The 2016 Annual Public Educational Forum

Anxiety, Depression, and Dementia/Alzheimer Disease: What are the Links?

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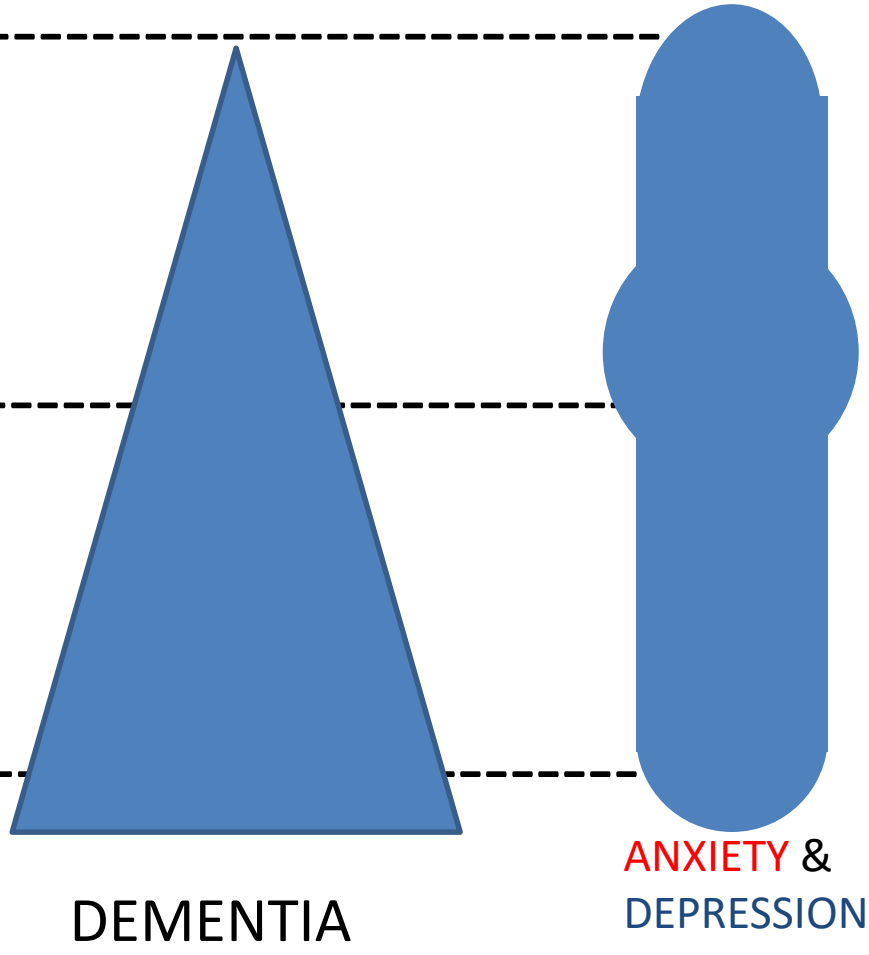
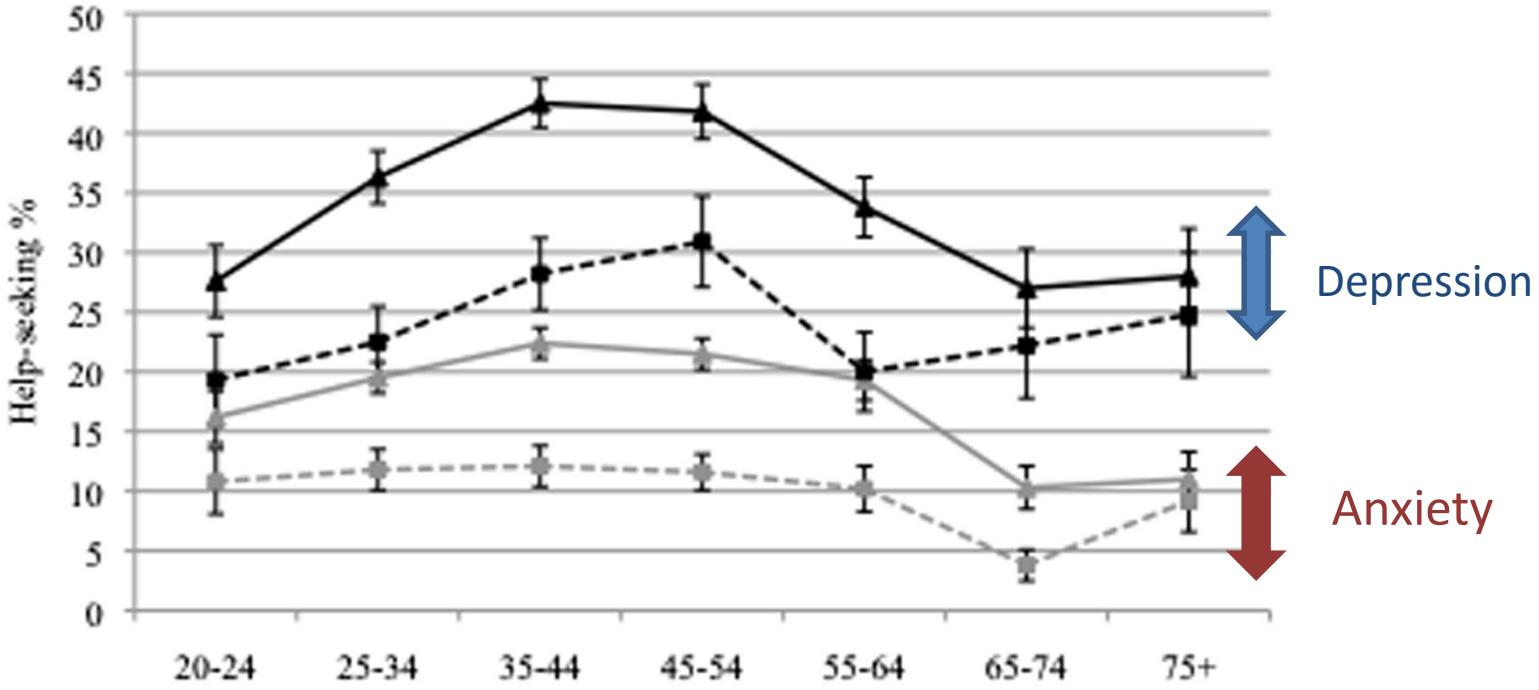
Why talk about hese conditions?

- Alzheimer Disease (AD) and other dementias become increasingly common as we grow older.
- Anxiety and depression are common throughout adulthood.

- Early Adulthood----------
- Middle Adulthood----------
- Late Adulthood----------



Depression and Anxiety * Across adulthood

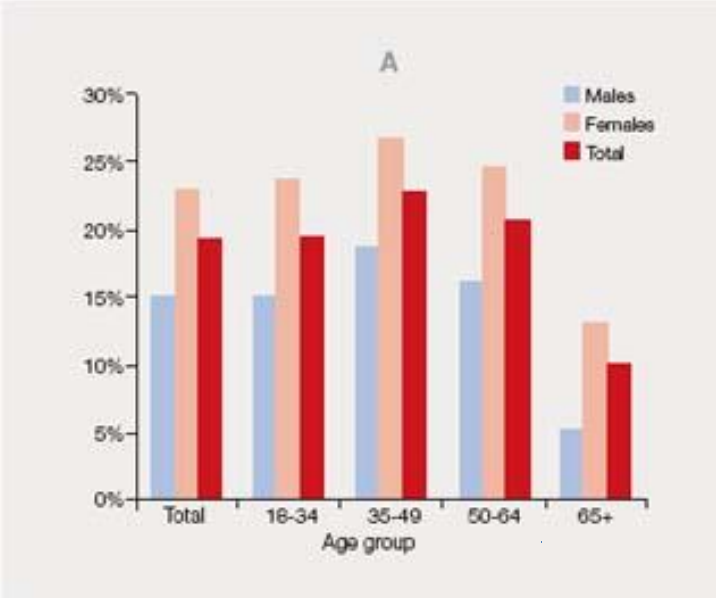


* % seeking help for these conditions

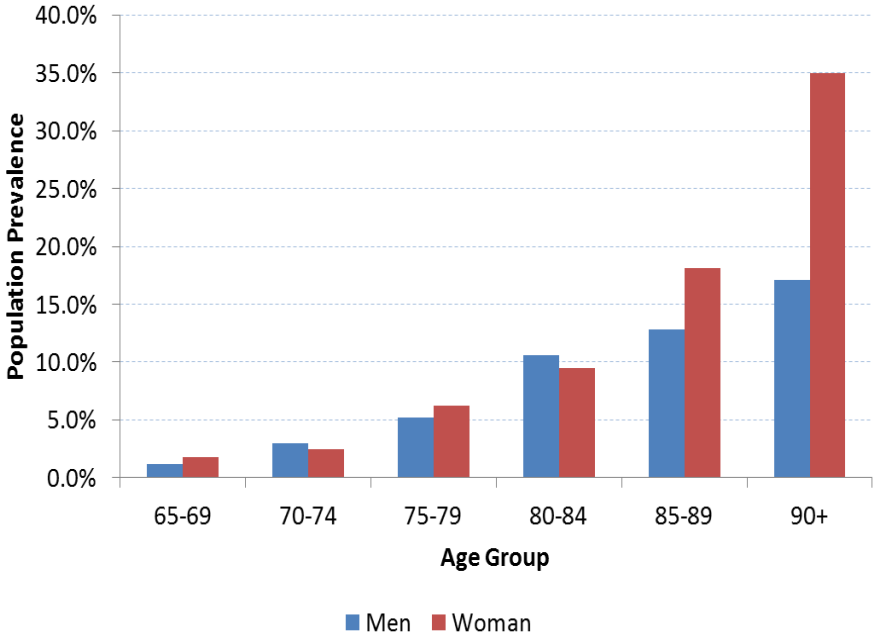
Mackenzie C. et al., Depression and Anxiety, 2012, 29 (3):234-242

Prevalence

Depression

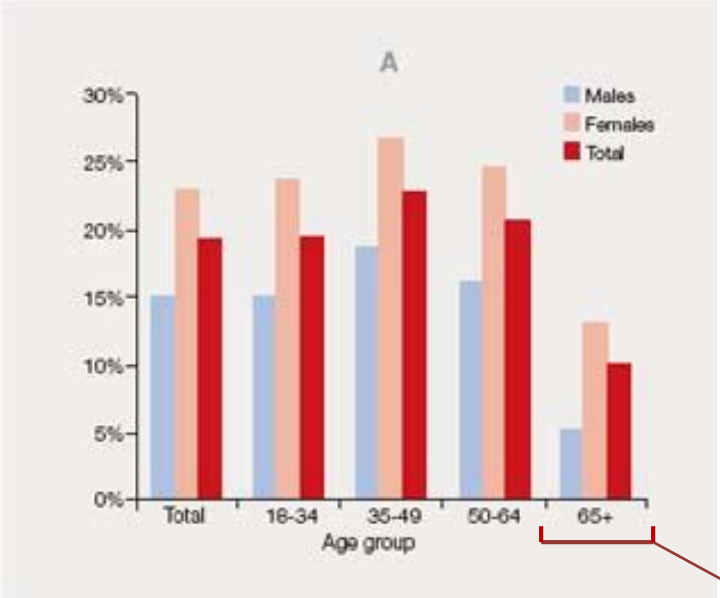


Dementia

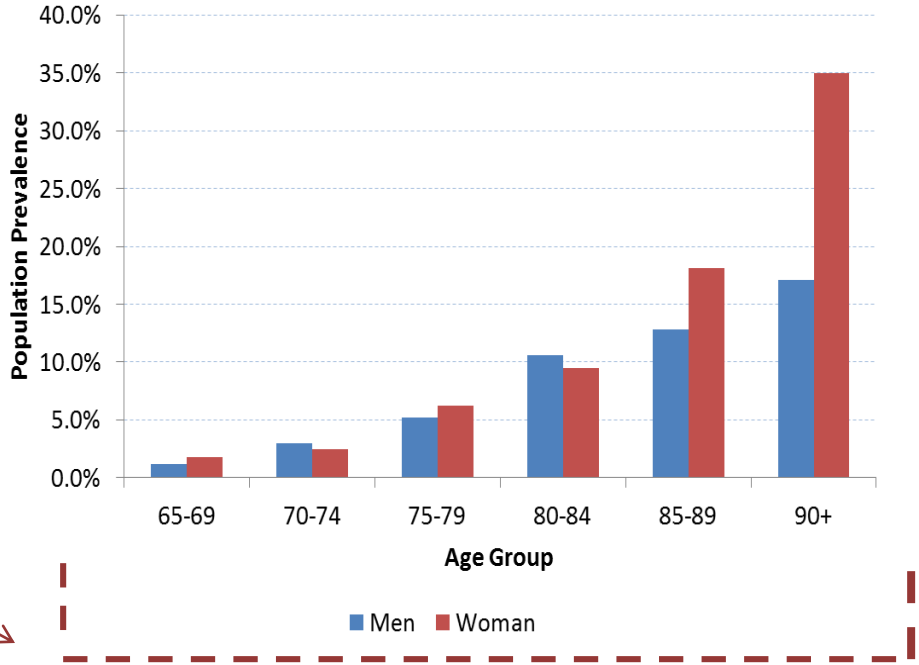


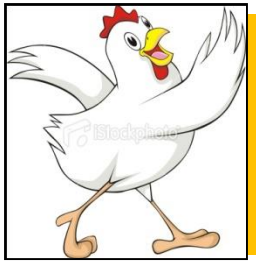
Prevalence

Depression

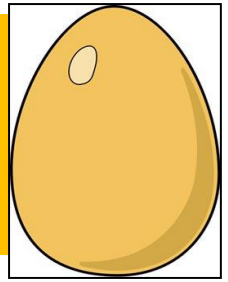


Dementia



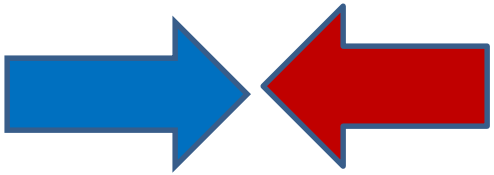


Chicken Or Egg?



Depression

Anxiety



Dementia

Causes?

Consequences?

Coincidence?

In basic terms

- People who experience anxiety and depression early in life may have an increased chance of showing signs of AD when they get older.
  - Timely and appropriate treatment for anxiety and depression may help lower this chance.

However…

- Not everyone who was anxious or depressed earlier will develop dementia later.
- Many people who get dementia have never been anxious or depressed before.
- Some people become anxious or depressed for the first time when they are older.

And in those folks…

Among those who become anxious and depressed *for the first time* in late adulthood:

- In some, the anxiety and depression may simply be a reaction to their increasing difficulties with remembering , organizing, and thinking that are due to their AD.
- In others, the anxiety and depression may be the first symptoms of the brain changes of AD, appearing even before memory loss.

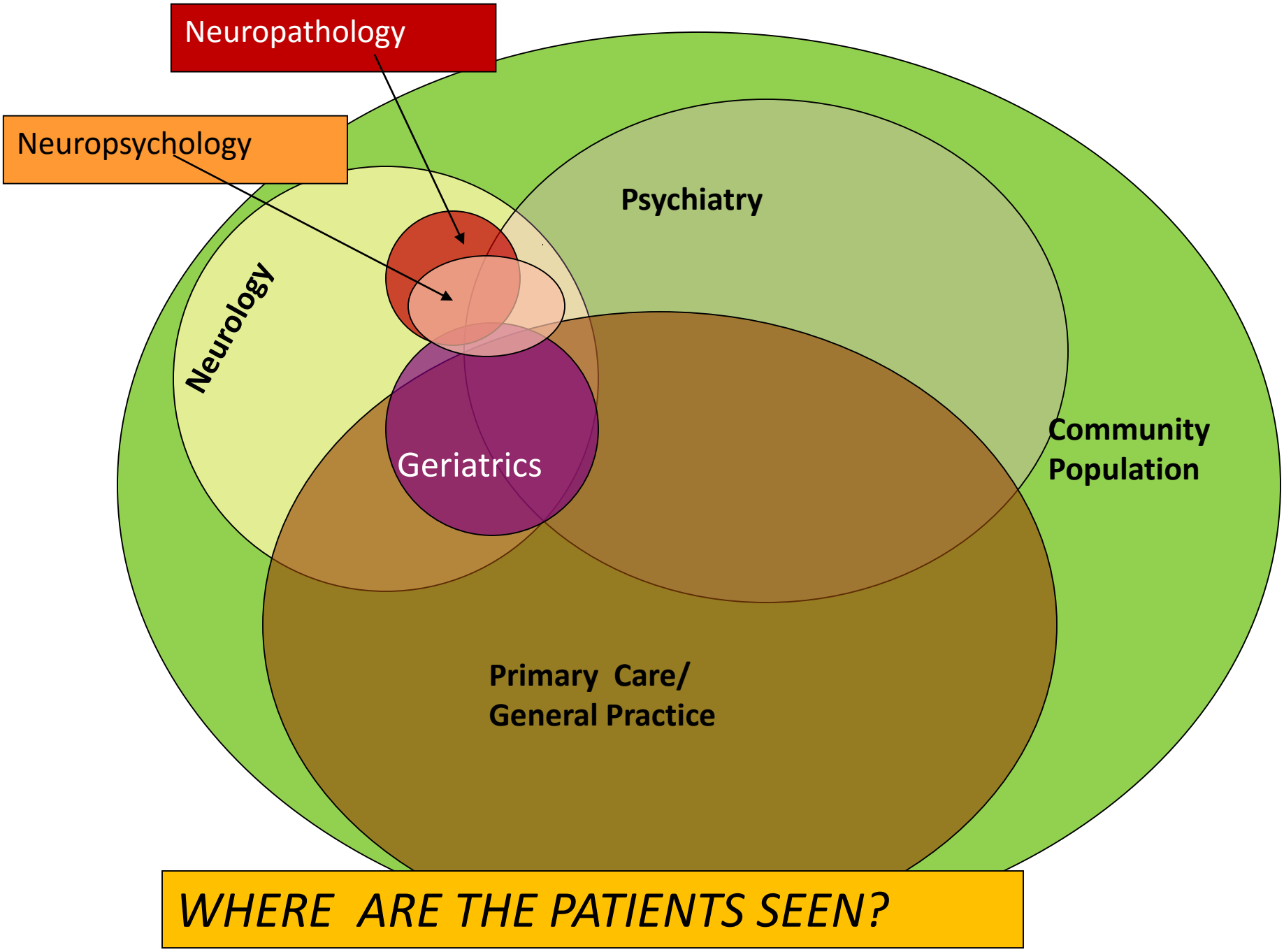
Depression and Dementia: the clinician's perspective

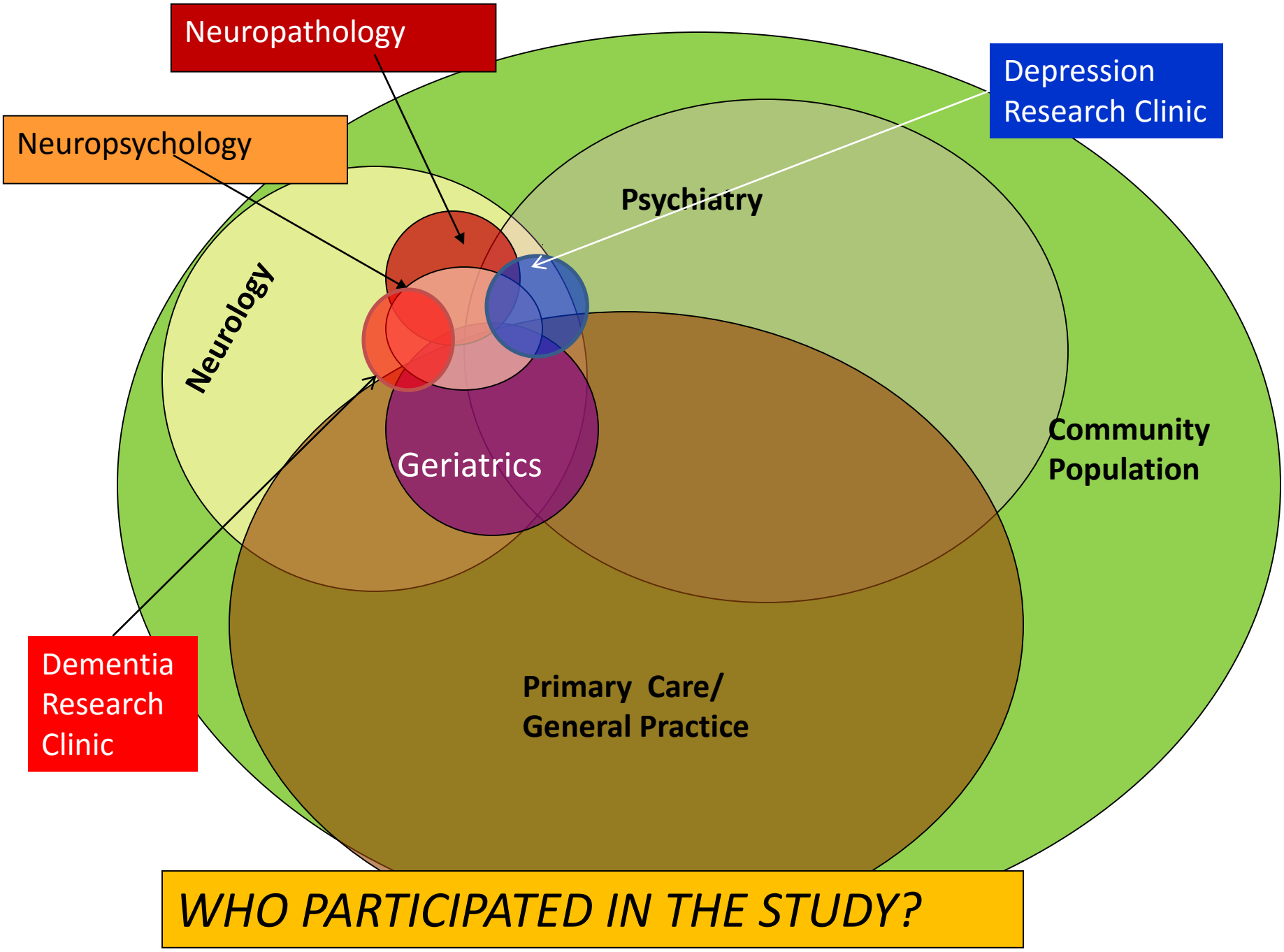
- Clinicians often see older patients who are **both** depressed **and** cognitively impaired.
- Cognitive functioning often **improves** when depression is treated.
- ***?*** Does this information have *clinical implications* for prognosis and treatment of patients?
- ***?*** Does this information help us understand the *underlying relationship and/or mechanisms*?

What does the research tell us?

Different studies appear to have conflicting results, depending on:

- ✓ The setting/population for the study.
- ✓ The design of the study.
- ✓ The assessments/measurements used in the study.
- ✓ The specific research question being asked (hypothesis being tested) in the study.


Neuropathology
Neuropsychology
Psychiatry
Neurology
Geriatrics
Community Population
Primary Care/ General Practice
WHERE ARE THE PATIENTS SEEN?


Neuropathology
Depression Research Clinic
Neuropsychology
Psychiatry
Neurology
Geriatrics
Community Population
Dementia Research Clinic
Primary Care/ General Practice
WHO PARTICIPATED IN THE STUDY?

What was the design of the study?

- **Who participated**? Memory clinic patients? Primary care patients? Volunteers? Randomly selected community members? Nursing home residents?
- **Time-line:** Was the study cross-sectional, retrospective, or prospective?
- Were participants **depressed or depression-free** at the time of selection?
- Were participants **cognitively impaired or cognitively intact** at the time of selection?
- What was the **outcome** studied? Cognitive decline? Clinical dementia? Brain imaging findings? Autopsy findings? Biomarkers (e.g. plasma or CSF amyloid)?

What did different studies/ articles mean by "Depression?"

- **Scores on Depression Symptom Scales**:
  - Self-report questionnaires, e.g., CES-D, GDS, PHQ-9
  - Clinician-rated scale, e.g., Ham-D
  - Prime-MD
- **Depressive Syndromes**:
  - Standard diagnostic criteria: DSM, ICD.
    - Clinician diagnosis
    - Diagnostic algorithm, e.g., SCID, CIDI
- **Depressive Disorders**:
  - Major depression (unipolar), bipolar disorder.
  - Depression secondary to other disorders *
  - Dysthymia
  - "Subsyndromal" or sub-threshold depression

** Including neurodegenerative and vascular brain disease*

What is meant in different studies by "Cognitive Impairment?"

- **Self-report : subjective difficulty** with memory, concentration, organization.
  - Spontaneous complaints.
  - History elicited by questioning.
- **Performance on objective cognitive tests.**
  - Brief general mental status test, e.g., MMSE, MoCA.
  - More extensive global test, e.g. 3MS, Mattis DRS.
  - Neuropsychological tests of specific cognitive domains *(attention, processing speed, learning/recall, language, visuospatial/constructional, executive functioning*)
  - Need appropriate norms for age, race/ethnicity, gender, education, language/dialect.
- Cognitive impairment resulting in *functional impairment.*

What is meant in different studies by "Functional Impairment?"

- **Basic** self-maintenance Activities of Daily Living (**ADLs**):
  - Self-maintenance: feeding, toileting, grooming, mobility
- **Instrumental ADLs**:
  - Familiar household items, appliances.
  - Driving car, cash management, medication management.
  - Higher-order activities.
- Change in everyday functioning *related to cognitive impairment* (Clinical Dementia Rating- **CDR** scale):
  - Memory, orientation, judgment, home/hobbies, community activities, self-care.

What do different studies mean by "Cognitive Decline?"

- **Subjective**: reports by individual or family (or observation by clinician) of **CHANGE**: loss of cognitive ability compared to previous level.
- **Objective**: **decline** in scores on cognitive tests, demonstrated by repeated testing.

? More than expected for age? (norms available?)

? Accounting for learning/practice effects?

? All potential causes considered?

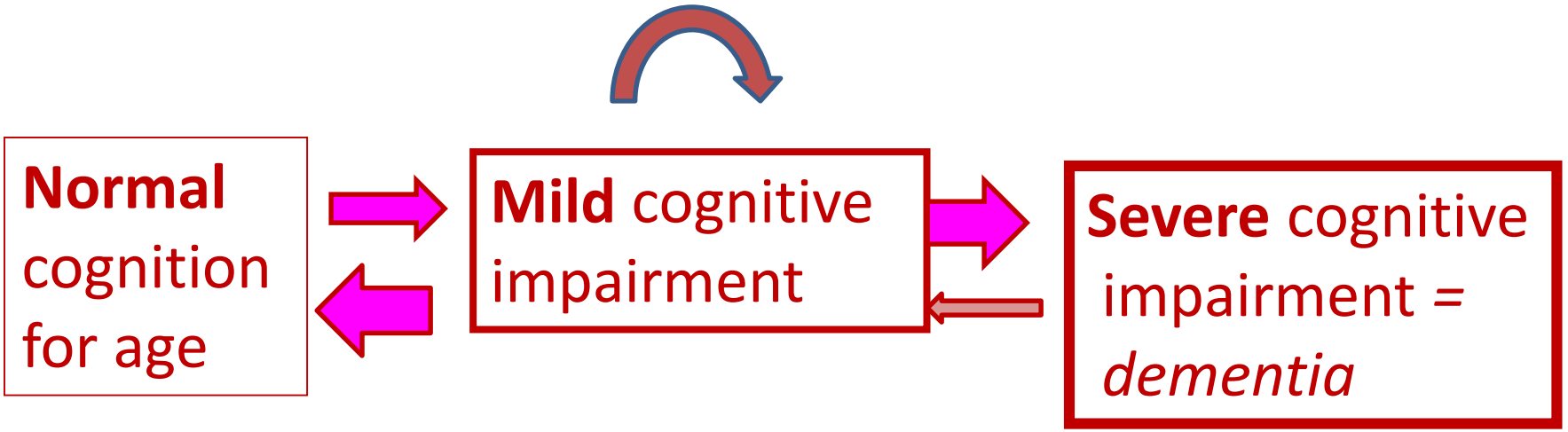
What do different studies mean by "DEMENTIA?"

- Clinical Dementia Rating (**CDR**) *(based on functional loss only)*
- DSM-diagnostic criteria? *(loss of memory and other cognitive domains sufficient to interfere with functional independence)*
- ICD criteria?
- Neuropsychological definition (*test scores >=2 standard deviations below the mean in two cognitive domains*)?
- A specific etiologic subtype of dementa (Alzheimer's, vascular, other)?

What do different studies mean by "Mild Cognitive Impairment (MCI)?"*

- A cognitive state **intermediate** between normal-for-age and dementia. *("intermediate" ≠ "transitional")*
- Has elevated probability of progressing to dementia.
- In memory clinic populations, majority with MCI progress to dementia (usually Alzheimer's) *(many studies)*
- In the community at large, the majority remain mildly impaired *(many studies)*
- Current criteria are International Working Group 2004 *(Winblad et al.)* but studies vary in how they interpret and implement the criteria.

*(*Petersen et al., 1999; Winblad et al., 2004)*


Normal cognition for age
Mild cognitive impairment
Severe cognitive impairment = *dementia*

What do the data tell us?

- Late-life depression is characterized by slowed information processing, which affects all realms of cognition. *Butters MA et al. 2004*
- Most older individuals who are cognitively impaired during a depressive episode remain impaired when their depression remits.
- A lot of older depressed patients who are cognitively intact when depressed are likely to be impaired one year later, although their depression has remitted.

  Bhalla R et al. 2006

Depressive symptoms in cognitively intact elderly were associated with increased probability of subsequent MCI, independent of vascular disease.

Barnes et al., 2006

Depressive symptoms predict cognitive decline in old age.

Wilson et al., 2004

Clinically significant *depressive symptoms* in women aged 65 or older are independently associated with greater incidence of MCI and probable dementia

Goveas et al., 2011

There was **no** increased risk of developing dementia in amnestic MCI patients with depression.

In contrast, amnestic MCI patients with *apathy* had significantly increased risk of progressing to dementia.

Palmer et al., 2010

Our group's findings on depression and cognitive decline

Dividing people into one group who later developed dementia and another group who remained dementia-free,

- Depressive symptoms are cross-sectionally associated with cognitive impairment, especially in those who continued to remain dementia-free.
- Dementia-free individuals undergo minimal cognitive decline over time;
- Depression is not associated with rate of subsequent cognitive decline in either group.

Ganguli et al., 2006

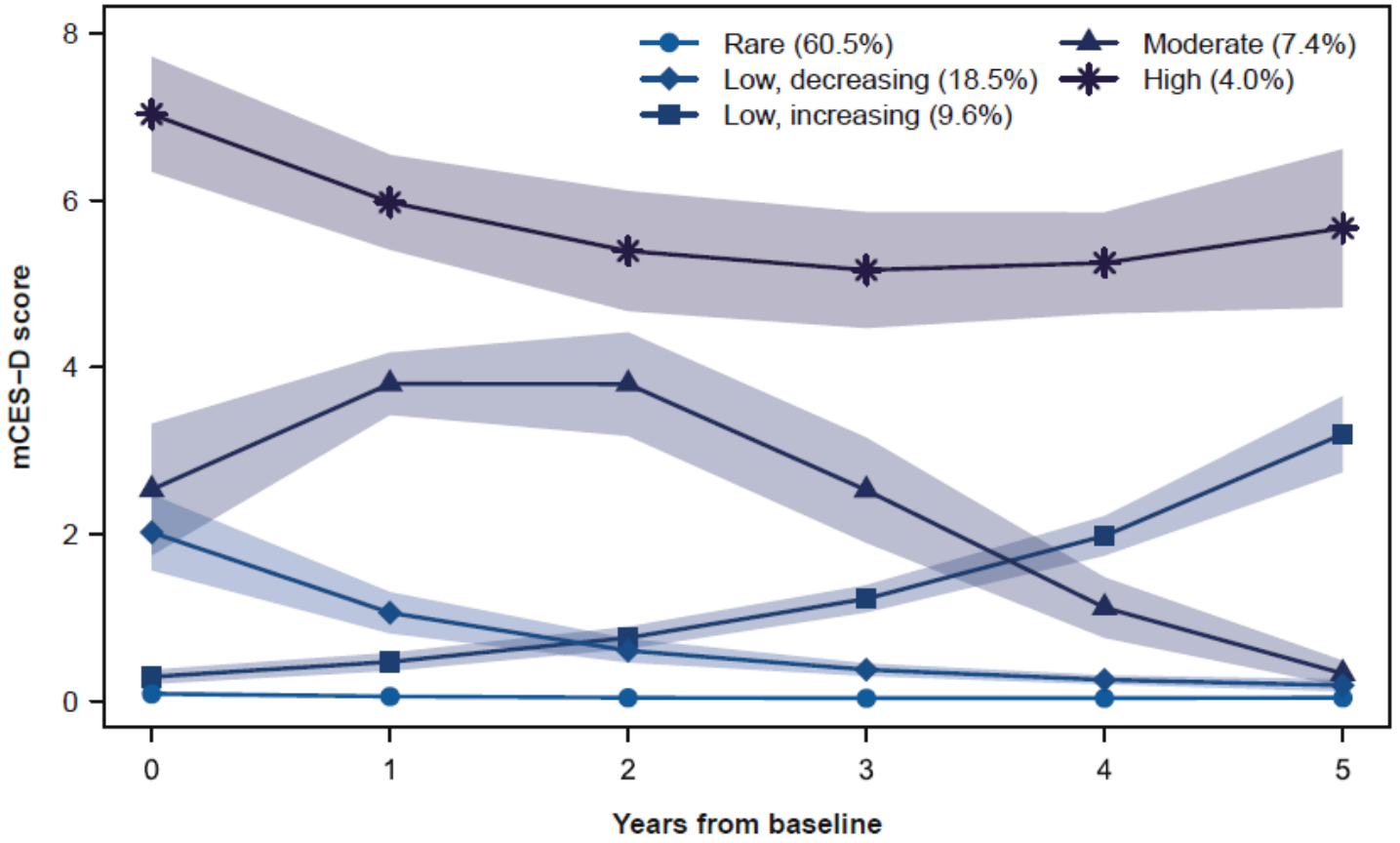
- Depressive symptoms were significantly more likely to be present in individuals **after the onset of dementia** than in persons without dementia.
- Depressive symptoms appeared to be **early manifestations, rather than predictors**, of Alzheimer's disease in this community sample.

Chen et al., 1999

- …after partially controlling for genetic influences, late-life depression for many individuals **may be a prodrome rather than a risk factor** for dementia.

Bromelhoff et al., 2009

Maybe it's not one-time depression but the course of depression over time



Graziane et al., 2015

"Fifty Shades of Blue"

Dual trajectories of depression and cognitive trajectories over time

- Moderate depressive symptoms, and low-grade but increasing symptoms, were the most strongly associated with consistently poor cognitive function.
- High-grade depressive symptoms were **not** strongly associated with consistently poor cognitive function except in attention/processing speed.

Graziane et al., 2015

Systematic Reviews and Meta-Analyses

- A **history** of depression may confer an increased later risk of developing AD, and may be an independent risk factor.

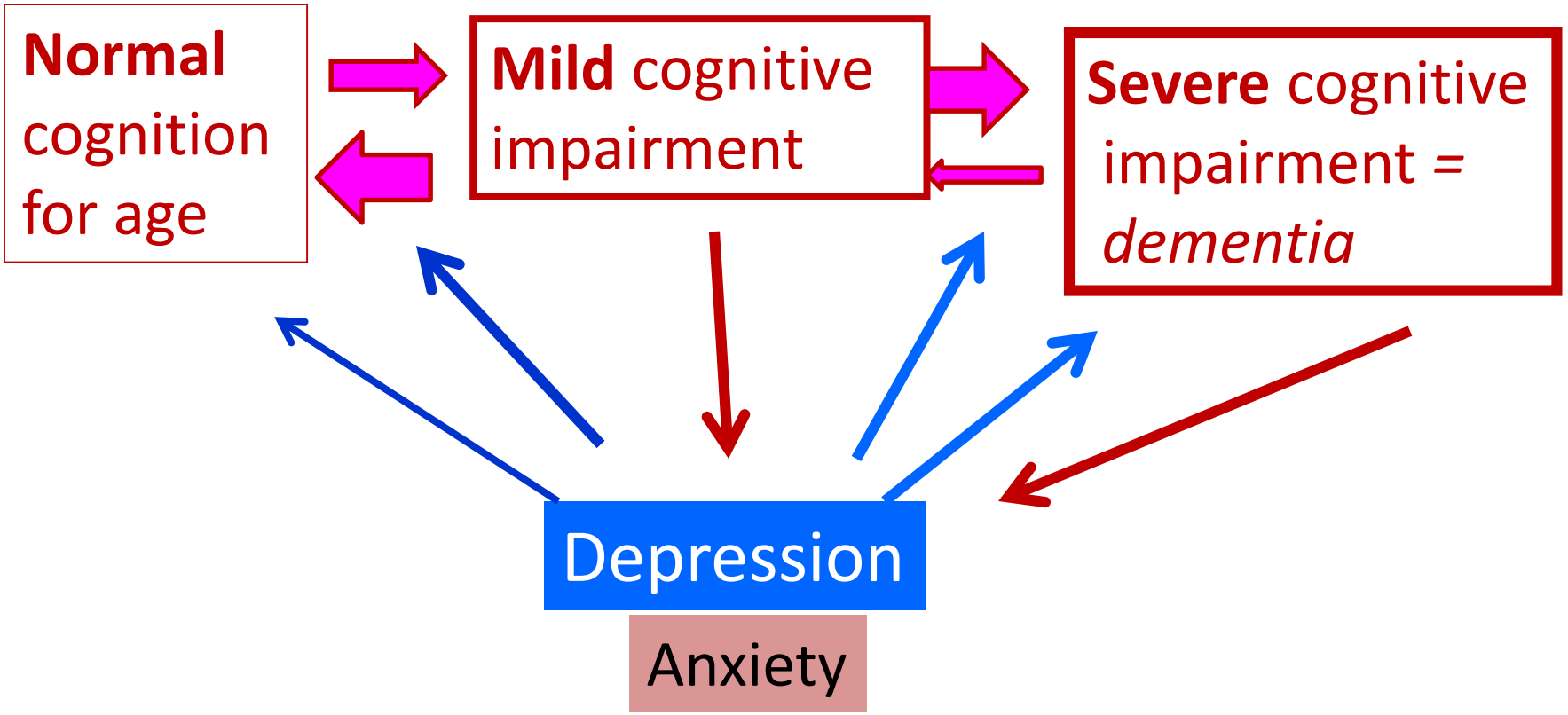
  Ownby et al., 2006.

- **Interval** between diagnoses of depression and AD was positively related to increased risk of AD.
- Assuming that MCI may be the earliest identifiable clinical state of dementia, **depressive symptoms may be an early manifestation rather than a risk factor** for dementia and Alzheimer's disease. *Panza et al., 2010.*

Anxiety may mean different things

- Recent onset, acute anxiety was associated with non-amnestic MCI;
- Chronic, severe anxiety was associated with all forms of MCI;
- Chronic, mild worry was not associated with MCI

  – *Andreescu et al., 2013*


Normal cognition for age
Mild cognitive impairment
Severe cognitive impairment = *dementia*
Depression
Anxiety

One way to resolve the apparent inconsistencies

- Major depression in **early life**, and
- **Recurrent major depression and chronic anxiety throughout life**,

*may be independent **risk factors** for dementia.*

- New depression/anxiety occurring in **late life**

*is more likely to be an **early manifestation or prodrome** of a dementing disease.*

Possible mechanisms-1

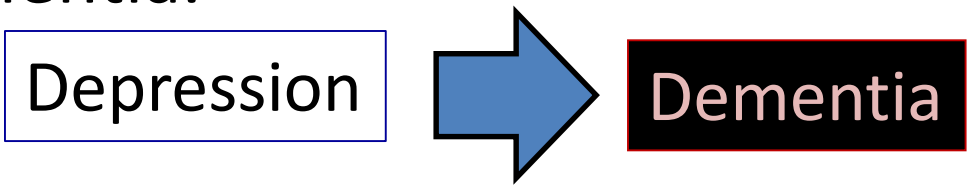
1. Glucocorticoid theory:

Major depression and anxiety is associated with **cortisol elevation**.

Sustained hypercortisolaemia is toxic to the **hippocampus**.

In these patients, the hippocampus becomes particularly vulnerable to neurodegenerative pathology in old age.

Here, depression is an independent risk factor for dementia.



Some Data

- Longer durations of untreated depressive episodes were associated with reduced hippocampal volume.
- No significant relationship between hippocampal volume loss and time depressed while taking antidepressant medication, or with lifetime exposure to antidepressants.
- Antidepressants may have a neuroprotective effect during depression.

Sheline et al., 2003

More data

Postmortem Study;

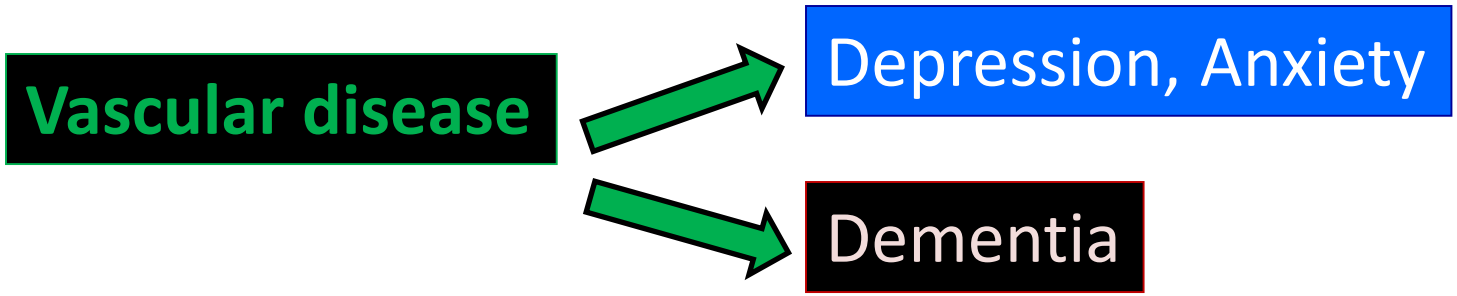
Brains of 102 deceased nursing home patients, all with Alzheimer's disease, half of whom had lifetime history of major depression

In AD, the presence of a **lifetime history of depression** corresponds to increases in AD-related neuropathological changes in the hippocampus.

Rapp et al., 2006

Possible mechanism -2.

- With increasing age, there is increasing **cerebrovascular (blood vessel) pathology** in the brain.
- “Vascular depression” can accompany “vascular cognitive impairment/vascular dementia.”
- Here, depression <u>is not</u> an independent risk factor for dementia.



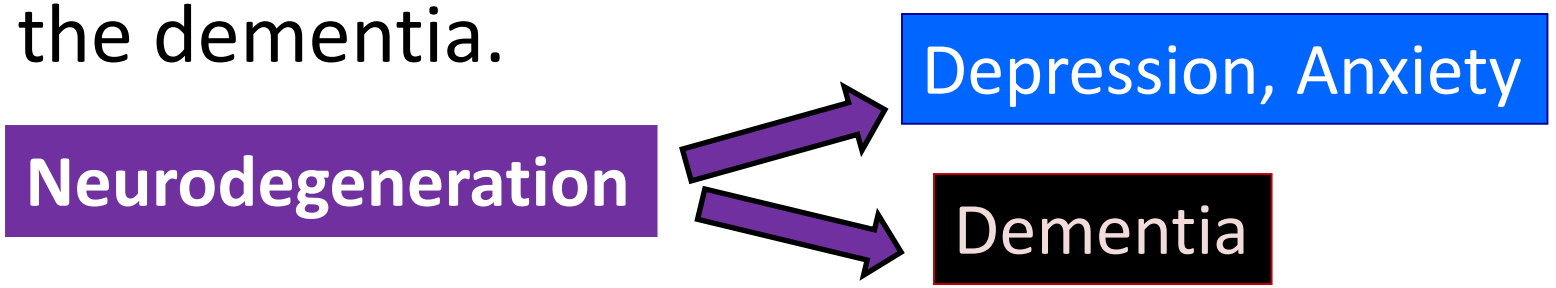
Data

- Prospective study of 3837 primary care patients with diabetes
- Patients with *major depression plus diabetes* had an increased risk of developing dementia compared to those with diabetes alone.
- These data add to recent findings showing that **depression was associated with an increased risk of macrovascular and microvascular complications** in patients with diabetes.

Katon et al., 2010

Possible mechanism - 3

- Neurodegenerative disease causes cognitive impairment/dementia.
- Neurodegenerative disease also causes apathy, anxiety, depression, and other behavioral disturbance.
- These behavioral disturbances precede or accompany MCI and may be the first sign of the dementia.



Some Data

Cross-sectional study of homebound elderly using AD biomarkers Aβ40 and Aβ42

- Patients with depression had lower plasma Aβ42 levels and a higher ratio of Aβ40: Aβ42 than those without depression.
- "Amyloid-associated depression" was associated with greater memory impairment than non-amyloid associated depression.
- "**Amyloid-associated depression" may be a prodrome of AD**.

Sun et al., 2008

Another set of ideas

Homeostasis:

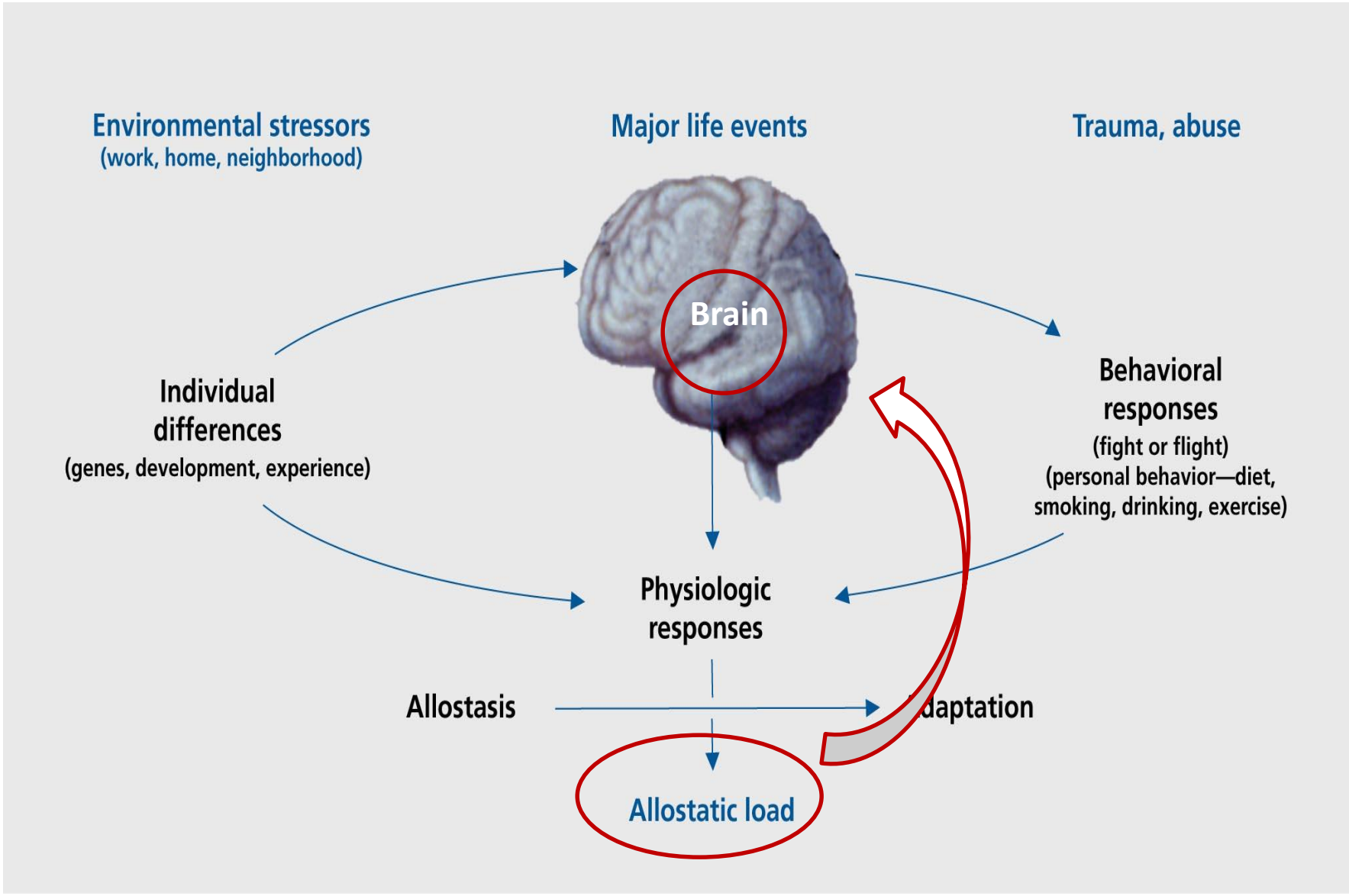
- A state of everything being stable in the body.

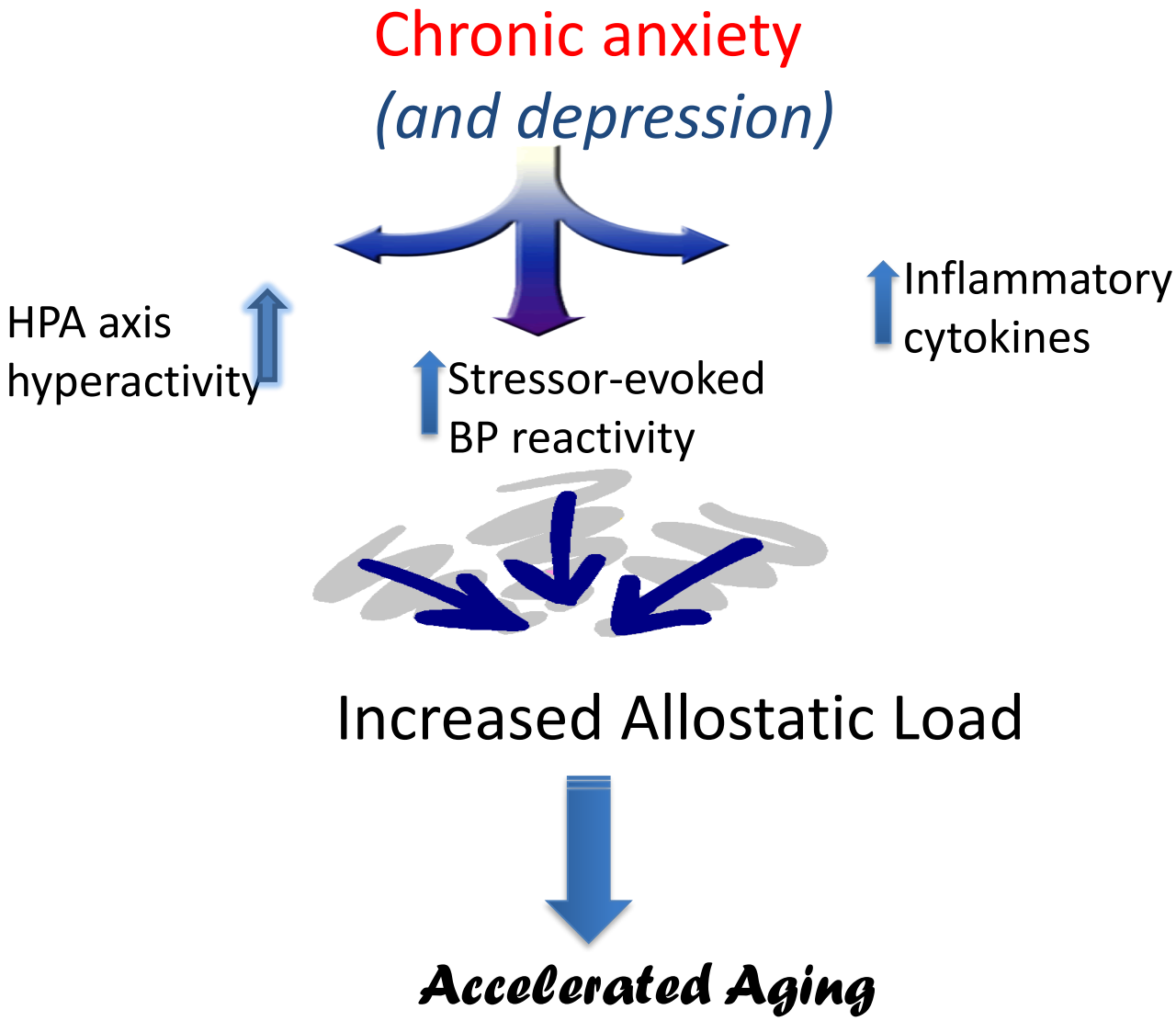
Allostasis:

- The body's physiological efforts to keep everything stable (to maintain homeostasis) in the face of challenges and change.

Allostatic Load:

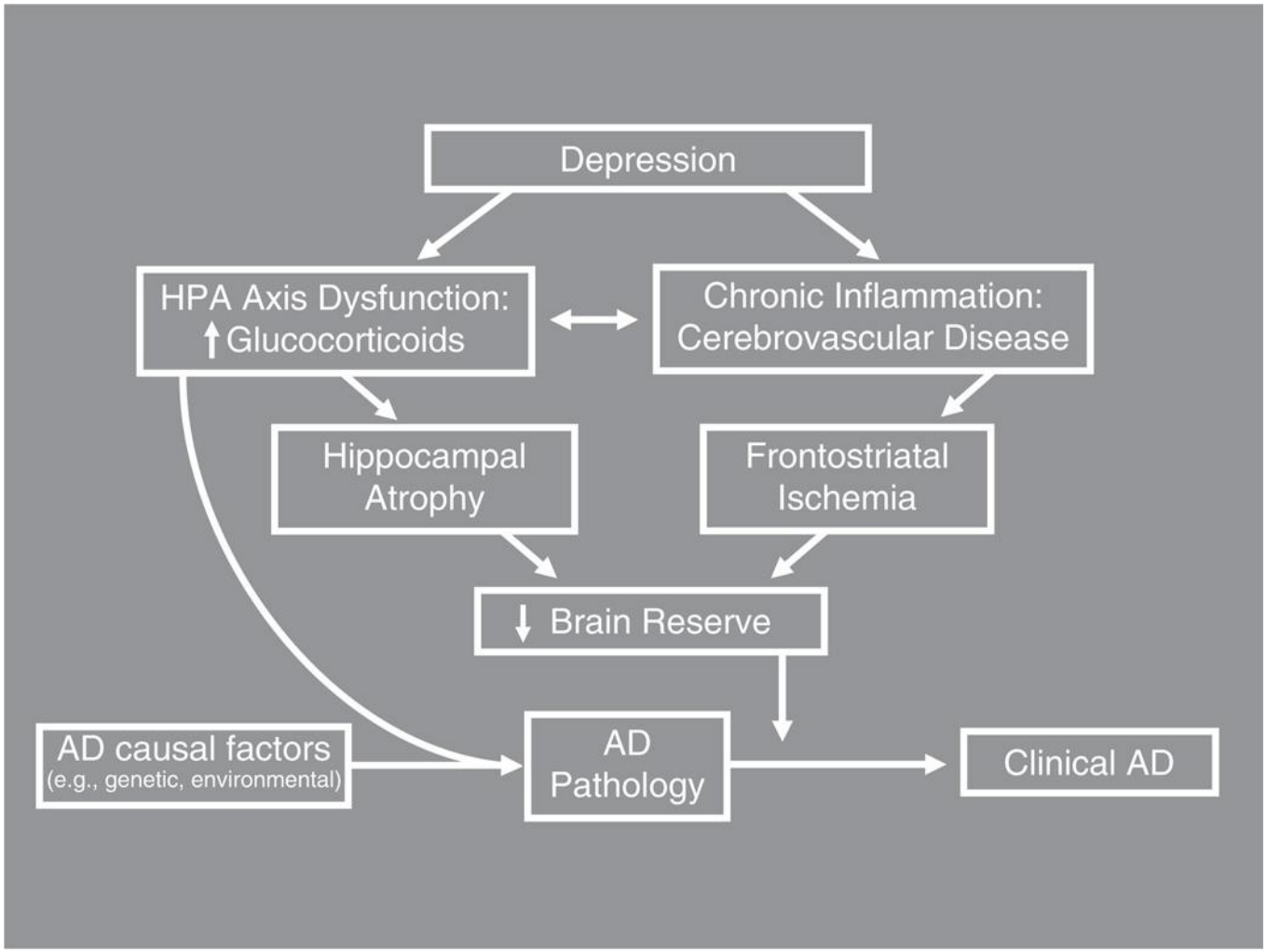
- The "wear and tear" negative consequences on the body of trying to keep everything stable through allostasis.
- Reflected by effects like inflammation, increased cortisol, cardiovascular risk.


Environmental stressors
(work, home, neighborhood)
Major life events
Trauma, abuse
Brain
Individual differences
(genes, development, experience)
Behavioral responses
(fight or flight)
(personal behavior—diet, smoking, drinking, exercise)
Physiologic responses
Allostasis
daptation
Allostatic load



Andreescu C, unpublished, 2015

Combining all models



Koenig, Bhalla, and Butters, JINS 2014

Conclusion

- Depression/Anxiety and Dementia frequently occur in the same people.
- The **direction of causality may vary**.
- Early onset depression and chronic anxiety may be risk factors for dementia.
- Adequate treatment for depression and anxiety may have a protective effect.
- **Late onset depression and anxiety** may be an early manifestation of the same disease (degenerative or vascular) that is causing the dementia.

Take-home message

- Don’t walk around being anxious or depressed at any age.

  Get help:
  - Medication
  - Talk therapy
  - Exercise
  - Meditate
  - Maintain physically and socially active lifestyle
- You’ll feel better
- You may also reduce your risk of dementia.