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TRAJECTORY MODELS IN COGNITIVELY HEALTHY ELDERS

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"Quando ci si avvicina

ad un traguardo,

ci si rende conto del

viaggio intrapreso,

di tutti i momenti passati,
vissuti, superati,

e di chi e come,

gli è stato accanto."

Ottavia Eleonora Ferraro

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Abbreviations

ADL	Activities of Daily Living
ARC	Ageing Research Center
CI	Confidence Interval
DSM IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
GBTM	Group-Based Trajectory Models
InveCe.AB	Invecchiamento Cerebrale Abbiategrasso
MMSE	Mini Mental State Examination
RRR	Relative Risk Ratio
SD	Standard Deviation
SNAC-K	Swedish National Study in Aging and Care in Kungsholmen
WHO	World Health Organization

Abstract

The old-age population is increasing at a considerably faster rate than the world's total population [1]. According to the United Nation report (2017), currently Europe has the highest proportion of elderly people of all the continents, but it is remarkable that in 2050 there will be an increase in the number of people over 60 also in China, in some nations of Africa and in Latin America [2].

However, the increase in elderly people is notable because aging brings important changes in health status: cognitive and physical functioning, together with the degree of disability, are important indicators used to try to quantify the quality of health, in the later stages of life. Moreover aging is also frequently related to non-communicable diseases.

Among brain disorders and non-communicable diseases, dementia, which is "an umbrella term for several diseases", is the major cause of disability among older adults having major consequences on cognitive impairment and on mortality [11].

The general aim of this thesis was to study in depth the health status using trajectory models of cognitive function, physical activity, and disability in a cohort of elderly people. Its specific aims were to identify trajectory and multi-trajectory trends of cognitive, physical functioning and disability on non-demented elderly people living in the North of Italy in order to profile each multi-trajectory group identified. Besides another aim was to describe trajectories of cognitive decline for a part of the older adults of the Italian population-based cohort and for the Swedish population-based cohort.

This PhD thesis is based on data gathered from the two population-based studies: the Italian InveCe.Ab (Invecchiamento Cerebrale in Abbiategrasso, i.e.,

Brain aging in Abbiategrasso) study conducted by the Golgi-Cenci Foundation, Abbiategrasso (Milan) and the Swedish database of SNAC-K study (Swedish National Study on Aging and Care-Kungsholmen) carried out by the Stockholm Gerontology Research Center in collaboration with Aging Research Center (ARC), Karolinska Institutet.

To achieve the aims, three outcomes were used in the present work.

Cognitive function was assessed using the Mini Mental State of Examination (MMSE) scale administered at every follow-up time in both studies.The physical status was assessed using the walking test as gait speed. To test the preservation from disability during all the follow-up times the Activity Daily Living scale was administered (ADL). This scale takes into account difficulty in daily living activities, such as bathing, using the toilet, dressing, feeding and moving from one room to another.

To describe different courses of the three outcomes, the statistical methodology of Group-Based Trajectory Model (GBTM) was applied.

This method uses the trajectory groups as a statistical device to find the unknown distribution of trajectories across subjects. The groups identified by using the GBTM were profiled and compared using a multinomial logistic regression model.

The main results, coming from the analysis of the single outcome, were: the MMSE score is the best outcome using the GBTM model to describe the aging trajectories in the subgroup of individuals with dementia.

The walking tests, performed with or without the speaking task, give different trajectories with respect to the performance. Both tests require much more effort from the subgroup including subjects with dementia, especially in the subgroup characterized by the worst physical function.

Trajectories on ADL score give a scenario of an increased disability in the course of time: difficulty to perform daily activities becomes considerable in the last period of the follow-up when subjects get older;

On the other hand, the results described by the multi-trajectories are good for most of the elderly: they have quite stable cognitive, physical function and they are free from disability in daily activities.

For the last specific aim, Italian and Swedish subcohorts have a similar trajectory for cognitive function (MMSE score) in the group with the best cognitive status. In the worst groups in both the Italian and the Swedish cohort show the greatest number of subjects with dementia identified with GBTM: 100% for the Swedish and 53% for the Italian.

Aging is a real, concrete and complex issue for human beings.

This rapid increase in the number of old-age people should prompt us to think what is the best solution to improve the health status of the elderly in order to avoid an increase in demand for longcare services which in turn will lead to a rise in the health costs [5].

Constancy, perseverance and well planned research are the keys to deepen in order to have a better knowledge of this phenomenon and its lifespan.

The knowledge either of the effect of the combination of old-age diseases with dementia over time or of the aspects which have the strongest impact on the old people's life may be helpful for the young to adopt preventive behaviours that contribute to a good aging process, and for families to provide a solid support from a public health perspective.

Introduction

Aging population: a worldwide phenomenon

The old-age population (i.e. people aged 60 years and older) is increasing at a considerably faster rate than the world's total population (Figure 1) [1].

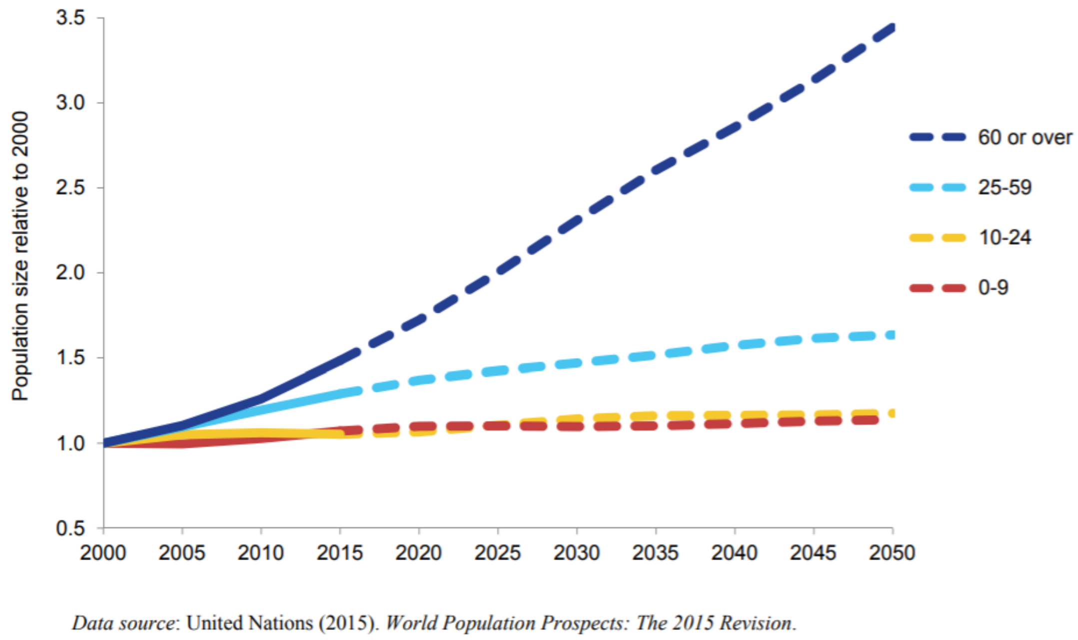
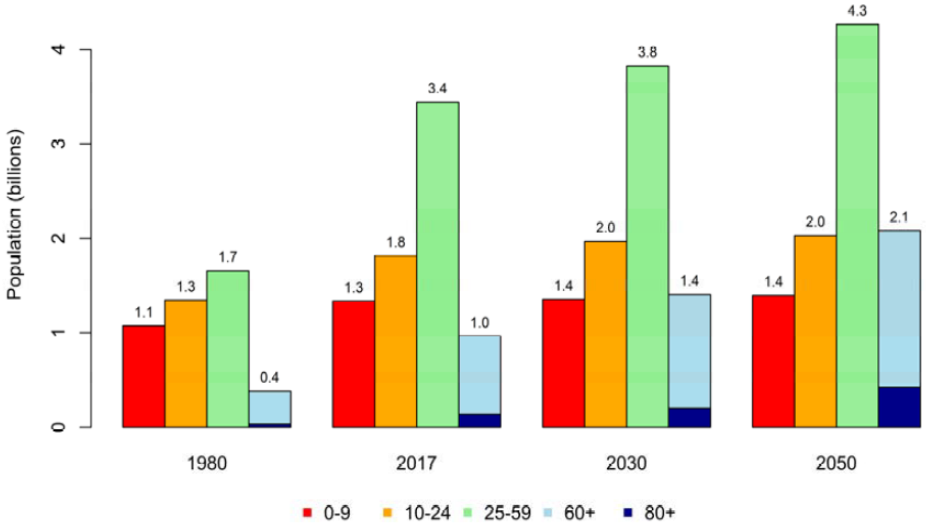


Figure 1 *– Increase in world population relative to 2000, by broad age group, 2000-2050. Reprinted from "United Nations, 2015- World Population Prospects: The 2015 Revision".*

In absolute number, by 2050 projections indicate that 2.1 billion (21.4%) of the worldwide population will be almost 60 years old and around 434 million will be 80 years old or more [2] (Figure 2): a steady rise, especially in the proportion of the elderly, is expected to increase twofold in the next 30 years.



Data source: United Nations (2017). *World Population Prospects: The 2017 Revision*.

Figure 2 *– Global population by broad age groups, 1980,2017,2030 and 2050. Reprinted from "United Nations, 2017- World Population Prospects: The 2017 Revision".*

According to the United Nation report (2017), currently Europe has the highest proportion of elderly people of all the continents, but it is remarkable that in 2050 there will be an increase in the number of people over 60 also in China, in some nations of Africa (e.g. Egypt and Tunisia) and in Latin America (e.g. Brazil, Chile, and Colombia), highlighted by darker colours as reported in Figure 3 [2].

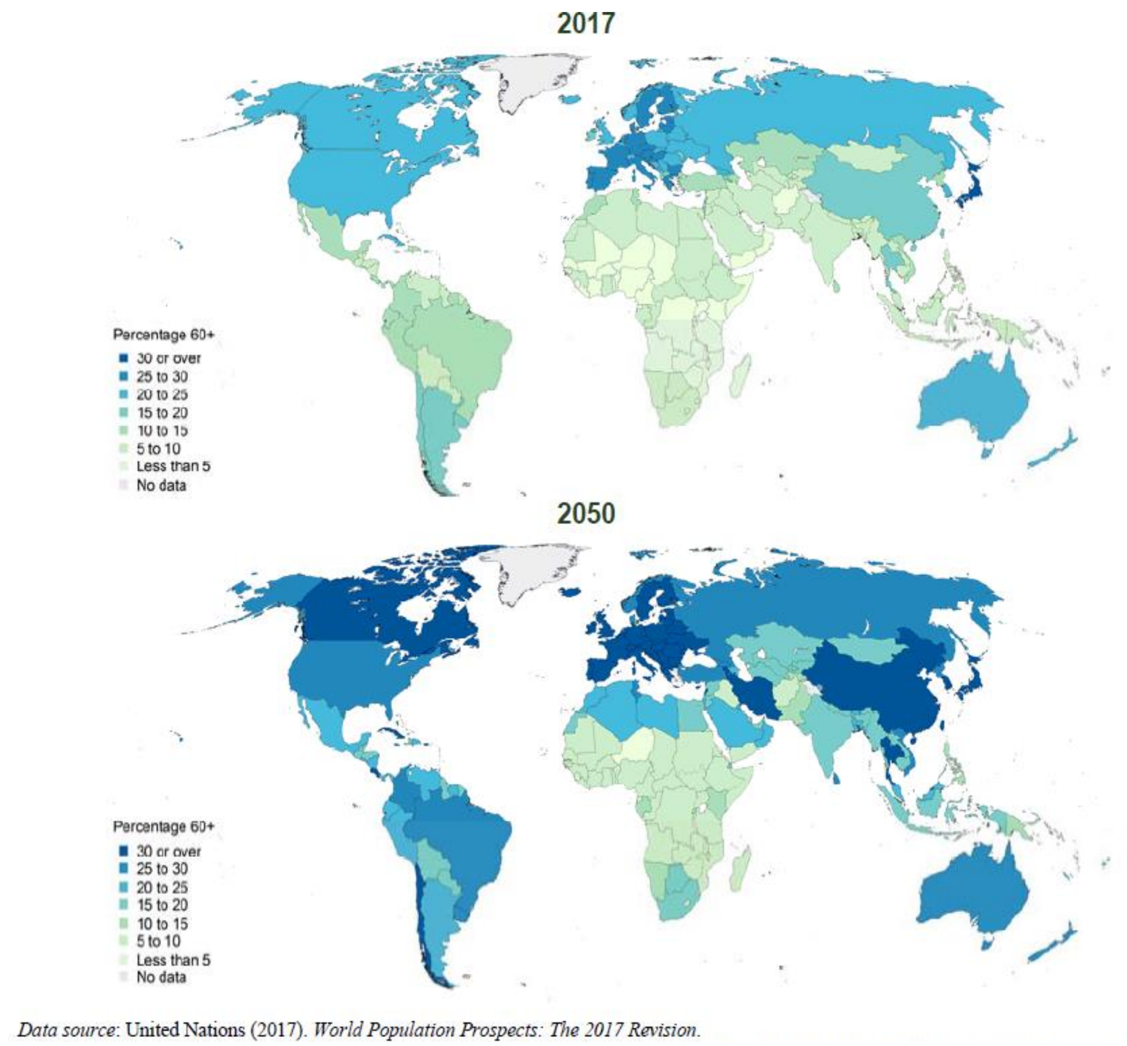


Figure 3 *– Projection of composition by age of world population. Reprinted from "United Nations, 2017-World Population Prospects: The 2017 Revision".*

Heterogeneity within the proportion of old-age people as well as within time variation characterizes European Union (EU) countries. In Italy, the proportion of the elderly in the '80s was less than 18%, so it did not appear in the top 10 of the countries with the largest proportion of over sixties. But the number of elderly people in Italy in 2017 was around 29% and will increase to approximately 37% in 2030, and to more than 40% in 2050. On the other hand Sweden, which ranked first in the World Population Prospect in 1980 with 22% of people aged 60 years or more, was not in the "top ten countries" neither in 2017 nor it will be in 2050: Swedish welfare strategies regarding family and their high rate of new-born [1,3] supported a non-increase in percentage of people aged 60 or more (Table 1).

	1980		2017		2050	
Rank	Country or area	Percentage aged 60 years or over	Country or area	Percentage aged 60 years or over	Country or area	Percentage aged 60 years or over
1	Sweden	22.0	Japan	33.4	Japan	42.4
2	Norway	20.2	Italy	29.4	Spain	41.9
3	Channel Islands	20.1	Germany	28.0	Portugal	41.7
4	United Kingdom	20.0	Portugal	27.9	Greece	41.6
5	Denmark	19.5	Finland	27.8	Republic of Korea	41.6
6	Germany	19.3	Bulgaria	27.7	China, Taiwan Province of China	41.3
7	Austria	19.0	Croatia	26.8	China, Hong Kong SAR	40.6
8	Belgium	18.4	Greece	26.5	Italy	40.3
9	Switzerland	18.2	Slovenia	26.3	Singapore	40.1
10	Luxembourg	17.8	Latvia	26.2	Poland	39.5

Data source: United Nations (2017). *World Population Prospects: The 2017 Revision*.
* Of 201 countries or areas with at least 90,000 inhabitants in 2017.

Table 1 *– The first 10 countries with the highest proportion of over 60 in the world situation in 1980 and 2017, and estimation for 2050. Reprinted from "United Nations, 2017-World Population Prospects: The 2017 Revision".*

Reasons for global aging: the demographic transition

In order to understand the phenomenon of global aging, the trend of two demographic indexes must be taken into account: the decrease in fertility rate, and the mortality rate. As reported in Figure 4, the fertility rate has globally shown a decline since 1958, whereas in Europe this negative trend seems to have stopped and to be slightly growing.

In regard to Italy, the fertility rate, after 1970, has had a decrease from 2.5 to 1.5 children per woman and this trend has overlapped that of Europe. In

Sweden a decreasing trend was present until the ‘80s, but then the fertility rate has inverted with values higher than the European mean.

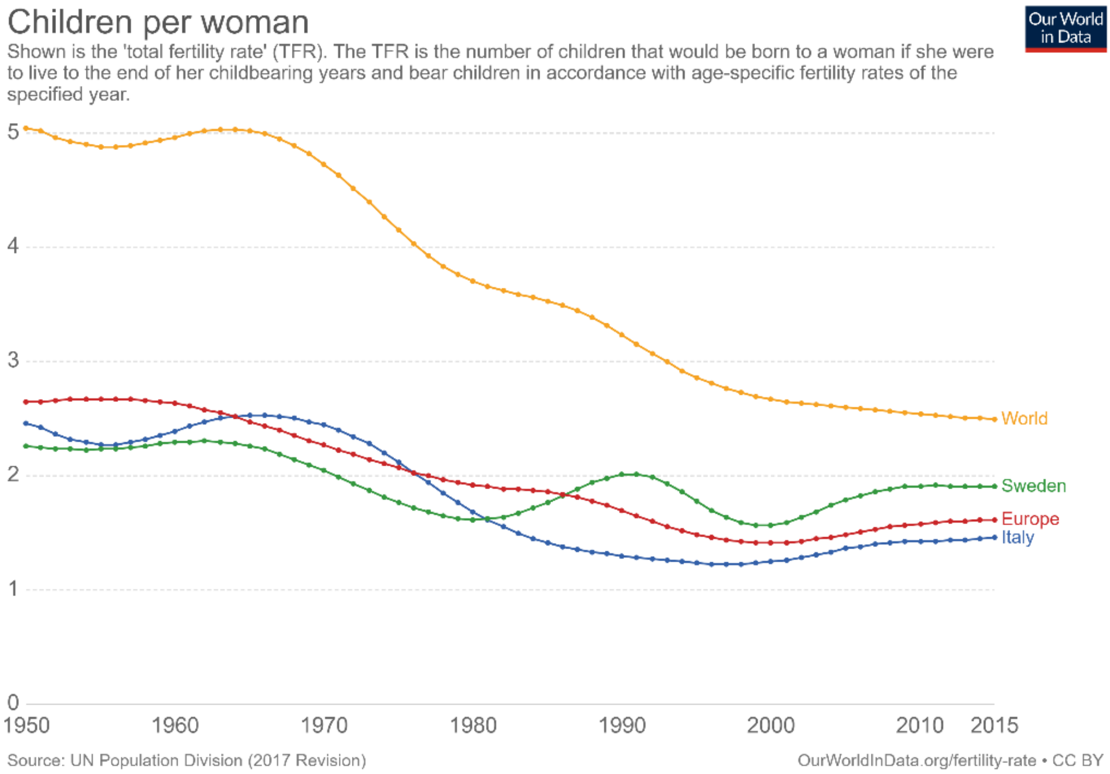


Figure 4 *– The Total Fertility Rate (TFR) is the number of children that would be born to a woman if she were to live to the end of her childbearing years and bear children in accordance with age-specific fertility rates of the specified years. Reprinted from "One World in Data.org/fertility-rate – Source United Nations Population Division, 2017".*

The decline in mortality was consistent if compared with the 19th century. As shown in Figure 5: the mortality rate in both Swedish and Italian populations declined from 1862 to 2014. More precisely, in regard with both countries, there was a consistent fall in rate: from 31 to 10 deaths per 1000 residents in Italy and from 21 to 10 deaths per 1000 residents in Sweden. The decrease was more marked in Italy.

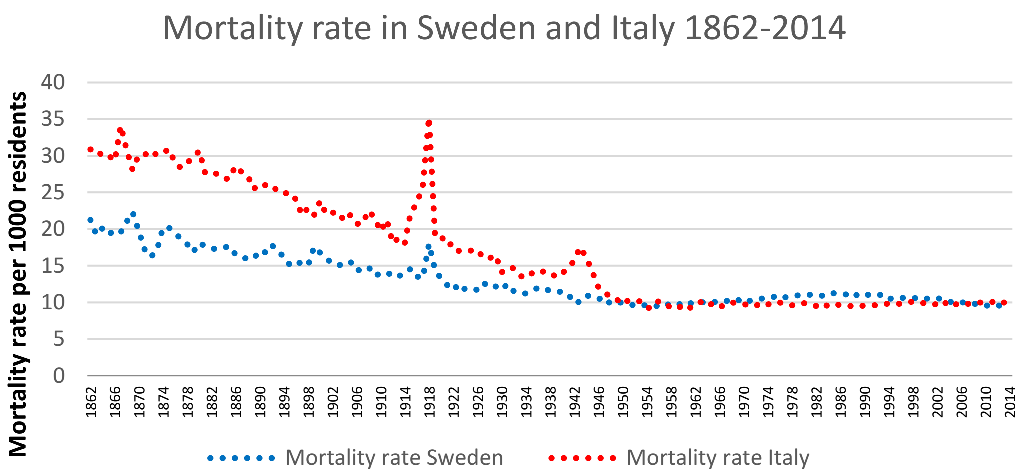


Figure 5 *– Trend of mortality rate in Italy and Sweden. Data from Statistics Sweden, Population and Economic Welfare statistics unit and ISTAT Italian National Statistics Institution.*

The decrease in mortality rate and the increase of elderly people are mostly due to the improvement in the quality of life occurred in the last 50 years and in the health care system, which has brought a large number of new therapies. Also, a considerable progress in medicine has been made. These preventive strategies together have led to a higher expectancy of life (Figure 6).

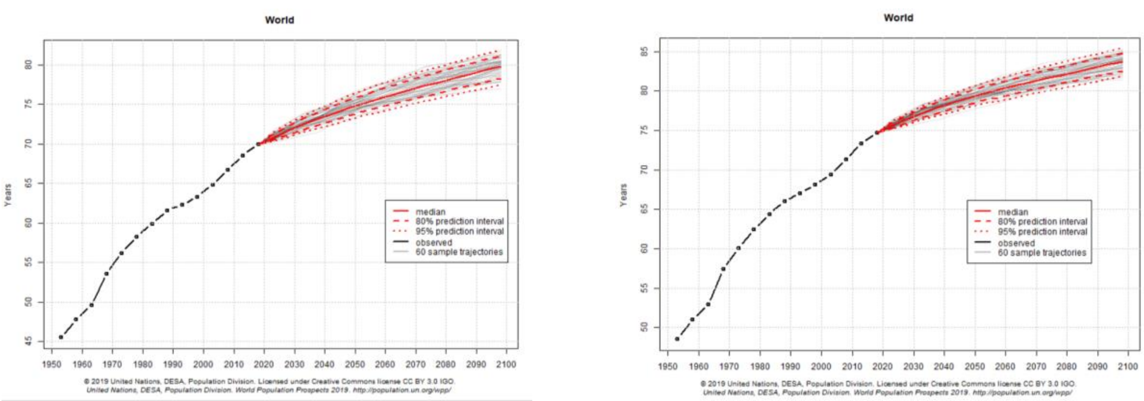


Figure 6 *– Expectancy of life for both sex, males and females respectively, made through probabilistic projections by Population Division on World Population Projects. Reprinted from "United Nations Population Division, 2019".*

In 2050 women's life expectancy at birth will be around 80 years and men's around 75 years, 21 and 30 years more than in 1950, respectively (Figure 6). Moreover, in Europe it was also estimated that, in 2014, people aged 65, could expect to live an additional 20 years [4].

This rapid increase in the number of old-age people should prompt us to think what is the best solution to improve the health status of the elderly in order to avoid an increase in demand for long care services which in turn will lead to a rise in the health costs [5].

On the other hand, the low birth rate may render it necessary to plan how to support society if there were a low occurrence among the younger generations.

Aging and health status

Aging brings about important changes in health status. Some indicators are useful to clinicians and also to researchers to understand the health status of the elderly and to plan health policies.

Cognitive and physical functioning, together with the degree of disability, are important indicators used to try to quantify the quality of health, in the later stages of life.

Cognitive function

During aging, one of the most relevant signs that may imply a decrease in health status is cognitive decline.

Cognitive decline is a complex theme since it has different levels and types of deterioration. The Mini Mental State Examination (MMSE) [6] is a tool implemented to catch if there is cognitive impairment, and at which level, in order to give an indication of a possible diagnosis of dementia. In other words, MMSE is a measure of the global cognitive level.

Physical Functioning

In literature, there are several indicators based on balance, strength, mobility implemented to quantify the level of well-being during aging and to test performance. The walking speed test is one of them and gives a measure of physical functioning: it is an easy and safe way to evaluate if a person may be at risk of negative outcomes due to physical deterioration [7].

Disability

It is known that disability, in particular in household activities, is a condition for old people, that had an impact on their lives [8]. So, together with cognitive and physical functioning, the degree of disability is an important indicator of impairment condition during aging.

Activity Daily Living (ADL) is a good instrument to measure the decline and the severity in general functioning that could affect the daily household activities.

Aging and dementia

Aging, as seen, is a complex phenomenon from a health status point of view, but it is also frequently related to non-communicable diseases. These diseases are known to have an important role in mortality and often are related to multi-morbidity [9].

It was estimated that the non-communicable diseases will represent, in 2030, the 87% of all burden diseases: they will affect more than one-half and more than three-fourths of the burden of the illness in the low and middle-income nation, respectively [10].

Among brain disorders and non-communicable diseases, dementia, which is "an umbrella term for several diseases", is the major cause of disability among older adults having major consequences on cognitive impairment and on mortality [11].

Alzheimer's disease is the most common form of dementia followed by vascular dementia, dementia with Lewy bodies and frontotemporal dementia [11].

Globally, although the number of old-age people who could be reasonably at risk of dementia is increasing, the incidence of dementia seems to have a tendency to decrease [12 –14]. In regard to prevalence, the debate is still open: the estimation is around 9.9 million new cases each year, one every three seconds [11].

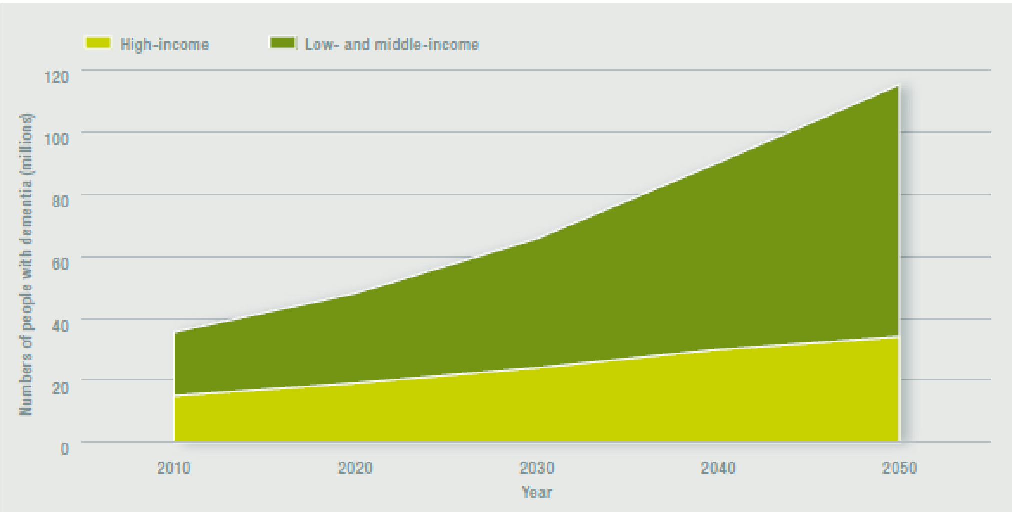


Figure 7 *– Growth in numbers of people with dementia in high-income and low-middle income countries. Reprinted from WHO, Dementia a Public Health Priority, 2012.*

WHO in 2012 [13] also reported that in the middle and low-income countries there will be a large increase in the number of elderly people affected by dementia for their rapid rise in population (Figure 7) in comparison with Europe, where the trend will remain quite the same (Figure 8).

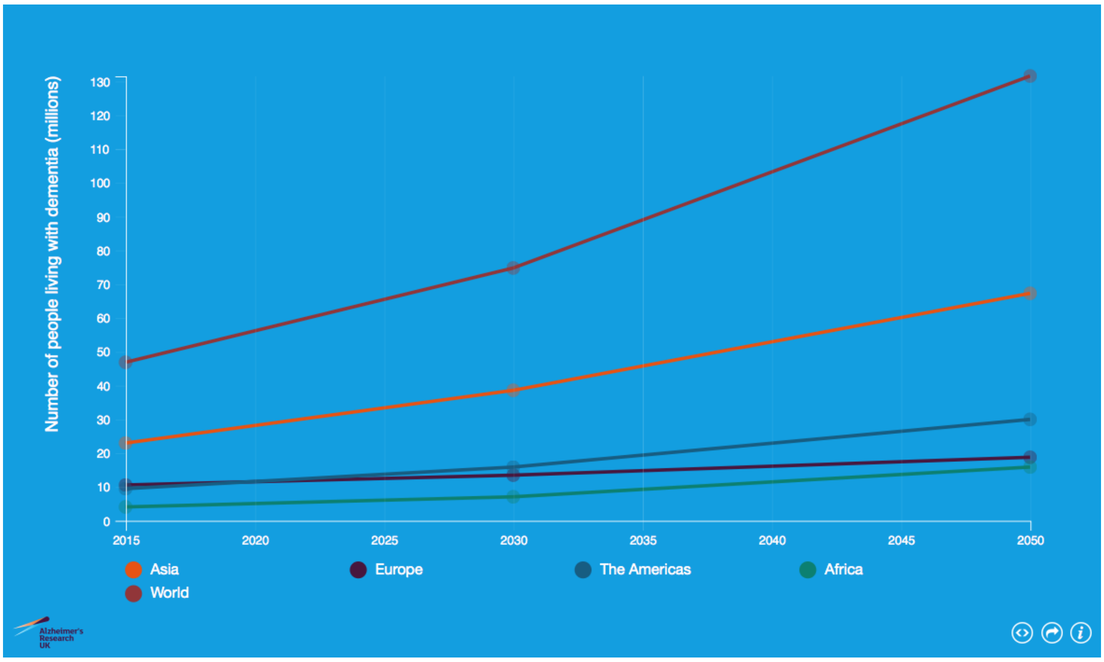
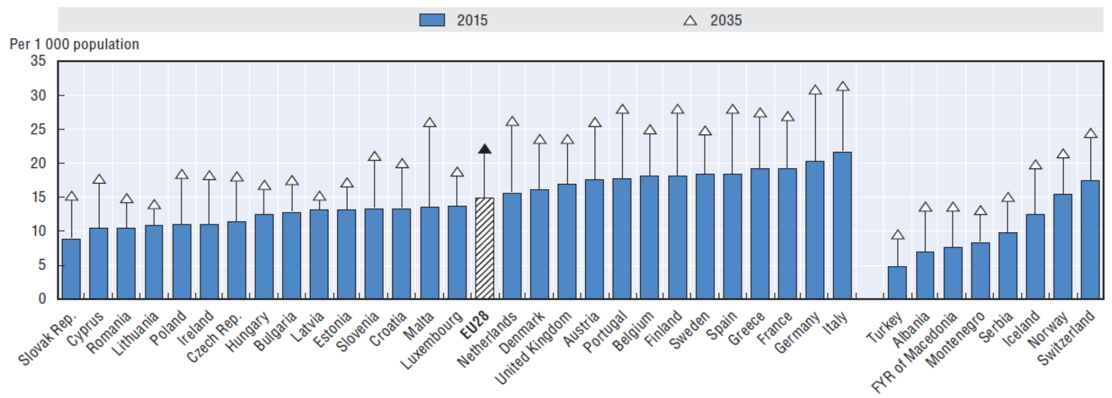


Figure 8 *– Trend of people living with dementia. Reprinted from Prince, M et al (2015). World Alzheimer's Report 2015, The Global Impact of Dementia: An analysis of prevalence, incidence, cost, and trends. Alzheimer's Disease International.*

The European Association of Alzheimer's disease reported in EU a prevalence of dementia in average of 1.55% for 2013. The same report indicated that both in Italy and in Sweden prevalences of people with different types of dementia was higher than in EU, 2.09% and 1.82% respectively [15].

According to the report, made by OECD [16], a remarkable increase in dementia is expected in the EU in the future, since the aging speed will be considerable.

It was estimated that in 2035 countries characterized by a huge rise in the number of older adults, like Germany and Italy, will see an increase in the incidence of dementia from 20 cases recorded in 2015, to more than 30 new cases out of 1000 people (Figure 9). On the other hand, in countries like Sweden with a small increase in aging, the prevalence will change from 18 cases occurred in 2015 to 25 cases of people with dementia out of 1000 people in 2035 [4].



Source: OECD analysis of data from Prince et al. (2013) and the United Nations.

StatLink http://dx.doi.org/10.1787/888933428892

Figure 9 *– The estimated prevalence of dementia per 1000 population, 2015 and 2035. Reprinted from "Prince M. et al (2013) and the United Nations".*

Although aging is the strongest risk factor for dementia, other risk factors are well known.

Some studies showed a relation of dementia to vascular diseases, in particular diabetes [17], to midlife hypertension [18], obesity [19], and physical inactivity [20]. Another risk factor playing a role in cognitive impairment and dementia together with social isolation was the educational status [21]. Furthermore, data showed that good aging will also be possible by means of a good social interaction through the social network [22].

The social support is very important for people with dementia [11]: cognitive impairment, as well as all the disorders causing mental impairment, influences the quality of life of the elderly people, who need to be constantly supported by their families or caregivers, also in regard to common habits of their daily living. The civil society is involved in the management of results coming from dementia, too. Infact, the burden of dementia is not only related to indirect costs due to daily living, but it has also a huge economic weight for the entire society: this cost was estimated to be US$ 604 billion per year [13] and it may increase to around US$ 2 trillion [23], if the number of patients shoots up getting larger.

Figure 10 *– Integrated caregiving system. Reprinted from WHO, Dementia a Public Health Priority, 2012.*

In few words, dementia is a global issue: initially it affects common people and ends in involving international organizations for its weight into human society.

The research activity works together with the Public Health Agency and European and International Associations on dementia, by identifying other possible modifiable risk factors, in order to improve, as much as possible, the prevention of dementia diseases and to relieve the human burden as well as to find new ways for dementia care (Figure 11).

Countries where aging is ongoing and where old-age people experience a good everyday life may be the model to follow in order to achieve the best results.

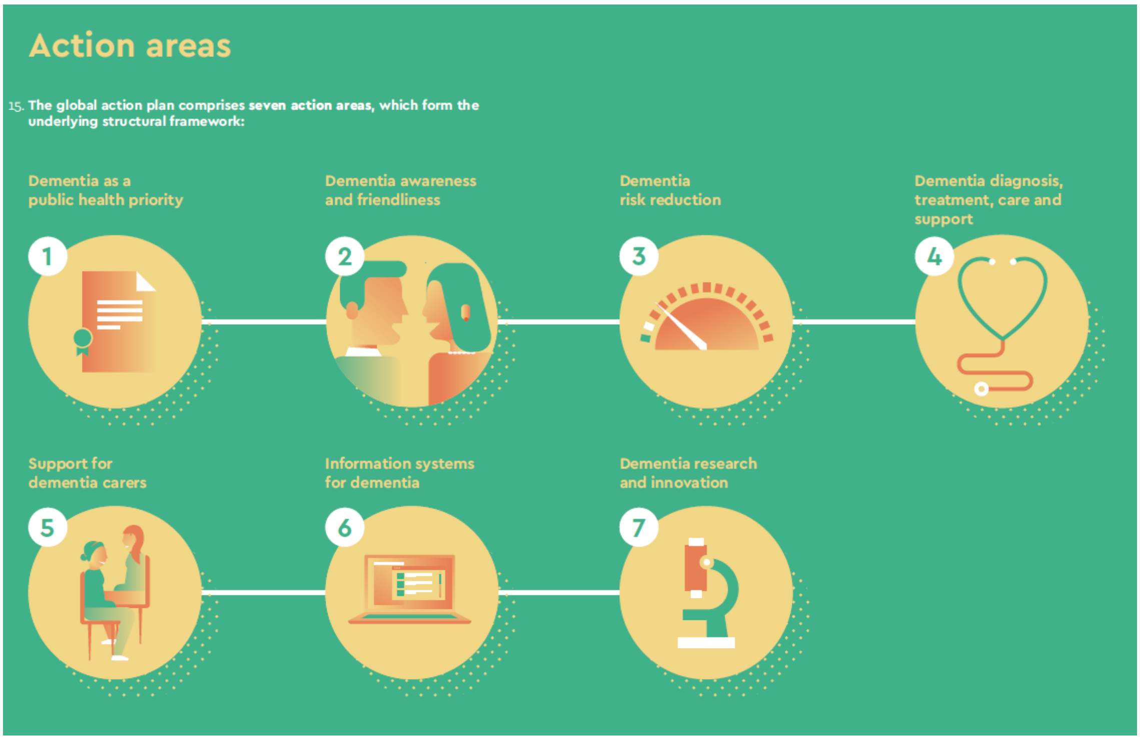


Figure 11 *– Action areas for dementia. Reprinted from "WHO, Global action plan on the public health response to dementia 2017–2025".*

Aims

General aim

The general aim of this PhD thesis was to study in depth the health status using trajectory models of cognitive status, physical activity, and disability in a cohort of elderly people. Two populations of elderly, Italian and Swedish, were investigated using the same analytic approach.

Specific aims

The specific aims were:

1. to identify trajectory trends of cognitive, physical functioning and disability on non-demented elderly people living in the North of Italy;
2. to identify a multi-trajectory trend of cognitive, physical functioning and disability on non-demented elderly people living in the North of Italy;
3. to profile each multi-trajectory group identified, in order to understand which are the main differences that characterize subjects with different trends;
4. to describe trajectories of cognitive decline for a part of the older adults of the Italian population-based cohort and for the Swedish population-based cohort.

Material and Methods

This PhD thesis is based on data gathered from the two population-based studies: the Italian InveCe.Ab (Invecchiamento Cerebrale in Abbiategrasso, i.e., Brain aging in Abbiategrasso) study conducted by the Golgi-Cenci Foundation, Abbiategrasso (Milan) and the Swedish database of SNAC-K study (Swedish National Study on Aging and Care-Kungsholmen) carried out by the Stockholm Gerontology Research Center in collaboration with Aging Research Center (ARC), Karolinska Institutet.

The Italian InveCe.Ab Study

Population and study design

The InveCe.Ab is a community-based cohort study on cognitive decline and dementia that was launched in 2010 [24].

The eligible population was made of 1773 older adults born between 1935 and 1939 living in Abbiategrasso, a small town near Milan, in the North of Italy. 20 % of them refused to participate in the study: 1321 participants were the respondents to the first step (Figure 12). After baseline assessment two follow-ups were completed in 2012 and in 2014. A 3rdfollow-up is ongoing.

Endpoints

The evaluation of dementia was made using the DSM IV, and the global cognition was assessed with Mini Mental Score Examination (MMSE). The proxy for the physical condition was obtained using the walking speed test and the disability was assessed with Activities of Daily Living (ADL) score.

Other information

Clinical variables, such as anthropometric measurements, walking test and drugs consumption were collected by a physician during the visits as well as social behaviour, lifestyle and demographic characteristics [24].

Instruments and data collection

All the non-instrumental information was collected by means of an ad hoc questionnaire (Appendix 1).

Data were collected by physicians and psychologists during each phase of the study. Visits took place at the Fondazione Golgi-Cenci in Abbiategrasso. In a few cases only they were conducted at participants' home.

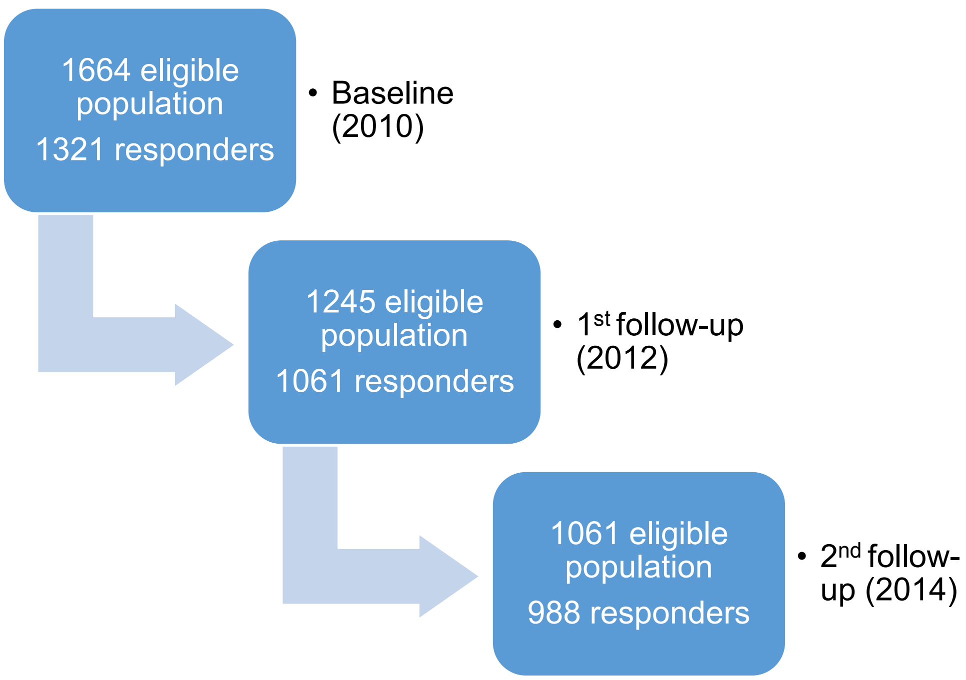


Figure 12 *– Flow chart of InveCe.Ab study.*

The Swedish SNAC-K study

Population and study design

The SNAC-K study is an ongoing longitudinal population-based study of individuals aged 60 years or older living in their own house or in an institution in the Kungsholmen area of Stockholm [25].

In 2001 a random sample of 5111 older adults, stratified across 11 birth cohorts (born between 1892 and 1939), were invited to participate in the study. At baseline, 3363 participants among the eligible population were examined from March 2001 to June 2004. After baseline assessment, the youngest cohorts (<78 years old at baseline) were followed every six years (2007-2013) and the oldest cohorts (≥78 years old at baseline) every three years (2004-2007-2010-2013-2016).

In Figure 13 the baseline assessment is shown in grey (B), the first follow-up in red (F1) , the second follow-up time in light-blue (F2), the third follow-up time in yellow (F3), the fourth follow-up in light green (F4) and the fifth assessment in violet (F5).

Endpoints

A physician using MMSE for global cognition and DSM-IV for dementia made the clinical examination of the patients.

Other information

Nurses enrolled in the study collected information on socio-demographics, work experience, lifestyle factors, daily living activities, anthropometric and arterial parameters from all participants in a two-hours assessment. Other information about other clinical diagnoses and medication use were collected by means of self-report information from participants or proxies.

Data collection

At each time of follow-up information on participants' status and medical history was collected through interviews, clinical examinations, and specific tests performed by trained staff (nurse, physicians and psychologists). The SNAC-K data were also linked with the Swedish National Patient Registry. (http://www.snac-k.se/).

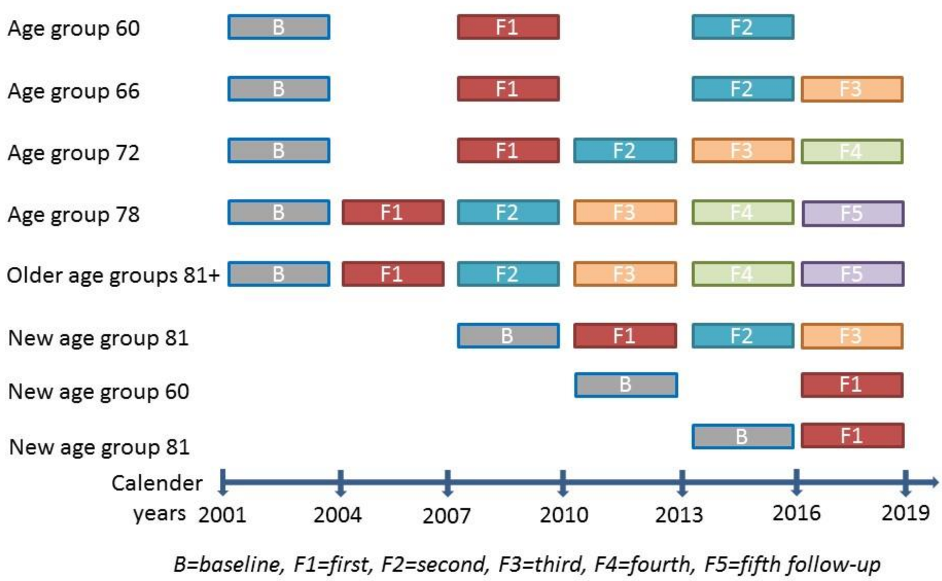


Figure 13 *– Flow chart of SNAC-K study. Reprinted from https://www.snac-k.se/about/study-plan/.*

Outcomes

To achieve the aims, three outcomes were used in the present work.

Cognitive function

Cognitive function was assessed using the MMSE scale administered at every follow-up time in both studies. The MMSE was composed of several items exploring different basic cognitive domains as memory, language, executive and visuospatial functioning and orientation in space and time. The items were associated with a score used to compute the MMSE score, ranging from 0 to 30, from poor to good cognitive status respectively.

Walking test

The physical status was assessed using the walking test as gait speed. This test can be done in two ways: both were employed in the studies used as a source of data.

More precisely, the time for each subject was reported after walking 10 meters subdivided in 5 meters back and forth (simple walking test). In the dual-task assessment of the walking speed, people had to walk for 10 meters reciting a number of personal names that came to their mind and they had to turn them to the opposite gender. This second version of walking test was more complex:it required higher cognitive ability due to the management, at the same moment, of cognitive and physical skills.

Disability

To test the preservation from disability during all the follow-up times the Activity Daily Living scale was administered (ADL). This scale takes into account difficulty in daily living activities, such as bathing, using the toilet, dressing, feeding and moving from one room to another. At each item of the scale a score equal to 0 was assigned if the subject did not have any problems in performing daily activities and more than 1 if there was at least one difficulty. The overall ADL score was calculated by summing these single scores: the higher score is a plausible index of a severe disability.

Statistical Methods

Trajectories models

In the present work a less known statistical methodology of trajectories was applied.

The trajectory can be an alternative method to describe different courses of an outcome. The simple use of this methodology gives results quickly, in order to underline which profiles characterize the health status decline during time, thus helping to plan the good management of these groups profiles.

Trajectories in GBTM

The trajectories on older people were implemented using the group-based trajectory models (GBTM) [27].

The idea of trajectory pinpointed in this model was directly retrieved from the words of Daniel Nagin, the developer of this methodology: "*A developmental trajectory describes the course of an outcome over age or time.*" This modeling strategy *"...provides a formal basis for determining the number of groups that best fits the data and an explicit metric, the posterior probability of group membership, for evaluating the precision of group assignments "*[26].

Group-based trajectory models

The first step of the GBTM is to analyze the distribution of the outcome (which is chosen according to the aims) conditionally on time. More precisely, a random vector Y_i for each *i-subject* with all longitudinal data and a vector $Time_i$ for each time point of follow-up will be generated.

Using a finite mixture model of unknown order *J*, the group-based trajectory assumes a nonparametric maximum likelihood estimator to design the distribution of the trajectories coming from the data collected from the population under study.

Practically speaking, the model is based on the construction of the likelihood function that requires the aggregation of the *J* conditional likelihood functions, based on the *j* group, $P^j(Y_i)$, to form the unconditional probability of the data.

It is possible to summarize the GBTM using the following equation:

$$P(Y_i | \mathrm{Time}_i) = \sum_{j=1}^{J} \pi_j \, P(Y_i | \mathrm{Time}_i, j; \beta_j)$$

where (π_j) is the probability of memberships in group *j*, and the conditional distribution of Y_i given membership in *j* is index by the unknown parameter vector β_j that gives the shape of group-specific trajectory a polynomial function of time [28].

Specifically, the unconditional probability of a sequence of measurements on individual *i* (Y_i), collected during the study time (Time_i), is equal to the sum across the j groups of the probability of Y_i given *i*'s memberships in group *j*, weighted by the probability of membership in group *j*.

The name *"finite mixture"* is due to the *finite number* of discrete unobserved *mixture subgroups* that compose the population.

Since the conditional independence at the level of the latent trajectory group is assumed, at the population level outcomes are not conditionally independent, because they depend on a latent construct of trajectory group membership.

So the specific equation of outcome distribution becomes:

$$P(Y_i | Time_i j; \beta_j) = \prod_{j=1}^{J} p(y_{it} | time_{it}, j; \beta_j)$$

where p(...) is the distribution of y_{it} conditional on membership in group j at the time t for individual i and could be a Normal or censored Normal, a Poisson or a Zero-inflated Poisson distribution.

Multi-trajectory model

The GBTM could be used also to analyze the trajectories deriving from the use of multiple outcomes.

If we have M number of outcomes and Y_i^m is the random vector for subject i of the m_{th} outcome and P_m (Y_i^m | $time_i$, m; β_i^m) represents the distribution of that vector conditional on group j and with the unknown parameter vector β_i^m, since conditional on memberships in the j_{th} group, Y_i^m are independently distributed with $P_J (Y_i^1, Y_i^2, ... Y_i^M) = P_{1j}(Y_i^1) ... P_{Mj}(Y_i^M)$, the likelihood for each individual conditional on the number of j groups may be written as

$$P_J(Y_i^1, Y_i^2, ... Y_i^M \mid time_i) = \sum_{j=1}^{J} \pi_J [\prod_{m=1}^{M} P_m(Y_i^m | time_i, j; \beta_j^m)]$$

With

$$P_m(Y_i^m | time_i, j; \beta_j^m)] = \prod_{t=1}^{T^m} p_m(y_{it}^m, j; \beta_j^m)]$$

where T^m implies that each of the m outcomes does not have to be measured over the same number of periods.

Note that the m outcomes are conditionally independent at the level of the latent trajectory group, but they are not conditionally independent at population level due to a latent construct of trajectory group membership.

Criteria for the best model selection

To select the best model the conventional index used was the Bayesian information criterion (BIC)[29] :

$$BIC = log\ (L) - 0.5k\ \log(N)$$

where L is the maximized likelihood, N denotes the sample size and k is the number of parameters considered in the model.

The highest values of this index should provide the best reasonable number of groups that can be used in the final model for the mixture model that underlies the GBTM.

The BIC is the methodological way to assess the best GBTM model but its author recommended to follow the other 6 points to have a good estimation from real data [27].

More precisely, beside the BIC value, these aspects should be evaluated to choose the final GBTM model:

- the *parsimonious* model which fitted the data well;
- an adequate sample numbers for each group;
- an average posterior probability (AvePP) value greater than 0.7 for each group;
- a similar proportion between each group's estimated probability and the effective proportion of each group computed using the maximum posterior probability assignment rule;

- the odds of correct classification major of 5 on the posterior probabilities of group membership for each group;
- reasonably narrow confidence intervals of the mean estimation by the model.

Goodness of fit

In addition to BIC two other indexes to evaluate the goodness of fit may be used:

- The probability that a model with j groups is the best model from a set of J different models that are changing for the number of groups found:

$$\frac{e^{BIC_j - BIC_{max}}}{\sum_j e^{BIC_j - BIC_{max}}}$$

Where BIC_j is the BIC of the j model and the BIC_{max} the maximum BIC score among all the BIC found from different Jmodels.

- An approximation of the Bayes factor (B_{ij}) estimated as :

$$B_{ij} = e^{BIC_i - BIC_j}$$

Where BIC_j is the BIC of the j model and the BIC_i the one found for the i model.

A B_{ij}< 0.1 reveals that there is strong evidence for model j, while $B_{ij} \geq 10$ for model i.

Differences among methodologies on modelling the trajectories

There are several methods in literature that show a quite similar aim to develop a model based on trajectories: the growth curve model (GCM) and the growth mixture model (GMM).

The main difference is "...*the approach to modelling individual-level heterogeneity...*"[26], such as each methodology using different assumptions concerning the distribution of the trajectories.

For GCM methodology the main assumption is that all subjects in a population have a similar development: differences are due to variability brought by each subject during time.

The GMM is based on mixture finite models where subpopulations have different trajectories that cannot be captured with random effects of each subject.

The GBTM is always based on finite mixture theory instead, but it uses the trajectory groups as a statistical device to find the unknown distribution of trajectories across subjects.

More precisely, this methodology aims to obtain the trajectory for each group, summarizing individual differences through polynomial functions of age or time.

The GBTM is based on the idea that who is following the same developmental course may have peculiar characteristics which differ from other groups and they may follow different developmental courses during time.

Descriptive statistics and multivariate models

The groups identified by using the trajectory models were profiled and compared. Continuous variables were summarized using mean and standard deviation (sd) in case of normality distribution respected, otherwise median and interquartile range (25^{th}-75^{th}percentile) were used. The qualitative variables were described as a percentage.

Profiles, on groups identified for the Italian cohort, were explored first with univariate analysis and then with multinomial logistic regression. In the first case, for quantitative variables the Analysis of Variance (ANOVA) followed by posthoc test was conducted using the *"best-performance"* group as reference. The Bonferroni's correction for multiple comparison test was applied (k=2 contrasts). If the assumptions were not respected the Kruskal-Wallis test was used, and the posthoc analyses were made by means of the Wilcoxon test. For qualitative variables the Chi-square test or Fisher exact test with Fisher-Freeman-Halton correction was applied. The characteristic under investigation are gender, age at baseline, ApoE-Ɛ4, education level, obesity. The Relative Rate Ratio with 95% Confidence Interval (95%CI) was reported for multinomial logistic model in which the same reference group of ANOVA was used.

A pvalue less than 0.05 was considered significant, apart from that of posthoc test: in this case, the significant level was 0.025 for the multiple comparison correction. In any case, the final pvalue was reported as 0.05.

Statistical software

Analyses were made using Stata, version 15. (StataCorp LP, College Station, TX).The plugin used to estimates the GBTM was named "TRAJ" in Stata.

Quality control and building of subsamples

Before starting with trajectory models the data control was made in order to have good features and, consequently, to obtain precise results.

On an Italian cohort made of 1319 subjects, each outcome was studied separately.

For each one a sensitivity analysis on two different subsamples was performed comparing if results could change. This preliminary analysis helped to identify bias due to lost information.

Namely, one subsample model was composed of all subjects with complete data for each studied outcomes and the second subsamples model was constrained using subjects with at least two observations on the outcomes during the follow-up time.

The final subsample was chosen by using both the best BIC, by testing several combinations of polynomial functions for each group, but also by trying to capture the data features in a more parsimonious and comprehensible way. Moreover, this methodology also provides the possibility to explore the role of potential critical covariates as risk factors, which do not vary over time, that may influence the probability of a subject to belong to a group.

For all the models fitted dementia was introduced as a cross-sectional outcome measured. Consequently, in all the analyses, the portion of people with dementia at baseline was excluded in order to explore which was the estimated proportion of people with dementia at the end of the study, in each group and for each outcome.

So the Italian cohort of 1319 elderly was reduced by 39 people with dementia identified at baseline. At the end of the second follow-up participants with dementia were 60.

Assessment of the subsamples to describe older adults in the two populations

With regard to the second aim, Italian and Swedish cohorts were used.
Since most of the population enrolled in the SNAC-K and in the InveCe.Ab study were of different ages and had a different follow-up time, the description of the cognitive trend in time for the two populations were implemented on subjects with similar follow-up time and ages in the first time point of the trajectory.

The description of cognitive trend, in these two European countries, was made using MMSE score and once again subjects with a diagnosis of dementia at baseline were excluded.

So the Italian cohort was composed of 352 subjects born between 1935 and 1936.

From SNAC-K 264 subjects born between 1929 and 1931 and with follow-up time from 2007 to 2013 were chosen, instead.

Results

Italian Cohort

The free-from dementia respondents of the Italian cohort showed a good cognitive function: the MMSE was quite stable with the value of the median 28 for all the follow-up times.

The walking test had a trend substantially stable during follow-up, while ADL score showed an increase in time if the mean values were evaluated (data not shown). The presence of obese subjects was quite stable, instead the median number of drugs taken daily rose in time (Table 2).

Variables	Follow-up		
	Baseline 2010	***1st Follow-up 2012***	***2nd Follow-up 2014***
MMSE in points	n=1196	n=1060	n=973
Median(25th -75th)	28 (27-29)	28 (27-29)	28 (26-29)
Walking test m/s	n=1217	n=1004	n=877
Median(25th -75th)	13(12-15)	13.03(11.68-14.79)	13.13(11.81-14.87)
Walking test (dual task) m/s	n=1213	n=1004	n=877
Median(25th -75th)	15(13-18)	15.03 (13.03-17.9)	15.37 (13.41-18.5)
Disability ADL in points	n=1317	n=1108	n=1003
Median(25th -75th)	0 (0-0)	0 (0-1)	0 (0-1)
Obesity	n=1305	n=1305	n=1000
Yes in % (n)	17.01% (222)	17.10% (223)	16.7% (167)
Daily number of drugs	n=1306	n=1099	n=1003
Median(25th -75th)	3 (2-5)	4 (2-5)	4 (2-6)

Table 2 *– Characteristics of the Subcohort for each time of follow-up.*

Trajectories for MMSE score

The trajectories of MMSE were investigated on the subjects having at least two MMSE scores in different follow-up times. Therefore, a subcohort of 1068 non-demented elderly was examined.

The distribution chosen to perform trajectories, for MMSE score, was the censored Normal in order to take into account the continuous nature of this variable and its possible range (0-30).

The GBTM model was fitted with unique risk factor as explicative variable the education expressed in years of study.

The process has consisted in modeling GBTM starting from the most economic model (without explicative) (Table 3).

The GBTM model with education showed a better BIC than the empty model and a high probability to be a good model for trajectory using only the cognitive function. Precisely, three groups with linear trajectories in cognitive function were estimated (Table 3): order 1st group characterized by low MMSE score, order 2nd group including subjects with medium MMSE score, order 3rd group composed of elderly with high MMSE (the most represented). As explained in the Methods section, other indexes must be used to support the goodness of trajectories identified by GBTM model.

The GBTM model presented an adequate number of subjects in each identified group (Table 4), a very good correspondence between the proportion estimated on posterior probability and the one estimated by each group, an average posterior probability greater than 0.70 in each group (Table 5), the odds of correct classification higher than 5 in all the groups (Table 6), even if the one with high MMSE presented a value slightly higher than cut-off.

Model	**Trajectory shapes**^			**BIC** Based on the number of observation n=3012	**Probabilityco rrect model**	**Bayes Factor**
	Order 1st Group	Order 2nd Group	Order 3rd Group			
Without risk factor	1	1	1	***-6012.51***	<0.001	1.01
Education *in years*	1	1	1	***-5922.54***	>0.90	0.99

^Possible trajectory shapes; 0=zero-order; 1=linear; 2=quadratic; 3=cubic.

Table 3 *– Different characteristics obtained from the model for the cognitive outcome are reported: type of model,risk factors, order found for each group and goodness of fit of the model.*

Order group	MMSE trajectory group	Number of units	Proportion of group	Proportion estimated on Posterior Probability
1st	*Low* **MMSE score**	65	0.061	0.063
2nd	*Medium* **MMSE score**	286	0.268	0.283
3rd	*High* **MMSE score**	717	0.671	0.654

Table 4 *– Number of people by groups found with GBTM, the proportion for each group and the proportion of final groups using the max posterior probability obtained from the estimation of the model.*

Order group	MMSE trajectory group	Average Posterior Probabilityin each group
1st	*Low* **MMSE score**	0.963
2nd	*Medium* **MMSE score**	0.919
3rd	*High* **MMSE score**	0.844

Table 5 *– Average posterior probability for each group.*

Order group	Group	Odds of correct classification *
1st	*Low* **MMSE score**	388.89
2nd	*Medium* **MMSE score**	13.69
3rd	*High* **MMSE score**	5.96

*based on the weighted posterior probability group assignment

Table 6 *– The odds of correct classification, due to the posterior probability of group membership.*

Finally, the confidence interval at 95% of the estimated MMSE mean score was always very tight (Table 7).

From Table 7 and even better from the trajectories of the subjects, in the final groups, it can be inferred that in all groups the trajectories declined in time but in different ways. In general the elderly with a bad cognitive function at baseline showed the worst time trajectories with a faster decline than those with a better cognitive function (Figure 14).

Year	MMSE score trajectory group		
	Low (n=65)	***Medium*** (n=286)	***High*** (n=717)
2010			
Observed mean	24.27	27.00	28.82
Predicted mean	24.28	27.15	28.842392
(95% CI)	(23.82-24.73)	(26.75-27.55)	(28.68-29.00)
2012			
Observed mean	21.45	26.76	28.85
Predicted mean	21.46	26.47	28.71
(95% CI)	(21.16-21.73)	(26.07-26.87)	(28.56-28.86)
2014			
Observed mean	18.65	25.61	28.51
Predicted mean	18.64	25.77	28.57
(95% CI)	(18.08-19.21)	(25.27-26.27)	(28.36-28.78)

Table 7 *–Confidence Interval of estimated means of MMSE score in each group at every time points. The observed mean of MMSE was also reported.*

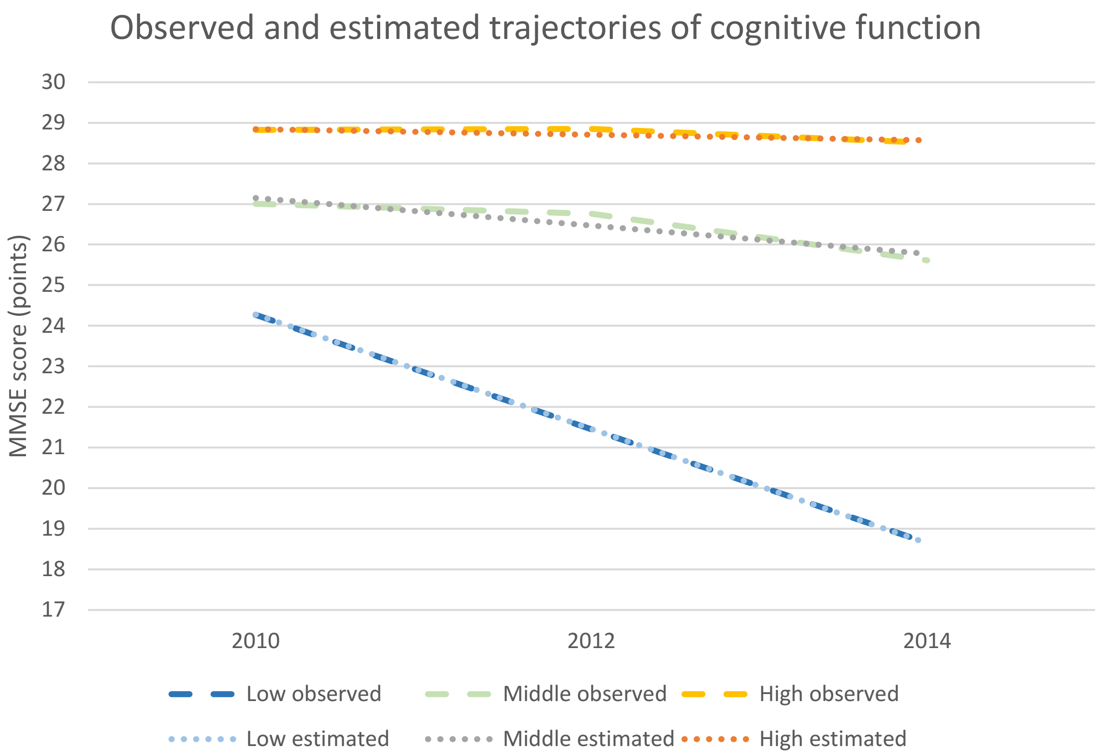


Figure 14 *– Observed and estimated trajectories of cognitive function.*

The first group, called "Low MMSE score", included the subjects with the lowest MMSE score at baseline and the most marked decreasing trend in the follow-up time: an average in MMSE score lower than 3 points in the score between the beginning and the end of the follow-up.

The "Medium MMSE score" group had a slight decrease in time with an average annual decrease of less than 0.4 points. On the other hand, the "High MMSE score" identified by the yellow line showed a quite stable MMSE score, of around 28 points in the follow-up time.

Trajectories for MMSE score constrained with no missing for each time

The next GBTM model reported the trajectories found using the data retrieved from participants with all the MMSE scores collected in the InveCe.Ab study.

As shown in Table 8 it is possible to find 3 groups, the first one characterized by low MMSE score, the second one including subjects with medium MMSE score, and the third group composed of elderly people with high MMSE (the most represented). In this subsample, too, the model adjusted for the education showed a better BIC than the empty model. A difference underlined in this GBTM model is that the best model without education had for the third group with the higher MMSE score a zero-order function index of none differences in cognitive function during the follow-up time.

Model	**Trajectory shapes^**			**BIC** Based on number of observation n=2628	**Probability correct model**	**Bayes Factor**
	Order 1st Group	Order 2nd Group	Order 3rd Group			
Without risk factor	1	1	0	-5066.18	<0.001	1.01
Education *in years*	1	1	1	-5000.38	>0.90	0.99

^Possible trajectory shapes; 0=zero-order; 1=linear; 2=quadratic; 3=cubic.

Table 8 *– Different characteristics obtained from the model for the cognitive outcome are reported: type of model, risk factors, order found for each group and goodness of fit of the model.*

This GBTM model presented an adequate number of subjects in each identified group (Table 9), a very good correspondence between the proportion estimated on posterior probability and the one estimated by each groups, an average posterior probability greater than 0.70 in each group (Table 10), the odds of correct classification higher than 5 in all the groups (Table 11). In these results as well the confidence interval at 95% of the estimated MMSE mean score was always very tight (Table 7).

Order groups	MMSE trajectory group	Number of units	Proportion of group	Proportion estimated on Posterior Probability	Average Posterior Probability in each group	Odds of correct classification *
1st	*Low* **MMSE score**	34	0.039	0.038	0.953	509.77
2nd	*Medium* **MMSE score**	233	0.266	0.281	0.854	15.03
3rd	*High* **MMSE score**	609	0.695	0.681	0.926	5.86

*based on the weighted posterior probability group assignment

Table 9 *– Number of people by groups found with GBTM, the proportion for each group and proportion of final groups using the max posterior probability obtained from the estimation of the model, average posterior probability for each group and the odds of correct classification, due to the posterior probability of group membership.*

Year	MMSE score trajectory group		
	Low (n=34)	***Medium*** (n=233)	***High*** (n=609)
2010			
Observed mean	23.98	27.16	28.89
Predicted mean	24.24	27.32	28.92
(95% CI)	(23.68-24.79)	(26.91-27.74)	(28.76-29.08)
2012			
Observed mean	22.38	27.00	28.92
Predicted mean	21.88	26.68	28.78
(95% CI)	(21.52-22.25)	(26.30-27.06)	(28.64-28.93)
2014			
Observed mean	19.53	25.86	28.58
Predicted mean	19.53	26.02	28.64
(95% CI)	(18.79-20.27)	(25.56-26.48)	(28.43-28.85)

***Table 10** – Confidence Interval of estimated means of MMSE score in each group at every time points. The observed mean of MMSE was also reported.*

From Table 10 and even better from the trajectories of the subjects in the final groups, found with GBTM, it can be inferred that in the low and middle groups the trajectories declined in time but always in different ways. The elderly with a bad cognitive function at baseline showed the worst time trajectories with a faster decline than those with a middle cognitive function. The high MMSE group, instead, reported a stable score during time (Figure 15).

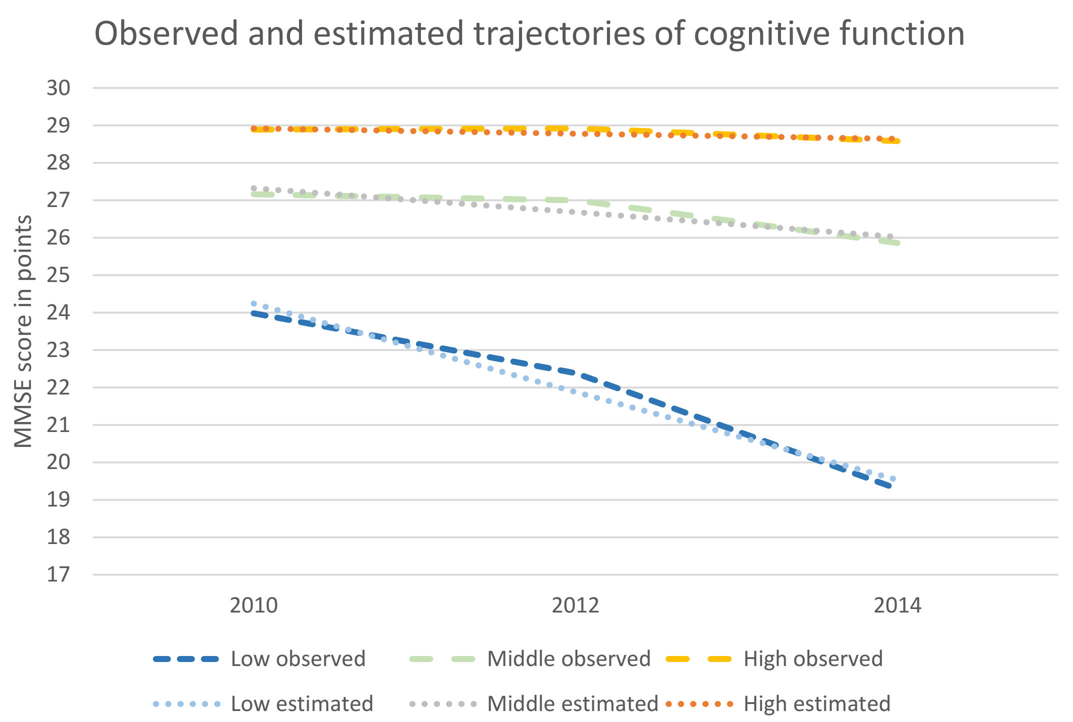


***Figure 15** – Observed and estimated trajectories of cognitive function. Subcohort with no missing data for each time.*

However, the observed mean showed an annual decrease of 1.1 points slightly lower for the Low group in comparison with the one found by the first model equal to 1.4 points. Besides, as highlighted in Figure 15, subjects in the "low" group had a decrease less linear than the one observed with the previous model with a higher decline between the first and the second follow-up, probably due to some worst conditions developed over time.

In general, the trajectories identified by the sensitivity analyses were similar to the previous model and described a decline in cognitive function in the groups with low and medium MMSE score.

MMSE and dementia

On the basis of the estimated MMSE score trajectories groups, it is possible to evaluate the proportion of the elderly with dementia by using the posterior probability from GBTM (Table 11).

This result was similar to the one found in the proportion of the elderly with dementia using final groups. Both results are achieved by means of the subcohort of subjects with at least two follow-ups completed and the subcohort with no missing for each time (Tables 11 and 12 respectively).

	n	***Proportion of older adults with dementia using posterior probability***	***Proportion of older adults with dementia using final groups***
Low **MMSE score**	65	0.482 (0.367-0.600)	0.462
Medium **MMSE score**	286	0.086 (0.060-0.123)	0.064
High **MMSE score**	717	0.003 (0.001- 0.011)	0.005

Table 11 *– Model with at least 2 times of follow-up completed (n=1068).*

Group	***n***	***Proportion of older adults with dementia using posterior probability***	***Proportion of older adults with dementia using final groups***
Low **MMSE score**	34	0.697 (0.528-0.825)	0.663
Medium **MMSE score**	233	0.100 (0.068-0.143)	0.068
High **MMSE score**	609	0.002 (0.0009- 0.009)	0.003

Table 12 *– Model with no missing data for each time (n=876).*

In both cases, the proportion of old-age people with dementia was similar, independently of the estimation (Posterior probability using final groups).

Moreover, the estimation by the model using the small size of subjects, with all data completed, gave a higher proportion of people with dementia (Table 12) than the estimation retrieved from the model using more subjects (Table 11).

This difference was more evident among the groups with low MMSE scores. Namely, the model deriving from subcohort with completed data estimated that at the end of the study there was around 66% of people with dementia in the group with low MMSE score, 7% in the middle one and less than 1% in the group with high MMSE score.

In the model based on a greater number of old-age people the proportion of people with dementia inside each group found with GBTM was 46.2%, 6.4%, and less than 1% in the low, middle and high MMSE groups respectively.

For both models, the elderly with the diagnosis of dementia were prevalently distributed in the group with low MMSE score: 55% were in the model with a smaller number of subjects and 58% in the one with at least two records (Table 13).

Group	***Model with at least 2 times of follow-up***	***Model with all data completed***
	n=52	n=40
Low **MMSE score**	*58%(n=30)*	55% (n=22)
Medium **MMSE score**	*36%(n=19)*	40% (n=16)
High **MMSE score**	*6% (n=3)*	5% (n=2)

***Table 13** – Distribution of elderly with a diagnosis of dementia at the end of the second follow-up in the 3 groups.*

Trajectories for walking speed test without speaking

To describe the trend of physical function, the score used to account for it was the walking speed without speaking.

The distribution chosen to perform trajectories, for the walking speed without speaking, was the Normal in order to take into account the continuous nature of this variable.

The best GBTM model came from the cohort of subjects who participated at least in two follow-up times. As reported in Table 14, the trajectories were linear for the third group, which was characterized by the slowest walking speed compared to the other two groups identified (Table 15).

Model	**Trajectory shapes**^			**BIC**
	Order 1st Group	Order 2nd Group	Order 3rd Group	Based on the number of observation n=2882
Without risk factor	0	0	1	***-6479.96***

^Possible trajectory shapes; 0=zero-order; 1=linear; 2=quadratic; 3=cubic.

Table 14 *– Different characteristics obtained from the model for walking speed are reported: type of model, risk factors, the order found for each group and goodness of fit of the model.*

Unlike the model fitted for MMSE score, for walking speed it was not possible to find any risk factors related to the outcome that was constant in time in order to adjust trajectories.

The model presented an adequate number of subjects in each group, a good correspondence between the estimated proportion by each group and the one estimated on posterior probability. The values of average posterior probability and the odds of correct classification were both major than the cut-off (Table 15).

Order group	Walking speed without talking trajectory group	Number of units	Proportion of group	Proportion estimated on Posterior Probability	Average Posterior Probabilityin each group	Odds of correct classification *
1st	*High* ***speed***	606	0.592	0.581	0.906	6.97
2nd	*Middle* ***speed***	339	0.331	0.341	0.850	10.96
3rd	*Low* ***speed***	78	0.076	0.077	0.947	210.65

*based on the weighted posterior probability group assignment

Table 15 *– Number of people by groups found with GBTM, the proportion for each group and proportion of final groups using the max posterior probability obtained from the estimation of the model, average posterior probability for each group and the odds of correct classification, due to the posterior probability of group membership.*

Year	Walking speed trajectory group		
	High speed n=606	Medium speed n=339	Low speed n=78
2010			
Observed mean	11.97	14.80	18.36
Predicted mean (95% CI)	12.00 (11.84-12.15)	14.80 (14.53-15.08)	18.51 (18.08-18.95)
2012			
Observed mean	11.86	14.65	19.69
Predicted mean (95% CI)	12.00 (11.84-12.15)	14.80 (14.53-15.08)	19.40 (18.08-18.95)
2014			
Observed mean	12.18	14.98	20.06
Predicted mean (95% CI)	12.00 (11.84-12.15)	14.80 (14.53-15.08)	20.28 (18.08-18.95)

Table 16 *– Confidence Interval of estimated means of walking speed test in each group at every time points. The observed mean of walking speed was also reported.*

In agreement with the coefficient in the model (0 0 1) (Table 14), quite stable trajectories were identified for the high and middle groups (table 16). On the contrary, an increase in trajectory was described for the group with the low walking speed test (Figure 16).

More precisely, with the best and middle group walking speed test showed trajectories which were constantly around 12 and about 15 seconds, respectively.

In the slow group, instead, the walking speed got worse from baseline to the end of the follow-up: the subjects started with a test in an average of 18 seconds to walk 10 meters and they reached 20 seconds in the next four years with an average increase of half-second during the follow-up time (Table 16).

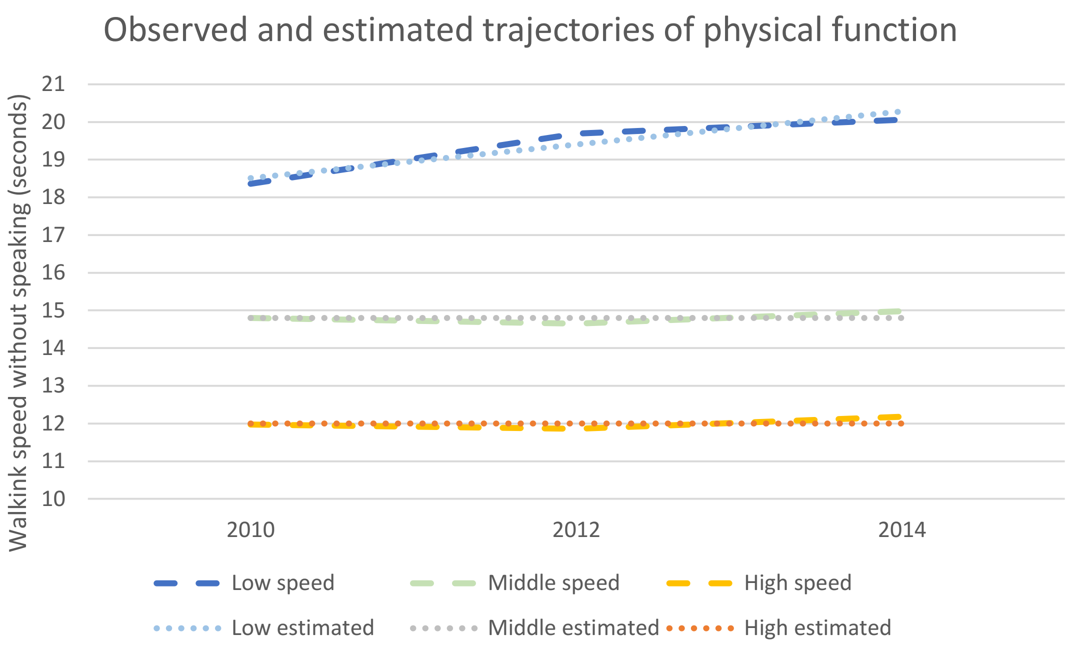


Figure 16 *– Observed and estimated trajectories of physical function.*

Trajectories for walking speed test without speaking constrained with no missing for each time

The GBTM model, constrained on subjects with completed data in the follow-up time, gave trajectories with similar polynomial function in comparison with the previous one (Table 17) and once again it proves to be a good model (Table 18).

Model	**Trajectory shapes^**			**BIC**
	Order 1st Group	Order 2nd Group	Order 3rd Group	Based on the number of observation n=2508
Without risk factor	0	0	1	-5499.58

^Possible trajectory shapes; 0=zero-order; 1=linear; 2=quadratic; 3=cubic.

Table 17 *– Different characteristics obtained from the model for walking speed are reported: type of model, risk factors, the order found for each group and goodness of fit of the model on subcohort with completed data of follow-up.*

Order groups	Walking speed without talking trajectory group	Number of units	Proportion of group	Proportion estimated on Posterior Probability	Average Posterior Probability in each group	Odds of correct classification *
1st	*High* ***speed***	487	0.582	0.575	0.910	7.458
2nd	*Middle* ***speed***	294	0.352	0.357	0.855	10.618
3rd	*Low* ***speed***	55	0.066	0.068	0.944	229.411

*based on the weighted posterior probability group assignment

Table 18 *– Number of people by groups found with GBTM, proportion for each group and proportion of final groups using the max posterior probability obtained from the estimation of the model, average posterior probability for each group and the odds of correct classification, due to the posterior probability of group membership on the Subcohort with completed data of follow-up.*

Year	**Walking speed trajectory group**		
	High speed **n=487**	**Middle speed** ***n=286***	***Low speed*** ***n=55***
2010			
Observed mean	11.89	14.64	17.94
Predicted mean (95% CI)	11.91 (11.74-12.08)	14.59 (14.30-14.88)	17.90 (17.44-18.36)
2012			
Observed mean	11.75	14.35	18.77
Predicted mean (95% CI)	11.91 (11.74-12.08)	14.59 (14.30-14.88)	18.84 (18.47-19.21)
2014			
Observed mean	12.09	14.78	19.82
Predicted mean (95% CI)	11.91 (11.74-12.08)	14.59 (14.30-14.88)	19.78 (19.23-20.34)

Table 19 *– Confidence Interval of estimated means of walking speed test in each group at every time points. The observed mean of walking speed was also reported.* Subcohort with no missing for each time.

In detail, three groups with different trajectories were identified by the GBTM model on greater subcohort and the trajectories retrieved overlapped the previous model. The group with slow speed was estimated to have an increasing trend in walking speed during the follow-up: at the last follow-up the speed was slightly higher compared to the baseline (Table 19).

On the other hand, it was estimated a quite stable timing in the other two groups (Table 19). The trend in walking speed in time is better represented in Figure 17.

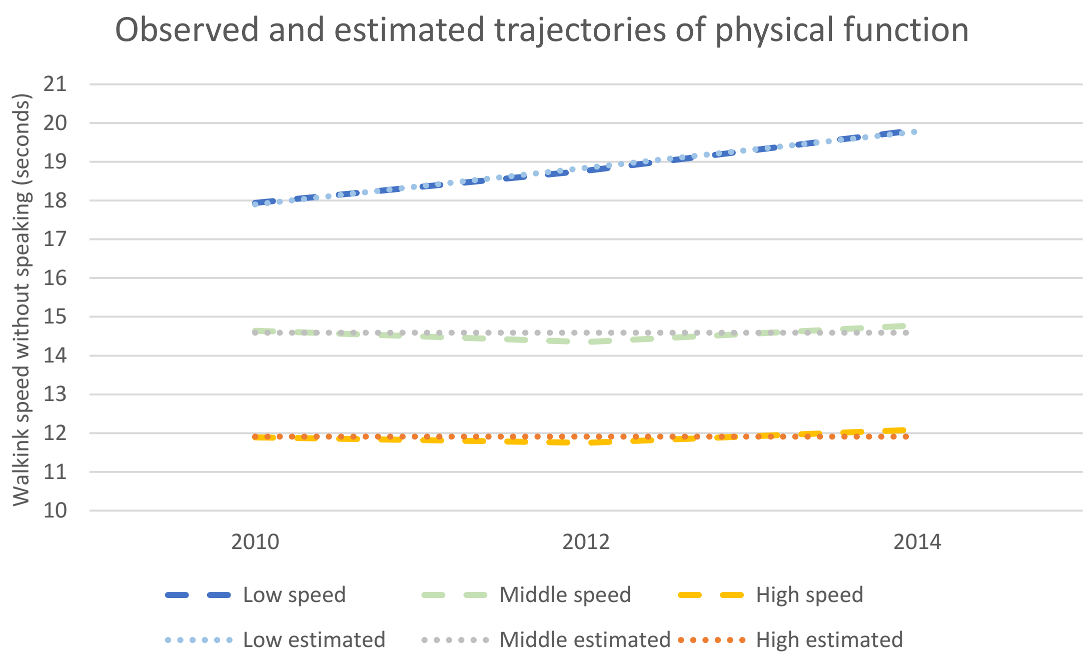


Figure 17 *– Observed and estimated trajectories of physical function.* Subcohort with no missing data for each time.

Walking speed test without speaking and dementia

As it was done with MMSE trajectories, the proportion of people with dementia for each group found was estimated on the basis of two different approaches (Table 19 and 20), the former deriving from the model implemented with at least two measures of follow-up completed, the latter with all data completed.

Two approaches estimated a similar proportion of people with dementia above all on constrained cohorts (Table 20).

Trajectories of walking speed without speaking gave worse results in comparison with the MMSE score.

A lower proportion of demented people was estimated in comparison with the MMSE score: 38 were identified by the model with more subjects (Table 20) and 22 by the one with constrained data (Table 21).

Group	***n***	***Proportion of older adults with dementia using posterior probability***	***Proportion of older adults with dementia using final groups***
High ***speed***	606	0.012 (0.006-0.025)	0.015
Middle ***speed***	339	0.061 (0.041-0.092)	0.052
Low ***speed***	78	0.151 (0.089-0.246)	0.145

Table 20 *– Model with at least 2 times of follow-up completed (n=1023).*

Group	***n***	***Proportion of older adults with dementia using posterior probability***	***Proportion of older adults with dementia using final groups***
High ***speed***	487	0.011 (0.005- 0.025)	0.013
Middle ***speed***	294	0.045 (0.026- 0.075)	0.039
Low ***speed***	55	0.079 (0.033-0.179)	0.077

Table 21 *– Model with no missing data for each time (n=836).*

In regard to the distribution of demented people across groups identified by models, it was found that the middle group had, in both models, the highest percentage of demented people: around 50% for the constrained subcohort and 47% for the greater subcohort. Finally, only 18% (n=4) as to constrained data and nearly 30% (n=11) as to the greater cohort were in the group with lower walking speed (Table 22).

Group	***Model with at least 2 times of follow-up***	***Model with all data completed***
	n=38	n=22
High ***speed***	*24%(n=9)*	32% (n=7)
Middle ***speed***	*33%(n=18)*	50% (n=11)
Low ***speed***	*29% (n=11)*	18% (n=4)

Table 22 *– Distribution of elderly with a diagnosis of dementia at the end of second follow-up in the 3 groups.*

Trajectories for dual-tasking walking speed test

By using data available from subjects with at least two measurements (n=1022), in the dual-tasking walking test, the best model was the one with polynomial order 0 0 1 (BIC=-7965.32) for the first, the second and the third group, respectively. No risk factors were useful to improve the fit and the distribution chosen, to perform trajectories, was the Normal in order to take into account the continuous nature of this variable.

The GBTM model had all the secondary indexes good, as highlighted in Table 23.

However, the GBTM model with the dual-tasking walking speed test showed a worse BIC than the GBTM model with a simple walking test without speaking (Table 14).

The most represented groups were the ones with high walking speed. In these groups, the trajectory was stable in time (Figure 18) as reported from value in Table 24: the speed, on average, did not change during the follow-up and it was 2 seconds greater than the speed taken from walking speed test without speaking (Table 19).

On the contrary, the group with a low number of old people with low speed showed the worst performance: they started with a mean of walking test of about 26 seconds and they reached 33 seconds at the last follow-up time as reported in Table 24. Nevertheless, this time was more than 10 seconds higher in comparison with the one registered during the walking speed test without speaking (Table 19).

Order group	Dual-tasking walking speed test trajectory group	Number of units	Proportion of group	Proportion estimated on Posterior Probability	Average Posterior Probabilityin each group	Odds of correct classification *
1st	*High* ***speed***	719	0.704	0.694	0.945	70.64
2nd	*Middle* ***speed***	267	0.261	0.269	0.878	190.46
3rd	*Low* ***speed***	36	0.035	0.037	0.957	5880.75

*based on the weighted posterior probability group assignment

Table 23 *– Number of people by groups found with GBTM, the proportion for each group and proportion of final groups using the max posterior probability obtained from the estimation of the model, average posterior probability for each group and the odds of correct classification, due to the posterior probability of group membership.*

Year	**Dual-tasking walking speed test trajectory group**		
	High speed n=719	**Middle speed *n=267***	***Low speed n=36***
2010			
Observed mean	14.08	20.06	25.71
Predicted mean (95% CI)	14.21 (14.02-14.40	19.83 (19.45-20.21)	25.34 (24.29-26.40)
2012			
Observed mean	14.08	19.27	28.16
Predicted mean (95% CI)	14.21 (14.02-14.40)	19.83 (19.45-20.21)	28.88 (28.08-29.68)
2014			
Observed mean	14.51	20.21	32.96
Predicted mean (95% CI)	14.21 (14.02-14.40)	19.83 (19.45-20.21)	32.42 (31.13-33.70)

Table 24 *– Confidence Interval of estimated means of walking speed test in each group at every time points. The observed mean of walking speed was also reported.*

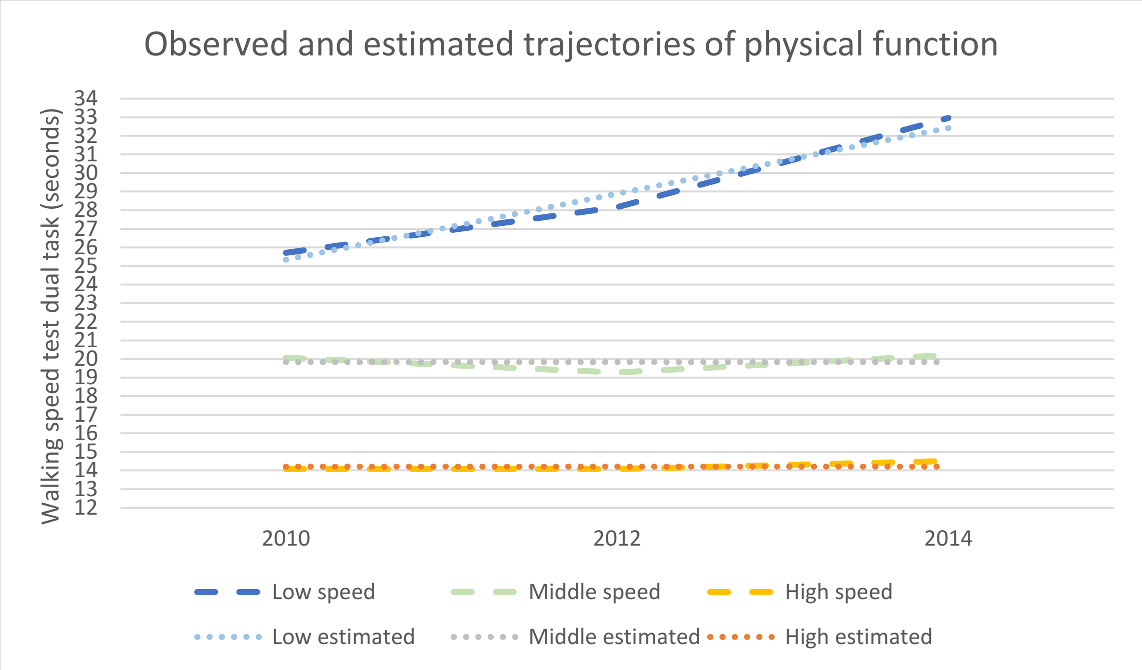


Figure 18 *– Observed and estimated trajectories of physical function using dual-tasking walking speed test.*

It seems that this version of walking speed test adds more difficulty: the fact that the subjects have to recite a number of names during the walking test worsens the physical performance.

On the other hand, by using the subcohort with all complete information (n=833) the best model has a lower BIC (BIC= -6769.38) in comparison with the subcohort with at least two records. From the polynomial order of the three groups, it can be inferred that the first and the third groups had a linear trend, whereas the second one is characterized by a non-linear order as a possible indication of a quite stable average in walking speed.

Again, all the indexes of goodness were over the cut-off (Table 25) and the number of subjects by the group was adequate.

Order group	Dual-tasking walking speed test trajectory group	Number of units	Proportion of group	Proportion estimated on Posterior Probability	Average Posterior Probability in each group	Odds of correct classification *
1st	*High* ***speed***	563	0.676	0.673	0.951	9.47
2nd	*Middle* ***speed***	228	0.274	0.278	0.878	19.03
3rd	*Low* ***speed***	42	0.050	0.050	0.914	202.86

*based on the weighted posterior probability group assignment

Table 25 *– Number of people by groups found with GBTM, proportion for each group and proportion of final groups using the max posterior probability obtained from the estimation of the model, average posterior probability for each group and the odds of correct classification, due to the posterior probability of group membership in Subcohort with complete data.*

Trajectories for dual-tasking walking speed test constrained with no missing for each time

The group with the best performance, as found with GBTM model on the largest cohort in dual-task walking speed, had increased by around 1 second in all the follow-up time (Table 26).

For the group with low speed a linear increase was confirmed (Figure 19) even if the rise was slightly smaller (Table 26).

Year	**Walking speed dual task trajectory group**		
	High speed n=563	**Middle speed *n=228***	***Low speed n=42***
2010			
Observed mean	13.78	19.54	24.13
Predicted mean (95% CI)	13.69 (13.43-13.96)	19.06 (18.63-19.49)	23.38 (22.35-24.41)
2012			
Observed mean	13.79	18.28	24.68
Predicted mean (95% CI)	13.97 (13.77-14.16)	19.06 (18.63-19.49)	26.17 (25.31-27.02)
2014			
Observed mean	14.33	19.36	29.69
Predicted mean (95% CI)	14.24 (13.98 -14.50)	19.06 (18.63-19.49)	28.95 (27.61-30.29)

Table 26 *– Confidence Interval of estimated means of walking speed test in each group at every time points. The observed mean of walking speed was also reported. Subcohort with no missing data for each time.*

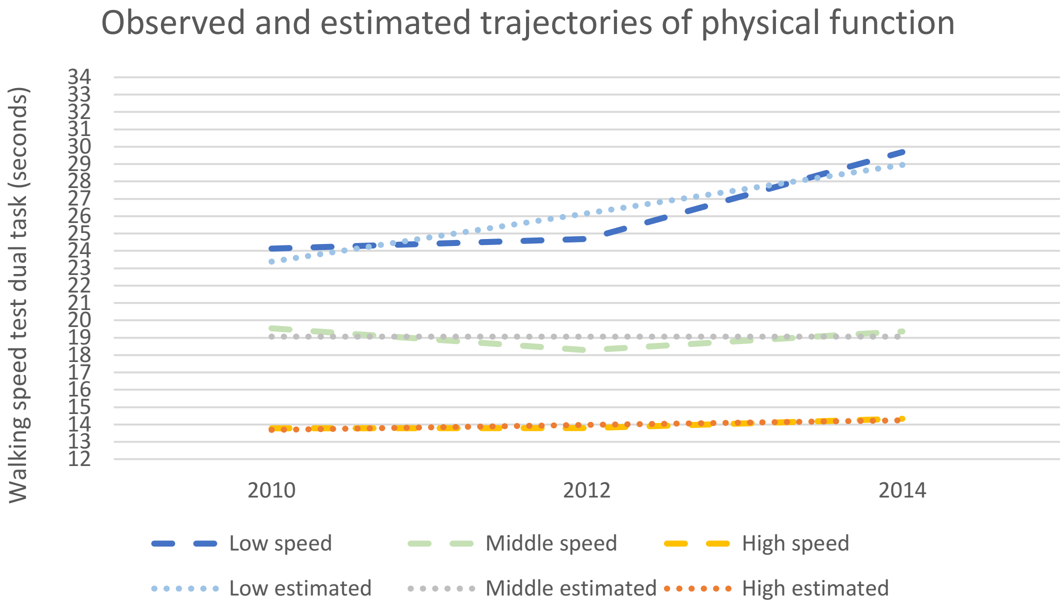


***Figure 19** – Observed and estimated trajectories of physical function using dual-tasking walking speed. Subcohort with no missing data for each time.*

Dual-tasking walking speed test and dementia

The highest proportion of people with dementia was found in the group with low speed by the GBTM model fitted by using a large number of subjects (Table 27), twofold greater than the one estimated by the model with few people (Table 28).

Group	*n*	***Proportion of older adults with dementia using posterior probability***	***Proportion of older adults with dementia using final groups***
High ***speed***	719	0.012 (0.006-0.023)	0.014
Middle ***speed***	267	0.094 (0.065-0.135)	0.079
Low ***speed***	36	0.193 (0.098-0.345)	0.187

Table 27 *– Model with at least 2 times of follow-up completed (n=1022).*

Group	***n***	***Proportion of older adults with dementia using posterior probability***	***Proportion of older adults with dementia using final groups***
High ***speed***	563	0.011 (0.005-0.023)	0.012
Middle ***speed***	228	0.057 (0.033-0.094)	0.049
Low ***speed***	42	0.104 (0.042-0.233)	0.099

Table 28 *– Model with no missing data for each time (n=833).*

In regard to the distribution of demented people, across groups identified by models, it was found that the middle group had, in both models, the highest percentage of demented people, i.e. around 50% for constrained subcohort and 53% for the greater subcohort. (Table 29).

Group	***Model with at least 2 times of follow-up***	***Model with all data completed***
	n=38	n=22
High ***speed***	*29%(n=11)*	32% (n=7)
Middle ***speed***	*53%(n=20)*	50% (n=11)
Low ***speed***	*18% (n=7)*	18% (n=4)

Table 29 *– Distribution of elderly with a diagnosis of dementia at the end of the second follow-up in the 3 groups.*

Trajectories for ADL score

Since the subjects were not so older to have a high degree of disability, the distribution chosen to perform trajectories was the zero-inflated Poisson in order to take into account the large number of zero.

The best GBTM model for ADL (BIC= -2485.84), using greater subcohort was characterized by three groups for which the trajectories were a linear function for the second and third groups only (that is, the middle and the worst one). Other indexes of fit (Table 30) were respected for this model.

As reported in table 31, the group with high disability showed a consistent increasing level of disability in time: at baseline, the ADL score was threefold greater than in the other two groups characterized by subjects with a mean value around 0 for ADL score and then raised until 7.4 points at the second follow-up.

The most represented group was the Free-Low disability where the mean of ADL score remained constant during the follow-up. The mean of ADL increase by 1 point for the middle group from the baseline to the end of the follow-up.

This scenario is more clearly illustrated in Figure 20.

Order group	ADL score trajectory group	Number of units	Proportion of group	Proportion estimated on Posterior Probability	Average Posterior Probability in each group	Odds of correct classification *
1st	*High* ***disability***	53	0.048	0.047	0.944	343.14
2nd	*Middle* ***disability***	417	0.374	0.433	0.921	15.20
3rd	*Free- Low* ***disability***	644	0.578	0.520	0.851	5.29

*based on weighted posterior probability group assignment

Table 30 *– Number of people by groups found with GBTM, proportion for each group and proportion of final groups using the max posterior probability obtained from the estimation of the model, average posterior probability for each group and the odds of correct classification, due to the posterior probability of group membership.*

Year	**ADL score trajectory group**		
	Free-Low disability n=644	**Middle disability *n=417***	***High* disability *n=53***
2010			
Observed mean	0.01	0.23	3.37
Predicted mean (95% CI)	0.02 (0.00-0.05)	0.26 (0.21-0.32)	3.47 (2.89-4.05)
2012			
Observed mean	0.02	0.59	5.13
Predicted mean (95% CI)	0.02 (0.00-0.05)	0.52 (0.42-0.62)	13.97 (4.58-5.67)
2014			
Observed mean	0.03	0.98	7.44
Predicted mean (95% CI)	0.02 (0.00-0.05)	1.01 (0.81-1.22)	7.57 (6.68-8.46)

Table 31 *– Confidence Interval of estimated means of ADL score in each group at every time points. The observed mean of ADL score was also reported.*

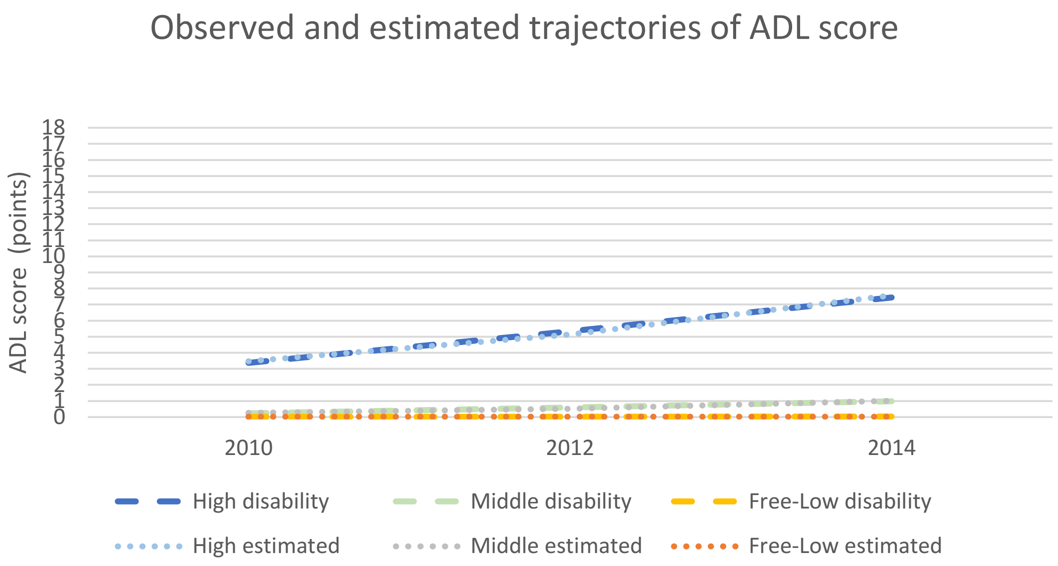


Figure 20 *– Observed and estimated trajectories of disability.*

Trajectories for ADL score constrained with no missing for each time

Similarly, the best model fitted using subcohort with completed ADL score for all follow-up time (BIC= -2181.77 (n=951)) identified three orders of groups with a zero-order trajectory for the best group and linear trajectories for the middle and the worst group (Table 32).

Order group	ADL score trajectory group	Number of units	Proportion of group	Proportion estimated on Posterior Probability	Average Posterior Probability in each group	Odds of correct classification *
1st	*High* ***disability***	33	0.035	0.036	0.977	1139.29
2nd	*Middle* ***disability***	123	0.129	0.144	0.841	31.52
3rd	*Free-Low* ***disability***	795	0.836	0.821	0.959	5.12

*based on the weighted posterior probability group assignment

Table 32 *– Number of people by groups found with GBTM, the proportion for each group and proportion of final groups using the max posterior probability obtained from the estimation of the model, average posterior probability for each group and the odds of correct classification, due to the posterior probability of group membership. Subcohort with completed data.*

Year	ADL score trajectory group		
	Free-Low disability n=795	**Middle disability *n=123***	***High* disability *n=33***
2010			
Observed mean	0.02	0.70	3.80
Predicted mean (95% CI)	0.04 (0.02-0.05	1.16 (0.97-1.36)	3.77 (3.07-4.46)
2012			
Observed mean	0.12	1.13	5.55
Predicted mean (95% CI)	0.10 (0.07-0.12)	1.16 (0.97-1.36)	5.62 (4.98-6.25)
2014			
Observed mean	0.26	1.66	8.41
Predicted mean (95% CI)	0.27 (0.22-0.32)	1.16 (0.97-1.36)	8.38 (7.34-9.41)

Table 33 *– Confidence Interval of estimated means of ADL score in each group at every time points. The observed mean of ADL score was also reported. Subcohort with complete data.*

Nevertheless, the most marked linear trend was found for the group with a high-degree disability (Figure 21). Subjects belonging to this group showed an increasing level of ADL score in time (Table 33): in other words, the worst group in terms of disability had a worse trajectory.

The elderly in this group started with a high level of disability from the baseline, and during time, this level saw an increase as reported previously in the first model as well.

On the contrary, subjects within the group with the best condition remained free from disability during time (Table 33), while older adults in the middle group started to have disability at the end of the follow-up when the mean of ADL score was greater than 1.5.

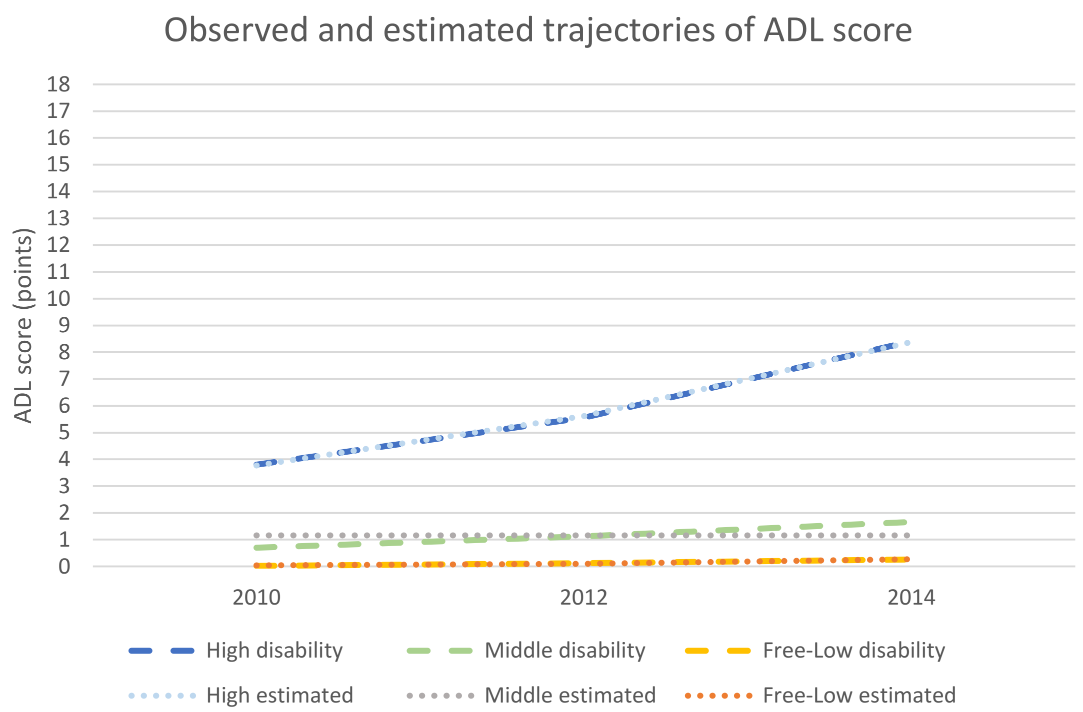


Figure 21 *– Observed and estimated trajectories of disability. Subcohort with no missing data for each time.*

The models estimated 59 and 47 people with dementia. Namely, the model fitted on the greater subcohort (Table 34) found that the 45% was affected by dementia within the groups with high disability, the 6% in the middle groups and the 1.5% in the group without disability.

The model fitted on restricted subcohort (Table 35) predicted 50% of people with dementia in the group with high-degree disability and 8% and 2.6% in those with middle and free-low disability, respectively.

Group	***n***	***Proportion of older adults with dementia using posterior probability***	***Proportion of older adults with dementia using final groups***
High ***disability***	53	0.483 (0.353-0.615)	0.449
Middle ***disability***	417	0.068 (0.049-0.094)	0.062
Free-Low ***disability***	644	0.011 (0.005-0.024)	0.015

Table 34 *– Model with at least 2 times of follow-up completed (n=1114).*

Group	***n***	***Proportion of older adults with dementia using posterior probability***	***Proportion of older adults with dementia using final groups***
High ***disability***	33	0.506 (0.346-0.665)	0.493
Middle ***disability***	123	0.057 (0.095-0.156)	0.083
Free-Low ***disability***	795	0.024 (0.015-0.037)	0.026

Table 35 *– Model with no missing data for each time (n=951).*

The 59 subjects with dementia were distributed among disability groups as follows: 41% in the high disability group, 42% in the middle disability one and 17% in the group with no or low disability. On the contrary, in the constrained model, the distribution was slightly different: a higher percentage of subjects with dementia was in the high disability group, followed by the middle group represented by 34% and the last 21% of older adults with dementia was in the free-low disability group (Table 36).

Group	***Model with at least 2 times of follow-up***	***Model with all data completed***
	n=59	n=47
High ***disability***	*41% (n=24)*	45% (n=21)
Middle ***disability***	*42%(n=25)*	34% (n=16)
Free-Low ***disability***	*17%(n=10)*	21% (n=10)

Table 36 *– Distribution of elderly with diagnosis of dementia at the end of second follow-up in the three groups.*

Multi-trajectory model

Since aging is a complex phenomenon, the next models provide the trajectories by grouping older adults who follow similar trajectories across the three outcomes of interest on cognitive, physical and disability function, thus responding to the second specific aim. As mentioned in the previous section, two different models were performed on the basis of the walking test: without speaking and dual-task.

Multi-trajectory model with walking speed test without speaking

The best multi trajectory model has settled on 993 subjects with at least 2 data collection from the baseline to the second follow-up (BIC=-14025.82): three order group trajectories were identified for each outcome reported in Table 37. All the indexes of goodness for the GBTM were verified as shown in Table 38.

Model	**Trajectory shapes^**		
	Order 1st Good scenario	Order 2nd Middle scenario	Order 3rd Severe scenario
MMSE score	1	1	1
Walking speed test	0	0	1
ADL score	1	1	1

^Possible trajectory shapes; 0=zero-order; 1=linear; 2=quadratic; 3=cubic.

Table 37 *– Trajectories shape of the multi-trajectory model with MMSE score, Walking speed test without speaking and ADL score.*

The multi-trajectory showed a linear shape of trajectory for all the groups in MMSE and ADL, whereas, in regard to the walking speed test, it was only detected in the severe scenario. Namely, in this group there is a linear increase in time in the walking speed and in the degree of disability, while a linear decrease in cognitive function was registered.

A multi-scenario can be retrieved from the multi-trajectory model as shown in Figure 22.

Among these 993 subjects, without dementia at baseline, different patterns on cognitive, physical and disability trend were identified.

It was possible to state that the worst trajectories in time among all the outcomes were identified for the group with "severe scenario" made of 4.3% of subjects (n=42) (Figure 22):

- the cognition was lower than 27 points at baseline and declined in time to around 21 points at the end of the study, with a 1.5 points annual loss in MMSE score;
- the walking speed had an increase around by 4 seconds on average during the entire period;
- disability showed low level at baseline but increased around by 3 points at the end of the second follow-up.

The first group with the best scenario showed the best trend from all of the outcomes during the follow-up time. In regard to the disability, the subjects included in the group with a middle scenario needed help in one of the daily living activities at the end of the study.

Order groups	Trajectory group	Number of units	Proportion of group	Proportion estimated on Posterior Probability	Average Posterior Probability in each group	Odds of correct classification *
1st	***Good scenario***	703	0.708	0.702	0.958	9.79
2nd	***Middle scenario***	248	0.250	0.255	0.895	25.54
3rd	***Severe scenario***	42	0.042	0.043	0.956	485.40

*based on the weighted posterior probability group assignment

Table 38 *– Number of people by groups found with GBTM, the proportion for each group and proportion of final groups using the max posterior probability obtained from the estimation of the model, average posterior probability for each group and the odds of correct classification, due to the posterior probability of group membership.*

Good scenario Middle scenario Severe scenario

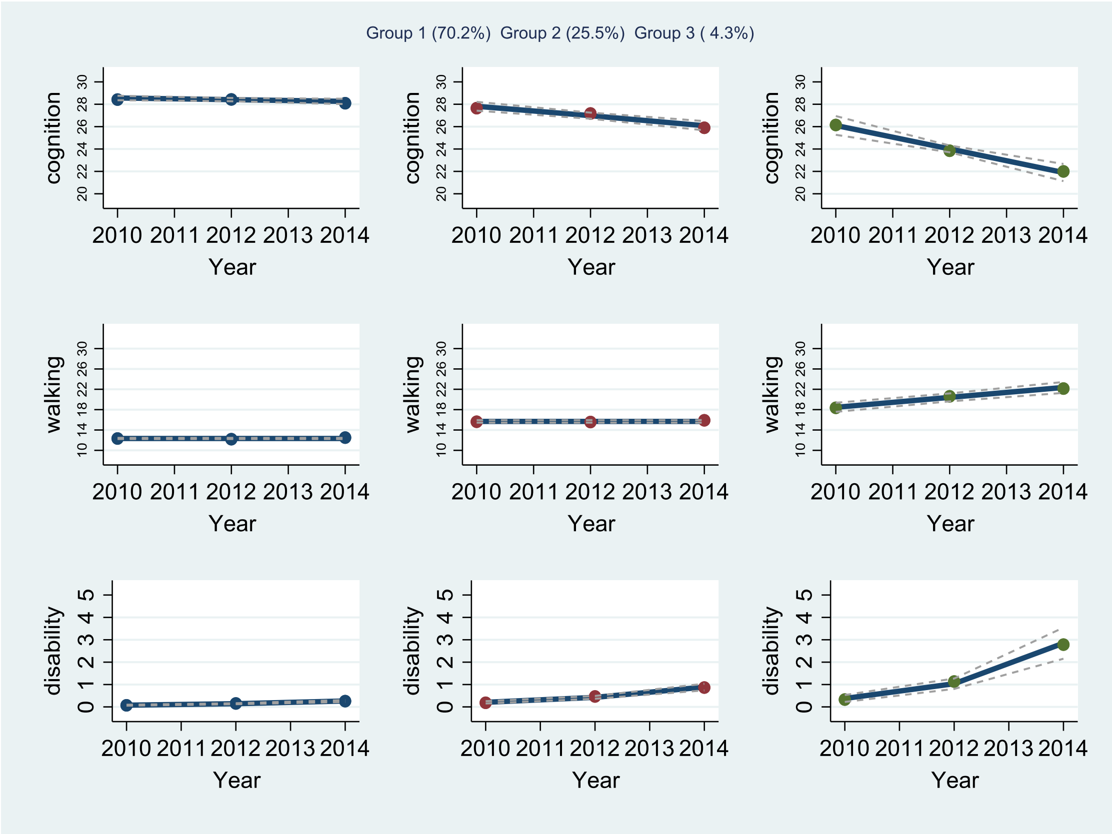


Figure 22 *– Reading the figure in column: the trend for each outcome for the same group was presented. Reading the figure in line the same outcome was depicted divided in the three order groups.*

Similarly to the GBTM model fitted on simple outcome, the multi-trajectory model was fitted on the costrained subcohort of older adults with full data on every outcome.

The best model was characterized by a BIC=-11012.29. The model always identified three orders of trajectories but the shapes were different from the previous ones: the polynomial function was non linear in the walking speed as reported in Table 39.

The other indexes of goodness respected the recommended criteria (Table 40).

Moreover, a different number of subjects was allocated across groups with respect to the best multi-trajectory model fitted on the greater subcohort: the large number of subjects was in the middle group 46.1% (n=360) and not in the group with the best scenario (Table 40).

Model	**Trajectory shapes^**		
	Order 1st Good scenario	Order 2nd Middle scenario	Order 3rd Severe scenario
MMSE score	1	1	1
Walking speed test	0	0	0
ADL score	0	1	1

^Possible trajectory shapes; 0=zero-order; 1=linear; 2=quadratic; 3=cubic.

Table 39 *– Trajectories shape of the multi-trajectory model with MMSE score, Walking speed test without speaking and ADL score. Subcohort of subjects with completed data.*

Order groups	Trajectory group	Number of units	Proportion of group	Proportion estimated on Posterior Probability	Average Posterior Probability in each group	Odds of correct classification *
1st	***Good scenario***	345	0.435	0.428	0.867	8.74
2nd	***Middle scenario***	360	0.461	0.465	0.868	7.58
3rd	***Severe scenario***	81	0.104	0.107	0.931	112.72

*based on the weighted posterior probability group assignment

Table 40 *– Number of people by groups found with GBTM, the proportion for each group and proportion of final groups using the max posterior probability obtained from the estimation of the model, average posterior probability for each group and the odds of correct classification, due to the posterior probability of group membership. Subcohort with completed data.*

As shown in Figure 23, three trajectories for each group were more stable due to the constrain on subjects with all the information, considering that they were the elderly with the highest survival time since they completed the second follow-up of the study.

More precisely, the increase in disability was lower for all the three groups than in the previous model. With regard to walking speed, the values were higher but stable for all the three groups. Evaluating the multi-trajectories within the scenario, the worst had, on average, only one point in the entire follow-up in comparison with the three points found in the previous model.

The cognitive function always declined in time, but the decrease is around by 0.5 points for each year in the follow-up time, less marked (Figure 23). The other two groups showed quite stable trajectories in all the outcomes (Figure 23).

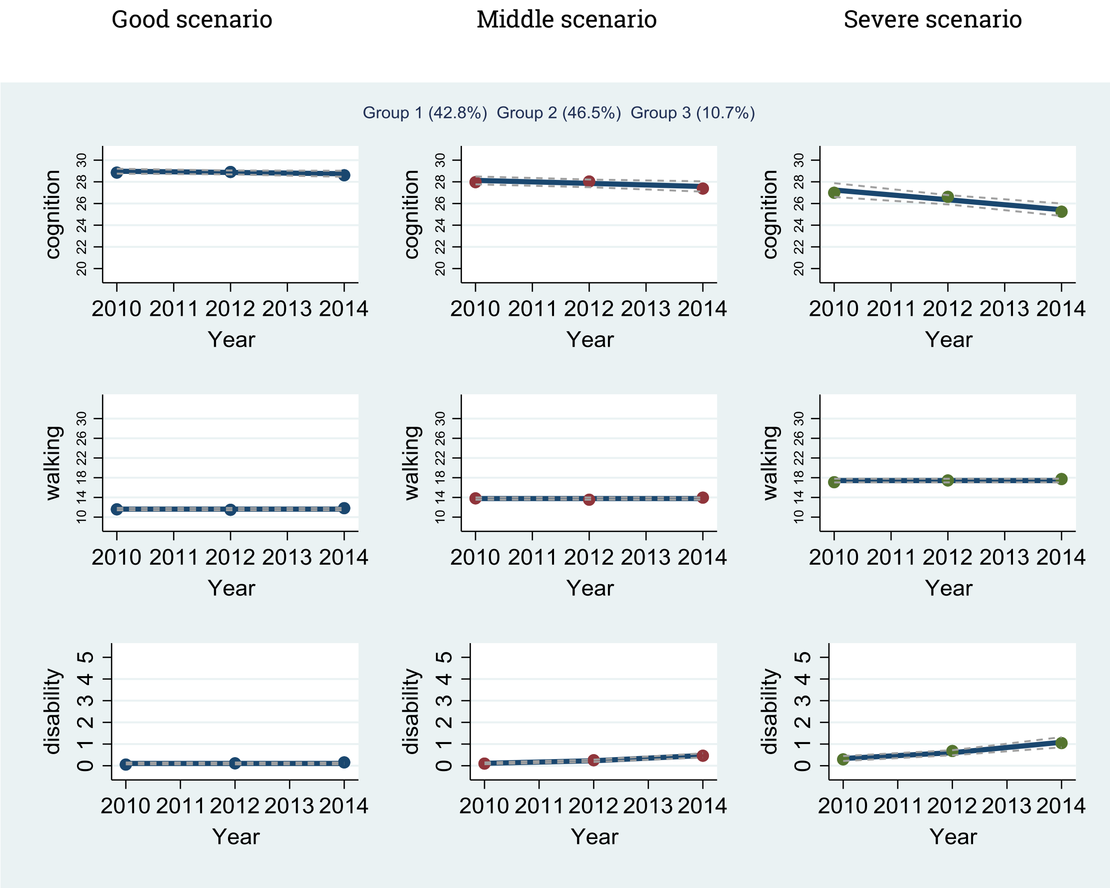


Figure 23 *– Reading the figure in column: the trend for each outcome for the same group was presented. Reading the figure in line the same outcome was depicted divided in the three order groups. Subcohort with complete data.*

Multi-trajectory with walking speed test without speaking and dementia

The multi-trajectory models identified a smaller number of people with dementia than models in which the outcomes were investigated separately.

Namely, at the end of the study only 36 and 20 people with dementia were estimated by both models respectively.

According to the multi-trajectory model fitted on the elderly with at least 2 times in follow-up with complete data for all the outcomes, the proportion of people with dementia based on final group overlapped the one based on posterior probability in every scenario.

Moreover, the worst scenario presented the highest amount of dementia compared with the other two (Table 41). The evidence from multi-trajectory model on constrained cohort (Table 42) was different: the number of subjects with dementia in the severe scenario was markedly smaller than the one estimated by the model with the greatest number of elderly people (13.1% vs 35.3%) as well as in the other two scenarios.

Finally, in the first model the distribution of people with dementia was 42% in the group with severe scenario, 39% in the middle group and 19% in the group with good scenario. In the second model, instead, it was 55%, 35% and 10% respectively.

Group	*n*	*Proportion of older adults with dementia using posterior probability*	*Proportion of older adults with dementia using final groups*
Good *scenario*	703	0.007 (0.003-0.016)	0.008
Middle *scenario*	248	0.073 (0.047-0.112)	0.063
Severe *scenario*	42	0.372 (0.243-0.521)	0.353

Table 41 *– Model with at least 2 times of follow-up completed (n=993).*

Group	*n*	*Proportion of older adults with dementia using posterior probability*	*Proportion of older adults with dementia using final groups*
Good *scenario*	345	0.003 (0.000-0.01)	0.004
Middle *scenario*	360	0.025 (0.014-0.047)	0.022
Severe *scenario*	81	0.145 (0.085-0.236)	0.131

Table 42 *– Model with no missing data for each time (n=781).*

Multi-trajectory model with dual-task walking speed test

The multi-trajectory model was fitted using dual-task walking speed test as outcome of functional activity on the subjects with at least two observations on all the outcomes (n=992) and then on the costrained subcohort (n=780), as usual. The best model describing the trajectory on 992 people showed a BIC of -15595.82 and three different orders of trajectory as specified in Table 43.

Model	**Trajectory shapes^**		
	Order 1st Good scenario	Order 2nd Middle scenario	Order 3rd Severe scenario
MMSE score	1	1	1
Walking speed test	0	0	1
ADL score	0	1	1

^Possible trajectory shapes; 0=zero-order; 1=linear; 2=quadratic; 3=cubic.

Table 43 *– Trajectories shape of the multi-trajectory model with MMSE score, Walking speed test dual-task and ADL score. Subcohort of subjects with completed data.*

As multi-trajectory in Table 40, all addition indexes of goodness were satisfied (Table 44).

Order group	Trajectory group	Number of units	Proportion of group	Proportion estimated on Posterior Probability	Average Posterior Probability in each group	Odds of correct classification *
1st	***Good scenario***	645	0.650	0.637	0.929	7.43
2nd	***Middle scenario***	285	0.287	0.301	0.868	15.34
3rd	***Severe scenario***	62	0.063	0.062	0.920	175.36

Table 44 *– Number of people by groups found with GBTM, the proportion for each group and proportion of final groups using the max posterior probability obtained from the estimation of the model, average posterior probability for each group and the odds of correct classification, due to the posterior probability of group membership.*

In contrast to the multi-trajectory model fitted on the same cohort with at least two times of completed data, this model identified another shape for the trajectories: these were linear for MMSE score and ADL score, in all the three order groups and the worst group.

The increasing trend in walking speed and in ADL score showed a worsening of disability and functional activities (Figure 24). Specifically, the group with best trajectory had more subjects showing a bad walking speed at baseline than the model with simple walking speed (mean value 14 sec vs 13 sec). Similarly, the baseline means for the other two groups were higher than in the model with a simple walking test. Disability in the group with severe scenario, in this last model with dual-task walking speed test, showed a worsening in time. The group with the worst scenario showed a less marked deterioration of functional activity than in the one measured with simple walking speed.

Good scenario Middle scenario Severe scenario

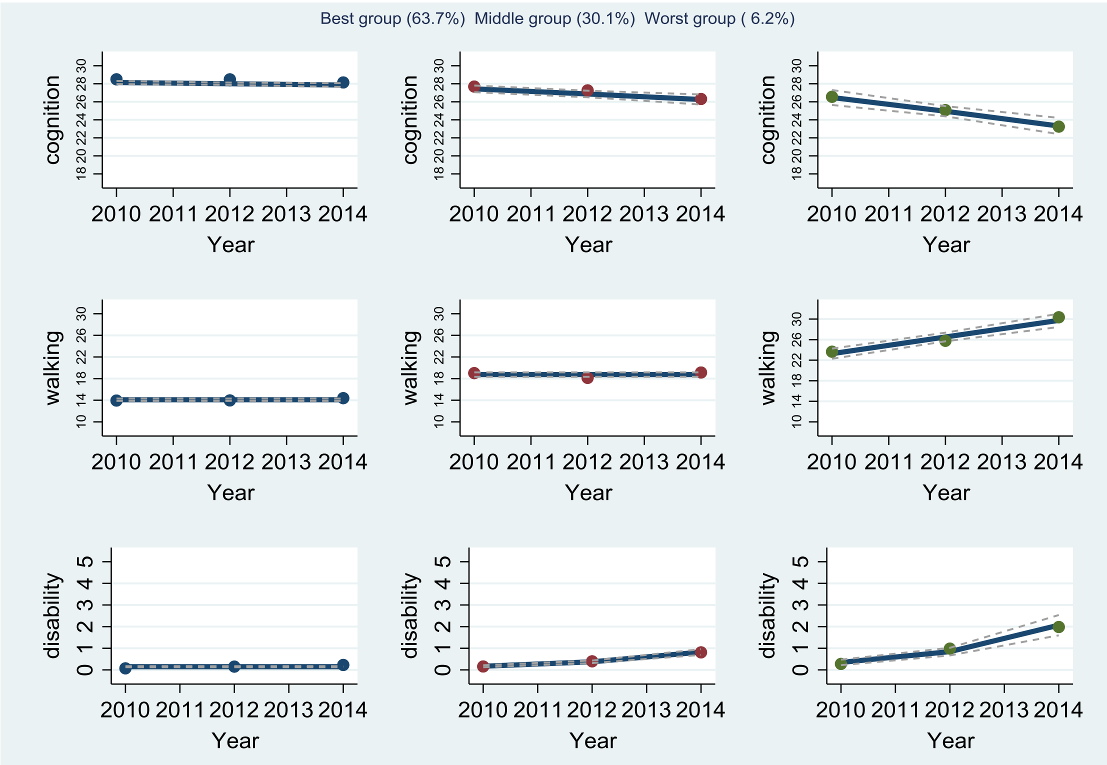


***Figure 24** – Reading the figure in column: the trend for each outcome for the same group was presented. Reading the figure inline the same outcome was depicted divided in the three order groups.*

Finally, the decreasing trend in MMSE was less remarkable from this model compared to the same model fitted by using walking speed (see Figure 24 vs Figure 22) in every scenario.

The best multi-trajectory model found using the constrained subcohort with all completed data on all outcomes (n=780, BIC=-12299.72) identified three final orders for the groups characterized by a trajectory shape similar to that one on a larger number of subjects (Table 45).

The additional indexes of goodness were verified and respected (Table 46).

Model	**Trajectory shapes^**		
	Order 1st Good scenario	Order 2nd Middle scenario	Order 3rd Severe scenario
MMSE score	1	1	1
Walking speed test	0	1	1
ADL score	1	1	1

^Possible trajectory shapes; 0=zero-order; 1=linear; 2=quadratic; 3=cubic.

Table 45 *– Trajectories shape of the multi-trajectory model with MMSE score, Walking speed test dual-task and ADL score. Subcohort with completed data.*

Order group	Trajectory group	Number of units	Proportion of group	Proportion estimated on Posterior Probability	Average Posterior Probability in each group	Odds of correct classification
1st	***Good scenario***	515	0.660	0.657	0.948	9.44
2nd	***Middle scenario***	225	0.288	0.291	0.878	17.63
3rd	***Severe scenario***	40	0.051	0.052	0.944	306.984

Table 46 *– Number of people by groups found with GBTM, the proportion for each group and proportion of final groups using the max posterior probability obtained from the estimation of the model, average posterior probability for each group and the odds of correct classification, due to the posterior probability of group membership. Subcohort with all completed data.*

As represented in Figure 25, this model brought some different results from the one with more subjects only for the group with the worst scenario: the increase in time in walking speed is near to 8 seconds, when in the previous model it was by around 9 seconds.

In the best and in the middle groups the scenarios were analogous with the model with at least 2 points data collected: performance had a quite stable trend.

There was also a slightly decrease in cognition with an approximately 1 point loss, on average, in MMSE score during all the period under study, while when the information used was not complete this loss was greater, of around 3 points. At least the disability got worse, but it had a smaller decrease: in 2014 the ADL mean score was near to 1 and not to 3 as reported previously.

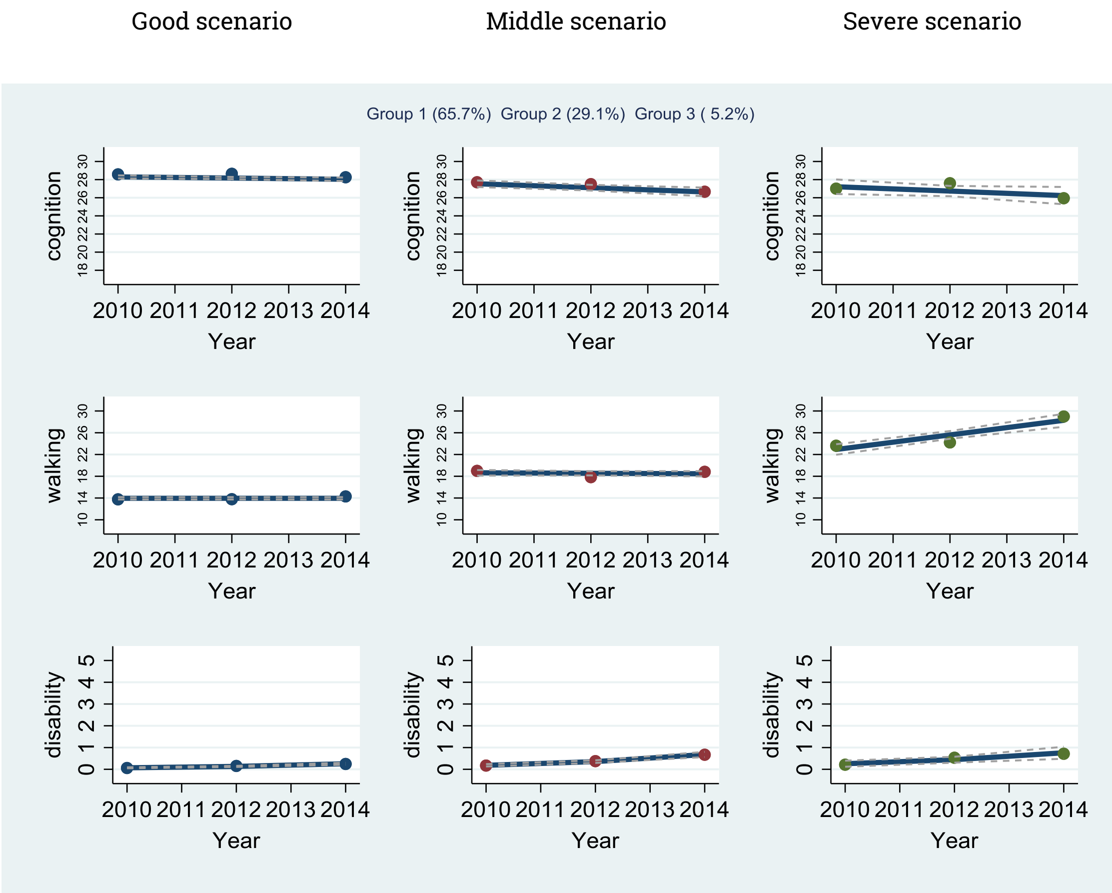


__Figure 25__ – Reading the figure in column: the trend for each outcome for the same group was presented. Reading the figure inline the same outcome was depicted divided in the three order groups.

Multi-trajectory with dual task-walking speed test and dementia

The models with dual-task walking speed gave different proportion of people with dementia only for the group with the worst scenario, changing the subset of analysis (Tables 47 and 48).

In the first model there were 36 subjects with dementia, mainly distributed in the group with severe and middle scenario (42% and 39% respectively) and in the second model there were 20 ones with dementia, mostly distributed in the group with the middle scenario (65%). The 20% was in the worst one.

By using data on proportion of people with dementia, in each group, the most noticeable change was found in the worst group.

If the proportion of people with dementia is compared between the model with dual-task walking test and the one with the simple walking test it is evident that there was a "loss" of information especially in the group with severe scenario from the cohort with at least two times of follow-up completed: around 29.3% (Table 47) compared to 35.3% (Table 41).

Group	*n*	***Proportion of older adults with dementia using posterior probability***	***Proportion of older adults with dementia using final groups***
Good *scenario*	645	0.004(0.001-0.012)	0.005
Middle *scenario*	285	0.064 (0.042-0.098)	0.052
Severe *scenario*	42	0.323 (0.219-0.447)	0.293

Table 47 *– Model with at least 2 times of follow-up completed (n=992).*

Group	*n*	***Proportion of older adults with dementia using posterior probability***	***Proportion of older adults with dementia using final groups***
Good *scenario*	515	0.004 (0.001-0.015)	0.005
Middle *scenario*	225	0.072(0.045-0.113)	0.057
Severe *scenario*	40	0.112 (0.047-0.244)	0.109

Table 48 *– Model with no missing data for each time (n=780).*

The 36 individuals with dementia identified from the multi-trajectory model on more subjects were distributed across three scenarios as follows: 8% in the best scenario, 39 in the middle and 53% in the severe one. On the other hand, in the constrained model among the 20 old-age people with dementia the 65% was in the middle scenario, the 20% in the severe and the 15% in the best one.

Group	***Model with at least 2 times of follow-up***	***Model with all data completed***
	n=36	n=20
Good *scenario*	*8%(n=3)*	15% (n=3)
Middle *scenario*	*39%(n=14)*	65% (n=13)
Severe *scenario*	*53% (n=19)*	20% (n=4)

Table 49 *– Distribution of elderly with diagnosis of dementia at the end of second follow-up in the three groups.*

Groups profile

The profiles of each group were made for the subjects identified by the multi-trajectory classic version of the walking speed test performed on subjects having at least two records: this choice ensures a larger amount of information.

The group with good scenario including the largest number of elders (n=703) was composed of 53.2% males. The mean age at baseline was 72.7 years (±1.4 years) and the years of education on average were 7.6. They regularly consumed on average 3.3 daily (±2.2) drugs, 18% (n=129) were ApoE-Ɛ4 carriers and near 12% were obese.

The second group (n=253) with the "middle" trend consisted in 65% females, with a 72.9 years (± 1.4 years) mean age at baseline and 5.8 years (± 2.6 years) of study on average. In this group, 24% were obese, 20% were ApoE-Ɛ4 carriers and they took regularly 4.2 drugs (± 2.3) on average.

The last group, displaying a severe scenario and involving a small number of older people (n=42), mostly included women (76%), who were slightly older than in the previous two groups (mean age 73.4 ±1.2 years) and with similar use of drugs 4.3 (±2.2). The average in terms of years of education was low (4.5 ± 3.2 years), 36% were obese and 19% were ApoE-Ɛ4 carriers.

No significant differences were found across the group as for the percentage of ApoE-Ɛ4 carriers (x^2 = 0.395, pvalue=0.815).

On the other hand, the profile of subjects in the three groups was different in terms of age, gender, educational level and obesity.

Namely, the elderly in the groups with the worst and middle scenario were older than those in the best one (pvalue <0.001 for both comparison).

Also the two aforementioned groups had a higher number of obese subjects (pvalue <0.001 for both comparison).

Subjects in the best scenario had the highest numbers of years of education (pvalue<0.001 and pvalue=0.018 respectively) and the lowest number of female subjects compared with the subjects in the middle and worst scenarios (pvalue<0.001 for both).

	RRR	**Std. Err.**	**[95% CI]**		**Pvalue**
Best Scenario	(base outcome)				
Middle Scenario					
Age at baseline	1.11	0.06	0.99	1.23	0.065
Gender	1.81	0.29	1.32	2.47	**<0.001**
ApoE-ε4	1.21	0.24	0.83	1.77	0.330
Obesity	2.13	0.42	1.45	3.13	**<0.001**
Years of education	0.84	0.03	0.79	0.89	**<0.001**
Worst Scenario					
Age at baseline	1.43	0.18	1.12	1.82	**0.005**
Gender	2.93	1.13	1.38	6.24	**0.005**
ApoE-ε4	1.24	0.53	0.54	2.87	0.610
Obesity	3.50	1.27	1.72	7.14	**0.001**
Years of education	0.63	0.06	0.53	0.75	**<0.001**

Table 50 *– Multinomial logistic model for multi-trajectory groups.*

The risk of being older was higher only in the group with the worst trajectories compared with the best group. To be more precise, it was 1.4 times greater (Table 50). In the worst group the risk of being a female was 2.9 times higher compared with the best group and in the middle group it was 1.8 times greater if compared to the group with the best scenario.

Education level was also heterogeneous among groups: if it was higher, the risk of being included in the worst group was lower than that of being in the best group (Table 50). Similarly, the risk of being in the middle group compared with that of being in the best group was inversely related to the level of education.

In respect of the clinical profile, only the obesity showed a remarkable difference across the three groups with different trajectories on cognitive status, disability and functional activity. To be more specific, the risk of being obese in the group with the worst scenario and in the middle group was 3.5 times and 2.1 times greater, respectively than in the best group (Table 50).

Swedish Cohort

In order to achieve the fourth specific aim a preliminary explorative analysis on different subcohorts of SNAC-K study was conducted.

The explorative analysis on GBTM model was always applied by means of the MMSE score, index of cognitive function, as the outcome.

In the first scenario explored 1044 subjects aged 60 and 66 and with data collection made for 3 times of follow-up (2001-2007-2013) were examined.

The trajectories were identified without risk factors. The best model (BIC= -4707.73 (n=2933)) identified two groups with different linear trajectories (Figure 26).

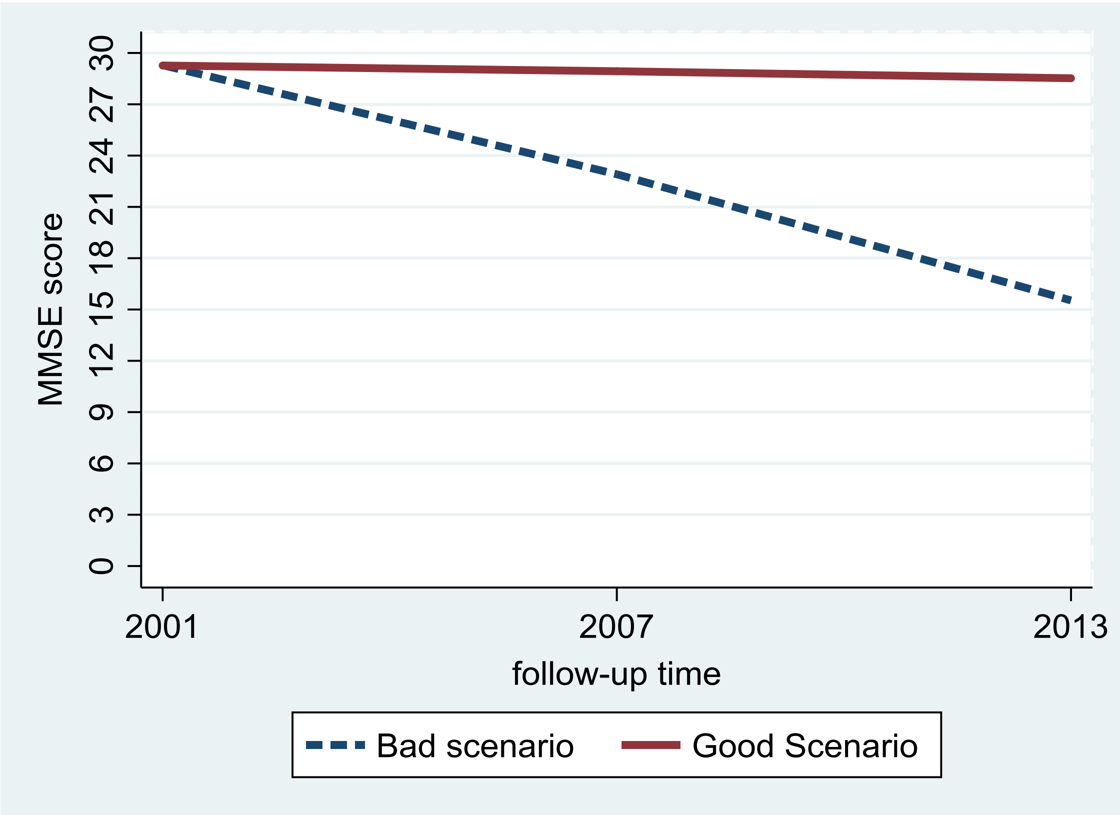


Figure 26 *– Groups from best GBTM on subject from SNAC-K with 60 and 66 years in 2001.*

The other indexes of goodness were respected (data not reported), except for the number of subjects in each group, which was a little weak.

The best group was characterized by a constant trend of 29 points in MMSE score during 13 years of follow-up and only 1.6% of people with dementia. The second group was composed of 17 subjects with an annual decrease approximately by 1 point during all the follow-up time. Among these 17 subjects 47% were females and 88% were diagnosed with dementia.

In the second scenario 344 subjects without dementia aged 72 in 2001 and with at least two records completed in the four follow-up times (2001,2007,2010 e 2013) were studied.

The best GBTM model (BIC= -2634.10 (n=1188) divides subjects in two orders of groups characterized once again by linear trajectories. As before, the additional indexes of goodness were respected (data not reported).

The best group of 72 year-old subjects (Figure 26) showed a stable MMSE during time of around 29 points on average: 13.7% of them had a diagnosis of dementia (n=44).

The group of elders with bad time trend in MMSE score (Figure 27) showed an annual decrease approximately by 1.5 points during the follow-up time. In comparison with younger older adults in the previous scenario, the worst group (n=22) had a slightly lower MMSE score also at baseline (they started at 28 vs 29 points on MMSE) and a higher percentage of women (around 63%). With respect to dementia, in the worst group all the people were diagnosed with it.

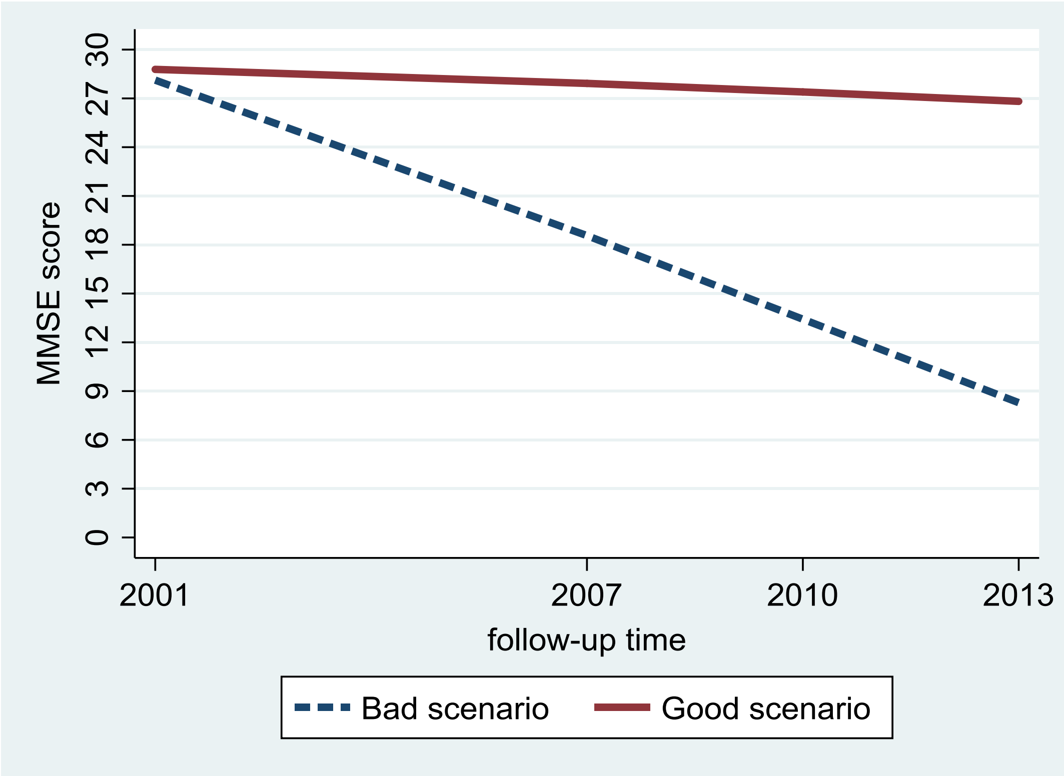


***Figure 27** – Groups from best GBTM on subject from SNAC-K aged 72 in 2001.*

The third scenario explored showed results on 888 older adults aged more than 78 at baseline and five times of follow-up (2001,2004,2007,2010,2013).

The best GBTM model (BIC=-7765.66) identified 2 trajectories as found in the other two subcohorts but some differences were found.

The numbers of elders in each group was more adequate: 734 elders in the best scenario and 153 in the worst trajectory group. The subjects in the worst group (Figure 27) showed an annual decrease by 2 points in MMSE score. The proportion of Swedish older people with a bad scenario in cognitive function was higher - around 17.3% (n=153) - in comparison with the two subsets with younger older people.

In regard to dementia in the worst group 94.2% (n=145) had a diagnosis of dementia and 76% were women. In the best group, instead, 20.6% (n=151) had a diagnosis of dementia and women were 70%.

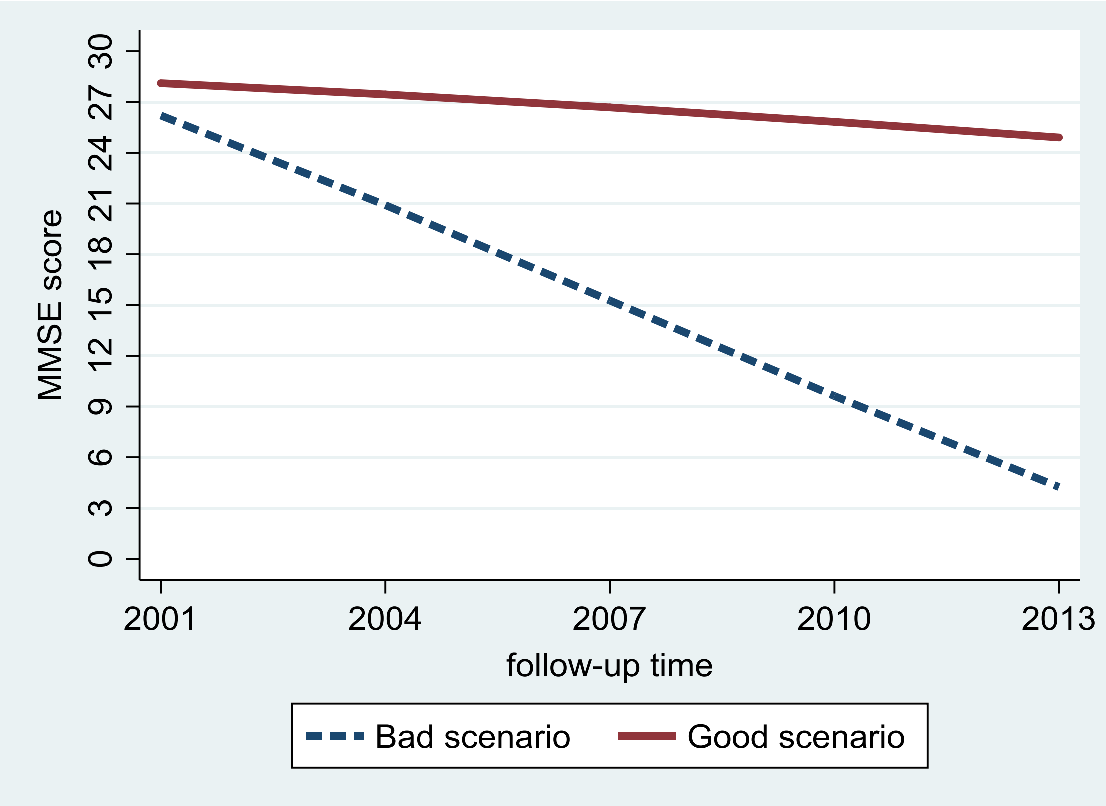


Figure 28 *– The best GBTM on subject of SNAC-K aged 78 or more in 2001.*

Sweden and Italy: a description of cognitive trends among older adults

The last scenario explored the description of cognitive trends in Sweden and Italy.

From the best GBTM model (BIC= -1639.60), 264 subjects composed the sample gathered from SNAC-K.

These participants had similar characteristics to the Italian cohort, in terms of age and follow-up time. To be more specific, mean age was 76.81 years (sd 0.87 years), 61% were women and the subjects had six years of follow up (2007-2010-2013). On the other hand, the Italian subcohort was composed of 352 older adults with a mean age of 74.51 years (sd 0.50 years), 53% were women and they had a four years follow-up (2010-2012-2014).

The best GBTM model for the Swedish population grouped subjects in two different MMSE trajectories (Figure 29). The additional indexes of goodness were satisfied (data not reported).

In particular, the number of subjects with the best scenario was 248 and they had a stable MMSE score near to 28 points. Among them, only 10%(n=24) developed dementia over the follow-up time.

The group with the worst MMSE score included individuals with an average annual decline of more than 2 points in MMSE score. This group is entirely composed of individuals who developed dementia over the follow-up.

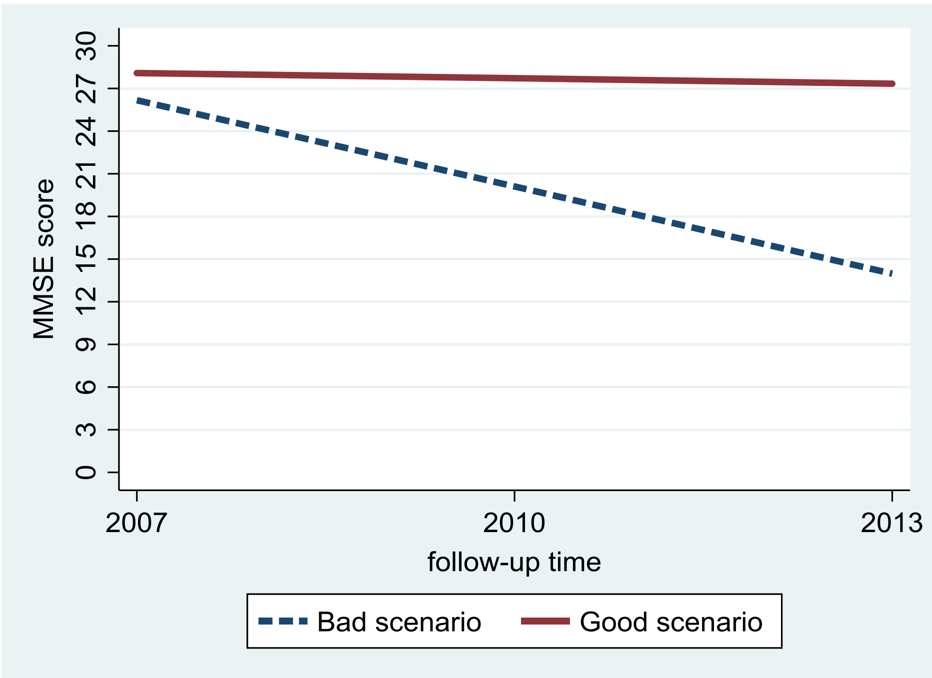


Figure 29 *– The best GBTM on the subject of Swedish cohort.*

With regard to the Italian cohort, the best model (BIC= -2114.46), was composed of three groups characterized by different trajectories (Figure 30). The subjects with a stable trend (n=275) showed an MMSE score in time that was higher than 27 points: less than 1.5% (n=4) had dementia. The middle group presented a slight annual decline in MMSE score of less than 1 point on average: 24% (n=15) were people with dementia. The group with the worst trajectory was formed of a small number of elders, half of them with a diagnosis of dementia (53%) and an average annual decline of 2 points in MMSE.

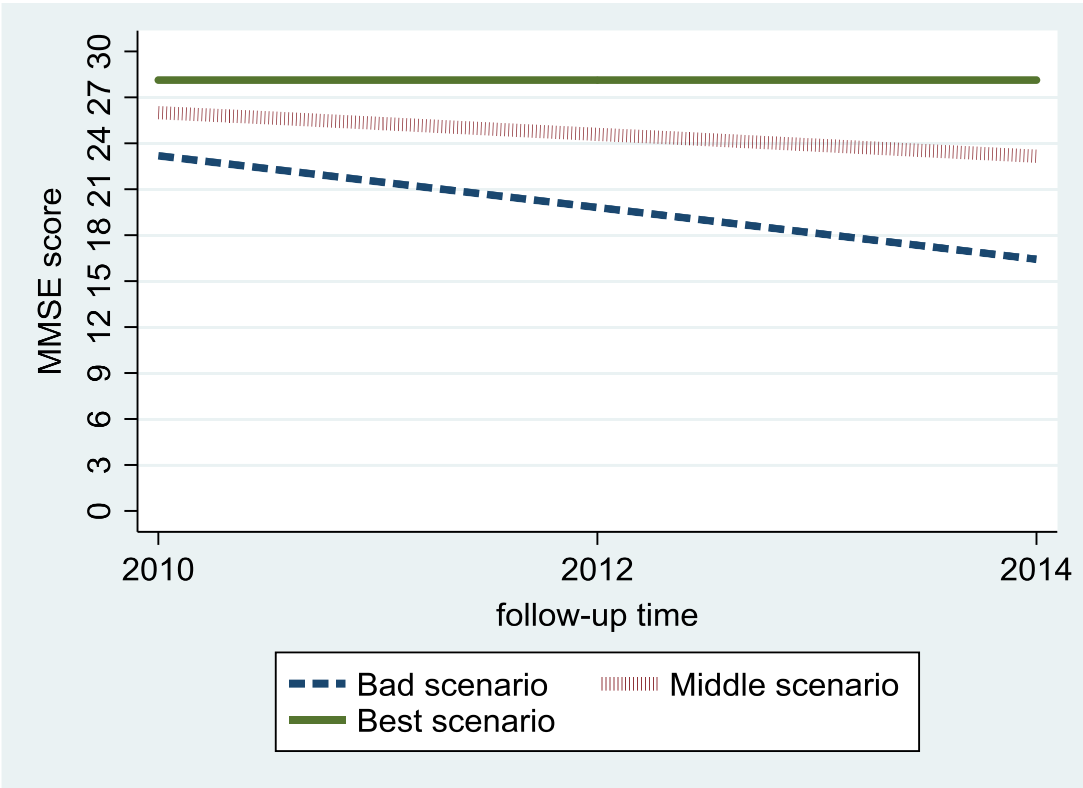


Figure 30 *– The best GBTM on subjects from the Italian cohort.*

The trajectories identified for the two subcohorts show that the majority of Italian and Swedish older adults had good and stable cognitive trajectories

(Figures 28 and 29), around 27 MMSE points. Most of the elderly examined belonged to this group: namely, 93.7% in Sweden and 76.6% in Italy.

In the groups with the steepest decline in cognitive function, the proportion of subjects with dementia captured by GBTM was 53% and 100% for Italy and Sweden respectively.

Unlike the Swedish subcohort, the GBTM model for the Italian one identified a group with a middle cognitive decline.

Discussion

The main findings can be summarized by the following points:

- the MMSE score is the best outcome using the GBTM model to describe the aging trajectories in the subgroup of individuals with dementia;
- the walking tests, performed with or without the speaking task, give different trajectories with respect to the performance. Both tests require much more effort from the subgroup including subjects with dementia, especially in the subgroup characterized by the worst physical function;
- trajectories on ADL score give a scenario of an increased disability in the course of time: difficulty to perform daily activities becomes considerable in the last period of the follow-up when subjects get older;
- multi-trajectories are good for most of the elderly: they have quite stable cognitive, physical function and they are free from disability in daily activities;
- the subjects belonging to the middle group show higher values in relation to time performance of the walking test and a low score in MMSE. Furthermore, on average the number of individuals with no disability is smaller;
- elders with a health status worsening over time, at the end of the study often have a diagnosis of dementia;
- the profile of the worst group, where subjects have a decline in all of the outcomes, is characterized by a higher presence of old women, who are obese and with low level of education;

- Italian and Swedish subcohorts have a similar trajectory for cognitive function (MMSE score) in the group with the best cognitive status;
- the worst groups in both the Italian and the Swedish cohort show the greatest number of subjects with dementia identified with GBTM: 100% for the Swedish and 53% for the Italian. This difference can be due to the presence of three groups in the InveCe.Ab cohort, whereas in SNAC-K the groups are two.

Italian elders over time

A large number of the Italian elders in the InveCe.Ab cohort, as stated in the results, grow older in a stable way with a good cognitive status, a good function activity and no impairment in daily activities. This result is consistent with the previous findings published by Christensen et al.[30] where the quality of life of people aged between 65 and 85 in the last 20 years has improved in comparison with the one of the previous cohort of elders.

These results, retrieved from the GBTM, are similar in terms of grouping subjects either using every single outcome or all the outcomes together. All the best models previously reported gathered subjects into three scenarios: worst, middle and best. Differences among models lie in the ability of these ones to identify within the worst groups the number of subjects with dementia.

The single analysis on the MMSE score gives the highest proportion of people with dementia in the worst group: 46.2%, compared with around 30% when the outcomes of cognitive, physical and disability function were analysed together in the multi-trajectories model.

With regard to the profile deriving from the multi-trajectory model, it is evident that in the worst scenario with the highest presence of subjects with dementia with respect to the middle and the best scenarios (5% and less than 1%, respectively) aging has the primary role in the development of dementia, but also obesity and educational level are important risk factors.

In the worst and in the middle scenarios, a higher presence of subjects with obesity is found. It is known that there may be a possible connection between obesity and cognitive and physical decline [19,21,31]. Moreover, obesity is identified as a modifiable risk factor for cognitive decline [32].

The education level is a well-known protective factor for cognitive decline [33 –35].

In the present work, the probability of not being included in the best physical, cognitive and disability-free scenario increased either for the subjects in the middle or for those ones in the worst scenario.

Understanding what are the factors, and which ones can be preventable, is very important not only for researchers in this field, but also for all the people who have to cope with dementia, from families to health and social professionals. This understanding may help the caregivers with the management of the elders as well as the patients with dementia.

Furthermore, it may support health professionals and policy makers in planning action for promoting a good aging strategy.

Sweden and Italian elders and cognitive function over time

Although different for several cultural, social and economic aspects, Italy and Sweden show common aspects about their cognitive function: a similar high percentage of older adults with good and stable cognitive trajectories - to be more specific, 93.7% in Sweden and 76.7% in Italy -, around 27 MMSE points over time. Despite this similarity, an important difference comes from GBTM: the number of groups with different trajectories is three for the Italian and two for the Swedish. This difference is probably due to the fact the Swedish typically have a higher education level in comparison with the Italian people.

In the groups with the steepest decline in cognitive function, the proportion of subjects with dementia captured by GBTM was between 53% and 100% for Italy and Sweden respectively.

This last result is probably due to the old age of people belonging to the SNAC-K cohorts characterized by subjects who reached the old age of 90 at the end of the study.

The GBTM fitted by using information only on cognitive function over time seems to consistently capture and group together a great proportion of people with dementia in the group with the worst cognitive trajectory.

To the best of our knowledge, this is the first time that the GBTM model has been used to describe cognitive trajectories in two different cohorts. Further studies need to be undertaken to better characterize people belonging to different cognitive trajectories.

Strengths and limitations

The GBTM is an easy way to assemble groups in order to find differences among them due to their main characteristics and to predict the time trend of the investigated outcomes. This offers the possibility of planning prevention activities and care management.

This methodology allows to take into consideration multiple different outcomes at the same time and/or to adjust or to predict other variables.

The GBTM model can be applied if the same information is measured repeatedly in the course of time, that is, in longitudinal studies.

Issues on the available data

The present study highlights that sometimes the loss of information can modify the composition of the groups.

The comparison among models with a different number of subjects due to their presence in all the follow-up times shows differences in the trajectories: this may be a problem, since the lack of stability may affect preventive planning.

Attrition is the main reason for the loss of information in longitudinal studies, given the so called attrition bias.

In respect of the relation between attrition and GBTM, the results reported give different views. The best model, according to the goodness of fit reported as BIC, is always the one with fewer subjects but all data completed. On the other hand, the more subjects are used, the more complete scenarios are given by the results, by means of all the information available.

The use of complete data only may give an overview in which only healthy subjects are represented, which does not reflect the population of reference, thus introducing some bias in the results.

Issues on the best version of the walking speed test

Another aspect highlighted in this work is related to the use of the walking test either in its classical or in the dual-task version.

For its higher complexity the dual-task walking test shows, as expected, a worse performance in terms of time in older individuals. However, the use of this version of the test allows to measure both physical and cognitive functions, thus giving more complete information on functional performances.

Random and systematic error

Systematic errors represent a risk in the epidemiological studies.
In the InveCe.Ab study selection bias was avoided by using a meticulous style of recruitment based on the personalization to contact subjects that brought a higher response rate, around 80%.

Furthermore, a bias which is often associated with studies involving the elders and which may have occurred in the InveCe.Ab and in the SNAC-K cohorts - thus undermining the validity of the information collected - is the recall bias: memory has a biological decrease, which, after a certain age, may lead to misclassification due to wrong answers. In any case, this bias is difficult to keep under control.

Finally, any other source of bias (information) has been controlled by using a crossed evaluation of diagnosis and, when necessary, by contacting family doctors, at least in the InveCe.Ab study.

Conclusion

Aging is a real, concrete and complex issue for human beings.

Constancy, perseverance and well-planned research are the keys to deepen in order to have a better knowledge of this phenomenon and its lifespan.

The evidence emerging from the present thesis contributes to expand on trajectories on different outcomes related to aging.

This represents a first investigation on trajectories on Italian elders: many other factors or relationships may be found by improving this methodology.

The creation of a national and/or international database including similar subjects within the same range of ages and with a standardized diagnosis of dementia by using a precise index on cognitive function may represent an oustanding achievement as well as a considerable step towards the prevention of dementia.

Collections of data gathered by means of longer observation periods and yearly visits may offer more accurate results in order to catch when the change in the course of time is important for the quality of life.

National data can offer much more homogeneous results from the exposure and life-style point of view. However, international data can give the entire scenario of the burden of this disease, showing factors that may increase or decrease its prevalence or incidence.

Future directions

Further exploration of these cohorts are needed to improve knowledge of other aspects related to older people's health and aging.

A successful application of our findings on other cohorts with similar characteristics to the InveCe.Ab cohort may be the first step to prove the usefulness of this methodology.

Understanding different patterns on homogeneous age cohorts can help to experience a better aging process and to prevent, as much as possible, all the potential risk factors.

The knowledge either of the effect of the combination of old-age diseases with dementia over time or of the aspects which have the strongest impact on the old people's life may be helpful for the young to adopt preventive behaviours that contribute to a good aging process, and for families to provide a solid support from a public health perspective.

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Appendix

Appendix 1

FONDAZIONE GOLGI CENCI
RICERCHE E STUDI PER GLI ANZIANI

ALZHEIMER ITALIA®
La forza di non essere soli.

ALLEGATO A

QUESTIONARIO AUTOCOMPILATO

Studio InveCe.Ab
Invecchiamento Cerebrale Abbiategrasso

Questionario di

COGNOME...Nome...................................

Gentile Signore/a,

La preghiamo di compilare il presente questionario in cui troverà delle domande sui Suoi dati anagrafici e sulle Sue abitudini di vita.
Queste informazioni, infatti, sono molto preziose per la Ricerca sullo stato di salute della popolazione e ci permetteranno eventualmente di ricontattarLa in futuro.

Grazie per la collaborazione!

N.B: *Questa parte verrà compilata dal personale sanitario:*
Codice DB:
visita n°:
data:

FONDAZIONE GOLGI CENCI
Piazza C. Golgi, 11 – 20081 Abbiategrasso (MI) - Tel. 02.94.85/21/ 2930/ 2444

A. INFORMAZIONI ANAGRAFICHE

Data della compilazione : □□ / □□ / □□□□
giorno mese anno

N° di Codice Fiscale: □□□□□□□□□□□□□□□□

Cognome ______________________________ **Nome**_________________________

Indirizzo: Via___________________________ **n°** _____

Comune ________________________________ **CAP** ______________ **Prov.** _______

n° di telefono: __________________________

1. Comune di nascita ___________________

2. Data di nascita □□ / □□ / □□□□
giorno mese anno

3. Sesso (Segnare con **una** crocetta **una** sola risposta)**:**
- □ maschio
- □ femmina

4. Nazionalità (Segnare con **una** crocetta **una** sola risposta)**:**
- □ italiana
- □ altra

Il Suo Medico di base è :

Cognome: _______________________________ Nome _________________________

n° di telefono: ________________________

B. DATI SOCIO-AMBIENTALI

1. Per quanti anni è andata/o a scuola? (Segnare con **una** crocetta **una** sola risposta)**:**

- non è andato a scuola
- 1
- 2
- 3
- 4
- 5 (5a elementare)
- 6
- 7
- 8 (3a media)
- 9
- 10
- 11
- 12 magistrali
- 13 (licei, Itc, ecc.)
- 14
- 15
- 16
- 17 corsi di laurea di 4 anni
- 18 corsi di laurea di 5 anni
- 19 corso di laurea in Medicina
- 20 Dottorato o Specializzazioni
- 99 Non sa

2. Attualmente lei è (Segnare con **una** crocetta **una** sola risposta)**:**

- pensionato e non lavora
- pensionato e lavora ancora
- non pensionato e lavora
- non pensionato e non lavora

3. Principale occupazione durante la vita lavorativa (Segnare con **una** crocetta **una** sola risposta)**:**

- operaio, artigiano, agricoltore,
- casalinga
- impiegato, assistente tecnico, infermiere, commerciante, segretaria
- professionista (medico, avvocato, commercialista, insegnante, manager, direttore, imprenditore)
- non occupato
- non sa

3.1. Considera il lavoro che ha prevalentemente svolto, fisicamente (Segnare con **una** crocetta **una** sola risposta) :

- non impegnativo
- poco impegnativo
- abbastanza impegnativo
- molto impegnativo

3.2. Considera il lavoro che ha prevalentemente svolto, in generale (Segnare con **una** crocetta **una** sola risposta):

- non stressante
- poco stressante
- abbastanza stressante
- molto stressante

3.3. Giudica il lavoro che ha prevalentemente svolto nella sua vita lavorativa (segnare con **una** crocetta **una** sola risposta):

- molto piacevole
- abbastanza piacevole
- poco piacevole
- per nulla piacevole

4. Stato civile (segnare con **una** crocetta **una** sola risposta):

- coniugato/a
- convivente
- separato/a;divorziato/a
- vedovo/a
- celibe/nubile
- altro

5. Ha avuto figli ?

- SI
- NO

Se sì

5.1. quanti? (n° di figli) ____

6. Nell'ultimo anno per la maggior parte del tempo lei ha vissuto (segnare con **una** crocetta **una** sola risposta):

- con il coniuge e altri (per es. figli, genitori)
- con il coniuge soltanto
- con altri familiari (senza coniuge)
- solo
- ricoverato (specificare): _______________
- altro (specificare): _________________________________

7. Situazione economica

7.1. Qual è la sua principale fonte di guadagno? (E' possibile segnare più di una risposta)

- Pensione
- Lavoro
- Altro
- Nessuna

7.1.1. Se pensionato/a quale tipo di Pensione (è possibile segnare più di una risposta):

- Di lavoro
- Di superstite (reversibilità)
- Di invalidità
- Sociale

7.2. Ritiene il suo reddito (pensione e altro) adeguato alle sue necessità? (Segnare con **una** crocetta **una** sola risposta)

- Adeguato
- Appena sufficiente
- Inadeguato
- Non risponde

7.3. Nella sua situazione attuale (segnare con **una** crocetta **una** sola risposta):

- ha gravi preoccupazioni e debiti
- deve stare attento alle spese e limitarsi
- è abbastanza tranquillo da un punto di vista economico
- ha buone disponibilità economiche

7.4. Ci sono stati periodi della vita in cui ha avuto improvvise e gravi difficoltà economiche(es. debiti, fallimenti, perdita stipendio)?

- NO · SI

Se sì:

7.4.1. Per quanto tempo?

- tanto tempo
- poco tempo

C. ORA QUALCHE DOMANDA SU COME AFFRONTA LE ATTIVITA' DI TUTTI I GIORNI

1. Attività di base della vita quotidiana (deve segnare con una crocetta il modo con cui nel mese scorso ha svolto la funzione indicata, una sola risposta per ogni domanda)

1.1. Abitualmente come fa a FARSI IL BAGNO (vasca, doccia)?

- Fa il bagno da solo (entra ed esce dalla vasca da solo).
- Ha bisogno di assistenza soltanto nella pulizia di una parte del corpo (es. dorso).
- Ha bisogno di assistenza per più di una parte del corpo

1.2. Abitualmente come fa a VESTIRSI? (prendere i vestiti dall'armadio e/o cassetti, inclusa biancheria intima, mettere i vestiti, uso delle allacciature e delle bretelle se utilizzate)

- Prende i vestiti e si veste senza bisogno di assistenza.
- Prende i vestiti e si veste senza bisogno di assistenza eccetto che per allacciare le scarpe.
- Ha bisogno di assistenza nel prendere i vestiti o nel vestirsi oppure non si veste (ad esempio perché rimane a letto o in pigiama)

1.3. Abitualmente come usa il GABINETTO?

- Va in bagno da solo, si pulisce e si riveste senza bisogno di assistenza *(può utilizzare mezzi di supporto come bastone, deambulatore o seggiola a rotelle).*
- Ha bisogno di assistenza nell'andare in bagno, nel pulirsi e/o nel rivestirsi.
- Non si reca in bagno per l'evacuazione

1.4. Come fa a SPOSTARSI ?

- Si sposta dentro e fuori dal letto ed in poltrona senza assistenza (può utilizzare mezzi di supporto come bastone, deambulatore)
- Compie questi trasferimenti solo se aiutato
- Allettato, non esce dal letto

1.5. E' continente per FECI E URINE?

- Controlla completamente feci e urine
- "Incidenti" occasionali
- Necessita di supervisione o aiuto per il controllo di feci e urine, usa il catetere, è incontinente

1.6. Abitualmente come fa ad ALIMENTARSI?

- Non ha bisogno di assistenza
- Ha bisogno di assistenza solo per tagliare la carne o versare le bevande
- Ha bisogno di assistenza per portare il cibo alla bocca (o usa la nutrizione artificiale)

2. Attività strumentali della vita quotidiana (deve segnare con una crocetta il modo con cui <u>nel mese scorso</u> ha svolto la funzione indicata, una sola risposta per ogni domanda)

2.1. Abitualmente come usa IL TELEFONO ?

- Usa il telefono di propria iniziativa: cerca il numero e lo compone.
- Compone solo pochi numeri ben conosciuti.
- Risponde al telefono, ma non compone i numeri.
- E' incapace di usare il telefono.
- *non ha /non usa il telefono*

2.2. Abitualmente come FA LA SPESA?

- Si prende cura della spesa e la fa in maniera autonoma.
- E' capace di effettuare solo piccoli acquisti.
- Ha bisogno di essere accompagnato/a per qualunque tipo di acquisto.
- Non è in grado di fare la spesa.
- *non fa mai la spesa, ma se necessario sarebbe in grado in farla*

2.3. Abitualmente come PREPARA I PASTI?

- Pianifica i pasti, li prepara adeguatamente e li porta in tavola in maniera autonoma.
- Prepara i pasti solo se ha a disposizione tutti gli ingredienti.
- E' in grado di riscaldare cibi già pronti oppure prepara i cibi in maniera non costante
- Ha bisogno di cibi già preparati e di essere servito.
- *Non prepara mai i pasti, ma se necessario sarebbe in grado*

2.4. Abitualmente come si prende CURA DELLA CASA?

- Riesce ad occuparsi della casa autonomamente o con occasionale aiuto per i lavori pesanti.
- Riesce ad effettuare i lavori domestici leggeri come lavare i piatti, rifare il letto, ecc.
- Riesce ad effettuare i lavori domestici leggeri, ma le riesce difficile mantenere un livello adeguato di pulizia.

- Ha bisogno di aiuto per tutte le pulizie della casa.
- *Non se ne occupa mai, ma se necessario sarebbe in grado di farlo*

2.5. Abitualmente come FA IL BUCATO?
- Lava tutta la propria biancheria
- Lava solo piccoli indumenti
- Tutto il bucato deve essere fatto da altri
- *Non se ne occupa mai, ma se necessario sarebbe in grado di farlo*

2.6. Abitualmente come si muove FUORI CASA?
- Viaggia autonomamente, servendosi dei mezzi pubblici o della propria automobile
- Non è capace di usare i mezzi pubblici da solo e viaggia in automobile solo se guidano altri
- Viaggia sui mezzi pubblici solo se assistito o accompagnato da altri
- Viaggia in macchina solo quando è assistito o accompagnato da altri anche per entrare e uscire dall'auto
- *Non esce mai di casa*

2.7. Abitualmente come gestisce i PROPRI FARMACI?
- Assume correttamente le medicine, senza aiuto
- Assume le medicine solo se in precedenza già preparate e separate da altri
- Per assumere le medicine ha bisogno dell'aiuto di altri
- *non assume nessun farmaco*

2.8. Abitualmente come USA DEL PROPRIO DENARO?
- Provvede in modo autonomo alle proprie finanze (conti, fare assegni, pagare l'affitto e le altre spese, andare in banca) controlla le proprie entrate.
- Provvede alle spese ed ai conti quotidiani, ma ha bisogno di aiuto per le operazioni maggiori (andare in banca, fare assegni, fare grosse spese, ecc.)
- Non maneggia mai il denaro, neppure per le spese quotidiane

3. Attualmente ha problemi di vista che <u>riducono la sua capacità di compiere tutte le attività quotidiane?</u>

- SI · NO

4. Attualmente ha problemi di udito che riducono la sua capacità di compiere tutte le attività quotidiane?

- SI · NO

D. ED ORA QUALCHE DOMANDA SULLE SUE ABITUDINI DI VITA

1. Alimentazione

1.1 Con quale frequenza mangia pesce ?
- mai · 1 volta/sett · 2/ volte sett · 3 o più volte

1.2. Prima dei 60 anni questo consumo di pesce era

- uguale - di più - di meno

1.3. Con quale frequenza mangia verdura fresca?
- mai - 1 volta/sett - 2/ volte sett - 3 o più volte

1.4. Prima dei 60 anni questo consumo di verdura fresca era
- uguale - di più - di meno

1.5. Con quale frequenza mangia frutta fresca?
- mai - 1 volta/sett - 2/ volte sett - 3 o più volte

1.6. Prima dei 60 anni questo consumo di frutta fresca era
- uguale - di più - di meno

1.7. Come giudica le sue abitudini alimentari? (Segnare con **una** crocetta **una** sola risposta)
- Equilibrate: mangia un po' di tutto e non sempre la stessa cosa
- Tende a mangiare sempre la stessa cosa
- Sta seguendo una dieta per dimagrire o perché consigliata dal medico

1.8. Qual'è il pasto principale della giornata? (Segnare con **una** crocetta **una** sola risposta)
- Prima colazione
- Pranzo
- Cena
- Non sa indicare

1.9. La quantità di cibo che mangia di solito è diminuita o aumentata nell'ultimo anno? (Segnare con **una** crocetta **una** sola risposta)
- Rimasta uguale
- Aumentata
- Diminuita di poco
- Diminuita molto

1.10. Come giudica il suo appetito? (Segnare con **una** crocetta **una** sola risposta)
- Scarso
- Normale
- Buono

1.11. Il suo appetito è stato sempre così? (Segnare con **una** crocetta **una** sola risposta)
- Si
- No, aumentato
- No, diminuito

1.11.1. Se diminuito, da quanto tempo? (Segnare con **una** crocetta **una** sola risposta)
- Negli ultimi 3 mesi
- Ultimi 3-12 mesi
- Da più di 1 anno

1.11.2. Quale è stata la causa? (Segnare con **una** crocetta **una** sola risposta)
- Nessuna specifica

- Malattia
- Farmaci
- Evento traumatico

1.12. Il suo peso, negli ultimi 12 mesi? (Segnare con **una** crocetta **una** sola risposta)
- E' rimasto uguale
- E' aumentato
- E' diminuito

1.12.1. Se è diminuito, quanto peso ha perso? Kg _______

1.13. Ha difficoltà a masticare?
- NO
- SI

Se sì:

1.13.1. perché? (Segnare con **una** crocetta **una** sola risposta)
- Senza denti o quasi
- Protesi che funziona male
- Non per problemi di denti

2. Fumo di tabacco

2.1. Lei fuma o fumava? (Segnare con **una** crocetta **una** sola risposta)
- mai fumatore
- ex-fumatore
- fumatore

Se non ha mai fumato passi direttamente alla domanda 3

2.2. Se fumatore o ex-fumatore: a che età ha iniziato? anni________

2.3. Se ex-fumatore: a che età ha smesso? anni________

2.4. Se fumatore o ex-fumatore: che cosa fuma o ha fumato prevalentemente?
- sigarette
- sigari
- pipa

2.5. Per i fumatori ed ex-fumatori: quante sigarette fumava in media al giorno dieci anni fa? _______________

2.6. Se fumatore di sigarette: quante sigarette fuma in media al giorno?__________

3 Consumo di alcoolici

3.1. Lei beve o beveva bevande alcooliche (vino, birra, liquori)?
- NO
- SI

Se sì:

3.1.1. Quando? (Segnare con **una** crocetta **una** sola risposta)
- ai pasti

- anche fuori pasto

3.1.2. Quando è stata l'ultima volta che ha bevuto più di 4 (se donna) o 5 (se uomo) bicchieri di bevande alcooliche in un giorno? (Segnare con **una** crocetta **una** sola risposta)
- meno di una settimana fa
- un mese fa
- 6 mesi fa
- un anno fa
- mai

4. Consumo di caffè, the

4.1. Lei beve o beveva caffè/the? ▪ NO ▪ SI

4.1.2 Se sì: quanti caffè/the al giorno? _____

4.1.3 Se ha smesso: a che età? _____

5. Sonno

5.1. Il suo sonno di solito è (segnare con **una** crocetta **una** sola risposta):
- regolare
- disturbato o con uso di sonniferi

5. 2. A che ora va a dormire la sera? _______

5.3. A che ora si alza al mattino? _______

5.4. Pensando all'ultimo mese, quando dorme:

Le capita di:	Mai	Qualche volta (1-2 volte al mese)	Spesso (3 o più volte al mese)
Non prendere sonno prima di 30 min			
Svegliarsi spesso la notte o presto al mattino			
Durante il sonno deve andare in bagno			
Durante il sonno non respira bene			
Durante il sonno ha tosse o russo			
Durante il sonno sente freddo			
Durante il sonno sente caldo			
Durante il sonno fa brutti sogni			
Durante il sonno ha dolore (es. crampi muscolari)			
Svegliarsi al mattino ed essere già stanco/a			

5.5. Come giudica la qualità del sonno dell'ultimo mese ? (Segnare con **una** crocetta **una** sola risposta)
- Ottima · Buona · Scarsa · Scadente

5.6. Con quale frequenza ha fatto uso di sonniferi? (Segnare con **una** crocetta **una** sola risposta)
- Mai · Qualche volta · Spesso

5.7. Quante volte le capita di avere colpi di sonno durante il giorno? (Segnare con **una** crocetta **una** sola risposta)
- Mai · Qualche volta · Spesso

5.8. Quanto spesso le capita di fare un riposino pomeridiano? (Segnare con **una** crocetta **una** sola risposta)
- Mai · qualche volta · spesso

5.9. C'è qualcuno che dorme nel suo stesso letto o nella stessa stanza?
- NO · SI

6. Attività fisica

6.1. Quale di queste frasi descrive meglio il suo ambito di movimento? (Segnare con **una** crocetta **una** sola risposta)

- Esco di casa quasi tutti giorni e mi reco fuori dal mio quartiere; a volte vado anche in altre città
- Esco di casa ma solo nei dintorni di casa mia, per fare spese o altro, e non mi allontano mai dai dintorni di casa mia
- Mi muovo solo all'interno della casa
- Ho difficoltà a muovermi anche all'interno della casa

6.2. Se è grado di uscire di casa, per svolgere le sue attività quotidiane :

	NO	1/2 volte alla settimana	3/4 vv la settimana	Tutti i giorni
Cammina per più di mezz'ora				
Usa la bicicletta				

6.3. Lei svolge attività fisica per divertimento o per mantenersi in forma?
- NO · SI

6.3.1 Nell'attività fisica che lei svolge le capita di sudare?
- NO · SI

6.4. Segni con una crocetta **quante volte nell'ultimo mese** ha praticato una delle seguenti attività <u>solo per divertimento o per mantenersi in forma</u>- *ad esempio se usa la bicicletta per fare la spesa non è da segnare, se la usa per fare un giro o per allenarsi la deve segnare*:

	Mai	1 volta la settimana	2 vv la settimana	3 o più volte
Cammino per più di mezz'ora al giorno				
Cammino per meno di mezz'ora al giorno				
Bicicletta				
Ballo				
Ginnastica di gruppo				
Nuoto				
Corsa				
Tennis				
Aerobica				
Altro				

7. **Reti sociali**

7.1. Lei trascorre del tempo abitualmente con amici o familiari (contatti con presenza fisica di persone , non solo telefonici) ?

- NO · SI

Se sì:

7.1.1. Con quante persone complessivamente: …..….. (n° di persone)

7.2. Segni con una crocetta se ha trascorso del tempo e quante volte nell'ultimo mese con*:*

	Non ce ne sono	Ci sono ma non li vedo mai	Li vedo qualche volta (1-3 volte al mese)	Li vedo spesso (4 o più volteal mese)
Vicino/a di casa				
Amici di vecchia data				
Nuove conoscenze				
Figlio				
Figlia				
Sorella				
Fratello				
Colleghi di lavoro				
Altro				

7.3. Lei è soddisfatto/a delle Sue relazioni familiari? (Segnare con **<u>una</u>** crocetta **<u>una</u>** sola risposta):

- Molto
- Abbastanza
- Poco
- Per niente
- Non risponde

7.4. Lei è soddisfatto/a delle Sue relazioni con gli amici? (Segnare con **una** crocetta **una** sola risposta):

- Molto
- Abbastanza
- Poco
- Per niente
- Non risponde

E. PERCEZIONE DELLO STATO DI SALUTE

1. Giudizio soggettivo

1.1. Come giudica il Suo stato di salute? Nel complesso come si sente ora? (Segnare con **una** crocetta **una** sola risposta)

- Molto male
- Abbastanza male
- Così così
- Abbastanza bene
- Molto bene

1.2. Come si sente rispetto ad un anno fa? (Segnare con **una** crocetta **una** sola risposta)

- Molto peggio
- Lievemente peggio
- Allo stesso modo
- Meglio
- Molto meglio

1.3. Pensa che negli ultimi due mesi ci siano stati dei cambiamenti nel Suo stato di salute?

- NO
- SI

Se sì

1.3.1 specificare :

- peggiorato
- migliorato

1.4. Si sente mentalmente più giovane, uguale o più vecchia/o della sua età reale?

- più giovane
- uguale
- più vecchia

1.5. Si sente fisicamente più giovane, uguale o più vecchia/o della sua età reale?

- più giovane
- uguale
- più vecchia

2. Avvenimenti della vita

2.1 Di seguito sono elencati degli avvenimenti che possono o no esserle successi: risponda **si** se sono occorsi nell'ultimo anno, **no** in caso contrario, *mettendo una crocetta nella casella corrispondente*

		si	no
1	difficoltà finanziarie importanti		
2	pensionamento		
3	perdita improvvisa del lavoro		
4	una nuova e importante malattia fisica (comparsa nel corso dell'ultimo anno)		
5	avere comunque altre malattie importanti che durano da lungo tempo		
6	difficoltà ad avere sostegno professionale adeguato , ad esempio dal medico o da un avvocato		
7	una malattia fisica importante di un membro stretto della famiglia		
8	incidenti o traumi		
9	aver subito un crimine (es: aggressioni, furti in casa o nell'appartamento)		
10	morte del coniuge		
11	morte di un figlio/a		
12	morte di un genitore		
13	morte di un fratello o una sorella		
14	morte di un altro parente o un amico molto vicino		
15	morte di un animale domestico (es: cane, gatto)		
16	obbligato a lasciare o a perdere la casa (es: sfratto)		
17	cambio di residenza volontario		
18	separazione o divorzio		
19	altre difficoltà con il coniuge		
20	problemi e conflitti rilevanti con altri che non sia il coniuge		
21	problemi rilevanti con amici o vicini		
22	interruzione di relazioni che duravano da lungo tempo, diverse dal matrimonio		
23	interruzione di rapporti con ogni altro parente o amico intimo		
24	una persona si è allontanata dalla sua casa (escludendo fine o interruzione del matrimonio o della convivenza)		
25	una persona è venuta a vivere in casa sua		
26	si prende cura di un parente o di un amico		

2.2 Di tutti queste situazioni, fra quelle cui ha risposto di "sì", qual è quella che l'ha colpita maggiormente? La situazione (ne indichi una sola) n°………….

F. ADESSO ALCUNE DOMANDE SULL'USO DELLA TECNOLOGIA (segni per favore con <u>una</u> crocetta <u>una sola risposta</u> ad ogni domanda)

1. Usa l'automobile? SI · NO ·
2. Usa il telecomando del televisore? SI · NO ·

3. Usa il bancomat ? SI ▪ NO ▪

4. Usa il cellulare? SI ▪ NO ▪

5. Usa il computer ? SI ▪ NO ▪

Se si :

5.1. Usa INTERNET? SI ▪ NO ▪

G. Risponda adesso alle ultime tre domande:

1. Ha problemi di udito ?

   SI ▪ NO ▪

2. Ha problemi di vista per cui ha dovuto farsi leggere il questionario?

   SI ▪ NO ▪

3. Ha compilato il questionario (segni una sola risposta):

   ▪ da solo/a ▪ con aiuto

Con riferimento alla Legge 196/2003 autorizzo la Fodazione Golgi Cenci al trattamento dei dati personali per eventuali comunicazioni a me e a scopo epidemiologico e di ricerca scientifica in forma anonima.

Firma

…………………………………………….

Grazie per la collaborazione!