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Longitudinal Analyses Of Frailty Trajectories Among European Older Adults

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LONGITUDINAL ANALYSES OF FRAILTY TRAJECTORIES AMONG EUROPEAN OLDER ADULTS

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LONGITUDINAL ANALYSES OF FRAILTY TRAJECTORIES AMONG EUROPEAN OLDER ADULTS

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Finally, I dedicate this dissertation to my husband, Ca beo, who provided unlimited support and endured my depressing moments when my research was stuck. Although we are already husband and wife, I want to take this opportunity to officially respond to the proposal written in his dissertation 3 years ago: Yes, I do!

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SUMMARY

Frailty is a common geriatric syndrome characterized by decreased adaptability to stressors and increased vulnerability to adverse health outcomes. Frailty is not simply about ageing, but is where ageing has taken its toll. The risk of becoming frail, thus, is regulated by genetic and environmental factors via epigenetic mechanisms. This makes the older population considerably heterogeneous concerning frailty. Therefore, understanding frailty profiles and frailty trajectories is helpful for tailoring ageing health policies and interventions.

The dissertation consists of two studies to present complementary perspectives of frailty trajectories in the European older population. The studies conducted secondary analyses on data extracted from the Survey of Health, Ageing, and Retirement in Europe (SHARE). The first study compared frailty trajectories of older adults across eleven European countries and found universal parabolic age trends and country-specific cohort effects. The second study took a latent-class modeling approach to model the heterogeneity of frailty in the elderly population. The study found four distinct health profiles in the study population and a predominant tendency for state stability or dying over time. Noteworthily, there was a relatively noticeable proportion of transitions to a better health state, highlighting the potential for frailty reversal. In considering the gender effect, the two studies together reflect the long-described male-female health-survival paradox.

While the first study provides the population-level perspective of frailty trends, the second one examines the individual-level progression of frailty. The former provides a big picture of frailty trends, which can help assess and plan interventions. The latter can find its application in clinical practice, ageing research as well as policy applications. Given that data were drawn from nationally representative samples, our findings are greatly generalizable.

CHAPTER 1
INTRODUCTION

1.1 Background

The world's older population is growing dramatically, both in its size and share. The 60+ age group comprised 13 percent (about 962 million people) of the global population in 2017 and is growing at an estimated rate of 3 percent per year, faster than all younger age groups [1]. Population ageing has economic and social implications for public and private interests. The shrinking working population would directly impact the economic growth; but fiscal and political challenges regarding public systems of healthcare and welfare to accommodate the needs of such a growing older population are more pressing [1]. For private interests, the increasing dependency, in any aspects, of older persons may affect their quality of life and cause psychological, social and health consequences to their families and caregivers [2]. Therefore, a lot of attention has been paid to ageing heath research in recent decades, with frailty being one of important topics.

Frailty is a critical condition in ageing process where an individual's overall well-being and ability to function independently are reduced. Frailty results from cumulative loss of physiological reserves. Specifically, many organ systems, in a healthy state, are able to produce more materials than the amount needed for survival, providing physiological reserves necessary to repair disease-related or age-related changes [3]. As molecular and cellular damages accumulate with age, reserve capacity diminishes gradually. When age-related deficits reach a certain aggregated level [4], the depletion of physiological reserves is accelerated, leading to the failure of homoeostasis mechanisms [5, 6]. Consequently, frail individuals are less able to cope with stressors - i.e., even a minor stressor can trigger rapid and dramatic health decline [7, 8]. Indeed, frailty has been

associated with impairments in many organ systems, increased disability and elevated mortality risk in the older population.

1.1.1 Frailty clinical progression

Frailty is often regarded as a medical syndrome and the progression of frailty is a reversible process involving three states, i.e. non-frail, pre-frail and frail [9, 10, 11, 12, 13, 14]. When the multi-system reduction in physical reserve capacity reaches or past a threshold of symptomatic clinical failures, health conditions in many organs would occur [7]. Bandeen-Roche et al. identified the co-occurrence of the five frailty-defining criteria in the phenotype model. Among subsets of people with similar profiles of criteria co-occurrence, they observed the prevalence of each criterion increased with the frailty severity of subsets [9]. This provides evidence to consider frailty as a syndrome and justification for categorizing frailty into three groups [14]. Specifically, pre-frailty identifies a subgroup of high risk progressing to frail, with a lower level of structural and functional damage and fewer clinical signs [14]. The transitions between frailty states were studied by Gill et al., on a sample of 755 participants during three consecutive 18-month intervals [11]. 58% of the sample had at least one transition between two different states; 38% of all transitions were from a less frail state to a more frail one, but recovery from frail to non-frail was extremely rare [11]. This reversibility property of frailty is fundamental to interventions of frailty rehabilitation and healthy aging promotion.

Frailty displays symptoms in many organs, but several common functional changes in daily life are considered as clinical precursors of frailty. Although not specific to frailty, extreme fatigue, weight loss and frequent infections are commonly the first warning signals [8, 15]. More specific signs are falls, delirium and unstable disability. Falls occur due to reduced postural balance that fails to maintain gait integrity. Especially, in severe frailty, with the simultaneous reduction of vital postural systems (e.g. vision, balance,

strength), safe navigation capability no longer responds properly to demanding environment, spontaneous falls often occur repeatedly [8]. This, even worse, causes fear of falls, which limits individuals' mobility and life space [16, 17]. Delirium is characterized by acute onset and fluctuating courses of confusion and impaired cognition [18, 19]. A review of human and animal models has postulated that delirium is a cognitive harbinger of frailty [20]. Moreover, due to physiological reserves decline, body functions of a frail individual are compromised by minor external events and fluctuates markedly [7], which gives rise to unstable and intermittent disability [8].

Structural and functional changes of systems in frailty are regulated by genetic factors and environmental factors through epigenetic mechanisms. Previous studies have identified many genes that play a crucial role in frailty, especially in inflammatory pathway and cellular response to stress [21, 22, 23]. Besides, social and environmental factors such as childhood experiences, social support, economic hardship have been associated with frailty [24, 25, 26]. Social determinants probably have the largest contribution to frailty, moderating the effect of genetic factors [13]. By targeting on modifiable environmental determinants, interventions could potentially reverse or decelerate the progression of frailty [13, 27]. For instance, nutrition and physical activity interventions seem effectively prevent and 'treat' frailty [27].

1.1.2 Measurements of frailty

Clinical signs and symptoms make frailty clinically recognizable, but operationally defining frailty remains a challenge. Two main approaches corresponding to its clinical presentations and pathophysiology are the phenotype model and the cumulative deficits model, respectively.

The frailty phenotype model has been established by Fried et al. [28] with five variables indicating compromised energetics: unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength. The presence of three out

of five criteria defines frailty, while meeting one or two criteria denotes a pre-frail stage [28]. This model ties closely to clinical presentations, suggesting that it can be a basis for diagnosis in routine care. However, it omits common and important features of frailty such as declined cognition and increased disability.

The cumulative deficit model defines frailty as the cumulative effect of individual deficits. Although every single deficit may carry no obvious threat, deficits cumulatively contribute to the progress towards adverse health outcomes and death. An included deficit can be any age-related symptom or abnormality. A typical measure based on this model is the 70-item frail index (FI) coined by Rockwood et al., which includes 70 deficits in physical health, ability in activities in daily living (ADLs), cognitive function and mental health [29]. FI is calculated as the number of deficits present divided by the number of deficits measured, and ranges from 0 to 1. FI assigns old people into 7 categories: very fit, well, well with treated comorbid disease, apparently vulnerable, mildly frail, moderately frail and severely frail.

In short, the phenotype model considers frailty as a state, while the cumulative deficit model looks at frailty as a medical syndrome. Although conceptually different, the models have shown an overlap in frailty identification and statistical convergence [30, 31]. This is demonstrated by the convergent predictive validity of adverse health outcomes between the two models. To date, several adaptations have been developed, which fall into the spectrum between the two approaches [32]. Some widely used, validated measures include Edmonton Frail Scale, FRAIL scale, Tilburg Frailty Indicator, Groningen Frailty Indicator, frailty index based on a Comprehensive Geriatric Assessment (FI-CGA). However, these instruments focus on variability in the total number of health deficits but not on specific patterns of deficits combination.

1.1.3 Gender differences in frailty

The literature of health-related gender inequality has long described the 'male-female health survival paradox' (also known as 'gender paradox') in which women experience more medical conditions but live longer than men [33]. As a multidimensional measure of health status of the elderly, frailty reflects similar gender differences - despite being more frail, females have survival advantage. To be specific, previous studies have shown that females, at all ages, have higher frailty scores [34, 35, 36, 37], and that females have a lower mortality rate at any level of frailty [34, 38]. The disparities result from a variety of gender differences in biological factors (e.g., genetic and physiology) as well as behavioral and social characteristics (e.g., risk-related behaviors and social roles). The pathogenesis of the gender paradox , however, remains unclear; and several hypotheses have been proposed, such as (i) females are more likely to have chronic diseases with low mortality [39], (ii) females have more physiological reserves [40], (iii) males and females have different failure thresholds due to different evolutionary designs [41, 42], or (iv) health measures currently used, including frailty, do not adequately capture deficits in males [43, 44].

In summary, the growing older population pose pressing challenges to improve quality and quantity of social and health care services. As frailty is associated with poor health outcomes, such as increased dependency, hospitalization, institutionalization and death, frailty places large burdens on the public systems as well as family and friend caregivers. However, increased use of healthcare resources does not necessarily improve health outcomes or quality of care of the elderly. To be effective, heath care interventions should be tailored to individuals or targeted subgroups. Therefore, it is important to continue to explore classification of older individuals into pragmatically meaningful groups as well as trajectories, stability and change of frailty construct during the late life.

1.2 Dissertation aims

The primary goal of this dissertation is to explore frail trajectories in the European older population. The secondary goal is to explore gender differences in frailty trajectories.

This dissertation addresses the following research objectives:

1. To explore how levels of dependency in the elderly vary across birth cohorts by examining differences in frailty trajectories, including stratification by gender (Chapter 2).

2. To explore frailty classes and their evolution over time, as well as gender differences in the frailty progression (Chapter 3).

1.3 Overview of dissertation chapters

Following this introductory chapter (Chapter 1), there are three dissertation chapters.

Chapter 2 addresses the first objective of this dissertation. The study takes the age-period-cohort (APC) approach to decompose frailty trends into temporal component (biological age, period and birth cohort), and provides a comparison of APC effects across European countries of interest. Frailty trajectories are stratified by gender to investigate gender disparity in frailty across ages and cohorts. This chapter provides insights of ageing health trends in studied countries, which is useful for localization of ageing policies.

Chapter 3 addresses the second objective of this dissertation, using a latent class modeling framework. The study first categorize individuals to frailty classes based on patterns of associations among a set of observed variables by latent class analysis. Subsequently, the study examine transitions across frailty classes and to death over time by latent transition analysis. Gender differences in transition patterns are also examined. The chapter presents some means to differentiate individuals into more homogenous subgroups and underscores the dynamic of older people health and social needs.

Finally, chapter 4 summarizes the findings and concludes with recommendations for future research.

CHAPTER 2

CROSS-NATIONAL COMPARISON OF FRAILTY TRAJECTORIES AMONG OLDER PEOPLE IN EUROPEAN COUNTRIES BETWEEN 2004 AND 2017: AN AGE-PERIOD-COHORT ANALYSIS

2.1 Introduction

Global population ageing has profound social and economic consequences for public and private interests [1]. Healthy ageing, hence, becomes the pivotal aim of eldercare in order to allow older adults to maximize the number of years of productive and quality life free from disease and disability. Epidemiological investigation into ageing trajectories is informative for social policy development and resource distribution, which are important in meeting changing needs of eldercare. Compared with trends in other health outcomes, trends in frailty would provide a more comprehensive perspective of the ageing population, as frailty encompasses age-related declines in multiple systems and is predictive of adverse health outcomes such as increased dependency, disability, hospitalization, institutionalization, and mortality.

Being home to the world's oldest population, Europe bears an onerous burden of ageing health problems, including frailty. In this study, we take APC approach to compare frailty trajectories among the community-dwelling elderly across nine European countries during the 2004-2016 period, including stratification by gender. Although a previous work examined the impact of socio-economic positions on frailty trajectories in European countries [45], the study took cohort effect into account only in all-country model but not country-specific models . Without decomposing secular trends into temporal components (biological age, period and birth cohort), it is largely unclear whether the trends were driven solely by the biological ageing process or also by intergenerational differences.

Moreover, cohort effects are expected to be dependent on population-specific factors. European countries, though sharing cultural and social similarities, have many differences in historical and socio-economic contexts, so cohort effects may represent idiosyncrasies for countries. A comparison of APC effects among European countries will provide valuable contributions to the advancement of ageing health trends documented in scientific literature as well as to localization of ageing policies.

In addition, health-related gender inequality has been widely documented to reveal the 'male-female health-survival paradox', in which women have longer age-specific life expectancy but shorter healthy life expectancy [33]. The greater burden of morbidity and disability in women result from a variety of biological, psychological and socio-economic differences between men and women [46, 47, 48, 42, 49]; especially, women are primary providers of informal care for spouses and relatives [48]. Regarding frailty, gender differences in frailty incidences and determinants have been observed in many populations [50, 51]. By stratifying frailty trajectories by gender, our aim is to investigate gender disparity in frailty across ages and birth cohorts amongst studied countries.

2.2 Methods

2.2.1 Data

Study sample

Data were extracted from the Survey of Health, Ageing, and Retirement in Europe (SHARE), a cross-national panel survey targeting to non-institutionalized individuals aged 50 or over and their spouse in participating countries. SHARE started in 2004 and then has been conducted biannually since the second wave in 2007. In general, population-based samples were drawn, mostly via multi-stage sampling. All SHARE respondents in any previous waves are included in the longitudinal sample. From Wave 2 onward, in order to ensure the sample's representativeness, refreshment samples were

recruited to include subjects who newly became age-eligible and compensate panel attrition. Descriptions of sampling and data collection procedures can be found in [52, 53, 54].

Wave 3, administered in 2009 and referred as the SHARELIFE module, focuses on life history and did not include frailty measure; therefore, this was excluded from our analysis. Until now, twenty-eight European countries and Israel have joined SHARE, with some variation in participation in each data collection wave [53]. Nine countries that participated in all waves (i.e. the 2004, 2007, 2011, 2013, 2015, and 2017 waves), namely Austria, Belgium, Switzerland, Germany, Denmark, Spain, France, Italy, and Sweden were included.

Frailty index (FI) construction

Frailty status, the outcome of this study, was measured by the frailty index of accumulated deficits (FI-CD) [31]. FI construction follows the standard protocol proposed by Searle and colleagues [55]. Specifically, deficits were only included to FI calculation if satisfying criteria: (1) available in all study waves, (2) health-related, (3) age-associated, (4) neither too common (present in $\geq 80\%$ people aged 80 and older), nor too uncommon (present in $\leq 1\%$ of the study population); and finally, the deficits must cover a range of systems when considered as a whole [55]. Variable selection for FI construction was guided by additional published studies [56, 57, 58]. A detailed list of 49 indicators for FI construction is presented in Study 1: Items used to construct frailty index in the SHARE.

Frailty index was calculated as the proportion of the number of deficits present among those measured, potentially ranging from 0 to 1. In instances where data were missing for some indicators, FI was calculated with reduced denominator. Because an inverse relationship between FI and health was found when at least 30 deficits were included in FI construction [59], we only included individuals if they had at least non-missing values for 30 or more indicators.

Predictors and covariates

Age and cohort were the main predictors of frailty index in our analysis. We derived seven distinct birth cohorts - before 1925 (reference group), 1925-1929, 1930-1934, 1935-1939, 1940-1944, 1945-1949 and 1950-1954. Gender was also included in the model as a covariate.

2.2.2 Modeling

Beta regression model

There are several possible choices for modeling a response variable naturally bounded between 0 and 1 (i.e., $0 \leq y \leq 1$). A suitable candidate of model is beta regression. Beta regression models the response variable at its original scale, producing less biased estimates and more straightforward statistical inference than transformation-based solutions [60, 61, 62].

The use of beta regression is based on the assumption that frailty index is beta distributed. Beta density is given by:

$$f(y;\alpha,\beta) = \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} y^{(\alpha-1)}(1-y)^{(\beta-1)}$$

where $y \in (0,1), \alpha > 0, \beta > 0$ and $\Gamma(.)$ denotes the gamma function. "Shape" parameters α and β pull density toward 0 and 1 respectively [60], allowing beta distribution to flexibly take different shapes. Beta distribution can be inflated at 0 and/or 1, meaning that the dependent variable can take value 0s and/or 1s [63]. Response variable is modeled as a mixture of Bernoulli and beta distributions. To make the two parameters more meaningful in a regression framework, several possible methods of parametrization in terms of mean and precision are available and applied in statistical packages (see [63], [64], [65] for more details).

The age-cohort-period (APC) model

The response variable, frailty index, in our sample has a right-skewed distribution bounded in the range [0, 1), with a decent number of 0s, in all countries (see Figure 2.1). Therefore, we employed zero-inflated beta regression for analysis. Two sub-models were conducted simultaneously: i) a zero-inflated model (logistic regression) that predicts the probability of frailty index taking a value of 0, and ii) beta regression model that predicts the value of frailty index. We analyzed repeated-measures data using a hierarchical modeling framework, which accounts for dependencies among observations, handles subject's missing data points, and allows unequal time intervals.

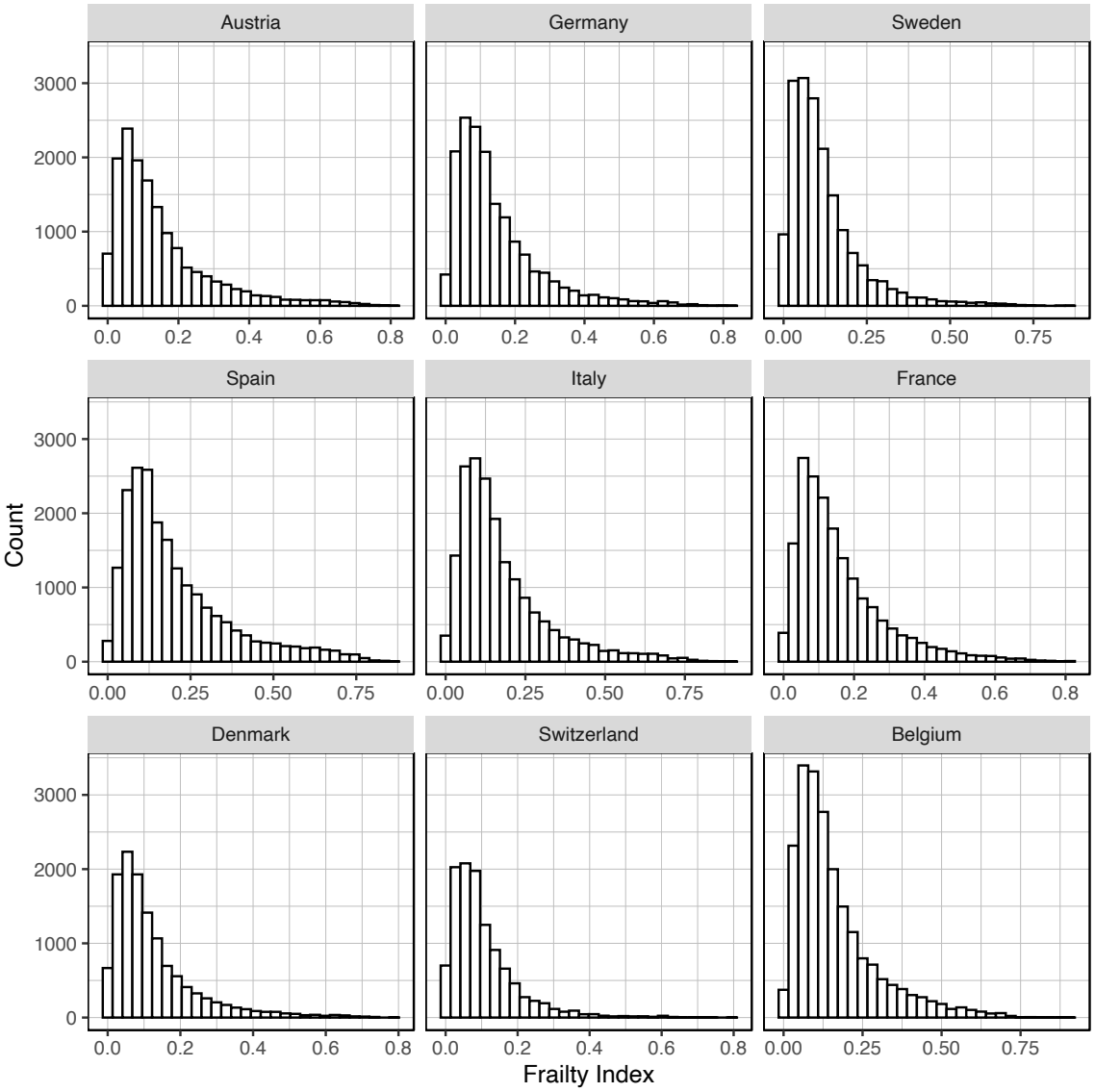
Following Yang and Land (2006), and Bell and Jones (2014) [66, 67], we modeled age effect with linear and quadratic terms, with the linear term specified as random to capture individual variation besides the universal effect of the biological ageing process. The cohort effect was specified as fixed because of unique lifetime health-related exposures of each birth cohort, which would not be appropriately represented by a random component assumed to be normally distributed. We constrained the period linear trend to zero, assuming that period effects were absorbed partly by age and cohort effects and the remaining was reflected by period residual term. Specifying the period effect as random is reasonable because there is no reason to believe that any of the four years of survey have had a unique effect on frailty status. However, the period residual term was estimated at an extremely small estimate ($\approx \mathrm{e}{-10}$) and the inclusion of this term did not improve model fit (i.e., no decline in the Akaike information criterion (AIC) and the Baysian information criterion (BIC)). Hence, the period residual term was dropped in the final model.

We fitted a series of zero-inflated beta regression models. Beta regression part was specified as a multi-level model, with logit link function, given by:

Micro-level model (within individual):

$$FI_{ti} = \beta_{0i} + \beta_{1i} age_{ti} + \beta_{2i} age_{ti}^2 + e_{it}$$

Figure 2.1: Distribution of frailty index



Macro-level model (between individuals):

$$\beta_{0i} = \gamma_{00} + \gamma_{01} cohort_i + u_{0i}$$

$$\beta_{1i} = \gamma_{10} + \gamma_{11} cohort_i + u_{1i}$$

$$e_{it} \sim N(0, \sigma_e^2), \quad u_{0i} \sim N(0, \sigma_0^2), \quad u_{1i} \sim N(0, \sigma_1^2),$$

where FI_{ti} is frailty index of an individual i measured at occasion t, and $cohort_i$ is the cohort membership of individual i, treated as a continuous variable. By adding $cohort_i$ and random term u_{1i} in the formula of slope β_{1i}, we allowed differential age effects between cohorts and between individuals. For the ease of model estimability and interpretability, we rescaled age by subtracting 50 from age and then dividing by 10. Cohort was treated as a categorical variable, with the before-1925 cohort being reference group.

In zero-inflated part, we initially specified a model with the same terms as in the beta regression part. However, the inclusion of too many terms in the zero-inflated part caused model non-convergence for some countries. As the objective of the current work is for a cross-national comparison, the same model specification for all studied countries is required. Therefore, we finally included the linear term of age as the only predictor in the zero-inflated part.

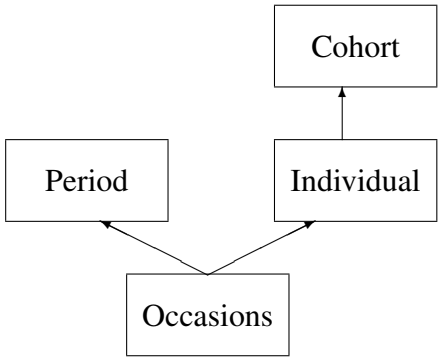


Figure 2.2: The hierarchical structure of panel data in APC analysis. Adapted from [67]

Subsequently, we included gender and its interaction terms with age and cohort into

beta regression model, and added a corresponding term into zero-inflated model. With gender included, macro-level model in beta regression was modified to:

$$\beta_{0i} = \gamma_{00} + \gamma_{01} cohort_i + \gamma_{02} gender_i + \gamma_{03} cohort_i * gender_i + u_{0i}$$

$$\beta_{1i} = \gamma_{10} + \gamma_{11} cohort_i + \gamma_{12} gender_i + u_{1i}$$

Analyses were conducted for each country separately with *glmmTMB* package [68] and *ggeffects* [69] in R 3.5.1 [70].

2.3 Results

A total sample of 51,354 participants from nine countries with sufficient non-missing indicators for FI construction were included into our analysis. The dataset has an average of 2.95 observations per individual (out of a possible total of six). A summary of sample characteristics for each country is presented in Table 2.1. Female participants accounted for a larger proportion in the samples of Austria and France (57.24% and 54.92%,respectively), while the sex ratio in other countries' samples was reasonably balanced. Frailty index tended to increase slightly across the waves of survey, with the difference between two consecutive periods being no more than 0.2 points.

Table 2.2 - 2.10 provides results of zero-beta regression models predicting frailty index. Across countries, the odds of being frailty-free statistically significantly decrease with age (in zero-inflated sub-models: $\beta_{Age} < 0$, $p < 0.001$). Regarding the level of frailty index, Figure 2.3 - 2.5, constructed from estimated coefficients, provide graphic representation of frailty trajectories, age and cohort effects. Figure 2.3 illustrates overall frailty trajectories, in which each line represents frailty trajectory of a particular cohort starting from the middle age in 2004 and tracking changes until 2017, and shade region denotes 95% prediction interval. An overall parabolic age trend of frailty, and cohort differences at overlapping ages can be seen from the figure.

Figure 2.4 displays conditional age effects, stratified by gender. The parabolic age trend is clear, with an accelerating increase in frailty level after the age of 75. The growth rate of frailty level after 75 years old in Italy, Germany and Switzerland is slower than in other countries. Whilst females generally have higher frailty level than males, gender-specific age trends are approximately parallel (except in Belgium), indicating the gender gap in frailty levels holds through life course. The frailty gender gap is quite noticeable in Spain, Italy, and Belgium but is negligible in other countries. Interestingly, the gender difference in Denmark reverse after the age of 75, though the gap is just minimal.

Figure 2.5 presents age-adjusted frailty level by birth cohort, stratified by gender. Across countries, frailty level is typically lowest in cohorts born before 1930, followed by a marked increase in the 1930s birth cohorts. Except in Italy and Spain, frailty level remains relatively stable in the 1935-1939 birth cohort and thereafter. Cohort effects appear to matter more for males than females (i.e. more between-cohort differences in males); and gender differentials in frailty attenuate in recent cohorts.

Apart from the similarities shared by all, three distinct patterns of conditional cohort effects emerge from studied countries. First, the Swiss, Swedish and Danish ageing populations appear the healthiest, with the overall age-adjusted frailty levels stable around or below 0.10 across cohorts. Frailty gender differentials are basically narrow. Second, the samples of Belgium, France, Germany and Austria follow very similar patterns, but the overall frail levels are higher (though staying under 0.15). Third, the elderly in Spain and Italy, in contrast, seem the least healthy, with the overall frailty levels exceeding 0.15. Cohort trend of Spain and Italy has a hill shape, with its peak being around the 1930-1934 and 1935-1939 cohorts, where frailty-related gender gap is also at the maximum. Gender differences in frailty level are persistently broad, though significantly narrowing after the peak. It is worth-noting that cohort-specific age-adjusted frailty levels of countries diverge for earlier cohorts but pretty much converge for most recent cohorts whose frailty level of Italy and Spain being similar to that of Austria, Belgium, Germany, and France.

Table 2.1: Sample characteristics across countries and time periods.

	Austria		**Belgium**		**Denmark**		**France**		**Germany**		**Italy**		**Spain**		**Sweden**		**Switzerland**	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Birth cohort																		
Before 1925	246	4.85	460	6.71	261	6.52	483	7.73	296	4.42	292	4.58	545	7.73	406	6.90	198	5.61
1925-1929	350	6.91	556	8.11	293	7.32	576	9.22	507	7.57	400	6.27	669	9.49	449	7.64	260	7.36
1930-1934	478	9.43	789	11.51	413	10.32	779	12.47	647	9.66	755	11.84	985	13.97	603	10.26	391	11.07
1935-1939	818	16.14	930	13.57	501	12.52	810	12.97	1169	17.46	1057	16.57	992	14.07	875	14.88	507	14.35
1940-1944	1106	21.82	1019	14.87	717	17.91	893	14.30	1318	19.68	1230	19.29	1168	16.56	1142	19.42	651	18.43
1945-1949	1025	20.22	1477	21.55	928	23.18	1273	20.38	1228	18.34	1424	22.33	1292	18.32	1328	22.59	764	21.63
1950-1954	1045	20.62	1622	23.67	890	22.23	1431	22.91	1531	22.86	1220	19.13	1401	19.87	1077	18.32	761	21.55
Gender																		
Male	2162	42.66	3230	47.13	1918	47.91	2815	45.08	3243	48.43	3028	47.48	3340	47.36	2819	47.94	1681	47.59
Female	2906	57.34	3623	52.87	2085	52.09	3430	54.92	3453	51.57	3350	52.52	3712	52.64	3061	52.06	1851	52.41
Frailty index, Mean (SD)																		
Wave 1 (2004)	0.13	0.11	0.14	0.11	0.12	0.11	0.14	0.12	0.13	0.11	0.16	0.12	0.20	0.14	0.11	0.11	0.10	0.08
Wave 2 (2007)	0.15	0.12	0.15	0.12	0.12	0.11	0.15	0.12	0.13	0.12	0.18	0.14	0.20	0.15	0.12	0.11	0.10	0.09
Wave 4 (2011)	0.14	0.13	0.17	0.13	0.12	0.11	0.16	0.13	0.15	0.13	0.18	0.14	0.22	0.17	0.13	0.12	0.10	0.09
Wave 5 (2013)	0.15	0.14	0.17	0.14	0.13	0.12	0.16	0.13	0.15	0.13	0.19	0.15	0.20	0.17	0.12	0.11	0.10	0.09
Wave 6 (2015)	0.16	0.15	0.17	0.14	0.13	0.12	0.17	0.14	0.15	0.13	0.17	0.15	0.20	0.16	0.12	0.10	0.11	0.10
Wave 7 (2017)	0.17	0.15	0.18	0.14	0.13	0.12	0.17	0.14	0.16	0.13	0.18	0.15	0.21	0.17	0.13	0.11	0.11	0.10
All waves	0.15	0.14	0.16	0.13	0.12	0.12	0.16	0.13	0.14	0.12	0.18	0.14	0.20	0.16	0.12	0.11	0.10	0.09

Figure 2.3: Predicted frailty index by age and birth cohort

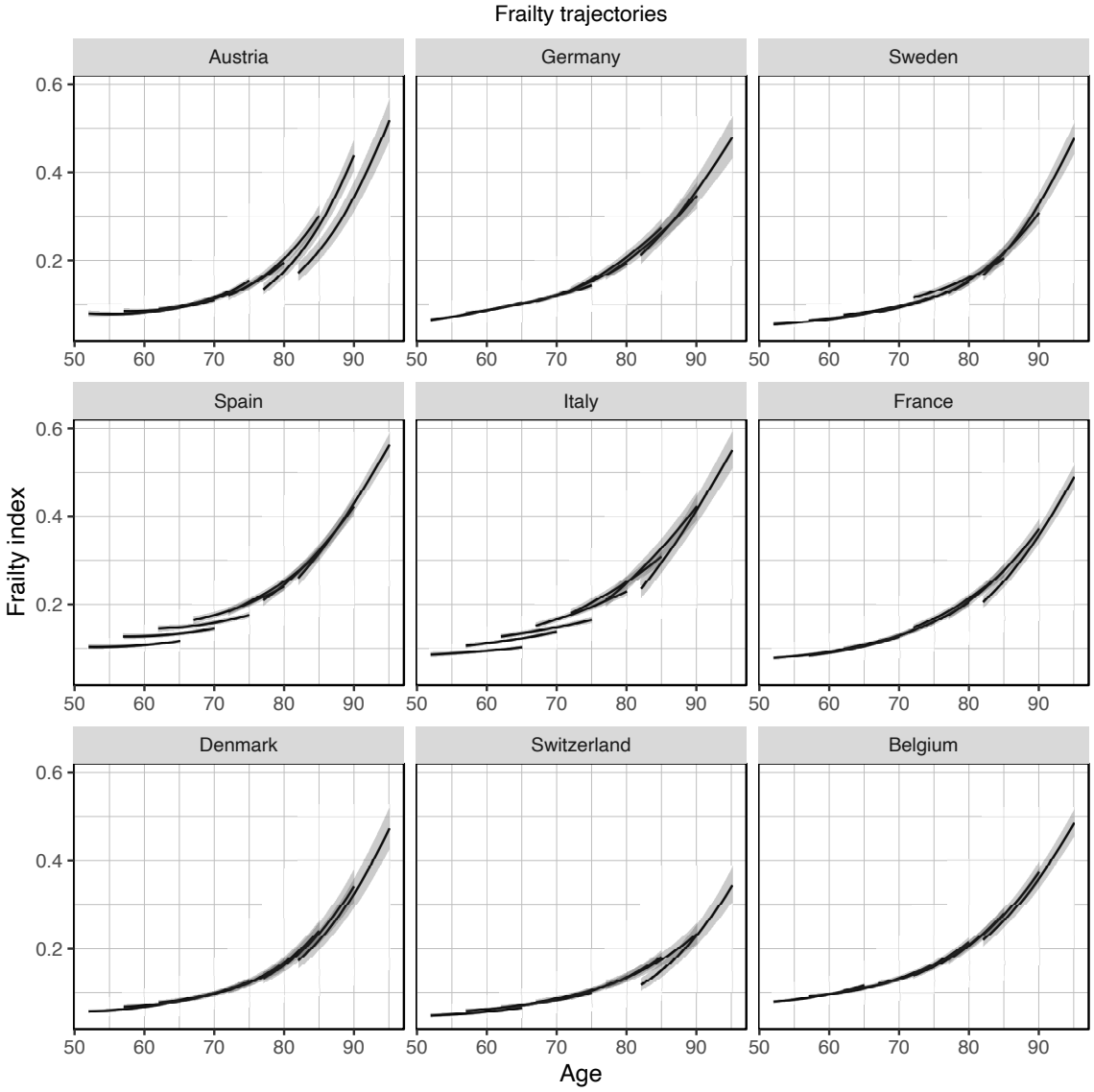


Figure 2.4: Conditional age effects, stratified by gender

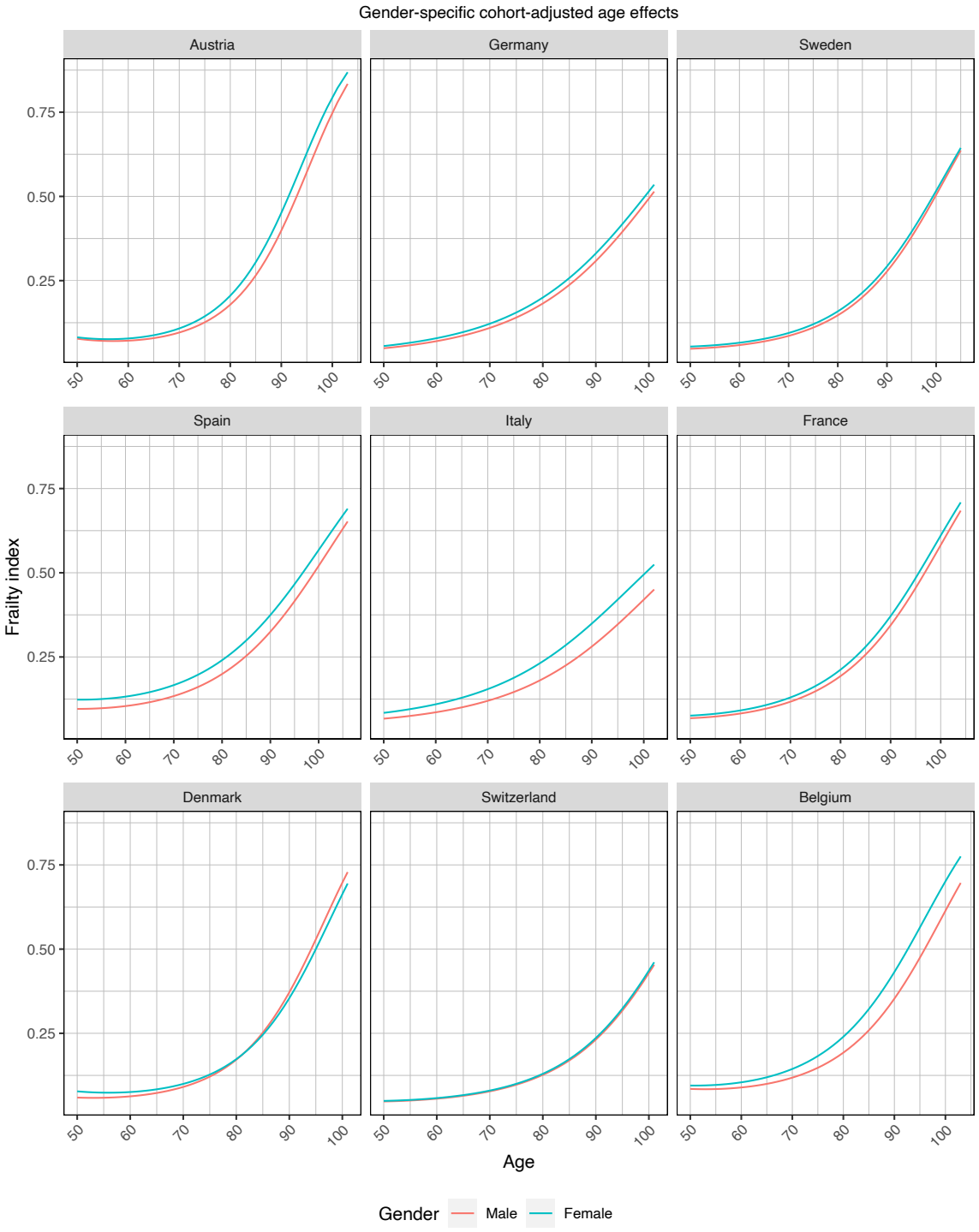
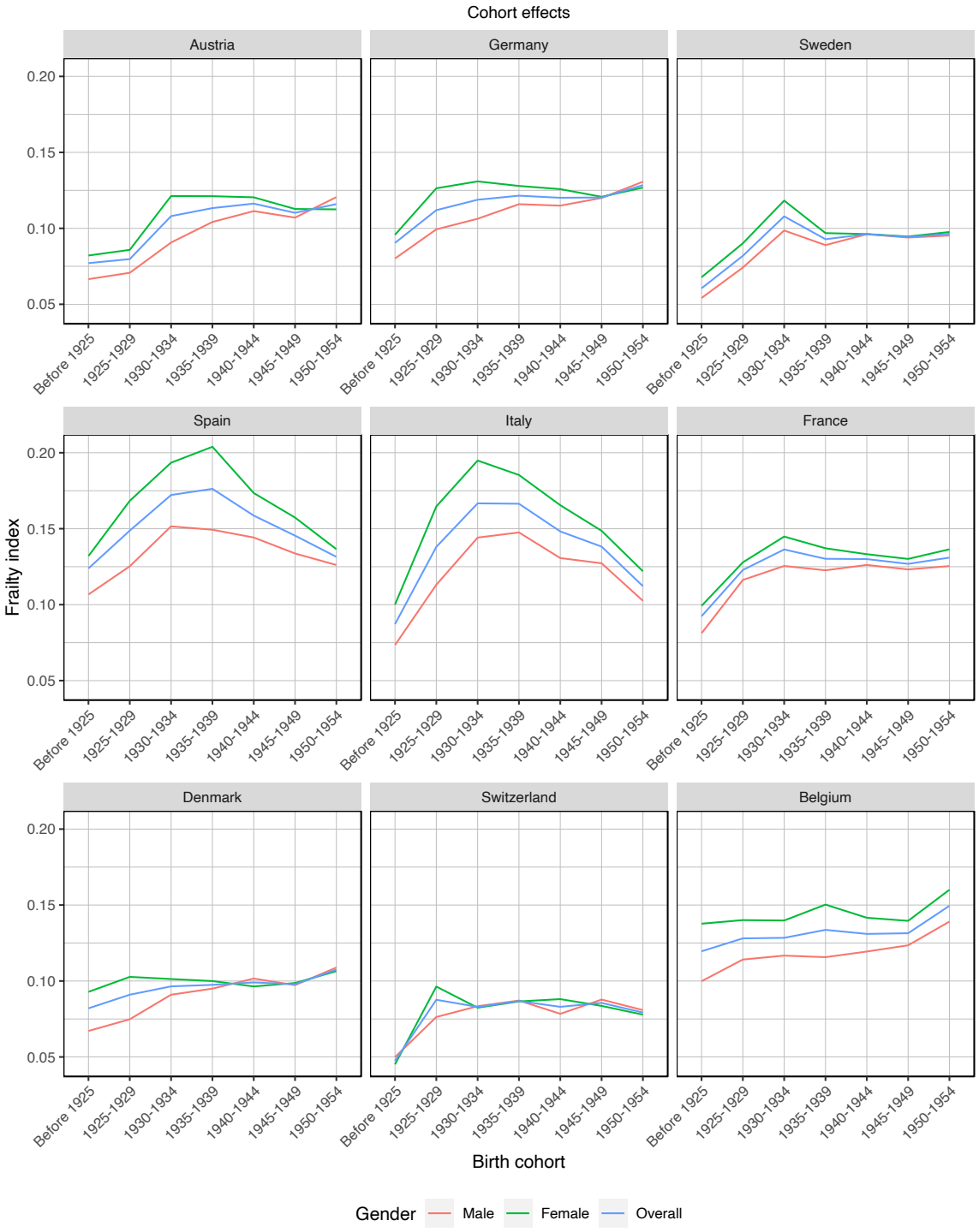


Figure 2.5: Conditional cohort effects, stratified by gender [1]



[1] 'Age' variable is kept constant at the sample mean(i.e., 70 years old)

Table 2.2: Results of zero-inflated beta regression models for Austria

Parameter	**Estimate**	**SE**	**Estimate**	**SE**
	Model 1		Model 2	
Beta model (logit link function)				
Fixed part coefficient estimates				
Intercept	-2.71	0.48***	-2.99	0.58***
Age	-0.29	0.22	-0.34	0.23
Age^2	0.20	0.03***	0.20	0.03***
Birth cohort				
Before 1925 (Ref)	0		0	
1925-1929	-0.32	0.34	-0.27	0.46
1930-1934	0.31	0.35	0.16	0.46
1935-1939	0.58	0.38	0.71	0.47
1940-1944	0.42	0.41	0.66	0.50
1945-1949	0.46	0.44	0.75	0.53
1950-1954	0.29	0.46	0.80	0.55
Cohort*Age				
Before 1925 (Ref)	0		0	
1925-1929	0.18	0.10	0.18	0.10
1930-1934	0.03	0.10	0.04	0.10
1935-1939	-0.08	0.12	-0.08	0.11
1940-1944	0.02	0.13	0.02	0.13
1945-1949	-0.03	0.15	-0.03	0.15
1950-1954	0.08	0.18	0.08	0.17
Female			0.15	0.19
Cohort*Female				
Before 1925 (Ref)			0	
1925-1929			-0.02	0.18
1930-1934			0.10	0.17
1935-1939			-0.06	0.16
1940-1944			-0.14	0.16
1945-1949			-0.17	0.17
1950-1954			-0.31	0.17
Age*Female			0.04	0.03
Zero inflated model				
Intercept	-3.81	0.20***	-3.81	0.20***
Age	-0.41	0.10***	-0.41	0.10***

Note: *p $<$ 0.05; **p $<$ 0.01; ***p $<$ 0.001

Age is in 10-year unit.

Table 2.3: Results of zero-inflated beta regression models for Belgium

Parameter	**Estimate**	**SE**	**Estimate**	**SE**
	Model 1		Model 2	
Beta model (logit link function)				
Fixed part coefficient estimates				
Intercept	-2.38	0.28***	-2.76	0.33***
Age	-0.07	0.13	-0.16	0.14
Age^2	0.13	0.02***	0.13***	0.02
Birth cohort				
Before 1925 (Ref)	0		0	
1925-1929	0.09	0.20	0.28	0.26
1930-1934	0.09	0.20	0.32	0.26
1935-1939	0.15	0.22	0.23	0.27
1940-1944	0.16	0.24	0.41	0.29
1945-1949	0.06	0.26	0.39	0.31
1950-1954	-0.09	0.28	0.20	0.32
Cohort*Age				
Before 1925 (Ref)	0		0	
1925-1929	-0.01	0.06	-0.00	0.06
1930-1934	-0.00	0.06	0.01	0.06
1935-1939	-0.01	0.07	0.00	0.07
1940-1944	-0.03	0.08	-0.02	0.08
1945-1949	0.02	0.09	0.03	0.09
1950-1954	0.17	0.11	0.19	0.11
Female			0.26	0.11*
Cohort*Female				
Before 1925 (Ref)			0	
1925-1929			-0.13	0.11
1930-1934			-0.16	0.11
1935-1939			-0.06	0.10
1940-1944			-0.17	0.10
1945-1949			-0.22	0.10*
1950-1954			-0.20	0.11
Age*Female			0.05	0.02**
Zero inflated model				
Intercept	-4.39	0.22***	-4.39	0.22***
Age	-0.71	0.14***	-0.71	0.14***

Note: *p $<$ 0.05; **p $<$ 0.01; ***p $<$ 0.001
Age is in 10-year unit.

Table 2.4: Results of zero-inflated beta regression models for Denmark

Parameter	**Estimate**	**SE**	**Estimate**	**SE**
	Model 1		Model 2	
Beta model (logit link function)				
Fixed part coefficient estimates				
Intercept	-2.81	0.41***	-3.66	0.50***
Age	-0.13	0.20	0.01	0.20
Age^2	0.16	0.02***	0.16	0.02***
Birth cohort				
Before 1925 (Ref)	0		0	
1925-1929	0.15	0.29	0.14	0.41
1930-1934	0.25	0.29	0.64	0.40
1935-1939	0.37	0.32	0.86	0.41*
1940-1944	0.32	0.35	0.98	0.44*
1945-1949	0.21	0.38	0.75	0.46
1950-1954	-0.00	0.40	0.60	0.48
Cohort*Age				
Before 1925 (Ref)	0		0	
1925-1929	-0.02	0.09	-0.01	0.09
1930-1934	-0.04	0.09	-0.04	0.09
1935-1939	-0.09	0.10	-0.10	0.10
1940-1944	-0.06	0.12	-0.06	0.12
1945-1949	-0.01	0.14	-0.00	0.14
1950-1954	0.15	0.16	0.15	0.16
Female			0.54	0.17**
Cohort*Female				
Before 1925 (Ref)			0	
1925-1929			-0.00	0.18
1930-1934			-0.23	0.17
1935-1939			-0.30	0.16
1940-1944			-0.41	0.16*
1945-1949			-0.34	0.16*
1950-1954			-0.38	0.17
Age*Female			-0.09	0.03**
Zero inflated model				
Intercep	-3.17	0.15***	-3.17	0.15***
Age	-0.59	0.09***	-0.59	0.09***

Note: *p $<$ 0.05; **p $<$ 0.01; ***p $<$ 0.001
Age is in 10-year unit.

Table 2.5: Results of zero-inflated beta regression models for France

Parameter	**Estimate**	**SE**	**Estimate**	**SE**
	Model 1		Model 2	
Beta model (logit link function)				
Fixed part coefficient estimates				
Intercept	-3.23	0.31***	-3.59	0.37***
Age	0.28	0.15	0.28	0.15
Age^2	0.09	0.02***	0.10	0.02***
Birth cohort				
Before 1925 (Ref)	0		0	
1925-1929	0.58	0.20**	0.77	0.27**
1930-1934	0.86	0.21***	0.96	0.27***
1935-1939	0.81	0.24***	0.97	0.29***
1940-1944	0.79	0.26**	1.05	0.31***
1945-1949	0.73	0.29*	1.00	0.34**
1950-1954	0.75	0.30*	0.96	0.35**
Cohort*Age				
Before 1925 (Ref)	0		0	
1925-1929	-0.13	0.06*	-0.13	0.06*
1930-1934	-0.21	0.06***	-0.21	0.06***
1935-1939	-0.21	0.07**	-0.21	0.07**
1940-1944	-0.20	0.09*	-0.20	0.09*
1945-1949	-0.19	0.10	-0.19	0.10
1950-1954	-0.18	0.12	-0.18	0.12
Female			0.22	0.11
Cohort*Female				
Before 1925 (Ref)			0	
1925-1929			-0.11	0.11
1930-1934			-0.05	0.10
1935-1939			-0.09	0.10
1940-1944			-0.16	0.10
1945-1949			-0.16	0.10
1950-1954			-0.12	0.11
Age*Female			-0.00	0.02
Zero inflated model				
Intercept	-4.19	0.22***	-4.19	0.22***
Age	-0.79	0.14***	-0.79	0.14***

Note: *p $<$ 0.05; **p $<$ 0.01; ***p $<$ 0.001
Age is in 10-year unit.

Table 2.6: Results of zero-inflated beta regression models for Germany

Parameter	**Estimate**	**SE**	**Estimate**	**SE**
	Model 1		Model 2	
Beta model (logit link function)				
Fixed part coefficient estimates				
Intercept	-3.68	0.41***	-4.04	0.49***
Age	0.59	0.19**	0.61	0.19**
Age^2	0.05	0.02*	0.05	0.02*
Birth cohort				
Before 1925 (Ref)	0		0	
1925-1929	0.53	0.33	0.47	0.41
1930-1934	0.61	0.33	0.57	0.41
1935-1939	0.87	0.34*	1.03	0.42*
1940-1944	1.09	0.36**	1.26	0.44**
1945-1949	1.04	0.39**	1.35	0.46**
1950-1954	0.94	0.40*	1.32	0.48**
Cohort*Age				
Before 1925 (Ref)	0		0	
1925-1929	-0.15	0.10	-0.15	0.10
1930-1934	-0.15	0.10	-0.15	0.10
1935-1939	-0.27	0.10**	-0.27	0.10**
1940-1944	-0.39	0.12***	-0.39	0.12**
1945-1949	-0.36	0.13**	-0.36	0.13**
1950-1954	-0.27	0.15	-0.27	0.15
Female			0.22	0.16
Cohort*Female				
Before 1925 (Ref)			0	
1925-1929			0.08	0.15
1930-1934			0.04	0.14
1935-1939			-0.08	0.14
1940-1944			-0.09	0.14
1945-1949			-0.19	0.14
1950-1954			-0.23	0.15
Age*Female			-0.01	0.03
Zero inflated model				
Intercept	-4.13	0.24***	-4.13	0.24***
Age	-0.76	0.15***	-0.76	0.15***

Note: *p $<$ 0.05; **p $<$ 0.01; ***p $<$ 0.001
Age is in 10-year unit.

Table 2.7: Results of zero-inflated beta regression models for Italy

Parameter	**Estimate**	**SE**	**Estimate**	**SE**
	Model 1		Model 2	
Beta model (logit link function)				
Fixed part coefficient estimates				
Intercept	-4.09	0.39***	-4.56	0.46***
Age	0.81	0.18***	0.78	0.18***
Age^2	0.03	0.02	0.03	0.02
Birth cohort				
Before 1925 (Ref)	0		0	
1925-1929	1.00	0.29***	0.85	0.37*
1930-1934	1.64	0.29***	1.62	0.36***
1935-1939	1.87	0.31***	1.96	0.38***
1940-1944	2.00	0.34***	2.07	0.40***
1945-1949	1.84	0.36***	2.07	0.42***
1950-1954	1.71	0.38***	1.91	0.44***
Cohort*Age				
Before 1925 (Ref)	0		0	
1925-1929	-0.24	0.08**	-0.23	0.08**
1930-1934	-0.45	0.08***	-0.44	0.08***
1935-1939	-0.57	0.10***	-0.56	0.09***
1940-1944	-0.70	0.11***	-0.68	0.11***
1945-1949	-0.66	0.13***	-0.65	0.13***
1950-1954	-0.72	0.15***	-0.70	0.15***
Female			0.32	0.14*
Cohort*Female				
Before 1925 (Ref)			0	
1925-1929			0.10	0.15
1930-1934			0.02	0.13
1935-1939			-0.07	0.13
1940-1944			-0.06	0.13
1945-1949			-0.16	0.13
1950-1954			-0.14	0.14
Age*Female			0.01	0.02
Zero inflated model				
Intercept	-4.54	0.30***	-4.54	0.30***
Age	-0.71	0.17***	-0.71	0.17***

Note: *p $<$ 0.05; **p $<$ 0.01; ***p $<$ 0.001
Age is in 10-year unit.

Table 2.8: Results of zero-inflated beta regression models for Sweden

Parameter	**Estimate**	**SE**	**Estimate**	**SE**
	Model 1		Model 2	
Beta model (logit link function)				
Fixed part coefficient estimates				
Intercept	-4.06	0.36***	-4.47	0.41***
Age	0.48	0.17**	0.51	0.17**
Age^2	0.09	0.02***	0.09	0.02***
Birth cohort				
Before 1925 (Ref)	0		0	
1925-1929	0.75	0.25**	0.77	0.31*
1930-1934	1.56	0.26***	1.61	0.32***
1935-1939	1.21	0.29***	1.41	0.33***
1940-1944	1.36	0.31***	1.70	0.36***
1945-1949	1.27	0.34***	1.60	0.38***
1950-1954	1.19	0.36***	1.49	0.40***
Cohort*Age				
Before 1925 (Ref)	0		0	
1925-1929	-0.21	0.07**	-0.20	0.07**
1930-1934	-0.47	0.08***	-0.46	0.08***
1935-1939	-0.37	0.09***	-0.37	0.09***
1940-1944	-0.43	0.10***	-0.42	0.10***
1945-1949	-0.39	0.12***	-0.39	0.12**
1950-1954	-0.34	0.14*	-0.33	0.14*
Female			0.28	0.13*
Cohort*Female				
Before 1925 (Ref)			0	
1925-1929			-0.03	0.13
1930-1934			-0.04	0.12
1935-1939			-0.15	0.11
1940-1944			-0.24	0.11*
1945-1949			-0.23	0.12*
1950-1954			-0.21	0.12
Age*Female			-0.02	0.02
Zero inflated model				
Intercept	-3.10	0.14***	-3.10	0.14***
Age	-0.61	0.08***	-0.61	0.08***

Note: *p $<$ 0.05; **p $<$ 0.01; ***p $<$ 0.001
Age is in 10-year unit.

Table 2.9: Results of zero-inflated beta regression models for Spain

Parameter	**Estimate**	**SE**	**Estimate**	**SE**
	Model 1		Model 2	
Beta model (logit link function)				
Fixed part coefficient estimates				
Intercept	-2.88	0.39***	-3.42	0.44***
Age	0.27	0.18	0.35	0.19
Age^2	0.09	0.02***	0.09	0.02***
Birth cohort				
Before 1925 (Ref)	0		0	
1925-1929	0.45	0.25	0.34	0.30
1930-1934	0.90	0.26***	0.90	0.31**
1935-1939	1.11	0.30***	0.98	0.34**
1940-1944	1.17	0.33***	1.30	0.37***
1945-1949	1.01	0.36**	1.19	0.40**
1950-1954	0.73	0.38	1.07	0.42**
Cohort*Age				
Before 1925 (Ref)	0		0	
1925-1929	-0.12	0.07	-0.13	0.07
1930-1934	-0.26	0.07***	-0.28	0.07***
1935-1939	-0.35	0.09***	-0.36	0.09***
1940-1944	-0.44	0.11***	-0.47	0.11***
1945-1949	-0.41	0.13**	-0.44	0.13***
1950-1954	-0.33	0.15*	-0.36	0.15*
Female			0.28	0.12*
Cohort*Female				
Before 1925 (Ref)			0	
1925-1929			0.10	0.10
1930-1934			0.05	0.09
1935-1939			0.14	0.10
1940-1944			-0.02	0.10
1945-1949			-0.05	0.10
1950-1954			-0.15	0.11
Age*Female			-0.02	0.02
Zero inflated model				
Intercept	-4.38	0.30***	-4.38	0.30***
Age	-0.89	0.18***	-0.89	0.18***

Note: *p $<$ 0.05; **p $<$ 0.01; ***p $<$ 0.001
Age is in 10-year unit.

Table 2.10: Results of zero-inflated beta regression models for Switzerland

Parameter	**Estimate**	**SE**	**Estimate**	**SE**
	Model 1		Model 2	
Beta model (logit link function)				
Fixed part coefficient estimates				
Intercept	-4.07	0.52***	-3.92	0.58***
Age	0.35	0.24	0.36	0.24
Age^2	0.09	0.03**	0.09	0.03**
Birth cohort				
Before 1925 (Ref)	0		0	
1925-1929	1.30	0.36***	0.73	0.44
1930-1934	1.11	0.37**	0.98	0.43*
1935-1939	1.29	0.41**	1.16	0.46*
1940-1944	1.30	0.45**	0.96	0.50
1945-1949	1.20	0.48*	1.14	0.53*
1950-1954	1.07	0.51*	0.99	0.56
Cohort*Age				
Before 1925 (Ref)	0		0	
1925-1929	-0.32	0.10**	-0.32	0.10**
1930-1934	-0.25	0.11*	-0.26	0.11*
1935-1939	-0.32	0.12**	-0.33	0.12**
1940-1944	-0.35	0.14*	-0.36	0.14*
1945-1949	-0.28	0.16	-0.29	0.16
1950-1954	-0.26	0.19	-0.27	0.19
Female			-0.11	0.17
Cohort*Female				
Before 1925 (Ref)			0	
1925-1929			0.36	0.16*
1930-1934			0.09	0.15
1935-1939			0.10	0.15
1940-1944			0.23	0.15
1945-1949			0.05	0.15
1950-1954			0.07	0.16
Age*Female			0.00	0.03
Zero inflated model				
Intercept	-3.07	0.20***	-3.07	0.20***
Age	-0.85	0.12***	-0.85	0.12***

Note: *p $<$ 0.05; **p $<$ 0.01; ***p $<$ 0.001
Age is in 10-year unit.

2.4 Discussion

Using a six-wave dataset spanning 13 years from the SHARE, the present work extends and complements current understanding of frailty trajectories in nine European countries by decomposing frailty trajectories into age and cohort effects. Our analyses reveal consistent parabolic age trends across countries, whereas patterns of cohort effects were more country-specific. Throughout old age, women were inclined to be more frail than their counterparts; and gender differentials in frailty narrowed substantially in successively younger cohorts.

Our finding of the upward parabolic shape of age trends is consistent with the findings of previous studies [57, 71, 72], further supporting the idea of accelerated accumulation of deficits with age [6, 5]. Additionally, this phenomenon might be a life-course outcome of advances in living conditions and healthcare that increase survival of frail individuals, with the impact being most pronounced at the oldest ages where the risk of frailty is greatest [71]. This, however, casts a gloom over prolonged life expectancy, as it is associated with additional years spent in frailty and greater healthcare costs. From another perspective, the disproportionate speed-up of frailty progression starting from the age of 75 might reflect biases in ageing health policy and practice that are largely concerned with the "young-old" rather than the "old-old" in European countries [73]. Although the driving forces behind the slower after-75-year-old growth rate of frailty level in Italy, Germany and Switzerland are not well-understood, one can speculate that it is partly attributed to the better inclusion of the "old-old" in active ageing policy and ageing-friendly environment, enabling them to be more proactive, resilient and capable. It is interesting to note that the eldercare in Italy is characterized by familistic orientation more than in other European countries. In close-knit families rooted in Italian culture, seniors would receive mental and physical support from family members [74].

The present study showed lower age-adjusted frailty levels of the cohorts born before 1930 compared with recent cohorts across countries. This result is in accord with other

studies which examined cohort-specific frailty trajectories in the U.S., England and Hongkong and reported lower frailty levels in early cohorts compared to recent cohorts [71, 72, 75]. Similar findings were also observed in Hongkong for cohort-specific trajectories of multimorbidity [76]. It is possibly due to healthy survivor effect, in which respondents in earlier cohorts are healthier individuals who can live long enough to be surveyed.

In addition, our finding of markedly higher age-adjusted frailty levels in the cohorts born from 1930 and thereafter may demonstrate a real deterioration in late-life health of generations who spent their *in utero* stage and formative years during the Great Depression, the World War II (WW2) , and the subsequent economic recovery period. This is in agreement with the literature on the impact of economic hardship and wartime exposure during *in utero* period and childhood on later life health [77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88]. Malnutrition, starvation, and trauma are major problems during the Great Depression and WW2 [80, 81, 89] that may have long-term health effects. In epidemiology studies of famines, fetal undernutrition has been found associated with a broad spectrum of health consequences in adulthood, including lower self-reported health [82], heart disease [82], and adult antisocial personality disorders [83], diabetes [84] and schizophrenia [84, 85]. An analysis of the Seige of Leningrad evidenced the association between starvation and war trauma in childhood or adolescence and elevated risk of cardiovascular disease, breast cancer, and higher blood pressure at middle age [86]. Of the SHARE sample, respondents experiencing war were found to have an increased probability of suffering from lower self-rated health, heart disease, diabetes, and depression as a result of hunger, dispossession, persecution, and having an absent father [81]. However, a US-based study of the 1930s birth cohort found little evidence of the effect of *in utero* economic hardship on late-life health [90]. This suggests that long-term health effects of the Great Depression and the World War II may vary greatly from country to country, depending on its unique conditions.

Our analyses revealed contrasting patterns of age-adjusted frailty levels across the cohorts born from 1935 and thereafter amongst countries - specifically, a noticeable downtrend was observed in Italy and Spain, whereas there was no substantial difference across cohorts in the others. A possible explanation for age-adjusted cohort differences in Italy and Spain might be their welfare regime. Although cohorts born between 1940 and 1955 were generally more income-privileged than previous cohorts, such generational inequalities were stronger in conservative welfare states[2], especially in Italy and Spain [93]. Lower income, in turn, has been found associated with worse health outcomes, including frailty [94, 95, 96]. The association between income and health would be amplified by Southern European welfare regime[3], which is characterized by a fragmented system of welfare provision and a healthcare with partial and limited coverage [98]. Correspondingly, in Italy and Spain, the 1930s cohorts had higher frailty levels than successively younger cohorts. On the other hand, the lack of evidence for cohort differences in other countries is in line with the result from a British analysis, which also found little evidence of differences in frailty levels across recent cohorts (aged 50 to 70 in 2002) [71]. In a recent study of grip strength trajectories in Germany, Sweden, and Spain, using data from the SHARE, no clear pattern of cohort effects was detected for Sweden, and an increasing trend across late birth cohorts was reported for Spain [99]. These findings agree with our results, as an inverse relationship between grip strength and frailty is expected. However, the study reported a hill-shaped pattern with the highest grip strength in the 1940-1945 cohort for Germany, which disagrees with our results. This illustrates the potential for variability in cohort differences across different domains of health.

[2]Esping-Andersen's typology classifies welfare states into three regime types (Liberal, Conservative, Social Democratic). Of our studied countries, Austria, Belgium, Germany, France, Italy, and Spain are classified as conservative welfare states; Denmark and Sweden as social democratic welfare states; Switzerland as a liberal welfare state [91, 92].

[3]Ferrera's four-fold typology makes a distinction between the Scandinavian (Social Democratic), Anglo-Saxon (Liberal), Bismarckian (Conservative) and Southern European countries. Of our studied countries, Italy and Spain are classified as Southern European welfare states instead of Bismarckian (conservative) ones as in Esping-Andersen's typology [97].

We observed a variation in overall age-adjusted frailty levels across countries: (i) lowest in Denmark, Sweden, and Switzerland; (ii) higher in Austria, Belgium, Germany, and France; (iii) and highest in Italy and Spain; however, in recent cohorts, frailty level of Italy and Spain were similar to that of Austria, Belgium, Germany, and France. In accordance with the present results, previous cross-sectional studies of self-reported health outcomes on the SHARE sample have demonstrated that Scandinavian respondents were the healthiest and respondents living in Southern Europe were the least healthy [100, 101, 102]. This cross-country discrepancy could be attributed to idiosyncrasies in historical development of each country, especially regarding the Great Depression and WW2. In WW2, Denmark, Sweden, and Switzerland adopted a neutral position and were not or little afflicted by war[4] [104, 105]. Despite some economic slowdowns due to the Great Depression and WW2, generally these countries experienced a consistent economic growth, as reflected by GDP per capita (see Appendix B). Conversely, the economic impact of WW2 was much more destructive for the countries involved, and the Great Depression also hit these countries harder, especially for Italy with a stagnant economic growth until post-war period (see Appendix B). As for Spain, the 1936-1945 period witnessed a disastrous civil war, and subsequent fierce oppression and economic slump [106]. Spanish economy remained sluggish until late 1950s, while other countries' post-WW2 economy recovered strongly thanks to financial aid under the Marshall Plan [107] (see Appendix B). Further, among war-afflicted countries, age-adjusted frailty levels vary from country to country for earlier cohorts but converge to similar levels for post-war cohorts, suggesting historical milestones as a key driver of cross-country differences in frailty levels. Without catastrophic, traumatic events that affected countries differently such as the Great Depression and wars, cohort effects would be rather similar across the countries.

Moreover, cultural differences in health perception and response styles may contribute

[4] "Although mainland Denmark was under German occupation from April 1940 to the end of WW2, it was never affected by major war events" [103]

to the cross-country variations observed. It has ben shown that respondents from Denmark and Sweden had tendency to largely over-rate their health whereas Germans tend to under-rate their health [100]. If differences in reporting styles are taken into account, cross-national variations in frailty levels would be reduced but not eliminated.

We further explored gender-stratified frailty trajectories and found higher frailty levels in women than in men, which corroborates the findings of a great deal of previous works in the 'male-female health-survival paradox' [42, 101, 102, 108, 37, 109]. Nevertheless, except in Italy and Spain, gender differential in cohort-adjusted frailty levels was relatively small. The wider gender gap seen for Southern European countries might be attributed to their welfare system, which is often criticized for worsening women position and health [110, 111]. The 'age gradient' of frailty progression was similar for men and women in most countries, except Belgium where frailty gender gap was widening with age. This reflects cumulative disadvantages of women over life-course [112], but also suggests that the 'cumulative disadvantage' effect would vary between countries. Furthermore, our analysis revealed that across countries, gender inequality in age-adjusted frailty levels was attenuated progressively in recent cohorts, which appears to be encouraging for the global effort to close gender gap. However, for several countries, this seemingly improving trend was at the expense of increased frailty score for males. A possible explanation is that the more pronounced increase in life expectancy of men in recent cohorts makes stronger healthy survivor effect in men. Yet the reasons behind the phenomenon of men losing their health advantage remain unclear and call for future research.

Our study is subject to some limitations. First, as in other cross-national comparative studies, an important concern is the incomparability of available data due to translation and adaptation of instruments [113]. It is not always possible to find words in different languages that can convey the exact meaning of a construct [114]; and different modes of survey administration can have an effect on responses [113]. Second, the inherent limitation

of APC analysis is that for model identification, it is logically infeasible to completely tease age, period and cohort effects apart. As shown in Bell and Jones (2014) [67], age and cohort effects could be overestimated if there is a period trend. Another limitation pertains to selection bias, as healthier individuals may be more likely to respond to the survey.

2.5 Conclusion

Using an age-cohort-period approach, this study compared frailty trajectories of older adults across a sample European countries, teasing apart age and cohort effects in frailty trends. The study found universal parabolic age trends, but country-specific cohort effects. Women were generally more frail than men at any age, and the gender gap was narrowed in more recent cohorts. Our research adds a new cross-nationally comparative perspective about frailty trends to the literature.

CHAPTER 3
HEALTH STATUS TRANSITIONS AMONG COMMUNITY-LIVING ELDERLY IN EUROPE: A LATENT TRANSITION ANALYSIS

3.1 Introduction

The global population is ageing, posing increasing challenges in the eldercare to governments, families, and health service providers. This requires care interventions tailored to individuals' problems and needs. For this purpose, frailty, a dynamic state involving the interaction of different functioning domains, was introduced as a proxy for the severity of the ageing process and has become a critically important health problem in late-life care. Frailty is associated with, but distinct from, morbidities and disabilities [115]. Thus, frailty provides a conceptual framework for moving away from the organ- and disease-based approaches towards a health-based, integrative approach [116].

However, in the absence of a gold standard, the conceptualization and operationalization of frailty remain debatable. Most frailty definitions greatly emphasize physical deficiencies, with characteristics such as unintentional weight loss, slowness, or morbidities. From a broader approach, which sees human beings as 'more than the sum of their parts', researchers have also explored social and psychological domains of frailty [117]. These domains are characterized by cognitive impairments, mood changes, or social factors. Such an integral definition of frailty, corresponding to the definition of health of the World Health Organization (WHO), is: "Frailty is a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social), which is caused by the influence of a range of variables and which increases the risk of adverse outcomes" [116].

Frailty might be conceptualized as a continuum between non-frail and frail (e.g.,

Frailty Index [31]), or as categories (e.g., Frailty phenotype [28]). While the former captures the dynamic nature of frailty, where the actual state of a frail older person can be positioned along this continuum, the latter sets boundaries to distinguish between different levels of frailty severity. Nevertheless, because of the interaction between domains [117], their combinations would create considerable heterogeneity in the group of people labeled frail, and it remains unclear which specific combinations lead to adverse health outcomes. Differentiating those people into more homogenous subgroups would facilitate interventions more targeted to underlying problems.

Specifying older people to frailty subgroups based on severity or deficit domains, however, is questionable. Severity-based classification typically relies on the total score of considered deficits, which assumes that all deficits equivalently measure frailty severity. Domain-based classification appears to ignore evidence showing that deficits in different domains are highly correlated and that many older adults suffer from deficits in multiple domains.

To uncover unobserved subgroups of frailty within our study sample, we choose a latent class modeling framework, which is person-centered analyses. Individuals are categorized based on patterns of associations among a set of observed variables. While there have been a number of studies using latent class models for exploring frailty topologies and trajectories, few have considered social functioning domain and examined changes in membership over time [118, 119]. Of interest in this current study are whether there are meaningful subgroups of European older people who present similar constellations of health problems, and how individuals change their membership over time. Two aims of the research are: i) to identify distinct frailty classes, with socio-psychological domains taken into account, at each time point by latent class analysis, and ii) to study transitions across frailty classes and to death over three time points by latent transition analysis.

3.2 Methods

LTA requires a step-wise approach to appropriately capture transitions in health status over time. In this section, we first provide a brief overview of LCA and LTA, followed by an application to the data derived from the Survey of Health, Ageing and Retirement in Europe (SHARE) to answer our research questions.

3.2.1 Overview of LCA and LTA framework

Latent class analysis (LCA) LCA is a model-based clustering method. Unobserved subgroups of a population are explored based on the conditional probabilities of response patterns to a set of observable indicators given a postulated latent class model. Data for the analysis are the pairs of a response pattern and its frequency count. With all indicators being categorical in LCA, the multinomial distribution of the data arises naturally, and the general unrestricted LCA model takes the form of a multinomial probability model [120, 121]. Two sets of parameters specify the model: i) the γ parameters represent the overall probabilities of cluster membership, and ii) the ρ parameters represent the probabilities of observing a given response conditional on cluster membership [120]. The classical LCA approach relies on three assumptions as follows:

- A1. The population is partitioned into exhaustive and mutually exclusive subgroups.
- A2. Latent classes are uniquely characterized by the conditional probabilities of response patterns $\rho's$. The quantities fully define latent classes and distinguish them from each other.
- A3. Within a class, the observed indicators are statistically independent of each other (i.e., local/conditional independence).

Violation of the local independence assumption (i.e., the existence of locally dependent item pairs) would be the main cause of model misfit, which is picked up by overall fit

statistics and information criteria. The assumption violation can be remedied simply by including additional classes to account for the local dependence. However, this assumption is too restrictive and can be unrealistic in many practical applications [122]. For example, when searching for distinct syndromes, for each pair of symptoms, it seems unlikely that the occurrence of any one symptom will be unrelated to the other for any diagnostic category [123]. The pursuant additional latent classes would be spurious and/or of no scientific interest, so a model with fewer classes is preferred [124, 125]. Therefore, relaxing the local independence assumption may be necessary to obtain substantive and interpretable subgroups.

Class enumeration is based on the compromise of standard fit statistics, classification diagnostics, interpretability, and parsimony [126, 127, 128]. First, a series of LCA models is conducted by sequentially adding classes until a model fits data well, as indicated by absolute and relative fit statistics. Overall model fit of a particular model is often evaluated with likelihood ratio Chi-square goodness-of-fit test, where an insignificant result shows model-data consistency. Chi-square test, however, is well-known for being sensitive to a negligible, inconsequential model misfit in large samples [126, 129]. It is suggested that a closer inspection of standardized residuals ($stdres$) could assess whether a model is close enough to a good fit. Specifically, a well-fitting model is expected to have a small proportion (i.e., less than 5%) of response patterns with large standardized residuals (i.e., $|stdres| \geq 3$) [126]. Also, this test is not appropriate with large sparse tables - a particular concern of a mixture model with many categorical indicators, since the test statistic (denoted as G^2) deviates from the asymptotic Chi-square distribution [130]. Even in cases appropriate for its use, the Chi-square goodness-of-fit test indicates the overall model misfit but does not help detect the source of the misfit. In addition to global model fit, a local fit measure called bivariate residual (BVR) can be used to detect local dependencies between item pairs [124]. The BVR has the same form as Pearson residual, and some rules of thumb are available for the use of BVR - for example, one rule suggests a value of

greater than 3.84 as an indication of significant misfit, while another rule recommends a cut-off at 1.0 [131]. However, for reasons of model stability and identifiability, it is not advisable to relax all local dependencies [132]. When local dependencies present between multiple item pairs, the most severe violations, as guided by BVRs, should be freed [132, 133].

Relative fit statistics are used for comparison between two or more competing models, which include the Akaike information criterion (AIC) [134], the Bayesian information criterion (BIC) [135], sample size adjusted BIC (ssaBIC) [135], the Lo-Mendell-Rubin likelihood ratio test (LMR-LRT) [136], the adjusted version of LMR-LRT (aLMR-LRT) [136], and the bootstrapped likelihood ratio test (BLRT) [137, 138]. Smaller values of information criteria indicate better model fit; hence, a model with the lowest AIC or BIC among the set of considered models is preferred. However, there is no guarantee that information criteria will arrive at a single lowest value before reaching the maximum number of classes considered. In such cases, exploring the marginal gains in model fit via 'elbow' plots of these indices can guide class enumeration [126]. LRT tests provide a comparison of two nested models, with $p < 0.05$ suggesting the k-class model fits significantly better than the (k-1)-class model. However, as with other statistical tests, these LRT tests depend on sample size [139]. A statistically significant test result does not necessarily mean a practical difference in model fit in very large samples.

Despite the exploratory nature of LCA, the model selected by statistical analysis is useful only if it can supply theoretically interpretable latent classes [128]. The selection of the final model should be guided by the conceptual meaningfulness and plausibility of classes. Latent classes are interpreted and labeled on the basis of the probabilities of responses to each observed variable for each class (ρ's). It is qualitative and quantitative differences between latent classes that characterize the latent variable.

After selecting the best-fitting model, it is critical to evaluate how well the candidate model has assigned individuals into latent classes [126]. Class assignment for each

individual is not definite, but the probabilities of being in each of the latent classes are estimated by the model and are often called estimated posterior class probabilities. A widely used index summarizing the overall accuracy of membership classification for the whole sample across all latent classes is entropy, given by:

$$EN = -\sum_{i=1}^{N}\sum_{j=1}^{J}\alpha_{ij}log\alpha_{ij}$$

, where N denotes the number of observations, and J denotes the number of classes. Entropy is bounded in $[0, +\infty)$, where a higher value indicates a larger amount of uncertainty in classification. Relative entropy is a rescaled version of entropy:

$$REN = 1 - \frac{EN}{NlogJ}$$

, ranging from 0 to 1 where a higher value indicates a better classification [140]. Although there is no clear cut-off of REN, Clark and Muthén suggested values of 0.80, 0.60, and 0.40 representing high, medium, and low entropy, respectively [141]. Two indices of class-specific assignment quality are average posterior class probability (AvePP) and odds of correct classification (OCC). Latent classes with AvePP $\geq$ 0.70 and OCC $\geq$ 5.0 are considered well-separated and adequately accurate [142]. These diagnostics should not be used to evaluate model fit but are more relevant to the utility of latent class membership in subsequent analyses [126]. An entropy level of 0.60 or higher has been found sufficiently good class separation in a multistage classify-analyze approach, and the analysis is expected to work as efficiently as the 1-step approach [141, 143].

Latent transition analysis (LTA)

LTA is a latent Markov model, estimating membership transition patterns of dynamic constructs over time. Stage membership is not observed but is identified by a set of observed variables. Thus, LTA consists of a measurement component (usually LCA) that

captures latent classes and a structural component where the latent class variable at time $(t+1)$ is auto-regressed on the latent class variable at time t.

Measurement invariance (MI): MI refers to the stability of a latent class solution, characterized by equality of conditional item probabilities across time. Specifications of MI vary from full MI to partial MI and full measurement non-invariance. Full MI is often assumed in LTA applications since it indicates latent classes at different time points are defined identically, allowing a straightforward interpretation of transition probabilities [144]. However, depending on the nature of the construct, observed variables measuring it, and considered timeframe, full MI may not be plausible. Thus, both theoretical and practical reasons determine whether measurement invariance should be assumed. Statistically, MI can be checked by comparing fit indices (i.e., AIC, BIC, ssaBIC) of models with and without MI. MI can also be formally tested using a likelihood ratio test, with a significant test result rejecting MI [145].

Analysis strategy: The standard one-step LTA simultaneously estimates its measurement and structural components by a joint model. This approach efficiently incorporates classification uncertainties into the regression analysis. However, the involvement of autocorrelations and/or auxiliary variables could alter the structure and meaning of latent classes if the associations between latent classes and indicator variables are not sufficiently strong [143, 146]. Conversely, the two-step classify-analyze approach frees latent class formation the influence of structural model and/or auxiliary variables, but treating latent classes as true states (i.e., ignore measurement errors in classifications) can lead to biased estimates in subsequent analyses [141]. The two-step approach, hence, is no longer recommended [147].

The three-step approach offers a separate treatment of measurement and structural models while taking the inherent uncertainty in classification estimates into account. First, the unconditional latent class structure is estimated independently from the structural

model to create a variable N for each observation's most likely latent class. Second, the measurement error for the variable N is computed from the estimated posterior class probabilities. Third, the structural model is estimated with the latent class variable measured by N with uncertainty rates prefixed at the values obtained from step two [143]. This approach is an improvement over the two-step approach because of the adjustment for classification uncertainties and is expected to work as efficiently as the one-step approach with an entropy level of 0.60 or higher. More details about the three-step LTA procedure can be found in [143, 148].

Despite its advantages over the one-step approach, the three-step relies on the assumption of no direct effects of auxiliary variables on the indicators used in the measurement model, which is often violated in practice [149]. Ignoring such direct effects has been shown to lead to biased parameter estimates and alter the intended meaning of the latent class [143]. One possible solution is to include direct effects in the measurement model in Step 1 [143, 150]. This approach, however, still leaves a certain amount of bias [151]. Hence, Vermunt and Magidson recently proposed a modification of the three-step approach, characterized by the inclusion of covariates with direct effects in the step-one model and the classification error correction matrix in step three [151]. Specifically, the step-one model should contain relevant direct effects as well as the effects of the included covariates on the latent classes; and in step three, the classification error correction matrix is allowed to differ across categories of the covariates with direct effects (see [151] for more details).

3.2.2 Application to SHARE data

Data

Secondary data analysis was conducted on data from wave 4 to wave 6 of the Survey of Health, Ageing and Retirement in Europe (SHARE)[53]. Description of the SHARE was provided in Chapter 2. We limited our analysis to individuals aged 60 or older in 2011

(interview year of wave 4) in twelve countries - Austria, Germany, Sweden, Spain, Italy, France, Denmark, Switzerland, Belgium, Czech Republic, Slovenia, and Estonia.

Measures

We included categorical indicators belonging to six domains as described below. These indicators, if treated as continuous variables, show an apparent floor effect, which leads to a non-meaningful and non-discriminatory classification with a giant, dominant class, regardless the number of classes fitted. Therefore, the indicators were categorized based on levels commonly accepted in the clinical setting.

- Self-rated health was measured by a single item about how the individual would say about his/her health at present, ranging from 1 (Excellent) to 5 (Poor), with a higher score indicating worse self-rated health. Responses were recoded into three categories: Good or better, Fair and Poor.

- Cognitive functioning was captured through cognition tests of performance in verbal fluency, immediate recall, and delayed recall were used, as they are sensitive measures for discriminating between cognitively healthy individuals and those with MCI or dementia [152, 153, 154]. Threshold performance scores for impairment were set in relation to scores previously shown to be indicative of MCI or AD, as follows: verbal fluency scores < 15; immediate recall scores < 5; and delayed recall scores < 4 [153, 154]. A single indicator assessing memory functioning is coded as 'Impaired' if at least one of the recall tests indicates impairment.

- Social functioning was assessed by asking respondents whether they performed any of the following five activities in the last month: i) doing voluntary or charity work, ii) attending an educational or training course, iii) visiting a sport, social, or other kinds of club, iv) participating in a political or community-related activity, and v) play cards or games like chess . If at least one activity was undertaken almost every

week or two activities were undertaken almost every month, social functioning is coded as 'Good'.

- Mental health was measured by the EURO-D scale as a binary indicator [155]. The EURO-D scale includes 12 items about recent moods, where having four or more symptoms denotes clinically-verified depression [155].

- Morbidity status was based on self-reported information about chronic diseases (cardiovascular disease, hypertension, high blood cholesterol, stroke or cerebral vascular disease, diabetes, chronic lung disease, arthritis, and stomach or duodenal ulcer). The variable is recoded to 'None', '1 disease', and '$\geq$ 2 diseases'.

- Functional limitation was measured using the Global Activity Limitation Indicator (GALI), the Activities of Daily Living Index (ADL), and Instrumental Activities of Daily Living Index (IADL). GALI is a single-item measure of activity limitation in the last six months, with three possible responses - 'Not limited', 'Limited, but not severely', and 'Severely limited' [156]. ADL is a binary indicator adapted from the Katz ADL scale [157], indicating whether a subject had any limitations in performing 'dressing', 'bathing/showering', 'eating, cutting up food', 'walking across a room' and 'getting in or out of bed'. IADL is another binary indicator adapted from the Lawton IADL scale [158], indicating whether a subject had any limitations in performing 'telephone calls', 'taking medications', 'managing money', 'shopping for groceries and 'preparing a hot meal'.

If all items constructing the indicator were missing, the indicator was assigned a missing value. Otherwise, missing values in items were imputed as 0.

Analysis plan

Using Latent GOLD 5.1, we conducted latent transition analyses using the three-step approach, following the model-building strategy described in [151]. First, we started with

an exploration of measurement model alternatives for cross-sectional data. LCA models with 1 to 9 classes were successively fitted to data at each occasion T_1, T_2, T_3. The optimal number of classes was first selected using standard relative fit statistics. The chosen model was then checked for local and global fit by examining BVRs and Chi-square goodness-of-fit. Local independence assumption was relaxed by stepwise adding log-linear local dependency terms of the violated pairs of indicators. Local dependency terms were added one at a time, followed by re-checking local independence. The process was repeated until the adequate global and local model fit was achieved. Although several pairs of items had a violation for model identifiability, only the most severe violations of local independence were relaxed [132, 133] (also see Appendix). Based on the patterns of the probabilities of item endorsement, we examined if each class is meaningful and interpretable. The quality of classification was then evaluated using REN and AvePP.

Once an appropriate unconditional latent class model was identified, two covariates (baseline age and gender) were included in the analysis to validate emergent classes. Each covariate was included in the model one at a time and determined whether it had direct effects on the indicators based on BVRs. Subsequently, covariates with direct effects were simultaneously in the model, where not only the identified direct effects but also the effects of the covariates on the latent classes were specified.

Step three in the model-building strategy proposed by Vermunt and Magidson [151] requires a special option DIF, which has yet to be available in the currently released Latent GOLD version [1]. Therefore, following Nylund-Gibson et al. [148], if the emergent latent classes and the relative size of classes remained stable across the LCA model with and without covariates, covariate results from the three-step approach did not differ much from the one-step approach and we proceeded with the usual three-step approach.

In the next step, we assessed the implausibility of MI across time points and conducted three-step LTAs. The models were estimated using the long data format and including

[1] Option DIF is made available in Latent GOLD version 6 [151]. The most recently released version at the time of writing this manuscript is version 5.

death and lost to follow-up (LTF) as known classes, which minimizes attrition bias. MI was checked by comparing fit indices and an LRT between models with and without allowing latent class parameters to vary across time [2]. In the third step of LTA, we specified a first-order autoregression model, estimating the probabilities of transitioning between latent classes and to death or LTF over the study period. We first fitted an LTA model without covariates and then a model with baseline age and gender.

Under the assumption of missing completely at random (MCAR) or missing at random (MAR), missing latent class indicators were modeled by full information maximum likelihood (FIML). Conversely, case-wise deletion was used for missing covariates in the regression steps. LATENT GOLD syntax is provided in Appendices.

3.3 Results

3.3.1 Sample Description

The baseline sample consists of 33,330 respondents between 60 to 104 years old, with the mean age of 71.27 (SD: 8.09) and 55.84% females. The distribution of observed indicators shown in Table 3.1 reveals a great heterogeneity in the sample. There are negligible differences in the distribution of demographic variables and health indicators on three occasions, suggesting that for observed variables, individuals who died or were lost to follow-up were similar to those remaining in the study. Given the low proportions of missingness (less or slightly greater than 5%), the assumption of MAR is reasonable.

3.3.2 Frailty profiles

Table 3.2 and Figure 3.1 present fit statistics of 1-class to 9-class models. For each time point, the elbow plot of BIC indicates that the most substantial reduction in the information criteria had occurred by the number of class equal 4 (k=4) and flattened out

[2] In testing MI, LATENT GOLD requires users to specify parameters that vary across time points, whereas Mplus requires users to indicate which parameters are the same across time points.

afterward, even though these fit statistics had the lowest values at k=8 (BIC) or higher (AIC and SSAIC). Inconsistent with information criteria, the LRTs were significant for all estimated models, which is not unexpected for our huge sample. The lack of consensus among model fit measures, however, is not uncommon. In such a case, it is advisable to compromise between statistical fit and interpretability in the model selection [128]. Therefore, we considered the number of latent classes k=4 for subsequent steps.

The local independence 4-class model M_0 appears to be a model misfit. As our sample size is very large, a significant G^2 test result does not necessarily mean significant and consequential model misfit. Unfortunately, standardized residuals are not available in Latent GOLD for a closer inspection as Masyn (2013) suggested [126]; hence, we relied on BVRs to evaluate absolute model fit. BVRs calculated under M_0 are displayed in Table 3.3. It can be seen that BVRs were substantially large for the local dependencies between two pairs of indicators - (1) cognitive functioning and social functioning, and (2) cognitive functioning and self-rated health. Based on this, we formulated a model M_1 allowing the log-linear local dependence parameters corresponding to the two indicator pairs to be freely estimated. BVRs under model M_1 reflected great improvement in model fit over model M_0, as presented in Table 3.3 presents.

Table 3.4 and Figure 3.2 show class-specific health indicators probabilities for the four classes after relaxing local dependencies in M_1. The four emergent classes were remarkably similar in structure but differed in their probabilities of item endorsement. In general, the probabilities of impairment in health indicators were increasing across classes, and the two most impaired classes were best distinguished by the high probabilities of ADL and IADL. Thus, the classes differentiated individuals' frailty conditions based on degree rather than type. The classes were labeled to reflect this feature.

Health indicators at T_1 clustered into the four following classes:

1. The **Relative Healthy** class (39%)consists of individuals with good self-rated health

who reported relatively low probabilities of chronic diseases (i.e., morbidities and depression) and manifested low probabilities of cognitive disorders, functional limitations, and disability.

2. The **Pre-frail** class (38%) comprises people who reported a moderate probability of fair self-rated health and had comparatively higher probabilities of chronic diseases, cognitive disorders, and activity limitations but were unlikely to be disabled.

3. The **Independent Frail** class (12%) consists of people with fair or poor self-rated health who reported even higher probabilities of chronic diseases (especially with co-morbidity), cognitive disorders, and activity limitations. The likelihood for them to present with ADL or IADL disability was minimal.

4. The **Dependent Frail** class (10%) comprises individuals with fair or poor self-rated health who reported the highest probabilities of impairments in health indicators of interest. They differ from those in the Independent Frail class in terms of the substantially high probabilities of functional limitations and disability.

The structure of classes was reproduced for T_2 and T_3, and the distribution of classes did not differ significantly. At all three times, the classification derived from M_1 is of good quality with medium entropy (REN=0.72, 0.72, and 0.73 respectively) and all AvePPs well above 70%, as shown in Table 3.5. This warrants the use of a three-step procedure in subsequent LTA.

Figure 3.1: Elbow plot of BIC index of LCA models at each time point.

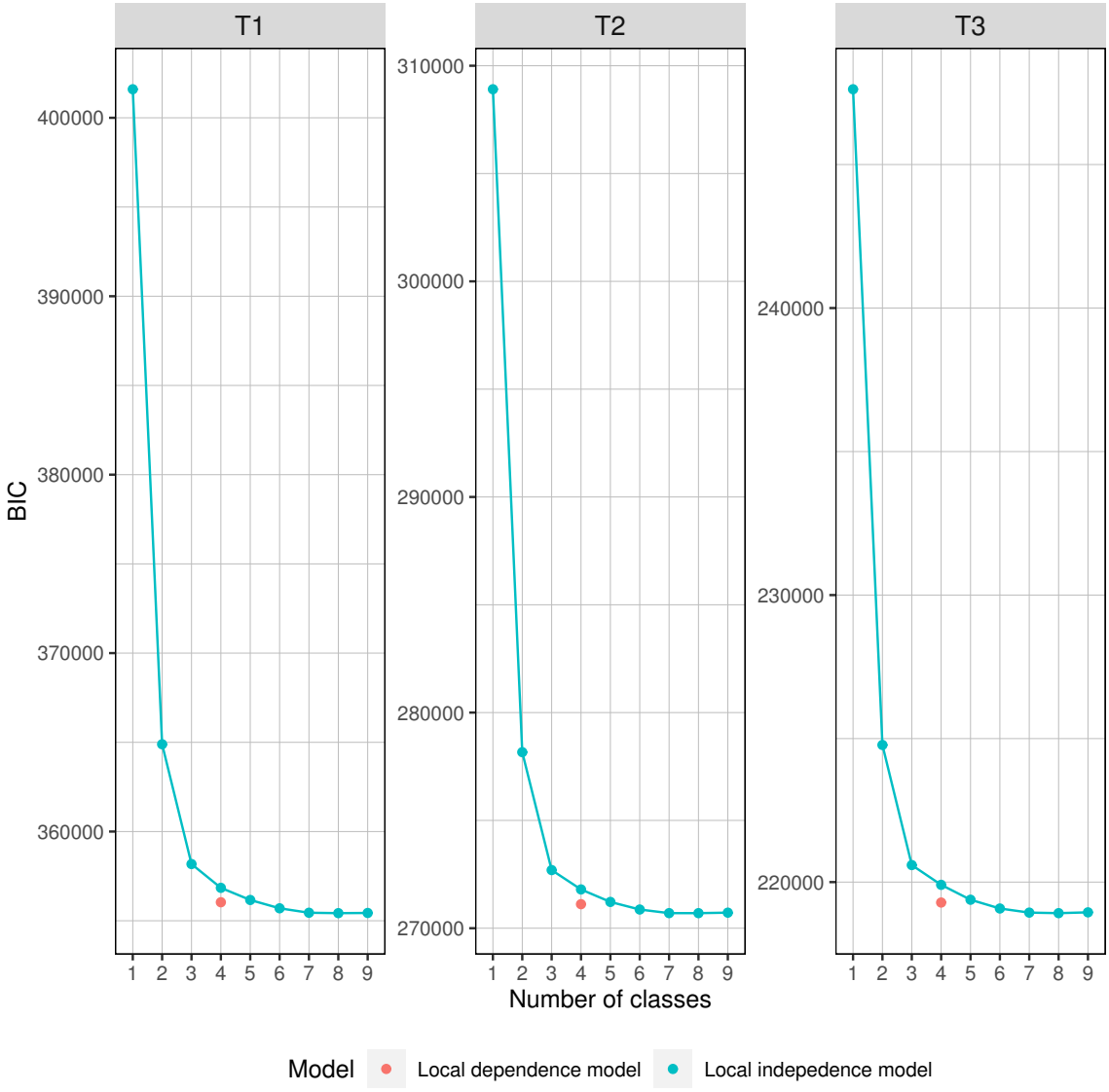


Table 3.1: Sample description at each time point

Variable (Label)	T1 (N = 33330)		T2 (N=25485)		T3 (N=20496)	
	n	%	n	%	n	%
Self-rate health						
Male	14719	44.16	11080	43.48	8764	42.76
Female	18611	55.84	14405	56.52	11732	57.24
Baseline age, Mean (SD)	71.27	8.09	70.80	7.71	70.36	7.41
Self-rate health						
Good or better (0)	18158	54.47	13773	54.04	10897	53.17
Fair	10561	31.69	8157	32.01	6874	33.54
Poor	4579	13.74	3541	13.89	2721	13.28
Missing	32	0.09	14	0.05	4	0.02
Social functioning						
Good	8435	25.31	6623	25.99	5409	26.39
Poor	24322	72.97	18252	71.62	14040	69.50
Missing	573	1.72	610	2.4	1047	5.11
Cognitive functioning						
None impaired	12813	38.43	10608	41.62	8815	43.01
Fluency OR memory impaired	12143	34.43	8747	34.32	6804	33.20
Fluency & memory impaired	7212	21.64	5187	20.35	3903	19.04
Missing	1162	3.48	943	3.70	974	4.75
ADL limitations						
No	28471	85.42	21494	84.34	17161	83.73
Yes	4819	14.46	3979	15.61	3321	16.20
Missing	40	0.12	12	0.05	14	0.07
IADL limitations						
No	29349	88.06	22111	86.76	17638	86.06
Yes	3941	11.82	3362	13.19	28.44	13.87
Missing	40	0.12	12	0.05	14	0.07
GALI						
Not limited	15566	46.70	12127	47.58	9341	45.57
Limited but not severe	11671	35.02	8544	22.53	7075	34.52
Severely limited	6075	18.23	4802	18.84	4076	19.89
Missing	18	0.05	12	0.05	4	0.02
Chronic diseases						
None	8195	24.59	6091	23.90	4671	22.79
1 disease	10307	30.92	8048	31.58	6241	30.45
$\geq$ 2 diseases	14791	44.38	11300	44.34	9572	46.70
Missing	37	0.11	46	0.18	12	0.06
Depression						
No	22726	68.18	17547	68.85	14105	68.82
Yes	9509	28.53	7094	27.84	5416	26.42
Missing	1095	3.28	844	3.31	975	4.76

Table 3.2: Model fit statistics of LCA at each time point

Model	**Log-likelihood**	**AIC**	**BIC**	**SSABIC**	G^2	**df**	G^2 **p-value**
Baseline T_1							
1-class LCA	-200737	401499	401600	401561	52862	7596	<0.0001
2-class LCA	-182316	364682	364892	364812	16019	7583	<0.0001
3-class LCA	-178891	357858	358178	358057	9170	7570	<0.0001
4-class LCA	-178157	356417	356846	356684	7702	7557	0.12
5-class LCA	-177749	355626	356165	355961	6886	7544	1.0
6-class LCA	-177449	355051	355699	355454	6285	7531	1.0
7-class LCA	-177256	354691	355449	355162	5898	7518	1.0
8-class LCA	-177177	354559	**355426**	355098	5740	7505	1.0
9-class LCA	-177114	354459	355436	355862	5615	7492	1.0
4-class LCA-RC	-177732	355574	356036	355862	6851	7553	1.0
Two-year follow-up T2							
1-class LCA	-154394	308811	308909	308871	44654	6627	<0.0001
2-class LCA	-138955	277960	278164	278085	13777	6614	<0.0001
3-class LCA	-136155	272386	272696	272575	8177	6601	<0.0001
4-class LCA	-135640	271382	271798	271636	7147	6588	<0.0001
5-class LCA	-135284	270696	271218	271015	6435	6575	0.89
6-class LCA	-135042	270239	270866	270621	5951	6562	1.0
7-class LCA	-134893	269967	270700	270414	5653	6549	1.0
8-class LCA	-134826	269859	**270698**	270370	5519	6536	1.0
9-class LCA	-134772	269776	270721	270353	5411	6523	1.0
4-class LCA-RC	-135278	270666	271114	270939	6423	6584	0.92
Four-year follow-up T3							
1-class LCA	-123752	247527	247623	247585	34765	5709	<0.0001
2-class LCA	-112265	224579	224778	224698	11792	5696	<0.0001
3-class LCA	-110108	220291	220593	220472	7478	5683	<0.0001
4-class LCA	-109699	219500	219905	219743	6661	5670	<0.0001
5-class LCA	-109357	218878	219386	219182	6012	5657	0.0005
6-class LCA	-109158	218469	219080	218835	5578	5644	0.74
7-class LCA	-109201	218223	218936	218650	5305	5631	1.0
8-class LCA	-108947	218101	**218918**	218590	5157	5618	1.0
9-class LCA	-108897	218026	218945	218576	5056	5605	1.0
4-class LCA-RC	-109371	218851	219288	219113	6004	5666	0.0009

*All likelihood ratio tests for comparing k-class model to (k-1)-class model are statistically significant.

Figure 3.2: Latent classes at each time point

Table 3.3: Bivariate residuals under M_0 and M_1 at three time points

Item pair	T1		T2		T3	
	M0	M1	M0	M1	M0	M1
Self-rated health $\longleftrightarrow$ Social functioning	8.19	18.62	5.79	15.35	11.63	24.11
Self-rated health $\longleftrightarrow$ Cognitive functioning	0.78	4.98	0.62	4.54	0.23	2.60
Self-rated health $\longleftrightarrow$ ADL	11.49	11.91	4.53	5.01	9.27	10.08
Self-rated health $\longleftrightarrow$ IADL	1.16	0.72	1.94	1.58	1.64	1.28
Self-rated health $\longleftrightarrow$ GALI	14.90	11.91	14.66	11.66	14.92	12.30
Self-rated health $\longleftrightarrow$ Morbidity	2.27	2.15	1.51	1.49	2.20	2.19
Self-rated health $\longleftrightarrow$ Depression	6.25	8.46	11.27	13.35	8.94	10.82
Social functioning $\longleftrightarrow$ Cognitive functioning	**293.76**	**0.03**	**232.81**	**0.03**	**199.93**	**0.00**
Social functioning $\longleftrightarrow$ ADL	9.14	3.88	11.23	5.67	18.25	11.04
Social functioning $\longleftrightarrow$ IADL	3.18	7.27	0.82	3.62	0.61	3.05
Social functioning $\longleftrightarrow$ GALI	17.62	9.80	11.20	5.65	21.84	13.71
Social functioning $\longleftrightarrow$ Morbidity	20.67	13.83	10.65	6.24	8.57	5.07
Social functioning $\longleftrightarrow$ Depression	1.68	1.38	0.64	0.76	0.00	0.24
Cognitive functioning $\longleftrightarrow$ ADL	1.53	0.65	2.22	0.67	2.23	0.85
Cognitive functioning $\longleftrightarrow$ IADL	16.94	20.44	14.09	16.97	11.92	14.86
Cognitive functioning $\longleftrightarrow$ GALI	21.59	13.63	14.93	8.21	19.12	11.56
Cognitive functioning $\longleftrightarrow$ Morbidity	8.85	5.40	9.72	6.60	4.40	2.39
Cognitive functioning $\longleftrightarrow$ Depression	**26.42**	**0.10**	**21.88**	**0.09**	**34.08**	**0.04**
ADL $\longleftrightarrow$ IADL	7.06	5.62	5.97	4.68	3.90	3.14
ADL $\longleftrightarrow$ GALI	16.57	14.44	7.38	5.80	9.98	7.90
ADL $\longleftrightarrow$ Morbidity	2.94	2.68	1.72	1.36	2.75	2.07
ADL $\longleftrightarrow$ Depression	3.61	5.52	2.48	3.81	0.06	0.35
IADL $\longleftrightarrow$ GALI	1.74	1.60	1.22	0.88	1.51	1.26
IADL $\longleftrightarrow$ Morbidity	2.69	2.37	1.66	1.56	1.39	1.37
IADL $\longleftrightarrow$ Depression	0.67	1.77	0.09	0.66	0.36	1.37
GALI $\longleftrightarrow$ Morbidity	17.30	12.89	19.65	14.74	13.42	9.88
GALI $\longleftrightarrow$ Depression	0.83	0.66	2.30	1.98	1.97	1.81
Morbidity $\longleftrightarrow$ Depression	7.20	7.58	3.85	4.20	0.08	0.10

Table 3.4: Probabilities of health indicators per frailty profiles obtained from unconditional LCA model M_1

	Relatively Healthy			Pre-frail			Independent frail			Dependent frail		
	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
Class Size	0.39	0.40	0.41	0.38	0.37	0.38	0.13	0.11	0.10	0.10	0.11	0.12
Self-rate health												
Good or better	0.96	0.96	0.95	0.41	0.39	0.36	0.00	0.00	0.00	0.08	0.09	0.09
Fair	0.03	0.04	0.05	0.58	0.59	0.62	0.42	0.43	0.41	0.30	0.31	0.34
Poor	0.00	0.00	0.00	0.01	0.02	0.02	0.57	0.57	0.59	0.62	0.61	0.57
Social functioning												
Good	0.40	0.42	0.42	0.21	0.20	0.22	0.11	0.10	0.11	0.03	0.04	0.05
Poor	0.60	0.58	0.58	0.79	0.80	0.78	0.89	0.90	0.89	0.97	0.96	0.95
Cognitive functioning												
No impairment	0.54	0.58	0.60	0.36	0.38	0.39	0.26	0.29	0.34	0.11	0.12	0.15
One impairment	0.35	0.33	0.30	0.41	0.39	0.40	0.42	0.40	0.39	0.29	0.28	0.31
Two impairments	0.11	0.09	0.10	0.23	0.22	0.21	0.32	0.30	0.27	0.61	0.59	0.54
ADL limitations												
No	0.99	0.99	0.99	0.91	0.91	0.90	0.76	0.74	0.76	0.18	0.16	0.19
Yes	0.01	0.01	0.01	0.09	0.09	0.10	0.24	0.26	0.24	0.82	0.84	0.81
IADL limitations												
No	0.99	1.00	0.99	0.95	0.94	0.94	0.93	0.91	0.95	0.09	0.08	0.08
Yes	0.01	0.00	0.01	0.05	0.06	0.06	0.07	0.09	0.05	0.91	0.92	0.92
GALI												
Not limited	0.85	0.86	0.84	0.32	0.33	0.29	0.04	0.02	0.03	0.02	0.02	0.03
Limited but not severe	0.14	0.13	0.15	0.59	0.57	0.59	0.41	0.42	0.39	0.19	0.18	0.20
Severely limited	0.01	0.01	0.01	0.09	0.09	0.12	0.55	0.56	0.58	0.78	0.80	0.77
Morbidity												
None	0.45	0.41	0.39	0.13	0.14	0.13	0.07	0.07	0.06	0.11	0.12	0.12
1 disease	0.35	0.37	0.36	0.33	0.33	0.30	0.18	0.18	0.19	0.22	0.23	0.23
$\geq$ 2 diseases	0.20	0.22	0.25	0.53	0.54	0.56	0.76	0.75	0.76	0.67	0.65	0.66
Depression												
No	0.90	0.91	0.91	0.70	0.70	0.70	0.39	0.37	0.37	0.27	0.28	0.32
Yes	0.10	0.09	0.09	0.30	0.30	0.30	0.61	0.63	0.63	0.73	0.72	0.68

Table 3.5: Quality of classification obtained from unconditional LCA model M_1

	T1	T2	T3
AvePP (%)[1]			
Relatively Healthy	82.58	87.34	88.72
Pre-frail	86.96	80.33	79.32
Independent Frail	80.22	78.45	86.33
Dependent Frail	91.35	90.38	92.56
Relative entropy	0.72	0.72	0.73

[1] Average posterior class probability.

Table 3.6: Bivariate residuals for the covariates obtained by including one at a time in the M_1 model

Time	Independent	Self-rate health	Social functioning	Cognitive functioning	ADL	IADL	GALI	Morbidity	Depression
T1	Age	16.26	2.73	184.09	2.54	53.02	8.33	7.71	7.32
	Gender	8.10	4.83	89.81	3.32	0.03	9.65	1.31	495.27
T2	Age	10.59	7.94	139.89	0.08	24.56	11.12	6.42	0.01
	Gender	5.49	0.05	66.70	3.13	0.02	9.29	2.06	371.63
T3	Age	10.29	5.29	90.42	0.74	34.57	4.66	2.09	3.58
	Gender	4.08	2.42	56.89	1.66	0.50	3.78	1.65	289.03

Table 3.7: Conditional probabilities of health indicators per frailty profiles in the LCA model including direct effects of covariates on indicators M_2.

	Relatively Healthy			Pre-frail			Independent frail			Dependent frail		
	T0	T1	T2	T1	T2	T3	T1	T2	T3	T1	T2	T3
Class Size	0.40	0.40	0.41	0.39	0.38	0.38	0.13	0.12	0.10	0.09	0.10	0.11
Self-rate health												
Good or better	0.96	0.95	0.94	0.41	0.41	0.35	0.01	0.00	0.00	0.08	0.09	0.08
Fair	0.04	0.05	0.06	0.57	0.57	0.62	0.40	0.43	0.37	0.29	0.30	0.34
Poor	0.00	0.00	0.00	0.02	0.02	0.02	0.59	0.56	0.63	0.63	0.61	0.58
Social functioning												
Good	0.38	0.41	0.40	0.22	0.22	0.23	0.11	0.10	0.10	0.03	0.05	0.06
Poor	0.62	0.59	0.60	0.78	0.78	0.77	0.89	0.90	0.90	0.97	0.95	0.94
Cognitive functioning												
No impairment	0.53	0.57	0.59	0.37	0.40	0.41	0.26	0.29	0.33	0.11	0.13	0.16
One impairment	0.35	0.33	0.31	0.41	0.38	0.39	0.42	0.40	0.39	0.29	0.29	0.31
Two impairments	0.12	0.10	0.11	0.22	0.21	0.21	0.33	0.31	0.28	0.60	0.59	0.53
ADL limitations												
No	0.99	0.99	0.99	0.91	0.91	0.89	0.72	0.73	0.70	0.17	0.14	0.19
Yes	0.01	0.01	0.01	0.09	0.09	0.11	0.28	0.27	0.30	0.83	0.86	0.81
IADL limitations												
No	0.99	1.00	0.99	0.95	0.94	0.93	0.92	0.88	0.97	0.01	0.07	0.00
Yes	0.01	0.00	0.01	0.05	0.06	0.07	0.08	0.12	0.03	0.99	0.94	1.00
GALI												
Not limited	0.86	0.88	0.85	0.31	0.32	0.26	0.04	0.02	0.02	0.02	0.01	0.02
Limited but not severe	0.13	0.11	0.14	0.61	0.59	0.61	0.39	0.41	0.35	0.18	0.17	0.20
Severely limited	0.01	0.01	0.01	0.09	0.09	0.13	0.58	0.57	0.63	0.80	0.81	0.78
Morbidity												
None	0.45	0.42	0.39	0.12	0.13	0.12	0.07	0.07	0.06	0.11	0.12	0.12
1 disease	0.35	0.37	0.36	0.33	0.33	0.30	0.18	0.18	0.19	0.22	0.23	0.22
$\geq$ 2 diseases	0.20	0.21	0.25	0.55	0.54	0.58	0.76	0.75	0.75	0.67	0.65	0.66
Depression												
No	0.90	0.91	0.91	0.70	0.71	0.70	0.38	0.37	0.35	0.27	0.28	0.32
Yes	0.10	0.09	0.09	0.30	0.29	0.30	0.62	0.63	0.65	0.73	0.72	0.68

Table 3.8: Covariate effects (odds ratio (OR)) in the LCA model with direct effects M_2.

Covariate	Latent class	T1	T2	T3
Age	Relatively Healthy (ref)	1.00	1.00	1.00
	Pre-frail	1.07	1.07	1.06
	Independent Frail	1.09	1.09	1.08
	Dependent Frail	1.17	1.18	1.18
Female	Relatively Healthy (ref)	1.00	1.00	1.00
	Pre-frail	1.33	1.33	1.33
	Independent Frail	1.33	1.37	1.27
	Dependent Frail	1.51	1.55	1.61

All p-values of Wald tests < 0.0001.

Table 3.9: Fit indices of measurement invariance testing

	Log-likelihood	BIC	AIC	SABIC
Measurement invariance	-485092	971116	970345	970858
Measurement non-invariance	-474269	951243	949007	950496

Table 3.10: Transition probabilities based on unconditional model

	T2 latent class					
	Relatively Healthy	Pre-frail	Independent Frail	Dependent Frail	Deceased	LTF [1]
T1 latent class						
Relatively Healthy	**0.721**	0.077	0.005	0.004	0.014	0.179
Pre-frail	0.049	**0.628**	0.054	0.047	0.039	0.183
Independent Frail	0.002	0.132	**0.460**	0.139	0.094	0.173
Dependent Frail	0.001	0.012	0.050	**0.508**	0.232	0.197
	T3 latent class					
	Relatively Healthy	Pre-frail	Independent Frail	Dependent Frail	Deceased	LTF
T2 latent class						
Relatively Healthy	**0.750**	0.085	0.003	0.004	0.014	0.144
Pre-frail	0.032	**0.697**	0.063	0.041	0.037	0.129
Independent Frail	0	0.103	**0.495**	0.168	0.088	0.146
Dependent Frail	0	0.041	0.047	**0.515**	0.253	0.145

[1] Lost to follow-up.

[2] Death and LTF are absorbing states.

[3] Values in diagonal (in bold) present the probabilities of stayers. Values in the upper triangular represent the probabilities of progressing to a more frail and disabled class. Values in the lower triangular represent the probabilities of reversing to a better health class.

Table 3.11: Transition probabilities from T1 to T3 based on unconditional model

With LTF included						
			T3 latent class			
	Relatively Healthy	Pre-frail	Independent Frail	Dependent Frail	Deceased	LTF [1]
T1 latent class						
Relatively Healthy	**0.543**	0.116	0.010	0.009	0.028	0.294
Pre-frail	0.057	**0.449**	0.069	0.059	0.080	0.286
Independent Frail	0.006	0.145	**0.243**	0.154	0.175	0.277
Dependent Frail	0.001	0.034	0.049	**0.271**	0.365	0.280

With LTF excluded					
		T3 latent class			
Relatively Healthy	Pre-frail	Independent Frail	Dependent Frail	Deceased	
T1 latent class					
Relatively Healthy	**0.769**	0.164	0.014	0.013	0.040
Pre-frail	0.080	**0.629**	0.097	0.083	0.112
Independent Frail	0.008	0.201	**0.336**	0.213	0.242
Dependent Frail	0.001	0.047	0.068	**0.376**	0.507

[1] Lost to follow-up.

[2] Values in diagonal (in bold) present the probabilities of stayers. Values in the upper triangular represent the probabilities of progressing to a more frail and disabled class. Values in the lower triangular represent the probabilities of reversing to a better health class.

Table 3.12: Covariate effects (odds ratio (OR)) on the transition to a state versus staying in the same state

Covariate	**Latent class at time *T***	**Latent class at time *T+1***					
		Relatively Healthy	Pre-frail	Independent Frail	Dependent Frail	Deceased	LTF [1]
Age	Relatively Healthy	**1.00**	1.08*	0.98	1.20*	1.10*	0.99
	Pre-frail	0.95*	**1.00**	1.02*	1.15*	1.13*	1.01*
	Independent Frail	1.02	0.98*	**1.00**	1.08*	1.05*	1.01
	Dependent Frail	1.13	1.01	0.93*	**1.00**	1.07*	1.01
Female	Relatively Healthy	**1.00**	0.93	0.63	0.85	0.61*	0.92*
	Pre-frail	0.92	**1.00**	0.90	1.02	0.66*	0.93
	Independent Frail	0.03	0.97	**1.00**	1.03	0.35*	0.89
	Dependent Frail	0.01	1.06	2.04*	**1.00**	0.48*	0.96

[1] Lost to follow-up.
[2] Reference class varies with the origin state (in bold).
[3] *p < 0.05

Table 3.13: Overall transition probabilities, adjusting for time-heterogeneity, baseline age and gender

Latent class at time *T*	**Latent class at time *T+1***					
	Relatively Healthy	Pre-frail	Independent Frail	Dependent Frail	Deceased	LTF [1]
Relatively Healthy	**0.742**	0.071	0.005	0.004	0.014	0.164
Pre-frail	0.059	**0.654**	0.044	0.045	0.038	0.159
Independent Frail	0.000	0.145	**0.443**	0.154	0.091	0.165
Dependent Frail	0.001	0.029	0.045	**0.509**	0.244	0.171

[1] Lost to follow-up.
[2] Death and LTF are absorbing states.
[3] Values in diagonal (in bold) present the probabilities of stayers. Values in the upper triangular represent the probabilities of progressing to a more frail and disabled class. Values in the lower triangular represent the probabilities of reversing to a better health class.

3.3.3 Covariates in LCA

Table 3.6 reports BVRs for baseline age and gender obtained by including one at a time in the M_1 model. It shows that age has direct effects on cognitive functioning and IADL, and gender has direct effects on cognitive function and depression, as corresponding BVRs are substantially larger than the rest. Consequently, we specified and estimated a model (M_2) with baseline age and gender as covariates and included the encountered direct effects. For all three occasions, comparing the solutions of M_1 and M_2, there are no significant shifts in the classes once covariates are included. Thus, because of the stability of the emergent classes, accompanied by good quality of classification, we proceeded with the three-step LTA in a usual way and used the classification obtained from M_1. Table 3.6 reports BVRs for baseline age and gender obtained by including one at a time in the M_1 model. It shows that age has direct effects on cognitive functioning and IADL, and gender has direct effects on cognitive function and depression, as corresponding BVRs are substantially larger than the rest. Consequently, we specified and estimated a model (M_2) with baseline age and gender as covariates and included the encountered direct effects. For all three occasions, comparing the solutions of M_1 and M_2, there are no significant shifts in the classes once covariates are included. Thus, because of the stability of the emergent classes, accompanied by good quality of classification, we proceeded with the three-step LTA in a usual way and used the classification obtained from M_1.

Baseline age and gender consistently proved to be significant predictors of a class assignment (see Table 3.8). Older individuals were more likely to be in a more compromised health state. Gender differentiated Dependent Frail from other classes, with females more likely to be in Dependent Frail state. No clear gender differences were found between Pre-frail and Dependent Frail; however, females were about 1.3 times more likely to be in these classes instead of the Relatively Healthy class.

3.3.4 LTA

A comparison of fit statistics of models with and without measurement invariance is shown in Table 3.9. Results indicate the model with uniform DIF significantly improved model fit. This implies the item probabilities of the four classes may be different across time. However, given the remarkable consistency in the item profile plots across time, it is reasonable to assume measurement invariance for practical applications [144].

Table 3.10 presents the transition probabilities describing patterns of changes from T_1 to T_2, and from T_2 to T_3 based on the unconditional LTA model. Overall, the results indicate that the Relative Healthy individuals were very unlikely to progress to Frail states (i.e., Independent Frail and Dependent Frail), and individuals in Frail states were also improbable to reverse to Relative Healthy states (less than 0.5%). The probability of dying within two years positively correlated with the severity of frailty, while the LTF rate after two years was roughly equivalent across all classes. Specifically, from T_1 to T_2, 50.8% of the individuals in the Dependent Frail class were predicted to remain in that state, 23.2% were predicted to die within two years, and about 6% transitioned to less disabled states: 5.0% to Independent Frail and 1.2% to Pre-frail. Among the Independent Frail individuals, 46.0% were expected to remain in the state, 13.2% reversed to Pre-frail, 13.9% transitioned to Dependent Frail, and 9.4% died. For the individuals in the Pre-frail class, 62.8% were predicted to stay in the same state, 3.9% died, and the probabilities of transitioning to other states were relatively equivalent, around 5%. The Relative Healthy individuals had a high probability (72.1%) of remaining healthy and a probability of 7.7% to progress to Pre-frail, and only 1.4% of them died within two years.

Frailty progression from T_2 to T_3 has similar patterns, with quantitative differences. Individuals were more likely to stay in the origin state or transition to a more compromised health state, and were less likely to reverse to an improved health state, except among the Dependent Frail individuals whose probability of transitioning to Pre-frail increased to 4.1% (as opposed to 1.2% from T_1 to T_2). In addition, the mortality rate of the Dependent

Frail individuals increased 25.3%. These differences must be considered in light of the decreased completing risk of being LTF.

The transition probabilities from T_1 to T_3 were obtained by multiplying transition matrices T_1T_2 and T_2T_3, and is presented in Table 3.11. The 4-year transition exhibited a similar but more pronounced pattern. After 4 years, about one-third of participants in each class were lost to follow up. Transition probabilities of those remaining in the study is also provided in the lower part of the table. Most strikingly, the Dependent Frail individuals had very poor 4-year prognosis, with 50.7% deceasing and 37.6% staying in the same class. The Independent Frail class also demonstrated undesirable progression (24.2% died and 21.3% transitioned to Dependent Frail); however, 20.9% reversed to a better health state, although only 0.8% returned to the Relatively Healthy class.

Table 3.12 and 3.13 show the effects of covariates on the transition probabilities between states and the overall covariate-adjusted transition probabilities in the LTA model, including age and gender. There was a consistent effect of age for all classes, indicating that older people were significantly more likely to transition to more disabled states and death (ORs > 1, $p < 0.05$) and were significantly less likely to transition to less disabled states (ORs < 1, $p < 0.05$). Females in all classes were significantly less likely to die within two years (ORs < 1, $p < 0.05$), and females in the Dependent Frail class were significantly more likely to reverse to the Independent Frail class (OR=2.04, $p < 0.05$). Age and gender, in general, had no or minor effects on the probability of being LTF.

3.4 Discussion

By considering frailty as an unobserved, latent variable, this study aimed to explore whether distinct frailty profiles exist in the community-dwelling individuals aged 60 or older and whether there were meaningful transitions among the profiles over time. Results showed that four probable subgroups with stable underlying structures sufficiently captured the heterogeneity of frailty in our sample while maintaining stability and interpretability, and

that individuals' health states were sensitive to change over three occasions two years apart.

The same four frailty profiles emerged across all three studied occasions, and they are better described according to the degree, rather than type, of frailty. Our ordinal classification of frailty is consonant with Fried's frailty phenotype [28], with frail state further classified into two subgroups based on the degree of disability. Being disabled and dependent can be an outcome of frailty as well as a manifestation of severe frailty, indicating the need for long-term care. In general population samples, previous works using LCA have revealed various frailty typologies with 3-7 classes [14, 118, 119, 159, 160], but the relative ordering of classes is consonant with our solution. Especially, despite using different indicators, the four frailty classes characterized in this study had very similar meanings to those identified by Liu and colleagues [161].

To evaluate the validity of emergent classes, the study incorporated age and gender as covariates. The inclusion of these covariates in the model is justified by the definition of frailty as an age-related deterioration syndrome, and the well-documented male-female health-survival paradox [33]. In line with these justifications, our results indicate that females and older individuals were more likely to be in more compromised health states. Further, the 2-year mortality risk has been shown to increase with the severity of compromised states in the LTA results. Taken together, the emergent latent classes are clinically valid and meaningful.

Latent class analysis of transition patterns between occasions two years apart revealed a predominant tendency for state stability or dying. Across all latent classes, a greater portion of individuals (at least 46%) stayed in the same class they were two years ago; especially, up to about 70% of the Relative Healthy continued to maintain healthy. Nevertheless, relatively high probabilities of transitions were found. Consistent with prior works [11, 14], most transitions occurred between adjacent states - specifically, the likelihood of transitioning between Relatively Health and Frail states (i.e., Independent Frail and Dependent Frail) was extremely rare. This marks Pre-frail as the transition

threshold in the final pathway to frailty. In addition, we found pretty noticeable probabilities of transitioning to a better health state, which is in agreement with the theory of frailty reversibility [11, 27, 162, 163].

However, the transition patterns are not stationary - as the study sample got older, the probabilities of deteriorating transitions increased, and the probabilities of ameliorating transitions generally decreased. In addition, the model with covariates showed that the older individuals were, the more likely they progressed to compromised health states or death. Together, these results suggest the acceleration of physiological reserves depletion in the ageing process and the resultant failure of homeostatic mechanism [5, 6]. The exception of the increased probability converting from Dependent Frail to Pre-Frail ($T_2 \rightarrow T_3$ in comparison with $T_1 \rightarrow T_2$) remains an open question but can be partly explained by attrition bias, in which healthier people were more likely to stay in the survey.

The classification provides more prognostic value on a longer time frame. The Dependent Frail class appears had very poor prognosis, appearing as end-of-life health state. Half of the Dependent Frail individuals dying within 4 years and the majority of survivors remaining in this class. Although the Independent Frail individuals also had undesirable prognosis with high probabilities of mortality and progressing to Dependent Frail, there was a considerable likelihood of transitioning to an improved health state (about 21%, mostly to the Pre-Frail class). The differences in transition patterns of the Dependent Frail and Independent Frail classes suggest that functional limitation has significant prognostic value of the elder's health.

Females exhibited better tolerance to health problems than their male counterparts with a lower 2-year mortality risk for all latent classes, indicative of the survival part of the gender paradox [33]. Especially, we observed a higher likelihood of the reversal from Dependent Frail to Independent Frail in females. Although the driving forces behind the reversal are unclear, this gender difference can be explained by the theory that females have greater physiological reserves [40], making them more resilient in the face of severe

frailty. Another possible explanation is differences in social assets and health-related behaviors between males and females. Females have been shown to be more active in help-seeking and healthcare utilization [164, 165], and experience a slower decline in social connectedness [166]; hence, they may receive more medical and non-medical supports for health recovery.

The current study provides empirical evidence supporting the ordinal classification of frailty embedded in the Fried's phenotype model but also highlights that three states are not sufficient to capture the heterogeneity of frailty. Although the underlying nature of an ordinal classification basically is continuous, it offers discriminatory power for old adults with different risk levels of homeostasis failure and poor health outcomes. Thus, in longitudinal trajectory of frailty, the ordinal classification is particularly useful in capturing critical changes in individuals' health state which can disproportionately cause adverse health outcomes. Furthermore, to our best knowledge, this is the first study to explore transition patterns of frailty in the community-dwelling population aged 60 or older, revealing the potential of frailty reversal and the effects of age and gender. As the study analyzed data from nationally representative samples of twelve European countries, its findings are generalizable to the general population of these countries.

Nevertheless, it is also crucial to keep in mind the limitations of the study. First, our findings must be interpreted in consideration of the inherent drawbacks of LCA and LTA models. Model selection in mixture models is a challenging task, as little is known about the statistical power of those models. For very large samples as in our study, available fit statistics may be ineffective in measuring and comparing models' fit, and model selection is best conducted if emphasis is placed on model interpretability [128]. In addition, although a new feature in Latent GOLD accounting for differential item functioning (DIF) in the three-step LTA model was introduced in a recent article [151], the feature has yet to be available in the currently released version. Without accounting for DIF, our analysis left a certain possibility for bias in the results. Another limitation pertains to attrition. Unable to control

for other individual effects other than age and gender, we can not exclude selection bias. However, the proportions of LTF individuals in frailty profiles did not differ significantly and capturing LTF individuals in LTA as absorbing states allowed us to limit attrition bias.

3.5 Conclusion

Within a person-centered framework, this study encompassed multiple dimensions of heath into a small number of health profiles that can explain the inter-relationships between health dimensions. Our classification of individuals into pragmatically meaningful groups can be useful for clinical practice, ageing research, and policy applications. In addition, the study demonstrated a transition pattern between resultant profiles over time, highlighting the potential for frailty reversal. Future studies, however, are necessary to shed light on the frailty reversal mechanism. Gender-related difference in frailty progression was also found, reflecting the well-documented male-female health-survival paradox.

CHAPTER 4

CONCLUSION

Frailty is a common geriatric syndrome, characterized by decreased adaptability to stressors and increased vulnerability to adverse health outcomes. Frailty is not simply about ageing, but is where ageing has taken its toll. The risk of becoming frail, thus, is regulated by genetic and environmental factors via epigenetic mechanisms. This makes the older population greatly heterogenous with respect to frailty. Therefore, understanding of frailty profiles as well as frailty trajectories is useful for tailoring ageing health policies and interventions.

The first study (Chapter 2) compared frailty trajectories of older adults across eleven European countries. The study took an age-cohort-period approach to decompose frailty trends to age and cohort effects. We found universal parabolic age trends, with an accelerating increase in frailty level after the age of 75. The growth rate of frailty level in Italy, Germany and Switzerland is slower than in other countries. The cohort effects, however, are country-specific. The Swiss, Swedish and Danish elderly appeared the healthiest, followed by the older population in Belgium, France, Germany and Austria; the elderly in Spain and Italy seemed the least healthy. With respect to gender effect, women were found more frail than men at any age, and the gender gap was narrowed in more recent cohorts. Our findings add new insights of a cross-national comparison of frailty trend over ages and of frailty trend over birth cohorts. The findings are useful in evaluating country-specific contextual effects on frailty trend, which allows better localization of ageing health policies and interventions.

The second study (Chapter 3) took a latent-class modeling approach to model the heterogeneity of frailty in the elderly population. Latent class analysis allowed us to encompass multiple dimensions of heath into four health profiles that can explain the

inter-relationships between health dimensions. Our classification is based on the degree of frailty rather than the type of frailty, and yields pragmatically meaningful groups. The classification can be useful for clinical practice, ageing research as well as policy applications. Subsequently, latent transition analysis demonstrated a transition pattern between resultant profiles over time. There was a predominant tendency for state stability or dying. Most of transitions were made between adjacent states, with transitions between non-adjacent states being extremely rare. Noteworthily, we found a quite noticeable proportion of transitioning to better states, highlighting the potential for frailty reversal. Regarding gender effect, women showed better tolerance to poor health and greater likelihood of frail reversal.

Overall, the two studies present complementary perspectives of frailty trajectories in the European older population. While the first study considers population-level frailty trends , the second one examines the individual-level progression of frailty. The former provides a big picture of frailty trends, which can be helpful in assessing and planning interventions. The latter can find its application in clinical practice, ageing research as well as policy applications. In considering gender effect, the two studies together reflect the long described male-female health-survival paradox. Given that data were drawn from nationally representative samples, our findings are greatly generalizable.

Several questions raised by our studies are worth exploring in future studies. In the first study, we observed that gender differentials in frailty attenuated in younger successive cohorts at the expense of men of recent cohorts having higher frailty scores. Despite of our attempt to explain it by survivor healthy effect, the observation calls for future studies. In addition, the second study found a decent proportion of transitions to better health states. It will be of great importance to explore determinants and mechanisms of frailty reversal.

Appendices

APPENDIX A

STUDY 1: ITEMS USED TO CONSTRUCT FRAILTY INDEX IN THE SHARE

Topic/Variable	**Response cut-off point**
General health:	
Self-perceived health	Excellent = 0, Very good = 0.25, Good = 0.5, Fair = 0.75, Poor = 1
Physical measures:	
BMI: weight/height^2 (Kg/m^2)	$18.5 \leq$ BMI ≤ 25 = 0 (Normal) $25 <$ BMI < 30 = 0.5 (Overweight) BMI < 18.5 = 1 (Underweight) BMI ≥ 30 = 1 (Obese)
Grip strength (Kg): (Left + Right hand)/2	Men: BMI ≤ 24 and strength ≤ 29 = 1 BMI 24.1–26 and strength ≤ 30 = 1 BMI 26.1–28 and strength ≤ 30 = 1 BMI >28 and strength ≤ 32 = 1 Women: BMI ≤ 23 and strength ≤ 17 = 1 BMI 23.1–26 and strength ≤ 17.3 = 1 BMI 26.1–29 and strength ≤ 18 = 1 BMI >29 and strength ≤ 21 = 1
Comorbidities:	
Chronic lung disease	Yes = 1, No = 0
Osteoporosis	Yes = 1, No = 0
Parkinson's disease	Yes = 1, No = 0

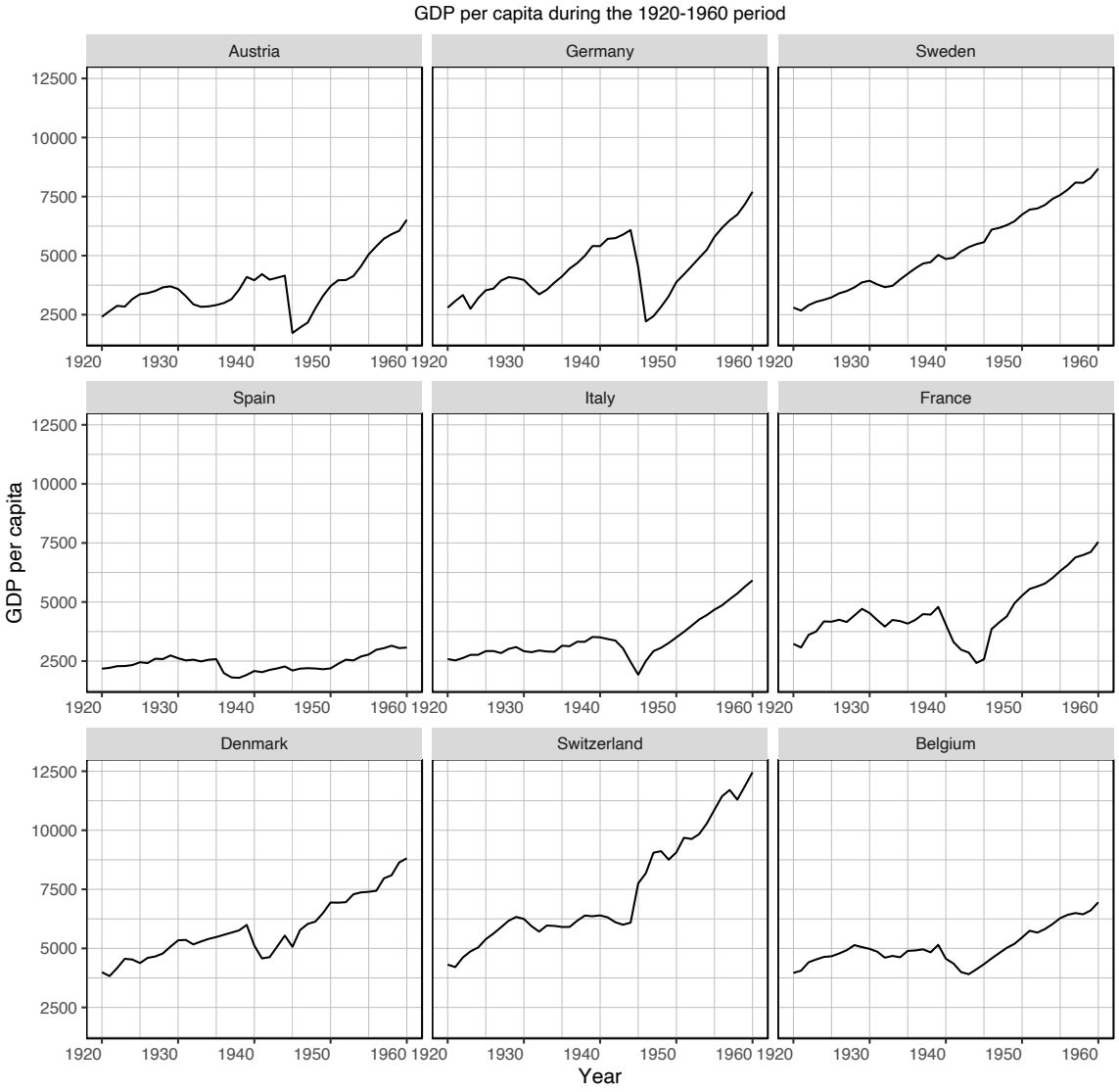
Diabetes mellitus or high blood sugar	Yes = 1, No = 0
Asthma	Yes = 1, No = 0
Cancer	Yes = 1, No = 0
Cataracts	Yes = 1, No = 0
High blood cholesterol	Yes = 1, No = 0
Heart attack	Yes = 1, No = 0
Stroke or CVD	Yes = 1, No = 0
High blood pressure	Yes = 1, No = 0
Arthritis	Yes = 1, No = 0
Stomach or duodenal ulcer	Yes = 1, No = 0
Hip or femoral fracture	Yes = 1, No = 0
Mobility Limitations:	
Climbing several flights of stairs	Yes = 1, No = 0
Walking 100 m	Yes = 1, No = 0
Sitting for about 2 hours	Yes = 1, No = 0
Getting up from a chair	Yes = 1, No = 0
Climbing several flights of stairs without resting	Yes = 1, No = 0
Climbing one flight of stairs without resting	Yes = 1, No = 0
Stooping/kneeling/crouching	Yes = 1, No = 0
Reaching or extending arms	Yes = 1, No = 0
Pulling/pushing large objects	Yes = 1, No = 0
Lifting/carrying weights >5 kg	Yes = 1, No = 0
Picking up a small coin from table	Yes = 1, No = 0
Functional Limitations:	
Dressing, including shoes and socks	Yes = 1, No = 0
Walking across a room	Yes = 1, No = 0
Bathing/showering	Yes = 1, No = 0

Eating, such as cutting up your food	Yes = 1, No = 0
Getting in or out of bed	Yes = 1, No = 0
Using the toilet, including getting up or down	Yes = 1, No = 0
Using a map to figure out how to get around in a strange place	Yes = 1, No = 0
Preparing a hot meal	Yes = 1, No = 0
Shopping for groceries	Yes = 1, No = 0
Making telephone calls	Yes = 1, No = 0
Taking medications	Yes = 1, No = 0
Doing work around house/garden	Yes = 1, No = 0
Managing money, such as paying bills and keeping track of expenses	Yes = 1, No = 0
Signs/symtomps:	
Eyesight for seeing things at a distance	Excellent = 0, Very good = 0.25, Good = 0.5, Fair = 0.75, Poor = 1
Hearing problems	Excellent = 0, Very good = 0.25, Good = 0.5, Fair = 0.75, Poor = 1
Bothered by: falling down	Yes = 1, No = 0
Bothered by: fear of falling down	Yes = 1, No = 0
Bothered by: dizziness, faints or blackouts	Yes = 1, No = 0
Cognition:	
Orientation	score $<$ 2/4 = 1
Mathematical performance	score $<$ 3/4 =1
Immediate recall test	score $<$ 5 = 1
Delayed recall test	score $<$ 4 =1
Verbal fluency test	score $<$ 15 =1
Mentality:	

EURO-D score	score $\geq$ 4 = 1

APPENDIX B

STUDY 1: GDP PER CAPITA DURING THE 1920-1960 PERIOD



Source: The Maddison Project. Retrieved from: http://www.ggdc.net/maddison/historical_statistics/horizontal-file_03-2007.xls

APPENDIX C

STUDY 2: LATENT GOLD SYNTAX FOR LCA

Input: Cross-sectional data at each time point.

```
options
   maxthreads=6;
   algorithm
      tolerance=1e-008 emtolerance=0.01 emiterations=250 nriterations=50 ;
   startvalues
      seed=0 sets=50 tolerance=1e-005 iterations=200;
   bayes
      categorical=1 variances=1 latent=1 poisson=1;
   montecarlo
      seed=0 sets=0 replicates=500 tolerance=1e-008;
   quadrature  nodes=10;
   missing  includedependent; /*to evoke FMIL*/
   output
      parameters=first
betaopts=wl standarderrors profile probmeans=posterior
      loadings bivariateresiduals estimatedvalues=model
      reorderclasses;
variables
   dependent sph nominal, socialfunc nominal, cogfunc nominal,
      adl nominal, iadl nominal, gali nominal, morbidity nominal,
      depress nominal;
   latent
      Cluster nominal 4;
equations
   Cluster <- 1;
   sph <- 1 + Cluster;
```

```
socialfunc <- 1 + Cluster;
cogfunc <- 1 + Cluster;
adl <- 1 + Cluster;
iadl <- 1 + Cluster;
gali <- 1 + Cluster;
morbidity <- 1 + Cluster;
depress <- 1 + Cluster;
```

APPENDIX D

STUDY 2: LATENT GOLD SYNTAX FOR LCA, RELAXING LOCAL INDEPENDENCE ASSUMPTION

Input: Cross-sectional data at each time point.

```
options
   maxthreads=6;
   algorithm
      tolerance=1e-008 emtolerance=0.01 emiterations=250 nriterations=50 ;
   startvalues
      seed=0 sets=50 tolerance=1e-005 iterations=200;
   bayes
      categorical=1 variances=1 latent=1 poisson=1;
   montecarlo
      seed=0 sets=0 replicates=500 tolerance=1e-008;
   quadrature  nodes=10;
   missing  includedependent;
   output
      parameters=first
betaopts=wl standarderrors profile probmeans=posterior
      loadings bivariateresiduals classification estimatedvalues=model
      reorderclasses;
variables
   dependent sph nominal, socialfunc nominal, cogfunc nominal,
      adl nominal, iadl nominal, gali nominal, morbidity nominal,
      depress nominal;
   latent
      Cluster nominal 4;
equations
   Cluster <- 1;
```

```
sph <- 1 + Cluster;
socialfunc <- 1 + Cluster;
cogfunc <- 1 + Cluster;
adl <- 1 + Cluster;
iadl <- 1 + Cluster;
gali <- 1 + Cluster;
morbidity <- 1 + Cluster;
depress <- 1 + Cluster;
cogfunc <-> socialfunc;
depress <-> cogfunc; /* adding residual correlation */
```

APPENDIX E

STUDY 2: LATENT GOLD SYNTAX FOR LCA, RELAXING LOCAL INDEPENDENCE ASSUMPTION. CHECKING DIF WITH COVARIATE.

Input: Cross-sectional data at each time point.

```
options
   maxthreads=6;
   algorithm
      tolerance=1e-008 emtolerance=0.01 emiterations=250 nriterations=50 ;
   startvalues
      seed=0 sets=50 tolerance=1e-005 iterations=200;
   bayes
      categorical=1 variances=1 latent=1 poisson=1;
   montecarlo
      seed=0 sets=0 replicates=500 tolerance=1e-008;
   quadrature  nodes=10;
   missing  includedependent;
   output
      parameters=first
betaopts=wl standarderrors profile probmeans=posterior
      loadings bivariateresiduals classification estimatedvalues=model
      reorderclasses;
variables
   dependent sph nominal, socialfunc nominal, cogfunc nominal,
      adl nominal, iadl nominal, gali nominal, morbidity nominal,
      depress nominal;
   independent age;
   latent
      Cluster nominal 4;
equations
```

```
Cluster <- 1 + age;

sph <- 1 + Cluster;

socialfunc <- 1 + Cluster;

cogfunc <- 1 + Cluster;

adl <- 1 + Cluster;

iadl <- 1 + Cluster;

gali <- 1 + Cluster;

morbidity <- 1 + Cluster;

depress <- 1 + Cluster;

cogfunc <-> socialfunc;

depress <-> cogfunc;
```

APPENDIX F

STUDY 2: LATENT GOLD SYNTAX FOR LCA, RELAXING LOCAL INDEPENDENCE ASSUMPTION AND INCLUDING COVARIATES WITH DIRECT EFFECTS.

Input: Cross-sectional data at each time point.

```
options
   maxthreads=6;
   algorithm
      tolerance=1e-008 emtolerance=0.01 emiterations=250 nriterations=50 ;
   startvalues
      seed=0 sets=250 tolerance=1e-005 iterations=1000;
   bayes
      categorical=1 variances=1 latent=1 poisson=1;
   montecarlo
      seed=0 sets=0 replicates=500 tolerance=1e-008;
   quadrature  nodes=10;
   missing  includedependent;
   output
      parameters=first
betaopts=wl standarderrors profile probmeans=posterior
      loadings bivariateresiduals classification estimatedvalues=model
      reorderclasses;
variables
   dependent sph nominal, socialfunc nominal, cogfunc nominal,
      adl nominal, iadl nominal, gali nominal, morbidity nominal,
      depress nominal;
   independent age, gender;
   latent
      Cluster nominal 4;
```

```
equations
   Cluster <- 1 + age + gender;
   sph <- 1 + Cluster;
   socialfunc <- 1 + Cluster;
   cogfunc <- 1 + Cluster +age + gender;
   adl <- 1 + Cluster;
   iadl <- 1 + Cluster + age;
   gali <- 1 + Cluster;
   morbidity <- 1 + Cluster;
   depress <- 1 + Cluster + gender;
   cogfunc <-> socialfunc;
   depress <-> cogfunc;
```

APPENDIX G

STUDY 2: LATENT GOLD SYNTAX FOR STEP 1 AND 2 OF LTA, ASSUMING MEASUREMENT INVARIANCE

Input: All-wave data is presented in long-table format.

```
options
   maxthreads=6;
   algorithm
      tolerance=1e-008 emtolerance=0.01 emiterations=250 nriterations=50 ;
   startvalues
      seed=0 sets=50 tolerance=1e-005 iterations=200;
   bayes
      categorical=1 variances=1 latent=1 poisson=1;
   montecarlo
      seed=0 sets=0 replicates=500 tolerance=1e-008;
   quadrature  nodes=10;
   missing  includedependent;
   output
      parameters=first
betaopts=wl standarderrors profile probmeans=posterior
      loadings bivariateresiduals estimatedvalues=model reorderclasses;
variables
   dependent sph nominal, socialfunc nominal, cogfunc nominal, adl nominal,
      iadl nominal, gali nominal, morbidity nominal,
      depress nominal;
   latent
      Cluster nominal 6 knownclass=survival(0: 0 0 1 1 1 1, 1: 1 0 0 0 0 0,
      2: 0 1 0 0 0 0);
      /*absorbing states modeled by specifying as known classes */
equations
```

```
Cluster <- 1;
sph <- 1 + Cluster;
socialfunc <- 1 + Cluster;
cogfunc <- 1 + Cluster;
adl <- 1 + Cluster;
iadl <- 1 + Cluster;
gali <- 1 + Cluster;
morbidity <- 1 + Cluster;
depress <- 1 + Cluster;
cogfunc <-> socialfunc;
depress <-> cogfunc;
```

APPENDIX H

STUDY 2: LATENT GOLD SYNTAX FOR STEP 1 AND 2 OF LTA, ASSUMING MEASUREMENT NON-INVARIANCE

Input: All-wave data presented in long-table format.

```
options
   maxthreads=6;
   algorithm
      tolerance=1e-008 emtolerance=0.01 emiterations=250 nriterations=50 ;
   startvalues
      seed=0 sets=50 tolerance=1e-005 iterations=200;
   bayes
      categorical=1 variances=1 latent=1 poisson=1;
   montecarlo
      seed=0 sets=0 replicates=500 tolerance=1e-008;
   quadrature  nodes=10;
   missing  includedependent;
   output
      parameters=first
betaopts=wl standarderrors profile probmeans=posterior
      loadings bivariateresiduals estimatedvalues=model reorderclasses;
  outfile
'frailty_classification.sav' /*to save classification for Step 3 analysis*/
      classification      keep id, gender, age;
variables
   dependent sph nominal, socialfunc nominal, cogfunc nominal, adl nominal,
      iadl nominal, gali nominal, morbidity nominal,
      depress nominal;
   independent time nominal;
   latent
```

```
      Cluster nominal 6 knownclass=survival(0: 0 0 1 1 1 1, 1: 1 0 0 0 0 0,
      2: 0 1 0 0 0 0);
equations
   Cluster <- 1 + time;
   sph <- 1 + Cluster + time + Cluster*time;
   socialfunc <- 1 + Cluster + time + Cluster*time;
   cogfunc <- 1 + Cluster + time + Cluster*time;
   adl <- 1 + Cluster + time + Cluster*time;
   iadl <- 1 + Cluster + time + Cluster*time;
   gali <- 1 + Cluster + time + Cluster*time;
   morbidity <- 1 + Cluster + time + Cluster*time;
   depress <- 1 + Cluster + time + Cluster*time;
         cogfunc <-> socialfunc;
   depress <-> cogfunc;
```

APPENDIX I

STUDY 2: LATENT GOLD SYNTAX FOR STEP 3 OF LTA, ASSUMING A STATIONARY MARKOV MODEL.

Input: Output file from Step 1 and 2 of LTA.

```
options
   maxthreads=6;
   algorithm
      tolerance=1e-008 emtolerance=0.01 emiterations=250 nriterations=50 ;
   startvalues
      seed=0 sets=50 tolerance=1e-005 iterations=200;
   bayes
      categorical=1 variances=1 latent=1 poisson=1;
   montecarlo
      seed=0 sets=0 replicates=500 tolerance=1e-008;
   quadrature  nodes=10;
   missing  includeall;
   output
      parameters=first standarderrors profile estimatedvalues=model;
   step3 modal ml;
variables
   caseid id;
   independent time nominal, age, gender;
   latent
      State dynamic nominal posterior = ( Cluster#1 Cluster#2 Cluster#3
      Cluster#4 Cluster#5 Cluster#6 ) ;
equations
  State[=0] <- 1 + age + gender;
  State <- (~tra) 1 | State[-1] + (~tra) time|State[-1] + (~tra) age|State[-1]
  + (~tra) gender|State[-1];
```

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