Universitair Medisch Centrum Groningen

Cognitieve stoornissen bij depressie

19 mei 2015 – Symposium *'Nooit te oud om te leren!'*
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DISCLOSURE BELANGEN MARIJ ZUIDERSMA

(potentiële) belangenverstrengeling	**Geen**
Voor bijeenkomst mogelijk relevante relaties met bedrijven	
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	• • • •

DEPRESSION IN LATE LIFE

Point prevalence MDD: 7.2%
Point prevalence depressive symptoms: 17.1%

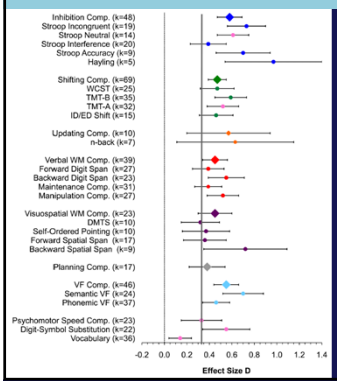
Luppa et al. *JAD* 2012

DEPRESSION AND COGNITIVE DEFICITS

DEPRESSION AND COGNITIVE DEFICITS

Depression – cognitive deficits

DEPRESSION AND COGNITIVE DEFICITS



Relation between MDD and executive function

113 studies
3936 MDD
3771 controls

Snyder, Psychological Bulletin 2013

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Cognitive deficits in MDD

Table 3. Associations between depression status and depression severity with cognitive functioning

	DEPRESSED PERSONS ($n = 378$) MEAN (SE)	NON-DEPRESSED CONTROLS ($n = 132$) MEAN (SE)	F	p	COHEN'S D	ASSOCIATION WITH DEPRESSION SEVERITY β	t	p
Episodic memory								
Immediate recall	31.8 (0.34)	33.4 (0.61)	4.56	0.03	0.24	−0.16	−3.52	<0.001
Delayed recall	5.89 (0.11)	6.37 (0.20)	4.05	<0.05	0.22	−0.14	−2.89	0.004
Z-score episodic memory	−0.04 (0.05)	0.17 (0.08)	5.17	0.02	0.23	−0.16	−3.52	<0.001
Processing speed								
Stroop card I	20.5 (0.28)	19.6 (0.50)	2.19	0.14	0.17	−0.05	−1.08	0.28
Stroop card II	26.6 (0.34)	24.3 (0.61)	10.81	0.001	0.35	−0.22	−4.79	<0.001
Z-score processing speed	−0.05 (0.05)	0.20 (0.08)	6.92	0.01	0.27	−0.15	−3.20	0.001
Interference control								
Z-score interference control	−0.07 (0.05)	0.26 (0.09)	9.57	0.002	0.34	−0.14	−2.98	0.003
Working memory								
Digit span forward	8.17 (0.09)	8.09 (0.16)	0.18	0.68	0.05	−0.10	−2.03	0.04
Digit span backward	5.29 (0.10)	5.41 (0.17)	0.34	0.56	0.06	−0.07	−1.54	0.12
Z-score working memory	0.004 (0.04)	0.013 (0.08)	0.01	0.92	0.01	−0.10	−2.11	0.04

Korten et al. International Psychogeriatrics 2014

DEPRESSION AND COGNITIVE DEFICITS

DEPRESSION AND COGNITIVE DEFICITS

Burden for patient, environment and society
Disability
Institutionalization (Gaugler et al. *BMC Geriatr* 2007; Harris & Cooper, *JAGS* 2006)
Mortality (Cuijpers et al. *JAD* 2002; Sachs et al. *Ann Int Med* 2012)

DEPRESSION AND COGNITIVE DEFICITS

????

DEPRESSION AND COGNITIVE DEFICITS

Overlap in symptoms
Concentration problems
Indecisiveness
Loss of interest/initiative
Psychomotor slowness

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Am J Psychiatry 136:7, July 1979

Pseudodementia

BY CHARLES E. WELLS, M.D.

Pseudodementia is the syndrome in which dementia is mimicked or caricatured by functional psychiatric disorders. The author describes 10 patients with pseudodementia and compares its clinical features with those of true dementia. The syndrome occurred in patients with various psychiatric diagnoses, but a striking feature in most patients was marked dependency. The recognition of this clinical syndrome should obviate the need for many neurological diagnostic studies and lead to earlier and more effective psychiatric treatment.

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"Patients with pseudodementia are at risk of therapeutic neglect and superfluous diagnostic procedures."

DEPRESSION INCREASES RISK OF DEMENTIA

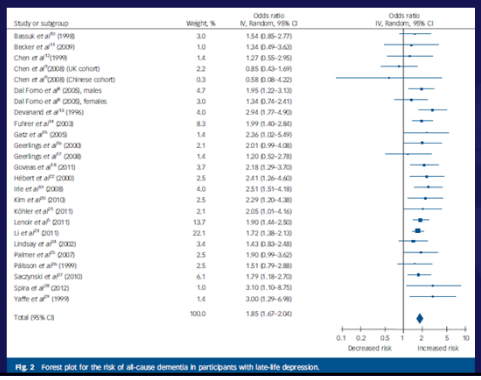


Fig. 2 Forest plot for the risk of all-cause dementia in participants with late-life depression.

Diniz et al. BJP 2013

POPULATION ATTRIBUTABLE RISK OF ALZHEIMER'S DISEASE

	Prevalence*	PAR (95% CI)	Number of attributable cases in 2010 (95% CI)†
Europe			x1000
Diabetes mellitus	6·9%	3·1% (1·4–5·0)	222 (98–364)
Midlife hypertension	12·0%	6·8% (1·9–13·0)	492 (136–934)
Midlife obesity	7·2%	4·1% (2·4–6·2)	299 (172–448)
Physical inactivity	31·0%	20·3% (5·6–35·6)	1461 (401–2564)
Depression	18·5%	10·7% (7·2–14·5)	774 (520–1049)
Smoking	26·6%	13·6% (3·8–24·2)	978 (277–1745)
Low educational attainment	26·6%	13·6% (8·5–18·6)	978 (614–1342)
Combined‡	..	54·0% (27·2–73·7)	3891 (1959–5311)
Adjusted combined§	..	31·4% (15·3–46·0)	3033 (1472–4332)

Norton et al. Lancet Neurology 2014

EXECUTIVE DYSFUNCTION AND LONG-TERM DEPRESSION OUTCOMES

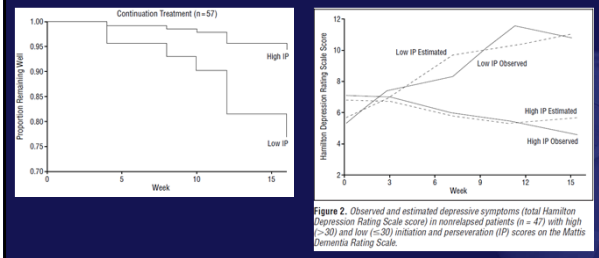
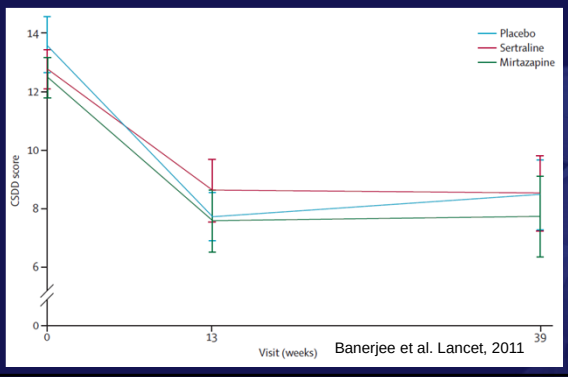


Figure 2. *Observed and estimated depressive symptoms (total Hamilton Depression Rating Scale score) in nonrelapsed patients (n = 47) with high (>30) and low (≤30) initiation and perseveration (IP) scores on the Mattis Dementia Rating Scale.*

Alexopoulos et al. *Arch Gen Psych* 2000

TREATMENT OF DEPRESSION IN DEMENTIA PATIENTS WITH SSRI'S



Banerjee et al. Lancet, 2011

PSYCHOLOGICAL TREATMENT OF DEPRESSION IN DEMENTIA/MCI PATIENTS

Figure 4. Forest plot of comparison: 1 Psychological treatment versus treatment as usual, outcome: 1.1 Depression.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Burgener 2008	3.3	2.9	19	4.3	3.4	14	7.4%	-0.31 [-1.01, 0.38]
Burns 2005	5.4	2.6	20	5.5	3.1	20	9.3%	-0.03 [-0.65, 0.59]
Spector 2012	10.38	5.835	21	16.72	7.283	18	8.0%	-0.95 [-1.62, -0.28]
Stanley 2012	8.2	2.86	11	7.8	5.95	15	5.9%	0.08 [-0.70, 0.86]
Tappen 2009	15.13	9.54	15	19.13	7.37	15	6.8%	-0.46 [-1.18, 0.27]
Waldorff 2012	5.05	4.61	130	5.77	5.07	141	62.7%	-0.15 [-0.39, 0.09]
Total (95% CI)			**216**			**223**	**100.0%**	**-0.22 [-0.41, -0.03]**

Heterogeneity: Chi² = 6.33, df = 5 (P = 0.28); I² = 21%
Test for overall effect: Z = 2.30 (P = 0.02)

Std. Mean Difference IV, Fixed, 95% CI
Favours treatment Favours usual care

Orgeta et al. Cochrane database 2014

TO WHAT EXTENT ARE COGNITIVE DEFICITS A MANIFESTATION OR BYPRODUCT OF DEPRESSION?

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TO WHAT EXTENT IS DEPRESSION A SIGNAL OF BEGINNING COGNITIVE DISORDERS?

REMITTED DEPRESSION AND COGNITIVE PERFORMANCE IN YOUNG AND OLD ADULTS

Meta-analysis by Bora et al. 2013: Cognitive deficits in all domains in remitted patients compared to healthy controls

Cognitive domain	No of studies	MDD (n)	HC (n)	Cohen's d	95% CI	p
Global	30	895	993	0.47	0.38-0.57	<0.001
Processing speed	20	647	745	0.47	0.31-0.64	<0.001
Visual memory	12	393	495	0.54	0.33-0.76	<0.001
Verbal memory	15	428	460	0.48	0.23-0.73	<0.001
Executive function	24	714	794	0.59	0.44-0.74	<0.001
Working memory	14	475	496	0.39	0.20-0.57	<0.001
Attention	10	228	231	0.53	0.33-0.72	<0.001

Bora et al. *Psychological Medicine* 2013

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Processing speed	20	647	745	0.47	0.74	<0.001
Visual memory	12	393	495	0.54	0.60	<0.001
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Attention	10	228	231	0.53	X	<0.001

Onset first episode between 50-65 years: even more pronounced

Bora et al. *Psychological Medicine* 2013

COGNITIVE DEFICITS PERSIST EVEN AFTER REMISSION OF DEPRESSION

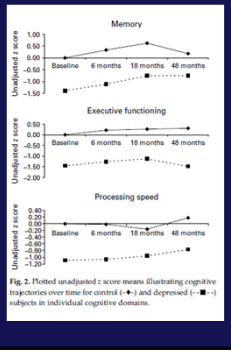
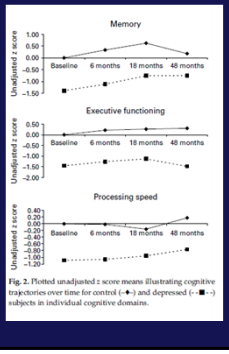


Fig. 2. Plotted unadjusted z score means illustrating cognitive trajectories over time for control (-●-) and depressed (--■--) subjects in individual cognitive domains.

Köhler et al. Psychological Medicine, 2010

COGNITIVE DEFICITS PERSIST EVEN AFTER REMISSION OF DEPRESSION



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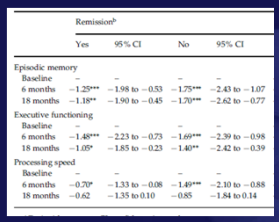

	Remission[b]			
	Yes	95% CI	No	95% CI
Episodic memory				
Baseline	–	–	–	–
6 months	−1.25***	−1.98 to −0.53	−1.75***	−2.43 to −1.07
18 months	−1.18**	−1.90 to −0.45	−1.70***	−2.62 to −0.77
Executive functioning				
Baseline	–	–	–	–
6 months	−1.48***	−2.23 to −0.73	−1.69***	−2.39 to −0.98
18 months	−1.05*	−1.85 to −0.23	−1.40**	−2.42 to −0.39
Processing speed				
Baseline	–	–	–	–
6 months	−0.70*	−1.33 to −0.08	−1.49***	−2.10 to −0.88
18 months	−0.62	−1.35 to 0.10	−0.85	−1.84 to 0.14

Köhler et al. Psychological Medicine, 2010

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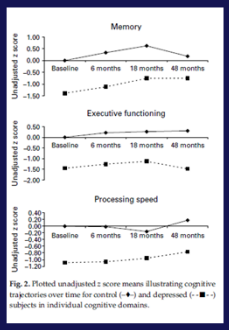

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Köhler et al. Psychological Medicine, 2010
Also:
Douglas and Porter, Aust N.ZJ Psych 2009
Bhalla et al. Am J Ger Psych 2006
Maeshima et al. J Aff Disorders 2013
O'Brien et al. Am J Psych 2004
Portella et al. Int J Ger Psych 2003

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DO COGNITIVE DEFICITS PERSIST EVEN WHEN DEPRESSION REMITS?

NESDO
Netherlands Study on Depression in Older Persons

DEPRESSION AND COGNITIVE DEFICITS

CROSSECTIONAL ASSOCIATIONS

NESDO
Netherlands Study on Depression in Older Persons

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Z-score episodic memory	−0.04 (0.05)	0.17 (0.08)	5.17	0.02	0.23	−0.16	−3.52	<0.001
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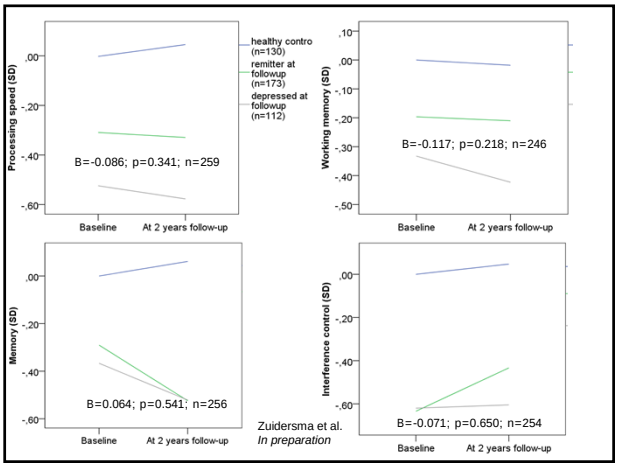
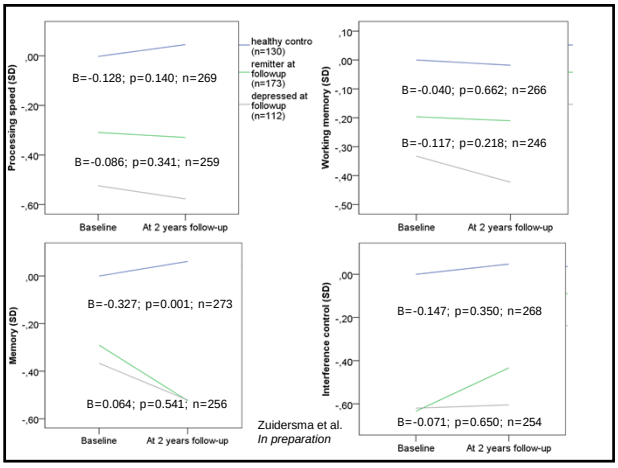
Korten et al. International Psychogeriatrics, 2014



Zuidersma et al.
In preparation



Zuidersma et al.
In preparation

COGNITIVE DEFICITS PERSIST EVEN AFTER REMISSION OF DEPRESSION

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Potential explanations

-Depressed group may have contained preclinical Alzheimer's disease

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-Depressed group may have contained preclinical Alzheimer's disease

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-Common underlying mechanism (vascular lesions, white matter hyperintensities)

ARE COGNITIVE DEFICITS A MANIFESTATION OR BYPRODUCT OF DEPRESSION?

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NOT ALWAYS

ARE COGNITIVE DEFICITS A MANIFESTATION OR BYPRODUCT OF DEPRESSION?

NOT ALWAYS

IS IT REALLY DEPRESSION?

DEPRESSION INSTRUMENTS MEASURE ONLY DEPRESSION?

DEPRESSION INSTRUMENTS MEASURE ONLY DEPRESSION?

Depression

Something else: beginning cognitive problems?

'DEPRESSIVE' SYMPTOM PROFILE AND COGNITIVE DEFICITS IN 303 OLDER PERSONS WITHOUT DEPRESSION

Backman et al. J Abnorm Psychol 1996

'DEPRESSIVE' SYMPTOM PROFILE AND COGNITIVE DEFICITS IN 303 OLDER PERSONS WITHOUT DEPRESSION

Factor analysis on 8 DSM symptoms of depression

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Mood-related symptoms
- Dysphoria
- Appetite disturbance
- Feelings of guilt
- Suicidal thoughts

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Motivation-related symptoms
- Lack of interest
- Concentration difficulties
- Psychomotor change
- Loss of energy

Backman et al. J Abnorm Psychol 1996

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Factor analysis on 8 DSM symptoms of depression

Mood-related symptoms	Motivation-related symptoms
- Dysphoria	- Lack of interest
- Appetite disturbance	- Concentration difficulties
- Feelings of guilt	- Psychomotor change
- Suicidal thoughts	- Loss of energy

Table 3
Correlations Among Independent and Dependent Variables

Variable	1	2	3	4	5	6	7	8	9
1. Age	—	−.08	.10	.00	−.01	−.23**	−.23**	−.28**	−.27**
2. Education		—	−.23**	−.05	−.02	.20**	.24**	.28**	.20**
3. Gender*			—	.08	.13*	−.03	−.02	−.07	−.01
4. Mood-related symptoms				—	.12*	−.08	−.11	−.12*	−.11
5. Motivation-related symptoms					—	−.19**	−.19**	−.12*	−.12*
6. FR–RR						—	.51**	.48**	.39**
7. FR–SR							—	.55**	.51**
8. FR–O								—	.75**
9. CR–O									—

Note. FR = free recall; RR = rapidly presented random words; SR = slowly presented random words; O = organizable words; CR = cued recall.
* Men were coded as 1, and women were coded as 2.
* $p < .05$. ** $p < .01$.

Backman et al. J Abnorm Psychol 1996

‘DEPRESSIVE’ SYMPTOM PROFILE AND PRESENCE OF ALZHEIMER IN NON-DEPRESSED OLDER PERSONS

TABLE 3. Symptoms of depression reported by the collateral sources of controls and subjects with DAT according to the CDR scale.

	Initial evaluation		15-Month evaluation			34-Month evaluation		
	Controls	CDR 1	Controls	CDR 1	CDR 2	Controls	CDR 1	CDR 2
n =	58	44	55	16	13	51	6	10
Dysphoria (%)	16	39	2	19	25	10	0	30
Appetite disturbance (%)	5	11	4	19	8	2	0	0
Sleep disturbance (%)	16	14	11	13	15	14	0	30
Energy (%)	14	52**	11	56*	46	16	50	70
Psychomotor change (%)	5	27	7	50*	67**	12	33	40*
Loss of interest (%)	0	39**	0	56**	77**	2	40	70**
Guilt (%)	0	11	0	13	0	0	17	20
Thinking/concentration disturbance (%)	2	86**	2	100**	100**	4	100**	90**
Thoughts of death or suicide (%)	2	20	0	6	31*	0	20	20

Comparisons between controls and subjects with dementia were made using Fisher's exact χ^2. * $p \leq 0.001$, ** $p \leq 0.0001$.

Burke et al. Alzheimer’s disease and associated disorders, 1988

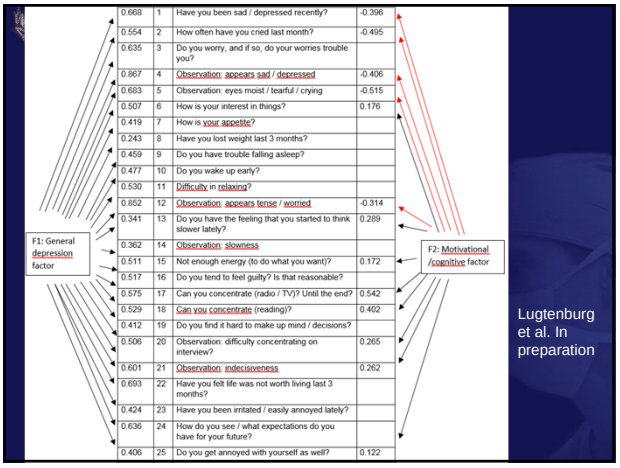
DEPRESSION AND COGNITIVE DEFICITS

Overlap in symptoms
Concentration problems
Indecisiveness
Loss of interest/initiative
Psychomotor slowness

AMSTERDAM STUDY OF THE ELDERLY (AMSTEL)

- N=1908 older persons from general population
- No dementia, no cognitive problems
- GMS agecat to assess depressive symptoms
- 2 years later: incident dementia assessed (n=93 cases)
- **Bifactor analysis on depressive symptoms**

Lugtenburg et al. In preparation



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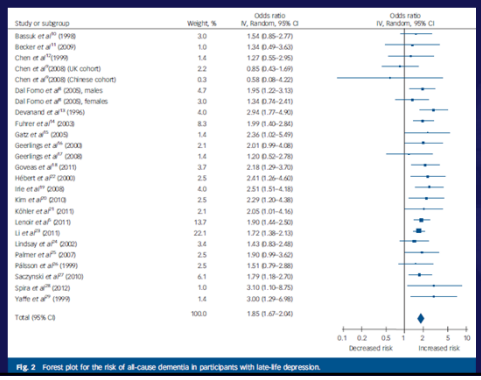
DEPRESSION INSTRUMENTS MEASURE ONLY DEPRESSION?

Depression

Something else: beginning cognitive problems?

DEPRESSION INCREASES RISK OF DEMENTIA



Diniz et al. BJP 2013

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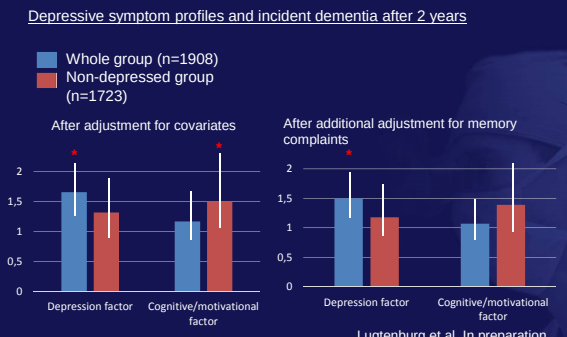


Lugtenburg et al. In preparation

SWEDISH NATIONAL STUDY ON AGING AND CARE IN *KUNGSHOLMEN* (SNAC-K)

- N=2690 older persons from general population
- No dementia, no cognitive problems at baseline
- MADRS to assess depressive symptoms
- **Bifactor analysis on depressive symptoms**
- At baseline and 6 years later: cognitive performance

Zuidersma et al. In preparation

SWEDISH NATIONAL STUDY ON AGING AND CARE IN *KUNGSHOLMEN* (SNAC-K)

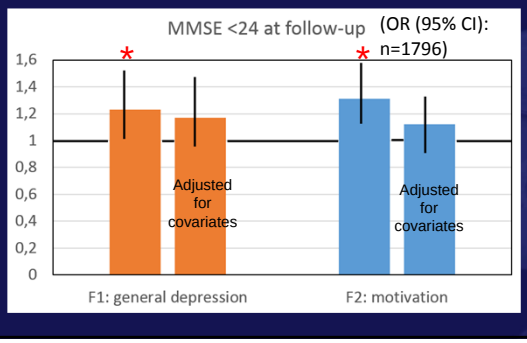
n=2690

0.84*	Depression	-0.20*
0.61*	Anxiety thoughts	
0.34*	Sleep disturbance	
0.55*	Reduced appetite	0.30*
0.58*	Concentration	
0.60*	Lassitude / lack of initiative	0.48*
0.72*	Inability to feel	
0.75*	Pessimistic thoughts	-0.17*
0.81*	Suicidal thought	
0.77*	Depression observed	-0.23*

General depression Factor

Motivation factor

SWEDISH NATIONAL STUDY ON AGING AND CARE IN *KUNGSHOLMEN* (SNAC-K)



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SUMMARY

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- Cognitive deficits persist even after remission of depression
- Motivational and cognitive symptoms of 'depression' occur in non-depressed older people with cognitive deficits
- In older people from the general population depression instruments capture variance due to depression and variance unrelated to depression (dominated by motivational/cognitive symptoms)
- Both depression and reduced motivation in the absence of depression are related to an increased risk of dementia and cognitive decline

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Case – Bep, 66 years

CASE: BEP, 66 YEARS

Intake

Complaints:
- loss of initiative
- loss of energy
- Rumination
- Tense
- stopped hobbies

IDS-total score: 45

16 wk treatment with 20 mg Citalopram of GP doesn't help

→ Conclusion after intake: moderate to severe depressive disorder with comorbid generalized anxiety disorder

CASE: BEP, 66 YEARS

START TREATMENT AT UCP
- Shortly after intake complete loss of daily structure

→ Start CBT treatment
→ Citalopram → duloxetine

COGNITIVE SCREENING
- No subjective cognitive complaints
- Father known with Alzheimer's disease at age 50-60
- MMSE 27/30
- CAMCOG 88/102

→ No indication for cognitive disorder

CASE: BEP, 66 YEARS

EFFECTIVITY CBT
- IDS: 45 → 38
- Discrepancy between sessions and home
- Subjective complaints of memory and planning (housework and new telephone)

→ Not effective

CASE: BEP, 66 YEARS

MEMORY CLINIC
- Increasing deficits in memory and planning → not enough for MCI or dementia
- No neurological abnormalities
- No abnormalities in liquor (β-amyloid-42, total tau, phosphorylated tau)

→ Memory and executive deficits not large enough for MCI or dementia
→ Alzheimer's disease unlikely

CASE: BEP, 66 YEARS

FOLLOW-UP POLICY: DULOXETINE → NORTRYPTILINE

→ IDS 38 → 18
→ Bep feels well
→ Husband still complains about loss of initiative / being passive

Additional information from liquor: abnormal β-amyloid-40
→ Risk factor for Alzheimer's disease

CASE: BEP, 66 YEARS

DEPRESSIVE SYMPTOM PROFILES

	START	DULOXETINE	NORTRIPTYLINE
SOMSCORE	45	38	18
Somber voelen	■	■	
Angstig of gespannen voelen	■		
Gedachten aan de dood en zelfmoord	■	■	
Negatieve toekomstverwachtingen	■	■	
Negatief zelfbeeld	■	■	
Te vroeg ontwaken			
Inslaapproblemen	■	■	
Prikkelbaar voelen			
Verminderde eetlust	■	■	
Gewichtsafname			
Concentratieproblemen / besluiteloos	■	■	■
Algemene interesse			■
Gebrek aan energie	■	■	■
Zwaar gevoel of gebrek aan energie.	■	■	■
Traagheid in denken, spreken, bewegen		■	■
Pijnklachten	■	■	■
Overige lichamelijke klachten			
Verstopping en/of diarree	■	■	■
Gevoeligheid voor afwijzing anderen			
Slaapproblemen gedurende de nacht			
Teveel slapen	■	■	■
Geen reactieve stemming	■		
Dagschommeling stemming			
Andere kwaliteit van de stemming	■		
Toegenomen eetlust			
Gewichtstoename afgelopen 2 weken			
Geen plezier ervaren en/of genieten	■		
Afgenomen belangstelling voor seks	■	■	■

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- Clinicians must take cognitive deficits in depressed older persons seriously

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- Cognitive deficits are not merely a manifestation of depression
- Clinicians must take cognitive deficits in depressed older persons seriously
- Both depression and a specific 'depressive' symptom profile dominated by loss of initiative and absence of low mood are associated with cognitive decline

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Thank you

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