Interplay of mood and Cognition in late life

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Disclosures

- No Conflicts of interest
- Involved in treatment trials for escitalopram, nabilone, and brain stimulation interventions for cognition and behavioural symptoms of dementia
- Membership in Guideline Panel for behavioural and psychological symptoms of dementia

Objectives

- To discuss the diagnosis and treatment of late life major depression
- To discuss major depression, depressive symptoms, and risk of dementia
- To discuss diagnostic challenges for depression in dementia
- To discuss treatment of major depression in dementia
- To discuss treatment of depressive symptoms in dementia

Major Depression

- Five or more – for two weeks (at least one symptom has to be either depressed mood, or loss of interest or pleasure
  - **Depressed mood most of the day, nearly every day…….**
  - **Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day……..**
  - Significant weight loss when not dieting or weight gain…..
  - Insomnia or hypersomnia nearly every day….
  - Psychomotor agitation or retardation…..
  - Fatigue or loss of energy nearly every day…..
  - Feelings of worthlessness or excessive or inappropriate guilt …..
  - Diminished ability to think or concentrate……
  - Recurrent thoughts of death…or suicidal ideation…
- The symptoms cause clinically significant distress or impairment ……..
- The episode is not attributable to the **physiological effects of a substance or another medical condition.**
- Responses to a significant loss (e.g., bereavement, serious medical illness or disability….)

DSM-5 TR

General Adult versus Late Life Depression

Symptom Domain	Adult Presentation	Geriatric Presentation
Mood	Depressed mood, anhedonia, suicidal thoughts	Depressed, **hopeless, feels worthless, psychic anxiety**, thoughts of death
Somatic	Sleep changes, appetite changes, activity changes	Activity changes, **general somatic symptoms**
Cognitive	Decreased concentration, indecisiveness	**Decreased processing speed, executive function, selective attention, working memory, verbal fluency, spatial planning**

Portella 2003, Diniz 2013, Aziz 2017

Major Depressive Disorder (MDD) Versus Depressive Symptoms

- Major depressive episode (MDE)
- Major depressive disorder (MDD)
  - The person has to meet full criteria for major depressive episode
  - Other etiologies (substance use, Breavement, medical condition, disability) should be ruled out

- Sub-syndromal depression or depressive symptoms

- Particularly relevant for diagnosing depression in late life and may have important implications for treatment

Treatment of MDD in late life

- First line psychotherapies- cognitive behaviour therapies (CBT – both individual and group) and problem-solving therapy (PST).
- Second line psychotherapies- supportive therapy, behavioural activation, reminiscence, psychodynamic psychotherapy and interpersonal psychotherapy
- Emerging evidence for virtual therapies (iCBT)
- First line Pharmacotherapies- Sertraline/duloxetine, esitalopram/citalopram (Goal should be full remission)
- If no-response or Incomplete response, Switch medication or augmentation with Lithium, Antipsychotic (Aripiprazole), or psychotherapy augmentation (CBT, IPT or PST)

CCSMH Depression Guidelines 2021

Brain Stimulation Treatments for MDD in late life

- Electroconvulsive therapy
  - failed to respond to 1 or more adequate antidepressant trials
  - first-line treatment in those at high risk of poor outcomes
  - May be first line in MDD with psychosis
- Transcranial Magnetic Stimulation
  - Modest response rates- comparable to antidepressants
  - Recent studies with higher stimulation dose have shown better efficacy
  - May be appropriate for those who fail at least one antidepressant, or if there are concerns above cognitive adverse effects from ECT.

Treatment of Depressive Symptoms in late life

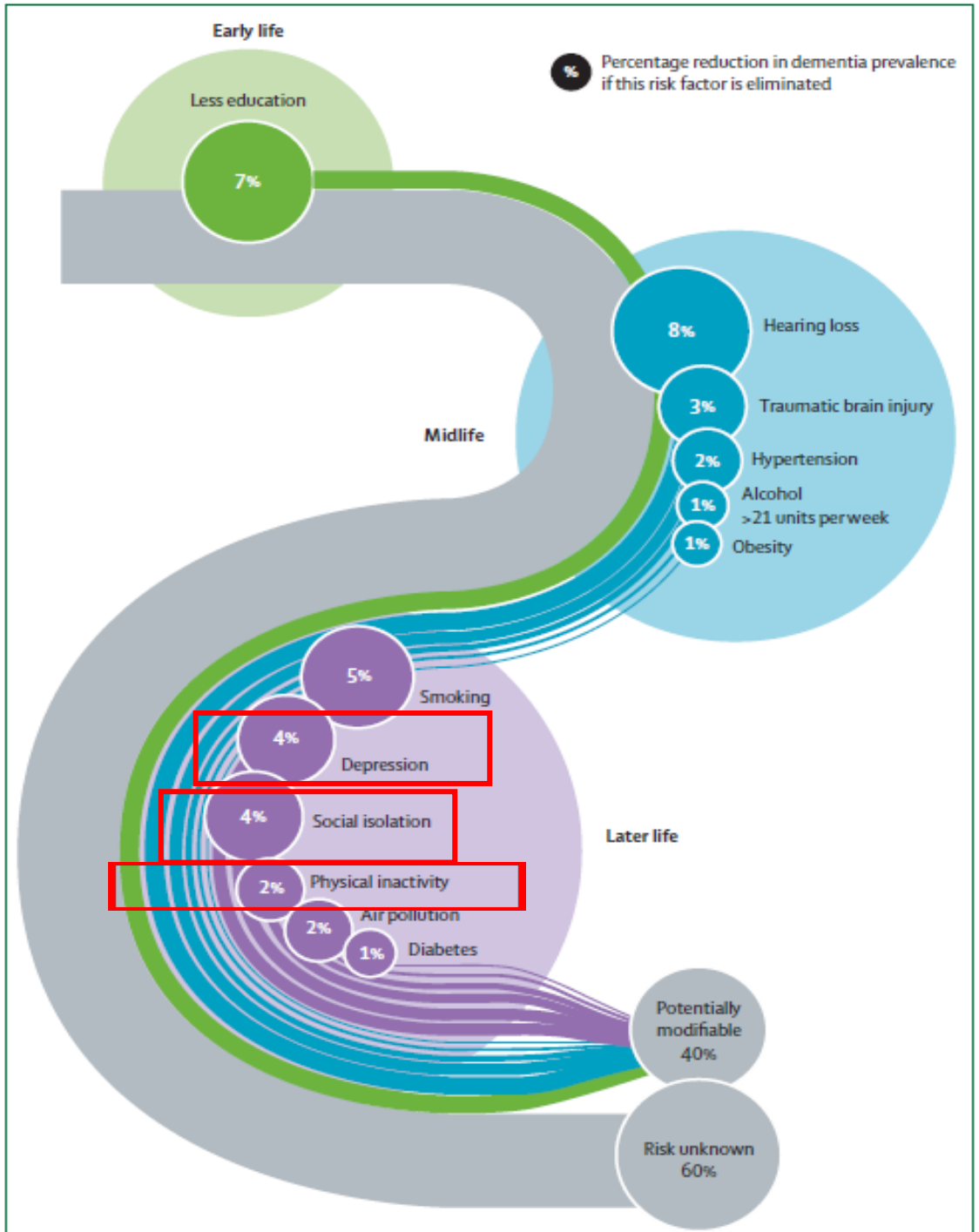
- Stepped Care approach consisting of watchful waiting, bibliotherapy, problem solving therapy, monitoring by primary care
- Interventions aimed at reducing social isolation and/or loneliness
- Physical activity (particularly for those with lower level of activity)
- Limited evidence for efficacy of antidepressants
- There may be increase risk of adverse effects

CCSMH Depression Guidelines 2021

Risk Factors for dementia

- Depression (4%)
- Social Isolation (4%)
- Physical Inactivity (2%)

- Out of total modifiable risk of 40%



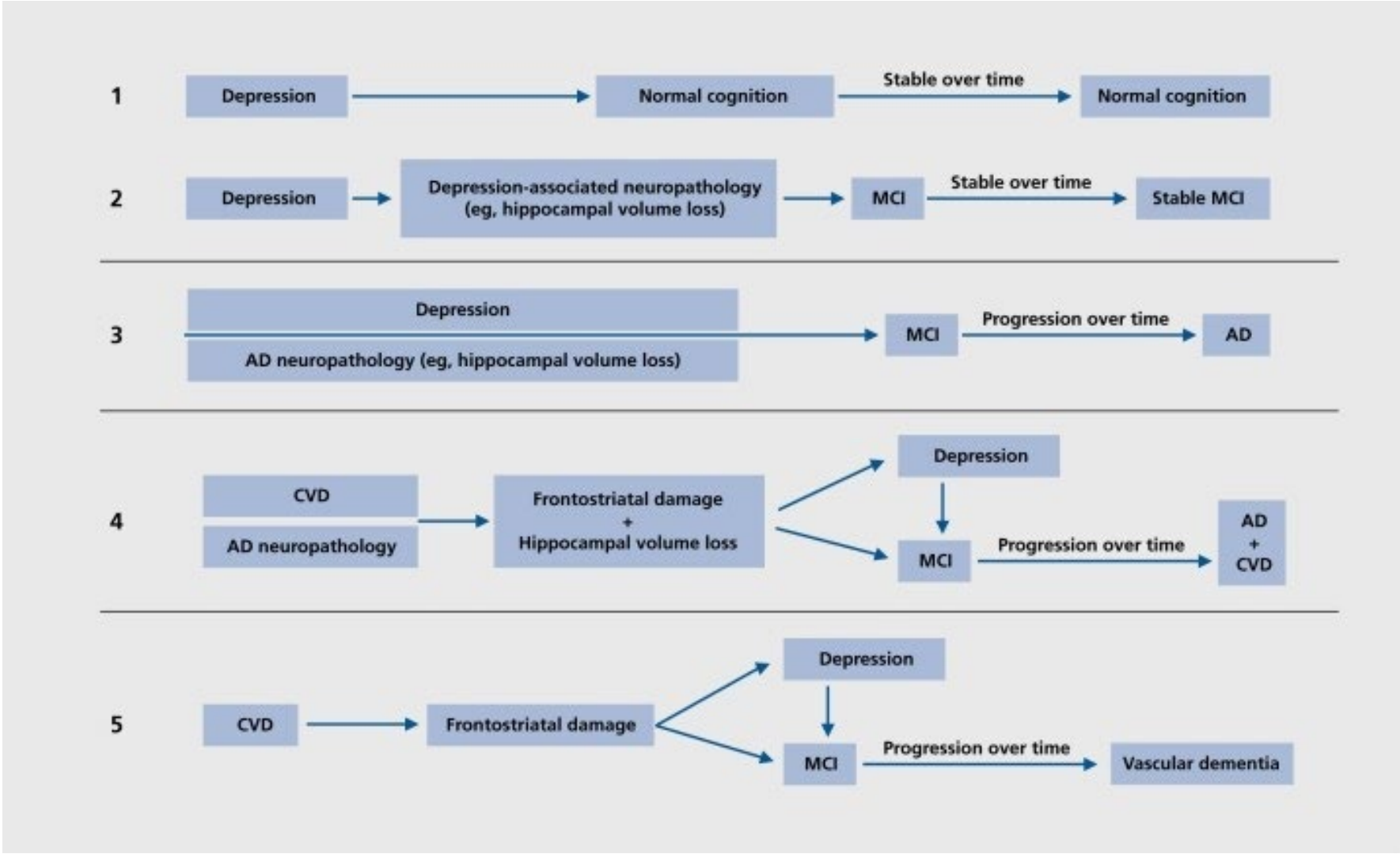
Lancet Commission report 2020

Presentation of Depression and Cognitive Impairment in late life

- Early onset MDD -> late life MDD
- Late onset MDD (onset after age 60 or 65)
- Depression as a prodromal condition for dementia
- Depression symptoms arise concurrently with cognitive decline
- Depressive symptoms in individuals with a diagnosed cognitive disorder
- Major Depression in individuals with a diagnosed cognitive disorder

Cognitively Normal → Mild Cognitive Impairment → Dementia

Long Term Impact of Depressive illness on Cognition



Butters 2008

Depression as a Risk Factor for Dementia

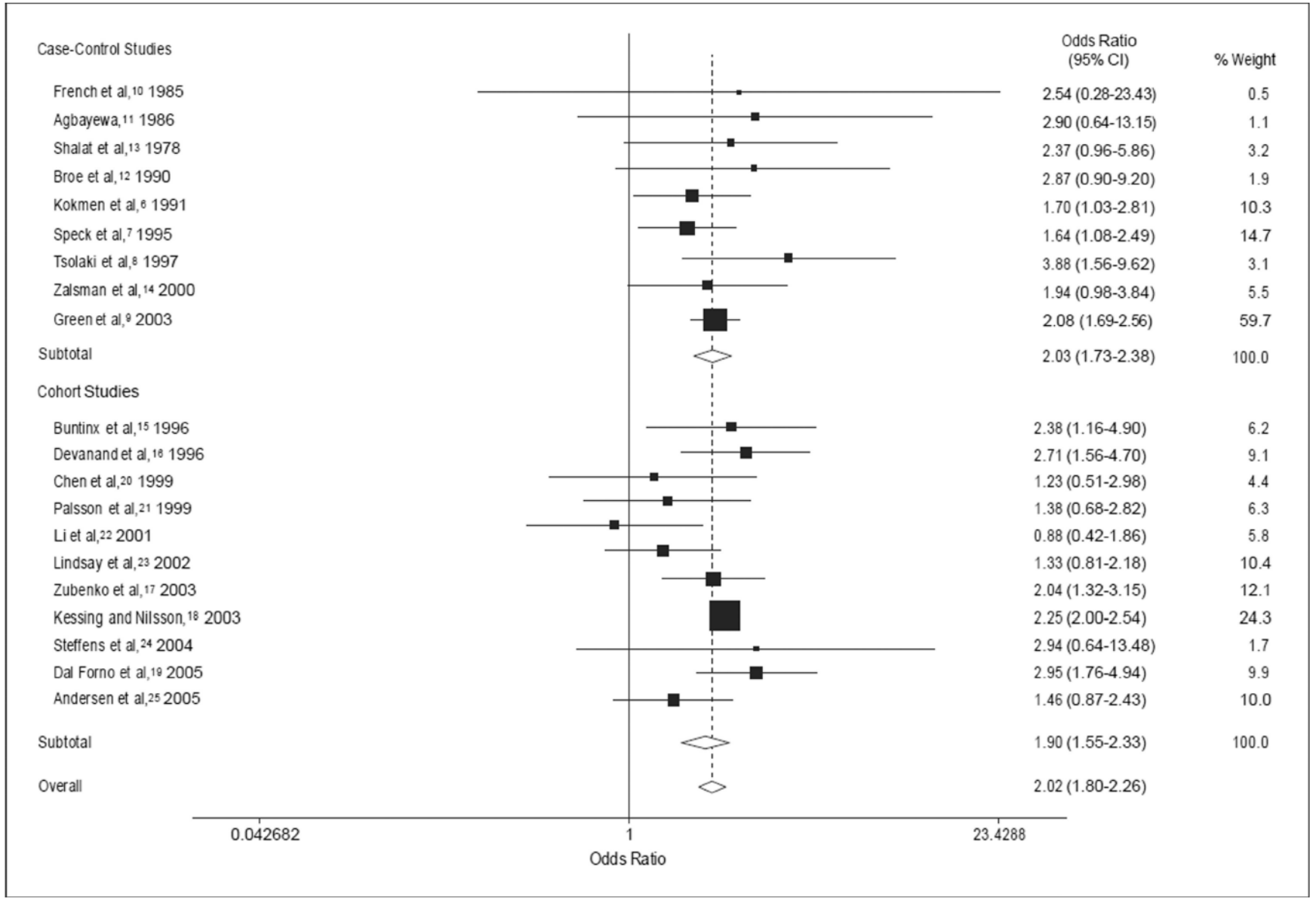
20 studies
N = 102172 persons across 8 countries.

Case-control studies
Pooled odds ratios = 2.03 (95% confidence interval, 1.73–2.38)

Cohort Studies
Pooled odds ratios =1.90 (95% confidence interval, 1.55–2.33)

Combined = 2.02

Interval between diagnoses of depression and AD was positively related to increased risk of developing AD

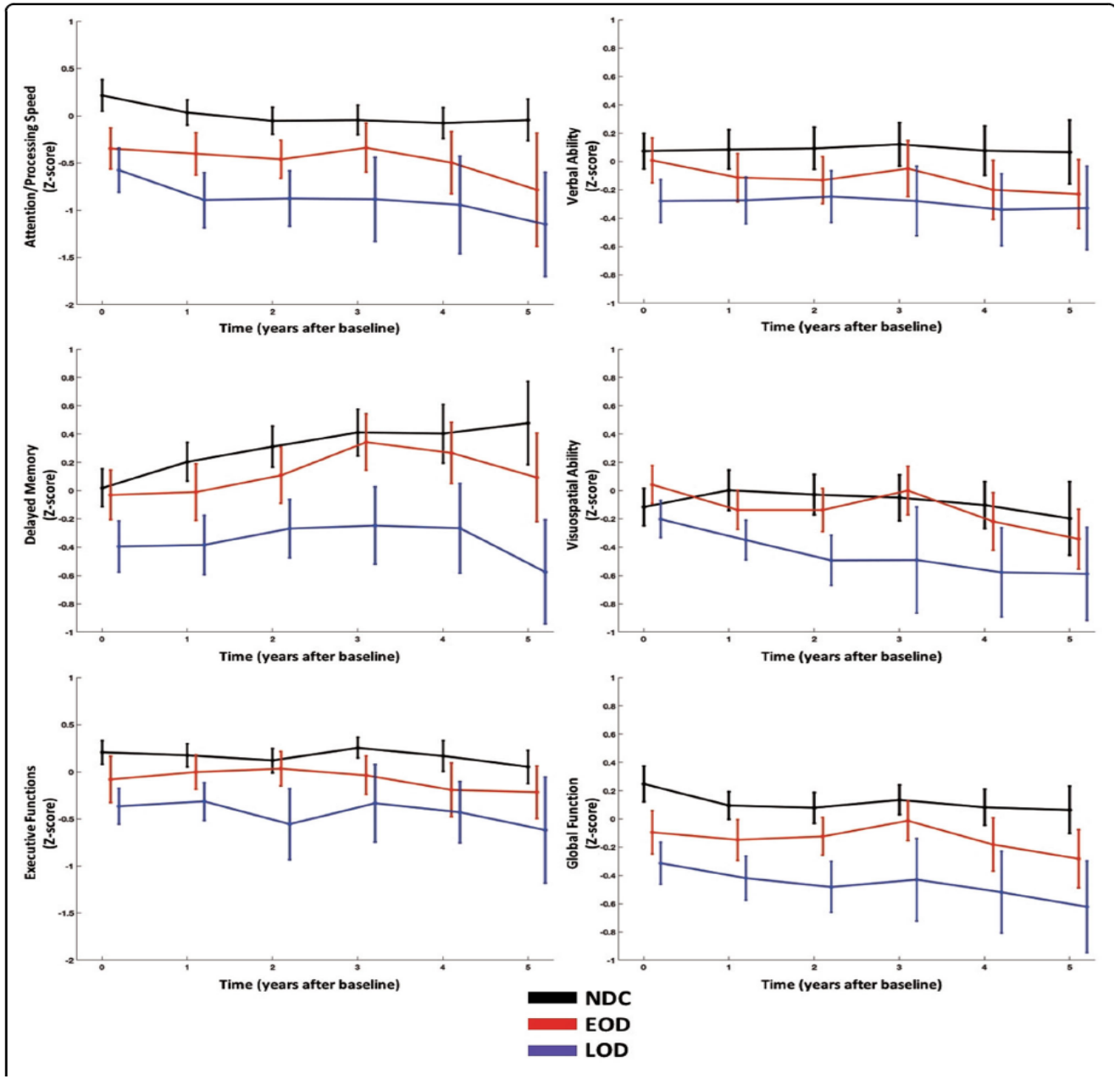


Ownby et al. 2006

Early versus Late onset Depression as a Risk Factor for Dementia

N
No Depression =114
Early onset depression = 100
Late onset depression = 85

- Baseline impairment may lower the threshold for those with LLD to develop dementia
- EOD and LOD may represent distinct phenotypes
- Higher risk of progressive decline with LOD



Ly et al. 2021

Depression as Risk factor and a Prodromal Syndrome

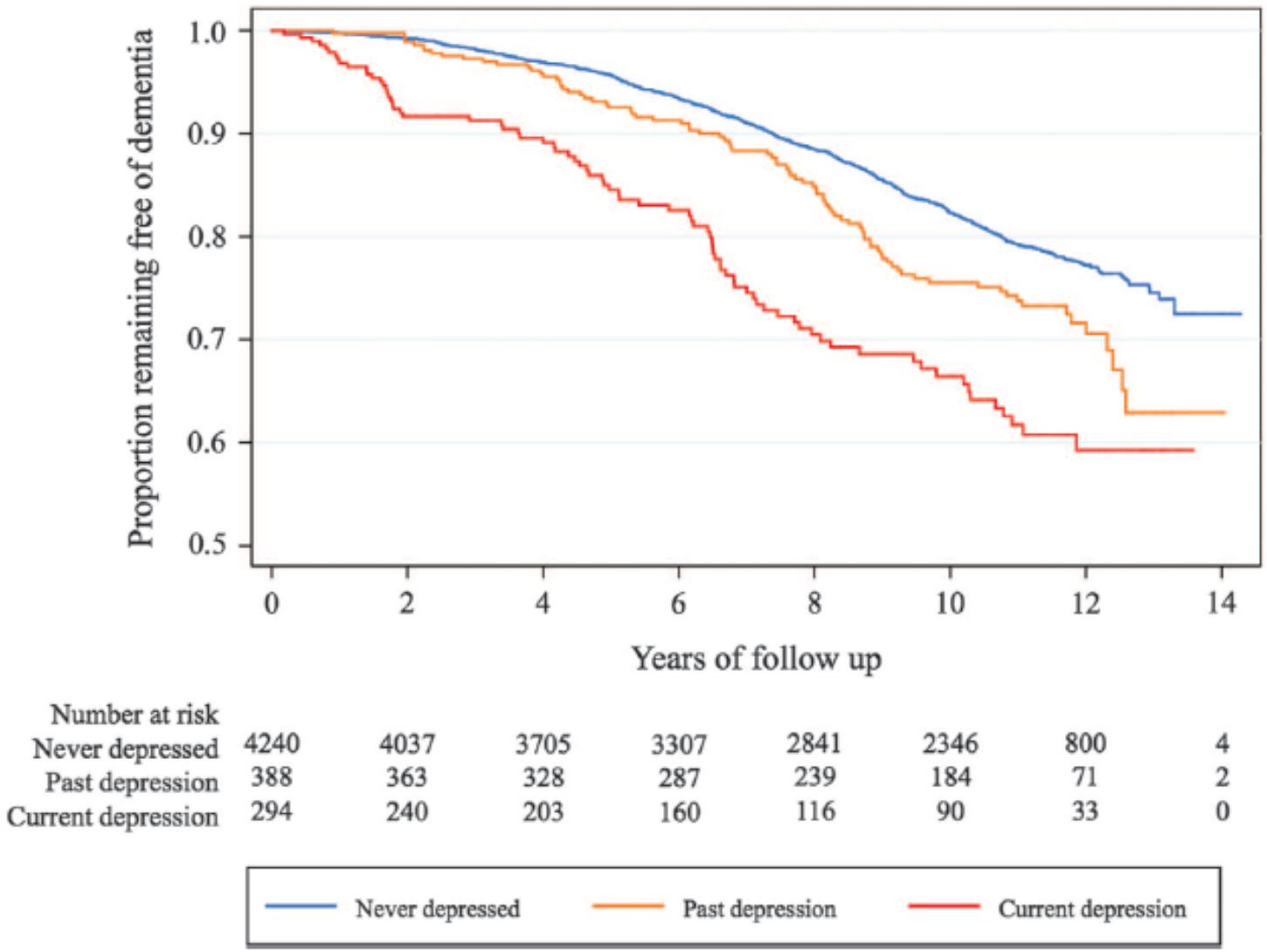
Sub-hazard ratios (SHRs) of dementia for men with past depression = 1.3 (95% (CI) =1.0, 1.6)

Current Depression = 1.5 (95% CI = 1.2, 2.0).

Questionable Depression = 1.2 (95% CI = 1.0, 1.4),
Mild-to-moderate = 1.7 (95% CI = 1.4, 2.2)
Severe depressive = 2.1 (95% CI = 1.4, 3.2)

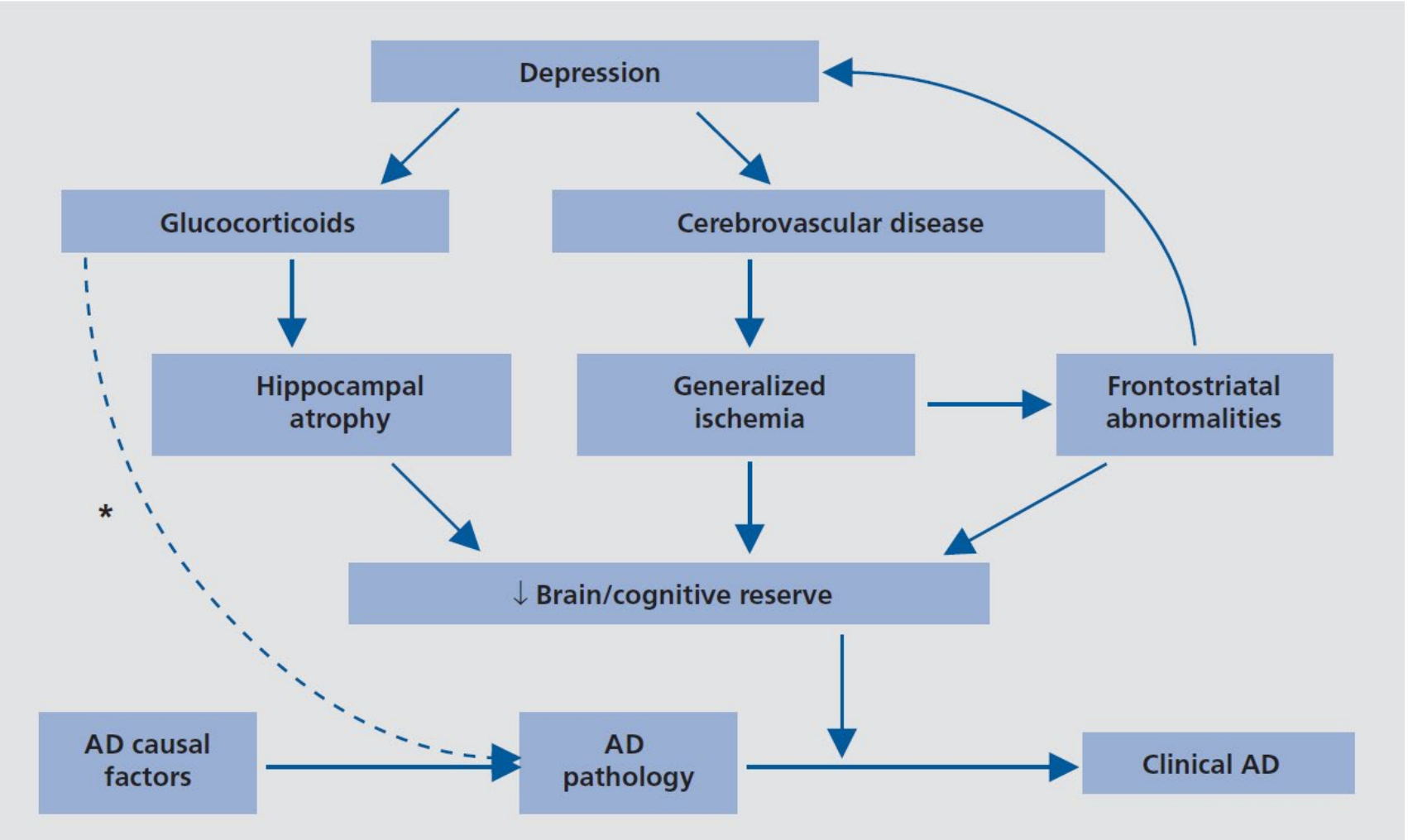
The Associations were only significant in the initial 5 years of follow-up.

There were no effects of antidepressant treatment



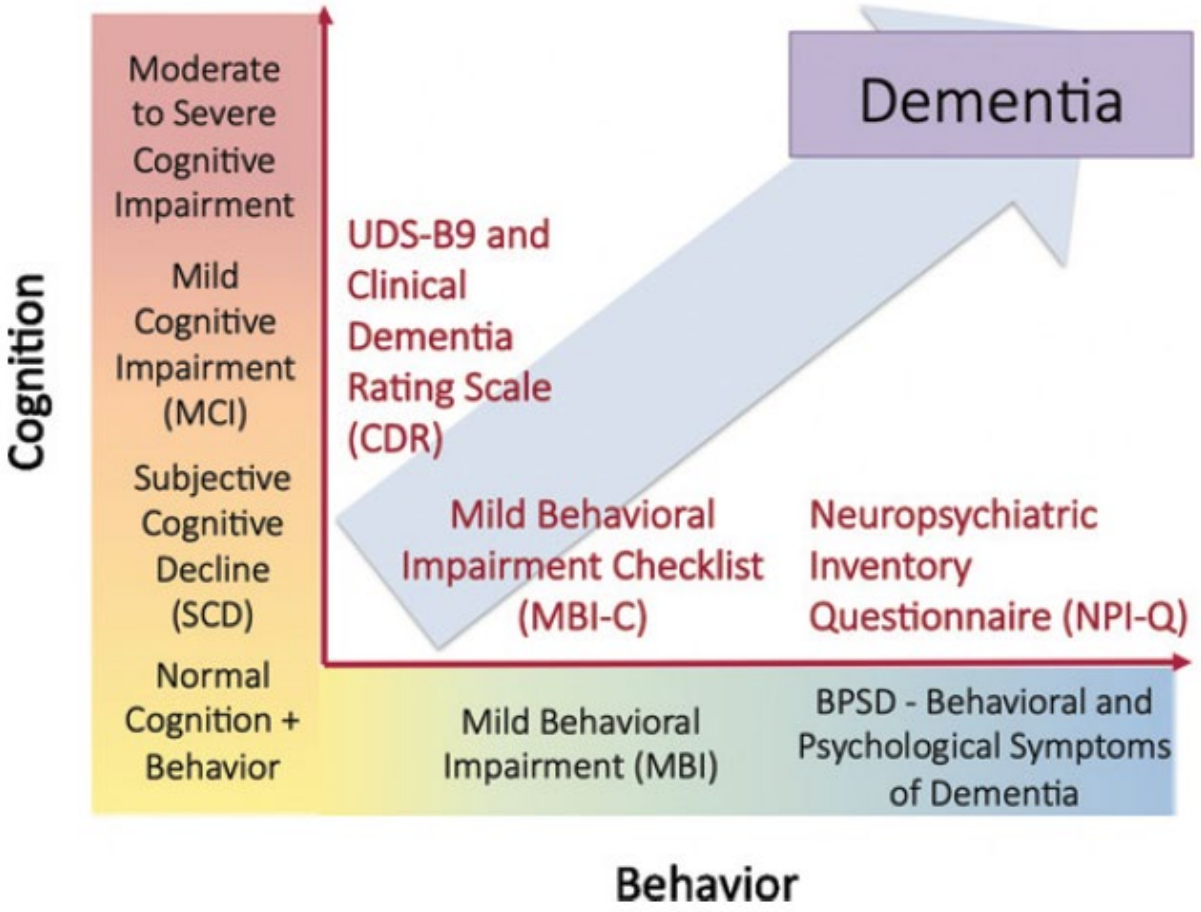
Almeida 2017- Health in Men study

Potential Mechanisms underlying the association of depression with dementia risk



Butters et al. 2008

MBI, Affective Dysregulation and Dementia Risk



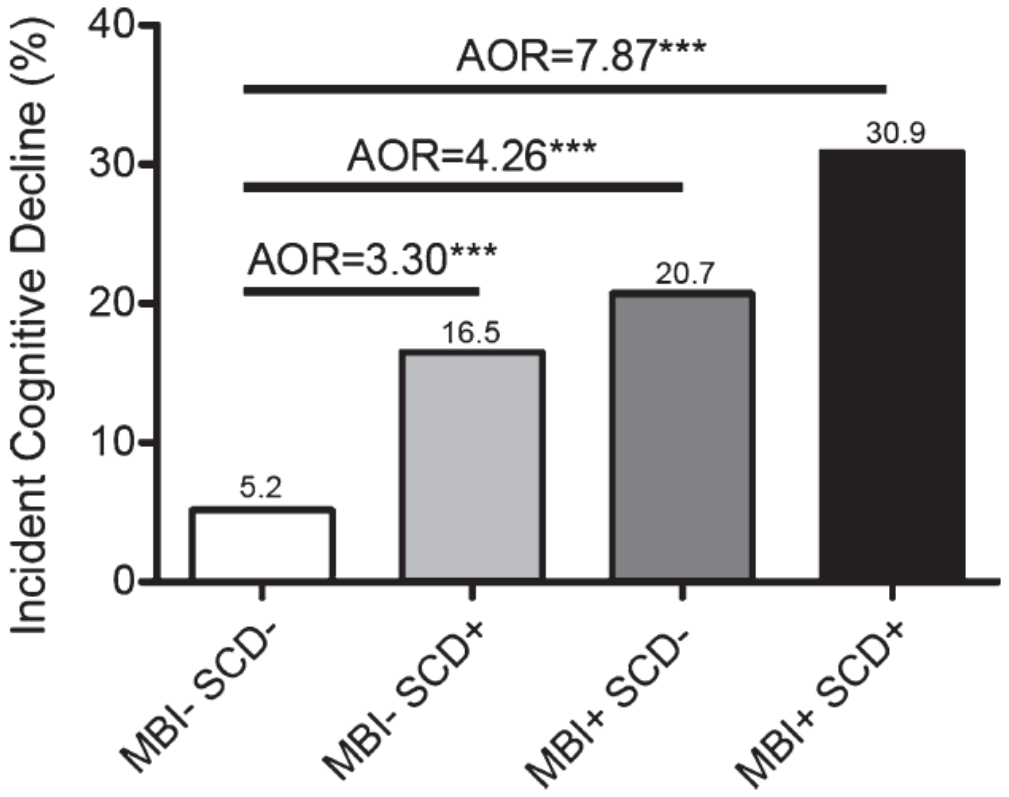


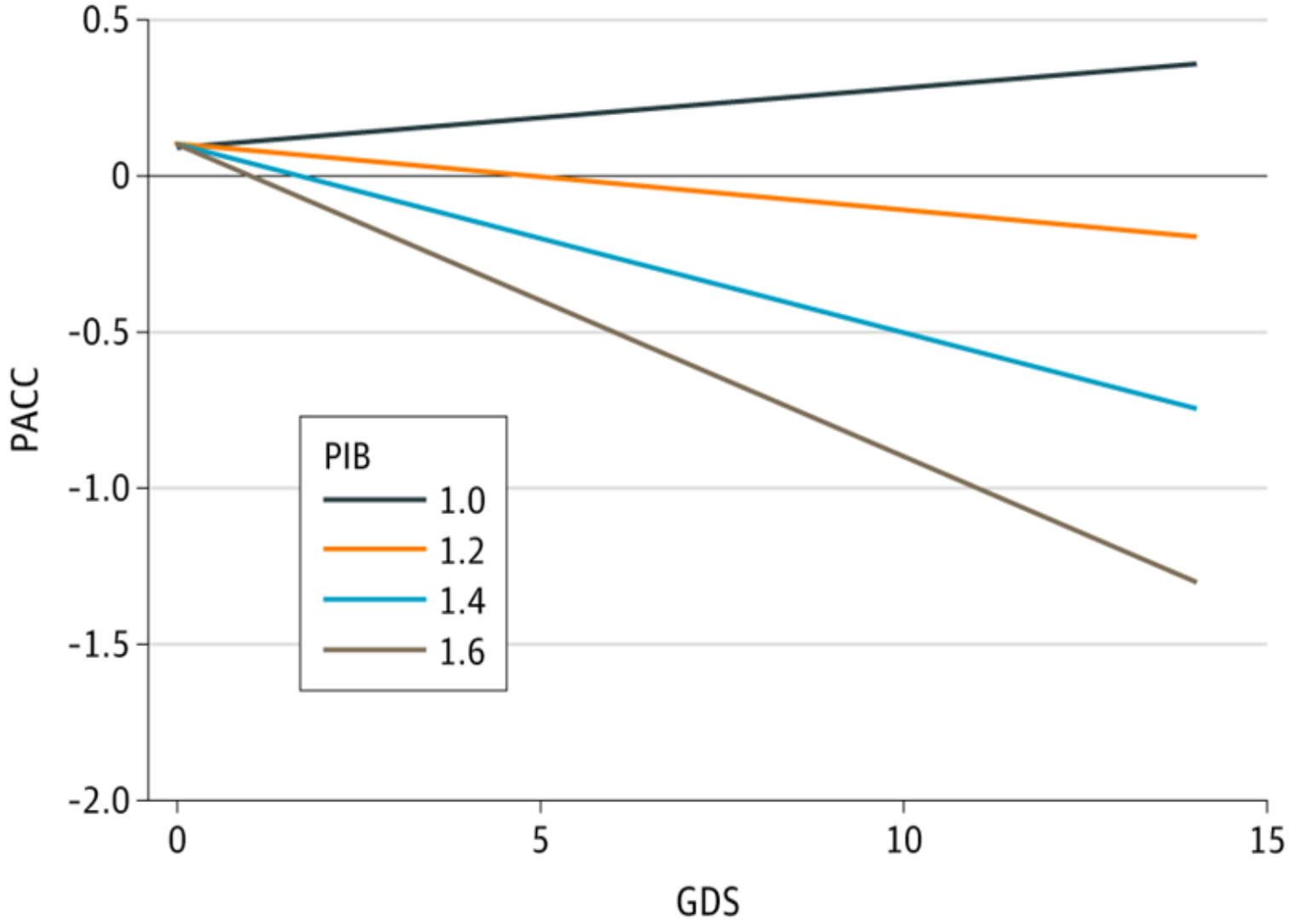
Fig. 3. Odds of CDR > 0 after three years versus MBI/SCD grouping.

Ismail 2021

Depressive symptoms and Amyloid pathology

N = 276 older adults,
Cognitively unimpaired
Mild depression at study entry

- Worsening depressive symptoms over 2 to 7 years in the presence of cortical amyloid were significantly associated with declining cognition.



Gatchel 2019

MDD and Amyloid- Negative association

- The proportion of amyloid positivity in the LLD group was 19.3% compared to 31.1% in ND group
- Global Aβ was not associated with lifetime number of depressive episodes, lifetime length of depression, length of lifetime SSRI use, or lifetime length of untreated depression

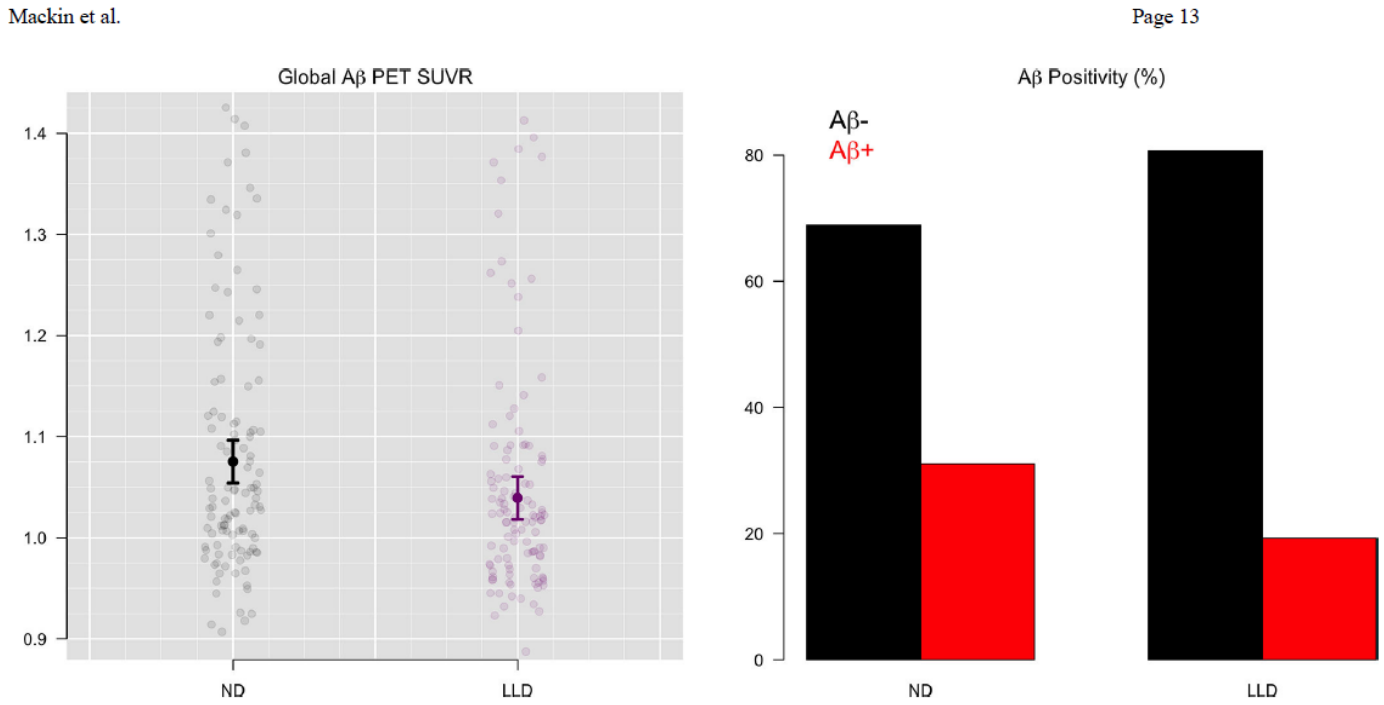
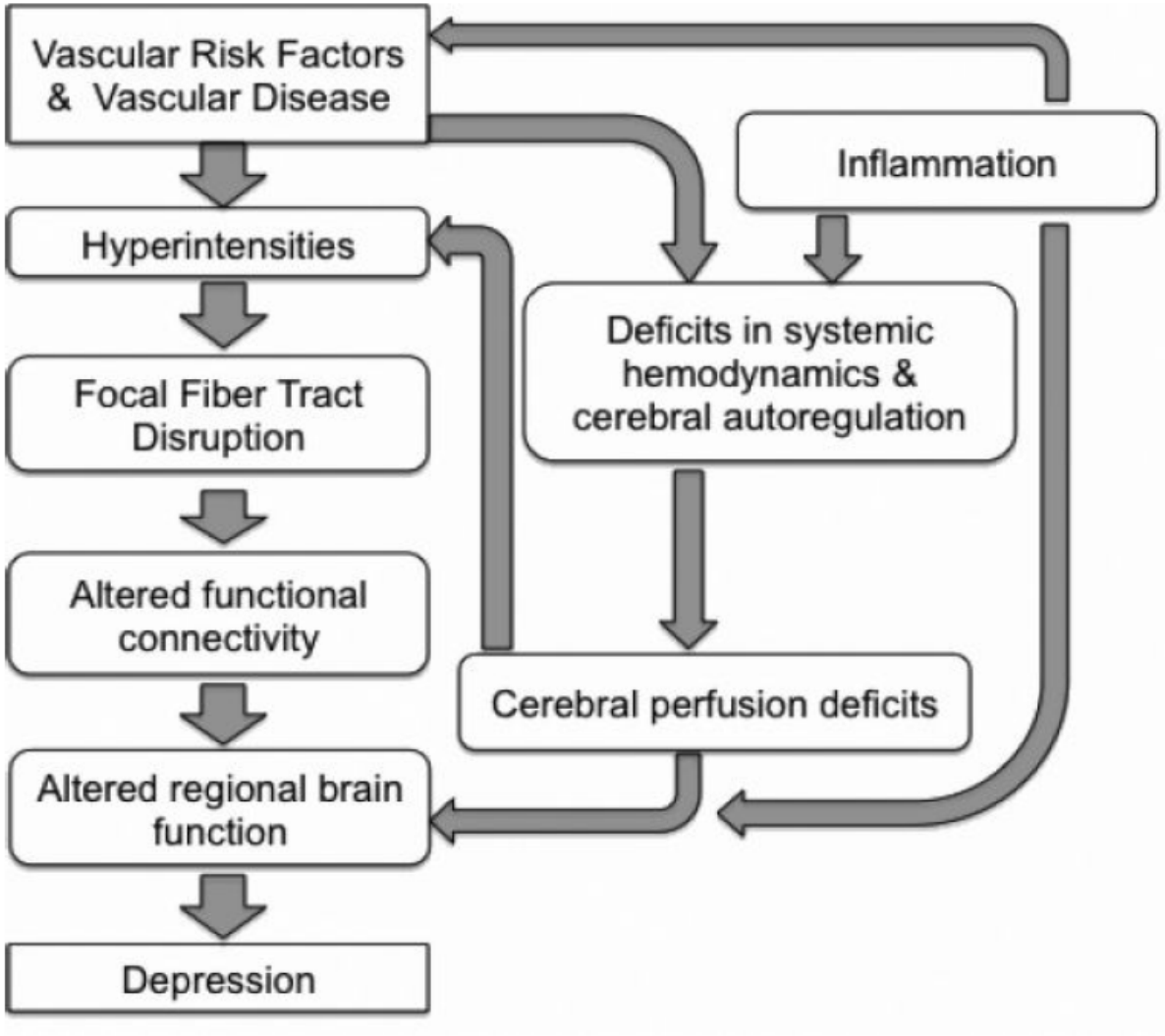


Figure 1.
Global Aβ PET Uptake and Amyloid Positivity for LLD and ND groups (n=238)

Mackin 2021

Vascular Factors and Late life depression- Model

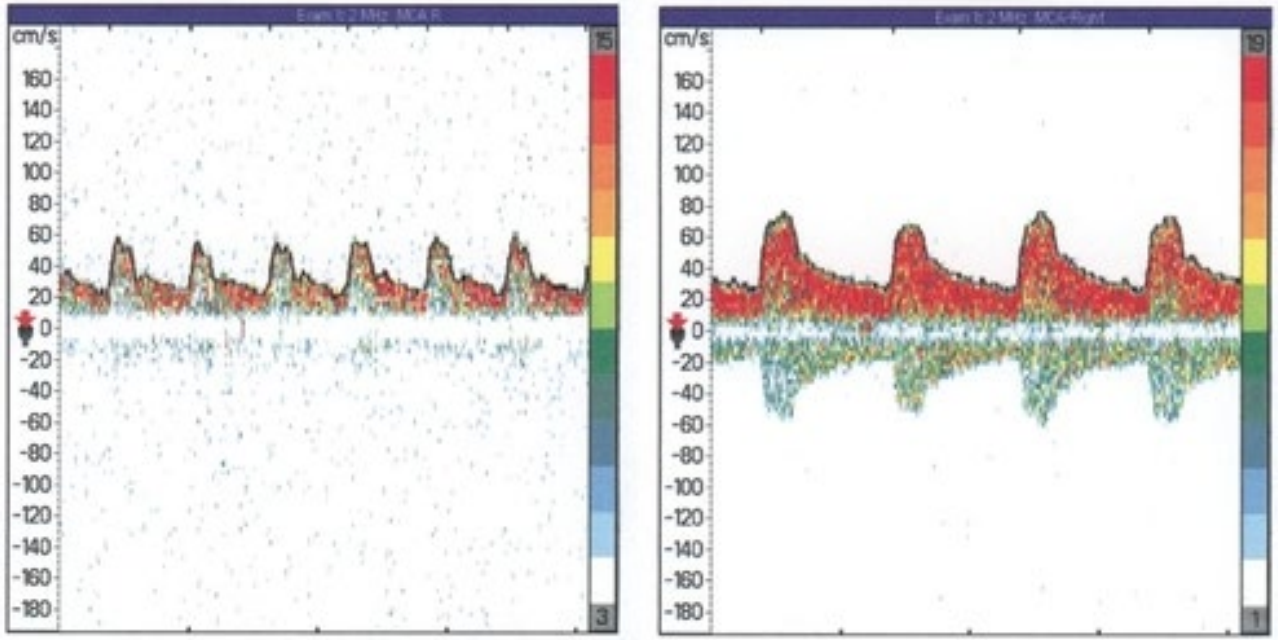
- Late Life Depression
- Executive dysfunction
- Other Cognitive deficits
- White Matter Hyperintensities
- Hypoperfusion
- Inflammation



Taylor 2013

Vascular LLD

- Silent Strokes
- Basal Ganglia Lacunar Infarcts
- Reduced Blood Flow
- Disruption of cortico-striato-pallido-thalamo-cortical (CSPTC) pathways
- More psychomotor retardation, apathy, and lack of insight, and less agitation and guilt
- Poor treatment response



Blood flow velocity In the middle cerebral artery in an 82 -year-old patient with major depression (left) and a 79-year-old psychiatrically normal subject (right).

Alexopoulos 2022

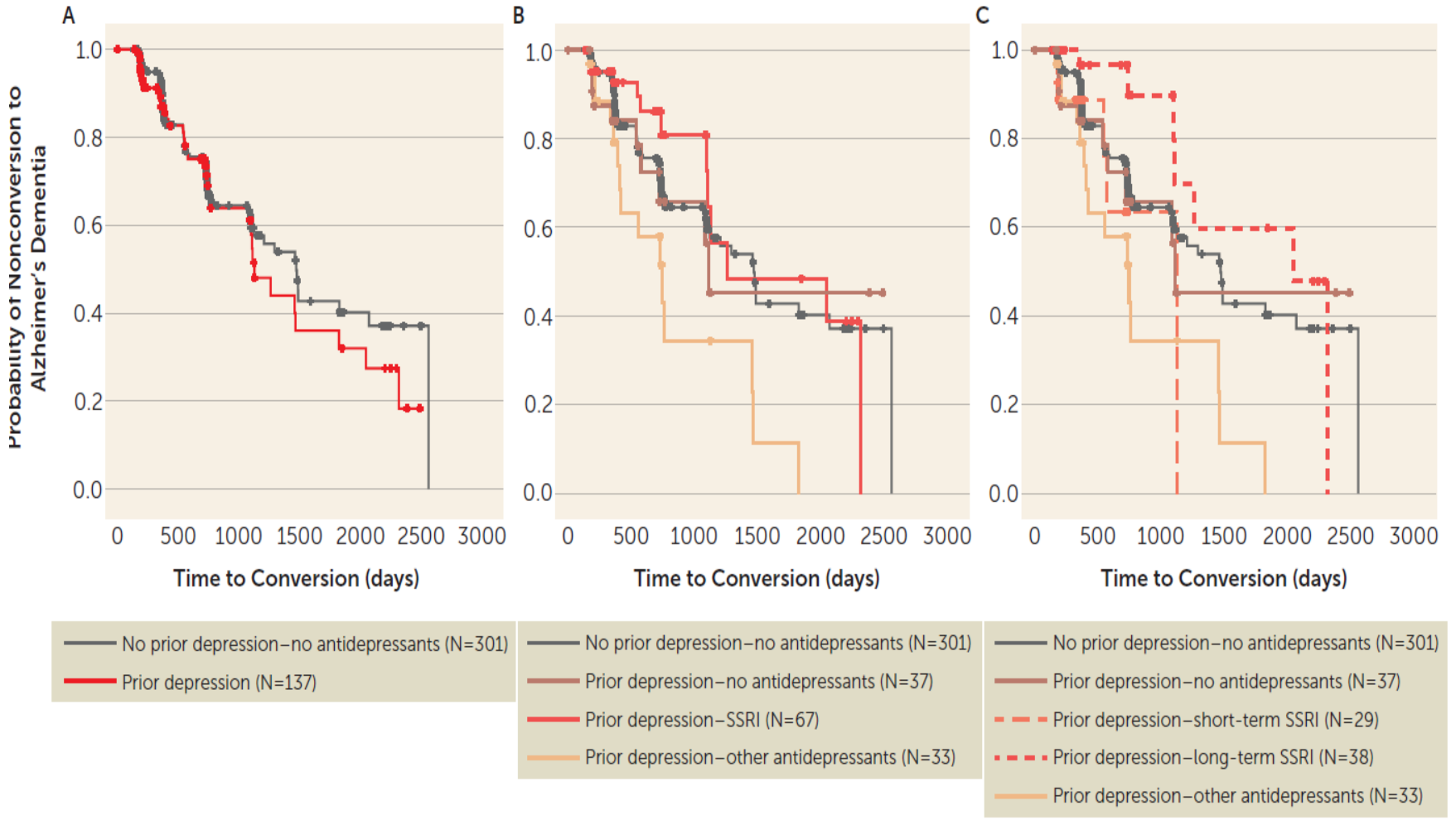
Impact of Depression Treatment on Dementia Risk

755 ADNI participants

- MCI (2.6 times) or AD (3.2 times) was associated with h/o depression
- h/o depression was not associated with rate of conversion to AD

- In MCI + h/o depression, long-term SSRI treatment (4 years) was associated with a delayed progression to AD

- There was no impact of SSRI t/t on CSF biomarkers of AD



Bartels 2018

Assessment of Depression in Dementia

- GDS and PHQ-9 which are validated measures for detection of late life depression may not be appropriate in those with cognitive impairment
- Observer-rated instruments, such as the Cornell Scale for depression in dementia should be used
- Evaluation should take into consideration level of cognitive impairment, psychosocial environment, medical comorbidities, and possibility of hypoactive delirium.
- Apathy might confound the assessment of depression in dementia

MDD in Dementia

- Large Metanalysis form prevalence of MDD in dementia

N = 55 studies, 13172 participants

- MDD prevalence all-cause dementia = 15.9% (95% CI, 12.6%-20.1%).
- Vascular dementia= 24.7%
- Alzheimer's disease =14.8%
- Dementia with Lewy bodies = 21.46%

Asmer 2018

Depression as one of the Neuropsychiatric Symptoms in Dementia

- 75%- 95% have at least one NPS during the course of their illness

Point prevalence's of specific symptoms

- Depression (50-77%)
- Apathy (71%)
- Anxiety (62%)
- Agitation /hyperactivity (30-80%)
- Psychosis (50%)

(Tariot 1999 J clin Psy, Lyketsos 2002, JAMA, Aalten 2005 IJGP)

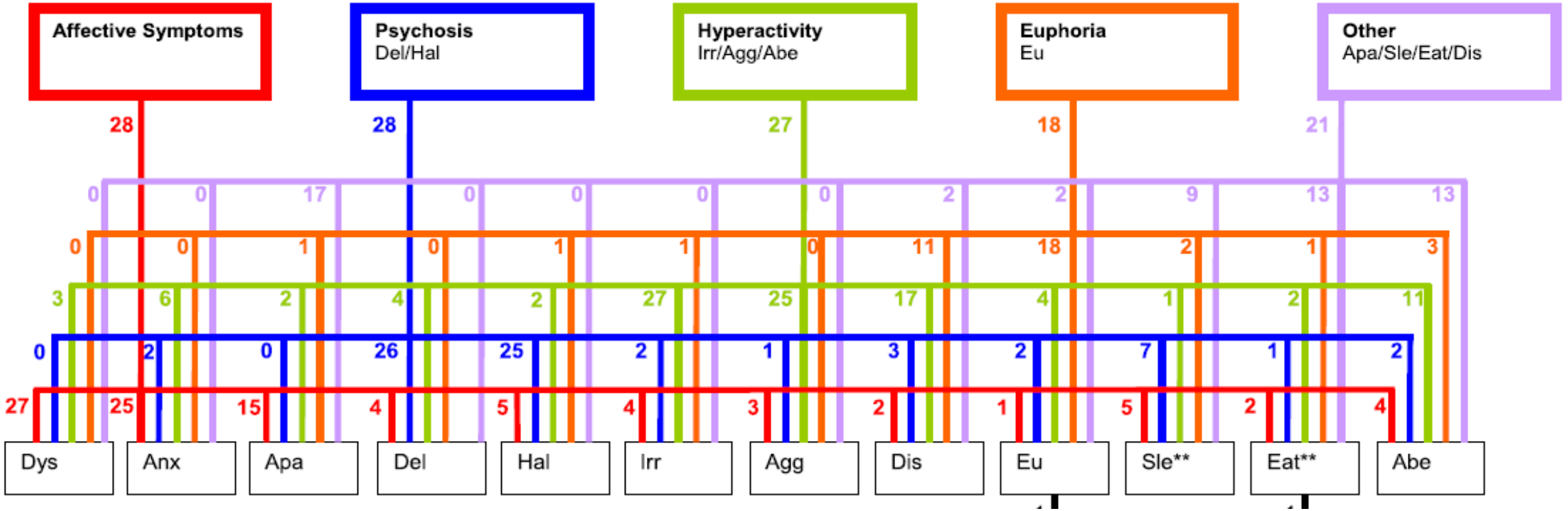
(Jeste DV, Finkel SI, 2000, AJP, Steinberg 2008 IJGP, Garcia-Martin 2022, BMC Geriatrics)

Depressive Symptoms Across Neurodegenerative Disorders

- PD and DLB-
  - Any Symptom (80%)
  - Depression (30-40%)
  - Apathy (17-70%)
  - psychosis (50 -70%)
- FTD –
  - Any Symptoms (90%- 100%)
  - **Apathy,** anxiety and aberrant motor activity were most frequent
- VCD- Depressive symptoms very common (~50%)

Aarsland 2009 & 2015, movement disorders, JPD, Fields 2017, Arch Clin Neuropsych., Martínez 2008, Dement Geriatr Cogn Disorders, Banks 2008, J Geriatr Psychiatry Neurol, Srikanth 205, Journal of the Neurological Sciences, Lyketsos 2002, JAMA

Grouping of NPS



Most Studies included patients with Dementia, Not Clear in MCI

Van der Linde 2013 IJGP
Siafarikas 2018, Int Psychogeriatrics

Canadian Psychiatric Association
Association des psychiatres du Canada

Original Research

The Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie
1-12

DOI: 10.1177/07067437221147443
TheCJP.ca | LaRCP.ca
SAGE

Neuropsychiatric Symptom Burden across Neurodegenerative Disorders and its Association with Function

La charge des symptômes neuropsychiatriques dans les troubles neurodégénératifs et leur association avec la fonction

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Results - (ONDRI cohort) –Frequency

Table 2. Percentage of Participants in Each Cohort (AD, ALS, FTD, PD, and CVD) Showing Symptoms (Mild, Moderate, or Severe) Evaluated on the NPI-Q.

NPI-Q Symptom	AD ($n=126$)	ALS ($n=40$)	FTD ($n=53$)	PD ($n=140$)	CVD ($n=161$)	*P* value*
Delusions	8.7%	2.5%	13.5%	2.9%	7.3%	.06
Hallucinations	4.3%	2.5%	3.8%	9.5%	2.0%	.06
Aggression	28.2%	22.5%	40.4%	17.4%	24.5%	.02
Depression	32.5%	37.5%	37.3%	37.7%	25.8%	.2
Anxiety	25.6%	17.5%	46.2%	21.7%	15.9%	<.001
Euphoria	5.1%	5.0%	15.4%	2.9%	3.3%	.02
Apathy	38.3%	27.5%	56.9%	23.2%	23.2%	<.001
Disinhibition	23.0%	7.5%	43.1%	12.3%	14.6%	<.001
Irritability	37.9%	22.5%	59.6%	27.5%	38.0%	<.001
Motor	12.8%	12.8%	30.8%	5.0%	8.6%	<.001
Night-time behaviours	22.8%	26.3%	53.8%	52.9%	33.6%	<.001
Appetite	28.0%	41.0%	55.8%	27.5%	22.5%	<.001

Significant differences in the NPS frequency among cohorts ($\chi 2$ (4)=34.4, $p < .001$)

Results- (ONDRI cohort) – NPS Association with IADLs

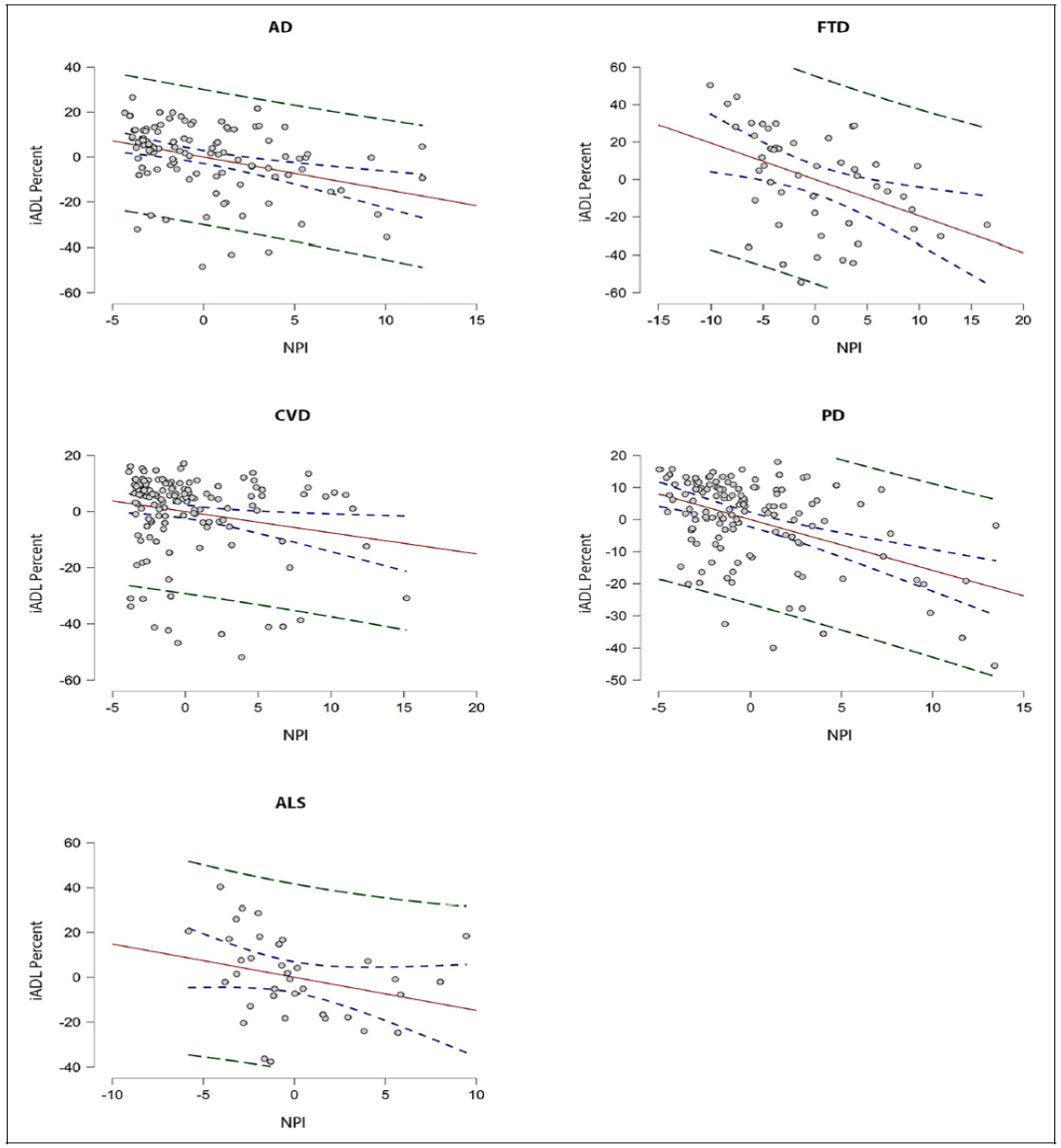
- Within individual Cohorts
  - AD – NPIQ, MoCA, and age contributed to IADLs.

  $(F(4,103) = 15.8, R^2 = .36, p < .001)$
  - PD – NPIQ and age contributed to IADLs.

  $(F(5,126) = 12.2, R^2 = .30, p < .001)$
  - FTD - NPIQ alone contributed to IADLs.

  $(F(4,45) = 4.3, R^2 = .21, p < .01)$
  - CVD-NPIQ alone contributed to IADLs.

  $(F(4,138) = 2.9, R^2 = .05, p = .03)$



Results- (ONDRI cohort) – NPS Association with ADLs

- Multivariable linear regression model for cohorts was **Significant.**
- Post-hoc differences between the FTD, and CVD, and between CVD and PD
- Within cohorts
  - AD- NPIQ and age contributed to ADLs

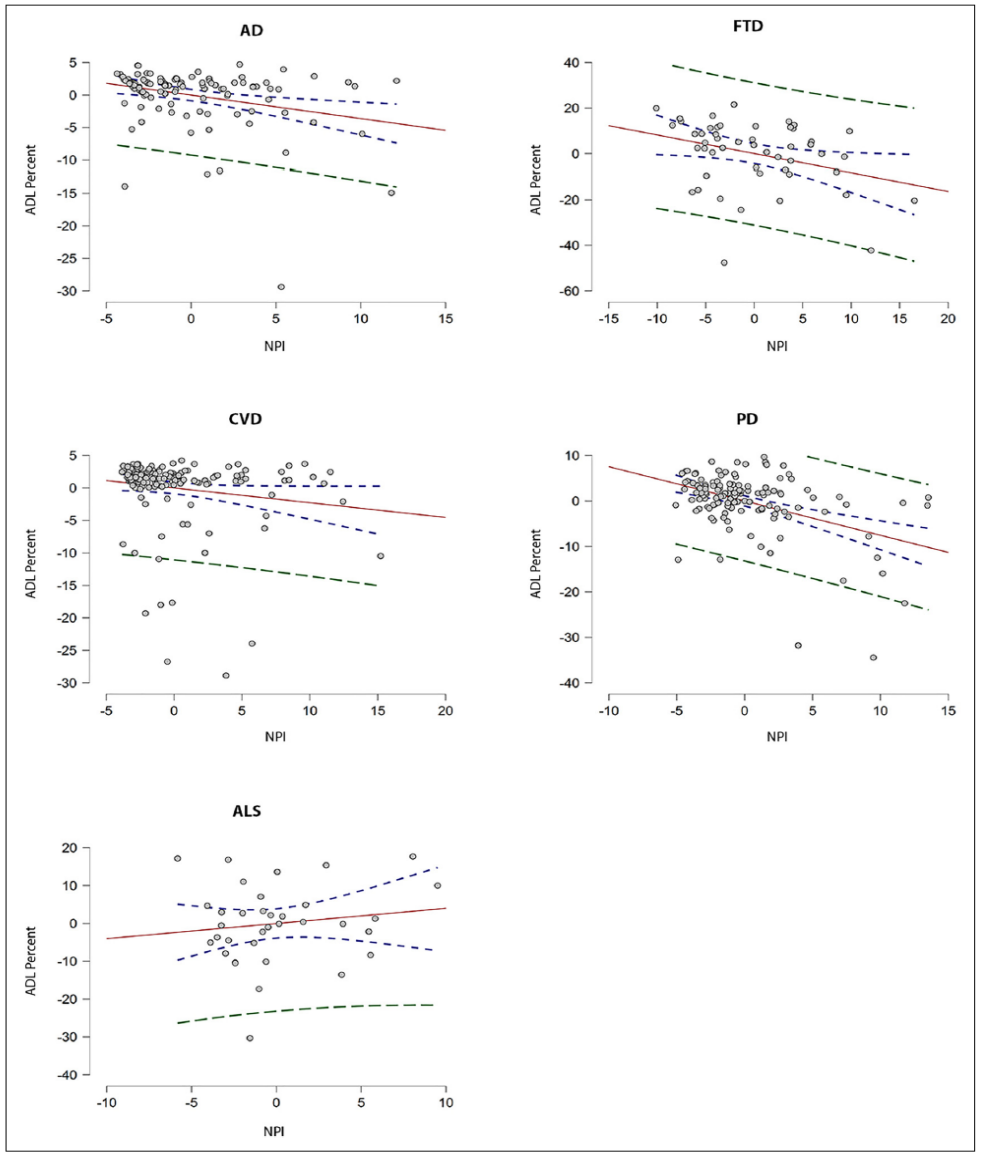
(F(4,104)=4.6, R^2=.12, p=.002).

  - FTD- NPIQ alone contributed to ADLs

(F(4,45)= 3.1, R^2=.14, p=.026)

  - PD – NPIQ and motor contributed to ADLs

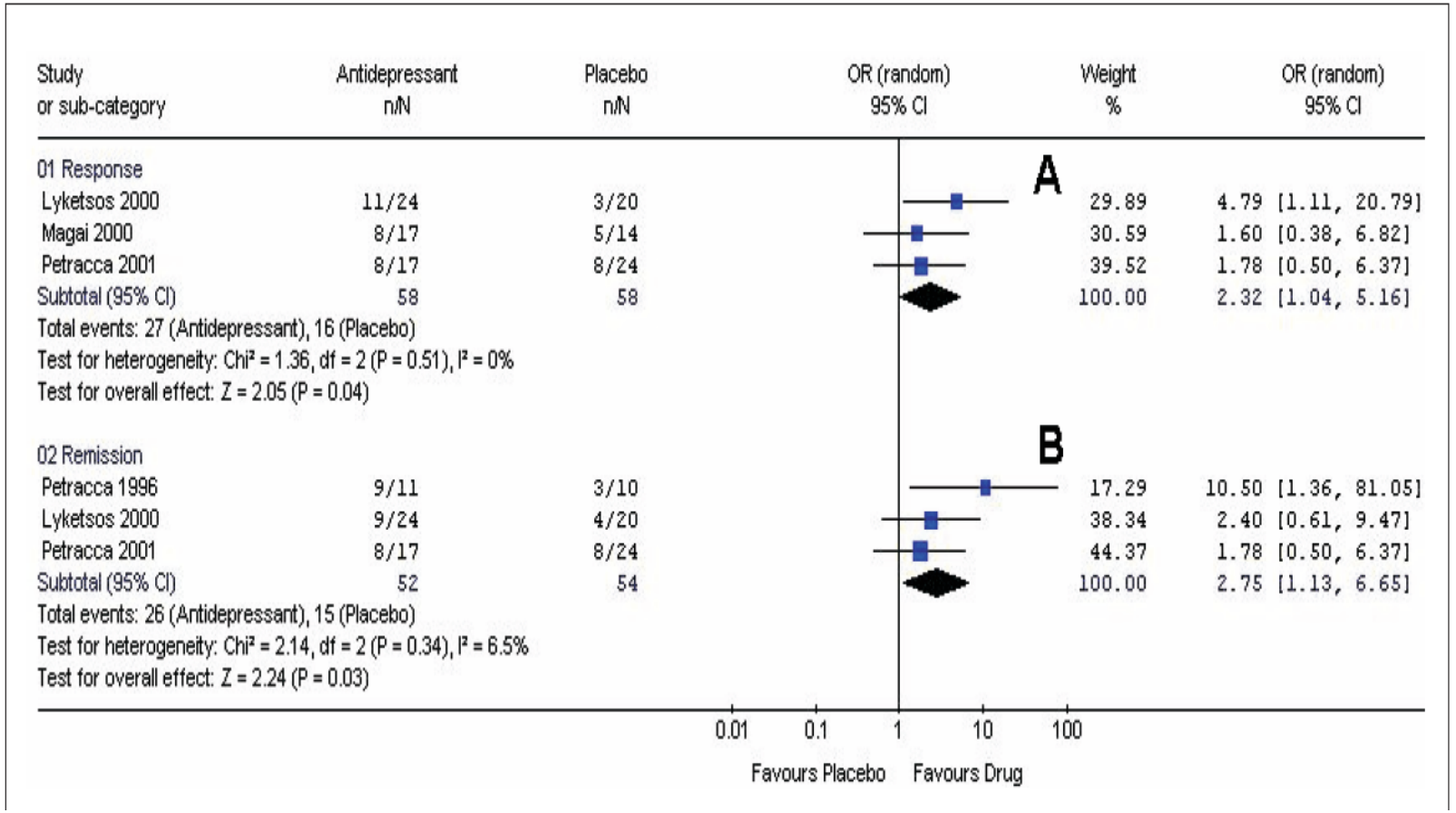
(F(5,129)=15.0, R^2=.34, p <.001)



Treatment of MDD in Dementia

- Antidepressants are efficacious in the treatment of depression in AD.
- Tolerability of antidepressants in AD appears to be similar to placebo.
- TCAs may be associated with a decline in cognition.

Figure 1 Response to treatment of depressive symptoms in Alzheimer's disease patients: antidepressant compared with placebo. Panel A, response; Panel B, remission



Thompson 2007

Treatment of MDD in dementia

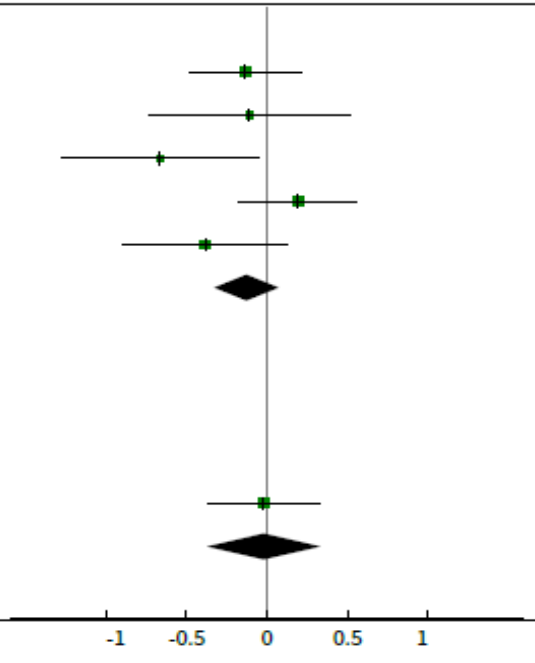
- 10 studies, 1592 patients
- High-quality evidence of little or no difference in scores on depression symptom rating scales between the antidepressant and placebo at 6 to 13 weeks
- No difference between groups at six to nine months
- Remission rate was higher in the antidepressantgroup than the placebo group (antidepressant: 40%, placebo: 21.7%; OR 2.57, 95% CI 1.44 to 4.59; 240 participants; 4 studies; moderate quality evidence).
- No change in Cognition or IADLs
- Slightly higher Adverse effects (dry mouth, dizziness) with Antidepressants

Dudas 2018, Chochrane

Treatment of MDD in dementia

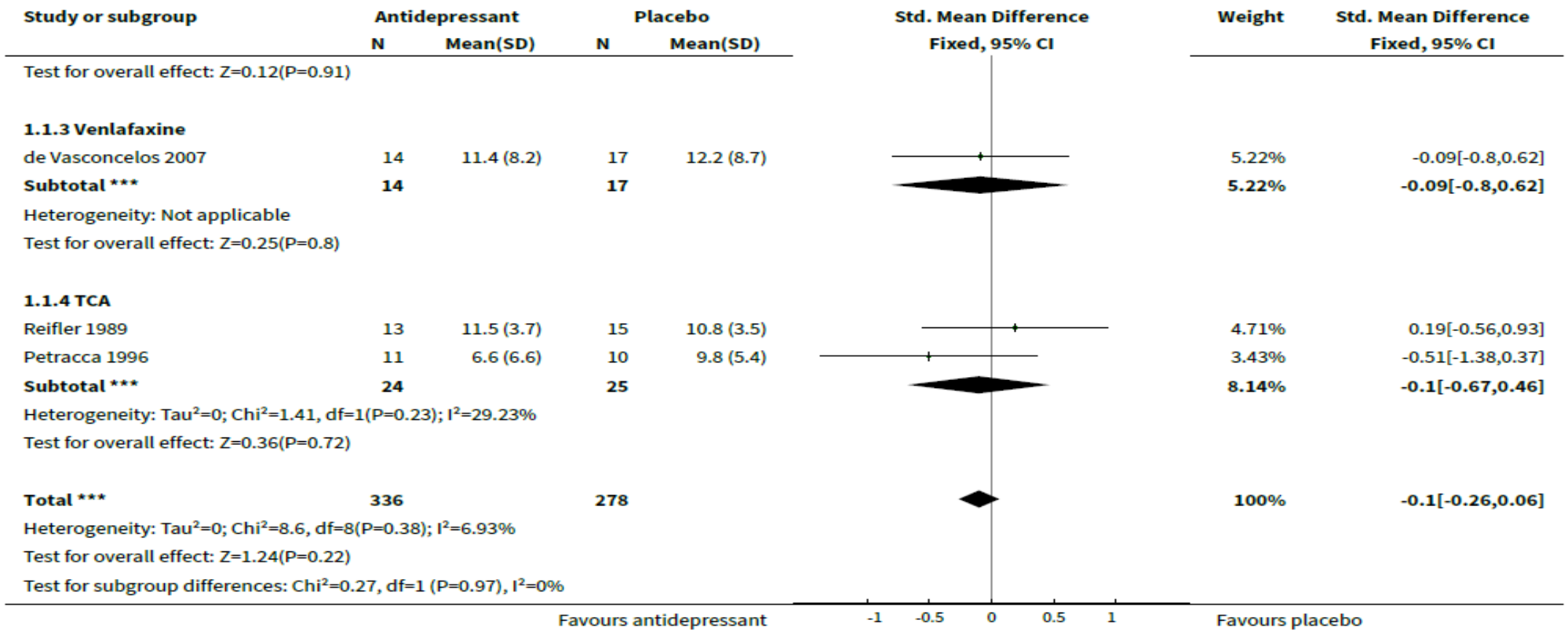
Analysis 1.1. Comparison 1 Antidepressant versus placebo, Outcome 1 Depression endpoint mean scores at 6-13 weeks.

Study or subgroup	Antidepressant N	Antidepressant Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.1.1 SSRIs							
Rosenberg 2010	67	6 (7.2)	64	7.1 (7.9)		22.22%	-0.14[-0.48,0.21]
Petracca 2001	17	9.4 (5.7)	24	10 (5.1)		6.76%	-0.11[-0.73,0.51]
Lyketsos 2003	24	10.3 (7.7)	20	14.9 (5.5)		7%	-0.66[-1.28,-0.05]
Banerjee 2011	78	8.6 (4.9)	46	7.7 (4.1)		19.6%	0.19[-0.17,0.56]
An 2017	27	4.1 (4.5)	33	5.9 (4.8)		9.91%	-0.38[-0.9,0.13]
Subtotal ***	**213**		**187**			**65.49%**	**-0.13[-0.33,0.07]**
Heterogeneity: $Tau^2=0$; $Chi^2=6.91$, df=4(P=0.14); $I^2=42.12\%$							
Test for overall effect: Z=1.26(P=0.21)							
1.1.2 Mirtazapine							
Banerjee 2011	85	7.6 (5)	49	7.7 (4.1)		21.15%	-0.02[-0.37,0.33]
Subtotal ***	**85**		**49**			**21.15%**	**-0.02[-0.37,0.33]**
Heterogeneity: $Tau^2=0$; $Chi^2=0$, df=0(P<0.0001); $I^2=100\%$							



Dudas 2018, Chochrane

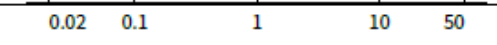
Treatment of MDD in Dementia



Treatment of MDD in dementia

Analysis 1.6. Comparison 1 Antidepressant versus placebo, Outcome 6 Number of patients with remission (ITT) at 6-12 weeks.

Study or subgroup	Antidepressant n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.6.1 SSRI					
Lyketsos 2003	9/24	3/20		14.06%	3.4[0.77,14.93]
Petracca 2001	8/17	8/24		24.14%	1.78[0.5,6.37]
Rosenberg 2010	22/67	12/64		56.65%	2.12[0.94,4.76]
Subtotal (95% CI)	**108**	**108**		**94.85%**	**2.22[1.2,4.12]**
Total events: 39 (Antidepressant), 23 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.45$, df=2(P=0.8); $I^2=0\%$					
Test for overall effect: Z=2.54(P=0.01)					
1.6.2 TCA					
Petracca 1996	9/12	3/12		5.15%	9[1.42,57.12]
Subtotal (95% CI)	**12**	**12**		**5.15%**	**9[1.42,57.12]**
Total events: 9 (Antidepressant), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.33(P=0.02)					
Total (95% CI)	**120**	**120**		**100%**	**2.57[1.44,4.59]**
Total events: 48 (Antidepressant), 26 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=2.44$, df=3(P=0.49); $I^2=0\%$					
Test for overall effect: Z=3.19(P=0)					
Test for subgroup differences: $Chi^2=1.98$, df=1 (P=0.16), $I^2=49.51\%$					



Favours placebo

Favours antidepressant

Treatment of Depressive Symptoms in Dementia

- Metanalysis: 213 studies; 25177 persons with dementia
- Non-Drug Interventions found to be more effective
  - cognitive stimulation (mean difference −2.93, 95% CI −4.35 to −1.52),
  - Cognitive stimulation combined with a cholinesterase inhibitor (−11.39, −18.38 to −3.93),
  - massage and touch therapy (−9.03, −12.28 to −5.88),
  - Multidisciplinary care (−1.98, −3.80 to −0.16),
  - occupational therapy (−2.59, −4.70 to −0.40),
  - exercise combined with social interaction and cognitive stimulation (−12.37,−19.01 to −5.36),
  - reminiscence therapy (−2.30, −3.68 to −0.93).

Watt et al. 2021

Conclusions

- Depressive Symptoms and Major Depressive disorder are common in late life and are associated with cognitive dysfunction.
- Depression in late life should be treated with psychotherapy, pharmacotherapy or Brain Stimulation interventions.
- Depression appears to significantly increase the risk of dementia in late life.
- Specifically late onset depression might carry a higher risk for later dementia and may also be a prodromal syndrome for dementia.
- It might be challenging to diagnose major depression in dementia and observer report might be more reliable.
- Behavioural treatments are first line for treatment of major depression and depressive symptoms in dementia
- Antidepressants should be reserved for treatment of severe depression in dementia.

Questions / Comments

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