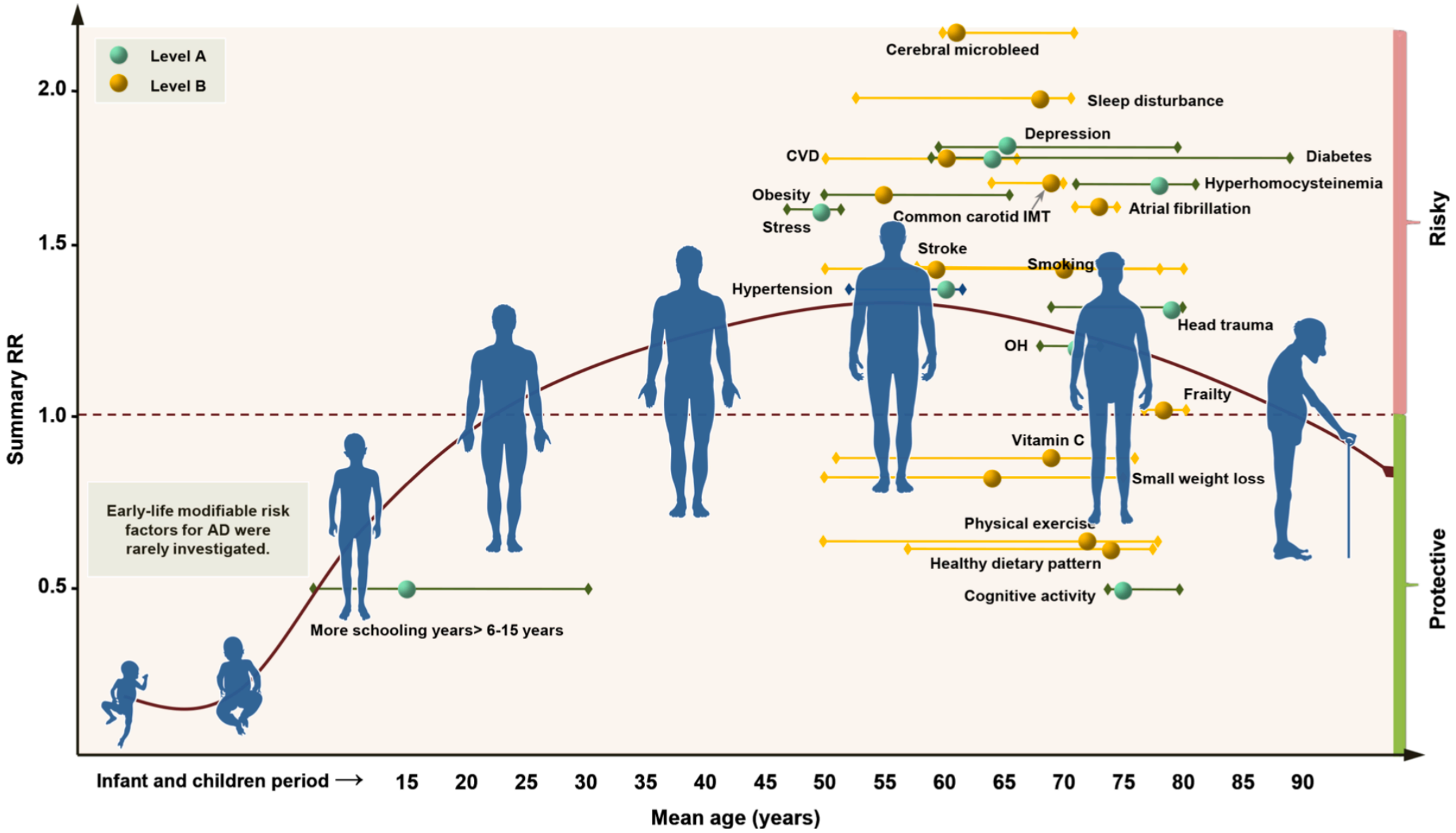
# What factors contribute to dementia prevention?




- Lancet commission
  - 14 modifiable factors
  - Conservative estimate (45% of dementias)
- Missing risk factors include:
  - Sleep
  - Diet quality and nutrient status
  - Late life cognitive activity
  - Oral health
- Others estimate 47—73%
  - UK Biobank data

Livingston *et al.*, Lancet 2024;
Zhang *et al.*, Nature Human Behavior 2023

# An increasing number of potentially modifiable risk factors




Yu J-T, et al. J Neurol Neurosurg Psychiatry 2020

# Dementia prevention – lists upon lists

## Summary of Alzheimer's Prevention

- Exercise regularly
- Eat more plants, reduce saturated fats
- Keep blood pressure ~ 120/80
- Keep LDL cholesterol ~ 70 mg/dl
- Manage diabetes
- Identify and treat sleep apnea
- Avoid smoking
- Reduce or avoid alcohol
- Address mental health issues
- Minimize chances of head traumas
- Address social isolation
- Address hearing loss
- Keep a healthy weight
- Engage in lifelong, meaningful and complex cognitive activities

| Risk factor | Relative risk[a] |
|---|---|
| Early life (age <45 years) | |
| Less education (primary school only) | 1.6 |
| Midlife (age 45–65 years) | |
| Hearing loss | 1.9 |
| Traumatic brain injury | 1.8 |
| Hypertension (>135–140/85–90)[S9,c] | 1.6 |
| Alcohol consumption (>21 units per week) | 1.2 |
| Obesity (body-mass index ≥30) | 1.6 |
| Late life (age >65 years) | |
| Smoking | 1.6 |
| Depression | 1.9 |
| Social isolation | 1.6 |
| Physical inactivity | 1.4 |
| Diabetes | 1.5 |
| Air pollution | 1.1 |

Frisoni et al. Lancet Regional – Europe 2023

# Dementia prevention – where to start?

- Prevailing opinion suggests most dementia may be preventable
- A large number of risk factors have been identified
- It's unclear how we implement those at the individual level
  - Relationships are assumed to be linear
    - We know this isn't the case
  - No hierarchy
  - No framework to understand how it all connects

# A (possible) solution!

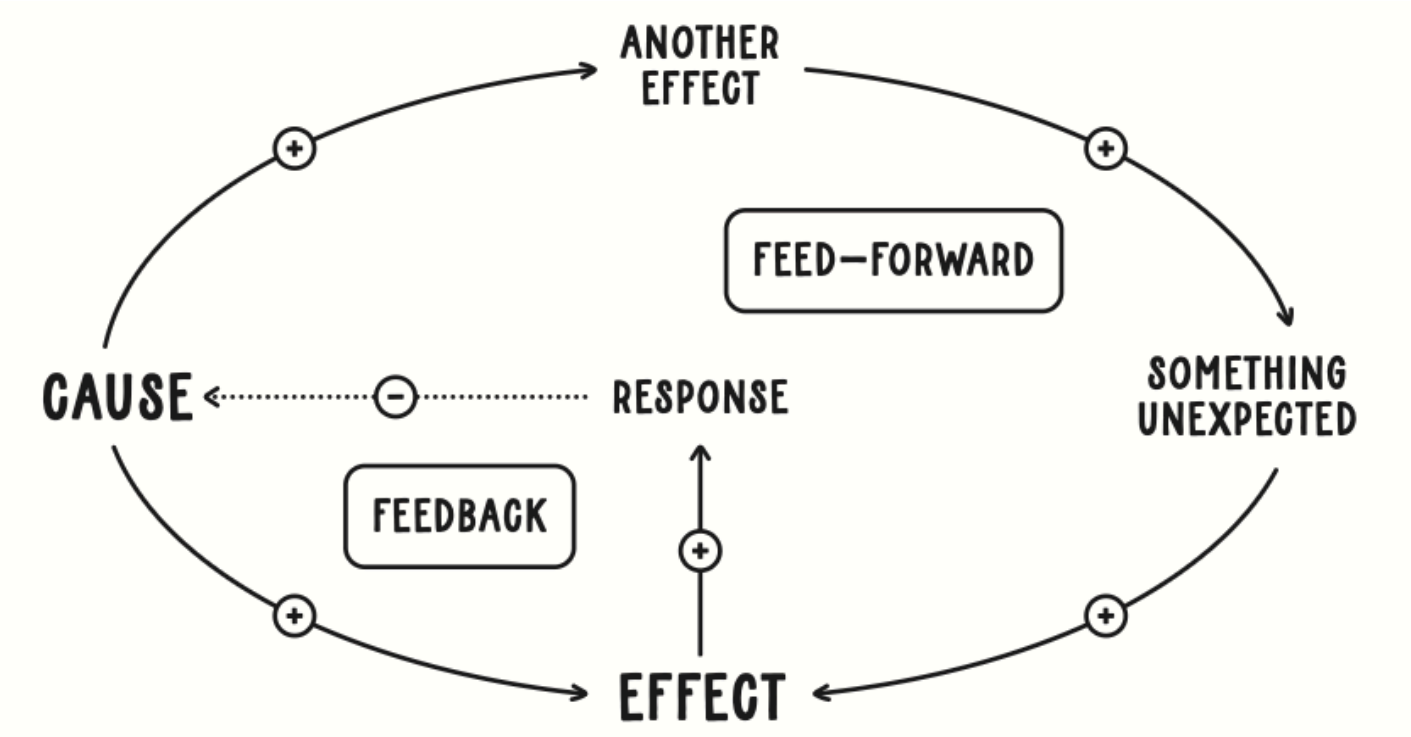
The Demand-Driven Theory of Age-Related Cognitive Decline and Dementia

(DDToARCDD)

TL;DR - Why Your Brain Is Like Your Biceps

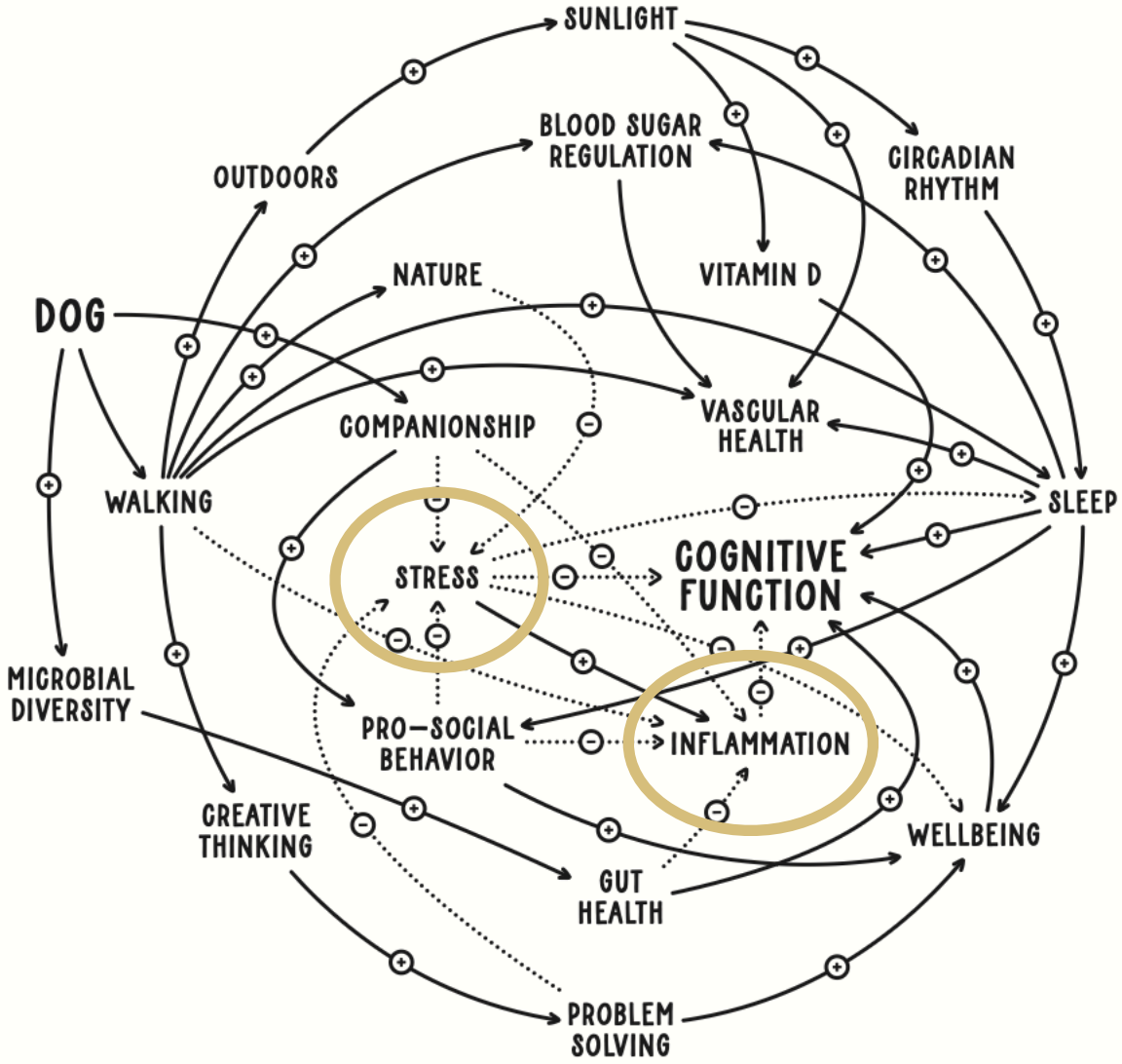
Turknett and Wood, Cells 2022

# Taking a systems approach




From *The Stimulated Mind* (Penguin Random House, 2026)

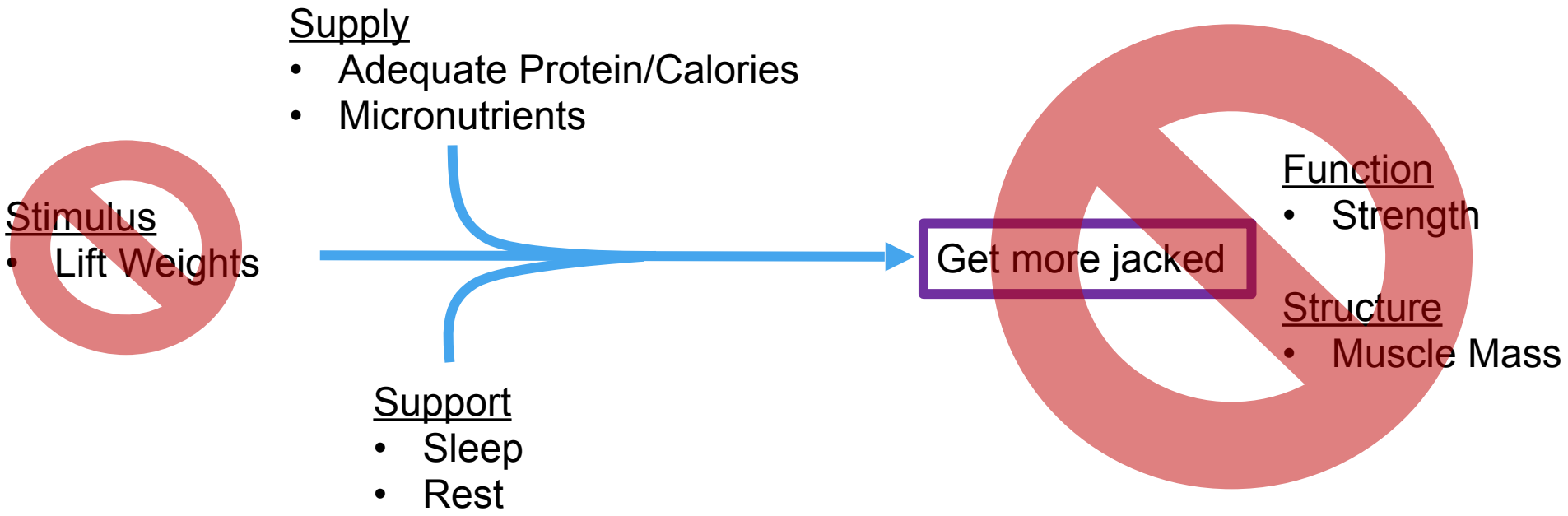
# Finding common nodes of action



# The 3 S Model

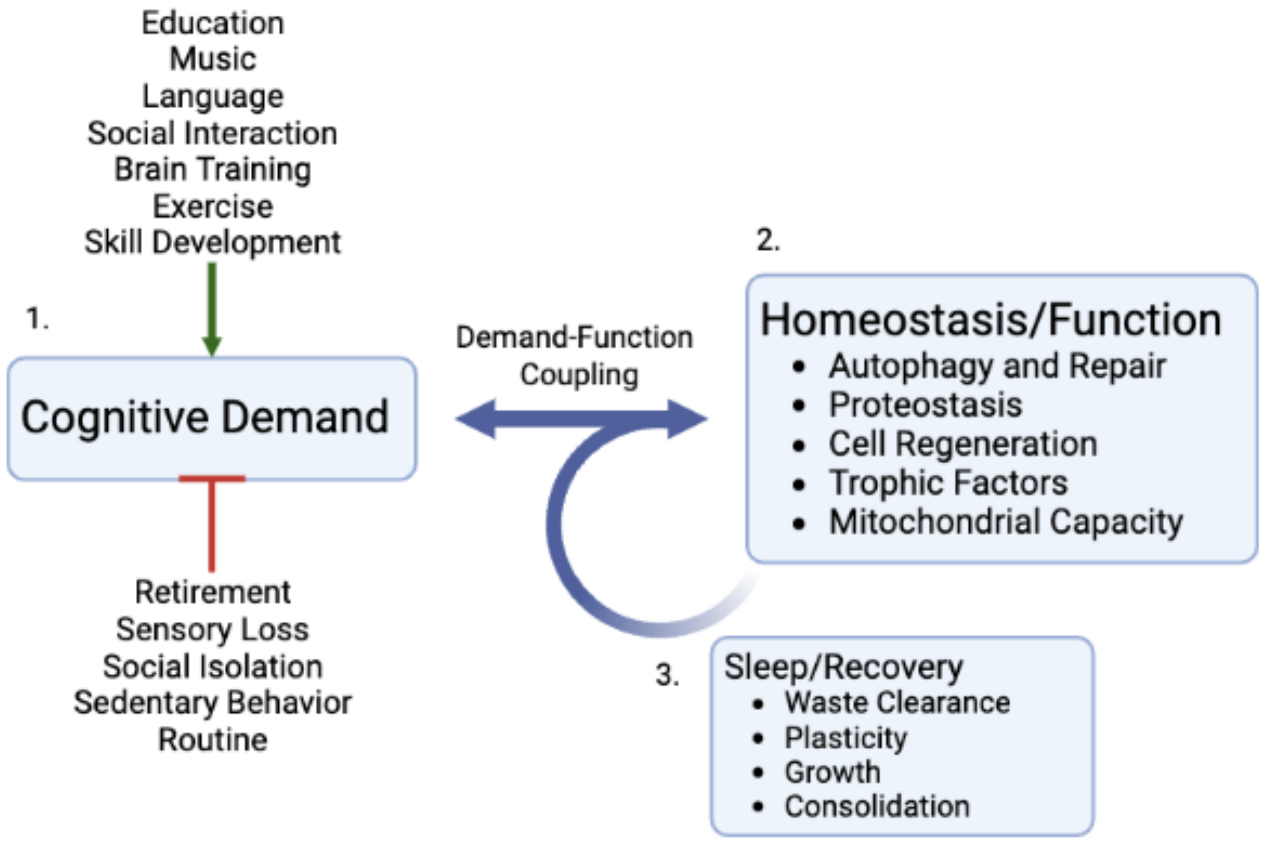
- Multiple interacting factors determine cognitive function
- Stimulus
  - Physical activity, cognitive, and social activity
- Supply
  - Vascular/metabolic health and nutrient status
- Support
  - Sleep/rest and trophic support, avoiding chronic stress/toxic exposures

# A simplified model of building muscle



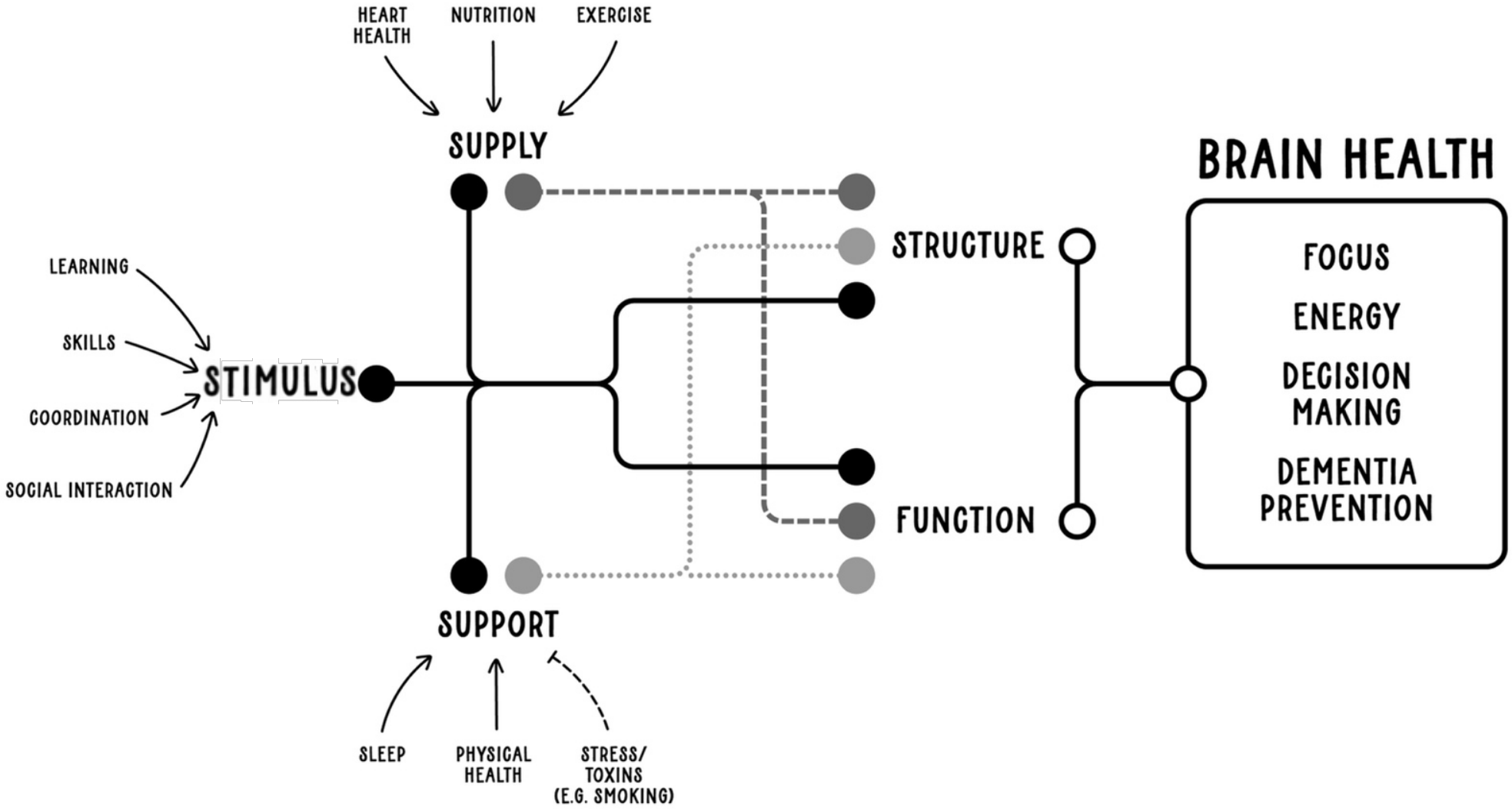
# Demand-function coupling

- The function of a tissue is determined by the stimulus
  - Same as with exercise and fitness/strength
- Similar across all stages of life




Turknett and Wood, Cells 2022

# The 3 S model of brain function




From *The Stimulated Mind* (Penguin Random House, 2026)

# Summary

- Brain health is an interconnected system underpinned by:
  - How the brain is used and challenged
  - The supply of substrates to respond to inputs
  - Providing the environment that supports adaptation
  - How these factors work together improve brain structure and function

- The system is synergistic
  - Risk factors are not a list where everything has to be perfect
  - Small changes in a few areas can have a big overall impact
  - When you change *one* thing, you're changing many things

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