Head Office: Università degli Studi di Padova

Department of General Psychology

Department of Philosophy, Sociology, Education and Applied Psychology

---

Ph.D. COURSE IN: Brain, Mind and Computer Science

CURRICULUM: Neuroscience, Technology and Society

SERIES: XXXVI

Modifiable lifestyle factors for cognitive health:

The role of Cognitive Reserve and Motor Reserve

Coordinator: Ch.ma Prof.ssa Anna Spagnolli

Supervisor: Ch.ma Prof.ssa Sara Mondini

Co-Supervisor: Ch.ma Prof.ssa Ombretta Gaggi

Ph.D. Student: Dott.ssa Veronica Pucci

«If you have everything under control,

you are not moving fast enough.»

M.M.

TABLE OF CONTENTS

Abstract

Lifestyle factors such as cognitive, social, and physical activities have been examined in the literature as potential enhancers of cognitive health in healthy individuals and those with pathological conditions. The knowledge, skills, and experiences acquired throughout lifespan contribute to Cognitive Reserve (CR), which refers to the ability to utilise available brain resources flexibly and efficiently. It is commonly observed that individuals with higher CR tend to have more efficient brain networks that enable them to cope with pathology through compensatory mechanisms. This compensation is attributed to the accumulation of cognitive resources gained through prolonged exposure to stimulating activities during education, occupation, and leisure activities.

Furthermore, Physical Activity (PA) has recently been explored due to its potential to prevent age-related diseases and maintain or enhance cognitive functioning in healthy individuals. Emerging evidence suggests that PA can improve cognition in healthy adults, reduce the incidence of dementia, and enhance the health of individuals with existing dementia. PA carried out throughout the lifespan may also influence cognition. For instance, the literature shows that PA during teenage may lead to less decline in executive functioning in older age. In line with this evidence, we hypothesised a Motor Reserve (MR), a flexible and dynamic construct that accumulates over the years, possibly compensating for age-related cognitive decline. MR encompasses not only physical exercise and structured activities typically performed to improve and maintain physical fitness but also incidental PA, which includes unstructured daily activities that involve a metabolic cost above the baseline, such as walking, housekeeping, and workplace activities.

Considering this background, this thesis investigates the relationship between Cognitive Health, Cognitive Reserve, and Motor Reserve. We hypothesised that the greater CR and MR, the better the Cognitive Health. We explored these relationships in diverse populations, including healthy adults, fragile individuals (Oldest-Old and Subjective Cognitive Decline), people with neurological disorders (Multiple Sclerosis) and individuals with genetic

conditions (Intellectual Developmental Disability). In addition, we integrated the concept of CR within the neuropsychological assessment by developing new cognitive tests that consider CR to generate cut-offs, guaranteeing a more accurate interpretation of examinees' performance.

Investigating the effect of CR and MR on cognitive health in adults, older adults and pathological populations provided guidelines for developing new preventive protocols for cognitive decline and rehabilitation programs for people with existing neurological diseases.

1. Cognitive reserve

1.1 Cognitive reserve definition

Cognitive reserve (CR) encompasses all the learning and skills acquired throughout the lifespan, constituting a repository of cognitive abilities and knowledge that enhances the complexity of brain networks and cognitive efficiency. CR is a modifiable factor that can be changed or improved, and this is the basic theory behind cognitively, mentally, and physically stimulating activities to improve cognitive health and cope with age-related cognitive decline and dementia (Clare et al., 2017; Reed et al., 2010).

The concept of CR was prefigured in the late sixties of the past century (Blessed et al., 1968), and later, it was further developed in the area of Alzheimer's disease during the nineties (Katzman et al., 1988; Satz, 1993; Stern et al., 1992). The CR was born to explain the heterogeneity of the cognitive profile of people with Alzheimer’s disease. Nevertheless, several studies indicate that there is no direct relationship between the severity of brain damage (or neuropathology) and the onset of clinical manifestations. In 1988, in a post-mortem analysis of 137 individuals, Katzman and collaborators found that some brains exhibited signs compatible with the neuropathology of Alzheimer’s disease. However, these individuals had never shown any symptoms during their lives. This incongruity led researchers to hypothesise that these individuals had a greater “reserve” capacity due to the weight and size of their above-average brains and their higher number of neurons. Consistent with this finding, Snowdon and collaborators (1997) examined the post-mortem brains of 678 women of the same convent in a longitudinal study. They found that many individuals in the mild to moderate stages of Alzheimer’s disease exhibited no symptoms of cognitive impairment. Through decreased neurodegeneration and increased reserve, a significant percentage of participants with the same degree of Alzheimer's disease pathology resisted the clinical expression of symptoms. Pathological changes in Alzheimer's disease do not necessarily result in clinical manifestations, just as brain damage of similar severity can lead to different levels of cognitive deficits (Steffener & Stern, 2012). This evidence implies the existence of a series of processes that could contrast the effects of a loss in the brain, all encompassed within the notion of reserve.

According to SCOPUS, the term “Cognitive Reserve” (CR) was included either in the title or in the abstract or was among the keywords of 321 articles in 2022 (search run on February 9, 2023). On average, this is almost one per day. This extraordinary success stems from a few ideas left unnoticed for quite some time. In this century, CR has found its first definitions and applications, and since the Twenties, many studies on CR or using CR have been recorded. The CR construct has been exported from dementia - with increasing success - to areas that involve other pathological conditions, such as Parkinson’s disease (Lucero et al., 2015), multiple sclerosis (Santangelo et al., 2019), traumatic brain injury (Fraser et al., 2019; Menardi et al., 2020), stroke (Umarova et al., 2019), psychiatric disorders (Herrero et al., 2020), and, not least, healthy cognitive ageing (Cabeza et al., 2002), and adolescence (Conte et al., 2023).

It is essential to consider how CR interacts with adjacent constructs. The landscape of CR's definitions and conceptual frameworks has undergone significant changes over the past century, encompassing a spectrum of nuances ranging from simple synonyms to closely related or partially convergent terminologies (Pettigrew & Soldan, 2019). According to the most recent consensus document (Stern et al., 2020), it is now possible to assert that the terms "cognitive reserve," "brain reserve," and "brain maintenance" best represent our field of study and are the ones around which there is the most agreement. Recently, a laudable initiative (https://reserveandresilience.com) has promoted a series of meetings to collaborate on a consensus document collecting shared definitions. Stern, a significant contributor to the CR concept, defines “reserve” as the adaptability of cognitive processes that explains the differential susceptibility of cognitive abilities or day-to-day function to brain ageing pathology or insult (Stern et al., 2020, p. 1306).

1.2 How to measure Cognitive Reserve

1.2.1 Methodological insights about CR measurement

In addition to the proliferation of studies related to the Cognitive Reserve (CR), there has been notable progress in the quantitative assessment of CR. This advancement required the precise definition of the essence of CR, which is intrinsically linked to the epistemological foundations of the underlying models.

CR is widely accepted as a latent variable, meaning a construct that cannot be directly observed or measured. Therefore, a critical step in studying CR is identifying indicators that accurately measure and quantify the construct. According to Borsboom (2003), the ontological characterisation of a latent variable can be delineated into two distinct categories. The first category is *realism*, where the latent variable is posited to exist independently of its measurement. For example, from a realist perspective, intelligence is considered a latent variable that exists independently of any specific Intelligence Quotient (IQ) test or measurement method. In this view, intelligence is an inherent and unobservable trait that individuals possess to varying degrees. IQ tests or other measurements are tools designed to tap into this pre-existing intelligence. In contrast, the second category is *anti-realism*, where the latent variable or a phenomenon is argued to lack existence without effective measurement. For example, according to the anti-realist perspective, emotional intelligence is a construct that lacks independent existence without effective measurement through the assessment with specific tools.

Borsboom (2005) states that the realist perspective is the only epistemologically defensible position from a scientific point of view. Within this framework, the relationship between the construct and its proxies becomes crucial, and two models can again be distinguished: *reflective* and *formative* (Diamantopoulos & Siguaw, 2006; Jones et al., 2011).

In the reflective model (Figure 1), the observed indicators (X1, X2 and X3 in Figure 1) are direct effects (i.e., reflections) of the underlying latent variable. This model is extensively used in psychology for measuring intelligence or depression, owing to its effectiveness in manipulating latent variables and the diverse set of associated observable indicators. For instance, a reflective indicator of intelligence might be the performance on a test presumed to measure intelligence, and a reflective indicator of depression could be a person’s response to a questionnaire about their experience of deflected mood or loss of interest in daily activities. The foundation of the reflective model lies in the concept that the observed data (X1, X2 and X3) are outcomes of an unobserved variable: a high level of depression leads individuals to respond affirmatively to questions concerning emotions of sadness (Jones et al., 2011).

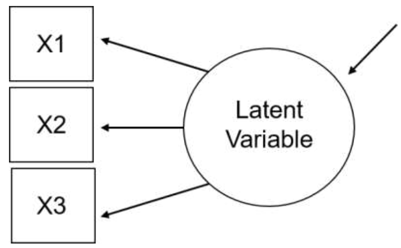

Figure 1. A Reflective measurement model (adapted from Jones et al., 2011).

In the formative model, the latent variable is a direct consequence of the indicator (X1, X2, X3) and not their cause (Figure 2). This model is commonly employed in sociology or economics; socioeconomic status is a suitable example. For instance, individuals may have a low educational level because they have a low socioeconomic status. Conversely, a high educational level may initiate a cascade of life events that could elevate an individual's socioeconomic status.

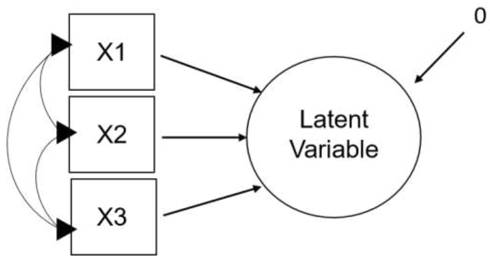

Figure 2. A Formative measurement model (adapted from Jones et al., 2011).

As the example of education and socioeconomic status, several indicators of CR are partially consistent with both formative and reflective models, and, in fact, nowadays, there are no elements in favour of either model for the estimation of CR (Ikanga et al., 2017).

1.2.2 Proxies for Cognitive Reserve

Since the mechanisms underlying the concept of CR are not directly measurable, researchers rely on proxy determinants related to brain resilience and cognitive efficiency (Ahmadi et al., 2017). Proposed proxies of CR include several factors, such as years of formal education (Roe et al., 2007; Valenzuela & Sachdev, 2006), measures of intelligence (Boyle et al., 2021), occupational attainment (Myung et al., 2017), level of literacy (Contador et al., 2017) and engagement in cognitively stimulating activities (Wilson et al., 2007).

Among these CR proxies, educational level is the most widely studied, and it is not uncommon to find research where education alone stands in for the concept of cognitive reserve (Valenzuela & Sachdev, 2006). The theoretical rationale for using an indicator such as education as a proxy for reserve seems reasonable: education may increase brain reserve by promoting synaptic growth (White et al., 1994) and foster CR by generating new cognitive strategies (Manly et al., 2005; Stern, 2002).

Other indicators of cognitive reserve include occupational status. Valenzuela and Sachdev (2006) found that “high” occupational status (unskilled, semi-skilled, trade, and clerical workers versus managerial, technical, and professional occupations) was associated with approximately a 50% reduction in the risk for dementia. However, a notable limitation of many CR measures is their association with neuropsychological test performance, which may follow various alternative paths, not exclusively via the hypothesised reserve mechanisms.

CR proxies also encompass activities outside formal education and occupational environments. An increasing body of research has demonstrated a positive correlation between healthy cognitive ageing and leisure activities that stimulate cognitive efficiency. Observational studies indicate that a lifestyle that includes the engagement in activities such as reading, writing, and participating in cultural events at different stages of life is linked to enhanced cognitive functioning (Pozzi et al., 2023; Rajan et al., 2015; Sugita et al., 2021). Additionally, these activities are associated with a deceleration in cognitive decline and a reduced risk of cognitive impairment (Brewster et al., 2014; Fancourt & Steptoe, 2018; Rajan et al., 2018). Furthermore, social engagement has emerged as a significant factor associated with cognitive health in older adults. Interactions within social networks, group activity participation, and meaningful social connections have been shown to contribute positively to cognitive health (DaWalt et al., 2019; Fratiglioni et al., 2020).

While proxies offer several advantages when quantifying CR, there is a parallel need for a comprehensive measure derived from a standardised tool. For instance, widely recognised instruments such as the Cognitive Reserve Index questionnaire (CRIq, Nucci et al., 2012) or the Cognitive Reserve Scale (CRS, Leoń et al., 2014) have been developed to provide a more rigorous and replicable assessment of CR. These standardised tools offer the advantage of uniformity in measurement across diverse populations, allowing researchers to compare results across studies and draw more robust conclusions. Striking a balance between the understanding gained from proxies and the precision afforded by a standardised measure is crucial for advancing our comprehension of CR dynamics in diverse populations and contexts.

1.2.3 The short Cognitive Reserve Index questionnaire

Mondini, S., Pucci, V., Pastore, M., Gaggi, O., Tricomi, P.P., & Nucci, M. (2023). s-CRIq: the online short version of the Cognitive Reserve Index questionnaire. Aging Clinical and Experimental Research.

Introduction

Kartschmit and colleagues (2019) outlined the most commonly used tools for measuring cognitive reserve. Their work focused on the important features and properties of these instruments. One such tool is the Cognitive Reserve Index questionnaire (CRIq; Nucci et al., 2012). The CRIq is a semi-structured interview that collects demographic information, including birthdate, place of birth, sex, place of residence, nationality, and marital status. It comprises twenty items divided into three categories - education, working activity, and leisure time - each contributing to a row score (CRI-Education, CRI-WorkingActivity, CRI-LeisureTime).

CRI-Education gathers information on years of education and any relevant training courses lasting at least six months. CRI-WorkingActivity records data on professions pursued during adult life, categorising them into five distinct occupational levels based on cognitive demands and responsibilities: (1) unskilled manual work (e.g., farmer, car driver, call centre operator); (2) skilled manual work (e.g., carpenter, plumber, electrician); (3) skilled non-manual or technical work (e.g., IT specialist, dental hygienist, laboratory technician); (4) professional occupation (e.g., architect, social worker, pharmacist); (5) highly intellectual occupation (e.g., researcher, investment banker, manager). To calculate the raw score for this section, the occupation level (from 1 to 5) is multiplied by the number of years practised. CRI-LeisureTime focuses on activities outside the workplace and educational settings, consisting of sixteen items associated with various intellectual, social, and physical activities. The score is determined by considering the frequency of each activity and years of practice.

To account for the age effect, the authors employed three linear regression models, as age demonstrated a significant correlation with the row scores of the three CRIq sections.

Age was set as the independent variable, and the row scores of each section were chosen as dependent variables. The residuals from these regression models were standardised and adjusted to a scale with a mean of 100 and a standard deviation of 15. This scoring allows comparisons among participants of the same age group. The average of the three sub-indices, once again standardised and transposed to a scale with a mean of 100 and a standard deviation of 15, represents the total CRI score. The CRIq was designed to be administered by a professional and typically lasts approximately 15 minutes.

Currently, CRIq has been widely used in both clinical settings and research. Until now, CRIq has been translated (and in some cases adapted and validated) into 19 different languages (Table 1).

#	Language	Adaptation	Normative data; sample size	Authors and years
1	Arabic (Lebanon)	yes	yes; N=226	Farran & Darwish, 2023
2	Bulgarian	no	yes; N=114	Yaneva et al., 2019
3	Catalan	no	no	Tr. requested by authors of CRIq
4	Chinese	no	yes; N=371	Cao et al., 2022
5	Czech	no	no	Tr. by Vil´ımovsk´y, 2016 - unpublished
6	Dutch	no	no	Tr. by Kessels & Oosterman 2016 – unpublished
7	English	no	no	Tr. by Jarema & Kehaya - unpublished
8	French	no	no	Tr. by Jarema & Kehaya - unpublished
9	German	no	no	Tr. requested by authors of CRIq
10	Greek	yes	yes; N=591	Maiovis et al., 2016
11	Hungarian	no	no	Tr. by Bozzai & Karádi - unpublished
12	Indonesian	no	yes; N=66	Kusumaningrum et al., 2021
13	Korean	yes	yes; N=358	Choi et al., 2016

14	Latvian	no	no	Tr. by Sneidere & Harlamova, 2017 - unpublished
15	Malay	no	yes; N=80	Abdullah et al., 2021
16	Persian	no	yes; N=385	Hatami et al., 2020
17	Portuguese	no	no	Tr. requested by authors of CRIq
18	Russian	no	no	Tr. by Кутиков & Никишкова, 2020 - unpublished
19	Serbian	yes	yes; N=117	Volarov et al., 2020
20	South African (IsiZulu)	yes	no	Narsi et al., 2020
21	Spanish	no	no	Tr. requested by authors of CRIq
22	Turkish	no	yes; N=499	Ozakbas et al., 2021
23	Turkish	yes	yes; N=175	Çebi & Kulce, 2022

Table 1. The table shows all the CRIq translated and adapted, listed alphabetically by language.

The widespread adoption and utilisation of the CRIq have led many professionals to employ this tool for research and clinical purposes. More than ten years after the first publication of the CRIq, it is desirable to revisit specific aspects of the original tool, especially considering feedback from professionals and researchers who routinely adopt the CRIq in their work. The four primary areas identified for attention include (1) the complete digitalisation of the tool, (2) allowing self-administration of the questionnaire, (3) reducing the number of items to allow a quicker test administration, and (4) updating normative data to reflect the contemporary Italian population. These four points are discussed below.

(1) *Digitalisation*. Digital instruments are almost always more prevalent in the toolkits of clinical psychologists and researchers (Ostermann et al., 2021). They enable experts to obtain accurate measurements, save data more securely, and work more sustainably (Marcopulos & Łojek, 2019). Professionals may safely store vast amounts of data using digital tools, facilitating data sharing with other professionals. In addition, digital instruments simplify the scoring process, reducing the need for manual data processing, and they allow for a more standardised procedure of administration, which reduces human error and ensures reliable

and replicable results. The digitalisation of tests promotes sustainability by reducing the consumption of physical resources and eliminating the need for paper-based assessments and data storage, contributing to environmental conservation.

(2) *Self-administration*. The adaptation of a test for self-administration means that respondents can complete the questionnaire at their convenience, reducing the time employed in in-person visits and, in case of a research purpose, enabling access to a broader and more diverse sample of participants (e.g., from different geographical areas).

(3) *Shorter version*. A shorter questionnaire allows quicker administration, enhancing its suitability for professionals and participants with time constraints. Lengthy assessments may induce participant fatigue, potentially compromising response quality. A shorter version aids in sustaining participant engagement and focus. Moreover, a briefer tool proves more practical for routine use in clinical settings where time is often limited. In large-scale research studies, opting for a shorter version enables researchers to assess more participants efficiently.

(4) *Updated normative data*. Over time, the demographic characteristics of a population can shift due to factors such as migration, changes in birth rates, and lifestyle modifications. Updating normative data ensures that the assessment tool remains relevant and applicable to the current characteristics of the Italian population.

Thus, we have proposed a fully digitised version of the questionnaire, encompassing administration and data storage. We have also updated the normative sample by designing a new, online, self-administered, abbreviated version: the short Cognitive Reserve Index questionnaire (s-CRIq). This effort aims to introduce the revised version of the CRIq and to compare its results with those obtained from both previous paper-and-pencil and online versions of the CRIq.

Methods and Materials

Data, data analyses and the link for the online administration of s-CRIq (Italian and English versions) are freely available at the OSF link https://osf.io/efzhs/. All the analyses were conducted with R software (R Core Team, 2022).

s-CRIq development and description

In the new online short version, we aimed to simplify the information-gathering process, ensuring that s-CRIq is user-friendly for self-administration. The questionnaire begins by collecting personal information, including name, surname,[1] sex, date of birth, place of birth, residence, and nationality. In this section, we have excluded non-essential data to quantify CR, such as marital status. The only mandatory fields in this section are the place of birth, which is essential for calculating the age of the examinees, and nationality, which is crucial for selecting a normative sample from the same cultural background as the examinee.

The CRI-Education section is equivalent to the original CRIq; however, in the s-CRIq, the online administration allows a more agile collection of this information. Education is recorded by directly selecting the achieved level, eliminating the need to calculate years of education. The CRI-WorkingActivity section is similar to the original CRIq, but we simplified the data acquisition process. In the s-CRIq, examinees can directly write and select their occupation from an extensive database embedded within the tool. The database comprises more than 6000 jobs derived from the International Standard Classification of Occupation (ISCO-08; ILO, 2012). The international community supports this classification as an accepted standard for international labour statistics in Europe. ISCO-08 classifies each working activity with numbers on a continuum, where the higher the number, the lower the complexity of the occupation in terms of skills and cognitive resources involved (ranging from 1111 to 9629; e.g., 3153 is for “astronaut”, 7533 is for a “toy maker” and 9333 is for “porter”). The s-CRIq still classifies each job into five levels of cognitive load, as in the original CRIq. However, the

[1] To guarantee the examinees’ privacy this information is not stored in the database.

occupation is classified into one of them automatically, according to the cognitive load and responsibility involved.

The CRI-LeisureTime section is the most diverse to the original CRIq. The s-CRIq records only six items, five selected from the original seventeen of the CRI-LeisureTime, plus a new one (which includes some activities from three of the original items). The item selection was based on data collected in 2019 using the original CRIq. The selection procedure is grounded on two different approaches: Item Response Theory (IRT) and Confirmatory Factor Analysis (CFA). Both these methods yield a score which estimates how capable an item is of detecting the construct of interest. The five items selected for the s-CRIq were those with the highest scores in both methods (Table 2 and Figure 3). A new item has been added to the five selected ones. It is related to activities carried out during free time, chosen by 92 individuals in an informal survey. The same activities had all been described separately in the original version of the questionnaire, while in the s-CRIq, they are all included as examples in the new item.

		Confirmatory Factor Analysis (R^2)	Item Response Theory (β)
Item 1	**Newspapers**	**0.400**	**1.401**
Item 2	Household	0.247	0.767
Item 3	Driving	0.254	0.946
Item 4	Hobby/sports	0.253	0.864
Item 5	New technologies	0.047	0.510
Item 6	Social activities	0.133	0.567
Item 7	Cinema/theatre	0.233	0.927
Item 8	Caring	0.111	0.424
Item 9	Gardening	0.192	0.773
Item 10	Volunteering	0.105	0.777
Item 11	Artistic activities	0.091	0.464
Item 12	**Concerts/conferences**	**0.292**	**1.251**
Item 13	**Travelling**	**0.370**	**1.461**
Item 14	**Books**	**0.488**	**2.109**
Item 15	**Children**	**0.066**	**0.639**
Item 16	Pet	0.071	0.291
Item 17	Bank account	0.390	1.248

Table 2. The table shows the values of R^2 (deriving via Confirmatory Factor Analysis) and of β (deriving via Item Response Theory). The two approaches were used to select the best items of the CRI-LeisureTime section of CRIq: the five items with the highest scores in both approaches were chosen for the s-CRIq (in bold).

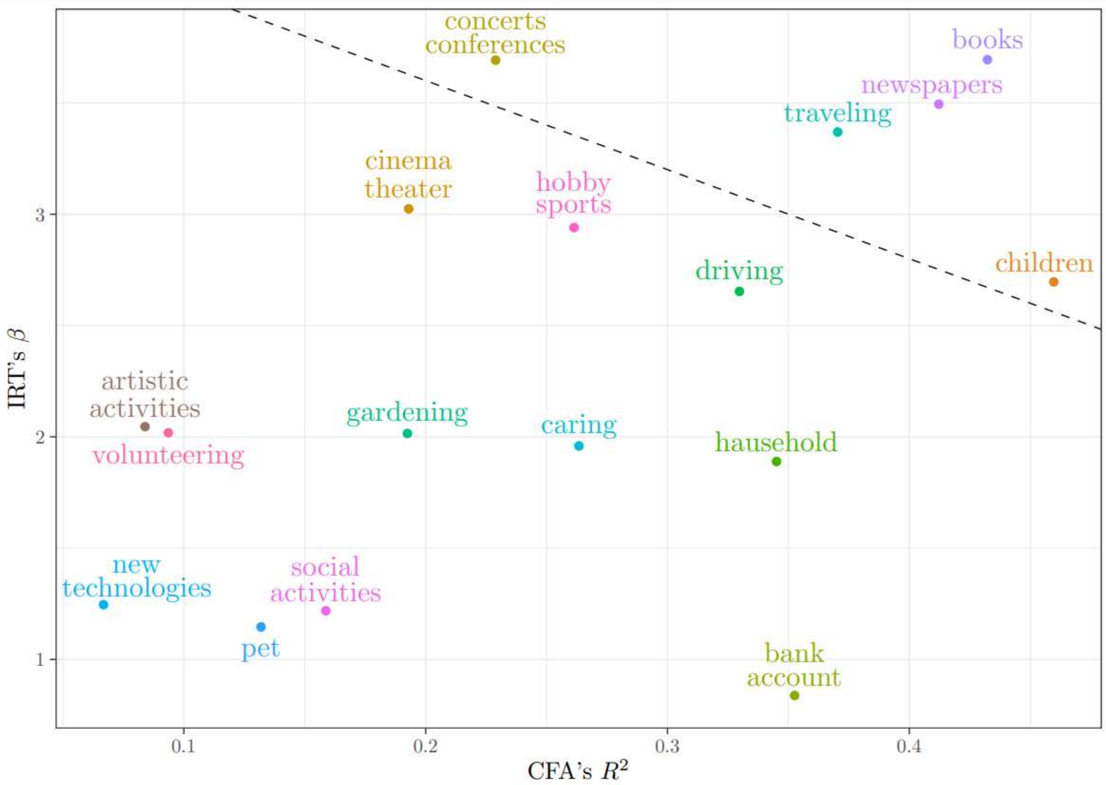

Figure 3. The figure shows the items selected for the s-CRIq via the two statistical approaches (Confirmatory Factor Analysis and Item Response Theory). On the x-axis is reported the β of IRT, and on the y-axis is reported the R^2 of the CFA. All items above the dotted line are the chosen ones. *Note.* CFA=Confirmatory Factor Analysis; IRT=Item Response Theory.

s-CRIq scores calculation

The s-CRIq scores are calculated using the same algorithm as in the original. The following information is gathered and counted as the raw score for each s-CRIq section:

(1) CRI-Education: Years of education are automatically counted following the level of education (e.g., a bachelor's degree corresponds to 16 years of education). Any other structured course with a minimum duration of six months is also considered (0,5 for each six months).

(2) CRI-WorkingActivity: According to the cognitive load and responsibilities involved, years of occupation are recorded in one of five classes. Only the three most relevant working activities are considered for the scoring.

(3) CRI-LeisureTime: the number of years that the six leisure activities are carried out continuously for at least one year. Depending on the type of activity, its frequency - weekly, monthly, or yearly - is considered.

The three sub-scores of the s-CRIq are the residuals of three corresponding linear regressions, where the raw score of the three sections (CRI-Education, CRI-WorkingActivity and CRI-LeisureTime) is the dependent variable, and the age of the examinee is the independent one. The best-predicted value of the raw score for each s-CRIq section is estimated using the model parameters and the examinee's age. The residual (i.e., the difference between the predicted and the observed values) represents the score of each of the three sub-indices of the s-CRIq. Using the residuals of the linear model as scores has at least two advantages. The first is that the scores are not correlated with age, although they are closely linked to the years in which the activities have been carried out. For example, a CRI-Education of 110 gives the same information about either a 30-year-old individual or an 80-year-old individual. In other words, the s-CRIq scores quantify the frequency and regularity of the engagement of cognitive abilities over time, regardless of age. An effect of this is that the variability of s-CRIq scores in the population grows as age increases (at age 20, people have very similar CRI, whereas, at 80, the CRI score can be very different). A second advantage of using the linear model is that a person is compared with individuals of the same generation, that is, those who share the same "world" - the historical, socio-economic, and cultural background where the person has lived. For example, a person with just eight years of education reached a time in which it was hard to go to school (because of wartime or other social issues) has a high CRI-Education score. On the other hand, a person with the same years of schooling but achieved in a period in which everyone averaged at least ten years has a low CRI-Education score. This same reasoning can be applied to the other two sub-indices.

For the sake of readability, the residuals were then standardised and transposed into a scale with M=100 and SD=15. Finally, the total score of s-CRIq, named Cognitive Reserve Index (hereafter CRI), was the average of the three sub-scores, again standardised and transposed to a scale with M=100 and SD=15. The result is that the higher the CRI score, the higher the estimated CR. CRI scores are conventionally classified into five ordered levels: Low (<70), Medium-low (70-84), Medium (85-114), Medium-high (115-130) and High (more than 130).

Data collection

Data collection was carried out at different intervals of time. From 2008 to 2010, data were gathered via the original paper-and-pencil questionnaire as a semi-structured interview. This first database is the one on which the questionnaire was initially built (Nucci et al., 2012), and it represented the normative database of the CRIq. We named this original database *Administered Long Paper* (hereafter ALP). From 2018 to 2019, the same CRIq was administered as a semi-structured interview to a new sample of Italian participants through the online version of the questionnaire. We named this database *Administered Long Online* (hereafter ALO). From 2021 to 2022, the s-CRIq was administered to a new sample of participants using the short online version of the questionnaire. We named this database *Administered Short Online* (hereafter ASO). Finally, at the same time, we acquire data through the online s-CRIq in a self-administered modality. We named this last database *Self-administered Short Online* (hereafter SSO).

Results

Descriptive statistics and distribution overlapping

The sample from the four databases (ALP, ALO, ASO and SSO) included 1807 individuals. The characteristics of the participants of the databases are reported in Table 3.

Database name	ALP	ALO	ASO	SSO	Tot
Sample size (N)	588	344	435	440	1807
Male/Female (%)	55/45	60/40	59/41	65/35	59/41
Age M (SD)	50.2 (19.7)	50.2 (21.3)	51.9 (19.7)	44.6 (18.3)	49.3 (19.8)
18-37 (N)	174	122	125	180	601
38-57 (N)	217	85	127	158	587
58-77 (N)	124	83	132	80	419
≥ **78** (N)	73	54	51	22	200

Table 3. The Table shows the main characteristics of the four databases (ALP, ALO, ASO and SSO). *Note.* ALP: Administered, Long, Paper-and-Pencil CRIq; ALO: Administered, Long, Online CRIq; ASO: Administered, Short, Online CRIq; SSO: Self-administered, Short, Online CRIq.

The new norms of CRI-LeisureTime were calculated only on the five items shared by all databases. At the same time, the original parameters of the first data collection, i.e., ALP, were used to calculate the total CRI and the other two sub-indexes. The descriptive statistics of the CRI total and the three sub-indexes are reported in Table 4.

We aimed to compare the four databases utilising descriptive indexes and their empirical shape data distributions. We analysed the area intersected by empirical density functions measured by the Overlapping Index (Pastore, 2018; Pastore & Calcagnì, 2019) to measure the similarity between the empirical shape distributions.

Database name	ALP	ALO	ASO	SSO
	Mean (SD)			
CRI-Education	100 (15)	102.4 (14.0)	103.1 (15.9)	107.7 (17.7)
CRI-WorkingActivity	100 (15)	100.6 (15.2)	97.8 (15.7)	101.8 (14.8)
CRI-LeisureTime	100 (15)	106.6 (20.2)	109.3 (20.8)	112.7 (21.2)
CRI	100 (15)	104.2 (17.3)	104.4 (17.2)	109.7 (17.9)

Table 4. The Table shows the means and the standard deviations of CRI and CRI sub-scores of the four databases. *Note*. ALP: Administered, Long, Paper-and-Pencil CRIq; ALO: Administered, Long, Online CRIq; ASO: Administered, Short, Online CRIq; SSO: Self-administered, Short, Online CRIq.

CRI-Education

The empirical density distributions of CRI-Education across the four databases show strong positive skew and high uniformity. As expected, the mean and mode of the distributions are more right shifted for more recent databases (Figure 4), demonstrating a constant rise in the population's level of education. The SSO sample has a higher mean and a more pronounced right tail than the other databases. Overall, 64% of the areas of the four empirical density distributions are shared, and 84% are shared by at least two.

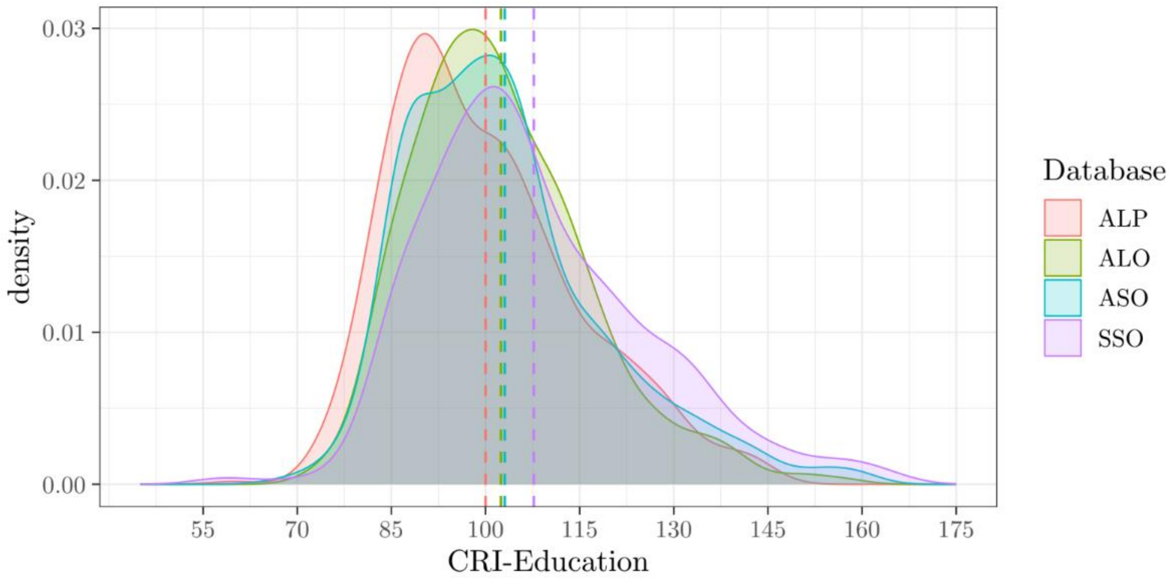

Figure 4. The figure shows the empirical density distributions of CRI-Education of the four databases. Dotted vertical lines signal the means of each distribution. *Note.* ALP Administered, Long, Paper-and-Pencil CRIq, ALO Administered, Long, Online CRIq, ASO Administered, Short, Online CRIq, SSO Self-administered, Short, Online CRIq

CRI-WorkingActivity

The empirical density distributions of CRI-WorkingActivity across the four databases are the most similar. They have an almost equivalent mode and very similar mean and shape (Figure 5). The more recent SSO and ASO databases have slightly distinct traits, with SSO having the highest mean scores and ASO having the lowest mean scores among the four databases. Overall, 70% of the areas of the four empirical density distributions are shared, and 87% are shared by at least two.

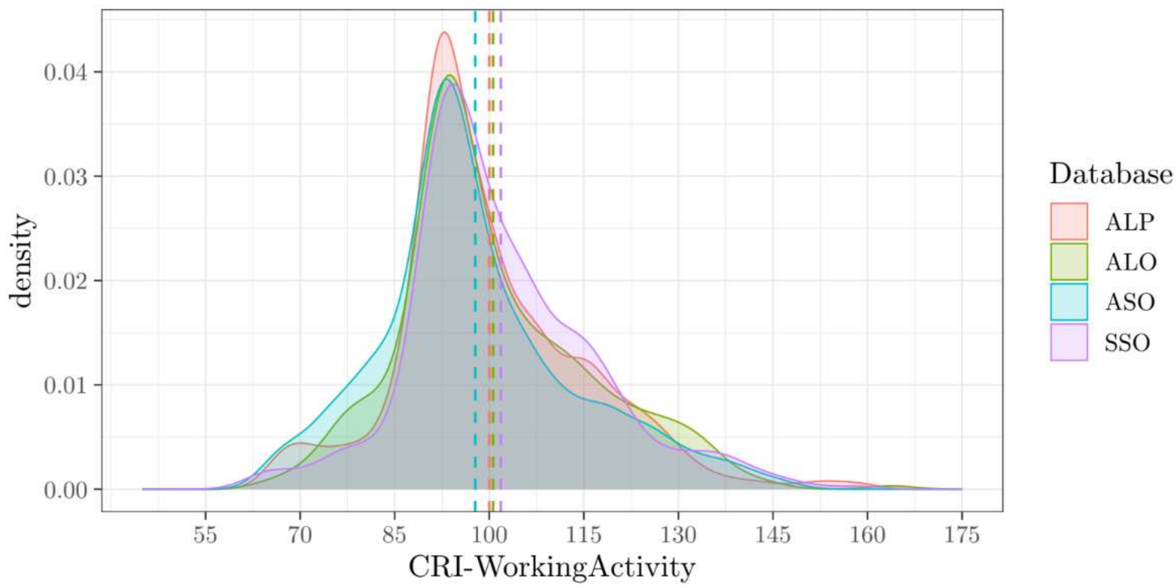

Figure 5. The figure shows the empirical density distributions of CRI-WorkingActivity of the four databases. Dotted vertical lines signal the means of each distribution. *Note.* ALP Administered, Long, Paper-and-Pencil CRIq, ALO Administered, Long, Online CRIq, ASO Administered, Short, Online CRIq, SSO Self-administered, Short, Online CRIq.

CRI-LeisureTime

The empirical density distributions of CRI-LeisureTime (this index was calculated on the five items of the s-CRIq in all four databases) differ the most. The means of the four distributions differ the most from one another (Figure 6). As in the case of CRI-Education, the most recent databases are shifted to the right, and the distance between means is very noticeable, especially compared to the original database (ALP). Remarkably, CRI-LeisureTime gives rise to distributions with the most substantial positive skew. In particular, the differences are clear and consistent for the three most recent databases (ALO, ASO and SSO) compared to the original one (ALP). Overall, 60% of the areas of the four empirical density distributions are shared, and 87% are shared by at least two.

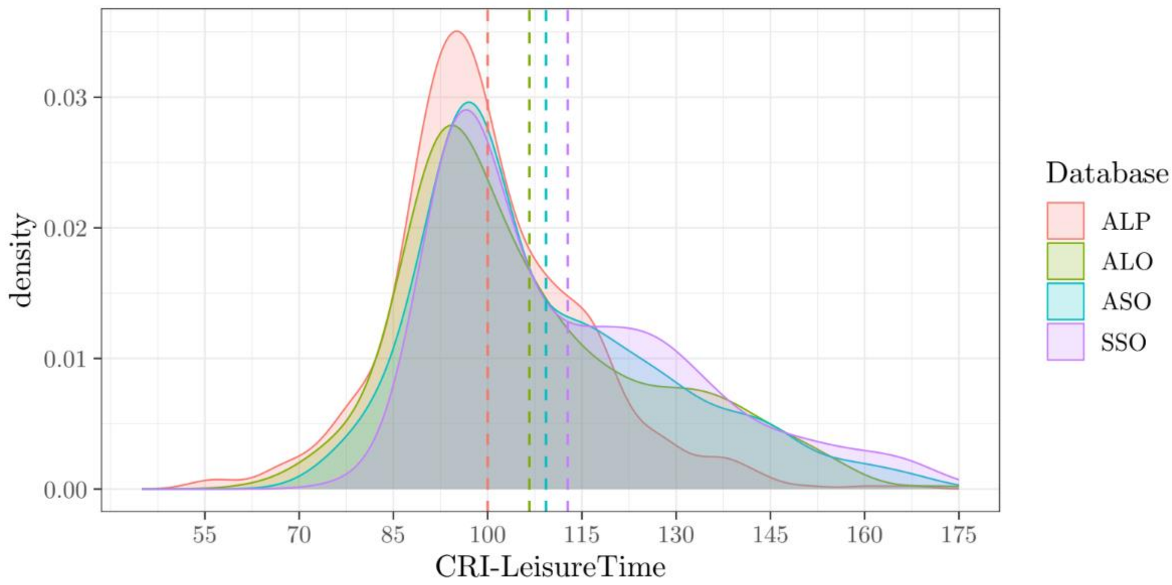

Figure 6. The figure shows the empirical density distributions of CRI-LeisureTime of the four databases. Dotted vertical lines signal the means of each distribution. *Note.* ALP Administered, Long, Paper-and-Pencil CRIq, ALO Administered, Long, Online CRIq, ASO Administered, Short, Online CRIq, SSO Self-administered, Short, Online CRIq.

Total CRI

As expected, the empirical density distributions of the CRI in the four databases summarise those observed in the three sub-indexes. The mean shows a trend to increase in the more recent databases from ALP to SSO, although ALO and ASO are almost equivalent (Figure 7). The shape of the distributions appears broadly overlapped, with marked positive skewness and nearly equal mode in the four distributions. All four empirical density distributions share 65% of their areas, and at least two share 86%.

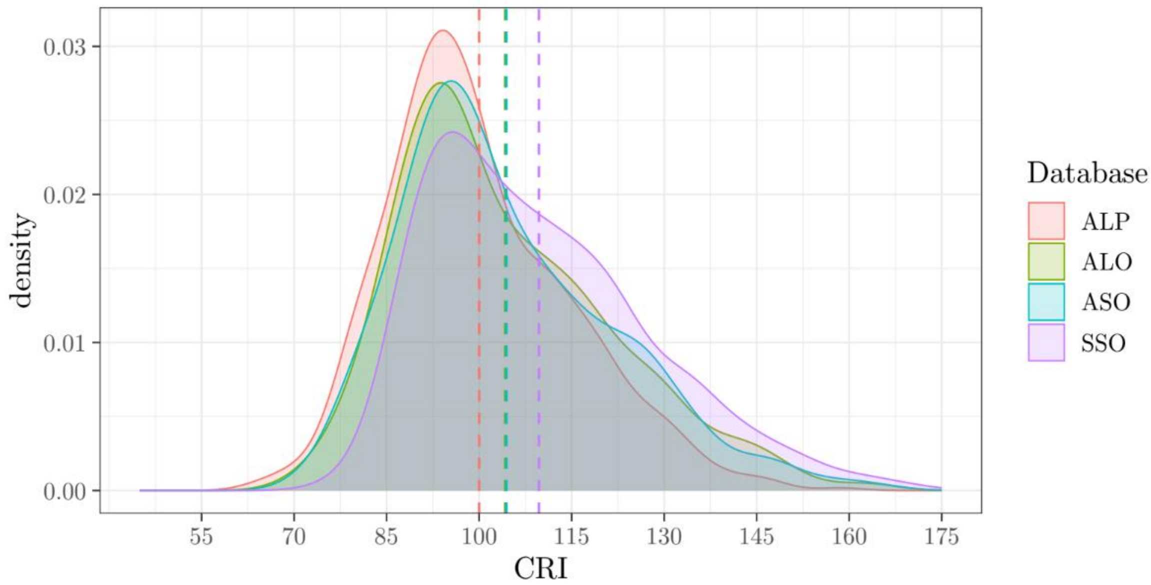

Figure 7. The figure shows the empirical density distributions of the CRI Total score of the four databases. Dotted vertical lines signal the means of each distribution. *Note.* ALP Administered, Long, Paper-and-Pencil CRIq, ALO Administered, Long, Online CRIq, ASO Administered, Short, Online CRIq, SSO Self-administered, Short, Online CRIq.

Discussion

In this work, we have introduced a new short and online version of the Cognitive Reserve Index questionnaire (s-CRIq). The primary objective of this adaptation was to address several critical issues that emerged while using the original questionnaire (CRIq, Nucci et al., 2012). After completing the process of adaptation and digitalisation of the questionnaire, we analysed the various datasets collected over time using the different questionnaire formats. These analyses allowed us to assess the comparability of the scores of the various questionnaire formats and gain insights into the evolving lifestyle patterns within the Italian population. It is essential to underline that cultural and historical changes play a crucial role in shaping the habits and routines of individuals.

The comparison of these four databases shows that some of the variables of interest change over time in the Italian population. From the initial database (ALP) to the most recent ones (ALO, ASO, SSO), the most evident change emerged with educational level and the practice of leisure time activities. Education levels have progressively increased within the population, reflecting a broader trend in Italy, as reported by Istat in 2021. In fact, in 2007, Italy extended mandatory schooling from 14 to 16 years of age, and this change is visible in our current period. Similarly, the activities people engage in during their leisure time show a consistent upward trend in the average scores across various databases. However, the most recent data demonstrates more pronounced variability. This shift can be attributed to the heightened sense of well-being experienced by individuals in Italy, increased access to a broader range of leisure activities, and the growing integration of these activities into daily routines and lifestyles. It was plausible to think that as the educational level increased, the "high-level work" increased, too. Unexpectedly, working activity scores do not show a comparable increase, although means and shapes are the most similar between databases. The fact that the unemployment rate has increased while the number of people with a high degree of education has increased may help to explain this contradictory result (Istat, 2021).

Additionally, the CRI total score shows a clear overlap in the distributions and a modest rightward shift in the average scores. The distribution shape of the most recent database (SSO) exhibits a discernible difference pattern in all sub-indices. Its right tail (highest estimated CR) is consistently higher than the right tails of the other datasets. This result may be explained by at least two factors: first, the youngest individuals are included in the most recent sample; second, the sample may not be wholly randomised. In this latter case, the recruitment of these individuals was likely biased toward high-functioning individuals who could easily complete the online questionnaire. These observed differences required updating the normative sample considering only the more recent databases (ALO, ASO, SSO). The new parameters for CRI calculation are available on the website (https://www.cognitivereserveindex.org/NewEdition/), and they will be regularly updated following the new data gathered through the website.

The s-CRIq offers several benefits: it is shorter than the original (CRI-LeisureTime is decreased from 17 to 6 items), more user-friendly, intuitive, and quick to administer, and it can be entirely completed online and self-administered. As a result, it might be widely and regularly adopted in both research and clinical contexts. In this regard, a promising use of s-CRIq is in interpreting scores of cognitive tests. For example, Montemurro et al. (2022) recently showed that the more comprehensive life-experience CR proxy is better than considering only education in predicting expected cognitive performance. In particular, adding CR to age and education when interpreting test scores improves the accuracy of cut-offs in the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005) in healthy older adults. Also, two new cognitive tests, the Global Examination of Mental State (GEMS, Mondini et al., 2022) and the "Esame Neuropsicologico Breve 3" (tr. Short neuropsychological examination 3, Mondini et al., 2022), allow considering s-CRIq when comparing performance within the normative sample (see also chapter 1.4 of this thesis).

Although using the s-CRIq in self-administration mode is a clear time saver, this should be used cautiously in a clinical context. Patients may find comprehending or responding to the questions challenging, so their answers may be incomplete or inaccurate. In these situations, a semi-structured interview conducted by a professional is strongly recommended.

CRIq has so far been translated into several different languages. However, there is strong evidence that a person's cultural background and country of origin affect cognition and performance on cognitive tests, as disciplines like "Cultural psychology" and "Cultural neuropsychology" have highlighted (Fernández & Abe, 2018). This is even more so as far as the CRIq is concerned, as it collects life experiences, which can be very different across cultures and times. The new s-CRIq is based on data from the current Italian population and is representative since it reflects today's life experiences typical of this European country. Thus, before using s-CRIq in a new language, it should be translated and adapted to that culture, and normative data collection would be necessary (see, for example, Maiovis et al., 2015 for the Greek CRIq).

Like any new instrument, s-CRIq is not exempt from limitations. The small number of items compared to the long version of CRIq may reduce accuracy. This is more evident when the CR score falls on the tails of the distribution (i.e., people with very low or very high estimated CR). Additionally, minor differences may arise in the case of self-administration. Individuals, when self-evaluating, appear more indulgent and tend to overestimate the depth and richness of their life experiences. The informatisation of data collection will allow for comparison results and provide different norms for each version.

In conclusion, the s-CRIq allows the quick and effective collection of an individual's detailed and comprehensive personal lifestyle activities. This tool can be helpful in research and clinical settings for better assessment quality and more personalised treatment promoting precision medicine.

1.3 Cognitive Reserve and cognitive health in fragile and pathological conditions

The Cognitive Reserve theory, initially introduced to account for symptom variability in people with dementia (Steffener & Stern, 2012), has been extensively investigated in Alzheimer's disease. Specifically, CR was introduced to explain the variability in brain ageing and clinical manifestations among individuals with similar extent of brain damage (Stern & Barulli, 2009). Several studies have shown that higher levels of CR correspond to a lower incidence of dementia, potentially influencing cognitive performance by increasing information processing capacity (Tucker & Stern, 2011). Subsequently, research has explored CR applicability in other neurological conditions such as Parkinson's disease (Ciccarelli et al., 2022; Gu & Xu, 2022; Lucero et al., 2015; Prete et al., 2023) and multiple sclerosis (Santangelo et al., 2019; Stein et al., 2023). Furthermore, studies have examined CR in the context of cognitive outcomes following traumatic and acquired brain injuries (Basagni et al., 2023; Fraser et al., 2019; Menardi et al., 2020) and stroke (Contador et al., 2023; Umarova et al., 2019). Notably, CR has been applied to investigations of healthy ageing, explicitly addressing age-related cognitive changes. In the field of healthy ageing, CR has been observed to enhance cognitive efficiency in late life and also during middle age (Cabeza et al., 2018; Ferreira et al., 2017; Jin et al., 2023).

In the present chapter, four studies will be presented examining the application of CR in the context of cognitive health across distinct fragile and clinical populations. Rather than focusing only on individuals with dementia, our investigation extends to fragile conditions, involving the oldest-old demographic and individuals with Subjective Cognitive Decline (SCD). Additionally, we explore CR in other pathological conditions, including multiple sclerosis (MS) and Intellectual Developmental Disability (IDD). The motivation behind our exploration lies in the recognition that CR may exert influence over cognitive outcomes in populations facing unique challenges. By examining these and clinical populations, our work aims to offer insights into the role of CR, uncovering potential protective mechanisms and intervention strategies.

Through these studies, we aim to contribute to a more comprehensive understanding of how CR interfaces with cognitive health across diverse populations, thereby addressing critical gaps in the literature.

1.3.1 Cognitive Reserve and Oldest-old

Carta, E., Riccardi, A., Marinetto, S., Mattivi, S., Selini, E., Pucci, V., & Mondini, S. (2023). *Over ninety years old: Does high cognitive reserve still help brain efficiency? Psychological Research.*

Introduction

Ageing is a universal and multifactorial process characterised by progressive development, maturation and decline of the organism from birth to death. It is denoted by a gradual and progressive loss of functional capacity and increased comorbidity, directly proportional to age (Paolisso & Boccardi, 2014). Age represents a significant risk factor for dementia onset, as do low education, poor physical activity, and vascular factors (Pierce et al., 2017). Even though the loss of functional and cognitive abilities is physiological, it remains essential to distinguish between normal and pathological ageing and to identify factors that play a role in this time of life. Only very few studies have investigated non-pathological cognitive functioning in the oldest-old (aged over 90, World Health Organization, 2017). This population's cognitive profile is characterised by a general decline, particularly in memory, attention, and executive functions (Salthouse, 1998).

In Italy, the number of people over 65 years old is constantly growing, and it is expected to reach 35% of the whole population around 2045-2050 (Istat, 2021). At the same time, life expectancy is increasing (5 years or more in 2070), and the number of people who will reach the age of 90 or more will very likely increase, too. Studying the relationship between Cognitive Reserve and cognitive performance in the oldest-old population seems fitting. In recent years, some communities worldwide have been discovered where survival into very old age is not episodic but occurs in a significant part of the population. One of these populations lives in the Blue Zone, on the Mediterranean island of Sardinia. Much interest surrounds this area and its population because it could be reasonable ground to study what makes individuals live longer and stay cognitively and physically healthy (Pes et al., 2020). Many hypotheses have been proposed, focusing on different lifestyle factors. For example, Herbert et al. (2022) highlighted the importance of the physical activity of centenarians in this zone. Daily moving, besides hobbies and work beyond the expected retirement age, would have a crucial role in their well-being. In addition, the sociocultural context of the Blue Zone promotes autonomy in facing daily life in older adults and encourages their active role in the community, passing on local traditions and cultural values to younger people (Ruiu et al., 2022).

Consequently, depression symptoms are significantly reduced compared to people from other rural areas of Sardinia. Nieddu et al. (2020) compared two long-lived populations: one living in Costa Rica (Nicoya peninsula) and the other in the Sardinia Blue Zone. They found that the two populations shared a particular plant-based diet and concluded that this could be the basis of their optimal health and long-lasting functional and physical capacity. A high-functioning brain in older age is another factor that accompanies active life and is promoted by cognitive reserve, as shown by many studies in older adults (Cabeza et al., 2018).

In the present study, we would like to go further and investigate the oldest-old individuals living in Sardinia as a reference population to explore the relationship between their CR and their cognitive performance.

The study was approved by the Ethical Committee of the School of Psychology, University of Padua (N= 4857) and conducted following the Declaration of Helsinki.

Materials and Methods

Participants

Sixty-seven participants (47 female) aged between 90 and 105 (M=93.7; SD=3.2) were enrolled in this study. All participants were born and resided in Sardinia, mainly in the province of Nuoro. They lived at home and were autonomous in their daily life: twenty lived alone, while the others lived with their partners or a son/daughter. Participants with neurological issues or recent hospitalisations were excluded from the sample. The mean education of the sample was 4.7 years (SD=2.9), ranging from 0 to 18. The overall educational level of the sample was very low: 25 people had attended primary school, with only 12 completing the five-year course. Only two people had a university degree, and one had never attended school, although she had learnt to read and write independently. This low level of formal education reflects the social and cultural context of the 1920s/1930s in Sardinia. During data collection, seven individuals were still working: four shepherds, aged 91, 91, 96 and 97, a priest aged 91, a florist aged 91 and a shopkeeper aged 101. All participants were bilingual because they used both the Sardinian and Italian languages daily. Many participants spent their free time doing activities such as reading, needlework, poetry, gardening, and travelling. Some of them even used social networks.

Materials

Two instruments were used in the present study: the Brief Neuropsychological Battery 2 (Esame Neuropsicologico Breve 2 - ENB2; Mondini et al., 2011), made up of 16 tests to measure different cognitive functions, and the Cognitive Reserve Index questionnaire (CRIq, Nucci et al., 2012) to quantify participants' Cognitive Reserve (See chapter 1.2.3 of this thesis for a complete CRIq description).

ENB-2 (Mondini et al., 2012)

ENB-2 is a neuropsychological battery often used in Italy with older adults (e.g., Zangrossi et al., 2021). It includes sixteen tests to assess different cognitive functions: Digit span (repetition of series of digits) for short-term memory; Immediate and Delayed recall prose memory (repetition of a short story at two different delays), to evaluate long-term memory; Interference memory at 10 seconds and 30 seconds (memorizing 3 letters while counting by two) to evaluate capacity to perform a dual-task and divided attention; Trial making test, part A (linking numbers in ascendent order with a line on a sheet of paper), to evaluate selective attention; Trial making test, part B (alternating linking with a line numbers, in ascendent order, and letters, following the alphabet, on a sheet of paper), to evaluate selective and switching attention; Token test (executing simple and precise verbal orders), to evaluate verbal comprehension; Phonemic fluency test (producing words beginning with the same letter), to evaluate access to lexicon and executive functions in strategy of searching; Abstract reasoning test (finding the semantic category shared between two concepts), to evaluate abstract thinking and reasoning; Cognitive estimation test (finding the closest answer to unknown and unusual questions), to evaluate capacity of estimation and executive functions in finding solutions; Overlapping figures test (recognition of individual shapes within a complex image with overlapping meaningful figures), to evaluate visual perception and executive functions in selecting different figures from a background; Spontaneous drawing test (drawing a daisy with a stem and one leaf), to evaluate imagery and drawing abilities; Copy drawing test (copying the drawing of a house), to evaluate praxis and visuo-constructional abilities; Clock drawing test (drawing a clock with all the numbers and placing the hands at a specific time), to evaluate imagery, planning and visual constructional abilities; and Praxis test (executing meaningful gestures or copying meaningless gestures with hands and arms), to evaluate praxis abilities, that is, the capacity to use parts of the body to make specific gestures. The battery provides a score for each single cognitive task and a total score that reflects the overall cognitive profile.

Procedure

The recruitment was carried out by accessing municipal registers. People were contacted and asked to participate voluntarily in the study. After the procedure was explained to the participants, their written informed consent was obtained. The neuropsychological assessment was conducted in one session at participants' homes, lasting approximately one hour and a half. Participants often felt more competent speaking Sardinian than Italian, so answers in both languages were accepted.

Results

Data were analysed using R Software (R Core Team, 2022). Participants’ Cognitive Reserve Index (CRI) was quite heterogeneous, ranging from 88 to 165 (M=111, SD=16.7). Descriptive statistics of participants' demographic features and their performance in each ENB-2 task and global score (ENB-2 tot) are reported in Table 11.

Variable	Mean	Median	Mode	SD	Min	Max	Skewness	Kurtosis
Age	93.7	92	92	3.2	90	105	1.5	2.4
Education	4.7	5	5	2.9	0	18	2.2	7.9
CRI	115.7	111	104	16.7	88	165	2.1	6.8
Digit span	4.5	4	4	0.8	3	7	0.8	0.3
Immediate memory	6.8	7	6	2.4	3	15	0.9	1.6
Delayed memory	8	7	5	4	0	20	0.8	0.7
Interference memory (10s)	3	2	2	2.2	0	9	0.8	-0.1
Interference memory (30s)	2.5	2	2	2	0	8	0.6	-0.3
TMT-A	277.2	183	999	282.1	34	999	2	2.6
TMT-B	329.7	296	121	166.3	121	708	0.9	0.2
Token	4.6	4.5	5	0.5	3	5	-1.2	0.6
Fluency	6.4	5.6	3.6	3.2	1.6	17	1.3	1.9
Abstraction	3.8	4	4	1.6	1	6	-0.2	-0.9
Overlapped figures	14.6	14	14	6.5	0	33	0.5	0.4
Cognitive estimation	3.8	3	3	6.5	1	5	-0.2	-0.4
Copy drawing	0.8	1	1	0.7	0	2	0.3	-1.1
Spontaneous drawing	1.2	1	1	0.8	0	2	-0.4	-1.1
Clock	4.8	4	4	2.5	0	9.5	-0.1	-0.5
Praxis	5.8	6	6	0.5	3	6	-3.6	14.4
ENB-2 tot	47.9	47	43	9.7	28	69	0.2	-0.3

Table 11. Descriptive statistics of the sample demographic features (age, education and CRI) and all scores obtained in all ENB-2 tasks and ENB-2 total score. *Note:* CRI=Cognitive Reserve Index (Nucci et al., 2012); ENB-2=Esame Neuropsicologico breve 2 (Mondini et al., 2011); TMT-A=Trail Making Test Part A; TMT-B=Trail Making Test Part B.

Regression analyses were carried out to verify the predictive value of CRI for participants' cognitive performance at ENB-2 in every single task and as global performance (ENB-2 tot). Age was not considered a covariate because of its low variability (range: 90-105). Education was also not considered a covariate to avoid collinearity, as CRI includes years of education. A statistically significant effect of CRI was found for the ENB-2 total score (R^2=0.182, p<.001), and for 7 out of 16 single tasks: Interference memory at 10s (R^2=0.145, p=0.015), Interference memory at 30s (R^2=0.072, p=0.028), TMT-B (R^2=0.223, p=0.047), Token (R^2=0.081, p=0.019), Fluency (R^2=0.323, p<0.001), Abstraction (R^2=0.092, p=0.012) and Overlapped figures (R^2=0.132, p=0.002). Table 12 summarises the regression models used.

	Model fit measures		Model coefficients	
			Intercept	CRI-Estimate
Tasks	R^2	*p*		
Digit span	0.052	0.063	3.225	0.011
Immediate memory	0.032	0.149	3.844	0.026
Delayed memory	0.019	0.270	4.222	0.033
Interference memory (10s)	0.145	**<0.001**	-2.773	0.050
Interference memory (30s)	0.072	**0.028**	-1.159	0.032
TMT-A	0.022	0.228	568.110	-2.515
TMT-B	0.223	**0.048**	809.684	-3.854
Token	0.081	**0.019**	3.538	0.009
Fluency	0.323	**<0.001**	-6.261	0.110
Verbal abstraction	0.092	**0.012**	0.348	0.030
Overlapped figures	0.132	**0.002**	-1.641	0.141
Cognitive estimation	0.036	0.122	1.947	0.013
Copy drawing	0.003	0.683	0.590	0.002
Spontaneous drawing	0.033	0.141	0.267	0.008
Clock	0.019	0.267	2.507	0.020
Praxis	<.001	0.855	5.739	<.001
ENB-2 tot	0.182	**<0.001**	19.388	0.247

Table 12. Details of regression models having ENB-2 tasks as dependent variables and CRI as the independent variable. *Note:* CRI=Cognitive Reserve Index (Nucci et al., 2012); ENB-2=Esame Neuropsicologico breve 2 (*tr.* Brief Neuropsychological Examination; Mondini et al., 2011); TMT-A=Trail Making Test Part A; TMT-B=Trail Making Test Part B.

Discussion

This study aimed to explore the relationship between cognitive reserve (CR; measured with the Cognitive Reserve Index questionnaire; Nucci et al., 2012) and neuropsychological performance in nonagenarians and centenarians living in a specific area of Sardinia, the Blue Zone. Our interest was to understand whether CR can modulate neuropsychological performance also in oldest-old individuals. Our analysis shows that high CR predicts better cognitive efficacy, especially in executive function tasks. Participants generally showed a mean ENB-2 total score well above the cut-off for over 80. However, as the normative data of ENB-2 do not adequately represent their age range, ENB-2 may have underestimated their performance.

Considering the single tests of ENB-2, regression analyses show that CR predicts better performance on several tests such as Token, Interference memory (10 and 30 seconds), TMT-B, Fluency, Abstraction and Overlapping figures. Except for the Token test, all these tasks involve executive function. Other data in the literature confirm the link between CR and executive function. For example, Oosterman et al. (2021; see also Colangeli et al., 2016; Roldán-Tapia et al., 2012; Satz et al., 2011; Siedlecki et al., 2009) showed that CR attenuates the effect of age on executive functioning in old to very old adults. As executive functions are core mechanisms of cognition, they may represent the compensatory mechanisms of CR (Tucker & Stern, 2011).

Another interesting point is that, although this population has very low average education and low cognitive demanding working activities, their CR is at a medium-high level due to stimulating leisure activities. Some participants, for example, knew by heart a few of the great classics of literature, such as The Divine Comedy and The Iliad, and participated in poetry competitions. Others organised and led hunting parties went on holiday to thermal areas or went on pilgrimages. According to previous studies (Lee et al., 2020), cognitively challenging leisure activities play a fundamental role in the construction of CR, especially in people with low levels of education, and that is the case for our special participants.

The power of CR in this population clearly shows how an active lifestyle benefits older adults and promotes well-preserved ageing. Whatever activity requires engaging, thinking, and social collaboration maintains our brain functioning and reduces hospitalisation and independence in daily living. Thus, promoting a cohesive and socially active community could be an excellent strategy for our advanced societies.

Even with the value of our results, the study has some limitations. Our sample was relatively small, and to verify the generalizability of our data, future research should increase the sample size to achieve a large open-access database of the Italian population. A control group should also be included, for example, a group of younger Sardinian elders or a group of oldest-old living in other areas of Italy, to evaluate and compare performances. Future studies should consider these points to understand more in-depth the co-occurrence of these variables in determining healthy ageing.

In conclusion, as the literature has underlined, environmental and genetic factors undoubtedly contribute to high brain maintenance[2] and cognitive performance. On the other hand, we found that cognitive reserve, mainly derived from leisure activities, continues to modulate, and strengthen cognitive functioning. In addition to brain maintenance, cognitive reserve contributes to the oldest-old's mental health and general well-being. Although biological changes strongly affect cognitive functioning at this age, CR still has a role in preserving cognitive health and the ability to function successfully.

[2] Brain maintenance refers to the relative absence of change in neural resources over time as a determinant of preserved cognition in older age. Brain maintenance and cognitive reserve are complementary concepts. One refers to relative preservation of the brain while the other refers to sustaining cognition in the face brain changes. Both brain maintenance and cognitive reserve can be influenced by multiple genetic and environmental factors, operating at various points across the lifespan (reserveandresilience.com).

1.3.2 Cognitive Reserve and Subjective Cognitive Decline

Mondini, S., Pucci, V., Montemurro, S., & Rumiati, R. I. (2022). *Protective factors for subjective cognitive decline individuals: trajectories and changes in a longitudinal study with Italian elderly. European Journal of Neurology, 29(3), 691–697.*

Introduction

Subjective Cognitive Decline (SCD) refers to the individual perception of cognitive decline, representing a midway condition along the continuum between healthy and pathological ageing (Jessen et al., 2014). The criteria for the identification of SCD are: (1) self-experienced persistent decline in cognitive capacity in comparison with a previous status and unrelated to an acute event; (2) normal age-, sex-, and education-adjusted performance on standardised cognitive tests, which are used to classify cognitive impairment (Jessen et al., 2014). Evidence shows that SCD is related to a higher risk of Mild or Major Neurocognitive Disorders (American Psychiatric Association, 2013). People with SCD frequently show Alzheimer's disease-related brain pathology, including impaired functional connectivity, increased deposition of cerebral β-amyloid, atrophy, and reduced glucose metabolism in hallmark regions associated with Alzheimer's disease (La Joie et al., 2016). Since the assessment of SCD is less invasive and expensive than measuring cerebrospinal fluid or neuroimaging biomarkers, SCD can potentially become a biomarker of Alzheimer's disease (Ossenkoppele & Jagust, 2017). However, not all individuals with SCD will necessarily turn into overt cognitive impairment (Jessen et al., 2020). Therefore, it is crucial to identify individuals with SCD who are likely to progress to objective cognitive decline and make a tailored diagnostic procedure because early diagnosis and intervention can effectively improve their prognosis (Li et al., 2022).

SCD may be of particular interest in studying the effects of CR since it is widely acknowledged that both genetic and environmental risk factors co-occur to influence the likelihood of individuals with SCD progressing to dementia. In addition, a recent meta-analysis

(Xu et al., 2015) showed that one-third of these risk factors are modifiable, highlighting the feasibility and importance of early prevention (Wen et al., 2021).

Within this framework, we aimed to explore possible protective factors for individuals with SCD, which are less investigated than Major Neurocognitive Disorders (MajorND) or Mild Neurocognitive Disorders (MildND), although they represent a midway condition along the continuum between healthy and pathological ageing. In a retrospective and longitudinal study, the effect of demographic factors (age and sex), comorbidities, and Cognitive Reserve proxies (education and occupation) on cognitive health were investigated.

Materials and Methods

From a cohort of 4,638 consecutive individuals with various brain disorders who had arrived at their first neuropsychological assessment, 3,081 with a referral question of possible cognitive decline were selected for the study. These individuals were sent to the Clinical Service of the University of Padua (Italy) from 2002 to 2016, under the indication of the family doctor or the worries of a family member. Subsequently, we analysed the data of a sub-group of 543 individuals who came a second time for a follow-up and a further sub-group of 125 individuals who underwent a third evaluation.

At all assessments, participants underwent a complete neuropsychological evaluation. However, for the aim of this study, we considered only six tests able to detect cognitive abilities known as being prone to decline in older adults progressively:

1) The Mini-Mental State Examination (MMSE; Folstein et al., 1975): a screening test used to obtain a global measure of the cognitive state (Italian version, Magni et al., 1996). The maximum score is 30/30.

2) The Story recall test, for short Memory (taken from the battery ENB2, Mondini et al., 2011) to evaluate episodic memory; it requires first the repetition of a short story and then the delayed recall of the same story after five minutes. This study uses the sum of the immediate and delayed recall scores. The maximum score is 56/56.

3) The Famous Face naming test, for short Faces, requires recognising and naming 15 pictures of famous contemporary and historical personages selected and validated (Semenza et al., 2003). Maximum score is 16/16.

4) The verbal fluency test, for short Fluency (taken from the battery ENB2, Mondini et al., 2011) to measure lexical access and executive function. It requires the production of as many words as possible, starting through three specific phonemes (i.e., C, S, P). The average mean of words produced is the score used in this study.

5) The Trial Making Test-A, for short TMT-A (taken from the battery ENB2, Mondini et al., 2011) for measuring selective and spatial attention and psychomotor speed; it requires rapidly connecting in sequence with a line a series of numbers distributed on a paper; the processing time is taken as score and the faster, the better.

6) The Clock drawing test, for short Clock (taken from the battery ENB2, Mondini et al., 2011) was used to measure visuospatial abilities, planning and praxis. It requires filling up a drown circle (the circumference of a clock) with all numbers in the correct sequence and positions and then placing the hands at a given time (i.e. 2:45 pm). The sequence of numbers, their correct positions and their hands give a maximum score of 10/10.

Among the possible variables which may predict the cognitive outcomes, we considered two socio-demographical ones, i.e., Age and Sex, one clinical, i.e., Comorbidity and two proxies of CR, i.e., Education and Occupation.

Comorbidity was classified into four levels depending on the number of concomitant relevant pathologies (0, 1, 2, 3), such as hypertension, diabetes, tremors, cardiovascular diseases, or mood disorders (the classification of the comorbidity and their frequency on the sample is reported on the Appendix 1). Education was considered as the number of years of schooling. Occupation was considered in terms of cognitive skills and cognitive resources required and was operationalised through the International Standard Classification of Occupations (ISCO, 2008). As described above (Chapter 1.2.3), ISCO-08 has been developed to facilitate international comparison of occupations. The international community fully supports it as an accepted standard for international labour statistics. This system classifies each working activity along a continuous numeric value. The higher the numerical code, the lower the complexity of the occupation in terms of skills and cognitive resources involved.

The study was conducted following the Declaration of Helsinki, and it was approved by the Ethical Committee of the University of Padua.

Baseline study

Participants

A sample of 3081 individuals (2010 females and 1069 males) was selected for the Baseline study. Participants' mean Age was 78.2 years old (SD=7.79), ranging from 45 to 99. The average Education was 6.99 years (SD=3.85), ranging from 0 (3 illiterate individuals had no formal education) to 25 years. The variable Occupation was reported in our sample for 2648 participants (in 433 cases, the occupation was not reported in the clinical record). According to ISCO-08, the mean was 6266 (SD=2586), ranging from 110 to 9622. Participants with 0 comorbidity were 813 (26%); 503 participants (16%) had one comorbidity; 431 participants (14%) had two comorbidities; 1344 participants (43%) had three or more comorbidities. Figure 8 shows the distribution of the predictors considered.

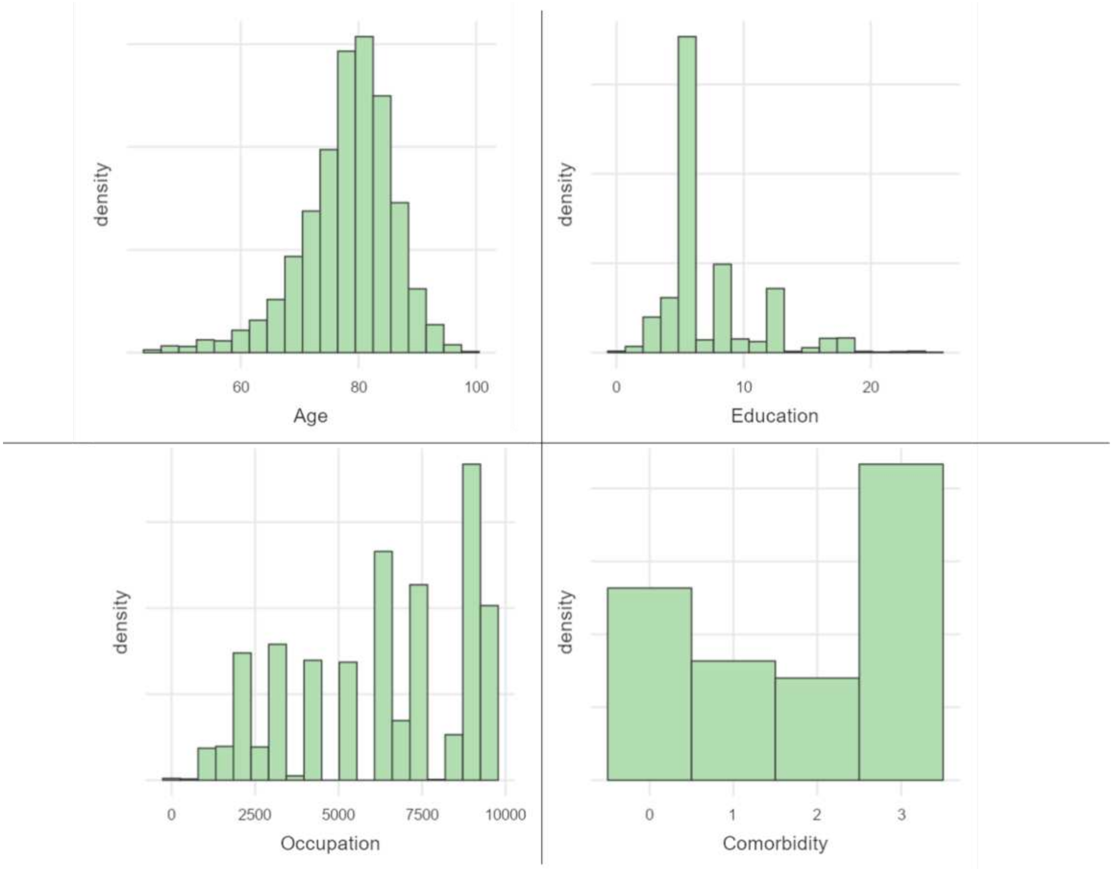

Figure 8. The figure represents the distributions of Age, Education, Occupation and Comorbidity of participants.

Three diagnostic groups were identified based on psychometric data and anamnestic and clinical information. Two categories were defined according to the DSM-5 (American Psychiatric Association, 2013): 1) Major Neurocognitive Disorder due to Alzheimer's disease (MajorND, 1980 participants, 64% of the total); 2) Mild Neurocognitive Disorder (MildND, 584 participants, 19% of the total). The third group without a clinical diagnosis was named 3) Subjective Cognitive Decline (SCD, 507 participants, 17% of the total) and included participants who did not show any objective impairment (Jessen et al., 2020).

Results

Descriptive statistics of the sample features and the performance at cognitive tests are presented in Table 5.

	Mean (SD)	Range	Median	Mode
Age	78.2 (7.8)	45-99	79	80
Education	6.99 (3.8)	0-25	5	5
Occupation	6265 (2585.9)	110-9622	6121	9111
MMSE	19.77 (5.9)	0-30	20	21
Memory	12.4 (10.5)	0-52	10	0
TMT	112.54 (72.8)	9-300	88	177
Clock	4.42 (3.72)	0-10	4	0
Fluency	5.85 (3.83)	0-23	6	0
Faces	6.94 (4.01)	0-18	7	6

Table 5. The table reports descriptive statistics of participants' characteristics and performance at tests. *Note.* MMSE=Mini-Mental State Examination (Folstein et al., 1975); TMT=Trail Making Test (taken from Mondini et al., 2011).

Subsequently, linear regression models were carried out to verify whether and how Age, Sex, Education, Occupation and Comorbidities could predict participants' cognitive performance in the six tests. Entering one predictor at a time, the Models with the best fit (based on R^2) were those with all five predictors, and all these models were significant (see model fit measure in Table 6). A consistent effect of Age and Education was expected, but interestingly, Occupation was also found to be predictive on all tests except for Clock and TMT. Sex and Comorbidity played a minor role and predicted only two tests each. Females outperformed males in naming faces, whilst males outperformed females in the clock. A similar verbal/visuospatial sex difference had been observed in a previous study on the effect of CR on ageing (Le Carret et al., 2003), whilst Tappen (2019) found that in an older adult population, men were better than women in the clock test.

	Predictors (Beta and *p*)											
	Age		Sex		Education		Occupation		Comorbidity		Model fit measure	
Models	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	R^2	*p*
MMSE	-.250	**<.001**	.030	.135	.259	**<.001**	-.048	**.037**	-.030	.111	.164	**<.001**
Memory	-.312	**<.001**	.003	.952	.246	**<.001**	-.067	**.017**	-.020	.367	.201	**<.001**
Faces	-.300	**<.001**	-.140	**.013**	.212	**<.001**	-.066	**.042**	-.039	.141	.175	**<.001**
Fluency	-.213	**<.001**	.021	.065	.268	**<.001**	-.067	**.016**	-.077	**<.001**	.166	**<.001**
TMT	.250	**<.001**	-.035	.497	-.271	**<.001**	.052	.083	.083	**<.001**	.192	**<.001**
Clock	-.193	**<.001**	.187	**<.001**	.247	**<.001**	-.017	.568	-.006	.803	.134	**<.001**

Table 6. The Table shows the contribution of each predictor to the model. Model fit measures indicate the significance of models with all covaried predictors. The significant probability for each test is indicated in bold. *Note:* MMSE=Mini-Mental State Examination; TMT=Trail Making Test-A.

The effect of Age and Education persisted within each of the three diagnostic groups (SCD, MildND, MajorND), and although Occupation did not play a role within each group, it differed significantly between them (F(2,900)=31.0, p<0.001): SCD had the lowest score (i.e., more complex jobs), whilst MajorND had the highest score (i.e., less complex jobs) (Figure 9).

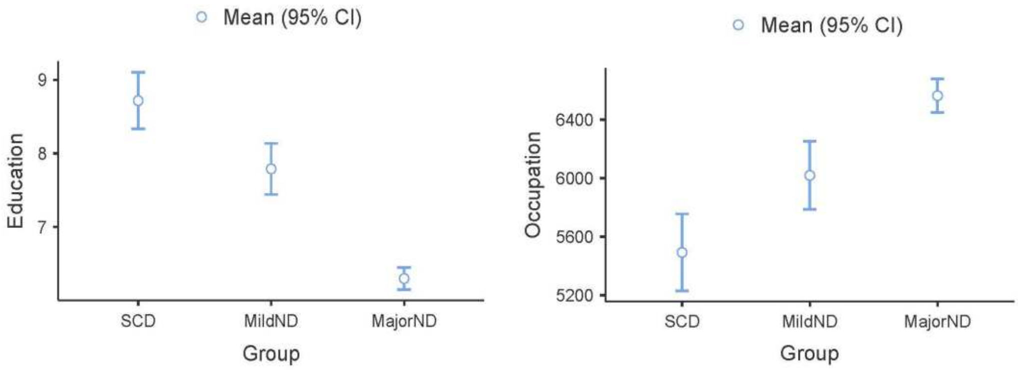

Figure 9. Predictors in the groups. The graphs show the mean differences in age (years), education (years) and occupation (ISCO-08 codes: the lower the scores the more complex the occupations) resulting from one-way ANOVA between the three groups (SCD, MildND and MajorND). *Note.* SCD=Subjective Cognitive Decline; MildND=Mild Neurocognitive Disorder; MajorND=Major Neurocognitive Disorder.

Follow-up studies

Participants

A total of 543 individuals from the baseline study underwent a second assessment (T2), and 125 underwent a third assessment (T3). In all assessments, the same six neuropsychological tests were administered. As a whole group, participants from T1 to T2 showed a lower average score on all tests, but for the Fluency and Clock, the only two which remained stable. Participants from T2 to T3 diminished their average scores on all tests except Fluency, which remained stable. Participants were then sorted into two groups based on clinical evidence and their cognitive performance in the tests. At T2 and T3, individuals who performed worse than in the previous assessment were aggregated in a single group and named *declining*. This group also included MajorND participants who maintained the same clinical diagnosis but had a worsened cognitive performance (no MajorND patient improved on cognitive tests). Participants who at T2 (or T3) did not worsen their profile were aggregated in a single group and named *resistant* (Table 7). The time interval between assessments (from T1 to T2) was different amongst participants: *short* (1 year; 242 participants), *medium* (2–3 years; 207 participants) and *long* (more than 3 years; 94 participants). Assuming that the longer the time, the higher the possible cognitive decline, this analysis aimed to verify if the effect of CR proxies changed depending on the time elapsed between assessments.

N	From T1 to T2		N	From T2 to T3	
434	***Declining***		**104**	***Declining***	
13	SCD	MildND	7	SCD	MildND
13	SCD	MajorND	6	SCD	MajorND
74	MildND	MajorND	30	MildND	MajorND
302	MajorND	MajorND	61	MajorND	MajorND
109	***Resistant***		**21**	***Resistant***	
35	SCD	SCD	7	SCD	SCD
52	MildND	MildND	8	MildND	MildND
18	MildND	SCD	6	MildND	SCD
543	*Total*		*125*	*Total*	

Table 7. The table shows the changing profile of participants from T1 to T2 among 543 participants who had a second assessment (T2) and from T2 and T3 among the 125 participants who underwent a third assessment (T3). *Note.* SCD=Subjective Cognitive Decline; MildND=Mild Neurocognitive Disorder; MajorND=Major Neurocognitive Disorder.

Results

As for the Baseline study, we carried out a series of linear regression models where Age, Sex, Education, Occupation and Comorbidity were introduced as predictors and participants' performance in the six cognitive tests as the dependent variable. At T2, all models were significant in predicting the outcomes of the cognitive tests. The effect of Education was confirmed in all six tests, and Age had an effect only in two. No other effect was found. At T3, Education was the only significant predictor in three tests.

At each assessment, the *declining* group showed lower average scores at T2 than at T1 and at T3 than at T2 on four out of six tests. Instead, the average scores on all six tests of the *resistant* group did not change at either T2 or T3 (Table 8).

	Declining					
	From T1 to T2			From T2 to T3		
	t (df)	*mean diff.*	*p-value*	*t (df)*	*mean diff.*	*p-value*
MMSE	11.4 (399)	2.80	**<.001**	5.92 (92)	2.47	**<.001**
Memory	4.15 (220)	0.64	**.005**	5.35 (51)	4.75	**<.001**
Faces	3.92 (83)	0.99	**<.001**	3.17 (17)	1.33	**.006**
Fluency	1.18 (176)	0.24	.240	1.62 (52)	0.63	.111
TMT	-3.08 (182)	-14.25	**.002**	-1.97 (54)	-15.38	.054
Clock	1.75 (225)	0.37	.082	2.26 (64)	0.79	**.027**
	Resistant					
	From T1 to T2			From T2 to T3		
	t (df)	*mean diff.*	*p-value*	*t (df)*	*mean diff.*	*p*
MMSE	0.32 (81)	0.11	.710	1.20 (15)	1.00	.248
Memory	1.29 (87)	1.06	.200	0.87 (17)	1.28	.398
Faces	1.58 (29)	0.73	.125	2.61 (3)	1.25	.080
Fluency	0.32 (83)	0.13	.751	-1.99 (17)	-1.52	.066
TMT	-0.42 (29)	-1.56	.672	-1.46 (15)	-6.63	.165
Clock	-1.04 (60)	-0.34	.301	0-38 (13)	0.18	.707

Table 8. The table shows paired sample t-tests, which show the mean difference of the six tests between T1 and T2 and between T2 and T3 in the two groups separately (declining and Resistant). The significant probability for each test is indicated in bold. *Note*: MMSE=Mini-Mental State Examination; TMT=Trail Making Test-A.

At T2, as expected, the resistant group had a higher education than the declining group (t=8.04, mean difference 2.43, p<0.001) at all time intervals: short (t=5.67, mean difference 2.77, p<0.001), medium (t=3.02, mean difference 1.34, p=0.003) and long (t=5.43, mean difference 3.77, p<0.001). More interestingly, the resistant showed higher occupation than the declining (t=−4.80, mean difference −979, p<0.001) across the three-time intervals: short (t=−2.69, mean difference −819, p=0.007); medium (t=−2.60, mean difference −858, p=0.01) and long (t=−3.30, mean difference −1565, p=0.001). Notably, the resistant had the highest education and more complex occupations when the interval was the longest (Figure 10).

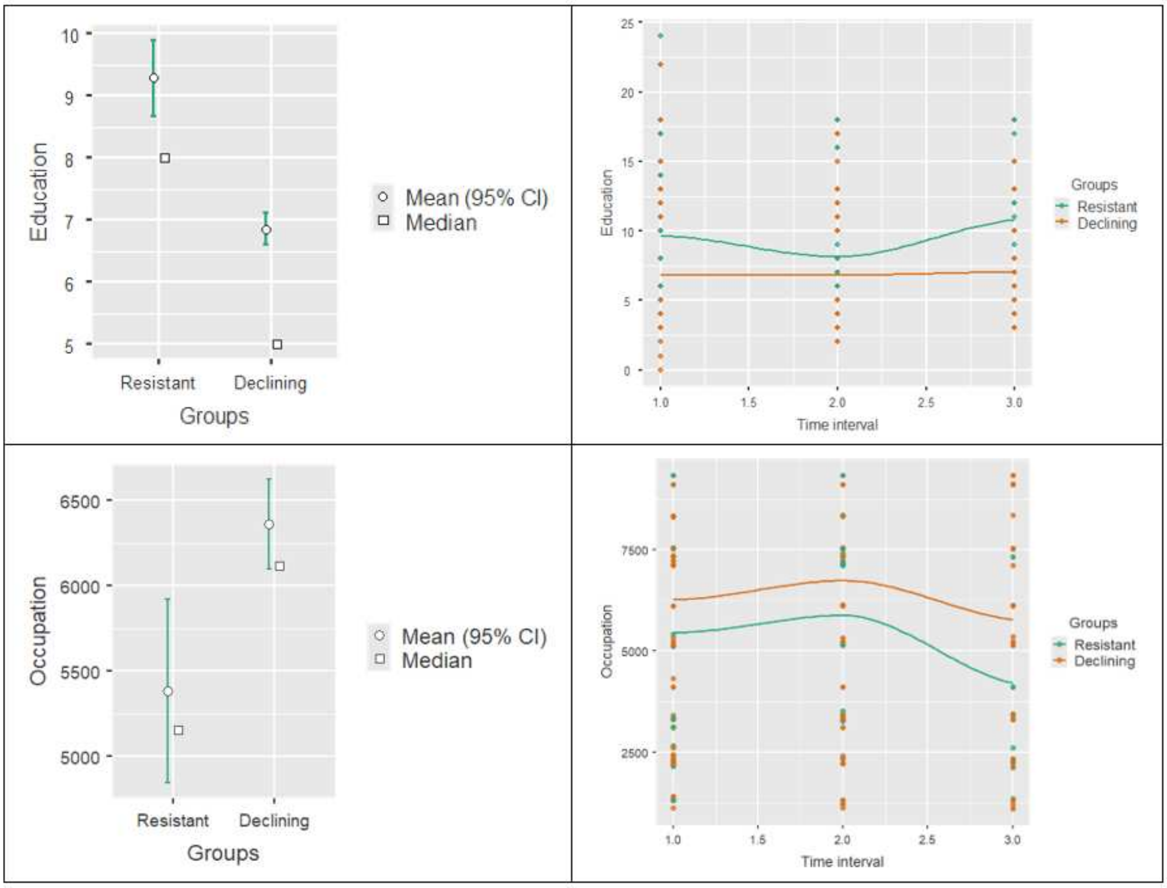

Figure 10. Education and occupation effects on resistant and declining individuals at the second assessment, at different time intervals. The two graphs on the left-hand side show the mean difference in education and occupation between resistant and declining, whilst the two graphs on the right-hand side show the mean difference in education and occupation between resistant and declining at the three time intervals.

Of the 125 participants who underwent a third assessment (T3), 104 were declining (83.9%) and only 21 (16.1%) were resistant. Once again, the resistant group were not only more educated ($t=3.86$, mean difference 2.49, $p<0.001$) but held a more complex occupation than the declining ($t=2.25$, mean difference −941, $p=0.025$) (Figure 11). The time intervals between assessments were not considered in this analysis.

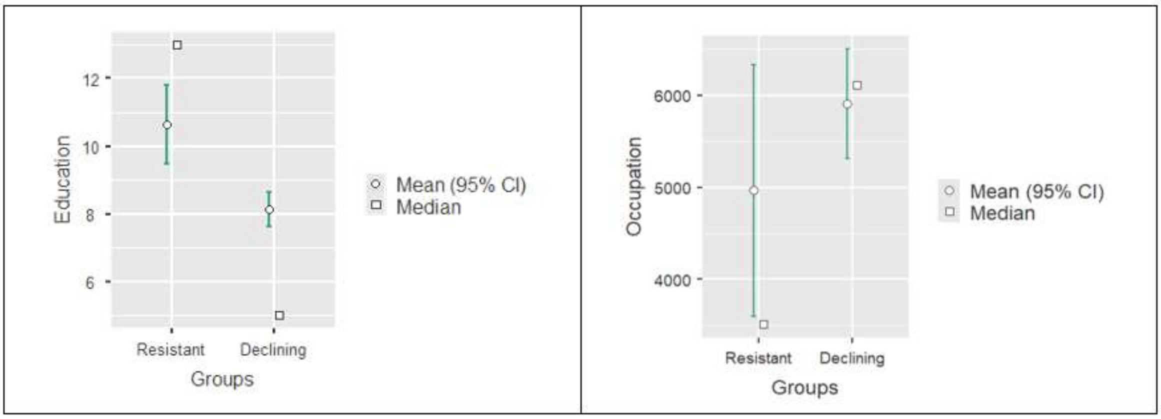

Figure 11. Education and occupation effects on resistant and declining individuals at the third assessment. The graphs represent the mean difference in education (on the left-hand side) and occupation (on the right-hand side) between the resistant and the declining at the third assessment.

Discussion

This study aimed to identify which factors may modulate cognition in ageing and how such an effect may change over time. In the baseline study, the higher the education, the better the performance, an effect already well-known and reported in the literature. However, this study makes a new contribution to the field by demonstrating the role of occupation as a good predictor of participants' performance. The younger participants, the more educated and those with more complex jobs showed better cognitive performance. While cognition deteriorates with ageing, particularly in less educated people (Chan et al., 2018), the clear-cut effect of occupation found in this study points to the relevance of occupation in operationalising CR. Different from education, which is mostly, although not exclusively, acquired during the first part of life, occupation is built on activities carried out during adulthood. This result demonstrates the benefits of lifelong learning mechanisms. Adult learning effectively preserves cognition in older adults (Clare et al., 2017; Valenzuela & Sachdev, 2006). Age and education were confirmed as modulators of performance in all three diagnostic groups (SCD, MildND and MajorND).

It was found that education protects people potentially at risk of developing cognitive decline (SCD group). Interestingly, these same individuals also held more complex jobs than the other two groups. Thus, less impaired individuals seemed to have CR proxies to the highest degree.

Across assessments, the explanatory power of predictors seems progressively attenuated. In fact, as age increases, many factors affect cognitive health and give rise to huge heterogeneity (Netz et al., 2019). Education was the only variable that continued to affect the performance over time, although its effect decreased at the two follow-ups. When considering all participants, most tests found progressive worsening from one assessment to the next. However, when sorted into resistant (i.e., those who maintained their profile) or declining (i.e., those whose profile worsened), the former showed significantly higher education and a more complex occupation than the latter at both T2 and T3. This result suggests a critical role of CR proxies in characterising the evolution of dementia.

There are some limitations of this retrospective study. First, the patients in our sample could have been misdiagnosed because of the lack of precise biomarkers. However, structural and functional neuroimaging information was used to obtain the clinical diagnosis at baseline. It is noted that the number of participants between assessments decreased significantly, as is usual in most studies considering an older population with a percentage of pathological individuals. Another limitation may be that the concept of CR in this study was confined to education and occupation, even though CR is likely to be more than that. As this is a retrospective study, further useful data and information (e.g., lifestyle, place of residence) could not be obtained to understand how our participants aged. Although SCD individuals within the continuum between normal and pathological ageing are considered, including non-clinical participants in future studies would be appropriate.

This is one of the few studies that include the category of SCD individuals when CR is used as a potential modulator of age-related trajectories. Moreover, the importance of working activities carried out during adulthood was a critical factor in CR and cognitive performance in SCD individuals (Bessi et al., 2018; Lojo-Seoane et al., 2018).

In conclusion, our longitudinal study on healthy and pathological participants maintains that with social connectedness, an ongoing sense of purpose and the ability to function independently, higher levels of CR contribute to mental health and general well-being along the different trajectories of ageing.

1.3.3 Cognitive Reserve and Multiple Sclerosis

Maffezzini, S., Pucci, V., Riccardi, A., Montemurro, S., Puthenparampil, M., Perini, P., Rinaldi, F., Gallo, P., Arcara, G., & Mondini, S. (2023). *Clinical Profiles in Multiple Sclerosis: Cognitive Reserve and Motor Impairment along Disease Duration. Behavioral Sciences, 13(9).*

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, degenerative disease affecting both grey and white matter of the central nervous system (Dobson & Giovannoni, 2019). MS is related to a wide range of symptoms, including sensory deficit, arm or leg movement disorders, fatigue, coordination and balance deficits, and psychological and cognitive problems. Cognitive impairment occurs in up to 70% of individuals with MS (Chiaravalloti & DeLuca, 2008; Oreja-Guevara et al., 2019; Sumowski et al., 2018), who typically show affected cognitive functioning in sustained attention, information processing speed, memory, and executive functions (Benedict et al., 2020; Grzegorski & Losy, 2017; Rocca et al., 2015) among other changes in their quality of life. For this reason, assessing the neuropsychological status of people with MS is essential for the diagnosis, and in monitoring the disease progression (Oreja-Guevara et al., 2019). Although cognitive impairment is one of the most frequent symptoms of MS, it is not clear why some individuals do not show such dysfunctions (Benedict & Zivadinov, 2011; Ghaffar et al., 2012), whereas others show a decline. These latter individuals are usually older (Brochet & Ruet, 2019) and have a more extended history of the disease (Tremblay et al., 2020).

Other studies have focused on the description of cognition in individuals with MS based on their motor disability, measured on the Expanded Disability Status Scale (EDSS, Kurtze, 1983), a routinely used method for quantifying motor disability in MS and monitoring changes over time. Recent longitudinal studies have indeed shown that higher motor disability is correlated with lower cognitive functioning (Heled & Achiron, 2021; Yigit et al., 2021), even if the relationship between motor and cognitive impairment is still controversial (Amato et al., 2010).

In recent years, cognitive reserve (CR) has been considered a construct that can explain the possible variance of cognitive impairment in individuals with MS (Da Silva et al., 2015; Rocca et al., 2015). In general, the results of such studies have shown that high levels of CR are associated with lower cognitive dysfunction (Ifantopoulou et al., 2019; Santangelo et al., 2019). Instead, with old age, low CR levels are among the most significant predictors of cognitive decline in individuals with MS (Amato et al., 2019; Nunnari et al., 2016).

However, relatively few studies have focused on the precise role of CR in the cognition of individuals with MS, also considering clinical indices such as the duration of the disease, age of onset, and the level of motor disability. Rimkus and colleagues (2018) suggested that the protective effect of CR is strongest in the early years after the disease onset when there is a reduced effect of inflammatory activity on cognitive abilities. A meta-analysis (Santangelo et al., 2019) has highlighted the only effect of CR on cognitive performance and not on other clinical variables such as disease severity, disease duration, motor disability (measured with EDSS), and type of MS. Furthermore, Artemiadis et al. (2020) underlined that in individuals with the same level of motor disability, those with a higher CR showed a better cognitive performance in a series of neuropsychological tasks.

These findings, however, are controversial and further investigation is needed. Indeed, CR was quantified through a heterogeneous pool of proxies and, in most cases, without a composite index. Tremblay and colleagues' investigation (2023) is one of the few previous studies that considered a composite measure of CR using the standardised and reliable Cognitive Reserve Index questionnaire (CRIq; Nucci et al., 2012). The authors found that CR moderated the relationship between EDSS and cognition. However, this investigation did not consider the duration of the disease.

The present work aimed to verify whether a higher level of CR may interact with the duration of the disease and motor disability in predicting cognitive outcomes. We hypothesised that, despite duration of the disease and motor impairment, a higher level of CR may allow individuals with MS to maintain good cognitive efficiency. Due to the multiple factors considered in our hypothesis, we analysed the data through Generalised Additive Models

(GAMs; Wood, 2017), a statistical approach which allowed us to verify the complex interaction among multiple continuous variables.

Materials and Methods

Participants

In this cross-sectional study, 100 individuals with MS were enrolled: 88 with relapsing-remitting MS and 12 with progressive MS (according to the recent guidelines by Lublin et al., 2014). Participants' (72 Female, ratio F:M=2.6:1) mean age was 50.9±9.25 (range 30-74), mean education was 12.5±3.53 years (range 5-21), the duration of the disease ranged from 1 to 37 years (mean=14.82±9.28), and motor disability, measured through the EDSS, ranged from 1 to 8 (mean=3±1.89). Most participants were treated with first- or second-line drugs, whereas 7% of them had no pharmacological therapy for some reasons (e.g., personal choice, no availability of appropriate drugs for the typology of MS).

The inclusion criteria were: (i) age >18, (ii) no history/evidence of psychiatric or neurological disorders other than MS, (iii) no history of alcohol or drug abuse, (iv) no hearing difficulties, (v) Italian mother tongue, and (vi) no recent relapse of the disease.

All participants were recruited between January and July 2021 at the Multiple Sclerosis Centre of the University Hospital of Padua, where they arrived for a first diagnosis or clinical follow-ups. When a participant suitable for this study was at the Multiple Sclerosis Centre, the EDSS was administered by a trained neurologist. An expert psychologist scheduled the telephonic cognitive assessment up to one week later. The entire procedure of this study was conducted remotely, by telephone. Each participant was informed about the purpose of the research, and their consent was acquired via audio recording. The examiner ensured that the room was quiet and distraction-free and that the telephone connection was stable.

The study was approved by the Ethical Committee of the Hospital of Padua (Prot. N 19669), and it was conducted following the Declaration of Helsinki.

Materials

For each participant, clinical variables, cognitive reserve, and neuropsychological measures were collected. Clinical variables: included (i) the duration of the disease (in years) registered in the clinical report and personal anamnesis; (ii) motor disability, assessed through the EDSS (Kurtzke, 1983) administered by neurologists. Cognitive reserve was measured with the Cognitive Reserve Index questionnaire (CRIq; Nucci et al., 2012; see chapter 1.2.3 of the present thesis for a complete description of the questionnaire). Neuropsychological assessment aimed to evaluate cognitive functioning through the Tele-Global Examination of Mental State (Tele-GEMS, Montemurro et al., 2023), a new cognitive screening tool that is administered remotely using a telephone and consists of ten tasks investigating different cognitive domains. It provides an index of global cognitive functioning, which reflects the balanced contribution of each task to a total score that ranges from 0 to 100. The administration lasts about 10 minutes.

Statistical Analysis

All statistical analyses were performed with R software (R Core Team, 2022). First, an independent sample t-test was carried out to analyse possible differences according to sex to verify whether to include this variable in the subsequent analyses. Descriptive correlation analyses among our predictors were calculated through Pearson's *r*. Generalised additive models (GAMs, Wood, 2017) of increasing complexity were used to investigate the interaction between clinical variables (EDSS and duration of the disease) and cognitive reserve (CRI) on the one side and cognitive functioning (Tele-GEMS) on the other.

The main advantage of GAMs over the more traditionally used GLMs is their ability to model efficiently based on smooth functions and nonlinear relationships between the predictors and the dependent variable. Although this is also possible with GLMs, in GAMs, nonlinearity must be specified explicitly a priori. In contrast, the modelling procedure in a GAM uses a bottom-up approach to estimate whether a nonlinear relationship improves the fit. In GAMs, the relationship between the predictor and the expected value of the dependent variable is modelled through a smooth function, which in turn may follow any exponential family distribution or have a known mean-variance relationship, allowing a quasi-likelihood approach.

The models were built from simpler to more complex to examine the best pattern of variables that would fit our data. The goodness of fit of the models was assessed with the Akaike Information Criterion (AICc), and GCV was used to check for any possible overfitting (Burham & Anderson, 2002; Symonds & Moussalli, 2011). We also calculated the Akaike Information Criterion weights (AICw), which is the probability of a model being the best among a given set of models and, as such, can be used for model selection. The best model was chosen according to the AICw (R^2 and AIC are also reported), and a series of diagnostic tests were carried out to check the appropriateness of the model's characteristics. We also checked the quality of the GAMs by visual inspection of the residuals.

Results

Descriptive statistics of the variables (age, education, disease duration, EDSS, CRI, and Tele-GEMS) are reported in Table 9. Our sample did not differ between males and females on Tele-GEMS performance (t(98)=−0.79, p=0.43); thus, sex was not a predictor in the GAMs.

	Mean	SD	Median	Min	Max	Kurtosis	Skewness	Q1	Q3
Age	50.89	9.25	51	30	74	0.09	0.04	46	56
Education	12.53	3.53	13	5	21	-0.65	0.04	8	13
Duration of the disease	14.82	9.28	13	1	37	-0.75	0.45	7	21
EDSS	3.04	1.90	2.50	1	8	-0.31	0.86	1.5	4
CRI	105.67	13.58	104	78	142	-0.29	0.33	96	115
Tele-GEMS	76.74	15.65	81.8	19.5	98.3	1.78	-1.31	60.08	87.73

Table 9. Descriptive statistics of the sample of the study. ***Note.*** EDSS=Expanded Disability Status Scale (Kurtzke, 1983); CRI=Cognitive Reserve Index (Nucci et al., 2012); Tele-GEMS=Tele-Global Examination of mental State (Montemurro et al., 2023).

Correlational analyses showed that Tele-GEMS correlated positively with CRI (r=0.50, p<0.001) and negatively with age (r=−0.29, p=0.003), EDSS (r=−0.44, p<0.001), and the duration of the disease (r=−0.23, p=0.02). Correlations among all variables of interest (Tele-GEMS, CRI, age, EDSS, and disease duration) are reported in Figure 12.

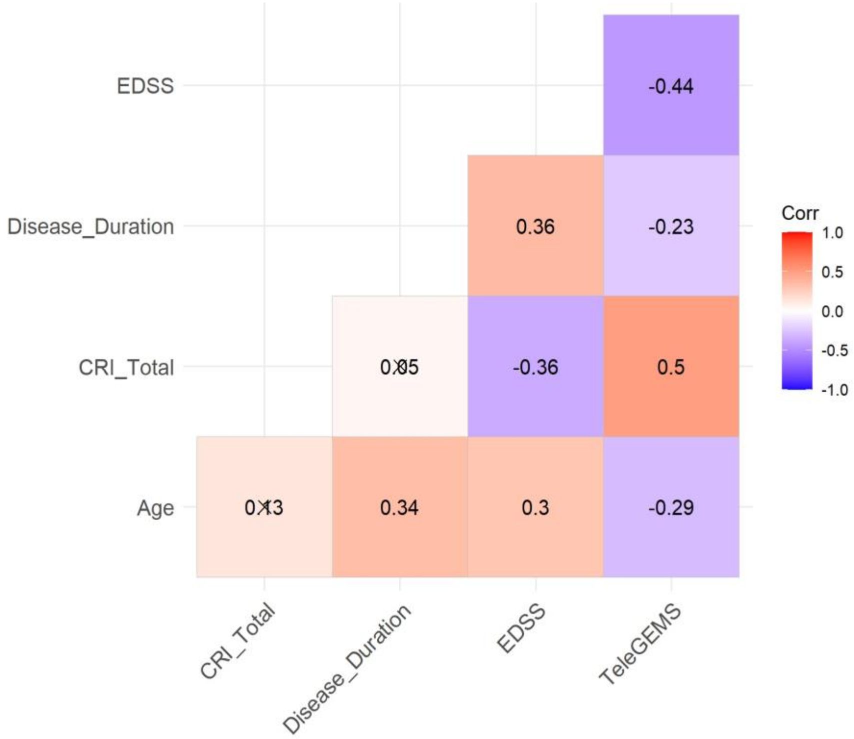

Figure 12. The figure reports the correlations among the variables considered in this work. *Note.* Barred values are not significant. EDSS=Expanded Disability Status Scale (Kurtzke, 1983); CRI=Cognitive Reserve Index (Nucci et al., 2012); Disease Duration=duration of the disease (in years); Tele-GEMS=Tele-Global Examination of mental State (Montemurro et al., 2023).

Generalised additive models (GAMs) analyses underlined that the best model was the one assessing the possible influence between CRI and EDSS, also considering age and the duration of the disease (Model 4). In particular, Model 4 had the highest R^2 (R^2=0.458, Deviance = 50.9) and the lowest AIC. Model 4 was the best according to its AICw (Table 10). A series of diagnostic tests (R function '*gam.check*') showed appropriate characteristics for the tensors referring to the interaction effects (for CRI*Disease Duration: k′=4, p= 0.78; for CRI*EDSS: k′=4, p=0.99).

#	Generalised Additive Models: Interaction between Cognitive Reserve, Disease Duration and EDSS Tele-GEMS = Dependent Variable											
	Intercept			Smooth Terms				Model Fit				
	Estimate (Standard error)	t	p	Terms	Edf	F	p	R^2	Dev	AIC	Model weights
1	76.74 (1.19)	64.71	<.001	s(Age)	1	3.49	0.065	0.43	46.5%	787.9	0.100
				s(CRI)	3.87	8.56	<.001				
				s(DD)	1	1.54	0.217				
				s(EDSS)	1	1.82	0.180				
2	76.67 (1.18)	64.71	<.001	s(Age)	1	2.71	0.103	0.44	49.5%	786.9	0.183
				s(CRI)	3.94	7.67	<.001				
				s(DD)	1	1.64	0.203				
				s(EDSS)	1.29	0.74	0.337				
				ti(CRI,DD)	1.93	1.41	0.257				
3	76.13 (1.32)	57.59	<.001	s(Age)	1	3.71	0.567	0.43	47.6%	788.4	0.079
				s(CRI)	4.13	8.13	<.001				
				s(DD)	1	1.94	0.167				
				s(EDSS)	1	2.54	0.114				
				ti(CRI,EDSS)	1	1.05	0.307				
4	75.05 (1.36)	55.03	<.001	s(Age)	1	3.37	0.070	0.46	50.9%	784.3	0.638
				s(CRI)	4.27	8.55	<.001				
				s(DD)	1	2.47	0.120				
				s(EDSS)	1	2.79	0.098				
				ti(CRI,DD)	1	5.70	0.019				
				ti(CRI,EDSS)	1	4.98	0.028				

Table 10. Results of generalised additive models with Tele-GEMS as the dependent variable and age, CRI, disease duration, and EDSS as covariates, with CRI and disease duration and CRI and EDSS in interaction. The table shows, for the four GAMs carried out, the result associated with the intercept, the smooth terms, and the model fit. Within the intercept, the table shows the standard error, t-value, and p-value associated with the standard error. Within the smooth terms, the table reports the names of smooth terms, estimated degrees of freedom (Edf), F-value, and p-value associated with the smooth terms. Within the model fit, the table shows the R-squared with the percentage of deviance explained, the AIC, and the model weights, representing the probability of a model being the best among the given set of models. *Note.* EDSS=Expanded Disability Status Scale (Kurtzke, 1983); DD=duration of the disease; CRI=Cognitive Reserve Index (Nucci et al., 2012); Tele-GEMS=Tele-Global Examination of mental State (Montemurro et al., 2023).

A visual inspection of Model 4 related to the interaction between CRI and the duration of the disease is shown in Figure 13, and a similar inspection related to the interaction between CRI and EDSS is shown in Figure 14. These two figures provide additional insights into how the interaction between CRI and EDSS and the duration of the disease predicts cognitive performance (i.e., Tele-GEMS). Tele-GEMS scores are represented with different colours: the darker shades of blue in the contour plot represent lower scores, while the darker shades of yellow represent higher scores. Figure 13 shows the interaction between CRI and the duration of the disease, highlighting that high levels of CRI (on the x-axis) are associated with a better Tele-GEMS (on the y-axis) even when the duration of the disease (on the z-axis) is very high. However, a negative effect of the duration of the disease is found on the Tele-GEMS in persons with a low CR. Figure 2 shows the interaction between CRI and EDSS, indicating that high levels of CRI (on the x-axis) correspond to a higher Tele-GEMS (on the y-axis) but that such a positive effect of CRI is significantly attenuated when the EDSS (on the z-axis) is very high (i.e., severe motor disability). This effect is evident in Figure 14 (right side) in correspondence with the dark blue in the upper right-hand-side corner. In the case of a low CR, instead, the Tele-GEMS is low at any level of EDSS.

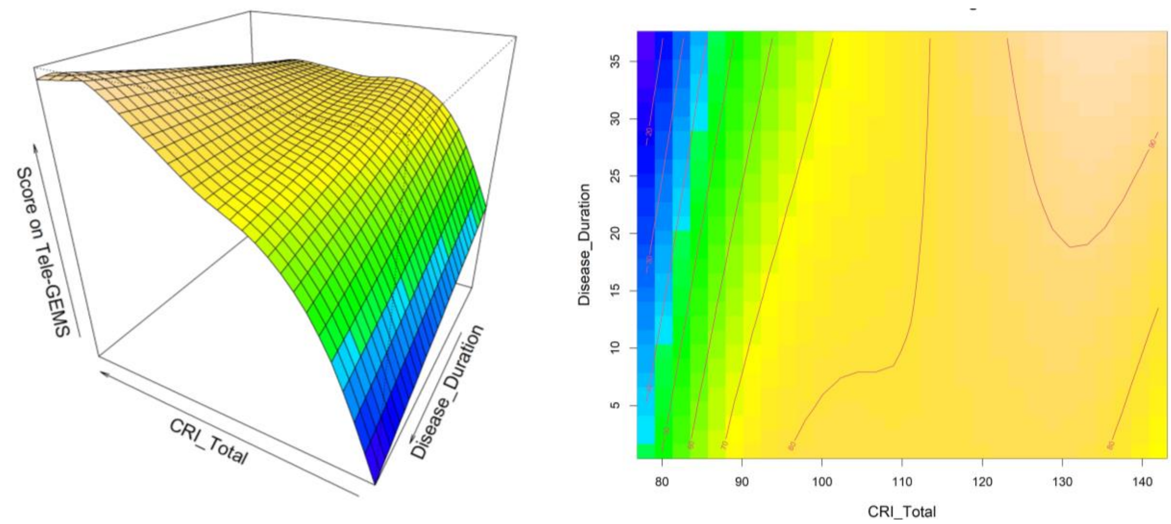

Figure 13. Interaction effect of CRI and disease duration on Tele-GEMS. The figure shows the effect of the tensor surface associated with the interaction between CRI and disease duration (in three-dimensional mode on the left side and two-dimensional mode on the right side). CRI is on the x-axis, disease duration is on the y-axis, and Tele-GEMS is on the z-axis on the left side and is represented by the red lines on the right side. The darker blue in the contour plots shows a lower Tele-GEMS, whereas darker shades of yellow show a higher Tele-GEMS. ***Note.*** CRI=Cognitive Reserve Index (Nucci et al., 2012); Disease Duration=duration of the disease (in years); Tele-GEMS=Tele-Global Examination of mental State (Montemurro et al., 2023).

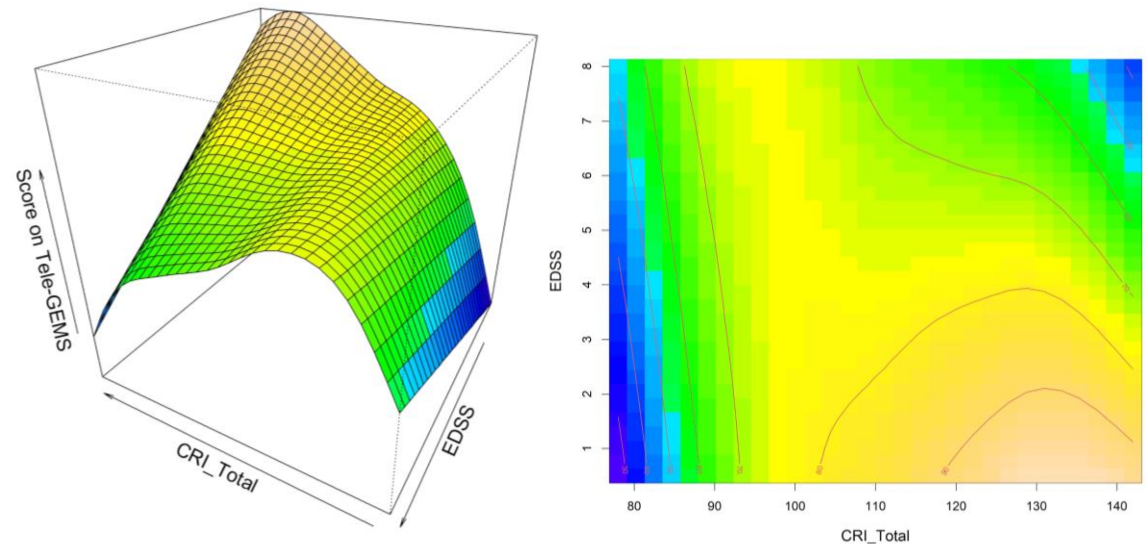

Figure 14. Interaction effect of CRI and EDSS on Tele-GEMS. The figure shows the effect of the tensor surface associated with the interaction between CRI and EDSS (in three-dimensional mode on the left side and two-dimensional mode on the right side). CRI is on the x-axis, EDSS is on the y-axis, and Tele-GEMS is on the z-axis on the left side and is represented by the red lines on the right side. The darker blue in the contour plots shows a lower Tele-GEMS, whereas darker yellow shows a higher Tele-GEMS. *Note.* EDSS=Expanded Disability Status Scale (Kurtzke, 1983); CRI=Cognitive Reserve Index (Nucci et al., 2012); Tele-GEMS=Tele-Global Examination of mental State (Montemurro et al., 2023).

Discussion

The present study aimed to investigate the impact of relevant factors such as CR, disease duration, and motor disability on the cognitive efficiency of people with multiple sclerosis. It is well known that high levels of CR are associated with better cognitive performance in both healthy (Opdebeeck et al., 2016) and pathological people, such as those who have dementia (Nelson et al., 2021) or MS (Sumowski & Leavitt, 2013). Our results, obtained with a sample of 100 people with MS, are in line with what has already been reported in the literature (Heled et al., 2021; Tremblay et al., 2020): cognitive efficiency is negatively correlated with the duration of the disease and motor disability but positively correlated with CR. The added value of the present study is the methodological approach adopted. Indeed, the use of GAMs allowed us to consider the potentially complex interaction between different clinical variables and socio-demographic variables, at the same time disentangling their respective effects: controlling for age, the data showed that motor disability and the duration of the disease in interaction with CR were significant predictors of cognitive performance. These results confirm the positive effect of CR in predicting a better cognitive profile regardless of the duration of the disease and motor disability but not in the case of severe motor impairment (i.e., EDSS=6–7, corresponding to needing bilateral assistance to walk 100 m). As MS is a degenerative disorder, our findings (i.e., an extended positive effect of CR throughout the disease) are crucial since they suggest that patients with a high CR may maintain a suitable quality of life for longer. However, at a high level of motor impairment, CR is no longer protective and, at this point in the disease, a cognitive decline appears inevitable. In line with our results, Tremblay et al.'s (2023) research highlighted the modulating effect of CR on motor disability and underlined its effect on specific cognitive domains (i.e., visuospatial memory and processing speed); however, they had not considered disease duration, which we found to be an important clinical variable that we cannot neglect.

This positive effect of CR on cognitive health could be explained in terms of the corresponding brain reserve (including the richness of networks and dendritic spines, synaptic density, compensation mechanisms, and brain plasticity). In other words, CR strictly correlates to the variations of cerebral capacity according to the environment and plasticity processes. In particular, two processes are involved; the first is the one the healthy brain uses to execute various intellectual tasks, which implies a more efficient use of neural networks. The second, the compensatory mechanism, is activated in the event of brain injury, and the neural networks utilised for cognitive functions differ from those observed in individuals with a well-preserved neurological function. These brain/cognitive mechanisms support and maintain better cognitive efficiency (Stern et al., 2020).

The present cross-sectional investigation is not exempt from limitations. First, MS is a progressive disorder, and any possible effect of CR over time should be further investigated through longitudinal observations, in which the clinical changes are systematically monitored. Secondly, neuroimaging data was not available for this study. However, on the one hand, using such data would have allowed us to characterise brain deterioration; on the other hand, GAMs provided a solid pool of information accounting for the complex interaction among different clinical variables. Other variables were possibly at play in our sample's cognitive health, such as perceived fatigue, type of medication, mood deflection, and psychological traits. These confounding factors have not been considered in the present study, and thus, further investigation will be necessary to deepen and examine the interaction between CR and cognitive MS symptoms. In addition, the cognitive assessment was conducted remotely, which may represent a possible limitation in the reliability of the cognitive measures. However, we adopted a standardised cognitive screening test (Tele-GEMS) administered by an expert psychologist. Tele-GEMS was explicitly designed for telephone-based assessment and has been proven to be equivalent to in-person cognitive screenings (Montemurro et al., 2023).

In conclusion, this study reveals that accounting for the interplay between CR and the duration of the disease, as well as between CR and motor disability, may explain a significant degree of variance in cognitive performance. Our results, which will be helpful to clinicians and researchers, indicate that high levels of CR are related to improved cognitive performance even in prolonged disease duration. However, severe motor disability may, at some point, attenuate this "protective effect".

1.3.4 Cognitive Reserve and Intellectual Developmental Disability[3]

Pucci, V., La Face, A., Kilpcera, B., & Mondini, S. Cognitive Reserve Proxies for Individuals with Intellectual Developmental Disability: a Scoping Review. Under review in The Journal of Applied Research in Intellectual Disability.

Introduction

Intellectual Developmental Disabilities (IDD; DSM 5, American Psychiatric Association, 2013) are neurodevelopmental disorders that begin in childhood and are characterised by impairment in conceptual, social, and practical living areas (Boat & Wu, 2015). The main characteristics of these conditions are significant limitations in intellectual functioning, adaptive behaviour functioning, and onset in developmental age (see ICD 11; World Health Organization, 2019).

Due to specific genetic and physiological risk factors (Munir, 2016), IDD is linked to a significant co-occurrence of mental, behavioural, and neurodevelopmental disorders (ICD-11, World Health Organization, 2019). For instance, individuals with IDD, especially those with Down Syndrome, are genetically predisposed to premature ageing (Batty et al., 2007; Janicki et al., 1999; Kilgour et al., 2010; Malegiannaki et al., 2019), and advanced age is the major risk factor for neurodegenerative diseases (Hou et al., 2019). As a result, the increase in life expectancy among people with IDD has led to a considerably increased risk of dementia (Coppus, 2013).

The prevalence of Alzheimer's disease in people with IDD is almost three times greater than in the general population (Strydom et al., 2007), and the onset occurs on average ten years earlier (Dodd et al., 2008). According to Cooper et al. (2004), some people with IDD never exhibit the clinical signs of dementia, although almost all of them exhibit neuropathology consistent with Alzheimer's disease by the age of 40. In other words, there is not always a

[3]This part of the project took place at the University of Graz; Karl-Franzens-Universität, Institute of Education Research and Teacher Education. Country: Austria. Address: Merangasse 70/II, Graz.

linear link between the degree of brain damage and the severity of the symptomatology (Arvio & Bjelogrlic-Laakso, 2021).

As already reported in the previous chapters of this Thesis (see Chapter 1.1), in the general population, this discrepancy between clinical symptoms and brain damage has been explained using the concept of Cognitive Reserve (CR; Stern, 2009). CR, indeed, may account for the adaptability of cognitive processes to pathology or insult and to age-related changes, and it refers to knowledge, abilities and skills acquired during the lifespan (Stern et al., 2020).

One of the underpinning processes of the CR is brain neuroplasticity, defined as the ability to create new neuronal pathways in response to personal experiences during the lifespan (Cramer et al., 2011; Fuchs & Flügge, 2014). Evidence of neuroplasticity has also been found in people with IDD, proven through behavioural as well as neuropsychological measures (Lifshitz & Rand, 1999). This means that also people with IDD may accumulate CR and benefit from its protective effects later in life. Despite this, to the best of our knowledge, the concept of CR has never been systematically studied in this population.

Considering the growing importance of providing care for people with dementia and IDD, it is essential to ascertain which lifestyle factors (CR proxies) may offer them primary protection against dementia. Currently, instruments for estimating CR rely on proxies such as educational attainment, level of responsibility and cognitive demands in the workplace, engagement in intellectually stimulating hobbies, caring for relatives or children, financial management, and other similar factors (e.g., Nucci et al., 2012). However, given that the experiences of people with IDD often differ from those of the general population, those CR proxies may not be suitable for them (Dodd et al., 2008). For example, a high percentage of these people are unmarried (marriage estimates rate: 5%; Beber & Biswas, 2009), have no children (e.g., the fertility rate of women with IDD is 19%, Rubenstein et al., 2022), or are not in paid employment (20% are in paid employment, Bell, 2020; Innes et al., 2012). They often have fewer possibilities and opportunities to engage in cognitively stimulating activities (Arvio & Bjelogrlic-Laakso, 2021) or complex jobs. They usually engage in passive leisure activities when assistance and support are unavailable (Reppermund & Trollor, 2016).

For these reasons, the CR proxies used for the general population may not be sensitive to detect interpersonal differences in this population, and other proxies could be highly relevant when estimating the CR of a person with IDD. On this ground, the present scoping review aimed to identify lifestyle factors that contribute to CR in people with IDD.

Methods

In this study, we explored the concept of CR in IDD using Arksey & O'Malley's (2005) scoping review methodology. Scoping reviews aim «to map rapidly the key concepts underpinning a research area and the main sources and types of evidence available, and can be undertaken as stand-alone projects in their own right, especially where an area is complex or has not been reviewed comprehensively before» (Mays et al., 2001; p. 194). Our review follows the 5-stage structure of such an approach: (1) identifying the initial research question, (2) selecting studies on the topic, (3) choosing the relevant studies, (4) charting the data, and (5) collecting, summarising, and reporting results. This approach guarantees transparency by facilitating the replicability of the search strategy. The screening process is in line with the PRISMA-ScR guidelines (Page et al., 2021).

Identifying the initial research question

The present review aims to identify lifestyle factors that may enhance CR in individuals with IDD. Therefore, the aim was to systematise the primary sources of inter-individual variability in the daily activities and experiences of people with IDD. We then selected the variables found to positively affect cognitive function and/or those leading to improvements in daily functioning.

Selecting studies on the topic

Arksey and O'Malley (2005) suggest that a wide array of keywords for search terms be adopted in order to glean broad coverage of the available literature. The following search terms were therefore entered into the databases Scopus and PubMed:

(“Intellectual Disabilit” OR “Down Syndrome” OR “mental retardation” OR ”cognitive disabilit*” OR “profound intellectual disabilit*”) AND (“cognitive reserve" OR “education" OR "physical activit*" OR “lifestyle” OR ”compensation theory” OR “leisure” OR “daily function*” OR “cognitive activit*” OR “stimulating activit*” OR “recreational activit*”) AND ("Adult*" OR “Aging” OR “Ageing” OR “Elder*”) AND (“psycholog*” OR “neuropsycholog*” OR “sociolog*”)*.

The search fields comprised title, abstract and keywords for Scopus, and title and abstract for PubMed. No date limit was set. Only full-text contributions and peer-reviewed in English were considered. Contributions from non-psychology-related fields were excluded. Searches were re-run prior to charting the data. We included studies on adults with IDD where possible CR proxies were considered in relation to the cognitive outcome (i.e., cognitive efficiency or everyday functioning). We also included relevant outcomes from studies conducted using theoretical frameworks other than the CR theory (e.g., the Compensation Age Theory, Lifshit et al., 2020).

Choosing the relevant studies

The search strategy identified N=1239 potentially relevant articles (search run on June 10, 2022). After duplicate removal, N=1103 articles were screened independently by two authors (V.P. and A.L.F.), experts in CR and cognitive impairment in IDD. Selections were recorded via Rayyan (https://rayyan.qcri.org/welcome). N=1002 contributions were excluded as they met one or more of the following exclusion criteria: 1) unsuitable study type (review or meta-analysis); 2) unsuitable population (e.g., samples consisted of parents/siblings/caregivers of people with IDD or people with IDD under the age of 18); 3) irrelevant outcome (i.e., studies not focused on cognitive efficiency as one of the outcomes); 4) no CR proxies; 5) full text not available. The two authors were blinded to each other's decisions, and a third independent rater resolved disagreements (B.G.K).

The same authors independently assessed the eligibility of the remaining N=102 contributions. A template for standardised data extraction and data coding processes was collaboratively created prior to the full-text review, and the contributions were then read entirely against inclusion criteria. Any discrepancies between authors were discussed until a consensus was reached. Communication between authors throughout the screening process strengthened the eligibility criteria. N=85 articles were excluded after screening for eligibility, and N=17 were included in the present scoping review.

The data extracted were recorded on an Excel spreadsheet, which showed the first author and year of publication, type of study, country of the study, number of participants, biographical information of the participants, clinical features of participants (e.g., diagnosis, severity, IQ), CR proxies (e.g., education, occupation, physical activity), outcomes (cognitive functioning; quality of life), link/correlation between CR proxies and outcomes. The screening process followed the PRISMA-ScR guidelines and is illustrated in the flow chart in Figure 15.

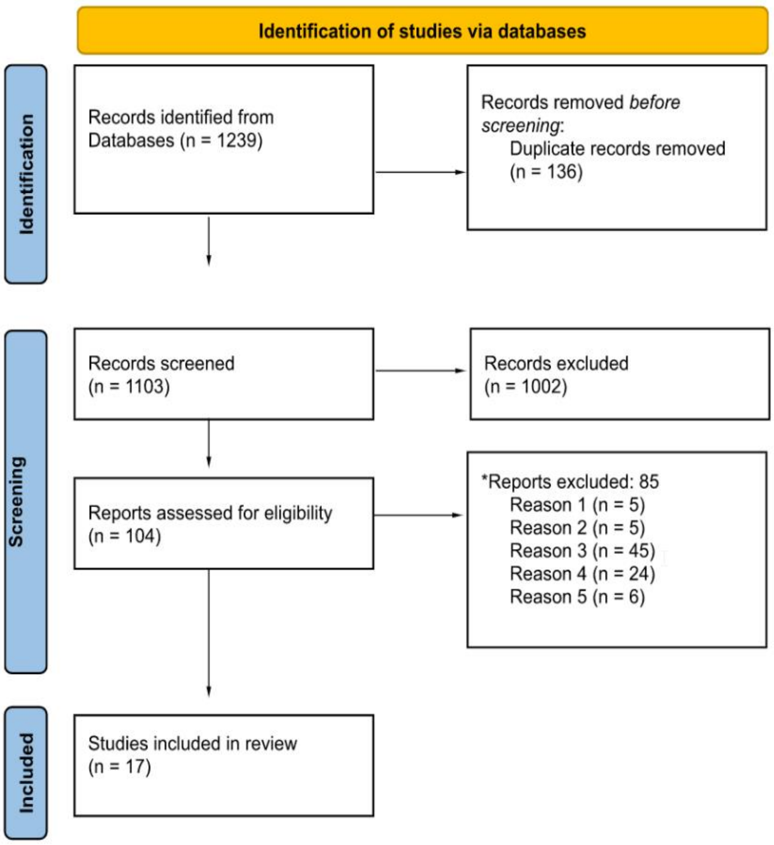

Figure 15. PRISMA 2020 flow diagram. *Note.* Reason 1=study type (Review or Meta-analysis); Reason 2=population (no sample with IDD); Reason 3=outcome (no cognitive outcome); Reason 4=No proxies of cognitive reserve; Reason 5=No full text available. Figure adapted from Page et al., 2020.

Charting the data

A qualitative and narrative summary of findings is reported in Table 13. For each of the 17 papers, the following information is reported: author and year of publication, country, main sample´s features, ID aetiology, CR proxies, outcomes, and main findings.

#	Authors and year	Type of study	Country	Population N (M/F)	IDD aetiology and associated conditions	Proxies of CR	Outcomes	Main findings
1	**Belfiore et al., 1993**	Cross-Sectional and Observational	USA	4 (3/1) individuals with profound IDD	NA	**Environmental stimulation:** a) more than 15 people present throughout the 20-minute session; (b) above-normal indoor lighting was maintained; (c) a jukebox, radio, or television was audible.	**Observed adaptive behaviour:** Eye contact, inactivity, head orienting to a specific stimulus, movement without orienting.	In high-stimulating community settings, participants showed more adaptive behaviours.
2	**Biggs et al., 2016**	Cross-Sectional	USA	389 caregivers of 389 (271/118) individuals with IDD or autistic spectrum disorder aged 13-21 (M=16.4; SD=2.5)	IDD (N=157; 89/68) autistic spectrum disorder (N=232; 182/50)	**Community activities:** out-of-school activities´ frequency reported by caregivers.	**Quality Of Life** (Physical well-being, Mood, Autonomy, social supports, daily activity) KIDSCREEN-27 (Ravens-Sieberer et al., 2007) **Functional Abilities:** 4-item scale developed for the National Longitudinal Transition Study-2 **Support needs** (scale adapted by Lee et al., 2008).	Frequency of Community Activities positively correlates with functional Abilities and negatively correlates with support needed.
3	**Chen et al., 2015**	Cross-Sectional	USA	20 (15/17) individuals with IDD aged 15-30 (M=20.6; SD= 5.7)	Down Syndrome	**Physical Activity**: 20-min of treadmill walking at moderate intensity	**Executive functions**: Attention shifting (Dimensional Change Card Sort Test; Zelazo, 2006); Inhibition (The Knock-Tap; NEPSY, Korkman et al., 1998); Choice-response time	Improved inhibition performance after the intervention.
4	**Couzens et al., 2012**	Longitudinal	Australia	89 (48/41) individuals with IDD	Down Syndrome	**Maternal Educational Level:** demographic questionnaire **Type of schooling:** segregated special school, special class or unit in a regular school, regular class with ‘pull-out’ supports, inclusive class	**Cognitive functioning** (Stanford-Binet IV, Couzens et al., 2004)**:** Fluid abilities (Memory for Sentences, Pattern Analysis, Bead Memory) and Crystallized abilities (Vocabulary, Comprehension, Quantitative)	Better cognitive outcome related to higher maternal educational Level and attendance at regular elementary school

5	**Dressler et al., 2021**	Cross-Sectional	Italy	54 (32/22) individuals with IDD aged 16-52 (M=28.6; DS=8.8)	Down Syndrome	**Type of schooling:** Inclusive schooling **Parents´ educational level**	**Adaptive Functioning:** Vineland Adaptive Behavior Scales (Communication; Daily Living Skills, Socialization; Sparrow et al., 2003) **Cognitive functioning:** Raven's Coloured Progressive Matrices (CPM; Lifshit et al., 2020) **Occupation** **Social participation**	Better adaptive functioning related to attendance of inclusive schooling and higher maternal educational level.
6	**Fleming et al., 2021**	Cross-Sectional	USA	61 (28/33) individuals with IDD aged 22-55 (M=37.5, SD=7.9)	Down Syndrome	**Physical activity in everyday life:** data from accelerometer	**Cognitive functioning:** Memory (The Cued Recall Test; Zimmerli & Devenny, 1995); Executive functioning (The Stroop Dog and Cat Task; Nash & Snowling, 2008); Visuospatial ability (Block Design; Wechsler, 2004 and Haxby extension; Haxby, 1989); Motor planning and control (The Purdue Pegboard; Vega, 1969); Dementia Symptoms (Down Syndrome Mental Status Examination; Haxby,1989 and Dementia Questionnaire for People with Learning Disabilities; Evenhuis, 2018) **Alzheimer Disease´s biomarker**: PET Aβ, tau PET; WM integrity	A higher amount of physical activity related to higher executive functioning, higher episodic memory, higher visuospatial construction ability and fewer symptoms of dementia.
7	**Haddad et al., 2018**	Cross-Sectional	Australia	175 (97/78) caregivers of individuals with IDD aged 16-31 (M=23.6)	Down Syndrome	**Sociodemographic factors**: Parents´ education; Occupation (full-time work, part-time work, not working) and Savings (No savings; a bit every now and again; a lot) **Friendships**: (no friends; 1-2 friends; 3 or more friends) **Physical activity:** weekly frequency **Daily occupation**: in an open work environment; in a sheltered service environment; post-secondary classes.	**Health-related quality of life:** Kidscreen-27 Parent Proxy Report (Physical well-being, Mood, Autonomy, social supports, daily activity; Bourke et al., 2008) **Functioning in activities of daily living** (ADL): Index of Social Competence (Communication Skills, Community skills, Self-care McConkey & Walsh, 1982)	Better health-related quality of life is related to physical activity 3 or more days per week; three or more friends, family savings; occupation in a sheltered service environment and better functioning In activities In daily life.

8	**Kenshole et al., 2017**	Cross-Sectional	UK	57 (38/19) individuals with IDD aged 46–78 (M=57.5)	Down Syndrome (N=30); Down Syndrome + Alzheimer Disease (N=27)	**Physical Activity:** high/Moderate/ Low level **Current and Past Living Place(s):** independent living/supported living (with relatives or in supported living accommodation); institutionalized living (in residential accommodation) **Education** **Occupation**: yes/no **Cognitive activity:** High/Moderate/ Low level	**Cognitive functioning:** British Picture Vocabulary Scale (severity of learning disability: mild, moderate, severe; Dunn et al., 1997)	Better cognitive functioning related to higher levels of cognitive activity.
9	**Lifshitz-Vahav et al., 2016**	Cross-Sectional	Israel	32 (18/14) individuals with IDD aged 22-55 (M=40.9, SD=8.9)	NS (N=18); Down Syndrome (N=14)	**Participation in Cognitively Stimulating Activities**: cognitive activity (e.g., chess, checkers, or cards, reading, using laptops, participating in academic courses, drama), Leisure activity (e.g., listening to the radio, watching TV, dancing, music, sports, karaoke, cooking, pet care).	**Cognitive functioning: Fluid abilities** (Trail Making Test Reitan, 1955; Homophone Meaning Generation Test, Mashal & Kasirer, 2011; Metaphoric Triad Test, Kogan et al., 1980; Novel Metaphors Test, Mashal & Kasirer, 2011); **Crystallized abilities:** (Phonemic fluency, Kavé et al., 2010; Synonyms, Glanz, 1989; Idiom comprehension, Mashal & Kasirer, 2011; Conventional Verbal Metaphor, Mashal & Kasirer, 2011; The Standard Progressive Matrices, Raven et al., 1986)	Higher cognitive and recreational activities correlate with higher crystallized and fluid abilities.
10	**Lifshitz-Vahav et al., 2021**	Cross-Sectional	Israel	80 (38/42) individuals with IDD aged 16-69	Down Syndrome	**Leisure activities´ frequency and cognitive load**: Participation in Cognitively Stimulating Activities Questionnaire (Lifshitz-Vahav et al., 2016). High-stimulation activities: playing cards, checkers or chess, radio listening, TV watching, socializing, reading, using technologies, attending courses, acting, drawing, painting, and photography.	**Cognitive functioning: Fluid abilities** (Vocabulary and Similarities, WAIS-III HEB, Wechsler, 2001); **Crystallized abilities** (Block Design, WAIS-III HEB, Wechsler, 2001; Raven Standard Progressive Matrices; Raven et al., 1986)	Participation in highly cognitively stimulating leisure activities contributed positively to crystallized and fluid abilities.

						Low-stimulation activities: listening to music, dancing, making jewellery, gardening, doing sports, karaoke, cooking/baking, and pet care.		
11	**Mihaila et al., 2019**	Longitudinal	USA	65 (34/31) individuals with IDD aged 30-54 (M=37.9, SD=7.4)	Down Syndrome	**Sociodemographic information:** Mental age (Stanford-Binet, Fifth Edition Abbreviated Battery, Janzen et al., 2004; Type of residence (Family; Group home; Supported apartment; Independently); Occupation (Full or part-time; Full or part-time with support; Supported workshop; Volunteer; Not employed) **Frequency of participation in leisure activities (Physical and Social)**: Victoria Longitudinal Study Questionnaire (Jopp & Hertzog, 2007)	**Cognitive functioning:** Episodic memory (Cued Recall Test, Zimmerli & Devenny, 1995; Pictures Recognition, (Wilson et al., 1991) **Brain β-amyloid**: pet-scan	Higher frequency of cognitively stimulating activities related to better episodic memory at baseline. Higher frequency of social and cognitively stimulating activities related to smaller declines in episodic memory from baseline to follow-up. β-amyloid accumulation was related to fewer episodic memory decline.
12	**Ptomey et al., 2018**	Cross-Sectional and Case-Control	USA	27 (16/11) individuals with IDD aged 18-35 years (M=27.9; SD=7.3)	Down Syndrome	**Physical exercise**: 12-week at-home group program (1 session per week vs. 2 sessions per week)	**Cognitive functioning:** Cantab dementia battery for iPad (Égerházi et al., 2007; reaction time, pair associated learning, attention switching task)	2 sessions/week condition related to better performance in the Paired Associates Learning tasks, the attention switching task and reaction time.

13	**Raspa et al., 2018**	Cross-Sectional	USA and Portugal	732 parents of 1176 individuals with IDD aged 5-67 years (M=19.5; SD=11.1)	X-Fragile with and without Autism	**Measures of independence in daily living** **Occupation**: job in the community; sheltered workshop or work centre; volunteer job; adult day services **Living arrangement:** alone; with roommates; with parents; in a group home; in a residential facility.	**Functional academic skills:** Time and schedules, money, math, reading, writing. **Daily living skills**: hygiene, cooking, laundry, housekeeping, transportation, safety.	Functional academic and daily living skills predict having or not having a job in the community. Living alone or with a roommate is predicted by functional academic and daily living skills.
14	**Sinai et al., 2017**	Cross-Sectional	UK	251 individuals with IDD (139/112)	Down Syndrome + Alzheimer's Disease	**Living situation:** living with family or away from family	**Age at diagnosis of dementia:** time in years between date of diagnosis and date of birth **Survival rate:** time from the initial date of diagnosis of dementia until the date of death or last follow-up	Lower age at diagnosis of dementia is predicted by living with family. Survival rate is positively associated with earlier diagnosis of dementia, minor severity of IDD and living with family.
15	**van Schijndel-Speet et al., 2017**	Cross-Sectional and Case-Control	Ned	66 individuals with IDD aged 44–83 (M=58.2; SD=NA)	intellectual disability from mild to severe	**Physical activity**: 8 months physical activity and fitness program, 3 sessions/week at moderate intensity.	**Activity of Daily Living:** Barthel Index (Mahoney & Barthel, 1965) **Instrumental Activities of Daily Living:** Lawton IADL scale (Lawton & Brody, 1969). **Cognitive Functioning:** Dementia Questionnaire for Persons with Mental Retardation (Evenhuis, 1996).	Physical activity training correlated with an improvement in cognitive functioning.
16	**Azaiza et al., 2011**	Cross-Sectional	Israel	156 individuals with IDD aged 18-65 (M=29.9; SD=8.7)	intellectual disability	Participation in **Leisure Activities**	**Cognitive Functioning** **Activities of Daily Living (ADL)** and **Instrumental Activities of Daily Living (IADL)**	Participation in Leisure Activities correlates with ADL; IADL and Cognitive Functioning

17	**Temple et al., 2001**	Cross-Sectional	Canada	35 individuals with IDD aged 29- 67 (M=46; SD=NA)	Down Syndrome	**Frequency of recreational activities:** Residential Lifestyles Inventory (RLI; Kennedy et al., 1990) **Employment:** (1) no employment; (2) part-time in a workshop; (3) part-time in the community; (4) full-time in a workshop; (5) full-time with some competitive employment in the community; (6) full-time work with mostly competitive employment **Educational Level:** (1) no schooling; (2) finished grade school; (3) finished secondary school; (4) secondary school plus continuing education. **Years spent in an institution**	**Cognitive functioning:** personal information and orientation; confrontation naming (Boston Naming Test; Kaplan et al.1978), reading (Wide Range Achievement Test; Jastak & Wilkinson, 1984), vocabulary (Peabody Picture Vocabulary; Dunn & Dunn, 1997),verbal fluency (category fluency for animal sand names), memory (Fuld Object-Memory test; Fuld, 1981), visual motor ability (Visual Motor Integration Test; Beery & Buktenica, 1997), constructional ability (WISC-III block design; Wechsler, 1989), fine motor skills (hole foam pegboard), apraxia (tests of upper and lower limbs, whole body and bucco-facial), grip strength (Hand Dynamometer), adaptive behaviour (Adaptive Behaviour Scale; Nihira et al., 1974) **Dementia Symptoms**: Dementia Scale for Down Syndrome (Gedye 1995)	Cognitive functioning associated with a higher educational level, fewer years in an institution and more challenging employment.

Table 13. Description of the selected studies for the present Scoping Review.

Collecting, summarising, and reporting results

Studies description

Of the 17 studies included, 6 were conducted in the USA (35%), 3 in Israel (18%), 2 in Australia, 2 in the UK, 1 in Italy, 1 in the Netherlands, 1 in Portugal and 1 in Canada. Twelve studies were cross-sectional (71%), 2 longitudinal (12%), 2 case-control (12%), and 1 observational (6%). The 17 studies included 2737 individuals with IDD (777 Male, 527 Female, 1433 not reported), with an average age of 34.8 years (SD=NA; range=5-83). In 10 studies (59%), the participants were people with Down Syndrome; in 3 studies, people with not further specified IDD; in 2 studies, people with Down Syndrome and autistic spectrum disorders (ASD); in 1 study, people with ASD and IDD, and in 1 study with ASD and X-Fragile syndrome.

CR Proxies

Within the Cognitive Reserve (CR) framework, we considered all lifestyle factors proven to enhance or be associated with cognitive efficiency as CR proxies. Within the 17 studies, the following factors were identified as potential CR proxies: Environmental stimulation (N=1; 6%); Community and social activities (N=3; 18%); Physical activity (N=6; 36%); Parental educational level (N=3; 18%); Education (N=2; 12%); Type of schooling (N=2; 12%); Occupation (N=5; 29%); Living place (N=4; 24%) and Leisure activities (N=5; 29%). Further details of the proxies are given below, including how they were operationalised and the associated results. The order of their presentation follows the frequency of appearance in the selected paper.

Physical activity. Physical activity (PA) and physical exercise (PE) are bodily movements produced by skeletal muscles that result in energy expenditure. PE refers to structured and planned activities to improve or maintain physical fitness (Caspersen et al., 1985), while PA refers to any movement resulting from everyday activities that leads to a metabolic cost above the baseline (Bherer et al., 2013). Three studies examined the role of PE in delivering short-term training (Chen et al., 2015; Ptomey et al., 2018; van Schijndel-

Speet et al., 2017). Others focused on the amount of PA in everyday life, quantified via (a) accelerometers (Fleming et al., 2021), (b) weekly frequency (Haddad et al., 2018) and (c) PA intensity (Kenshole et al., 2017). Six studies found that the higher the level of PA, the better the cognitive functioning, specifically episodic memory (Fleming et al., 2021; Ptomey et al., 2018), visuoconstructional abilities (Fleming et al., 2021), executive functions (Chen et al., 2015; Fleming et al., 2021; Ptomey et al., 2018), and daily activities (Haddad et al., 2018).

Leisure activities. Four studies analysed the link between leisure activities and cognitive or functional outcomes. The focus was on the frequency of engaging in recreational activities (Mihaila et al., 2019; Temple et al., 2001), on the cognitive load of the activities (Lifshitz-Vahav et al., 2016) or on both variables (Azaiza et al., 2011). Results showed that engaging in leisure activities was associated with better cognitive performance cognitive (Azaiza et al., 2011; Lifshitz-Vahav et al., 2016; Mihaila et al., 2019) and with better functioning in daily life (Azaiza et al., 2011). One study found that highly cognitively stimulating activities had affected crystallised and fluid abilities, while lower cognitively stimulating leisure activities did not (Lifshitz et al., 2016).

Occupation. The variable Occupation was included in five of the analysed studies. Haddad and collaborators (2018) operationalised the variable in three categories: (a) full-time, (b) part-time and (c) not employed. Kenshole and collaborators (2017) used a dichotomous categorisation (occupation: yes/no). Mihaila and colleagues (2019) operationalised the variable in terms of 5 categories: (a) Full- or part-time job; (b) Full- or part-time job with support; (c) Supported workshop; (d) Volunteer; (e) Not employed. Raspa and colleagues (2018) distinguished between (a) jobs in the community; (b) sheltered workshops or work centres; (c) volunteer jobs; and (d) adult day services. Temple and colleagues (2001) operationalised the variable Occupation by considering different types of employment: (a) no employment; (b) part-time employment in a workshop; (c) part-time employment in the community; (d) full-time employment in a workshop; (e) full-time work with some competitive employment in the community; (f) full-time work with most competitive employment. Results showed that having a job positively affects cognitive and functional outcomes (Raspa et al., 2018). In turn, improvements in health-related quality of life were only found for those participants working in a sheltered environment (Haddad et al., 2018). In addition, the more challenging the employment, the stronger the positive effect on cognitive functioning (Temple et al., 2001).

Living place. Kenshole et al. (2017) operationalised Living place as a dichotomous variable: (a) independent living or supported living (with relatives or in supported living accommodations); (b) institutionalised living (in residential accommodations). Raspa and collaborators (2018) considered living arrangements such as living (a) alone, (b) with a roommate, (c) with parents, (d) in a group home or (e) in a residential treatment facility. Sinai et al. (2017) differentiated between living with or away from the family. Lastly, Temple et al. (2001) examined the years spent in an institution. Results showed that living alone, with families or roommates, was linked to better daily living skills (Raspa et al., 2018). Furthermore, living with the family, in contrast to living in an institutional setting, allowed for better health care, earlier detection of cognitive impairments and earlier diagnosis of dementia, resulting in a higher survival rate after diagnosis (Sinai et al., 2017). In line with these results, Temple et al. (2001) found that the fewer years spent in an institution, the better the overall cognitive functioning.

Parental educational level. Two studies considered the years of education of both parents (Dressler et al., 2021; Haddad et al., 2018), and one only considered the maternal educational level (Couzens et al., 2012). Results showed that parental educational level correlated with the child's health-related quality of life (Haddad et al., 2018) and that the higher the mother's education, the better the child's cognitive functioning (Couzens et al., 2012; Dressler et al., 2021).

Community and Social activities. Activities carried out outside the educational or working environment were clusterised within Community and Social activities. Biggs et al. (2016) considered the frequency of out-of-school activities during the week. Haddad and colleagues (2018) considered the variable Friendships on three levels: no friends; 1-2 friends; 3 or more friends. Mihaila et al. (2019) considered the frequency of participation in social activities. These studies found that being more engaged in community activities positively correlated with functional abilities in everyday life and negatively correlated with the need for support in primary care (Lee et al., 2008). Moreover, Biggs et al. (2016) showed that a higher number of friends was correlated with better health-related quality of life, including physical well-being, mood, autonomy in daily activities and social support (Kidscreen-27 Parent Proxy Report; Bourke et al., 2008). In a PET study, Mihaila and collaborators (2019) showed that more frequent participation in social activities was related to a smaller decline in episodic memory over time and moderated the association between β-amyloid accumulation and episodic memory decline.

Education. The variable Education was operationalised as years of education (Kenshole et al., 2017) and as a categorical variable: (a) no schooling; (b) graded school; (c) secondary school; (d) secondary school plus continuing education (Temple et al., 2001). Temple and colleagues (2001) found that a higher educational level was related to better cognitive outcomes.

Type of schooling. The variable Type of schooling was operationalised in one study (Couzens et al., 2012) in four categories, depending on different approaches of teaching: (a) segregated special school; (b) special class or unit in a regular school; (c) regular class with “pull-out” support; (d) inclusive class. Dressler and colleagues (2021) asked their participants whether a special school (characterised by the presence of a support teacher or by specific and individual treatments) had been attended. Attending an inclusive regular school was shown to be linked to better adaptive functioning (Dressler et al., 2021) and better cognitive outcomes (Couzens et al., 2012).

Environmental stimulation. According to Belfiore and collaborators (1993), an environment is considered stimulating when (a) more than 15 people are present, (b) above-normal indoor lighting is maintained, and (c) a jukebox, radio, and/or television is audible. In this observational study, the authors found that in high-stimulating environments, participants with severe IDD showed more adaptive behaviours (e.g., orienting their heads towards a specific stimulus and making eye contact).

Discussion

The results of this scoping review broadly picture all lifestyle factors and life experiences that positively correlate with cognitive performance or daily functioning in people with IDD. These variables have been considered possible proxies of CR for the population with IDD, even when not explicitly labelled as such in the studies included in the review.

Some of the proxies identified overlap with those commonly adopted to quantify CR in the general population: Physical activity, Leisure activities, Occupation, Community and Social activities, and Education (see, for example, the Cognitive Reserve Index questionnaire; Nucci et al., 2012). Other identified CR proxies are generally not considered as such for the general population, and they might represent specific CR proxies for individuals with IDD: Living place, Parental educational level, Type of schooling and Environmental stimulation. All found proxies and their adaptation for people with Intellectual Developmental Disability will be discussed below.

The most frequently considered proxy in the studies included in this review is Physical activity (PA). PA has been shown in six studies to be associated with the cognitive efficiency of individuals with IDD, and it may increase their CR in the same way it does for individuals without IDD (Cheng, 2016). The contribution of PA to CR has already been largely highlighted (Amato et al., 2010): PA can boost cognitive performance by producing better brain oxygenation (Umegaki et al., 2021). However, the level of PA of people with IDD generally does not meet that recommended by the World Health Organization (Goenarjo et al., 2020). In fact, for people living with disability, the WHO recommends at least 150–300 minutes of moderate-intensity aerobic physical activity a week, muscle-strengthening activities at a moderate or greater intensity that involve all major muscle groups two or more days a week. As shown by several reviews (Bossink et al., 2017; Jacinto et al., 2021; McGarty & Melville, 2018), the prevailing sedentary lifestyle in this population is attributed to numerous physical and social barriers that hinder their possibility to engage in physical exercise. Therefore, it might be necessary to consider the level of structured PA and incidental PA (e.g., walking, manual labour, household activities) when operationalising this proxy of CR for people with IDD. By doing so, it would be possible to differentiate levels of CR between people whose cognitive or motor impairments limit their range of activities.

The second most frequently mentioned proxy in the studies identified in the review is Leisure activities. It was considered in terms of frequency and cognitive load of the activities carried out, as done for the general population (Anstey & Christensen, 2014). However, given the high inter-individual variability of the cognitive abilities of people with IDD, a broader range of activities should be considered, particularly those with low cognitive demand. It would allow distinguishing CR levels in people with different severity of disability.

Occupation, a pivotal proxy of CR in the population without IDD (e.g., Mondini et al., 2022), has been shown to be a possible proxy of CR in people with IDD. Usually, the cognitive load and level of responsibility of the job are considered when estimating CR. However, for people with IDD, other job features may additionally influence the level of CR. Worthy of consideration might be, for example, the amount of time spent at work (part-time or full-time jobs, Haddad et al., 2018), the amount of autonomy (working with or without support; Mihaila et al., 2019), and working with other people or alone (Raspa et al., 2018). Even having or not having a job may make a difference in determining CR variability in people with IDD.

Community and social activities are often considered CR proxies in the population without IDD (Harrison et al., 2015), and they are usually operationalised in terms of frequency of practice and cognitive load. However, other features of social life should be considered for people with IDD. For example, Haddad and colleagues (2018) found that the number and quality of friendships positively affect the cognitive and functional outcomes of people with IDD.

Education is the most widespread proxy for estimating CR, and it has repeatedly been shown to be linked to overall cognitive functioning (Anstey & Christensen, 2014). Generally, education is quantified in terms of level or years of education. However, for people with IDD, education should also be considered in terms of the Type of schooling (e.g., regular, or special education), an additional proxy found in the selected studies. In the present review, two studies found a difference in the cognitive outcome of people with IDD depending on the type of school attended: segregated special school, special class or unit in a regular school, regular class with “pull-out” support, inclusive class, special school with the presence of a support teacher, and specific and individual treatments (Couzens et al., 2012; Dressler et al., 2021). Attending an inclusive regular school was linked to better adaptive functioning (Dressler et al., 2021) and better cognitive performance (Couzens et al., 2012). These results are in line with some other evidence from the literature: longitudinal studies show that students with special educational needs achieve better school performance in integrative educational settings (Myklebust, 2006), probably because inclusive schools offer a richer social and language environment (Guralnick & Weinhouse, 1984; Law et al., 1996). Segregated education services offer unique advantages, like a more individualised education, small class sizes, specialised teachers, and emphasis on functional skills (Kauffman, 1994). However, empirical assessments of the advantages and disadvantages of the two forms of education still need to be more consistent and satisfactory (Gasteiger-Klicpera et al., 2013). In addition, their respective potential to enhance CR has not been investigated yet. Further investigation is necessary to disentangle the benefits offered by attending different school settings to build CR in people with IDD.

The parents' educational level affects the cognitive and adaptive functioning of their kid with IDD, in addition to the child's education. Parental education and socio-economic level indirectly shape children's environment and experiences during development (Baranyi et al., 2022; Conte et al., 2023; Kessler et al., 2010). However, while this variable is not always considered a relevant proxy of CR for adults without intellectual disabilities, it has been found in three of the included studies to be potentially relevant for the CR of people with IDD. Parents of children with IDD are likely involved more directly, persistently and over a more prolonged period in their children's choices than parents of children without IDD. Parents with higher education may be more prone to let their children join social and physical activities and be more effective in promoting their development than parents with lower education (Szumski et al., 2018; Vilaseca et al., 2019). Evidence shows that parental education correlates positively with health-related quality-of-life measures for people with IDD (Haddad et al., 2018). However, in two studies included in this review (Couzens et al., 2012; Dressler et al., 2021), only the maternal educational level, positively correlated with their children's cognitive functioning. Maternal education is indeed known in the literature to be strongly related to children's language, cognitive and academic development (Magnuson et al., 2009). The disparity observed between the influence exerted by mothers and fathers on their children's development may be explained by the fact that mothers usually spend more time with their children and take more responsibility for childcare than fathers, thus possibly having a greater influence on their children's development. However, this conventional mother-based caring of children is progressively changing among the new generations (Perry-Jenkins & Gerstel, 2020). The more recent model of roles within families could make this advantage of the mother's influence on the child's development no longer of significance. Despite distinctions based on the historical and socio-cultural context, it is undeniable that the educational level of parents (and their socio-economic level and resources in general) has an impact on parents´ involvement in their children's lives, environmental enrichment, learning experiences and quality of childcare (Conte et al., 2023). Given that individuals with IDD typically have more extensive interactions with their parents, it makes sense for this demographic to consider the parents' educational level when determining the child's CR. To sum up, the educational level of both parents and the primary caregiver(s) could be considered a proxy of CR in this population, as it is linked to a more cognitively stimulating environment, especially during the most sensitive developmental period.

The variable Living place can be interpreted as a possible proxy of CR based on the results of four studies included in this review. These underlined a link between more autonomous living settings and better cognitive functioning and skills in daily living (Kenshole et al., 2017; Raspa et al., 2018; Sinai et al., 2017; Temple et al., 2001). However, due to the cross-sectional nature of these studies, it is impossible to determine the direction of this relationship. On the one hand, it is reasonable to assume that living in a non-institutional setting (independently, with a flatmate or with family) may provide a greater number of opportunities for cognitive stimulation and self-determination, thus enhancing the cognitive and functional outcomes of the person (Ansado et al., 2013; Stancliffe et al., 2007). On the other hand, people with IDD with a higher level of cognitive functioning at baseline are more likely to live independently (Nota et al., 2007). People with severe impairment, with a lower level of functioning at baseline, generally need constant professional support and are more likely to live in an institution. Longitudinal studies are therefore still needed to identify which specific living conditions may contribute to the CR of individuals with IDD.

Different living places might also offer different levels of environmental stimulation, for example, depending on the number of flatmates, the noise and light level or the presence of television or radio. In one study (Belfiore et al., 1993), these features of the living place were related to the functioning of people with severe IDD, thus being a possible proxy of CR for them. While it may be assumed that this proxy is also relevant for people without IDD, in the study just mentioned above (e.g., listening to music, type of lighting, and number of people present in a room), this is likely to be particularly relevant for people with severe IDD, who are generally less able to actively engage in activities that enhance CR and might benefit from passive stimulation.

Although this scoping review provides valuable insights into the proxies of CR for people with IDD, some proxies, such as Living place, Type of schooling and Occupation, may partially overlap with the degree of intellectual disability. Individuals with a higher level of cognitive functioning at baseline may have more chances to get a high-responsibility job, to be able to live independently in non-institutional settings or to be educated in regular schools. Nonetheless, these proxies can be tailored by considering the baseline level of cognitive functioning. At an equivalent level of cognitive functioning, this approach would allow for differentiation of the factors contributing to increasing CR.

Conclusion

The present scoping review is the first step towards the systematic study of Cognitive Reserve in the population with Intellectual Developmental Disability. This nascent field of research aims to allow people with IDD to exercise their rights to healthy ageing and barrier-free participation in community life. Being aware of the lifestyle factors that enhance CR may allow professionals to promote lifestyle-related interventions supporting optimal ageing outcomes (Amoretti et al., 2019), especially in light of the high incidence and early onset of dementia among them. Life experiences and lifestyle choices are, in fact, among the primary sources of protection against cognitive decline, probably also for people with IDD (Arvio & Bjelogrlic-Laakso, 2021). Notably, community-based activities are most effective, as they foster social engagement and feelings of inclusion and belonging (Mihaila et al., 2019). Much more effort should therefore be devoted to overcoming the many barriers (e.g., lack of trained staff, insufficient supervision, and difficulties with physical access; Buttimer & Tierney, 2005) people with IDD meet every day to guarantee access to cognitively and socially stimulating activities that build CR. Developing evidence-based guidelines and interventions for people working with individuals with IDD is crucial. Professionals should be equipped with the knowledge and resources to support individuals with IDD in making healthy lifestyle choices that contribute to their cognitive health. By fostering interdisciplinary collaborations and partnerships, stakeholders can share knowledge, expertise, and resources to target the needs of this population by enhancing the opportunities offered by the specific socio-cultural contexts in which they live. The goal of this common work should be to enable individuals with IDD to age healthily, experience barrier-free participation in community life, promote cognitive well-being and enhance CR.

1.4 Cognitive Reserve and Neuropsychological Assessment

Introduction

According to Lezak and colleagues (2012), the goal of a neuropsychological assessment is to identify the presence, nature, and severity of cognitive dysfunction. Neuropsychological tests[4] aim to evaluate cognitive functions that are not directly observable (Mondini et al., 2023). The test score interpretation depends on reference values or cut-off scores, indicating a threshold below which the performance is considered impaired, signalling potential cognitive dysfunction (Gregory, 2015; Mitrushina et al., 2005; Piccininni et al., 2023). These cut-off scores are determined through normative samples that estimate the observed examinees' performance, considering factors known to influence cognitive efficiency. These factors in neuropsychological assessments usually include age, education, and sex (Strauss et al., 2006). However, other variables may be at play and influence cognition (e.g., socio-behavioural or socioeconomic factors; see Fratiglioni et al., 2004; Livingston et al., 2017; Mondini et al., 2022; Ward et al., 2015).

From this perspective, cognitive reserve may represents a more reliable and comprehensive measure of abilities and knowledge acquired during life (Stern & Barulli, 2009), and thus, a modulator of cognitive performance. CR is a crucial factor in explaining the variance between age-related brain alterations and pathological conditions. In essence, CR is instrumental in understanding differences in performance under similar brain conditions (Stern et al., 2020). Education, widely acknowledged as a proxy for estimating CR, has been extensively employed for this purpose (Borland et al., 2017; Busch & Chapin, 2008; Cesar et al., 2019; Malek-Ahmadi et al., 2015; Siciliano et al., 2019). However, despite the diffusion of education in quantifying CR, its validity has been challenged, as the CR mechanism is unlikely to be solely represented by the link between education and cognition in later life (Anatürk et al., 2021).

[4] A *neuropsychological test* is defined as a systematic procedure for observing and describing an individual's behaviour using numerical scales or category systems (Cronbach, 1970).

Several studies in this domain emphasize the role of a broad spectrum of enriching life experiences occurring throughout adulthood (Fratiglioni et al., 2004; Livingston et al., 2017; Reed et al., 2011; Ward et al., 2015). Key activities in this context encompass occupational attainment and leisure-time activities (Butler & Snowdon, 1996; Snowdon, 1997; Stern et al., 1995). Assessing the potential contribution of these lifestyle activities to CR involves considering the type of activity, the effort invested, and the frequency of engagement (Scarmeas et al., 2001; White et al., 1994). This evaluation applies to diverse responsibilities and demands associated with specific jobs and physical activities like sports that require regularity, resistance, and concentration or hobbies involving acquiring new skills, such as music or art courses.

Given the significance of considering education alongside other socio-demographic variables identified as protective factors in longitudinal studies (Mondini et al., 2022; Ward et al., 2015), it is strongly recommended to enhance the reliability of normative data by adopting a composite proxy for CR in the determination of cut-off scores.

As described in the Chapter 1.2.3 of the present Thesis, the Cognitive Reserve Index questionnaire (CRIq, Nucci et al., 2012) serves as a tool to estimate CR by incorporating education, occupational activity, and leisure-time activities, recognizing their crucial role in building CR (Chan et al., 2018; Livingston et al., 2017; Scarmeas & Stern, 2003; Stern et al., 1995; Ward et al., 2015). In fact, while education is a practical and easily quantifiable measure, it can only capture formal education and may lose effectiveness over time (Berggren et al., 2018). The CRIq holds the advantage of being a validated and standardised measure, and it has been repeatedly used in studies assessing the relationship between cognition and CR.

Given this background, test scores should be adjusted for CR rather than merely age and education to have a clearer and more precise picture of the examinees' performance. In the present chapter, four novel neuropsychological instruments will be presented and discussed, focusing on their common novel feature: the incorporation of the CR in the process of interpreting row scores. The aim was to enhance the accuracy and depth of neuropsychological assessment. Unlike conventional tools, these allow for comparing the row scores, considering not only age, education, and sex but also the individual's CR - a more comprehensive and reliable reflection of one's lifestyle and, thus, of their available cognitive resources.

Materials and Methods

Materials[5]

This section will briefly describe the four cognitive tests developed and validated, which considered the Cognitive Reserve of the examinees to generate and interpret cut-off scores.

Global Examination of Mental State (GEMS; Mondini et al., 2022)

GEMS is a cognitive screening test encompassing 11 tasks designed to assess various cognitive functions: orientation, memory, working memory, visuospatial and constructional abilities, planning abilities, perceptual and visual attention language skills, including naming, comprehension, verbal fluency, and pragmatics. GEMS is administrable in person and typically lasts 10 minutes. The screening provides a global score of cognitive efficiency (range: 1-100). GEMS is available online at the OSF link: https://osf.io/4t5a8, with instructions and an Excel file to convert the raw scores and cut-offs.

Tele-Global Examination of Mental State (Tele-GEMS; Montemurro et al., 2023)

Tele-GEMS is a cognitive screening test developed to be administered remotely via telephone or videoconference. Tele-GEMS mirrors GEMS's structure and items, assessing the same cognitive functions: orientation, memory, working memory, visuospatial and planning abilities, perceptual and attention language skills, including naming, comprehension, verbal fluency, and pragmatics. Some tasks were adapted to the remote administration. Tele-GEMS administration typically lasts 10 minutes and it provides a global score of cognitive efficiency

[5] Each cognitive test presented here is derived from a standalone work or paper: each instrument was developed and validated with a normative sample, and the psychometric properties were calculated individually. In the present thesis, they will be aggregated and presented, focusing only on the relationship between cognitive performance and cognitive reserve.

(range: 0-100). The materials are available online at the OSF link (https://osf.io/t3bma/) with instructions for the examiners, an Excel file to calculate Tele-GEMS total score, and cut-offs according to age, education, and Cognitive Reserve Index (CRI).

Auto-Global Examination of Mental State (Pucci et al., under review)

Auto-GEMS is a cognitive screening test developed to be self-administered via computer. Auto-GEMS mirrors GEMS and Tele-GEMS structure and items assessing the same cognitive functions: orientation, memory, working memory, visuospatial and constructional abilities, planning capabilities, perceptual and visual attention language skills, including naming, comprehension, verbal fluency, and pragmatics. Some tasks were adapted to be suitable for the self-administration. Auto-GEMS administration typically lasts 10 minutes. The screening provides a global score of cognitive efficiency (range: 0-100).

Esame Neuropsicologico Breve-3 (ENB-3; tr. Brief Neuropsychological Examination, Mondini et al., 2022)

ENB-3 is a neuropsychological test battery available in both paper-and-pencil and digital forms. ENB-3 includes sixteen tasks to assess different cognitive functions: Digit span (forwards and backwards); Immediate and Delayed; Interference memory at 10 seconds and 30 seconds; Trial making test, part A; Verbal commands; Phonemic fluency; Abstract reasoning; Cognitive estimation; Overlapping figures; Spontaneous drawing; Copy drawing; Clock drawing; and Praxis. The battery provides a score for each single cognitive task and a total score that reflects the overall cognitive profile. The ENB-3 administration lasts about 40 minutes. The battery provides a global score of cognitive efficiency (range: 0-100).

Participants

The four instruments have their specific normative sample from which psychometric properties and cut-offs were calculated. All the individuals (of all four samples) were recruited from different social groups, organisations, and other environments without connections with clinical settings. Inclusion criteria were age over 18, Italian mother tongue, and autonomy in daily living activities. People with neurological or psychiatric diseases were excluded. All participants were assessed with the specific cognitive test (GEMS, Tele-GEMS, Auto-GEMS or ENB-3) and with the Cognitive Reserve Index questionnaire (CRIq; Nucci et al., 2012 – see chapter 1.2.3 of the present thesis for a complete description of the questionnaire). All four samples were adequately distributed for age, education, and sex. In Table 14, the size and main features of the four samples are reported. All participants took part voluntarily in the study, signed the informed consent, and were aware they could stop and withdraw from the testing at any time.

The Ethical Committee of the School of Psychology (University of Padua) approved these studies, and they adhered to the Declaration of Helsinki.

Test	Sample size	Variable	Mean	SD	Median	Min	Max
GEMS	N=635	Age	51.8	21.5	54	18	98
		Education	12.8	4.9	13	0	25
		CRI	103.8	16.9	100	65	181
		GEMS Total	83.45	12.8	87.5	21	100
Tele GEMS	N=601	Age	51.5	19.3	54	18	93
		Education	13.8	4.7	13	0	30
		CRI	108.6	18.6	105	63	194
		Tele-GEMS Total	83.4	10.8	86	37	100
Auto-GEMS	N=1308	Age	51.2	18	55	18	93
		Education	13.3	4.1	13	5	21
		CRI	123.3	16.6	122	74	208
		Auto-GEMS Total	81.8	11.4	83.5	27.8	100
ENB-3	N=1051	Age	51.5	20.9	54	15	99
		Education	12.7	4.6	13	0	28
		CRI	107.8	17.9	104	63	184
		ENB-3 Total	77	13	80	25	98

Table 14. Descriptive statistics of the demographic features of the four samples and their scores for each cognitive task (GEMS, Tele-GEMS, Auto-GEMS and ENB-3). *Note.* GEMS=Global Examination of Mental State (Mondini et al., 2022); Tele-GEMS=Tele-Global Examination of Mental State (Montemurro et al., 2023); Auto-GEMS=Auto-Global Examination of Mental State (Pucci et al., under review); ENB-3=Esame Neuropsicologico Breve-3 (*tr.* Brief Neuropsychological Examination, Mondini et al., 2022); CRI=Cognitive Reserve Index (Nucci et al., 2012).

Statistical analysis

We calculated descriptive statistics of participants' features (age, education and CRI) and of their cognitive performance. Correlational analyses were performed using Pearson's *r* coefficient. We deeper assessed the relationship between age, sex, education, CRI, and cognitive performance (GEMS, Tele-GEMS, Auto-GEMS and ENB-3) by multiple regressions, entering the total score of the test as the dependent variable. Age, sex, education, and CRI were included in multiple regressions. The best model among the regression models was then visually inspected following the procedure used by Montemurro et al. (2022). We explored the possibility of improving the fit by allowing non-linear terms. We tested whether adding quadratic terms yielded better models for all the variables that showed a non-linear trend in inspecting partial residuals. The model with the lowest AIC was then chosen as the best one, and clinical cut-offs were obtained using the regression-based method by Crawford and Garthwaite (2007). The analyses were performed with the free statistical software R (R Core Team, 2022).

Results

GEMS

GEMS total score correlated negatively with age (r=-0.62, p<0.001), meaning that the younger participants performed better than the older. GEMS total score correlated positively with education (r=0.62, p<0.001) and CRI (r=0.27, p<0.001), meaning that the higher the education and the CRI, the better the performance. The relationship between age, sex, education, and CRI (as a proxy of CR) with GEMS was further assessed through multiple regressions, with the total GEMS score as the dependent variable. Age, education and CRI were included in multiple regressions as continuous predictors, whereas sex was included as a factorial variable. Results show that age, education, and CRI were significant predictors of GEMS, whereas sex had no effect. Age had a negative relationship with GEMS, whereas education and CRI had a positive one. Interestingly, the main effect of CRI was stronger than that of education. Visual inspection of the partial residuals indicated that age, education, and CRI were non-linearly related to GEMS. Models 4, 5 and 6 were thus built to check whether including nonlinear terms would improve the model fit. Model 6, including age, sex, and CRI, and the quadratic terms for age (age2), education (education2), and CRI (CRI2) showed the minimum loss of information (Burnham et al., 2011), and it was used for generating cut-offs. For more details, see Figure 16 and Table 15.

GEMS cut-offs were calculated using Crawford and Garthwaite's (2007) approach. Participant score is predicted from demographic variables (age, sex, education, and CRI) using Model 6, reported in Table 15. An essential feature of this method is that it considers the problem of the estimate for extreme values of the predictors, and it is specifically designed to compare a single case to a control group. The precise cut-offs for all possible combinations of sociodemographic variables (age, sex, education, and CRI) can be calculated using a Shiny App available on the OSF.

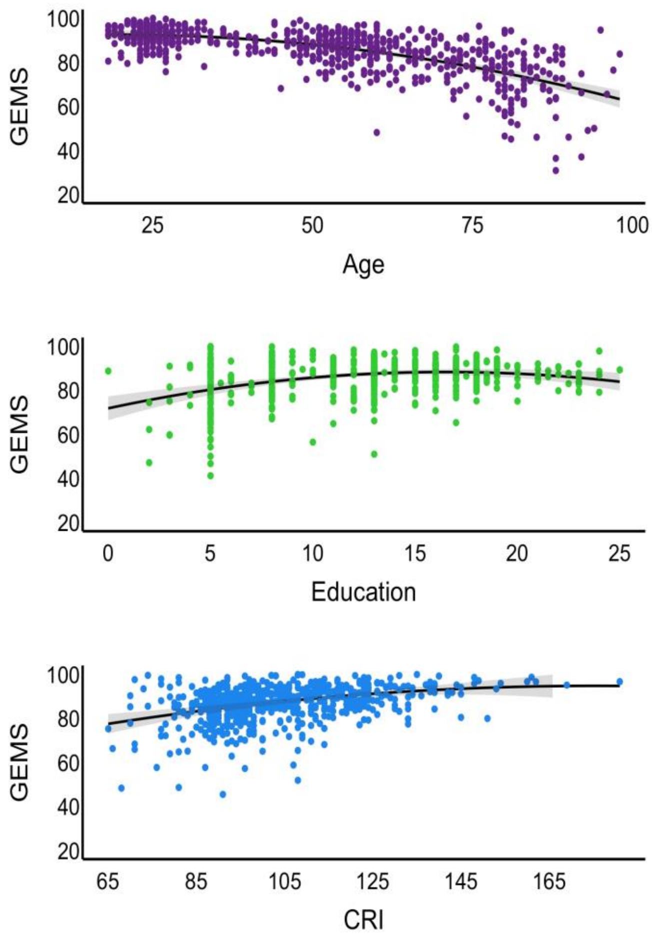

Figure 16. Effect of age, education, and cognitive reserve on GEMS scores. Age, education, and CRI are reported on the x-axis, and GEMS scores are reported on the y-axis. Quadratic terms of age, education, and CRI are included in the regression models. *Note.* GEMS=Global Examination of Mental State; CRI=Cognitive reserve Index.

Regression Models – dependent variable: GEMS score							
Model	Predictor	Beta (SE)	t-value	*p*	Adj. R^2	AICc (df)	AICw
Model 1	Intercept	103.32 (1.09)	94.94	<0.001*	0.392	4794 (4)	0.000
	Age	-0.37 (0.02)	-19.91	<0.001*			
	Sex	-1.43 (0.81)	-1.75	0.080			
Model 2	Intercept	83.26 (1.93)	43.11	<0.001*	0.504	4664 (5)	0.000
	Age	-0.24 (0.02)	-11.86	<0.001*			
	Sex	-1.58 (0.74)	-2.15	0.031*			
	Education	1.04 (0.09)	12.06	<0.001*			
Model 3	Intercept	71.40 (2.17)	32.78	<0.001*	0.568	4548 (6)	0.000
	Age	-0.38 (0.02)	-15.96	<0.001*			
	Sex	-0.52 (0.69)	-0.75	0.452			
	Education	0.25 (0.11)	2.19	0.028*			
	CRI	0.28 (0.02)	9.76	<0.001*			
Model 4	Intercept	64.56 (2.35)	27.47	<0.001*	0.596	4508 (7)	0.000
	Age	0.24 (0.09)	2.49	0.012*			
	Age^2	-0.0 (0.00)	-6.59	<0.001*			
	Sex	-0.49 (0.67)	-0.73	0.464			
	Education	0.34 (0.11)	3.04	0.002*			
	CRI	0.19 (0.03)	6.37	<0.001*			
Model 5	Intercept	4.64 (2.99)	18.26	<0.001*	0.612	4483 (8)	0.349
	Age	0.20 (0.09)	2.15	0.003*			
	Age^2	-0.0 (0.00)	-5.6	<0.001*			
	Sex	-0.07 (0.66)	-0.11	0.908			
	Education	2.19 (0.37)	5.87	<0.001*			
	Education^2	-0.06 (0.01)	-5.19	<0.001*			
	CRI	0.17 (0.03)	5.76	<0.001*			
Model 6	Intercept	39.00 (9.14)	4.26	<0.001*	0.612	4482 (9)	0.651
	Age	0.17 (0.09)	1.78	0.075			
	Age^2	-0.0 (0.00)	-5.23	<0.001*			
	Sex	-0.02 (0.66)	-0.03	0.971			
	Education	2.00 (0.38)	5.16	<0.001*			
	Education^2	-0.06 (0.01)	-4.51	<0.001*			
	CRI	0.49 (0.17)	2.75	0.005*			
	CRI^2	-0.0 (0.00)	-1.80	0.070			

Table 15. The Table reports the model name (first column); the intercept and the predictors entered in the regression model (second column); Beta (standard estimate) and standard error within brackets (third column); t-value associated with the model (fourth column); p-value associated with the model in

which asterisks indicate p-value minor of 0.05 (fifth column); adjusted R^2 associated with the model (sixth column); a modified version of the Akaike Information Criterion values (AICc, seventh column), in which the lowest the AICc value, the better the model fit; Akaike Weights associated with the model (AICw, eighth column): the probability of a model to be the best among the given set of models. *Note.* GEMS=Global Examination of Mental State; CRI=Cognitive reserve Index.

Tele-GEMS

Tele-GEMS score correlated with age (r=−0.53, p<.001), with education (r=0.51, p<.001), and with CRI (r=0.20, p<.001). To further assess the relationship between cognitive performance and age, education and CRI, we used a regression-based approach. Inspection of the partial residuals of a full model, i.e., with age, education, and CRI, showed that such predictors were non-linearly related to Tele-GEMS. Thus, subsequent regressions were performed to check whether including non-linear terms would improve the fit (see Table 16 for more details). The final model (model 6; F=89.55, p<.001, adjusted R^2=0.47) included age, education, CRI, and sex and non-linear terms for age and education (Figure 17). The results of this model can be summarised as follows: the higher the education, the better the Tele-GEMS score, with a decreased effect at the highest education levels, possibly due to the smaller size of observation at the highest range. Notably, the higher the CRI, the higher the Tele-GEMS score, indicating the relevance of CRI in explaining the variance of cognitive performance. Sex showed a non-significant effect on performance. All the predictors included in the final model were considered for the computation of cut-offs. We calculated clinical cut-offs by applying Crawford and Garthwaite's (2007) regression-based method to the results of model 6. Tele-GEMS scores associated with p=0.05 were rounded to the nearest integer to calculate these cut-offs. The materials to calculate the Tele-GEMS total score and obtain Cut-offs are available at the OSF link: https://osf.io/t3bma/.

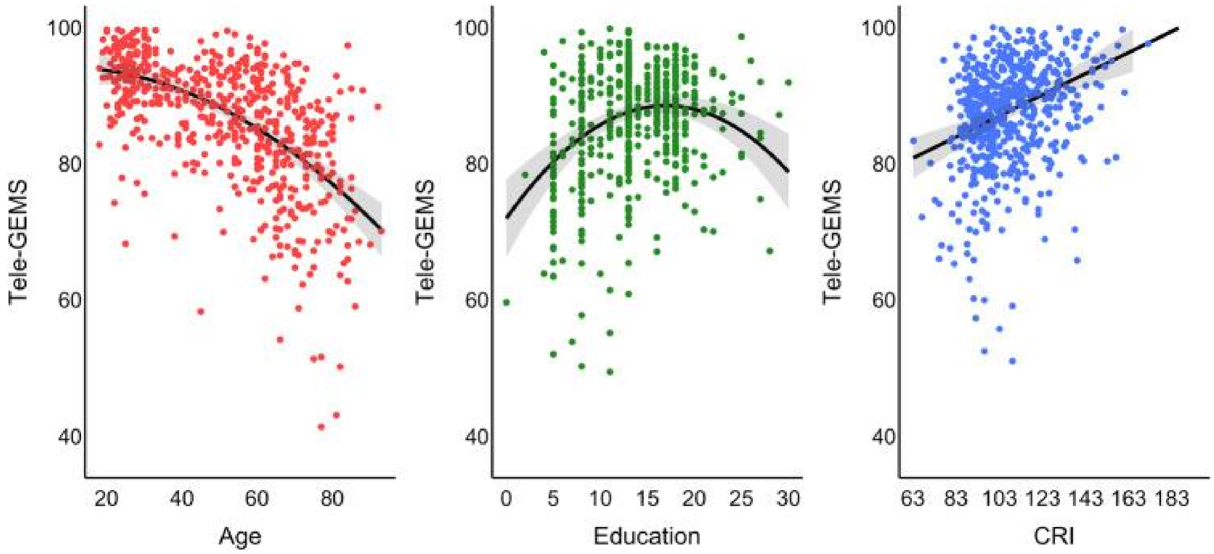

Figure 17. Effect of age, education, and the Cognitive Reserve Index (CRI) on Tele-GEMS total score. Age, education, and CRI are reported on the x-axis, while Tele-GEMS total score is reported on the y-axis. Quadratic terms of age and education are included in this figure, according to the final regression model, which best fits Tele-GEMS data. *Note.* Tele-GEMS=Tele-Global Examination of Mental State; CRI=Cognitive Reserve Index.

Regression Models – dependent variable: Tele-GEMS score						
Model	Predictor	Beta (SE)	t-value	*p*	Adj. R^2	AICc (df)
Model 1	Intercept	100.84 (1.12)	89.72	<0.001*	0.28	4374 (4)
	Age	-0.29 (0.01)	-15.19	<0.001*		
	Sex	-1.40 (0.75)	-0.53	0.59		
Model 2	Intercept	85.63 (1.84)	46.53	<0.001*	0.39	4226 (5)
	Age	-0.21 (0.01)	-11.10	<0.001*		
	Sex	-0.24 (0.69)	-0.35	0.072		
	Education	0.80 (0.08)	10.02	<0.001*		
Model 3	Intercept	78.13 (2.04)	38.26	<0.001*	0.43	4227 (6)
	Age	-0.34 (0.02)	-13.47	<0.001*		
	Sex	-0.02 (0.66)	0.03	0.970		
	Education	0.15 (0.11)	1.35	0.170		
	CRI	0.21 (0.02)	7.32	<0.001*		
Model 4	Intercept	71.33 (2.65)	26.88	<0.001*	0.45	4213 (7)
	Age	0.07 (0.11)	0.70	0.48		
	Age^2	-0.00 (0.00)	-3.94	<0.001*		
	Sex	-0.32 (0.66)	-0.49	0.62		
	Education	0.16 (0.11)	1.41	0.15		

	CRI	0.18 (0.02)	6.45	<0.001*		
Model 5	Intercept	61.21 (3.23)	18.91	<0.001*	0.47	4188 (8)
	Age	0.04 (0.10)	0.45	0.65		
	Age^2	-0.0 (0.00)	-3.14	0.001*		
	Sex	0.01 (0.65)	0.02	0.97		
	Education	1.94 (0.35)	5.43	<0.001*		
	Education^2	-0.05 (0.01)	-5.24	<0.001*		
	CRI	0.15 (0.02)	5.31	<0.001*		
Model 6	Intercept	57.45 (8.53)	6.73	<0.001*	0.47	4190 (9)
	Age	0.03 (0.11)	0.30	0.76		
	Age^2	-0.0 (0.00)	-2.93	0.003*		
	Sex	0.01 (0.65)	0.02	0.98		
	Education	1.87 (0.38)	4.82	<0.001*		
	Education^2	-0.05 (0.01)	-4.65	<0.001*		
	CRI	0.23 (0.17)	1.37	0.16		
	CRI^2	-0.0 (0.00)	-0.47	0.63		

Table 16. Results of Regression Analyses with different demographic variables as predictors of interest and Tele-GEMS as dependent variable. The table shows the model's name (first column); the name of the term entered in the regression model (second column); coefficient estimate and standard error within round brackets (third column); t-value associated with the term (fourth column); p-value (fifth column), with an asterisk "*" denotes significant terms; adjusted R^2 associated with each Model (sixth column); Akaike Information Criterion values (seventh column). The lower the AIC value, the better the model fits. *Note.* Tele-GEMS=Tele-Global Examination of Mental State; CRI=Cognitive Reserve Index; AIC=Akaike Information Criterion.

Auto-GEMS

Auto-GEMS global score negatively correlates with age (r=-0.59; p<0.001), positively with education (r=0.53; p<0.001) and positively with CRI (r=0.27; p<0.001). No difference between males and females was observed (t=0.926, p=0.354). Regression models were devised to verify their effect on the Auto-GEMS score and derive cut-off. The model with all four predictors (age, education, CRI and sex - Model 4) had the best fit. The results of this model can be summarised as follows: the ones with younger age and with higher education have the better the Auto-GEMS score. Notably, the higher the CRI, the higher the Auto-GEMS score, indicating the relevance of CRI in explaining the variance of cognitive performance. See Table 17 for more details. Cut-offs were calculated using the regression-based approach by Crawford and Garthwaite (2007). These variables were identified as relevant by comparing different regression models and choosing the model with the best fit.

Model	Predictor(s)	Model coefficients		Model fit measures		
		Beta	*p*	R^2	F test (*p*)	AIC
Model 1	Age	-0.37	<0.001	0.344	685.4 (<0.001)	9541
Model 2	Age	-0.28	<0.001	0.434	500.6 (<0.001)	9350
	Education	0.95	<0.001			
Model 3	Age	-0.29	<0.001	0.439	339.4 (<0.001)	9335
	Education	0.81	<0.001			
	CRI	0.05	0.001			
Model 4	Age	-0.29	<0.001	0.441	256.9 (<0.001)	9331
	Education	0.81	<0.001			
	CRI	0.05	0.002			
	Sex	-1.14	0.018			

Table 17. The table shows the results of the three linear regression models that tested the demographic variables' effect on the Auto-GEMS. The first column shows the name of the model; the second, the predictors entered in the models; the third, the values of model coefficient (Beta and p); the fourth, the model fit measures (R squared, F test and associated p-value and Akaike Information Criterion). *Note*. CRI=Cognitive Reserve Index; Auto-GEMS=Auto-Global Examination of Mental State, AIC= Akaike Information Criterion.

ENB-3

ENB-3 global score negatively correlates with age (r=-0.62; p<0.001), positively with education (r=0.56; p<0.001) and positively with CRI (r=0.29; p<0.001). The effect of age, sex, education, and CRI was further investigated via multiple regressions. Inspection of the partial residuals of a full model showed that age, education and CRI were non-linearly related to ENB-3 score. Thus, subsequent regressions were performed to check whether including non-linear terms would improve the fit (see Table 18). The final model, i.e., that best fitted ENB-3 scores (model 6; p<.001, adjusted R^2=0.60), included age, education, CRI, and sex and non-linear terms for age, education and CRI. The results of this model can be summarised as follows: the higher the age, the worse the performance and the higher the education, the better the performance. Notably, the higher the CRI, the higher the ENB-3 score, emphasising its importance in the context of cognitive testing. All the predictors included in the final model were considered for the computation of cut-offs.

Regression Models – dependent variable: ENB-3 total score						
Model	Predictor	Beta (SE)	t-value	*p*	Adj. R^2	AICc (df)
Model 1	Intercept	0.939 (0.01)	129.68	<0.001*	0.39	-1996 (4)
	Age	-0.01 (0.07)	-22.63	<0.001*		
	Sex	-0.01 (0.01)	-2.13	0.033*		
Model 2	Intercept	0.79 (0.01)	67.47	<0.001*	0.52	-2197 (5)
	Age	-0.00 (0.01)	-18.44	<0.001*		
	Sex	-0.01 (0.00)	-1.97	0.049*		
	Education	0.01 (0.00)	15.21	<0.001*		
Model 3	Intercept	0.73 (0.01)	51.93	<0.001*	0.57	-2211 (6)
	Age	-0.00 (0.00)	-19.30	<0.001*		
	Sex	-0.00 (0.00)	-1.32	0.187		
	Education	0.00 (0.00)	4.47	<0.001*		
	CRI	0.21 (0.02)	7.32	<0.001*		
Model 4	Intercept	0.00 (0.00)	39.99	<0.001*	0.58	-2239 (7)
	Age	-0.00 (0.00)	-0.102	0.918		
	Age^2	-0.00 (0.00)	-5.49	<0.001*		
	Sex	-0.00 (0.00)	-1.47	0.141		
	Education	0.00 (0.00)	4.81	<0.001*		
	CRI	0.00 (0.00)	7.85	<0.001*		
Model 5	Intercept	0.00 (0.00)	27.19	<0.001*	0.59	-2264 (8)
	Age	0.00 (0.00)	0.01	0.995		
	Age^2	-0.00 (0.00)	-5.20	<0.001*		
	Sex	-0.00 (0.00)	-1.27	0.204		
	Education	0.00 (0.00)	6.42	<0.001*		
	Education^2	-0.00 (0.00)	-5.23	<0.001*		
	CRI	0.00 (0.00)	7.01	<0.001*		
Model 6	Intercept	0.00 (0.00)	5.38	<0.001*	0.60	-2275 (9)
	Age	-0.00 (0.00)	-1.32	0.188		

	Age^2	-0.00 (0.00)	-3.83	<0.001*		
	Sex	-0.00 (0.00)	-1.24	0.214		
	Education	0.00 (0.00)	5.60	<0.001*		
	Education^2	-0.00 (0.00)	-4.64	<0.001*		
	CRI	0.00 (0.00)	4.56	<0.001*		
	CRI^2	-0.00 (0.00)	-3.54	<0.001*		

Table 18. Results of Regression Analyses with different demographic variables as predictors of interest and ENB-3 as dependent variable. The table shows the model's name (first column); the name of the term entered in the regression model (second column); coefficient estimate and standard error within round brackets (third column); t-value associated with the term (fourth column); p-value (fifth column), with an asterisk "*" denotes significant terms; adjusted R^2 associated with each Model (sixth column); Akaike Information Criterion values (seventh column). The lower the AIC value, the better the model fits.

Discussion

This Chapter presents new cognitive tests to investigate global cognition and impairments of any origin or aetiology. The main aim of these works was to provide new tools capable of generating cut-offs considering not only age and education but also the more comprehensive score of CR (measured by the Cognitive Reserve Index questionnaire), which provides a more precise expectation of performance and a better understanding of the possible evolution of the cognitive profile. While most neuropsychological tests typically reveal declining performance with increasing age and improved performance with higher education (Mondini et al., 2023; Scheffels et al., 2023), various other factors may impact cognitive health and performance on neuropsychological tests.

The effect of age, education and CRI on cognitive performance was investigated via linear regressions, and we found that age and education predicted global performance: the younger and the more educated participants obtained higher scores. Notably, our analyses showed a robust and positive relationship of CRI with scores: the higher the CRI, the better the performance. This latter result is consistent with the literature showing a strong relationship between CR proxies and cognitive functioning. Thus, a more comprehensive life-experience proxy is more effective than age and education only in capturing and predicting cognitive efficiency. We then also used CR as a factor for generating clinical cut-offs. The integration of CR into the cut-off scores provides a more precise evaluation of cognitive health, offering information into the potential trajectory of cognitive profiles over time. Recognizing CR as a critical determinant in cognitive performance encourages a holistic approach to cognitive assessments, acknowledging the multifaceted nature of factors contributing to cognitive health.

To the best of our knowledge, this work provides, for the first time, normative data using a CR proxy for calculating the cut-offs, providing a precise and individualized approach to score interpretation. This novel approach underscores the need for a comprehensive understanding of cognitive health beyond traditional demographic factors, recognizing diverse cognitive trajectories shaped by individual experiences.

Conclusion

In conclusion, the comprehensive consideration of CR across these cognitive tests emphasizes its crucial role in shaping cognitive performance. Incorporating CR into neuropsychological assessments enhances cognitive evaluations' precision, relevance, and individualization, guaranteeing a more holistic understanding of cognitive functioning. This evidence underscores the significance of recognizing and integrating CR into the landscape of neuropsychological testing, contributing to advancing precision medicine in cognitive assessment. Incorporating CR within the norms allows a tailored comparison of each examinee, ensuring a more accurate assessment of cognitive functioning and promoting precision medicine.

2. Motor Reserve and Physical Activity

Lifestyle factors, encompassing cognitive, social, and physical activities, have been extensively explored in the literature as potential contributors to cognitive health in healthy and pathological conditions (Arenaza-Urquijo et al., 2015).

The first part of the present Thesis focuses on the effect of life-long cognitively stimulating activity on cognitive health. The acquisition of knowledge, skills, and experiences throughout the lifespan collectively shapes Cognitive Reserve (CR), reflecting an individual's capacity to flexibly and efficiently utilize available brain resources. A well-established observation is that individuals with higher CR exhibit more efficient brain networks, enabling effective coping with pathology through compensatory mechanisms (Stern, 2002; Stern & Barulli, 2009).

Beyond cognitive-stimulating activities, recent attention has been directed towards the role of physical activity (PA) due to its potential in preventing age-related diseases and maintaining or enhancing cognitive functioning in healthy individuals. Evidence indicates that Physical Activity (PA) holds the potential to enhance cognitive functions in healthy adults, reduce dementia incidence, and enhance overall health in individuals with existing dementia (Angevaren et al., 2008; Blondell et al., 2014; Sofi et al., 2011). Notably, PA engaged in over an individual's lifespan may exert a lasting impact on cognition. Aligning with recent findings, the second section of this Thesis will introduce a new possible kind of reserve: Motor Reserve (MR), which is conceptualized as a dynamic and accumulative construct possibly able to compensate for age-related cognitive decline. Exploring the Motor Reserve's influence on cognitive health across adults, older adults, and populations with neurological disorders will offer insights guiding the development of novel preventive protocols for cognitive decline and rehabilitation programs tailored for individuals with pre-existing neurological conditions.

2.1 Introduction

Physical activity (PA) is defined as bodily movements produced by skeletal muscles that result in energy expenditure (World Health Organization, 2022). Two types of PA can be distinguished: physical exercise and incidental physical activity. Physical exercise includes planned and structured activities, usually to improve or maintain physical fitness (Caspersen et al., 1985), such as swimming, biking, or playing sports. Incidental physical activity is non-purposeful PA resulting from daily activities that imply movements, such as working, housekeeping or walking (Bherer et al., 2013; Fratiglioni et al., 2004). In a systematic review, Reynolds and colleagues (2014) systematised all types of daily activities considered incidental physical activity. The authors highlighted that increasing incidental energy expenditure via practical day-to-day tasks has substantial public health potential, partly because more adults participate in non-organized physical activity than in organized physical activity (Australian Sports Commission, 2010). See Figure 18 for some examples of physical exercise and incidental physical activity.

Physical Activity	
Physical Exercise	Incidental Physical Activity
e.g. • running • swimming • biking • football, rugby, hockey • skipping • aerobics • gymnastics • martial arts	*e.g. (by Reynolds et al., 2014)* • Taking the stairs • Walk or cycle (active transportation) • Gardening or other maintenance work including: chopping wood, sweeping patio, heavy lifting, shoveling snow, digging and raking in the garden • Household chores, housework, including: carrying light loads, sweeping, washing windows, scrubbing floors • Caring for your family. • Occupational physical activity, including: heavy lifting, digging, heavy construction; climbing up stairs; carrying light loads; repeated lifting, pushing and pulling heavy objects; repeated bending, twisting and reaching; working with hand-held or hand-operated vibrating tools and machinery • Walking the dog/working with other animals, e.g. horse

Figure 18. Examples of Physical Exercise and Incidental Physical Activity.

The health benefits of physical activity are undeniable, and virtually everyone can benefit from becoming more physically active (Warburton & Bredin, 2017). Regular PA is an effective primary and secondary preventive measure for more than 25 chronic medical conditions and premature mortality (Pedersen & Saltin, 2015; Warburton et al., 2010). The World Health Organization reports that approximately 3.2 million deaths occur annually due to physical inactivity, making it the fourth highest risk factor for global mortality (World Health Organization, 2010).

Several medical conditions can benefit from the regular practice of PA, such as cardiovascular diseases, diabetes, metabolic disorders, cancer and musculoskeletal diseases. For example, regular physical activity reduces chronic heart diseases by enhancing cardiovascular efficiency. This improvement involves the reinforcement of the contraction and relaxation of the heart, ensuring effective blood pumping and circulation. Additionally, regular exercise increases lung capacity, facilitating optimal oxygen intake, and promotes the dilation of blood vessels (Soares-Miranda et al., 2012). This process decreases heart disease and stroke risk factors, including high blood pressure and abnormal blood lipid profiles (Cornelissen & Fagard, 2005; Kodama, 2007). Moreover, engaging in physical activity improves blood glucose control and delays the onset of type 2 diabetes (Colberg et al., 2010). Physical activity reduces the risk of diabetes through both long-term and short-term enhancements in insulin action, leading to better glucose control. Notably, two months of exercise training in older men significantly improved insulin sensitivity and fasting glycaemia (Ibañez et al., 2005).

The amount of physical activity is also related to obesity and related metabolic diseases. Individuals with sedentary lifestyles tend to have a lower metabolic rate, leading to weight gain and eventual obesity over time (Kim et al., 2017). Obesity has become a global epidemic, affecting nearly half of the world's population (Lavie et al., 2019). For instance, the European Union reported that, in 2008, 23% of women and 20% of men in European countries were overweight or obese (Finucane et al., 2011). Inadequate physical activity and a more sedentary lifestyle are significant factors causing increased obesity and overweight in Europe.

A high level of physical activity leads to increased energy expenditure, reducing stored fats (adiposity) and lowering body mass index. Moreover, this combination helps lower the risk of diabetes and high blood pressure while improving the lipid profile (Colberg et al., 2010).

The protective effects of physical activity have also been studied in relation to cancer. Literature indicates that a physically active lifestyle in men reduces 30-40% the risk of colon cancer, while women have a 20-30% lower risk of breast cancer (Lee, 2003). The risk reduction associated with physical activity is attributed to the reduction of long-term inflammation which helps in preventing cancer. Additionally, physical activity enhances the immune system's ability to combat cancer and improves hormone balance, lowering the overall risk of cancer (Warburton et al., 2010).

Regarding skeletal muscle health, regular physical activity fosters increased bone density, supports the health of joints, and strengthens muscles, tendons, and ligaments. Moreover, regular physical activity enhances functional abilities in older adults, enabling them to lift, carry, climb stairs, and perform various activities. This contributes to a reduced risk of conditions such as osteoporosis and fractures (Schmitt et al., 2009).

Advanced age does not preclude physical activity; in fact, it can prevent morbidity and disability in older adults. According to the WHO (World Health Organization, 2007) guidelines, exercise is an efficient and cost-effective way of preventing the decline of older people’s functional capacity. Generally, physical activity in older adults enhances muscular tone and movement ability, reduces the risk of osteoporosis, and stimulates the release of neurohormonal mediators, such as endorphins and serotonin, that contribute to a sense of overall well-being. Physical activity enhances muscle strength, endurance, flexibility, and balance, reducing the fear of falling (Chou et al., 2012). Moreover, physical activity serves as a preventive measure against the development of frailty in older adults, promoting greater autonomy and independence in their daily activities.

Engaging in physical activity also has positive effects on brain structure and cognition. PA directly influences cognitive functioning associated with structural and functional changes in the brain and improves psychophysical well-being (Colcombe & Kramer, 2003).

Neuroimaging studies demonstrated that moderate amounts of physical activity support a healthy brain: PA can induce positive changes in grey matter volume, white matter integrity, functional brain activity, and cerebral perfusion (Festa et al., 2023). In a cross-sectional study (Weinstein et al., 2012), it was observed that increased levels of physical activity correlated with greater brain volumes in the prefrontal cortex and anterior cingulate cortex. These findings, in turn, were linked to enhanced cognitive performance, particularly in memory and attention.

Moreover, Erickson and colleagues (2009) found a positive association between higher fitness levels and increased hippocampal volume. From a cognitive perspective, this correlation translated into improved memory and spatial memory task performance. Consistently Szabo and colleagues (2011) found that older adults with elevated fitness levels exhibited greater preservation of hippocampal volume. This preservation, in turn, correlated with more accurate and faster spatial memory, and fewer episodes of forgetfulness. Similarly, Arenaza-Urquijo et al. (2017) reported that older individuals engaged in physical activity had greater gray matter volume in the prefrontal, insular, and motor cortices, and this result remained significant even after accounting for potential confounders.

The benefits of physical activity are also observable in the white matter. Using Diffusion Tensor Imaging, Tseng et al. (2013) found that older adult athletes exhibited greater white matter integrity and fewer hyperintensities (white matter insults) compared to sedentary individuals of the same age. These findings suggest that lifelong exercise is associated with reduced white matter hyperintensities and may preserve white matter microstructural integrity related to motor control and coordination in late adulthood.

Through fMRI studies, Colcombe et al. (2004) found that higher physical activity levels were linked to increased brain activation in the prefrontal and parietal cortex, along with reduced activation in the anterior cingulate cortex during attention-demanding tasks. A similar result was reported by Vidoni and collaborators (2013), who found an inverse association between cardiorespiratory fitness and anterior cingulate activity in participants without dementia.

Increased cerebral perfusion is one mechanism through which physical activity supports cognitive performance in late adulthood. Xu et al. (2014) reported that women engaging in strength training at least once per week exhibited significantly greater cerebrovascular perfusion than those who did not. These findings suggest that regular strength training can benefit women's cerebrovascular health.

Another aspect of the impact of physical activity on the brain is related to neurotrophins, essential modulators of physical activity-induced neural plasticity. The Brain-Derived Neurotrophic Factor (BDNF), a widely distributed neurotrophins in the brain, plays a crucial role in maintaining, growing, and facilitating synaptic plasticity of neurons underlying emotion and cognition, as well as modifying neuronal excitability (Cowansage et al., 2014). Both resistance and aerobic exercise can increase BDNF levels when a sufficient intensity of physical activity is achieved. Moderate levels of physical activity have been shown to mitigate cognitive decline in older adults, and some proposed mechanisms involve BDNF (Phillips, 2017). The ability of physical activity to increase BDNF release, enhance synapse functioning, and activate other cellular pathways contributing to plasticity is central to homeostatic processes that preserve, protect, and reorganize impaired networks in older adults (Lu et al., 2008; Patterson, 2015).

Therefore, from a brain-structure point of view, physical activity and cardiovascular fitness can decelerate age-related processes of neuronal and volumetric loss, reduce lesions in white matter, and mitigate myelin loss, facilitating better oxygenation and blood supply to the brain.

While several works in the literature have explored exercise-induced benefits on body and brain health, only in recent years the study of the relationship between PA and cognition received considerable attention. Emerging evidence suggests that physical activity (PA) can enhance cognitive health in individuals without dementia, reduce the incidence of dementia, and improve health in those with existing dementia (Angevaren et al., 2008; Blondell et al., 2014; Sofi et al., 2011).

Increased physical activity may offer a neuroprotective mechanism, reducing the cognitive decline and providing protection against dementia (Kirk-Sanchez & McGough, 2013). For instance, Dustman et al. (1984) conducted an intervention with a sample of healthy but sedentary older individuals. They found that engaging in aerobic PA training led to improvements over the baseline in memory, information processing speed, and inhibitory control. Consistent results were found by Kramer et al. (1999), which compared healthy older adults practising brisk walking with a control group involved in stretching-and-toning exercises. Compared with the control group, the experimental group demonstrated improvements in several cognitive domains, especially those related to executive functioning (Kramer et al., 1999). Other studies have shown that physical activity benefits overall cognitive functioning, mainly focusing on executive functions (Angevaren et al., 2008; Hindin & Zelinski, 2012; Smith et al., 2010). These results may suggest a domain-specific effect of physical activity, warranting further analysis.

A meta-analysis (Colcombe & Kramer, 2003) of randomised controlled trials indicated that aerobic exercise interventions have stronger effects when complemented by resistance exercises than when aerobic exercises are practised in isolation. Subsequent investigations into the effectiveness of resistance training found that six months of training significantly increased some measures of cognitive functioning in older adults (Cassilhas et al., 2007). Others, such as Liu-Ambrose et al. (2010), reported a domain-specific effect of resistance training, suggesting positive influences on selective attention and inhibitory response in older women.

These positive results obtained with the healthy populations prompted researchers to explore the effects of physical activity among individuals suffering from diseases linked to ageing, especially dementia and Mild Cognitive Impairment (MCI). For example, a study in older adults with MCI suggested sex-specific effects, with women showing improvements in cognitive performance after PA interventions (McWeeny et al., 1987). Conversely, another study reported that both aerobic and endurance training could enhance the memory domain in individuals with MCI (Nagamatsu et al., 2012). It is plausible that sedentary individuals with

MCI may experience positive effects from the practice of physical exercise, and some authors hypothesise that sex differences in glucometabolic and hypothalamic-pituitary-adrenal axis responses to exercise may explain the observed gender effect in this population category. Modest amounts of exercise may be an effective and low-cost method of improving cognitive function in individuals with MCI or in the early stages of dementia (Lautenschlager et al., 2010).

A positive overall effect of physical activity interventions on cognitive function is observable also in people with dementia (Groot et al., 2016). This effect extends beyond cognitive functioning measured by psychometric tests, as significant improvements in everyday activities have been observed. These findings suggest that physical activity interventions may serve as an alternative or complementary approach to pharmacological treatment for patients with dementia.

The overall health benefits of PA are not only related to structured physical exercise but also connected with incidental physical activity. A recent study Wallmann-Sperlich et al. (2022) reported that more than 75% of the PA carried out during a week is assigned to incidental lifestyle PA and that a substantial amount was spent engaging in vigorous-intensity activity. Several studies reported that the amount of incidental physical activity is also related to better overall health. For example, incidental physical activity is associated with better scores on cognitive tasks, an increased EEG frequency, and better physiological status, which suggests that incidental physical activity may be protective against age-related deterioration (Sanchez-Lopez et al., 2018). This data underlines the importance of promoting a physically active lifestyle next to structured PA and points to the need for future research to understand the health potential of incidental lifestyle PA (Wallmann-Sperlich et al., 2022).

2.2 The Motor Reserve Hypothesis

While most of the studies discussed so far have focused on the effects of physical activity (PA) training implemented over specific periods, recent findings suggest that the beneficial impact on cognition is wider than interventions applied solely in older age. Instead, lifelong exercise, regularly undertaken since early adulthood, may positively affected cognitive efficiency. For instance, Reas and colleagues (2019) conducted a cross-sectional study involving 1826 individuals aged 60-99. Their research showed that physical activity during teenage years may contribute to a reduced decline in executive functioning later in life. In this study, participants underwent cognitive tests, and health and lifestyle information were collected through self-administered questionnaires. Participants retrospectively reported the frequency of engagement in light, moderate, or strenuous exercise during different life stages: teenage years, age 30, age 50, and current age (referred to as older age). Each life stage was categorized as regularly active (3 or more times per week) or inactive. Regular physical activity at various life stages correlated with better late-life function across multiple cognitive domains. The most robust association was observed with the current level of physical activity, particularly in executive functions and episodic memory. Physical activity in youth and midlife, especially during teenage years, was linked to improved cognition in later adulthood. Additionally, individuals active both during their teenage years and in older age outperformed those active only during one of the two periods.

This evidence prompted the consideration that physical activity can accumulate over time, representing a distinct kind of *reserve* alongside cognitive reserve, known as *Motor Reserve* (MR). Motor Reserve reflects the cumulative impact of a physically active lifestyle at every stage of life, potentially leading to enhanced cognitive functioning in late adulthood. MR may be associated with a greater ability to cope with normal or pathological motor skill decline expected in late adulthood (Bastos & Barbosa, 2022). In line with what has already been repeatedly demonstrated at the cognitive level, this construct has been named Motor Reserve.

As mentioned above and reported in the literature, the factors contributing to increasing MR might also increase CR. However, it is reasonable to assume that factors determining high CR (i.e., education, work, cognitively stimulating leisure activities) do not necessarily increase MR.

2.3 How to measure Motor Reserve

The instruments commonly employed in the literature to assess physical activity (PA) were considered inadequate for accurately capturing the Motor Reserve (MR) construct for two primary reasons. Firstly, MR encompasses both incidental physical activity and structured physical exercise, and no standardised tool is available for precisely quantifying daily incidental physical activity. Secondly, MR reflects the cumulative amount of PA across the entire lifespan, while most questionnaires in the literature concentrate only on the recent period. For these reasons, we developed an ad-hoc questionnaire for measuring MR: the Motor Reserve Index questionnaire (MRIq, Pucci et al., 2023).

Considering the evidence in the literature regarding the short-term impact of physical activity on cognitive health, we developed another questionnaire, the Current Physical Activity questionnaire, using the same items as the MRIq. This tool aims to quantify the level of physical activity, encompassing incidental and structured physical activity, over the past twelve months. The process of development and validation for both instruments is detailed below.

2.3.1 The Motor Reserve Index questionnaire

The Motor Reserve Index questionnaire (MRIq) is a semi-structured questionnaire administered by a professional, specifically developed for this study to quantify both incidental and structured physical activity (PA) carried out across a person's lifespan. The MRIq comprises 17 items covering six areas (or sections in the questionnaire) of daily activities: Housework, Active Transportation, Free Time Activity, Physical Exercise, Caring Activity, and Workplace Activity. The different sections are described below.

Section I – Housework activities: This section comprises three items according to the type and intensity of housework: soft (e.g., sweeping and washing dishes), moderate (e.g., ironing, washing floors, or washing clothes by hand), and strenuous (e.g., cleaning windows or carrying heavy objects).

Section II – Active Transportation: In this section, three items investigate how much a person walks daily. Participants are asked if they walk short distances (less than 1 km), long distances (more than 1 km), and if they use stairs.

Section III – Leisure activities: Two items evaluate the practice of activities during free time. The first concerns soft leisure activities practised while sitting (e.g., knitting or bricolage). The second item concerns strenuous leisure activities practised standing up (e.g., gardening or playing a musical instrument).

Section IV – Physical exercise: Two items evaluate structured physical activity. The first refers to light and moderate exercises (e.g., yoga, pilates, or bowling), while the second refers to vigorous ones (e.g., football or basketball).

Section V – Care activity: Two items evaluate daily activities that involve energy expenditure to care for other people or pets. The first item refers to caring for children or pets, while the second refers to caring for older or sick people.

Section VI – Workplace activities: Five items quantify a person’s physical activity in the workplace. Participants are asked whether their work involves physical activity of light, moderate, or vigorous intensity, whether the work is carried out mainly by sitting or standing, and whether the work involves active transportation.

Each item gives a score based on the frequency and years of practice, starting from 18. The score of each item is calculated in hundredths proportionally to the maximum possible raw scores. For example, a 58-year-old person who has done soft housework activities from 28 will have 30 years of activity (58 minus 28) out of a possible 40 (58 minus 18). The final score in cents will be 75 (i.e., 30/40, then multiplied by 100). A person who carried out daily soft housework activities from 18 will obtain 100 at the item investigating "soft housework activities"; conversely, if they have never done domestic activities, they will get 0. The overall score (range: 0-100) is the average of the mean score of each section. The questionnaire is easy to understand and takes about 5 minutes to administer (in Table 19 the items of the MRIq are reported).

Motor Reserve Index questionnaire	
Section I – Housework activities	For how many years have you engaged in housekeeping of SOFT intensity, such as washing dishes or sweeping?
	For how many years have you engaged in housekeeping of MODERATE intensity, such as ironing or washing floors?
	For how many years have you engaged in housekeeping of HIGH intensity, such as transporting wood, washing windows, or whitewashing?
Section II – Active Transportation	For how many years have you climbed flights of stairs?
	For how many years have you walked short distances (<1 km)?
	For how many years have you walked long distances (>1 km)?
Section III – Leisure activities	For how many years have you engaged in leisure activities while SITTING DOWN, such as crafts, puzzles, or knitting?
	For how many years have you engaged in leisure activities while STANDING UP, such as gardening or hunting?
Section IV – Physical exercise	For how many years have you participated in LIGHT/MODERATE sports, such as bowls, dancing, or running?
	For how many years have you participated in STRENUOUS/COMPETITIVE sports, such as jogging, cycling, tennis, football, basketball, or volleyball?
Section V – Care activity	For how many years did you take care of young children or pets?
	For how many years have you cared for an elderly or sick person, such as a spouse or parent?
Section VI – Workplace activities	For how many years were you involved in work with MILD intensity?
	For how many years were you engaged in work that involved MODERATE activity leading to an increased heart rate or breathing, like fast-paced walking?
	For how many years were you involved in work with HIGH-intensity activities that led to an increase in heart rate or breathing, such as moving heavy loads?

	For how many years did you have a job that required standing for more than 1 hour at a time?
	For how many years did you have a job that involved walking?

Table 19. The Table reports the items of the Motor Reserve Index questionnaire divided into six sections.

2.3.2 The Current Physical Activity questionnaire

The Current Physical Activity questionnaire (CPAq) was developed using the same items as the MRIq but asking participants to consider only the previous twelve months. CPAq as MRIq is administered by an examiner as a semi-structured interview. It comprises 17 items covering six areas, 5 for all participants and one for those still working during the data collection. For each item, four alternatives based on weekly frequency can be selected: never, rarely (once a week), sometimes (two/three times a week), and often (more than three times a week). The questionnaire is easy to understand and quick to administer (about 5 minutes). The global CPAq score is obtained by summing up the item scores (range 0–51). In Table 20 the items of the CPAq are reported.

Current Physical Activity questionnaire		**Scores**			
		Never	Rarely	Sometimes	Always
Section I – Housework activities	How often have you engaged in housekeeping of SOFT intensity, such as washing dishes or sweeping in the last twelve months?	0	1	2	3
	How often have you engaged in housekeeping of MODERATE intensity, such as ironing or washing floors in the last twelve months?	0	1	2	3
	How often have you engaged in housekeeping of HIGH intensity, such as transporting wood, washing windows, or whitewashing in the last twelve months?	0	1	2	3
Section II – Active Transportation	How often have you climbed flights of stairs in the last twelve months?	0	1	2	3
	How often have you walked short distances (<1 km) in the last twelve months?	0	1	2	3
	How often have you walked long distances (>1 km) in the last twelve months?	0	1	2	3

Section III – Leisure activities	How often have you engaged in leisure activities while SITTING DOWN, such as crafts, puzzles, or knitting in the last twelve months?	0	1	2	3
	How often have you engaged in leisure activities while STANDING UP, such as gardening or hunting in the last twelve months?	0	1	2	3
Section IV – Physical exercise	How often have you participated in LIGHT/MODERATE sports, such as bowls, dancing, or running in the last twelve months?	0	1	2	3
	How often have you participated in STRENUOUS/COMPETITIVE sports, such as jogging, cycling, tennis, football, basketball, or volleyball in the last twelve months?	0	1	2	3
Section V – Care activity	How often did you take care of young children or pets in the last twelve months?	0	1	2	3
	How often have you cared for an elderly or sick person, such as a spouse or parent in the last twelve months?	0	1	2	3
Section VI – Workplace activities	How often were you involved in work with MILD intensity in the last twelve months?	0	1	2	3
	How often were you engaged in work that involved MODERATE activity leading to an increased heart rate or breathing, like fast-paced walking in the last twelve months?	0	1	2	3
	How often were you involved in work with HIGH-intensity activities that led to an increase in heart rate or breathing, such as moving heavy loads in the last twelve months?	0	1	2	3
	How often did you have a job that required standing for more than 1 hour at a time in the last twelve months?	0	1	2	3
	How often did you have a job that involved walking in the last twelve months?	0	1	2	3

Table 20. The Table reports the items of the Current Physical Activity questionnaire divided into six sections.

Validation of Motor Reserve Index questionnaire and Current Physical Activity questionnaire

The Motor Reserve Index questionnaire (MRIq) and Current Physical Activity questionnaire (CPAq) were developed ad hoc for this study, and their psychometric properties were evaluated. Content validity was assessed using the Content Validity Index (Polit & Beck, 2006), internal consistency was determined through Cronbach's alpha, and test-retest reliability was assessed using Pearson's r.

Content Validity

A gold standard measure of Motor Reserve was unavailable in the literature. Consequently, no tool could be employed to assess convergent validity. Therefore, our approach involved evaluating Content Validity, defined as the extent to which elements of an instrument are pertinent to and representative of the targeted construct (in this case, Motor Reserve) (Cook & Beckman, 2006). Thus, a panel of 13 experts in cognition and physical activity evaluated the items of the questionnaire, indicating whether each was essential for evaluating the amount of physical activity undertaken by an individual. The Content Validity Ratio (CVR) for each item was computed using the following formula:

$$(Ne - N/2)/(N/2)$$

where Ne represents the total number of experts deemed the item as essential, and N corresponds to the total number of experts (here N=13). CVR values for items ranged from 0.23 to 1. The Content Validity Index (CVI=0.59) was determined as the average score of CVR for each item. Additional details about the CVI calculation process are provided in Table 21. Despite two items yielding low CVR values (Item1 = 0.23; Item7 = 0.23), all items were included in the questionnaire. This decision was made to maintain the ability to differentiate between individuals who are entirely physically inactive and those who are less active.

Item	Exp1	Exp2	Exp3	Exp4	Exp5	Exp6	Exp7	Exp8	Exp9	Exp10	Exp11	Exp12	Exp13	Ne	CVR
1	1	1	0	1	0	1	0	0	1	0	1	1	1	8	0.23
2	1	1	0	1	0	1	1	0	1	0	1	1	1	9	0.39
3	1	1	0	1	1	1	1	1	1	1	1	1	1	12	0.85
4	1	1	0	1	1	1	1	1	0	1	1	1	1	10	0.54
5	1	1	1	1	0	1	1	1	0	0	1	1	1	10	0.54
6	1	1	1	1	1	1	1	1	1	1	1	1	1	13	1
7	1	0	0	1	0	1	0	0	1	1	1	1	1	8	0.23
8	1	0	0	1	0	1	1	0	1	1	1	1	1	9	0.39
9	1	1	0	1	0	1	1	0	1	1	1	1	1	10	0.54
10	1	1	1	1	1	1	1	1	1	1	1	1	1	13	1
11	1	0	0	1	0	1	0	1	1	1	1	1	1	9	0.39
12	1	0	0	1	0	1	1	1	1	1	1	1	1	10	0.54
13	1	0	1	1	0	0	1	1	1	0	1	1	1	9	0.39
14	1	0	1	1	0	0	1	1	1	1	1	1	1	10	0.54
15	1	1	1	1	1	1	1	1	1	1	1	1	1	13	1
16	1	0	1	1	0	1	1	1	1	0	1	1	1	10	0.54
17	1	1	1	1	1	1	1	1	1	1	1	1	1	13	1
														CVI = 0.53	

Table 21. The table shows the judgment of the 17 items of each of the 13 experts. "0" = experts who judged the item as not essential; "1" = experts who judged the item as essential; Ne = total number of experts who judged each item as essential; CVR = Content Validity Ratio, calculated as (Ne-N/2)/(N/2), where N is the sample size of experts (13); CVI = Content Validity Index, average of CVR scores.

The two questionnaires were then administered to a sample of 350 individuals (220 female; see Table 22 for the sample's descriptive statistics).

	Mean	SD	Mode	Median	Min	Max
Age	55.8	17.2	55	58	19	96
Education	13.1	4.2	13	13	4	29
CRI-Total	114.5	20.0	126	112	70	194
CRI-Education	106.5	14.9	106	105	66	203
CRI-WorkingActivity	106.7	16.8	93	104	69	163
CRI-LeisureTime	119.5	23.5	95	117	71	194

Table 22. Descriptive statistics of the sample (N=350) who underwent the Motor Reserve Index and Current Physical Activity questionnaires. *Note*. CRI = Cognitive Reserve Index.

Internal Consistency

Internal consistency was calculated through Cronbach's alpha on all items. A standardized alpha was used based on the correlations. Results showed a high internal consistency for MRI (0.83, range=0.81-0.84) and slightly higher for CPA (0.54, range=0.48-0.54). This low Cronbach's alpha is not surprising. Since the items evaluated the amount of physical activity in different areas of life, it is possible that an individual is very active in one of these areas (e.g., workplace activity) but not in another (e.g., physical exercise). In other words, a poor correlation between the items does not reflect a poor psychometric property. In fact, MRIq and CPAq can be considered reflective tools (Borsboom et al., 2003; see also chapter 1.2.1 of this thesis), measuring a latent construct. Within this framework, a high Cronbach's alpha is not required. We reported here the values as an additional description of the questionnaires' properties. A very similar result was found by Nucci and collaborators (2012) when developing and validating the Cognitive Reserve Index questionnaire. Table 23 shows Cronbach's alpha values obtained for the 17 MRI and the CPA items.

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
MRIq	.82	.82	.82	.81	.81	.82	.83	.82	.83	.82	.84	.82	.83	.83	.84	.82	.83
CPAq	.54	.52	.52	.51	.52	.51	.57	.53	.52	.54	.55	.54	.51	.48	.52	.56	.58

Table 23. The table shows the Cronbach's alpha values for each of the 17 items of the MRI and CPA. *Note:* MRIq = Motor Reserve Index questionnaire; CPAq = Current Physical Activity questionnaire.

Test-retest reliability

To calculate the test-retest reliability, a sub-sample of 20 participants was reassessed after around two months: Pearson's r resulted acceptable (r=0.73 for MRI and r=0.67 for CPA), indicating a good test-retest reliability.

Discussion

The development and validation of the Motor Reserve Index questionnaire (MRIq) and Current Physical Activity questionnaire (CPAq) represent a significant contribution to the standardised assessment of physical activity engagement in daily life. These tools were carefully designed to provide a comprehensive picture of individuals' physical activity levels across different life areas. Both questionnaires cover a spectrum of daily activities, including housework, active transportation, leisure activities, physical exercise, care activities, and workplace activities. The inclusion of experts in cognition and physical activity in the evaluation process ensured content validity, even though two items had relatively low Content Validity Ratios. MRIq and CPAq's ability to capture incidental and structured activities, as well as their high internal consistency and test-retest reliability, support their effectiveness as reliable tools. Both questionnaires offer distinct advantages: the MRIq provides a comprehensive overview of a person's lifelong engagement in physical activity, while the CPAq offers a dynamic framework of current activity levels. Notably, these questionnaires fill a crucial gap in assessing motor reserve, for which no gold standard measure exists.

In conclusion, the MRIq and CPAq are reliable and valid instruments for assessing motor reserve and current physical activity. Researchers and professionals can confidently use these tools to gain valuable information about individuals' physical activity patterns, contributing to understanding its potential implications for overall health and well-being.

2.4 Motor Reserve and cognitive health in healthy ageing

Pucci, V., Guerra, C., Barsi, A., Nucci, M., & Mondini, S. (2023)*. How long have you exercised in your life? The effect of motor reserve and current physical activity on cognitive performance. Journal of the International Neuropsychological Society, 1–7.*

Introduction

Time-related changes can negatively impact cognitive functioning, affecting an individual's quality of life and independence (Reas et al., 2019). As a result, current research in medicine and psychology aims at identifying potential preventive measures. Several studies have shown that short-term cognitive training or stimulation can improve cognitive functioning (Woods et al., 2012).

As reported in the previous chapters, the literature shows how an active lifestyle and engagement in structured PA can positively impact the brain. For example, it can lead to an increase in grey matter volume (e.g., Arenaza-Urquijo et al., 2017; Weinstein et al., 2012), white matter integrity (e.g., Johnson et al., 2012; Tseng et al., 2013), functional brain activity (e.g., Vidoni et al., 2013), and cerebral perfusion (Xu et al., 2014). PA seems to slow down the process of age-related neuronal and volumetric loss and reduce both lesions in the white matter and myelin loss, promoting better oxygenation and blood supply to the brain (Goenarjo et al., 2020).

The present study aimed to analyse the impact on cognitive performance of (a) PA across the lifespan (i.e., MR proxy) and (b) Current Physical Activity (CPA) in healthy adults. We expected that the higher the MR and the CPA, the better the cognitive performance. Moreover, following the most recent literature, we expected a stronger effect on executive functions.

Materials and Methods

The study was conducted following the Declaration of Helsinki, and it was approved by the Ethical Committee of the School of Psychology of the University of Padua (Protocol n°4109, Numero Univoco = 41D39A3D2D925510CD898DD310574A5A).

Participants

A sample of 75 healthy volunteers was recruited from organisations without connection with clinical settings. The inclusion criteria considered participants over 50, Italian native speakers without neurological or psychiatric diseases and not in pharmacological or chemotherapy treatment. Furthermore, their raw score on the Mini-Mental State Examination (MMSE, Folstein et al., 1975; Italian version, Magni et al., 1996) had to be greater than or equal to 25 (out of 30) to exclude individuals with potential impairment.

Participants' education was classified into five levels according to years of schooling. This sub-division was due to the automatic registration of the computerized test battery used in this study (Cognitive Function Dementia – Jahn & Hessler, 2020): 1, less than 8 years (9 participants, 12% of the total); 2, from 8 to 10 years (27 participants, 36% of the total); 3, from 10 to 12 years (19 participants, 25.3% of the total); 4, from 12 to 13 years (10 participants, 13.3% of the total); and 5 for more than 13 years (10 participants, 13.3% of the total). See Table 24 for details about participants' characteristics.

	Mean		SD		Mode		Median		Min		Max	
	Adults	Older adults	Adults	Older adults	Adults	Older adults	Adults	Older adults	Adults	Older adults	Adults	Older adults
Age	55.8	75.2	2.7	2.9	52	71	54	74	50	65	64	89
Education	2.9	2.7	1	1.4	2	2	3	2	2	1	5	5
CRI	109.8	109.3	12.7	16.9	111	110	109	110	85	76	145	153
MRI	51.9	40.4	11.9	11.3	47	38	51	41	28	16	76	63
CPA	25.7	16.5	6.2	5.4	27	21	27	18	12	3	36	27

Table 24. The table shows the descriptive statistics of the main characteristics of the two groups of the sample. *Note.* Adults sample size = 37 (22 female, 13 male); Older-adults sample size = 38 (23 female, 15 male). SD = Standard Deviation; CRI = Cognitive Reserve Index; MRI = Motor Reserve Index; CPA = Current Physical Activity.

Materials

The materials used to carry out this investigation included four different tools: (1) the Motor Reserve Index questionnaire (MRIq) to quantify participants' Motor reserve, (2) the Current Physical Activity questionnaire to quantify the participants' current level of physical activity (CPAq) (see chapter 2.3 for a complete description of MRIq and CPAq), (3) the Cognitive Reserve Index questionnaire (CRIq, Nucci et al., 2012; see chapter 1.2.3 of the present thesis for a complete description of the questionnaire) to quantify participants' cognitive reserve, and (4) Cognitive Function Dementia (CFD; Jahn & Hessler, 2020) to assess the cognitive profile of participants (see below for a full description of this instrument).

Cognitive Function Dementia (CFD; Jahn & Hessler, 2020)

The CFD test is a comprehensive battery of tests to assess all types of cognitive impairment. Tests are administered in a standard sequence on a touchscreen computer, and the whole administration lasts about 60 minutes. The CFD test battery is designed for individuals aged 50 or older without computer experience. Due to older individuals' difficulties using the mouse and keyboard, all tests within the CFD test set are accessible via a touchscreen. We utilised a laptop with a touchscreen that rotates 360 degrees, allowing them to function as tablets. While conducting the CFD test set, both the screen position in relation to the device and the device position in relation to the respondent or supervisor are essential. Depending on the test, the screen should either be opened and face the test supervisor (test supervisor mode) or flipped over to face the respondent (test respondent mode). Figure 19 illustrates the two types of screen positions.

Testing mode	Screen position	Comment
Test supervisor mode		Screen open and facing supervisor
Test respondent mode		Screen flipped over toward test respondent

Figure 19. The Figure illustrates the two types of screen positions.

The device's position is recommended depending on the testing mode (test supervisor or test respondent mode), as shown in Figure 20 below.

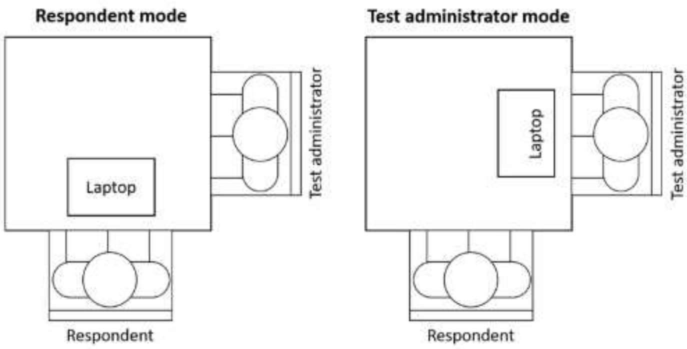

Figure 20. Position of the device depending on testing mode.

CFD detects subtle differences among healthy participants, avoiding the ceiling effect. The cognitive domains and sub-dimensions assessed with the CFD test set align with the DSM-5 diagnostic criteria for neurocognitive disorders and relevant research findings in dementia diagnostics. Figure 21 illustrates the cognitive domains and sub-dimensions evaluated by the CFD test set and the individual tests included. The tests included in the CFD battery are detailed below.

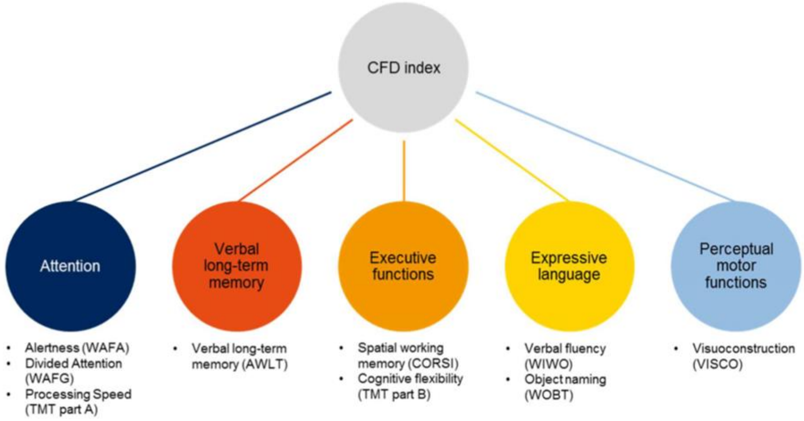

Figure 21. Cognitive domains and sub-dimensions in the CFD battery.

a. *Vienna Verbal Fluency Test*: it is a task to assess the richness of vocabulary and executive functioning. The task consists of a two-minute generation of words within a semantic category (i.e., animal, sem-FLU) and a specific phoneme (i.e., letter L, phon-FLU).

b. *Auditory Word List Learning Test:* in this task, the examinee must learn and recall a list of 12 words with delay. The test includes a learning phase (WL-T0) followed by a recall phase with two different delays: after 5 minutes (WL-T1) and after 20 minutes (WL-T2) and a final recognition phase (WL-Rec).

c. *Alertness*: this test measures 1) alertness, a general readiness to react to simple visual stimuli (AL-1), and 2) the ability to modulate the attentional level when an auditory cue is presented before the stimulus (AL-2).

d. *Divided Attention:* the test measures the ability to orient attention towards several information channels simultaneously. Visual and auditory stimuli are presented simultaneously, and the participant must respond only when one of the target stimuli changes twice in sequence. Reaction times are measured (RTs).

e. *Trail-Making Test Part A* – (TMT-A; Langensteinbach Version; Reitan, 1955): it evaluates the processing speed in detecting simple numerical stimuli using part A of the TMT test. The score (TMT-A) depends on both processing time and accuracy (number of errors).

f. *Trail-Making Test Part B* – (TMT-B; Langensteinbach Version; Reitan, 1955): TMT-B (measure of executive functioning) measures the ability to rapidly switch between two different reference systems (numbers and letters), tapping each stimulus in sequence. The score (TMT-B) considers processing time and accuracy (number of errors).

g. *Backward CORSI Block-Tapping Test*: this test evaluates visuospatial working memory and executive functioning. The participant must watch the same sequence of blocks in a matrix and reproduce it backwards. The sequence length increases as the test progresses until the participant cannot perform the sequence correctly. The score is the Immediate Block Span Backwards (bk-CORSI).
h. *Vienna Object Naming Test*: the test measures the ability to retrieve the names of objects. A cue (phonemic or semantic) can be given in the case of anomia. The score is the number of named objects without cues (ob-NAM).
i. *Visuoconstruction Test*: this test evaluates visual constructive ability and requires participants to reconstruct a complex figure in 60 seconds, starting from two triangles. The final score is the number of figures correctly completed (FIG).

Procedure

All participants were informed about the study's general aims and the administration time (about 1 hour and 30 minutes). The MMSE, CRIq, and CFD were administered first, and subsequently, the participants underwent CPAq and MRIq. All participants signed an informed consent after the experimental procedure was explained to them.

Data analyses and results

R software (version 4.1.0, RStudio Team, 2022) was used for the analyses. The sample (N=75), aged between 50 and 89 years old (M=65.6; SD=11.7), showed a percentage of females of 60%. The participants' cognitive reserve index (CRI) ranged from 76 to 153 (M=110, SD=16.4); MRI (M=45.9, SD=12.9, rang =16–76) and CPA (M=21.1, SD=7.40, range= 3–36) were distributed as a Gaussian curve (MRI: S-W p = .69; CPA: S-W p = .67). Age was not correlated with CRI (r=−0.07), but it was negatively correlated with MRI (r=−0.48) and CPA (r=−0.71). CRI showed no significant correlation with MRI (r=0.03) and CPA (r=0.04). MRI was positively correlated with CPA (r=0.53).

A multiple linear regression approach was adopted. The dependent variable was the Global Cognitive Functioning index, while Age, CRI and MRI or CPA were the predictors. In both models, all predictors were significant within the model (See Table 25 for more details).

	Global Cognitive Functioning			
	Model 1 - MRI		Model 2 - CPA	
	Covariates	β (*p*)	Covariates	β (*p*)
Model coefficients	**Age**	-0.05 (<0.001)*	**Age**	-0.05 (<0.001)*
	CRI	0.26 (<0.001)*	**CRI**	0.27 (<0.001)*
	MRI	0.20 (0.023)*	**CPA**	0.22 (0.042)*
Model fit measures	R^2 = 0.62 (<.001)		R^2 = 0.61 (<0.001)	
Model coefficients	**Age group**	0.95 (<0.001)*	**Age group**	0.72 (<0.001)*
	CRI	0.30 (<0.001)*	**CRI**	0.30 (<0.001)*
	MRI	0.28 (0.004)*	**CPA**	0.38 (<0.001)*
Model fit measures	R^2 = 0.52 (*p* <0.001 *)		R^2 = .54 (*p* <0.001 *)	

Table 25. Values of the model coefficients (standardized β and *p*-value) and the model fit measures of the four models. *indicates significant F-tests. *Note.* CRI = Cognitive Reserve Index; MRI = Motor Reserve Index; CPA = Current Physical Activity.

To evaluate the effect of PA in different age groups, the sample was divided into two groups according to their age: Adults (range 50–64 years old, N=37) and Older adults (range 65–89 years old, N=38). This division is based on data in the literature (e.g., Salthouse, 2016), which showed relevant cognitive changes in people when they reach 60–65 years. Two additional regression models were used for the Global Cognitive Functioning index: Model 1, with Age as factor, and CRI and MRI as covariates, and Model 2, with Age as factor, and CRI and CPA as covariates.

Model 1 predicted about 52% of the Global cognitive functioning index variability (R2=0.52), and all three predictors were significant within the model (βAge=0.95; Adults performed better than Older adults; βCRI=0.30, p<0.001; βMRI=0.28, p=0.004). MRI was significant also when considered as a single predictor in the model (R2=0.25, p<0.001). The section of the MRIq with the greatest influence on the Global cognitive functioning index was the one concerning workplace activities (R2=0.22; p<0.001).

Model 2 explained about 54% (R2=0.54, p<0.001) of Global cognitive functioning index variability, and all three predictors were significant within the model (βAge=0.72, p<0.001; that is, Adults performed better than Older adults; βCRI=0.30, p<0.001; βCPA=0.38, p<0.001). CPA was also significant when considered a single predictor in the model (R2=0.38; p<0.001). The section of CPAq with the greatest influence on the Global cognitive functioning index was the one concerning workplace activities (R2=0.35; p<0.001). See Table 25 and Figure 22 for more details about the models.

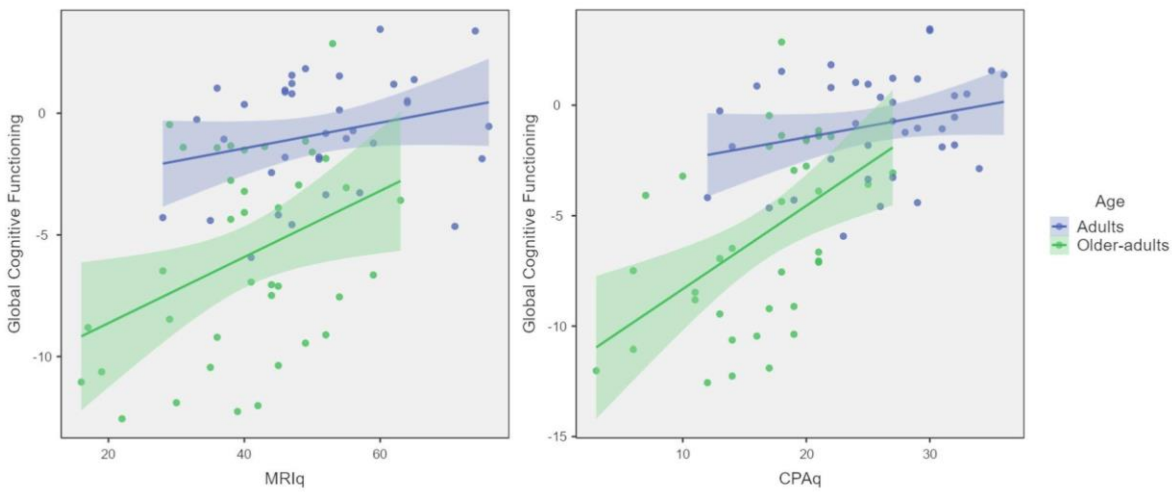

Figure 22. The two graphs show the effect of MRI (on the left-hand-side) and CPA (on the right-hand-side) on Global Cognitive Functioning in the two Age groups.

Single tasks of global cognitive functioning

The effect of MR (Model 1) and CPA (Model 2), including Age and CRI as predictors for each model, was also evaluated also on every single task of the CFD battery (complete results are reported in Table 26). The p-values were adjusted for the False Discovery Rate (Benjamini & Hochberg, 1995).

In Model 1, MRI was significant in predicting Alertness, backwards CORSI, and Phonemic Fluency tasks. In Model 2, CPA was found significant in predicting Trail Making

Test-A and Test-B, Object Naming task and Visuoconstruction task (See Table 36 for more details). For each test, the section concerning the workplace activity of MRI and CPA showed the greatest influence on the dependent variables.

	MRI Models					CPA Models				
	Predictors (β and p)			Model fit measures		Predictors (β and p)			Model fit measures	
Tasks	Age	CRI	MRI	R^2	*p*	Age	CRI	CPA	R^2	*p*
AL-1	**.75** ***p*=.011**	.11 *p*=.378	-.21 *p*=.154	.27	**<.001**	**.82** ***p*=.01**	.11 *p*=.451	-.10 *p*=.583	.24	**<.001**
AL-2	.51 *p*=.086	-.07 =.536	**-.28** ***p*=.05**	.22	**<.001**	.50 *p*=.142	-.07 *p*=.588	-.21 *p*=.225	.18	**.003**
TMT-A	**.88** ***p*=.002**	-.17 *p*=.173	-.11 *p*=439	.28	**<.001**	.53 *p*=.092	-.16 *p*=.159	**-.37** **p=.015**	.36	**<.001**
Div-RTs	**.75** ***p*=.011**	-.02 *p*=.896	-.05 *p*=.744	.16	**<.001**	**.87** **p=.015**	.01 *p*=.953	.08 *p*=.66	.16	**.008**
WL-T0	**-.93** ***p*<.001**	.19 *p*=.116	.16 *p*=.214	.35	**<.001**	**-.80** **p=.015**	.19 *p*=.117	.22 *p*=.152	.36	**<.001**
WL-T1	**-.73** ***p*=.011**	.09 *p*=.471	.17 *p*=.231	.23	**<.001**	**-.64** ***p*=.05**	.09 *p*=.549	.17 *p*=.312	.22	**<.001**
WL-T2	**-.71** ***p*=.011**	0 *p*=.974	.21 *p*=.163	.24	**<.001**	**-.72** ***p*=.03**	0 *p*=962	.15 *p*=.451	.21	**<.001**
WL-Rec	-.42 *p*=.175	.03 *p*=.834	.19 *p*=.214	.12	**.035**	-.21 *p*=.583	.03 *p*=.887	.29 p=.107	.14	**.014**
TMT-B	**.78** ***p*=.005**	**-.31** ***p*=.011**	-.12 *p*=.362	.31	**<.001**	.45 *p*=.138	**-.29** ***p*=.01**	**-.36** ***p*=.01**	.38	**<.001**
bk-CORSI	-.51 *p*=.08	.12 *p*=.362	**.29** ***p*=.05**	.23	**<.001**	-.46 *p*=.153	.12 *p*=.42	.23 *p*=.116	.20	**.001**
Sem-FLU	-.38 *p*=.175	**.43** ***p*<.001**	.10 *p*=.459	.28	**<.001**	-.34 *p*=.312	**.46** ***p*<.001**	.08 *p*=.635	.269	**<.001**
Phon-FLU	-.36 *p*=.185	**.38** ***p*=.003**	**.21** ***p*=.05**	.26	**<.001**	-.25 *p*=.451	**.38** ***p*=.005**	.23 *p*=.116	.26	**<.001**
Ob-NAM	-.36 *p*=.185	**.43** ***p*<.001**	.21 *p*=.116	.30	**<.001**	-.10 *p*=.771	**.42** ***p*<.001**	**.35** ***p*=.01**	.34	**<.001**

FIG	-.28 *p*=.361	**.28** ***p*=.05**	.21 *p*=.172	.17	**.005**	-.02 *p*=.962	**.26** ***p*=.05**	**.39** ***p*=.01**	.23	**<.001**

Table 26. The table shows the effect of the predictors in Model 1 (MRI) and Model 2 (CPA) in the 14 different tasks. *P-values* are adjusted for the False Discovery Rate (Benjamini & Hochberg, 1995). ***Note.*** CRI = Cognitive Reserve Index; MRI = Motor Reserve Index; CPA = Current Physical Activity; AL-1 = Simple Alertness; AL-2 = Complex Alertness; TMT-A = Trail-making Test Part A; Div-RTs = Divided Attention task; WL-T0 = Learning Phase of the Auditory Word List Learning task; WL-T1 = Short Term Recall of the Auditory Word List Learning task; WL-T2 = Long Term Recall of the Auditory Word List Learning task; WL-Rec = Recognition Phase of the Auditory Word List Learning task; TMT-B = Trail Making Test part B; bk-CORSI = Backwards Corsi Block-tapping test; Sem-FLU = Semantic Fluency task; Phon-FLU = Phonemic Fluency task; Ob-NAM = Vienna Object Naming task; FIG = Visuoconstruction task.

Discussion

This cross-sectional study aimed to verify whether PA carried out during the lifespan (proxy of MR) and CPA (carried out in the previous 12 months) could predict cognitive performance similarly to CR in adults and older adults (Petkus et al., 2019). The expectations were that both MR and CPA would have a critical role in cognition, in addition to age and CR.

Results show that age affects the global cognitive functioning: the Adult group performed better than the Older adult group. The same trend was found for most tasks (i.e., Alertness task, TMT-A and TMT-B, Divided Attention task and all Memory tasks). This result is in line with the literature showing relevant cognitive changes with ageing.

CR is known to influence cognitive functioning (e.g., Pettigrew & Soldan, 2019), and in the present study, indeed, high levels of CR predicted better performance overall (i.e., Global Cognitive Functioning Index) and several tasks in both age groups: TMT-B, Phonemic and Semantic fluency, Object Naming task, and Visuo-constructive task. TMT-B, Semantic and Phonemic fluency tasks have been repeatedly shown to be strictly dependent on CR (e.g., Llinàs-Reglà et al., 2017; Santos Nogueira et al., 2016). The Naming task involves low-frequency and culture-based items (e.g., pretzel) in which CR can play a crucial role (Montemurro et al., 2019). Finally, CR was predictive for the Visuo-constructive task, probably because it is highly demanding for individuals unfamiliar with the touchscreen, as many were in our sample (Darby et al., 2017; Stern, 2009; Valenzuela, 2019).

For our main research question, data showed that MR predicted: (1) Global cognitive functioning index and performance in some individual tasks; (2) Reaction times to an alert cue (AL-2 task); (3) Backwards CORSI task; and (4) Phonemic fluency task. The MR effect on Global cognitive functioning underscores that PA carried out across the lifespan is crucial in maintaining good cognitive health, mainly in individuals aged 65 and over. The MR effect, indeed, is markedly higher in the Older adults group than the Adults group. Regarding the specific tasks, in Reaction times with an alert cue (AL-2 task), participants had to inhibit the response to auditory stimulus and correctly respond as quickly as possible to the visual target. This could be considered an inhibition task involving executive functions, and, as the literature reports (Liu-Ambrose et al., 2010), the effect of PA is prominent in that domain. The same reasoning could explain the results of the bk-CORSI task and the Phonemic fluency task, which are both measures of executive functions, working memory, and cognitive flexibility.

We found a significant relationship between age and MR as it is plausible to think that, with ageing, people tend to reduce the amount of daily PA. However, MR explained additional variance within the regression models, meaning it should be a factor to consider when cognitive performance needs to be interpreted.

It must be underlined that when MR is taken as a single predictor within the regression models, it predicts the performance in almost all cognitive tasks. Thus, MR can be considered a crucial factor in predicting and interpreting cognitive performance, in addition to age and CR. Moreover, we found that the MRIq section devoted to Workplace activity is always the most relevant component of MR in predicting the outcome of all tasks, as people usually spend a lot of time in the workplace in their productive years.

However, a higher MR level does not correspond to a higher CR level, underlining that they are two different and independent types of reserve, both of which contribute in a different way to good cognitive functioning.

Regarding CPA (performed in the previous 12 months), data show that it predicts Global cognitive functioning and performance in several tasks. The effect of CPA on global cognitive functioning underlines that having an active lifestyle in the previous 12 months is important to maintain better global cognition. This finding is in line with the literature that shows that short-term PA training could lead to cognitive improvement. Our findings confirm a previous meta-analysis (Northey et al., 2018) showing that PE training improved cognitive functioning in participants over 50, regardless of their cognitive status at baseline.

We found MR and CR to be two independent predictors of better cognition. On the one hand, CR increases brain network connectivity and cognitive functionality (Varela-López et al., 2022). On the other, MR may lead to better brain oxygenation, which indirectly sustains better cognition (Kane et al., 2007; O'Brien et al., 2021). In addition, during ageing, individuals are more exposed to cerebrovascular diseases accompanied by several cognitive deficits (Gorelick et al., 2011). MR might help in preventing age-related motor disabilities, as well as neurodegenerative and vascular diseases, thus promoting better general cognitive functioning and quality of life (see also Siciliano et al., 2022).

Moreover, any type of PA implies the connections of individuals with the environment and their bodies. These activities involve numerous and coordinated actions, all requiring cognitive functioning. For example, perception and cognitive estimation of distance, size, shape and weight of objects or spaces; planning of movements of harms and legs and the correct sequence and timing of moves and gauging the necessary strength to reach the goal. Finally, correctly executing actions requires cognitive functioning in modulating the motor response and calibrating the action within the surrounding space. Thus, motor functions are highly interconnected with sensory and cognitive functions, which mutually yield functional behaviour.

This work is not exempt from limitations: (1) we used self-reported measures to quantify MR and the current status of PA, which may be biased by participants' answers; (2) the small size of our sample does not allow us to generalise our results; however, it could be a starting point for future investigations; (3) the cross-sectional nature of the study design does not allow to evaluate the genuine effect of PA over time. (4) we also reported only preliminary evidence of the psychometric properties and the usability of the MR Index and the current PA questionnaires. In particular, test-retest reliability was calculated in a small sample.

In conclusion, we found that, similarly to CR, MR and CPA are reliable predictors of global cognitive functioning and specific tasks involving executive functioning. Maintaining an active lifestyle in older age in terms of PA is just as essential as regular practice across the lifespan, not only for physical well-being but also for cognition. This highlights the intrinsic relationship between the two.

2.5 Motor Reserve and cognitive health in pathological conditions: preliminary evidence and future perspectives

The impact of motor reserve on the cognitive health of healthy older adults represents a valuable result within the framework of lifestyle and cognitive well-being. Together with Cognitive Reserve, Motor Reserve can be a potential modulator of the trajectories of ageing, allowing a more comprehensive understanding of the variability in the behavioural manifestation of cognitive ageing. Motor Reserve should be considered and integrated into prevention and intervention programs to guarantee older individuals the best possible quality of life for as long as possible.

Given our results in the healthy population, further investigations are needed to verify MR applicability and predictive value in clinical populations. A systematic exploration of the predictive implications of motor reserve would be crucial for a comprehensive understanding of cognitive health in neurological disorders or other health conditions. Examining the interplay between motor reserve and cognition in conditions where both motor function and cognition are affected, such as in multiple sclerosis or Parkinson's disease, holds promise for yielding insights into the relationship between these constructs and their role in predicting cognitive health.

Evidence supporting the relationship between cognition and MR in pathological conditions derived from a study by Siciliano and colleagues (2022). The authors explored the impact of motor reserve, measured by the Motor Reserve Index questionnaire (MRIq, Pucci et al., 2023), on motor and cognitive disability in individuals with spinocerebellar ataxia type 2 (SCA2). This subtype of cerebellar ataxia is a genetic neurological disorder characterized by progressive atrophy of the cerebellum characterized by motor (trunk ataxia, dysarthria, slowed saccadic movements, and chorea) and cognitive deficits. This work revealed a relationship between the MR of patients with SCA2 and their ability to manage motor and cognitive dysfunction. In particular, a higher MR correlated with milder motor symptoms and enhanced cognitive efficiency, especially in long-term memory and processing speed. Therefore, measuring MR at various times and in the early phases of SCA2 using specific instruments like the MRIq could be helpful in the implementation of early and tailored interventions that increase benefits and enhance the quality of life of those individuals.

Further preliminary corroboration derives from our study on multiple sclerosis (MS), presented and discussed in Chapter 1.3.3 of this thesis. In a cohort of 100 participants with MS, our investigation explored the combined impact of CR, disease duration, and motor disability (assessed by the Expanded Disability Status Scale, EDSS) in predicting cognitive health. As expected, we found that CR was related to improved cognitive performance even in case of prolonged disease duration. However, severe motor disability may attenuate this "protective effect". In other words, at a high level of motor impairment, CR is no longer protective and, at this point of the disease, a cognitive decline appears inevitable. This strengthens the brain-body connection, affirming the holistic nature of health where the functions intricately influence one another. The identification of a diminishing protective effect of CR in the case of severe motor disability highlights the need for tailored interventions that address both cognitive and motor aspects. Clinicians and healthcare professionals should go beyond traditional cognitive-focused strategies, recognizing the integral role of motor function in shaping the trajectory of cognitive health. This implies the development of comprehensive interventions that address the complex relations between the motor and cognitive domains. This will eventually lead to the development of a more advanced and successful clinical approach for people with severe motor disabilities in diseases like MS. A systematic study of this phenomenon in people with MS is necessary. However, it is reasonable to assume that MR could modulate both the extent of motor disability and cognitive efficiency.

The study of the relationship between motor reserve and cognitive efficiency could yield interesting results even when conducted in individuals with Intellectual Developmental Disability (IDD). Also, in this case, we do not have systematic results confirming this, but preliminary evidence suggests that it might align with our expectations. In the Scoping Review presented and discussed in Chapter 1.3.4, our findings underscore the pivotal role of daily physical activity (both structured and incidental) in improving the cognitive health of individuals with IDD. This underscores the interconnectedness of lifelong PA and cognitive well-being in this population. A future step would be the adaptation of the Motor Reserve Index questionnaire for individuals with IDD. This approach aims to provide a comprehensive understanding of how MR may influence the cognitive trajectory of individuals with IDD. This research also sets the stage for targeted interventions. As shown by several reviews (Bossink et al., 2017; Jacinto et al., 2021; McGarty & Melville, 2018), the prevailing sedentary lifestyle in this population is attributed to numerous physical and social barriers that hinder their possibility to engage in physical exercise. The concept of MR in people with IDD may facilitate personalized and effective strategies to enhance cognitive outcomes in this specific population.

In conclusion, understanding how motor and cognitive health interact opens up new possibilities for individualised and tailored interventions and early prevention programs. It also highlights how crucial Motor Reserve may be in determining the trajectory of cognitive well-being in various populations, from healthy older adults to neurological or even genetic conditions. In essence, fostering an increase in Motor Reserve level remains a tangible prospect, affirming that lifestyle modifications can serve as a dynamic means to enhance both motor and cognitive resilience, thereby offering the potential for improved quality of life across varied health conditions.

3. Conclusions

The aim of this PhD thesis was to further investigate the relationship between Cognitive Health and lifestyle factors. In particular, we explored how Cognitive Reserve (CR) and Motor Reserve (MR) are related with cognitive performance. Our hypothesis was that the greater Cognitive and Motor Reserves, the better the Cognitive Health in terms of cognitive performance. These relationships were explored in diverse populations, including healthy adults, fragile groups of individuals (Oldest-old and Subjective Cognitive Decline), people with neurodegenerative disorders (Multiple Sclerosis) and individuals with genetic conditions (Intellectual Developmental Disability). In addition, we integrated the concept of CR within the neuropsychological assessment, by developing new cognitive tests that also consider CR to generate cut-offs, thus, guaranteeing a more accurate interpretation of the examinee's performance.

Our investigation into the effects of CR and MR on cognitive health in adults, older adults, and pathological populations has provided valuable insights for the development of new protocols to prevent cognitive decline and rehabilitation programs for those with existing neurological diseases.

3.1 Summary of the findings and of their implications

While CR has emerged as a crucial concept in understanding the adaptive capacity of cognitive processes in the face of pathology, age-related changes, and neurological conditions, there are open questions that need further exploration. To address these gaps, the present PhD thesis investigated the interplay between CR and cognitive health across fragile (Oldest-old and Subjective Cognitive Decline) and clinical (Multiple Sclerosis and Intellectual Developmental Disability) populations, where the construct of CR was never systematically studied.

In the first study we involve a group of fragile individuals: people over ninety years. Advanced age represents a significant risk factor for cognitive decline, ad it is essential identify factors which play protective a role in this time of life (Pierce et al., 2017). Only very few studies have investigated non-pathological cognitive functioning in the people over 90 years. For this reason, we would to go further and investigate the oldest-old individuals to explore the relationship between their CR and their cognitive health. Our results shows that high CR predicts better cognitive efficiency, especially in executive function tasks. The power of CR in this population clearly shows how an active lifestyle benefits older adults and promotes well-preserved cognitive ageing. Whatever activity requires engaging, thinking, and social collaboration maintains our brain functioning and reduces hospitalisation and independence in daily living. Thus, promoting a cohesive and socially active community could be an excellent strategy for our advanced societies.

In the second study we involve Individuals with Subjective Cognitive Decline, who may be of particular interest in studying the effects of CR since both genetic and environmental risk factors co-occur to influence the likelihood of individuals with SCD progressing to dementia. In addition, one-third of these risk factors are modifiable, highlighting the feasibility and importance of early prevention (Wen et al., 2021). In this retrospective and longitudinal study, we found that individuals with SCD have higher CR, compared to individuals with Mild or Major Neurocognitive Disorders, suggesting a critical role of CR proxies in characterising the evolution of dementia and related neurocognitive disorders. These findings emphasize the critical role of lifestyle factors in promoting cognitive health, general well-being, and independence across the diverse trajectories of aging, reinforcing the significance of social connectedness and a sense of purpose in maintaining cognitive health.

In the third study, we investigated whether a higher level of CR may interact with the duration of the disease and motor disability in predicting cognitive health in individuals with Multiple Sclerosis (MS). Our results show as high CR level predict a better cognitive profile regardless of disease duration but not in the case of severe motor impairment. As MS is a degenerative disorder, our findings (i.e., an extended positive effect of CR throughout the disease) are crucial since they suggest that patients with a high CR may maintain a suitable quality of life for longer. Our results, which will be helpful to clinicians and researchers, indicate that high levels of CR are related to improved cognitive performance even in prolonged disease duration.

Cognitive reserve (CR) has not been studied in people with Intellectual Developmental Disability, a population with a high incidence of dementia. Commonly adopted CR proxies should be adapted to reflect more specifically the experiences of people with Intellectual Developmental Disability. In light of this, in the fourth study, we conducted a scoping review to identify CR proxies specifically relevant to people with this condition. Some of the identified proxies overlap with those commonly used for the general population: Education, Occupation, Physical activity, Leisure and Community and Social activities. Others were found to be specifically relevant for this population: Type of schooling, Parental educational level, Environmental stimulation and Living place. These proxies need to be considered in addition to the ones already used in studies on CR and Intellectual Developmental Disability and in clinical practice. Research on the interaction between CR and Intellectual Developmental Disability aims to encourage policies promoting lifestyle-based educational and preventive interventions and overcome participation barriers for people with Intellectual Developmental Disability.

In the literature, most neuropsychological tests typically reveal declining performance with increasing age and improved performance with higher education (Scheffels et al., 2023; Mondini et al., 2023). However, several other factors may impact cognitive health and, thus, performance on neuropsychological tests. The extensive body of research on CR and cognitive performance, prompted us to broaden our perspective and apply this construct to neuropsychological assessment. In the present thesis four new cognitive tools (GEMS, Tele-GEMS, Auto-GEMS and ENB-2) were presented. The common novel factor of these tools regards the cut-off scores that are generated considering not only age, education and sex, but also the CR. Using a regression-based approach (Crowford & Garthwaite 2007), we verify that

CR explain a substantial portion of the variance of the test scores, significantly improving the model fit, thus, allowing for a more precise interpretation of performance. The comprehensive consideration of CR across these studies emphasizes its crucial role in shaping cognitive performance. Incorporating CR into neuropsychological assessments enhances cognitive evaluations' precision, relevance, and individualization, guaranteeing a more holistic understanding of cognitive functioning. This evidence underscores the significance of recognizing and integrating CR into the neuropsychological testing, contributing to advancing precision medicine in cognitive assessment.

The second part of the present PhD thesis has been focused on the beneficial effect of physical activity (PA) on cognitive health. The positive effect of PA on body, brain and cognition has been extensively studied in the literature, concentrating mainly on the effects of PA training implemented over specific periods of time and on the effect of structured PA (i.e., physical exercise), but not on the daily incidental physical activity. We hypothesised that the beneficial effects of PA (both incidental and structured) may accumulate over time, representing a distinct kind of reserve: the Motor Reserve (MR). MR reflects the cumulative impact of a physically active lifestyle at every stage of life, potentially leading to enhanced cognitive functioning in late adulthood. This construct comes from attributing cumulative power to a physically active lifestyle at every stage of life, which may be associated with a greater ability to cope with normal or pathological motor skill decline expected in late adulthood (Bastos & Barbosa, 2020). In a study with healthy older adults, we found that similarly to CR, MR is reliable predictors of cognitive health. Maintaining a physically active lifestyle in older ages just as essential as the regular practice across the lifespan, not only for physical well-being but also for cognition. This result highlights the intrinsic relationship between motor and cognitive health, highlighting the long-term significance of a lifetime habit of physical activity for mental and physical health.

In conclusion, this thesis expands our understanding of how lifestyle factors influence cognitive health across diverse populations. The integration of CR into assessments and the identification of MR emphasize the enduring impact of a physically and cognitively active lifestyle. These findings have implications for personalized interventions, emphasizing the potential for long-term benefits and improved quality of life. The holistic approach presented here, encompassing both cognitive and motor reserves, paves the way for advanced strategies in cognitive assessment and intervention programs.

3.2 Limitations and future perspective

While these works offer valuable insights, certain limitations merit acknowledgment. Firstly, the cross-sectional design of some studies restricts the establishment of causality. Longitudinal studies could provide a more robust understanding of the dynamic relationships observed. Secondly, the focus on specific populations may limit the generalizability of findings. Future research should aim for more diverse samples to enhance the external validity of results. Additionally, the incorporation of multimodal assessments, such as neuroimaging and biomarkers, could deepen the understanding of the biological mechanisms underlying the observed relationships. Furthermore, expanding the investigation into the impact of sociodemographic factors, genetic predispositions, and cultural variations on CR and MR would enrich the scope of this research. Lastly, interventions tailored to enhance both cognitive and motor reserves could be explored, with the potential to offer more effective strategies for promoting cognitive health across the lifespan. In essence, this research lays the groundwork for interdisciplinary studies into the intricacies of lifestyle, cognition, and well-being.

ACKNOWLEDGMENTS

The realisation of this three-year PhD journey has been made possible by the voices, presence, and collaboration of numerous individuals, and I extend my gratitude to all those who have been a part of this experience. My sincere appreciation goes to my supervisor, Sara Mondini, whose guidance has been instrumental throughout this academic voyage. Prof. Mondini's encouragement of my curiosity and involvement in diverse projects has not only shaped me as a clinician and researcher but has also provided opportunities for exploration across a broad spectrum of topics. I express deep gratitude to professionals and experts, particularly Massimo Nucci, Giorgio Arcara, and Sonia Montemurro, whose experience and guidance in the research world have been invaluable. I would extend my appreciation to all collaborators of *Mondini's Lab*, whose contributions have made each research step feasible with their precious insights. A special acknowledgement to Giulia Sebastianutto, whose role and support in recent months have been indispensable.

I am grateful for the support of my PhD colleagues, who have turned this challenging journey into a collective achievement. We have never felt in competition, and the achievement of one of us has always been an achievement for all of us: Giulia, Giovanna, Silvia, Susanna, Chiara, and Pier Paolo, your support has made the doctorate more than just a "job."

I owe a debt of gratitude to my family for their support in my personal and professional evolution. Last but not least, my heartfelt thanks to Federico, my life partner, whose enduring love has made this journey less daunting.

References

Abdullah, A. H., Sharip, S., Rahman, A. H. A., & Bakar, L. (2021). Cognitive reserve in stroke patients. *PsyCh Journal*, *10*(3), 444–452. https://doi.org/https://doi.org/10.1002/pchj.423

Ahmadi, M. M., Lu, S., Chan, Y., Perez, S. E., Chen, K., & Mufson, E. J. (2017). Static and Dynamic Cognitive Reserve Proxy Measures: Interactions with Alzheimer's Disease Neuropathology and Cognition. *Journal of Alzheimer's Disease & Parkinsonism*, *07*(06). https://doi.org/10.4172/2161-0460.1000390

Amato, M. P, Portaccio, E., Goretti, B., Zipoli, V., Iudice, A., Della Pina, D., Malentacchi, G., Sabatini, S., Annunziata, P., Falcini, M., Mazzoni, M., Mortilla, M., Fonda, C., & De Stefano, N. (2010). Relevance of cognitive deterioration in early relapsing-remitting MS: a 3-year follow-up study. *Multiple Sclerosis*, *16*(12), 1474–1482. https://doi.org/10.1177/1352458510380089

Amato, M. P., Prestipino, E., Bellinvia, A., Niccolai, C., Razzolini, L., Pastò, L., Fratangelo, R., Tudisco, L., Fonderico, M., Mattiolo, P. L., Goretti, B., Zimatore, G. B., Losignore, N. A., Portaccio, E., & Lolli, F. (2019). Cognitive impairment in multiple sclerosis: An exploratory analysis of environmental and lifestyle risk factors. *PLoS ONE*, *14*(10). https://doi.org/10.1371/journal.pone.0222929

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

Amoretti, S., Cabrera, B., Garriga, M., Torrent, C., Vieta, E., & Bernardo, M. (2019). Cognitive Reserve Assessment Scale in Health (CRASH): the reliability and validity. *European Neuropsychopharmacology*, *29*, S313–S314. https://doi.org/10.1016/j.euroneuro.2018.11.486

Anatürk, M., Kaufmann, T., Cole, J. H., Suri, S., Griffanti, L., Zsoldos, E., Filippini, N., Singh-Manoux, A., Kivimäki, M., Westlye, L. T., Ebmeier, K. P., & de Lange, A. G. (2021). Prediction of brain age and cognitive age: Quantifying brain and cognitive maintenance in aging. *Human Brain Mapping*, *42*(6), 1626–1640. https://doi.org/10.1002/hbm.25316

Angevaren, M., Aufdemkampe, G., Verhaar, H. J. J., Aleman, A., & Vanhees, L. (2008). Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *The Cochrane Database of Systematic Reviews*, *3*, CD005381. https://doi.org/10.1002/14651858.CD005381.pub3

Ansado, J., Marsolais, Y., Methqal, I., Alary, F., & Joanette, Y. (2013). The adaptive aging brain: evidence from the preservation of communication abilities with age. *The European Journal of Neuroscience*, *37*(12), 1887–1895. https://doi.org/10.1111/ejn.12252

Anstey, K., & Christensen, H. (2014). Leisure activity associated with cognitive ability level, but not cognitive change. *Frontiers in Psychology*, *5*, 1–9. https://doi.org/10.3389/fpsyg.2014.01176

Arenaza-Urquijo, E. M., de Flores, R., Gonneaud, J., Wirth, M., Ourry, V., Callewaert, W., Landeau, B., Egret, S., Mézenge, F., Desgranges, B., & Chételat, G. (2017). Distinct effects of late adulthood cognitive and physical activities on gray matter volume. *Brain Imaging and Behavior*, *11*(2), 346–356. https://doi.org/10.1007/s11682-016-9617-3

Arenaza-Urquijo, E. M., Wirth, M., & Chételat, G. (2015). Cognitive reserve and lifestyle: Moving towards preclinical Alzheimer's disease. *Frontiers in Aging Neuroscience*, *7*, 1–12.

https://doi.org/10.3389/fnagi.2015.00134

Arksey, H., & O'Malley, L. (2005). Scoping studies: Towards a methodological framework. *International Journal of Social Research Methodology: Theory and Practice*, *8*(1), 19–32. https://doi.org/10.1080/1364557032000119616

Artemiadis, A., Bakirtzis, C., Ifantopoulou, P., Zis, P., Bargiotas, P., Grigoriadis, N., & Hadjigeorgiou, G. (2020). The role of cognitive reserve in multiple sclerosis: A cross-sectional study in 526 patients. *Multiple Sclerosis and Related Disorders*, *41*, 102047. https://doi.org/https://doi.org/10.1016/j.msard.2020.102047

Arvio, M., & Bjelogrlic-Laakso, N. (2021). Screening of dementia indicating signs in adults with intellectual disabilities. *Journal of Applied Research in Intellectual Disabilities*, *34*(6), 1463–1467. https://doi.org/10.1111/jar.12888

Azaiza, F., Rimmerman, A., Croitoru, T., & Naon, D. (2011). Participation in leisure activities by Arab adults with intellectual disabilities living in the community. *International Journal of Social Welfare*, *20*(1), 97–103. https://doi.org/10.1111/j.1468-2397.2009.00703.x

Baranyi, G., Welstead, M., Corley, J., Deary, I. J., Muniz-Terrera, G., Redmond, P., Shortt, N., Taylor, A. M., Ward Thompson, C., Cox, S. R., & Pearce, J. (2022). Association of Life-Course Neighborhood Deprivation With Frailty and Frailty Progression From Ages 70 to 82 Years in the Lothian Birth Cohort 1936. *American Journal of Epidemiology*, *191*(11), 1856–1866. https://doi.org/10.1093/aje/kwac134

Basagni, B., Di Rosa, E., Bertoni, D., Mondini, S., & De Tanti, A. (2023). Long term effects of severe acquired brain injury: A follow-up investigation on the role of cognitive reserve on cognitive outcomes. *Applied Neuropsychology: Adult*, *0*(0), 1–6. https://doi.org/10.1080/23279095.2022.2160251

Bastos, P. A. D., & Barbosa, R. (2022). Motor reserve: How to build neuronal resilience against ageing and neurodegeneration? *Revue Neurologique*, *178*(8), 845–854. https://doi.org/10.1016/j.neurol.2021.12.012

Batty, G. D., Deary, I. J., & Gottfredson, L. S. (2007). Premorbid (early life) IQ and Later Mortality Risk: Systematic Review. *Annals of Epidemiology, 17(4)*, 278–288. https://doi.org/10.1016/j.annepidem.2006.07.010

Beber, E., & Biswas, A. B. (2009). Marriage and family life in people with developmental disability. *International Journal of Culture and Mental Health*, *2*(2), 102–108. https://doi.org/10.1080/17447140903205317

Belfiore, P. J., Browder, D. M., & Charles Mace, F. (1993). Effects of community and center-based settings on the alertness of persons with profound mental retardation. *Journal of applied behavior analysis*, *26*(3), 401–402.

Bell, M. (2020). People with intellectual disabilities and labour market inclusion: What role for EU labour law? *European Labour Law Journal*, *11*(1), 3–25. https://doi.org/10.1177/2031952519882953

Benedict, R. H. B., Amato, M. P., DeLuca, J., & Geurts, J. J. G. (2020). Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. *The Lancet Neurology*, *19*(10), 860–871. https://doi.org/https://doi.org/10.1016/S1474-4422(20)30277-5

Benedict, R. H. B., & Zivadinov, R. (2011). Risk factors for and management of cognitive dysfunction in multiple sclerosis. *Nature Reviews Neurology*, *7*(6), 332–342. https://doi.org/10.1038/nrneurol.2011.61

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society*, *57*(1), 289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

Berggren, R., Nilsson, J., & Lövdén, M. (2018). Education does not affect cognitive decline in aging: A Bayesian assessment of the association between education and change in cognitive performance. *Frontiers in Psychology*, *9*, 1–9. https://doi.org/10.3389/fpsyg.2018.01138

Bessi, V., Mazzeo, S., Padiglioni, S., Piccini, C., Nacmias, B., Sorbi, S., & Bracco, L. (2018). From Subjective Cognitive Decline to Alzheimer's Disease: The Predictive Role of Neuropsychological Assessment, Personality Traits, and Cognitive Reserve. A 7-Year Follow-Up Study. *Journal of Alzheimer's Disease*, *63*, 1523–1535. https://doi.org/10.3233/JAD-171180

Bherer, L., Erickson, K. I., & Liu-Ambrose, T. (2013). A review of the effects of physical activity and exercise on cognitive and brain functions in older adults. *Journal of Aging Research*. https://doi.org/10.1155/2013/657508

Biggs, E. E., & Carter, E. W. (2016). Quality of Life for Transition-Age Youth with Autism or Intellectual Disability. *Journal of Autism and Developmental Disorders*, *46*(1), 190–204. https://doi.org/10.1007/s10803-015-2563-x

Blessed, G., Tomlinson, B. E., & Roth, M. (1968). The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *The British Journal of Psychiatry : The Journal of Mental Science*, *114*(512), 797–811. https://doi.org/10.1192/bjp.114.512.797

Blondell, S. J., Hammersley-Mather, R., & Veerman, J. L. (2014). Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. *BMC Public Health*, *14*(1), 1–12. https://doi.org/10.1186/1471-2458-14-510

Boat, T. F., & Wu, J. T. . (2015). *Mental Disorders and Disabilities Among Low-Income Children* (National Academies Press (ed.)). 10.17226/21780

Borland, E., Nägga, K., Nilsson, P. M., Minthon, L., Nilsson, E. D., & Palmqvist, S. (2017). The Montreal Cognitive Assessment: Normative Data from a Large Swedish Population-Based Cohort. *Journal of Alzheimer's Disease*, *59*(3), 893–901. https://doi.org/10.3233/JAD-170203

Borsboom, D. (2005). Measuring the Mind: Conceptual Issues in Contemporary Psychometrics. In *Measuring the Mind: Conceptual Issues in Contemporary Psychometrics.* Cambridge University Press. https://doi.org/10.1017/CBO9780511490026

Borsboom, D., Mellenbergh, G. J., & Van Heerden, J. (2003). The Theoretical Status of Latent Variables. *Psychological Review*, *110*(2), 203–219. https://doi.org/10.1037/0033-295X.110.2.203

Bossink, L. W. M., van der Putten, A. A., & Vlaskamp, C. (2017). Understanding low levels of physical activity in people with intellectual disabilities: A systematic review to identify barriers and facilitators. *Research in Developmental Disabilities*, *68*, 95–110. https://doi.org/10.1016/j.ridd.2017.06.008

Bourke, J., Ricciardo, B., Bebbington, A., Aiberti, K., Jacoby, P., Dyke, P., Msall, M., Bower, C., & Leonard, H. (2008). Physical and mental health in mothers of children with Down syndrome. *The Journal of Pediatrics*, *153*(3), 320–326. https://doi.org/10.1016/j.jpeds.2008.02.047

Boyle, R., Knight, S. P., De Looze, C., Carey, D., Scarlett, S., Stern, Y., Robertson, I. H., Kenny, R. A., & Whelan, R. (2021). Verbal intelligence is a more robust cross-sectional measure of cognitive reserve than level of education in healthy older adults. *Alzheimer's Research and Therapy*, *13*(1). https://doi.org/10.1186/s13195-021-00870-z

Brewster, P. W. H., Melrose, R. J., Marquine, M. J., Johnson, J. K., Napoles, A., MacKay-Brandt, A., Farias, S., Reed, B., & Mungas, D. (2014). Life experience and demographic influences on cognitive function in older adults. *Neuropsychology*, *28*(6), 846–858. https://doi.org/10.1037/neu0000098

Brochet, B., & Ruet, A. (2019). Cognitive Impairment in Multiple Sclerosis With Regards to Disease Duration and Clinical Phenotypes. *Frontiers in Neurology*, *10*.. https://doi.org/10.3389/fneur.2019.00261

Burham, K. P., & Anderson, D. R. (2002). *Model selection and multi-model inference: Vol. Springer*.

Burnham, K. P., Anderson, D. R., & Huyvaert, K. P. (2011). AIC model selection and multimodel inference in behavioral ecology: Some background, observations, and comparisons. *Behavioral Ecology and Sociobiology*, *65*(1), 23–35. https://doi.org/10.1007/s00265-010-1029-6

Busch, R. M., & Chapin, J. S. (2008). Review of Normative Data For Common Screening Measures Used to Evaluate Cognitive Functioning in Elderly Individuals. *The Clinical Neuropsychologist*, *22*(4), 620–650. https://doi.org/10.1080/13854040701448793

Butler, S. M., & Snowdon, D. A. (1996). Trends in mortality in older women: findings from the Nun Study. *The Journals of Gerontology*, *51*(4), S201-8. https://doi.org/10.1093/geronb/51b.4.s201

Buttimer, J., & Tierney, E. (2005). Patterns of leisure participation among adolescents with a mild intellectual disability. *Journal of Intellectual Disabilities*, *9*(1), 25–42. https://doi.org/10.1177/1744629505049728

Cabeza, R., Albert, M., Belleville, S., Craik, F. I. M., Duarte, A., Grady, C. L., Lindenberger, U., Nyberg, L., Park, D. C., Reuter-Lorenz, P. A., Rugg, M. D., Steffener, J., & Rajah, M. N. (2018). Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. *Nature Reviews Neuroscience*, *19(11),* 701–710. Nature Publishing Group. https://doi.org/10.1038/s41583-018-0068-2

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *NeuroImage*, *17*(3), 1394–1402. https://doi.org/10.1006/nimg.2002.1280

Cao, T., Zhang, S., Yu, M., Zhao, X., & Wan, Q. (2022). The Chinese Translation Study of the Cognitive Reserve Index Questionnaire. *Frontiers in Psychology*, *13*. https://doi.org/10.3389/fpsyg.2022.948740

Carta, E., Riccardi, A., Marinetto, S., Mattivi, S., Selini, E., Pucci, V., & Mondini, S. (2023). Over ninety years old: Does high cognitive reserve still help brain efficiency? *Psychological Research*. https://doi.org/10.1007/s00426-023-01881-1

Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical Activity, Exercise, and Physical Fitness: Definitions and Distinctions for Health-Related Research CARL. *Public Health Reports*, *100*(2), 126–131. https://doi.org/10.1093/nq/s9-IX.228.365-f

Cassilhas, R. C., Viana, V. A. R., Grassmann, V., Santos, R. T., Santos, R. F., Tufik, S., & Mello, M. T. (2007). The impact of resistance exercise on the cognitive function of the elderly. *Medicine and Science in Sports and Exercise*, *39*(8), 1401–1407. https://doi.org/10.1249/mss.0b013e318060111f

Çebi, M., & Kulce, S. N. (2022). The Turkish translation study of the Cognitive Reserve Index Questionnaire (CRIq). *Applied Neuropsychology. Adult*, *29*(6), 1536–1542. https://doi.org/10.1080/23279095.2021.1896519

Cesar, K. G., Yassuda, M. S., Porto, F. H. G., Brucki, S. M. D., & Nitrini, R. (2019). MoCA Test: normative and diagnostic accuracy data for seniors with heterogeneous educational levels in Brazil. *Arquivos de Neuro-Psiquiatria*, *77*(11), 775–781. https://doi.org/10.1590/0004-282x20190130

Chan, D., Shafto, M., Kievit, R., Matthews, F., Spink, M., Valenzuela, M., & Henson, R. N. (2018). Lifestyle activities in mid-life contribute to cognitive reserve in late-life, independent of education, occupation, and late-life activities. *Neurobiology of Aging*, *70*, 180–183. https://doi.org/https://doi.org/10.1016

Chen, C. C., Ringenbach, S. D. R., Crews, D., Kulinna, P. H., & Amazeen, E. L. (2015). The association between a single bout of moderate physical activity and executive function in young adults with Down syndrome: A preliminary study. *Journal of Intellectual Disability Research*, *59*(7), 589–598. https://doi.org/10.1111/jir.12163

Cheng, S. T. (2016). Cognitive Reserve and the Prevention of Dementia: the Role of Physical and Cognitive Activities. *Current Psychiatry Reports*, *18*(9). https://doi.org/10.1007/s11920-016-0721-2

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *The Lancet Neurology*, *7*(12), 1139–1151. https://doi.org/https://doi.org/10.1016/S1474-4422(08)70259-X

Choi, C. H., Park, S., Park, H.-J., Cho, Y., Sohn, B. K., & Lee, J.-Y. (2016). Study on Cognitive Reserve in Korea Using Korean Version of Cognitive Reserve Index Questionnaire. *Journal of Korean Neuropsychiatric Association*, *55*(3), 256–263. https://doi.org/10.4306/jknpa.2016.55.3.256

Chou, C.-H., Hwang, C.-L., & Wu, Y.-T. (2012). Effect of Exercise on Physical Function, Daily Living Activities, and Quality of Life in the Frail Older Adults: A Meta-Analysis. *Archives of Physical Medicine and Rehabilitation*, *93*(2), 237–244. https://doi.org/10.1016/j.apmr.2011.08.042

Ciccarelli, N., Colombo, B., Pepe, F., Magni, E., Antonietti, A., & Silveri, M. C. (2022). Cognitive reserve: a multidimensional protective factor in Parkinson's disease related cognitive impairment. *Aging, Neuropsychology, and Cognition*, *29*(4), 687–702. https://doi.org/10.1080/13825585.2021.1892026

Clare, L., Wu, Y. T., Teale, J. C., MacLeod, C., Matthews, F., Brayne, C., & Woods, B. (2017). Potentially modifiable lifestyle factors, cognitive reserve, and cognitive function in later life: A cross-sectional study. *PLoS Medicine*, *14*(3), 1–14. https://doi.org/10.1371/journal.pmed.1002259

Colangeli, S., Boccia, M., Verde, P., Guariglia, P., Bianchini, F., & Piccardi, L. (2016). Cognitive Reserve in Healthy Aging and Alzheimer's Disease. *American Journal of Alzheimer's Disease and Other Dementias*, *31*(5), 443–449. https://doi.org/10.1177/1533317516653826

Colberg, S. R., Sigal, R. J., Fernhall, B., Regensteiner, J. G., Blissmer, B. J., Rubin, R. R., Chasan-Taber, L., Albright, A. L., & Braun, B. (2010). Exercise and Type 2 Diabetes. *Diabetes Care*, *33*(12), e147–e167. https://doi.org/10.2337/dc10-9990

Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., Webb, A., Jerome, G. J., Marquez, D. X., & Elavsky, S. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(9), 3316–3321. https://doi.org/10.1073/pnas.0400266101

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychological Science*, *14*(2), 125–130. https://doi.org/10.1111/1467-9280.t01-1-01430

Contador, I., Alzola, P., Stern, Y., de la Torre-Luque, A., Bermejo-Pareja, F., & Fernández-Calvo, B. (2023). Is cognitive reserve associated with the prevention of cognitive decline after stroke? A Systematic review and meta-analysis. *Ageing Research Reviews*, *84*. https://doi.org/10.1016/j.arr.2022.101814

Contador, I., del Ser, T., Llamas, S., Villarejo, A., Benito-León, J., & Bermejo-Pareja, F. (2017). Impact of literacy and years of education on the diagnosis of dementia: A population-based study. *Journal of Clinical and Experimental Neuropsychology*, *39*(2), 112–119. https://doi.org/10.1080/13803395.2016.1204992

Conte, F., Rinaldi, L., Gerosa, T., Mondini, S., Costantini, G., & Girelli, L. (2023). Cognitive Reserve Potential: Capturing Cognitive Resilience Capability in Adolescence. *Assessment*, *0*(0), 10731911231183364. https://doi.org/10.1177/10731911231183363

Cook, D. A., & Beckman, T. J. (2006). Current Concepts in Validity and Reliability for Psychometric Instruments: Theory and Application. *The American Journal of Medicine*, *119*(2), 166.e7-166.e16. https://doi.org/10.1016/j.amjmed.2005.10.036

Cooper, S.-A., Melville, C., & Morrison, J. (2004). People with intellectual disabilities. *British Medical Journal*, *329*(7463), 414–415. https://doi.org/10.1136/bmj.329.7463.414

Coppus, A. M. W. (2013). People with intellectual disability: What do we know about adulthood and life expectancy? *Developmental Disabilities Research Reviews*, *18*(1), 6–16. https://doi.org/10.1002/ddrr.1123

Cornelissen, V. A., & Fagard, R. H. (2005). Effects of Endurance Training on Blood Pressure, Blood Pressure–Regulating Mechanisms, and Cardiovascular Risk Factors. *Hypertension*, *46*(4), 667–675. https://doi.org/10.1161/01.HYP.0000184225.05629.51

Couzens, D, Cuskelly, M., & Jobling, A. (2004). The Stanford Binet fourth edition and its use with individuals with Down Syndrome: cautions for clinicians. *International Journal of Disability, Development and Education*, *51*(1), 39–56. https://doi.org/10.1080/1034912042000182193

Couzens, D., Haynes, M., & Cuskelly, M. (2012). Individual and Environmental Characteristics Associated with Cognitive Development in Down Syndrome: A Longitudinal Study. *Journal of*

Applied Research in Intellectual Disabilities, *25*(5), 396–413. https://doi.org/10.1111/j.1468-3148.2011.00673.x

Cowansage, K. K., Shuman, T., Dillingham, B. C., Chang, A., Golshani, P., & Mayford, M. (2014). Direct Reactivation of a Coherent Neocortical Memory of Context. *Neuron*, *84*(2), 432–441. https://doi.org/10.1016/j.neuron.2014.09.022

Cramer, S. C., Sur, M., Dobkin, B. H., O'Brien, C., Sanger, T. D., Trojanowski, J. Q., Rumsey, J. M., Hicks, R., Cameron, J., Chen, D., Chen, W. G., Cohen, L. G., deCharms, C., Duffy, C. J., Eden, G. F., Fetz, E. E., Filart, R., Freund, M., Grant, S. J., … Vinogradov, S. (2011). Harnessing neuroplasticity for clinical applications. *Brain : A Journal of Neurology*, *134*(6), 1591–1609. https://doi.org/10.1093/brain/awr039

Crawford, J. R., & Garthwaite, P. H. (2007). Using regression equations built from summary data in the neuropsychological assessment of the individual case. *Neuropsychology*, *21*(5), 611–620. https://doi.org/10.1037/0894-4105.21.5.611

Cronbach, L. J. (1970). *Essentials of Psychological Testing, 3rd edition.* New York: Harper & Row.

Da Silva, A. M., Cavaco, S., Moreira, I., Bettencourt, A., Santos, E., Pinto, C., Gonçalves, A., Coutinho, E., Samões, R., Dias, C. C., Teixeira-Pinto, A., Da Silva, B. M., & Montalban, X. (2015). Cognitive reserve in multiple sclerosis: Protective effects of education. *Multiple Sclerosis*, *21*(10), 1312–1321. https://doi.org/10.1177/1352458515581874

Darby, R. R., Brickhouse, M., Wolk, D. A., & Dickerson, B. C. (2017). Effects of cognitive reserve depend on executive and semantic demands of the task. *Journal of Neurology, Neurosurgery and Psychiatry*. https://doi.org/10.1136/jnnp-2017-315719

DaWalt, L. S., Usher, L. V., Greenberg, J. S., & Mailick, M. R. (2019). Friendships and social participation as markers of quality of life of adolescents and adults with fragile X syndrome and autism. *Autism*, *23*(2), 383–393. https://doi.org/10.1177/1362361317709202

de Medeiros Rimkus, C., Avolio, I. M. B., Miotto, E. C., Pereira, S. A., Mendes, M. F., Callegaro, D., & da Costa Leite, C. (2018). The protective effects of high-education levels on cognition in different stages of multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *22*, 41–48. https://doi.org/https://doi.org/10.1016/j.msard.2018.03.001

Diamantopoulos, A., & Siguaw, J. A. (2006). Formative versus reflective indicators in organizational measure development: A comparison and empirical illustration. *British Journal of Management*, *17*(4), 263–282. https://doi.org/10.1111/j.1467-8551.2006.00500.x

Dobson, R., & Giovannoni, G. (2019). Multiple sclerosis – a review. *European Journal of Neurology*, *26*(1), 27–40. https://doi.org/https://doi.org/10.1111/ene.13819

Dodd, P., Guerin, S., McEvoy, J., Buckley, S., Tyrrell, J., & Hillery, J. (2008). A study of complicated grief symptoms in people with intellectual disabilities. *Journal of Intellectual Disability Research : JIDR*, *52*(Pt 5), 415–425. https://doi.org/10.1111/j.1365-2788.2008.01043.x

Dressler, A., Perelli, V., Bozza, M., Bargagna, S., Benninger, F., Kosheleva, A., & Schernhammer, E. (2021). The surplus effect in adaptive behaviour in down syndrome: What can promote it? *Brain Sciences*, *11*(9). https://doi.org/10.3390/brainsci11091188

Dunn, M., Dunn, L. M., & Nelson, N. (1997). *The British Picture Vocabulary Scale Second Edition.*

NFER-Nelson.

Dustman, R. E., Ruhling, R. O., Russell, E. M., Shearer, D. E., Bonekat, H. W., Shigeoka, J. W., Wood, J. S., & Bradford, D. C. (1984). Aerobic exercise training and improved neuropsychological function of older individuals. *Neurobiology of Aging*, *5*(1), 35–42. https://doi.org/10.1016/0197-4580(84)90083-6

Égerházi, A., Berecz, R., Bartók, E., & Degrell, I. (2007). Automated Neuropsychological Test Battery (CANTAB) in mild cognitive impairment and in Alzheimer's disease. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *31*(3), 746–751. https://doi.org/https://doi.org/10.1016/j.pnpbp.2007.01.011

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Hu, L., Morris, K. S., White, S. M., Wójcicki, T. R., McAuley, E., & Kramer, A. F. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus*, *19*(10), 1030–1039. https://doi.org/10.1002/hipo.20547

Evenhuis, H. (2018). The Dementia Questionnaire for People with Learning Disabili- ties. Prasher, V. (Ed.), Neuropsychological Assessments of Dementia in Down Syndrome and Intellectual Disabilities. *Springer*.

Evenhuis, H. M. (1996). Further evaluation of the Dementia Questionnaire for Persons with Mental Retardation (DMR). *Journal of Intellectual Disability Research*, *40*(4), 369–373. https://doi.org/https://doi.org/10.1046/j.1365-2788.1996.786786.x

Fancourt, D., & Steptoe, A. (2018). Cultural engagement predicts changes in cognitive function in older adults over a 10 year period: Findings from the English Longitudinal Study of Ageing. *Scientific Reports*, *8*(1). https://doi.org/10.1038/s41598-018-28591-8

Farran, N., & Darwish, H. (2023). *behavioral sciences Validation of the Cognitive Reserve Index Questionnaire (CRIq) in Arabic*. *Behavioral sciences*, *13*(12), 1006. https://doi.org/10.3390/bs13121006

Fernández, A. L., & Abe, J. (2018). Bias in cross-cultural neuropsychological testing: problems and possible solutions. *Culture and Brain*, *6*, 1–35.

Ferreira, D., Machado, A., Molina, Y., Nieto, A., Correia, R., Westman, E., & Barroso, J. (2017). Cognitive variability during middle-age: Possible association with neurodegeneration and cognitive reserve. *Frontiers in Aging Neuroscience*, *9*. https://doi.org/10.3389/fnagi.2017.00188

Festa, R. R., Jofré-Saldía, E., Candia, A. A., Monsalves-Álvarez, M., Flores-Opazo, M., Peñailillo, L., Marzuca-Nassr, G. N., Aguilar-Farias, N., Fritz-Silva, N., Cancino-Lopez, J., Soto-Sánchez, J., Sepulveda, C., Huerta Ojeda, Á., Núñez-Espinosa, C., Valladares-Ide, D., & Jannas-Vela, S. (2023). Next steps to advance general physical activity recommendations towards physical exercise prescription: a narrative review. *British Medical Journal Open Sport & Exercise Medicine*, *9*(4), e001749. https://doi.org/10.1136/bmjsem-2023-001749

Finucane, M. M., Stevens, G. A., Cowan, M. J., Danaei, G., Lin, J. K., Paciorek, C. J., Singh, G. M., Gutierrez, H. R., Lu, Y., Bahalim, A. N., Farzadfar, F., Riley, L. M., Ezzati, M., & Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). (2011). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. *Lancet*, *377*(9765), 557–567. https://doi.org/10.1016/S0140-6736(10)62037-5

Fleming, V., Piro-Gambetti, B., Patrick, A., Zammit, M., Alexander, A., Christian, B. T., Handen, B., Cohen, A., Klunk, W., Laymon, C., Ances, B. M., Plante, D. T., Okonkwo, O., & Hartley, S. L. (2021). Physical activity and cognitive and imaging biomarkers of Alzheimer's disease in down syndrome. *Neurobiology of Aging*, *107*, 118–127. https://doi.org/10.1016/j.neurobiolaging.2021.07.016

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. https://doi.org/https://doi.org/10.1016/0022-3956(75)90026-6

Fraser, E. E., Downing, M. G., Biernacki, K., McKenzie, D. P., & Ponsford, J. L. (2019). Cognitive reserve and age predict cognitive recovery after mild to severe traumatic brain injury. *Journal of Neurotrauma*, *36*(19), 2753–2761. https://doi.org/10.1089/neu.2019.6430

Fratiglioni, L., Marseglia, A., & Dekhtyar, S. (2020). Ageing without dementia: can stimulating psychosocial and lifestyle experiences make a difference? *The Lancet Neurology*, *19*(6), 533–543. https://doi.org/https://doi.org/10.1016/S1474-4422(20)30039-9

Fratiglioni, L., Paillard-Borg, S., & Winblad, B. (2004). An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurology*, *3*(6), 343–353. https://doi.org/10.1016/S1474-4422(04)00767-7

Fuchs, E., & Flügge, G. (2014). Adult neuroplasticity: more than 40 years of research. *Neural Plasticity*, 541870. https://doi.org/10.1155/2014/541870

Gasteiger-Klicpera, B., Klicpera, C., Gebhardt, M., & Schwab, S. (2013). Attitudes and experiences of parents regarding inclusive and special school education for children with learning and intellectual disabilities. *International Journal of Inclusive Education*, *17*(7), 663–681. https://doi.org/10.1080/13603116.2012.706321

Ghaffar, O., Fiati, M., & Feinstein, A. (2012). Occupational Attainment as a Marker of Cognitive Reserve in Multiple Sclerosis. *PLoS ONE*, *7*(10). https://doi.org/10.1371/journal.pone.0047206

Goenarjo, R., Bosquet, L., Berryman, N., Metier, V., Perrochon, A., Fraser, S. A., & Dupuy, O. (2020). Cerebral Oxygenation Reserve: The Relationship Between Physical Activity Level and the Cognitive Load During a Stroop Task in Healthy Young Males. *International Journal of Environmental Research and Public Health*, *17*(4). https://doi.org/10.3390/ijerph17041406

Gorelick, P. B., Scuteri, A., Black, S. E., DeCarli, C., Greenberg, S. M., Iadecola, C., Launer, L. J., Laurent, S., Lopez, O. L., Nyenhuis, D., Petersen, R. C., Schneider, J. A., Tzourio, C., Arnett, D. K., Bennett, D. A., Chui, H. C., Higashida, R. T., Lindquist, R., Nilsson, P. M., … Seshadri, S. (2011). Vascular Contributions to Cognitive Impairment and Dementia. *Stroke*, *42*(9), 2672–2713. https://doi.org/10.1161/STR.0b013e3182299496

Gregory, R. (2015). *Psychological Testing: History, Principles, and Applications. 7th ed. Essex*. UK: Pearson Education Limited.

Groot, C., Hooghiemstra, A. M., Raijmakers, P. G. H. M., van Berckel, B. N. M., Scheltens, P., Scherder, E. J. A., van der Flier, W. M., & Ossenkoppele, R. (2016). The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. *Ageing*

Research Reviews, *25*, 13–23. https://doi.org/10.1016/j.arr.2015.11.005

Grzegorski, T., & Losy, J. (2017). *Cognitive impairment in multiple sclerosis – a review of current knowledge and recent research*. *28*(8), 845–860. https://doi.org/doi:10.1515/revneuro-2017-0011

Gu, L., & Xu, H. (2022). Effect of cognitive reserve on cognitive function in Parkinson's disease. *Neurological Sciences*, *43*(7), 4185–4192. https://doi.org/10.1007/s10072-022-05985-1

Guralnick, M. J., & Weinhouse, E. (1984). Peer-related social interactions of developmentally delayed young children: Development and characteristics. *Developmental Psychology*, *20*, 815–827. https://doi.org/10.1037/0012-1649.20.5.815

Haddad, F., Bourke, J., Wong, K., & Leonard, H. (2018). An investigation of the determinants of quality of life in adolescents and young adults with Down syndrome. *PLoS ONE*, *13*(6). https://doi.org/10.1371/journal.pone.0197394

Harrison, S. L., Sajjad, A., Bramer, W. M., Ikram, M. A., Tiemeier, H., & Stephan, B. C. M. (2015). Exploring strategies to operationalize cognitive reserve: A systematic review of reviews. *Journal of Clinical and Experimental Neuropsychology*, *37*(3), 253–264. https://doi.org/10.1080/13803395.2014.1002759

Hatami, J., Feizi khajeh, A., Rahiminezhad, A., Farahani, H., & Rezapour, T. (2020). Validation of Persian Version of Cognitive Reserve Index Questionnaire (CRIq). *Journal of Applied Psychological Research*, *11*(1), 87–99. https://doi.org/10.22059/japr.2020.288425.643348

Haxby, J. V. (1989). Neuropsychological evaluation of adults with Down's syndrome: patterns of selective impairment in non-demented old adults. *Journal of Intellectual Disability Research*, *33*(3), 193–210. https://doi.org/https://doi.org/10.1111/j.1365-2788.1989.tb01467.x

Heled, E., Aloni, R., & Achiron, A. (2021). Cognitive functions and disability progression in relapsing-remitting multiple sclerosis: A longitudinal study. *Applied Neuropsychology: Adult*, *28*(2), 210–219. https://doi.org/10.1080/23279095.2019.1624260

Herbert, C., House, M., Dietzman, R., Climstein, M., Furness, J., & Kemp-Smith, K. (2022). Blue Zones: Centenarian Modes of Physical Activity: A Scoping Review. *Journal of Population Ageing*. https://doi.org/10.1007/s12062-022-09396-0

Herrero, P., Contador, I., Stern, Y., Fernández-Calvo, B., Sánchez, A., & Ramos, F. (2020). Influence of cognitive reserve in schizophrenia: A systematic review. *Neuroscience and Biobehavioral Reviews*, *108,* 149–159. https://doi.org/10.1016/j.neubiorev.2019.10.019

Hindin, S. B., & Zelinski, E. M. (2012). Extended practice and aerobic exercise interventions benefit untrained cognitive outcomes in older adults: a meta-analysis. *Journal of the American Geriatrics Society*, *60*(1), 136–141. https://doi.org/10.1111/j.1532-5415.2011.03761.x

Hou, Y., Dan, X., Babbar, M., Wei, Y., Hasselbalch, S. G., Croteau, D. L., & Bohr, V. A. (2019). Ageing as a risk factor for neurodegenerative disease. *Nature Reviews Neurology*, *15*(10), 565–581. https://doi.org/10.1038/s41582-019-0244-7

Ibañez, J., Izquierdo, M., Argüelles, I., Forga, L., Larrión, J. L., García-Unciti, M., Idoate, F., & Gorostiaga, E. M. (2005). Twice-Weekly Progressive Resistance Training Decreases Abdominal Fat and Improves Insulin Sensitivity in Older Men With Type 2 Diabetes. *Diabetes Care*, *28*(3), 662–667. https://doi.org/10.2337/diacare.28.3.662

Ifantopoulou, P., Artemiadis, A. K., Bakirtzis, C., Zekiou, K., Papadopoulos, T.-S., Diakogiannis, I., Hadjigeorgiou, G., Grigoriadis, N., & Orologas, A. (2019). Cognitive and brain reserve in multiple sclerosis-A cross-sectional study. *Multiple Sclerosis and Related Disorders*, *35*, 128–134. https://doi.org/https://doi.org/10.1016/j.msard.2019.07.027

Ikanga, J., Hill, E. M., & MacDonald, D. A. (2017). The conceptualization and measurement of cognitive reserve using common proxy indicators: Testing some tenable reflective and formative models. *Journal of Clinical and Experimental Neuropsychology*, *39*(1), 72–83. https://doi.org/10.1080/13803395.2016.1201462

ILO. (2012). *International Standard Classification of Occupations 2008 (ISCO-08): Structure, group definitions and correspondence tables*.

Innes, A., McCabe, L., & Watchman, K. (2012). Caring for older people with an intellectual disability: a systematic review. *Maturitas*, *72*(4), 286–295. https://doi.org/10.1016/j.maturitas.2012.05.008

ISTAT. (2021). *Previsioni della popolazione residente e delle famiglie – base 1.1.2020, Statistiche Report. https://www.istat.it. Accessed Nov 2021*.

Jacinto, M., Vitorino, A. S., Palmeira, D., Antunes, R., Ferreira, J. P., Bento, T., & Matos, R. (2021). Perceived barriers of physical activity participation in individuals with intellectual disability—A systematic review. *Healthcare*, *9*(11), 1–12. https://doi.org/10.3390/healthcare9111521

Jahn, T., & Hessler, J. (2020). *Manual Cognitive Function Dementia, Version 2*. Schuhfried.

Janicki, M. P., Dalton, A. J., Henderson, C. M., & Davidson, P. W. (1999). Mortality and morbidity among older adults with intellectual disability: health services considerations. *Disability and Rehabilitation*, *21(5-6)*, 284–294.

Janzen, H. L., Obrzut, J. E., & Marusiak, C. W. (2004). Test Review: Roid, G. H. (2003). Stanford-Binet Intelligence Scales, Fifth Edition (SB:V). Itasca, IL: Riverside Publishing. *Canadian Journal of School Psychology*, *19*(1–2), 235–244. https://doi.org/10.1177/082957350401900113

Jessen, F., Amariglio, R. E., Buckley, R. F., van der Flier, W. M., Han, Y., Molinuevo, J. L., Rabin, L., Rentz, D. M., Rodriguez-Gomez, O., Saykin, A. J., Sikkes, S. A. M., Smart, C. M., Wolfsgruber, S., & Wagner, M. (2020). The characterisation of subjective cognitive decline. *The Lancet Neurology*, *19*(3), 271–278). https://doi.org/10.1016/S1474-4422(19)30368-0

Jessen, F., Amariglio, R. E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chételat, G., Dubois, B., Dufouil, C., Ellis, K. A., van der Flier, W. M., Glodzik, L., van Harten, A. C., de Leon, M. J., McHugh, P., Mielke, M. M., Molinuevo, J. L., Mosconi, L., Osorio, R. S., Perrotin, A., … Wagner, M. (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *10*(6), 844–852. https://doi.org/10.1016/j.jalz.2014.01.001

Jin, Y., Lin, L., Xiong, M., Sun, S., & Wu, S. (2023). Moderating effects of cognitive reserve on the relationship between brain structure and cognitive abilities in middle-aged and older adults. *Neurobiology of Aging*, *128*, 49–64. https://doi.org/https://doi.org/10.1016/j.neurobiolaging.2023.04.003

Jones, R. N., Manly, J., Glymour, M. M., Rentz, D. M., Jefferson, A. L., & Stern, Y. (2011). Conceptual and measurement challenges in research on cognitive reserve. *Journal of the International*

Neuropsychological Society, *17*(4), 593–601. https://doi.org/10.1017/S1355617710001748

Jopp, D., & Hertzog, C. (2007). Activities, Self-Referent Memory Beliefs, and Cognitive Performance: Evidence for Direct and Mediated Relations. *Psychology and Aging*, *22*(4), 811–825. https://doi.org/10.1037/0882-7974.22.4.811

Kane, M. J., Brown, L. H., McVay, J. C., Silvia, P. J., Myin-Germeys, I., & Kwapil, T. R. (2007). For Whom the Mind Wanders, and When. *Psychological Science*, *18*(7), 614–621. https://doi.org/10.1111/j.1467-9280.2007.01948.x

Kartschmit, N., Mikolajczyk, R., Schubert, T., & Lacruz, M. E. (2019). Measuring Cognitive Reserve (CR) – A systematic review of measurement properties of CR questionnaires for the adult population. *PLoS ONE*, *14*(8), 1–23. https://doi.org/10.1371/journal.pone.0219851

Katzman, R., Terry, R., DeTeresa, R., Brown, T., Davies, P., Fuld, P., Renbing, X., & Peck, A. (1988). Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Annals of Neurology*, *23*(2), 138–144. https://doi.org/10.1002/ana.410230206

Kauffman, J. M. (1994). Places of Change: Special Education's Power and Identity in an Era of Educational Reform. *Journal of Learning Disabilities*, *27*(10), 610–618. https://doi.org/10.1177/002221949402701001

Kavé, G., Kukulansky-Segal, D., Avraham, A., Herzberg, O., & Landa, J. (2010). Searching for the Right Word: Performance on Four Word-Retrieval Tasks Across Childhood. *Child Neuropsychology*, *16*(6), 549–563. https://doi.org/10.1080/09297049.2010.485124

Kennedy, C. H., Horner, R. H., Newton, J. S., & Kanda, E. (1990). Measuring the activity patterns of adults with severe disabilities using the Resident Lifestyle Inventory. *Journal of the Association for Persons with Severe Handicaps*, *15*(2), 79–85.

Kenshole, A. V., Gallichan, D., Pahl, S., & Clibbens, J. (2017). Lifestyle factors and Alzheimer's disease in people with Down syndrome. *Journal of Applied Research in Intellectual Disabilities*, *30*, 58–66. https://doi.org/10.1111/jar.12369

Kessler, R. C., McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., Aguilar-Gaxiola, S., Alhamzawi, A. O., Alonso, J., Angermeyer, M., Benjet, C., Bromet, E., Chatterji, S., de Girolamo, G., Demyttenaere, K., Fayyad, J., Florescu, S., Gal, G., Gureje, O., … Williams, D. R. (2010). Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *British Journal of Psychiatry*, *197*(5), 378–385. https://doi.org/10.1192/bjp.bp.110.080499

Kilgour, A. H. M., Starr, J. M., & Whalley, L. J. (2010). Associations between childhood intelligence (IQ), adult morbidity and mortality. *Maturitas*, *65*(2), 98–105. https://doi.org/10.1016/j.maturitas.2009.09.021

Kim, B.-Y., Choi, D.-H., Jung, C.-H., Kang, S.-K., Mok, J.-O., & Kim, C.-H. (2017). Obesity and Physical Activity. *Journal of Obesity & Metabolic Syndrome*, *26*(1), 15–22. https://doi.org/10.7570/jomes.2017.26.1.15

Kirk-Sanchez, N. J., & McGough, E. L. (2013). Physical exercise and cognitive performance in the elderly: Current perspectives. *Clinical Interventions in Aging*, *9*, 51–62.

https://doi.org/10.2147/CIA.S39506
Kodama, S. (2007). Effect of Aerobic Exercise Training on Serum Levels of High-Density Lipoprotein Cholesterol. *Archives of Internal Medicine*, *167*(10), 999. https://doi.org/10.1001/archinte.167.10.999
Kogan, N., Connor, K., Gross, A., & Fava, D. (1980). Understanding Visual Metaphor: Developmental and Individual Differences. *Monographs of the Society for Research in Child Development*, *45*(1), 1–78. https://doi.org/10.2307/1165832
Korkman, M., Kirk, U., & Kemp, S. (1998). NEPSY: A Developmental Neuropsychological Assessment Manual. *San Antonio, TX: The Psychological Corporation*.
Kramer, A. F., Hahn, S., Cohen, N. J., Banich, M. T., McAuley, E., Harrison, C. R., Chason, J., Vakil, E., Bardell, L., Boileau, R. A., & Colcombe, A. (1999). Ageing, fitness and neurocognitive function. *Nature*, 400(6743), 418–419. https://doi.org/10.1038/22682
Kurtze, J. F. (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*, *33*(11), 1444–1452.
Kusumaningrum, P., Andoko, D., Damping, C. E., & Nasrun, M. W. S. (2021). The Role of Cognitive Reserve as Measured by Cognitive Reserve Index Questionnaire Indonesia Version in Geriatric Delirium Cases. *EJournal Kedokteran Indonesia*, *9*(1), 44. https://doi.org/10.23886/ejki.9.29.44
La Joie, R., Perrotin, A., Egret, S., Pasquier, F., Tomadesso, C., Mézenge, F., Desgranges, B., de La Sayette, V., & Chételat, G. (2016). Qualitative and quantitative assessment of self-reported cognitive difficulties in nondemented elders: Association with medical help seeking, cognitive deficits, and β-amyloid imaging. *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring*, *5*, 23–34. https://doi.org/10.1016/j.dadm.2016.12.005
Lautenschlager, N. T., Cox, K., & Kurz, A. F. (2010). Physical activity and mild cognitive impairment and Alzheimer's disease. *Current Neurology and Neuroscience Reports*, *10*(5), 352–358. https://doi.org/10.1007/s11910-010-0121-7
Lavie, C. J., Carbone, S., Kachur, S., O'Keefe, E. L., & Elagizi, A. (2019). Effects of Physical Activity, Exercise, and Fitness on Obesity-Related Morbidity and Mortality. *Current Sports Medicine Reports*, *18*(8), 292–298. https://doi.org/10.1249/JSR.0000000000000623
Law, M., Cooper, B., Strong, S., Stewart, D., Rigby, P., & Letts, L. (1996). The Person-Environment-Occupation Model: A Transactive Approach to Occupational Performance. *Canadian Journal of Occupational Therapy*, *63*(1), 9–23. https://doi.org/10.1177/000841749606300103
Lawton, M. P., & Brody, E. M. (n.d.). *Assessment of Older People: Self-Maintaining and Instrumental Activities of Daily Living 1*.
Le Carret, N., Lafont, S., Letenneur, L., Dartigues, J. F., Mayo, W., & Fabrigoule, C. (2003). The effect of education on cognitive performances and its implication for the constitution of the cognitive reserve. In *Developmental Neuropsychology*. https://doi.org/10.1207/S15326942DN2303_1
LEE, I.-M. (2003). Physical Activity and Cancer Prevention???Data from Epidemiologic Studies. *Medicine & Science in Sports & Exercise*, *35*(11), 1823–1827. https://doi.org/10.1249/01.MSS.0000093620.27893.23
Lee, S.-H., Wehmeyer, M. L., Palmer, S. B., Soukup, J. H., & Little, T. D. (2008). Self-Determination

and Access to the General Education Curriculum. *The Journal of Special Education*, *42*(2), 91–107. https://doi.org/10.1177/0022466907312354

Lee, S. Y., Kang, J. M., Kim, D. J., Woo, S. K., Lee, J. Y., & Cho, S. J. (2020). Cognitive Reserve, Leisure Activity, and Neuropsychological Profile in the Early Stage of Cognitive Decline. *Frontiers in Aging Neuroscience*, *12*. https://doi.org/10.3389/fnagi.2020.590607

Leoń, I., Garciá-García, J., & Roldań-Tapia, L. (2014). Estimating cognitive reserve in healthy adults using the cognitive reserve scale. *PLoS ONE*, *9*(7), 39–43. https://doi.org/10.1371/journal.pone.0102632

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). Neuropsychological assessment, 5th ed. In *Neuropsychological assessment, 5th ed.* (pp. xxv, 1161–xxv, 1161). Oxford University Press.

Li, W., Yue, L., & Xiao, S. (2022). *Subjective cognitive decline is associated with a higher risk of objective cognitive decline: A cross-sectional and longitudinal study*. *Frontiers in psychiatry*, *13*, 950270. https://doi.org/10.3389/fpsyt.2022.950270

Lifshit, H. B., Bustan, N., & Shnitzer-Meirovich, S. (2020). Intelligence trajectories in adolescents and adults with down syndrome: Cognitively stimulating leisure activities mitigate health and ADL problems. *Journal of Applied Research in Intellectual Disabilities*, *34*(2), 491–506. https://doi.org/10.1111/jar.12813

Lifshitz-Vahav, H., Shnitzer, S., & Mashal, N. (2016). Participation in recreation and cognitive activities as a predictor of cognitive performance of adults with/without Down syndrome. *Aging and Mental Health*, *20*(9), 955–964. https://doi.org/10.1080/13607863.2015.1047322

Lifshitz, H., & Rand, Y. (1999). Cognitive Modifiability in Adult and Older People With Mental Retardation. *Mental Retardation*, *37*(2), 125–138. https://doi.org/10.1352/0047-6765(1999)037<0125:CMIAAO>2.0.CO;2

Liu-Ambrose, T., Nagamatsu, L. S., Graf, P., Beattie, B. L., Ashe, M. C., & Handy, T. C. (2010). Resistance training and executive functions: a 12-month randomized controlled trial. *Archives of Internal Medicine*, *170*(2), 170–178. https://doi.org/10.1001/archinternmed.2009.494

Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., Ballard, C., Banerjee, S., Burns, A., Cohen-Mansfield, J., Cooper, C., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Larson, E. B., Ritchie, K., Rockwood, K., Sampson, E. L., … Mukadam, N. (2017). Dementia prevention, intervention, and care. *The Lancet*, *390*(10113). https://doi.org/10.1016/S0140-6736(17)31363-6

Llinàs-Reglà, J., Vilalta-Franch, J., López-Pousa, S., Calvó-Perxas, L., Torrents Rodas, D., & Garre-Olmo, J. (2017). The Trail Making Test: Association With Other Neuropsychological Measures and Normative Values for Adults Aged 55 Years and Older From a Spanish-Speaking Population-Based Sample. *Assessment*, *24*(2), 183–196. https://doi.org/10.1177/1073191115602552

Lojo-Seoane, C., Facal, D., Guàrdia-Olmos, J., Pereiro, A. X., & Juncos-Rabadán, O. (2018). Effects of Cognitive Reserve on Cognitive Performance in a Follow-Up Study in Older Adults With Subjective Cognitive Complaints. The Role of Working Memory. *Frontiers in Aging Neurosciencw, 10*, 189. https://www.frontiersin.org/article/10.3389/fnagi.2018.00189

Lu, Y., Christian, K., & Lu, B. (2008). BDNF: A key regulator for protein synthesis-dependent LTP and long-term memory? *Neurobiology of Learning and Memory*, *89*(3), 312–323. https://doi.org/10.1016/j.nlm.2007.08.018

Lublin, F. D., Reingold, S. C., Cohen, J. A., Cutter, G. R., Soelberg Sørensen, P., Alan Thompson, Dms. J., Wolinsky, J. S., Balcer, L. J., Brenda Banwell, M., Barkhof, F., Bebo, B., Calabresi, P. A., Clanet, M., Comi, G., Fox, R. J., Freedman, M. S., Goodman, A. D., Inglese, M., Kappos, L., … Polman, C. H. (2014). *VIEWS & REVIEWS Defining the clinical course of multiple sclerosis The 2013 revisions*. *Neurology*, *83*(3), 278–286. https://doi.org/10.1212/WNL.0000000000000560

Lucero, C., Campbell, M. C., Flores, H., Maiti, B., Perlmutter, J. S., & Foster, E. R. (2015). Cognitive reserve and β-amyloid pathology in Parkinson disease. *Parkinsonism and Related Disorders*, *21*(8), 899–904. https://doi.org/10.1016/j.parkreldis.2015.05.020

Maffezzini, S., Pucci, V., Riccardi, A., Montemurro, S., Puthenparampil, M., Perini, P., Rinaldi, F., Gallo, P., Arcara, G., & Mondini, S. (2023). Clinical Profiles in Multiple Sclerosis: Cognitive Reserve and Motor Impairment along Disease Duration. *Behavioral Sciences*, *13*(9). https://doi.org/10.3390/bs13090708

Magni, E., Binetti, G., Bianchetti, A., Rozzini, R., & Trabucchi, M. (1996). Mini-mental state examination: A normative study in Italian elderly population. *European Journal of Neurology*, *3(*3), 198–202. Blackwell Publishing. https://doi.org/10.1111/j.1468-1331.1996.tb00423.x

Magnuson, K. A., Sexton, H. R., Davis-Kean, P. E., & Huston, A. C. (2009). Increases in maternal education and young children's language skills. *Merrill-Palmer Quarterly*, *55*(3), 319–350. https://doi.org/10.1353/mpq.0.0024

Mahoney, F. I., & Barthel, D. W. (1965). Functional evaluation: the barthel index. *Maryland State Medical Journal*, *14*, 61–65.

Maiovis, P., Ioannidis, P., Nucci, M., Gotzamani-Psarrakou, A., & Karacostas, D. (2016). Adaptation of the Cognitive Reserve Index Questionnaire (CRIq) for the Greek population. *Neurological Sciences : Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *37*(4), 633–636. https://doi.org/10.1007/s10072-015-2457-x

Malegiannaki, A. C., Katsarou, D., Liolios, A., & Zisi, V. (2019). Ageing and Down syndrome: Neurocognitive characteristics and pharmacological treatment. *Hellenic Journal of Nuclear Medicine*, *22*, 123–132.

Malek-Ahmadi, M., Powell, J. J., Belden, C. M., O'Connor, K., Evans, L., Coon, D. W., & Nieri, W. (2015). Age- and education-adjusted normative data for the Montreal Cognitive Assessment (MoCA) in older adults age 70–99. *Aging, Neuropsychology, and Cognition*, *22*(6), 755–761. https://doi.org/10.1080/13825585.2015.1041449

Manly, J. J., Schupf, N., Tang, M.-X., & Stern, Y. (2005). Cognitive decline and literacy among ethnically diverse elders. *Journal of Geriatric Psychiatry and Neurology*, *18*(4), 213–217. https://doi.org/10.1177/0891988705281868

Marcopulos, B., & Łojek, E. (2019). Introduction to the special issue: Are modern neuropsychological assessment methods really "modern"? Reflections on the current neuropsychological test armamentarium. *The Clinical Neuropsychologist*, *33*(2), 187–199.

https://doi.org/10.1080/13854046.2018.1560502
Mashal, N., & Kasirer, A. (2011). Thinking maps enhance metaphoric competence in children with autism and learning disabilities. *Research in Developmental Disabilities*, *32*(6), 2045–2054. https://doi.org/https://doi.org/10.1016/j.ridd.2011.08.012
Mays, N., Roberts, E., & Popay, J. (2001). *Synthesising research evidence.* Routledge.
McConkey, R., & Walsh, J. (1982). An index of social competence for use in determining the service needs of mentally handicapped adults. *Journal of Intellectual Disability Research*.
McGarty, A. M., & Melville, C. A. (2018). Parental perceptions of facilitators and barriers to physical activity for children with intellectual disabilities: A mixed methods systematic review. *Research in Developmental Disabilities*, *73*, 40–57. https://doi.org/10.1016/j.ridd.2017.12.007
McWeeny, K. H., Young, A. W., Hay, D. C., & Ellis, A. W. (1987). Putting names to faces. *British Journal of Psychology*, *78*(2), 143–149. https://doi.org/doi:10.1111/j.2044-8295.1987.tb02235.x
Menardi, A., Bertagnoni, G., Sartori, G., Pastore, M., & Mondini, S. (2020). Past Life Experiences and Neurological Recovery: The Role of Cognitive Reserve in the Rehabilitation of Severe Post-Anoxic Encephalopathy and Traumatic Brain Injury. *Journal of the International Neuropsychological Society*, *26*(4), 394–406. https://doi.org/10.1017/S1355617719001231
Mihaila, I., Handen, B. L., Christian, B. T., Lao, P. J., Cody, K. A., Klunk, W. E., Tudorascu, D. L., Cohen, A. D., Okonkwo, O. C., & Hartley, S. L. (2019). Leisure Activity, Brain β-amyloid, and Episodic Memory in Adults with Down Syndrome. *Developmental Neurobiology*, *79*(7), 738–749. https://doi.org/10.1002/dneu.22677
Mitrushina, M., Boone, K., & Razani, J. (2005). *Handbook of Normative Data for Neuropsychological Assessment. 2nd ed.* New York, NY: Oxford University Press.
Mondini, S., Pucci, V., Montemurro, S., & Rumiati, R. I. (2022). Protective factors for subjective cognitive decline individuals: trajectories and changes in a longitudinal study with Italian elderly. *European Journal of Neurology*, *29*(3). https://doi.org/10.1111/ene.15183
Mondini, S., Cappelletti, M., & Arcara, G. (2023). *Methodology in Neuropsychological Assessment: An Interpretative Approach to Guide Clinical Practice*. Routledge.
Mondini, Sara, Mapelli, D., Arcara, G., Bisiacchi, P. S., Gaggi, O., Montemurro, S., Pucci, V., & Vestri, A. (2022). *Esame Neuropsicologico Breve 3*. Raffaello Cortina Editore.
Mondini, Sara, Mapelli, D., Vestri, A., Arcara, G., & Bisiacchi, P. (2011). *Esame neuropsicologico breve 2*. Raffaello Cortina Editore.
Mondini, S., Montemurro, S., Pucci, V., Ravelli, A., Signorini, M., & Arcara, G. (2022). Global Examination of Mental State: An open tool for the brief evaluation of cognition. *Brain and Behavior*, *12*(8), 1–8. https://doi.org/10.1002/brb3.2710
Mondini, S., Pucci, V., Montemurro, S., & Rumiati, R. I. (2022). Protective factors for subjective cognitive decline individuals: trajectories and changes in a longitudinal study with Italian elderly. *European Journal of Neurology*, *29*(3), 691–697. https://doi.org/https://doi.org/10.1111/ene.15183
Mondini, S., Pucci, V., Pastore, M., Gaggi, O., Tricomi, P. P., & Nucci, M. (2023). s-CRIq: the online short version of the Cognitive Reserve Index Questionnaire. *Aging Clinical and Experimental Research*. https://doi.org/10.1007/s40520-023-02561-1

Montemurro, S., Daini, R., Tagliabue, C., Guzzetti, S., Gualco, G., Mondini, S., & Arcara, G. (2022). Cognitive reserve estimated with a life experience questionnaire outperforms education in predicting performance on MoCA: Italian normative data. *Current Psychology*. https://doi.org/10.1007/s12144-022-03062-6

Montemurro, S., Mondini, S., Crovace, C., & Jarema, G. (2019). Cognitive Reserve and Its Effect in Older Adults on Retrieval of Proper Names, Logo Names and Common Nouns. *Frontiers in Communication*, *4*(April), 1–12. https://doi.org/10.3389/fcomm.2019.00014

Montemurro, S., Mondini, S., Pucci, V., Durante, G., Riccardi, A., Maffezzini, S., Scialpi, G., Signorini, M., & Arcara, G. (2023). Tele-Global Examination of Mental State (Tele-GEMS): an open tool for the remote neuropsychological screening. *Neurological Sciences*, *44*(10), 3499–3508. https://doi.org/10.1007/s10072-023-06862-1

Munir, K. M. (2016). The co-occurrence of mental disorders in children and adolescents with intellectual disability/intellectual developmental disorder. *Current Opinion in Psychiatry*, *29*(2), 95–102. https://doi.org/10.1097/YCO.0000000000000236

Myklebust, J. O. (2006). Class placement and competence attainment among students with special educational needs. *British Journal of Special Education*, *33*(2), 76–81. https://doi.org/10.1111/j.1467-8578.2006.00418.x

Myung, W., Lee, C., Park, J. H., Woo, S., Kim, S., Kim, S., Chung, J. W., Kang, H. S., Lim, S.-W., Choi, J., Na, D. L., Kim, S. Y., Lee, J.-H., Han, S.-H., Choi, S. H., Kim, S. Y., Carroll, B. J., & Kim, D. K. (2017). Occupational Attainment as Risk Factor for Progression from Mild Cognitive Impairment to Alzheimer's Disease: A CREDOS Study. *Journal of Alzheimer's Disease*, *55*, 283–292. https://doi.org/10.3233/JAD-160257

Nagamatsu, L. S., Handy, T. C., Hsu, C. L., Voss, M., & Liu-Ambrose, T. (2012). Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment. *Archives of Internal Medicine*, *172*(8), 666–668. https://doi.org/10.1001/archinternmed.2012.379

Narsi, K., Tomita, A., & Ramlall, S. (2020). Cognitive Reserve and Its Determinants in Newly HIV Diagnosed Antiretroviral-Naive Adults From Periurban and Informal Settlements: Evidence From an HIV Hyperendemic South African Setting. *Journal of Acquired Immune Deficiency Syndromes*, *85*(3), 387–393. https://doi.org/10.1097/QAI.0000000000002457

Nash, H. M., & Snowling, M. J. (2008). Semantic and phonological fluency in children with Down syndrome: Atypical organization of language or less efficient retrieval strategies? *Cognitive Neuropsychology*, *25*(5), 690–703. https://doi.org/10.1080/02643290802274064

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Nelson, M. E., Jester, D. J., Petkus, A. J., & Andel, R. (2021). Cognitive Reserve, Alzheimer's Neuropathology, and Risk of Dementia: A Systematic Review and Meta-Analysis. *Neuropsychology Review*, 31(2), 233–250. https://doi.org/10.1007/s11065-021-09478-4

Netz, Y., Lidor, R., & Ziv, G. (2019). Small samples and increased variability – discussing the need for restricted types of randomization in exercise interventions in old age. *European Review of Aging and Physical Activity*, *16*(1), 17. https://doi.org/10.1186/s11556-019-0224-3

Nieddu, A., Vindas, L., Errigo, A., Vindas, J., Pes, G. M., & Dore, M. P. (2020). Dietary habits, anthropometric features and daily performance in two independent long-lived populations from nicoya peninsula (Costa rica) and ogliastra (sardinia). *Nutrients*, *12*(6). https://doi.org/10.3390/nu12061621

Northey, J. M., Cherbuin, N., Pumpa, K. L., Smee, D. J., & Rattray, B. (2018). Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. *British Journal of Sports Medicine*, *52*(3), 154–160. https://doi.org/10.1136/bjsports-2016-096587

Nota, L., Ferrari, L., Soresi, S., & Wehmeyer, M. (2007). Self-determination, social abilities and the quality of life of people with intellectual disability. *Journal of Intellectual Disability Research*, *51*(11), 850–865. https://doi.org/10.1111/j.1365-2788.2006.00939.x

Nucci, M., Mapelli, D., & Mondini, S. (2012). Cognitive Reserve Index questionnaire (CRIq): a new instrument for measuring cognitive reserve. *Aging Clinical and Experimental Research*, *24*(3), 218–226. https://doi.org/10.3275/7800

Nunnari, D., De Cola, M. C., Costa, A., Rifici, C., Bramanti, P., & Marino, S. (2016). Exploring cognitive reserve in multiple sclerosis: New findings from a cross-sectional study. *Journal of Clinical and Experimental Neuropsychology*, *38*(10), 1158–1167. https://doi.org/10.1080/13803395.2016.1200538

O'Brien, M. W., Kimmerly, D. S., & Mekari, S. (2021). Greater habitual moderate-to-vigorous physical activity is associated with better executive function and higher prefrontal oxygenation in older adults. *GeroScience*, *43*(6), 2707–2718. https://doi.org/10.1007/s11357-021-00391-5

Oosterman, J. M., Jansen, M. G., Scherder, E. J. A., & Kessels, R. P. C. (2021). Cognitive reserve relates to executive functioning in the old–old. *Aging Clinical and Experimental Research*, *33*(9), 2587–2592. https://doi.org/10.1007/s40520-020-01758-y

Opdebeeck, C., Martyr, A., & Clare, L. (2016). Cognitive reserve and cognitive function in healthy older people: a meta-analysis. *Aging, Neuropsychology, and Cognition*, *23*(1), 40–60. https://doi.org/10.1080/13825585.2015.1041450

Oreja-Guevara, C., Blanco, T. A., Ruiz, L. B., Pérez, M. Á. H., Meca-Lallana, V., & Ramió-Torrentà, L. (2019). Cognitive dysfunctions and assessments in multiple sclerosis. *Frontiers in Neurology*, *10*. https://doi.org/10.3389/fneur.2019.00581

World Health Organization (2019). *International statistical classification of diseases and related health problems (11th ed.)*.

Ossenkoppele, R., & Jagust, W. J. (2017). The Complexity of Subjective Cognitive Decline. *JAMA Neurology*, *74*(12), 1400–1402. https://doi.org/10.1001/jamaneurol.2017.2224

Ostermann, T., Röer, J. P., & Tomasik, M. J. (2021). Digitalization in psychology: A bit of challenge and a byte of success. *Patterns*, *2*(10). https://doi.org/10.1016/j.patter.2021.100334

Ozakbas, S., Yigit, P., Akyuz, Z., Sagici, O., Abasiyanik, Z., Ozdogar, A. T., Kahraman, T., Bozan, H. R., & Hosgel, I. (2021). Validity and reliability of "Cognitive Reserve Index Questionnaire" for the

Turkish Population. *Multiple Sclerosis and Related Disorders*, *50*, 102817. https://doi.org/10.1016/j.msard.2021.102817

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical Research Ed.)*, *372*(71). https://doi.org/10.1136/bmj.n71

Paolisso, G., & Boccardi, V. (2014). L'invecchiamento della popolazione: i dati dell'Osservatorio ARNO Population aging: results of ARNO Study Invecchlamento della popolazlone. In *Gerontology, 62*.

Pastore, M. (2018). Overlapping: a R package for Estimating Overlapping in Empirical Distributions. *Journal of Open Source Software*, *3*(32), 1023. https://doi.org/10.21105/joss.01023

Pastore, M., & Calcagnì, A. (2019). Measuring distribution similarities between samples: A distribution-free overlapping index. *Frontiers in Psychology*, *10*, 1–8. https://doi.org/10.3389/fpsyg.2019.01089

Patterson, S. L. (2015). Immune dysregulation and cognitive vulnerability in the aging brain: Interactions of microglia, IL-1β, BDNF and synaptic plasticity. *Neuropharmacology*, *96*, 11–18. https://doi.org/10.1016/j.neuropharm.2014.12.020

Pedersen, B. K., & Saltin, B. (2015). Exercise as medicine – evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scandinavian Journal of Medicine & Science in Sports*, *25*(3), 1–72. https://doi.org/10.1111/sms.12581

Perry-Jenkins, M., & Gerstel, N. (2020). Work and Family in the Second Decade of the 21st Century. *Journal of Marriage and Family*, *82*(1), 420–453. https://doi.org/https://doi.org/10.1111/jomf.12636

Pes, G. M., Errigo, A., Tedde, P., & Dore, M. P. (2020). Sociodemographic, Clinical and Functional Profile of Nonagenarians from Two Areas of Sardinia Characterized by Distinct Longevity Levels. *Rejuvenation Research*, *23*(4), 341–348. https://doi.org/10.1089/rej.2018.2129

Petkus, A. J., Resnick, S. M., Rapp, S. R., Espeland, M. A., Gatz, M., Widaman, K. F., Wang, X., Younan, D., Casanova, R., Chui, H., Barnard, R. T., Gaussoin, S., Goveas, J. S., Hayden, K. M., Henderson, V. W., Sachs, B. C., Saldana, S., Shadyab, A. H., Shumaker, S. A., & Chen, J. C. (2019). General and domain-specific cognitive reserve, mild cognitive impairment, and dementia risk in older women. *Alzheimer's and Dementia: Translational Research and Clinical Interventions*, *5*, 118–128. https://doi.org/10.1016/j.trci.2019.02.003

Pettigrew, C., & Soldan, A. (2019). Defining Cognitive Reserve and Implications for Cognitive Aging. *Current Neurology and Neuroscience Reports*, *19*(1). https://doi.org/10.1007/s11910-019-0917-z

Phillips, C. (2017). Lifestyle modulators of neuroplasticity: How physical activity, mental engagement, and diet promote cognitive health during aging. *Neural Plasticity*, *2017*. Hindawi Limited. https://doi.org/10.1155/2017/3589271

Piccininni, M., Rohmann, J. L., Wechsung, M., Logroscino, G., & Kurth, T. (2023). Should Cognitive Screening Tests Be Corrected for Age and Education? Insights From a Causal Perspective. *American Journal of Epidemiology*, *192*(1), 93–101. https://doi.org/10.1093/aje/kwac159

Pierce, A. L., Bullain, S. S., & Kawas, C. H. (2017). Late-Onset Alzheimer Disease. *Neurologic Clinics*, *35*(2), 283–293. https://doi.org/https://doi.org/10.1016/j.ncl.2017.01.006

Polit, D. F., & Beck, C. T. (2006). The content validity index: Are you sure you know what's being reported? critique and recommendations. *Research in Nursing & Health*, *29*(5), 489–497. https://doi.org/10.1002/nur.20147

Pozzi, F. E., Appollonio, I., Ferrarese, C., & Tremolizzo, L. (2023). Can Traditional Board Games Prevent or Slow Down Cognitive Impairment? A Systematic Review and Meta-Analysis. *Journal of Alzheimer's Disease*, *95*, 829–845. https://doi.org/10.3233/JAD-230473

Prete, M., Cellini, N., Ronconi, L., & Di Rosa, E. (2023). Cognitive reserve moderates the relationship between sleep difficulties and executive functions in patients with Parkinson's disease. *Sleep Medicine*, *111*, 82–85. https://doi.org/https://doi.org/10.1016/j.sleep.2023.09.009

Ptomey, L. T., Szabo, A. N., Willis, E. A., Gorczyca, A. M., Greene, J. L., Danon, J. C., & Donnelly, J. E. (2018). Changes in cognitive function after a 12-week exercise intervention in adults with Down syndrome. *Disability and Health Journal*, *11*(3), 486–490. https://doi.org/10.1016/j.dhjo.2018.02.003

Pucci, V., Guerra, C., Barsi, A., Nucci, M., & Mondini, S. (2023). How long have you exercised in your life? The effect of motor reserve and current physical activity on cognitive performance. *Journal of the International Neuropsychological Society*, 1–7. https://doi.org/10.1017/s135561772300022x

R Core Team. (2022). *R: A language and environment for statistical computing.* R Foundation for Statistical Computing. https://www.r-project.org/

Rajan, K. B., Barnes, L. L., Skarupski, K. A., Mendes de Leon, C. F., Wilson, R. S., & Evans, D. A. (2015). Physical and Cognitive Activities as Deterrents of Cognitive Decline in a Biracial Population Sample. *The American Journal of Geriatric Psychiatry*, *23*(12), 1225–1233. https://doi.org/https://doi.org/10.1016/j.jagp.2015.07.008

Rajan, K. B., Rajan, R. S., Manning, L. K., & Evans, D. A. (2018). Aging Audiences: Association of Live Performance Attendance and Cognitive Decline in a Biracial Sample. *Journal of Aging and Health*, *30*(3), 445–457. https://doi.org/10.1177/0898264316682907

Raspa, M., Franco, V., Bishop, E., Wheeler, A. C., Wylie, A., & Bailey, D. B. (2018). A comparison of functional academic and daily living skills in males with fragile X syndrome with and without autism. *Research in Developmental Disabilities*, *78*, 1–14. https://doi.org/10.1016/j.ridd.2018.04.024

Raven, J. C., Court, J. H., & Raven, J. (1986). *Manual for raven's progressive matrices and vocabulary scales.* Psychologists Press.

Ravens-Sieberer, U., Auquier, P., Erhart, M., Gosch, A., Rajmil, L., Bruil, J., Power, M., Duer, W., Cloetta, B., Czemy, L., Mazur, J., Czimbalmos, A., Tountas, Y., Hagquist, C., Kilroe, J., Fuerth, K., Czerny, L., Simeoni, M. C., Robitail, S., … Phillips, K. (2007). The KIDSCREEN-27 quality of life measure for children and adolescents: Psychometric results from a cross-cultural survey in 13 European countries. *Quality of Life Research*, *16*(8), 1347–1356. https://doi.org/10.1007/s11136-007-9240-2

Reas, E. T., Laughlin, G. A., Bergstrom, J., Kritz-Silverstein, D., Richard, E. L., Barrett-Connor, E., & McEvoy, L. K. (2019). Lifetime physical activity and late-life cognitive function: The Rancho Bernardo study. *Age and Ageing*, *48*(2), 241–246. https://doi.org/10.1093/ageing/afy188

Reed, B. R., Dowling, M., Tomaszewski Farias, S., Sonnen, J., Strauss, M., Schneider, J. A., Bennett, D. A., & Mungas, D. (2011). Cognitive Activities During Adulthood Are More Important than Education in Building Reserve. *Journal of the International Neuropsychological Society*, *17*(4), 615–624. https://doi.org/10.1017/S1355617711000014

Reed, B. R., Mungas, D., Farias, S. T., Harvey, D., Beckett, L., Widaman, K., Hinton, L., & DeCarli, C. (2010). Measuring cognitive reserve based on the decomposition of episodic memory variance. *Brain*. https://doi.org/10.1093/brain/awq154

Reitan, R. M. (1955). The relation of the trail making test to organic brain damage. *Journal of Consulting Psychology*, *19*(5), 393–394. https://doi.org/10.1037/h0044509

Reppermund, S., & Trollor, J. N. (2016). Successful ageing for people with an intellectual disability. *Current Opinion in Psychiatry*, *29*(2), 149–154. https://doi.org/10.1097/YCO.0000000000000228

Reynolds, R., McKenzie, S., Allender, S., Brown, K., & Foulkes, C. (2014). Systematic review of incidental physical activity community interventions. *Preventive Medicine*, *67*, 46–64. https://doi.org/10.1016/j.ypmed.2014.06.023

Rocca, M. A., Amato, M. P., De Stefano, N., Enzinger, C., Geurts, J. J., Penner, I. K., Rovira, A., Sumowski, J. F., Valsasina, P., & Filippi, M. (2015). Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. *The Lancet Neurology*, *14*(3), 302–317. https://doi.org/10.1016/S1474-4422(14)70250-9

Roe, C. M., Xiong, C., Phillip Miller, J., & Morris, J. C. (2007). Education and Alzheimer disease without dementia Support for the cognitive reserve hypothesis. *Neurology*, *68*(3), 223–228. https://doi.org/10.1212/01.wnl.0000251303.50459.8a

Roldán-Tapia, L., García, J., Cánovas, R., & León, I. (2012). Cognitive Reserve, Age, and Their Relation to Attentional and Executive Functions. *Applied Neuropsychology: Adult*, *19*(1), 2–8. https://doi.org/10.1080/09084282.2011.595458

Rubenstein, E., Ehrenthal, D. B., Nobles, J., Mallinson, D. C., Bishop, L., Jenkins, M. C., Kuo, H. H., & Durkin, M. S. (2022). Fertility rates in women with intellectual and developmental disabilities in Wisconsin Medicaid. *Disability and Health Journal*, *15*(3). https://doi.org/10.1016/j.dhjo.2022.101321

Ruiu, M., Carta, V., Deiana, C., & Fastame, M. C. (2022). Is the Sardinian Blue Zone the New Shangri-La for mental health? Evidence on depressive symptoms and its correlates in late adult life span. *Aging Clinical and Experimental Research*, *34*(6), 1315–1322. https://doi.org/10.1007/s40520-021-02068-7

Salthouse, T A. (1998). Independence of age-related influences on cognitive abilities across the life span. *Developmental Psychology*, *34*(5), 851–864.

Salthouse, Timothy A. (2016). Continuity of cognitive change across adulthood. *Psychonomic Bulletin and Review*, *23*(3), 932–939. https://doi.org/10.3758/s13423-015-0910-8

Sanchez-Lopez, J., Silva-Pereyra, J., Fernández, T., Alatorre-Cruz, G. C., Castro-Chavira, S. A., González-López, M., & Sánchez-Moguel, S. M. (2018). High levels of incidental physical activity are positively associated with cognition and EEG activity in aging. *PLOS ONE*, *13*(1), e0191561. https://doi.org/10.1371/journal.pone.0191561

Santangelo, G., Altieri, M., Gallo, A., & Trojano, L. (2019). Does cognitive reserve play any role in multiple sclerosis? A meta-analytic study. *Multiple Sclerosis and Related Disorders*, *30*, 265–276. https://doi.org/10.1016/j.msard.2019.02.017

Santos Nogueira, D., Azevedo Reis, E., & Vieira, A. (2016). Verbal Fluency Tasks: Effects of Age, Gender, and Education. *Folia Phoniatrica et Logopaedica*, *68*(3), 124–133. https://doi.org/10.1159/000450640

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology*, *7(*3), 273–295. https://doi.org/10.1037/0894-4105.7.3.273

Satz, P., Cole, M. A., Hardy, D. J., & Rassovsky, Y. (2011). Brain and cognitive reserve: Mediator(s) and construct validity, a critique. *Journal of Clinical and Experimental Neuropsychology*, *33*(1), 121–130. https://doi.org/10.1080/13803395.2010.493151

Scarmeas, N, Levy, G., Tang, M. X., Manly, J., & Stern, Y. (2001). Influence of leisure activity on the incidence of Alzheimer’s disease. Neurology, 57(12), 2236–2242. https://doi.org/10.1212/wnl.57.12.2236

Scarmeas, Nikolaos, & Stern, Y. (2003). Cognitive reserve and lifestyle. In *Journal of Clinical and Experimental Neuropsychology*, *25*(5), 625–633. https://doi.org/10.1076/jcen.25.5.625.14576

Scheffels, J. F., Ballasch, I., Scheichel, N., Voracek, M., Kalbe, E., & Kessler, J. (2023). The Influence of Age, Gender and Education on Neuropsychological Test Scores: Updated Clinical Norms for Five Widely Used Cognitive Assessments. *Journal of Clinical Medicine*, *12*(16), 5170. https://doi.org/10.3390/jcm12165170

Schmitt, N. M., Schmitt, J., & Dören, M. (2009). The role of physical activity in the prevention of osteoporosis in postmenopausal women—An update. *Maturitas*, *63*(1), 34–38. https://doi.org/10.1016/j.maturitas.2009.03.002

Semenza, C., Mondini, S., Borgo, F., Pasini, M., & Sgaramella, M. T. (2003). Proper names in patients with early Alzheimer’s disease. *Neurocase*, *9*(1), 63–69. https://doi.org/10.1076/neur.9.1.63.14370

Siciliano, L., Olivito, G., Urbini, N., Silveri, M. C., & Leggio, M. (2022). “Mens Sana in Corpore Sano”: The Emerging Link of Motor Reserve with Motor and Cognitive Abilities and Compensatory Brain Networks in SCA2 Patients. *Biomedicines*, *10*(9), 2166. https://doi.org/10.3390/biomedicines10092166

Siciliano, M., Chiorri, C., Passaniti, C., Sant’Elia, V., Trojano, L., & Santangelo, G. (2019). Comparison of alternate and original forms of the Montreal Cognitive Assessment (MoCA): an Italian normative study. *Neurological Sciences*, *40*(4), 691–702. https://doi.org/10.1007/s10072-019-3700-7

Siedlecki, K. L., Stern, Y., Reuben, A., Sacco, R. L., Elkind, M. S. V., & Wright, C. B. (2009). Construct validity of cognitive reserve in a multiethnic cohort: The Northern Manhattan Study. *Journal of the International Neuropsychological Society*, *15*(4), 558–569. https://doi.org/10.1017/S1355617709090857

Sinai, A., Mokrysz, C., Bernal, J., Bohnen, I., Bonell, S., Courtenay, K., Dodd, K., Gazizova, D., Hassiotis, A., Hillier, R., McBrien, J., McCarthy, J., Mukherji, K., Naeem, A., Perez-Achiaga, N., Rantell, K., Sharma, V., Thomas, D., Walker, Z., & Whitham, S. (2017). Predictors of Age of Diagnosis and Survival of Alzheimer's Disease in Down Syndrome. *Journal of Alzheimer's Disease*, *61*(2), 717–728. https://doi.org/10.3233/JAD-170624

Smith, P. J., Blumenthal, J. A., Hoffman, B. M., Cooper, H., Strauman, T. A., Welsh-Bohmer, K., Browndyke, J. N., & Sherwood, A. (2010). Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosomatic Medicine*, *72*(3), 239–252. https://doi.org/10.1097/PSY.0b013e3181d14633

Snowdon, D. A. (1997). Aging and Alzheimer's disease: lessons from the Nun Study. *The Gerontologist*, *37*(2), 150–156. https://doi.org/10.1093/geront/37.2.150

Soares-Miranda, L., Siscovick, D. S., & Mozaffarian, D. (2012). Abstract MP014: Physical Activity and Risk of Coronary Heart Disease and Stroke in Older Adults: The Cardiovascular Health Study. *Circulation*, *125*(suppl_10), 147–155. https://doi.org/10.1161/circ.125.suppl_10.amp014

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G. F., Casini, A., & Macchi, C. (2011). Physical activity and risk of cognitive decline: A meta-analysis of prospective studies. *Journal of Internal Medicine*, *269*(1), 107–117. https://doi.org/10.1111/j.1365-2796.2010.02281.x

Sparrow, S. S., Balla, D. A., Cicchetti, D. V, Balboni, G., Pedrabissi, L., Doll, E. A., & Service, A. G. (2003). *Vineland Adaptive Behavior Scales Intervista, Forma Completa, Manuale, Adattamento Italiano a Cura di Giulia Balboni e Luigi Pedrabissi*. 266.

Stancliffe, R. J., Lakin, K. C., Doljanac, R., Byun, S.-Y., Taub, S., & Chiri, G. (2007). Loneliness and living arrangements. *Intellectual and Developmental Disabilities*, *45*(6), 380–390. https://doi.org/10.1352/1934-9556(2007)45[380:LALA]2.0.CO;2

Steffener, J., & Stern, Y. (2012). Exploring the neural basis of cognitive reserve in aging. *Biochimica et Biophysica Acta*, *1822*(3), 467–473. https://doi.org/10.1016/j.bbadis.2011.09.012

Stein, C., O'Keeffe, F., Strahan, O., McGuigan, C., & Bramham, J. (2023). Systematic review of cognitive reserve in multiple sclerosis: Accounting for physical disability, fatigue, depression, and anxiety. *Multiple Sclerosis and Related Disorders*, *79*, 105017. https://doi.org/https://doi.org/10.1016/j.msard.2023.105017

Stern, Y, Alexander, G. E., Prohovnik, I., Stricks, L., Link, B., Lennon, M. C., & Mayeux, R. (1995). Relationship between lifetime occupation and parietal flow: implications for a reserve against Alzheimer's disease pathology. *Neurology*, *45*(1), 55–60. https://doi.org/10.1212/wnl.45.1.55

Stern, Y. (2002). *What is cognitive reserve ? Theory and research application of the reserve concept*. 448–460.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*(10), 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004

Stern, Y., Alexander, G. E., Prohovnik, I., & Mayeux, R. (1992). Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. *Annals of Neurology*, *32*(3), 371–375. https://doi.org/10.1002/ana.410320311

Stern, Y., Arenaza-Urquijo, E. M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., Ewers, M., Franzmeier, N., Kempermann, G., Kremen, W. S., Okonkwo, O., Scarmeas, N., Soldan, A., Udeh-Momoh, C., Valenzuela, M., Vemuri, P., Vuoksimaa, E., Arenaza Urquiljo, E. M., Bartrés-Faz, D.,

… Vuoksimaa, E. (2020). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's and Dementia*, 1305–1311. https://doi.org/10.1016/j.jalz.2018.07.219

Stern, Y., & Barulli, D. (2009). Cognitive reserve. *Handbook of Clinical Neurology*, *167*(10), 181–190. https://doi.org/10.1016/B978-0-12-804766-8.00011-X

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). A compendium of neuropsychological tests: Administration, norms, and commentary, 3rd ed. Oxford University Press.

Strydom, A., Livingston, G., King, M., & Hassiotis, A. (2007). Prevalence of dementia in intellectual disability using different diagnostic criteria. *British Journal of Psychiatry*, *191*, 150–157. https://doi.org/10.1192/bjp.bp.106.028845

Sugita, A., Ling, L., Tsuji, T., Kondo, K., & Kawachi, I. (2021). Cultural engagement and incidence of cognitive impairment: A 6-year longitudinal follow-up of the Japan gerontological evaluation study (JAGES). *Journal of Epidemiology*, *31*(10), 545–553. https://doi.org/10.2188/jea.JE20190337

Sumowski, J. F., Benedict, R., Enzinger, C., Filippi, M., Geurts, J. J., Hamalainen, P., Hulst, H., Inglese, M., Leavitt, V. M., Rocca, M. A., Rosti-Otajarvi, E. M., & Rao, S. (2018). Cognition in multiple sclerosis. *Neurology*, *90*(6), 278. https://doi.org/10.1212/WNL.0000000000004977

Sumowski, J. F., & Leavitt, V. M. (2013). Cognitive reserve in multiple sclerosis. *Multiple Sclerosis Journal*, *19*(9), 1122–1127. https://doi.org/10.1177/1352458513498834

Symonds, M. R. E., & Moussalli, A. (2011). A brief guide to model selection, multimodel inference and model averaging in behavioural ecology using Akaike's information criterion. *Behavioral Ecology and Sociobiology, 65*(1), 13–21. https://doi.org/10.1007/s00265-010-1037-6

Szabo, A. N., McAuley, E., Erickson, K. I., Voss, M., Prakash, R. S., Mailey, E. L., Wójcicki, T. R., White, S. M., Gothe, N., Olson, E. A., & Kramer, A. F. (2011). Cardiorespiratory fitness, hippocampal volume, and frequency of forgetting in older adults. *Neuropsychology*, *25*(5), 545–553. https://doi.org/10.1037/a0022733

Szumski, G., Firkowska-Mankiewicz, A., Lebuda, I., & Karwowski, M. (2018). Predictors of success and quality of life in people with borderline intelligence: The special school label, personal and social resources. *Journal of Applied Research in Intellectual Disabilities*, *31*(6), 1021–1031. https://doi.org/10.1111/jar.12458

Tappen, R. (2019). *The Clock Drawing Test*. *12*(1), 2–4. https://doi.org/10.2307/1130982

Temple, V., Jozsvai, E., Konstantareas, M. M., & Hewitt, T. A. (2001). Alzheimer dementia in Down's syndrome: The relevance of cognitive ability. *Journal of Intellectual Disability Research*, *45*(1), 47–55. https://doi.org/10.1046/j.1365-2788.2001.00299.x

Tremblay, A, Charest, K., Brando, E., Roger, E., Duquette, P., & Rouleau, I. (2020). The effects of aging and disease duration on cognition in multiple sclerosis. *Brain and Cognition*, *146*, 105650. https://doi.org/https://doi.org/10.1016/j.bandc.2020.105650

Tremblay, Alexandra, Charest, K., Brando, E., Roger, E., Duquette, P., & Rouleau, I. (2023). Cognitive reserve as a moderating factor between EDSS and cognition in multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *70*, 104482. https://doi.org/https://doi.org/10.1016/j.msard.2022.104482

Tseng, B. Y., Gundapuneedi, T., Khan, M. A., Diaz-Arrastia, R., Levine, B. D., Lu, H., Huang, H., & Zhang, R. (2013). White matter integrity in physically fit older adults. *NeuroImage*, *82*, 510–516. https://doi.org/10.1016/j.neuroimage.2013.06.011

Tucker, A. M., & Stern, Y. (2011). Cognitive reserve in aging. In *Current Alzheimer Research*, *8*(1). https://doi.org/10.2174/156720511795745320

Umarova, R. M., Sperber, C., Kaller, C. P., Schmidt, C. S. M., Urbach, H., Klöppel, S., Weiller, C., & Karnath, H. O. (2019). Cognitive reserve impacts on disability and cognitive deficits in acute stroke. *Journal of Neurology*, *266*(10), 2495–2504. https://doi.org/10.1007/s00415-019-09442-6

Umegaki, H., Sakurai, T., & Arai, H. (2021). Active Life for Brain Health: A Narrative Review of the Mechanism Underlying the Protective Effects of Physical Activity on the Brain. *Frontiers in Aging Neuroscience*, *13*, 1–11. https://doi.org/10.3389/fnagi.2021.761674

Valenzuela, M. J. (2019). *Cognitive Reserve in the Aging Brain*. Oxford University Press. https://doi.org/10.1093/acrefore/9780190236557.013.338

Valenzuela, M. J., & Sachdev, P. S. (2006). Brain reserve and dementia: a systematic review. *Psychological Medicine*, *36*(4), 441–454. https://doi.org/DOI: 10.1017/S0033291705006264

van Schijndel-Speet, M., Evenhuis, H. M., van Wijck, R., van Montfort, K. C. A. G. M., & Echteld, M. A. (2017). A structured physical activity and fitness programme for older adults with intellectual disabilities: results of a cluster-randomised clinical trial. *Journal of Intellectual Disability Research*, *61*(1), 16–29. https://doi.org/10.1111/jir.12267

Varela-López, B., Cruz-Gómez, Á. J., Lojo-Seoane, C., Díaz, F., Pereiro, A. X., Zurrón, M., Lindín, M., & Galdo-Álvarez, S. (2022). Cognitive reserve, neurocognitive performance, and high-order resting-state networks in cognitively unimpaired aging. *Neurobiology of Aging*, *117*, 151–164. https://doi.org/10.1016/j.neurobiolaging.2022.05.012

Vega, A. (1969). Use of Purdue Pegboard and finger tapping performance as a rapid screening test for brain damage. *Journal of Clinical Psychology*, *25*(3), 255–258.

Vidoni, E. D., Gayed, M. R., Honea, R. A., Savage, C. R., Hobbs, D., & Burns, J. M. (2013). Alzheimer disease alters the relationship of cardiorespiratory fitness with brain activity during the stroop task. *Physical Therapy*, *93*(7), 993–1002. https://doi.org/10.2522/ptj.20120465

Vilaseca, R. M., Rivero, M., Bersabé, R. M., Cantero, M. J., Navarro-Pardo, E., Valls-Vidal, C., & Ferrer, F. (2019). Demographic and parental factors associated with developmental outcomes in children with intellectual disabilities. *Frontiers in Psychology*, *10*. https://doi.org/10.3389/fpsyg.2019.00872

Volarov, M., Miladinović, P., Gligorijević, A., Poznanović, M., Obradović, J., Nikolić, N., & Bugarski-Ignjatović, V. (2020). Serbian cognitive reserve index questionnaire: Adaptation and validation. *Approaches and Models in Special Education and Rehabilitation – Thematic Collection of International Importance, 2020, 11-24*. https://hdl.handle.net/21.15107/rcub_rfasper_3508

Wallmann-Sperlich, B., Düking, P., Müller, M., Froböse, I., & Sperlich, B. (2022). Type and intensity distribution of structured and incidental lifestyle physical activity of students and office workers: a retrospective content analysis. *BMC Public Health*, *22*(1), 634. https://doi.org/10.1186/s12889-022-12999-z

Warburton, D. E., Charlesworth, S., Ivey, A., Nettlefold, L., & Bredin, S. S. (2010). A systematic review of the evidence for Canada's Physical Activity Guidelines for Adults. *International Journal of Behavioral Nutrition and Physical Activity*, *7*(1), 39. https://doi.org/10.1186/1479-5868-7-39

Warburton, D. E. R., & Bredin, S. S. D. (2017). Health benefits of physical activity: a systematic review of current systematic reviews. *Current Opinion in Cardiology*, *32*(5), 541–556. https://doi.org/10.1097/HCO.0000000000000437

Ward, D. D., Summers, M. J., Saunders, N. L., & Vickers, J. C. (2015). Modeling cognitive reserve in healthy middle-aged and older adults: the Tasmanian Healthy Brain Project. *International Psychogeriatrics*, *27*(4), 579–589. https://doi.org/10.1017/S1041610214002075

Wechsler, D. (2001). *Wechsler Adult Intelligence Scale - Fourth Edition (WAIS–IV).* TX: Psychological Corporation.

Wechsler, D. (2004). *Wechsler Memory Scale- Fourth Edition: Administration and scoring manual.* . The Psychological Corporation.

Weinstein, A. M., Voss, M. W., Prakash, R. S., Chaddock, L., Szabo, A., White, S. M., Wojcicki, T. R., Mailey, E., McAuley, E., Kramer, A. F., & Erickson, K. I. (2012). The association between aerobic fitness and executive function is mediated by prefrontal cortex volume. *Brain, Behavior, and Immunity*, *26*(5), 811–819. https://doi.org/10.1016/j.bbi.2011.11.008

Wen, C., Hu, H., Ou, Y. N., Bi, Y. L., Ma, Y. H., Tan, L., & Yu, J. T. (2021). Risk factors for subjective cognitive decline: the CABLE study. *Translational Psychiatry*, *11*(1). https://doi.org/10.1038/s41398-021-01711-1

White, L., Katzman, R., Losonczy, K., Salive, M., Wallace, R., Berkman, L., Taylor, J., Fillenbaum, G., & Havlik, R. (1994). Association of education with incidence of cognitive impairment in three established populations for epidemiologic studies of the elderly. *Journal of Clinical Epidemiology*, *47*(4), 363–374. https://doi.org/https://doi.org/10.1016/0895-4356(94)90157-0

Wilson, B., Ivani-Chalian, C. F., & Aldrich, F. (1991). *Rivermead Behavioral Memory Test for Children.* Bury St Edmunds, UK: Thames Valley Test Co.

Wilson, R. S., Scherr, P. A., Schneider, J. A., Tang, Y., & Bennett, D. A. (2007). Relation of cognitive activity to risk of developing Alzheimer disease. *Neurology*, *69*(20), 1911–1920. https://doi.org/10.1212/01.wnl.0000271087.67782.cb

Wood, S. N. (2017). *Generalized additive models: an introduction with R*.

Woods, B., Aguirre, E., Spector, A. E., & Orrell, M. (2012). Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD005562.pub2

World Health Organization. (2017). *Decade of Healthy Ageing 2020–2030*.

Xu, W., Tan, L., Wang, H.-F., Jiang, T., Tan, M.-S., Tan, L., Zhao, Q.-F., Li, J.-Q., Wang, J., & Yu, J.-T. (2015). Meta-analysis of modifiable risk factors for Alzheimers disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *86*(12), 1299–1306. https://doi.org/10.1136/jnnp-2015-310548

Xu, X., Jerskey, B. A., Cote, D. M., Walsh, E. G., Hassenstab, J. J., Ladino, M. E., Clark, U. S., Labbe, D. R., Gunstad, J. J., Poppas, A., Cohen, R. A., Hoge, R. D., & Sweet, L. H. (2014). Cerebrovascular perfusion among older adults is moderated by strength training and gender. *Neuroscience Letters*, *560*, 26–30. https://doi.org/10.1016/j.neulet.2013.12.011

Yaneva, A., Massaldjieva, R., Mateva, N., & Bakova, D. (2019). Assessment of Cognitive Reserve: a pilot study for Bulgarian Population. *European Journal of Public Health*, *29*(4), ckz186.578. https://doi.org/10.1093/eurpub/ckz186.578

Yigit, P., Acikgoz, A., Mehdiyev, Z., Dayi, A., & Ozakbas, S. (2021). The relationship between cognition, depression, fatigue, and disability in patients with multiple sclerosis. *Irish Journal of Medical Science*, *190*(3), 1129–1136. https://doi.org/10.1007/s11845-020-02377-2/Published

Zangrossi, A., Montemurro, S., Altoè, G., & Mondini, S. (2021). Heterogeneity and Factorial Structure in Alzheimer's Disease: A Cognitive Perspective. *Journal of Alzheimer's Disease*, *83*, 1341–1351. https://doi.org/10.3233/JAD-210719

Zelazo, P. D. (2006). The Dimensional Change Card Sort (DCCS): a method of assessing executive function in children. *Nature Protocols*, *1*(1), 297–301. https://doi.org/10.1038/nprot.2006.46

Zimmerli, E., & Devenny, D. A. (1995). Cued recall as ascreen for dementia in the MR population. *Paper Presented at the Gatlinburg Confer-Ence on Research and Theory in Mental Retar-Dationanddevelopmentaldisabilities*.

Appendix

Appendix 1. Type and frequency of the comorbidities of the sample (N=3081).

Type of comorbidity	N (frequency)
Bon diseases (e.g., arthrosis, arthritis, spondyloarthrosis, discopathy, rachialgia)	341 (11%)
Cardiac diseases (e.g., atrial fibrillation, heart failure, brady/tachy-cardia)	618 (20%)
Cerebrovascular diseases (e.g., multi-infarct vascular encephalopathy, stroke, transient ischemic attack)	540 (18%)
Cholesterol dysfunction (e.g., hypercholesterolemia)	150 (5%)
Diabetes	319 (10%)
Epilepsy	40 (1%)
Falls	207 (7%)
Hypertension	999 (32%)
Infective diseases (e.g., tuberculosis, poliomyelitis, hepatitis, leukoencephalopathy)	80 (3%)
Migraine (e.g., cephalalgy, frequent headache, migraine)	40 (1%)
Motor (e.g., extrapyramidal symptoms, tremor, postural and gait disorders, hemiplegia, dysarthria)	514 (17%)
Neurovegetative disorders (e.g., insomnia, syncope, lipothymic episodes, vasovagal crises)	190 (6%)
Other medical conditions (e.g., ulcer, anemia, colon polyposis, hyperuricemia, dyslipidaemia, diverticulitis, scleroderma metabolic syndrome)	499 (16%)
Psychiatric disorders (e.g., anxiety, depression, delirium, behavioural disorders)	737 (24%)
Respiratory diseases (e.g., pulmonary thromboembolism, bronchitis, apnea)	187 (6%)
Sensory deficit (e.g., hypovisus, hearing loss, cataracts, glaucoma, retinopathy)	383 (12%)
Substance abuse	49 (2%)
Thyroid diseases (e.g., hypothyroidism, hyperthyroidism, goitre)	138 (4%)
Traumatic Brain Injury	86 (3%)
Tumours	161 (5%)
Vascular disorders (e.g., vasculopathy, carotid atheromasia, arteriopathy, phlebothrombosis)	221 (7%)
Vitamin deficiency (e.g., B12, folic acid)	63 (2%)