Frailty was associated with **cognitive decline** in the control arms of anti-dementia clinical trials.

Higher baseline frailty, identified by routinely collected laboratory safety data, is associated with greater cognitive decline in clinical trials of anti-dementia drugs.

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BACKGROUND

- The degree of frailty can be quantified with a **frailty index** based on the accumulation of deficits in routine blood work and vital signs: the **FI-Lab** [1].
- Frailty moderates the effect of neuropathology in the expression of dementia [2].

OBJECTIVE

- To use an **FI-Lab**, constructed from clinical trial laboratory safety data, in evaluating the relationship between **frailty** and **ADAS-Cog** progression in dementia clinical trials.

METHODS

N = 2097 (out of 6500) subjects from 7 (out of 24) trials. (No trial was excluded due to insufficient lab data, save for ApoE genotype.)

- Coalition Against Major Diseases (**CAMD**) database.
- Control arm data only.
- Sufficient lab data at screening (≥20 items).
- Baseline and ≥1 follow-up **ADAS-Cog 11** score.
- ApoE ε4 genotype.

FI-Lab $= (\sum_i^n x_i)/n$

- Each of a subject's n items (lab tests + vital signs at screening) are scored $x_i = 0$ (normal) or 1 (abnormal).
- Ranges from **0 (fit)** → **1 (frail)**.

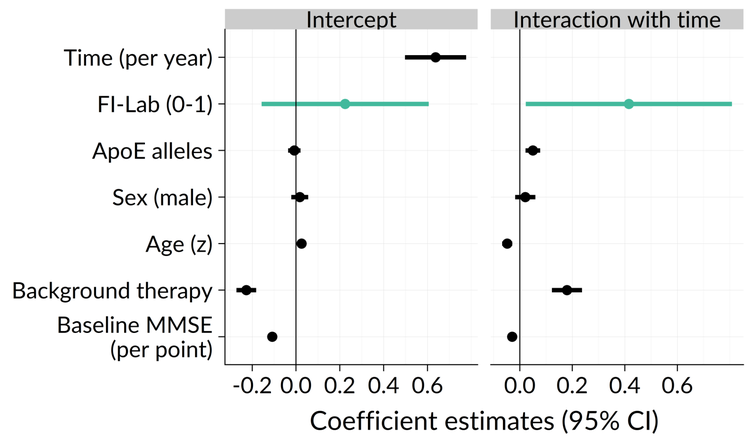
Longitudinal regression model

- Dependent: **ADAS-Cog 11**, beta-distributed.
- Fixed effects:
  - Time from baseline.
  - **FI-Lab**: [0-1].
  - Age [45-90+].
  - Sex.
  - Baseline MMSE: [0-30].
  - ApoE ε4 alleles: [0, 1, 2].
  - Background anti-dementia medication: [0, 1].
    - Cholinesterase inhibitors and/or memantine.
- Random effects: subject-specific slopes and intercepts.

RESULTS

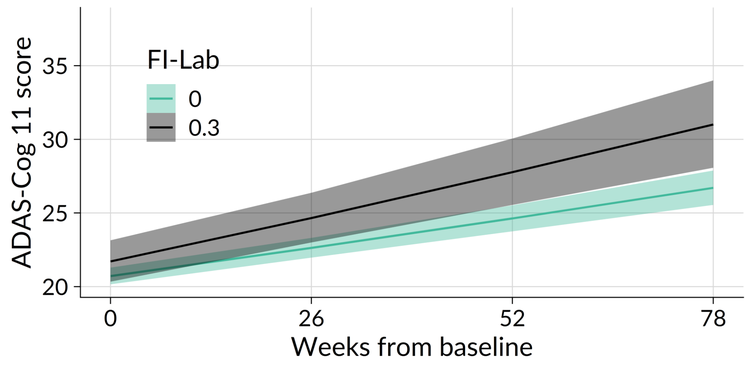
- Mean (SD) **FI-Lab** = 0.07 (0.05).
- **FI-Lab** had a modest effect on **ADAS-Cog 11** progression: β (95% CI) = **0.41 (0.02, 0.81)**.

Figure 1. Longitudinal model coefficient estimates.



- This correspond to a one-year increase of **6.1 (3.8, 8.3)** ADAS-Cog points for a **frail** individual, compared to **3.9 (3.0, 4.8)** for a **fit** individual.

Figure 2. Predicted ADAS-Cog progression (95% CI) for an *average* CAMD subject (see Table S1).



DISCUSSION

- In the **CAMD** database of control arm subjects with mild cognitive impairment or Alzheimer disease, **higher frailty** at screening was associated with greater **cognitive decline** over 12-78 weeks.
- These trials enrolled a fitter sample than most of their demented or non-demented age peers.

Table S1. Subject demographics and characteristics.

Study	Duration (weeks)	N	Age, mean (SD)	Female (%)	AD diagnosis (%)	Baseline MMSE, mean (SD)	Baseline ADAS-Cog , mean (SD)	Background medication use (%)	ApoE positive (%)	FI-Lab, mean (SD)
1009	12	157	74.2(6.3)	54.1	100	20.7 (3.8)	23.7 (11.1)	0	47.8	0.07 (0.06)
1056	54	466	72.9 (8.1)	56.2	100	20 (4.1)	23.9 (10.3)	100	59	0.06 (0.05)
1057	54	465	74.0 (8.0)	61.5	100	19.5 (4.1)	25.2 (10.8)	100	56.6	0.06 (0.05)
1058	24	153	72.5 (8.6)	60.1	100	19.6 (4.1)	24.8 (10.0)	0	50.3	0.06 (0.05)
1105	78	221	72.9 (8.9)	49.8	100	20.9 (3.5)	22.2 (9.6)	100	57.9	0.10 (0.05)
1132	52	282	70.5 (10.2)	43.3	0	26.9 (1.6)	19.1 (3.1)	0	41.8	0.10 (0.05)
1142	78	353	76.0 (7.8)	55.8	100	21.0 (3.4)	22.3 (8.4)	95	66.6	0.07 (0.04)
Total	-	**2097**	**73.4 (8.5)**	**55.0**	**86.6**	**21.1 (4.3)**	**23.2 (9.6)**	**70.9**	**55.8**	**0.07 (0.05)**

Figure S1. FI-Lab score distribution.

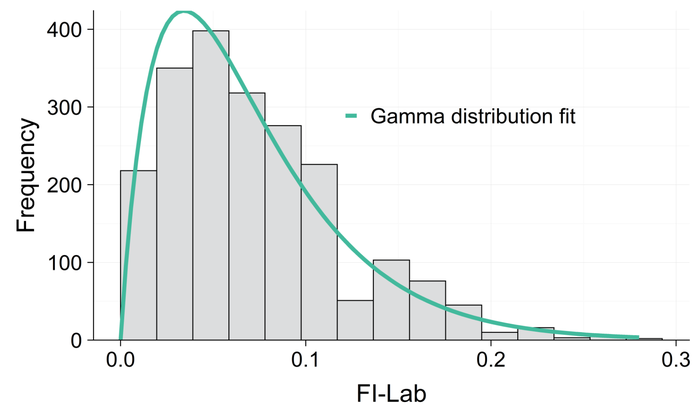


Table S2. Items included in FI-Lab construction.

Category	Test	# subjects	# studies	Units	Normal range*	% abnormal
Blood	Alanine Aminotransferase	2090	7	IU/L	0-48	2.2%
Blood	Albumin	2089	7	g/L	32-50	2.7%
Blood	Alkaline Phosphatase	2091	7	IU/L	20-125	3.4%
Blood	Aspartate Aminotransferase	2084	7	IU/L	0-42	1.9%
Blood	Basophils	2063	7	10^9/L	0-0.2	0.5%
Blood	Bilirubin	854	3	mg/dL	0.20-1.19	3.9%
Blood	Bilirubin, Direct	1393	4	umol/L	0-6	0.1%
Blood	Bilirubin, Indirect	1235	4	umol/L	0-22	2.6%
Blood	Calcium	2086	7	mmol/L	2.12-2.56	5.3%
Blood	Chloride	1930	6	mmol/L	95-108	3.9%
Blood	Cholesterol	511	5	mmol/L	0-5.17	55.9%
Blood	Creatine Kinase	2089	7	IU/L	0-190	7.3%
Blood	Creatinine	2090	7	umol/L	44-124	5.3%
Blood	Eosinophils	2063	7	10^9/L	0.05-0.55	8.3%
Blood	Erythrocytes	1909	6	10^12/L	3.8-5.5	5.9%
Blood	Folate	750	3	nmol/L	7-45	52.1%
Blood	Gamma Glutamyl Transferase	1428	4	IU/L	0-75	5.0%
Blood	Glucose	2089	7	mmol/L	3.9-6.9	10.6%
Blood	Hematocrit	1907	6	%	35-48	6.2%
Blood	Hemoglobin	2065	7	g/L	118-158	6.0%
Blood	Hemoglobin A1c	1322	5	%	0-6.4	9.9%
Blood	Leukocytes	2065	7	10^9/L	3.8-10.8	4.3%
Blood	Lymphocytes	2063	7	10^9/L	0.85-4.1	6.2%
Blood	Mean Corpuscular Hemoglobin	1691	5	pg	27-35	5.1%
Blood	Mean Corpuscular Volume	1845	6	fL	80-103	4.1%
Blood	Monocytes	2063	7	10^9/L	0.2-1.1	4.8%
Blood	Neutrophils	2063	7	10^9/L	1.8-8	3.7%
Blood	Percent Basophils	1570	5	%	0-2	0.9%
Blood	Percent Eosinophils	1570	5	%	0-7	2.8%
Blood	Percent Lymphocytes	1570	5	%	16-46	9.0%
Blood	Percent Monocytes	1570	5	%	0-12	2.0%
Blood	Percent Neutrophils	1570	5	%	40-75	11.5%
Blood	Phosphate	1293	4	mmol/L	0.7-1.4	3.5%
Blood	Platelets	2047	7	10^9/L	130-400	3.5%
Blood	Potassium	2084	7	mmol/L	3.5-5.3	3.0%
Blood	Protein	1932	6	g/L	60-81	2.2%
Blood	Sodium	1866	6	mmol/L	135-146	3.0%
Blood	Thyrotropin	2049	7	mIU/L	0.4-5.5	6.8%
Blood	Triglycerides	580	5	mmol/L	0.63-2.71	17.9%
Blood	Urea	1931	6	mmol/L	2.5-10.5	6.4%
Blood	Vitamin B12	2010	7	pmol/L	148-812	9.6%
Urine	Erythrocytes	508	2	/HPF	Negative-Trace	4.1%
Urine	Glucose	789	3	mg/dL	Negative-Trace	2.3%
Urine	Ketones	633	2	-	Negative	2.4%
Urine	Lactate Dehydrogenase	1574	5	IU/L	0-270	2.0%
Urine	pH	632	2	-	5-8	0.1%
Urine	Protein	788	3	mg/dL	Negative-Trace	3.9%
Urine	Specific Gravity	633	2	ratio	1.006-1.03	3.8%
Vital Sign	Diastolic Blood Pressure	2052	7	mmHg	60-90	4.8%
Vital Sign	Heart Rate	2051	7	beats/min	60-100	16.5%
Vital Sign	Pulse Pressure	2051	7	mmHg	30-60	33.8%
Vital Sign	Respiratory Rate	817	3	breaths/min	12-30	1.1%
Vital Sign	Systolic Blood Pressure	2052	7	mmHg	90-140	26.4%
Vital Sign	Temperature	820	3	C	36.1-37.2	17.7%

*Normal ranges varied both between and within studies. Reported numbers are median lower and upper ranges.

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References

[1] Howlett et al. *BMC Med.* 12: 171 (2014).
[2] Wallace et al. *Lancet Neurol.* 18: 177-184 (2019).