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Factors associated with changes of the frailty status after age 70: Findings in the MAPT study

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ABSTRACT

Purpose: Frailty has become a major issue in the prevention of functional decline and disability in aged populations. Using repeated measurements of frailty over 3 years, this work aimed to describe transitions between frailty states and associated factors.
Methods: This study used the data from the Multidomain Alzheimer Preventive Trial and included the 842 participants aged 70 and over who did not receive the multidomain intervention. Frailty was assessed using the phenotype proposed by Fried et al. at baseline and at 6, 12, 24, and 36 months. Factors influencing the transitions across frailty states were examined using multistate modeling.
Results: The study population included 548 women and 294 men, mean age 75.4 ± 4.5 years. At baseline, 430 (53%) participants were nonfrail, 349 (43%) prefrail, and 28 (4%) frail. A total of 2271 pairs of consecutive measurements of frailty status were available over the 3 years of follow-up, with no change in frailty status in 1548 of them (68%), a worsening of frailty status in 426 of them (19%), and an improvement in frailty status in the remaining 297 (13%). Polypharmacy (i.e., ≥6 drugs) and probable

Ethics: The study protocol was approved by the French Ethics Committee located in Toulouse (CPP SOOM II) on December 6, 2007 and authorized by French health authority (Ministry of Health) on December 31, 2007. Written consent was obtained from all participants. The protocol is registered on a public-access clinical trial database (https://www.clinicaltrials.gov) [NCT00672685)].

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depression were associated with incident prefrailty. Female gender was systematically associated with a lower probability of recovering from prefrailty and frailty. Older age, overweight, comorbidity, and abnormal C-reactive protein also reduced the probability of recovery from frailty or prefrailty.
Conclusions: This study sheds light on factors that should be further investigated in future research to help the prevention and management of frailty.

Introduction

Frailty is defined as an ageing-related state, resulting from a decrease in physiological reserves across multiple systems, increasing vulnerability to stressors [1]. From this theoretical basis, multiple operational definitions of frailty have emerged [2]. The most commonly used is the frailty phenotype, which is based on a set of five criteria exploring physical strength, physical activity, nutrition, mobility, and energy [3]. Frailty has been shown to affect between 11 and 14% of people aged 65 years and over and to be a predictor of adverse health outcomes, such as falls, institutionalization, and mortality [4,5].

As such, frailty has become a major issue in the prevention of functional decline and disability in aged populations [6,7]. The concept of frailty is now incorporated in public health policies, and primary care physicians are encouraged to screen their patients for frailty and to refer them, where necessary, to day hospitals for a full frailty assessment, enabling the provision of personalized interventions to delay health and functional decline. A wide range of interventions are available, including improved management of chronic conditions, physical activity, and nutritional skills [8,9].

Much research has focused on the dynamic of frailty in longitudinal settings to understand the multiple causes of and risk factors for prefrailty and frailty. Valuable studies in the field [10–20] have contributed to the description of frailty transitions. However, large intervals between measurements of the frailty phenotype (from 18 months to more than 4 years depending on the study) fail to take into account any change in frailty status that occurred within shorter intervals and may result in transitions being related to risk factors that may have changed since the previous assessment (e.g., number of medications). The close follow-up of participants included in the control arms of prevention trials can provide useful information about the natural history of frailty. Because of eligibility criteria, participants in prevention trials are initially mostly nonfrail, enabling us to observe the occurrence of frailty longitudinally [20].

In this context, this study aimed to describe changes in frailty status among individuals included in the nonmultidomain intervention arms of the Multidomain Alzheimer Preventive Trial (MAPT) during the first 3 years of their participation and the factors associated with the different transitions.

Material and methods

Study design and population

The MAPT study is a phase III, multicenter (n = 13), randomized, placebo-controlled trial, using a four-arm design with three treatment groups (omega-3 alone, multidomain intervention alone, and omega-3 plus multidomain intervention) and a placebo group [21]. The MAPT study was designed to assess the efficacy of isolated supplementation with omega-3 fatty acid, an isolated multidomain intervention (consisting of nutritional counseling, physical exercise, and cognitive stimulation) or a combination of the two interventions on changes in cognitive function in community-dwelling individuals aged 70 years and older for a period of 3 years. Participants were recruited between May 2008 and February 2011 from community-dwelling elderly people aged 70 years or older who met at least one of three criteria:

- Spontaneous memory complaint expressed to the general practitioner;
- Limitation in one instrumental activity of daily living (IADL, i.e., ability to use the telephone, shop, prepare meals, do housekeeping, do one's laundry, use transportation, follow a medication schedule, or manage money);
- Slow walking speed (lower than 0.8 m per s, i.e., more than 5 seconds required to walk 4 meters).

Subjects with dementia were excluded as well as subjects with a mini mental state examination score lower than 24, subjects assessed as dependent for any of the basic activities of daily living (an ADL score lower than 6 [range: 0–6]), and subjects with any disease that could compromise their participation. In addition, subjects who had taken omega-3 supplements within the past 6 months were not included.

The MAPT study included 1680 participants, of whom only those included in the nonmultidomain intervention arms were considered in the present study (420 in the control arm and 423 in the omega-3 arm). As mentioned previously, the use of the control arm was intended to enable observation of the natural history of frailty in the absence of specific interventions. To increase the power of the study and because the omega-3 supplementation did not significantly affect frailty status over time in the MAPT study [22], the subjects included in the omega-3 arm were also considered in the analysis. Although the multidomain intervention did not affect frailty status either, caution prompted us to exclude the individuals who received the multidomain intervention; multidomain interventions are one of the most promising strategies for modifying the course of frailty among older adults [23], and the MAPT study was not designed to assess the efficacy of the multidomain intervention on frailty. One subject withdrew from the omega-3 arm, resulting in a final sample of 842.

Data collection

Follow-up visits were scheduled every 6 months up to 36 months. Assessment of frailty and other variables was conducted at baseline, 6 months, and annually at 1, 2, and 3 years by research staff blinded to the intervention.

Frailty

Frailty phenotype was determined according to the following five criteria, adapted from Fried et al [3]:

- Unintentional weight loss >4.5 kg in the past year;
- Fatigue measured by two questions from the CES-D depression scale;

Table 1
Characteristics of the study sample at baseline by frailty status

Variables	Total (N = 807)	Nonfrail (N = 430)	Prefrail (N = 349)	Frail (N = 28)	P^*
General information					
Arm of the MAPT trial					
Placebo	401 (49.7)	224 (52.1)	166 (47.6)	11 (39.3)	.242
Omega 3	406 (50.3)	206 (47.9)	183 (52.4)	17 (60.7)	—
Gender					.177
Male	285 (33.3)	141 (49.5)	131 (37.5)	13 (4.6)	
Female	522 (64.7)	289 (67.2)	218 (62.5)	15 (53.6)	
Age					<.001
70–74 y	396 (49.1)	249 (57.9)	137 (39.3)	10 (35.7)	
75–79 y	262 (32.5)	134 (31.2)	120 (34.4)	8 (28.6)	
80 y and over	149 (18.5)	47 (10.9)	92 (26.4)	10 (35.7)	
ADCS score at baseline					<.001
41–45 (less disabled)	428 (53.3)	259 (60.7)	163 (46.8)	6 (21.4)	
0–41 (more disabled)	375 (46.7)	168 (39.3)	185 (53.2)	22 (78.6)	
BMI (kg/m^2)					<.001
16–24 kg/m^2	336 (41.8)	208 (48.6)	122 (36.2)	6 (21.4)	
25–29 kg/m^2	336 (41.8)	173 (40.4)	147 (42.4)	16 (57.1)	
30 kg per m^2 and over	131 (16.3)	47 (11.0)	78 (22.5)	6 (21.4)	
Health information					
Polypharmacy (≥6 drugs)	284 (35.2)	128 (29.8)	148 (42.4)	8 (28.6)	.001
Cognitive impairment	132 (16.4)	61 (14.2)	61 (17.5)	10 (35.7)	.009
Probable depression	142 (17.7)	48 (11.2)	83 (24.0)	11 (39.3)	<.001
Number of health disorders, mean ± SD	4.8 ± 2.6	4.4 ± 2.5	5.3 ± 2.6	5.1 ± 2.5	<.001
Biochemical abnormalities					
Total cholesterol	347 (43.9)	185 (43.7)	148 (43.7)	14 (50.0)	.804
Triglycerides	295 (37.2)	145 (34.2)	133 (39.0)	17 (60.7)	.013
Creatinine	119 (15.2)	51 (12.3)	59 (17.3)	9 (32.1)	.006
CRP	86 (11.9)	39 (9.9)	41 (13.4)	6 (25.0)	.045
Hemoglobin	50 (6.3)	19 (4.4)	27 (7.9)	4 (14.3)	.025
Frailty criteria					
Unintentional weight loss	39 (4.8)	0	32 (9.2)	7 (25.0)	—
Fatigue	135 (16.7)	0	110 (31.5)	25 (89.3)	—
Low grip strength	194 (24.0)	0	171 (49.0)	23 (82.1)	—
Slow walking speed	22 (2.7)	0	13 (3.7)	9 (32.1)	—
Low level of physical activity	124 (15.4)	0	101 (28.9)	23 (82.1)	—

Figures are n (%), except for the number of diseases.
* χ^2 test or Fisher's exact test for categorical variables and analysis of variance for continuous variables.

- Low grip strength based on the best of three measurements with preferred hand;
- Slow walking speed based on the best of two measurements over 4 meters;
- Low level of physical activity expressed in weekly energy expenditure relating to time spent doing leisure and physical activities [24].

Further details about the assessment of frailty (exact formulation of the questions and coding) are given in Appendix 1.

Frail subjects were those meeting three or more of the five criteria. Those meeting one or two of the five criteria were considered prefrail. The frailty phenotype could only be determined if information about all five criteria was available (no imputation of missing data).

Other variables

Baseline information included age, gender, and treatment arm, as well as the following variables that were also collected at each follow-up:

- Body mass index;
- Polypharmacy defined as more than or equal to 6 drugs [25];
- Health disorders using the MedDRA System Organ Class classification (considering diseases up to 12 months before baseline);
- Probable depression measured by a Geriatric Depression Scale 15-item version (GDS-15) score of >5 [26];
- Cognitive impairment measured by a mini mental state examination score less than or equal to 26 [27];
- Functional ability as measured by the Alzheimer's Disease Cooperative Study-Activities of Daily Living Prevention Instrument (ADCS-ADL PI) [28], dichotomized according to the median value in the study sample;
- Biochemical abnormalities (whether clinically significant or not) reported by investigators in the case report form. Based on individual test results (not available for the present study), the investigators rated for each parameter whether the result was normal or not and, if not, whether a clinical effect could be related to the biochemical abnormality.

All variables except gender were updated at each follow-up.

Statistics

The characteristics of the participants were described for the study sample and by frailty group in terms of proportions for categorical variables and means ± standard deviation for continuous variables. Comparison between groups used χ^2 test or Fisher's exact test for categorical variables and analysis of variance for continuous variables.

As recommended for panel data where individuals are observed at arbitrary continuous times, here periodical medical visits, we used multistate modeling to describe how individuals moved between frailty states during the follow-up (states were unknown between observation times). Intensity of transition (i.e., instantaneous risk of moving from one state to another) may depend on time t (but we

assume here time-homogenous intensities) or, more generally, on a set of individual-level or time-dependent explanatory variables. Factors associated with the four main transitions (from nonfrail to prefrail, from prefrail to frail, from frail to prefrail, and from prefrail to nonfrail) were assessed by introducing covariates in the multistate model. The model was specified so that covariates applied to all intensities. Time-dependent covariates were assumed to be constant between the times they were observed, and the transition probability between a pair of times (t_1; t_2) is assumed to depend on the covariate value at t_1. Variables significantly associated with at least one transition in bivariate analysis were introduced in the final model (namely gender, age, ADCS-ADL score, body mass index category, polypharmacy, number of health disorders, probable depression, and abnormal C-reactive protein [CRP]). More details about the model are given in Appendix 2. Results are given in terms of transition intensities with adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for each covariate. Analyses were performed using Stata v13 and R (MSM package) [29].

Results

Characteristics of the study sample at baseline

The study sample was composed of 65.1% women and mean age was 75.4 ± 4.5. Memory complaint was the main reason for inclusion (n = 836; 99.3%), far ahead of IADL limitations (54; 6.4%), and slow walking speed (68; 8.1%). We were able to determine the frailty phenotype of 807 individuals at baseline (95.8%). Of these, 430 (53.3%) were nonfrail, 349 (43.2%) prefrail, and 28 (3.5%) frail. Fatigue, low grip strength, and low level of physical activity were the factors that contributed most to frailty. The characteristics of the study sample by frailty status are described further in Table 1.

Follow-up of frailty

We were able to determine the frailty phenotype of 711 individuals at 6 months (86.8%), 626 at 12 months (83.0%), 550 at 24 months (81.7%), and 562 at 36 months (84.6%). The proportion of nonfrail individuals decreased during the follow-up (Fig. 1). We recorded 18 deaths during the follow-up.

A total of 2271 pairs of consecutive measurements of frailty status were available over the 3 years of follow-up, with no change in frailty status in 1548 of them (68%), a worsening of frailty status in 426 of them (19%), and an improvement in frailty status in the remaining 297 (13%). The transition matrix (Table 2) shows that nonfrail and prefrail people often remained in the same state from one assessment to another; 70.8% of nonfrail people remained nonfrail and 67.4% of prefrail people remained prefrail. Worsening transitions represented 29.1% of consecutive measurements from the nonfrail state and 8.2% from the prefrail state. Transitions in the direction of recovery amounted to 24.4% of consecutive measurements from the prefrail state and to 64.8% of those from the frail state. Of note, direct transitions from nonfrail to frail or from frail to nonfrail were very rare.

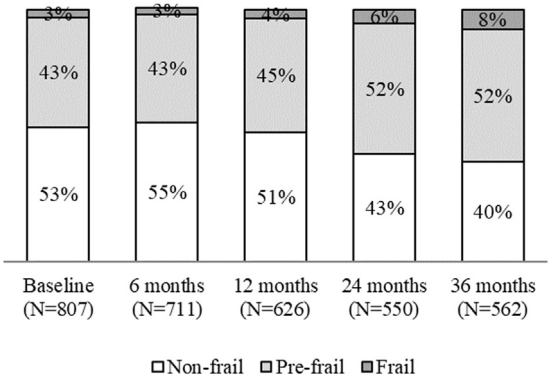

Fig. 1. Evolution of the proportion of individuals in each frailty state during the follow-up.

Table 2
Transition matrix

From	To			Total
	Nonfrail	Prefrail	Frail	
Nonfrail	831 (70.8)	335 (28.6)	7 (0.6)	1173 (100.0)
Prefrail	251 (24.4)	692 (67.4)	84 (8.2)	1027 (100.0)
Frail	5 (7.0)	41 (57.8)	25 (35.2)	71 (100.0)

Figures are n (%).
Transitions are defined between two consecutive assessments of frailty.

Factors influencing transitions

Results of the multistate model are presented in Table 3. We did not identify factors associated with the transition from prefrail to frail states. The only factors associated with the transition from nonfrail to prefrail state were polypharmacy and probable depression. Female gender was systematically associated with a lower probability of recovering from prefrailty and frailty. Older age, overweight, comorbidity, and abnormal CRP also reduced the probability of recovering from frailty or prefrailty. Of note, the arm in the MAPT trial (control or omega-3) was not included in the final model because it did not influence the likelihood of the transitions in bivariate analysis.

Discussion

Transitions between frailty states

Nested in a prevention trial among older adults reporting memory or physical complaints, this study enabled us to describe transitions between frailty states over relatively short time intervals. We confirm that transitions occur most commonly between adjacent frailty states [10,13,16,17,30], reinforcing the hypothesis of a progressive evolution across the frailty continuum. Our results are also in line with previous findings showing that chances of recovery from frailty are usually equal or superior to chances of recovery from prefrailty in longitudinal settings [10,13,16,17], probably because of a selection effect where the most frail are more likely to be lost to follow-up [31].

Factors associated with the transitions

The analysis of the factors associated with the transitions showed that incident prefrailty was associated with polypharmacy, defined as more than or equal to 6 drugs according to the recommended threshold for studies in the area of frailty [25]. The potential contribution of medications to frailty has been suggested previously [32], often based on cross-sectional associations [33,34]. Our results supplement those of Wang et al and Saum et al who demonstrated that polypharmacy increased the risk of incident phenotypic frailty in longitudinal settings [35,36]. Although contradictory results exist [14] and residual confounding bias by comorbidity cannot be excluded, this association seems plausible. Indeed, polypharmacy may increase the risk of receiving inappropriate prescriptions and of experiencing adverse drug events that

Table 3
Multistate model assessing factors influencing transitions between frailty states

Variables	Transitions between frailty states			
	From nonfrail to prefrail (N = 335)	From prefrail to nonfrail (N = 251)	From prefrail to frail (N = 84)	From frail to prefrail (N = 41)
Gender				
Male	1	1	1	1
Female	1.12 (0.82–1.53)	**0.70 (0.49–0.98)**	0.69 (0.30–1.58)	**0.32 (0.12–0.84)**
Age				
70–74 y	1	1	1	1
75–79 y	1.05 (0.78–1.41)	**0.57 (0.40–0.81)**	0.94 (0.37–2.38)	0.36 (0.11–1.12)
80 y and over	1.45 (0.98–2.16)	**0.43 (0.27–0.68)**	1.27 (0.47–3.44)	0.39 (0.12–1.31)
ADCS score <41	1.13 (0.84–1.52)	0.93 (0.66–1.29)	1.79 (0.84–3.85)	1.50 (0.55–4.08)
Body mass index				
16–24 kg/m^2	1	1	1	1
25–29 kg/m^2	1.09 (0.81–1.46)	**0.64 (0.45–0.90)**	0.52 (0.21–1.30)	0.52 (0.15–1.77)
30 kg per m^2 and over	1.26 (0.84–1.91)	0.64 (0.40–1.02)	1.79 (0.58–5.54)	1.28 (0.28–5.94)
Polypharmacy (≥6 drugs)	**1.44 (1.07–1.96)**	1.19 (0.83–1.69)	0.98 (0.44–2.20)	0.85 (0.29–2.46)
Number of health disorders (+1)*	1.02 (0.97–1.08)	0.98 (0.92–1.05)	0.92 (0.78–1.07)	**0.75 (0.61–0.93)**
Probable depression	**1.49 (1.01–2.18)**	0.72 (0.48–1.10)	1.92 (0.81–4.55)	0.86 (0.26–2.18)
Abnormal CRP	1.16 (0.79–1.70)	**0.58 (0.35–0.97)**	1.20 (0.51–2.81)	1.05 (0.37–2.98)

Values are adjusted hazard ratios + 95% CI.
Significant associations are indicated in bold.
* Hazard ratios for each additional health disorder; for instance each additional health disorder reduced the probability of recovery from frailty to pre-frailty of 25%.

can, in turn, cause or precipitate frailty [37]. Probable depression, assessed using the Geriatric Depression Scale 15-item version, was also associated with incident prefrailty, consistent with previous results from a U.S. cohort that reported that depressive symptoms and antidepressant use increased the risk of incident frailty among women aged 65 and older and not frail at baseline [38].

Other factors identified in the transition analysis were negatively associated with recovery. Among them, female sex and higher age were negatively associated with improvement in frailty status. The former association brings new elements to the "male-female health-survival paradox" [39], that is, the fact that women live longer despite bearing a larger burden of health deficits than men. The latter association has been previously shown in Chinese and Italian cohorts [13,17]. The same pattern was found regarding improvement of cognitive/physical function in older adults included in the New Mexico Aging Process Study [40]. Comorbidity also diminished the chances of recovery from frailty. Consistent with the strong overlap between frailty and comorbidity, diversity of health disorders was found to be associated with frailty transitions in the literature, notably respiratory, cardiovascular, metabolic, malignant diseases, osteoarthritis, and stroke [13,16,17].

The role of overweight and obesity in frailty transitions is controversial. In an Italian cohort of older adults, overweight and obesity raised the risk of prefrailty among nonfrail individuals, whereas prefrail individuals seemed to benefit from being overweight [17]. Here, the results indicated the deleterious effect of overweight, with lower odds of recovery from a prefrail state in overweight individuals compared with those not overweight.

Cross-sectional associations between frailty and increased levels of inflammatory mediators, especially IL-6 and its surrogate CRP, have been reported [41]. In a sample of >5000 older men in the United States, Pollack et al found that men with high levels of inflammatory markers were more likely to progress in frailty (CRP in highest quartile) and less likely to improve (IL-6 in the highest quartile) [16]. We confirmed the latter finding by showing that abnormal levels of CRP were negatively associated with recovery from prefrailty to nonfrail status.

Strength and limitations

The main strength of this study is the repeated assessment of the frailty phenotype over 3 years, with objective measurements of grip strength and walking speed. Intervals of 6–12 months between visits reduced the possibility of missed transitions over short intervals. Limitations included the low number of frail subjects at baseline. The prevalence of frailty was 3.5%, whereas it is expected to be about 15% in a population of mean age 75 years [34]. This low prevalence may be explained by the fact that this study was conducted as part of randomized controlled trial whose population may not be representative of the elderly population [42]. The low number of frail individuals at baseline (n = 28) limited the power of this study to detect factors associated with worsening or improving frailty and made stratified analyses by age or gender impossible. Furthermore, this selection bias may have been aggravated by the fact that prefrail and frail individuals were more likely to be lost to follow-up compared to nonfrail ones, the proportions of individuals lost to follow-up at 36 months being 23%, 28%, and 36% in nonfrail, prefrail, and frail individuals at baseline, respectively. As a consequence of the low number of frail individuals at baseline and of the attrition of the study sample, the generalizability of our results remains limited. Lastly, we did not have thorough information about biochemical parameters, except doctor-diagnosed abnormalities, nor could we take into account social factors.

Conclusion

In a sample of older adults participating in a 3-year prevention trial, this study showed that polypharmacy and depressive mood increased the risk of incident prefrailty. On the other hand, we identified factors associated with poorer odds of recovery among frail or prefrail individuals. They were female gender, older age, multiple health problems, overweight, and elevated CRP. The findings of this study should be confirmed in larger settings to guide policies directed at preventing or managing frailty.

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Appendix

Appendix 1
Details of frailty assessment

Frailty criterion	Measurement	Response or cut-off corresponding to frailty for the criterion
Unintentional weight loss	"In the last year, have you lost more than 4.5 Kg unintentionally (i.e., not due to dieting or exercise)?"	"Yes"
Fatigue	Using the CES–D Depression Scale, the following two statements are read. (a) I felt that everything I did was an effort; (b) I could not get going. The question is asked "How often in the last week did you feel this way?" 0 = rarely or none of the time (=1 day), 1 = some or a little of the time (1–2 d), 2 = a moderate amount of the time (3–4 d), or 3 = most of the time.	Answer "2" or "3" to either of these questions
Low grip strength	Grip strength based on the best of three measurements with preferred hand, results stratified by gender and body mass index (BMI)	*Men*: BMI ≤24 Kg per m^2: ≤29 Kg 24.1 ≤ BMI ≤28 Kg per m^2: ≤30 Kg BMI >28 Kg per m^2: ≤32 Kg *Women*: BMI ≤23 Kg per m^2: ≤17 Kg 23.1 ≤ BMI ≤26 Kg per m^2: ≤17.3 Kg 26.1 ≤ BMI ≤29 Kg per m^2: ≤18 Kg BMI >29 Kg per m^2: ≤21 Kg
Slow walking speed	Walking speed based on the best of two measurements over 4 meters, results stratified on gender and height	*Men*: Height ≤173 cm: ≥7 seconds Height > 173 cm: ≥6 seconds *Women*: Height ≤159 cm: ≥7 seconds Height > 159 cm: ≥6 seconds
Low level of physical activity	Questionnaire about the time spent doing 15 activities during the previous 2 weeks: walking, chores (moderately strenuous), mowing the lawn, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golf, gymnastic, and swimming. Kcals per week expended are calculated using standardized coefficients per activity (*Ainsworth BE, Haskell WL, Leon AS, Jacobs DR, Jr., Montoye HJ, Sallis JF et al. Compendium of physical activities: classification of energy costs of human physical activities. Medicine and science in sports and exercise. 1993;25(1):71–80*).	*Men*: <383 Kcal per week *Women*: <270 Kcal per week

Appendix 2. Details about the multi-state model

By supposing $\{X(t);\ t \geq 0\}$ a stochastic process which can take three possible states (1: for "non-frail" state; 2: for "pre-frailty" state and 3: for "frailty" state), we defined the associated transition intensities, $\alpha_{ij}(t)$ (with i and j vary between 1 and 3), as the following hazard function:

$$\alpha_{ij}(t, Z(t)) = \lim_{\Delta t \to 0} \frac{P(X(t + \Delta t) = i | X(t) = j, Z(t))}{\Delta t}$$

where Z(t) is the vector of covariates considered, and α_{ij}, the coefficient of interest, included in a 3*3 transition matrix verifying:

$$\alpha_{ii} = -\sum_{j \neq i} \alpha_{ij}$$

In this study, $\alpha_{ij}(t)$ is estimated by a cox model which could be written as following:

$$\alpha_{ij}(t, Z(t)) = \alpha_{0ij}(t) \exp\left(Z(t)^t \beta_{ij}\right)$$

where α_{0ij} corresponded to the baseline non parametric hazard function and β the vector of unknown parameters linked to covariates.