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Original Research

High prevalence of frailty in patients with adrenal adenomas and adrenocortical hormone excess: a cross-sectional multi-centre study with prospective enrolment

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Abstract

Objective: Frailty, characterized by multi-system decline, increases vulnerability to adverse health outcomes and can be measured using Frailty Index (FI). We aimed to assess the prevalence of frailty in patients with adrenal disorders (based on hormonal sub-type) and examine association between FI and performance-based measures of physical function.

Design: Multi-centre, cross-sectional study (March 2019-August 2022).

Methods: Adult patients with adrenal disorders (non-functioning adrenal adenomas [NFA], mild autonomous cortisol secretion [MACS], Cushing syndrome [CS], primary aldosteronism [PA]) and referent subjects without adrenal disorders completed a questionnaire encompassing 47 health variables (comorbidities, symptoms, daily living activities). FI was calculated as the average score of all variables and frailty defined as FI $\geq$ 0.25. Physical function was assessed with hand grip, timed up-and-go test, chair rising test, 6-minute walk test, and gait speed.

Results: Compared to referent subjects ($n = 89$), patients with adrenal disorders ($n = 520$) showed increased age, sex, and body mass index-adjusted prevalence of frailty (CS [odds ratio—OR 19.2, 95% confidence interval—CI 6.7-70], MACS [OR 12.5, 95% CI 4.8-42.9], PA [OR 8.4, 95% CI 2.9-30.4], NFA [OR 4.5, 95% CI 1.7-15.9]). Prevalence of frailty was similar to referent subjects when post-dexamethasone cortisol was <28 nmol/L and was higher when post-dexamethasone cortisol was 28-50 nmol/L (OR 4.6, 95% CI 1.7-16.5). FI correlated with all measures of physical function ($P < .001$).

Conclusions: Whilst frailty prevalence was highest in patients with adrenocortical hormone excess, even patients with NFA demonstrated an increased prevalence compared to the referent population. Future longitudinal studies are needed to evaluate the impact of various management strategies on frailty.

Keywords: Cushing syndrome, cortisol, aldosterone, non-functioning, dexamethasone suppression test

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Significance

In this multi-centre study, using the Frailty Index (FI) tool, we demonstrated an increased burden of frailty in patients with adrenal disorders (adenomas or adrenocortical hormone excess) compared to referent subjects without adrenal disorders. Although frailty prevalence was highest in patients with adrenocortical hormone excess, we noted an increased prevalence even in those with non-functioning adrenal adenomas and post-dexamethasone cortisol of 28-50 nmol/L. The increased burden of frailty observed in patients with non-functioning adrenal adenoma highlights that even subtle degree of cortisol excess (below the standard cut-off) has negative health implications. Identifying patients with adrenocortical adenomas at increased health risk is challenging in current practice. We propose the adrenal-specific FI as a simple tool with the potential to assist in identifying these patients.

Introduction

Adrenal adenomas are frequently encountered in clinical practice and can be seen in up to 7% of individuals undergoing cross-sectional abdominal imaging.[1,2] Only a minority of patients with adrenal adenomas demonstrate features of overt hormone excess, such as Cushing syndrome (CS) or primary aldosteronism (PA). More than 90% of patients with adrenal adenomas are asymptomatic and incidentally discovered. Based on the overnight 1 mg oral dexamethasone suppression test (DST), adrenal incidentalomas can be classified as non-functioning adrenal adenoma (NFA) when post-DST morning cortisol is ≤ 50 nmol/L (1.8 mcg/dL) or adenomas with mild autonomous cortisol secretion (MACS), when post-DST morning cortisol is >50 nmol/L.[3–5] Patients with MACS have been reported to demonstrate an increased prevalence and incidence of cardiovascular risk factors such as hypertension, obesity, type 2 diabetes mellitus, abnormal body composition, dyslipidaemia, chronic kidney dysfunction, and arrhythmias, and subsequently increased risk of cardiovascular events, and mortality.[6–12] In addition, patients with MACS are reported to have a higher prevalence and incidence of both symptomatic and asymptomatic fragility fractures.[13,14] Limited data also suggest that even patients with NFA demonstrate an increased risk of developing diabetes and altered body composition, highlighting that even lower levels of autonomous cortisol secretion may be harmful.[12,15,16]

Previous studies in MACS and NFA investigated the prevalence and incidence of a limited number of comorbidities associated with hormone excess.[7,9] Adrenalectomy was reported to result in variable improvement of certain parameters (hypertension, diabetes mellitus, excessive weight, dyslipidaemia) in both patients with MACS and NFA.[17] Identifying patients with adrenal incidentaloma at risk for cardiovascular events and increased morbidity is challenging, and as such adrenalectomy has been recommended only for a minority of patients with MACS, mainly in those with established cardiovascular risk factors.[3]

Frailty is a multidimensional syndrome characterized by physiological and functional decline, thereby resulting in an increased vulnerability to adverse health outcomes.[18] Frailty can be quantified using validated tools such as Frailty Index (FI) or performance-based measures that assess an individual's overall health status and accurately predict the risk of worsening health, hospitalization, and mortality.[19,20] FI is a self-reported questionnaire designed to assess health variables covering a range of systems and works on the concept of deficit accumulation. On the other hand, performance-based measures evaluate physical function (muscle strength or physical performance) using direct measures of handgrip strength, gait speed, or chair rising test.[21,22] Whilst FI relies on dichotomous self-reporting, performance-based measures are time-consuming and challenging to implement in routine clinical practice.

To evaluate the impact of MACS more accurately on patients' overall health, we previously constructed an FI for patients with adrenal adenomas using 47 health variables that included activities of daily living and patients' symptoms in addition to comorbidities.[10] Following the initial development of the FI for patients with adrenal adenomas, we designed a prospective multi-centre study with the following objectives: (1) to determine the prevalence of frailty in adrenal disorders based on hormonal sub-type and (2) to examine association between FI and performance-based measures of frailty (muscle strength and physical function).

Methods

Study design

We conducted a multi-centre, cross-sectional study with prospective enrolment of participants between March 28, 2019 and August 20, 2022. The study protocol was approved by the Mayo Clinic Ethics Committee followed by the local ethics committee from the respective participating institutions prior to data collection. Informed consent was obtained from all participants. This research complies with the Declaration of Helsinki.

Participant selection

Participants included adult patients with NFA, MACS, CS, PA, and referent subjects without adrenal disorders. Patients were identified either during outpatient clinic visit or via electronic medical search. To avoid imaging bias, referent subjects were recruited via a letter addressed to individuals who underwent an abdominal scan for reasons other than an adrenal disorder at Mayo Clinic, Rochester, and were eligible if they had a negative history of an adrenal disorder and the abdominal scan demonstrated no adrenal mass. Patients with CS included those with either corticotropin (ACTH)-independent or ACTH-dependent aetiology and were diagnosed based on the presence of clinical features and biochemical evidence of hyper-cortisolism per the standard clinical practice guidelines.[23] Similarly, patients with PA were diagnosed according to standard clinical practice guidelines.[24] Based on the 2016 clinical practice guidelines,[3] MACS was defined by a morning serum cortisol of > 50 nmol/L after 1-mg DST and the absence of clinical features of CS (facial plethora, moon face, supraclavicular fullness, dorsocervical fat pad, large violaceous striae, proximal myopathy). Those with morning serum cortisol $\leq$50 nmol/L after 1-mg DST were categorized as NFA. In the instances when overnight 8-mg DST was performed (in lieu of 1-mg DST), morning serum cortisol of >28 nmol/L was

Table 1. Health variables used to calculate Frailty Index.

	Points assigned
Comorbidities	
Body mass index, kg/m^2	<18.5 or ≥30 = 1 25 to <30 = 0.5 18.5 to <25 = 0
Hypertension	Yes = 1, No = 0
Diabetes	Yes = 1, No = 0
Hyperlipidaemia	Yes = 1, No = 0
Chronic kidney disease	Yes = 1, No = 0
Coronary artery disease	Yes = 1, No = 0
Cardiac arrhythmia	Yes = 1, No = 0
Atrial fibrillation	Yes = 1, No = 0
Congestive heart failure	Yes = 1, No = 0
Stroke	Yes = 1, No = 0
Cancer	Yes = 1, No = 0
Dementia	Yes = 1, No = 0
Chronic obstructive pulmonary disease	Yes = 1, No = 0
Asthma	Yes = 1, No = 0
Depression	Yes = 1, No = 0
Anxiety	Yes = 1, No = 0
Substance use disorders	Yes = 1, No = 0
Osteoporosis	Yes = 1, No = 0
Fragility fracture	Yes = 1, No = 0
Arthritis	Yes = 1, No = 0
Symptoms	
Excessive bruising	Yes = 1, No = 0
Joint pain/stiffness	Yes = 1, No = 0
Muscle pain/stiffness	Yes = 1, No = 0
Back pain/stiffness	Yes = 1, No = 0
Weakness in arms/legs	Yes = 1, No = 0
Tendency to fall easily	Yes = 1, No = 0
Weight gain of >10 pounds in last year	Yes = 1, No = 0
Sleep difficulty	Yes = 1, No = 0
Sad most of the time	Yes = 1, No = 0
Restless and irritable	Yes = 1, No = 0
Anxious or nervous	Yes = 1, No = 0
Difficulty concentrating	Yes = 1, No = 0
Little interest in relationship or activities	Yes = 1, No = 0
Activities of daily living	
Need help with preparing meals	Yes = 1, No = 0
Need help with eating	Yes = 1, No = 0
Need help with dressing	Yes = 1, No = 0
Need help with using toilet	Yes = 1, No = 0
Need help with housekeeping	Yes = 1, No = 0
Need help climbing stairs	Yes = 1, No = 0
Need help with bathing	Yes = 1, No = 0
Need help with walking	Yes = 1, No = 0
Need help with using transportation	Yes = 1, No = 0
Need help with getting in/out of bed	Yes = 1, No = 0
Need help with medications	Yes = 1, No = 0
Depend on assistive devices (walker, cane, etc.)	Yes = 1, No = 0
Need assistive device for breathing	Yes = 1, No = 0
Can climb 2 flights of stairs	No, can't do at all = 1 Yes, with difficulty = 0.5 Yes, with no difficulty = 0

used to diagnose MACS based on our institutional practice. We excluded individuals younger than 18 years old, those unable to consent, and those with exogenous CS, adrenal malignancy, and pheochromocytoma.

Protocol

All participants completed a questionnaire at the time of enrolment and prior to any planned surgical intervention. The questionnaire comprised 47 health variables covering 3 major domains—20 chronic comorbidities, 13 symptoms, 14 activities of daily living.[10] All variables were assigned a value of "1" point when present and "0" points when not present, with the exception of body mass index (BMI) (<18.5 kg/m^2 [underweight] or > 30 kg/m^2 [obese] = 1; BMI 25-29.9 kg/m^2 [overweight] = 0.5; BMI 18.5-24.9 kg/m^2 [normal weight] = 0), and ability to climb 2 flights of stairs without rest (no, can't do at all = 1; yes, with difficulty = 0.5; yes, with no difficulty = 0), Table 1. In instances of missing data (0.14% in entire cohort), a value of "0" point was assigned to the specific variable. The FI was calculated as the sum of all variables divided by 47. Based on FI, participants were categorized as frail (FI ≥ 0.25), pre-frail (FI 0.11–0.24), non-frail (FI < 0.11).[10]

Participants from one centre (Mayo Clinic) were asked to participate in optional performance-based measurement of muscle strength and physical function (handgrip strength, timed up-and-go test, gait speed, 6-minute walk test, chair rising test). Hand grip strength (in kilograms) was measured using a Jamar dynamometer and the average of three readings in each hand was calculated.[25] The timed up-and-go test included the time (in seconds) taken by participant to stand up from a chair, walk 3 m, turn around and sit down.[26] Gait speed (as metre per second) involved the time taken to cover a standard distance of 4.57 m on flat ground.[27] The 6-minute walk test entailed the measurement of distance (in metres) covered by the participant in 6 min.[28] Chair rising test involved the number of sit to stands a participant could complete in 30 s.[22]

Information on demographics, BMI, smoking status, alcohol consumption, tumour imaging characteristics (location and maximum diameter), and hormonal work-up was collected during the health interview and based on the review of medical record at the time of enrolment.

Outcomes

FI questionnaire with assessment of prevalence of frailty and sub-components (comorbidities, symptoms, activities of daily living) in patient with adrenal disorders and referent subjects. Relationship of FI with post–1-mg-DST cortisol and performance-based measures of frailty.

Statistical analysis

We presented categorical data as counts and percentages, and continuous data as medians and interquartile ranges. Association between variables was assessed using the chi-square test and rank sum test. Logistic regression models were used to test for group differences in prevalence of frailty (adjusted for age and sex, and BMI), and sub-components (adjusted for age and sex). The relationship of FI with post–1-mg-DST cortisol and performance-based measures of frailty was assessed using Spearman correlations (adjusted for age and sex). *P*-value of <.05 was considered significant. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between March 28, 2019 and August 20, 2022, 520 patients (median age 59.3 years [50.6-67.2], 69% women) and 89 referent subjects (median age 54.1 years [44.9-62.3], 73% women) from 7 international centres (4 centres in the United States, 1 in Croatia, 1 in Poland, and 1 in Greece) participated in this cross-sectional study. Of the 520 patients, 163 (31%) were

Table 2. Characteristics of patients with adrenal disorders and referent subjects.

		Patients with adrenal disorders			
	Referent subjects	Non-functioning adrenal adenomas	Primary aldosteronism	Mild autonomous cortisol secretion	Cushing syndrome[a]
N	89	163	81	212	64
Age, years	54.1	62.9	51.2	61.0	51.6
Median (IQR)	(44.9-62.3)	(55.5-69.0)	(44.2-62.0)	(52.9-68.5)	(39.5-59.3)
Women, *n* (%)	65 (73%)	107 (66%)	41 (51%)	155 (73%)	57 (89%)
Race, *n* (%)					
Missing	0	2	0	0	0
African American	0 (0%)	10 (6%)	11 (14%)	6 (3%)	1 (2%)
American Indian or Alaskan Native	0 (0%)	2 (1%)	0 (0%)	1 (0%)	0 (0%)
Asian	4 (4%)	1 (1%)	8 (10%)	2 (1%)	2 (3%)
Hispanic	4 (4%)	2 (1%)	2 (2%)	5 (2%)	1 (2%)
Mixed	0 (0%)	1 (1%)	3 (4%)	0 (0%)	1 (2%)
Native Hawaiian or Pacific Islander	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
White	81 (91%)	144 (89%)	57 (70%)	198 (93%)	59 (92%)
BMI, kg/m^2	26.4	30.5	32.9	30.5	32.5
Median (IQR)	(24.1-31.2)	(27.1-35.5)	(28.3-36.9)	(25.9-35.3)	(29.3-36.9)
Smoking, *n* (%)					
Missing	0	3	0	2	0
Active	3 (3%)	29 (18%)	6 (7%)	69 (33%)	10 (16%)
Former	28 (31%)	59 (37%)	22 (27%)	72 (34%)	15 (23%)
Never	58 (65%)	72 (45%)	53 (65%)	69 (33%)	39 (61%)
Current daily alcohol use, in units					
Missing	0	0	0	1	0
0	19 (21%)	92 (56%)	38 (47%)	118 (56%)	45 (70%)
≤1	60 (67%)	55 (34%)	32 (40%)	79 (37%)	16 (25%)
1-2	7 (8%)	14 (9%)	8 (10%)	9 (4%)	3 (5%)
≥3	3 (3%)	2 (1%)	3 (4%)	5 (2%)	0 (0%)
Tumour size, largest diameter, in mm					
Missing/not applicable	89	1	17	3	38
Median (IQR)	—	20 (15-26)	14 (10-19)	30 (20-38)	30 (26-37)
Location of adrenal tumour, *n* (%)					
Bilateral	—	37 (23%)	16 (20%)	79 (37%)	8 (13%)
Left	—	79 (48%)	28 (35%)	84 (40%)	11 (17%)
Right	—	47 (29%)	20 (25%)	49 (23%)	7 (11%)
None	—	0 (0%)	17 (21%)	0 (0%)	38 (59%)
Post–1-mg-DST cortisol, in nmol/L					
Missing/not applicable	89	0	31	10	8
Median (IQR)	—	30 (28-39)	30 (28-39)	86 (66-132)	350 (185-516)
Post–8-mg-DST cortisol[b], in nmol/L					
Missing/not applicable	89	163	81	174	51
Median (IQR)	—	—	—	69 (44-94)	69 (44-182)
Frail Index score category					
Non-frail	61 (69%)	44 (27%)	20 (25%)	47 (22%)	7 (11%)
Pre-frail	24 (27%)	83 (51%)	34 (42%)	76 (36%)	19 (30%)
Frail	4 (4%)	36 (22%)	27 (33%)	89 (42%)	38 (59%)

BMI, body mass index; DST, overnight dexamethasone suppression test; IQR, interquartile range.
To convert nmol/L to mcg/dL, divide by 27.7.
[a]Adrenal Cushing syndrome ($n = 26$) + Pituitary Cushing syndrome ($n = 35$) + Ectopic Cushing syndrome ($n = 3$).
[b]Only 8 participants were classified based on the post–8-mg-DST cortisol results.

diagnosed with NFA, 212 (41%) with MACS, 64 (12%) with CS, and 81 (16%) with PA. When compared to all patients with adrenal disorders combined, referent subjects had similar proportion of women, whites, and alcohol users, but were younger, had lower BMI, and a lower proportion of active or former smokers, Table 2. These results differed based on the adrenal disorder sub-group, Table 2.

In patients with adrenal tumours, the median tumour size was largest in patients with CS and MACS, followed by those with NFA and PA, Table 2. Bilateral tumours were seen in 140 (27%) patients overall, with the highest proportion in those with MACS (37%). Median post–1-mg-DST cortisol was 58 nmol/L (33-105), and, as expected highest in patients with CS, Table 2.

Prevalence of frailty

Overall, 194 (32%) participants were frail and 236 (39%) were pre-frail. Unadjusted prevalence of frailty (37% versus 4%, $P < .001$) and pre-frailty (41% versus 27%, $P < .001$) was higher in patients when compared to referent subjects. Among patients, unadjusted prevalence of frailty was highest in patients with CS (59%), followed by MACS (42%), PA (33%), and NFA (22%), Table 2. Compared to referent subjects and after adjusting for age, sex, and BMI, the prevalence of frailty was highest in patients with CS (odds ratio—OR 19.2, 95% confidence interval—CI 6.7-70.0, $P < .001$) followed by MACS (OR 12.5, 95% CI 4.8-42.9, $P < .001$), PA (OR 8.4, 95% CI 2.9-30.4, $P < .001$), and NFA (OR 4.5, 95% CI 1.7-15.9, $P < .001$), Table 3. When

Table 3. Sex-, age-, and BMI-adjusted prevalence of frailty in participant groups.

	Compared to referent subjects Odds ratio (95% CI)	Compared to patients with non-functioning adrenal adenomas Odds ratio (95% CI)
Adrenal disorder categories		
Non-functioning adrenal adenomas	4.5 (1.7-15.9)	—
Primary aldosteronism	8.4 (2.9-30.4)	1.9 (1.0-3.8)
Mild autonomous cortisol secretion	12.5 (4.8-42.9)	2.8 (1.7-4.6)
Cushing syndrome	19.2 (6.7-70.0)	4.1 (2.1-8.3)
Primary aldosteronism sub-groups[a]		
Without post–1-mg-DST cortisol[b]	6.3 (1.7-27.5)	1.6 (0.6-4.2)
With post–1-mg-DST cortisol ≤50 nmol/L	7.7 (2.5-29.4)	1.8 (0.8-3.9)
With post–1-mg-DST cortisol >50 nmol/L	11.8 (3.5-48.4)	3.0 (1.2-7.3)
Cushing syndrome sub-groups[c]:		
ACTH-independent (adrenal)	27.8 (7.5-135)	3.9 (1.5-10.0)
ACTH-dependent (pituitary + ectopic)	39.0 (10.8-185)	4.8 (2.0-11.8)
Post–1-mg-DST cortisol[d]		
<28 nmol/L	3.5 (0.6-18.7)	—
28-50 nmol/L	4.6 (1.7-16.5)	—
51-83 nmol/L	10.5 (3.7-38.1)	2.4 (1.3-4.4)
>83 nmol/L	14.9 (5.5-52.8)	3.3 (1.8-5.9)

Post–1-mg-DST cortisol: serum cortisol after overnight 1 mg dexamethasone suppression test.
[a]After excluding patients with Cushing syndrome or mild autonomous cortisol secretion alone (ie, patients with concomitant primary aldosteronism and mild autonomous cortisol secretion included).
[b]Patients with primary aldosteronism who did not have the overnight 1 mg dexamethasone suppression test.
[c]After excluding patients with primary aldosteronism or mild autonomous cortisol secretion.
[d]After excluding patients with Cushing syndrome or primary aldosteronism alone (ie, patients with concomitant primary aldosteronism and mild autonomous cortisol secretion included).

compared to NFA, the age-, sex- and BMI-adjusted prevalence of frailty was increased in patients with CS (OR 4.1, 95% CI 2.1-8.3, $P < .001$) and MACS (OR 2.8, 95% CI 1.7-4.6, $P < .001$), and to a lesser degree in PA (OR 1.9, 95% CI 1.0-3.8, $P = .049$), Table 3. Similar results were obtained after adjusting for smoking and alcohol consumption (data not shown).

Subgroup analysis of patients with PA demonstrated an increased prevalence of frailty in patients with abnormal DST (OR 11.8, 95% CI 3.5-48.4) followed by patient with normal DST (OR 7.7, 95% CI 2.5-29.4) when compared to referent subjects, Table 3. However, when compared to patients with NFA, only those with PA and abnormal DST demonstrated an increased prevalence of frailty (OR 3.0, 95% CI 1.2-7.3), Table 3.

Patients with CS had the highest prevalence of frailty of all hormonal sub-types, and further subgroup analysis of CS subtype demonstrated a higher prevalence in patients with ACTH-dependent CS when compared to referent subjects (OR 39.0, 95% CI 10.8-185), and non-functioning adrenal adenomas (OR 4.8, 95% CI 2.0-11.8), Table 3.

Frailty sub-components in patients with MACS and NFA, and referent subjects

When comparing individual health variables in patients with MACS to patients with NFA (Table S1), after adjusting for age and sex, patients with MACS more frequently reported chronic kidney disease (OR 3.8, 95% CI 1.6-10.5), a diagnosis of depression (OR 1.8, 95% CI 1.0-3.0), unusual bruising (OR 1.8, 95% CI 1.1-3.1), tendency to fall easily (OR 2.2, 95% CI 1.1-4.3), feeling sad (OR 1.8, 95% CI 1.0-3.4), being anxious (OR 1.9, 95% CI 1.2-3.1) and irritable (OR 2.6, 95% CI 1.6-4.4), difficulties concentrating (OR 3.0, 95% CI 1.9-4.8), little interest or pleasure in relationships or activities (OR 3.5, 95% CI 2.1-6.1), needing help with cooking (OR 4.5, 95% CI 1.5-19.5), housekeeping (OR 2.3, 95% CI 1.2-5.0), and walking (OR 11.0, 95% CI 2.2-201), Figure 1, Table S2.

When comparing individual health variables to referent subjects, patients with MACS and NFA more frequently reported comorbidities of hypertension, diabetes mellitus, dyslipidaemia, cancer, and symptoms of unusual bruising, muscle pain or stiffness, joint pain or stiffness, back pain or stiffness, weakness in arms or legs, weight gain of more than 10 pounds in the past year, sleep difficulties, feeling sad, irritable and anxious, difficulties concentrating and little interest or pleasure in relationships, and inability to climb two flights of stairs. Compared to referent subjects, patients with MACS but not NFA more frequently reported chronic kidney disease, depression, a tendency to fall easily, needing help with housekeeping, and being dependent on a breathing device, Figure 1, Table S3.

Relationship between FI and post–1-mg-DST cortisol

Amongst all patients, a positive correlation was noted between the FI score (adjusted for age and sex) and post–1-mg-DST cortisol level (adjusted $r = 0.20$, $P < .001$), Figure 2, Table 4. Sex-based differences were noted, with FI score (adjusted for age) having a stronger correlation in women ($r = 0.25$, $P < .001$) compared to men ($r = 0.10$, $P = .242$), Figure 2, Table 4. After excluding patients with CS, the age-, sex-, and BMI-adjusted prevalence of frailty of patients with post–1-mg-DST cortisol <28 nmol/L was similar to referent subjects (OR 3.5, 95% CI 0.6-18.7). However, prevalence of frailty increased with the degree of autonomous cortisol secretion, with OR of 4.6 (95% CI 1.7-16.5) when DST was 28-50 nmol/L, OR of 10.5 (95% CI 3.7-38.1) when DST was 51-83 nmol/L, and OR of 14.9 (95% CI 5.5-52.8) when DST was >83 nmol/L, Table 3.

Correlation of FI and performance-based measures of frailty

Of the 609 subjects in this study, performance-based measures of frailty were completed in 317 (52%) participants for

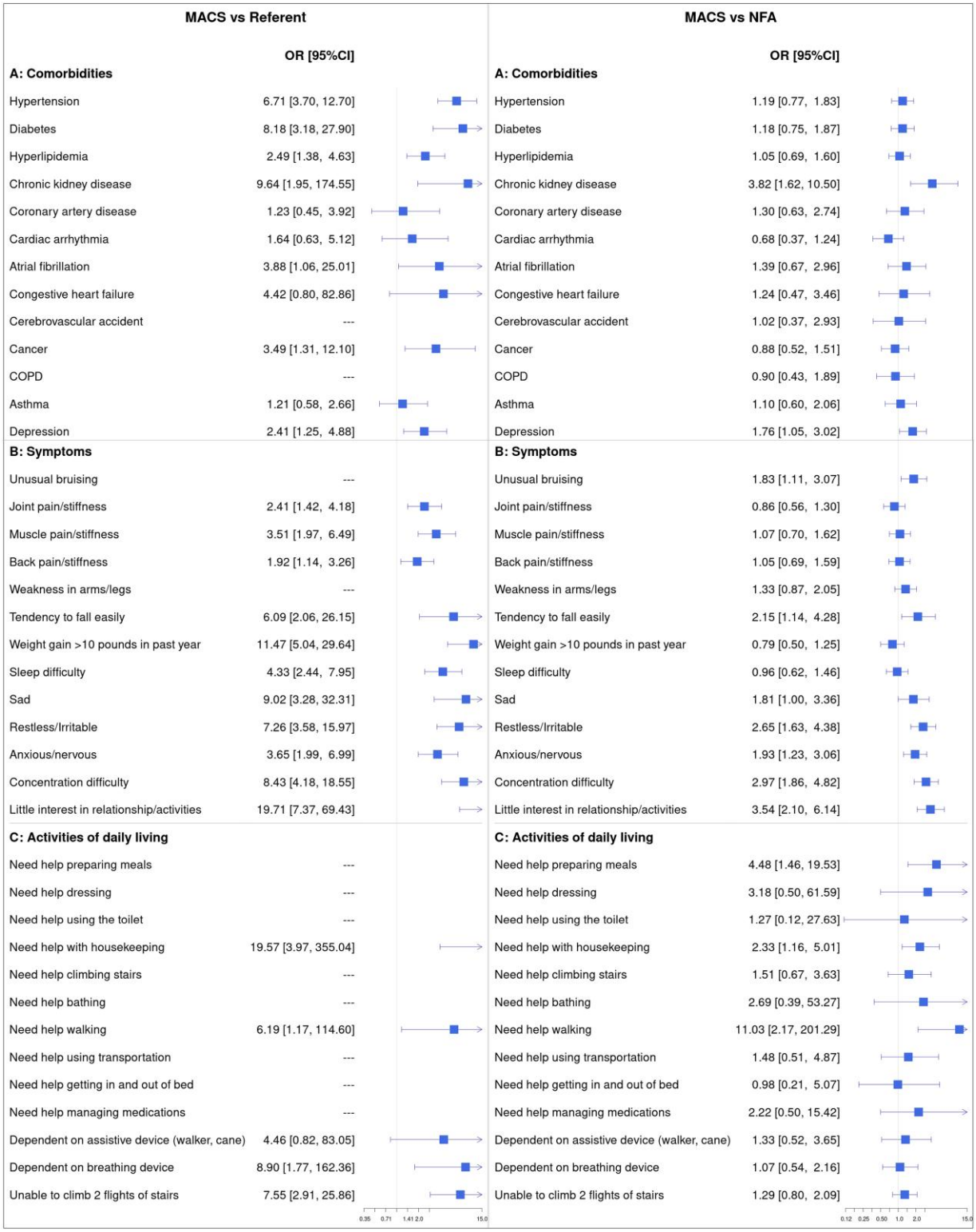

Figure 1. Age- and sex-adjusted logistic model demonstrating Frailty Index health variables that include comorbidities (A), symptoms (B), and activities of daily living (C) in patients with mild autonomous cortisol secretion (MACS) versus referent subjects (left panel), and patients with MACS versus patients with non-functioning adenoma (NFA) (right panel). OR, odds ratio; 95% CI, 95% confidence interval. In the case of zero events in a comparator group, the logistic regression model could not be applied.

handgrip strength, 282 (46%) participants for timed up-and-go test, 199 (33%) participants for gait speed, 142 (23%) participants for 6-minute walk test, and 115 (19%) participants for chair rising test. After adjusting for age and sex, higher FI score was associated with the lower handgrip measurement ($r = -0.30$, $P < .001$), lower chair rising test ($r = -0.34$, $P < .001$), shorter 6-minute walk test ($r = -0.56$, $P < .001$), longer duration of timed up-and-go test ($r = 0.32$, $P < .001$), and lower gait speed ($r = -0.34$, $P < .001$), Figure 2, Table 4. Sex differences were observed for the hand grip strength and timed

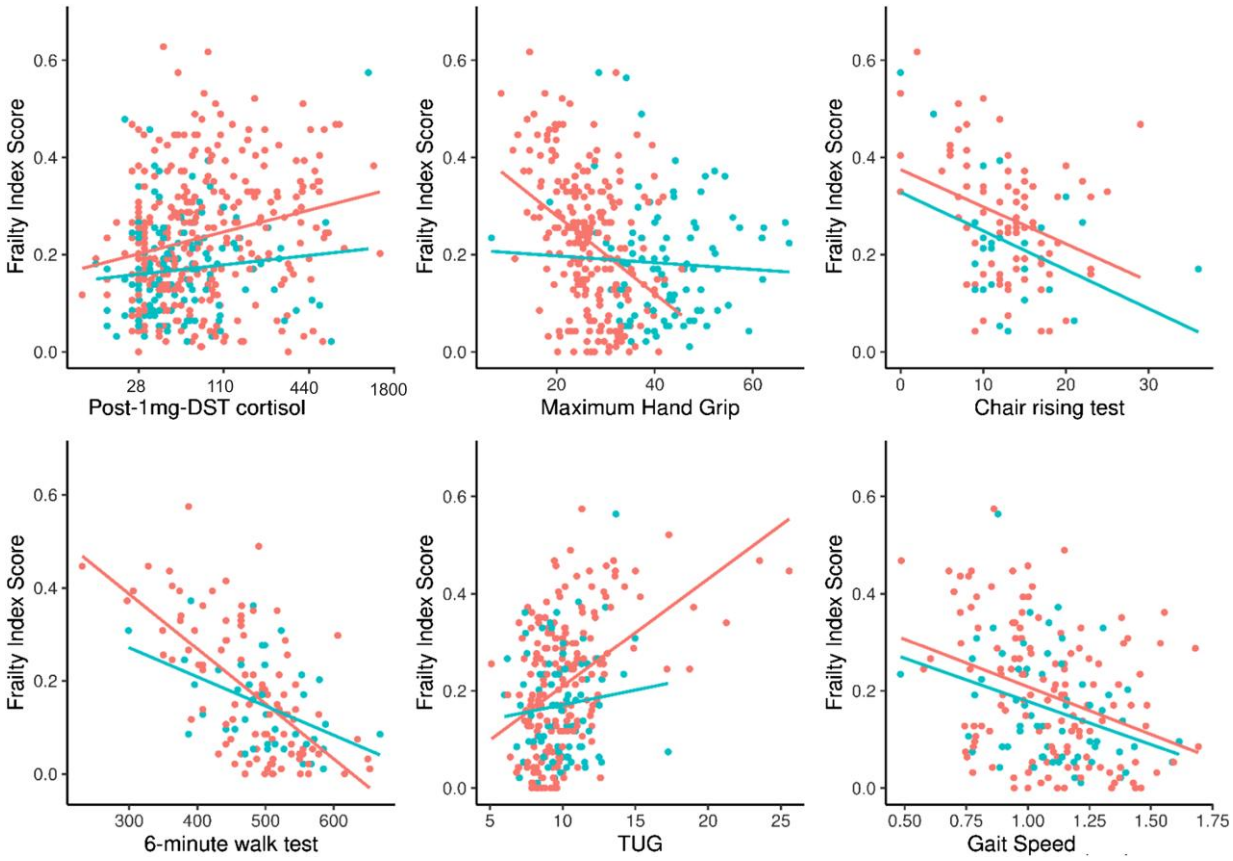

Figure 2. Scatter plots with regression lines by sex (red for females and teal for males) of Frailty Index score with cortisol following 1 mg dexamethasone overnight administration (post–1-mg-DST cortisol), hand grip strength (in kilograms), chair rising test (number of stands in 30 s), 6-minute walk test (distance covered in metres), timed up-and-go (TUG) test (in seconds), and gait speed (in metres per second).

up-and-go test with a higher association with the FI in women when compared to men, Figure 2, Table 4.

Discussion

In this prospective multi-centre cross-sectional study, we present the concept of FI in the evaluation of patients with adrenal adenomas and those with adrenocortical hormone excess. We found that patients with incidentally discovered, "asymptomatic" adrenal nodules, including those with MACS and NFA, demonstrate increased burden of frailty, and that the prevalence increased with post-DST cortisol. Finally, in a subset of patients, we demonstrate FI correlates well with the various performance-based measures of frailty.

Frailty is a state of multi-system decline, predisposing an individual to disability, increased morbidity, and mortality.[19,29] FI is a cumulative deficit tool that works on the principle that multiple, small deficits may not be clinically significant; however, when coexisting can negatively impact the overall health, and contribute to biological ageing.[29,30] In patients with MACS, the absence of overt features of hyper-cortisolism results in delayed diagnosis and prolonged exposure to abnormal cortisol secretion, potentially culminating in a premature ageing process. In our study, we observed an increased prevalence of depression, anxiety, irritability, concentration difficulties and anhedonia in patients with MACS compared to referent population and patients with NFA. Furthermore, in patients with MACS, the higher prevalence of unusual bruising, extremity weakness, tendency to fall easily, and need for assistance with daily activities such as preparing meals, housekeeping, and walking could reflect the negative impact of abnormal cortisol secretion on skin fragility and muscular strength. These symptoms are considered to be a part of CS, and their presence (to a lesser degree) in patients with MACS is not usually recognized during routine physical exam. We found that patients with MACS have an increased prevalence of hypertension, diabetes mellitus, and dyslipidaemia compared to referent subjects but not NFA, an observation different from previous studies comparing cardiometabolic burden between MACS and NFA.[6,8,9] The likely explanation is the difference in study methodology, where previous studies employed retrospective data collection compared to self-reporting of health variables in the current study. Notably, we also found an increased prevalence of chronic kidney disease in patients with MACS, a finding also noted in a population-based study that included a mix of patients with NFA and MACS.[10] Among cardiovascular risk factors, chronic kidney disease was the only comorbidity that was much more frequent in patients with MACS when compared to patients with NFA, possibly due to a more severe associated cardiovascular morbidity, or potentially due to a direct impact of cortisol excess on kidney function. Notably, misclassification of some patients with MACS could have occurred as false-positive DST results are more common with impaired kidney function.[31]

Based on current clinical practice guidelines, in the absence of PA, adenomas with post–1-mg-DST cortisol ≤50 nmol/L are categorized as "non-functioning".[3] However, studies using urinary steroid profiling show elevated glucocorticoid metabolite excretion in patients with NFA compared to referent

Table 4. Adjusted Spearman correlation analysis with Frailty Index.

	Combined			Female			Male		
	N	*r*	*P*-value	*N*	*r*	*P*-value	*N*	*r*	*P*-value
Post–1-mg-DST cortisol	471	0.20	<.001	333	0.25	<.001	138	0.10	.242
Maximum hand grip strength	317	−0.30	<.001	224	−0.36	<.001	93	−0.03	.801
Chair rising test	115	−0.34	<.001	87	−0.32	.002	28	−0.37	.059
6-minute walk test	142	−0.56	<.001	102	−0.60	<.001	40	−0.44	.005
Time up-and-go test	282	0.32	<.001	198	0.41	<.001	84	0.06	.574
Gait speed	199	−0.34	<.001	136	−0.34	<.001	63	−0.36	.004

Post–1-mg-DST cortisol: morning serum cortisol after overnight 1 mg dexamethasone suppression test.

subjects,[16,32] and limited literature suggests that patients with NFA are prone to develop diabetes mellitus, have an altered body composition (increased visceral fat and lower muscle mass), exhibit increased carotid-intima thickness and endothelial dysfunction, and experience higher rates of metabolic syndrome.[12,15,33,34] In our study, we observed that the prevalence of frailty and its components was higher in patients with NFA when compared to referent subjects reflecting the continuum of cortisol secretion in patients with adrenal incidentalomas and underscoring that the term "non-functioning" could be misleading. Furthermore, we noted an increasing prevalence of frailty proportional to post–1-mg-DST cortisol and found that even patients with post–1-mg-DST cortisol between 28 and 50 nmol/L had a higher frailty burden compared to the referent group without adrenal tumour.

Performance-based measures of muscle strength and physical function is a validated method to assess frailty.[21,22,25–28] However, the process can be cumbersome, time-consuming, and thus, not routinely used in clinical practice. We found that our FI correlated with the performance-based measures, especially in women. As such FI could be a much more simple and quick way to assess the overall health status of a patient with adrenal adenoma.

The strengths of our study include a large sample size and prospective enrolment of participants from multiple international centres, making these results generalizable to a broader population. With inclusion of patients with different hormone sub-types (NFA, MACS, CS, PA) and referent subjects, we were able to demonstrate the entire spectrum of hormone secretion and association with frailty and its components. Our study also has the advantage of avoiding imaging bias as we included only referent subjects with available normal adrenal imaging. Nonetheless, our study does have certain limitations. We acknowledge a selection bias, as patients with adrenal disorders were recruited from referral centres, primarily from endocrine clinics, and referent subjects were recruited from a single centre. As our study used a survey, recall bias was also possible. Despite a multi-centre design, our study included a predominantly white population which may limit the application of our observations to other races. The duration of exposure to abnormal cortisol secretion was not possible to ascertain in patients without features of overt hormone excess as most adrenal adenomas are discovered incidentally. Furthermore, our referent group had a modest sample size and was not matched for age, sex, and BMI. Nevertheless, we adjusted our analyses to account for these variables. Given that multiple conditions can impact the results of DST, we also acknowledge the possibility of misclassification of some participants. Lastly, though we noted the increased prevalence of frailty and many of its components (comorbidities, symptoms, daily living activities) in patients with adrenal adenomas, we cannot establish causality based on the cross-sectional design of our study.

In conclusion, patients with MACS and, to a lesser degree, those with NFA experience an increased burden of frailty, thereby predisposing these individuals to poorer health outcomes and quality of life. FI is a potentially useful and simple clinical tool that provides an overall assessment of health and may help clinicians identify patients with adrenal adenomas that are at increased risk for adverse health outcomes and assist with clinical decision-making. Future longitudinal studies are needed to determine the impact of treatment on reversibility of frailty in patients with adrenal adenomas.

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Supplementary material

Supplementary material is available at *European Journal of Endoicrinology* online.

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Data availability

De-identified data sets will be shared upon reasonable request to the corresponding author.

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