Relationship between frailty and biomarkers of Alzheimer's disease: a scoping review.

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MSVU Centre on Aging, June 16th, 2016

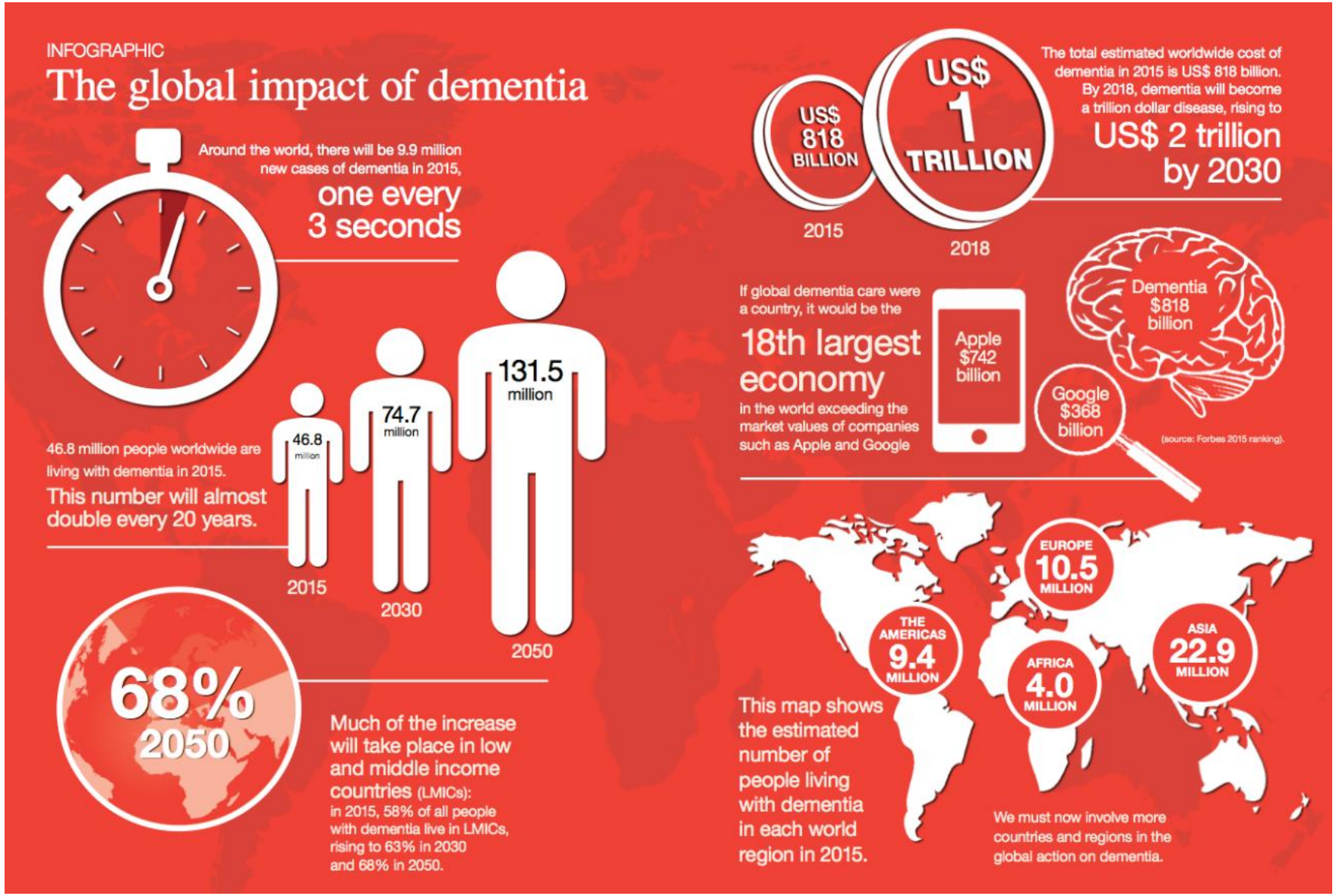
DALHOUSIE UNIVERSITY

GERIATRIC MEDICINE RESEARCH

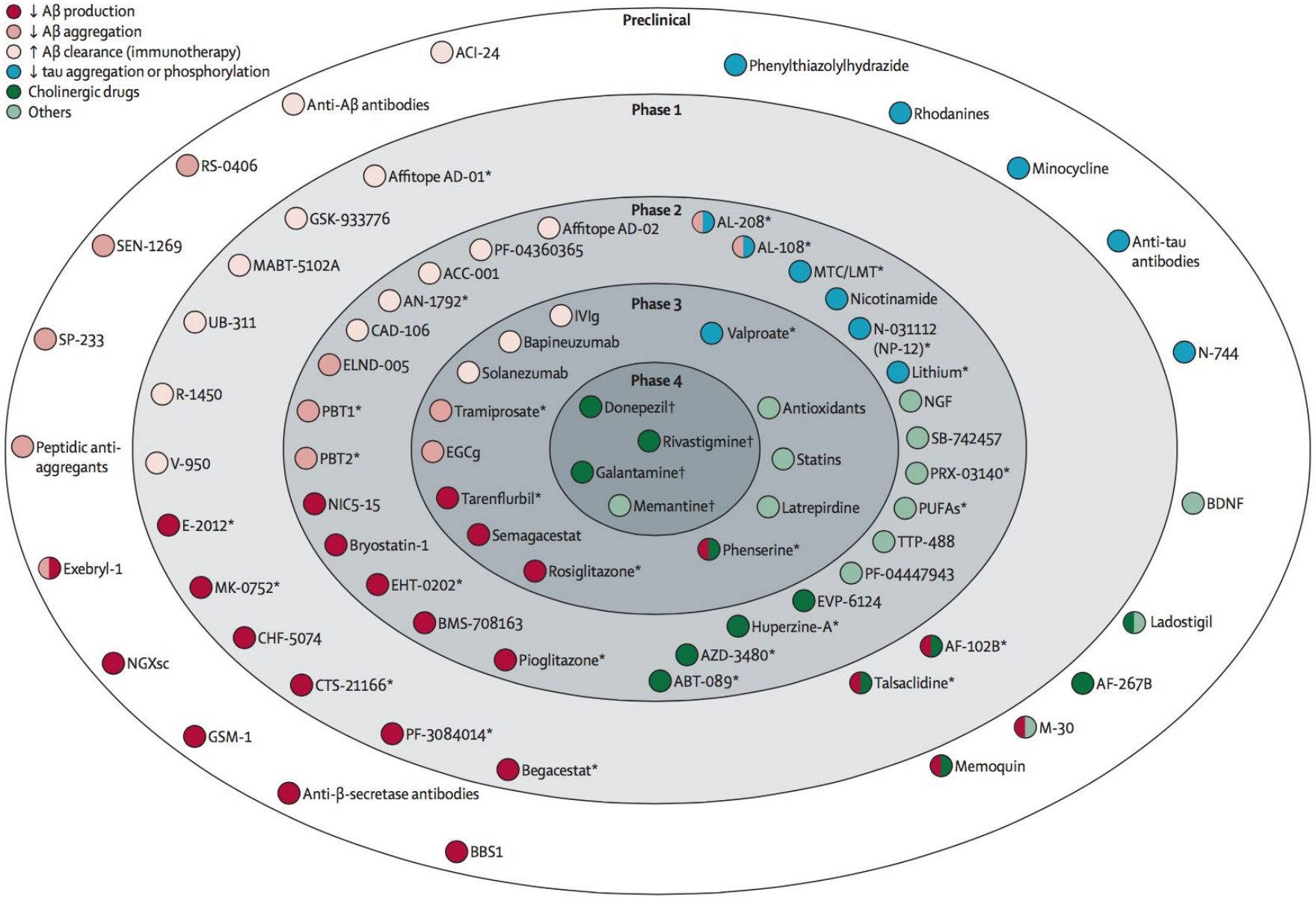
nova scotia health authority

CCNA CCNV

Alzheimer Society CANADA



World Alzheimer Report 2015, Alzheimer's Disease International

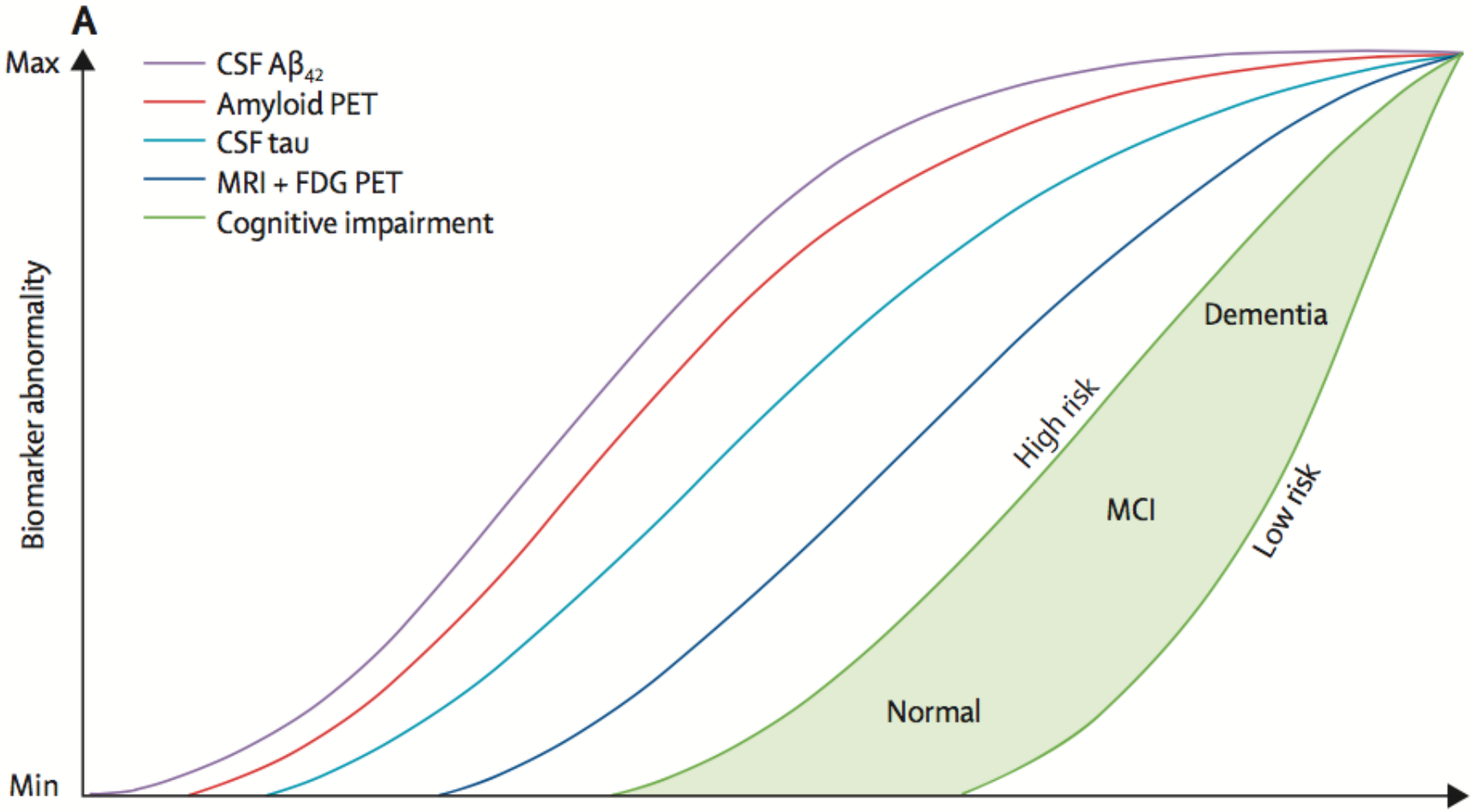


Mangialasche et al., *Lancet Neurol,* 2010

Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers

Clifford R Jack Jr, David S Knopman, William J Jagust, Ronald C Petersen, Michael W Weiner, Paul S Aisen, Leslie M Shaw, Prashanthi Vemuri, Heather J Wiste, Stephen D Weigand, Timothy G Lesnick, Vernon S Pankratz, Michael C Donohue, John Q Trojanowski

Lancet Neurol, 2013



Rationale & Objective

- Alzheimer's disease (AD) and frailty are closely linked, both are highly related to advanced age and vulnerability to health outcomes.
- Given that neuropathological features of AD are poorly correlated with its clinical presentation, it is possible that frailty interacts with biomarkers of AD to increase vulnerability to cognitive decline.
- **Objective**: to systematically assess the state of the published literature on associations between frailty and biomarkers of AD to better understand its pathophysiological trajectory.

Methods

- **Databases searched**: PubMed, Embase, PsycInfo
- **Search terms**: ‘frail elderly’ AND ‘Alzheimer disease’ AND ‘neuropathology’ + synonyms
- **Inclusion criteria**: original articles that measured a ‘biomarker’ of Alzheimer’s disease and measured frailty
  - ***What are AD biomarkers?*** (McKhann et al., *Alz Dement*, 2011): low CSF $A\beta_{42}$, positive PET amyloid imaging, elevated CSF tau, decreased ^{18}fluorodeoxyglucose (FDG) uptake on PET in temporoparietal cortex, disproportionate atrophy on structural magnetic resonance imaging
- **Exclusion criteria:** written in a language other than English or French, involved subjects other than humans
- **Screening process**: two independent reviewers at all levels; all conflicts resolved by consensus

	PUBMED	EMBASE	PSYCINFO
2			
3	"alzheimer disease"[MeSH] OR	alzheimer disease'/exp OR	DE "alzheimer disease" OR
4	"dementia"[MeSH] OR	dementia'/exp OR	DE "dementia" OR
5	"mild cognitive impairment"[MeSH] OR	mild cognitive impairment'/exp OR	-
6	"memory disorders"[MeSH] OR	memory disorders'/exp OR	DE "memory disorder" OR
7	alzheimer* [tiab] OR	alzheimer*:ab,ti OR	TI alzheimer* OR AB alzheimer* OR
8	"dementia"[tiab] OR	dementia':ab,ti OR	TI dementia OR AB dementia OR
9	"cognitive"[tiab] OR	cognitive':ab,ti OR	TI cognitive OR AB cognitive OR
10	"cognition"[tiab] OR	cognition':ab,ti OR	TI cognition OR AB cognition OR
11	"memory"[tiab] OR	memory':ab,ti OR	TI memory OR AB memory OR
12	senil*[tiab]	senil*:ab,ti	TI senil* OR AB senil*
13			
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15	frail* [tiab] OR	frail*':ab,ti OR	TI frail* OR AB frail* OR
16	"deficit accumulation" [tiab] OR	deficit accumulation':ab,ti OR	TI "deficit accumulation" OR AB "deficit accumulation" OR
17	prefrail* [tiab] OR	prefrail*:ab,ti OR	TI prefrail* OR AB prefrail* OR
18	pre-frail* [tiab] OR	pre-frail*:ab,ti OR	TI pre-frail* OR AB prefrail* OR
19	non-frail* [tiab] OR	non-frail*:ab,ti OR	TI non-frail* OR AB non-frail* OR
20	nonfrail* [tiab]	nonfrail*:ab,ti	TI nonfrail* OR AB nonfrail*
21			
22	"amyloidosis"[MeSH Terms] OR	amyloidosis'/exp OR	-
23	"neurofibrillary tangles"[MeSH Terms] OR	neurofibrillary tangles'/exp OR	DE "neurofibrillary tangles" OR
24	"Amyloid beta- peptides" [MeSH] OR	amyloid beta- peptides'/exp OR	DE "amyloid precursor protein" OR
25	"amyloid plaque"[MeSH] OR	amyloid plaque'/exp OR	-
26	"positron emission tomography" [MeSH] OR	positron emission tomography'/exp OR	DE "positron emission tomography" OR
27	"tauopathies" [MeSH] OR	tauopathies'/exp OR	-
28	"tau Proteins" [MeSH] OR	tau proteins'/exp OR	-
29	"biological markers"[MeSH] OR	biological markers'/exp OR	DE "biological markers" OR
30	-		DE "neuropathology" OR
31	-		DE "neurodegeneration" OR
32	"magnetic resonance imaging"[MeSH] OR	magnetic resonance imaging'/exp OR	DE "magnetic resonance imaging" OR
33	neuropath*[tiab] OR	neuropath*:ab,ti OR	TI neuropath* OR AB neuropath* OR
34	amyloid[tiab] OR	amyloid':ab,ti OR	TI amyloid OR AB amyloid OR
35	tau[tiab] OR	tau':ab,ti OR	TI tau OR AB tau OR
36	"neurofibrillary tangle*"[tiab] OR	neurofibrillary tangle':ab,ti OR 'neurofibrillary tangles':ab,ti OR	TI neurofibrillary N0 tangle* OR AB neurofibrillary N0 tangle* OR
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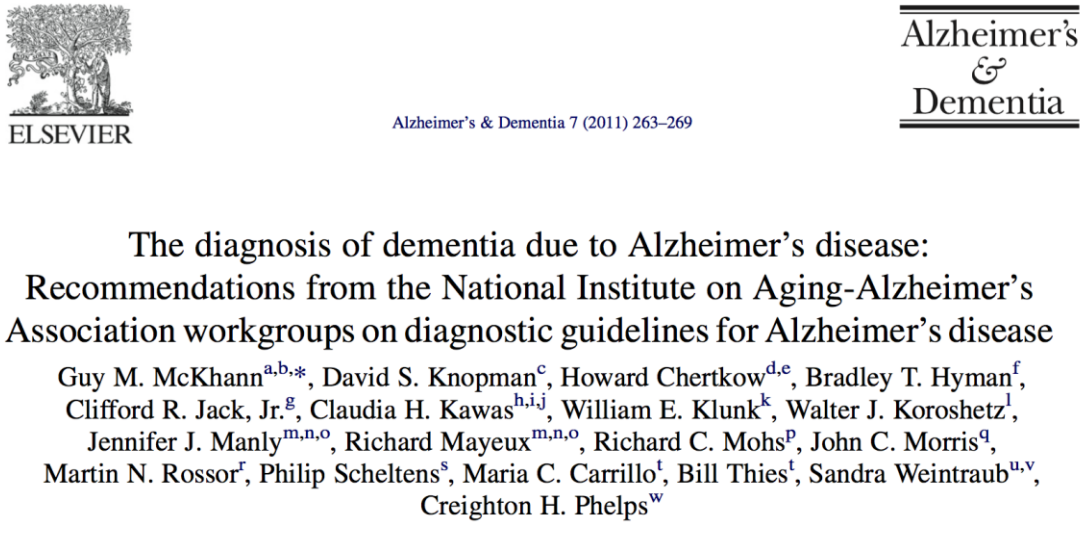
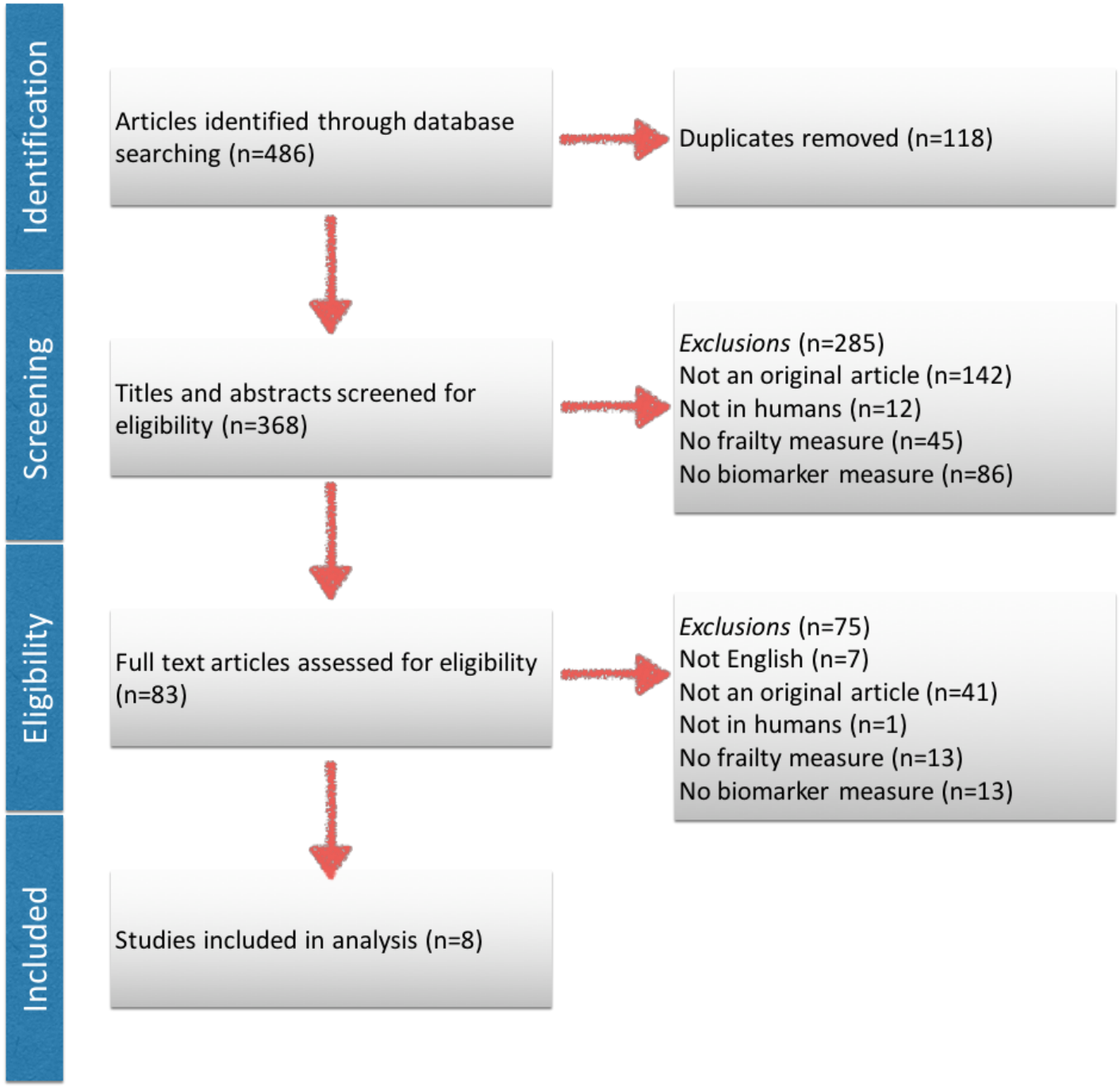
45	"neurodegeneration" [tiab]	neurodegeneration':ti,ab	TI neurodegeneration OR AB "neurodegeneration"

Pathophysiological (bio)markers of AD



- Low CSF amyloid-beta
- Positive amyloid (PiB) PET imaging
- Elevated t-tau and p-tau in CSF
- Decreased FDG uptake on PET
- Brain atrophy as measured by MRI


Identification
Screening
Eligibility
Included
Articles identified through database searching (n=486)
Duplicates removed (n=118)
Titles and abstracts screened for eligibility (n=368)
Exclusions (n=285)
Not an original article (n=142)
Not in humans (n=12)
No frailty measure (n=45)
No biomarker measure (n=86)
Full text articles assessed for eligibility (n=83)
Exclusions (n=75)
Not English (n=7)
Not an original article (n=41)
Not in humans (n=1)
No frailty measure (n=13)
No biomarker measure (n=13)
Studies included in analysis (n=8)

	Sample size (% female; % cognitively impaired at baseline)	Average age of participants at baseline	Study design; average length of follow-up (years)	Study/ database	Biomarker measured	Frailty measurement	Main finding
Koch et al., Neurolog Disorders 2013	72 (sex not reported; 100% mild-moderate AD)	69.9 ± 7.0	Cross-sectional	Tertiary Care Centre in Rome, Italy	**CSF: $A\beta_{42}$, p-tau, t-tau levels**	Rapid or slow progressing AD (based on MMSE)	AD progression significantly associated with t-tau, but not p-tau or $A\beta_{42}$ in one-way ANOVAs.
Gabelle et al., Alzheimers Dement 2014	1147 (60.0% female; 43% MCI)	73.0 ± 4.9	Nested case-cohort; 5.7	French 3-City study (Bordeaux, Dijon, Montpellier)	**Blood plasma: Aβ (40,42,40/42) levels**	Fried Phenotype	Frailty did not significantly influence the relationship between plasma Aβ and mortality in Cox regression models.
Burns et al., Neurology 2008	121 (54% female; 47% early AD)	73.5 ± 6.5	Cross-sectional	Brain Aging Project (Kansas, USA)	**Normalized whole brain volume**	Physical Performance Test	Frailty did not influence the relationship between whole brain atrophy and cardiorespiratory fitness (VO_2 peak) in linear regression models.
Yamada et al., Geriatr Gerontol Int 2013	31 (74% female; 35% MCI, 65% mild AD)	78.9 ± 7.3	Cross-sectional	Memory clinic data from Kyoto, Japan	**Global brain atrophy index (VBM)***	Physical Performance Test	Global brain atrophy was significantly correlated with frailty.
Tay et al., J Nutr Health Aging 2015	99 (35.4% female; 16% MCI, 69% mild AD, 15% moderate AD)	76.6 ± 6.7	Prospective cohort study, 1.0	Memory clinic data from Singapore	**Medial temporal atrophy (T1 MRI, consensus based 0-4 score)**	Modified Fried Phenotype	Baseline frailty and medial temporal atrophy were significantly related, but 1 year change in frailty was not associated with baseline atrophy in regression models.
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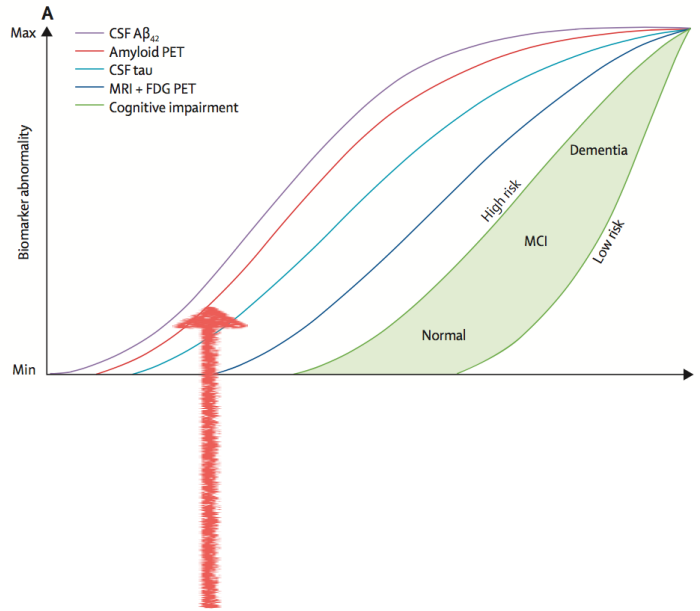

Table 1. General, Clinical, and Laboratory Characteristics of AD as Distinguished by Disease Progression Rate

	SP-AD	RP-AD
Age	70.5	69.2
MMSE	21.28	20.2
Tau	464.32 µg/L	1104.14 µg/L
$A\beta_{1-42}$	266.78µg/L	278.17 µg/L
Tau-p	67.4 µg/L	66.2 µg/L
CRP	2.08	1.83
Fibrinogen	319.74	308.82
ApoE	e3/e4	e3/e3

Slow Progressive AD (SP-AD); Rapidly Progressive RP-AD).

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Adjusting for physical frailty did not substantially alter the observed correlations between mortality and plasma $A\beta_{1-40}$ (HR = 1.21; 95% CI [1.04-1.40], p=0.02) or the $A\beta_{1-40}/_{1-42}$ ratio (HR 1.09; CI 95% [1.02-1.17], p=0.02).

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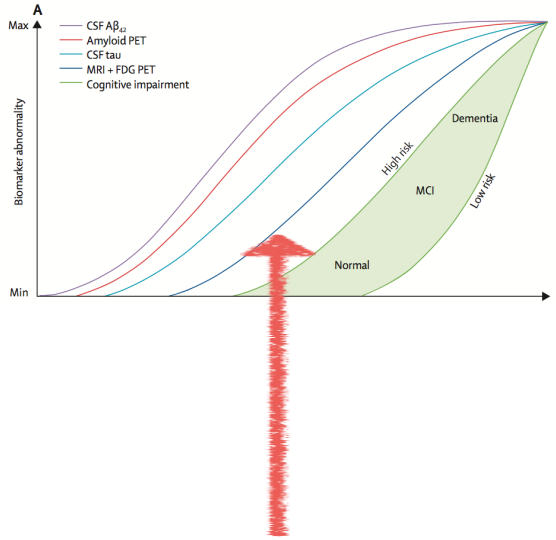

Table 2
Relationship of Brain Structure and Cognition with Fitness and Physical Activity

	Nondemented (n=64)		Early AD (n = 57)	
Dependent Variable	**Simple Correlation (r)**	**Age-Controlled (β)**	**Simple Correlation (r)**	**Age-Controlled (β)**
Brain Structure				
Whole Brain Volume	0.18	-0.20	0.54**	0.35*
White Matter Volume	0.15	0.04	0.39**	0.35*
Gray Matter Volume	0.08	-0.27 (p=0.06)	0.36**	0.13

Frailty did not significantly alter the age-controlled regression coefficients for any of the brain structure measures

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Table 2 Correlation coefficients for global brain atrophy and other measurements

	Global brain atrophy	Global brain atrophy (adjusted for age)
Characteristics		
Age	0.435	
Cognitive function		
Mini-Mental State Examination	0.019	–0.147
Word Fluency Test (animals)	–0.641	–0.522
Letter fluency Test (ka)	–0.320	–0.337
Clock Drawing Test	–0.338	–0.547
Trail Making Test Part-A	0.067	0.053
Physical function		
Comfortable walking time	0.555	0.205*
Maximum walking time	0.543	0.221*
Timed Up & Go Test	0.630	0.276
Functional reach	–0.121	–0.009
One-Leg Standing time	–0.581	–0.204*
Five Chair Stands	0.473	0.303

3 of the 6 PPT (frailty) measures were significantly correlated with age-adjusted global brain atrophy

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Medial Temporal Atrophy (MTA) was significantly different among frail and non-frail groups at baseline…

BUT, after controlling for immune-endocrine and cognitive factors, MTA did not predict baseline frailty OR 1 year progression in frailty in regression models

Table 2b
Multiple Logistic Regression Models for Baseline Frailty Status

	Odds Ratio (95% C.I)	p value
Model 3 (N=86)		
Age	1.04 (0.93-1.15)	0.510
Gender (female)	2.05 (0.52-8.10)	0.305
Immune-Endocrine status		
Non-proinflammatory & Non-endocrine deficient	1	
Proinflammatory & Non-endocrine deficient	3.07 (0.71-13.30)	0.134
Non-proinflammatory & Endocrine deficient	0.60 (0.06-6.51)	0.675
Proinflammatory & Endocrine deficient	1.59 (0.28-9.14)	0.604
MTA score	1.72 (0.90-3.25)	0.098
CMMSE	1.00 (0.88-1.13)	0.947

MTA=medial temporal atrophy; Model 1 (N=99) adjusted for age, gender and biomarker status: R2=14.4%; Model 2 (N=86) adjusted for age, gender, biomarker status and hippocampal atrophy: R2=13.4%; Model 3 (N=86) adjusted for age, gender, biomarker status, hippocampal strophy and CMMSE: R2=13.4%

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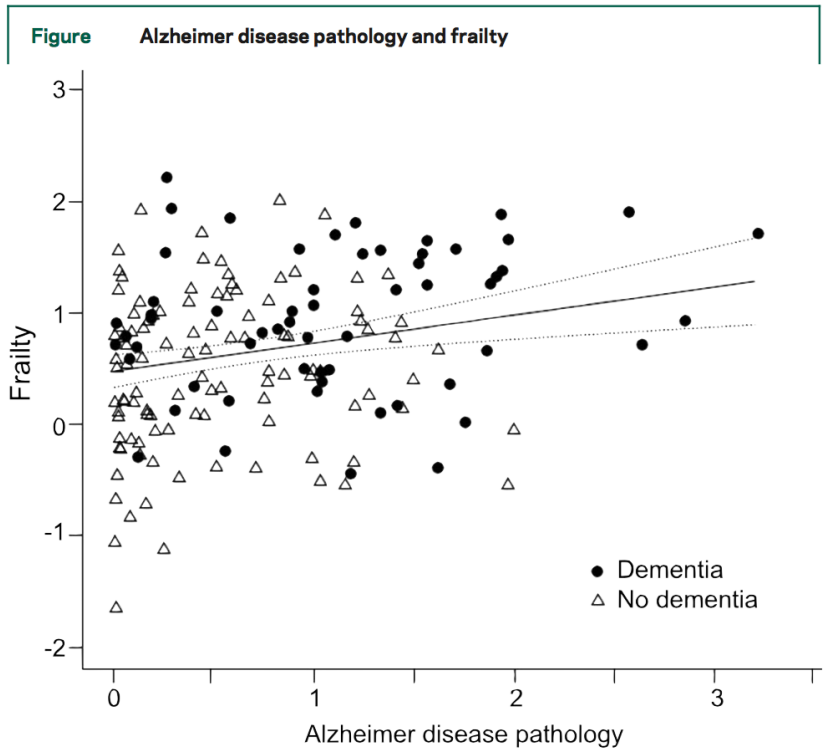

As frailty increases, so does the amount of AD pathology, with no effect of dementia diagnosis

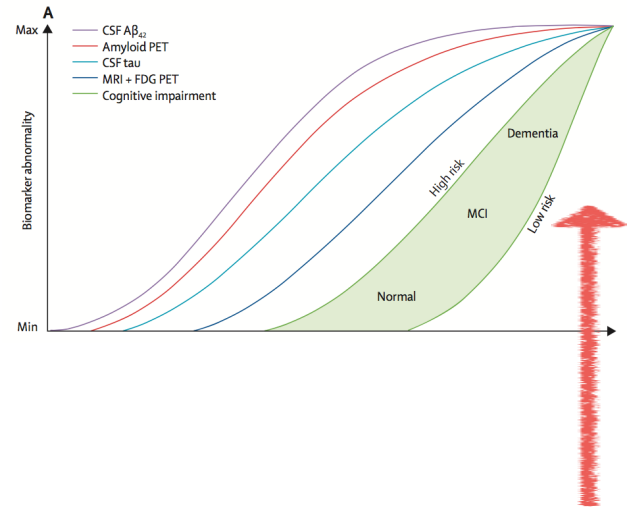

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Table 2 Brain pathology and progression of frailty in old age[a]

Model	Pathology	Level	Rate of change
A	Macroinfarcts	0.063 (0.042, 0.136)	0.023 (0.009, 0.010)
B	Microinfarcts	0.078 (0.045, 0.080)	−0.002 (0.009, 0.818)
C	Atherosclerosis	0.011 (0.013, 0.372)	0.003 (0.003, 0.342)
D	Arteriolosclerosis	0.079 (0.021, <0.001)	0.008 (0.005, 0.089)
E	Alzheimer disease pathology	0.004 (0.033, 0.903)	0.021 (0.007, 0.004)
F	Nigral neuronal loss	−0.031 (0.025, 0.208)	0.020 (0.005, <0.001)
G	Lewy body disease	0.004 (0.033, 0.903)	0.021 (0.007, 0.004)

[a] Estimated from 7 separate mixed-effect models examining the association of a different brain pathology with the level of frailty at study entry and the annual rate of change in frailty (time × pathology). Each model also included terms (not shown) controlling for age, sex, education, and their interaction with time: estimate (SE, *p* value).

AD pathology was not associated with baseline frailty, but was associated with frailty progression

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Figure 1 Person-specific paths of progressive frailty

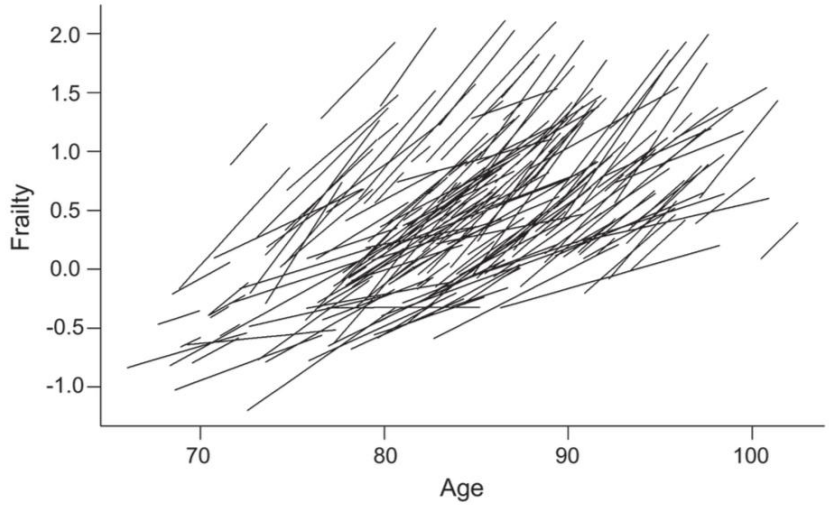
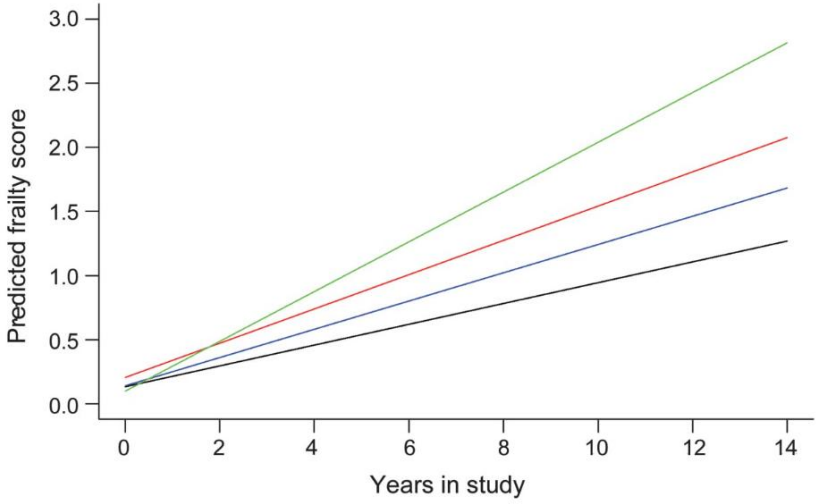


Figure 2 Effect of more brain pathology on the predicted paths of frailty



Green= high AD pathology + macroinfarcts + nigral neuronal loss
Red=high AD pathology + macroinfarcts
Blue= high level AD pathology
Black= low level AD pathology

	Sample size (% female; % cognitively impaired at baseline)	Average age of participants at baseline	Study design; average length of follow-up (years)	Study/ database	Biomarker measured	Frailty measurement	Main finding
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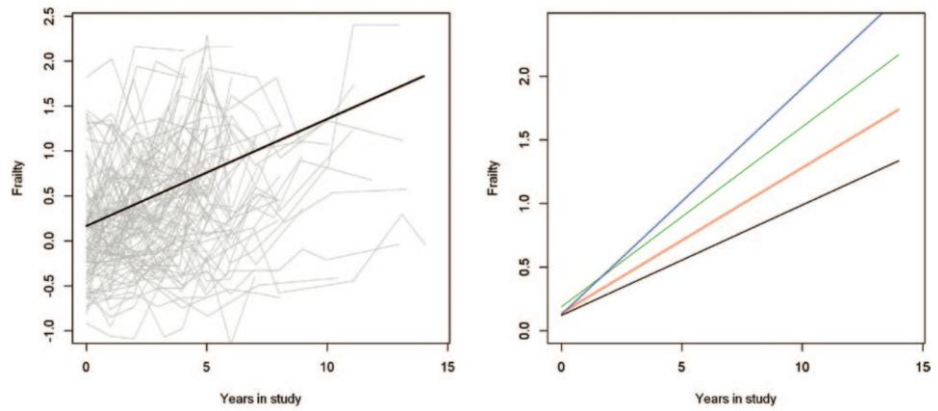
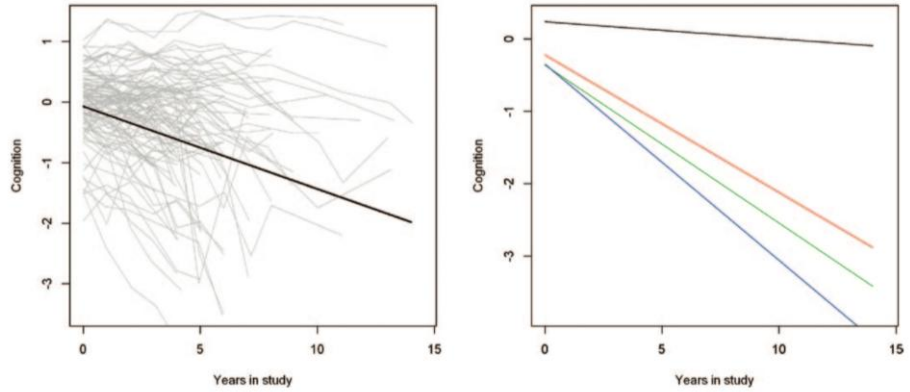


Frailty increases with time and this effect is stratified by pathologic burden



Cognition declines with time and this effect is stratified by pathologic burden

	Sample size (% female; % cognitively impaired at baseline)	Average age of participants at baseline	Study design; average length of follow-up (years)	Study/ database	Biomarker measured	Frailty measurement	Main finding
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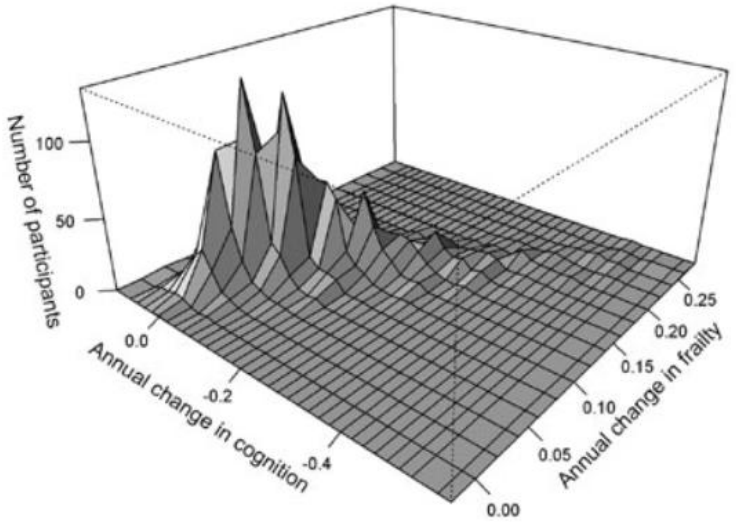

Change in cognition and frailty are linearly related; as people become more frail, their cognition declines

	Sample size (% female; % cognitively impaired at baseline)	Average age of participants at baseline	Study design; average length of follow-up (years)	Study/ database	Biomarker measured	Frailty measurement	Main finding
Koch et al., Neurolog Disorders 2013	72 (sex not reported; 100% mild-moderate AD)	69.9 ± 7.0	Cross-sectional	Tertiary Care Centre in Rome, Italy	**CSF: $A\beta_{42}$, p-tau, t-tau levels**	Rapid or slow progressing AD (based on MMSE)	AD progression significantly associated with t-tau, but not p-tau or $A\beta_{42}$ in one-way ANOVAs.
Gabelle et al., Alzheimers Dement 2014	1147 (60.0% female; 43% MCI)	73.0 ± 4.9	Nested case-cohort; 5.7	French 3-City study (Bordeaux, Dijon, Montpellier)	**Blood plasma: Aβ (40,42,40/42) levels**	Fried Phenotype	Frailty did not significantly influence the relationship between plasma Aβ and mortality in Cox regression models.
Burns et al., Neurology 2008	121 (54% female; 47% early AD)	73.5 ± 6.5	Cross-sectional	Brain Aging Project (Kansas, USA)	**Normalized whole brain volume**	Physical Performance Test	Frailty did not influence the relationship between whole brain atrophy and cardiorespiratory fitness (VO_2 peak) in linear regression models.
Yamada et al., Geriatr Gerontol Int 2013	31 (74% female; 35% MCI, 65% mild AD)	78.9 ± 7.3	Cross-sectional	Memory clinic data from Kyoto, Japan	**Global brain atrophy index (VBM)***	Physical Performance Test	Global brain atrophy was significantly correlated with frailty.
Tay et al., J Nutr Health Aging 2015	99 (35.4% female; 16% MCI, 69% mild AD, 15% moderate AD)	76.6 ± 6.7	Prospective cohort study, 1.0	Memory clinic data from Singapore	**Medial temporal atrophy (T1 MRI, consensus based 0-4 score)**	Modified Fried Phenotype	Baseline frailty and medial temporal atrophy were significantly related, but 1 year change in frailty was not associated with baseline atrophy in regression models.
Buchman et al., Neurology 2008	164 (56.4% female; 35.8% MCI or AD)	88.1 ± 5.7	Cross-sectional	Religious Orders Study/ Memory and Aging Project (USA)	**Post mortem index of AD pathology**	Modified Fried Phenotype	AD pathology was significantly associated with frailty status in adjusted linear regression models, no interaction with dementia diagnosis.
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Conclusions

- Few studies have examined the relationship between biomarkers of AD and frailty in the context of dementia
- The studies that have examined this topic have important limitations such as small sample size, cross-sectional design, poor measurement of frailty, and low variability of cognition at baseline
- Despite this, it is clear that frailty and biomarkers of AD are closely related although their mechanistic link is largely unknown; frailty appears to be most strongly related to biomarkers that appear in later disease stages, though the influence of frailty on relationships between biomarkers of AD and other health outcomes (e.g. mortality) remains equivocal

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Table 4. Percentage of the Variance of Rate of Change in Frailty and Cognition Explained by Demographics and Postmortem Indices

Term	Percentage of Variance of Change in Frailty	Percentage of Variance of Change in Cognition
Demographics	**9.19%**	**2.10%**
Age	6.37%	2.09%
Sex	0.00%	0.01%
Education	2.82%	0.00%
Pathologies	**8.06%**	**29.96%**
Macroinfarcts	3.42%	0.97%
Microinfarcts	0.20%	0.00%
AD pathology	1.53%	26.34%
Nigral neuronal loss	2.91%	2.63%
Total	**17.25%**	**32.04%**

Note: AD = Alzheimer's disease. Values in bold represent the total percentage of variance explained by demographic and pathology variables.

f Change in Frailty	
	Estimate (*SE*, *p* Value)
	0.002 (0.0006, .006)
	0.009 (0.009, .304)
ation	−0.003 (0.001, .006)
oinfarcts	0.032 (0.009, $p < .001$)
oinfarcts	0.009 (0.009, $p = 0.342$)
athology	0.020 (0.007, $p = .004$)
l neuronal loss	0.017 (0.005, $p < .001$)