University Medical Center Groningen

university of groningen

Depressed of just old?

The balance between frailty and mental health

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European Association of Geriatric Psychiatry (EAGP)

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The concept of frailty[1,2]

A **decrease in reserve capacity** of

different **physiological systems and organs**,

that a relatively **minor stressor**

can **disturb homeostasis** of the body

and lead to serious **adverse health consequences**.

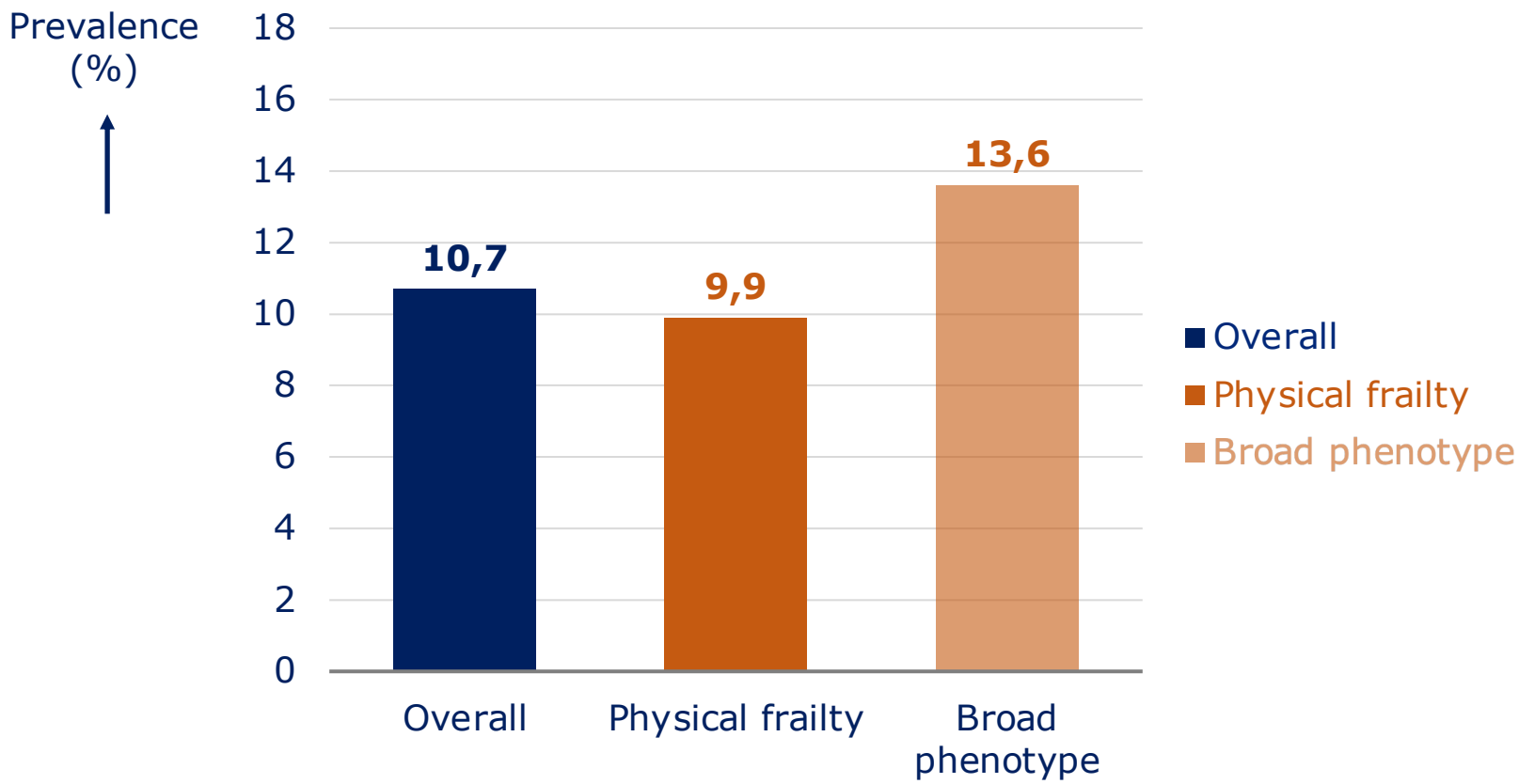
[1] Collard & Oude Voshaar, Tijdschr Psychiatrie 2011

[2] Hoogendijk et al, Lancet 2019

Frailty – a key concept in geriatric medicine[1]

- Identify patients at risk for adverse effects, dependency & death.
- To adjust medical treatment to prevent complications.

Meta-analysis: Prevalence of frailty[1]



[1] Collard et al, JAGS 2013

Two frailty became dominant in the literature

Kenneth Rockwood

Accumulation of
health deficits

Linda Fried

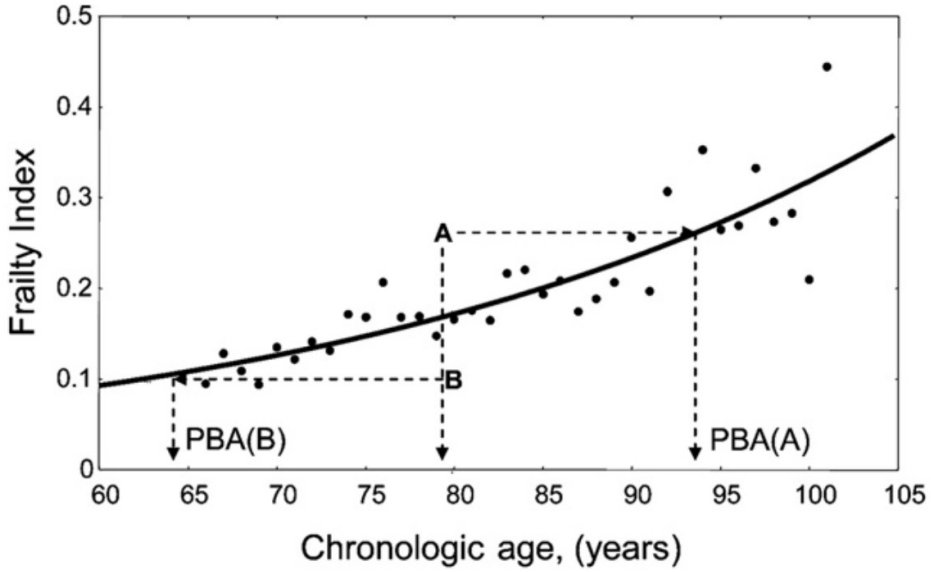
Biomedical
frailty syndrome

Kenneth Rockwood - Frailty index (FI)[1-3]

Biological ageing is a stochastic accumulation of health deficits

Frailty Index (FI, range 0 – 1)[1,2]

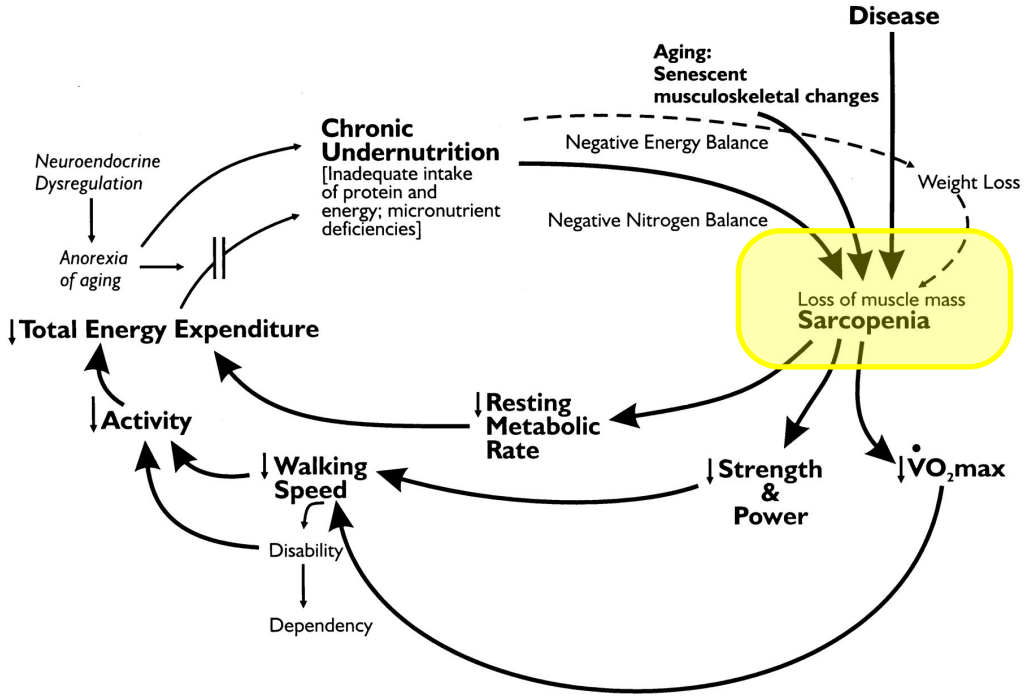
- FI = proportion of potential deficits
- FI ≥0.25 = frail
- Representative of biological age[3]



[1] Rockwood & Mitnitski, Clin Geriatr Med 2011
[2] Searle et al, BMC Geriatrics 2008
[3] Diebel & Rockwood, Current Oncology Reports 2021

Linda Fried - Frailty Phenotype[1]

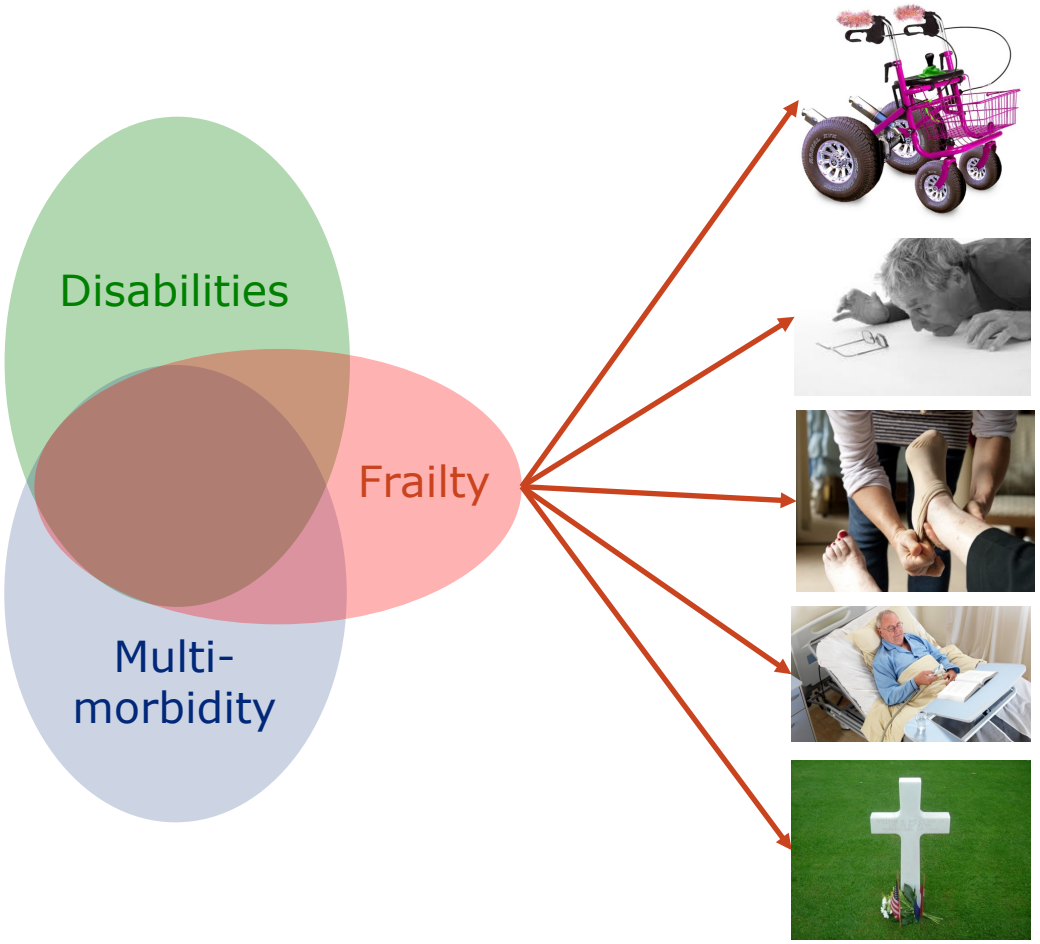
A physiological state of multisystem and energy dysregulation



Criteria (≥3/5 = frail):
1. Unintentional weight loss
2. Exhaustion/poor endurance
3. Weakness (muscle strength)
4. Slowness
5. Low physical inactivity

[1] Fried et al, J Gerontol Biol Sci Med Sci 2001

Validating the Physical Frailty Phenotype[1]

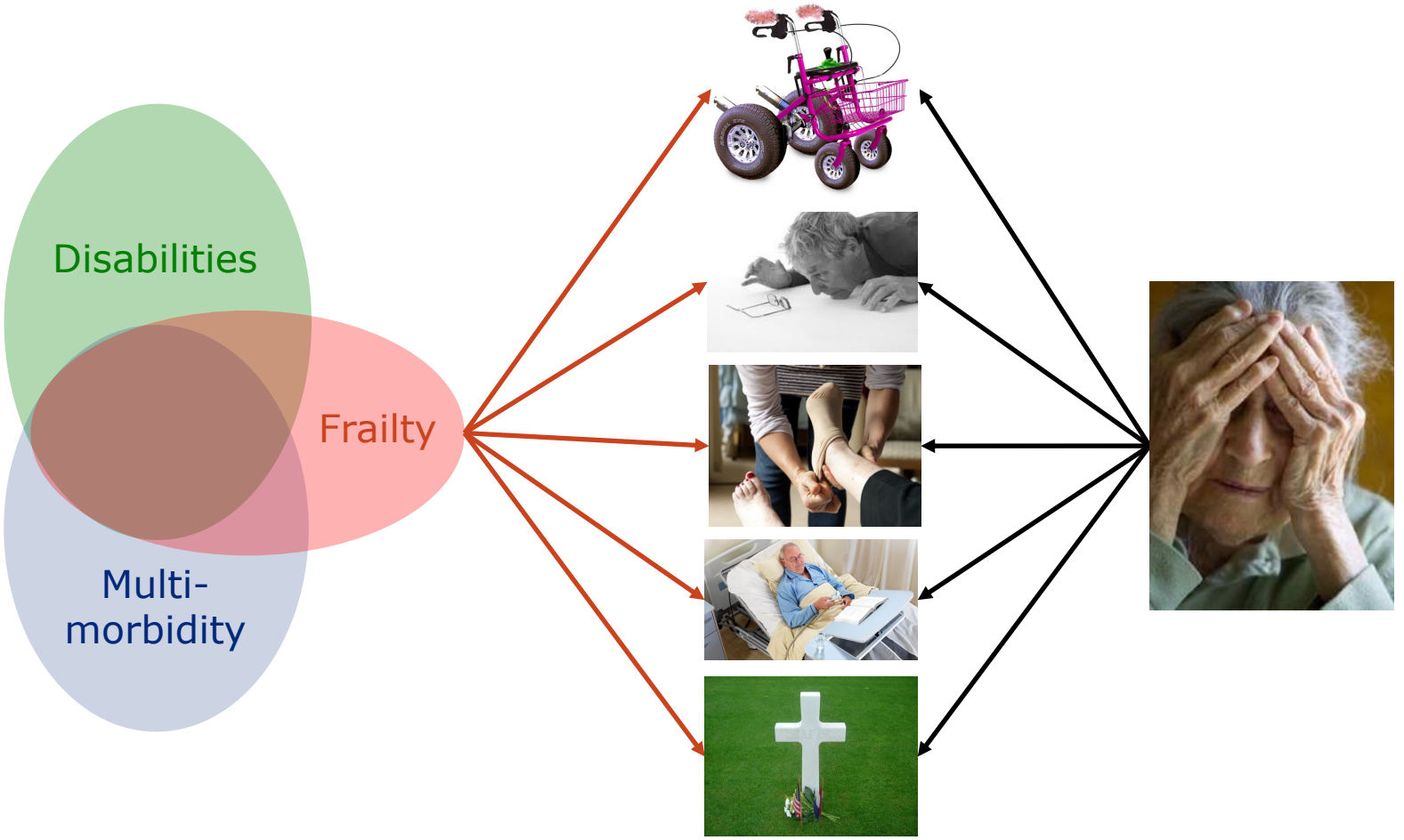


[1] Fried et al, J Gerontol A Biol Sci Med Sci 2001

[2] Mezuk et al, Int J Geriatr Psychiatry 2011

Validating the Physical Frailty Phenotype[1]

or validating depression?[2]



[1] Fried et al, J Gerontol A Biol Sci Med Sci 2001

[2] Mezuk et al, Int J Geriatr Psychiatry 2011

Two sides of the same coin?[1]

Determinants

Depressive disorder (DSM-IV criteria)

Depressed mood	Anhe-donia	Concen-tration	Death thoughts	Guilt	Sleep	Loss of appetite	Tired	Motor activity	Weight loss	Fatigue	Slowness	Weakness	Energy expense

Frailty (Fried criteria)

Consequences

[1] Mezuk et al, Am J Geriatr Psychiatry 2012

Depression & frailty a reciprocal relationship[1]

Systematic review & meta-analysis of 24 cohort studies

Frail older persons:

- Prevalence of depression: 39 %
- Incidence of depression: OR=1.9 [95% CI: 1.6–2.3]

Depressed older persons:

- Prevalence of frailty: 40 %
- Incidence of frailty: OR=3.7 [95% CI: 2.0–7.1]

[1] Soyal et al, Ageing Res Reviews 2017

Datasets underlying my lecture

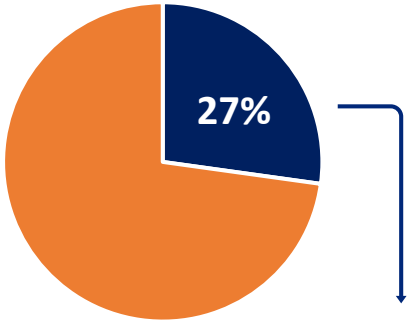
Netherlands Study of Depression in Older persons (NESDO):

- 378 depressed patients (DSM-IV criteria) aged ≥60 years
- 132 never-depressed older persons
- Follow-up for 6 years

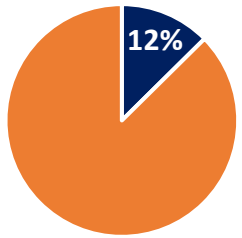
The LifeLines cohort study:

- Population-based cohort (n~150,000 adults) in the Northern Netherlands
- Depressive and anxiety disorders (DSM-IV criteria)
- Follow-up for 30 years (of which the 10-year follow-up is completed)

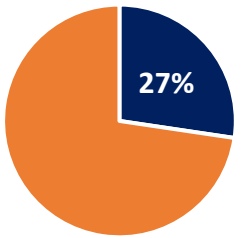
Prevalence of frailty in depressive disorder (DSM-IV)[1,2]



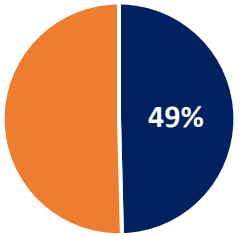
NESDO (n=378, 60+): Frail-depressed[1,2]



60-64 years



65-79 years



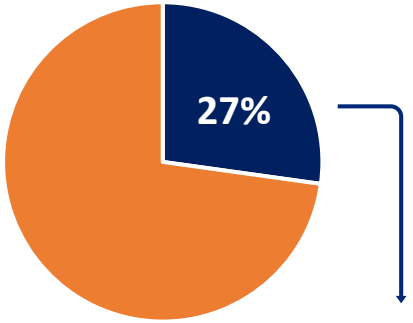
80+

Significantly more ($p<.05$) than 1 out of 10 persons in the population[2]

[1] Collard, … , Oude Voshaar, Ageing Ment Health 2014

[2] Collard, … , Oude Voshaar, J Am Geriatr Soc 2012

Prevalentie frailty bij depressie volgens DSM-criteria[1,2]



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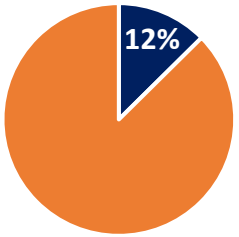
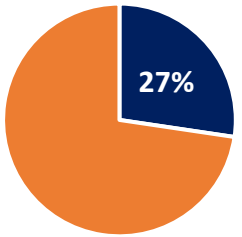
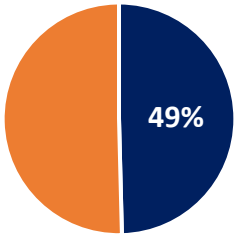


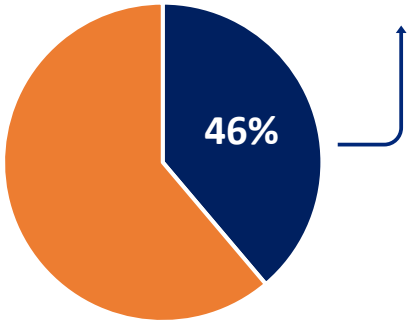
60-64 years

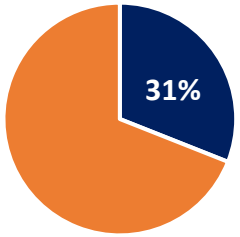


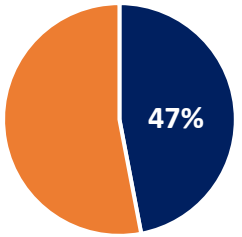
65-79 years

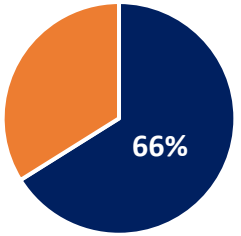


80+









[1] Collard, … , Oude Voshaar, Ageing Ment Health 2014

[2] Oude Voshaar et al, Int J Geriatr Psychiatry 2022

Clinical relevance of frailty in depression

- **Accelerated ageing**
- Mortality rate[1]
- Risk of falling
- Prognosis of depression
- Frailty management in mental health care

[1] Miloyan & Fried, World Psychiatry 2017

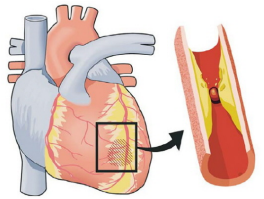
Clinical relevance - Depression and accelerated ageing[1,2]

RR=1.8
[1.6 – 2.1]

RR=1.6
[1.4 – 1.9]

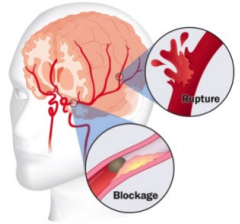
RR=1.1
[1.0 – 1.2]

RR=1.8
[1.5 – 2.2]



RR=1.7
[1.3 – 1.8]

RR=1.3
[1.2 – 1.5]

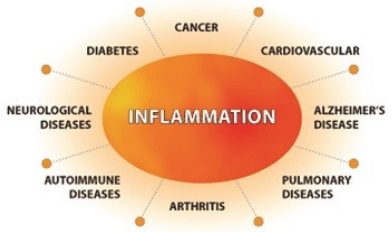


[1] Penninx et al, BMC Psychiatry 2013
[2] Miloyan & Fried, World Psychiatry 2017

Depression as a condition of accelerated ageing[1-8]

Depression → Incident somatic diseases & mortality[1]

↳ mediating mechanisms ↗



Low-graded inflammation[2,3,4]

Shortened telomere length[5,6,7]

Vitamin D deficiency[8]

[1] Penninx et al, BMC Psychiatry 2013
[2] Dowlati et al, Biol Psychiatry 2010
[3] Liu et al, J Affect Disord 2012
[4] Rottenberg et al, Biol Psychol 2007
[5] Monroy et al, World J Biol Psych 2017
[6] Lin et al, J Psychiatr Res 2016
[7] Darrow et al, Psychosom Med 2016
[8] Ju et al, J Nutr Health Aging 2013

Ageing-related biomarkers in NESDO: Not associated with depressive disorder[1-6]

No difference between depressed patients (n=378) and controls (n=132)

Low-graded inflammation[1,2,3]

- hsCRP[1,3]
- IL-6[1,3]
- GDF-15[2,3]

Leucocyte telomere length[4]

Vitamin D only cross-sectional[5,6]

[1] Vogelzangs et al, Brain Behav Immun 2014
[2] Teunisse et al, J Psychosom Res 2016
[3] Rozing et al, Psychoneuroendocrinol 2018
[4] Schaakxs et al, Am J Geriatr Psychiatry 2015
[5] Derks et al, Transl Psychiatry 2015
[6] Van den Berg et al, J Psychosom Res 2016

Ageing biomarkers in NESDO: Associated with frailty severity in depression[1-3]

Fully adjusted linear regression in depressed older patients (n=378):

Low-graded inflammation:

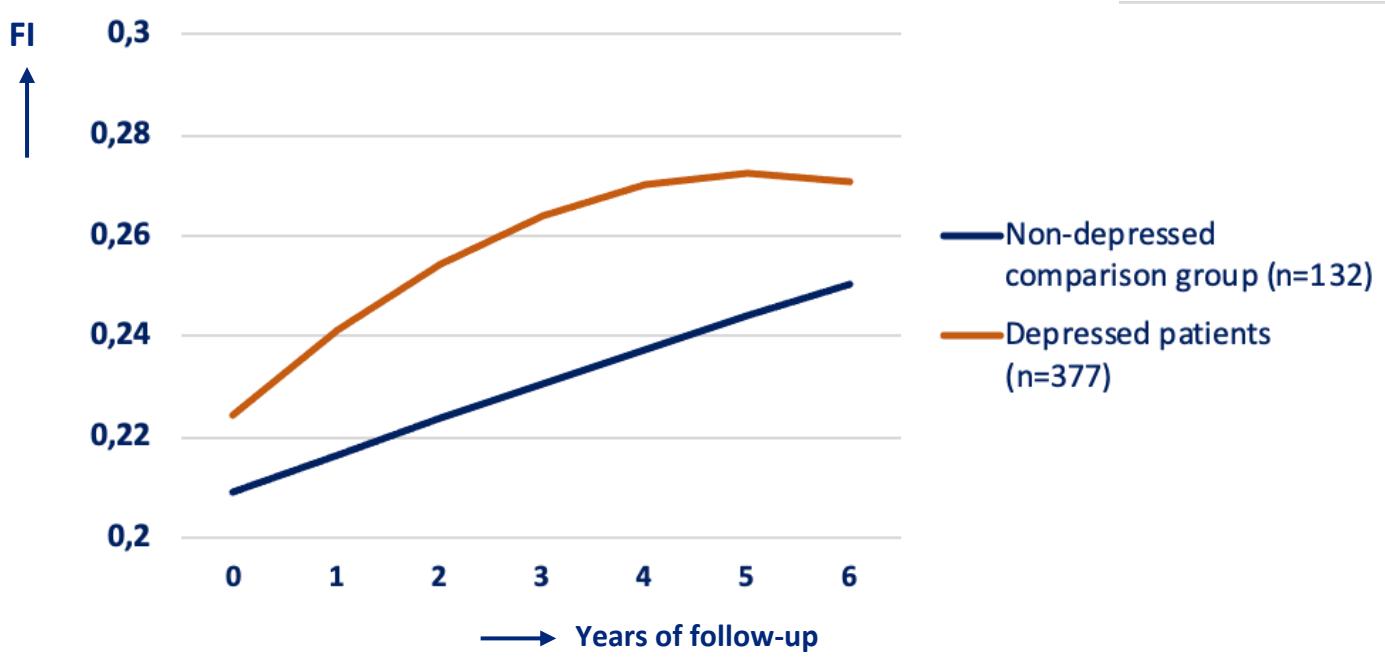
- hsCRP (β=.14, p=.031)[1]
- IL-6 (β=.13, p=.060)[1]
- NGAL (β=.14, p=.028)[1]

Telomere length (β=-.10, p=.048)[2]

Vitamin D level (β=-.15, p<.001)[3]

[1] Arts, … , Oude Voshaar, J Am Geriatr Soc 2015
[2] Arts, … , Oude Voshaar, Exp Gerontology 2018
[3] Vd Berg, … , Oude Voshaar, Ageing Ment Health 2018

Depression and accelerated ageing in NESDO[1]



Significant interaction terms of **time by group (p=.030)** and **time² by group (p=.033)** in **linear mixed models** adjusted for for age, sex, education, smoking, alcohol, physical activity, WC, cognition, somatic diseases, and depression severity

[1] Oude Voshaar et al, submitted

Depression and accelerated ageing in LifeLines[1]

Determinants of frailty severity (FI) at 5-year follow-up by linear regression adjusted frailty severity at baseline and potential confounders*

	Younger adults (≤59 years, n=77,036)		**Older adults** (60+ years, n=14,490)	
	β	*P*-value	β	*P*-value
• Depressive disorder	0.03	<.001	0.04	<.001
• Any anxiety disorder	0.02	<.001	0.01	.421

* Adjusted for age, sex, level of education, physical activity, BMI, alcohol, smoking, living alone (in addition to frailty severity at baseline, depressive disorder and any anxiety disorder)

[1] Borges, … , Oude Voshaar, JAGS 2022

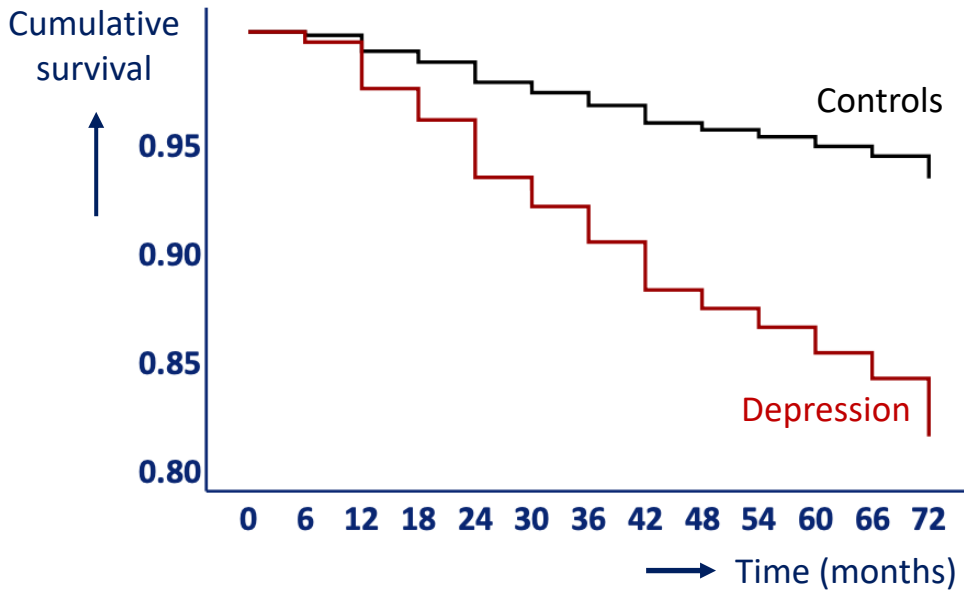
Prognostic and clinical relevance of frailty in depression

- Accelerated ageing
- **Mortality rate[1]**
- Risk of falling
- Prognosis of depression
- Frailty management in mental health care

[1] Miloyan & Fried, World Psychiatry 2017

NESDO: 6-year mortality risk of late-life depression[1]

Unadjusted analysis:

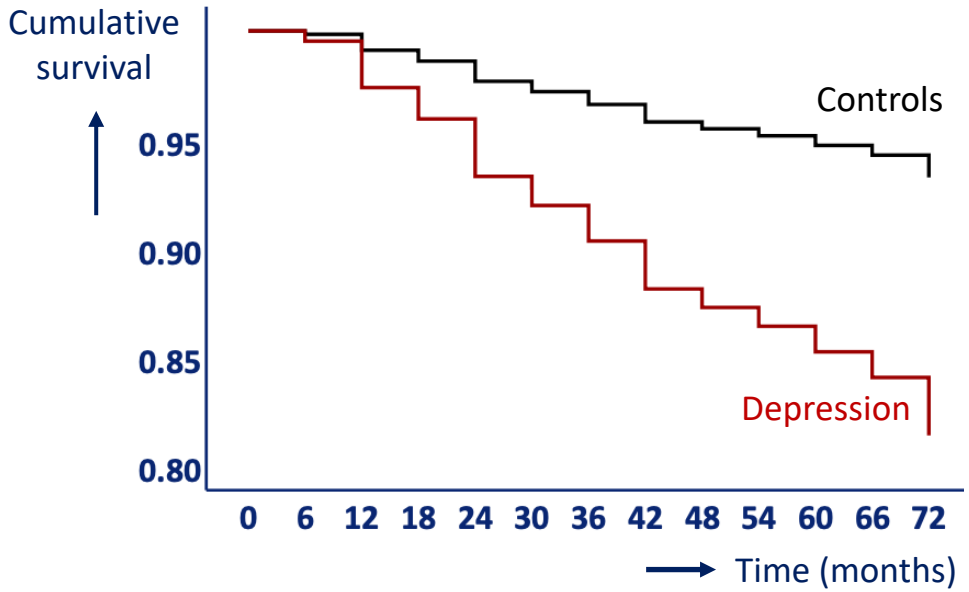


HR=3.0 [1.4 - 6.2], p=.004

[1] Jeuring, Oude Voshaar, et al, Am J Geriatr Psychiatry 2018

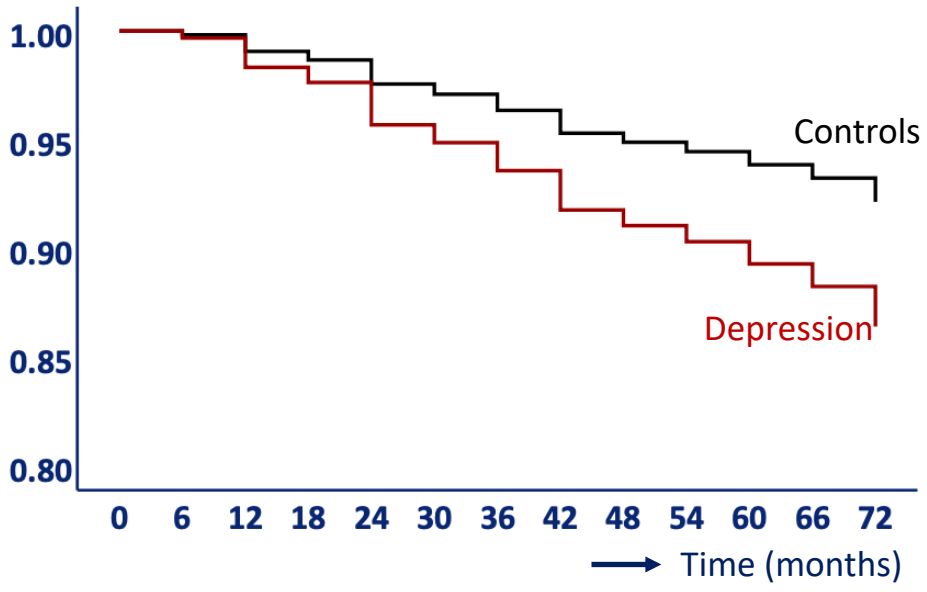
NESDO: 6-year mortality risk of late-life depression[1,2]

Unadjusted analysis:



HR=3.0 [1.4 - 6.2], p=.004

Adjusted for demographics, lifestyle & health:

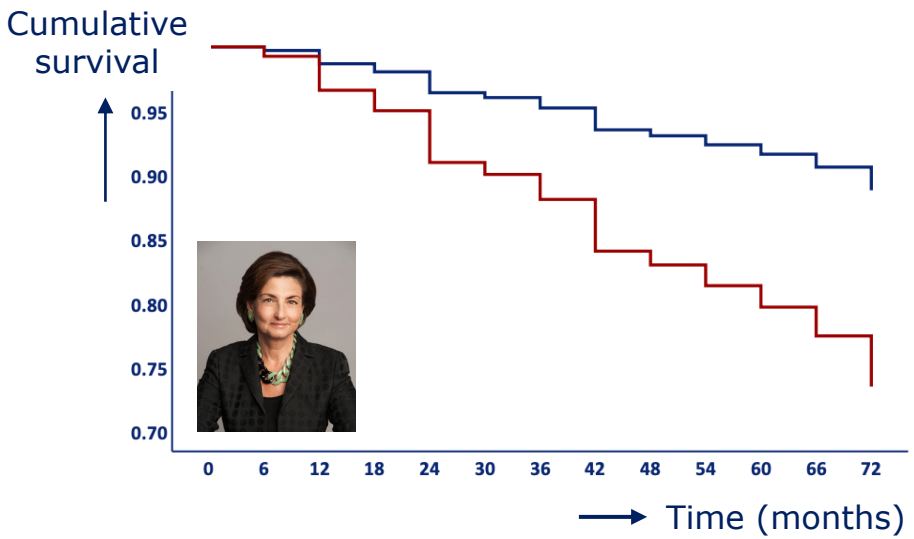


HR=1.8 [0.8 – 3.9], p=.162

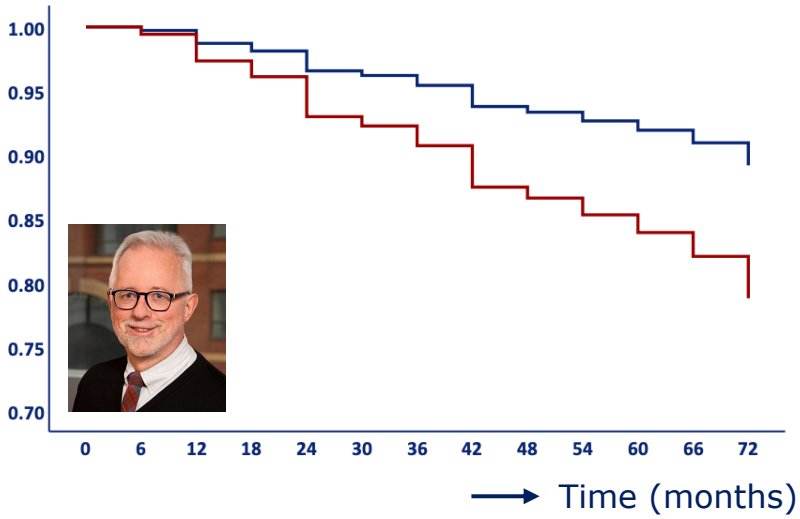
[1] Jeuring et al, Am J Geriatr Psychiatry 2018
[2] Van den Berg et al, Ageing Ment health 2020

NESDO: Does frailty predicts mortality in depression?[1,2]

HR_{FFP} = 2.9 [1.5 – 5.7], p=.002*



HR_{FI} = 2.0 [1.1 – 3.6], p=.026*



* Adjusted for age, sex, education, alcohol, smoking, physical activity, BMI, depression severity, somatic diseases & medication count

[1] Arts, …, Oude Voshaar, J Clin Psychiatry 2021
[2] Oude Voshaar et al, Int J Geriatr Psychiatry 2022

Does frailty in depression predicts mortality1,2

But, inflammatory markers:

- HR_{hsCRP} = 1.5 [1.1 – 1.9], p=.003
- $HR_{IL\text{-}6}$ = 1.2 [0.9 – 1.6], p=.132
- HR_{NGAL2} = 1.5 [1.2 – 1.8], p=.001

vitamin D:

- HR_{vitD} = 0.6 [0.4 – 0.8], p=.002

& leucocyte telomere length:

- HR_{LTL} = 0.7 [0.5 – 0.9], p=.007

also predict mortality in depression!

[1] Arts, …, Oude Voshaar, J Clin Psychiatry 2021
[2] Oude Voshaar et al, Int J Geriatr Psychiatry 2022

Does frailty in depression predicts mortality1,2

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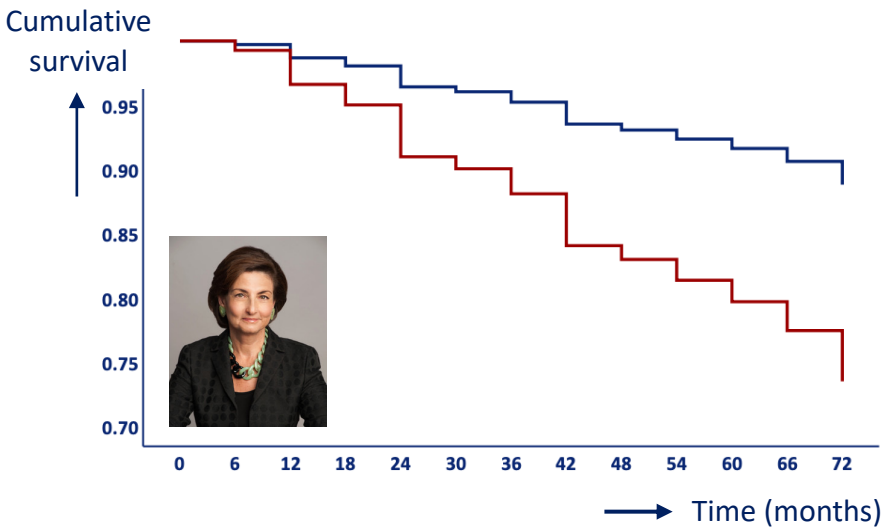

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[1] Arts, …, Oude Voshaar, J Clin Psychiatry 2021
[2] Oude Voshaar et al, Int J Geriatr Psychiatry 2022

Lifelines: Frailty explains excess mortality in depression[1]

10-year	Model 1		Model 2		Model 3		Model 4	
Mortality rate	HR	[95% CI]	HR	[95% CI]	HR	[95% CI]	HR	[95% CI]
Younger people:								
○ Depressive disorder	**2.7**	**[2.0-3.5]***	**2.1**	**[1.5-3.0]***	**2.0**	**[1.4-2.8]***	**1.6**	**[1.1-2.2]***
Older people:								
○ Depressive disorder	1.1	[0.6–1.8]	1.0	[0.5–1.7]	0.9	[0.5- 1.6]	0.7	[0.6-1.2]

Model 1: Adjusted for demographics (age, sex & level of education)

Model 2: Adjusted for demographics & lifestyle (smoking, alcohol, physical activity, smoking)

Model 3: Adjusted for demographics, lifestyle & multimorbidity

Model 3: Adjusted for demographics, lifestyle, multimorbidity & frailty

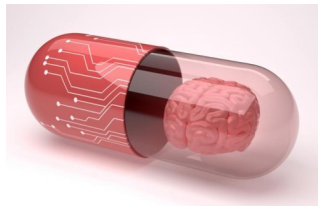
[1] Oude Voshaar et al, Eur Psychiatry 2021

Prognostic and clinical relevance of frailty in depression

- Accelerated ageing
- Mortality rate[1]
- **Risk of falling**
- Prognosis of depression
- Frailty management in mental health care

[1] Miloyan & Fried, World Psychiatry 2017

Clinical relevance frailty in depression II - Fall risk[1]



[1] Aprahamian, Oude Voshaar, et al, Aging Ment Health 2020

Impact of frailty on fall risk of SSRI's[1]

One-year, naturalistic FU study in geriatric outpatients (n=811):

- 82 years
- 73% females
- 38% frail
- 19% depressed (DSM-criteria)
- 31% GDS ≥6
- 37% uses an SSRI

Condition:	OR [95% B.I.]*	P-value
• No frailty, no SSRI	1.0 [REF]	-
• Frailty	1.3 [1.1 – 1.6]	.001
• SSRI	1.5 [1.3 – 1.8]	<.001
• **Frailty with SSRI**	**2.7 [2.5 – 2.9]**	**<.001**

* Adjusted for age, sex, level of education, depression, chronic somatic diseases, and medication.

[1] Aprahamian, Oude Voshaar, et al, Aging Ment Health 2020

A further case for integrated care in mental health care[1]

Psychiatric inpatients (n=178) at increased risk of geriatric syndromes compared to patients (n=687) hospitalized in a general hospital (adjusted for age and sex):

- OR_{falls} = 1.7 [1.2 – 2.6]
- $OR_{malnutrition}$ = 4.1 [2.7 – 6.4]
- $OR_{delirium}$ = 6.5 [4.2 – 9.9]
- $OR_{physical\ impairment}$ = 1.4 [0.9 – 2.1]

[1] Douiairi, Oude Voshaar, et al, J Frailty Aging 2023

Prognostic and clinical relevance of frailty in depression

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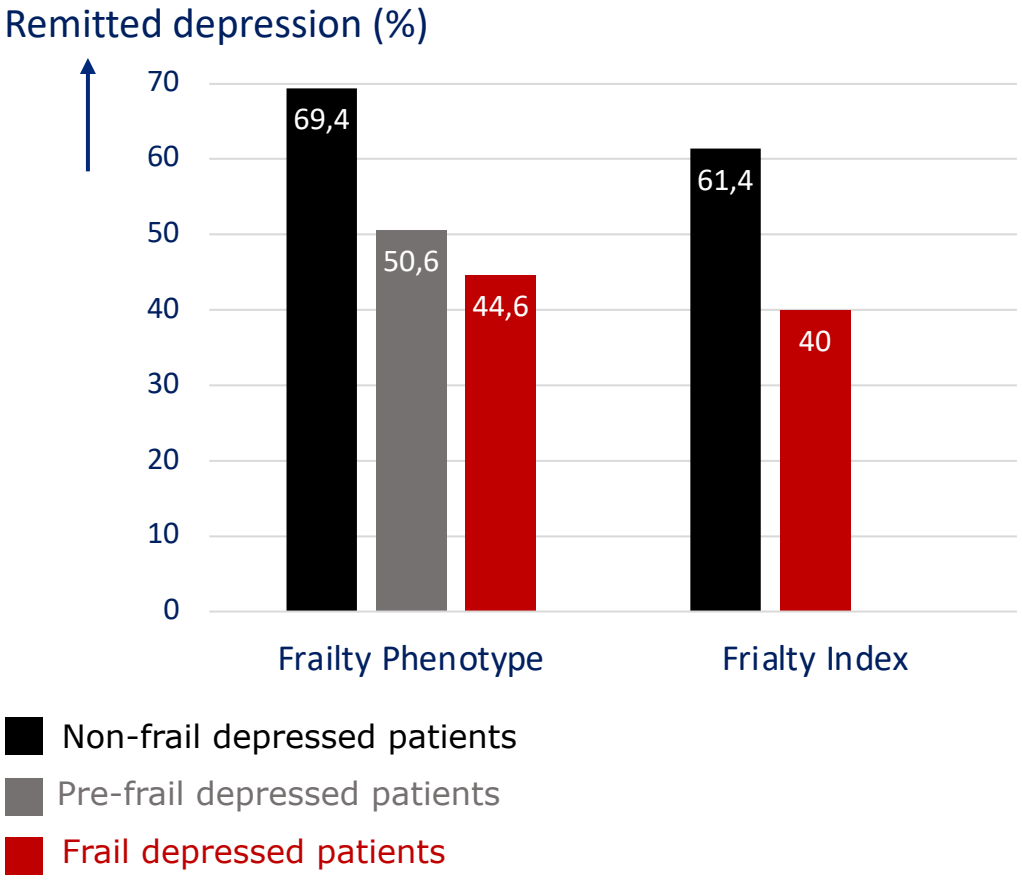
- **Prognosis of depression**
- Frailty management in mental health care

[1] Miloyan & Fried, World Psychiatry 2017

NESDO: Remission at 2-year follow-up (n=285)[1,2]



Prediction of non-remission:

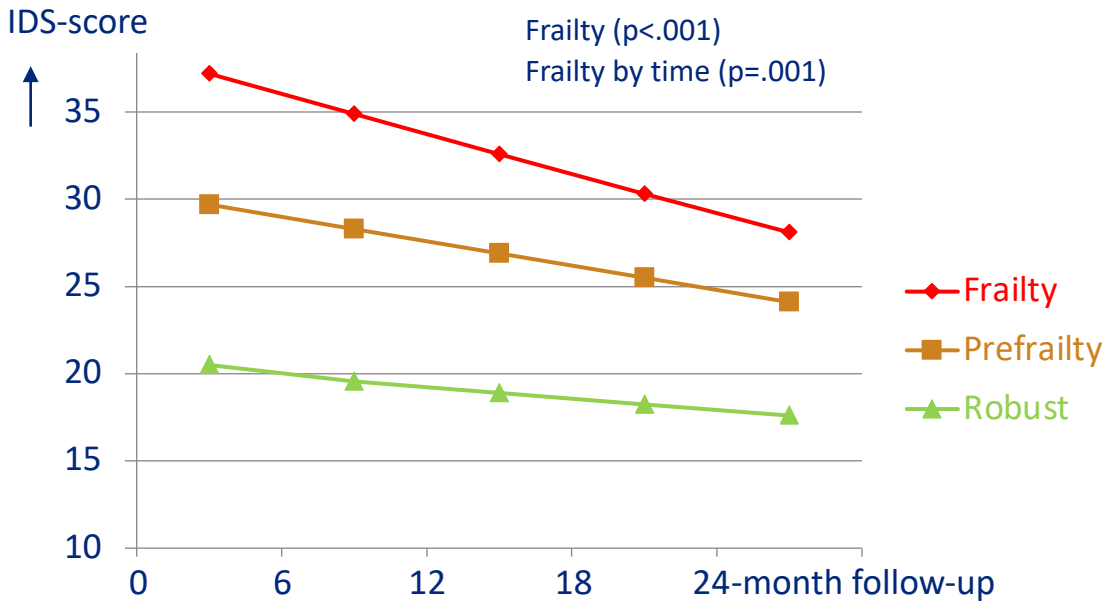
$OR_{prefrail}$ = 2.36 [1.16 – 4.80], p=.017

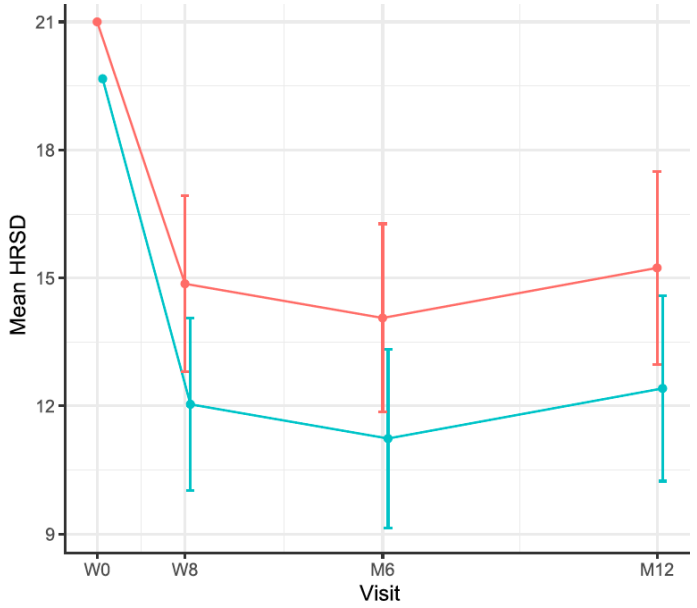
OR_{frail} = 2.66 [1.17 – 6.02], p=.019
(REF = robust)

OR_{frail} = 1.24 [1.01- 1.52], p=.040
(per frailty component)

[1] Collard & Oude Voshaar, Eur Psychiatry 2017
[2] Oude Voshaar et al, Int J Geriatr Psychiatry 2022

Course of depressive symptoms over time[1,2]



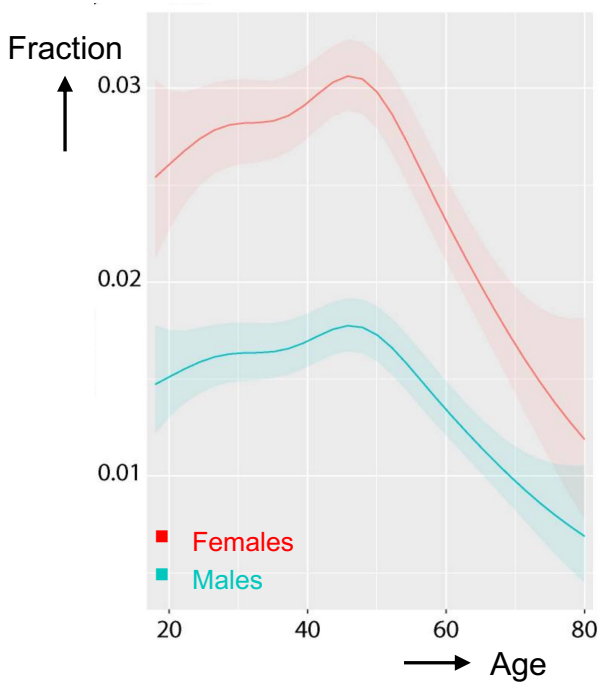


[1] Collard et al, Eur Psychiatry 2017

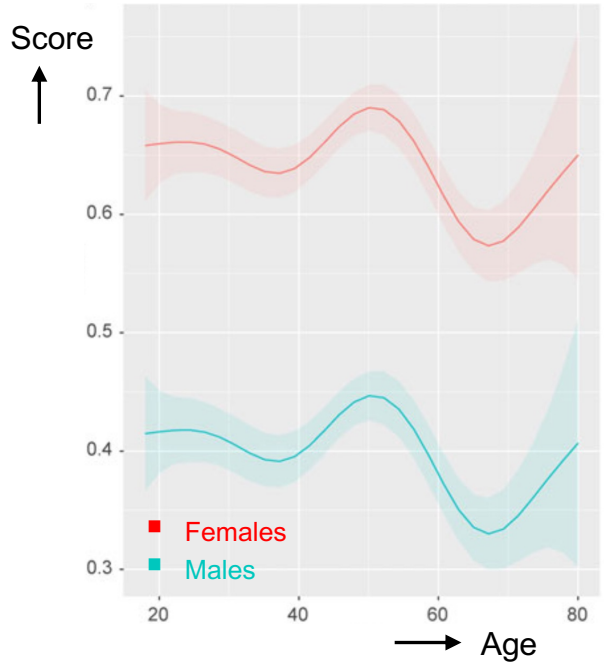
[2] Brown et al, Am J Geriatr Psychiatry 2021

Differential course depressive disorder - symptoms[1]

Prevalence of depression in the Lifelines Cohort study (n>140,000)[1]



Depressive disorder (DSM)



Depressive symptoms

[1] Van Loo et al, Psychol Med 2021

Age and prognosis of depressive disorder (NESDA/NESDO)[1]

Odd ratios [95% CI] for age (per 10 years) on two-year course of depression

(n=1042 depressed patients, age range 18 – 93 years)

	Persistence of a depressive disorder		Chronic depressive symptom course	
Models[1,2]	OR [95% CI]	p	OR [95% CI]	p
• Age[1]	1.11 [1.02 – 1.20]*	.016	1.25 [1.10 – 1.37]*	<.001
• Age[2]	1.05 [0.98 – 1.18]	.342	1.18 [1.04 – 1.31]*	.002

[1] Adjusted for demographics and psychopathology (no. of depressive episodes, anxiety, and ADs)

[2] Additionally adjusted for health (pain, chronic diseases, BMI) and social factors (loneliness, support)

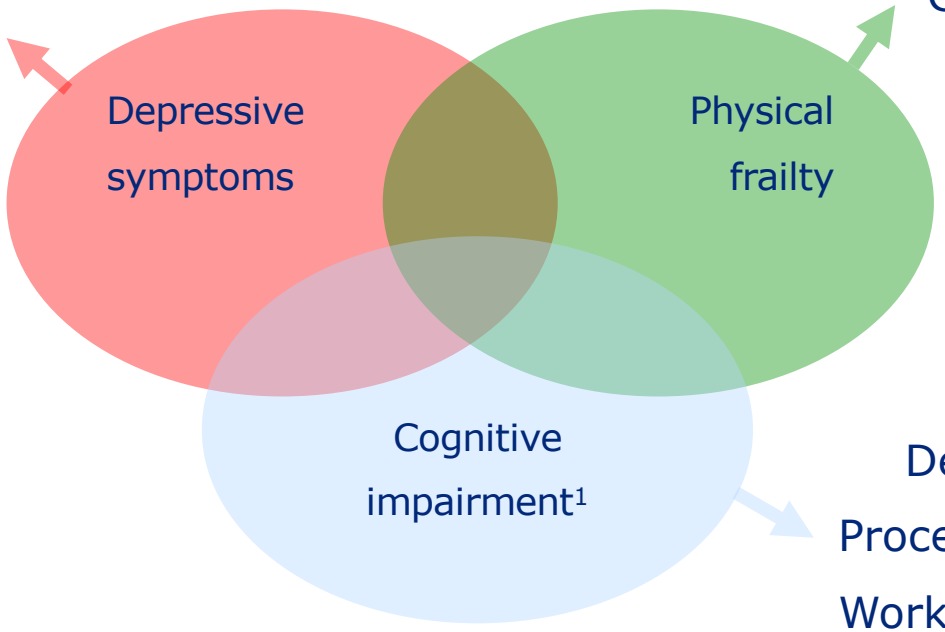
[1] Schaakxs et al, Lancet Psychiatry 2018

Data-driven subtyping of late-life depression based on depressive symptom dimensions, frailty and cognitive performance

Somatic-affective symptoms

Motivational symptoms

Mood symptoms



Hand grip strength

Gait speed

Delayed recall

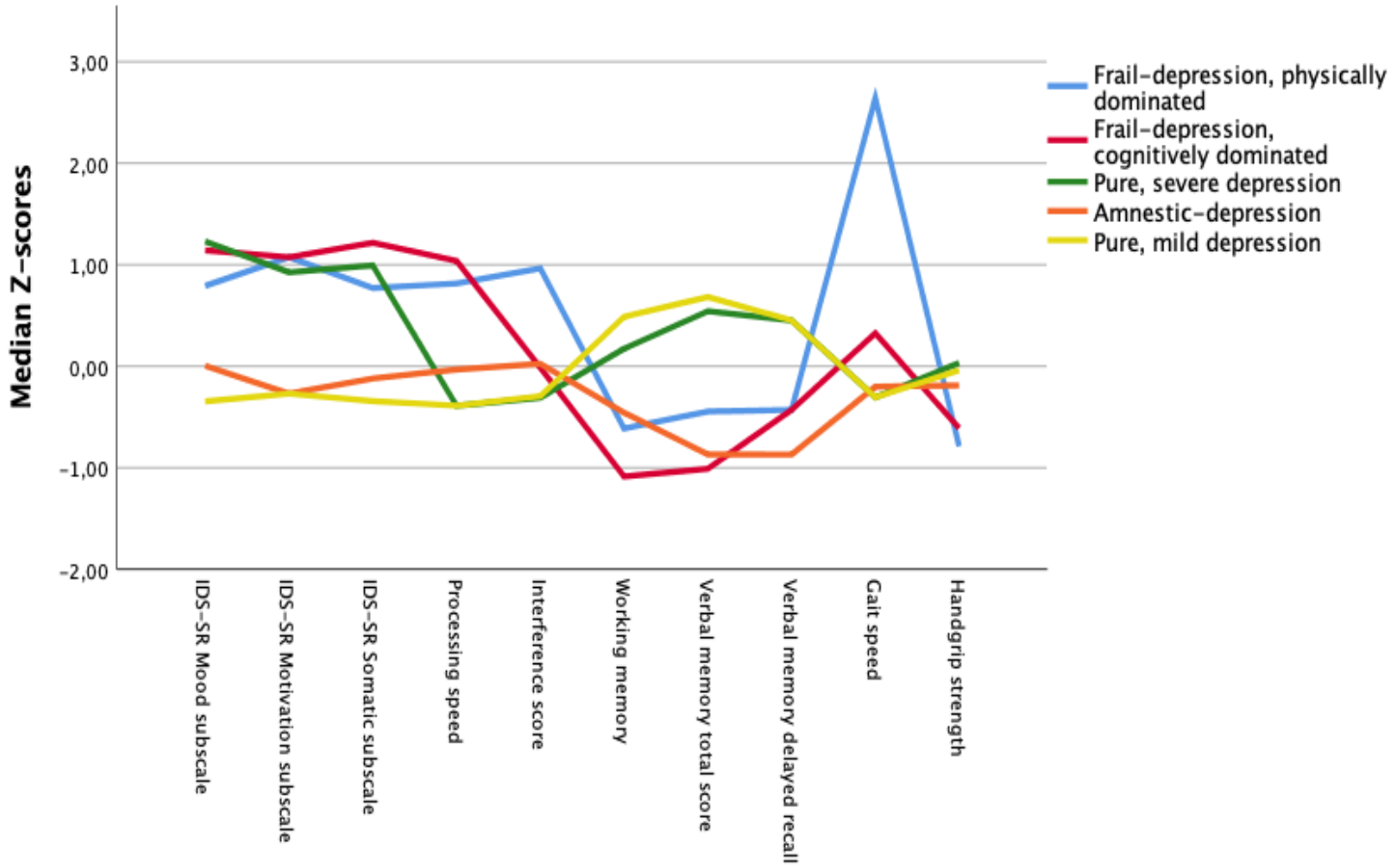
Processing speed

Working memory

Interference control

[1] Kelaiditi et al, J Nutr health Aging (2013)

Outcome Latent Profile Analysis (LPA, n=375)



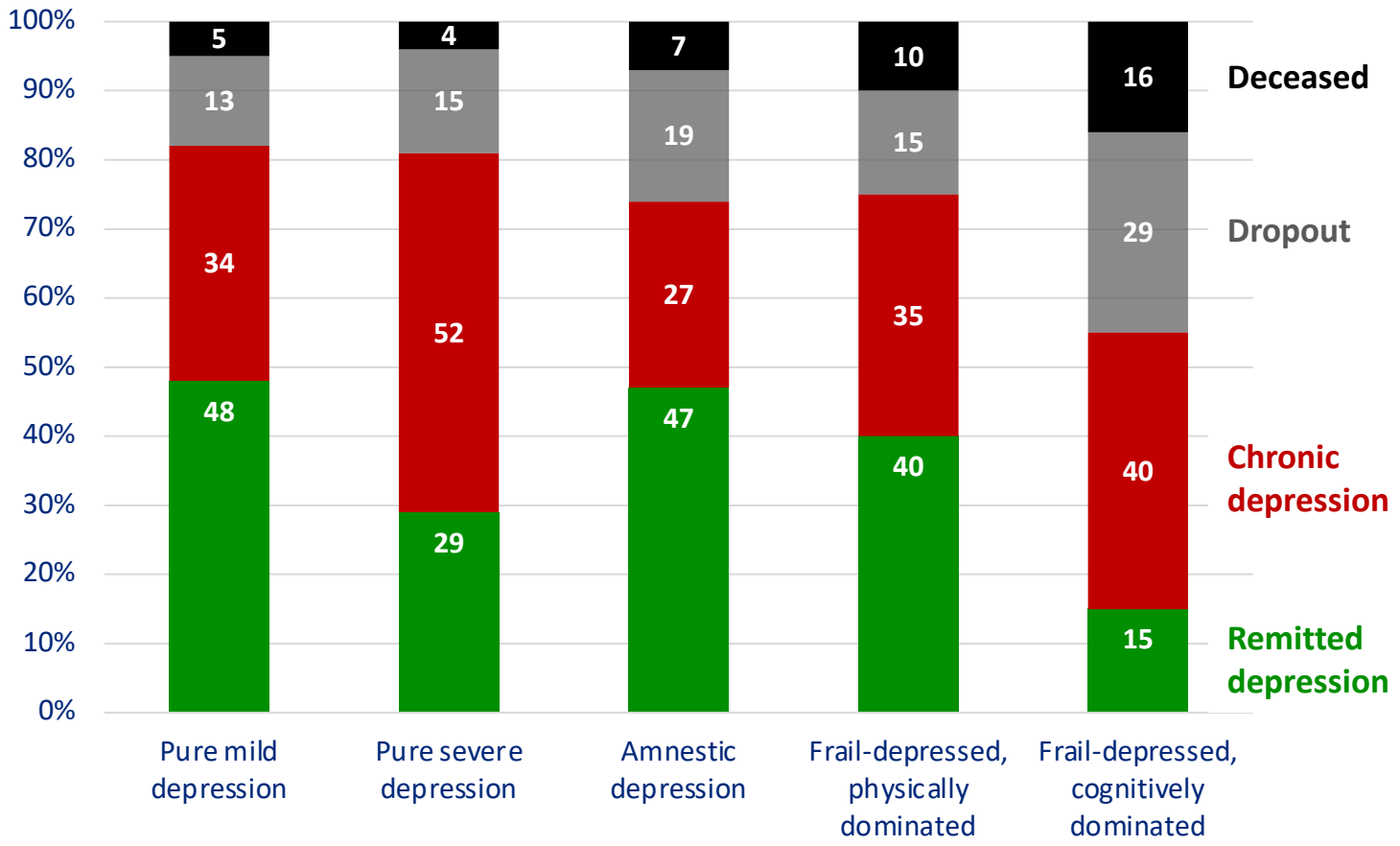
[1] Lugtenburg, … , Oude Voshaar, J Gerontol A Med Sci Biol Sci 2020

Interpretation Latent Profile Analysis (n=375)

LPA subgroups:	%	Depressive symptom severity	Low verbal memory	Low processing speed & executive dysfunctioning	Physical frail
• Pure mild depression	32.3	+	-	-	-
• Pure severe depression	22.7	+++	-	-	-
• Amnestic depression	27.7	+	++	-	-
• Frail-depressed, extreme frail	5.3	+++	++	++	+++
• Frail-depressed	12.0	+++	++	++	++

[1] Lugtenburg, … , Oude Voshaar, J Gerontol A Med Sci Biol Sci 2020

Two-year follow-up in LPA subgroups (in %)



[1] Lugtenburg, … , Oude Voshaar, J Gerontol A Med Sci Biol Sci 2020

Prognostic and clinical relevance of frailty in depression

- Accelerated ageing
- Mortality rate[1]
- Risk of falling
- Prognosis of depression
- **Frailty management in mental health care**

[1] Miloyan & Fried, World Psychiatry 2017

Frailty management[1]: A must for mental health care

Relevant for depressed older persons:

- 25 – 45% is frail
- Accelerated progression of frailty

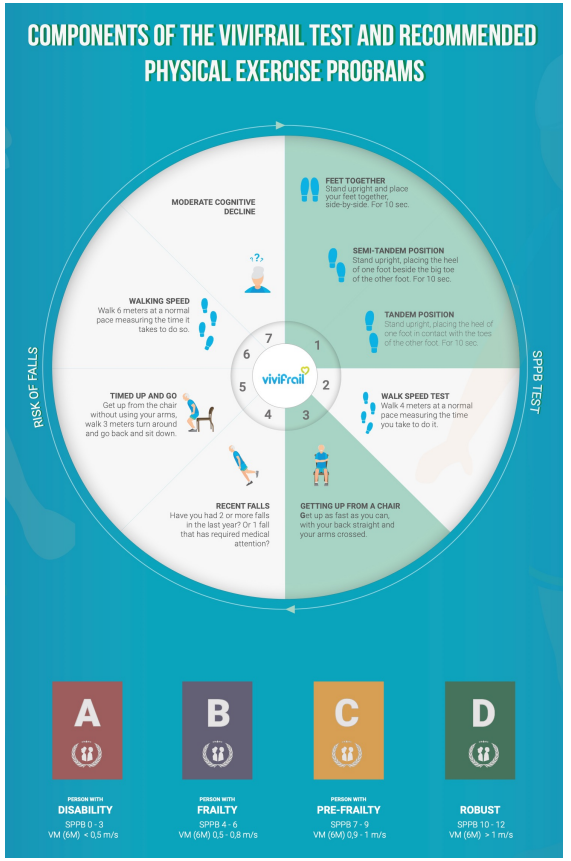
So relevant from age 60 year?

[1] Dent et al, J Nutr Health Aging 2019

VIVIFRAIL for the frail-depressed patiëent[1]

VIVIFRAIL

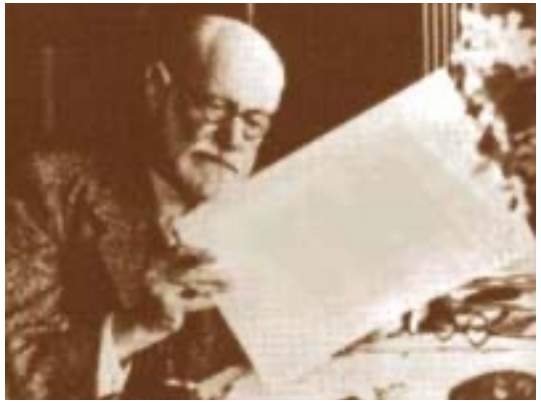
- Daily exercises (30 – 45 minutes)
- Adjusted to functional level of individual patients
- Feasible at home: Without supervision
  Without aids
- BUT psychiatric patients hard to motivate.



[1] www.vivifrail.com

Psychological care for frail elderly - Therapeutic nihilism

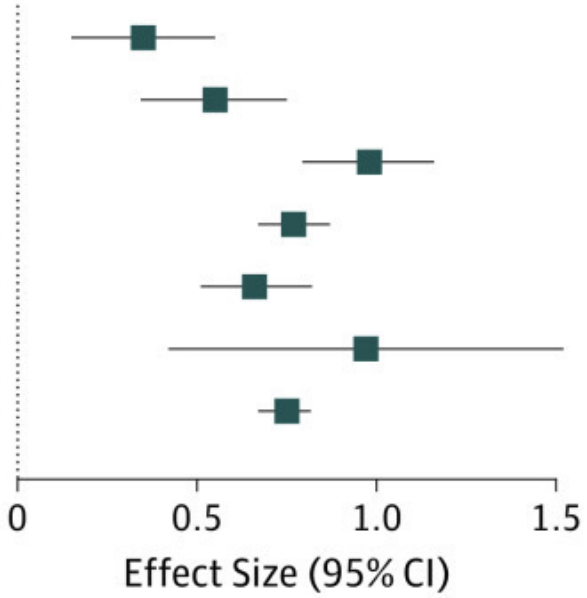
Above the age of 50 years, the plasticity of mental processes, needed for psychotherapy is generally absent.



- Older persons can’t be taught anymore -

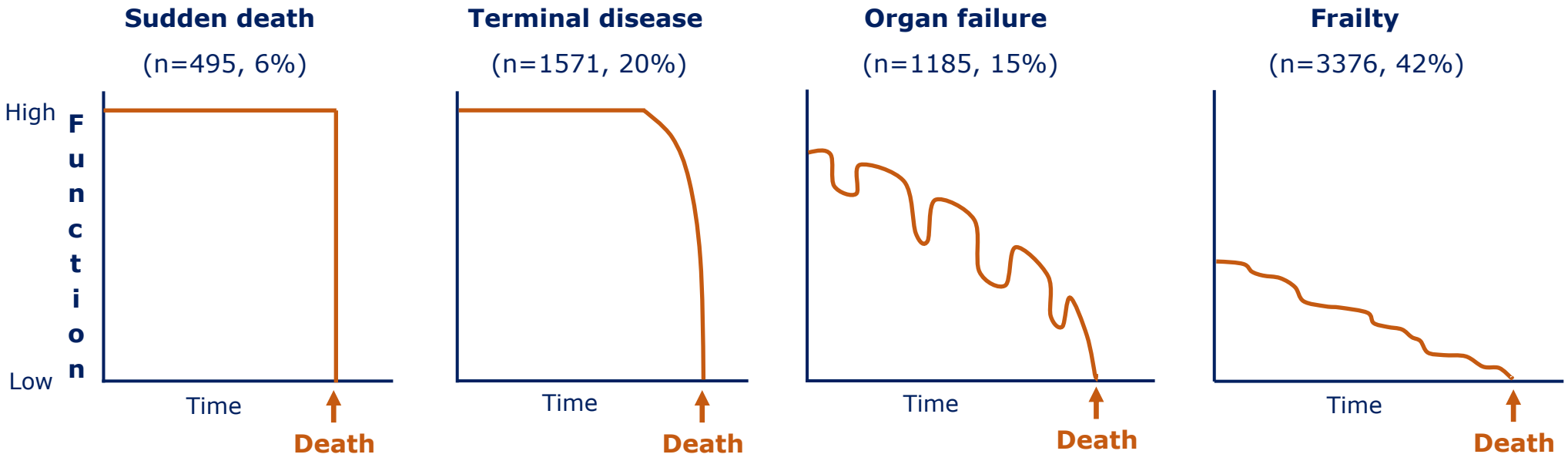
Meta-analysis psychotherapy ‘across the lifespan’[1]

Age Category	No.	Effect Size (95% CI)
Children	15	0.35 (0.15-0.55)
Adolescents	28	0.55 (0.34-0.75)
Young adults	27	0.98 (0.79-1.16)
Middle-aged adults	304	0.77 (0.67-0.87)
Older adults	69	0.66 (0.51-0.82)
Older old	10	0.97 (0.42-1.52)
All studies	453	0.75 (0.67-0.82)



[1] Cuijpers et al, JAMA Psychiatry 2020

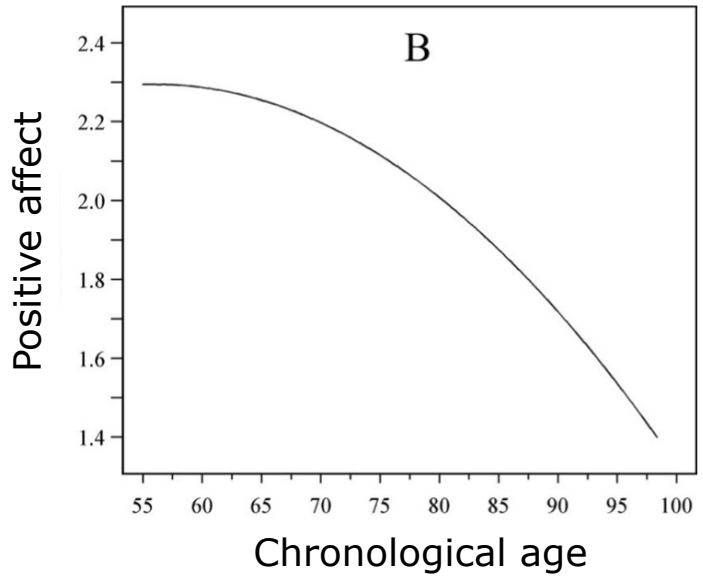
Trajectories of dying (of 7,966 people who died ≥65 year)[1]

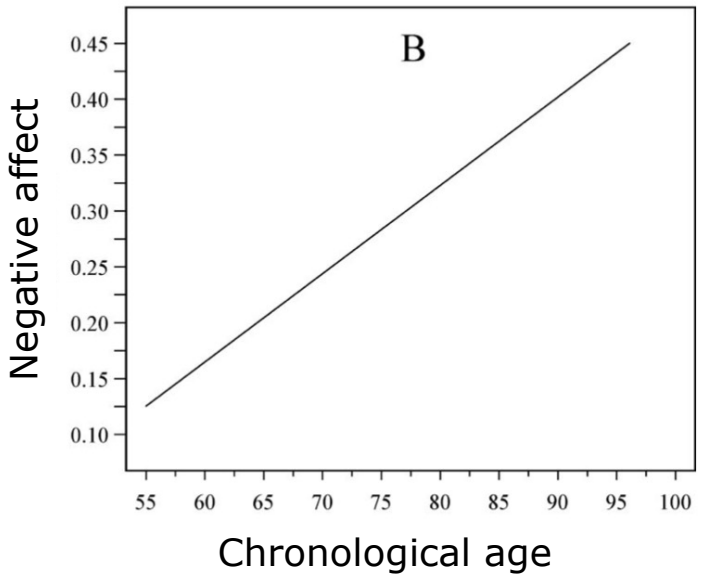


[1] Lunney et al, JAGS 2002

Course of positive and negative affect during ageing (55+, LASA) [1]

A higher age is associated with a lower level of positive and higher level of negative affect.

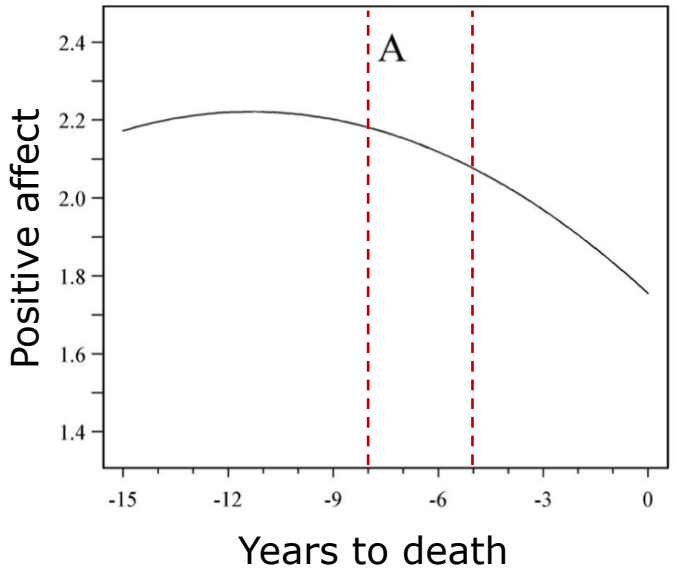


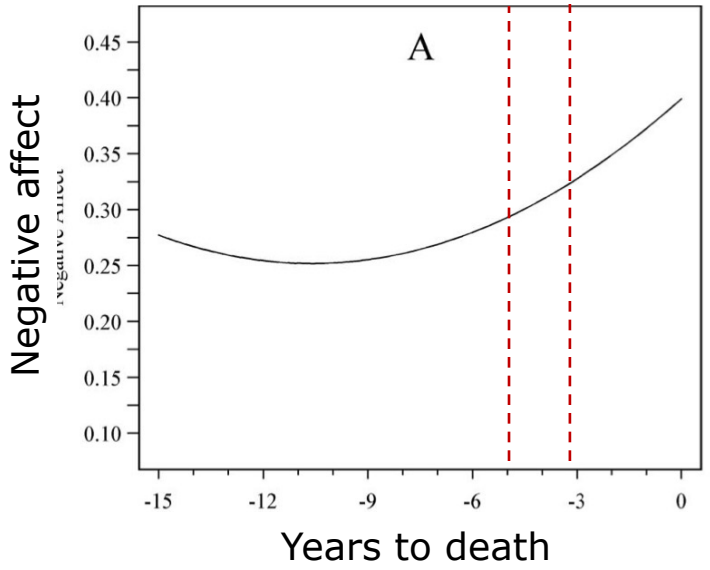


[1] Vogel et al, Psychology Aging 2013

Course of positive and negative affect during ageing (55+, LASA) [1]

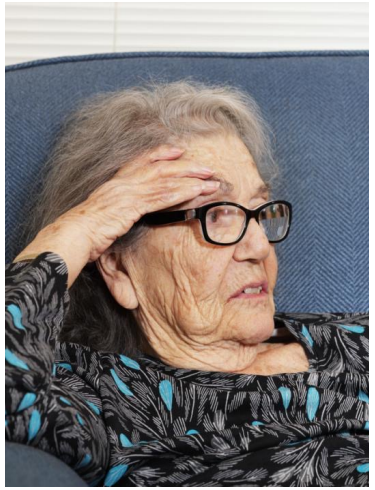
Change in positive/negative affect related to 'time-to-death' rather than chronological age





[1] Vogel et al, Psychology Aging 2013

Psychotherapy for frailty with low mood/depressive symptoms



Patient perspective:

- Frailty associated with disability and non-specific physical symptoms
- Wellbeing and QoL are more important than physical performance
- Frailty is associated with negative self-image (& maladaptive cognitions)
- Older people prefer psychotherapy (above psychotropic drugs)

Why Acceptance and Commitment Therapy (ACT) for frailty?

- ACT is aimed at meaning in life and a valuable life within one's own possibilities
- ACT is effective in affective disorders, cancer, chronic pain and chronic diseases (e.g. diabetes)
- Older people with chronic pain respond better to ACT, while younger people respond better to CBT[1]

[1] Wetherell et al, Int J Geriatr Pyschiatry 2016

umcg

Being present in the here and now, despite your vulnerabilities

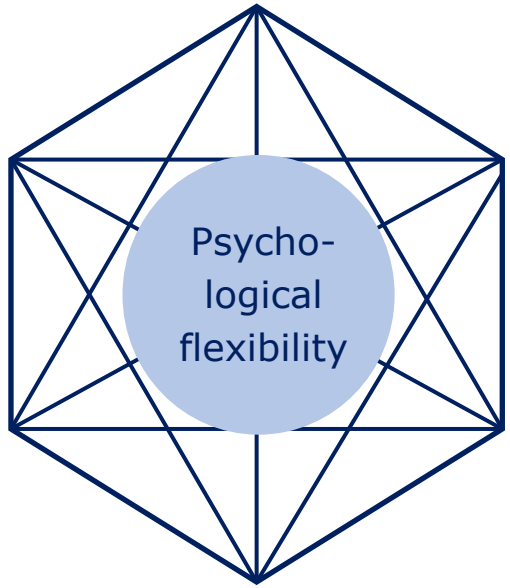
Being present

Willingness to stop fighting aging

Acceptance

Committed action

How can you live a valuable life despite obstacles?



Values

Identifying what's really important in life, despite the struggles of aging.

Cognitive defusion

Learning to differentiate the experience of aging from your struggles with thoughts or beliefs about aging

Self as context

Making the distinction between yourself and the physical vulnerabilities you struggle with.

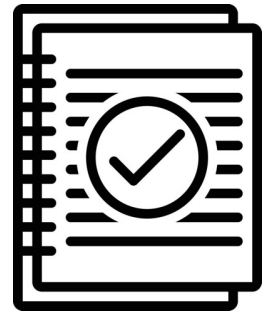
Development of ACT-frailty protocol

Therapy protocol

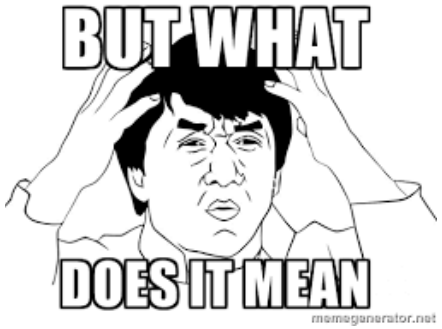
- Eight (weekly) sessions:
  - S1 – Case conceptualization
  - S2 – Creative helplessness
  - S3-8 Increasing of ACT-capabilities
- At the hospital, online, phone, home visits

Lesson’s learned: Valuable for most older people!

Do’s



Don’ts


BUT WHAT
DOES IT MEAN
memegenerator.net

Conclusion 1: Frailty in depression

- 25 - 45% of depressed older patients is frail.
  - Frailty in depression is associated with aging-related biomakers:
    - Inflammation
    - Telomere Length
    - Vitamin D
  - Prospectively associated with an increased fall risk.
  - Predicts mortality; partially explained by aging-related biomarkers

Conclusion 2: Clinical relevance of frailty in depression

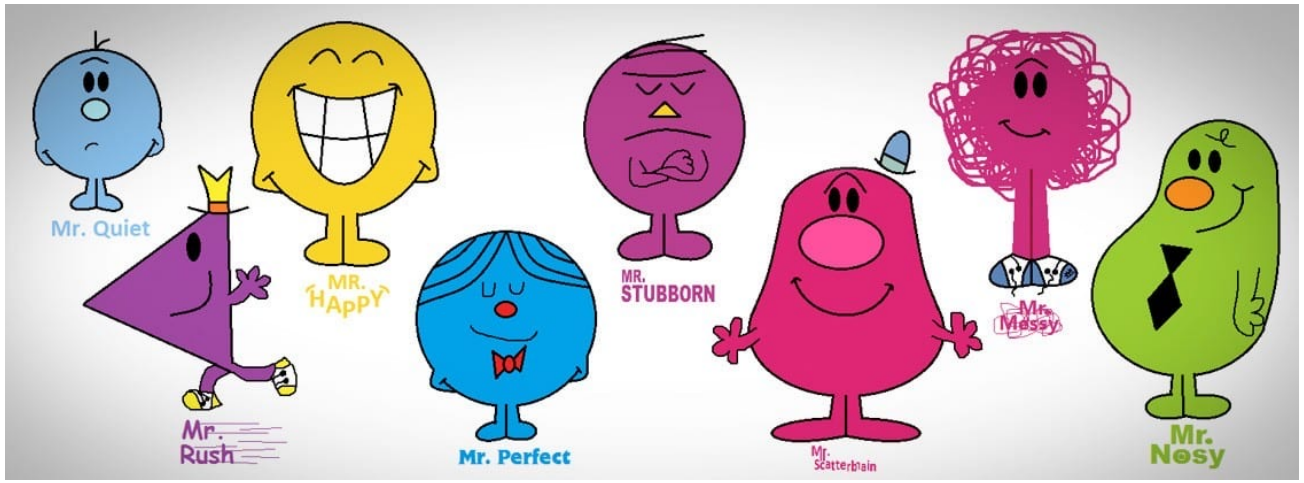
Frailty partly explains worse prognosis of late-life depression.

Discriminating frailty & depression is challenging, but relevant:

- Relevant for prevention of inappropriate use of antidepressants & overtreatment of depression
- Preference for psychotherapy in later life: Frailty Identity Crisis?
- More emphasis on geriatric rehabilitation?

Do ‘distal’ risk factors of depression also affect frailty?

Adverse Childhood Experiences (ACE)



Personality traits

Are ACE associated with the onset of frailty?[1]

Longitudinal Ageing Study Amsterdam (LASA):

- 1427 non-frail people (~72 years; 17-year FU)

Cox-regression analyses:

- <70 years: HR = 0.87 [0.69 – 1.11], p=.271
- >70 years: HR = 1.28 [1.01 – 1.63], p=.044

[1] Dimitriadis, … , Oude Voshaar, Age Ageing 2023

Are ACE associated with progression of sarcopenia?[1]

Canadian Longitudinal Study of Ageing (CLSA):

- 21 910 non-sarcopenic people (~62 years; 3-year FU)

Logistic regression:

- Non-depressed: OR = 0.98 [0.91 – 1.05], p=.522
- Depressed people: OR = 1.13 [1.01 – 1.28], p=.039

[1] Dimitriadis, … , Oude Voshaar, Age Ageing 2023

Is personality (BIG-5) associated with the course of frailty?[1]

Netherlands Study of Depression in Older persons (NESDO, n=510, two-year follow-up)

	Frailty Phenotype		Frailty Index	
Big-5 personality traits:	β	p	β	p
• **Neuroticism**	**0.11**	**.034**	-0.02	.627
• Extraversion	-0.06	.180	-0.05	.118
• **Agreeableness**	**-0.11**	**.004**	**-0.10**	**.002**
• **Conscientiousness**	**-0.09**	**.029**	-0.04	.236
• **Openness**	-0.02	.643	**-0.07**	**.028**

* Linear regression adjusted for sociodemographics (age, sex, education), depressive disorder, and somatic health status (number of somatic diseases and of prescribed medications)

[1] Bos, … , Oude Voshaar, Clin Gerontologist 2023