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ORIGINAL ARTICLE

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Associations between a laboratory frailty index and adverse health outcomes across age and sex

Joanna M. Blodgett[1] | Olga Theou[2] | Arnold Mitnitski[2] | Susan E. Howlett[2,3] | Kenneth Rockwood[2]

[1]MRC Unit for Lifelong Health and Ageing at UCL, London, UK

[2]Geriatric Medicine, Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

[3]Department of Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada

Correspondence
Joanna M. Blodgett, MRC Unit for Lifelong Health and Ageing at UCL, London, UK.
Email: joanna.blodgett.16@ucl.ac.uk

Abstract

Objective: Early frailty may be captured by a frailty index (FI) based entirely on vital signs and laboratory tests. Our aim was to examine associations between a laboratory-based FI (FI-Lab) and adverse health outcomes, and investigate how this changed with age.

Methods: Up to 8988 individuals aged 20+ years from the 2003-2004 and 2005-2006 National Health and Nutrition Examination Survey cohorts were included. Characteristics of the FI-Lab were compared to those of a self-reported clinical FI. Associations between each FI and health care use, self-reported health, and disability were examined in the full sample and across age groups.

Results: Laboratory-based FI scores increased with age but did not demonstrate expected sex differences. Women aged 20-39 years had higher FI scores than men; this pattern reversed after age 60 years. FI-Lab scores were associated with poor self-reported health (odds ratio[95% confidence interval]: 1.46[1.39-1.54]), high health care use (1.35[1.29-1.42]), and high disability (1.41[1.32-1.50]), even among those aged 20-39 years.

Conclusion: Higher FI-Lab scores were associated with poor health outcomes at all ages. Associations in the youngest group support the notion that deficit accumulation occurs across the lifespan. FI-Lab scores could be utilized as an early screening tool to identify deficit accumulation at the cellular and molecular level before they become clinically visible.

KEYWORDS
aging, epidemiology, frailty, pre-clinical

1 | INTRODUCTION

Frailty is defined as the increased vulnerability to poor health outcomes as a result of age-associated decline in multiple physiological systems.[1] In contrast to single measurements of physical capability, frailty represents the cumulative decline across several systems (i.e., mobility, cognition, comorbidities, vision, etc.) and is able to identify those at risk of poor health outcomes that may require intervention or additional care management.[2] Those with higher frailty are more likely to have poor health in subsequent years and have a higher risk of death.[3-6] The basis of frailty is rooted in aging, and the fact that some people are frailer than

others reflects that aging occurs at different rates.[2,7,8] Indeed, frailty can be a better predictor of mortality than chronological age itself.[9,10]

Understanding the mechanisms that underlie frailty is complex. Reflecting its intrinsic relationship with aging[7] and its multiple manifestations,[11] frailty represents an accumulation of deficits across multiple systems rather than a single system impairment. Despite substantial growth in frailty research over the last two decades, there is limited understanding of the cellular and molecular processes that dictate how these deficits scale up to become clinically visible.[12] Recent emergence in the geroscience field suggests that aging occurs first at the molecular and cellular level, before becoming clinically visible in an individual.[13,14] Building on animal models, increasingly, frailty research has focused on the assessment of subclinical frailty as a potential precursor to clinically visible frailty.[6,13,15] This research builds on the frailty index (FI) approach, which operationalizes frailty by calculating an index (theoretically between 0 and 1) of the proportion of health deficits present in an individual.[16] An FI built solely from vital signs and blood or urine tests (FI-Lab) demonstrates the well-established properties of a clinical FI and has been replicated across sexes,[13] countries,[6,13,15,17,18] and species.[19,20] FI-Lab deficits were commonly present in people with few clinically detectable health deficits; even in those with little evidence of frailty otherwise, laboratory test abnormalities increased the risk of death.[18]

These studies have primarily examined mortality as an outcome[13,15,17,18] with limited evidence on associations with other adverse health outcomes.[6] Furthermore, most of these studies considered an older cohort, with only a single study examining these associations across the full adult life course.[13] Despite the established phenomenon of females living longer, yet experiencing higher levels of frailty,[21,22] these studies have not examined sex differences in FI-Lab scores. For those reasons, we were interested in evaluating the relationship of abnormal laboratory test results (FI-Lab) with adverse health outcomes in a large, representative sample across the life course. Building on an initial report from our group on FI-Lab scores and premature mortality,[13] we sought to examine if FI-Lab scores were associated with disability, health care utilization, and self-reported health using data from the National Health and Nutrition Examination Survey (NHANES) and if these associations were present at all ages.

2 | METHODS

2.1 | Sample

Data from the NHANES 2003-2004 and 2005-2006 cohorts were utilized. NHANES is a nationally representative, cross-sectional study examining the health of American individuals. Up to 8898 individuals aged 20 years and older were included in analyses. Details of these individuals and missing data have been reported elsewhere.[13] Data are accessible through public access files on the NHANES website.[23]

2.2 | Measurement of frailty, disability, health care utilization, and self-reported health

Three frailty indices (FIs) were calculated for each study member. First, an FI-Lab consisted of 32 deficits measured with common blood and urine tests; examples of deficits are albumin, lactate dehydrogenase, and C-reactive protein. Next, an FI-Self Report was created using 36 deficits measured by a series of self-reported questions, such as history of angina, difficulty dressing, or memory impairment. Finally, these two FIs were combined to create a 68-item FI-Combined. Full details of the 68 items and abnormal references ranges have been previously published.[13]

Activities of daily living (ADL) disability was dichotomized as difficulty with any of the following: using a fork/knife, getting out of bed, getting dressed, or walking between rooms on the same floor.[24,25] Self-reported health was scored as "poor" if the individual answered *poor* or *fair* when asked how their general health was and "high" otherwise.[24] Health care utilization was scored as "high" if the individual had seen a doctor or health care professional four or more times in the last 12 months.[24]

2.3 | Statistical analysis

One-way analyses of variance and Tukey's post hoc examined if there were significant differences in FI scores between sexes, age groups, education levels, living status, and income categories. Logistic regressions examined the strength of the association between each FI and three adverse health outcomes: self-reported health, ADL disability, and health care utilization. Estimates represent the increased odds of having the adverse health outcome for every 0.10 increase in frailty score. Logistic regressions were performed in the full sample and then were stratified by age (ages 20-39, 40-59, 60+ years). Due to possible colinearity between the adverse health outcomes and FI-Self Report/Combined, deficits that were in both the FI and the outcome were removed from the index for their respective analyses. All statistical analyses were conducted in SPSS 20. An alpha level of 0.05 was used to determine statistical significance.

3 | RESULTS

Mean frailty scores increased with age with all three FIs (Figure 1). In the FI-Self Report and FI-Combined, there was an increase in frailty across all age groups (Table 1; $P < 0.001$). In the FI-Lab, those aged 20-39 years and 40-59 years had similar scores ($P = 0.31$), while those aged 60+ years had significantly higher scores than both younger groups ($P < 0.001$). At all ages, women had higher frailty levels than men in the FI-Self Report and FI-Combined. Women aged 20-39 years had higher FI-Lab frailty than their male counterpoints, while this pattern reversed during midlife leading to men having significantly higher FI-Lab scores in those aged 60+ years ($P < 0.005$; Figure 1A, Table 1). At age 40-59 years, there were no differences in FI-Lab frailty between men and women ($P = 0.85$).

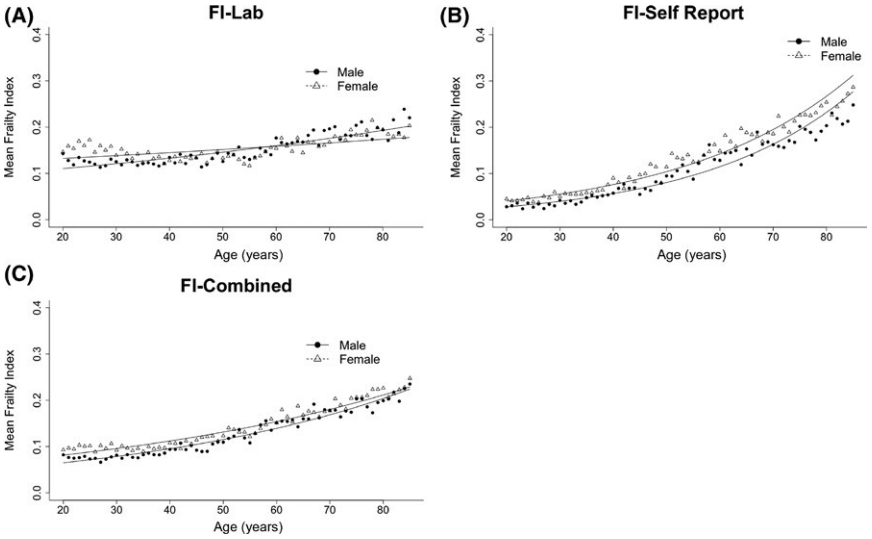

FIGURE 1 Increase in frailty index (FI) score with age by sex in (A) FI-Lab, (B) FI-Self Report, (C) FI-Combined

Those with higher levels of frailty were more likely to have lower educational attainment ($P < 0.05$) and income ($P < 0.001$); this held true in all three FIs across all age groups. There were significantly higher FI-Self Report ($P < 0.001$) and FI-Combined ($P < 0.001$) scores in those participants who were widowed (followed by divorced or separated, married, and finally not married). The same pattern was found in the FI-Lab ($P < 0.01$); however, there was no significant difference between those who were married and those who had never married ($P = 0.59$; Table 1).

A 0.1 increase in FI-Lab score was associated with a 1.46 (95% confidence interval [CI]: 1.39-1.54), 1.41 (1.32-1.50), and 1.35 (1.29-1.42) times higher risk of poor self-reported health, disability, and high health care use, respectively (Table 2). FI-Self Report or FI-Combined score was also associated with higher risk of these three outcomes; these odds ratios were larger than those of FI-Lab (Table 2). When stratified by age, FI-Lab score remained associated with higher risk of all adverse health outcomes at all ages and odds ratios were comparable between age groups. Similar patterns of association across age group were also seen for the FI-Self Report and FI-Combined (Table 2).

4 | DISCUSSION

In these cross-sectional analyses, higher FI-Lab scores were associated with higher risk of poor self-reported health, disability, and high health care utilization; notably, these associations were present across all age groups. FI-Lab scores were higher in women in early life, but this pattern reversed in midlife, and men had higher FI-Lab scores after age 60 years. When compared to the FI-Self Report (and FI-Combined), the FI-Lab demonstrated similar associations with demographic characteristics and similar, albeit smaller, associations with the adverse health outcomes.

Commonly, as here with self-report data (FI-Self Report scores), women have higher frailty levels than men.[26] In contrast, the FI-Lab scores were higher in women aged 20-39 years but higher in men after age 60 years. In the Irish Longitudinal Study on Ageing, women aged 50+ years had higher scores in a self-reported FI, but lower scores in a performance-based FI, suggesting possible sex bias with self-report data.[27] Mitnitski et al[28] showed that sex differences in self-reported FIs are not consistent across all ages, and can converge in late life. Similarly, Kulminski et al[7] showed convergence of FI scores for men and women at extreme ages; they proposed that the sex-specific excess in health deficits may vary according to the particular set of potential deficits used. A related study demonstrated that abnormalities in blood pressure, pulse, cholesterol, and glucose were more strongly associated with mortality in women.[29] Even so, the so-called major health deficits (such as disability) might result in qualitatively distinctive sex deficit acceleration patterns.[30] How laboratory tests fit as major/minor deficits is not clear.

Adding more deficits to the FI can strengthen its predictive ability[31,32]; here, the 68-item FI-Combined showed higher odds ratios with self-reported health and health care use than did the 36-item FI-Self Report and FI-Lab. Whether this reflects the nature of the items or increased information value due to more items is not clear.[33] Similarly, Howlett et al[18] showed that combining self-reported and laboratory measures increased the prediction of mortality. In contrast, the FI-Self Report was more strongly associated with ADL disability than was the FI-Combined. This is unsurprising: a self-reported FI might be expected to be better correlated with self-reported disability in a cross-sectional study than would lab values.

These findings replicate evidence that has shown an increased risk of poor outcomes in those with higher FI-Lab score.[6,13,15,17,18] In contrast to previous analyses of this NHANES cohort with mortality,[13] the odds ratios associated with FI-Lab were smaller than those of the FI-Self Report. This may be due to the cross-sectional data collection, where one would expect clinically visible frailty to demonstrate stronger associations with the adverse health outcomes than a sub-clinical FI. Longitudinal evidence could determine if subclinical frailty (FI-Lab), which may occur before clinical frailty

TABLE 1 Descriptive characteristics of the full sample by all three frailty indices

	FI-Lab	FI-Self Report	FI-Combined
Whole sample (n = 8898)			
Mean ± SD	0.15 ± 0.09	0.11 ± 0.11	0.13 ± 0.08
Median	0.13	0.07	0.11
Range	0.00-0.65	0.00-0.80	0.00-0.63
99th percentile	0.41	0.49	0.40
	Mean ± SD	**Mean ± SD**	**Mean ± SD**
Sex group			
Male (n = 4297)	0.13 ± 0.08	0.08 ± 0.10	0.11 ± 0.07
Female (*n* = 4601)	0.13 ± 0.08	0.11 ± 0.11	0.12 ± 0.08
Age group (y)			
20-39 (*n* = 3238)	0.14 ± 0.08	0.04 ± 0.05	0.09 ± 0.05
40-59 (n = 2637)	0.13 ± 0.08	0.10 ± 0.10	0.12 ± 0.07
60+ (n = 3023)	0.18 ± 0.09	0.19 ± 0.12	0.19 ± 0.09
Education group			
Less than high school (n = 2530)	0.16 ± 0.09	0.13 ± 0.13	0.14 ± 0.09
High school (n = 2170)	0.14 ± 0.08	0.10 ± 0.11	0.12 ± 0.08
Some college/AA degree (n = 2480)	0.13 ± 0.08	0.09 ± 0.10	0.11 ± 0.07
College graduate or more (n = 1706)	0.12 ± 0.07	0.07 ± 0.08	0.09 ± 0.06
Marital status group			
Married (n = 5519)	0.13 ± 0.08	0.09 ± 0.09	0.11 ± 0.07
Widowed (n = 866)	0.18 ± 0.10	0.21 ± 0.13	0.20 ± 0.10
Divorced/Separated (n = 1098)	0.14 ± 0.08	0.12 ± 0.12	0.13 ± 0.08
Never married (n = 1409)	0.13 ± 0.07	0.06 ± 0.08	0.09 ± 0.06
Income group			
Less than $20 000 (n = 2070)	0.16 ± 0.09	0.14 ± 0.13	0.15 ± 0.09
$20 000-$40 000 (n = 2797)	0.14 ± 0.08	0.11 ± 0.11	0.12 ± 0.08
$40 000-$75 000 (n = 1775)	0.13 ± 0.08	0.09 ± 0.09	0.11 ± 0.07
More than $75 000 (n = 1819)	0.11 ± 0.07	0.06 ± 0.07	0.09 ± 0.05

AA, Associate of Arts; FI, frailty index.

(FI-Self Report), is associated with health outcomes after a multi-year follow-up. However, it is notable that these associations were robust across all outcomes and all age groups. That all three FIs were significantly associated with poor self-reported health, high ADL disability, and high health care use in participants aged 20-39 years further supports the concept that the deficit accumulation of aging occurs across the lifespan.

The FI-Lab score in this same cohort was not previously associated with 8-year mortality in those aged 20-39 years.[13] However, mortality may not be an appropriate outcome to evaluate the predictive ability of the FI-Lab in younger people as mortality before the age of 50 years is very low and not commonly related to age-related illness within the general population. Indeed, the association between FI-Lab and adverse outcomes, such as disability, high health care use, and low self-reported health, may represent an intermediate stage of risk identification as each of these outcomes is associated with premature mortality.[34,35] Our findings show that subclinical deficits can be identified at any point in the adult lifespan.

The main limitation of this study is the cross-sectional design. Still, even recognizing that temporality is only one component of the Bradford Hill criteria for causation,[36] we have been careful not to make any causal claims and to comment only on associations between FI scores and three self-reported outcomes. Follow-up research should consider longitudinal outcomes to determine the predictive ability of the FI-Lab on clinically visible deficits in a young and middle-aged population. This could identify an aging pathway from cellular and molecular deficits to clinical deficits to adverse outcomes. In particular, future longitudinal research could examine the predictive validity of FI-Lab in a young population who have yet to show clinical deficits.

TABLE 2 Logistic regression examining the association between each FI and related adverse health outcomes

Model number	FI	Outcomes		
		Self-reported health Odds ratio (95% CI)	ADL disability Odds ratio (95% CI)	Health care use Odds ratio (95% CI)
Full sample (n = 8878)				
Proportion reporting outcome		n = 2039 (23.0%)	n = 1258 (12.2%)	n = 3744 (42.2%)
1	FI-Self Report	2.55 (2.40-2.71)	4.99 (4.56-5.45)	2.15 (2.02-2.27)
2	FI-Lab	1.46 (1.39-1.54)	1.41 (1.32-1.50)	1.35 (1.29-1.42)
3	FI-Combined	2.83 (2.63-3.04)	4.58 (4.16-5.04)	2.36 (2.21-2.52)
20-39 y old (n = 3238)				
Proportion reporting outcome		n = 473 (14.6%)	n = 101 (3.1%)	n = 1061 (32.8%)
4	FI-Self Report	2.51 (2.15-2.94)	15.13 (10.65-21.51)	2.16 (1.85-2.54)
5	FI-Lab	1.30 (1.17-1.45)	1.27 (1.02-1.58)	1.41 (1.29-1.55)
6	FI-Combined	2.22 (1.88-2.61)	7.23 (5.26-9.93)	2.41 (2.09-2.79)
40-59 y old (n = 2637)				
Proportion reporting outcome		n = 607 (23.0%)	n = 367 (13.9%)	n = 975 (37.0%)
7	FI-Self Report	3.16 (2.82-3.54)	5.84 (4.97-6.87)	2.70 (2.42-3.02)
8	FI-Lab	1.74 (1.57-1.92)	1.55 (1.38-1.75)	1.29 (1.18-1.41)
9	FI-Combined	4.22 (3.65-4.89)	6.23 (5.17-7.50)	2.83 (2.51-3.21)
60+ y old (n = 3023)				
Proportion reporting outcome		n = 959 (31.7%)	n = 790 (26.1%)	n = 1708 (56.5%)
10	FI-Self Report	2.51 (2.15-2.94)	3.80 (3.42-4.22)	1.93 (1.79-2.08)
11	FI-Lab	1.49 (1.38-1.6)	1.45 (1.34-1.57)	1.24 (1.15-1.33)
12	FI-Combined	2.67 (2.41-2.95)	3.84 (3.41-4.32)	2.01 (1.83-2.20)

ADL, activities of daily living; FI, frailty index.
Each odds ratio represents the increased association for every 0.1 increase in frailty score (each model is adjusted for age and sex).

The FI-Lab could be utilized as an early screening tool to identify those exhibiting patterns of frailty at the cellular/molecular level. Indeed, creating an FI-Lab using routine blood tests could be a more convenient and feasible option to identify those at increased risk, as recently shown by the electronic FI (e-FI), which calculates a frailty score using routinely available, primary care health records.[37]

Clinically visible deficits must arise as a consequence of what is happening at the organ, tissue, and cellular/subcellular levels. Exactly how subcellular deficits scale up to become clinically visible is not yet clear.[38,39] Linking FI-Lab changes to single aging biomarkers is proving to be tricky, as proven by experience with it and telomere length.[14,40,41] Some results suggest that the degree of frailty correlates with structural and functional changes at the cellular and organ levels.[42,43] In general, these changes suggest that how subcellular changes occur influences the propagation of deficits through a complex network.[32]

CONFLICT OF INTEREST

Kenneth Rockwood is President and Chief Science Officer of DGI Clinical, which in the last 5 years has had contracts with pharma and device manufacturers (Baxter, Baxalta, Shire, Hollister, Nutricia, Roche, Otsuka) on individualized outcome measurement. In 2017 he attended an advisory board meeting with Lundbeck. Otherwise any personal fees are for invited guest lectures and academic symposia, received directly from event organizers, chiefly for presentations on frailty. He is associate director of the Canadian Consortium on Neurodegeneration in Aging, which is funded by the Canadian Institutes of Health Research, and with additional funding from the Alzheimer Society of Canada and several other charities, as well as, in its first phase (2013-2018), from Pfizer Canada and Sanofi Canada. He receives career support from the Dalhousie Medical Research Foundation as the Kathryn Allen Weldon Professor of Alzheimer Research, and research support from the Canadian Institutes of Health Research, the QEII Health Science Centre Foundation, the Capital Health Research Fund, and the Fountain Family Innovation Fund of the QEII Health Science Centre Foundation. There are no conflicts of interest to report for the other authors.

AUTHOR CONTRIBUTIONS

All authors were involved in the concept and design of the manuscript and provided comments. J.B. conducted all statistical analyses. J.B., O.T., and K.R. drafted the manuscript with input from all authors.

ORCID

Joanna M. Blodgett https://orcid.org/0000-0001-7684-3571

Olga Theou https://orcid.org/0000-0001-6460-782X

Arnold Mitnitski https://orcid.org/0000-0003-4596-2847

Susan E. Howlett https://orcid.org/0000-0001-5351-6308

Kenneth Rockwood https://orcid.org/0000-0002-6674-995X

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