

ASSOCIATION BETWEEN HOSPITALIZATION AND CHANGE OF FRAILTY STATUS IN THE GAZEL COHORT

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Abstract: *Objectives:* To assess the relationship between changes of frailty status and intervening hospitalizations, using information of the GAZEL cohort, matched with the data of the French National Health Data System. *Design:* Observational cohort study. *Participants:* Community-dwelling adults of the GAZEL cohort (n = 12145; aged between 58 and 73 years in 2012). *Measurements:* Frailty was determined with the Strawbridge questionnaire in 2012, 2013 and 2014. Data regarding hospitalizations (notably their number, length of stay, emergency department use, and main diagnosis) were collected from the French National Health Data System. The relationship between intervening hospitalizations and changes of frailty status over time was assessed with multivariate Markov models. *Results:* The prevalence of frailty was 14% in 2012 and 2013 and 17% in 2014. A total of 2715 changes in frailty status were observed from 2012 to 2014. At least one hospitalization was recorded for 1453 people (12%) between the 2012 and 2013 questionnaires, and 1472 (13%) between the 2013 and 2014 questionnaires. No association was found between intervening hospitalizations and changes of frailty status (aHR 1.14 [0.97-1.35] for robust to frail transition and aHR 0.89 [0.73-1.08] for frail to robust transition). However, repeated hospitalizations, hospitalizations after emergency department use, surgery and several diagnosis groups were significantly associated with transitions towards frailty or its recovery. *Conclusion:* Hospitalizations encompass a wide range of clinical situations, some of them being associated with incident frailty. An early recognition of these situations could help to better prevent and manage frailty in the early old age.

Key words: Frailty, hospitalization, transition, cohort, aging.

Introduction

Frailty is defined as a syndrome of decreased physiological reserves, causing vulnerability to adverse outcomes (1). Two main conceptual frameworks of frailty exist: the frailty phenotype defined by Fried et al (1) and the index of deficit accumulation defined by Rockwood et al (2). In addition, a number of other definitions and tools have been developed to assess frailty, in line with an increased attention of the medical community regarding the early management of health and functional decline among the elderly. Indeed, frailty often precedes disability; early identification of frailty can hence help to prevent and delay functional impairments (3, 4). Epidemiological studies highlighted factors associated with transitions towards frailty among robust people, as well as transitions towards recovery among frail people (5-9). Some are constitutive and non-modifiable, such as age and gender, whereas others may be accessible to prevention and health policies, namely health disorders, lifestyle, social network, and healthcare system organization and use (5-9). However, little is known about acute precipitants of frailty.

Although hospitalizations stand among the potential consequences of frailty (10, 11), they may also constitute a precipitating factor for incident frailty (6, 7). Previous studies demonstrated the negative impact of hospitalizations on functional capacities (12-14). To our knowledge, 2 studies

investigated the relationship between hospitalizations and the dynamics of the frailty phenotype. Gill et al (7) assessed frailty every 18 months for 108 months among 754 North American people aged 70 years or older. They showed that intervening hospitalizations restrained recovery from pre-frail and frail states. Lee et al (6) assessed the Fried's frailty status among 3018 Chinese individuals, aged 65 or older, twice at 2 years of interval. In this study, intervening hospitalizations were significantly associated with a worsening of the frailty status and, for women, associated with impeded recovery. However these studies did not stratify the risk according to the characteristics of the hospitalizations, notably the reason for hospitalization, the duration or whether it was planned or not. Hospitalizations include a wide range of clinical situations, from minor life accident to vital emergencies. Taking into account detailed information about hospitalizations may help to further understand the role of hospitalizations in the frailty trajectories.

This study aimed to assess the relationship between changes in frailty status and intervening hospitalizations, using information of a prospective cohort, matched with the data of the French National Health Data System.

Methods

Study design and participants

This study was nested in the GAZEL cohort. Details regarding the study design have been described elsewhere (15). Briefly, in 1989, 20625 employees (5614 women and 15011 men aged 35-50 years) of the French national electricity and gas utility (Electricité de France - Gaz de France, EDF-GDF) accepted to participate. Every year, participants were invited to complete a postal questionnaire including a large set of items dealing with health status, lifestyle, socioeconomic and occupational factors. Data were also collected from national registers and personal and medical departments of EDF-GDF. Our study population included subjects for whom at least 2 consecutive measures of frailty were available between 2012 and 2014. Ages ranged from 58 to 73 years old. Among the 13104 participants who answered to at least 1 questionnaire over the study period, 124 (1.0%) were excluded because they returned only 1 questionnaire, 198 (1.5%) because the 2 measures were not consecutive, and 377 (2.9%) because of missing data about frailty. The final sample included 12405 (95%) individuals, with 3 measures of frailty for 11218 (90%) of them and 2 for 1187 (10%) of them.

Frailty assessment

Frailty was assessed according to the questionnaire established by Strawbridge et al. (16). Four domains were assessed through 16 items:

- four items assessed the physical domain (sudden loss of balance, weakness in the arms, weakness in the legs, becoming dizzy when standing up quickly);
- two items assessed the nutritive domain (unexplained weight loss, loss of appetite);
- four items assessed the cognitive domain (difficulty paying attention, difficulty finding the right word, difficulty remembering things, forgetting where things were put);
- six items assessed the sensory domain (difficulty reading newspapers, difficulty recognizing a friend across the street, difficulty reading signs at night, hearing over the phone, hearing a normal conversation, hearing a conversation in a noisy room).

Scores for the last 6 items ranged from 1 to 4, with 1 = no difficulty, to 4 = great deal of difficulty. Scores for the first 10 items were rated differently, with 1 = rarely or never had the problem in the last 12 months, to 4 = very often had the problem. Participants who scored 3 or 4 in at least 1 item were considered to have difficulty in the corresponding domain. Subjects were considered frail if they reported difficulty in 2 domains or more and robust otherwise (0 or 1). In case of missing data regarding items of the Strawbridge questionnaire, individuals were included in the analysis if available information enabled to classify them as frail (at least 2 impaired domains) (n = 122, 2.3% of all frail individuals) or non-frail

(absence of impairment in at least 3 domains) (n = 91, 0.3% of all robust individuals). Otherwise, they were excluded (n = 576, 4.4% of all participants).

Hospitalizations

The French National Health Data System comprises exhaustive data about the use of health care resources (17) for the whole study sample (excluding non-reimbursed care such as over-the-counter drugs), as well as information about hospitalizations in private and public hospitals. We extracted data from 2012 to 2014 about stays in medicine and surgery wards (excluding stays in rehabilitation and psychiatric wards). Participants were considered hospitalized if they stayed at least 1 night at the hospital. The following information about hospitalizations was used in the analysis:

- number of hospitalizations that occurred between 2 consecutive questionnaires;
- length of stay, dichotomized according to the median;
- severity according to a 4-level complications and comorbid conditions scale as defined in the French Diagnosis-Related-Groups (DRG) system (18) (1 = lowest to 4 = highest severity), dichotomized as low (grade 1-2) and high (grade 3-4) severity;
- major primary diagnosis category according to the 10th International Classification of Diseases (ICD-10);
- emergency department use;
- surgical act according to the French DRG system.

In case of multiple hospitalizations, the highest value was retained for length of stay and severity. Sensitivity analysis was conducted using the cumulative length of stay during the study period.

Covariates

Information about socio-demographic characteristics, behaviors, and health status was collected. Social situation was self-rated in 2013 using an 8-level Likert scale. A 3-level variable was created, corresponding to disadvantaged, intermediate, and comfortable social status. Family situation was defined as 'couple' if the participant was married or living with someone and 'alone' if separated, divorced, widowed or living alone. Three groups of body mass index (BMI) were defined (low if BMI ≤ 23 Kg/m² for males and 21 Kg/m² for female and, high if BMI > 27 Kg/m² for both males and females). Polypharmacy was assessed using data of reimbursement of the National Health Data System. A 3-level variable was created to define polypharmacy according to the mean number of drugs consumed per 3-month periods during the year preceding the questionnaire (19): no polypharmacy (0 to 4 drugs), moderate polypharmacy (5 to 9 drugs), and high polypharmacy (10 drugs or more). Seven self-reported diseases were considered: cancer, diabetes, high blood pressure, lung disease, heart disease, stroke and muscular or joint pain. A 3-level variable was defined (20), depending on the number

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Table 1
Characteristics of the study sample, by year

Variables		2012 (n=11891)	2013 (n=12405)	2014 (n=11732)
Sex	Female	3089 (26)	3233 (26)	3051 (26)
Age	less than 65	3847 (32)	2488 (20)	1165 (10)
	65 to 70	5492 (46)	6259 (50)	6125 (52)
	70 and over	2552 (21)	3658 (29)	4442 (38)
Frailty		1664 (14)	1766 (14)	1945 (17)
Hospitalization		1443 (12)	1563 (13)	1537 (13)
Body Mass Index	Low	1614 (14)	1638 (13)	1564 (13)
	Normal	5908 (50)	6010 (48)	5645 (48)
	High	4219 (35)	4344 (35)	4128 (35)
Tobacco	Non - smoker	10476 (88)	1079 (86)	9356 (80)
	Little smoker	537 (5)	546 (4)	485 (4)
	Medium and heavy smoker	359 (3)	333 (3)	290 (2)
Social situation	Disadvantaged	1214 (10)	715 (6)	645 (5)
	Intermediate	9094 (76)	9648 (78)	9132 (78)
	Comfortable	1582 (13)	2042 (16)	1955 (17)
Polypharmacy	0 to 4	6958 (59)	7193 (58)	6750 (58)
	5 to 9	3904 (33)	4153 (33)	4019 (34)
	10 or more	1029 (9)	1059 (9)	963 (8)
Comorbidity score	0	1973 (17)	2119 (17)	1827 (16)
	1	4941 (42)	4996 (40)	4672 (40)
	2 or more	4977 (42)	5290 (43)	5233 (45)
Depression		2943 (25)	3096 (25)	3247 (28)

Results expressed as number (percentage) for categorical data and as mean (standard deviation) for continuous data.

of self-reported diseases: 0/1/2 or more. Mental health was assessed through self-reported history of depression during the last 12 months.

Statistical analysis

We used prevalence to describe categorical variables and mean \pm standard deviation (SD) for continuous variables. Associations between hospitalizations and changes of frailty status were assessed using Markov multi-state models. Different multi-state models were run separately to evaluate the association with each characteristic of the hospitalizations. These models assumed time-homogenous intensities of transitions and, that future evolution depended on the current state. The state-transition matrix was set as a reversible robust-frail model. Transitions to death were disregarded due to low mortality (n = 363; 2.8%). The variables introduced in the model were chosen a priori and were the same for all the transitions considered by the model. Time-dependent covariates were assumed constant in between the times they were observed.

We reported results with adjusted hazard ratio (aHR) and

95% confidence intervals (95%CI). Analyses were performed using R software, version 3.4.1. and ‘msm’ package (21).

Results

Population

The study population was mostly composed of males (74%). Mean age was 67 (\pm 3.5) years in 2012 and ranged from 58 to 73 years. The prevalence of frailty varied between 14 and 17%, depending on the year considered. The most commonly impaired dimension was the sensory one; the least frequently impaired was the nutritional one. Most individuals (>80%) reported at least 1 health problem (Table 1).

Hospitalizations

During the first inter-questionnaire period (2012-2013), 1453 (12%) people were hospitalized, and 1472 (13%) during the second period (2013-2014). The median length of stay was 4 days with a majority of low severity diagnoses (86% and 83% of grade 1 or 2 severity, for the first and the second period respectively). Approximately 23% of the participants

Table 2
 Details of intervening hospitalization characteristics during the study period

Variables		First period interval	Second period interval
Number of hospitalized individuals		1453 (12)	1472 (13)
Number of hospitalizations	Continuous	1.47 (± 1.76)	1.50 (± 1.71)
	1	1092 (71)	1083 (74)
	2 to 4	334 (23)	356 (24)
	5 or more	27 (2)	33 (2)
Maximal ¹ duration (in days)	Continuous	6.19 (± 10.0)	6.66 (± 10.6)
	1	274 (19)	266 (18)
	2 to 3	447 (31)	461 (31)
	4 to 6	294 (20)	312 (21)
	a week or more	438 (30)	433 (30)
Cumulative ¹ duration (in days)	Continuous	8.2 (± 19.0)	8.9 (± 21.2)
	1	255 (18)	241 (16)
	2 to 3	402 (28)	427 (29)
	4 to 6	290 (20)	301 (21)
	a week or more	506 (35)	503 (34)
Emergency department use ²		319 (22)	357 (24)
Surgery classification in DRG ²		870 (60)	867 (59)
Maximal ¹ severity according to CC	1	974 (67)	930 (63)
	2	280 (19)	292 (20)
	3	137 (9.4)	164 (11)
	4	62 (4.3)	86 (5.8)
Major diagnostic categories ² according to ICD-10			
Certain infectious & parasitic diseases	A00-B99	15 (1.0)	18 (1.2)
Cancers	C00-D48	258 (18)	258 (18)
Diseases of the blood & blood-forming organs & certain disorders involving the immune mechanism	D50-D89	11 (0.8)	14 (1.0)
Endocrine, nutritional & metabolic diseases	E00-E90	38 (2.6)	31 (2.1)
Mental & behavioral disorders	F00-F99	19 (1.3)	7 (0.5)
Nervous system diseases	G00-G99	42 (2.9)	57 (3.9)
Eye & adnexa diseases	H00-H59	44 (3.0)	51 (3.5)
Circulatory system diseases	I00-I99	285 (20)	298 (20)
Lung diseases	J00-J99	52 (3.6)	50 (3.4)
Digestive system diseases	K00-K93	178 (12)	176 (12)
Skin & subcutaneous tissues diseases	L00-L99	16 (1.1)	13 (0.9)
Musculoskeletal system & connective tissues diseases	M00-M99	237 (16)	247 (17)
Genito-urinary system diseases	N00-N99	148 (10)	130 (8.8)
Symptoms, signs & abnormal clinical & laboratory findings, not elsewhere classified	R00-R99	99 (6.8)	92 (6.3)
Injury, poisoning & certain other consequences of external causes	S00-T98	92 (6.3)	99 (6.7)
Factors influencing health status & contact with health services	Z00-Z99	192 (13)	224 (15)

1. maximal value among hospitalizations; 2. observed at least once during individual follow-up; Results expressed as number (percentage) for categorical data and as mean (standard deviation) for continuous data; DRG: diagnostic related group; CC: comorbidities and complications classes; ICD-10: 10th International Classification of Diseases.

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Table 3
Factors associated with transitions in frailty status

Variables		Robust to frail	Frail to robust
Hospitalization	yes vs no	1.14 [0.97 – 1.35]	0.89 [0.73 – 1.08]
Sex	female	1.10 [0.94 - 1.28]	0.87 [0.73 - 1.03]
Age (ref. “less than 65”)	65 - 70	1.03 [0.84-1.26]	0.73 [0.59 - 0.90]
	70 & more	1.29 [1.05 - 1.58]	0.59 [0.48 - 0.74]
Social status (ref. “intermediate”)	disadvantaged	1.00 [0.78 - 1.30]	0.81 [0.62 - 1.07]
	comfortable	0.83 [0.70 - 0.99]	1.09 [0.89 - 1.33]
Live	alone	0.90 [0.77 -1.06]	0.93 [0.78 - 1.11]
Body Mass Index (ref. “normal”)	low	1.13 [0.95 - 1.35]	0.67 [0.55 - 0.83]
	high	0.92 [0.81 - 1.05]	0.87 [0.75 - 1.01]
Tobacco (ref. “non smoker”)	little smoker	1.03 [0.77 - 1.37]	1.20 [0.87 - 1.65]
	medium heavy smoker	1.06 [0.76 - 1.47]	0.77 [0.52 - 1.15]
Polypharmacy (ref. “0 to 4”)	5 to 9	1.33 [1.17 - 1.52]	0.88 [0.76 - 1.02]
	10 & more	1.61 [1.32 - 1.96]	0.76 [0.61 - 0.95]
Comorbidity score (ref. “no comorbidity”)	1	1.54 [1.23 - 1.92]	1.02 [0.80 - 1.32]
	2 & more	2.09 [1.67 - 2.61]	0.88 [0.69 - 1.13]
Depression	yes vs no	2.05 [1.81 - 2.32]	0.74 [0.64 - 0.85]

Results expressed as adjusted hazard ratio with 95% confidence interval

who were hospitalized used the emergency department. Nearly 60% of the participants who were hospitalized were submitted to at least one surgical procedure. The most frequent diagnoses were related to the circulatory system (I00-I99) (20% of hospitalized individuals in both periods), followed by cancer (C00-D48) (18%), and musculoskeletal system and connective tissue diseases (M00-M99) (16% and 17% respectively). Characteristics of the hospitalizations are further described in Table 2.

Frailty transitions

During the follow-up, 23623 pairs of consecutive measures of frailty were available; they included 2715 (12%) changes of frailty status. The most frequent transition was from the robust to the frail state (n=1519, 7.5%).

Crude hazards of changing of frailty status were significantly different between individuals who were hospitalized and those who were not (HR 1.41 [1.22 - 1.63] for robust to frail transition and HR 0.77 [0.65 - 0.91] for frail to robust transition), but not in multivariate analysis (Table 3). However, those who were hospitalized multiple times were more likely to become frail (R-F transition) (aHR 1.32 [1.01 - 1.74]). Hospitalizations involving the use of the emergency department were also associated with R-F transition (aHR 1.38 [1.03 - 1.85]), as well as hospitalizations without surgery (aHR 1.36 [1.08 - 1.73]), high severity conditions (aHR 1.50 [1.05 - 2.15]) and groups of diagnoses ‘Symptoms, signs & abnormal clinical & laboratory findings, not elsewhere classified’ (aHR 1.70 [1.01 - 2.86]) and ‘Factors influencing health status & contact

with health services’ (aHR 1.51 [1.06 - 2.14]) (Table 4). The group ‘Symptoms, signs & abnormal clinical & laboratory findings, not elsewhere classified’ mainly consisted in urinary retention, syncope and collapse, and unspecified chest pain, whereas ‘Factors influencing health status & contact with health services’ mainly included dialysis, chemotherapy, and polysomnography. The other factors associated with frailty transitions were older age, polypharmacy, comorbidity, and depression. A comfortable social status was associated with a lower risk of becoming frail.

On the other hand, some types of hospitalizations were negatively associated with recovery from frailty (F-R transition): hospitalizations involving surgery (aHR 0.74 [0.56 - 0.96]) and hospitalizations due to ‘musculoskeletal system & connective tissue’ diseases (aHR 0.59 [0.36 - 0.96]), a group of diagnosis that included arthrosis (coxarthrosis and gonarthrosis) and rotator cuff syndrome. Other factors lowering the chances of recovery from frailty were older age, low BMI, polypharmacy, and depression.

We did not find any association between the length of stay and changes of frailty status.

Discussion

Main results

In a French cohort of 12405 individuals aged 58 and over, followed from 2012 to 2014, we found no association between changes of frailty status according to the Strawbridge’s definition and intervening hospitalizations

Table 4
 Associations between characteristics of hospital stays and frailty transitions

Variables		Robust to Frail	Frail to Robust
≥1 hospitalization		1.14 [0.97 - 1.35]	0.89 [0.73 - 1.08]
Number of hospitalizations (+1)		1.03 [0.99 - 1.07]	0.95 [0.86 - 1.05]
Hospitalizations	unique	1.07 [0.88 - 1.30]	0.92 [0.74 - 1.14]
	multiple	1.32 [1.01 - 1.74]	0.78 [0.54 - 1.12]
Length of stay (maximum)	1 to 4 days	1.14 [0.92 - 1.42]	0.80 [0.61 - 1.05]
	4 days or more	1.13 [0.91 - 1.42]	0.97 [0.76 - 1.24]
Length of stay (cumulative)	1 to 4 days	1.15 [0.91 - 1.44]	0.83 [0.63 - 1.10]
	4 days or more	1.13 [0.91 - 1.40]	0.97 [0.73 - 1.19]
Severity	grade 1 or 2	1.08 [0.90 - 1.29]	0.85 [0.69 - 1.05]
	grade 3 or 4	1.50 [1.05 - 2.15]	1.09 [0.71 - 1.68]
Emergency department use	with	1.38 [1.03 - 1.85]	0.93 [0.66 - 1.32]
	without	1.07 [0.88 - 1.29]	0.87 [0.70 - 1.09]
Surgery	with	1.00 [0.81 - 1.23]	0.74 [0.56 - 0.96]
	without	1.36 [1.08 - 1.73]	1.08 [0.84 - 1.40]
Certain infectious & parasitic diseases	with	1.70 [0.48 - 5.95]	1.03 [0.34 - 3.11]
	without	1.13 [0.96 - 1.34]	0.88 [0.73 - 1.08]
Cancers	with	1.12 [0.78 - 1.61]	0.99 [0.62 - 1.57]
	without	1.15 [0.96 - 1.37]	0.87 [0.71 - 1.07]
Diseases of the blood & blood-forming organs & certain disorders involving the immune mechanism	with	2.65 [0.81 - 8.73]	0.46 [0.06 - 3.37]
	without	1.13 [0.96 - 1.34]	0.89 [0.74 - 1.08]
Endocrine, nutritional & metabolic diseases	with	1.65 [0.55 - 5.02]	2.42 [0.95 - 6.20]
	without	1.13 [0.96 - 1.34]	0.86 [0.71 - 1.05]
Mental & behavioral disorders	with	0.99 [0.23 - 4.26]	1.02 [0.29 - 3.56]
	without	1.14 [0.97 - 1.35]	0.88 [0.73 - 1.07]
Nervous system diseases	with	1.61 [0.80 - 3.20]	0.77 [0.23 - 2.53]
	without	1.12 [0.95 - 1.33]	0.89 [0.73 - 1.08]
Eye & adnexa diseases	with	1.20 [0.55 - 2.62]	0.80 [0.29 - 2.20]
	without	1.14 [0.96 - 1.33]	0.89 [0.73 - 1.08]
Circulatory system diseases	with	0.96 [0.68 - 1.35]	0.85 [0.57 - 1.25]
	without	1.19 [1.00 - 1.43]	0.90 [0.73 - 1.11]
Respiratory system diseases	with	0.77 [0.30 - 1.94]	1.21 [0.52 - 2.83]
	without	1.15 [0.98 - 1.37]	0.88 [0.72 - 1.07]
Digestive system diseases	with	1.27 [0.82 - 1.97]	1.00 [0.61 - 1.63]
	without	1.12 [0.94 - 1.34]	0.87 [0.71 - 1.07]
Skin & subcutaneous tissue diseases	with	1.39 [0.41 - 4.70]	0.60 [0.09 - 4.25]
	without	1.14 [0.96 - 1.34]	0.89 [0.73 - 1.08]
Musculoskeletal system & connective tissue diseases	with	1.25 [0.89 - 1.75]	0.59 [0.36 - 0.96]
	without	1.12 [0.93 - 1.34]	0.96 [0.78 - 1.17]
genito-urinary system diseases	with	0.93 [0.59 - 1.62]	1.01 [0.61 - 1.69]
	without	1.16 [0.98 - 1.38]	0.87 [0.71 - 1.07]
Symptoms, signs & abnormal clinical & laboratory findings, not elsewhere classified	with	1.70 [1.01 - 2.86]	1.10 [0.61 - 1.97]
	without	1.10 [0.93 - 1.31]	0.87 [0.71 - 1.07]
Injury, poisoning & certain other consequences of external causes	with	1.06 [0.60 - 1.87]	0.60 [0.28 - 1.29]
	without	1.15 [0.97 - 1.36]	0.91 [0.75 - 1.11]
Factors influencing health status & contact with health services	with	1.51 [1.06 - 2.14]	0.79 [0.49 - 1.29]
	without	1.08 [0.90 - 1.29]	0.90 [0.74 - 1.11]

All models were run separately, Results expressed as adjusted hazard ratio with 95% confidence interval; Adjustment : age, sex, marital status, social status, BMI, comorbidity score, tobacco consumption, polypharmacy, self-reported depression; reference group: "no hospitalization"

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when all hospitalizations were considered together. However, we found that hospitalizations were significantly associated with changes of frailty status in particular situations, being multiple hospitalizations, use of emergency department and hospitalizations because of 2 groups of diagnoses related to heterogeneous and chronic diseases.

Frailty and hospitalizations

In line with previous prevalence reported in studies by Strawbridge et al (16) and Matthews et al (22), the prevalence of frailty varied from 14% in 2012 and 17% in 2014 in this sample composed, of 74% of men. To our knowledge, this is the first time frailty transitions are studied using a multidimensional definition of frailty. We show that frailty is a transient state, consistently with the findings of studies using the frailty phenotype (6, 7). Indeed, more than 1/3 of frail individuals recovered from frailty during the follow-up.

Hospitalizations were described using the National Health Data System. Hospitalization prevalence and the main reasons for hospitalizations were consistent with national statistics reported by the French Technical Agency for Information on Hospitalization ('Agence Technique de l'Information sur l'Hospitalisation') (23).

Changes of frailty status and hospitalizations

Previous studies (6, 7) suggested an association between all-kind hospitalization and frailty transitions, whereas we did not confirm this result. Nevertheless, the extent of the comparison is limited by the use of different definitions to assess frailty, with either the multidimensional definition by Strawbridge et al, or the physical frailty phenotype. It can be assumed that a multidimensional approach of frailty is less sensitive than a physical definition to the impact of hospitalization. However, a higher risk of transition towards frailty was observed in the case of multiple hospitalizations, in line with previous studies.

We showed that hospitalization in emergency was associated with incident frailty, in accordance with the hypothesis that hospitalization in emergency is more stressful than planned hospitalization. It may also reflect a difficulty for general practitioner to manage individuals at the edge of frailty. Surprisingly, we found that hospitalization without surgery was associated with an increased risk of transition towards frailty. This result may actually reflect the association between the use of the emergency department and incident frailty, as hospitalization without surgery and the use of the emergency department were hospitalization features, strongly related to each other. Indeed, surgery was less frequent among people who were admitted through the emergency department (36% vs 67% in the first period and 38% vs 66% in the second period; p-value < 0.001).

This study did not enable to highlight specific diagnoses that would increase the risk of frailty, except two heterogeneous groups of diagnoses: 'Symptoms, signs & abnormal clinical & laboratory findings, not elsewhere classified' and 'Factors influencing health status & contact with health services'. The

first group comprises diagnoses without a clear identification of the underlying process or pathology. These unspecific signs may be related to undiagnosed chronic conditions such as prostate tumor or heart disease as already underlined by literature (24). They may also be part of the "geriatric syndrome" (25). The diagnoses included in the second group concerned heavy chronic conditions. In both cases, no difference in diagnosis was found between those who maintained a robust status and those who failed.

Other factors

As summarized in a recent systematic review (9), age, polypharmacy, comorbidity, depression and social situation were found to be significantly associated with increased risk of incident frailty. Others factors such as gender are inconsistently associated with frailty transitions in the literature. In the present study, gender was not associated with any kind of transition, probably because the analysis took into account depression and polypharmacy, which are two major determinants of frailty more often found among women (26, 27). High BMI, and tobacco consumption were not significantly associated with incident frailty. However, we did not take into account the history of exposure to these factors and, long-term effects may be under-evaluated in the present analysis.

Strength and limitations

The main strength of this study lies in its population size and follow-up. The French National Health Data System included an exhaustive record of hospitalizations even though it was not specifically built for epidemiological purposes.

However, several limitations must be acknowledged. First, the causality of events could not be ascertained. We did not know when changes in frailty states occurred nor their exact temporal relationship with hospitalizations. More frequent assessments of frailty, as previously done for disability (28) could help clarifying the temporality of the relationship. However, such a design would not eliminate indication bias, where the part of frailty attributable to an acute or chronic disease is difficult to disentangle from the part caused by the iatrogenic component of hospitalizations. Secondly, comorbidities were self-reported and their severity not assessed, preventing us to use more accurate comorbidity scales (29). Thirdly, hospitalizations characteristics were assessed in separate models due to collinearity issues. As a consequence, cumulative effects and interactions were not evaluated in this study. Finally, hospitalizations were considered as punctual and independent events. No information was available about stays in psychiatric ward or the use of rehabilitation services. This study did not take into account the diversity of care paths following hospitalizations (30, 31).

Implications and perspectives

Hospitalization features studied here could easily be collected, directly from hospital reports or patients. Practitioners might gain insights about the near future of

their patients after discharge. Hospitalization features can help identifying individuals for whom the follow-up must be reinforced after hospitalization to prevent frailty and, in turn, physical and functional impairments (32). Another application could be to identify patients likely to benefit from prehabilitation (33-35), before planned hospitalizations. However further work is needed to confirm our findings in other settings and to study how they could help improving the management of the hospitalized elderly.

Conclusion

This study showed that some kinds of hospitalizations are associated with incident frailty among robust individuals and impeded recovery among frail individuals. These results highlight the interrelationship between hospitalizations and frailty and should increase awareness of care providers towards hospitalized people at risk of frailty. Studies combining a wider spectrum of information at the individual (clinical information, care pathways) and contextual level (availability and coordination of health services) are required to improve our understanding and management of frailty.

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References

1. Fried LP, Tangen CM, Walston J, et al. Frailty in Older Adults: Evidence for a Phenotype. *Journals Gerontol Ser A Biol Sci Med Sci*. 2001;56(3):M146-M157. doi:10.1093/gerona/56.3.M146
2. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of Deficits as a Proxy Measure of Aging. *Sci World J*. 2001;1:323-336. doi:10.1100/tsw.2001.58
3. Acosta-Benito M, Sevilla-Machuca I. Using prefrailty to detect early disability. *J Fam Community Med*. 2016;23(3):140. doi:10.4103/2230-8229.189106
4. De La Rica-Escuin M, González-Vaca J, Varela-Pérez R, et al. Frailty and mortality or incident disability in institutionalized older adults: The FINAL Study. *Maturitas*. 2014;78(4):329-334. doi:10.1016/j.maturitas.2014.05.022
5. Trevisan C, Veronese N, Maggi S, et al. Factors Influencing Transitions Between Frailty States in Elderly Adults: The Progetto Veneto Anziani Longitudinal Study. *J Am Geriatr Soc*. 2017;65(1):179-184. doi:10.1111/jgs.14515
6. Lee JSW, Auyeung T-W, Leung J, Kwok T, Woo J. Transitions in Frailty States Among Community-Living Older Adults and Their Associated Factors. *J Am Med Dir Assoc*. 2014;15(4):281-286. doi:10.1016/j.jamda.2013.12.002
7. Gill TM, Gahbauer EA, Han L, Allore HG. The relationship between intervening hospitalizations and transitions between frailty states. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2011;66 A(11):1238-1243. doi:10.1093/gerona/glr142
8. Jansen KM, Bell JS, Hilmer SN, et al. Effects of Changes in Number of Medications and Drug Burden Index Exposure on Transitions between Frailty States and Death: The Concord Health and Ageing in Men Project Cohort Study. *J Am Geriatr Soc*. 2016;64(1):89-95. doi:10.1111/jgs.13877
9. Feng Z, Lugtenberg M, Franse C, et al. Risk factors and protective factors associated with incident or increase of frailty among community-dwelling older adults: A systematic review of longitudinal studies. *PLoS One*. 2017;12(6):1-18. doi:10.1371/journal.pone.0178383
10. Muscedere J, Waters B, Varambally A, et al. The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis. *Intensive Care Med*. 2017;43(8):1105-1122. doi:10.1007/s00134-017-4867-0
11. Hogan DB, Maxwell CJ, Afilalo J, et al. A Scoping Review of Frailty and Acute Care in Middle-Aged and Older Individuals with Recommendations for Future Research. *Can Geriatr J*. 2017;20(1):22-37. doi:10.5770/cgj.20.240
12. Covinsky KE, Pierluissi E, Story THEPS. CLINICIAN ' S CORNER Hospitalization-Associated Disability " She Was Probably Able to Ambulate , but I ' m Not Sure " -JAMA- 2011.pdf. 2015.
13. Zisberg A, Shadmi E, Gur-Yaish N, Tonkikh O, Sinoff G. Hospital-Associated Functional Decline: The Role of Hospitalization Processes Beyond Individual Risk Factors. *J Am Geriatr Soc*. 2015;63(1):55-62. doi:10.1111/jgs.13193
14. Kuys SS, Dolecka UE, Guard A. Activity level of hospital medical inpatients: An observational study. *Arch Gerontol Geriatr*. 2012;55(2):417-421. doi:10.1016/j.archger.2012.02.008
15. Goldberg M, Leclerc A, Bonenfant S, et al. Cohort profile: The GAZEL Cohort Study. *Int J Epidemiol*. 2007;36(1):32-39. doi:10.1093/ije/dyl247
16. William J. Strawbridge, Sarah J. Shema, Jennifer L. Balfour, Helen R. Higby and GAK. Antecedents of Frailty Over Three Decades in an Older Cohort. 1998:9-16.
17. Tuppin P, Rudant J, Constantinou P, et al. L'utilité d'une base médico-administrative nationale pour guider la décision publique: du système national d'information interrégimes de l'Assurance Maladie (SNIRAM) vers le système national des données de santé (SNDS) en France. *Rev Epidemiol Sante Publique*. 2017;65:S149-S167. doi:10.1016/j.respe.2017.05.004
18. Delahaye-Guillocheau V. Manuel Des Groupes Homogènes de Malades. Ministère des Aff Socia la Santé. 2017;1(2017/5 bis):1-53.
19. IRDES. La polymédication : définitions, mesures et enjeux - Revue de la littérature et tests de mesure. *Quest d'économie la santé*. 2014;204:8.
20. Alvarado BE, Zunzunegui M-V, Béland F, Bamvita J-M. Life course social and health conditions linked to frailty in Latin American older men and women. *J Gerontol A Biol Sci Med Sci*. 2008;63(12):1399-1406. http://www.ncbi.nlm.nih.gov/pubmed/19126855. Accessed January 12, 2018.
21. Jackson C. Multi-state modelling with R: the msm package. Cambridge, UK. 2007:1-53. ftp://218.193.60.3/software/rsoft/msm/doc/msm-manual.pdf.
22. Matthews M, Lucas A, Boland R, et al. Use of a questionnaire to screen for frailty in the elderly: an exploratory study. *Aging Clin Exp Res*. 2004;16(1):34-40. doi:10.1007/BF0324529
23. Hospitalière AT de l'information. Vieillesse de La Population et Évolution de l'activité Hospitalière 2007-2010: Focus Sur La Prise En Charge Des 80ans et Plus.; 2015.
24. Newman A B, Gottdiener JS, Mcburnie MA, et al. Associations of subclinical cardiovascular disease with frailty. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M158-66. doi:10.1093/gerona/56.3.M158
25. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric Syndromes: Clinical Research, and Policy Implications of a Core Geriatric Concept. *J Am Geriatr Soc*. 2007;55(5):780-791. doi:10.1111/j.1532-5415.2007.01156.x
26. Venturini CD, Engroff P, Ely LS, et al. Gender differences, polypharmacy, and potential pharmacological interactions in the elderly. *Clinics (Sao Paulo)*. 2011;66(11):1867-1872. http://www.ncbi.nlm.nih.gov/pubmed/22086515. Accessed January 12, 2018.
27. Li N, Chen G, Zeng P, et al. Prevalence of depression and its associated factors among Chinese elderly people: A comparison study between community-based population and hospitalized population. *Psychiatry Res*. 2016;243:87-91. doi:10.1016/j.psychres.2016.05.030
28. Gill TM. Disentangling the disabling process: Insights from the precipitating events project. *Gerontologist*. 2014;54(4):533-549. doi:10.1093/geront/gnu067
29. Sharabiani MTA, Aylin P, Bottle A. Systematic Review of Comorbidity Indices for Administrative Data. *Med Care*. 2012;50(12):1109-1118. doi:10.1097/MLR.0b013e31825f64d0
30. Røststad T, Garåsen H, Steinsbekk A, Håland E, Kristoffersen L, Grimsmo A. Implementing a care pathway for elderly patients, a comparative qualitative process evaluation in primary care. *BMC Health Serv Res*. 2015;15(1):1-9. doi:10.1186/s12913-015-0751-1
31. Van Oostveen CJ, Ubink DT, Huis In Het Veld JG, Bakker PJ, Vermeulen H. Factors and models associated with the amount of hospital care services as demanded by hospitalized patients: A systematic review. *PLoS One*. 2014;9(5). doi:10.1371/journal.pone.0098102
32. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a Predictor of Surgical Outcomes in Older Patients. *J Am Coll Surg*. 2010;210(6):901-908. doi:10.1016/j.jamcollsurg.2010.01.028
33. Sheshadri A, Johansen KL. Prehabilitation for the Frail Patient Approaching ESRD. *Semin Nephrol*. 2017;37(2):159-172. doi:10.1016/j.semnephrol.2016.12.006
34. Carli F, Awasthi R, Gillis C, Kassouf W. Optimizing a frail elderly patient for radical cystectomy with a prehabilitation program. *J Can Urol Assoc*. 2014;8(11-12):e884-e887. doi:10.5489/auaj.2025
35. Gill TM, Baker DI, Gottschalk M, et al. A prehabilitation program for physically frail community-living older persons. *Arch Phys Med Rehabil*. 2003;84(3 SUPPL. 1):394-404. doi:10.1053/apmr.2003.50020