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

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Short title: Factors associated with frailty transitions 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 Prevention Trial (MAPT) 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 modelling. **Results:** The study population included 548 women and 294 men, mean age 75.4 +/- 4.5 years. At baseline, 430 (53%) participants were non-frail, 349 (43%) pre-frail, 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 depression were associated with incident pre-frailty. Female gender was systematically associated with a lower probability of recovering from pre-frailty and frailty. Older age, overweight, comorbidity, and abnormal CRP also reduced the probability of recovery from frailty or pre-frailty. **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 in order to understand the multiple causes of and risk factors for pre-frailty and frailty. Valuable studies in the field¹⁰⁻²⁰ 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 (number of medications, for example). The close follow-up of participants included in the control arms of prevention trials can provide useful information

about the natural history of frailty. Due to eligibility criteria, participants in prevention trials are initially mostly non-frail, 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 non-multidomain 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/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 (MMSE) 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 non-multidomain intervention arms were considered in the present study (420 in the control arm and 423 in the omega-3 arm). As mentioned above, the use of the control arm was intended to enable observation of the natural history of frailty in the absence of specific interventions. In order to increase the power of the study and because the omega-3 supplementation did not significantly affect frailty status over time in the MAPT study²², 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 adults²³ 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 al³:

- Unintentional weight loss >4.5 kg in the past year;
- Fatigue, measured by 2 questions from the CES-D depression scale;
- Low grip strength, based on the best of 3 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 pre-frail. The frailty phenotype could only be determined if information about all 5 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 (BMI);
- Polypharmacy defined as ≥ 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 (MMSE) score of ≤ 26 ;²⁷
- Physical function 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 $\pm$ standard deviation for continuous variables. Comparison between groups used Chi-square 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 modelling 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 4 main transitions (from non-frail to pre-frail, from pre-frail to frail, from frail to pre-frail, and from

pre-frail to non-frail) 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, BMI category, polypharmacy, number of health disorders, probable depression, and abnormal CRP). More details about the model are given in Appendix 2. Results are given in terms of transition intensities with adjusted Hazard Ratios (HR) and 95% Confidence Intervals (CI) 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 non-frail, 349 (43.2%) pre-frail, 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.

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

	Total	Non-frail	Pre-frail	Frail	p*
	N=807	N=430	N=349	N=28	
General information					
Arm of the MAPT trial					
Placebo	401 (49.7)	224 (52.1)	166 (47.6)	11 (39.3)	0.242
Omega 3	406 (50.3)	206 (47.9)	183 (52.4)	17 (60.7)	
Gender					0.177
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					<0.001
70-74 years	396 (49.1)	249 (57.9)	137 (39.3)	10 (35.7)	
75-79 years	262 (32.5)	134 (31.2)	120 (34.4)	8 (28.6)	
80 years and over	149 (18.5)	47 (10.9)	92 (26.4)	10 (35.7)	
ADCS score at baseline					<0.001
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/m²)					<0.001
16-24 kg/m²	336 (41.8)	208 (48.6)	122 (36.2)	6 (21.4)	
25-29 kg/m²	336 (41.8)	173 (40.4)	147 (42.4)	16 (57.1)	
30 kg/m² 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)	0.001
Cognitive impairment	132 (16.4)	61 (14.2)	61 (17.5)	10 (35.7)	0.009
Probable depression	142 (17.7)	48 (11.2)	83 (24.0)	11 (39.3)	<0.001
Number of health disorders, mean+/-SD	4.8+/-2.6	4.4+/-2.5	5.3+/-2.6	5.1+/-2.5	<0.001
Biochemical abnormalities					
Total cholesterol	347 (43.9)	185 (43.7)	148 (43.7)	14 (50.0)	0.804

	Total	Non-frail	Pre-frail	Frail	p*
	N=807	N=430	N=349	N=28	
Triglycerides	295 (37.2)	145 (34.2)	133 (39.0)	17 (60.7)	0.013
Creatinine	119 (15.2)	51 (12.3)	59 (17.3)	9 (32.1)	0.006
CRP	86 (11.9)	39 (9.9)	41 (13.4)	6 (25.0)	0.045
Hemoglobin	50 (6.3)	19 (4.4)	27 (7.9)	4 (14.3)	0.025
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.

** Chi2 test or Fisher's exact test for categorical variables and analysis of variance for continuous variables*

Abbreviations: MAPT= Multidomain Alzheimer Preventive Trial, ADCS=Alzheimer's Disease Cooperative Study-Activities of Daily Living Prevention Instrument, BMI=Body Mass Index, CRP=C-Reactive Protein

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 non-frail individuals decreased during the follow-up (Figure 1). We recorded 18 deaths during the follow-up.

Figure 1. Evolution of the proportion of individuals in each frailty state 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 non-frail and pre-frail people often remained in the same state from one assessment to another; 70.8% of non-frail people remained non-frail

and 67.4% of pre-frail people remained pre-frail. Worsening transitions represented 29.1% of consecutive measurements from the non-frail state and 8.2% from the pre-frail state. Transitions in the direction of recovery amounted to 24.4% of consecutive measurements from the pre-frail state and to 64.8% of those from the frail state. Of note, direct transitions from non-frail to frail or from frail to non-frail were very rare.

Table 2. Transition matrix

		To			Total
		Non-frail	Pre-frail	Frail	
From	Non-frail	831 (70.8)	335 (28.6)	7 (0.6)	1173 (100.0)
	Pre-frail	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 (%).

Note: Transitions are defined between 2 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 pre-frail to frail states. The only factors associated with the transition from non-frail to pre-frail state were polypharmacy and probable depression. Female gender was systematically associated with a lower probability of recovering from pre-frailty and frailty. Older age, overweight, comorbidity, and abnormal CRP also reduced the probability of recovering from frailty or pre-frailty. 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.

Table 3. Multistate model assessing factors influencing transitions between frailty states

Variables	Transitions between frailty states			
	From non-frail to pre-frail	From pre-frail to non-frail	From pre-frail to frail	From frail to pre-frail
	N=335	N=251	N=84	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 years	1	1	1	1
75-79 years	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 years 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)
BMI				
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/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

Abbreviations: ADCS=Alzheimer's disease cooperative Study-Activities of Daily Living Prevention Instrument,

BMI=Body Mass Index, GDS=Geriatric Depression Scale, CRP=C-Reactive Protein

* 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%.

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 pre-frailty 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 pre-frailty was associated with polypharmacy, defined as ≥ 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 previously³², 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 exist¹⁴ 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 can, in turn, cause or precipitate frailty.³⁷ Probable depression, assessed using the GDS-15, was also associated with incident pre-frailty, consistent with previous results from a US 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 i.e. 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 pre-frailty among non-frail individuals whereas pre-frail individuals seemed to benefit from being overweight.¹⁷ Here, the results indicated the deleterious effect of overweight, with lower odds of recovery from a pre-frail 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 pre-frailty to non-frail 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 to 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 pre-frail and frail individuals were more likely to be lost to follow-up compared to non-frail ones, the proportions of individuals lost to follow-up at 36 months being 23%, 28% and 36% in non-frail, pre-frail 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 pre-frailty. On the other hand,

we identified factors associated with poorer odds of recovery among frail or pre-frail 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.

Statements

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 (www.clinicaltrials.gov) [NCT00672685].

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Competing interests

The authors have no conflicts of interest to declare.

Authors' contribution

All the authors meet the ICMJE criteria for authorship:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary material

Appendix 1. Details of frailty assessment

Frailty criterion	Measurement	Response or cut-off corresponding to frailty for the criterion
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	Exhaustion: 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 days), 2 = a moderate amount of the time (3–4 days), or 3 = most of the time.	Answer “2” or “3” to either of these questions
Weakness	Grip strength based on the best of 3 measurements with preferred hand, results stratified by gender and body mass index (BMI)	<p><i>Men:</i> BMI ≤24 Kg/m²: ≤29 Kg 24.1 ≤ BMI ≤28 Kg/m²: ≤30 Kg BMI >28 Kg/m²: ≤32 Kg</p> <p><i>Women:</i> BMI ≤23 Kg/m²: ≤17 Kg 23.1 ≤ BMI ≤26 Kg/m²: ≤17.3 Kg 26.1 ≤ BMI ≤29 Kg/m²: ≤18 Kg BMI >29 Kg/m²: ≤21 Kg</p>
Walking speed	Walking speed based on the best of 2 measurements over 4 meters, results stratified on gender and height	<p><i>Men:</i> Height ≤173 cm : ≥7 seconds Height > 173 cm : ≥6 seconds</p> <p><i>Women:</i> Height ≤159 cm : ≥7 seconds Height > 159 cm : ≥6 seconds</p>
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 (<i>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</i>).	<p><i>Men:</i> <383 Kcal per week <i>Women:</i> <270 Kcal per week</p>

Appendix 2. Details about the multi-state model

By supposing $\{X(t) ; t \geq 0\}$ a stochastic process which can take 3 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:

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

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:

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

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