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Neurocognitive and psychological reserves:

a multifactorial approach to aging

Candidato

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Ma i vecchi, i vecchi

Se avessi un'auto da caricarne tanti

Mi piacerebbe un giorno portarli al mare

Arrotolargli i pantaloni

E prendermeli in braccio tutti quanti

Sedia, sediola, oggi si vola

E attenti a non sudare.

(*I vecchi,* Claudio Baglioni)

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PREFACE

The present thesis embodies the results of my research activities conducted at the Department of Clinical and Experimental Medicine, Unit of Geriatrics, and focused on the fields of Psychogeriatrics and Psychology of Aging.

Under the supervision of Prof. Antonino Catalano, the discussed research activities were developed in collaboration with Prof. Giorgio Basile, whit whom a multidimensional approach to frailty evaluation was shared, and with Prof. Maria C. Quattropani, who leads the Clinical Psychology Research Group at the *Research and Psychological Intervention Center* (University of Messina) and co-tutored the present thesis.

The design and the development of the discussed research topics have been also enriched by the collaboration with Prof. George A. Bonanno from the Columbia University (USA), and with Dr. Francesca Morgante and Dr. Luciana Ricciardi from St. George's University of London (UK). Prof. Bonanno provided an expert intellectual contribution to the novel investigation of psychological resilience among elderly population; Dr. Morgante and Dr. Ricciardi contributed to an accurate interpretation of the association between cognitive and physical functioning among elderly, within the theoretical framework of Cognitive Reserve.

The first chapter of this thesis provides an introductory theoretical background concerning the nature of the link between cognition and physical functioning along aging trajectories, by presenting a recently published point of view.

The second chapter introduces the concept of Cognitive Reserve and provides an updated state of the art on the association between Cognitive Reserve and frailty among elderly, which represents the theoretical framework of our observations.

In the light of the theoretical background previously provided, the third chapter consists in the experimental section in which currently unpublished evidence on the interaction between Cognitive Reserve indexes and cognitive, physical and functional outcomes will be discussed.

The fourth chapter of the present thesis will focus on the construct of psychological resilience, and our related experimental observations will additionally be presented. In this context, the association between psychological resilience factors and age-related outcomes (e.g. frailty and quality of life) among elderly represent novel topics of research.

Eventually, the final chapter will provide comprehensive conclusions and clinical future implications in the light of the discussed evidence.

CHAPTER 1

From cognitive to motor impairment and from sarcopenia to cognitive impairment: a bidirectional pathway towards frailty and disability

(Basile G, Sardella A. Aging Clin Exp Res 2020; published online ahead of print)

The progressive decline of cognitive functions and the gradual reduction of motor/physical performances are broadly considered as outcomes associated with older age, which are indeed able to characterize aging trajectories, even though differently.

It is known that motor functioning declines with increasing age due to several influencing factors, either as part of the normal biological aging process, or either as consequence of lifestyle-related aspects (e.g. nutrition, physical activity). Moreover, faster rate of motor decline are associated with increased mortality, which suggests that the late life impairment of motor function might reflect forthcoming death rather than merely advancing age (Wilson et al., 2012). Equally, muscle strength, another broadly established index of health, declines with increasing age. Specifically, the course of decline in handgrip strength appears linear in the age span of 50 to 85 years, reaching a horizontal plateau in the oldest women (Frederiksen et al., 2006).

Similarly, even cognitive functions go through a period of accelerated decline during the last years of life, indicating that a faster cognitive decline in older adults might be considered not only as the consequence of neurodegenerative processes (e.g., leading to dementia), but also an expression of a wider biological decline in proximity to death. Additionally, a large longitudinal study displayed that the shape of pre-death cognitive modification, even though characterized by a sharp decline if compared with usual aging-related change, nonetheless still indicates a gradual decline rather than a precipitous drop (MacDonald et al., 2011). Interestingly, motor and cognitive performances also appear to share a common trajectory since a sharply accelerated decline occur about 2.5 years before death in both motor and cognitive status, with the onset of terminal motor decline which seems correlated with the onset of cognitive decline (Wilson et al., 2012).

Not to mention that several shared health-related factors underlie the decline of both cognitive and motor functions. Specifically, factors related to pathological mechanisms (e.g. inflammatory, cardiovascular, metabolic), aspects related to lifestyle (e.g. physical activity, smoke, alcohol), as well as psychosocial factors involved in the comprehensive construct of cognitive reserve equally affect cognitive and motor individual trajectories.

Although running parallel along the same temporal continuum, cognitive and motor/physical functions may evolve at different speeds along the entire lifespan, and with different impact on aging processes. Therefore, subjects simultaneously presenting a cognitive impairment and a reduction of motor/physical performances could differentiate among themselves in terms of precocity of the cognitive symptom compared to the motor/physical ones, or vice versa.

Over the past few years, this integrated perspective has become the common denominator for several studies investigating this brain-muscle loop (Lauretani et al., 2017), in line with the hypothesis that neurodegenerative damages as well as systemic, inflammatory and metabolic burden may represent potential shared determinants of both cognitive and motor impairment (Grande et al., 2019a). According to this perspective, negative aspects of neurocognitive aging (e.g. grey matter atrophy or white matter hyperintensities) jointly contribute to exhibited motor, cognitive and sensory functions, which are maintained by several functional compensation processes (e.g. bilaterality, neurogenesis or functional recruitment). Furthermore, motor, cognitive and sensory functions might benefit from cognitive enrichment factors (e.g. exercise, or cognitive training), which positively affect both functional compensation and neuropathological aspects (Li et al., 2018).

Consistently, performing physical exercise has been found to produce even structural changes in some brain regions involved in cognitive impairment. Accordingly, it was previously showed that 1-year moderate-intensity aerobic exercise was associated with an increased hippocampus volume and improved memory performances within older not-demented adults (Erickson et al., 2011), compared to a stretching-based exercise. Moreover, resistance exercises and resistance training were recently discussed as able to induce substantial functional brain changes even in the frontal lobe, together with improvement in executive functions, within healthy, Mild Cognitive Impairment (MCI) and early dementia older adults (Herold et al., 2019).

Thus, the investigation of the association between cognitive and motor/physical functions has represented a challenging subject of debate in the last decades. Physical disability and neurodegenerative diseases often share both cognitive and motor impairment, even though at different degree of severity. However, the direction of this cognitive-motor link still needs to be furtherly clarified.

From cognitive to motor impairment

A first pathway suggests that pre-clinical cognitive decline, such as the MCI, may have a negative impact not only on cognitive status, but similarly also on motor/physical performances. A recent meta-analysis has shown that patients with MCI, compared to healthy controls, exhibit a reduced walking speed during the execution of one or two cognitive tasks; additionally the authors suggest that subjects' attentional load in executing the cognitive tasks could play a significant role in the reduced motor performance. Furthermore, patients with MCI, compared to healthy controls, also show greater balance deficits; the possible explanation of this association might be due to the deficit in the visual information processing which is common in MCI, and which interferes with postural control, producing postural oscillations (Bahureksa et al., 2017).

Moreover, since cognitive decline and muscle weakness are equally prevalent negative outcomes in aging, several studies have also investigated the temporal relationship between decline of muscle strength and cognitive performance, suggesting the presence of an earlier cognitive decline compared to the physical one. Accordingly, early attention impairment has been previously associated to motor performances longitudinal decline among older community-dwellers with normal motor functioning at baseline (Inzitari et al., 2007). Similarly, better attention, processing speed and memory functioning have been associated with slower decline in handgrip strength at 4-years follow-up, in a large sample of oldest old (Taekema et al., 2012). The early presence of cognitive impairment has been also confirmed in a longitudinal observation on a large sample of elderly women, highlighting that cognitive decline preceded the progressive reduction of gait speed and handgrip strength (Atkinson et al., 2010).

Recently, evidence from a further longitudinal population-based study confirmed the above-mentioned cognitive-to-motor trend, highlighting in addition a potential difference across age: poorer cognitive performance was associated with precipitous decline in gait speed and handgrip strength among the older subjects (85–90 years) compared to younger ones (Stijntjes et al., 2017).

From sarcopenia to cognitive impairment

A specular pathway investigated over the years, suggests conversely the presence of earlier motor dysfunction as potentially predictor of further cognitive impairment. In line with this hypothesis, previous studies have pointed out that a reduction in walking speed may precede the onset of cognitive impairment in healthy subjects (Marquis et al., 2002; Waite et al., 2005). The evidence from a longitudinal study on a large sample of healthy subjects followed up for 20 years confirmed this association, also highlighting that a reduction in walking speed precedes cognitive impairment by almost a decade (Buracchio et al., 2010). Gait speed therefore assumes a relevant prognostic role for the detection of cognitive impairment and prodromal dementia (i.e all cause dementia, Alzheimer's disease (AD), vascular and non-AD dementia), in subjects with and without initial cognitive deficits (Grande et al., 2019a). Interestingly, the contemporary presence of gait and cognitive impairment has been considered also a potential better predictor of further risk of dementia than the cognitive-frailty construct (Montero-Odasso et al., 2016).

In this context, the so-called Motoric Cognitive Risk (MCR) syndrome certainly must be considered as a further confirmation of the close link between gait and cognition. MCR stands for a peculiar phenotype with a prevalent motor component, which affect about 8% and 6% of older persons in Europe and USA, respectively (Maggio & Lauretani, 2019), and which is characterized by a reduction in walking speed in the presence of cognitive complaints and preserved functional autonomy (Verghese et al., 2013).

Walking speed is thus commonly considered one of the markers of physical health, and it results often associated with the degree of functional autonomy in daily life, as well as it is considered one of the predictors of adverse outcomes, including falls and mortality (Chhetri et al., 2017). However, an equally important predictive role for the reduction of cognitive performance appears to be played by the loss of muscle mass and strength, which are common expression of sarcopenia. The association between sarcopenia and cognitive impairment has been a subject of debate in the past years, since these clinical conditions often share common risk factors such as malnutrition, sedentary lifestyle, or inflammatory processes (Chang et al., 2016).

Therefore, in line with this context, sarcopenia might be also considered a predictor of cognitive impairment. Accordingly, tight muscle cross sectional area (CSA) and skeletal muscle mass have been found to be associated with cognitive performance in a large sample of healthy subjects (Kohara et al., 2017).

Since handgrip strength is broadly considered a relevant index of sarcopenia, several studies have investigated the hypothesis that potential earlier strength impairment might be associated with further cognitive decline. A possible explanation of this association might be that grip strength, as well as gait speed, primarily reflects the integrity of neural processes required for muscle coordination, which is strongly associated with cognitive functioning (Boyle et al., 2010).

Reduced handgrip strength has been previously linked to lower cognitive performances, especially in terms of executive functions, attention, working memory, and overall cognitive status in non-demented older subjects. Moreover, several studies have reported that decreased handgrip strength at baseline appeared strongly associated with developing MCI; conversely higher handgrip strength at baseline might be a protective factor not only for functional status, mobility and mortality as expected, but also for cognitive functioning (Fritz et al., 2017; Carson, 2018). In line with this perspective, in an elderly Korean population a significant cross-sectional association between grip strength and Mini Mental State Examination (MMSE) at the baseline was found. Additionally, the study highlighted also a significant and independent longitudinal influence of the grip strength on the onset of cognitive impairment in those subjects with normal MMSE at baseline (Kim et al., 2019a).

Bidirectional perspective

A challenging research approach might combine the two specular perspectives that have been separately discussed. Despite still few, some studies have started to investigate the association between cognitive and motor/physical functions in a bidirectional way.

Accordingly, a recent longitudinal study conducted on an American population followed for 20 years, confirmed a significant predictive value of baseline grip strength on the onset of further cognitive decline, estimating proportionally lower risk to develop cognitive decline every 5 kg of increase in handgrip strength. However, interestingly, the authors also highlighted a significant bidirectional association in which the absence of cognitive deficit or the presence of different baseline cognitive deficit severity were associated with progressively higher risk to develop handgrip strength reduction (McGrath et al., 2019a).

Consistently, this evidence has been confirmed also in a Korean large population, followed up for 8 years, since it was shown a significant bidirectional relationship between muscular strength and cognitive functions, suggesting that these conditions might share common pathways such as oxidative stress or chronic inflammation (Kim et al., 2019b).

Conclusions

Several evidences have been discussed regarding the existing link between cognitive and physical functioning, as well as the suggested direction of this link (see Supplementary Material of Chapter 1).

Coexistent cognitive and motor/physical limitations establish a distinct risk profile for several adverse events in both community and institutionalized population. From a clinical perspective, routinely including measures of both handgrip strength and cognitive functions might help to identify patients at high risk for functional decline, since it is known that being both weak and cognitively impaired worsens the degree of autonomy in the performance of daily life activities (McGrath et al., 2019b). Moreover, concurrent, rather than isolated, cognitive impairment and reduced gait speed substantially increase the risk for developing disability (Grande et al., 2019b). Not to mention that co-occurring, rather than isolated, sarcopenia and cognitive impairment have been found to be relevant predictor of the 12 months-mortality in older adults, after discharge from acute care hospital (Zengarini et al., 2019).

The reduction of cognitive and motor/physical functions have been commonly considered as independent events, however they are often associated, and they also result mutually able to accelerate the evolution of each other. Therefore, cognitive and motor/physical decline could be alternatively considered a common way, rather than parallel pathways, able to lead to frailty and disability (Figure 1). This integrated perspective also promotes an increasingly multi-dimensional approach to frailty, together with a significant concern in the end of life stages such as disability and mortality.

In the light of these premises, according to a geriatric perspective, it appears essential always to proceed with the integrated evaluation of both cognitive and motor/physical functions, in order to achieve a comprehensive management of the patient and provide an accurate prognostic identification of peculiar aging trajectory.

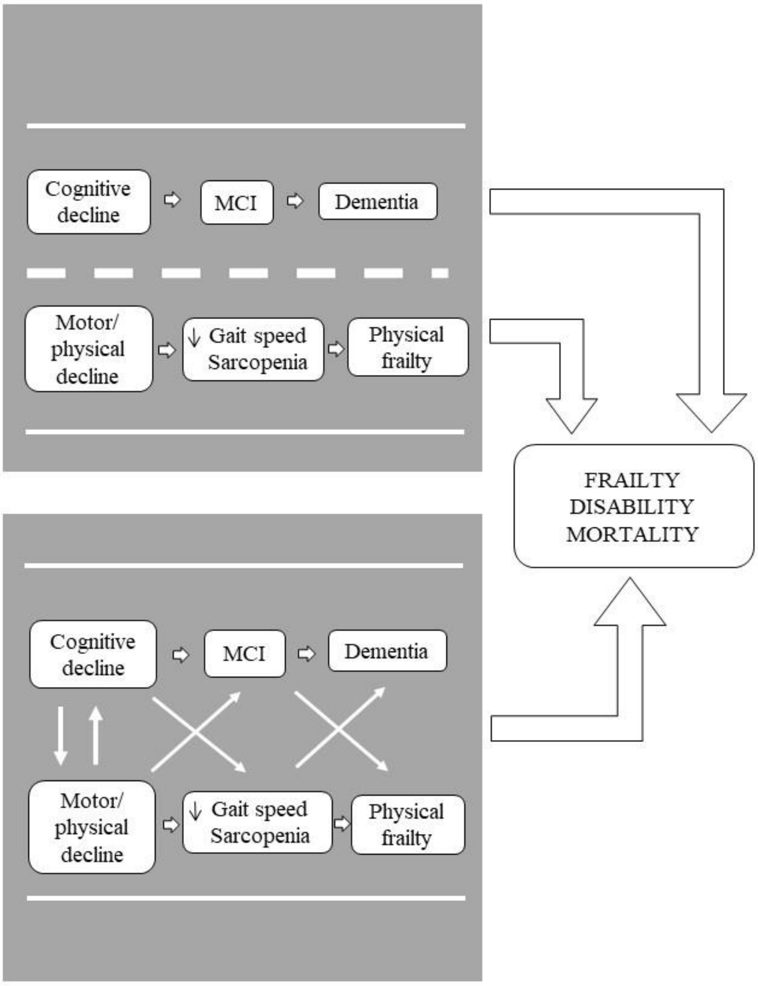

Figure 1: Top panel reproduces the scenario in which the progressive reduction of cognitive functions and the decrease of motor/physical performances, along their evolution towards dementia and physical frailty, respectively, are two potentially independent events leading to frailty and disability. The bottom panel reproduces an alternative scenario, considering these conditions associated and mutually able to accelerate the evolution of each other. Therefore, cognitive and motor/physical decline could be also considered a common way leading to frailty and disability, rather than just two separate, parallel pathways. *Abbreviations*: MCI = Mild Cognitive Impairment.

(Basile & Sardella, 2020, doi: 10.1007/s40520-020-01550-y)

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CHAPTER 2

State of the art on the association between Cognitive Reserve dimensions and frailty

The present chapter embodies the results from a structured narrative review, performed with the purpose to summarize the available evidence concerning the association between indexes of CR and frailty among elderly population, as well as to provide a theoretical framework for our experimental observations (Sardella et al., 2020).

Frailty: operational definitions and models

Frailty is a broadly investigated geriatric condition, which is characterized by an increased vulnerability to stressors due to reduced homeostatic reserves (Clegg et al., 2013). Frailty has been conceptualized as a dynamic condition along aging trajectories, frequently associated to the onset of adverse health outcomes in community population (Morley et al., 2012) and in clinical settings (Basile et al., 2019). Within the broad construct of frailty, both physical and psychological components have been acknowledged. In this context, although different approaches have been proposed in order to measure physical frailty, the two most representative models are the phenotype model described by Fried and colleagues (Fried et al., 2001), and the deficit model designed by Rockwood and colleagues (Rockwood et al., 2007). According to the first model, frailty is based on an a priori defined set of five criteria investigating specific physical variables (i.e., weight loss, fatigue, reduced gait speed, poor handgrip strength, and sedentary habits). Subjects can be clustered as robust, pre-frail, or frail depending on the number of presented criteria. Conversely, the Rockwood and colleagues' model conceives a multidimensional frailty resulting from of the age-related accumulation of deficits. Frailty is here operationalized into the so-called Frailty Index (FI), which is defined as the ratio between the deficits an individual presents and the number of age-related health variables considered in the evaluation.

The Fried's frailty phenotype and the Rockwood's frailty index have been commonly considered as alternative approaches. Accordingly, the frailty phenotype provides an immediate identification of non-disabled elderly at risk of negative events; conversely, the FI meets the needs of a comprehensive geriatric assessment, providing a marker of deficits accumulation. Since they have different purposes, these two instruments should be considered complementary, rather than alternative, in the evaluation of elderly subjects (Cesari et al., 2014).

To complete the theoretical framework of frailty models, a further model has been recently proposed to embrace a more comprehensive biopsychosocial perspective of the individual, combining physical, psychological and social domains. The model, proposed by Gobbens and colleagues, assumes that lifespan determinants have an effect on the occurrence of diseases and might affect the physical, psychological and social domains responsible for frailty (Gobbens et al., 2010)

Cognitive Reserve: the Stern model and its evolution towards years

Human aging is a complex and individualized process, which represents the product of the interaction between multiple bio-psycho-social factors. In this context, both progressive clinical and functional changes represent outcomes commonly associated with aging, which also allow physician to trace different trajectories able to differentiate healthy from pathological aging.

In the light of this vision, the concept of reserve has long been suggested as a potential protective factor against the onset of negative age-related outcomes, including functional impairments (Stern, 2012). Different models have been proposed for classifying the concept of reserve, mainly passive and active models. A well-known example of passive model is represented by the construct of brain reserve, according to which the individual's reserve derives from structural properties of the brain, such as brain size or neural count (Katzman et al., 1988). This approach is closely associated to the concept of brain reserve capacity (BRC), which presumes that individual differences in BRC can lead to different clinical manifestations. Indeed, this model suggests indeed that, once BRC is depleted and specific critical thresholds are exceeded, clinical deficits emerge with different degrees of severity (Satz, 1993). However, a widely discussed limitation of passive models of reserve is that they do not consider individual qualitative differences in the use of available resources.

In order to overcome this limitation, active models of reserve conversely suggest the existence of active processes, which are executed to compensate for emerging deficits. Accordingly, the concept of Cognitive Reserve (CR) has been developed in the last decades as a potential factor able to describe individual differences in vulnerability to cognitive, functional, or clinical decline along aging (Pettigrew et al., 2019). CR has been defined in terms of "adaptability that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult" (Stern et al., 2018). According to the original CR model, given the same level of brain reserve, patients with higher CR employ more efficient processing mechanisms, and might be able to take advantage of a wider range of alternate networks in order to better cope against the onset of deficit.

CR has been conceptualized as a broad construct which encompasses several different hallmarks of lifespan experiences. According to the Stern model, intelligence, education and occupational attainment were hypothesized as relevant dimensions of CR (Stern, 2002). Consistently, this hypothesis has been originally supported by epidemiological evidence suggesting that low educational and low occupational attainment were associated to an increased risk of developing dementia (Stern et al., 1994). Similarly, lower premorbid intelligence quotient (IQ) measured during childhood has been considered a significant risk factor for cognitive impairment and dementia in late life (Whalley et al., 2000). In light with CR model, also individual engagement in leisure activities might functionally improve cognitive networks and, consequently, might delay the onset of cognitive impairment and dementia (Scarmeas & Stern, 2003).

The impact of CR dimensions on healthy aging and dementia

The debate regarding the impact of CR on aging trajectories should not be disjointed from a life-course approach, which considers together biological, physical, and psychological factors acting over the lifespan (Wang et al., 2019). As it was previously stated, the CR hypothesis has primarily been proposed in order to better explain individual differences in clinical expression of cognitive aging, as well as the different subjects' adaptation to neurological diseases as dementia. Accordingly, subjects with higher CR (commonly expressed by educational level, job complexity, social and mental activity, intelligence) should be able to tolerate more brain pathology before the onset of cognitive symptoms, compared to those having lower CR. In this context, education has been broadly conceived as one of the most relevant indexes of CR, and one of the most widely accepted protective factors in the epidemiological studies on dementia (Meng et al., 2012). Furthermore, the potential protective role of premorbid IQ, as expression of CR, has been recently discussed, confirming the association between low childhood IQ and increased risk of dementia (Russ et al., 2017). Moreover, evidence derived from population-based studies has recently highlighted the beneficial impact of occupational status on cognitive aging, showing that performing complex jobs in adulthood is associated with reduced risk of dementia (Dekhtyar et al., 2016).

In this context, it has also been debated the potential role of leisure time activities in the prevention of cognitive decline and incident dementia in older persons

(Scarmeas & Stern, 2003). In particular, less social participation and social interactions constitute significant risk factors for the development of cognitive dysfunction (Penninkilampi et al., 2018). Conversely, an active and frequent social participation seems to affect the brain structure, resulting into an enhanced use of brain networks (Stern, 2012).

The association between CR indexes and frailty

The relationship between CR and frailty represents a fairly recent subject of investigation. Since frailty is considered as a multidimensional and dynamic condition, the hypothesis that CR dimensions might have an impact not only on cognitive trajectories but also on frailty has been increasingly debated during the last years. CR has been a challenging construct of investigation due to its wide heterogeneity, since it embraces several domains and related factors. In this context, education has commonly been considered one of the most representative surrogate of CR. As we stated earlier, the potential protective role of higher education has been broadly investigated for the risk of dementia. However, evidence that education plays a significant role in the delay of cognitive impairment appears also controversial (Cadar et al., 2016). A possible explanatory perspective is based on a passive theory of cognitive reserve, according to which people with higher levels of education will continue to perform at higher levels of cognitive functioning compared to lower educated subjects (Lenehan et al., 2015). As recently suggested, the link between higher education and lower risk of dementia might be likely attributable to the association between education with individual level of cognitive function before old age, rather than with the rate of cognitive changes (Wilson et al., 2019). According to the findings of the structured narrative review that we performed (see Supplementary Material of Chapter 2), education represents the most investigated index of CR among elderly subjects, and the beneficial role of education could be extended even on frailty status despite the heterogeneous evaluation of frailty status among the retrieved studies.

Occupation is considered a further source of CR and, recently, the association between occupational status and frailty has been systematically reviewed (Iavicoli et al., 2018). The Authors highlighted a noteworthy relationship between life-course occupation and frailty at older age, suggesting that manual, or blue-collar jobs might be considered as potential determinants of frailty at older age. Nevertheless, the heterogeneous frailty operationalization, as well as the limited description of potential contributing workplace-related factors among available studies, may not allow definitive conclusions yet. The findings of our review updated the available literature (see Supplementary Material of Chapter 2) consistently suggesting that unemployment and job quality should be more carefully accounted, jointly with psychosocial factors as potential determinants of frailty. In line with this life-course perspective, future studies should also aim at investigating individuals' characteristics which might be potentially related to job experiences, and that might interact also with the severity of age-related negative outcomes.

Consistently with the importance of integrating CR dimensions as potential protective factors for frailty, the role of leisure time has been explored in the last years even in association with frailty status. Leisure activity is commonly defined as the intentional use of own free time for activities outside the daily routine, therefore it represents one of the major components of a healthy lifestyle (Wang et al., 2012). Several evidences have discussed leisure activities as potential protective factor for dementia especially among elderly, exploring whether leisure activities could prevent or rather delay the onset of cognitive decline. The findings of our review are in line with this background, and additionally suggest that an active leisure time could be also associated with reduced odds of being frail among elderly subjects (see Supplementary Material of Chapter 2).

CR certainly represents a heterogeneous concept, and the conducted studies on this topic have faced several conceptual and methodological issues. An important limitation of some investigated CR dimensions is that they might impact on cognitive and functional aging trajectories via indirect alternative paths, and not only directly improving CR. For instance, the predictive role of education and occupation for negative age-related outcomes in elderly populations might be confounded by several factors linked to educational and occupational attainment, such as age, gender, intelligence, or available socioeconomic sources (Jones et al., 2011).

In the light of these premises, providing an operationalized definition of CR has been challenging over the past years, especially due to the multidimensional complexity of the construct and the heterogeneous methods of evaluation. CR has been widely conceptualized in terms of education, premorbid intelligence, occupational status, leisure time activities, employing these proxies independently or jointly (Adam et al., 2013; Chapko et al., 2018).

Since the multidimensional nature of CR, the use of standardized questionnaires and scales able to jointly intercept different domains of reserve has been encouraged in the last years. CR scoring evaluation has been increasingly proposed in the context of several clinical settings involving mostly patients with neurological or psychiatrics conditions, internal chronic diseases, as well as healthy community subjects (Kartschmit et al., 2019).

In conclusion, education, occupation, premorbid IQ and leisure time represent factors able to interact even with frailty status of elderly, rather that only with cognitive trajectories towards dementia. To the best of our knowledge, the operationalized assessment of CR is still lacking in the context of frailty among elderly population. In the light of these considerations, identifying the CR of elderly patients might lead clinicians to account the potential impact of these antecedent factors even on frailty status, contributing to a better definition of individual aging trajectories (Figure 1). The upcoming challenge would be to acknowledge CR as one of the potential individual reserves, along the mutual cognitive-functional trajectories leading to frailty (Basile & Sardella, 2020).

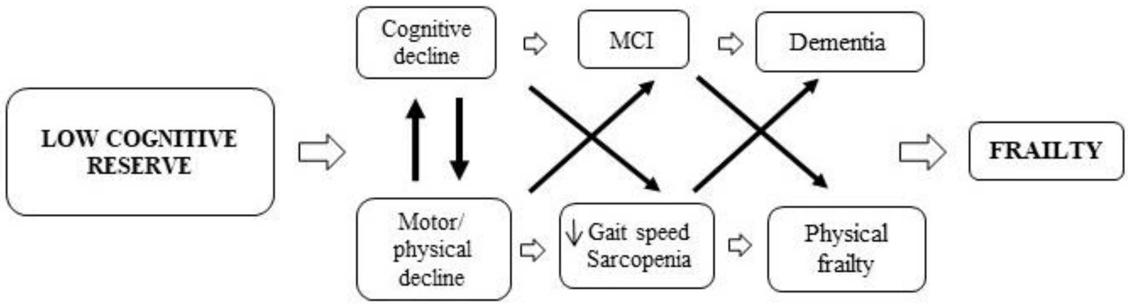

Figure 1: Hypothetical model, according to which low Cognitive Reserve (CR) might have a negative impact on individual aging trajectories, which are characterized by the joint cognitive and motor/physical decline, eventually leading to frailty.

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CHAPTER 3

Consistently with the theoretical frameworks explained in the previous chapters, the current chapter presents the unpublished results from our conducted analyses, which were aimed to explore the association between Cognitive Reserve (CR) dimensions and age-related multifactorial outcomes contributing to frailty among elderly.

Experimental section

Design, participants and setting

The design consists in a cross-sectional investigation of a sample of elderly outpatients. The Geriatric Outpatients Clinic of the University Hospital in Messina (Italy) represents the clinical setting of the study.

Patients were included if they had an age ≥65, and if they exhibited a Mini-Mental State Examination (MMSE) score ≥ 12; conversely, patients showing severe cognitive impairment were excluded, in order to facilitate the administration of the scales. Since the comprehensive performed evaluation involved additionally a physical and motor assessment, patients with severe functional limitations (e.g. patients on wheelchairs or not able to walk, patients with severe limitations to upper limbs), or severe diagnosed sensory deficits (severe visual or hearing impairment) were also excluded, in order to allow the execution of the required tasks.

Procedures

Each patient underwent a screening cognitive assessment, a physical and functional evaluation. A trained psychologist performed the cognitive assessment of each patient; an expert geriatrician performed the physical and the functional evaluations. All procedures completed were in accordance with the ethical standards of our institutional research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent was collected for all the participants. The Ethics Committee of the University Hospital of Messina approved the protocol of this study (Prot. 23/19 – University Hospital Ethics Committee). The recruitment took place from October 2018 to October 2019.

Main outcomes and measures

We used the MMSE to screen global cognitive functioning (Folstein et al., 1975). Physical performances were measured in terms of 4-meter gait speed (expressed as meter per second) and handgrip strength (expressed in kilograms, measured by a Jamar dynamometer). Patients' daily life autonomy was evaluated through the Basic Activities of Daily Life (BADL) and Instrumental Activities of Daily Life (IADL) scales (Katz et al., 1963; Lawton & Brody, 1969, respectively).

In addition, patients' frailty status was evaluated by a 35-item Frailty Index (FI) based on collected variables (see Supplementary Material of Chapter 3), according to the accumulation of deficits model (Rockwood & Mitnitski, 2007); patients with a FI ≥ 0.25 were categorized as frail, as usual (Basile et al., 2019).

Education level, occupation attainment, leisure activities and premorbid Intelligence quotient (IQ) were additionally investigated for each patient. Education, occupation and leisure time were accounted through the Cognitive Reserve Index questionnaire (CRIq), which is based on the theoretical framework of the Stern model for CR. The CRIq consists of three sections investigating subject's educational status, occupational level and leisure time activities; the questionnaire returns independent subscore for each domain together with a total score of CR (Nucci et al., 2012).

The pre-morbid IQ was estimated through the Italian Brief Intelligence Test (originally named *Test di Intelligenza Breve* - TIB), which was developed from the New Adult Reading Test (NART) (Nelson HE, O'Connell A 1978). Consistently, the TIB consists in reading thirty-four words of rare or uncommon use, with an irregular accent, together with additional twenty control-words of frequent use (Colombo et al., 2002). The TIB returns a total score of IQ calculated by a predefined algorithm, and represents a quick and easy to administer tool, which could be an advantage when elderly subjects are evaluated.

Statistical analyses

Data were analysed using IBM SPSS 22 statistical software. Spearman's rho was used to measure the degree of correlations between the accounted variables. We computed Chi-squared and Mann-Whitney test to evaluate differences between groups after classifying subjects in frail and non-frail according to the FI score (i.e. subjects exhibiting a FI ≥0.25 were classified as frail). Univariate and multivariate linear regressions were performed in order to explore significant associations between the investigated variables. Values of $p<0.05$ were considered statistically significant.

Study 1: The interaction between Cognitive Reserve indexes and cognitive, physical and functional status among elderly outpatients. (*Unpublished data*)

Main purpose

The study aimed to assess CR using two validated tools (CRIq and TIB) among an elderly sample. Specifically, we explored the interactions between the two operationalized CR indexes and the patients' cognitive, physical and functional status. Our purpose was to understand whether CR indexes could be independently associated to frailty status, or independently associated to different age-related factors (i.e. cognitive functioning), which commonly lead to frailty.

Main findings

The study involved 141 elderly outpatients (42 males, 99 females). Patients exhibited a mild-to-moderate cognitive impairment (MMSE mean score 22.6 ± 4.5), resulted partially autonomous in their basic and instrumental daily activities (BADL mean score 4.23 ± 1.5; IADL mean score 3.67 ± 1.4, respectively), and showed a mean FI score of 0.25 (with FI scores ranging from 0.05 to 0.50).

Elderly subjects classified as frail were marginally older ($p = 0.09$) and less educated compared to those classified as not frail. Furthermore, frail subjects reported significantly worse cognitive (MMSE), functional (BADL and IADL) and physical (handgrip and gait speed) performances compared to not frail subjects. Eventually, frail elderly exhibited worse cognitive reserve indexes, measured through TIB and CRIq, and a worse QoL, according to the SF12 score. The main sociodemographic and clinical characteristics of the sample are comprehensively summarized in Table 1. The sociodemographic and clinical differences between patients, according to frailty status are provided in Table 2.

Table 1: Main sociodemographic and clinical characteristics of the sample

	Patients (N=141)
Sociodemographic	
Age (years) (mean ± SD)	80.31 ± 6.84
Gender	
- Male (n, %)	42 (29.8)
- Female (n, %)	99 (70.2)
Education (years) (mean ± SD)	7.09 (± 3.83)
Marital status	
- Married (n, %)	71 (50.4)
- Widow/er (n, %)	56 (39.7)
- Other (n, %)	14 (9.9)
Clinical	
MMSE (mean ± SD)	22.61 (± 4.52) [lower score 12; higher score 30]
Handgrip strength (kg) (mean ± SD)	17.25 (± 7.15)
Gait speed (m/s) (mean ± SD)	0.64 (± 0.20)
BADL (mean ± SD)	4.23 (± 1.59)
IADL (mean ± SD)	3.67 (± 2.41)
FI (mean ± SD)	0.25 (± 0.11)
Frailty status	
- Frail (n, %)	71 (50.4)
- Not frail (n, %)	70 (49.6)

Abbreviations: SD= Standard deviation; MMSE: Mini Mental State Examination; BADL: Basic Activities of Daily Living; IADL: Instrumental Activities of Daily Living; FI: Frailty Index. Note: Patients with FI ≥ 0.25 were considered frail.

Table 2: Sociodemographic and clinical differences between patients, according to frailty status.

	Not frail (N=70)		**Frail** (N=71)		
	%		%		*p*
Gender (m/f)	25/45		16/55		0.09
	Mean	SD	Mean	SD	*p*
Age	79.51	6.04	81.1	7.499	0.093
Education	7.9	3.931	6.3	3.583	***0.006***
BADL	5.41	0.789	3.07	1.302	***<0.001***
IADL	5.11	2.096	2.24	1.777	***<0.001***
Handgrip	19.966	6.5195	14.572	6.7545	***<0.001***
Gait speed	0.7373	0.16304	0.5586	0.17603	***<0.001***
MMSE	25.61	2.886	19.68	4.744	***<0.001***
TIB	98.90	15.31	93.82	11.30	***0.002***
CRIq	88.17	14.026	78.55	13.48	***<0.001***

Abbreviations: MMSE: Mini Mental State Examination; BADL: Basic Activities of Daily Living; IADL: Instrumental Activities of Daily Living. TIB: Test di Intelligenza Breve; CRIq: Cognitive Reserve Index questionnaire. Note: values are expressed in terms of percentage, mean and standard deviation (SD).

Correlation analyses

Correlations between frailty, cognitive, physical and functional performances are graphically reported in Table 3. In summary, patients' cognitive, physical and functional performances were found to be jointly positively correlated; patients who presented poorer cognitive, physical and functional status showed also a higher FI, meaning that they exhibited a worse frailty status.

Table 3: Correlations between cognitive, physical and functional outcomes

	FI	MMSE	Handgrip	Gait speed	BADL	IADL
FI	-	-0.631**	-0.504**	-0.505**	-0.818**	-0.707**
MMSE	-0.631**	-	0.361**	0.269**	0.524**	0.591**
Handgrip	-0.504**	0.361**	-	0.369**	0.450**	0.349**
Gait speed	-0.505**	0.269**	0.369**	-	0.453**	0.399**
BADL	-0.818**	0.524**	0.450**	0.453**	-	0.660**
IADL	-0.707**	0.591**	0.349**	0.399**	0.660**	-

Abbreviations: FI: Frailty Index; MMSE: Mini Mental State Examination; BADL: Basic Activities of Daily Living; IADL: Instrumental Activities of Daily Living.
*= $p<0.05$; **= $p\leq0.001$

The CRIq score was positively correlated with MMSE score, handgrip strength, gait speed and ADL, meaning that subjects with higher CR presented also better cognitive, physical and functional performances. CRIq score was additionally negatively correlated with FI, meaning that higher level of CR corresponded to worse frailty status.

The TIB score was positively correlated with MMSE score, gait speed and IADL score, meaning that subjects with higher premorbid IQ presented also better cognitive functions, were faster on the 4-m walking task, and exhibited a better autonomy in instrumental daily activities. TIB score was also negatively correlated to FI, meaning that subjects with lower premorbid IQ presented a worse frailty status expressed by a higher FI score. Correlations of both CRIq and TIB are reported in Table 4.

Table 4: Correlations between Cognitive Reserve indexes and cognitive, physical, functional outcomes.

	CRIq		**TIB**	
FI	r = -0.329	***p* < 0.001**	r = -0.225	***p* = 0.007**
MMSE	r = 0.405	***p* < 0.001**	r = 0.387	***p* < 0.001**
Handgrip	r = 0.319	***p* < 0.001**	r = 0.099	*ns*
Gait speed	r = 0.260	***p* = 0.002**	r = 0.195	***p* = 0.02**
BADL	r = 0.276	***p* = 0.001**	r = 0.104	*ns*
IADL	r = 0.329	***p* < 0.001**	r = 0.245	***p* = 0.003**

Abbreviations: FI: Frailty Index; MMSE: Mini Mental State Examination; BADL: Basic Activities of Daily Living; IADL: Instrumental Activities of Daily Living; CRIq: Cognitive Reserve Index Questionnaire; TIB: Test di Intelligenza Breve.

Univariate linear regressions

We performed several univariate linear regressions considering the FI as the dependent variable. Moreover, we performed univariate linear regressions also considering the MMSE as the dependent variable (Tables 5, 6).

Table 5: Univariate linear regressions for Frailty (expressed by FI)

					95% CI	
	B	**SE(B)**	**β**	***p***	Lower	Upper
Age	0.003	0.001	0.180	***0.03***	0.000	0.005
Gender	0.034	0.019	0.148	0.08	-0.004	0.072
Education	-0.005	0.002	-0.168	***0.04***	-0.009	0.000
TIB	-0.001	0.001	-0.161	***0.05***	-0.003	0.000
CRIq	-0.002	0.001	-0.290	***<0.001***	-0.003	0.001
MMSE	-0.015	0.002	-0.637	***<0.001***	-0.018	-0.012
Handgrip	-0.007	0.001	-0.453	***<0.001***	-0.009	-0.004
Gait speed	-0.292	0.040	-0.528	***<0.001***	-0.372	-0.213
BADL	-0.054	0.003	-0.816	***<0.001***	-0.060	-0.048
IADL	-0.030	0.003	-0.681	***<0.001***	-0.035	-0.024

Abbreviations: SE(B): Standard Error for the unstandardized beta; MMSE: Mini Mental State Examination; BADL: Basic Activities of Daily Living; IADL: Instrumental Activities of Daily Living; FI: Frailty Index; CRIq: Cognitive Reserve Index questionnaire; TIB: Test di Intelligenza Breve.

As reported in Table 5, among the accounted sociodemographic variables, age (β= 0.180, p= 0.03) and years of education (β= -0.168, p= 0.04) were found significantly associated to FI, meaning that older and less educated patients exhibited a worse frailty status (expressed by a high FI score).

Furthermore, in addition to the cognitive (MMSE), physical (handgrip and gait speed) and functional scores (BADL and IADL, both the investigated CR indexes (CRIq and TIB) were also found significantly associated to FI (β= -0.290, p<0.001; β= -0.161, p= 0.05, respectively). Accordingly, higher CR and higher premorbid IQ were associated to lower FI, which is expression of a better health status.

Table 6: Univariate linear regressions for MMSE

					95% CI	
	B	**SE(B)**	**β**	***p***	Lower	Upper
Age	-0.085	0.056	-1.28	0.13	-0.195	0.025
Gender	-2.006	0.818	-0.204	***0.015***	-3.623	-0.389
Education	0.246	0.098	0.209	***0.013***	0.053	0.440
TIB	0.112	0.026	0.337	***<0.001***	0.059	0.164
CRIq	0.120	0.024	0.385	***<0.001***	0.071	0.168
Handgrip	0.220	0.050	0.348	***<0.001***	0.121	0.320
Gait speed	7.231	1.928	0.305	***<0.001***	3.418	11.044

Abbreviations: SE(B): Standard Error for the unstandardized beta; MMSE: Mini Mental State Examination; CRIq: Cognitive Reserve Index questionnaire; TIB: Test di Intelligenza Breve.

We performed different univariate linear regressions for cognitive status, expressed by MMSE. We tested the potential association of sociodemographic variables (i.e. age, gender, and years of education) with MMSE. Moreover, in line with the discussed existing link between cognitive and physical/motor performances, we tested the association of handgrip strength and gait speed with

MMSE. Eventually, we tested the association of CR indexes (expressed by CRIq and TIB) with cognitive status.

Gender (β= -0.204, p= 0.015) and years of education (β= 0.209, p= 0.013) resulted significantly associated to MMSE. The univariate linear regression also showed that handgrip (β= 0.340, p< 0.001) and gait speed (β= 0.305, p< 0.001) were significantly associated to cognitive functioning. Eventually, both the investigated CR indexes (CRIq and TIB) were also found significantly associated to MMSE (β= -0.385, p<0.001; β= 0.337, p<0.001, respectively).

Multivariate linear regression

In line with the findings of the previous univariate linear regressions, we performed two multivariate hierarchical linear regressions. Consistently, those variables that were found significantly associated in the univariate regressions were then hierarchically included in the multivariate models.

A first multivariate linear regression considered the FI as the dependent variable, in order to understand whether CR indexes (CRIq and/or TIB) could be independently associated to FI (Table 7). A second multivariate linear regression was performed considering the MMSE as the dependent variable, in order to understand whether CR indexes (CRIq and/or TIB) could be independently associated to cognitive status (Table 8).

Table 7: Multivariate linear regression for FI

	R^2	Adjusted R^2	F	*p*
Step 1	0.067	0.053	4.870	***0.009***
	SE(B)	**β**	**t**	***p***
Age	0.001	0.183	2.210	***0.029***
Education	0.002	-0.176	-2.127	***0.035***
	R^2	Adjusted R^2	**F**	***p***
Step 2	0.749	0.737	65.59	***<0.001***
	SE(B)	**β**	**t**	***p***
Age	0.001	-0.006	-0.131	0.89
Education	0.001	-0.084	-1.804	0.07
Handgrip	0.001	-0.098	-1.922	0.057
Gait speed	0.029	-0.117	-2.267	***0.025***
BADL	0.004	-0.594	-9.438	***<0.001***
IADL	0.003	-0.204	-3.343	***0.001***
	R^2	Adjusted R^2	**F**	***p***
Step 3	0.767	0.754	61.47	***<0.001***
	SE(B)	**β**	**t**	***p***
Age	0.001	0.004	0.091	0.92
Education	0.001	-0.068	-1.501	0.13
Handgrip	0.001	-0.074	-1.477	0.14
Gait speed	0.028	-0.124	-2.476	***0.015***
BADL	0.004	-0.541	-8.570	***<0.001***
IADL	0.003	-0.140	-2.235	***0.027***
MMSE	0.001	-0.177	-3.158	***0.002***

	R^2	Adjusted R^2	F	*p*
Step 4	0.772	0.756	48.40	***<0.001***
	SE(B)	**β**	**T**	***p***
Age	0.001	-0.003	-0.063	0.95
Education	0.002	-0.153	-2.244	***0.027***
Handgrip	0.001	-0.080	-1.566	0.12
Gait speed	0.028	-0.128	-2.543	***0.012***
BADL	0.004	-0.551	-8.642	***<0.001***
IADL	0.003	-0.133	-2.117	***0.036***
MMSE	0.001	-0.205	-3.472	***0.001***
TIB	0.00	0.031	0.599	0.55
CRIq	0.00	0.102	1.482	0.14

Abbreviations: MMSE: Mini Mental State Examination; BADL: Basic activities of daily living; IADL: Instrumental activities of daily living; TIB: Test di Intelligenza Breve; CRIq: Cognitive Reserve Index questionnaire; FI: Frailty Index.

The multivariate linear regression for FI was performed through four hierarchical steps: the sociodemographic variables age and education were included in the first step; the physical/functional factors involving handgrip strength, gait speed and daily autonomy were included in the second step, followed by the cognitive status expressed by the MMSE. The CR indexes (CRIq and TIB) were included in the final step. Even though each step resulted statistically significant, the final model was significantly explained by education (β= -0.153, p= 0.027), gait speed (β= -0.128, p= 0.012), BADL (β= -0.551, p<0.001), IADL (β= -0.133, p= 0.036), and MMSE (β= -0.205, p= 0.001). Accordingly, lower educational level, reduced gait speed, lower daily autonomy, and a worse cognitive status represents those clinical characteristics significantly associated to higher FI score, which corresponds to a worse frailty status. Both the tested CR indexes resulted not significantly associated to FI (CRIq: β= 0.102, p= 0.14; TIB: β= 0.031, p= 0.55), after adjusting for the other factors.

We additionally performed a multivariate linear regression considering the MMSE as the dependent variable. The multivariate linear regression was developed in three hierarchical steps: the first step involved age and education as sociodemographic variables; in the second step, the physical measures were incorporated; eventually, the CR indexes were included in the final step.

The first step resulted statistically significant and was substantially explained by the gender (β= -0.172, p= 0.04); the second step resulted similarly significant and was explained by the inclusion of the physical variables (handgrip: β=0.251, p= 0.015; gait speed: β= 0.199, p= 0.021). The final step (R^2= 0.306, $p<0.001$) showed that both TIB (β= 0.268, p= 0.002) and CRIq (β= 0.420, p= 0.001) were significantly associated to MMSE, together with handgrip strength β= 0.296, p=0.002). Accordingly, exhibiting greater CR and premorbid IQ, and higher handgrip strength are associated to a better cognitive status expressed by the MMSE score.

These findings appear in line with the existing cognitive-motor link, and suggest the presence of a significant interaction of both premorbid IQ and CR with cognitive status among elderly evaluated for frailty.

Table 8: Multivariate linear regression for MMSE

	R^2	Adjusted R^2	F	*p*
Step 1	0.070	0.056	5.119	***0.007***
	SE(B)	**β**	**T**	***p***
Gender	0.839	-0.172	-2.022	***0.04***
Education	0.103	0.163	1.910	0.058
	R^2	**Adjusted R^2**	**F**	***p***
Step 2	0.173	0.149	7.017	***<0.001***
	SE(B)	**β**	**T**	***p***
Gender	0.954	0.011	0.113	0.91
Education	0.098	0.129	1.574	0.11
Handgrip	0.064	0.251	2.456	***0.015***
Gait speed	2.019	0.199	2.336	***0.021***
	R^2	**Adjusted R^2**	**F**	***p***
Step 3	0.306	0.274	9.701	***<0.001***
	SE(B)	**β**	**T**	***p***
Gender	0.966	0.172	1.755	0.08
Education	0.138	-0.283	-2.469	***0.015***
Handgrip	0.060	0.296	3.124	***0.002***
Gait speed	1.880	0.148	1.865	0.064
TIB	0.028	0.268	3.134	***0.002***
CRIq	0.039	0.420	3.390	***0.001***

Abbreviations: MMSE: Mini Mental State Examination; BADL: Basic activities of daily living; IADL: Instrumental activities of daily living; TIB: Test di Intelligenza Breve; CRIq: Cognitive Reserve Index questionnaire.

Study 2: Preliminary evidence on the longitudinal association between CR indexes and cognitive status (*Unpublished data*)

Main purposes

Cross-sectional association between CR indexes and cognitive status, expressed by MMSE, were previously evidences. The purpose of this longitudinal observation was to understand whether the investigated CR indexes (i.e. CRIq and TIB) might be also considered potentially predictors of cognitive status at follow-up. An additional purpose of the study was to understand whether baseline physical and motor performances might also be longitudinally associated to cognitive status.

Statistical analysis

Data were analysed using IBM SPSS 22 statistical software. The Wilcoxon test was used to describe differences between baseline and longitudinal MMSE scores. Univariate and multivariate linear regressions were computed in order to explore significant associations between CR indexes and motor / physical factors previously assessed, and longitudinal MMSE (dependent variable).

Values of $p < 0.05$ were considered statistically significant.

Procedures

Since the progressive suspension of the Geriatric Outpatient Clinic activity (starting from March 2020) due to the Covid-19 pandemic, most patients included in our original sample have not been able to undergo the scheduled follow-up. The evaluation of cognitive status was therefore carried out by telephone, through the validated Italian Telephone version of the MMSE (Itel-MMSE) (Metitieri et al., 2001). Compared to the original MMSE, the Itel-MMSE includes each temporal / spatial orientation item, except for "In which floor are we". The original items concerning memory, attention and calculation were fully reported even in the Itel-MMSE. The principal difference from the original MMSE concerns the section dedicated to the evaluation of language and praxia. Accordingly, in the Itel-MMSE the patient is asked to name "the thing currently used to talk" to the examiner (i.e. telephone); the items dedicated to the execution of motor sequences, the execution of a written command (i.e. "Close your eyes"), the sentence writing and the copy of pentagons have not been included in the Itel-MMSE. The test administration usually lasts about five minutes; the total score ranges from 0 to 22, with higher scores expressive of better cognitive status. A regression equation allows to estimate the expected MMSE score based on the score obtained at Itel-MMSE:

$$\text{Expected MMSE} = 1.01 * \text{Itel-MMSE score} + 5.16$$

In order to avoid potential rater-related bias, a single trained psychologist conducted the phone calls and administered the questionnaire. The telephone procedure started in April; the phone calls were made during the morning hours, with an average of five phone calls per day.

Main findings

From the original sample, a total of 115 patients were tracked by telephone; however, eleven of them declined to undergo the evaluation; we were not able to contact the remaining twenty-six patients. The final number of patients included in the follow-up evaluation was 104.

The principal differences between baseline and longitudinal MMSE scores are summarized in Table 1. Compared to baseline, patients exhibited a significantly worse cognitive status on follow-up.

Table 1: Differences between baseline and longitudinal MMSE (N=104)

	Baseline (t0)	Longitudinal (t1)	z (t1 - t0)	*p*
MMSE	22.81 (± 4.32)	22.00 (±4.93)	-6.401	***<0.001***

Abbreviations: MMSE: Mini Mental State Examination. Note: values expressed in terms of mean and standard deviation.

Univariate linear regressions

We performed univariate linear regressions considering MMSE (t1) as the dependent variable, in order to find those baseline variables potentially associated to longitudinal cognitive status. Similarly to the cross-sectional observation, together with both the CRIq and the TIB, we included in the univariate analysis sociodemographic (age and gender), physical (handgrip strength), and motor (gait speed) variables (Table 2).

Table 2: Univariate linear regressions for MMSE (t1)

					95% CI	
	B	**SE(B)**	**β**	***p***	Lower	Upper
Age	-1.31	0.075	-0.169	0.084	-0.280	0.018
Gender	-1.802	1.028	-0.170	0.083	-3.841	0.237
Education	0.357	0.121	0.279	***0.004***	0.117	0.597
TIB	0.106	0.032	0.308	***0.001***	0.042	0.170
CRIq	0.142	0.031	0.409	***<0.001***	0.080	0.204
Handgrip	0.259	0.067	0.358	***<0.001***	0.127	0.391
Gait speed	8.468	2.964	0.273	***0.005***	2.588	14.348

Abbreviations: MMSE: Mini Mental State Examination; TIB: Test di Intelligenza Breve; CRIq: Cognitive Reserve Index questionnaire.

The univariate linear regressions showed that education was the only sociodemographic variable significantly associated to MMSE (t1). Both handgrip (β= 0.358, p<0.001) and gait speed (β= 0.273, p= 0.005) were significantly associated to longitudinal cognitive status, meaning that patients with baseline higher handgrip strength and faster gait speed exhibited better cognitive performances at follow-up. Eventually, both CRIq (β= 0.409, p<0.001) and TIB (β= 0.308, p= 0.001) were found significantly associated to MMSE (t1), meaning that patients with higher CR indexes at baseline exhibited higher MMSE scores at follow-up.

Multivariate linear regression

In line with the results from univariate linear regressions, we consequently performed a multivariate linear regression considering the MMSE (t1) as the dependent variable, and hierarchically including in the model each variable that resulted significant at the univariate (Table 3).

Each step of the model resulted significant. Education was included in first step (R^2= 0.072, p= 0.006); after the inclusion of handgrip and gait speed in the second step, education did not persist to be significant, and the step was substantially explained by handgrip β= 0.270, p= 0.008). In the final step (R^2= 0.252, p< 0.001) CRIq and TIB were included; eventually, CRIq (β= 0.291, p= 0.04) and TIB (β= 0.223, p= 0.029), together with handgrip (β= 0.235, p= 0.02), resulted significant predictors of MMSE (t1).

Table 3: Multivariate linear regression for MMSE (t1)

	R^2	**Adjusted R^2**	**F**	***p***
Step 1	0.072	0.063	7.833	***0.006***
	SE(B)	**β**	**T**	***p***
Education	0.126	0.268	2.799	***0.006***
	R^2	**Adjusted R^2**	**F**	***p***
Step 2	0.175	0.150	7.023	***<0.001***
	SE(B)	**β**	**T**	***p***
Education	0.129	0.141	1.437	0.15
Handgrip	0.072	0.270	2.705	***0.008***
Gait speed	3.050	0.146	1.478	0.14
	R^2	**Adjusted R^2**	**F**	***p***
Step 3	0.252	0.213	6.524	***<0.001***
	SE(B)	**β**	**T**	***p***
Education	0.178	-0.147	-1.090	0.27
Handgrip	0.072	0.235	2.362	***0.02***
Gait speed	3.051	0.076	0.775	0.44
TIB	0.035	0.223	2.215	***0.029***
CRIq	0.048	0.291	2.075	***0.04***

Abbreviations: MMSE: Mini Mental State Examination; TIB: Test di Intelligenza Breve; CRIq: Cognitive Reserve Index questionnaire.

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CHAPTER 4

Psychological resilience and aging

Aging represents the product of the interaction between several bio-psycho-social variables, which therefore concur to draw different trajectories from normal aging to disability. Consistently, a crucial purpose of aging research is to understand how the exposure to adverse and challenging events across the life span may influence individual health.

Psychological resilience has been considered a relevant factor able to contribute to the aging adaptation. In the context of psychological resilience, which represents a wide and heterogeneous construct, the process of emotional regulation has been additionally described to explain individual differences for both psychopathology and wellbeing (Aldao et al., 2010). Consistently, the importance of flexibility in emotion regulation has been accounted as a relevant regulatory factor, involving enhancement and suppression abilities: enhancement refers to an increased emotional reactivity to contextual situations; conversely, suppression describes the relative reduction of own emotional expression in specific contexts (Chen et al., 2018). Therefore, adaptation processes might depend on individual ability to flexibly enhance or suppress emotional expression (namely, expressive flexibility), in relation to the contextual demands (Burton & Bonanno, 2016). Previous researches have highlighted that expressive flexibility is a factor able to predict lower levels of psychopathology symptoms and better psychological adjustment (Bonanno et al., 2004; Lenzo et al., 2020a; Westphal et al., 2010). In line with the theoretical framework proposed by Bonanno and colleagues, context sensitivity in considered an additional factor, which contributes to define psychological resilience. Context sensitivity refers to the individual ability to accurately perceive cues to contextual demands across different life situations, and has been identified as a relevant factor of efficacious self-regulation (Bonanno et al., 2018); moreover, it has been previously suggested as a crucial factor involved in psychological adjustment and in the onset of psychopathology following stressful life events (Coifman & Bonanno, 2010).

Among psychological factors that might be additionally involved in a positive adaptation to aging, dispositional optimism has raised an increasing interest in the context of several clinical conditions. According to the original definition, optimism represents one of the two sides of life orientation (the latter is pessimism), which can be considered an expression of individual's psychological adaptability (Scheier & Carver, 1985). Dispositional optimism has been previously linked to a better individual cardiovascular health, especially regarding the choice of healthy related behaviours (e.g. avoiding smoke or performing physical activity) (Serlachius et al., 2015). Moreover, the positive role of optimism has been also discussed in the context of age-related clinical conditions, such as cognitive impairment (dos Santos et al., 2018) and diabetes (Faghani et al., 2018). Moreover, higher levels of optimism have been associated with a better

QoL among patients with heart failure (Kraai et al., 2018), and Parkinson's disease (Gison et al., 2014).

In line with these premises, the purpose of this chapter is to present our pilot observations aimed to explore for the first time the association between psychological resilience factors (i.e. expressive flexibility, context sensitivity, and additionally dispositional optimism) and common age-related outcomes (i.e. frailty and quality of life) among elderly subjects.

Experimental section

Study design, participants and the performed procedures were described in the previous Chapter 3.

Main outcomes

In addition to the cognitive, physical and functional evaluation, which are reported in the previous chapter, psychological resilience indexes were also explored among the elderly sample. Patients' dispositional optimism was explored through the Italian version of the revised Life Orientation Test (LOT-R) (Scheier et al., 1994; Giannini et al., 2008); LOT-R is a 10-item questionnaire based on a 5-points Likert scale ranging from "strongly disagree" to "strongly agree"; higher scores reflect a greater expectation of positive results.

The Context Sensitivity Index (CSI), a 20-item self-report questionnaire, was administered in order to assess the ability to accurately identify cues to contextual demands across different hypothetical situations (Bonanno et al., 2018). The CSI measures the individual ability to capture sensitivity in presence of contextual cues (CSI Cue Presence index), and in absence of contextual cues (Cue Absence index). An overall CSI score is then calculated by averaging the Cue Presence and Cue Absence indexes; the total CSI score was employed for our observations; higher scores are expression of a greater individual contextual sensitivity.

Eventually, we accounted patients' expressive flexibility through the Flexible Regulation of Emotional Expression (FREE) Scale, which is a 16-item self-report questionnaire assessing the ability to enhance and suppress emotions across different hypothetical contexts (Burton et al., 2016). Accordingly, the FREE scale provides two indexes, namely the ability to enhance emotional expression (FREE Enhancement) and the ability to suppress emotional expression (FREE Suppression), which are expressed by two subscores. An overall score is additionally provided, which is a global measure of expressive flexibility. Higher scores are representative of better expressive flexibility.

The Italian version of the Short Form-12 (SF-12) questionnaire was administered to assess the perception of patient's QoL (Ware et al., 1996).

SF-12 is a 12-item questionnaire assessing different QoL-related aspects (e.g. physical functioning, limitations due to physical health, pain, vitality, social functioning, and limitations due to emotional problems). The questionnaire provides two synthetic indexes: the Physical Component Summary (PCS) and the

Mental Component Summary (MCS), which are related to individual physical state and mental state, respectively.

Study 1. Association between Psychological resilience factors and frailty (*Unpublished data*)

Aim of the study

The main purpose of the present pilot research was to investigate the potential association between psychological resilience factors (i.e. expressive flexibility, context sensitivity, and additionally dispositional optimism) and frailty status among elderly outpatients. Since the calculated FI is based on the presence of several clinical deficits, as previously described, and it represents *per se* a health index, for this study's analyses, we did not account cognitive, physical and functional variables. Therefore, we aimed only to investigate which psychological factor could be associated to frailty status among our elderly sample.

Statistical analyses

Data were analysed using IBM SPSS 22 statistical software. Univariate and multivariate linear regressions were computed in order to explore significant associations between psychological resilience factors (independent variables) and frailty status (dependent variable). Values of $p < 0.05$ were considered statistically significant.

Main findings

The main sociodemographic and clinical characteristics of the sample have been extensively described in chapter 3. Description of frailty status and psychological factors are summarized in the following Table 1.

Table 1: Frailty status and psychological factors of the sample.

	Patients (N=141)
FI (mean ± SD)	0.25 (± 0.11)
Frailty status - Frail (n, %)	71 (50.4)
- Not frail (n, %)	70 (49.6)
LOT-R (mean ± SD)	18.20 (± 5.57)
FREE (mean ± SD)	7.06 (± 1.55)
FREE_supp (mean ± SD)	3.92 (± 0.92)
FREE_enha (mean ± SD)	3.84 (± 0.84)
CSI (mean ± SD)	18.94 (± 1.57)

Abbreviations: SD= Standard deviation; FI: Frailty Index; PCS: Physical Component Summary; MCS: Mental Component Summary; LOT: Life Orientation Test-Revised; FREE: Flexible Regulation of Emotional Expression; CSI: Context Sensitivity Index.

Univariate linear regressions

We performed several univariate linear regressions considering the FI as the dependent variable, in order to highlight the associations between psychological resilience factors and frailty; we also accounted age and gender as additional variables potentially associated to frailty (Table 2). The variable gender was originally dichotomised (0-1), as “0” corresponds to being male.

Table 2: Univariate linear regressions for FI

	B	SE(B)	β	*p*	95% CI Lower	95% CI Upper
Age	0.003	0.001	0.180	***0.03***	0	0.005
Gender	0.034	0.019	0.148	0.08	-0.004	0.072
FREE	-0.009	0.007	-0.141	0.19	-0.023	0.005
FREE_enha	-0.019	0.012	-0.178	0.10	-0.043	0.004
FREE_supp	-0.023	0.013	-0.193	0.07	-0.049	0.003
CSI	-0.022	0.007	-0.343	***0.002***	-0.036	-0.008
LOT-R	-0.006	0.002	-0.319	***0.001***	-0.009	-0.002

Abbreviations: LOT-R: Life Orientation Test-Revised; FREE: Flexible Regulation of Emotional Expression; FREE_supp: Suppression; FREE_enha: Enhancement; CSI: Context Sensitivity Index*;* FI: Frailty Index.

The univariate analyses showed that CSI (β = -0.343, *p*= 0.002) and LOT-R (β = -0.319, *p*= 0.001) were the two psychological factors associated to frailty, expressed by the FI. Accordingly, a better dispositional optimism and a better individual ability to perceive cues to contextual demands were associated to lower FI, expression of a better health status. The FREE Suppression index was only marginally associated to FI (β = -0.193, *p*= 0.07). Among the included sociodemographic variable, age resulted significantly associated to FI (β= 0.180, *p*= 0.002); gender did not reach a full statistical significance (β = 0.148, *p*= 0.08).

Multivariate linear regression

In line with the results of the univariate regressions, we consequently performed a multivariate linear regression considering the FI as the dependent variable, and hierarchically including those variables, which were found significantly associated to FI at the univariate analyses (Table 3).

Table 3: Multivariate linear regression for FI

	R^2	Adjusted R^2	F	*p*
Step 1	0.006	-0.007	0.453	0.50
	SE(B)	**β**	**t**	***p***
Age	0.002	0.077	0.673	0.50
	R^2	**Adjusted** R^2	**F**	***p***
Step 2	0.246	0.216	8.053	***<0.001***
	SE(B)	**β**	**t**	***p***
Age	0.002	0.005	0.050	0.96
LOT-R	0.002	-0.359	-3.55	***0.001***
CSI	0.007	-0.333	-3.25	***0.002***

Abbreviations: LOT-R: Life Orientation Test-Revised; CSI: Context Sensitivity Index.

The variable age was included in the first step of the model, which did not reach a statistical significance (R^2= 0.006, *p*= 0.50). LOT-R and CSI were included in the second step of the model, which resulted statistical significant (R^2= 0.246, *p*<0.001). LOT-R and CSI were found to be significantly associated to FI after adjusting for age (β = -0.359, *p*= 0.001; β = -0.333, *p*= 0.002, respectively).

We performed an additional multivariate regression, hierarchically including gender and FREE Suppression in the model, since these variables were found marginally associated to the FI in the univariate regression (*p*= 0.08; *p*= 0.07, respectively). Age and gender were included in the first step of the model; FREE Suppression was included in the second block together with LOT-R and CSI. After adjusting for age, gender and FREE_supp, LOT-R (β= -0.350, p= 0.001) and CSI (β= -0.330, p= 0.002) were confirmed independently associated to FI.

Study 2. Association between Psychological resilience factors and Quality of Life (QoL)

Aim of the study

The main purpose of the study was to investigate whether psychological resilience factors (i.e. expressive flexibility, context sensitivity, and additionally dispositional optimism) might interact with both physical and mental dimensions of QoL in our sample of elderly outpatients.

Statistical analysis

Data were analysed using IBM SPSS 22 statistical software. Univariate and multivariate linear regressions were computed in order to explore significant associations between psychological resilience factors (independent variables) and QoL dimensions (dependent variables). Since the calculated FI was based on the presence of several detected deficits (as previously described), and since it represents *per se* an index of health status able to influence individual QoL, we included the FI in the univariate linear regressions; additionally, we accounted the FI also in the multivariate analyses as a potential adjustment factor. Values of $p < 0.05$ were considered statistically significant.

Main findings

The main sociodemographic and clinical characteristics of the sample have been extensively described in chapter 3. The mean SF-12 score was significantly ($p<0.001$) different between subjects classified as frail (45.36 ± 6.19) and those classified as not frail (54.29 ± 10.94). PCS and the MCS scores were significantly different ($p <0.001$) between subjects classified as frail (PCS = 45.53 ± 6.30; MCS = 45.77 ± 7.50) and subjects classified as not frail (PCS = 54.13 ± 11.01; MCS = 53.91 ± 10.47).Description of QoL domains and psychological factors are summarized in the following Table 1

Table 1: QoL domains, frailty status and psychological factors of the sample.

	Patients (N=141)
FI (mean ± SD)	0.25 (± 0.11)
PCS (mean ± SD)	50 (± 10)
MCS (mean ± SD)	49.99 (± 9.99)
LOT-R (mean ± SD)	18.20 (± 5.57)
FREE (mean ± SD)	7.06 (± 1.55)
FREE_supp (mean ± SD)	3.92 (± 0.92)
FREE_enha (mean ± SD)	3.84 (± 0.84)
CSI (mean ± SD)	18.94 (± 1.57)

Abbreviations: LOT-R: Life Orientation Test-Revised; FREE: Flexible Regulation of Emotional Expression; FREE_supp: Suppression; FREE_enha: Enhancement; CSI: Context Sensitivity Index; PCS: Physical Component Summary; MCS: Mental Component Summary; FI: Frailty Index.

Univariate linear regressions

We performed several univariate linear regressions considering the QoL as the dependent variable, in order to highlight the associations between psychological resilience factors and QoL dimensions. Accordingly, we progressively considered the SF-12 total score, the PCS and the MCS score as the dependent variable, expression of global QoL, physical component and mental component of QoL, respectively. We additionally investigated through univariate linear regressions whether age, gender and the FI might be also potentially associated to QoL dimensions (Tables 2-4). The variable gender was originally dichotomised (0-1), as "0" corresponds to being male.

Table 2: Univariate linear regressions for global QoL (SF-12)

	B	**SE(B)**	**β**	***p***	**95% CI**	
					Lower	Upper
LOT-R	0.903	0.158	0.502	***<0.001***	0.589	1.217
FREE	1.536	0.708	0.232	***0.033***	0.129	2.943
FREE_supp	1.599	1.215	0.143	0.192	-0.818	4.016
FREE_enha	4.070	1.278	0.330	***0.002***	1.527	6.612
CSI	1.048	0.715	0.166	0.147	-0.377	2.472
Age	0.130	0.154	0.083	0.40	-0.176	0.436
Gender	-4.939	2.060	-0.231	***0.018***	-9.025	-0.854
FI	-43.565	8.664	-0.446	***<0.001***	-60.75	-26.37

Abbreviations: LOT-R: Life Orientation Test-Revised; FREE: Flexible Regulation of Emotional Expression; FREE_supp: Suppression; FREE_enha: Enhancement; CSI: Context Sensitivity Index*;* PCS: Physical Component Summary; MCS: Mental Component Summary; FI: Frailty Index.

The univariate linear regression for SF-12 showed that gender (β= -0.231, p= 0.018) was significantly associated to SF-12, meaning that being male was associated to a better QoL. Among the investigated psychological factors, LOT-R (β= 0.502, p< 0.001), the FREE total score (β= 0.232, p= 0.033) and the FREE Enhancement index (β= 0.330, p= 0.002) resulted significantly associated to SF-12. Accordingly, a higher dispositional optimism, a better global expressive flexibility, or a peculiar better ability to enhance emotional expression were associated to higher scores of SF-12, expression of a better QoL.

Eventually, also FI (β= -0.446, $p< 0.001$) was associated to SF-12, meaning higher FI was associated to a worse QoL expressed by SF-12.

Table 3: Univariate linear regressions for PCS

	B	**SE(B)**	**β**	***p***	**95% CI**	
					Lower	Upper
LOT-R	0.705	0.169	0.390	***<0.001***	0.370	1.041
FREE	1.095	0.723	0.164	0.134	-0.334	2.534
FREE_supp	0.941	1.233	0.083	0.448	-1.512	3.394
FREE_enha	3.896	1.296	0.313	***0.004***	1.318	6.475
CSI	0.938	0.730	0.146	0.203	-0.516	2.392
Age	0.062	0.155	0.040	0.68	-0.245	0.369
Gender	-5.565	2.044	-0.260	***0.008***	-9.620	-1.510
FI	-44.523	8.617	-0.455	***<0.001***	-61.61	-27.43

Abbreviations: LOT-R: Life Orientation Test-Revised; FREE: Flexible Regulation of Emotional Expression; FREE_supp: Suppression; FREE_enha: Enhancement; CSI: Context Sensitivity Index*;* PCS: Physical Component Summary; MCS: Mental Component Summary; FI: Frailty Index.

The univariate linear regression for PCS showed that gender (β= -0.260, $p= 0.008$) was significantly associated to the PCS, meaning that being male was associated to a better physical QoL. Among the investigated psychological factors, LOT-R (β= 0.390, $p< 0.001$), and the FREE Enhancement index (β= 0.313, $p= 0.004$) resulted significantly associated to PCS. Accordingly, a higher dispositional optimism, and a better ability to enhance emotional expression were associated to higher scores of PCS, expression of a better physical QoL. Eventually, also FI (β= -0.455, p< 0.001) was associated to PCS, meaning higher FI was associated to a worse physical QoL.

Table 4: Univariate linear regressions for MCS

	B	**SE**	**β**	***p***	**95% CI**	
					Lower	Upper
LOT-R	0.942	0.155	0.525	***<0.001***	0.634	1.249
FREE	1.748	0.692	0.267	***0.014***	0.370	3.125
FREE_supp	2.025	1.192	0.183	0.093	-0.347	4.396
FREE_enha	3.245	1.289	0.266	***0.014***	0.681	5.810
CSI	0.802	0.708	0.129	0.261	-0.607	2.212
Age	0.130	0.154	0.083	0.40	-0.176	0.437
Gender	-3.179	2.094	-0.149	0.13	-7.331	0.974
FI	-38.00	8.917	-0.389	***<0.001***	-55.68	-20.31

Abbreviations: LOT-R: Life Orientation Test-Revised; FREE: Flexible Regulation of Emotional Expression; FREE_supp: Suppression; FREE_enha: Enhancement; CSI: Context Sensitivity Index*;* PCS: Physical Component Summary; MCS: Mental Component Summary; FI: Frailty Index.

The univariate linear regression for SF-12 showed that, among the investigated psychological factors, LOT-R (β= 0.525, p< 0.001), the FREE total score (β= 0.267, p= 0.014) and the FREE Enhancement index (β= 0.266, p= 0.014) resulted significantly associated to MCS. Accordingly, a higher dispositional optimism, a better global expressive flexibility, or a peculiar better ability to enhance emotional expression were associated to a better mental QoL. Eventually, also FI (β= -0.389, p< 0.001) was associated to MCS, meaning higher FI was associated to a worse mental QoL.

Multivariate linear regressions

In line with the results of the previous univariate linear regressions, we performed different multivariate linear regressions for each index of QoL (SF-12, PCS and MCS), as dependent variables, hierarchically including in the model those variables which were statistically significant in the univariate regressions (Tables 5-7). The purpose was to investigate whether the retrieved significant psychological resilience factors could be independently associated to QoL. Moreover, we aimed to investigate whether such psychological resilience factors could be associated to QoL even after adjusting for FI.

Table 5: Multivariate linear regression for SF12

	R^2	Adjusted R^2	F	*p*
Step 1	0.031	0.020	2.692	0.10
	SE(B)	**β**	**T**	***p***
Gender	2.361	-0.177	-1.641	0.10
	R^2	Adjusted R^2	F	*p*
Step 2	0.218	0.199	11.421	***<0.001***
	SE(B)	**β**	**T**	***p***
Gender	2.134	-0.172	-1.765	0.08
FI	10.064	-0.432	-4.421	***<0.001***
	R^2	Adjusted R^2	F	*p*
Step 3	0.345	0.312	10.517	***<0.001***
	SE(B)	**β**	**T**	***p***
Gender	2.036	-0.147	-1.574	0.11
FI	10.213	-0.274	-2.769	***0.007***
LOT-R	0.178	0.371	3.765	***<0.001***
FREE_enha	1.050	0.098	1.044	0.30

Abbreviations: LOT-R: Life Orientation Test-Revised; FREE: Flexible Regulation of Emotional Expression; FREE_enha: Enhancement; FI: Frailty Index.

The variable gender was included in the first step, which resulted not statistically significant (R^2= 0.031, *p*= 0.10). The FI was added in the second step of the model, which reached a statistical significance ((R^2= 0.218, *p*< *0.001*); in this step, FI resulted significantly associated to SF-12 (β= -0.432, *p*< *0.001*). Eventually, LOT-R and FREE Enhancement were included in the third step, which resulted statistically significant (R^2= 0.345, $p<0.001$); in this step the two final variables significantly associated to SF-12 were FI (β= -0.274, p= 0.007) and LOT-R (β= 0.371, $p<0.001$).

Since even the FREE score was found significantly associated to SF-12 in the univariate linear regression, we performed an additional multivariate regression hierarchically including the FREE score in place of the FREE Enhancement, therefore accounting the global index of expressive flexibility. The results of the model did not differ from the previous in terms of variables significantly associated to SF-12: in fact, FI (β= -0.279, p= 0.005) and LOT-R (β= 0.341, p= 0.001) were confirmed significantly associated to SF-12; the FREE resulted only marginally associated to SF-12 (β= 0.167, p= 0.08).

Table 6: Multivariate linear regression for PCS

	R^2	**Adjusted R^2**	**F**	***p***
Step 1	0.040	0.028	3.462	0.06
	SE(B)	**β**	**T**	***p***
Gender	2.369	-0.200	-1.861	0.06
	R^2	**Adjusted R^2**	**F**	***p***
Step 2	0.235	0.216	12.599	***<0.001***
	SE(B)	**β**	**T**	***p***
Gender	2.128	-0.195	-2.020	***0.04***
FI	10.034	-0.442	-4.572	***0.001***
	R^2	**Adjusted R^2**	**F**	***p***
Step 3	0.283	0.247	7.876	***<0.001***
	SE(B)	**β**	**T**	***p***
Gender	2.147	-0.175	-1.795	0.07
FI	10.772	-0.347	-3.345	***0.001***
LOT-R	0.188	0.232	2.253	***0.02***
FREE_enha	1.107	0.040	0.409	0.68

Abbreviations: PCS: Physical Component Summary; LOT-R: Life Orientation Test-Revised; FREE: Flexible Regulation of Emotional Expression; FREE_enha: Enhancement; FI: Frailty Index.

The first step did not reach a statistical significance (R^2= 0.040, p= 0.06), considering gender as the first variable included in the model (β= -0.200, p= 0.06). The variable FI was included in the second step, which resulted significant (R^2=0.235, p< 0.001): in this step, both gender (β= -0.195, p= 0.04) and FI (β= -0.442, p< 0.001) resulted significantly associated to PCS. LOT-R and FREE Enhancement were finally included in the third step, which resulted significant (R^2= 0.283, p< 0.001): accordingly, LOT-R and FI were the two variables independently associated to PCS in the final step (β= 0.232, p= 0.02; β= -0.347, p= 0.001, respectively).

Table 7: Multivariate linear regression for MCS

	R^2	**Adjusted R^2**	**F**	***p***
Step 1	0.144	0.134	13.971	***<0.001***
	SE(B)	**β**	**t**	***p***
FI	10.338	-0.380	-3.738	***<0.001***
	R^2	**Adjusted R^2**	**F**	***p***
Step 2	0.329	0.304	13.246	***<0.001***
	SE(B)	**β**	**t**	***p***
FI	10.145	-0.189	-1.901	0.06
LOT-R	0.175	0.447	4.546	***<0.001***
FREE_enha	1.022	0.120	1.298	0.19

Abbreviations: MCS: Mental Component Summary; LOT-R: Life Orientation Test-Revised; FREE: Flexible Regulation of Emotional Expression; FREE_enha: Enhancement; FI: Frailty Index.

According to the results obtained from the relative univariate linear regressions, neither gender nor age were included in the multivariate regression for MCS. Therefore, the variable FI was included in the first step of the model, which reached a statistical significance (R^2= 0.144, p<0.001); FI resulted significantly associated to MCS (β= -0.380, p< 0.001). LOT-R and FREE Enhancement were included in the second step (R^2= 0.329, p< 0.001): after adjusting for FI and FREE Enhancement, LOT-R resulted the only variable independently associated to MCS (β= 0.447, p< 0.001).

Since even the FREE score was found significantly associated to MCS in the univariate linear regression, we performed an additional multivariate regression hierarchically including the FREE score in place of the FREE Enhancement, therefore accounting the global index of expressive flexibility. The result of the final step of the model confirmed that LOT-R was significantly associated to MCS (β= 0.421, p< 0.001); additionally, in the model FI resulted significantly associated to MCS (β= -0.198, p= 0.04). The FREE score resulted not significantly associated to MCS (β= 0.159, p= 0.08).

Study 3: Psychological resilience factors as predictors of QoL among elderly during the COVID-19 pandemic: preliminary longitudinal evidence.

Main purpose

The elderly denoted one of the most vulnerable and at risk categories during the Covid-19 pandemic. The progressive lockdown imposed by the national government represented a new and challenging condition for elderly subjects, who have not only had to face the worry and the fear of contagion, but they also had to cope with the distressing experiences of quarantine and isolation from relatives and friends.

Recent evidence have highlighted that the Covid-19 emergency had a negative impact on psychological status among elderly, often in terms of increased depressive and anxiety symptoms (Garcia-Portilla et al., 2020). The principal aim of this preliminary longitudinal investigation was to longitudinally explore QoL among our sample during the Covid-19 pandemic; at the same time, we additionally aimed to identify, among the investigated baseline psychological resilience factors, potential predictors of QoL.

Statistical analysis

Data were analysed using IBM SPSS 22 statistical software. The Wilcoxon test was used to describe differences between baseline and longitudinal QoL values.

Univariate and multivariate linear regressions were computed in order to explore significant associations between the psychological resilience factors previously assessed and longitudinal QoL dimensions (dependent variables). Since the calculated FI was based on the presence of several detected deficits (as previously described), and since it represents *per se* an index of health status able to influence individual QoL, we included the FI in the univariate linear regressions; additionally, we accounted the FI also in the multivariate analyses as a potential adjustment factor. Values of $p < 0.05$ were considered statistically significant.

Procedures

Due to the progressive suspension of the Geriatric Outpatient Clinic activity (starting from March 2020), most patients included in our original sample have not been able to undergo the scheduled follow-up. The evaluation of QoL through the SF-12 was therefore carried out by telephone. In order to avoid potential rater-related bias, a single trained psychologist conducted the phone calls and administered the questionnaire. The telephone procedure started in April; the phone calls were made during the morning hours, with an average of five phone calls per day.

Main findings

From the original sample, a total of 115 patients were tracked by telephone; however, eleven of them declined to undergo the evaluation; we were not able to contact the remaining twenty-six patients. The final number of patients included in the follow-up evaluation was 104.

Due to the COVID-19 outbreak, to date the main outcome of the follow-up evaluation was considered only the QoL, measured by SF-12. The principal differences between baseline and longitudinal QoL values are summarized in Table 1. Compared to baseline, patients exhibited a significantly worse general QoL, as well as significantly worse levels in both the physical and the mental component.

Table 1: Differences between baseline and longitudinal QoL values (N= 104)

	Baseline (t0)	Longitudinal (t1)	z (t1 - t0)	*p*
SF-12	49,99 (± 10)	46,46 (±10)	-8.22	***<0.001***
PCS	50 (± 10)	46,42 (± 10.28)	-8.67	***<0.001***
MCS	49,99 (± 9,99)	46,35 (± 10.06)	-8.27	***<0.001***

Abbreviations: PCS: Physical Component Summary; MCS: Mental Component Summary.
Note: values expressed in terms of mean and standard deviation.

Univariate analysis

Several univariate linear regression have been performed in order to investigate the association between baseline psychological factors and longitudinal levels of QoL (Tables 2-4).

Table 2: Univariate linear regressions for SF-12 (t1)

	B	**SE(B)**	**β**	***p***	**95% CI**	
					Lower	Upper
LOT-R	0.915	0.157	0.598	***<0.001***	0.603	1.228
FREE	1.889	0.684	0.290	***0.007***	0.528	3.251
FREE_supp	1.911	1.189	0.174	0.11	-0.454	4.275
FREE_enha	4.925	1.217	0.406	***<0.001***	2.506	7.345
CSI	1.204	0.700	0.193	0.09	-0.191	2.599
Age	0.014	0.155	0.009	0.92	-0.293	0.322
Gender	-4.778	2.066	-0.223	***0.023***	-8.876	-0.681
FI	-53.45	8.116	-0.546	***<0.001***	-69.55	-37.35

Abbreviations: LOT-R: Life Orientation Test-Revised; FREE: Flexible Regulation of Emotional Expression; FREE_enha: Enhancement; FREE_supp: Suppression; FI: Frailty Index.

The first univariate linear regressions considered the total score of SF-12 (t1) as the dependent variable. The gender resulted significantly associated to SF-12 (t1) (β= -0.223, p= 0.023), suggesting that being male was associated to higher levels of QoL. Furthermore, the FI calculated at baseline was significantly associated to SF-12 (t2) (β= -0.546, p< 0.001), meaning that a worse frailty status (i.e. higher FI) was associated to lower SF-12 scores. Among the psychological factors investigated at baseline, LOT-R (β= 0.598, p< 0.001), the total score of FREE (β= 0.290, p= 0.007), as well as the sole FREE Enhancement index (β= 0.406, p< 0.001) were found significantly associated to the SF-12 (t1). Accordingly, better dispositional optimism, better global expressive flexibility, and peculiarly better ability to enhance emotional expression were associated to better QoL.

Table 3: Univariate linear regressions for PCS (t1)

	B	**SE(B)**	**β**	***p***	**95% CI**	
					Lower	Upper
LOT-R	0.759	0.172	0.410	***<0.001***	0.418	1.099
FREE	1.322	0.727	0.196	0.07	-0.123	2.76
FREE_supp	1.160	1.244	0.102	0.35	-1.315	3.635
FREE_enha	4.279	1.297	0.340	***0.001***	1.689	6.859
CSI	1.074	0.734	0.166	0.14	-0.388	2.537
Age	-0.035	0.159	-0.022	0.82	-0.35	0.281
Gender	-5.484	2.108	-0.249	***0.011***	-9.66	-1.30
FI	-55.47	8.29	-0.552	***<0.001***	-71.93	-39.01

Abbreviations: PCS: Physical Component Summary; LOT-R: Life Orientation Test-Revised; FREE: Flexible Regulation of Emotional Expression; FREE_enha: Enhancement; FREE_supp: Suppression; FI: Frailty Index.

We performed univariate linear regressions also considering the PCS (t1) as the dependent variable. Even in this occasion, being female (β= -0.249, p= 0.011) and a higher FI calculated at baseline (β= -0.552, p< 0.001) resulted significantly associated to longitudinal lower physical QoL. The LOT-R score (β= 0.410, p<0.001) and the FREE Enhancement index were the psychological factors significantly associated to PCS (t1).

Table 4: Univariate linear regressions for MCS (t1)

	B	SE(B)	β	*p*	95% CI	
					Lower	Upper
LOT-R	0.961	0.155	0.532	***<0.001***	0.653	1.269
FREE	2.181	0.667	0.338	***0.002***	0.854	3.507
FREE_supp	2.543	1.163	0.233	***0.03***	0.229	4.856
FREE_enha	4.155	1.238	0.346	***0.001***	1.693	6.618
CSI	0.973	0.701	0.157	0.16	-0.424	2.369
Age	0.032	0.156	0.020	0.83	-0.277	0.341
Gender	-3.115	2.108	-0.145	0.14	-7.296	1.065
FI	-47.27	8.53	-0.481	***<0.001***	-64.21	-30.33

Abbreviations: MCS: Mental Component Summary; LOT-R: Life Orientation Test-Revised; FREE: Flexible Regulation of Emotional Expression; FREE_enha: Enhancement; FREE_supp: Suppression; FI: Frailty Index.

Eventually, we performed different univariate linear regressions considering the MCS (t1) as the dependent variable. None of the accounted sociodemographic variables (i.e. age and gender) were found significantly associated to the mental component of QoL. The FI resulted negatively associated to MCS (t1), meaning that a worse frailty status at baseline, expressed by higher FI, was associated to lower values in the mental component of QoL at follow-up ($\beta = -0.481$, $p<0.001$). Better dispositional optimism ($\beta = 0.532$, $p<0.001$), and better expressive flexibility ($\beta = 0.338$, $p = 0.002$) resulted associated to higher MCS (t1) values. Regarding the expressive flexibility domain, we found that, in addition to the total FREE score, both the Enhancement (β= 0.346, p= 0.001) and Suppression (β= 0.233, p= 0.03) indexes were also significantly associated to MCS (t1).

Multivariate linear regressions

In line with the results obtained from the univariate linear regressions, we consequently performed different multivariate linear regressions, in order to find significant predictors of QoL. Accordingly, we computed three different regression models, considering SF-12 (t1), PCS (t1) and MCS (t1) as the dependent variables, and hierarchically included in the models those variables that were significant at the univariate regressions (Tables 5-7)

Table 5: Multivariate linear regression for SF-12 (t1)

	R^2	**Adjusted R^2**	**F**	***p***
Step 1	0.025	0.013	2.134	0.14
	SE(B)	**β**	**t**	***p***
Gender	2.329	-0.158	-1.461	0.14
	R^2	**Adjusted R^2**	**F**	***p***
Step 2	0.285	0.268	16.356	***<0.001***
	SE(B)	**β**	**t**	***p***
Gender	2.006	-0.153	-1.634	0.10
FI	9.460	-0.510	-5.462	***<0.001***
	R^2	**Adjusted R^2**	**F**	***p***
Step 3	0.436	0.408	15.459	***<0.001***
	SE(B)	**β**	**t**	***p***
Gender	1.884	-0.165	-1.881	0.06
FI	9.216	-0.360	-3.954	***<0.001***
LOT-R	0.165	0.317	3.40	***0.001***
FREE	0.579	0.217	2.445	***0.01***

Abbreviations: LOT-R: Life Orientation Test-Revised; FREE: Flexible Regulation of Emotional Expression; FREE_enha: Enhancement; FI: Frailty Index.

Gender, FI, LOT-R and FREE were the variables hierarchically included in the multivariate linear regression for SF-12 (t1). The first step of the model accounted the variable gender, but did not reach a statistical significance (p=0.14). The second step resulted significant (R^2= 0.285, p<0.001) after the inclusion of the FI; gender persisted to be not significant, FI was instead statistically significant (β= -0.510, $p< 0.001$). In the final step (R^2= 0.436, $p<0.001$), the psychological variables were included: after a progressive adjustment, LOT-R (β= 0.317, p= 0.001) and FREE (β= 0.217, p= 0.01) resulted significant predictors of SF-12 (t1), in addition to FI (β= -0.360, $p< 0.001$).

Since the FREE Enhancement index resulted significantly associated to SF-12 (t1) in the univariate analysis, we performed an additional multivariate linear regression, hierarchically including FREE_enha in place of FREE. The final step of the model (R^2= 0.406, $p<0.001$) showed that LOT-R (β= 0.356, $p<0.001$) and FI (β= -0.356, $p<0.001$) significantly predict SF-12 (t1).

Table 6: Multivariate linear regression for PCS (t1)

	R^2	Adjusted R^2	F	*p*
Step 1	0.035	0.023	2.993	0.087
	SE(B)	**β**	**t**	***p***
Gender	2.401	-0.187	-1.730	0.087
	R^2	**Adjusted R^2**	**F**	***p***
Step 2	0.302	0.285	17.705	***<0.001***
	SE(B)	**β**	**t**	***p***
Gender	2.055	-0.181	-1.959	0.054
FI	9.690	-0.517	-5.597	***<0.001***
	R^2	**Adjusted R^2**	**F**	***p***
Step 3	0.350	0.317	10.758	***<0.001***
	SE(B)	**β**	**t**	***p***
Gender	2.066	-0.161	-1.734	0.087
FI	10.365	-0.421	-4.264	***<0.001***
LOT-R	0.180	0.234	2.370	***0.020***
FREE_enha	1.065	0.043	0.455	0.65

Abbreviations: PCS: Physical Component Summary; LOT-R: Life Orientation Test-Revised; FREE: Flexible Regulation of Emotional Expression; FREE_enha: Enhancement; FI: Frailty Index

The multivariate regression for PCS (t1) was developed in three hierarchical steps. The variable gender was included in the first step, which did not reach a statistical significance (R^2= 0.035, p= 0.087); the second step resulted significant (R^2= 0.302, p<0.001), and it was substantially explained by the inclusion of the FI in the model (β= -0.517, p<0.001). The psychological factors expressed by LOT-R and FREE_enha were added in the final step (R^2= 0.350, p<0.001). Eventually, both FI (β= 0.421, p<0.001) and LOT-R (β= 0.234, p= 0.020) were found to be independent predictors of PCS (t1), meaning that a worse baseline frailty status and lower baseline levels of dispositional optimism predicted reduced physical QoL.

Table 7: Multivariate linear regression for MCS (t1)

	R^2	**Adjusted R^2**	**F**	***p***
Step 1	0.204	0.195	21.285	***<0.001***
	SE(B)	**β**	**t**	***p***
FI	9.933	-0.452	-4.614	***<0.001***
	R^2	**Adjusted R^2**	**F**	***p***
Step 2	0.408	0.378	13.765	***<0.001***
	SE(B)	**β**	**t**	***p***
FI	9.468	-0.254	-2.693	***0.009***
LOT-R	0.167	0.402	4.228	***<0.001***
FREE_enha	1.070	0.089	0.911	0.36
FREE_supp	1.206	0.155	1.548	0.12

Abbreviations: MCS: Mental Component Summary; LOT-R: Life Orientation Test-Revised; FREE: Flexible Regulation of Emotional Expression; FREE_enha: Enhancement; FREE_supp: Suppression; FI: Frailty Index.

The multivariate linear regression for MCS (t1) was developed only in two steps, since none of the accounted sociodemographic variables were found significantly associated to MCS (t1) in the univariate regressions.

Consistently, we included the variable FI in the first step, which resulted statistically significant (R^2= 0.204, $p<0.001$). LOT-R, and both the FREE indexes Enhancement and Suppression were hierarchically included in the final step (R^2= 0.408, $p<0.001$); at the end of the model, FI (β= -0.245, p=0.009) and LOT-R (β=0.402, $p<0.001$) resulted the two factors able to significantly predict MCS (t1).

Since even the total FREE score was previously found significantly associated to the MCS (t1), we performed an additional multivariate regression analysis including the FREE score in place of both the FREE_enha and FREE_supp, in order to understand whether the global expressive flexibility index could be associated to MCS (t1). The first step of the regression included the FI, and resulted statistically significant (R^2= 0.204, $p<0.001$). LOT-R and FREE were additionally included in the final step (R^2== 0.414, $p<0.001$); eventually, LOT-R (β= 0.398, $p<0.001$), FREE (β= 0.224, p= 0.012), and FI (β= -0.270, p= 0.004) were found to be predictors of MCS (t1), with LOT-R and FI that contributed most to explaining the model.

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CONCLUSIONS

The present thesis embodied the unpublished results from several conducted studies aimed to explore CR and psychological resilience among a sample of elderly patients. Specifically, the main purpose was to investigate the interaction between CR indexes and psychological resilience factors with common age-related clinical outcomes such frailty and QoL.

CR was discussed in the context of the theoretical model proposed by Yaakov Stern, according to which educational level, occupational status and leisure time are considered the most representative indexes of CR, together with the premorbid IQ. In line with this theoretical framework, we measured CR though two validated screening tools, the CRIq and the TIB. The operationalized evaluation of CR in the context of frailty represents a novel research approach; as well original is the employment of unitary screening tools in order to investigate CR in the context of the joint cognitive, physical and functional evaluation among elderly subjects.

Despite in our cross-sectional observations CRIq and TIB scores resulted significantly associated to frailty status, both of them did not persist to be significant after adjustment for common frailty-related factors such physical, motor and cognitive performances. A possible explanation of this evidence might allow us not to consider CR a factor able to directly influence frailty status, at least in the context of the investigated elderly outpatients' sample, but rather a factor able to possibly interact with intermediary domains, whose evolution along lifespan commonly lead to frailty. To support at least partially this hypothesis, our findings showed that both CRIq score and IQ were cross-sectionally, significantly associated to patients' cognitive status expressed by MMSE, even after adjusting for sociodemographic (i.e. age and years of education) and physical factors (i.e. handgrip strength and gait speed). Additionally, in line with our preliminary longitudinal results, even though partially limited due to the Covid-19 emergency, CRIq and TIB were both found to be significant predictors of cognitive status at follow-up, even after adjusting for sociodemographic (i.e. years of education) and physical factors (i.e. handgrip strength and gait speed). This preliminary findings suggest that CR might have a positive role along the cognitive trajectory leading to frailty. Furthermore, consistently with a joint cognitive-motor approach to aging, the positive role of CR could assume significance in the evolution of a cognitive frailty, which refers to a clinical condition characterized by the presence of both physical frailty and cognitive impairment, in the absence of a manifest diagnosed dementia (Canevelli & Cesari, 2017).

CR denotes a multifaceted construct in which different factors are involved, as we accordingly evaluated through CRIq and TIB; similarly, the FI employed in our sample provides a multifactorial measure of frailty and it represents a useful tool for assessing the complexity of the outpatients. Therefore, the absence of a direct significant association between these two wide factors could find an explanation indeed in the complex nature of our studied sample, based on outpatients.

We acknowledge that this selection bias might represent a limitation, potentially influencing the generalizability of our findings. At the same time, the hypothesized positive role of CR along the cognitive trajectory leading to frailty represents an original starting point. However, further longitudinal and larger studies are needed and strongly encouraged in order to better elucidate the potential protective role of CR along age-related cognitive-motor trajectories (Figure 1).

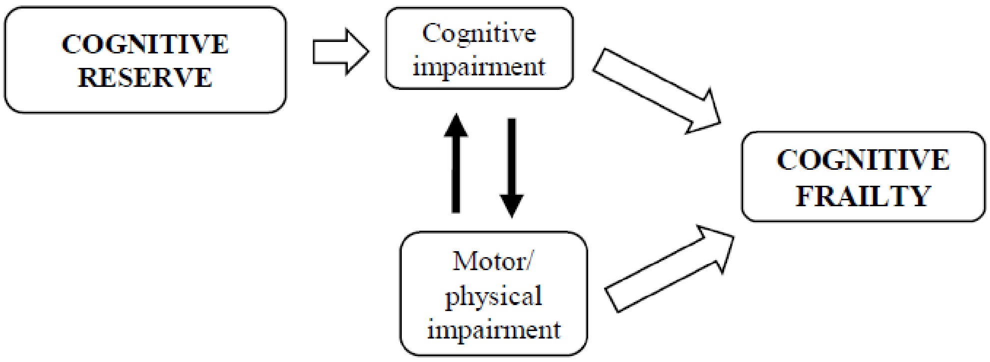

Figure 1: Hypothetical model according to which CR might have a positive role along the cognitive trajectory leading to frailty. Consistently with a joint cognitive-motor approach to aging, the positive role of CR could possibly assume significance in the trajectories of cognitive frailty.

One of the geriatric framework that could be enriched by the additional evaluation of CR is the Comprehensive Geriatric Assessment (CGA), which perfectly summarizes a bio-psycho-social approach, providing an integrated assessment of elderly outpatients (Parker et al., 2018). The employment of the CRIq has been recently suggested in the context of the CGA among patients with dementia, since the established interaction between CR factors and the onset and the progression of cognitive impairment (Devita et al., 2020). Furthermore, the TIB may also provide an additional and useful support in the context of GCA. TIB represents a quick and easy to administer tool, which could be an advantage when elderly subjects are evaluated. This test was originally proposed to estimate premorbid IQ in subjects with cognitive impairment, and it has been already employed for the same purpose among non-demented elderly patients with Parkinson's disease, together with the CRIq (Caffò et al., 2016).

In line with the need to encourage the CR evaluation even in the context of aging trajectories towards frailty, it might be also possible to consider CR dimensions as a potential novel target of intervention among elderly, as recently suggested for subjects with dementia (Wang et al., 2019). The behind hypothesis should be based on improving and promoting those healthy and protective lifestyles which are linked to reduced cognitive and functional decline, parallel to the treatment of the pathological conditions that underlie frailty. In the context of a bio-psycho-social approach to elderly health, enhancing and valuing CR dimensions could also allow individuals to increase the awareness of their needs, promoting the choice of healthy lifestyles, as well as improving the adherence to therapies and the care for their health.

The present thesis additionally embodied several conducted observations aimed to explore psychological resilience factors among elderly subjects.

Throughout the last years, the investigation of psychological resilience has been increasingly aimed to recognize those related factors mainly involved in adaptation processes. Aging represents *per se* the result of several adaptation processes; consistently, evaluating the impact of psychological resilience factors on different age-related negative outcome (such as frailty, disability, and poor quality of life) acquires significance in the context of elderly population, which need to adapt well to changes in older life. The behind hypothesis is that those who develop and encourage resilient characteristics and strategies over the life course may leverage them against health-related challenges (Taylor et al., 2020).

We accounted dispositional optimism, context sensitivity and expressive flexibility as those psychological resilience factors to explore in our conducted studies. Dispositional optimism represents an interesting factor, which has been previously investigated in several clinical settings, and which has been suggested as potentially able to motivate individuals to assume healthy behaviours. Consistently, recent systematic reviews and meta-analyses highlighted the general association between optimism and physical health in adults, and the beneficial role of optimism for the treatment of subjects suffering from chronic medical conditions, such as cardiovascular diseases, cancer, diabetes, neurological pathologies (Rasmussen et al., 2009; Schiavon et al., 2017).

Context sensitivity and expressive flexibility represent the core factors of a psychological resilience model proposed and validated by Bonanno and colleagues (Bonanno et al., 2004), according to which resilience is the result of individual ability to maintain a stable equilibrium after being exposed to stressful and traumatic situations. In line with this theoretical framework, positive or negative adaptation processes depends on individual ability to flexibly enhance or suppress emotional expression in accordance with the contextual demands. (Burton et al., 2016). Emotion regulation is commonly considered a psychological factor able to interact with individual well-being; therefore, a flexible emotion regulation should take into account both regulatory efforts and the context in which such regulatory strategies are applied (Chen et al., 2018). The effect of a flexible emotion regulation has been previously investigated in different community and clinical settings, suggesting a potential protective role of expressive flexibility for reducing psychopathology symptoms and supporting psychological adjustment (Rodin et al., 2017; Southward & Cheavens, 2017).

The investigation of psychological resilience, expressed by dispositional optimism, context sensitivity and expressive flexibility, and its association with frailty status represents a novel research topic among elderly subjects. We measured frailty in terms of number of deficit accumulated along older life course, and the resulted FI can be read as a multifactorial index of health. The question behind our observations was whether psychological resilience factors could interact with a comprehensive patients' health status expressed by the FI, assuming the need for patients to put into practice positive adaptation processes to their progressive frailty status.

Our conducted cross-sectional observations showed that dispositional optimism, measured by the LOT-R, and context sensitivity, evaluated by the CSI, were significantly associated to frailty status, even adjusting for age and the remaining investigated psychological factors. These preliminary findings suggest that higher levels of optimism and a better individual ability to perceive cues to contextual demands were associated to a lower FI (expression of a better health status) among elderly subjects. Since QoL commonly denotes a further aspect that mainly contributes to the aging adaptation process, and it is strongly related to frailty, we additionally explored the association between psychological resilience factors and QoL dimensions in our sample. The findings from our cross-sectional conducted studies showed that, together with frailty status, dispositional optimism was the only resilience factors significantly associated to both physical and mental dimensions of QoL. Even though partially limited by the Covid-19 emergency, we also performed longitudinal observations with the purpose to investigate whether baseline psychological resilience factors might also predict QoL at follow-up. Accordingly, our preliminary longitudinal evidence confirmed that dispositional optimism was a significant predictor of both physical and mental dimensions of QoL, together with frailty status. Additionally, the longitudinal analyses showed that also the comprehensive index of expressive flexibility (but not the single enhancement nor the suppression factors measured by the FREE), was a significant predictor of the global QoL and the mental dimension of QoL.

Dispositional optimism, context sensitivity and expressive flexibility represent original research topics among elderly outpatients, specifically in their association with frailty and QoL. Our pilot findings, despite strongly limited by the Covid-19 pandemic, provide for the first time information on novel psychological factors potentially involved in aging adaptation processes.

The impact of psychological resilience factors on frailty, and on related outcome such QoL, appears a worthy and challenging research topic, which needs to be better explored by future longitudinal studies, in order to further enrich the geriatric multidimensional approach to elderly subjects. Identifying psychological resilience factors involved to health and wellbeing might also be practically translated into the implementation of intervention programs, focused on improving those modifiable antecedent factors that may promote health along the course of older life.

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APPENDIX

Supplementary Material:

1. Supplementary Material of Chapter 1:

- Table 1: Main characteristics of the most representative studies discussed in the review, supporting the association between cognitive and motor impairment

2. Supplementary Material of Chapter 2:

- Table 1: Summary of included studies (alphabetically listed)
- References

3. Supplementary Material of Chapter 3:

- Variables included in the Frailty Index

Supplementary material of chapter 1

Table 1: Main characteristics of the most representative studies discussed in the review, supporting the association between cognitive and motor impairment

			From cognitive to sarcopenia and motor impairment			
Study	**Article Type**	**Study Design**	**Sample Characteristics**	**Cognitive Measure**	**Motor/physical Measure**	**Main Findings**
Inzitari et al., 2007	Original article	Longitudinal 3 year-follow up	Community population (N = 1052)	MMSE; Test di Babcock (memory); Digit cancellation test (attention)	Motor performance battery	Attention impairment predicts motor performances decline among older community-dwellers with normal baseline motor functioning. Attentional and executive dysfunction may be a major determinant of mobility disability in elderly persons.
Atkinson et al., 2010	Original article	Longitudinal 6-year follow up	Community women population (N = 1793)	MMSE	Gait speed; chair stands; handgrip strenght	Baseline global cognitive function and change in global cognitive function were associated with physical performance change, but baseline physical performance was not associated with cognitive change in this cohort.
Taekema et al., 2012	Original article	Prospective 4-year follow up	Community population (85 years) (N=555)	Neuropsychological battery	Handgrip strenght	Baseline cognitive performance was associated with decline in handgrip strength. Baseline handgrip strength was not associated with cognitive decline
Stijntjes et al., 2017	Original article	Longitudinal 5-12 year follow up	Two community population (different ranges of age)	Neuropsychological battery	Handgrip strenght and gait speed	Over all age groups, poorer executive function was associated with a steeper decline in gait speed. From the age of 85 years, this relationship was found across

			(N=2545; N=434)			all cognitive and physical domains. From the age of 65 years, slower gait speed and/or weaker handgrip strength were associated with steeper declines in global cognitive function. In the age group of 75–85 year, slower gait speed and/or weaker handgrip strength were associated with steeper declines across all cognitive domains.

From sarcopenia and/or motoric decline to cognitive impairment

Study	Article Type	Study Design	Sample Characteristics	Cognitive Evaluation	Motor/physical Measure	Main Findings
Marquis et al., 2002	Original article	Prospective longitudinal 6-year follow up	Cognitively healthy subjects (N = 108)	MMSE, Wechsler Memory Scale–Revised	Gait speed	Gait speed independently predicted the onset of persistent cognitive impairment at follow up.
Waite et al., 2005	Original article	Longitudinal 6-year follow up	Community elderly population (age ≥75 years; N = 630)	MMSE	Gait speed	Gait speed at baseline was one of the predictors of the onset of dementia over 6-year follow up. Subjects with cognitive impairment in combination with gait slowing were the most likely to develop dementia.
Buracchio et al., 2010	Original article	Longitudinal 20-year follow up	Community healthy population (N=204)	MMSE	Gait speed	Motor decline expressed by gait speed was found to precede up to 12 years the onset of MCI.
Montero-Odasso et al., 2016	Original article	Longitudinal 5-year follow up	Community population (N=254)	MMSE, MoCA	Gait speed	The combination of slow gait and cognitive impairment predicted the highest risk for progression to dementia; additionally, it was considered a potential

						better predictor of further risk of dementia than the cognitive-frailty construct.
Verghese et al., 2013	Original article	Longitudinal 36.9-month follow up	Community population (age ≥70; N = 997)	Neuropsychological battery	Gait speed	The Motoric-Cognitive Risk (MCR) Syndrome is characterized by an earlier reduction in walking speed, subjective cognitive complaints and preserved functional autonomy. MCR provides a clinical approach to identify individuals at high risk for dementia, especially vascular dementia.
Kohara et al., 2017	Original article	Cross sectional	Community population (age ≥55; N=1518)	Touch Panel-type Dementia Assessment Scale	Thigh muscle cross-sectional area (CSA) and skeletal muscle mass	The Touch Panel-type Dementia Assessment Scale score was positively associated with thigh muscle CSA in men and skeletal muscle mass in women. Muscle mass decline in the bottom 10% of participants on both sarcopenia indices was independently related to cognitive impairment in women.
Boyle et al., 2010	Original article	Prospective cohort study	Residential facilities population (N = 761)	Neuropsychological battery	Handgrip strenght, gait speed	The authors employed the construct of physical frailty, which was based on four components (i.e., handgrip strength, gait speed, body composition and fatigue). Physical frailty was associated with a substantially increased risk of incident MCI (each one-unit increase in physical frailty was associated with a 63% increase in the risk of MCI).

Kim et al., 2019	Original article	Prospective 8-year follow up	Community population (age ≥65; N= 2378)	MMSE (Korean version)	Handgrip strenght	The baseline handgrip strength was positively associated with the baseline MMSE score. Higher handgrip strength at baseline can predict MMSE scores positively over time; the change of handgrip strength over time was a predictor of high MMSE scores over the study period.

Bidirectional perspective

Study	**Article Type**	**Study Design**	**Sample Characteristics**	**Cognitive Evaluation**	**Motor/physical Measure**	**Main Findings**
McGrath et al., 2019	Original article	Longitudinal 20-year follow up	Community population (N= 14775)	Telephone Interview of Cognitive Status	Handgrip strenght	Significant predictive value of baseline handgrip strength on the onset of further cognitive decline (proportionally lower risk to develop cognitive decline every 5 kg of increase in handgrip strenght). The absence of cognitive deficit or the presence of different baseline cognitive deficit severity were associated with progressively higher risk to develop handgrip strength reduction.

Kim et al., 2019	Original article	Longitudinal 8-year follow up	Community population (N=5995)	MMSE (Korean version)	Handgrip strenght	Subjects with greater handgrip strength showed a subsequent reduction (approximately 50%) in the risk of cognitive impairment, compared to those in the lowest quartile of handgrip strenght. Conversely, cognitive impairment was a significant predictor of reduced muscular strength for participants with dementia compared with those with normal cognitive function.

Abbreviations: MMSE = Mini Mental State Examination; MoCA = Montreal Cognitive Assessment; MCI = Mild Cognitive Impairment.

Supplementary material of chapter 2

Table 1. Summary of included studies (alphabetically listed)

Study	Design / Participants	Frailty quantification	Cognitive reserve dimension	Main findings
Aguillar-Navarro et al, 2015[1]	Longitudinal Community population	Frailty phenotype	Education	Education was expressed by the total number of years achieved. Participants classified at baseline as frail showed lower education, compared to those classified as non-frail and pre-frail ($p < 0.001$).
Alexandre et al, 2014[2]	Cross sectional Community population	Frailty phenotype	Education	Education was expressed by the total number of years achieved. Education was significantly associated to Exhaustion (OR (CI 95%) =0.92 [0.86, 0.99]), Weakness (OR (CI 95%) =0.92 [0.85, 0.99]) and Slowness (OR (CI 95%) =0.88 [0.82, 0.95]) in men ($p \leq 0.05$). Education was significantly associated to Weakness (OR (CI 95%) =0.92 [0.87, 0.98]) and Slowness (OR (CI 95%) =0.94 [0.88, 0.99]) in women ($p \leq 0.05$).
Alvarado et al, 2008[3]	Cross sectional Community population	Frailty phenotype	Education Occupation	Education was expressed by: no schooling, primary, secondary and postsecondary. Occupation recorded according to the International Standard Classification of Occupations (ISCO-88). Less than secondary schooling and low-skilled occupation were associated to greater odds of frailty.
Avila-Funes et al, 2008[4]	Longitudinal Community population	Frailty phenotype	Education	Education was expressed as having a high educational level (> 12years). Participants classified at baseline as frail showed lower education, compared to those classified as non-frail and pre-frail ($p= 0.029$)
Biritwum et al, 2016[5]	Cross sectional Community population	Deficit-accumulation Frailty Index (FI)	Education	Education was expressed as: no education, less than primary, primary, secondary and higher. The odds of frailty were lower for subjects with any educational level (less than primary, primary, higher) compared to subjects with no formal education. Higher education (beyond secondary school) was associated with the greatest reduction in odds of frailty. The adjusted odds ratio (aOR) for frailty showed higher odds of frailty for subjects with secondary school education in Ghana (aOR=1.90) and for those with less than primary school in Mexico (aOR=2.39).
Buch et al, 2018[6]	Cross sectional Community population	Adapted Morley 5 Frail Scale	Education	Education was expressed by the total number of years achieved. Subjects classified as frail showed significantly lower educational level (9.35±5.52) compared to those classified as pre-frail (9.91±5.20) and robust (12.34±4.70).

Buchman et al, 2013[7]	Longitudinal Community population	Frailty phenotype	Education	Education was expressed by the total number of years achieved. Frailty was associated with education (r= -0.14; p<0.001). For each additional year of education at baseline there was a 2.6% slower rate of increasing frailty (time × education: estimate -0.003, SE 0.001, p=0.009) at follow-up.
Carneiro et al, 2016[8]	Cross sectional Community population	Edmonton Frail Scale (EFS)	Education	Education expressed as: up to four years of study, and more than four years of study. Education level of 0-4 years was associated to frailty (PR: 1.209; 95% CI=1.12-1.30; p= <0.001), even after multivariate analysis (PR: 1.112; 95% CI=1.03-1.18; p=0.002)
Castell et al, 2013[9]	Cross sectional Community population	Frailty phenotype	Education Occupation	Education was expressed as: low, medium, high educational level achieved. The prevalence of frailty was 14.9% (95% CI=11.7-18.7) in subjects with low education level, significantly higher compared to the prevalence in those with completed primary education (p <0.001). Information about subjects' social status were collected, in terms of low, medium and high quality of job. The prevalence of frailty was 14% (95% CI= 11.3-17.5) in subjects with low social status, significantly higher compared to the prevalence in those with medium-high social status.
Chamberlain et al, 2016[10]	Cohort study Community population	Deficit-accumulation Frailty Index (FI)	Education	Education was expressed as: less than high school, high school/college, 4-year college/postgraduate. Less than high school education was significantly associated to increased odds of baseline higher frailty index in subjects aged 60-69 ((OR (95% CI) 4.98 (3.72 to 6.67)), compared to subjects with college graduate education or higher. Less than high school education was significantly associated to increased odds of baseline higher frailty index in subjects aged 70-79 ((OR (95% CI) 2.94 (2.32 to 3.73)), compared to subjects with college graduate education or higher. Less than high school education was a significant predictor to a worse frailty trajectory in subjects aged 60-69 ((OR (95% CI) 1.98 (1.32 to 2.96)), compared to subjects with college graduate education or higher. Less than high school education was a significant predictor to a worse frailty trajectory in subjects aged 70-79 ((OR (95% CI) 1.57 (1.12 to 2.22)), compared to subjects with college graduate education or higher.
Chang et al, 2011[11]	Cross sectional Community population	Frailty phenotype Edmonton Frail Scale (EFS)	Education	Education expressed as: 0 years, < 7 years, and > 7 years of former education. The majority of subjects classified as frail according to Fried Frailty Index (FFI) showed no former education (41.9%) or < 7 years of education (51.6%). The majority of subjects classified as frail according to EFS showed no former education (56.1%) or <7 years of education (26.8%). After multinomial logistic regression, no former education (OR (95% CI) 10.60 (1.18–95.07)) and <7 years of education (OR (95% CI) 13.40 (1.55–116.24)) were significantly associated to FFI (p=0.035; p=0.019, respectively), but not associated with EFS.
Chaudhary et al, 2019[12]	Cross sectional Community population	Deficit-accumulation Frailty Index (FI)	Education	Education expressed as: no education, less than primary, primary, secondary and higher. The odds of frailty were significantly lower for those subjects with secondary (OR=0.73, 95% CI=0.39-0.59) and higher education (OR=0.48 CI=0.39 0.59), compared to those with no formal education.

Chen et al, 2010[13]	Cross sectional Community population	Frailty phenotype	Education	Education expressed as: Illiteracy, Elementary, Junior high, Senior high. Subjects who were classified as frail significantly showed poor education (illiteracy: 52.5%; elementary: 32.8%).
Chen et al, 2014[14]	Cross sectional Community population	Frailty phenotype	Education Leisure activities	Education expressed as: no formal education, elementary, junior high and above. Leisure activities were expressed as: chatting with neighbours, religious activities, leisure activities, visiting friends and relatives, gathering, and as the total number of performed activities. Poor education level was not found to be significantly associated to frailty (p=0.454). The majority of subjects classified as frail was involved in ≤ 1 activity (p<0.001). Leisure activities, religious activities, chatting with neighbours, and visiting friends and relatives were also significantly associated to frailty. The number of performed activities was significantly associated to increased odds of frailty (OR 2.39 (95% CI 1.50-3.82)).
Chon et al, 2018[15]	Cross sectional Community population	Frailty phenotype	Education Leisure activities	Education was expressed as: < elementary, elementary graduate, or ≥ middle school. Leisure activities was assessed as the frequency of contact with family, friends, or neighbours, by the Korean Frailty and Aging Cohort Study (KFACS) questionnaire. The majority of subjects classified as frail significantly showed less than elementary education (20.3%) or elementary education (10.2%). Having rare contacts with family, compared to daily contacts, was only associated to higher odds of pre-frail status (OR, 1.43; 95% CI, 1.00–2.04). Having rarely and weekly contacts with neighbours, compared to daily contacts, was associated to lower odds of frailty status (OR, 0.45; 95% CI, 0.25–0.81; OR, 0.39; 95% CI, 0.23–0.68, respectively). Having rare contacts with friends, compared to daily contacts, was associated to higher odds of pre-frail status (OR, 1.87; 95% CI, 1.17–2.99) and frail status (OR, 3.23; 95% CI, 1.58–6.61). Having monthly contacts with friends, compared to daily contacts, was associated to pre-frail status (OR, 2.02; 95% CI, 1.27–3.20) and frail status (OR, 5.04; 95% CI, 2.29–11.08).
Cohen et al, 2016[16]	Cross sectional Oncology Unit Outpatients	Deficit-accumulation Frailty Index (FI)	Education	Education expressed as: Missing, ≤ high school, college, graduate school. Compared to robust patients, the majority of pre-frail patients (41.6%) and frail patients (54.7%) significantly showed less education (≤ high school). Poor education (≤ high school) was associated to higher odds of pre-frail status (OR (95%CI) 1.48 (0.99-2.22); p=0.06), compared to robust status. Poor education (≤ high school) was associated to higher odds of frail status (OR (95%CI) 2.38 (1.28-4.43); p=0.006), compared to robust status.
Cramm et al, 2013[17]	Cross sectional Community population	Tilburg Frailty Indicator (TFI)	Education	Education was dichotomized as poor (primary school or less = 1) or good (more than primary school = 0). Poor education was significantly associated to the majority of subjects classified as frail (25.9%). Multilevel logistic regression did not show any significant relationship between poor education and frailty (OR 1.150 (1.121–1.180).
da Silva et al, 2018[18]	Cross sectional	Frailty phenotype	Education	Education expressed as years of study: >4 years, ≤ 4 years. The majority of subjects (81%) classified as frail showed an education level ≤ 4 years, significantly less than non-frail subjects. Crude analysis between educational level and frailty showed a significant

	Community population			association between ≤ 4 years of education and frailty (OR (95% CI) 2.35 (1.36–4.04); p=0.002). Adjusted analysis between educational level and frailty did not show a significant association between ≤ 4 years of education and frailty (OR (95% CI) 1.64 (0.88–3.07); p=0.120).
Dent & Hoogendijk 2014[19]	Prospective Observational Geriatrics Unit Inpatients	Frailty phenotype	Leisure activities	Leisure activities were expressed as social activities and social relationships, and assessed by the Older People's Quality of Life questionnaire. On admission, social activities (lowest quartile) and social relationships (lowest quartile) were not significantly associated to frailty status (OR (95% CI) 2.24 (0.77–6.52); p=0.141); (OR (95% CI) 1.34 (0.63–2.84); p=0.444), respectively. Frail subjects with a poor level of social activities had increased odds of being discharged to higher level care (OR (95% CI) 3.36 (1.01-11.22); p<0.05).
Etman et al, 2012[20]	Observational Longitudinal Community population	Frailty phenotype	Education	Education expressed as: low = 0-10 years; years, high= 11-25 years, according to the 1997 International Standard Classification of Education (ISCED-97). The majority of participants at baseline presented a low education level (59.4%). Considering the overall sample, at 2-years follow-up a significant higher risk of worsening in frailty state was found for lower educated subjects as compared with higher educated subjects (OR 1.40, 95% CI 1.28-1.54). Significant associations between level of education and worsening in frailty state was found for six countries, with a risk of lower educated subjects ranging from 1.35 (95% CI 1.08 to 1.70) in Belgium to 1.64 (95% CI 1.03 to 2.63) in Spain as compared with higher educated subjects.
Etman et al, 2015[21]	Observational Longitudinal Community population	Frailty phenotype	Education Leisure activities	Education expressed as: low = 0-10 years; years, high= 11-25 years, according to the 1997 International Standard Classification of Education (ISCED-97). Leisure activities was expressed as self-reported involvement in social activities within the last month. Associations between education and frailty have been previously discussed (Etman et al, 2012). Poor (or any) social participation was significantly associated to worsening in frailty, over 2-years follow-up (OR (CI 95%) 1.18 (1.08-1.30); p<0.001).
Eyigor et al, 2015[22]	Cross sectional Physical Medicine and Rehabilitation Clinic Outpatients	Frailty phenotype	Education Occupation	Education expressed as: University, high School, primary-secondary school, illiterate. Occupation was clustered as: retired, housewife, civil servant, worker, other. The majority of subjects classified as frail showed less education level (48.7% no former education; 37.2% primary or secondary school). A significant difference in education level was found within pre-frail, frail and non-frail subjects. The majority of subjects classified as frail showed a poor occupational status (45.7% were housewives). A significant difference in occupational status was found within pre-frail, frail and non-frail subjects. Single regression analysis showed that having no former education, having primary/secondary school education and being housewife increased the risk of frailty (OR 95% 13.161, 5.733- 30.216, p<0.001; OR 95% 4.668, 2.155- 10.112, p<0.001; OR 95% 2.153, 1.006- 4.610, p=0.048, respectively).

Gale et al, 2016[23]	Cross sectional Community population	Frailty phenotype	Intelligence quotient (IQ) Education	IQ was measured at the age of 11 years, by the Moray House Test No 12. Education was expressed as: no qualifications, O level or equivalent, A level or equivalent, semiprofesssional or professional qualifications, degree. IQ at 11 years old was associated to a significant higher RR of pre-frailty (RR 95% CI: 1.25 (1.08 to 1.45), p<0.01). IQ at 11 years old was associated to a significant higher RR of frailty (RR 95% CI: 1.57 (1.21 to 2.03), p<0.001. Highest education level was associated to a significant higher RR of frailty (RR 95% CI: 0.70 (0.52 to 0.96).
Garcia-Garcia et al, 2011[24]	Observational Community population	Frailty phenotype	Education Occupation	Education expressed as: None, uncomplete school, school and more. Occupation expressed as: white collar, blue collar, non-qualified workers, and housewives. The prevalence of frailty in subjects with no former education was 8.6% (CI 95% 7.0-10.5); that in subjects with uncomplete school was 9.8% (CI 95% 6.6-13.9); that in subjects with higher education level was 6.1% (CI 95% 3.6-9.6). The prevalence of frailty in white collars was 5.4% (CI 95% 3.0–8.7); that in blue collars was 7.0% (CI 95% 3.7–12.0); that in non-qualified workers was 8.4% (CI 95% 6.4–10.8); that in housewives was 10.0% (CI 95% 7.6–31.9). However, differences were not significant.
Gardiner et al, 2016[25]	Observational Longitudinal Community population	FRAIL Scale	Education Occupation	Education expressed as: Post high school, high school, less than high school. Occupation clustered as: Professional, sales/administration, trade/manual, other/missing, never worked. Adjusted regression model showed that less than high school education was associated to low vs increasing frailty trajectory (RR 0.76 (CI 95% 0.65-0.90), p<0.05) and high vs increasing frailty trajectory (RR 1.31 (CI 95% 1.13-1.51), p<0.05). Adjusted logistic regression model showed that a sales/administration job was associated to low vs increasing frailty trajectory (RR 0.83 (CI 95% 0.70-0.99), p<0.05). A trade/manual job was associated to low vs increasing frailty trajectory (RR 0.71 (CI 95% 0.56-0.87), p<0.05), and high vs increasing frailty trajectory (RR 1.41(CI 95% 1.19-1.70), p<0.05). Other/missing job was associated to high vs increasing frailty trajectory (RR 1.34 (CI 95% 1.14-1.57), p<0.05). No former job was associated to low vs increasing frailty trajectory (RR 0.76 (CI 95% 0.58-0.99), p<0.05), and high vs increasing frailty trajectory (RR 1.33 (CI 95% 1.08-1.63), p<0.05).
Herr et al, 2015[26]	Cross sectional Community population	Deficit-accumulation Frailty Index (FI)	Education Occupation	Education was expressed as: low (≤ 7 years), high level (10 years). Occupation was clustered as: low (blue-collar workers), intermediate (intermediate white-collar workers, employees, and shopkeepers), and high (high-level white-collar workers). Mean FI (±SD) in subjects with high educational level was 0.149 (±0.111); mean FI (±SD) in subjects with intermediate education level was 0.190 (±0.128); mean FI (±SD) in subjects with low education level was 0.235 (±0.143). Differences in FI mean were statistically significant. Mean FI (±SD) in subjects with high occupation level was 0.160 (± 0.123); mean FI (±SD) in subjects with intermediate occupation level was 0.193 (± 0.129); mean FI (± SD) in subjects with low occupation level was 0.215 (± 0.142). Differences in FI mean were statistically significant. Low education level was significantly associated to higher odds of frailty (OR (95% CI) 1.45 (1.17-1.80),

				p<0.001). Intermediate education level was significantly associated to higher odds of frailty (OR (95% CI) 1.45 (1.12-1.87), p=0.004). Low occupation level was significantly associated to higher odds of frailty (OR (95% CI) 1.38 (1.06-1.79), p=0.015).
Hoogendijk et al, 2014[27]	Longitudinal Community population	Frailty phenotype	Education	Education level indicated by the relative index of inequality (RII). Frailty prevalence was significantly different between subjects with low (14.8%), medium (8.8%) and high (7.3%) education level (p<0.001). In a full-adjusted model, educational differences in frailty were for a large part explained (76%; OR 1.47; 95% CI 0.85-2.54) by additional variables.
Hsu & Chang, 2015[28]	Observational Longitudinal Community population	Frailty phenotype	Education Leisure activities	Education was expressed as the total number of years achieved. Leisure activities expressed as social participation (participating in community activities or being engaged in voluntary work). Educational level was a significant predictor of being in the developing frailty group (B= -0.13; SE 0.04; p<0.001) or the high risk of frailty group (B= -0.15; SE 0.04; p<0.001). Social participation was a significant predictor of being in the high risk of frailty group (B= -0.80; SE 0.22; p<0.001).
Ihle et al, 2017[29]	Cross sectional Community population	Handgrip strenght	Education Occupation Leisure activities	Education was expressed as the total number of years achieved. Leisure activities were expressed as the self-reported average time per day spent for cognitively stimulating activities. Occupation was clustered as: higher and low cognitive level job. The correlation of education, job level, and stimulating leisure activities to cognitive status (expressed by MMSE) were larger in subjects with lower handgrip strength.
Jurschik et al, 2012[30]	Cross sectional Community population	Frailty phenotype	Education Leisure activities	Education expressed as: Illiterate, no education, primaries, first degree, second degree, college degree. Leisure activities expressed as family ties, social participation, social ties, social support and social engagement. There were not statistically significant differences between frail and non-frail subjects in terms of education level (p= 0.31). Social participation (p=0.001), having social ties (p<0.001), and social engagement (p<0.001) were significantly associated to frailty status. Logistic regression showed that having poor social ties (OR 0.57; 95% CI 0.43–0.77; p< 0.001) was a significant predictor of frailty status.
Lee et al, 2016[31]	Cross sectional Community population	Frailty phenotype	Education	Education expressed as: ≤high school, vocational or college degree, > college. Low education was not significant associated with frailty status (OR 0.7; 95% CI 0.5–1.0; p= 0.09)
Lu et al, 2017[32]	Cross sectional Community population	Deficit-accumulation Frailty Index (FI)	Occupation	Occupation was clustered as: full time employment, part-time employment, and other activities. The female mean FI was significantly different between groups (p=0.008), according to employment history (Full time job 0.16; Not employed 0.18; Weak attachment 0.17; Long career break 0.16; Short career break 0.14; Family care→ Full time 0.15; Full time→ Part time 0.17).
Mlynarska et al, 2018[33]	Cross sectional	Tilburg Frailty Indicator (TFI)	Education	Education expressed as the total number of years achieved. The majority of subjects classified as frail showed a basic education (47.74%; p<0.001) and a secondary

	Elettrocardiology Department (Inpatients)			education (47.73%; p=0.0046). In a multiple regression model, number of years of education was a significant predictor of higher frailty level (p=0.0001), higher physical frailty (p=0.0001) and higher social frailty (p=0.0001).
Moreira & Lourenco, 2016[34]	Cross sectional Community population	Frailty phenotype	Education	Education expressed as: Illiterate, 1 to 5, 6 to 11, ≥12 years. Univariate logistic regression showed that education of 6-11 years was significantly associated to higher odds of frailty (OR 1.42; 95% CI 1.12-1.71; p=0.001). Data not shown for 1-5 years of education and no former education. Multivariate logistic regression showed that 1-5 years of education and no former education was significantly associated to odds of frailty (OR 0.56; 95% CI 0.39-0.80; p=0.002; and OR 2.12; 95% CI 1-4.62; p=0.048).
Poli et al, 2017[35]	Cross sectional Community population	FRAIL Scale	Education Occupation Leisure activities	Education level and occupation were merged as socioeconomic status. The level of education was scored according to the International Standard Classification of Education: 0 = no qualification; 1 = primary school; 2 = secondary school; 3 = vocational school of 2–3 years; 4 = high school; 5 = bachelor's degree; 6 = PhD. Occupation was clustered as: unskilled workers; (b) less-qualified workers; (c) qualified workers and lower service class; (d) middle-class city-dwellers; (e) white-collar workers and (f) entrepreneurs, managers and higher service class. Leisure activities expressed by the frequency (null, rare, frequent and daily) of several activities. As solely described, low education level was associated to frailty (p<0.001). Socioeconomic status was associated with frailty only considering the difference between frail and robust subjects (average vs. lower socioeconomic level/status: OR = 0.29, 95 % CI 0.10–0.85, higher vs. lower: OR = 0.20, 0.07–0.63). Subjects with an average level of cultural fruition had a more reduced risk of being frail (OR = 0.47, 95 %CI 0.22–1.01) than subjects with a lower level, while subjects with a higher or above average level of cultural fruition had 75 % reduced risk of frailty than subjects with a lower level (OR = 0.24, 95 %CI 0.08–0.73).
Serra-Prat et al, 2016[36]	Cross sectional Community population	Frailty phenotype	Education	Education expressed by the frequency of subjects with ≥ secondary education. These subjects had: a reduced risk of frailty (OR 0.26; CI 95 0.08-0.88; p=0.001) in the whole sample; a reduced risk of frailty in men (OR 0.70; CI 95 0.15-3.39; p=0.001); a reduced risk of frailty in women (OR 0.14; CI 95 0.02-1.12; p=0.001).
Sewo Sampaio et al, 2016[37]	Cross sectional Community women population	Kihon Checklist (KCL)	Education Occupation Leisure activities	Education was expressed as: Elementary school, junior high school, high school, technical school, university. Occupation was clustered as: None/retired, formal work, informal work, volunteer, other. Leisure activities are described as number of times per week that participants left home. There were no significant differences between frail and robust subjects in terms of elementary education level (p=0.107) and no former occupation/retirement (p=0.319). Leaving home less than once a week was significantly associated with frailty (p<0.001).
Shah et al, 2019[38]	Cross sectional Retrospective	Deficit accumulation Frailty Index (FI)	Education	Education was expressed as the prevalence of subjects with highest level of education—12[th] grade[A]. The prevalence of subjects with the highest level of education was not significantly different between robust (53.2%), pre-frail (63.1%) and frail subjects (66.2%) (p=0.285).

	Community male veterans			
Simone & Haas, 2013[39]	Cross sectional Community population	Groningen Frailty Indicator (GFI)	Education Leisure activities	Education expressed as the total number of years achieved. Leisure activities evaluated by a Check-list of several activities. There were no significant differences between Frail and Not Frail subjects in terms of year of education (p=0.97). There were no significant differences between Frail and Not Frail subjects in terms of Leisure activities engagement (number of different social leisure activities p=0.07; number of different solitary leisure activities p=0.54; total leisure activities p=0.18).
Siriwardhana et al, 2019[40]	Cross sectional Community population	Frailty phenotype	Education Occupation	Education was expressed according to the International Standard Classification of Education. Occupation was explored by the Sri Lanka Standard Classification of Occupation, based on the International Standard Classification of Occupations 2008. No formal/primary education was associated to increased odds of being frail compared to being robust (age/sex adjusted model, OR 4.04; CI 95% 1.67-9.77; p<0.05). Less than secondary education was associated to increased odds of being frail compared to being robust (age/sex adjusted model, OR 2.30; CI 95% 1.09-4.88; p<0.05). No former occupation/poor skilled job was associated to increased odds of being frail compared to being robust (fully adjusted model, OR 3.43; CI 95% 1.31-8.98; p<0.05). A medium skilled job was associated to increased odds of being frail compared to being robust (age/sex adjusted model, OR 2.92; CI 95% 1.12-7.62; p<0.05).
Soler-Vila et al, 2016[41]	Observational Longitudinal Community population	Frailty phenotype	Education Occupation Leisure activities	Education expressed as: Primary or less, secondary, university. Occupation clustered as: manual work, non-manual work. The only variable inferenced as leisure activities was hours/week in reading books. Compared to men with university education, men with secondary education and men with primary or less education did not show significant higher odds of frailty incidence (OR 0.80 CI 95% 0.26-2.45; OR 1.63 CI 95% 0.69-3.84, respectively). Compared to women with university education, women with secondary education and women with primary or less education showed higher odds of frailty incidence (OR 1.58 CI 95% 0.54-4.62; OR 3.02 CI 95% 1.25-7.30, respectively). Adjusted OR of frailty incidence for women with lower education was 2.00 (CI 95% 0.76-5.23). Compared with subjects with a non-manual occupation, manual workers had an OR for incident frailty of 0.85 (CI 95% 0.39-1.82) in men and of 2.24 (CI 95% 1.41-3.56) in women. Regarding leisure activities, ORs for incident frailty were not significant in men nor women (OR 0.78 CI 95 0.60-1.00; OR 0.84 CI 95% 0.67-1.06, respectively).
Stolz et al, 2017[42]	Cross sectional Community population	Deficit accumulation Frailty Index (FI)	Education Occupation	Education was measured using the International Standard Classification of Education (ISCED-97); Occupational class was measured through The European Socio-economic Classification, based on the International Standard Classification of Occupations (ISCO-88). The FI mean was higher in subjects with primary education, evaluated in 2004-2005 and in 2013 (FI=0.13 (CI 95% 0.13-0.13) and FI=0.20 (CI 95% 0.19-0.20), respectively).

				The FI mean was higher in working class subjects, evaluated in 2004-2005 and in 2013 (FI=0.11 (CI 95% 0.11-0.11) and FI=0.17 (CI 95% 0.16-0.17), respectively). Subjects at the age of 67, with primary education and a working class occupation (together with the lowest income and wealth) was equally frail (FI=0.165, CI 0.157 to 0.174) as a subject at the age of 74, with the highest level of education and occupational class (together with the highest income and wealth) (FI=0.167, CI 0.157 to 0.181), that is, 7 years later.
Syddall et al, 2010[43]	Cross sectional Community population	Frailty phenotype	Education Occupation	Education was discussed in terms of age of leaving full-time education. Occupation was discussed in terms of social class (Professional, management and technical, skilled non-manual, skilled manual, partly skilled, unskilled). Univariate OR for frailty was 0.50 (CI 95% 0.25-1.01; p=0.05) per older year of leaving full time education in men. Univariate OR for frailty was 1.65 (CI 95% 0.99-2.77; but p=0.06) per lower band of social class in men.
Szanton et al, 2010[44]	Cross sectional Community women population	Frailty phenotype	Education	Education was clustered as <12, 12, or >12 years achieved. Adjusted OR for frailty was higher in women with less than 12 years of education (OR 3.01(95% CI=1.99-4.54).
van der Linden et al, 2019[45]	Longitudinal Community population	Frailty phenotype	Education Occupation	Education expressed as the total number of years achieved. Occupation clustered as high skill and low skill job. Lower education was associated to higher odds of pre-frailty and frailty in women (OR 0.97 CI 95% 0.95-0.99; p<0.05). Lower education was associated to higher odds of pre-frailty and frailty in men (OR 0.98 CI 95% 0.96-1.00; p<0.05). Low skilled job was associated to higher odds of pre-frailty and frailty in women (OR 1.20 CI 95% 1.02-1.40; p<0.05). Low skilled job was associated to higher odds of pre-frailty and frailty in men (OR 1.29 CI 95% 1.07-1.55; p<0.01).
Wade et al, 2017[46]	Longitudinal Community population	Deficit accumulation Frailty Index (FI)	Occupation	Occupation measured using the National Statistics-Socio-Economic Classification scheme (NS-SEC): Managerial and professional, intermediate, routine and manual. Subjects who were robust/prefrail at Wave 2, and frail at Wave 6 presented a routine/manual job (51.7%; p≤ 0.001).
Woo et al, 2005[47]	Cross sectional Community population	Deficit accumulation Frailty Index (FI)	Education Occupation	Education expressed as secondary and above, primary, no formal. Occupation clustered as with collar, other jobs. Men FI mean score was significantly lower in subjects with white collar jobs, compared to other jobs (0.114±0.070; p<0.001. Women FI mean score was lower in subjects with white collar jobs, compared to other jobs, but not significant in a fully adjusted model (0.132±0.083). Men FI mean score was lower in subjects with secondary education level or above (0.118±0.073; p value not significant in a fully adjusted model). Women FI mean score was lower in subjects with secondary education level or above (0.138±0.092; p value not significant).
Woo et al, 2015[48]	Cross sectional	Deficit accumulation Frailty Index (FI)	Education	Education was used as the prevalence of subjects with education level ≤ middle school, which was significantly associated to a higher crude OR of frailty in Beijing rural

	Community population			subjects (4.21 CI 95% 1.53-11.60) and in Hong Kong subjects (1.98 CI 95% 1.55-2.53) compared to Beijing urban subjects (1.27 CI 95% 1.11-1.45) ($p<0.05$).
Wu et al, 2017[49]	Cross sectional Community population	Frailty phenotype	Education	Education expressed as: no formal education/ illiterate, can read but did not finish elementary school, elementary school/traditional Chinese school, middle school, and high school or above. The majority of subjects with no formal education/illiterate and less than elementary education were classified as prefrail (56.7%, and 53.2%, respectively) and frail (11.4%, and 6.0%, respectively). The majority of subjects with middle school education or high school education/above were classified as robust (51.6%, and 56.5%, respectively).
Yang & Pang, 2018[50]	Cross sectional Community population	Deficit accumulation Frailty Index (FI)	Education Occupation Leisure activities	Education and Occupation information were merged in a socioeconomic vulnerability index (SEVI), together with family economic status and access to health care services. Leisure activities were considered playing chess or poker, singing or dancing, traveling, and chatting with others; a computed score was calculated based on the participation. SEVI and social activities were associated to FI ($\gamma = 0.25$; $\gamma = -0.14$; respectively; both $p < 0.001$).
Ye et al, 2018[51]	Cross sectional Community population	FRAIL Scale	Education Occupation Leisure activities	Education expressed as illiteracy, primary school, junior high school, senior high school, and university. Occupation expressed as work status (employed, other). Leisure activities information can be inferenced by the social participation measure assessed in the study (engagement in social activities in the past 12 months) Subjects with higher education level had half the risk of frailty compared with those who were illiterate (OR 0.52 CI 95% 0.34-0.79; p=0.002). The associations between occupation and frailty disappeared after age-gender adjustment (OR 0.85 CI 95% 0.69-1.06; p=0.146). Compared to subject in the first quartile of social participation (subjects with the lowest level of social participation), the ORs of frailty for those in the second, third and fourth quartiles were 0.76 (95% CI: 0.59–0.97), 0.59 (95% CI: 0.45–0.77) and 0.59 (95%CI: 0.45–0.77), respectively.
Yu et al, 2018[52]	Longitudinal Community population	Deficit accumulation Frailty Index (FI)	Education Occupation Leisure activities	Education was expressed as: no education, primary, secondary, post-secondary. Occupation was clustered as: unemployed/retired/others, working full-time, working part-time. Leisure activities expressed as the prevalence of subjects involved in social activities Completing secondary education or higher was associated to decreased FI (−0.0029 (95% CI −0.0038, −0.0021)). Working full-time/part-time similarly decreased the FI (−0.0051 (95% CI −0.0062, −0.0039)), compared to being unemployed/retired. Participation in social activities was associated with a lower risk of frailty (−0.0023 (95% CI −0.0027, −0.0019)).
Zheng et al, 2016[53]	Longitudinal Community population	Deficit accumulation Frailty Index (FI)	Education	Education expressed as the total number of years achieved. For subjects without frailty and disability at baseline, low education increased the odds of developing frailty (OR 1.4; $p<0.05$).

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Supplementary material of chapter 3

Table 1. Variables included in the Frailty Index (FI)

Hospitalization	Pain	Urinary incontinence	Hearth failure	Cerebrovascular disease
Fractures	Bathing	Faecal incontinence	Chronic Obstructive Pulmonary Disease	Handgrip strenght
Caregiver	Dressing	Telephone	BMI	Parkinsonism
Cognitive status	Walking	Drugs	Cancer	Gait speed
Malnutrition	Getting up / Sitting down	Hypertension	Cirrhosis	Medications
Deshydratation	Feeding	Diabetes	Chronic kidney failure	Benzodiazepines
Oral health	Toileting	Hearth disease	Obesity	Neuroleptics
			Total number of detected deficits	***Frailty Index***
			__ / 35	

Note: The FI is expressed as a ratio of health deficits present to the total number of deficits considered; the greater the number of health deficits, the higher the degree of frailty. According to this approach, patients with a FI ≥0.25 are commonly considered frail.