64° CONGRESSO NAZIONALE SIGG
Continuità di affetti, continuità di cure
ROMA, 27/30 NOVEMBRE 2019 - AUDITORIUM DELLA TECNICA

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

Role of NAFLD fibrosis score and frailty on the risk of dementia: the Italian Longitudinal Study on Aging

Custodero C, Ciavarella A, Di Fino L, Mastropierro V, Mazzoccoli C, Elia V, Carbonara C, Mastrofilippo T, Pilotto A, Sabbà C, Solfrizzi V

Medicina Interna e Geriatria «C. Frugoni», Dipartimento Interdisciplinare di Medicina

Università degli Studi di Bari

Background

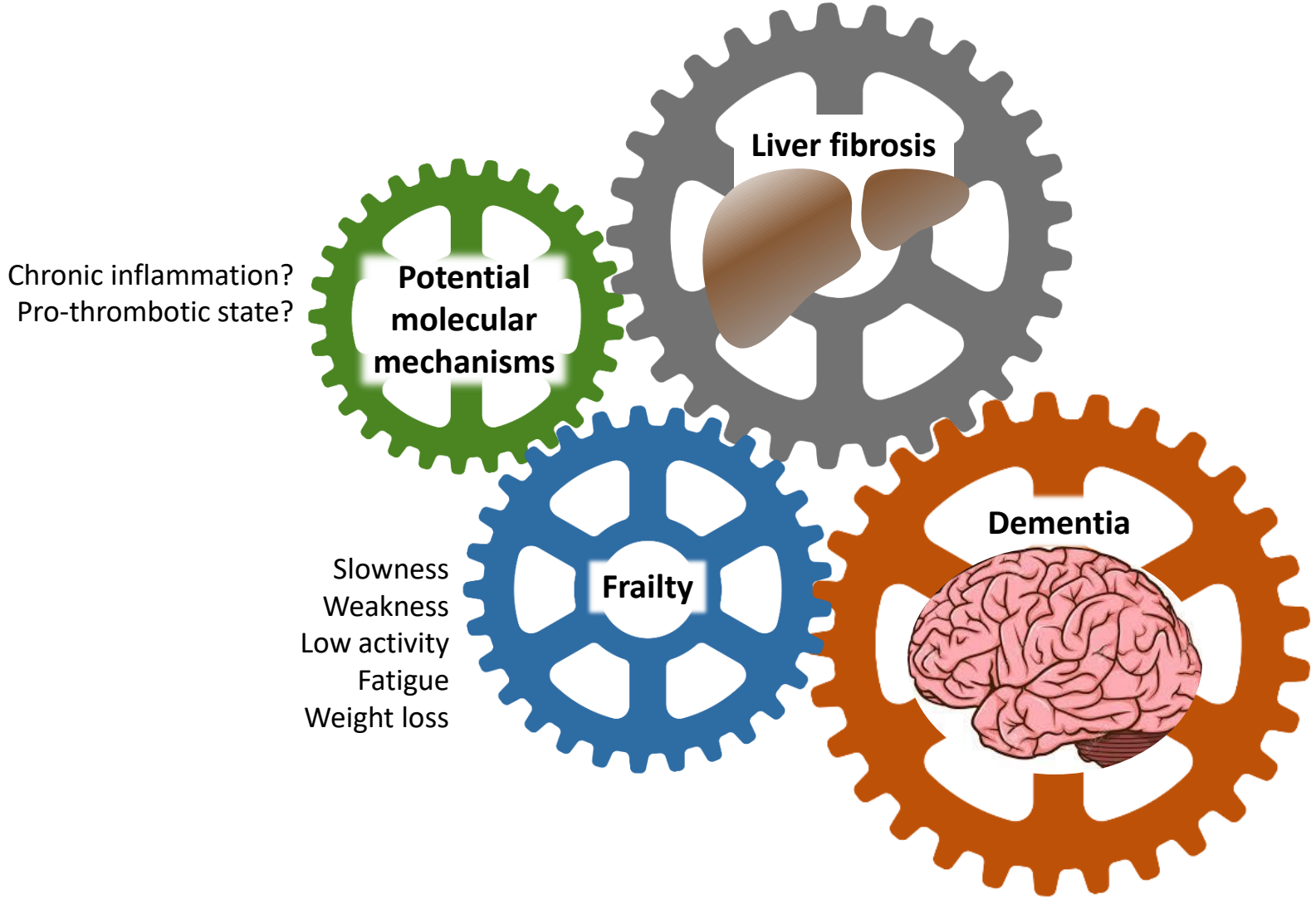
- Chronic liver diseases (CLDs) are a major cause of morbidity and mortality worldwide, mainly driven by rising impact of non-alcoholic fatty liver disease (NAFLD)
- Liver fibrosis:

  1) the main determinant of hepatic disease progression and of poor prognosis in patients with chronic liver diseases

  2) largely unrecognized in subjects with previously unknown liver disease and highly prevalent among older adults
- Middle-aged and older adults with higher degrees of liver fibrosis have poorer cognitive performance

Caballeria L, et al. Clin Gastroenterol Hepatol 2018
Weinstein G, et al. Liver Int 2019

Hypothesis
A Brain-Liver axis?



Aims

To determine :

1) Whether liver fibrosis severity is a risk factor for all-dementias, Alzheimer's Disease (AD), and Vascular Disease (VaD) in older adults
2) The role of frailty as possible effect modifier

NAFLD fibrosis score (NFS)

Algorithm:

-1.675 + 0.037 x age [*years*] + 0.094 x BMI [kg/m^2] + 1.13 x impaired fasting glucose (IFG) or type 2 diabetes [*yes = 1, no = 0*] + 0.99 x aspartate transaminase (AST) to alanine transaminase (ALT) ratio – 0.013 x platelet [$x\ 10^9/L$] – 0.66 x albumin [*g/dl*]

Classification:

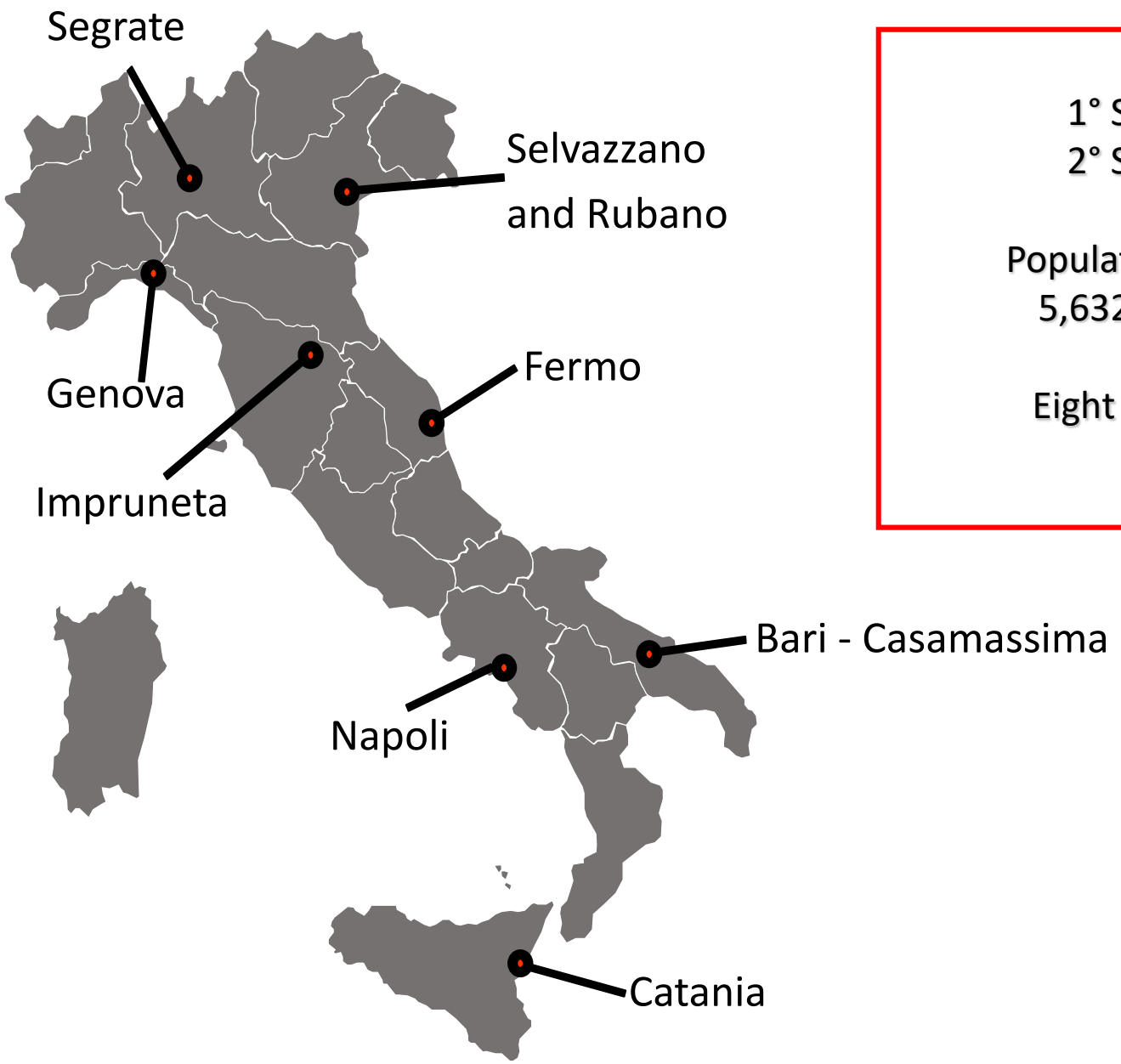
1) high probability of advanced fibrosis (F3-F4): NFS > 0.676,
2) indeterminate probability of advanced fibrosis: -1.455 < NFS ≤ 0.676,
3) low probability of advanced fibrosis (F0-F2): NFS < -1.455

Characterization of frailty

- Weight loss (unintentional Weight loss >5kg in the last year)
- Exhaustion (GDS Score ≥ 10 and negative answer to the question: “do you feel full of energy?”)
- Weakness (negative chair-stand test: inability to stand from a chair unaided and without using the arms)
- Slowness (time ≥ 7 seconds spent to walk 5 meters)
- Low activity (physical activity questionnaire: inactive or light physical activity ((no sweating) 2–4 h/wk)

Frailty defined for presence of 3 or more criteria

Italian Longitudinal Study On Aging - ILSA



1° Survey (1992-1993)
2° Survey (1995-1996)

Population – based sample of
5,632 subjects (65-84 yrs)

Eight Italian Municipalities

Methods

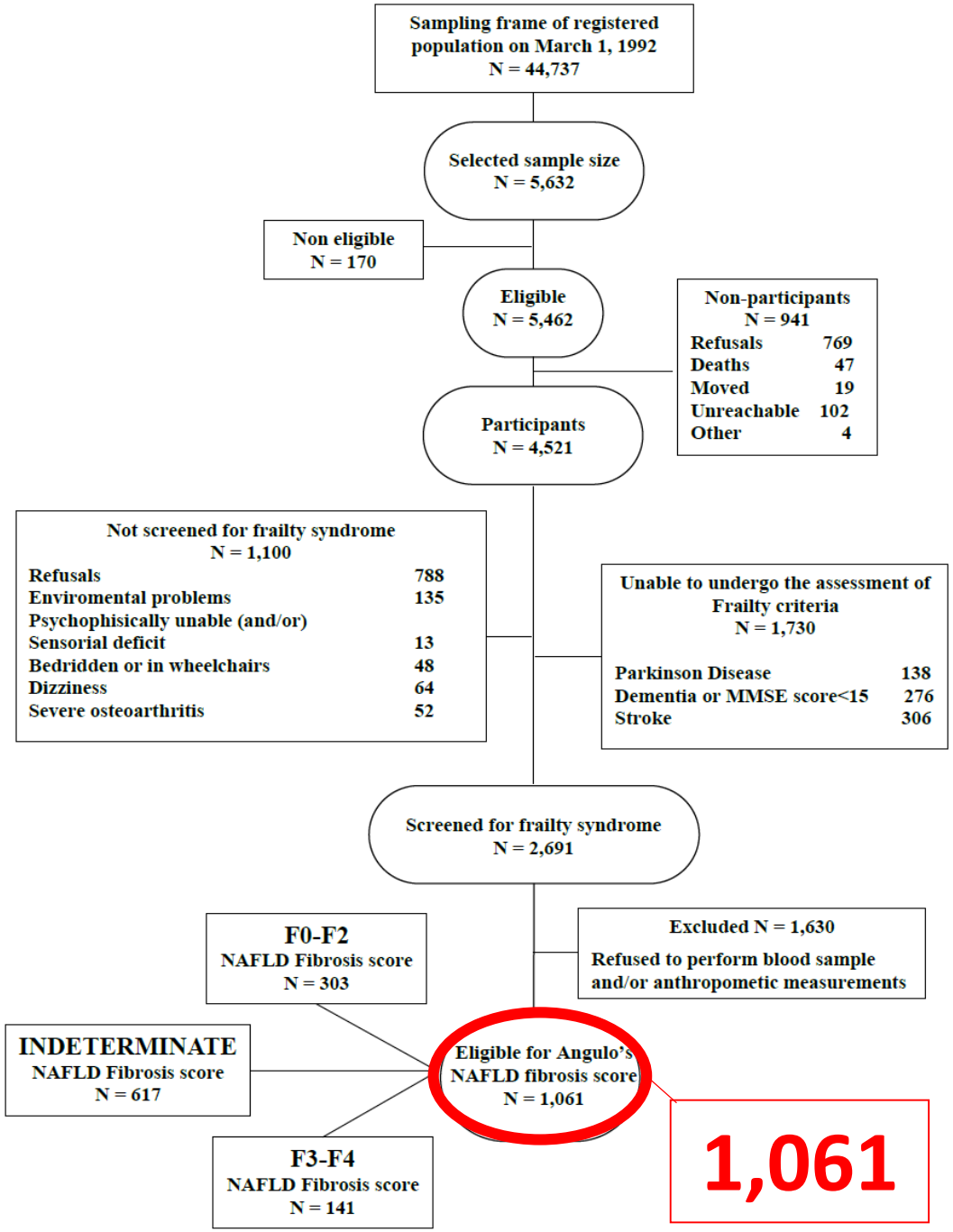
- Assessment of liver fibrosis (NAFLD Fibrosis Score - NFS)
- Screening for frailty (Fried's criteria)
- Diagnosis of dementia disorders:
  - DSM-III-R criteria for dementia syndrome
  - the NINCDS/ADRDA criteria for possible and probable AD
  - the ICD-10 criteria for VaD

<u>Statistical analysis:</u>

Incidence rates of dementia for the F3-F4 NFS and each frailty components (number of events per 1000 person-years)

Cox proportional hazards models for time to new events of all-dementias, AD, VaD

We verified the effect modifier of frailty status on the risk of all dementias, AD, and VaD due to NAFLD liver fibrosis



Results

Prevalence of NFS F3-F4: **15.66%**

- Increased with age (65-69 years: 7.63%; 69-74 years: 11.04%; 75-79 years: 17.54%; 80-84 years: 25.65%, test for trend odd ratio (OR) 1.65, 95% CI 1.39 to 1.95)
- Higher in men than in women (men: 18.46%, women: 12.02%, OR 1.65, 95% CI 1.04 to 2.17)
- Associated to frailty independently by age (OR 1.96, 95% CI 1.07 to 3.58) and sex (OR 2.99, 95% CI 1.66 to 5.38)

	Entire sample (n=1061)	NFS F0-F2 (n=303)	NFS indeterminate (n=617)	NFS F3-F4 (n=141)	P value
Women (%)	473 (44.58)	146 (48.18)	276 (44.81)	51 (36.17)	0.060
Age, years	72.39 (5.34)	70.64 (4.85)	72.70 (5.28)[‡]	74.76 (5.48)[*,†]	0.0001
Education, years	6.81 (5.00)	8.13 (5.62)	6.30 (4.55)[‡]	6.15 (4.95)[*]	0.0001
Pack-years	17.24 (26.16)	16.41 (24.42)	17.52 (26.96)	17.83 (26.36)	0.8734
Alcohol consumption (%)	192 (18.20)	63 (20.86)	109 (17.78)	20 (14.29)	0.6719
BMI, kg/m2	26.94 (4.35)	25.54 (3.60)	27.17 (4.20)[‡]	28.97 (5.36)[*,†]	0.0001
MMSE	26.10 (3.93)	26.65 (3.91)	26.06 (3.74)	25.06 (4.53)[*,†]	0.0001
IADL	8.04 (3.25)	7.68 (2.80)	8.00 (3.06)	8.96 (4.52)[*,†]	0.0515
GDS	8.96 (5.69)	8.41 (5.65)	9.35 (5.63)	8.47 (5.94)	0.005
Charlson Comorbidity Index	0.94 (0.80)	0.87 (0.81)	0.95 (0.78)	1.04 (0.87)	0.5041
Hypertension (%)	588 (55.42)	147 (48.51)[§]	369 (59.81)[¶]	72 (51.06)	0.003
Type 2 diabetes (%)	126 (12.33)	48 (16.49)[§]	61 (10.30)	17 (12.23)	0.031
Coronary artery disease (%)	104 (9.80)	32 (10.56)	60 (9.72)	12 (8.51)	0.792
Stroke (%)	12 (1.17)	4 (1.37)	5 (0.84)	3 (2.16)	0.404
Congestive heart failure (%)	92 (8.67)	22 (7.26)	49 (7.94)	21 (14.89)[§]	0.018
Metabolic syndrome (%)	450 (42.41)	115 (37.95)	271 (43.92)	64 (45.39)	0.169
Albumin, mg/dL	4.31 (0.41)	4.49 (0.40)	4.27 (0.39)[‡]	4.10 (0.39)[*,†]	0.0001
B/A1	0.88 (0.43)	0.92 (0.53)	0.88 (0.40)	0.84 (0.25)	0.2688
Frailty N (%)	65 (6.6)	14 (4.86)	33 (5.78)	18 (13.53)[¶]	0.002

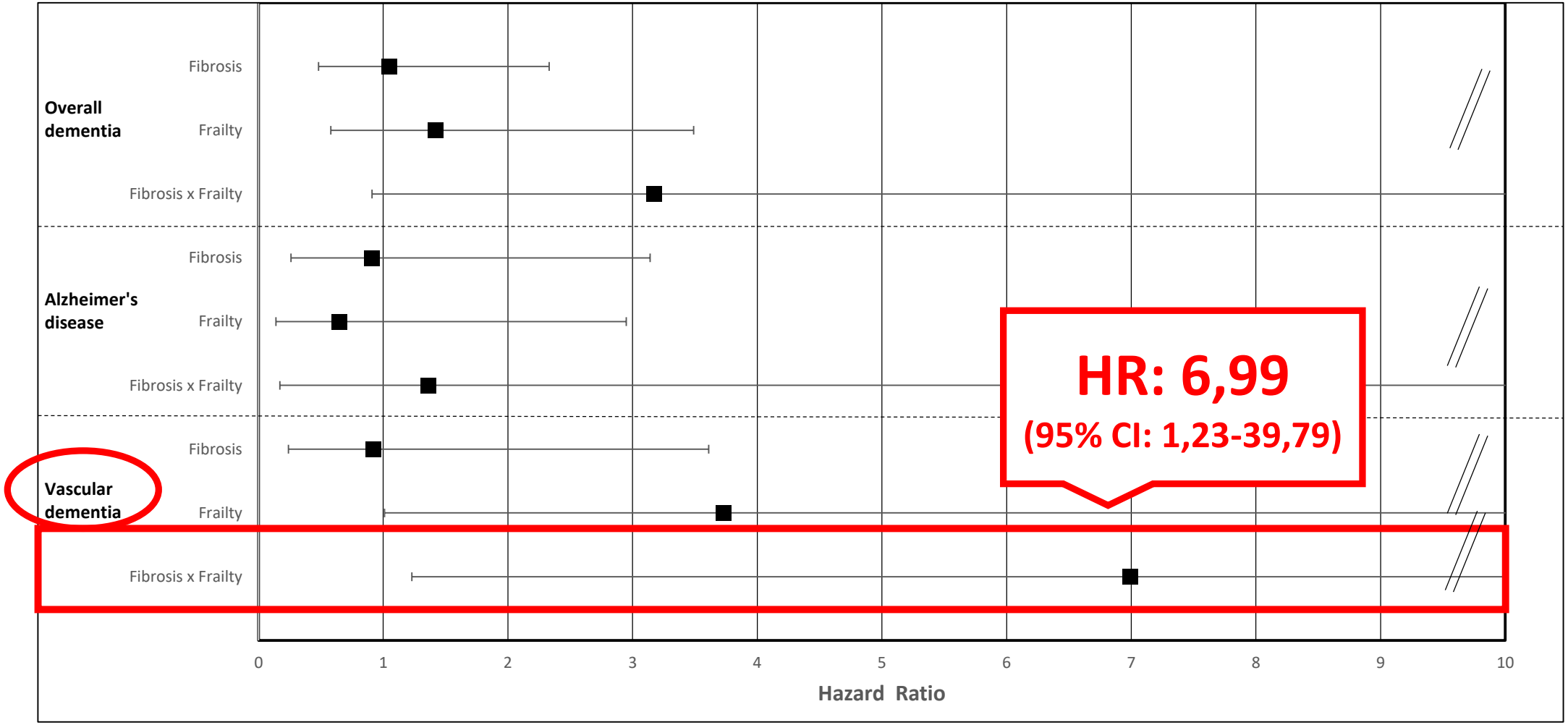
Incidence rates of all dementias in the NFS F3-F4

	Characteristics of frailty	New events	Rate	CI 95%
Frailty*	Weight loss	-	-	-
	Weakness	2	44.41	11.11-177.56
	Exhaustion	2	25.02	6.26-100.06
	Slowness	7	39.83	18.99-83.55
	Low activity	8	30.76	15.38-61.51
	≥ 3 impaired characteristics	3	44.16	14.24-136.92
Without frailty	Weight loss	-	-	-
	Weakness	8	15.73	7.87-31.45
	Exhaustion	8	16.89	8.44-33.76
	Slowness	3	7.94	2.56-24.61
	Low activity	-	-	-
	< 3 impaired characteristics	6	12.99	5.83-28-90

~ 5 times higher

* Frailty condition defined according to Fried's criteria

Hazard Ratios of Incident Dementia



HR adjusted for age, sex, metabolic syndrome, alcohol intake, education, pack-years cigarettes, Instrumental Activities of daily Living score, Mini Mental Score Examination score at baseline, Charlson Comorbidity Index score, apolipoprotein B-to-apolipoprotein A-I ratio.

Conclusions

- The presence of liver fibrosis might be a potentially modifiable risk factor for vascular dementia in frail older adults
- Slowness followed by weakness and low activity had the highest incidence rate for all dementias in subjects with higher NFS
- These findings should encourage NFS assessment in older persons
- Randomized controlled trials are warranted to verify if strategies acting on frailty condition or potential underlying common mechanisms with liver fibrosis (e.g. inflammation, thrombosis) could reduce the dementia risk in people with liver fibrosis