Research Article

Nonesterified Fatty Acids and Hospitalizations Among Older Adults: The Cardiovascular Health Study

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Abstract

Background: We sought to determine associations between total serum concentrations of nonesterified fatty acids (NEFAs) and incident total and cause-specific hospitalizations in a community-living cohort of older adults.

Methods: We included 4715 participants in the Cardiovascular Health Study who had fasting total serum NEFA measured at the 1992/1993 clinic visit and were followed for a median of 12 years. We identified all inpatient admissions requiring at least an overnight hospitalization and used primary diagnostic codes to categorize cause-specific hospitalizations. We used Cox proportional hazards regression models to determine associations with time-to-first hospitalization and Poisson regression for the rate ratios (RRs) of hospitalizations and days hospitalized.

Results: We identified 21 339 hospitalizations during follow-up. In fully adjusted models, higher total NEFAs were significantly associated with higher risk of incident hospitalization (hazard ratio [HR] per SD [0.2 mEq/L] = 1.07, 95% confidence interval [CI] = 1.03–1.10, $p < .001$), number of hospitalizations (RR per SD = 1.04, 95% CI = 1.01–1.07, $p = .01$), and total number of days hospitalized (RR per SD = 1.06, 95% CI = 1.01–1.10, $p = .01$). Among hospitalization subtypes, higher NEFA was associated with higher likelihood of mental, neurologic, respiratory, and musculoskeletal causes of hospitalization. Among specific causes of hospitalization, higher NEFA was associated with diabetes, pneumonia, and gastrointestinal hemorrhage.

Conclusions: Higher fasting total serum NEFAs are associated with a broad array of causes of hospitalization among older adults. While some of these were expected, our results illustrate a possible utility of NEFAs as biomarkers for risk of hospitalization, and total days hospitalized, in older adults. Further research is needed to determine whether interventions based on NEFAs might be feasible.

Keywords: Diabetes, Mental, Metabolism, Musculoskeletal, Pneumonia

Nonesterified fatty acids (NEFAs) are carboxylic acids with carbon chains of various lengths and degrees of saturation. Circulating levels of NEFAs are potentially modifiable and hence attractive candidates to study as risk factors for chronic disease. Circulating levels reflect a balance between lipolytic factors (eg, catecholamines, natriuretic peptides), inhibitors of lipolysis (eg, adiponectin, insulin), and modifiable external factors (eg, exercise and diets rich in fat,

carbohydrate, or alcohol and low in protein intake) (1,2). NEFAs are well-established regulators of glucose metabolism and have been linked to adverse effects particularly on the cardiovascular system (3–6). Indeed, we previously showed that higher total serum concentrations of NEFAs are associated with higher risk of congestive heart failure and atrial fibrillation in the Cardiovascular Health Study (CHS) (7,8).

Importantly, the biological effects of NEFAs potentially occur across a wide variety of organ systems and tissues. Surprisingly, our previous work on mortality in (CHS) demonstrated that NEFAs were associated even more strongly with death related to dementia, infection, and respiratory disease than with cardiovascular death (9,10). Nonetheless, because of the limited number of deaths in CHS, and because some chronic conditions are uncommon proximal causes of death, the full set of diseases to which NEFA may contribute has not been comprehensively evaluated.

Hospitalizations are an attractive alternative endpoint to mortality for agnostic studies of metabolic exposures like NEFAs. Beyond their coincident morbidity, they are expensive, accounting for about a third of health care expenditures in the United States. In 2011, aggregate hospital costs were \$387.3 billion, a 63% increase from 1997 (11). Furthermore, because Medicare is the primary payor for hospitalizations of older adults in the United States, detailed information on the number, length, and primary cause of hospitalization is available for nearly all older adults.

Given the broad set of physiological effects of NEFAs, their potentially modifiable nature, and their known associations with several incident conditions (5,7–9), we sought to determine the broad-based associations of NEFAs with all-cause and disease-specific hospitalizations. We hypothesized that this agnostic method would enable us to identify potential effects of NEFAs that had not been previously identified using single candidate outcomes.

Research Design and Methods

CHS is a prospective cohort consisting of 5888 men and women aged ≥ 65 years who were randomly selected from Medicare-eligibility lists in 4 U.S. communities (Forsyth County, NC; Washington County, MD; Sacramento County, CA; and Pittsburgh, PA). A detailed description of methods and procedures in the CHS has previously been published (12). Briefly, persons eligible to participate were not institutionalized or wheelchair-dependent, did not require a proxy for consent, were not receiving treatment for cancer, and were expected to remain in their respective regions for 3 years. From 1989 to 1990, 5201 participants were recruited in the original cohort. Between 1992 and 1993, 687 participants (predominantly African American) were additionally recruited. Baseline evaluation of study participants included standardized questionnaires, physical examination, anthropometric measurements, resting electrocardiography, and laboratory examinations. From 1989 through 1999, participants were followed up every 6 months, alternating between telephone calls and clinic visits; biannual telephone calls have continued since then. The institutional review board at each center approved the study, and each participant gave informed consent.

For this analysis, the 1992–1993 clinic visit (ie, the first visit that incorporated the additional 687 participants that were recruited) was used as baseline. Of the 5265 participants present at the 1992–1993 clinic visit, 4715 had NEFA measured, forming the analytic sample for this study. Participants who underwent NEFA measurement were younger (74.9 years old vs 77.5 years old), healthier (79.1% vs 61.1%), and more educated (12th grade or higher: 45.7% vs 36.9%) than those without available NEFA measurements.

Measurement of Total Fasting Plasma NEFA

Plasma NEFA concentration was measured by the Wako enzymatic method at the CHS Central Laboratory at the University of Vermont. This technique relies on the acylation of CoA by the fatty acids in

the presence of added acyl-CoA synthetase. Acyl-CoA produced is oxidized by added acyl-CoA oxidase with generation of hydrogen peroxide and in the presence of peroxidase permits the oxidative condensation of 3-methyl-N-ethyl-N-(*b*-hydroxyethyl)-aniline with 4-aminoantipyrine to form a purple-colored adduct. The latter is then measured colorimetrically at 550 nm. The interassay CV was 3.5%–8.2% (detectable range 0.015–1.50 mEq/L).

Ascertainment of Hospitalizations

We defined hospitalization as care in a hospital that required admission as an inpatient and an overnight or longer stay. CHS has been linked to Medicare claims since 1991 and systematically queries hospitalizations during biannual telephone contacts. It is therefore well-suited to examine the association of NEFAs with the full range of causes of hospitalization in a systematic manner. Primary diagnosis groups using the first digit (ie, of “100s,” “200s,” “300s” etc.) were first used to categorize hospitalization. To determine with greater granularity which specific diseases drove significant category-level associations, we then examined individual ICD-9 codes for cause-specific hospitalizations within categories significantly associated with NEFAs. To ensure precision, we only examined individual ICD-9 codes for which at least 40 persons were hospitalized during follow-up. The ICD-9 nomenclature is outlined in [Supplementary Table 1](#).

Covariates

Baseline variables were used for statistical adjustment. These include age, gender, waist circumference, marital status (married or nonmarried); race (White or non-White); years of education, diabetes status (fasting glucose >125 mg/dL or use of antihyperglycemic medication), alcohol intake (in 3 categories), systolic blood pressure, hypertension medication use, hypolipidemic and hypoglycemic medication use, prevalent atrial fibrillation, and adjudicated prevalent cardiovascular disease (myocardial infarction, stroke, and congestive heart failure) (13–15). Disability was assessed by difficulty in 6 activities of daily living (dressing, eating, toileting, bathing, transferring, and walking across a room). Cognitive function was measured by the Modified Mini-Mental State Examination (16). The Lubben Social Network Scale (LSNS) score was used to assess social networks. Scores range from 0 to 50, with higher scores indicating more frequent contact with larger networks (17). General health status was self-reported in 5 categories from excellent to poor. Other biomarkers measured at the CHS Central Laboratory included albumin, cystatin-C (used to estimate glomerular filtration rate), C-reactive protein, insulin, total and HDL cholesterol, and triglycerides. Waist circumference was measured by technicians at the 1992–1993 clinic visit. Physical activity was estimated using the Minnesota Leisure-Time inventory.

Statistical Analyses

For robustness, we examined hospitalizations in 3 ways. First, for comparison with previous work, we constructed Cox proportional hazards regression models to estimate hazard ratios (HRs) for time-to-first hospitalizations (all-cause and cause-specific) as a function of total NEFAs. As in previous analyses, we modeled NEFA per standard deviation (SD) increment. Next, quasi-Poisson regression was used to estimate rate ratios for 2 related outcomes—the number

of hospitalizations and the total days of hospitalization, taking into account the time under follow-up as an offset. Our initial model included participants' age, sex, race, and clinic site. Our fully adjusted models included age, gender, race, clinic, waist circumference, smoking status, alcohol consumption, physical activity, diabetes, systolic blood pressure, hypertension medication use, prevalent atrial fibrillation, prevalent cardiovascular disease, general health status, C-reactive protein, albumin, total cholesterol, HDL cholesterol, triglycerides, insulin, and eGFR; we adjusted these models for prevalent diabetes, atrial fibrillation, and cardiovascular disease because we previously established these as related to NEFAs in published work (7,18–20). We also repeated our primary analyses with additional adjustment for baseline cognition, social network score, number of activities of daily living, and hypolipidemic and hypoglycemic medication use.

After examining total hospitalizations, we examined rate ratios for hospitalizations and days hospitalized attributable to each of the 15 major categories of hospitalization. Where suggestive associations with NEFA existed for these primary diagnosis groups, we then explored individual causes of hospitalizations in subcategories with at least 40 participants to minimize false positives; the threshold of 40 was defined arbitrarily but a priori. All analysis was conducted in R (R Development Core Team; 2019) (21).

Results

Of the 4715 CHS participants with NEFA measurements available, 41% were male, and 16.8% were African Americans. Participants were, on average, 74.9 years old. The mean (SD) total serum NEFA was 0.50 (SD 0.20) mEq/L.

Table 1 shows the demographic characteristics of participants according to NEFA quartiles. As expected, NEFA tended to be higher with older age, greater body mass index, and among women.

Participants were followed from their 1992–1993 visit until June 30, 2015, a median follow-up of 12 years. During this time, we identified over 21 000 separate hospitalizations. We observed a 7% increased likelihood of incident hospitalizations, a 4% increased likelihood of total number of hospitalizations, and a 6% increased likelihood of total number of days hospitalized, per SD increment in NEFAs, after adjusting for potential confounding variables (Table 2).

We observed significant associations of NEFAs (per SD increment) with several subtypes of hospitalizations, including mental (HR = 1.24, $p = .02$), neurologic (HR = 1.17, $p = .03$), respiratory (HR = 1.14, $p < .001$), and musculoskeletal disorders (HR = 1.12, $p = .01$). There were borderline associations of NEFAs with hospitalizations for digestive disorders (HR = 1.07, $p = .05$) (Table 3). Overall, mental disorders generally demonstrated the steepest associations, while respiratory and musculoskeletal disorders (which were far more common) manifested particularly strong statistical associations.

Table 4 shows the associations of NEFAs with cause-specific hospitalizations (where at least 40 persons were hospitalized). Significant associations were observed for diabetes (HR = 1.23, $p = .01$), pneumonia (HR = 1.14, $p = .01$), gastrointestinal hemorrhage (HR = 1.26, $p = .01$), and other disorders of bone and cartilage hospitalizations; the latter includes osteoporosis and pathological fractures (HR = 1.29, $p = .02$). A borderline association was observed for duodenal ulcer (HR = 1.31, $p = .05$). Similar findings were observed for number of days hospitalized

Table 1. Demographic Characteristics According to Quartile of NEFA

Variable	Total N = 4715	Q1 N = 1184	Q2 N = 1179	Q3 N = 1174	Q4 N = 1178	p Value
Age, y	74.9 ± 5.3	74.1 ± 4.9	74.7 ± 5.3	75.2 ± 5.4	75.4 ± 5.6	<.01
Male, %	1967 (41.7)	725 (61)	542 (46)	405 (35)	295 (25)	<.01
Black race, %	789 (16.7)	177 (15)	200 (17)	206 (18)	206 (18)	.29
Education ≥12 grade, %	2151 (45.7)	587 (50)	533 (45)	532 (45)	499 (43)	<.01
BMI, kg/m ²	26.9 ± 4.8	26.2 ± 4.0	26.8 ± 4.6	27.1 ± 5.0	27.3 ± 5.3	<.01
Waist circumference	97.4 ± 13.3	96.3 ± 11.3	97.2 ± 13.4	97.9 ± 13.7	98.3 ± 14.4	<.01
Alcohol, #/wk	2.1 ± 6.2	2.11 ± 4.8	2.06 ± 5.7	1.97 ± 8.0	2.29 ± 5.8	.57
Smoke, %						
Current	459 (9.9)	127 (11)	129 (11)	106 (9)	97 (8)	<.01
Former	2068 (44.7)	597 (51)	517 (45)	497 (43)	457 (40)	
Never	2100 (45.4)	441 (38)	511 (44)	545 (48)	603 (52)	
Systolic BP, mmHg	136.3 ± 21.5	131.7 ± 20.9	135.6 ± 21.6	137.20 ± 21.3	140.8 ± 2	<.01
Hypertension med, %	2387 (50.7)	557 (47.0)	572 (48.5)	588 (50.2)	670 (56.9)	<.01
AF, %	152 (3.2)	34 (2.9)	35 (3.0)	35 (3.0)	48 (4.1)	.10
MI, %	485 (10.3)	161 (14)	120 (10)	104 (9)	100 (9)	<.01
Stroke, %	259 (5.5)	66 (6)	55 (5)	63 (5)	75 (6)	.34
CHF, %	281 (6.0)	75 (6)	63 (5)	65 (6)	78 (7)	.50
Good health, %	3727 (79.1)	965 (82)	955 (81)	933 (80)	874 (74)	<.01
Albumin, gm/dL	3.92 ± 0.27	3.87 ± 0.28	3.9 ± 0.27	3.93 ± 0.27	3.96 ± 0.27	<.01
Glucose, mg/dL	108.3 ± 35.4	104.8 ± 30.7	105.4 ± 29.3	106.9 ± 31.8	116.4 ± 46.0	<.01
Insulin, IU/mL	14.3 ± 24.2	15.3 ± 29.1	13.1 ± 15.5	13.5 ± 19.7	15.3 ± 29.4	.91
LDL-C, mg/dL	127.3 ± 34.0	126.5 ± 32.33	128.3 ± 32.67	128.4 ± 34.91	125.9 ± 35.78	.73
HDL-C, mg/dL	53.2 ± 14.5	49.4 ± 12.81	52.2 ± 13.77	54.4 ± 14.5	57.0 ± 15.6	<.01
eGFR _{cys}	72.5 ± 19.0	71.5 ± 18.4	72.4 ± 19.0	72.7 ± 19.2	73.3 ± 19.4	.03

Notes: AF = atrial fibrillation; BMI = body mass index; BP = blood pressure; CHF = congestive heart failure; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NEFA = nonesterified fatty acid.

Table 2. The Association of Total NEFA per *SD* Increment With Risk of Incident Hospitalization and With Number and Days of Hospitalization

Outcome	N	Model 1			Model 2		
		HR/RR	95% CI	<i>p</i> Value	HR/RR	95% CI	<i>p</i> Value
First incident hospitalizations	4393	1.08	1.05–1.12	<.001	1.07	1.03–1.10	<.001
Total hospitalizations	21 339	1.06	1.03–1.10	<.001	1.04	1.01–1.07	.01
Total days hospitalized	124 098	1.09	1.04–1.13	<.001	1.06	1.01–1.10	.01

Notes: Model 1 adjusted for age, gender, race, and clinic. Model 2 adjusted for age, gender, race, clinic, waist circumference, smoking status, diabetes, systolic blood pressure, hypertension medication use, hypolipidemic and hypoglycemic medication use, prevalent atrial fibrillation, prevalent cardiovascular disease, C-reactive protein, albumin, eGFR, total cholesterol, HDL cholesterol, triglycerides, activities of daily living, cognition, social network score, general health, insulin, alcohol, and physical activity. HR = hazard ratio (from Cox proportional hazards regression analysis of NEFA and incident hospitalization); NEFA = nonesterified fatty acid; RR = rate ratio (from Poisson regression analyses of NEFA and number and days of hospitalization); *SD* = standard deviation.

Table 3. Association of Total NEFA per *SD* Increment With Subtypes of Hospitalization

Subtype	Hospitalizations				Days Hospitalized			
	N	RR	95% CI	<i>p</i> Value	N	RR	95% CI	<i>p</i> Value
Infectious and parasitic	746	1.05	0.95–1.16	.32	5345	1.14	1.01–1.29	.04
Neoplastic	1173	0.93	0.83–1.05	.25	9223	0.92	0.75–1.13	.41
Endocrine, nutritional, metabolic, and immune	755	1.08	0.97–1.19	1.11	4124	1.11	0.97–1.27	.15
Hematologic	216	0.88	0.71–1.09	.24	1007	0.91	0.68–1.22	.52
Mental	202	1.24	1.04–1.49	.02	1558	1.51	1.21–1.88	<.001
Neurologic	306	1.17	1.01–1.35	.03	1508	1.15	0.93–1.42	.18
Circulatory	6528	1.02	0.98–1.07	.37	37727	1.03	0.97–1.10	.32
Respiratory	2456	1.14	1.06–1.23	<.001	16010	1.15	1.04–1.26	.01
Digestive	2100	1.07	1.00–1.15	.05	12244	1.10	0.99–1.22	.07
Genitourinary	1164	0.95	0.87–1.02	.16	5842	1.00	0.90–1.12	.99
Dermatologic	312	1.05	0.89–1.24	.56	1957	1.04	0.85–1.29	.70
Musculoskeletal	1141	1.12	1.03–1.21	.01	5669	1.19	1.06–1.33	.003
Symptoms, signs, and ill-defined conditions	1525	1.04	0.96–1.11	.35	5185	1.07	0.96–1.20	.21
Injury and poisoning	2011	1.03	0.97–1.10	.38	12403	1.07	0.97–1.18	.17
External causes of injury	248	1.06	0.79–1.43	.70	1642	1.11	0.79–1.57	.55

Notes: Models adjusted for age, gender, race, clinic, waist circumference, smoking status, diabetes, systolic blood pressure, hypertension medication use, hypolipidemic and hypoglycemic medication use, prevalent atrial fibrillation, prevalent cardiovascular disease, C-reactive protein, albumin, eGFR, total cholesterol, HDL cholesterol, triglycerides, activities of daily living, cognition, social network score, general health, insulin, alcohol, and physical activity. NEFA = nonesterified fatty acid; *SD* = standard deviation.

for these conditions. In contrast, we did not observe individual diagnostic codes within neurologic and mental conditions that were responsible for the observed associations at the larger group level, in part because no single code accounted for most of the hospitalizations.

Analyses additionally adjusted for cognition, social support, functional status, and use of lipid- or glucose-lowering medications did not meaningfully alter the associations of NEFAs with hospitalization. The adjusted HR and 95% confidence interval for first hospitalization per *SD* in NEFA was 1.06 (1.03–1.10), and the incidence rate ratio and 95% confidence interval for all hospitalizations was 1.03 (1.00–1.06).

For comparative context, we also evaluated the associations of conventional lipids (total cholesterol, HDL-C, and triglycerides) with risk of hospitalizations. The adjusted HRs and 95% confidence intervals for incident hospitalization were 0.97 (0.93–1.00) for total cholesterol, 1.04 (1.00–1.09) for HDL-C, and 1.01 (0.97–1.05) for triglycerides. The comparable incidence rate ratio and 95% confidence intervals for total hospitalizations were 0.97 (0.94–1.00) for total cholesterol, 1.02 (0.98–1.06) for HDL-C, and 1.01 for triglycerides (0.98–1.04). Thus, in contrast to NEFA,

no conventional lipid was significantly associated with higher risk of hospitalization.

Discussion

In this community-living cohort of older adults, baseline levels of total serum NEFAs were consistently associated with incident hospitalizations and number and days of hospitalization. Using an agnostic approach across all hospitalizations, we found higher NEFAs to be significantly associated with increased likelihood of mental, neurologic, respiratory, and musculoskeletal disorders. Among specific disorders, higher NEFAs were significantly associated with increased likelihood of hospitalizations with primary diagnosis codes for diabetes, pneumonia, duodenal ulcer, gastrointestinal hemorrhage, and disorders of bone and cartilage.

To our knowledge, this is the first comprehensive study evaluating the association between NEFAs and hospitalizations, although it reinforces and complements our previous work on cause-specific mortality in CHS (10). In both cases, some expected associations were recapitulated but several disorders not previously demonstrated to be associated with NEFAs were also identified.

Table 4. Association of Total NEFA per SD Increment With Specific Hospitalizations

Variable	ICD-9	Hospitalizations				Days Hospitalized		
		N	RR	95% CI	p Value	RR	95% CI	p Value
Endocrine, nutritional, metabolic, and immune	Diabetes	144	1.23	1.05–1.44	.01	1.34	1.16–1.55	<.001
	Fluid electrolyte disorder	370	0.99	0.86–1.14	.91	1.00	0.84–1.19	.98
Neurologic	Other cerebral degenerations	59	1.10	0.82–1.49	.53	1.07	0.74–1.55	.72
Respiratory	Acute bronchitis	54	1.00	0.72–1.39	.99	0.91	0.57–1.45	.69
	Other bacterial pneumonia	137	1.12	0.90–1.41	.31	1.01	0.73–1.40	.96
	Pneumonia	710	1.14	1.03–1.25	.01	1.15	1.02–1.30	.03
Digestive	Diseases of esophagus	101	0.98	0.78–1.23	.85	1.10	0.80–1.50	.56
	Gastric ulcer	100	1.09	0.85–1.39	.50	1.12	0.86–1.46	.40
	Duodenal ulcer	59	1.31	1.00–1.71	.05	1.26	0.87–1.81	.22
	Gastritis and duodenitis	63	1.13	0.85–1.50	.39	1.25	0.90–1.72	.18
	Inguinal hernia	45	1.22	0.90–1.65	.21	1.18	0.75–1.86	.47
	Vascular insufficiency of intestine	56	1.18	0.80–1.76	.40	1.29	0.90–1.84	.17
	Other and unspecified noninfectious gastroenteritis and colitis	57	1.14	0.83–1.57	.42	1.42	1.04–1.94	.03
	Intestinal obstruction without mention of hernia	183	1.02	0.83–1.25	.85	0.98	0.77–1.26	.90
	Diverticula of intestine	223	0.91	0.76–1.09	.29	0.85	0.68–1.08	.18
	Functional digestive disorders not elsewhere classified	46	0.84	0.55–1.28	.42	0.78	0.49–1.24	.29
	Other disorders of intestine	97	0.94	0.73–1.20	.59	0.89	0.67–1.18	.43
	Cholelithiasis	173	1.03	0.87–1.21	.77	1.18	0.95–1.48	.14
	Diseases of pancreas	85	1.12	0.87–1.45	.38	1.04	0.67–1.63	.86
	Gastrointestinal hemorrhage	166	1.26	1.05–1.51	.01	1.24	1.01–1.54	.05
Musculoskeletal	Osteoarthritis and allied disorders	386	1.09	0.96–1.24	.20	1.04	0.90–1.21	.62
	Other and unspecified disorders of joint	41	0.99	0.70–1.39	.95	1.10	0.69–1.74	.69
	Intervertebral disc disorders	69	1.25	0.95–1.63	.11	1.27	0.93–1.72	.13
	Other and unspecified disorders of back	145	1.00	0.83–1.21	.97	0.98	0.79–1.21	.82
	Other disorders of bone and cartilage	132	1.29	1.05–1.58	.02	1.33	1.04–1.69	.02

Notes: Models adjusted for age, gender, race, clinic, waist circumference, smoking status, diabetes, systolic blood pressure, hypertension medication use, hypolipidemic and hypoglycemic medication use, prevalent atrial fibrillation, prevalent cardiovascular disease, C-reactive protein, albumin, eGFR, total cholesterol, HDL cholesterol, triglycerides, activities of daily living, cognition, social network score, general health, insulin, alcohol, and physical activity. NEFA = nonesterified fatty acid; SD = standard deviation.

The observed association between NEFAs and diabetes hospitalizations was among those considered expected, as NEFAs are known to inhibit glucose metabolism (4,5). Elevated levels of NEFAs exhibit a strong cytotoxic effect on the β -cells resulting in β -cell dysfunction and apoptosis (22,23). Metabolism of NEFAs in the peroxisomes leads to the formation of H_2O_2 which is thought to mediate the lipotoxicity of β -cells (24). The β -cells are particularly vulnerable to the toxic effects mediated by H_2O_2 because β -cells lack catalase. β -Cell dysfunction leads to impairment in insulin secretion, and ultimately, diabetes (25,26). In our previous work in CHS, NEFAs were associated with a higher risk of diabetes, particularly in the first 5 years of follow-up (19). As a consequence, total serum NEFAs are active targets for pharmacological development in the prevention and management of obesity and diabetes (2).

Although no previous research, to our knowledge, has linked pneumonia hospitalizations to NEFAs, plausible biological mechanisms exist to explain this association. Increased levels of saturated fatty acids could lead to dysfunctional monocyte maturation and neutrophil dysfunction, resulting in increased pneumonia risk and severity (27,28). Also, increased circulating NEFA may contribute directly to systemic inflammation, thereby increasing susceptibility to chronic inflammatory diseases, including respiratory disease (29).

Among musculoskeletal disorders, degenerative osteoarthritis is the most expensive to treat in U.S. hospitals, costing \$14.8 billion in 2011, and it was accordingly a common cause of hospitalization in CHS. Nonetheless, we found no consistent evidence to support an association with this condition. Instead, we observed a significant association with hospitalization for other disorders of bone and cartilage, a category that includes osteoporosis and pathological fractures. Of note, osteoblasts actively and extensively absorb and metabolize NEFAs (30), adding to the biological plausibility of this finding.

Among the digestive system diagnostic group, NEFAs were significantly associated with more hospitalizations for duodenal ulcer and gastrointestinal hemorrhage. These findings are supported by cellular and animal models, in which direct application of NEFAs or high-fat diets increases colonic mucosal inflammation and oxidative stress (31). Nonetheless, this observation represents a generally unexpected association that warrants confirmation in other cohorts.

We did not identify single specific causes of hospitalization that accounted for the category-level associations with mental and neurological disorders. Of note, we did not previously identify an association of NEFAs with incident stroke in CHS, but dementia-related mortality was strongly associated with NEFAs (10). NEFAs can cross the blood–brain barrier and induce neuronal toxicity (9), suggesting

that these associations may reflect effects of NEFAs across disorders of neuronal degeneration.

Research has shown that higher circulating levels of NEFAs promote oxidative stress (32). In oxidative stress, the production of reactive oxygen species in the peroxisome exceeds that which can be adequately detoxified (33,34). Micronutrients such as zinc (Zn^{2+}) play vital roles in the proper functioning of antioxidant enzymes (copper/zinc superoxide dismutase; Cu/Zn SOD). The availability of Zn^{2+} in plasma is regulated through buffering by serum albumin (35). Since NEFAs depend on serum albumin to move around in the bloodstream, higher circulating levels of NEFAs reduce the ability of serum albumin to bind Zn^{2+} . Given these interactions, the role of NEFAs in oxidative stress may explain their associations with hospitalization for the wide variety of disorders to which oxidative stress contributes (36–43).

Although we have discussed possible pathways by which NEFAs may contribute to some of the hospitalizations investigated, it is also noteworthy that NEFAs might be a nonspecific marker for poorer health in general. Circulating NEFA levels do not only reflect lipolytic factors (eg, catecholamines, natriuretic peptides), and inhibitors of lipolysis (eg, adiponectin, insulin), but they also tend to track with modifiable external factors related to overall health such as low socioeconomic status and obesity. As seen in Table 1, NEFAs appeared to be inversely associated with self-reported general health. Whether NEFAs are truly causally associated with the specific causes of hospitalization that we report will require interventional studies using pharmacological therapies specific to NEFAs.

Our study has several strengths. First, CHS provides high-quality data, with high rates of participant follow-up. In the case of hospitalizations, CHS has been linked to Medicare claims and participants are queried during biannual telephone contacts, so we were able to examine the association of NEFA with the full range of causes of hospitalization in a systematic manner. Second, our sample size of over 4000 participants is particularly large for studies of NEFA. Third, we had available an extensive list of potential covariates, including measures of obesity and inflammation. Finally, we had information on both hospitalizations and days hospitalized (an indirect measure of severity), and virtually all associations were consistent across these 2 linked but distinct outcomes.

Our study is not without limitations. First, we cannot rule out unmeasured or residual confounding as alternative explanation of observed results in this observational design. Second, our results apply directly only to older adults, as CHS is a cohort of older adults. While our study design provided ample power, given the large number of hospitalizations among older adults, it will be necessary to determine whether the results apply to younger adults in future studies. Third, the overall findings on incident hospitalization, number, and days of hospitalization are primary, and others are secondary, which will require independent replication owing to multiple comparisons. Even so, consistent findings with prior studies bolster support. Fourth, we have assessed NEFAs only at baseline, and hence any changes with time could affect our findings. Fifth, our analyses involved total NEFAs and the associations found may not be conclusive enough. Future studies with individual NEFA profiles may provide a more comprehensive picture. Finally, we found associations that may need further investigation, as ours is the first study to have examined many of these relationships. Nonetheless, our findings are consistent with the biology of the hospitalized conditions studied.

Conclusion

In this cohort of older adults followed for 2 decades, higher concentrations of total NEFAs were associated with a consistently higher risk of hospitalization. Hospitalizations due to mental, neurologic, respiratory, and musculoskeletal disorders were the main diagnostic groups that were significantly associated with higher NEFAs, and we found associations with specific causes of hospitalizations such as diabetes, pneumonia, gastrointestinal hemorrhage, and other disorders of bone and cartilage. Our results highlight the association of NEFA with hospitalizations, and total days hospitalized, due to a broad range of conditions in older adults, suggesting possible utility of NEFA as a biomarker.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

Author Contributions

All authors were involved in the conception and design of the study. P.B. performed the statistical analyses. All authors were involved in the interpretation of the data. P.D.A. wrote the manuscript, and all authors critically revised it. The final version of the manuscript was approved by all authors.

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