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Neuropsychological Studies in older adults: A comprehensive MMSE-MoCA conversion table – Prevention of postoperative delirium – Cognitive sequelae of atrial fibrillation

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Abstract

As life expectancy increases, so does the proportion of elderly individuals in most industrialized countries. As people age, they undergo both physical and cognitive changes. Thus, cognitive difficulties and other age-related pathologies such as cardiovascular and neurological diseases increase with age. In this context, atrial fibrillation (AF) and delirium are of great clinical relevance not only because of their epidemiological data but also, in particular, because of their major role in the development of cognitive dysfunction. Hence, sufficient knowledge and identification of potential risk factors of AF and delirium as well as early recognition are essential to take preventive measures. The present doctoral thesis aims to define corresponding scores for two widely used cognitive screening tools and provide insights into cognitive changes in elderly adults with atrial fibrillation and the validity of a preexisting preoperative delirium prediction model after cardiac surgery.

In study I, a comprehensive conversion table of two commonly used cognitive screening tests was created. We could define corresponding scores for the Mini-Mental Status Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) in 803 German-speaking Memory Clinic outpatients. Further, a systematic review of existing MMSE-MoCA conversions was conducted to create a comprehensive conversion table. This enables a direct comparison of cognitive test scores at screening examinations and over the course of disease in patients with predominantly neurocognitive disorders.

Study II investigated the associations between AF and cognition in aging. A small, constant increase in cognitive functioning over a median duration of 3.97 years in AF patients was found, presumably explained by learning effects that were less pronounced in non-paroxysmal AF patients, specifically in processing speed and executive functions. Some evidence suggests diabetes, history of stroke/transient ischemic attack (TIA) and depression being associated with faster cognitive decline in AF patients.

In study III, an independent external validation of an existing preoperative risk prediction model for delirium was provided in 348 patients who had undergone cardiac surgery. The evaluated predictive model showed poor discriminative capacity but fair calibration. As an outlook, reflections on future directions concerning the role of cognitive performance in AF and delirium are given as well as discussed.

Abbreviations

AF	Atrial fibrillation
AGS	American Geriatrics Society
AI	Artificial intelligence
AUROC	Area under the receiver operating characteristic curve
CI	Confidence Interval
CSVD	Cerebral small vessel disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
ICU	Intensive care unit
LR	Logistic regression
MCI	Mild cognitive impairment
MMSE	Mini-Mental Status Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NCD	Neurocognitive disorder
PND	Perioperative neurocognitive disorders
POCD	Postoperative cognitive dysfunction
POD	Postoperative delirium
SD	Standard deviation
TIA	Transient ischemic attack
WHO	World Health Organization

1. General introduction

The changing demographic landscape highlights a significant shift in the characteristics of the older adult population and its implications for cognitive function in advanced age (Sleeper, 2021). According to the World Health Organization (WHO), the proportion of the world's population aged 60 years and over is projected to almost double from 12% in 2015 to 22% in 2050 (Pas, Olde Rikkert, Bouwman, Kessels, & Buise, 2022; WHO, 2023). Elderly adults are more prone to be exposed to factors influencing cognitive function attributable to age-related conditions and chronic disease. Given these heightened risks, it is important to understand changes in cognition associated with age and factors that can negatively impact cognitive function (National Institute on Aging, 2023). For instance, simple instruments such as the Mini-Mental Status Examination (MMSE) or the Montreal Cognitive Assessment (MoCA) are commonly used as the initial step in assessing cognitive impairment, allowing for early and accurate detection of cognitive changes.

Cardiovascular and neurological diseases are among the most prevalent pathologies in the elderly (Afiune, Rassi, & Afiune Neto, 2022). Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia worldwide, characterized by uncoordinated atrial activation and ineffective atrial contraction. It has been suggested that AF may contribute to cognitive impairment and dementia (Chugh et al., 2014; Diener, Hart, Koudstaal, Lane, & Lip, 2019; Ding & Qiu, 2018; Koh et al., 2022), as well as being associated with higher rates of morbidity and mortality (Alonso & de Larriva, 2016; Bunch et al., 2010; Dublin et al., 2011; Gross & Stern, 2013; Kim et al., 2019; Ott et al., 1997; Singh-Manoux et al., 2017). Several predictors have been identified to increase the incidence of AF, with age being the most important risk factor. The prevalence of AF sharply increases after the age of 65 years (Giannone et al., 2022). An increase in atrial fibrillation is expected with age development in Western industrialized nations. However, the etiology of cognitive impairment associated with AF is not entirely clear (Shamloo et al., 2020). Before speculating about the potential treatment strategies to reduce the risk of cognitive impairment due to underlying AF a more precise estimation of that risk and identification of potential risk factors, especially in those patients having such arrhythmic diseases for a long time, remains essential (Zuin et al., 2021).

Therefore, longitudinal studies are needed to describe changes and investigate the causal linkages between cognitive performances in AF patients over time and identify potential mechanisms for prevention.

Coupled with the exponential growth of the aging population is an increased need or demand for surgical interventions (Wiggins et al., 2020). With advances in medicine these patients have acceptable survival rates after cardiac surgery for example, but poorly tolerate complications due to advanced age, frailty, and medical comorbidities (Story et al., 2010). Postoperative cognitive disorders after cardiac surgery are often seen as complications throughout the perioperative setting. They may manifest as postoperative delirium (POD) or later as postoperative cognitive dysfunction (POCD). Furthermore, besides older age, preexisting cognitive impairment is one of the leading risk factors for POD and POCD. Both are associated with increased morbidity and mortality as well as increased length of hospitalization resulting in increased suffering and costs (Gurlit & Möllmann, 2008). However, previous studies have shown that POD can be partially prevented by a targeted risk intervention strategy consisting of several components (Hshieh et al., 2015; Inouye et al., 1999; Salvi et al., 2020). In this context, it is essential to clearly identify the population at risk to provide better perioperative care (Kumar, Salzman, & Colburn, 2018). For this purpose, an accurate POD prediction model may be a powerful tool to facilitate early implementation of prevention measures in clinical practice (Menzenbach et al., 2020).

Summing up, given the increasing age of the population the incidence of cognitive difficulties and other age-related pathologies such as cardiovascular and neurological diseases will increase. Consequently, cognitive impairment is of particular interest because it is a clinically dominant comorbidity that can influence the presentation and management of underlying conditions (Perry et al., 2018). Hence, identifying potential risk factors of cognitive difficulties and other age-related pathologies is fundamental for developing preventive strategies. Moreover, early identification of cognitive impairment can significantly improve health outcomes and prevent devastating complications for the elderly (Algameel, Hawash, Abd Elrahman, & Wafik, 2021).

1.1 Cognitive impairment among elderly adults

As people age, changes to the structure and function of the brain may result in cognitive decline (Pottie et al., 2016). Therefore, increasing age counts as the strongest known risk factor for cognitive impairment and decline (Holsinger, Deveau, Boustani, & Williams, 2007). Cognitive impairment refers to problems with learning and memory, language, executive function attention, perceptual motor skills and social cognition (Jin, 2020). However, changes to the structure and function of the brain do not equally affect all cognitive domains or all people. This heterogeneity results from differences in the process of aging itself and in the chronic diseases that elderly adults may develop (Doroszkiewicz, 2022). There is a wide spectrum of cognitive impairment occurring in a continuum starting with aging-related cognitive decline, transitioning to mild cognitive impairment (MCI) and ending with dementia (Pottie et al., 2016). Moreover, MCI as an intermediate stage of cognitive impairment is often but not always a precursor of dementia (Petersen et al., 2014; Robertson et al., 2019). However, according to the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5; American Psychiatric Association [APA], 2013) disorders with a clinically significant acquired deficit in cognition resulting in a decline from a previously attained level of cognitive functioning referred to as neurocognitive disorder (NCD) (Sachdev et al., 2014; Strydom et al., 2016). The NCD cluster comprises three syndromes, each with a range of possible etiologies: delirium, mild neurocognitive disorder, and major neurocognitive disorder (dementia). The essential feature of delirium is an acquired and usually acute disturbance of attention accompanied by a change in cognition (Sachdev et al., 2014). In turn, the terms *major* and *mild* neurocognitive disorder are used to indicate severity of the impairment (Strydom et al., 2016). Major NCD is characterized by a decline in cognitive test performance of at least 2 standard deviations (SD) below the normative mean in at least one cognitive domain. Additionally, the cognitive deficits interfere with independent functioning in everyday activities. The minor form of NCD is referred to as mild NCD, the cognitive test performance falls in the range of one to two SD below the normative mean in at least one cognitive domain. Moreover, MCI does not interfere with the capacity for independence in everyday life. The underlying etiology varies among individuals but in the case of mild and major neurocognitive disorder (dementia) several subtypes have been recognized (i.e.,

Alzheimer`s disease, Frontotemporal lobar degeneration, human immunodeficiency virus infection, Huntington`s disease, Lewy body disease, Parkinson`s disease, Prion disease, Substance and/or medication use, Traumatic brain injury, Vascular disease, other medical condition, multiple etiologies, unspecified). To classify mild and major NCD the DSM-5 has defined the following six principal domains of cognitive function which should be assessed as part of an objective assessment: Complex attention, executive function, learning and memory, language, perceptual-motor function, and social cognition (APA, 2013; Sachdev et al., 2014).

Many elderly patients seen by surgical and medical specialists have significant cognitive impairment, often undiagnosed. Studies have shown that cognitive impairment is significantly associated with risk of adverse health outcomes (Hartley et al., 2017; Kallenberg et al., 2016). Moreover, unrecognized cognitive impairment represents a risk factor for medication non-adherence, poor compliance with behavioral recommendations, difficulties navigating the health care system, and caregiver stress. In this context, it is important to identify patients at risk to start early etiology-based and symptom-based treatment as signs of early cognitive impairment can be subtle and have often not been previously diagnosed (Pas et al., 2022). Although detailed neuropsychological testing is the gold standard for assessing specific neuropsychological functions, such extensive assessments are highly resource-dependent and time consuming. Thus, the use of briefer screening instruments assessing and monitoring global cognitive function is a more practical approach in clinical care (van Steenoven et al., 2014). Therefore, usually brief and reliable screening tests are used as an initial step in the process of assessing cognitive impairment (Ehrensperger et al., 2014). Screening tests require little training, are easy to administer and have demonstrated diagnostic utility (Damian et al., 2011) to differentiate patients with dementia from individuals with normal cognition (Freitas, Simões, Alves, & Santana, 2013). Many different brief screening tests for cognitive impairment are available (e.g., Mini-Mental Status Examination [Folstein, Folstein, & McHugh, 1975]; Montreal Cognitive Assessment [Nasreddine et al., 2005]; MiniCog [Borson, Scanlan, Chen, & Ganguli, 2003] and DemTect [Kalbe et al., 2004]). Screening tests generally include asking patients to perform a series of tasks that assess one or more selected neurocognitive domains and are then interpreted using a prespecified cut-off score (Block, Johnson-Greene, Pliskin, & Boake, 2017; Owens et al., 2020). A

positive screening test result should then lead to additional testing that can include blood tests, radiology examinations (e.g., magnetic resonance imaging [MRI]) and a medical as well as a neuropsychological evaluation to confirm the diagnosis of, e.g., dementia and determine its subtype.

The MMSE (Folstein et al., 1975) and MoCA (Nasreddine et al., 2005) are the most widespread psychometric cognitive screening tests worldwide (Owens et al., 2020). The MMSE was developed in 1975 and screens multiple domains (e.g., construction, learning and memory, language, and orientation). It can be administered in approximately 10 minutes. Raw scores range from 0 to 30 (lower scores representing poorer performance) with a proposed cut-off score below 27 to indicate cognitive impairment (Thalmann et al., 2002). Advantages of the MMSE include the number of cognitive domains available for screening and the predictive value for postoperative outcome (Price, Garvan, Hizel, Lopez, & Billings, 2017). Disadvantages include that scores are affected by age, education and cultural background as well as difficulty in identifying mild cognitive impairment (Lancu & Olmer, 2006). Additionally, the MMSE is restricted by copyright since 2001 which makes it less feasible for daily clinical use (Feldman & Newman, 2013).

A popular alternative to the MMSE is the MoCA which was developed 30 years later (2005) as a more challenging test than the MMSE. The MoCA takes about 12-15 minutes to complete and includes a broader range of cognitive functions such as higher-level language, executive function, and complex visuospatial processing to enable detecting mild cognitive impairment with less ceiling effect (Nasreddine et al., 2005). Furthermore, the MoCA takes into account the education level by adding one point for individuals with 12 years or less of education. The MoCA is also scored out of 30 (lower scores represent poorer performance) and an initially proposed cut-off score of 25/26 is considered to differentiate MCI or dementia from individuals with normal cognition (Nasreddine et al., 2005).

Concerning their usability, the MMSE is acknowledged as being more adequate for the detection of dementia, whereas the MoCA as being more sensitive to mild cognitive impairment (Lancu & Olmer, 2006). However, both tests have different strengths and weaknesses. Preferences regarding test selection may therefore differ in clinical trials and clinicians in everyday clinical practice vary in their use of the two scales. This makes comparisons in clinical routine as well as between studies, meta-analysis, and patient

cohorts in general difficult, as the direct comparison of MMSE and MoCA scores is complicated (Fasnacht et al., 2022; Roheger, Xu, Hoang, Eriksdotter, & Garcia-Ptacek, 2022). Scale conversion may facilitate the comparison and synthesis of cognitive data, enhance collaboration between clinicians, and inform clinical and policy decisions in the context of dementia (Hlavka, Kinoshita, Fang, & Hunt, 2021). Therefore, in study I, we aimed to define corresponding scores for the MMSE and MoCA to be able to create a comprehensive conversion table which enables a direct comparison of cognitive test scores at screening examinations and over the course of disease in patients with predominantly neurocognitive disorders. These findings can help to fully use existing research data and can serve as a reference for clinicians to continue clinical care using the MMSE in patients who were previously examined with MoCA screenings or vice versa (Roheger et al., 2022).

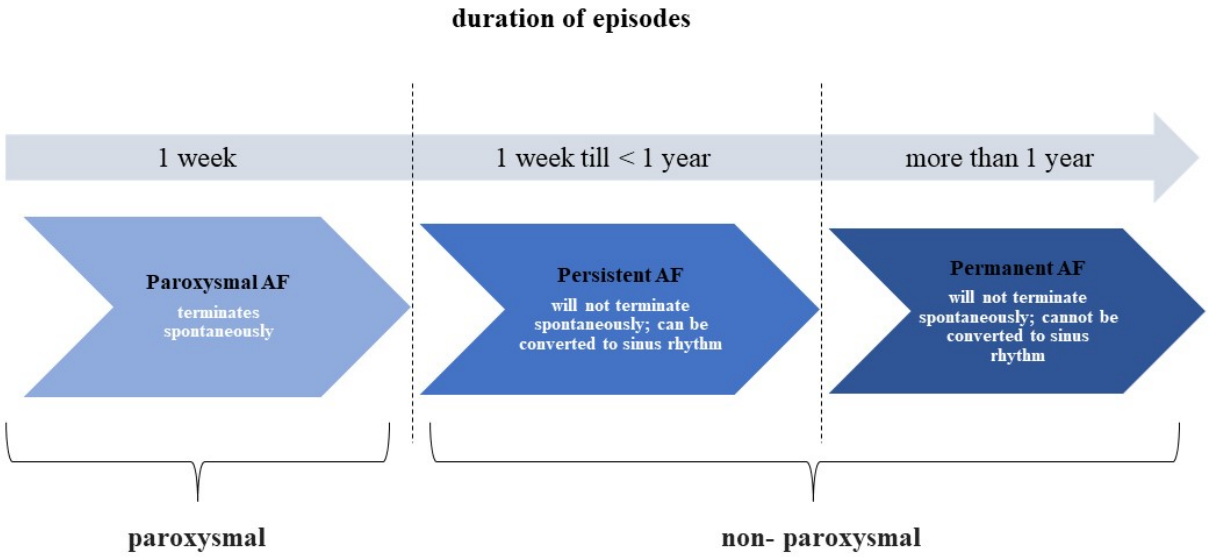
1.2 Atrial fibrillation among elderly adults

Atrial fibrillation is the most common cardiac arrhythmia affecting people of all ages (Kirchhof et al., 2016; Puccio et al., 2020). However, AF is strongly associated with age. The risk exponentially increases every decade after the age of 60 years and hereby (Alexander et al., 2015; Blum & Conen, 2023) increases the prevalence in older age (Chugh, Blackshear, Shen, Hammill, & Gersh, 2001; Heeringa et al., 2006; Staerk et al., 2018). In the European Union the prevalence of AF in adults older than 55 years was estimated to be 8.8 million in 2010 and was projected to rise to 17.9 million in 2060 (Krijthe et al., 2013). Atrial fibrillation is characterized by rapid and unsynchronized atrial excitation which leads to impaired atrial function (Al-Makhamreh et al., 2022). It can be detected on electrocardiogram (ECG) as irregular intervals between successive heartbeats (also called RR intervals) and distinct P waves. The P wave on the ECG represents atrial depolarization which results in atrial contraction or atrial systole (January et al., 2014). To characterize AF in clinical practice, the most frequent terms used are: *paroxysmal AF* (self-terminating, in most cases within 48 hours, might continue up to 7 days), *persistent AF* (episodes are sustained more than 7 days, including episodes that are terminated) and *permanent AF* (agreement between the physician and the patient

to accept the arrhythmia and not perform any antiarrhythmic treatment/procedure) (Blum & Conen, 2023; Kirchhof et al., 2016). Additionally, AF can be further divided into *paroxysmal* or *non-paroxysmal* (persistent or permanent) depending on the duration and frequency of the episodes (illustrated in Figure 1). This categorization may be useful in research (Al-Makhamreh et al., 2022).

Figure 1

Illustration of AF-type classification



Note. The sinus rhythm is the rhythm that originates from the sinus node and describes the characteristic rhythm of the healthy human heart. The normal heart rate has been considered to be between 60 and 100 beats per minute. In atrial fibrillation, the heart beats 120 to 160 times per minute, and in some as many as 200 times (Sauer & Olchansky, 2008).

Atrial fibrillation and cognitive decline are both strongly related to aging (Ott et al., 1997; Thacker et al., 2013) and frequently coexist affecting predominantly the elderly. An association between AF and cognitive impairment was first described in the Rotterdam Study (Ott et al., 1997). Since then, more than 30 studies have investigated the association between AF and cognitive impairment, and/or dementia in different populations along with underlying comorbid conditions (Dagres et al., 2018). Although some of these

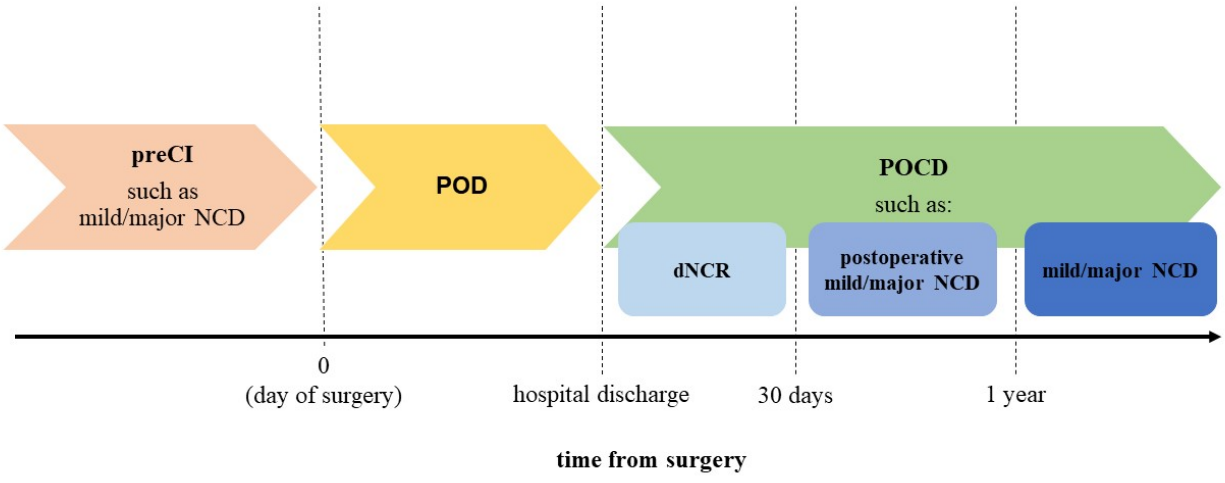
studies have reported no important differences between AF patients and controls in terms of cognitive function either at baseline (Park, Hildreth, Thomson, & O'Connell, 2007; Rastas et al., 2007) or during the follow-up period (12 months to 9 years) (Marengoni, Qiu, Winblad, & Fratiglioni, 2011; Park et al., 2007; Peters et al., 2009; Rastas et al., 2007), some others reported a positive relationship (Bilato et al., 2009; Bunch et al., 2010; Debette et al., 2007; Elias et al., 2006; Forti et al., 2007; Knecht et al., 2008; Koh et al., 2022; Tilvis et al., 2004) between AF and cognitive impairment (Shamloo et al., 2020). However, it seems that still not all possible pathophysiological aspects are fully understood between these two conditions (Ding & Qiu, 2018; Shamloo et al., 2020). Importantly, in addition to older age AF and cognitive decline share many cardiovascular risk factors such as diabetes, hypertension, and heart failure which could confound the association (Blum & Conen, 2023; Cheng, Huang, Deng, & Wang, 2012; Elias, Wolf, D'Agostino, Cobb, & White, 1993; Vogels, Scheltens, Schroeder-Tanka, & Weinstein, 2007). Moreover, beyond these shared risk factors AF may accelerate cognitive decline and increase the risk of dementia also in the absence of stroke through a plethora of pathways and mechanisms such as cerebral hypoperfusion, systemic inflammation, and cerebral small vessel diseases (CSVDs), such as white matter hyperintensities, microbleeds, silent cortical and subcortical infarction, reduced brain volume (Aldrugh, Sardana, Henninger, Saczynski, & McManus, 2017; Dietzel, Haeusler, & Endres, 2018; Ding & Qiu, 2018; Gallinoro et al., 2019; Kalantarian & Ruskin, 2016; Koh et al., 2022; Rivard & Khairy, 2017). Current evidence therefore suggests a broad overlap of risk factors for AF and cognitive decline making a close relationship plausible and likely (Blum & Conen, 2023; Koh et al., 2022). However, there is still a lack of a conclusive understanding of the complex relationship between these two conditions (Ding & Qiu, 2018; Shamloo et al., 2020) as well as the association of AF and its subtypes with change in cognitive function and the possible effects of comorbidities. Additionally, it is unknown if non-paroxysmal AF, characterized as persistent or permanent and with increased symptom severity, is more involved in change of cognitive function than paroxysmal AF (Kim et al., 2019). Thus, longitudinal studies are needed that investigate the association between AF subtype and longitudinal change in cognitive function. Accordingly, in study II we aimed at investigating longitudinal changes in cognitive functions in association with AF-type and comorbidities in a prospective, multicenter national observational Swiss-AF cohort.

1.3 Delirium among elderly adults

Delirium is highly prevalent among patients across all healthcare settings (Inouye, Westendorp, & Saczynski, 2014) and is generally reported to be more frequent in elderly, in those with preexisting cognitive impairment and in those admitted to the intensive care unit (ICU) (Grover & Kate, 2012). However, delirium respectively "perioperative neurocognitive disorders (PND)" according to the new nomenclature (Evered et al., 2018) after cardiac surgery are often seen as complications throughout the perioperative setting (Gurlit & Möllmann, 2008). They may manifest as postoperative delirium or later as postoperative cognitive dysfunction (illustrated in Figure 2). POD is a form of delirium that manifests in patients who have undergone surgical procedures and anesthesia usually occurring between one and three days after their operation (Whitlock, Vannucci, & Avidan, 2011).

Figure 2

Illustration of the nomenclature for perioperative neurocognitive disorders classification based on the time scales of development relative to surgery and anesthesia (adapted according to Safavynia, Goldstein, & Evered, 2022)



Note. preCI = preexisting cognitive impairment, POD = postoperative delirium, POCD= postoperative cognitive dysfunction, dNCR = delayed neurocognitive recovery, NCD = neurocognitive disorders.

According to the DSM-5, delirium is characterized by an acutely developing and fluctuating disturbance of awareness, attention, and cognition that is not better accounted for by a preexisting, established, or evolving dementia (APA, 2013; Ramineni & Dangayach, 2021; Wilson et al., 2020). In direct contrast to dementia which is a *chronic* confusional state, delirium is an *acute* confusional state (Inouye, 2006). Moreover, delirium may also be subdivided based on the pattern of symptoms into *hyperactive* (e.g., restlessness, agitation, hallucinations, and delusions), *hypoactive* (lethargy, reduced motor activity), and *mixed* subtypes (Ramineni & Dangayach, 2021). Among elderly adults the hypoactive form of delirium is more common and often goes unrecognized (Inouye, 2006).

Numerous epidemiologic studies report widely divergent data on the incidence of POD depending on the patient cohort studied (e.g., older vs younger patients), the type of surgical procedure, and treatment modalities (e.g., elective vs emergency surgery) (Aldecoa et al., 2017; Wilson et al., 2020). With an incidence ranging from 5% to 52% POD is the most frequent postoperative complication in elderly patients (American Geriatrics Society [AGS], 2015; Aldecoa et al., 2017; Buchan et al., 2020; Mossie et al., 2022). Although postoperative delirium is a common acute and transient condition, it is underdiagnosed by healthcare practitioners, at least 50% of the time (Caplan, 2011; Mistarz, Eliot, Whitfield, & Ernest, 2011), in part because of its fluctuating nature, lack of formal cognitive testing and its overlap with dementia (Inouye, 2006). Failure to detect delirium can lead to serious consequences such as increased mortality (McCusker, Cole, Dendukuri, & Belzile, 2003), worsening of cognitive trajectory (Inouye et al., 2014) greater need for long-term care and longer hospital stays (McCusker et al., 2003; Schubert et al., 2018) for those affected (Inouye, 2006; Marcantonio et al., 2005). Indeed, the association between delirium and risk for long-term cognitive decline in both medical and surgical populations was confirmed in a meta-analysis of 23 studies which reported a medium effect size (Hedges' g= 0.45; 95% Confidence Interval [CI] 0.34–0.57; $P < .001$) (Goldberg et al., 2020). Additionally, in a previous systematic review of postoperative delirium prediction rules, cognitive impairment was second only to age as the most commonly replicated predictor of delirium (van Meenen, van Meenen, de Rooij, ter Riet, 2014). Accordingly, it is also important to understand baseline cognitive functions of patients before considering the cognitive disturbances as part of the delirium (Kapoor et al., 2022).

In diagnosing delirium there are no definitive laboratory tests (Whitlock et al., 2011) and thus a thorough clinical evaluation is considered the gold standard. Currently, there are more than 40 instruments available which have been developed to assist with the screening and diagnosis of delirium. However, these tools vary greatly in sensitivity, specificity, staff training and administration time, and their overabundance challenges the selection of a specific tool as well as the direct comparisons and interpretation of results across studies (Barr et al., 2013; Helfand et al., 2021; Vasilevskis et al., 2011). However, the risk of the development of a later MCI or dementia increases threefold if POD occurs (Brown et al., 2018; Inouye et al., 2016; Rockwood et al., 1999; Saczynski et al., 2012; Sprung et al., 2016), and the progression of both pathologies is enhanced if they were already present preoperatively (Davis et al., 2012; Davis et al., 2017; Fong et al., 2009). Since it is assumed that delirium can be potentially preventable in some instances in up to 40% of cases (Inouye et al., 1999; Wang et al., 2020), prevention is therefore the most effective strategy for reducing its frequency and complications such as irreversible sequelae and higher health care costs (Gurlit & Möllmann, 2008; Inouye, 2006). In this context, it is important to identify patients at risk to start early etiology-based and symptom-based treatment (Aldecoa et al., 2017). Since the etiology of delirium is diverse, complex (Swarbrick & Partridge, 2022) and caused typically multifactorial (Inouye & Charpentier, 1996), preventive approaches that target multiple risk factors through a multicomponent strategy are the most effective and clinically relevant ones (Inouye et al., 1999; Inouye, 2006; Marcantonio, Flacker, Wright & Resnick, 2001; Siddiqi et al., 2016; Thom, Levy-Carrick, Bui, & Silbersweig, 2019). However, allowing interventions to be targeted appropriately and to maximize the use of resources (Inouye, et al., 1999; National Institute for Health and Care Excellence, 2023) an accurate and timely risk prediction model is needed. This model should combine the highest impact independent risk variables or features for POD into an algorithm that can help clinicians forecast which individuals are at a higher risk for developing POD (Adams & Leveson, 2012; Debray, Moons, Ahmed, Koffijberg, & Riley, 2013; Moons et al., 2012a; Reilly & Evans, 2006; Shining, Jingjing, Jian, Wenyan, & Zhang, 2022). To achieve this goal, the ideal postoperative delirium risk prediction tool would incorporate relevant and easily measurable predisposing (e.g., higher age, cognitive impairment) and precipitating (e.g., pharmacology, surgical factor) risk factors (Ormseth et al., 2023). Additionally, it should be brief and clinically feasible, have robust validation data

across different surgical specialties and balance sensitivity and specificity (Swarbrick & Partridge, 2022). In recent years, several studies have focused on the development of such postoperative delirium risk prediction tools especially in patients after cardiac surgery (Koster, Hensens, Schuurmans, & van der Palen, 2013; Mufti & Hirsch, 2017). This is not only because of its higher incidence in this population compared to others but also because the profound inflammatory response to cardiopulmonary bypass is thought to uniquely contribute to delirium in these patients (Rengel, Pandharipande, & Hughes, 2018). However, before a perioperative delirium prediction model can be applied in clinical practice, it is essential as well as mandatory to test the generalizability of the model and retest it using new data to assess its robustness to distributional shifts over time and settings (Debray et al., 2015; Moons et al., 2012b; Toll, Janssen, Vergouwe, & Moons, 2008). In study III a preexisting perioperative delirium prediction model (Rudolph et al., 2009) was externally validated in a prospective cohort study of patients who had undergone cardiac surgery to evaluate the model performance.

2. List of publications

I. Fasnacht, J. S.*, **Wueest, A. S.***, Berres, M., Thomann, A. E., Krumm, S., Gutbrod, K., Steiner, L. A.; Goettel, N., & Monsch, A. U. (2023). Conversion between the Montreal Cognitive Assessment and the Mini-Mental Status Examination. *Journal of the American Geriatrics Society*. *71*(3), 869-879. doi:10.1111/jgs.18124.

II. **Wueest, A. S.****, Zuber, P.****, Coslovsky, M., Rommers, N., Rodondi, N., Gencer, B., Moschovitis, G., De Perna, M. L., Beer, J. H., Reichlin, T., Krisai, P., Springer, A., Conen, D., Stauber, A., Mueller, A. S., Paladini, R. E., Kuehne, M., Osswald, S., Monsch, A. U., Bonati, L. H., & Swiss-AF Study Investigators. (2023). Mid-term Changes in Cognitive Functions in Patients with Atrial Fibrillation: A Longitudinal Analysis of the Swiss-AF Cohort. ***Under review***.

III. **Wueest, A. S.,** Berres, M., Bettex, D. A., Steiner, L. A., Monsch, A. U., & Goettel, N. (2023). Independent External Validation of a Preoperative Prediction Model for Delirium After Cardiac Surgery: A Prospective Observational Cohort Study. *Journal of Cardiothoracic and Vascular Anesthesia*, *37*(3), 415-422.

* Jael S. Fasnacht and Alexandra S. Wueest contributed equally to this study and share first authorship.

** Alexandra S. Wueest and Priska Zuber contributed equally to this study and share first authorship.

3. Study I

Conversion between the Montreal Cognitive Assessment and the Mini-Mental Status Examination

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Conversion between the Montreal Cognitive Assessment and the Mini-Mental Status Examination

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Abstract

Background: Early and accurate detection of cognitive changes using simple tools is essential for an appropriate referral to a more detailed neurocognitive assessment and for the implementation of therapeutic strategies. The Mini-Mental Status Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) are two commonly used psychometric tests for cognitive screening. Both tests have different strengths and weaknesses. Preferences regarding test selection may therefore differ among clinicians. The aim of this retrospective observational cohort study was to define corresponding scores for the MMSE and the MoCA.

Methods: We examined the relationship between the cognitive screening tests in 803 German-speaking Memory Clinic outpatients, encompassing a wide range of neurocognitive disorders. We produced a conversion table using the equipercentile equating method with log-linear smoothing. In addition, we conducted a systematic review of existing MMSE-MoCA conversions to create a table allowing for the conversion of MoCA scores into MMSE scores and vice versa using the weighted mean method.

Results: The Memory Clinic sample showed that the prediction of MMSE to MoCA was overall less accurate compared to the conversion from MoCA to MMSE. The 19 studies included after thorough literature search showed that MoCA scores were consistently lower than MMSE scores. Eleven of 19 conversion studies had addressed the conversion of the MoCA to the MMSE, while two studies converted MMSE to MoCA scores. Another six studies applied bi-directional conversions. We provide an easy-to-use table covering the entire range of scores and taking into account all currently existing conversion formulas.

Jael S. Fasnacht and Alexandra S. Wueest contributed equally to this study.

Conclusion: The comprehensive MMSE-MoCA conversion table enables a direct comparison of cognitive test scores at screening examinations and over the course of disease in patients with neurocognitive disorders.

KEYWORDS
conversion, equating, equipercentile, MMSE, MoCA

INTRODUCTION

The overall prevalence of dementia is increasing with the global aging of populations,[1] associated with substantial societal, social, and economic challenges. Early identification of cognitive impairment is crucial to allow for early treatment and appropriate advance care planning.[2] In order to comprehensively identify, describe, and quantify cognitive deficits, extensive neuropsychological diagnostics must take place.[3] Usually, brief and reliable screening tests are used as an initial step in the process of assessing cognitive impairment.[4] Most prominent screening tools are the Mini-Mental Status Examination (MMSE)[5] and the Montreal Cognitive Assessment (MoCA).[6] These instruments are widely used instruments screening tools, both in everyday clinical practice and in research. They require little training, are easy to administer, and have demonstrated diagnostic utility[7] to differentiate patients with dementia from individuals with normal cognition.[8] The MMSE has been criticized for its low sensitivity in patients with mild dementia or mild cognitive impairment (MCI).[6] Thus, clinicians migrated to prefer the MoCA over the MMSE.[9] The MoCA, which was developed to identify patients with MCI, is better suited to detect patients in early stages of neurocognitive disorders (NCD).[10] However, the MoCA might be too difficult for patients in advanced stages of NCD. Scale conversion may facilitate the comparison and synthesis of cognitive data, enhance collaboration between clinicians, and inform clinical and policy decisions in the context of dementia.[11] There are well-established methods for scale conversions such as equipercentile equating methods. This method was used in most previous studies[3,12–24] and enables direct and easy comparison of scores.[25] Some of these publications provided an MMSE-MoCA conversion table.[12–16,26] However, these studies were generally small sampled, did not appropriately reflect the heterogeneity of patients encountered in daily clinical practice and, therefore, have limited generalizability. Thus, conversions are needed that reflect the relationship between MoCA and MMSE for a broad range of causes of cognitive impairment as (a) patient populations are usually heterogeneous; (b) the cause of cognitive impairment during screening is unclear; and (c) comorbid diseases and conditions are often present.[17] Moreover, only a few studies considered a bi-directional score equation.[17,23–24,27–28] In most score conversion studies the uni-directional MoCA to MMSE translation was performed,[3,9,12–16,19–21,26] which leads to gaps and overrepresentations in the MMSE score range, making it difficult to unambiguously assign an equivalent MoCA score.[18] Specifically, it was found that multiple MMSE scores could correspond to one MoCA score at higher levels of cognitive function, while one MMSE score could correspond to multiple MoCA scores at lower levels of cognitive function. For example, in a previous study,[3] MMSE scores of 1, 3, 6, 8, 10, 12, 15, and 17 were absent from the conversion table. Additionally, more than one

Key points

- Early and accurate detection of cognitive changes using simple tools is essential for an appropriate referral to a more in-depth neurocognitive assessment and for the implementation of therapeutic strategies.
- The Mini-Mental Status Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) are two commonly used tests for cognitive screening and for an efficient and simple way to track cognition over time.
- We provide an easy-to-use table covering the entire ranges of both tools, which enables a direct comparison of cognitive scores at screening examinations and over the course of neurocognitive disorders.

Why does this paper matter?

Results from this study facilitate the comparison and synthesis of cognitive data from multicenter and longitudinal cohort research and thereby will enhance the communication between and within clinical and research settings.

TABLE 1 Demographic characteristics, clinical test scores, and diagnoses

Group	NF	Mild NCD	Major NCD	Total
n	118	329	356	803
Age in years	63.1 (13.4)	66.6 (13.8)	77.5 (9.8)	71.0 (13.5)
Range	19–88	19–91	19–92	19–92
Education in years	14.4 (3.0)	12.7 (2.9)	11.9 (2.9)	12.6 (3.0)
Range	8–20	7–20	7–20	7–20
Female %	45.8	51.1	57.6	53.2
MMSE score	29.2 (1.0)	27.6 (2.1)	23.9 (3.6)	26.2 (3.5)
Range	26–30	19–30	6–30	6–30
MoCA score	27.0 (2.1)	23.2 (3.8)	17.7 (4.2)	21.3 (5.2)
Range	20–30	12–30	2–30	2–30
Diagnoses %				
Alzheimer's disease	-	16.4	77.8	48.3
Vascular disease	-	6.4	0.6	3.4
Frontotemporal lobar degeneration	-	2.4	2.5	2.5
Lewy Body disease	-	0.3	1.4	0.9
Parkinson's disease	-	1.5	0.6	1.0
Traumatic brain injury	-	0.9	0.6	0.7
Brain tumor	-	0.9	0.6	0.7
Substance and/ or medication use	-	1.8	1.1	1.5
Epilepsy	-	1.2	0.6	0.9
Multiple sclerosis	-	4.9	2.0	3.4
Depression	-	8.5	0.6	4.4
Multiple etiologies	-	13.1	5.1	8.9
Other	-	15.2	3.1	8.9
Unspecified	-	26.4	3.7	14.6

Note: Demographic data and clinical test scores are presented as mean (SD). Clinical diagnoses are presented as percentages. Years of education was defined as the total number of years in school plus any professional education (not counting years needed to repeat). The maximum education was set at 20 years. In case of multiple specialized educations, only the longest one was counted.

Abbreviations: MMSE, mini mental status examination; MoCA, montreal cognitive assessment; NCD, neurocognitive disorder; NF, normal findings.

MoCA value corresponded to each of the MMSE scores 20, 22, 24, 26, 27, 28, 29, and 30. Thus, these scores were overrepresented. In order to promote the MoCA in clinical practice as a brief cognitive screening test in different domains and to facilitate interpretation of results, several authors recommend translating the full range of MoCA and MMSE scores in the future to make them comparable.[3,18] Additionally, the majority of previous studies originated from English-speaking samples,[9,12–16,19,22,26–27] while only a few conversion studies were based on German-speaking participants.[3,16] At present, no study has attempted to compile a comprehensive bi-directional MoCA-MMSE conversion based on all currently available studies. Thus, we aimed to create tables allowing for the conversion of MoCA scores into MMSE scores and vice versa.

METHODS

Participants

In this retrospective observational cohort study, German-speaking patients were referred for neuropsychological assessment to the outpatient Memory Clinic at the University Department of Geriatric Medicine FELIX PLATTER, Basel, Switzerland (clinicaltrials.gov, Registration No. NCT03581643). The local ethics committee (Ethikkommission Nordwest- und Zentralschweiz [EKNZ]) approved the study (N° EKNZ 2018-00737). The study was conducted in accordance with the most recent version of Declaration of Helsinki. Inclusion criteria were: (a) education ≥7 years; (b) fluent in the German

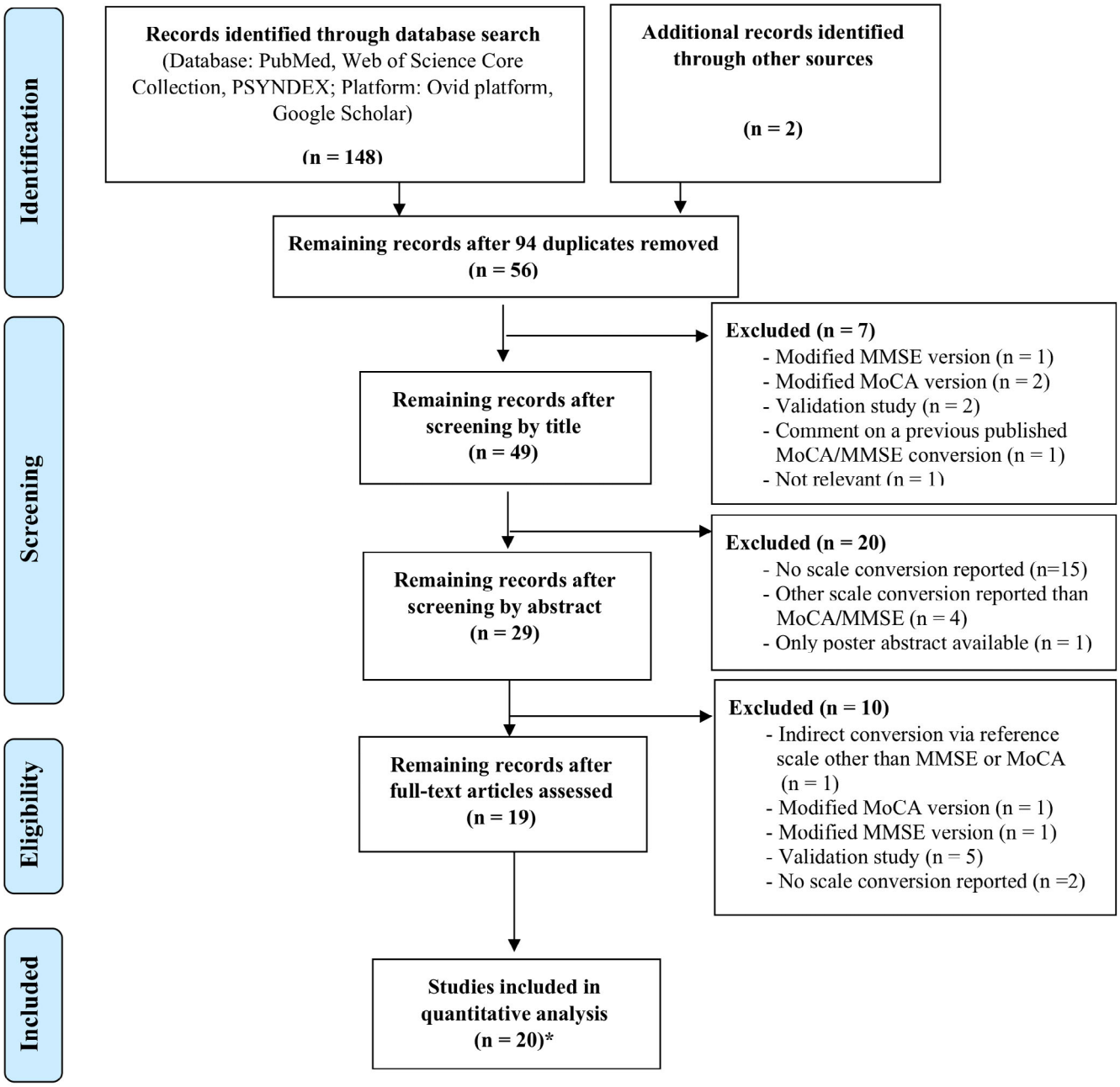

FIGURE 1 PRISMA flowchart for the selection of studies for the comprehensive MoCA-MMSE conversion table. *Including the current conversion study with 803 patients from the Memory Clinic FELIX PLATTER, Switzerland.

language; (c) initial neuropsychological testing in a clinical setting. This criterion was chosen to minimize the influence of learning effects from repeated testing on the relationship between MoCA and MMSE[29] and (d) availability of comprehensive neuropsychological assessment. Patients were excluded when cognitive performance was not validly quantifiable. Overall, 685 patients with mild or major NCD and 118 individuals with normal findings (NF) were included between March 2017 and May 2019. Table 1 depicts the demographic characteristics.

Procedures

All patients underwent comprehensive neuropsychological and medical assessments within the clinical setting.[30]

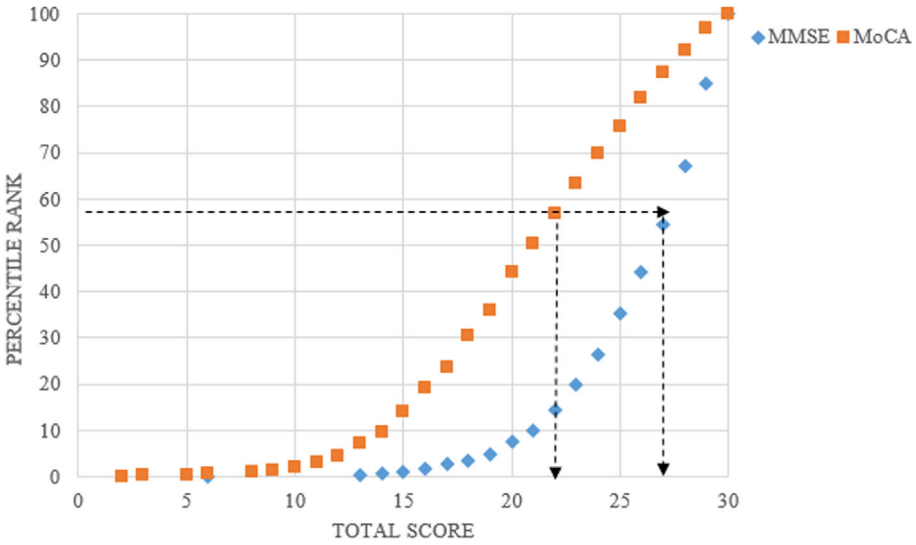

FIGURE 2 Equipercentile equating in MoCA and MMSE values in 803 patients from the Memory Clinic FELIX PLATTER, Switzerland. MMSE values are given in raw values. MoCA values correspond to education-adjusted values. The dotted lines indicate that MoCA and MMSE values are set equal when their corresponding percentile ranks are equal. MMSE, mini mental status examination; MoCA, montreal cognitive assessment.

For this, patients were assessed in the following order: (1) detailed patient and medical history; (2) neuropsychological screening including the MMSE and the clock drawing test; (3) the official German translation of the MoCA (Version 7, November 2004; http://www.mocatest.org); (4) assessment of symptoms of depression (15-item Geriatric Depression scale (GDS)[31] or Beck Depression Inventory (BDI))[32] and (5) one of two comprehensive neuropsychological test batteries assessing the patients' cognitive functioning, which have been described in detail elsewhere.[33] Briefly, for higher functioning patients the challenging battery was used and the standard battery for more impaired patients. A decision tree for choosing the appropriate neuropsychological battery is provided in Figure S1 (see Supplemental Material). The main difference in the two test batteries consists in the instruments assessing verbal and visual episodic memories. The comprehensive neuropsychological test battery was administered at the end of the assessment to avoid possible interference effects with the MoCA. Additionally, all patients were administered in a strictly standardized manner the MMSE followed by the MoCA (same version always, no alternate versions) on the same day to minimize extraneous influences upon cognitive performance at testing. Furthermore, the item concerning orientation, which is included in the MMSE as well as in the MoCA, was not performed twice in the same session. This means that if the patient answered the item in the MMSE incorrectly, it was also considered as incorrect in the MoCA. This also applied for correct answers. Education-adjusted MoCA scores (i.e., an additional point, when years of education was ≤12 years) were used for all analyses. Diagnostic consensus was reached in weekly held interdisciplinary diagnostic conferences of geriatricians, neurologists, neuropsychologists, psychiatrists, neuroradiologists, and nuclear medicine specialists within the clinical setting. The diagnoses were based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[10]

Comparison with international MoCA-MMSE conversions

For the comparison of international MoCA-MMSE conversions, a systematic literature search was performed to identify relevant studies. The selection criteria and detailed search strategy are included as Supplementary Text under Systematic Literature Review (see Text S1). Figure 1 shows details of the selection process in the PRISMA flowchart.

Statistical analysis

Score conversion

Patients' demographic characteristics, diagnoses, and MoCA and MMSE scores of the Memory Clinic sample were computed. The correlation between MoCA and MMSE scores were evaluated using Spearman's coefficient. In accordance with previous studies, we used the equipercentile equating method to develop a score conversion table between the MoCA and the MMSE (and vice versa).[12–15,25] A detailed explanation of this method is provided elsewhere.[34] Briefly, scores from two different measures are considered as equivalent within the same population if their corresponding percentile ranks are equal. For instance, if an individual with a score of 22 on the MoCA achieves a percentile rank of 55%, this means that 45% of individuals in that cohort performed better

TABLE 2 Conversion table for MoCA and MMSE scores based on equipercentile equating with log-linear smoothing in 329 mild NCD, 356 major NCD, and 118 NF

MoCA score	Equivalent MMSE	95% CI	MMSE score	Equivalent MoCA	95% CI
0	-	-	0	-	-
1	-	-	1	-	-
2	7	[2, 12]	2	-	-
3	9	[3, 15]	3	-	-
4	10	[5, 16]	4	-	-
5	12	[6, 17]	5	-	-
6	13	[8, 18]	6	2	[−1,4]
7	14	[10, 18]	7	2	[−1,5]
8	15	[12, 18]	8	2	[−1,6]
9	16	[14, 18]	9	3	[−1,7]
10	17	[15, 19]	10	4	[0,8]
11	18	[17, 19]	11	5	[1, 9]
12	19	[18, 20]	12	5	[1, 9]
13	20	[19, 21]	13	6	[3, 10]
14	21	[20, 22]	14	7	[4, 10]
15	22	[21, 23]	15	8	[6, 11]
16	23	[22, 23]	16	9	[7, 11]
17	24	[23, 24]	17	10	[8, 12]
18	25	[24, 25]	18	11	[10, 12]
19	25	[25, 26]	19	12	[11, 13]
20	26	[26]	20	13	[12, 14]
21	27	[26, 27]	21	14	[13, 15]
22	27	[27, 28]	22	15	[14, 16]
23	28	[28]	23	16	[15, 17]
24	28	[28, 29]	24	17	[17, 18]
25	29	[29]	25	19	[18, 19]
26	29	[29]	26	20	[19, 21]
27	30	[29, 30]	27	21	[21, 22]
28	30	[30]	28	23	[23, 24]
29	30	[30]	29	25	[25, 26]
30	30	[30]	30	28	[28, 29]

Note: MoCA was adjusted for the years of education (i.e., +1 point when years of education was ≤12 years).
Abbreviations: CI, confidence interval; MMSE, mini-mental status examination; MoCA, montreal cognitive assessment; NCD, neurocognitive disorder; −, values were not reported.

(i.e., achieved a score of 23 or higher on the MoCA). In the same cohort, the percentile rank distribution for the MMSE may be different: Here, an individual might score 27 and thus achieve the same percentile rank (55%) because the MMSE is cognitively less demanding. Thus, for both test scores in this example (MoCA: 22, MMSE: 27) 45% of the cohort performed above the rank achieved by this individual. In this way, MoCA scores are transformed to equivalent MMSE scores (Figure 2). The strength of this method is that the equated scores always fall within the range of possible scores; which is not always true when using traditional mean and linear equating methods. However, this method can lead to an irregular distribution of scores. We therefore implemented a log-linear transformation to smooth the raw scores of MoCA and MMSE into a regular distribution.[3,12] This ensures a higher equating accuracy. 95% confidence intervals (CI) were calculated

TABLE 3 Comprehensive conversion table for each possible MoCA and MMSE scores

	Equivalent MMSE score ($N = 9425$)			Equivalent MoCA score ($N = 4262$)	
Raw MoCA score	Weighted mean score	Range	Raw MMSE score	Weighted mean score	Range
0	5	0–15	0	0	0–1
1	7	2–15	1	0	0–1
2	9	2–16	2	0	0–1
3	10	5–16	3	0	0–1
4	11	6–17	4	0	0–1
5	12	8–17	5	0	0–2
6	13	10–18	6	0	0–3
7	14	11–19	7	1	0–4
8	15	12–19	8	1	0–4
9	16	14–20	9	2	0–5
10	17	15–20	10	3	0–5
11	18	16–21	11	4	0–6
12	19	17–21	12	4	0–7
13	20	18–22	13	5	0–8
14	20	19–22	14	6	0–8
15	21	20–23	15	7	0–9
16	22	21–23	16	8	2–10
17	23	22–24	17	9	4–11
18	24	22–25	18	10	6–12
19	25	23–26	19	11	8–13
20	25	24–26	20	12	10–14
21	26	25–27	21	13	12–17
22	27	26–28	22	14	13–18
23	27	26–29	23	16	15–18
24	28	27–30	24	17	16–19
25	28	28–29	25	19	18–20
26	29	28–30	26	20	20–21
27	29	29–30	27	22	21–23
28	29	29–30	28	23	22–25
29	30	30–30	29	26	23–27
30	30	30–30	30	28	24–29

Abbreviations: MMSE, mini mental status examination; MoCA, montreal cognitive assessment.

using 1000 bootstrap samples.[35] The upper limit of the 95% CI was censored at 30/30 points to facilitate clinical interpretation.[17] All estimating scores were rounded to the nearest integer, which restricted the range of the score from 0 to 30. Analyses were performed using R 3.6.3 software with its appropriate packages (The R Foundation for Statistical Computing, Vienna, Austria).[34] Continuous variables are expressed as means and standard deviations (SD) or median. Categorical variables are expressed as percentages.

Data extraction and data synthesis of the international MoCA-MMSE conversions

Key data were extracted from full-text studies by two authors (JSF, ASW) using a standard template. The formulas or tables for MoCA-MMSE conversion were extracted from each study (including our own conversion table) to build a comprehensive table in Excel (Microsoft, Redmond, WA, USA) as follows: (1) a range of all equivalent MMSE scores (min-max) was calculated for each

possible MoCA score; (2) the weighted mean method was used to provide one single score across all studies. This method took into account that some values contribute more than others due to the underlying sample size. We weighted the equivalent MMSE scores according to the sample size of each study before calculating a sum score. For the conversion from MMSE to MoCA, the same procedure as in step (1) and (2) was carried out.

RESULTS

Demographic and clinical characteristics

A detailed overview of patients' characteristics and test scores are provided in Table 1. The Spearman rank correlation coefficient between MoCA and MMSE total scores was significant ($rs = 0.80$, $p < 0.001$).

Accuracy of converted scores

Table 2 demonstrates the score conversion from MoCA to MMSE and vice versa. Data show that the 95% CI spans 3.24 MMSE points on average when predicting MMSE from the MoCA. For MoCA scores ≥11 points, the 95% CIs are much closer with 0–2 points in each direction than in the lower score range with more than 6 points. The MMSE to MoCA prediction is overall less accurate with an average span of the 95% CI of 3.68 MoCA points. For MMSE scores ≥18 points, the 95% CI included score points between 1 and 2.

Conversion table

Figure 2 presents the plot of equipercentile equivalents of MoCA and MMSE. For instance, a MoCA score of 22 points is equivalent to an MMSE score of 27 points, with both of these scores falling at approximately the same percentile rank of 55.

Comprehensive MoCA-MMSE conversion table

Table S1 (see Supplemental Material) presents a detailed overview of the demographic and clinical characteristics of the included transformation studies. Table 3 shows the comprehensive MoCA-MMSE conversion table. On the left side of the table, each possible MoCA score is presented with its equivalent weighted mean MMSE score and the range of equivalent MMSE scores. For instance, a MoCA score of 25 points is equivalent to a MMSE score between 28 and 29 points. The weighted mean MMSE score is 28 points. The MMSE and their equivalent MoCA scores (range and weighted mean score) are shown on the right side of Table 3.

DISCUSSION

Conversion table

This study revealed a positive correlation with a strong effect of MoCA and MMSE scores points. This is in line with the existing literature,[3,9,26] suggesting that both tests measure similar aspects of cognitive performance. However, a non-linear relationship was found between the two tests (Figure 2). This is not surprising, as the MMSE allocates more points for orientation (10 of 30 points) compared to only 6 of 30 points in the MoCA. In contrast, the MoCA places greater emphasis on visuospatial domains (4 of 30 points) compared to only 1 of 30 points with the MMSE.[7] As previously reported,[14] our data also showed a pronounced ceiling effect of the MMSE (Table 2). MoCA scores ≥21 points were translated into MMSE scores of 27–30 points, corresponding to the range of *normal* cognition in the MMSE. Overall, MoCA scores are consistently lower than MMSE scores, because visuospatial and executive domain items may be more difficult for most participants than items assessing orientation. This is consistent with other existing conversion tables.[3,12,17–18] Previous studies documented lower reliability for the MMSE-MoCA conversion than for the reverse equation.[17,36] In the present analysis, prediction of MoCA scores from MMSE data was also less accurate. Overall, the MMSE-MoCA conversion table presented here replicates existing tables for clinically heterogeneous samples with different neurodegenerative[17,24] and neurological diseases.[3] As previously reported,[3,17] the distribution of MoCA and MMSE scores was left-skewed, indicating the comparatively lower number of patients with severe cognitive impairment. Conversion scores in the lower score range should therefore be interpreted with caution, due to wide 95% CIs. In contrast with previous studies,[3,17] we could determine conversions for MoCA scores above 1 point and MMSE scores above 5 points based on actual data. This increases the generalizability of MoCA-MMSE conversion in clinically heterogeneous patient populations.[16] In addition, we used education-adjusted MoCA scores, since previous research found that MoCA scores are affected by education as the strongest non-cognitive factor.[6]

Comprehensive MoCA-MMSE conversion table

The 19 studies included from the literature show that MoCA scores are consistently lower than MMSE scores. Eleven[3,9,12–16,19–21,26] of 19 conversion studies have addressed the conversion from MoCA to the MMSE, while two studies[18,22] have converted MMSE to MoCA scores. Another six studies[17,23–24,27–28,36] have provided bi-directional conversions. The studies differed in the demographic and diagnostic composition of the patient cohort (see Table S1), making a direct comparison difficult. However, our review of existing MoCA-MMSE conversion tables suggested a high level of agreement for the higher score range. In the lower score range, both conversions showed a larger difference between the equivalent scores of the individual studies. Therefore, conversions in the lower part of the tests must be used with caution and the range should serve as a measure of uncertainty. Additionally, when applying the comprehensive MMSE-MoCA conversion table we recommend using the weighted mean, where each data point contributes equally to the final mean. However, there are various explanations for the large difference of equivalent scores in the lower score range: First, the number of patients with severe cognitive impairment was low in some studies, which increases the risk for sampling errors and reduces equating accuracy.[25] Three studies have reported extrapolated data for equivalent MMSE scores for raw MoCA scores <10[3,13] points or <8 points.[16] Other studies did not mention whether extrapolations have been made in the lower score range to correct for scarcity of data.[9,12,14–15,18–19,21,23–24,26–28] Second, different statistical conversion methods have been used. Scale equating using linear regression analysis does not adequately represent test-to-test differences in difficulty that vary along the scores,[9,27] which can reduce prediction accuracy, particularly in the lower and upper score ranges. In addition, the equivalent scores do not fall within a range of possible scores, as is the case with the equipercentile equating method.[14] Equivalent MMSE scores >30 points[9,27] and equivalent MoCA scores <0[27] must be set to 0/0 points and 30/30 points to facilitate clinical interpretation. Another point to mention is, that the majority of existing studies provide conversion tables for specific patient populations.[12–14,16,18–19,27,36] This is based on the assumption that the association between MoCA and MMSE is expected to differ between patients with primarily mnestic disorders and patients with executive dysfunction, since executive functions are not assessed in the MMSE.[13,17,24] It is possible that etiology-specific conversion tables are more reliable when the cause of the cognitive disorder is known.[24] A previous study demonstrated that the association between MoCA and MMSE is influenced by clinical diagnosis.[17] Nevertheless, the majority of authors have concluded that their results are comparable to previously published tables.[3,13,17,26] Additionally, it has been shown that tables created in patients with Parkinson's disease are comparably valid for use in patients with other causes of cognitive impairment.[37] Moreover, since screening procedures are only a snapshot of cognitive performance, variations in scores are possible due to factors other than etiology, such as fatigue, motivation, and anxiety.

The overview of existing conversion tables suggests that the ranges of equivalent scores (min-max) overlap across the scale range and are consistent with the conversions published to date.

Our study is not without limitations. First, the distribution of MoCA and MMSE scores in the current Memory Clinic sample was left-skewed, consistent with previous studies.[3,13] As previously highlighted, this increases the risk for sampling errors. Obtaining conversion scores based on actual data for MoCA scores <6 points is problematic from a practical and ethical perspective. Patients with such advanced cognitive impairments are rarely included in research.[16] Second, 48.3% of the current Memory Clinic sample were patients with Alzheimer's disease, potentially limiting clinical heterogeneity. However, this is not very likely to be clinically relevant, given that Alzheimer's disease is the most common cause of dementia, and thus, the most frequently encountered diagnosis in clinical practice. Third, according to standard institutional procedures[30] MMSE was performed followed by the MoCA in a strictly standardized manner and in the same order in all patients at our Memory Clinic. This may lead to a bias in MMSE-MoCA conversion.[17] Nevertheless, our results are comparable to a previous study, where the test administration did not take place in a fixed order to prevent exhaustion effects.[36] Fourth, the MMSE and MoCA in this study were both administered in a specific language and in specific versions, which can lead to a limited generalizability. However, the generalizability of the score conversion compared with other languages seems to have some consistency.[17,20–21] But for a more in-depth look, further research is needed in this regard, as this was beyond the scope of our paper. Fifth, MoCA and MMSE data were collected from baseline neuropsychological assessments. Since brief cognitive tests are also used in clinical practice to assess disease progression, the association between MoCA and MMSE should also be studied in patients with follow-up assessments to consider potential learning effects.[17] A previous study demonstrated that the correlation of MoCA and MMSE did not differ significantly

between baseline and follow-up examinations.[19] Nevertheless, this finding should be replicated in further studies.

AUTHOR CONTRIBUTIONS

Jael S. Fasnacht: conception design; acquisition of data; analysis and interpretation of data; drafting the article; revising the article critically for important intellectual content; final approval. Alexandra S. Wueest: acquisition of data; analysis and interpretation of data; drafting the article; revising the article critically for important intellectual content; final approval. Manfred Berres: interpretation of data; statistical analysis; revising the article critically for important intellectual content; final approval. Sabine Krumm: analysis and interpretation of data; revising the article critically for important intellectual content; final approval. Alessandra E. Thomann, Klemens Gutbrod, Luzius A. Steiner, and Nicolai Goettel: revising the article critically for important intellectual content; final approval. Andreas U. Monsch: conception design; revising the article critically for important intellectual content; final approval.

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CONFLICT OF INTEREST

Alessandra E. Thomann is a full-time employee and shareholder of F. Hoffmann-La Roche Ltd., her contribution to the submitted publication is related to work done at a previous employment. Nicolai Goettel has received consultancy fees from PIPRA AG, Zurich, outside the submitted work. The other remaining authors have no conflicts of interest to report.

SPONSOR'S ROLE

None.

REFERENCES

1. Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M. World Alzheimer report 2016. Improving Healthcare for People Living with Dementia: Coverage, Quality and Costs Now and in the Future 2016. Available at: https://www.alz.co.uk/research/world-report-2016. Accessed October 27, 2021.
2. Yaffe K. Modifiable risk factors and prevention of dementia: what is the latest evidence? *JAMA Intern Med*. 2018;178(2):281-282. doi:10.1001/jamainternmed.2017.7299
3. Scheffels JF, Kräling H, Kalbe E, Kessler J. Konversionen von kognitiven screenings: mini-mental-status-test vs. Montreal cognitive assessment vs. DemTect [conversions of cognitive screenings: mini-mental state examination vs. Montreal cognitive assessment vs. DemTect]. *Nervenarzt*. 2018;89(12):1371-1377. doi:10.1007/s00115-018-0583-4
4. Ehrensperger M, Taylor K, Berres M, et al. BrainCheck - a very brief tool to detect incipient cognitive decline: optimized case-finding combining patient- and informant-based data. *Alzheimers Res Ther*. 2014;6(9):69. doi:10.1186/s13195-014-0069-y
5. Folstein MF, Folstein SE, McHugh PR. "mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6
6. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-699. doi:10.1111/j.1532-5415.2005.53221.x
7. Damian AM, Jacobson SA, Hentz JG, et al. The Montreal cognitive assessment and the mini-mental state examination as screening instruments for cognitive impairment: item analyses and threshold scores. *Dement Geriatr Cogn Disord*. 2011;31(2):126-131. doi:10.1159/000323867
8. Freitas S, Simões MR, Alves L, Santana I. Montreal cognitive assessment: validation study for mild cognitive impairment and Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2013;27(1):37-43. doi:10.1097/WAD.0b013e3182420bfe
9. Larner AJ. Converting cognitive screening instrument test scores to MMSE scores: regression equations. *Int J Geriatr Psychiatry*. 2017;32:351-352. Doi. org/ 10. 1002/ gps. 4622.
10. American Psychiatric Association, ed. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.
11. Hlávka JP, Kinoshita AT, Fang S, Hunt A. Clinical outcome measure crosswalks in Alzheimer's disease: a systematic review. *J Alzheimers Dis*. 2021;83(2):591-608. doi:10.3233/JAD-210060
12. Roalf DR, Moberg PJ, Xie SX, Wolk DA, Moelter ST, Arnold SE. Comparative accuracies of two common screening instruments for classification of Alzheimer's disease, mild cognitive impairment, and healthy aging. *Alzheimers Dement*. 2013;9(5):529-537. doi:10.1016/j.jalz.2012.10.001
13. van Steenoven I, Aarsland D, Hurtig H, et al. Conversion between mini-mental state examination, Montreal cognitive assessment, and dementia rating scale-2 scores in Parkinson's disease. *Mov Disord*. 2014;29(14):1809-1815. doi:10.1002/mds.26062
14. Trzepacz PT, Hochstetler H, Wang S, Walker B, Saykin AJ. Alzheimer's disease neuroimaging I. relationship between the Montreal cognitive assessment and mini-mental state examination for assessment of mild cognitive impairment in older adults. *BMC Geriatr*. 2015;15:107. doi:10.1186/s12877-015-0103-3
15. Saczynski JS, Inouye SK, Guess J, et al. The Montreal cognitive assessment: creating a crosswalk with the mini-mental state examination. *J Am Geriatr Soc*. 2015;63(11):2370-2374. doi:10.1111/jgs.13710
16. Lawton M, Kasten M, May MT, et al. Validation of conversion between mini-mental state examination and Montreal

cognitive assessment. *Mov Disord*. 2016;31(4):593-596. doi:10.1002/mds.26498
17. Bergeron D, Flynn K, Verret L, et al. Multicenter validation of an MMSE-MoCA conversion table. *J Am Geriatr Soc*. 2017;65(5):1067-1072. doi:10.1111/jgs.14779
18. Wong A, Black SE, Yiu SYP, et al. Converting MMSE to MoCA and MoCA 5-minute protocol in an educationally heterogeneous sample with stroke or transient ischemic attack. *Int J Geriatr Psychiatry*. 2018;33(5):729-734. doi:10.1002/gps.4846
19. Monsell SE, Dodge HH, Zhou XH, et al. Neuropsychology work group advisory to the clinical task force. Results from the NACC uniform data set neuropsychological battery crosswalk study. *Alzheimer Dis Assoc Disord*. 2016;30(2):134-139. doi:10.1097/WAD.0000000000000111
20. Kopecek M, Stepankova H, Lukavsky J, Ripova D, Nikolai T, Bezdicek O. Montreal cognitive assessment (MoCA): normative data for old and very old Czech adults. *Appl Neuropsychol Adult*. 2017;24(1):23-29. doi:10.1080/23279095.2015.1065261
21. Yang H, Yim D, Park MH. Converting from the Montreal cognitive assessment to the mini-mental state Examination-2. *PLoS One*. 2021;16(7):e0254055. doi:10.1371/journal.pone.0254055
22. Melikyan ZA, Malek-Ahmadi M, O'Connor K, Atri A, Kawas CH, Corrada MM. Norms and equivalences for MoCA-30, MoCA-22, and MMSE in the oldest-old. *Aging Clin Exp Res*. 2021;33:3303-3311. doi:10.1007/s40520-021-01886-z
23. Aiello EN, Pasotti F, Appollonio I, Bolognini N. Equating mini-mental state examination (MMSE) and Montreal cognitive assessment (MoCA) scores: conversion norms from a healthy Italian population sample. *Aging Clin Exp Res*. 2022;34(7):1721-1724. doi:10.1007/s40520-022-02089-w
24. Roheger M, Xu H, Hoang MT, Eriksdotter M, Garcia-Ptacek S. Conversion between the mini-mental state examination and the Montreal cognitive assessment for patients with different forms of dementia. *J Am Med Dir Assoc*. 2022;S1525-8610(22):00288-2. doi:10.1016/j.jamda.2022.03.018
25. Kolen MJ, Brennan RL. *Test Equating, Scaling, and Linking*. Springer; 2004.
26. Helmi L, Meagher D, O'Mahony E, et al. Agreement and conversion formula between mini-mental state examination and Montreal cognitive assessment in an outpatient sample. *World J Psychiatry*. 2016;6(3):358-364. doi:10.5498/wjp.v6.i3.358
27. Solomon TM, de Bros GB, Budson AE, Mirkovic N, Murphy CA, Solomon PR. Correlational analysis of 5 commonly used measures of cognitive functioning and mental status: an update. *Am J Alzheimers Dis Other Dement*. 2014;29(8):718-722. doi:10.1177/1533317514534761
28. Yu RL, Lee WJ, Li JY, et al. Evaluating mild cognitive dysfunction in patients with Parkinson's disease in clinical practice in Taiwan. *Sci Rep*. 2020;10(1):1014. doi:10.1038/s41598-020-58042-2
29. Olin JT, Zelinski EM. The 12-month reliability of the mini-mental state examination. *Psychol Assess*. 1991;3(3):427-432. doi:10.1037/1040-3590.3.3.427
30. Monsch AU, Kressig RW. Specific care program for the older adults: memory clinics. *Eur Geriatric Med*. 2010;1(2):128-131. doi:10.1016/j.eurger.2010.03.006
31. Sheikh JI, Yesavage JA. *Geriatric Depression Scale (GDS): Recent Evidence and Development of a Shorter Version. Clinical Gerontology: A Guide to Assessment and Intervention 165–173*. The Haworth Press; 1986.
32. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:561-571. doi:10.1001/archpsyc.1961.01710120031004
33. Beck IR, Schmid NS, Berres M, Monsch AU. Establishing robust cognitive dimensions for characterization and differentiation of patients with Alzheimer's disease, mild cognitive impairment, frontotemporal dementia and depression. *Int J Geriatr Psychiatry*. 2014;29(6):624-634. doi:10.1002/gps.4045
34. Albano AD. Equate: an R package for observed-score linking and equating. *J Stat Softw*. 2016;74(8):1-36. doi:10.18637/jss.v074.i08WOS:000392514200001
35. Mooney CZ, Duval RD. *Bootstrapping: A Nonparametric Approach to Statistical Inference*. Sage Publications; 1993.
36. Chen X, Wen H, Wang J, Yi Y, Wu J, Liao X. Conversion between mini-mental state examination and Montreal cognitive assessment scores in older adults undergoing selective surgery using Rasch analysis. *J Adv Nurs*. 2021;77(2):729-741. doi:10.1111/jan.14638
37. Jung YI, Jeong EH, Lee H, et al. Validation of MoCA-MMSE conversion scales in Korean patients with cognitive impairments. *Dement Neurocogn Disord*. 2018;17(4):148-155. doi:10.12779/dnd.2018.17.4.148

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Figure S1. Decision tree used in the Memory Clinic FELIX PLATTER for choosing the appropriate neuropsychological battery (Standard or Challenging Battery).
Text S1. Systematic literature review.
Table S1. Demographic and clinical characteristics of the included transformation studies.

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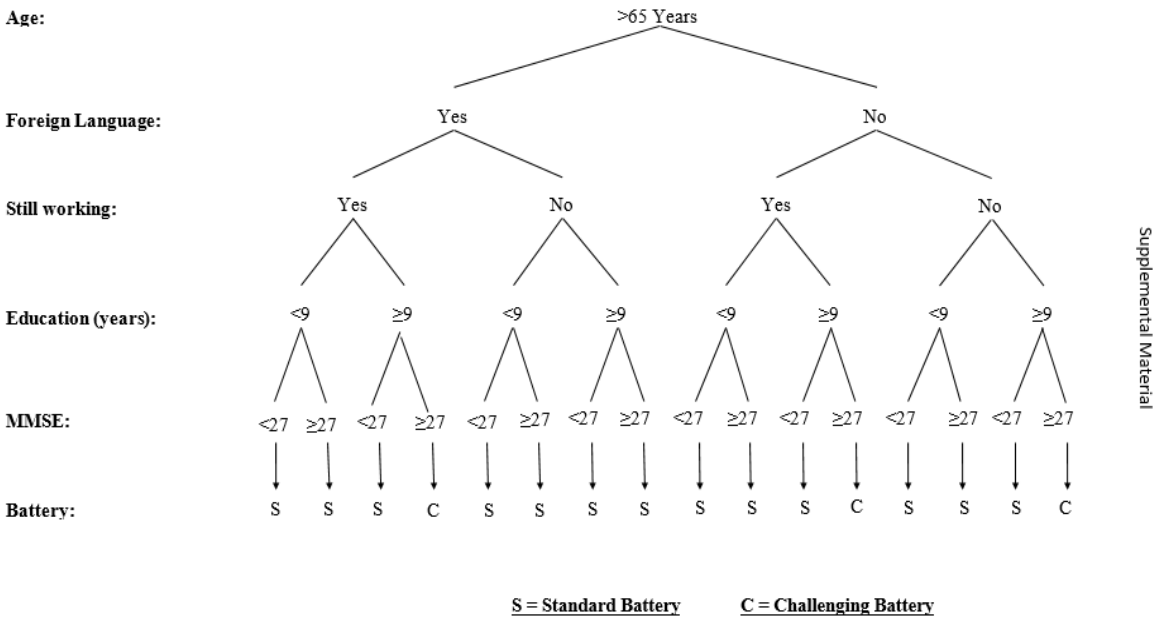

Supplemental Figure S1. Decision tree used in the Memory Clinic FELIX PLATTER for choosing the appropriate neuropsychological battery (Standard or Challenging Battery).

Supplementary Text S1. Systematic Literature Review

We performed a systematic review of existing MoCA-MMSE conversions using common online databases. Additional topic relevant publications were identified by screening reference lists of corresponding articles. The final systematic search was conducted on August 30, 2022. The search strategy required that the title or abstract contained at least one keyword of the following combinations: *Montreal Cognitive Assessment, MoCA, Mini Mental State Examination, MMSE* and *conversion, convert, equation, equating, equate, crosswalk.* There was no restriction in the year of publication. Three reviewers (JSF, ASW, SK) independently screened titles and abstracts. The identified studies were reviewed based on their full texts. Studies were included if they: (a) used the original versions of the MoCA and the MMSE (including translations); and (b) used either the MoCA or MMSE test as a reference scale to derive a conversion algorithm to allow unambiguous and direct assignment of scores. Exclusion criteria were: (a) modified test versions, such as short or literacy versions or versions with linguistic and cultural adaptations; (b) validation studies of previous conversions without additional contribution.

Supplemental Table S1. Demographic and clinical characteristics of the included transformation studies

Publication source	Language version	n	Sample	Female, (%)	Age, years	Education, years	Conversion method	Conversion direction	MoCA score	MMSE score	MoCA range	MMSE range
Aiello (2022)[23]	Italian	407	HC	59.5	60.6 (13.7)	12.2 (4.4)	EL	bi-directional	25.6 (3.8)	28.3 (1.9)	13–30	20–30
Bergeron (2017)[17]	Quebec-French	1492	HC, MCI, AD, VaD, psychiatric, other	52.5	69.0 (11.0)	11.6 (4.6)	E	bi-directional	-	-	15-30	20-30
Chen (2021)[36]	Chinese	124	Surgical	37.2	66.2 (4.7)	7.6 (3.6)	Rasch analysis	bi-directional	22.3 (4.1)*	27.5 (2.7)	7-30	10-30
Helmi (2016)[26]	Irish/English	70	Psychiatric	70.0	77.4 (7.1)	10.7 (2.5)	Circle Arc	MoCA→ MMSE	19.0 (6.4)	24.5 (4.9)	4-29	9-30
Kopecek (2017)[20]	Czech	540	HC	54.1	75.6 (9.1)	12.7 (3.5)	EL	MoCA→ MMSE	-	-	-	-
Larner (2017)[9]	English	147	HC, D	-	-	-	LR	MoCA→ MMSE	-	-	-	-
Lawton (2016)[16]	German/ English	2091	HC, PD	-	-	-	EL	MoCA→ MMSE	25.0 (3.5)*	27.6 (2.3)	8-30	13-30
Melikyan (2021)[22]	English	157	CU, oldest-old (age 90+)	66.9	93.5 (2.9)	15.1 (1.8)	EL	MMSE→ MoCA	24.2 (2.8)*	28.1 (1.8)	17-30	21-30
Monsell (2016)[19]	English	655	AD	-	-	-	EL	MoCA→ MMSE	-*	-	-	-
Roalf (2013)[12]	English	587	HC, MCI, AD	59.4	73.1 (8.5)	14.7 (3.8)	E	MoCA→ MMSE	20.3 (4.4)	24.8 (3.4)	-	-
Roheger (2022)[24]	Swedish	387	AD, VaD, PD, LBD, D and Stroke	54.7	79.0 (8.1)	-	EL	bi-directional	17.1 (4.4)	22.4 (4.2)	-	-
Saczynski (2015)[15]	English	199	AD, Delirium	63.0	84.0 (5.0)	-	E	MoCA→ MMSE	19.3 (6.6)*	24.1 (5.8)	0-30	2-30
Scheffels (2018)[3]	German	536	Neurological diseases	45.2	64.2 (16.0)	-	EL	MoCA→ MMSE	20.9 (5.6)*	25.2 (3.9)	1-30	1-30
Solomon (2014)[27]	English	101	MCI, AD	-	-	-	LR	bi-directional	-	-	-	-
Trzepacz (2015)[14]	English	618	HC, MCI, AD	40.5	76.5 (7.3)	16.1 (2.9)	EL	MoCA→ MMSE	21.4 (3.9)*	25.7 (2.6)	1-30	7-30

van Steenhoven (2014)[13]	English	197	Idiopathic PD	33.0	67.1 (9.5)	16.4 (2.8)	EL	MoCA→ MMSE	24.7 (4.2)*	27.7 (2.7)	10-30	12-30
Wong (2018)[18]	Chinese	623	Strroke, TIA	42.4	68.7 (10.9)	5.8 (4.5)	EL + P	MMSE→ MoCA	19.8 (6.2)*	25.0 (4.6)	-	-
Yang (2021)[21]	Korean	303	D, MCI, CU	57.1	70.5 (10.7)	7.8 (4.9)	EL	MoCA→ MMSE	14.9 (7.4)	21.4 (7.0)	-	-
Yu (2020)[28]	Chinese	168	Idiopathic PD	41.7	69.7 (9.5)	9.7 (5.4)	Log. R	bi-directional	21.8 (5.0)	25.5 (3.8)	5-30	12-30
Current study	German	803	HC, AD, VaD, FTLD, LBD, PD, TBI, psychiatric, Other	53.2	71.0 (13.5)	12.6 (3.0)	EL	bi-directional	21.3 (5.2)*	26.2 (3.5)	2-30	6-30

Studies are listed alphabetically, referenced by first author (year). Studies with * add +1 point in MoCA for education ≤ 12 years. Data are given as means (SD) unless otherwise specified.

Abbreviations: AD=Alzheimer's disease; CU=Cognitively unimpaired; D=Dementia; E=Equipercentile equating method; EL=Equipercentile equating method with log-linear smoothing; FTLD=Frontotemporal lobar degeneration; HC=Healthy control; LBD=Lewy body disease; Log. R=Logistic regression; LR=Linear Regression; MCI=Mild cognitive impairment; MMSE=Mini Mental Status Examination; MoCA=Montreal Cognitive Assessment; P=Poisson regression; PD=Parkinson's disease; TBI=Traumatic brain injury; TIA=Transient ischemic attack; VaD= Vascular dementia.

- = Values were not reported.

4. Study II

Mid-term Changes in Cognitive Functions in Patients with Atrial Fibrillation: A Longitudinal Analysis of the Swiss-AF Cohort

Mid-term Changes in Cognitive Functions in Patients with Atrial Fibrillation: A Longitudinal Analysis of the Swiss-AF Cohort

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ABSTRACT

Background: Longitudinal association studies of atrial fibrillation (AF) and cognitive functions have shown inconsistent results and an unclear role of AF-type. We therefore aim to investigate longitudinal changes in cognitive functions in association with AF-type (non-paroxysmal versus paroxysmal) and comorbidities in the Swiss-AF cohort.

Methods: 2,415 AF patients (mean age 73.2 years; 1,080 paroxysmal, 1,335 non-paroxysmal AF) participated in this Swiss multicenter prospective cohort study. Seven cognitive measures were administered up to five times. Age-education standardized scores were calculated and association between longitudinal change in scores and baseline AF-type investigated using linear mixed-effects models. Associations between AF-type and time to cognitive drop, an observed score of at least one standard deviation below individual's age-education standardized cognitive scores at baseline, were studied using cox proportional hazard models of each cognitive test, censoring patients at their last measurement. Models were adjusted for baseline covariates.

Results: Mean cognitive scores increased longitudinally (median follow-up 3.97 years). Non-paroxysmal AF patients showed smaller longitudinal increases in DSST, CoCo and TMT-B scores versus paroxysmal AF patients. Diabetes, history of stroke/TIA and depression were associated with worse performance on all cognitive tests. No differences in time to cognitive drop were observed between AF-types in any cognitive test.

Conclusion: We found a longitudinal increase in cognitive performance in AF patients, which was presumably explained by a learning effect that was less pronounced in non-paroxysmal AF patients, specifically in processing speed and executive functions. Time to cognitive drop was not associated to AF-type on any scores. We found some evidence for diabetes, history of stroke/TIA and depression being associated with faster cognitive decline in AF patients.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting people of all ages [1, 2]. As its incidence and prevalence increase with age, it is estimated that about 17.9 million adults aged over 55 years in 2060 will experience AF in the European Union [3]. Adjusting for age and predisposing conditions, AF has been associated with an increased risk of stroke [4], heart failure [5], and death [6, 7]. In addition, previous studies suggested an association between AF and cognitive functioning based on the increased risk for cerebral ischemia and stroke associated with AF [8–14].

Independent from other risk factors, a correlative study described an association between AF and a greater cognitive decline over 20 years in people with AF compared to people without AF [15]. Concerning the affected cognitive domain, AF has been associated with poorer performance and longitudinal decline in executive functions [16]. However, results on the relationship between AF and cognitive functioning have been challenged. While AF has been identified as a predictor of cognitive decline after five years, the association could not be confirmed at ten years of follow-up (FU) [8]. Furthermore, no change in cognitive functioning in a cohort of people with AF over a 36-months period was found even when comparing cognitive functions between AF patients and controls, or, AF patients treated with anti-thrombotic therapies [17].

Several reasons could account for these inconsistencies in the relationship between AF and cognitive change. First, studies differ in methodological aspects such as sample size, duration of follow-up periods and statistical methods, as well as with respect to the assessments of cognitive performance [1, 14]. Second, inconsistent results in the relationship between AF and cognitive change have been reported when adjusting for comorbidities. On the one hand, it has been described that patients with AF and a history of stroke have an increased risk for cognitive decline compared to patients without history of stroke [18], independently of shared comorbidities such as hypertension and diabetes. On the other hand, it has been described that patients with AF have an increased risk for cognitive decline independently of history of stroke [13, 15, 19, 20]. Finally, it has been shown that next to increasing age, the prevalence of heart failure, hypertension, diabetes, coronary artery, and cerebrovascular diseases increases with progression from

paroxysmal to non-paroxysmal (persistent or permanent) AF subtype [21]. However, the relationship of AF subtype and cognitive change has not been investigated [1].

Although the progression of AF and the development of cognitive decline share common risk factors [1], the association of AF and its subtypes with change in cognitive function, as well as the possible effects of comorbidities, are still not fully understood. Additionally, it is unknown if non-paroxysmal AF, characterized as persistent or permanent and with increased symptom severity, is more involved in change of cognitive function than paroxysmal AF [22]. Thus, longitudinal studies are needed that investigate the association between AF subtype and longitudinal change in cognitive function. In the Swiss-AF Cohort, we aim to investigate the association of AF subtype and change in cognitive functions over time in patients with AF, while accounting for comorbidities, using an extensive assessment of cognitive functioning with validated tests assessing multiple cognitive domains. Specifically, we aim to (1) describe the development of longitudinal cognitive functioning in a typical Swiss population of patients with AF; (2) assess whether changes of cognitive functions are associated with AF-type (i.e., paroxysmal or non-paroxysmal) and (3) describe the frequency of cases of cognitive drop over time, defined as an observed score of at least one standard deviation (SD) below the individual's age-education standardized cognitive test scores at baseline and assess the association with AF-type and comorbidities.

Materials and Methods

Study sample

The Swiss Atrial Fibrillation Study (Swiss-AF; NCT02105844) is an ongoing prospective, multicenter, observational, national cohort study in primarily elderly individuals with AF focusing on the interrelationships of AF and AF progression with structural and functional brain damage over time. Details about the sampling method and selection process are described elsewhere [23–25]. Briefly, a total of 2,415

subjects with a history of AF at baseline (BL) [23] were recruited by comprehensive screening of in- and outpatients in 14 participating centers in Switzerland between 2014 and 2017 and by contacting general practitioners in the area. Main inclusion criteria were age 65 years or older (with the exception of additional 315 patients aged between 37 and 65 years, which were enrolled to assess socio-economic aspects of AF in the working population) and presence of either paroxysmal or non-paroxysmal AF according to the guidelines of the European Society of Cardiology [26]. 87% of patients included in the present analysis were 65 years or older (n=2,100). Paroxysmal AF was defined as self-terminating AF lasting <7 days, did not require cardioversion and was documented at least twice within the past 5 years [26]. Persistent AF was defined as AF sustained for at least 7 days and/or AF requiring cardioversion, documented within the past 5 years by electrocardiography (ECG) or rhythm monitoring devices [26]. Permanent AF was defined as AF in which cardioversion therapy failed or was not attempted [26]. For the current study, participants were categorized as having paroxysmal and non-paroxysmal (including persistent and permanent) AF. Details about the assessment of AF-type are described in a previous publication [27]. Briefly, the local study investigator determined AF-type during the baseline visit based on all available clinical patient data over the years before enrollment, documented by medical records, ECG, and/or rhythm monitoring device. We excluded patients who were unable to provide informed consent, had any acute illness within the last 4 weeks or indicated only secondary, reversible episodes of AF (e.g., after cardiac surgery or severe sepsis). Regarding the integrity of cognitive abilities, no further requirements were defined since we aimed to establish a representative large sample of elderly patients with diagnosed AF.

Study procedures

Trained study personnel collected all data in a standardized manner. Specifically, a training video for the cognitive assessment was made available for all investigators at all sites. At enrollment, participants underwent a clinical examination and cognitive assessment. Detailed information on personal characteristics, risk factors and comorbidities were obtained through standardized case report forms (CRF).

The study was approved by the local Ethics Committee–Ethikkommission Nordwest- und Zentralschweiz (EKNZ number: PB_2016_00793) and conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent before participation. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. In the current analysis, we considered patients who were administered at least one cognitive test at baseline only or at any of the planned follow-up visits within 4 years (+50 days). Four yearly follow-up visits were planned per patient. The data for this analysis reflects the status of the Swiss-AF data base as on May 13, 2022, in which all patients were enrolled in the cohort for at least 4 years.

Assessment of cognitive function

The cognitive test battery consisted of five validated, widely used cognitive tests administered at each follow-up. The test battery included the Montreal Cognitive Assessment (MoCA) [28], Trail Making Test Part A (TMT-A) [29] Trail Making Test Part B (TMT-B) (TMT results calculated as number of correct connections per second) [29], Semantic Fluency test (SF) [30] and the Digit Symbol Substitution Test (DSST) [31], described in detail elsewhere [25]. All cognitive tests were administered in a paper-pencil format or, during the coronavirus disease 2019 (COVID-19) pandemic, in part (i.e., MoCA and SF) by telephone. Cognitive tests were administered in the main national languages of Switzerland, depending on patient's mother tongue (i.e., 72,4% German, 11,9% French and 10,2% Italian), except for the TMT and the DSST, which are language-independent tests. **Table S1** in the supplement provides an overview of the neuropsychological test battery, which consists of 17 outcome variables. The standard MoCA total score was calculated [28]. MoCA results administered by telephone (n=221) were discarded, since these results do not reflect the in-person test. Additionally, two derived cognitive measures were used, i.e., the ratio TMT-B / TMT-A and the Cognitive Construct (CoCo) derived from the total of 17 items comprised in the five validated neuropsychological tests used in the Swiss-AF cohort study. A previous study of the group has shown that using the CoCo score increased measurement sensitivity and allows to detect subtle changes

in cognitive function [25]. Cognitive drop was defined as an observed score of at least one SD below the individual's age-education standardized cognitive test scores at baseline [32]. All scores of the cognitive tests were standardized by age and years of education, which were used in all analysis to describe within-patient trajectories over time from the first visit and to compare cognitive functioning stratified by AF-type. For all cognitive tests, positive values represent better results.

Additional variables

Socio-demographic measures including age, sex and education (years) were obtained through standardized CRFs. Health behavior including smoking (yes/no) was collected from patients' self-reports. Chronic disease included history of diabetes (yes/no), history of hypertension (yes/no), history of stroke or transient ischemic attack (TIA) (yes/no) were self-reported from the patients as well as verified by medical records. Use of medication for cardiovascular disease (anticoagulants drugs) (yes/no) and glomerular filtration rate (GFR) (milliliter/minute) was collected from medical reports. Depression (yes/no) was assessed with the Geriatric Depression Scale (GDS; range 0-15, a value ≥5 indicating depression) [33].

Statistical analyses

Available information for each patient from baseline until follow-up 4, or until loss to any FU was used. Missing data were not imputed and patients with missing baseline covariates were excluded from the analysis. Due to the exploratory rather than confirmatory nature of the study, all results are presented as estimated effect sizes with 95% confidence intervals (CI). Continuous baseline characteristics are described via the mean and standard deviation or, if strongly skewed, using the median and interquartile range (IQR); frequencies and percentages are listed for categorical characteristics. All analyses were performed using the statistical software R version 4.2.2. The association between AF-type and evolution of cognitive functioning was assessed using linear mixed effects models with the age-education standardized cognitive score (see description in **Text S1**) as outcome and the time since first measurement, AF subtype and the interaction between them as fixed effects. To acknowledge the possibility of a practice effect, which seemed

largest between the first and second measurement [34], we added an additional variable, indicating whether it was the first measurement (yes/no). Time since first measurement was added to the model as a random slope, and random intercepts for each patient, nested within study center, were included. Separate models were constructed for each of the above-mentioned outcome measures. Model diagnostics were performed by examination of residuals. The association between AF-type and relevant cognitive drop was assessed using Cox proportional hazard models stratified by study center. Patients were censored at the last measured value (i.e., the last visit during which the cognitive test was performed) in case of death or drop out, or their administrative fourth follow-up, in case the patient had more follow-up visits available. Only the first drop in cognition per patient was considered for analysis. The analyses assumed that missing cognitive assessments were not associated with the event of cognitive drop (see section sensitivity analyses). The proportional hazard assumption was tested and the Schoenfeld residuals were visually inspected as model diagnostics. For none of the models we found strong deviations from this assumption.

Subgroup, sensitivity and posthoc analyses

To assess subgroup effects by sex, history of stroke, smoking status, or for patients with and without diabetes, hypertension, or depression are necessary, an interaction between each covariate of interest and AF subtype for each model was tested. For covariates with a signal of an interactive effect with AF subtype (interaction term p-value <0.05), we repeated the analyses in each level of the covariate (e.g. smokers versus non-smokers). The robustness of our previous assumptions was tested in several sensitivity analyses. First, we evaluated the assumption of the linear development of cognitive functioning over time, using scatter plots with local estimated scatterplot smoothing (LOESS) curves fit to describe the development over time for each of the cognitive tests. Second, we evaluated the appropriateness of the definition of cognitive drop at >1 SD decrease by using an arbitrary >1.5 SD for relevant cognitive drop and comparing the results. Lastly, the potential extent of an attrition bias was investigated by repeating the analyses using the analysis set which included all patients who were still part of the cohort after FU4, and who were able to perform at least one of the cognitive tests at FU4 (SF) with the patients who dropped out before or did not do cognitive

tests at FU4. Furthermore, taking losses to follow-up as (potentially) informative censoring events, we repeated the analysis using linear mixed effects models incorporating patients' inverse probability of censoring weights (IPCW) and comparing the results with the models from the main analysis. Due to the consistent relatively high estimates of three covariates (i.e., history of diabetes, depression, and history of stroke/TIA) on all cognitive tests we performed the above-described linear mixed effects as post hoc analyses to assess whether these variables were associated with an increase over time on one representative cognitive score (i.e., MoCA). The association of these covariates with cognitive drop are already explained in the above-described Cox-models.

Results

Patients' characteristics

Baseline characteristics are shown in **Table 1**. At study enrollment, mean age was 73.2±8.4 years, 27.4% of participants were women, and 90.4% were anticoagulated. 44.7% of the 2,415 included participants had paroxysmal AF, whereas 55.3% had non-paroxysmal AF.

Table 1 Baseline characteristics

	Overall	Paroxysmal	Non-paroxysmal
n	2,415	1,080	1,335
Age (years)	73.2 (8.4)	72.5 (8.5)	73.9 (8.3)
Sex = female (%)	662 (27.4)	345 (31.9)	317 (23.7)
Education groups (%)			
Basic*	288 (11.9)	130 (12.0)	158 (11.9)
Middle*	1,197 (49.6)	531 (49.2)	666 (50.0)
Advanced*	926 (38.4)	418 (38.7)	508 (38.1)
Education (years)	12.93 (3.2)	13.05 (3.3)	12.84 (3.2)
History of stroke/TIA (%)	480 (19.9)	235 (21.8)	245 (18.4)
History of diabetes (%)	422 (17.5)	173 (16.0)	249 (18.7)
History of hypertension (%)	1,691 (70.0)	721 (66.8)	970 (72.7)
Depression (%)	200 (8.3)	84 (7.8)	116 (8.7)
Oral anticoagulation medication (%)	2,182 (90.4)	932 (86.3)	1,250 (93.6)
GFR (ml/min.)	59.29 (19.1)	60.98 (19.9)	57.94 (18.3)
Active smoker (%)	175 (7.3)	87 (8.1)	88 (6.6)

Data are presented as mean (± SD) or counts (percentages). GFR: glomerular filtration rate; min.: minutes; ml: milliliter; TIA: transient ischemic attack; *Basic education: ≤6 years (less than compulsory education curriculum); middle education: 6 to ≤12 years (high school or similar); advanced education: ≥12 years (college or university degree).

For 2,358 participants data on all cognitive measures was available at baseline. The median FU was 3.97 years. **Table S2** presents the number of missing tests per visit. The number of missing test results gradually increased over the FU visits, being greater than 46% at FU4 for all cognitive tests except for SF. An overview of the number of cognitive tests completed per patient during each visit is available in **Table S3**. The number of performed cognitive assessment for MoCA, TMT-A, TMT-B, SF and DSST as well as for the two derived scores CoCo and TMT-B/TMT-A at baseline and at FU1-4 are provided in **Table 2.** The main reason for dropouts between BL-FU3 were (1) patient could not be reached (n=23); (2) consent was withdrawn (n=99); (3) death (n=253); (4) loss to follow-up / FU4 visit >50 days after 4 year mark (n=109). For a detailed overview, see **Table S4**. The reasons why cognitive assessments were missed or excluded

from the analysis were a constrained test situation or motivation, present incident of participant (e.g., health issue, emotional or mental incident), cognitive inability to perform the test, due to dropout or death or errors of administration by the examiner.

Table 2 Cognitive scores over the course of the study

	Baseline*		**Follow-up 1**		**Follow-up 2**		**Follow-up 3**		**Follow-up 4**	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
MoCA	2,402	24.9 (3.2)	2,108	25.5 (3.2)	1,889	25.9 (3.3)	1,531	26.3 (3.2)	990	26.5 (3.2)
SF	2,408	18.9 (5.4)	2,116	19.5 (5.7)	1,902	19.7 (5.8)	1,688	20.1 (6.1)	1,460	20.2 (6.4)
TMT-A	2,393	0.5 (0.2)	2,106	0.6 (0.2)	1,891	0.6 (0.2)	1,533	0.6 (0.2)	991	0.6 (0.2)
TMT-B	2,380	0.2 (0.1)	2,097	0.2 (0.1)	1,879	0.2 (0.1)	1,524	0.2 (0.1)	982	0.3 (0.1)
TMT B/A	2,380	0.4 (0.2)	2,097	0.4 (0.2)	1,876	0.4 (0.2)	1,523	0.4 (0.2)	982	0.4 (0.1)
DSST	2,396	43.6 (14.3)	2,096	45.1 (14.9)	1,871	45.9 (15)	1,520	47.6 (15.2)	987	48.2 (15.6)
CoCo	2,359	0 (0.5)	2,080	0 (0.5)	1,850	0.1 (0.6)	1,502	0.1 (0.6)	976	0.2 (0.6)

Data are presented as mean (± SD) or counts (percentages). CoCo: Cognitive construct; DSST: Digit Symbol Substitution Test; MoCA: Montreal Cognitive Assessment; SF: Semantic Fluency Test, animals; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B (number of correct connections per second); TMT B/A: ratio of Trail Making Test B/ Trail Making Test A.

*n=2,415

Development of cognitive functioning over time

The mean score for each of the cognitive tests increased over time, which is displayed in **Table 2** and visualized in **Figure 1**. Development over time for AF-type is displayed in supplementary material 1: **Figures S1-S2**.

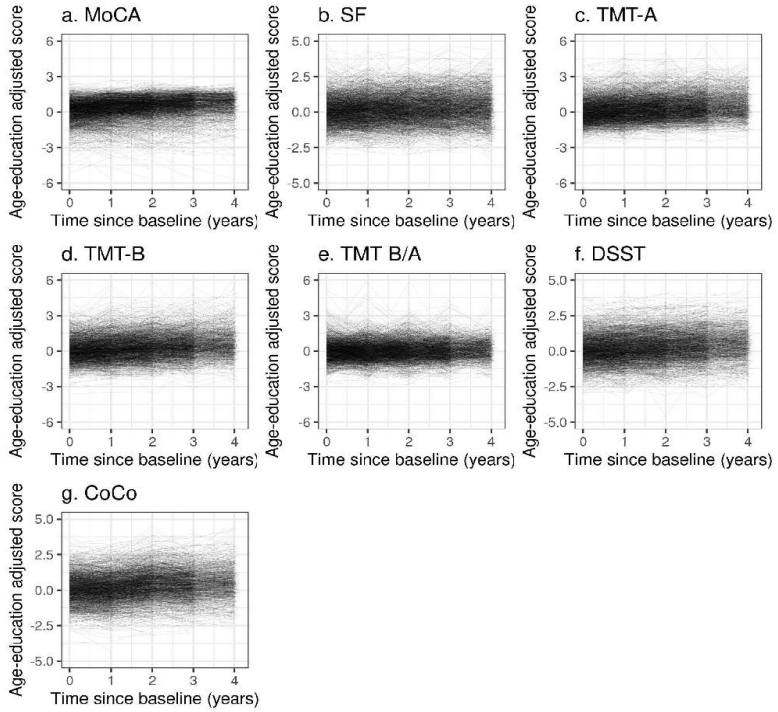

Figure 1 Spaghetti plots showing the evolution of the cognitive functioning over time (until FU4) for each of the age-education standardized cognitive measures for all AF patients. CoCo: Cognitive construct; DSST: Digit Symbol Substitution Test; MoCA: Montreal Cognitive Assessment; SF: Semantic Fluency Test, animals; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; TMT B/A: ratio of Trail Making Test B/ Trail Making Test A.

Cognitive development as a function of time and AF type

Based on visual inspection of the results, including fitting a LOESS curve for each endpoint (**Figure S3**), we accepted the assumption of a linear development of cognitive functioning over time. The age-education standardized score increased over time for the MoCA, SF, TMT-A, TMT-B, DSST and CoCo. Undertaking a cognitive test for the first time was estimated to differ from the mean of repeated undertakings by -0.09 units 95% CI [-0.13, -0.05] for the MoCA score, -0.07 units [-0.12, -0.03] for the SF score, -0.11 units [-0.16, -0.06] for the TMT-A score; -0.06 units [-0.11, -0.02] for the TMT-B score; -0.04 units [-0.07, -0.01] for the DSST score and 0.05 units [0.02, 0.08] for the CoCo score. The 95% CI for the interaction between AF-type and time laying completely below 0, suggested that the development in standardized TMT-B, DSST and CoCo score depended on AF-type, after adjustment for all covariates in the model. The point estimate of the interaction term suggested a smaller yearly increase in the DSST (0.07 compared to 0.09), CoCo score (0.11 compared to 0.14) and TMT-B (0.10 compared to 0.13) in patients with non-paroxysmal AF compared to patients with paroxysmal AF. For the other remaining cognitive tests, we found no interaction effect between AF-type and time, suggesting that the development in age-education standardized of the MoCA, SF, TMT-A and the TMT-B/TMT-A scores over time is not associated with AF-type. An overview is presented in **Table 3**.

The covariates depression, history of stroke or TIA and diabetes appeared to be associated with worse scores for all 7 standardized cognitive outcomes (**Figure 2**). An overview of the estimates and corresponding 95% CI for all variables in the linear fixed effects model describing the association between AF-type and the development of cognitive functioning in each cognitive test is presented in supplementary material 1: **Tables S5-S11**.

Table 3 Estimates with 95% CI for all 7 cognitive tests. The results for each covariate represent the effect after adjusting for all other variables in the model

Test	Variable	Estimate	95% CI
MoCA	AF-type (non-paroxysmal over paroxysmal)	-0.06	[-0.14, 0.01]
	Time (years)	0.09	[0.06, 0.12]
	AF-type*Time Interaction	-0.01	[-0.04, 0.01]
SF	AF-type (non-paroxysmal over paroxysmal)	-0.03	[-0.10, 0.05]
	Time (years)	0.03	[0.00, 0.05]
	AF-type*Time Interaction	0.01	[-0.02, 0.03]
TMT-A	AF-type (non-paroxysmal over paroxysmal)	-0.06	[-0.14, 0.02]
	Time (years)	0.09	[0.07, 0.12]
	AF-type*Time Interaction	-0.01	[-0.04, 0.01]
TMT-B	AF-type (non-paroxysmal over paroxysmal)	-0.03	[-0.11, 0.05]
	Time (years)	0.10	[0.07, 0.13]
	AF-type*Time Interaction	-0.03	[-0.05, -0.00]
TMT-B/A	AF-type (non-paroxysmal over paroxysmal)	0	[-0.07, 0.07]
	Time (years)	0.02	[-0.01, 0.05]
	AF-type*Time Interaction	-0.01	[-0.04, 0.01]
DSST	AF-type (non-paroxysmal over paroxysmal)	-0.07	[-0.15, 0.01]
	Time (years)	0.07	[0.06, 0.08]
	AF-type*Time Interaction	-0.02	[-0.04, -0.00]
CoCo	AF-type (non-paroxysmal over paroxysmal)	-0.05	[-0.13, 0.03]
	Time (years)	0.11	[0.09, 0.13]
	AF-type*Time Interaction	-0.03	[-0.04, -0.01]

CoCo: Cognitive construct; DSST: Digit Symbol Substitution Test; MoCA: Montreal Cognitive Assessment; SF: Semantic Fluency Test, animals; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B (number of correct connections per second); TMT B/A: ratio of Trail Making Test B/ Trail Making Test A.

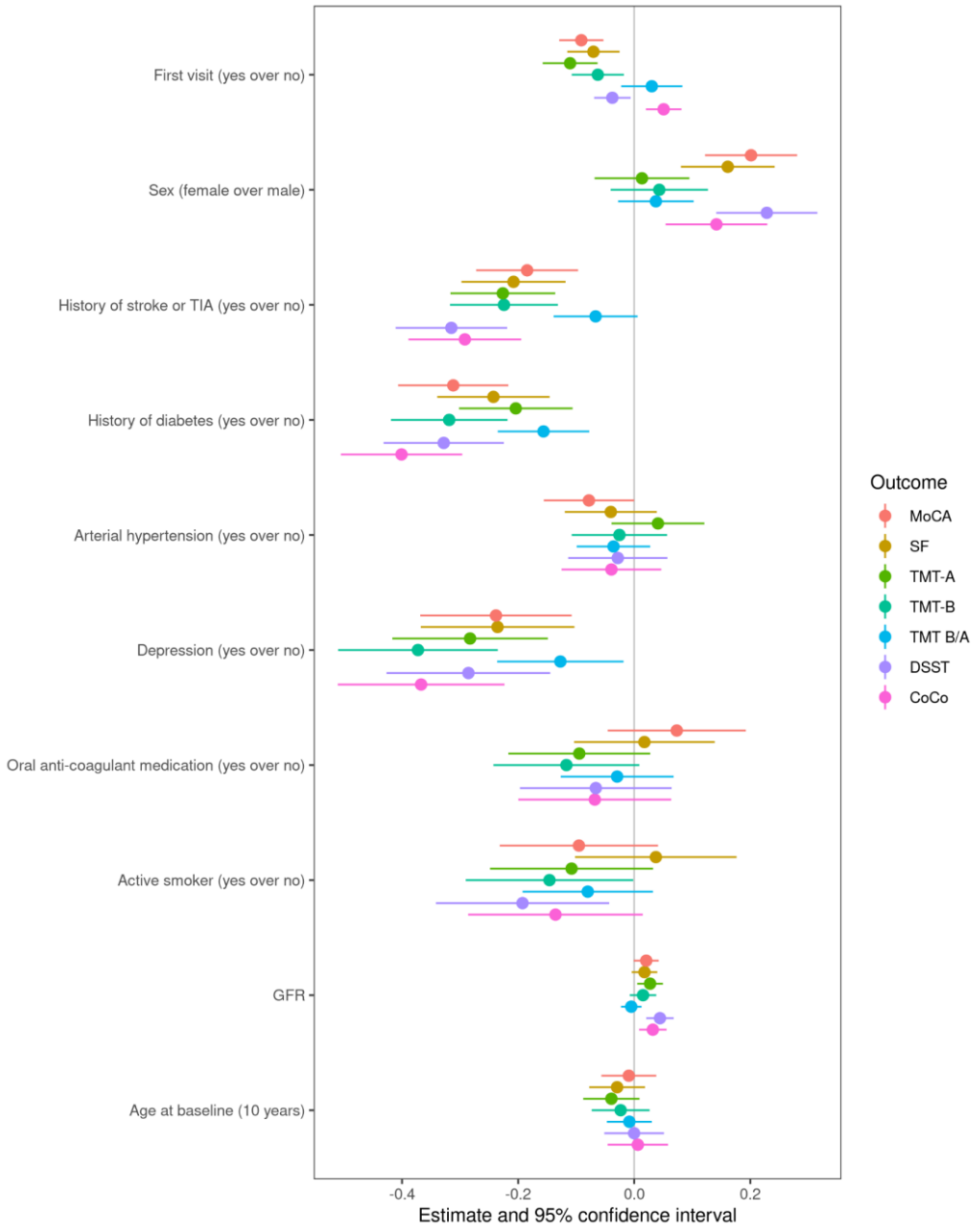

Figure 2 Forest plot visualizing the estimates and 95% CIs for the covariates in the linear mixed effects models of change in cognitive scores over time. Point estimates to the left of the vertical line mean worse cognitive function over time. CoCo: Cognitive construct; DSST: Digit Symbol Substitution Test; GFR: glomerular filtration rate; MoCA: Montreal Cognitive Assessment; SF: Semantic Fluency Test, animals; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; TMT B/A: ratio of Trail Making Test B/ Trail Making Test A.

Cognitive drop and the association with AF type

The threshold of cognitive drop >1 SD of the standardized baseline distribution was crossed by a total of 228 patients for MoCA, 472 for SF, 352 for TMT-A, 310 for TMT-B, 591 for TMT-B/TMT-A, 184 for DSST, and 190 for CoCo across all follow-up visits. **Table S12** presents an overview of the number of patients who crossed the threshold of 1 SD lower than the first test result per visit. AF-type did not appear to be associated with the hazard (HR) for cognitive drop for any of the cognitive tests in the model adjusted for all covariates. **Figure 3** shows the probability of cognitive drop by AF-type, unadjusted for other variables, and supplementary material 1: **Tables S13-S19** report the HRs and corresponding confidence intervals of all variables in the model for each cognitive test.

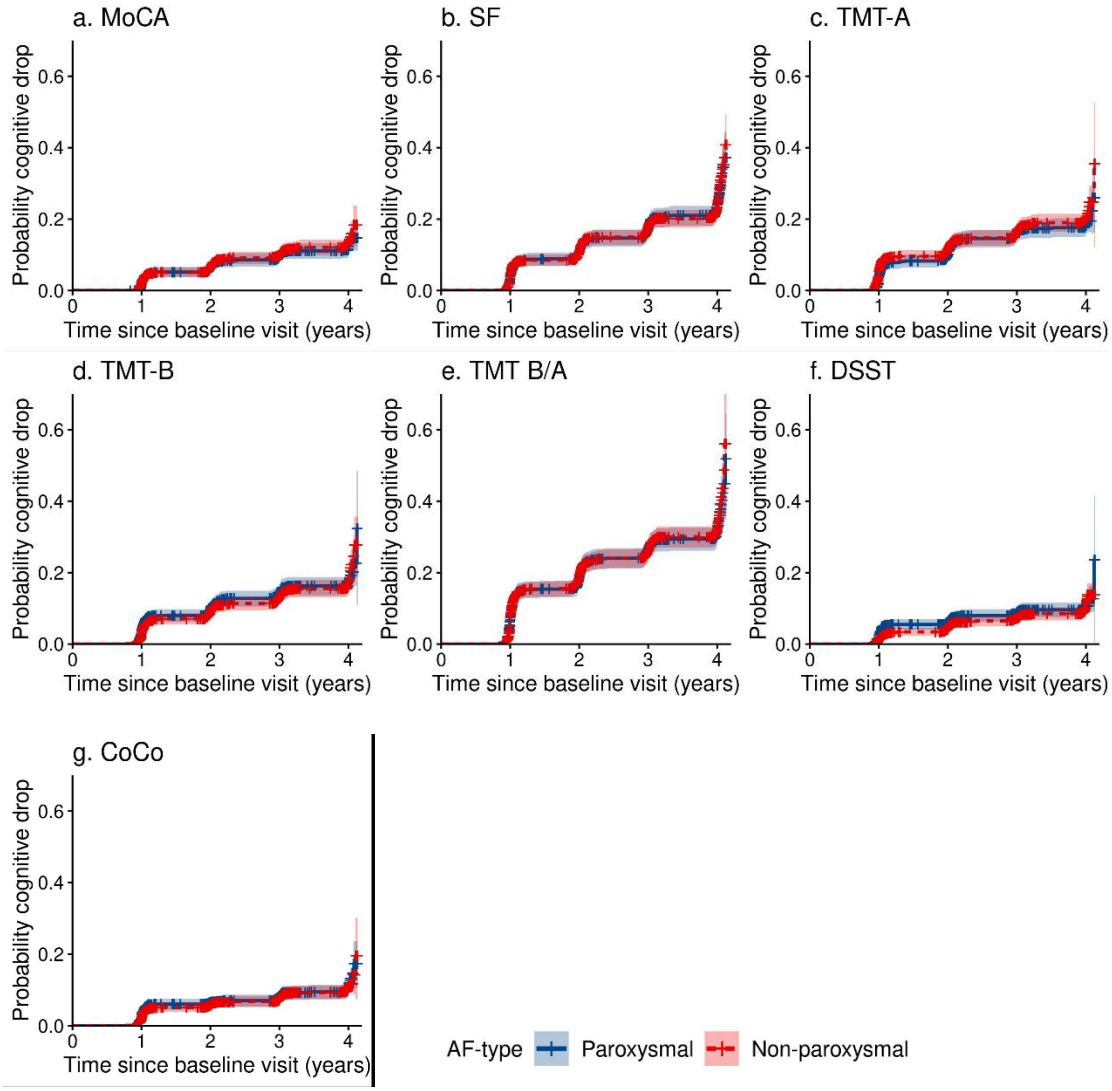

Figure 3 Cumulative probability of cognitive drop with 95% confidence interval according to all 7 cognitive tests by AF-type. Patients were censored at 4 years and 50 days from the baseline visit. CoCo: Cognitive construct; DSST: Digit Symbol Substitution Test; GFR: glomerular filtration rate; MoCA: Montreal Cognitive Assessment; SF: Semantic Fluency Test, animals; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; TMT B/A: ratio of Trail Making Test B/ Trail Making Test A.

Subgroup and sensitivity analyses

There was no association between AF-type and cognitive development and decline in the different subgroups with and without a history of diabetes, depression, or stroke/TIA, as well as by sex and smoking status. Only for a history of hypertension, we found a signal for a subgroup effect in the linear mixed models for MoCA, TMT-B, DSST, and CoCo (**Table S20** in the supplement). In the subgroup of patients without hypertension, we found a smaller increase in age-education standardized cognitive scores in patients with non-paroxysmal AF compared to patients with paroxysmal AF. The results of these models for the MoCA, TMT-B, DSST and CoCo are shown in supplementary material 1: **Tables S21-S24**. In the Cox models, we did not find signals for a potential subgroup effect. The different sensitivity analyses (**Figure S3**, **Tables S25-S30**), despite not alleviating the risk of attrition bias completely, suggested that in the observed time frame the effect of attrition is rather small, since the results of the analyses were similar when using patients who had all visits compared to the whole sample.

Post hoc analyses indicated an interaction between the time and history of stroke or TIA at baseline, suggesting a larger annual increase in MoCA score in patients without history of stroke or TIA compared to patients with history of stroke or TIA and are displayed in supplementary material 1: **Tables S31-S33**. The association between each covariate and cognitive drop can be found in **Table S13**. We visualized the unadjusted probability of cognitive impairment according to MoCA by history of stroke or TIA (**Figure S4**), depression (**Figure S5**), and diabetes (**Figure S6**) in the supplement. These analyses showed a higher cumulative incidence of cognitive drop over time among patients with history of stroke or TIA and among patients with depression.

Discussion

This large community-based cohort study of elderly patients with AF in Switzerland aimed at describing the development of cognitive functioning over time, its association with AF-type (paroxysmal or non-

paroxysmal) and accumulation of cases of cognitive drop over time and across AF-type and comorbidities. The results showed a longitudinal increase in all mean cognitive scores with a smaller increase in executive functioning and processing speed over time in patients with non-paroxysmal AF compared to patients with paroxysmal AF. No differences in the rate of accumulation of cognitive drop were observed between AF-types in any cognitive measure. The presence of diabetes, history of stroke/TIA and depression was associated with worse cognitive performance on all cognitive measures.

Previous work has described [15, 16, 35] but also questioned an association between cognitive drop and AF [8, 17]. Our results extend those findings in the sense that we found an increase in standardized mean scores of each cognitive test over time in a Swiss cohort of AF patients. Whereas the large number of AF patients and the avoidance of ceiling effects by performing validated cognitive testing on multiple domains in our study support the robustness of our results, two effects might explain our findings. First, longitudinal studies may be prone to attrition bias, indicating that participants who are most likely to remain in the study tend to be the healthiest, best educated, wealthiest, and have the highest scores on cognitive tests, whereas ill participants are less likely to return for study visits [36]. Under the limitation of our available data, sensitivity analysis using IPCW and comparison of full and dropout data sets suggested the attrition bias likely to be small, at least in the observed period. Second, longitudinal studies on cognition require repeated administration of cognitive tests, especially in a rather short period of time, which might lead to practice effects and improvement or maintenance of test scores despite a cognitive drop [37, 38]. Although we adjusted the analysis for one potential type of practice effect by accounting for the largest change between the baseline and the first follow-up, the increase over all cognitive tests remained. Thus, our study suggests an increase in cognitive performance over time in AF patients as the result of a practice effect.

While practice effects are typically considered as biases when interpreting longitudinal studies on cognition, their use as markers of cognitive performance has gained interest. A recent systematic review on 27 studies on practice effect as cognitive marker indicated that smaller practice effects were associated with neurodegeneration biomarkers and thus might act as a potential marker of cognitive decline [39]. Although our results showed a longitudinal increase in all cognitive measures due to practice effects, they indicate

smaller increases in executive functioning, processing speed and general cognitive performance over time in patients with non-paroxysmal AF compared to patients with paroxysmal AF. Additionally, our results indicated no difference between AF groups in accumulating cases of cognitive drop defined as a threshold of >1 SD in all cognitive measures. When we altered the threshold value to >1.5 SD in the sensitivity analysis, a decrease in the number of events per visit was visible, but no difference in the results compared to the main analysis was found. As thresholds are set as a decrease from the first measurement, the fact that a person with a high score on the first measurement has more room for decrease than a person who scored low at baseline is not accounted for; similarly, using a threshold as an outcome does not account for possible practice effects. Furthermore, thresholds can be biased through temporary worse test results due to i.e., lack of motivation or wellbeing on testing day. Consequently, comparing practice effects, taken as the ability to learn over time, might act as a more reliable marker of cognitive change in longitudinal studies. Since our results indicate smaller practice effects in executive functioning, processing speed and general cognitive functioning, they might reflect reduced cognitive functioning in the non-paroxysmal AF group.

This study is among the first to investigate the differences in cognitive functions between non-paroxysmal and paroxysmal AF over time. One recent study investigated group differences between 90 persistent, 90 paroxysmal AF patients and 90 healthy participants using cognitive tests on memory, language, and visuospatial functions. While both AF groups showed lower cognitive performance compared to the healthy group, persistent and paroxysmal AF patients showed no differences on a total score of cognitive functioning, but a tendency towards smaller visuospatial abilities in the persistent AF group [40]. Although no interaction between time and AF groups was found and permanent AF was not investigated by the authors, our results support the notion of lower cognitive abilities in the more sustained form of AF, which was categorized as non-paroxysmal AF in our study. Notably, our results indicated less practice effects in tasks addressing processing speed and executive functioning, which is in line with a previous study indicating an association between AF and a greater drop in executive functioning and processing speed [15]. In extension to those findings, our results indicate that this association might be only present in patients

with non-paroxysmal AF. Additional studies are needed to understand cognitive performance in the different subgroups more in detail, for example by addressing longitudinal change in different classifications of AF subtypes.

Next to executive functioning and processing speed, the difference between AF subgroups was also present in the cognitive construct (CoCo) score [25]. It has previously been shown that the CoCo score is likely to be more granular and more sensitive to detect small changes in cognitive function [25] which may be missed when examining each neurocognitive test alone [16, 41]. Thus, using derived measures on cognitive functioning as well as tests on executive functioning and processing speed might be most sensitive in detecting subtle changes in cognition in AF patients, even after considering practice effects.

Shared risk factors of AF and cognitive decline are an important possible mechanism linking AF to alterations in cognitive function. In our study, patients with pre-existing depression, history of stroke or TIA and diabetes performed worse on all cognitive tests. Nonetheless, the impact of AF-type on longitudinal cognition was present in multivariate models suggesting some genuine effect of AF-type on cognition. Although AF and cognitive drop are likely to share one or more underlying pathogenic mechanisms, their possible pathophysiological aspects are still not fully understood [1, 32]. Therefore, future studies with a control group are needed to explore the interplay between AF-type and other cardiovascular risk factors and comorbidities in relation to cognitive drop over time.

The large sample size of a comprehensively characterized, well-treated and representative cohort AF patients recruited from the main language regions of Switzerland, is a major strength of our study. Furthermore, brief composite measures (e.g., Mini-Mental State Examination) are commonly used as outcomes to assess cognitive performance, as they are time-efficient. Nevertheless, their assessment of cognitive functioning is limited by the insensitivity to detect subtle changes in various cognitive domains [16]. Thus, the standardized assessment of cognitive functions using five validated and widely used cognitive measures in addition to the derived CoCo score [25] in our study displays a further strength, as it allows to study attention, psychomotor speed, and mental flexibility (executive control) as well as short-

term memory, language, and visuospatial abilities. In addition, extensive information of AF-type, cardiac and neurological comorbidities were available and definitions of paroxysmal and non-paroxysmal AF were based on AF guidelines published in 2010 [26]. Appropriate CRFs, which have been previously validated, were used [23, 24]. Finally, all analyses were adjusted for potential confounders, and multiple sensitivity analyses provided consistent findings, supporting the robustness of the main findings.

Some limitations must be taken into account. First, understanding the role of AF itself in the changes in cognitive functioning would require the comparison to people without AF. We did not find a matching cohort of patient with no AF to perform such a comparison. The Swiss-AF CONTROL cohort is currently being recruited with the aim to make this analysis possible in the near future. Second, we identified 57 cases where MoCA and SF tests were not performed in the patient's mother tongue, which is a limitation to the results of these language dependent tests. Possibly more cases occurred, but it was not possible to precisely trace which cognitive tests were not performed in patients' mother tongue, since this information could only be extracted from notes within the database by the study personnel. Nevertheless, the identified number of such cases is small, and dropping these patients led to a negligible change in the results. Third, missing data occurred in our sample, especially at FU4 due to the COVID-19 pandemic that started during data collection and thus most cognitive tests could not be collected by phone (i.e., TMT-A, TMT-B, and DSST). Since the MoCA test conducted by telephone does not reflect the in-person test, we discarded those results. Participants were not included in the analyses if data was missing at baseline. Finally, although we adjusted our models to largest practice effects, identified primarily between the baseline and subsequent test measurements, the current study design did not allow for further statistical control for practice effects since time of FU and testing coincide almost completely. Nevertheless, our study supports previous notions that the lack of practice effect indicates a decline in cognitive performance over time. Future studies might further establish the role of practice effects as markers of cognitive decline by designing the study in a way that cognitive testing and follow-up are not at the same time point to control for the practice effect in subsequent measurements.

Conclusions

We found a small, constant increase in cognitive functioning over a median duration of 3.97 years in AF patients, which can probably be attributed to practice effects. Among patients with non-paroxysmal (i.e., persistent or permanent) AF, this practice effect was less pronounced in cognitive tests on processing speed and executive functioning compared to patients with paroxysmal AF. While these results might indicate persistent learning abilities and maintenance of cognitive functions in patients with AF, smaller practice effects, as it is the case in patients with non-paroxysmal AF, might represent a potential early marker of later cognitive decline. Longer follow-up is required to gauge the full impact of AF type on cognitive decline. Our study further highlights the importance of addressing comorbidities in AF early, as they contribute to worse cognitive performance. Therefore, future research should contribute to the understanding of underlying mechanisms in the relationship between AF and cognitive functioning.

Data availability statement

The datasets presented in this article are not readily available because restrictions by the Ethics Committee. Requests to access the datasets should be directed to the corresponding author.

Conflict of interest

NR received a grant from the Swiss Heart Foundation. ***GM*** has received consultant fees for taking part to advisory boards from Astra Zeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Gebro Pharma, Novartis and Vifor, all outside of the submitted work. ***JHB*** reports grants from the Swiss National Foundation of Science, the Swiss Heart Foundation, the Kardio foundation and received grant support and consultancy fees to the institution from Bayer, Sanofi, and Daitchii. ***TR*** reveived consulting honoraria or travel support from Abbott/SJM, Astra Zeneca, Brahms, Bayer, Biosense-Webster, Medtronic, Pfizer-BMS and Roche, all outside of the presented work. He reports research grants from the Swiss National Science Foundation

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Author contributions

ASW, PZ, MC, NRom, AUM and LHB conceived and design the analysis; ASW, PZ, MC, NRom analysed, interpreted the data and drafted the manuscript; NR, BC, GM, MLDP, JHB, TR, PK, AS, DC, AS, ASM, REP, MK, SO, AUM and LHB revised the manuscript and gave relevant intellectual contribution. All authors read and approved the final manuscript.

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REFERENCES

[1] Puccio D, Vizzini MC, Baiamonte V, Lunetta M, Evola S, Galassi AR, et al. Atrial fibrillation and cognitive disorders: An overview on possible correlation. Mech Ageing Dev. 2020;191:111326. doi: 10.1016/j.mad.2020.111326

[2] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg. 2016;50:E1–E88. doi: 10.1093/ejcts/ezw313

[3] Krijthe BP, Kunst A, Benjamin EJ, Lip GY., Franco OH., Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J. 2013;34:2746–2751. doi: 10.1093/eurheartj/eht280

[4] Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke. 1991;22:312–318. doi: 10.1161/01.str.22.3.312

[5] Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, et al. Temporal Relations of Atrial Fibrillation and Congestive Heart Failure and Their Joint Influence on Mortality. Circulation. 2003;107:2920–2925. doi: 10.1161/01.CIR.0000072767.89944.6E

[6] Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of Atrial Fibrillation on the Risk of Death. Circulation. 1998;98:946–952. doi: 10.1161/01.cir.98.10.946

[7] Chen LY, Sotoodehnia N, Bůžková P, Lopez FL, Yee LM, Heckbert SR, et al. Atrial Fibrillation and the Risk of Sudden Cardiac Death: The Atherosclerosis Risk in Communities Study and Cardiovascular Health Study. JAMA Intern Med. 2013;173:29–35. doi: 10.1001/2013.jamainternmed.744

[8] Tilvis RS, Kähönen-Väre MH, Jolkkonen J, Valvanne J, Pitkala KH, Strandberg TE. Predictors of cognitive decline and mortality of aged people over a 10-year period. J Gerontol A Biol Sci Med Sci. 2004;59:268–274. doi: 10.1093/gerona/59.3.m268

[9] Bunch TJ, Weiss JP, Crandall BG, May HT, Bair TL, Osborn JS, et al. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. Heart Rhythm. 2010;7:433–437. doi: 10.1016/j.hrthm.2009.12.004

[10] Dublin S, Anderson ML, Haneuse SJ, Heckbert SR, Crane PK, Breitner JC, et al. Atrial Fibrillation and Risk of Dementia: A Prospective Cohort Study. J Am Geriatr Soc. 2011;59:1369–1375. doi: 10.1111/j.1532-5415.2011.03508.x

[11] Elias MF, Sullivan LM, Elias PK, Vasan RS, D'Agostino Sr RB, Seshadri S, et al. Atrial Fibrillation Is Associated With Lower Cognitive Performance in the Framingham Offspring Men. J Stroke Cerebrovasc Dis. 2006;15:214–222. doi: 10.1016/j.jstrokecerebrovasdis.2006.05.009

[12] Marengoni A, Qiu C, Winblad B, Fratiglioni L. Atrial fibrillation, stroke and dementia in the very old: A population-based study. Neurobiol Aging. 2011;32:1336–1337. doi: 10.1016/j.neurobiolaging.2009.08.002

[13] Marzona I, O'Donnell M, Teo K, Gao P, Anderson C, Bosch J, et al. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. CMAJ. 2012;184:E329–E336. doi: 10.1503/cmaj.111173

[14] de Bruijn RF, Heeringa J, Wolters FJ, Franco OH, Stricker BH, Hofman A, et al. Association Between Atrial Fibrillation and Dementia in the General Population. JAMA Neurol. 2015;72:1288–1294. doi: 10.1001/jamaneurol.2015.2161

[15] Chen LY, Norby FL, Gottesman RF, Mosley TH, Soliman EZ, Agarwal SK, et al. Association of atrial fibrillation with cognitive decline and dementia over 20 years: The ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study). J Am Heart Assoc. 2018;7:e007301. doi: 10.1161/JAHA.117.007301

[16] Nishtala A, Piers RJ, Himali JJ, Beiser AS, Davis-Plourde KL, Saczynski JS, et al. Atrial fibrillation and cognitive decline in the Framingham Heart Study. Heart Rhythm. 2018;15:166–172. doi: 10.1016/j.hrthm.2017.09.036

[17] Park H, Hildreth A, Thomson R, O'Connell J. Non-valvular atrial fibrillation and cognitive decline: a longitudinal cohort study. Age Ageing. 2007;36:157–163. doi: 10.1093/ageing/afl164

[18] Madhavan M, Graff-Radford J, Piccini JP, Gersh BJ. Cognitive dysfunction in atrial fibrillation. Nat Rev Cardiol. 2018;15:744–756. doi: 10.1038/s41569-018-0075-z
[19] Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with Atrial fibrillation: A meta-analysis. Ann Intern Med. 2013;158:338–346. doi: 10.7326/0003-4819-158-5-201303050-00007
[20] Singh-Manoux A, Fayosse A, Sabia S, Canonico M, Bobak M, Elbaz A, et al. Atrial fibrillation as a risk factor for cognitive decline and dementia. Eur Heart J. 2017;38:2612–2618. doi: 10.1093/eurheartj/ehx208
[21] Chiang CE, Naditch-Brûlé L, Murin J, Goethals M, Inoue H, O'Neill J, et al. Distribution and Risk Profile of Paroxysmal, Persistent, and Permanent Atrial Fibrillation in Routine Clinical Practice. Circ Arrhythm Electrophysiol. 2012;5:632–639. doi: 10.1161/CIRCEP.112.970749
[22] Kim D, Yang PS, Yu HT, Kim TH, Jang E, Sung JH, et al. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a population-based cohort. Eur Heart J. 2019;40:2313–2323. doi: 10.1093/eurheartj/ehz386
[23] Conen D, Rodondi N, Müller A, Beer J, Auricchio A, Ammann P, et al. Design of the Swiss Atrial Fibrillation Cohort Study (Swiss-AF): structural brain damage and cognitive decline among patients with atrial fibrillation. Swiss Med Wkly. 2017;147:w14467. doi: 10.4414/smw.2017.14467
[24] Conen D, Rodondi N, Müller A, Beer JH, Ammann P, Moschovitis G, et al. Relationships of Overt and Silent Brain Lesions With Cognitive Function in Patients With Atrial Fibrillation. J Am Coll Cardiol. 2019;73:989–999. doi: 10.1016/j.jacc.2018.12.039
[25] Springer A, Monsch AU, Dutilh G, Coslovsky M, Kievit RA, Bonati LH, et al. A factor score reflecting cognitive functioning in patients from the Swiss Atrial Fibrillation Cohort Study (Swiss-AF). PLoS One. 2020;15:e0240167. doi: 10.1371/journal.pone.0240167
[26] Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;31:2369–2429.
[27] Bano A, Rodondi N, Beer JH, Moschovitis G, Kobza R, Aeschbacher S, et al. Association of Diabetes With Atrial Fibrillation Phenotype and Cardiac and Neurological Comorbidities: Insights From the Swiss-AF Study. J Am Heart Assoc. 2021;10:e021800. doi: 10.1161/JAHA.121.021800
[28] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695–699. doi: 10.1111/j.1532-5415.2005.53221.x
[29] Army Individual Test Battery: Manual of Directions and Scoring. War Department Adjutant General's Office. Washington D.C., 1944.
[30] Morris JC, Heyman A, Mohs RC, Rogers H. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assesment of Alzheimer's disease. Neurology. 1989;39:1159–1159. doi: 10.1212/wnl.39.9.1159
[31] Wechsler D. Wechsler Adult Intelligence Scale–Revised Manual New York: Psychological Corporation, 1981.
[32] Palmer K, Fratiglioni L, Winblad B. What is mild cognitive impairment? Variations in definitions and evolution of nondemented persons with cognitive impairment. Acta Neurol Scand. 2003;107:14–20. doi: 10.1034/j.1600-0404.107.s179.2.x
[33] Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982;17:37–49. doi: 10.1016/0022-3956(82)90033-4
[34] Bartels C, Wegrzyn M, Wiedl A, Ackermann V, Ehrenreich H. (2010). Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. BMC neuroscience. 2010,11:1-12. doi: 10.1186/1471-2202-11-118
[35] Small BJ, Dixon RA, McArdle JJ, Grimm KJ. Do changes in lifestyle engagement moderate cognitive decline in normal aging? Evidence from the victoria longitudinal study. Neuropsychology. 2012;26:144–155. doi: 10.1037/a0026579

[36] Van Beijsterveldt CE, van Boxtel MP, Bosma H, Houx PJ, Buntinx F, Jolles J. Predictors of attrition in a longitudinal cognitive aging study: The Maastricht Aging Study (MAAS). J Clin Epidemiol. 2002;55:216–223. doi: 10.1016/s0895-4356(01)00473-5

[37] Abner EL, Dennis BC, Mathews MJ, Mendiondo MS, Caban-Holt A, Kryscio RJ, et al. Practice effects in a longitudinal, multi-center Alzheimer's disease prevention clinical trial. Trials. 2012;13:217. doi: 10.1186/1745-6215-13-217

[38] Salthouse TA. Influence of age on practice effects in longitudinal neurocognitive change. Neuropsychology. 2010;24:563–572. doi: 10.1037/a0019026

[39] Jutten RJ, Grandoit E, Foldi NS, Sikkes SA, Jones RN, Choi SE, et al. Lower practice effects as a marker of cognitive performance and dementia risk: A literature review. Alzheimers Dement (Amst). 2020;12:e12055. doi: 10.1002/dad2.12055

[40] Gaita F, Corsinovi L, Anselmino M, Raimondo C, Pianelli M, Toso E, et al. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. J Am Coll Cardiol. 2013;62:1990–1997. doi: 10.1016/j.jacc.2013.05.074

[41] Gibbons LE, Carle AC, Mackin RS, Harvey D, Mukherjee S, Insel P, et al. A composite score for executive functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment. Brain Imaging Behav. 2012;6:517–527. doi: 10.1007/s11682-012-9176-1

[42] Smith SR, Servesco AM, Edwards JW, Rahban R, Barazani S, Nowinski LA, et al. Exploring the validity of the comprehensive trail making test. Clin Neuropsychol. 2008,22:507-518. doi: 10.1080/13854040701399269

[43] Matarazzo JD, Herman DO. Base rate data for the WAIS-R: test-retest stability and VIQ-PIQ differences. J Clin Neuropsychol. 1984;6:351-366. doi: 10.1080/01688638408401227

Mid-term Changes in Cognitive Functions in Patients with Atrial Fibrillation: A Longitudinal Analysis of the Swiss-AF Cohort

Supplementary Material:

Supplementary Tables, Supplementary Text and Supplementary Figures

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Table S1 Description of the neurocognitive test battery and all 17 items included in the cognitive assessment in the Swiss-AF study. Test description and items are grouped by test (MoCA, Trail Making Test Part A and B (TMT-A, TMT-B), Semantic Fluency Test (SF), and Digit Symbol Substitution Test (DSST). Information on definition of scores and measurement properties is also provided. The table was adapted according to Springer et al. [25].

Item No	**MoCA Items (scoring according to Manual; www.mocatest.org)** *The Test evaluates visuospatial and executive functions, confrontation naming, memory, attention, language and abstraction [28].*
1	MoCA-Trail Making Test with letters and numbers; scored as "completed" vs "not completed": [0, 1]
2	Copy Cube; scored as "completed" vs "not completed": [1, 0]
3	Clock Drawing; scored as to how many of the three features are correct: [0, 1, 2, 3]
4	Naming Animals; scored as to the number of animals correctly named: [0, 1, 2, 3]
5	Digit Span forward; scored as "completed" vs "not completed": [1, 0]
6	Digit Span backward; scored as "completed" vs "not completed": [1, 0]
7	Letter A; scored as "completed" if less than 2 errors occurred: [1, 0]
8	100–7 (Serial 7 Subtraction); scored as: 0 correct [0 points], 1 through 3 correct [1 point], 4 correct [2 points], 5 correct [3 points]; values range from: [0, 1, 2, 3]
9	Sentence Repetition; scored according to number of sentences repeated correctly: [0, 1, 2]
10	F-Words, i.e., naming as many words that begin with the letter F; the number of correct words beginning with the letter F given in one minute [0,. . .] (scoring within the MoCA total = 11 or more points [1], ten or less [0])
11	Abstraction; scored as the number of correct similarities [0, 1, 2]
12	Delayed Recall; scored as the number of words correctly recalled [0, 1, 2, 3, 4, 5]
13	Orientation; scored as the number of correct answers: [0, 1, 2, 3, 4, 5]
	Trail Making Test Part A, (TMT-A) Item *The test measures visual attention and psychomotor speed [29]. Internal consistency has been reported with Cronbach's alpha = .86 to .88 [42].*
14	Outcome: number of correct connections per second: [0,. . .]

	Trail Making Test Part B, (TMT-B) Item *The test assesses speed, accuracy and mental flexibility (e.g., task switching) [29]. Internal consistency has been reported with Cronbach's alpha = .86 to .88 [42].*
15	Outcome: number of correct connections per second: [0,. . .]
	Semantic Fluency, Animals (SF), Item *The test measures semantic fluency- a combination of semantic memory and executive functions, complementing phonemic fluency within the MoCA [30].*
16	Number of correct animal names given in one minute: [0,. . .]
	Digit Symbol Substitution Test (DSST), Item *The test assesses information processing speed, visuomotor coordination and attention [31]. DSST high test retest reliability has been reported. This test has high test–retest reliability [43].*
17	Number of correct symbols filled out in 120 seconds: [0,. . .]

Note. Cognitive Construct (CoCo) derived from the total of 17 items comprised in the five validated neuropsychological tests. Internal consistency for the coco score has been reported with Cronbach's alpha of .84 [25].

Text S1 Description of the age-education standardized cognitive function score

The Swiss-AF baseline data were used for standardization. A linear regression model was fit to the observed baseline data, for each subsequent observation the linear predictor was calculated. Finally, Z-scores were calculated by dividing the linear predictor by the residual standard error of the model. This model assumes a linear association between age and cognitive functioning, that was shown to be correct.

The standardization is performed via the following steps:

1. we fit a linear regression model to the observed values at baseline
2. for each subsequent observation (i.e. follow-up measurements) we calculate the linear predictor based on the model
3. to standardize (= calculate a Z-score) we divide the linear predictor by the residual standard error of the model (as fit using baseline values).

For purposes of the modeling, and to obtain meaningful expected values, we use as reference values (where relevant) the mean variable values for age and education level (years) at baseline based on the full Swiss-AF population. Thus, for example, we calculate the age and education adjusted Z-score for DSST using the following formula:

$$Z_{TMTA_i} = \frac{DSST_i - \beta_{age} \times (Age.at.visit - mean.age.BL) - \beta_{education-level} \times (Edu.Yrs - mean.edu.yrs.BL)}{\hat{\sigma}}$$

where $\hat{\sigma}$ is the square-root of the residual variance from the linear model.

Table S2 Number (and percentage) of missing tests per visit

	MoCA	SF	TMT-A	TMT-B	TMT B/A	DSST	CoCo
Baseline	13 (0.49)	7 (0.26)	22 (0.82)	35 (1.31)	35 (1.31)	19 (0.71)	56 (2.10)
Follow-up 1	279 (10.44)	271 (10.14)	281 (10.52)	290 (10.85)	290 (10.85)	291 (10.89)	307 (11.49)
Follow-up 2	399 (14.93)	386 (14.45)	397 (14.86)	409 (15.31)	412 (15.42)	417 (15.61)	438 (16.39)
Follow-up 3	648 (24.25)	491 (18.38)	646 (24.18)	655 (24.51)	656 (24.55)	659 (24.66)	677 (25.34)
Follow-up 4	941 (35.22)	471 (17.63)	940 (35.18)	949 (35.52)	949 (35.52)	944 (35.33)	955 (35.74)

Note. Patients who dropped out of the cohort are excluded already. CoCo: Cognitive construct; DSST: Digit Symbol Substitution Test; MoCA: Montreal Cognitive Assessment; SF: Semantic Fluency Test, animals; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; TMT B/A: ratio of Trail Making Test B/ Trail Making Test A.

Table S3 Number and percentage of cognitive measurements completed by visit

	n cognitive tests performed															
	0		**1**		**2**		**3**		**4**		**5**		**6**		**7**	
Visit	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	2	0.083	3	0.124	1	0.041	16	0.663	17	0.704	17	0.704	1	0.041	2,358	97.640
Follow-up 1	268	11.227	6	0.251	5	0.209	3	0.126	8	0.335	17	0.712	2	0.084	2,078	87.055
Follow-up 2	382	16.696	8	0.350	5	0.219	3	0.131	17	0.743	23	1.005	2	0.087	1,848	80.769
Follow-up 3	486	22.304	156	7.159	3	0.138	3	0.138	7	0.321	22	1.010	2	0.092	1,500	68.839
Follow-up 4	464	24.029	475	24.599	2	0.104	2	0.104	8	0.414	4	0.207	1	0.052	975	50.492

Table S4 Overview of the number of dropouts with reasons per visit

	Baseline	Follow-up 1	Follow-up 2	Follow-up 3
Patient could not be reached	3	5	5	10
Consent was withdrawn	25	26	21	27
Death	0	68	82	103
Loss to follow-up / FU4 visit late	0	0	0	109

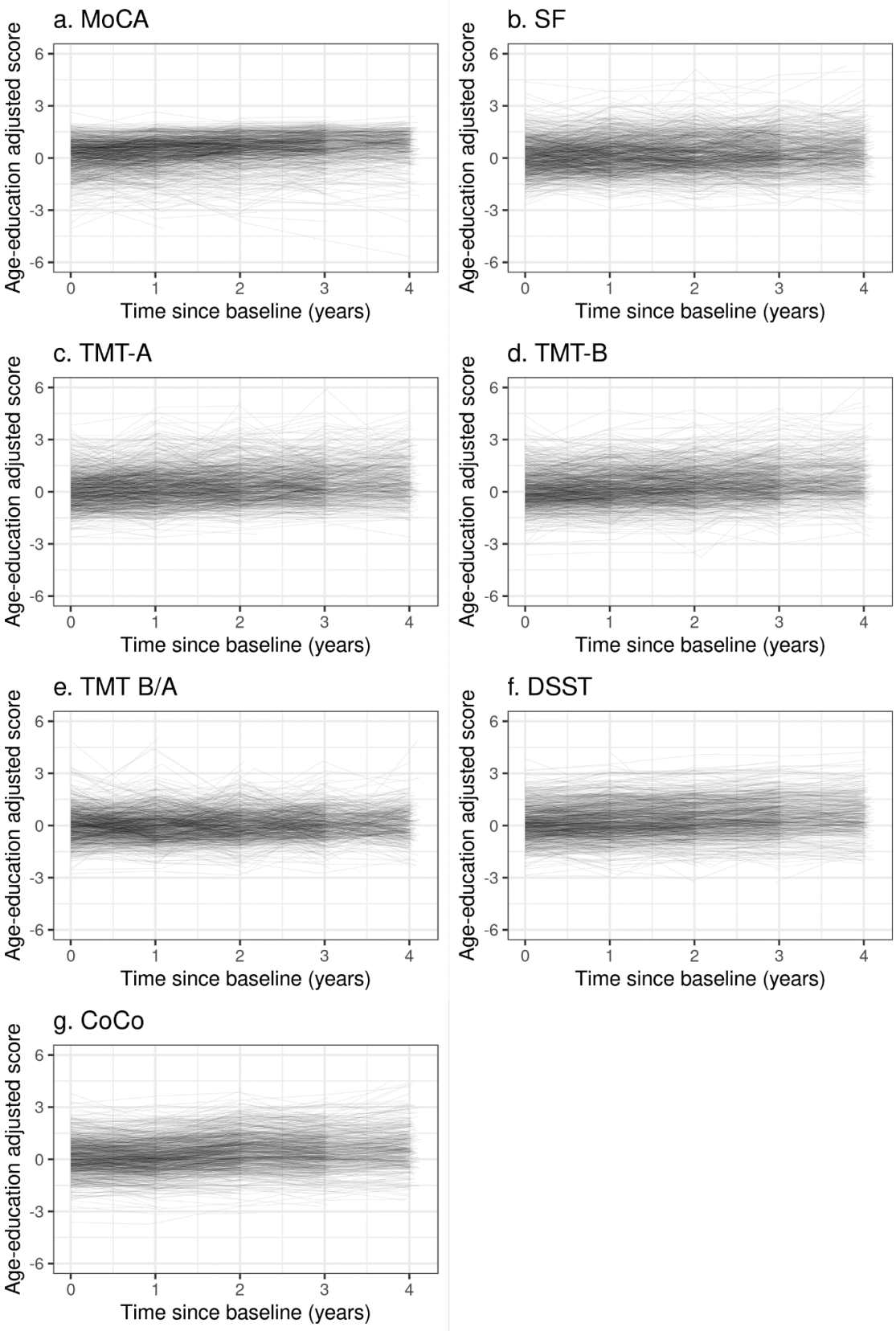

Figure S1 Spaghetti plots showing the evolution of the cognitive functioning until FU4 in patients with paroxysmal AF. CoCo: Cognitive construct; DSST: Digit Symbol Substitution Test; MoCA: Montreal Cognitive Assessment; SF: Semantic Fluency Test, animals; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; TMT B/A: ratio of Trail Making Test B/ Trail Making Test A.

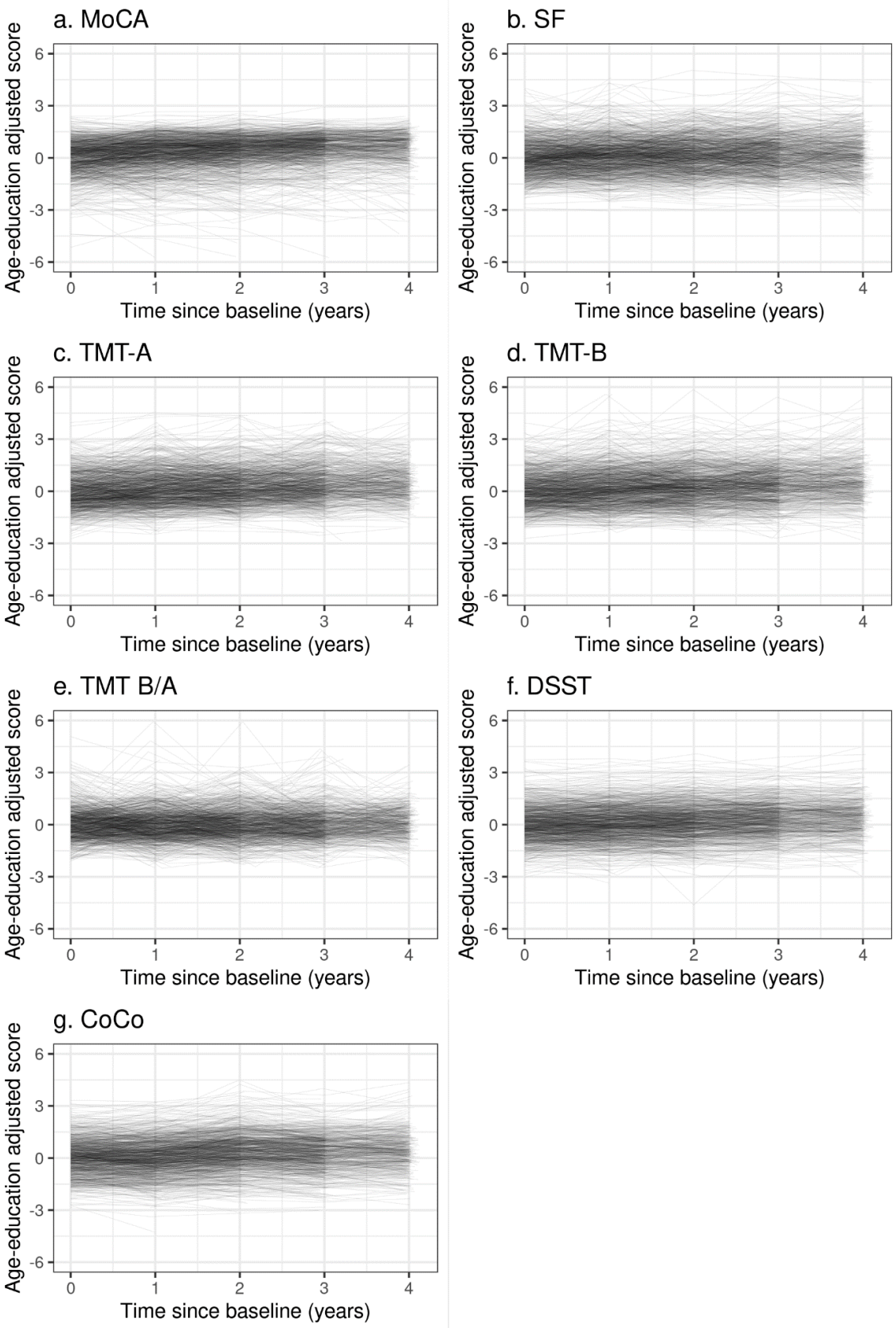

Figure S2 Spaghetti plots showing the evolution of the cognitive functioning until FU4 in patients with non-paroxysmal AF. CoCo: Cognitive construct; DSST: Digit Symbol Substitution Test; MoCA: Montreal Cognitive Assessment; SF: Semantic Fluency Test, animals; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; TMT B/A: ratio of Trail Making Test B/ Trail Making Test A.

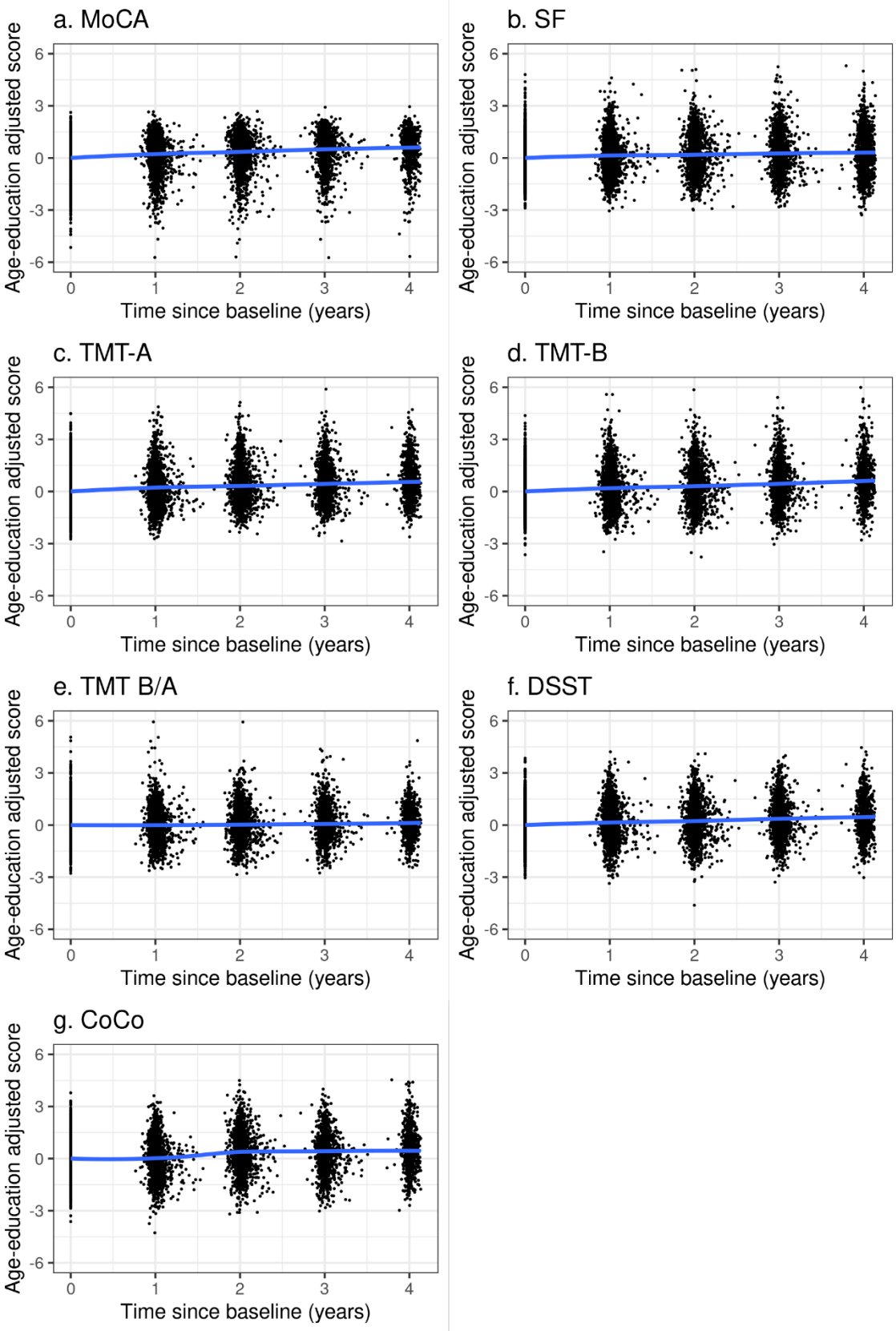

Figure S3 Scatter plot with spline to visualize the pattern of the cognitive functioning from baseline until FU4. CoCo: Cognitive construct; DSST: Digit Symbol Substitution Test; MoCA: Montreal Cognitive Assessment; SF: Semantic Fluency Test, animals; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; TMT B/A: ratio of Trail Making Test B/ Trail Making Test A.

Table S5 Estimates with 95% CI for MoCA. The results for each covariate represent the effect after adjusting for all other variables in the model

	estimate	95 % CI
AF-type (non-paroxysmal over paroxysmal)	-0.06	[-0.14, 0.01]
Time (years)	0.09	[0.06, 0.12]
First visit (yes over no)	-0.09	[-0.13, -0.05]
Sex (female over male)	0.20	[0.12, 0.28]
History of stroke or TIA (yes over no)	-0.18	[-0.27, -0.10]
History of diabetes (yes over no)	-0.31	[-0.41, -0.22]
Arterial hypertension (yes over no)	-0.08	[-0.16, -0.00]
Depression (yes over no)	-0.24	[-0.37, -0.11]
Oral anti-coagulant medication (yes over no)	0.07	[-0.05, 0.19]
Active smoker (yes over no)	-0.10	[-0.23, 0.04]
GFR (milliliter/minute)	0.02	[-0.00, 0.04]
Age at baseline (10 years)	-0.01	[-0.06, 0.04]
AF-type (non-paroxysmal over paroxysmal):Time (years)	-0.01	[-0.04, 0.01]

Note. AF: Atrial fibrillation; CI: Confidence interval; GFR: Glomerular filtration rate; MoCA: Montreal Cognitive Assessment; TIA: Transient ischemic attack.

Table S6 Estimates with 95% CI for SF. The results for each covariate represent the effect after adjusting for all other variables in the model

	estimate	95 % CI
AF-type (non-paroxysmal over paroxysmal)	-0.03	[-0.10, 0.05]
Time (years)	0.03	[0.00, 0.05]
First visit (yes over no)	-0.07	[-0.12, -0.03]
Sex (female over male)	0.16	[0.08, 0.24]
History of stroke or TIA (yes over no)	-0.21	[-0.30, -0.12]
History of diabetes (yes over no)	-0.24	[-0.34, -0.15]
Arterial hypertension (yes over no)	-0.04	[-0.12, 0.04]
Depression (yes over no)	-0.24	[-0.37, -0.10]
Oral anti-coagulant medication (yes over no)	0.02	[-0.10, 0.14]
Active smoker (yes over no)	0.04	[-0.10, 0.18]
GFR (milliliter/minute)	0.02	[-0.00, 0.04]
Age at baseline (10 years)	-0.03	[-0.08, 0.02]
AF-type (non-paroxysmal over paroxysmal):Time (years)	0.01	[-0.02, 0.03]

Note. AF: Atrial fibrillation; CI: Confidence interval; GFR: Glomerular filtration rate; SF: Semantic Fluency Test, animals; TIA: Transient ischemic attack.

Table S7 Estimates with 95% CI for TMT-A. The results for each covariate represent the effect after adjusting for all other variables in the model

	estimate	95 % CI
AF-type (non-paroxysmal over paroxysmal)	-0.06	[-0.14, 0.02]
Time (years)	0.09	[0.07, 0.12]
First visit (yes over no)	-0.11	[-0.16, -0.06]
Sex (female over male)	0.01	[-0.07, 0.09]
History of stroke or TIA (yes over no)	-0.23	[-0.32, -0.14]
History of diabetes (yes over no)	-0.20	[-0.30, -0.11]
Arterial hypertension (yes over no)	0.04	[-0.04, 0.12]
Depression (yes over no)	-0.28	[-0.42, -0.15]
Oral anti-coagulant medication (yes over no)	-0.09	[-0.22, 0.03]
Active smoker (yes over no)	-0.11	[-0.25, 0.03]
GFR (milliliter/minute)	0.03	[0.01, 0.05]
Age at baseline (10 years)	-0.04	[-0.09, 0.01]
AF-type (non-paroxysmal over paroxysmal):Time (years)	-0.01	[-0.04, 0.01]

Note. AF: Atrial fibrillation; CI: Confidence interval; GFR: Glomerular filtration rate; TMT-A: Trail Making Test A; TIA: Transient ischemic attack.

Table S8 Estimates with 95% CI for TMT-B. The results for each covariate represent the effect after adjusting for all other variables in the model

	estimate	95 % CI
AF-type (non-paroxysmal over paroxysmal)	-0.03	[-0.11, 0.05]
Time (years)	0.10	[0.07, 0.13]
First visit (yes over no)	-0.06	[-0.11, -0.02]
Sex (female over male)	0.04	[-0.04, 0.13]
History of stroke or TIA (yes over no)	-0.22	[-0.32, -0.13]
History of diabetes (yes over no)	-0.32	[-0.42, -0.22]
Arterial hypertension (yes over no)	-0.03	[-0.11, 0.06]
Depression (yes over no)	-0.37	[-0.51, -0.24]
Oral anti-coagulant medication (yes over no)	-0.12	[-0.24, 0.01]
Active smoker (yes over no)	-0.15	[-0.29, -0.00]
GFR (milliliter/minute)	0.02	[-0.01, 0.04]
Age at baseline (10 years)	-0.02	[-0.07, 0.03]
AF-type (non-paroxysmal over paroxysmal):Time (years)	-0.03	[-0.05, -0.00]

Note. AF: Atrial fibrillation; CI: Confidence interval; GFR: Glomerular filtration rate; TMT-B: Trail Making Test B; TIA: Transient ischemic attack.

Table S9 Estimates with 95% CI for TMT-B / TMT-A. The results for each covariate represent the effect after adjusting for all other variables in the model

	estimate	95 % CI
AF-type (non-paroxysmal over paroxysmal)	0.00	[-0.07, 0.07]
Time (years)	0.02	[-0.01, 0.05]
First visit (yes over no)	0.03	[-0.02, 0.08]
Sex (female over male)	0.04	[-0.03, 0.10]
History of stroke or TIA (yes over no)	-0.07	[-0.14, 0.01]
History of diabetes (yes over no)	-0.16	[-0.24, -0.08]
Arterial hypertension (yes over no)	-0.04	[-0.10, 0.03]
Depression (yes over no)	-0.13	[-0.24, -0.02]
Oral anti-coagulant medication (yes over no)	-0.03	[-0.13, 0.07]
Active smoker (yes over no)	-0.08	[-0.19, 0.03]
GFR (milliliter/minute)	-0.01	[-0.02, 0.01]
Age at baseline (10 years)	-0.01	[-0.05, 0.03]
AF-type (non-paroxysmal over paroxysmal):Time (years)	-0.01	[-0.04, 0.01]

Note. AF: Atrial fibrillation; CI: Confidence interval; GFR: Glomerular filtration rate; TMT B/A: ratio of Trail Making Test B/ Trail Making Test A; TIA: Transient ischemic attack.

Table S10 Estimates with 95% CI for DSST. The results for each covariate represent the effect after adjusting for all other variables in the model

	estimate	95 % CI
AF-type (non-paroxysmal over paroxysmal)	-0.07	[-0.15, 0.01]
Time (years)	0.07	[0.06, 0.08]
First visit (yes over no)	-0.04	[-0.07, -0.01]
Sex (female over male)	0.23	[0.14, 0.32]
History of stroke or TIA (yes over no)	-0.32	[-0.41, -0.22]
History of diabetes (yes over no)	-0.33	[-0.43, -0.22]
Arterial hypertension (yes over no)	-0.03	[-0.11, 0.06]
Depression (yes over no)	-0.29	[-0.43, -0.14]
Oral anti-coagulant medication (yes over no)	-0.07	[-0.20, 0.06]
Active smoker (yes over no)	-0.19	[-0.34, -0.04]
GFR (milliliter/minute)	0.04	[0.02, 0.07]
Age at baseline (10 years)	-0.00	[-0.05, 0.05]
AF-type (non-paroxysmal over paroxysmal):Time (years)	-0.02	[-0.04, -0.00]

Note. AF: Atrial fibrillation; CI: Confidence interval; DSST: Digit Symbol Substitution Test; GFR: Glomerular filtration rate; TIA: Transient ischemic attack.

Table S11 Estimates with 95% CI for CoCo. The results for each covariate represent the effect after adjusting for all other variables in the model

	estimate	95 % CI
AF-type (non-paroxysmal over paroxysmal)	-0.05	[-0.13, 0.03]
Time (years)	0.11	[0.09, 0.13]
First visit (yes over no)	0.05	[0.02, 0.08]
Sex (female over male)	0.14	[0.05, 0.23]
History of stroke or TIA (yes over no)	-0.29	[-0.39, -0.19]
History of diabetes (yes over no)	-0.40	[-0.51, -0.30]
Arterial hypertension (yes over no)	-0.04	[-0.13, 0.05]
Depression (yes over no)	-0.37	[-0.51, -0.22]
Oral anti-coagulant medication (yes over no)	-0.07	[-0.20, 0.06]
Active smoker (yes over no)	-0.14	[-0.29, 0.01]
GFR (milliliter/minute)	0.03	[0.01, 0.06]
Age at baseline (10 years)	0.01	[-0.05, 0.06]
AF-type (non-paroxysmal over paroxysmal):Time (years)	-0.03	[-0.04, -0.01]

Note. AF: Atrial fibrillation; CI: Confidence interval; CoCo: Cognitive construct; GFR: Glomerular filtration rate; TIA: Transient ischemic attack.

Table S12 Number (percentages) of new cases of cognitive drop per visit. Patients with a drop are excluded from analyses of later timepoints

	MoCA	SF	TMT-A	TMT-B	TMT B/A	DSST	CoCo
Follow-up 1	104 (3.9)	181 (6.8)	184 (6.9)	153 (5.7)	316 (11.8)	89 (3.3)	112 (4.2)
Follow-up 2	69 (2.6)	117 (4.4)	100 (3.7)	80 (3.0)	152 (5.7)	49 (1.8)	24 (0.9)
Follow-up 3	34 (1.3)	97 (3.6)	50 (1.9)	51 (1.9)	77 (2.9)	24 (0.9)	32 (1.2)
Follow-up 4	21 (0.8)	77 (2.9)	18 (0.7)	26 (1.0)	46 (1.7)	22 (0.8)	22 (0.8)

Note: Data are presented as counts (percentages). CoCo: Cognitive construct; DSST: Digit Symbol Substitution Test; MoCA: Montreal Cognitive Assessment; SF: Semantic Fluency Test, animals; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; TMT B/A: ratio of Trail Making Test B/ Trail Making Test A.

Table S13 HR with 95% CI for MoCA impairment. The results for each covariate represent the effect after adjusting for all other variables in the model

	HR	95 % CI
AF-type (non-paroxysmal over paroxysmal)	1.04	[0.80, 1.36]
Sex (female over male)	0.99	[0.73, 1.33]
History of stroke or TIA (yes over no)	1.43	[1.06, 1.93]
History of diabetes (yes over no)	1.39	[0.98, 1.96]
Arterial hypertension (yes over no)	0.97	[0.73, 1.31]
Depression (yes over no)	1.26	[0.79, 2.00]
Oral anti-coagulant medication (yes over no)	0.95	[0.60, 1.51]
Active smoker (yes over no)	1.55	[0.94, 2.53]
Age at baseline (10 years)	2.05	[1.70, 2.47]

Note. AF: Atrial fibrillation; CI: Confidence interval; MoCA: Montreal Cognitive Assessment; TIA: Transient ischemic attack.

Table S14 HR with 95% CI for SF impairment. The results for each covariate represent the effect after adjusting for all other variables in the model

	HR	95 % CI
AF-type (non-paroxysmal over paroxysmal)	1.01	[0.83, 1.22]
Sex (female over male)	0.87	[0.70, 1.08]
History of stroke or TIA (yes over no)	1.24	[0.99, 1.54]
History of diabetes (yes over no)	1.12	[0.86, 1.44]
Arterial hypertension (yes over no)	1.07	[0.87, 1.31]
Depression (yes over no)	1.00	[0.69, 1.44]
Oral anti-coagulant medication (yes over no)	1.19	[0.85, 1.66]
Active smoker (yes over no)	1.13	[0.78, 1.64]
Age at baseline (10 years)	1.17	[1.03, 1.32]

Note. AF: Atrial fibrillation; CI: Confidence interval; SF: Semantic Fluency Test, animals; TIA: Transient ischemic attack.

Table S15 HR with 95% CI for TMT-A impairment. The results for each covariate represent the effect after adjusting for all other variables in the model

	HR	95 % CI
AF-type (non-paroxysmal over paroxysmal)	1.15	[0.92, 1.43]
Sex (female over male)	0.99	[0.77, 1.26]
History of stroke or TIA (yes over no)	0.98	[0.74, 1.29]
History of diabetes (yes over no)	1.33	[1.01, 1.76]
Arterial hypertension (yes over no)	1.15	[0.90, 1.46]
Depression (yes over no)	0.84	[0.53, 1.34]
Oral anti-coagulant medication (yes over no)	1.19	[0.81, 1.76]
Active smoker (yes over no)	0.92	[0.60, 1.41]
Age at baseline (10 years)	0.92	[0.81, 1.05]

Note. AF: Atrial fibrillation; CI: Confidence interval; TMT-A: Trail Making Test A; TIA: Transient ischemic attack.

Table S16 HR with 95% CI for TMT-B impairment. The results for each covariate represent the effect after adjusting for all other variables in the model

	HR	95 % CI
AF-type (non-paroxysmal over paroxysmal)	0.94	[0.75, 1.19]
Sex (female over male)	1.02	[0.79, 1.32]
History of stroke or TIA (yes over no)	1.25	[0.95, 1.66]
History of diabetes (yes over no)	0.61	[0.41, 0.89]
Arterial hypertension (yes over no)	1.00	[0.78, 1.27]
Depression (yes over no)	0.84	[0.54, 1.32]
Oral anti-coagulant medication (yes over no)	1.04	[0.71, 1.52]
Active smoker (yes over no)	1.11	[0.72, 1.72]
Age at baseline (10 years)	1.11	[0.96, 1.28]

Note. AF: Atrial fibrillation; CI: Confidence interval; TMT-B: Trail Making Test B; TIA: Transient ischemic attack.

Table S17 HR with 95% CI for TMT-B/TMT-A impairment. The results for each covariate represent the effect after adjusting for all other variables in the model

	HR	95 % CI
AF-type (non-paroxysmal over paroxysmal)	0.98	[0.83, 1.16]
Sex (female over male)	1.02	[0.84, 1.22]
History of stroke or TIA (yes over no)	1.16	[0.95, 1.42]
History of diabetes (yes over no)	0.82	[0.64, 1.05]
Arterial hypertension (yes over no)	0.99	[0.83, 1.19]
Depression (yes over no)	0.78	[0.55, 1.12]
Oral anti-coagulant medication (yes over no)	0.90	[0.69, 1.19]
Active smoker (yes over no)	1.45	[1.06, 1.98]
Age at baseline (10 years)	1.36	[1.22, 1.51]

Note. AF: Atrial fibrillation; CI: Confidence interval; TMT B/A: ratio of Trail Making Test B/ Trail Making Test A; TIA: Transient ischemic attack.

Table S18 HR with 95% CI for DSST impairment. The results for each covariate represent the effect after adjusting for all other variables in the model

	HR	95 % CI
AF-type (non-paroxysmal over paroxysmal)	0.98	[0.72, 1.32]
Sex (female over male)	0.97	[0.69, 1.36]
History of stroke or TIA (yes over no)	1.46	[1.04, 2.04]
History of diabetes (yes over no)	1.66	[1.15, 2.40]
Arterial hypertension (yes over no)	0.86	[0.62, 1.18]
Depression (yes over no)	1.05	[0.59, 1.88]
Oral anti-coagulant medication (yes over no)	1.01	[0.61, 1.69]
Active smoker (yes over no)	1.58	[0.94, 2.66]
Age at baseline (10 years)	1.41	[1.16, 1.72]

Note. AF: Atrial fibrillation; CI: Confidence interval; DSST: Digit Symbol Substitution Test; TIA: Transient ischemic attack.

Table S19 HR with 95% CI for CoCo impairment. The results for each covariate represent the effect after adjusting for all other variables in the model

	HR	95 % CI
AF-type (non-paroxysmal over paroxysmal)	0.90	[0.67, 1.20]
Sex (female over male)	0.70	[0.49, 1.00]
History of stroke or TIA (yes over no)	1.47	[1.05, 2.05]
History of diabetes (yes over no)	1.06	[0.71, 1.59]
Arterial hypertension (yes over no)	0.92	[0.67, 1.26]
Depression (yes over no)	1.34	[0.79, 2.28]
Oral anti-coagulant medication (yes over no)	0.86	[0.53, 1.40]
Active smoker (yes over no)	1.62	[0.95, 2.77]
Age at baseline (10 years)	1.44	[1.18, 1.75]

Note. AF: Atrial fibrillation; CI: Confidence interval; CoCo: Cognitive construct; TIA: Transient ischemic attack.

Table S20 Results of three-way interactions with time and AF-type

Interaction term	Outcome	P-value
sex	MoCA	0.658
	SF	0.502
	TMT-A	0.558
	TMT-B	0.139
	TMT-A/B	0.641
	DSST	0.890
	CoCo	0.198
stroke	MoCA	0.502
	SF	0.412
	TMT-A	0.882
	TMT-B	0.690
	TMT-A/B	0.987
	DSST	0.502
	CoCo	0.990
smoking	MoCA	0.253
	SF	0.924
	TMT-A	0.360
	TMT-B	0.249
	TMT-A/B	0.426
	DSST	0.643
	CoCo	0.230
diabetes	MoCA	0.180
	SF	0.609
	TMT-A	0.931
	TMT-B	0.985
	TMT-A/B	0.405
	DSST	0.022
	CoCo	0.486
hypertension	MoCA	0.006
	SF	0.918
	TMT-A	0.432
	TMT-B	0.040
	TMT-A/B	0.307
	DSST	0.014
	CoCo	0.013
depression	MoCA	0.318
	SF	0.987
	TMT-A	0.619
	TMT-B	0.382
	TMT-A/B	0.259
	DSST	0.149
	CoCo	0.293

Note. CoCo: Cognitive construct; DSST: Digit Symbol Substitution Test; MoCA: Montreal Cognitive Assessment; SF: Semantic Fluency Test, animals; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; TMT B/A: ratio of Trail Making Test B/ Trail Making Test A.

Table S21 Estimate with 95% CI for MoCA in patients with (left) and without (right) a history of hypertension

	Hypertension		No Hypertension	
Variable	estimate	95 % CI	estimate	95 % CI
AF-type (non-paroxysmal over paroxysmal)	-0.04	[-0.13, 0.05]	-0.02	[-0.15, 0.11]
Time (years)	0.09	[0.07, 0.12]	0.13	[0.10, 0.16]
First visit (yes over no)	-0.09	[-0.13, -0.04]	-0.10	[-0.17, -0.04]
Sex (female over male)	0.21	[0.11, 0.31]	0.22	[0.08, 0.35]
History of stroke or TIA (yes over no)	-0.14	[-0.25, -0.03]	-0.26	[-0.42, -0.11]
History of diabetes (yes over no)	-0.39	[-0.50, -0.28]	-0.13	[-0.37, 0.11]
Depression (yes over no)	-0.19	[-0.36, -0.03]	-0.24	[-0.47, -0.00]
Oral anti-coagulant medication (yes over no)	0.18	[0.02, 0.35]	-0.03	[-0.21, 0.14]
Active smoker (yes over no)	-0.08	[-0.26, 0.09]	-0.22	[-0.47, 0.02]
GFR (milliliter/minute)	0.02	[-0.01, 0.04]	0.02	[-0.02, 0.06]
Age at baseline (10 years)	-0.06	[-0.12, 0.01]	0.02	[-0.05, 0.10]
AF-type (non-paroxysmal over paroxysmal):Time (years)	0.00	[-0.03, 0.03]	-0.06	[-0.10, -0.03]

Note. AF: Atrial fibrillation; CI: Confidence interval; GFR: Glomerular filtration rate; MoCA: Montreal Cognitive Assessment; TIA: Transient ischemic attack.

Table S22 Estimate with 95% CI for TMT-B in patients with (left) and without (right) a history of hypertension

	Hypertension		No Hypertension	
Variable	estimate	95 % CI	estimate	95 % CI
AF-type (non-paroxysmal over paroxysmal)	-0.04	[-0.13, 0.05]	0.03	[-0.11, 0.18]
Time (years)	0.08	[0.05, 0.10]	0.13	[0.09, 0.17]
First visit (yes over no)	-0.07	[-0.12, -0.02]	-0.05	[-0.13, 0.03]
Sex (female over male)	0.07	[-0.03, 0.17]	-0.03	[-0.19, 0.12]
History of stroke or TIA (yes over no)	-0.21	[-0.32, -0.10]	-0.22	[-0.40, -0.04]
History of diabetes (yes over no)	-0.33	[-0.44, -0.22]	-0.31	[-0.59, -0.03]
Depression (yes over no)	-0.33	[-0.49, -0.17]	-0.51	[-0.78, -0.25]
Oral anti-coagulant medication (yes over no)	0.13	[-0.04, 0.29]	-0.53	[-0.73, -0.33]
Active smoker (yes over no)	-0.10	[-0.27, 0.07]	-0.32	[-0.60, -0.04]
GFR (milliliter/minute)	0.02	[-0.01, 0.04]	-0.01	[-0.06, 0.03]
Age at baseline (10 years)	-0.01	[-0.08, 0.05]	-0.08	[-0.17, -0.00]
AF-type (non-paroxysmal over paroxysmal):Time (years)	-0.01	[-0.04, 0.02]	-0.06	[-0.11, -0.02]

Note. AF: Atrial fibrillation; CI: Confidence interval; GFR: Glomerular filtration rate; TMT-B: Trail Making Test B; TIA: Transient ischemic attack.

Table S23 Estimate with 95% CI for DSST in patients with (left) and without (right) a history of hypertension

	Hypertension		No Hypertension	
Variable	estimate	95 % CI	estimate	95 % CI
AF-type (non-paroxysmal over paroxysmal)	-0.08	[-0.17, 0.02]	-0.06	[-0.20, 0.08]
Time (years)	0.05	[0.03, 0.07]	0.10	[0.08, 0.12]
First visit (yes over no)	-0.04	[-0.08, -0.00]	-0.03	[-0.09, 0.02]
Sex (female over male)	0.25	[0.14, 0.35]	0.21	[0.05, 0.37]
History of stroke or TIA (yes over no)	-0.32	[-0.43, -0.20]	-0.30	[-0.48, -0.12]
History of diabetes (yes over no)	-0.34	[-0.45, -0.22]	-0.30	[-0.58, -0.01]
Depression (yes over no)	-0.25	[-0.42, -0.09]	-0.37	[-0.64, -0.10]
Oral anti-coagulant medication (yes over no)	0.18	[0.01, 0.35]	-0.42	[-0.62, -0.22]
Active smoker (yes over no)	-0.13	[-0.30, 0.05]	-0.39	[-0.68, -0.11]
GFR(milliliter/minute)	0.05	[0.02, 0.08]	0.03	[-0.02, 0.07]
Age at baseline (10 years)	0.01	[-0.05, 0.08]	-0.03	[-0.11, 0.06]
AF-type (non-paroxysmal over paroxysmal):Time (years)	-0.00	[-0.02, 0.02]	-0.05	[-0.08, -0.02]

Note. AF: Atrial fibrillation; CI: Confidence interval; DSST: Digit Symbol Substitution Test; GFR: Glomerular filtration rate; TIA: Transient ischemic attack.

Table S24 Estimate with 95% CI for CoCo in patients with (left) and without (right) a history of hypertension

	Hypertension		No Hypertension	
Variable	estimate	95 % CI	estimate	95 % CI
AF-type (non-paroxysmal over paroxysmal)	-0.05	[-0.15, 0.05]	-0.03	[-0.17, 0.11]
Time (years)	0.09	[0.07, 0.10]	0.13	[0.11, 0.16]
First visit (yes over no)	0.05	[0.01, 0.09]	0.05	[-0.01, 0.10]
Sex (female over male)	0.17	[0.06, 0.28]	0.10	[-0.05, 0.26]
History of stroke or TIA (yes over no)	-0.28	[-0.39, -0.16]	-0.30	[-0.48, -0.12]
History of diabetes (yes over no)	-0.43	[-0.54, -0.31]	-0.40	[-0.68, -0.12]
Depression (yes over no)	-0.31	[-0.47, -0.14]	-0.52	[-0.79, -0.26]
Oral anti-coagulant medication (yes over no)	0.20	[0.03, 0.37]	-0.47	[-0.67, -0.26]
Active smoker (yes over no)	-0.07	[-0.25, 0.11]	-0.34	[-0.63, -0.06]
GFR (milliliter/minute)	0.04	[0.01, 0.06]	-0.00	[-0.05, 0.05]
Age at baseline (10 years)	0.01	[-0.06, 0.07]	-0.03	[-0.12, 0.05]
AF-type (non-paroxysmal over paroxysmal):Time (years)	-0.01	[-0.03, 0.01]	-0.06	[-0.09, -0.03]

Note. AF: Atrial fibrillation; CI: Confidence interval; CoCo: Cognitive construct; GFR: Glomerular filtration rate; TIA: Transient ischemic attack.

Table S25 Number (and percentage) of new cases of cognitive drop per visit with the impairment threshold at 1.5 SD

	MoCA	SF	TMT-A	TMT-B	TMT B/A	DSST	CoCo
Follow-up 1	49 (1.83)	86 (3.22)	70 (2.62)	63 (2.36)	155 (5.80)	27 (1.01)	26 (0.97)
Follow-up 2	37 (1.38)	67 (2.51)	41 (1.53)	38 (1.42)	77 (2.88)	23 (0.86)	6 (0.22)
Follow-up 3	21 (0.79)	38 (1.42)	21 (0.79)	22 (0.82)	55 (2.06)	5 (0.19)	5 (0.19)
Follow-up 4	10 (0.37)	33 (1.24)	13 (0.49)	16 (0.60)	27 (1.01)	9 (0.34)	7 (0.26)

Note. CoCo: Cognitive construct; DSST: Digit Symbol Substitution Test; MoCA: Montreal Cognitive Assessment; SD: Standard deviation; SF: Semantic Fluency Test, animals; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; TMT B/A: ratio of Trail Making Test B/ Trail Making Test A.

Table S26 HR with 95% CI for SF impairment (cut-off 1.5 SD)

	HR	95 % CI
AF-type (non-paroxysmal over paroxysmal)	0.88	[0.67, 1.15]
Sex (female over male)	0.69	[0.49, 0.96]
History of stroke or TIA (yes over no)	1.12	[0.81, 1.56]
History of diabetes (yes over no)	1.17	[0.81, 1.68]
Arterial hypertension (yes over no)	1.01	[0.75, 1.36]
Depression (yes over no)	1.37	[0.84, 2.23]
Oral anti-coagulant medication (yes over no)	1.46	[0.87, 2.46]
Active smoker (yes over no)	1.03	[0.60, 1.77]
Age at baseline (10 years)	1.06	[0.90, 1.26]

Note. AF: Atrial fibrillation; CI: Confidence interval; SD: Standard deviation; SF: Semantic Fluency Test, animals; TIA: Transient ischemic attack.

Table S27 Estimates with 95% CI for the linear mixed effects model for SF including patients who did not miss any visit. The results for each covariate represent the effect after adjusting for all other variables in the model

	estimate	95 % CI
AF-type (non-paroxysmal over paroxysmal)	-0.00	[-0.10, 0.10]
Time (years)	0.04	[0.01, 0.06]
First visit (yes over no)	-0.10	[-0.15, -0.04]
Sex (female over male)	0.20	[0.10, 0.31]
History of stroke or TIA (yes over no)	-0.10	[-0.22, -0.02]
History of diabetes (yes over no)	-0.24	[-0.38, -0.11]
Arterial hypertension (yes over no)	-0.02	[-0.12, 0.08]
Depression (yes over no)	-0.41	[-0.59, -0.22]
Oral anti-coagulant medication (yes over no)	-0.10	[-0.25, 0.05]
Active smoker (yes over no)	0.19	[-0.00, 0.38]
GFR (milliliter/minute)	0.00	[-0.03, 0.03]
Age at baseline (10 years)	-0.02	[-0.08, 0.04]
AF-type (non-paroxysmal over paroxysmal):Time (years)	0.00	[-0.02, 0.03]

Note. AF: Atrial fibrillation; CI: Confidence interval; GFR: Glomerular filtration rate; SF: Semantic Fluency Test, animals; TIA: Transient ischemic attack.

Table S28 Estimates with 95% CI for the linear mixed effects model for SF in the group of patients that dropped out. The results for each covariate represent the effect after adjusting for all other variables in the model

	estimate	95 % CI
AF-type (non-paroxysmal over paroxysmal)	-0.07	[-0.20, 0.05]
Time (years)	-0.00	[-0.05, 0.04]
First visit (yes over no)	-0.03	[-0.11, 0.06]
Sex (female over male)	0.09	[-0.03, 0.22]
History of stroke or TIA (yes over no)	-0.27	[-0.40, -0.13]
History of diabetes (yes over no)	-0.19	[-0.33, -0.05]
Arterial hypertension (yes over no)	-0.04	[-0.18, 0.09]
Depression (yes over no)	-0.09	[-0.27, 0.10]
Oral anti-coagulant medication (yes over no)	0.20	[0.00, 0.40]
Active smoker (yes over no)	-0.12	[-0.33, 0.08]
GFR (milliliter/minute)	0.02	[-0.02, 0.05]
Age at baseline (10 years)	0.02	[-0.06, 0.10]
AF-type (non-paroxysmal over paroxysmal):Time (years)	0.03	[-0.02, 0.09]

Note. AF: Atrial fibrillation; CI: Confidence interval; GFR: Glomerular filtration rate; SF: Semantic Fluency Test, animals; TIA: Transient ischemic attack.

Table S29 Estimates with 95% CI for SF in the model with inverse probability of censoring weights added. The results for each covariate represent the effect after adjusting for all other variables in the model

	estimate	95 % CI
AF-type (non-paroxysmal over paroxysmal)	-0.03	[-0.10, 0.04]
Time (years)	0.05	[0.02, 0.07]
First visit (yes over no)	-0.07	[-0.15, -0.00]
Sex (female over male)	0.19	[0.14, 0.24]
History of stroke or TIA (yes over no)	-0.17	[-0.23, -0.12]
History of diabetes (yes over no)	-0.28	[-0.35, -0.22]
Arterial hypertension (yes over no)	-0.06	[-0.10, -0.01]
Depression (yes over no)	-0.30	[-0.38, -0.21]
Oral anti-coagulant medication (yes over no)	-0.04	[-0.12, 0.03]
Active smoker (yes over no)	0.04	[-0.05, 0.12]
GFR (milliliter/minute)	0.01	[-0.00, 0.03]
Age at baseline (10 years)	-0.04	[-0.07, -0.01]
AF-type (non-paroxysmal over paroxysmal):Time (years)	0.01	[-0.02, 0.04]

Note. AF: Atrial fibrillation; CI: Confidence interval; GFR: Glomerular filtration rate; SF: Semantic Fluency Test, animals; TIA: Transient ischemic attack.

Table S30 Number (and percentage) of new cases of cognitive improvement greater than 1 SD per visit

	MoCA	SF	TMT-A	TMT-B	TMT B/A	DSST	CoCo
Follow-up 1	390 (14.60)	340 (12.72)	341 (12.76)	252 (9.43)	278 (10.40)	129 (4.83)	66 (2.47)
Follow-up 2	186 (6.96)	193 (7.22)	233 (8.72)	200 (7.49)	195 (7.30)	97 (3.63)	176 (6.59)
Follow-up 3	117 (4.38)	127 (4.75)	136 (5.09)	135 (5.05)	124 (4.64)	71 (2.66)	69 (2.58)
Follow-up 4	56 (2.10)	86 (3.22)	58 (2.17)	69 (2.58)	58 (2.17)	52 (1.95)	50 (1.87)

Note. CoCo: Cognitive construct; CI: Confidence interval; DSST: Digit Symbol Substitution Test; MoCA: Montreal Cognitive Assessment; SD: Standard deviation; SF: Semantic Fluency Test, animals; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; TMT B/A: ratio of Trail Making Test B/ Trail Making Test A.

Table S31 Estimates with 95% CI for MoCA with the depression as predictor of interest. The results for each covariate represent the effect after adjusting for all other variables in the model

	estimate	95 % CI
Depression (yes over no)	-0.22	[-0.36, -0.08]
Time (years)	0.09	[0.06, 0.12]
First visit (yes over no)	-0.09	[-0.13, -0.05]
Sex (female over male)	0.2	[0.12, 0.28]
History of diabetes (yes over no)	-0.31	[-0.41, -0.22]
Arterial hypertension (yes over no)	-0.08	[-0.16, -0.00]
History of stroke or TIA (yes over no)	-0.18	[-0.27, -0.10]
Oral anti-coagulant medication (yes over no)	0.07	[-0.05, 0.19]
Active smoker (yes over no)	-0.1	[-0.23, 0.04]
AF-type (non-paroxysmal over paroxysmal)	-0.08	[-0.15, -0.01]
GFR	0.02	[-0.00, 0.04]
Age at baseline (10 years)	-0.01	[-0.06, 0.04]
Depression (yes over no):Time (years)	-0.02	[-0.06, 0.03]

Note. AF: Atrial fibrillation; CI: Confidence interval; GFR: Glomerular filtration rate; MoCA: Montreal Cognitive Assessment; TIA: Transient ischemic attack.

Table S32 Estimates with 95% CI for MoCA with the history of diabetes as predictor of interest. The results for each covariate represent the effect after adjusting for all other variables in the model

	estimate	95 % CI
History of diabetes (yes over no)	-0.32	[-0.41, -0.22]
Time (years)	0.09	[0.06, 0.11]
First visit (yes over no)	-0.09	[-0.13, -0.05]
Sex (female over male)	0.2	[0.12, 0.28]
Depression (yes over no)	-0.24	[-0.37, -0.11]
Arterial hypertension (yes over no)	-0.08	[-0.16, -0.00]
History of stroke or TIA (yes over no)	-0.18	[-0.27, -0.10]
Oral anti-coagulant medication (yes over no)	0.07	[-0.05, 0.19]
Active smoker (yes over no)	-0.1	[-0.23, 0.04]
AF-type (non-paroxysmal over paroxysmal)	-0.08	[-0.15, -0.01]
GFR	0.02	[-0.00, 0.04]
Age at baseline (10 years)	-0.01	[-0.06, 0.04]
History of diabetes (yes over no):Time (years)	0	[-0.03, 0.03]

Note. AF: Atrial fibrillation; CI: Confidence interval; GFR: Glomerular filtration rate; MoCA: Montreal Cognitive Assessment; TIA: Transient ischemic attack.

Table S33 Estimates with 95% CI for MoCA with the history of stroke or TIA as predictor of interest.

The results for each covariate represent the effect after adjusting for all other variables in the model

	estimate	95 % CI
History of stroke or TIA (yes over no)	-0.14	[-0.24, -0.05]
Time (years)	0.09	[0.06, 0.12]
First visit (yes over no)	-0.09	[-0.13, -0.05]
Sex (female over male)	0.2	[0.12, 0.28]
History of diabetes (yes over no)	-0.31	[-0.41, -0.22]
Arterial hypertension (yes over no)	-0.08	[-0.16, -0.00]
Depression (yes over no)	-0.24	[-0.37, -0.11]
Oral anti-coagulant medication (yes over no)	0.07	[-0.05, 0.19]
Active smoker (yes over no)	-0.1	[-0.23, 0.04]
AF-type (non-paroxysmal over paroxysmal)	-0.08	[-0.15, -0.01]
GFR	0.02	[-0.00, 0.04]
Age at baseline (10 years)	-0.01	[-0.06, 0.04]
History of stroke or TIA (yes over no):Time (years)	-0.04	[-0.07, -0.01]

Note. AF: Atrial fibrillation; CI: Confidence interval; GFR: Glomerular filtration rate; MoCA: Montreal Cognitive Assessment; TIA: Transient ischemic attack.

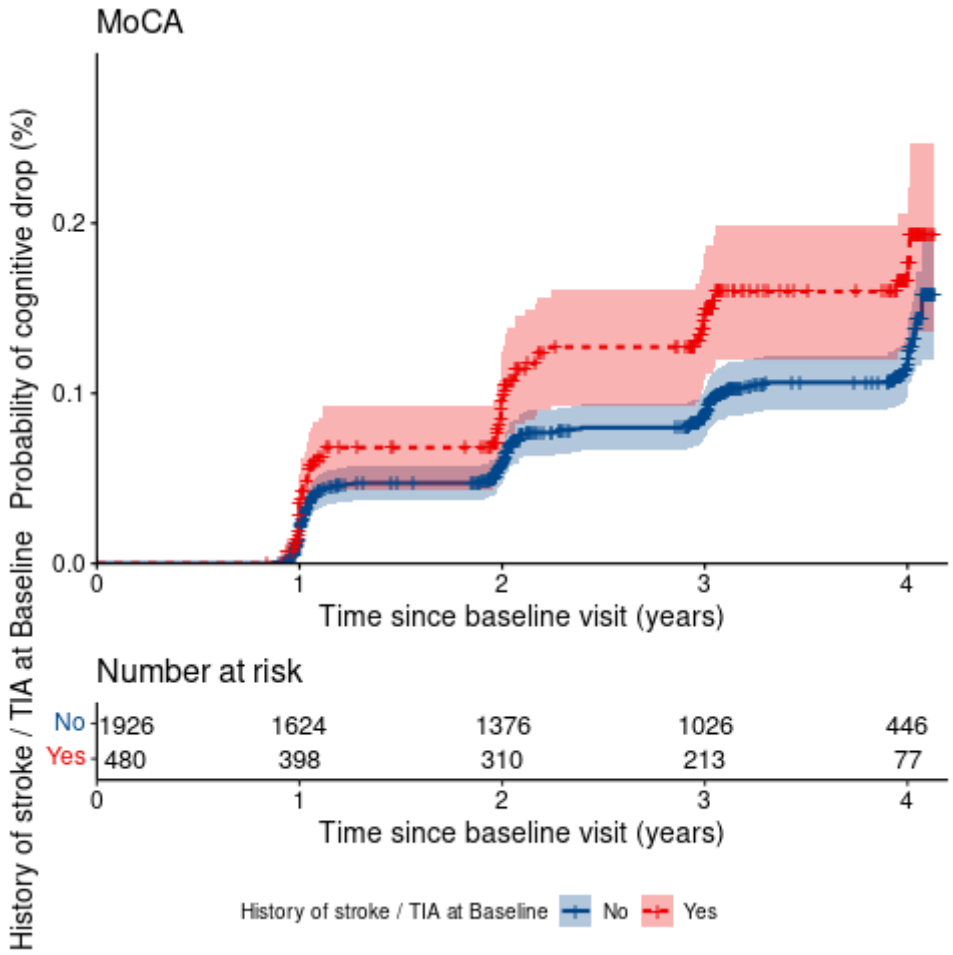

Figure S4 Cumulative probability of cognitive drop according to MoCA by history of stroke/ TIA. MoCA: Montreal Cognitive Assessment; TIA: Transient ischemic attack.

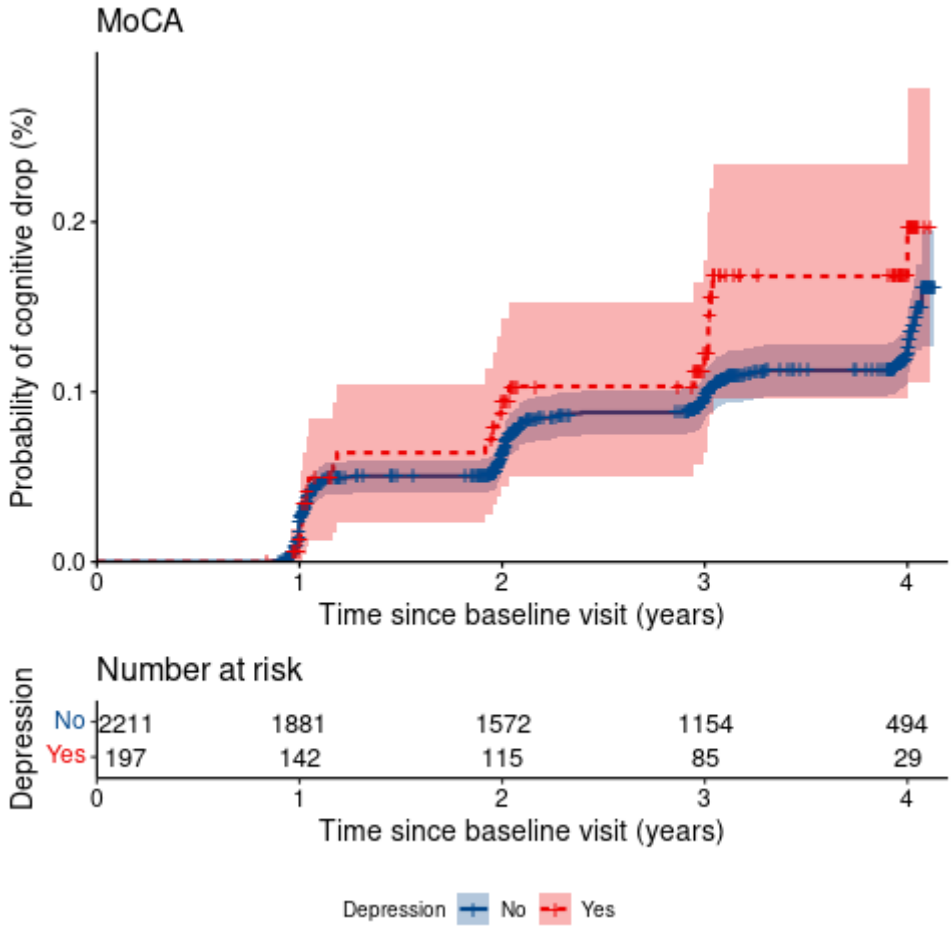

Figure S5 Cumulative probability of cognitive drop according to MoCA by depression. MoCA: Montreal Cognitive Assessment.

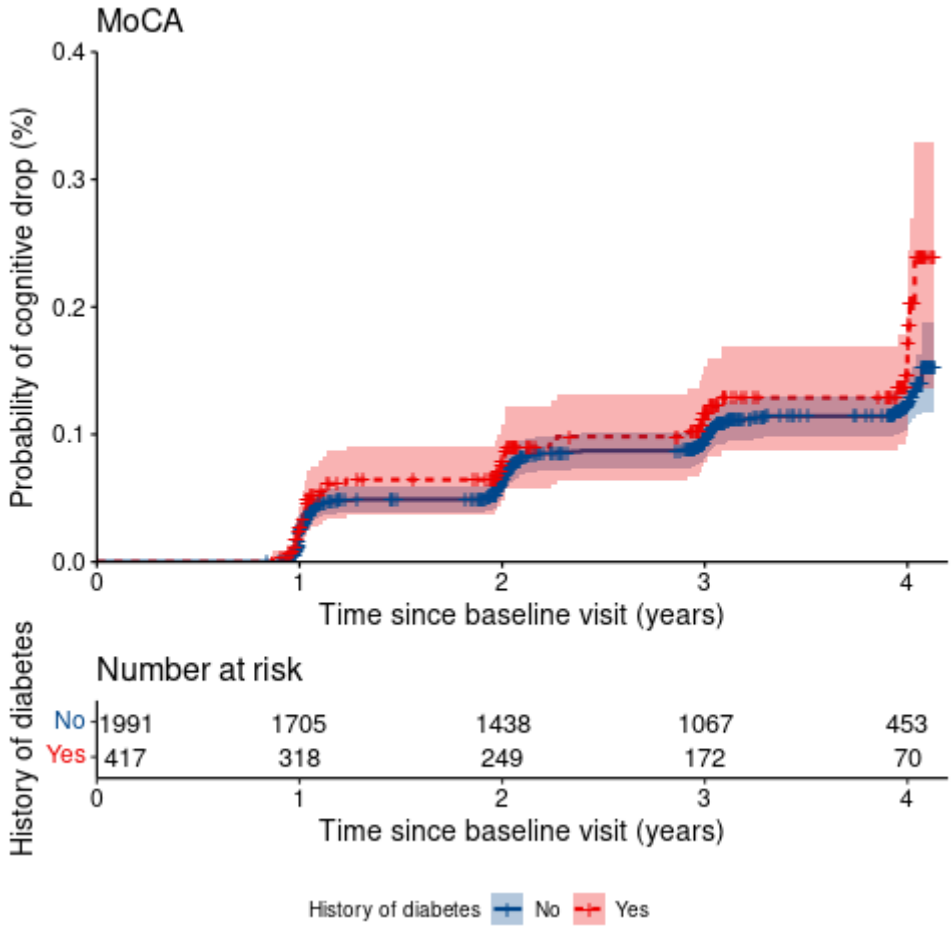

Figure S6 Cumulative probability of cognitive drop according to MoCA by history of diabetes. MoCA: Montreal Cognitive Assessment.

5. Study III

Independent External Validation of a Preoperative Prediction Model for Delirium After Cardiac Surgery:

A Prospective Observational Cohort Study

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Original Article

Independent External Validation of a Preoperative Prediction Model for Delirium After Cardiac Surgery: A Prospective Observational Cohort Study

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Objective: This investigation provided independent external validation of an existing preoperative risk prediction model.
Design: A prospective observational cohort study of patients undergoing cardiac surgery covering the period between April 16, 2018 and January 18, 2022.
Setting: Two academic hospitals in Switzerland.
Participants: Adult patients (≥60 years of age) who underwent elective cardiac surgery, including coronary artery bypass graft, mitral or aortic valve replacement or repair, and combined procedures.
Interventions: None.
Measurements and Main Results: The primary outcome measure was the incidence of postoperative delirium (POD) in the intensive or intermediate care unit, diagnosed using the Intensive Care Delirium Screening Checklist. The prediction model contained 4 preoperative risk factors to which the following points were assigned: Mini-Mental State Examination (MMSE) score ≤23 received 2 points; MMSE 24-27, Geriatric Depression Scale (GDS) >4, prior stroke and/or transient ischemic attack (TIA), and abnormal serum albumin (≤3.5 or ≥4.5 g/dL) received 1 point each. The missing data were handled using multiple imputation. In total, 348 patients were included in the study. Sixty patients (17.4%) developed POD. For point levels in the prediction model of 0, 1, 2, and ≥3, the cumulative incidence of POD was 12.6%, 22.8%, 25.8%, and 35%, respectively. The validation resulted in a pooled area under the receiver operating characteristics curve of 0.60 (median CI, 0.525-0.679).
Conclusions: The evaluated predictive model for delirium after cardiac surgery in this patient cohort showed only poor discriminative capacity but fair calibration.

Key Words: External validation; prediction; delirium; cardiac surgery

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WITH APPROXIMATELY 80 MILLION surgical procedures performed in Europe each year, postoperative delirium (POD) is a major complication of surgery, and poses a significant burden for patients, families, medical, and nursing staff, as well as the healthcare system.[1-3] Older patients undergoing surgery are more vulnerable to adverse postoperative outcomes due to advanced age, frailty, and medical comorbidities.[4] Postoperative delirium is characterized by an acutely developing and fluctuating disturbance of awareness, attention, and cognition, and is classified as a postoperative neurocognitive disorder according to the new nomenclature.[5] Although POD is an acute and transient condition, it has a serious impact on the outcome and prognosis of patients.[6] Numerous epidemiologic studies reported widely divergent data on the incidence of POD, depending on the cohort of patients studied (eg, older versus younger patients), the type of surgical procedure, and treatment modalities (eg, elective versus emergency surgery).[7] However, POD occurs predominantly after cardiac surgery,[8,9] with a reported incidence between 6% and 56%.[10]

Previous studies have shown that POD partially can be prevented by a targeted risk intervention strategy consisting of several components.[11-13] In light of continuous increases in the older population, given demographic aging in industrialized countries and clear interests in improving delirium care, an accurate POD prediction model may be a powerful tool to facilitate the early implementation of prevention measures in clinical practice.[6] Over the past few decades, numerous prediction models of POD,[14] such as the preoperative prediction model by Rudolph et al.,[15] have been developed for cardiac surgery. From a clinical standpoint, their prediction model appeared to be practical as it was based on just the following 4 risk factors: impaired cognition, depressive symptoms, prior stroke or TIA, and abnormal serum albumin.[15] Nevertheless, most of these prediction models either completely lacked internal or external validation[16,17] or only have been validated in a single external cohort (eg, the Rudolph et al. model).[18] These findings were consistent with results from systematic reviews in which the internal and external validations were performed a third (36%)[19] and a quarter (25%-29%)[19,20] of the time, respectively. Furthermore, the rate of prospective external validation of new risk-prediction models within 5 years after publication is small (16%).[20] A potential reason for the limited validations could be the much stronger academic incentives for the development of new models rather than the validation of previously published models.[21] However, it is essential, as well as mandatory, to test the generalizability of a model and to retest it according to new data in order to understand its robustness to distributional shifts over time and its settings before implementing it in clinical practice.[22-24] Likewise, previously existing prediction models should be tested prior to implementation.

The present study aimed to externally validate the Rudolph et al. preoperative prediction model (hereafter "the original model")[15] in a prospective cohort study of patients who had undergone cardiac surgery.

Methods

The study authors conducted and reported this prospective observational cohort study according to the Transparent Reporting of a multivariate prediction model for Individual Prognosis or Diagnosis guidelines.[25] The study protocol (No. 2020-00848) was approved by the institutional review board (Ethikkommission Nordwest- und Zentralschweiz) on July 27, 2020. A prior requirement for informed consent was later waived by Ethikkommission Nordwest- und Zentralschweiz.

Design and Selection Criteria

This broad prospective validation study was conducted at 2 academic medical centers in Basel and Zurich, Switzerland. The inclusion and exclusion criteria were identical to the derivation cohort used in the original model of Rudolph et al.[15] Briefly, the authors included patients aged ≥60 years who underwent elective cardiac surgery, including coronary artery bypass graft, mitral or aortic valve replacement or repair, and combined procedures. The exclusion criteria were non-German speaking, living >60 miles from the study center, emergency surgery, delirium before surgery, concurrent aortic or carotid surgical procedures, and medical instability limiting preoperative assessment.

Study Participants

The authors consecutively included 279 patients at the University Hospital Basel from April 16, 2018 to January 18, 2022, and 69 patients at the University Hospital Zurich from January 13, 2021 to January 18, 2022. The recruitment and inclusion process is shown in Figure 1.

Preoperative Assessment

The 4 preoperative predictors from the original model,[15] including the Mini-Mental State Examination (MMSE; range: 0-30 points, 0 = worst), the Geriatric Depression Scale (GDS; range: 0-15 points, 15 = worst), history of TIA and/or stroke, and serum albumin concentration were assessed during the routinely held preoperative anesthesia consultation. Demographic factors, age at the time of surgery, sex, and type of surgery were collected from the electronic medical record.

Outcome

The primary outcome was the incidence of delirium after cardiac surgery. POD was diagnosed using the Intensive Care Delirium Screening Checklist (ICDSC) with a score of ≥4 points (maximum score = 8) during the intensive care unit (ICU) or intermediate care unit stay. The ICDSC was administered 3 times per day by trained nursing staff, blinded to the predictor variables, until the patient was discharged from the ICU or intermediate care unit. The ICDSC is an 8-item screening instrument based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR criteria, which was specifically designed for the intensive care setting.[26] The checklist

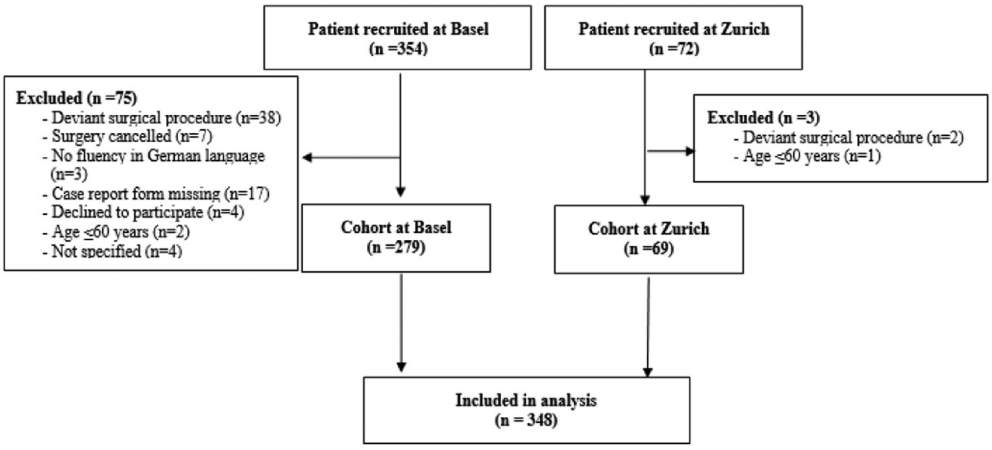

Fig 1. Flow chart of study participants.

contains the following items, which are rated as absent or present: (1) consciousness (ie, comatose, stuporous, awake, or hypervigilant); (2) orientation; (3) hallucinations or delusions; (4) psychomotor activity; (5) inappropriate speech or mood; (6) attentiveness; (7) sleep-wake cycle disturbances; and (8) fluctuation of symptoms. The items are rated on the patient's behavior at the time of screening, and interrater reliability among intensive care staff is considered adequate.[27]

Surgical Procedures

All patients underwent cardiac surgery under general anesthesia. The anesthesia protocol, the operative procedure, and the postoperative care (eg, pain control) were performed according to local hospital policies and practice protocols. The use of aortic cross-clamp, cardiopulmonary bypass, high-dose heparin, and hypothermia was at the discretion of the attending surgeon. The intraoperative data were extracted from the surgical notes.

Sample Size

There are no generally accepted approaches or empirical evidence to estimate the sample size requirements for validation studies of risk prediction models.[25] Therefore, the authors determined their sample size according to the events per variable rule. This common rule of thumb was originally adapted to ensure stability in regression covariates and postulates that at least 10 events (cases with POD) must occur for each candidate predictor in the model.[28] In the authors' analysis, they included 15 patients with POD per predictor variable. Therefore, the required sample size was a minimum of 60 patients presenting with POD (4 predictors × 15 events).

Missing Data

In the overall cohort, data on POD were missing in 5%, education was missing in 7%, GDS in 8%, MMSE in 6%, and the serum albumin concentration in 2%. There were no missing values of age, sex, and history of TIA and/or stroke. The authors assumed the missing data occurred at random, and they performed multiple imputations using the multivariate imputation by chained equation procedure with the predictive mean-matching method. The missing values were predicted based on the demographic variables (ie, age, sex, and education), all predictor variables, and outcome. The continuous variables were maintained as continuous in the imputation and only subsequently categorized for the final predictive model. In accordance with the original model, the authors created 20 multiple imputed datasets.[15] They reported all results from the pooled dataset. Rubin's rules were used to pool the regression coefficient estimates from the imputed datasets. The authors also reported the results of the original dataset with missing data.

Statistical Analysis

For descriptive analysis, all continuous variables are presented as mean ± SD. The categorical variables are reported as frequencies and percentages. The preoperative characteristics of patients from Basel were compared to those recruited from Zurich using a *t* test for the continuous variables. The categorical variables were compared with a chi-square test. Before applying the clinical prediction model, which was developed in a previous study, to the overall cohort dataset, the continuous risk factors were categorized using identical clinically meaningful cutoff points as used in the original model.[15] Therefore, GDS was dichotomized at >4 points, which indicates clinical depression. The MMSE was categorized as not impaired (range: 28-30 points), mild impairment (range: 24-27 points), and definitive impairment (≤23 points). The variables TIA and/or history of stroke were combined into one variable. Serum albumin concentration was classified into a normal value (3.6-4.4 g/dL) versus an abnormal value (≤3.5 or ≥4.5 g/dL). The clinical prediction model points were assigned as follows: MMSE ≤23 points received 2 points; MMSE 24 to 27 points, GDS >4 points, prior stroke/TIA, and abnormal serum albumin received 1 point each.[15] The incidence of POD is presented with increasing clinical prediction model points and a risk ratio relative to the lowest risk group.

Table 1
Baseline Characteristics of the External Swiss validation Cohort and the Derivation Cohort of Rudolph and Colleagues

Characteristic	Basel Cohort (n = 279)	Zurich Cohort (n = 69)	All (n = 348)	Derivation Cohort[15] (n = 122)
Data collection period	April 2018-January 2022	January 2021-January 2022	April 2018-January 2022	September 2002-October 2004
Study design	Prospective cohort	Prospective cohort	Prospective cohort	Prospective cohort
Setting	Academic medical center in Basel, Switzerland	Academic medical center in Zurich, Switzerland	2 academic medical centers in Switzerland	2 academic medical centers and 1 VA hospital
Outcome	Presence of POD	Presence of POD	Presence of POD	Presence of POD
Reference standard	ICDSC score ≥4	ICDSC score ≥4	ICDSC score ≥4	CAM/CAM-ICU
Incidence of POD	42 (15.1%) Missing: 17	18 (26.1%)	60 (17.4%) Missing: 17	63 (52%)
Age, y	71.0 (5.7)	70.4 (5.7)	70.9 (5.7)	74.7 (6.3)
Female sex	62 (22.0%)	10 (14.5%)	72 (20.7%)	25 (20%)
Education, y*	13.1 (3.4)	14.0 (3.3) Missing: 23	13.2 (3.4) Missing: 23	-†
TIA/stroke	40 (14.3%)	12 (17.4%)	52 (14.9%)	26 (22%)
GDS	1.6 (1.8) Missing: 29	1.2 (1.6)	1.5 (1.8) Missing: 29	3.3 (3.0)
MMSE	28.4 (1.5) Missing: 23	28.3 (1.8)	28.4 (1.6) Missing: 23	26.9 (2.6)
Albumin concentration, g/dL	Missing: 2	Missing: 4	Missing: 6	
3.6-4.4 (normal value)	219 (78.5%)	52 (75.4%)	271 (78.0%)	61 (64%)
≤ 3.5 or ≥4.5 (abnormal value)	58 (21.0%)	13 (19.0%)	71 (20.4%)	34 (36%)

NOTE. Data are shown as mean (SD) or n (%).
Abbreviations: CAM, Confusion Assessment Method; CAM-ICU, Confusion Assessment Method for Intensive Care Unit; GDS, Geriatric Depression Scale; ICDSC, Intensive Care Delirium Screening Checklist; MMSE, Mini-Mental State Examination; POD, postoperative delirium; TIA, transient ischemic attack; VA, Veteran's Affairs.
* Maximum is 20 years of education.
† Education was reported as follows: <high school: 19 (17%); high school: 44 (36%); >high school: 59 (49%).

The summary statistics of the original model in the derivation cohort are based on the bootstrapping method, which was used for variable selection. Because the authors did not perform variable selection (model selection), they did not require bootstrapping. However, to make the results of the derivation cohort comparable to their validation cohort, the authors calculated the raw risk ratio, including associated CIs of the prediction model for each score in their cohort and the derivation cohort of Rudolph et al. For model validation, the authors assessed the model performance using measures of discrimination and calibration. In the dataset, they assessed model discrimination with the area under the receiver operating characteristic curve (AUROC; identical to the c-statistics) in each imputed dataset, and reported the median AUROC. Calibration was assessed using the Hosmer-Lemeshow test for goodness of fit in the imputed datasets. In a sensitivity analysis, the authors examined the c-statistics, excluding "off-pump" patients. All analyses were computed using IBM SPSS Statistics V.28.0.1.0 (IBM SPSS, Inc, Armonk, NY) for Windows.

Results

Participants

Among the 348 patients in this combined external validation cohort, 17.4% (n = 60) developed POD after cardiac surgery. The baseline characteristics of patients from Basel and Zurich were similar, with the exception that patients from Zurich had a slightly higher incidence of POD. Compared to Zurich, patients from Basel were more likely to be female patients, have a low serum albumin concentration, and present with more depressive symptoms (Table 1). The mean patient age at surgery was 70.9 ± 5.7 years. Twenty-two patients underwent "off-pump" surgery.

In comparison to the original model in the derivation cohort, patients in this study were slightly younger (70.9 ± 5.7 *v* 74.7 ± 6.3 years), mostly male patients (79.3%), and showed a much lower incidence of POD (17.4% *v* 52%). The prevalence of TIA and/or stroke was lower (14.9% *v* 22%) for the authors' cohort, as well as the mean GDS (1.5 ± 1.8 *v* 3.3 ± 3.0 points). The mean MMSE was higher (28.4 ± 1.6 *v* 26.9 ± 2.6 points). Moreover, the authors' cohort had a higher percentage of the normal value of serum albumin concentration, but the abnormal serum albumin values were lower. Furthermore, most of the patients in their study had a high level of education (Table 1), similar to that reported by Rudolph et al.[15]

External Validation

The authors calculated the clinical prediction model points and applied them to the overall Swiss cohort. The increasing risk score was associated with an increased risk of POD. The number of patients with a score ≥3 was far too small (6 patients) and was not representative. However, POD was identified in 12.6% with a low-risk score, 22.8% with a moderate-risk score, 25.8% with a high-risk score, and 35% with a very-high-risk score. When applying the risk stratification system with no points as reference, the presence of ≥1 point increased the delirium risk by 1.5; 2 points or more doubled the delirium risk, and ≥3 points more nearly tripled the delirium risk (Table 2). The Hosmer-Lemeshow test for goodness of fit showed good agreement between the observed numbers and numbers estimated in the logistic regression model 1.000 (χ^2 = 0.000) in the imputed datasets. The median AUROC (identical to the c-statistics) was 0.60 (median CI, 0.525-0.679). Graphical representation of discrimination is shown in Figure 2. In the original dataset with missing data, the Hosmer-Lemeshow test showed good agreement between the observed numbers and numbers estimated in the logistic regression model 1.000

Table 2
Performance of the Clinical Prediction Model in the Swiss External Validation Cohort Compared to the Derivation Cohort of Rudolph and Colleagues

Risk Group	Prediction Model Points	Delirium Rate	Risk Ratio (95% CI)*	C-Statistic
Swiss validation cohort (n = 348)				0.60
	0	21.5/170 (12.6%)	Reference	
	1	29.5/129 (22.8%)	1.8 (1.1-3.0)	
	2	11.1/43 (25.8%)	2.0 (1.1-3.9)	
	≥3	2.1/6 (35%)	2.8 (0.9-8.8)	
Derivation cohort (n = 122)[15]				0.74
	0	5/25 (19%)	Reference	
	1	20/44 (47%)	2.3 (1.0-5.3)	
	2	23/36 (63%)	3.2 (1.4-7.3)	
	≥3	15/18 (86%)	4.2 (1.9-9.4)	

* The authors applied formulae for a single sample.

(χ^2 = 0.000) as well, and the AUROC was 0.60 (95% CI, 0.524-0.681). Excluding "off-pump" patients, the median AUROC was 0.61 (median CI, 0.530-0.685) in the imputed dataset; in the original dataset with missing data, the AUROC was 0.61 (95% CI, 0.529-0.688). Overall, compared to Rudolph et al., there was a degradation of model performance in the authors' validation cohort. The β coefficients for the logistic model based on the 4 preoperative predictors are presented in Table 1 in the supplement.

Discussion

The aim of this prospective observational study was to externally validate a previously published clinical prediction model for predicting POD in an independent cohort of cardiac surgery patients in Switzerland, in line with recent framework guidelines.[29] Independent of the authors' agreement with the inclusion and exclusion criteria according to Rudolph et al.,[15] the prediction model validated in their contemporary patient cohort was conflicting in that it showed fair calibration but a degradation (AUROC = 0.60) in the prediction of POD after cardiac surgery. To observe substantial decrements in discrimination during validations (compared with performance on the derivation dataset) was not surprising, as it was in line with previous reports.[20,30] There were several potential reasons for this. First, the observed magnitude of the AUROC may be explained by case mix and heterogeneity in the characteristics of the cohorts/populations. There was variability in the derivation and the authors' validation cohort, especially in the outcome measure of POD (52% *v* 17.4%), as well as in the predictor variables. In comparison to the original model of Rudolph et al.,[15] patients undergoing cardiac surgery in the authors' sample reported fewer depressive symptoms (1.5 ± 1.8 *v* 3.3 ± 3.0 points), showed a lower prevalence of TIA and/or stroke (14.9% *v* 22%), and performed better on the MMSE (28.4 ± 1.6 *v* 26.9 ± 2.6 points). Moreover, the authors' cohort had a higher percentage of normal-value serum albumin concentrations. However, the abnormal serum albumin values were lower compared to the original model.[15] In addition, Rudolph et al. validated their prediction model in a US population, whereas the authors evaluated the prediction model in Switzerland. However, according to a previous large-scale review, this substantially larger decrease in discriminatory performance might be expected to be more pronounced when models are evaluated in populations that are dissimilar to the derivation population.[21] Second, Rudolph et al. originally developed the clinical prediction model based on data from 2002 to 2004.[15] The prediction model may not be applicable to current patients undergoing cardiac surgery due to improvements in general healthcare, technical and technologic advances; and the establishment of preventive measures against delirium, such as dexmedetomidine infusion during surgery, at least in Zurich, may have resulted in a drift of the clinical prediction model performance over time.[30,31]

In this study, the authors used the ICDSC to diagnose POD. This corresponded to the standard procedure at the 2 academic institutions instead of the Confusion Assessment Method (CAM)

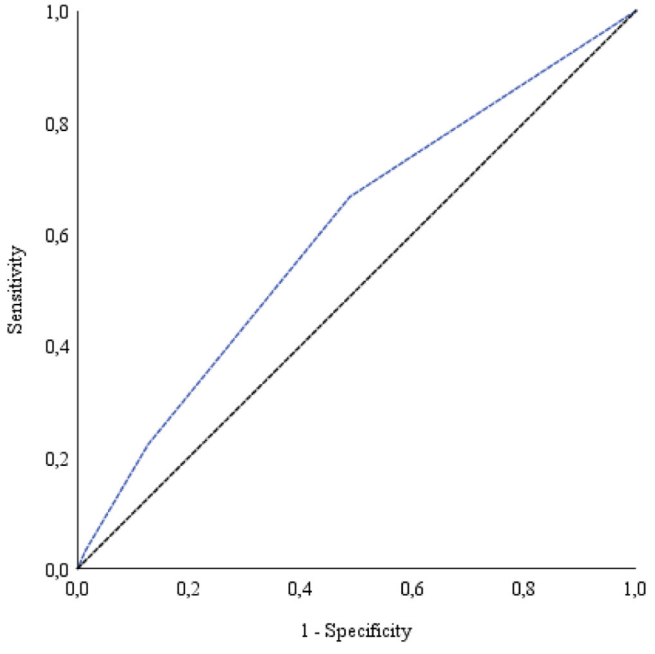

Fig 2. Area under the receiver operator characteristic curve (AUROC) showing the ability of the delirium prediction model by Rudolph et al. to correctly classify those with and without postoperative delirium after cardiac surgery in the underlying independent external Swiss validation cohort. AUROC = 0.5 indicates no discrimination, whereas AUROC = 1.0 indicates perfect discrimination. The *black dotted reference line* refers to no discrimination.

or CAM-ICU for intubated patients, which was used by Rudolph et al.[32] However, in 2 meta-analyses, the pooled sensitivity of CAM-ICU was found to be 75.5%-to-80.0%, and specificity was 95.8% to 95.9% for detection of delirium; whereas the pooled sensitivity for the ICDSC was found to be 74.0%-to-80.1%, and specificity was 74.6%-to-81.9%. Therefore, it can be assumed that both instruments are highly valid when compared to the gold standard (DSM-IV criteria) in detecting POD.[33,34]

Although some cases of delirium may have been missed, the observed incidence of POD in the authors' study was relatively low compared to the derivation cohort of Rudolph et al.[15] Several aspects may have contributed to this. First, the reported incidence of delirium varied from 6%-to-56%,[10] depending on the definition used, timing, characteristics of the studied population, selected assessment tool, type of surgical procedure, and the mode of treatment.[7] Rudolph et al. used further instruments in addition to the CAM and/or CAM-ICU, such as the Delirium Symptom Interview[35] and the Memorial Delirium Assessment Scale,[36] which also capture delirium symptoms and their severity. This may have contributed to the higher rate of POD in their sample. However, information regarding the duration of the CAM and/or CAM-ICU assessments, and whether the assessors were blind to the predictors, was lacking. This may have led to a possible bias in the POD rate. Second, the prevalence of delirium increases with age. Many studies have found age to be a significant predictive factor of POD, despite regression analysis to control for confounders. Age >60 years may be considered an implicit element of the original model by Rudolph et al., because patients <60 years were excluded. However, patients in the authors' cohort had a mean age of 70.9 years, which was younger than in the derivation cohort of Rudolph et al. (74.7 ± 6.3 years). Third, besides advanced age, baseline cognitive impairment is the most highly cited factor associated with an increased risk of delirium.[37,38] In the authors' cohort, patients had a better preoperative test performance (MMSE, 28.4 ± 1.6 points) compared to the derivation cohort (MMSE, 26.9 ± 2.6 points). According to established, clinically important ranges, 28.4 points indicate no impairment, whereas 26.9 points indicate mild impairment.[39,40] Fourth, the risk prediction model was applied retrospectively. Although this could have caused some errors in the risk stratification of individual patients, the authors herein think that this effect was small because all data used for the application of the Rudolph et al. prediction model were collected prospectively. Fifth, in recent years, guidelines have been developed that recommend the use of multicomponent, nonpharmacologic interventions to reduce delirium.[41] There are several simple, single-component interventions, such as reducing environmental stressors (eg, avoiding excessive noise, maintaining daylight and nighttime rhythm) and frequent orientation of patients to time and place, which can be implemented relatively easily.[12] However, although these measures seem relatively inexpensive at first sight, there are considerable "hidden costs," such as higher nurse-to-patient ratios and specific training requirements for caregivers. Given the high burden on scarce human and material resources, these multicomponent interventions are most cost-effective when targeted at high-risk patients.[11] Therefore, it is useful to identify patients with an increased risk of POD at an early stage (ie, before surgery) with specific tools.[42] In addition, there is high variability among different institutions, which may or may not apply preventative measures against delirium, and it is still uncertain as to which interventions are most effective. Therefore, the authors assumed that preventative measures, as administered in both participating institutions, may have played a role in lowering the incidence of POD in their cohort. Moreover, advances in surgical and anesthetic techniques and developments in cardiopulmonary bypass technology may have contributed to a lower delirium incidence as compared to 20 years ago.

Overall, the poor result of discriminative performance (AUROC = 0.60) of the Rudolph et al. prediction model in the authors' sample was in line with a previously published large head-to-head comparison study.[43] The aim of this previous study was to identify clinical prediction models for delirium developed and published since 1990, and to compare their performance head-to-head. In this large analysis, the model discrimination of the Rudolph et al. prediction model was considered poor (AUROC = 0.610).[43]

Strengths and Limitations

There were several important strengths to this study. To the best of the authors' knowledge, this was the first broad validation of the Rudolph et al. preoperative prediction model for POD after cardiac surgery in a German-speaking, Swiss population using real-world data and, therefore, was wholly independent of the development and validation sample of the original study. Furthermore, patients were recruited from more than 1 hospital in Switzerland. Second, the authors' sample size was larger (almost 3 times larger) compared to Rudolph et al. Third, the primary outcome (POD) was ascertained by investigators blinded to the predictor variables. Finally, the authors handled missing data using multiple imputations. This is a popular statistical methodology that replaces missing values with plausible values. One can explicitly account for the uncertainty inherent in the imputed values by creating multiple imputed data sets. Moreover, this approach is superior to more historic approaches such as complete case analysis, mean imputation, and single imputation.[44] However, a number of critical considerations pertaining to the authors' study can be made. First, the participants of this study were relatively well-educated (13.2 ± 3.4 years of education), which may have impacted the performance on the MMSE and the incidence of POD. Although all patients undergoing elective cardiac surgery at the participating institutions tested negative for SARS-CoV-2 preoperatively, possible effects of the COVID-19 pandemic during the recruitment period and seasonal variations should be kept in mind because this may limit the generalizability of the authors' findings.[45] Data on patients' history of prior SARS-CoV-2 infection were not available. Second, because the authors' purpose was to validate the prediction model externally and to avoid causing additional unnecessary distress to patients before surgery, they collected only a minimal number of variables from patients and medical reports. Hence, establishing or updating (eg, recalibrating or extending the model by adding newly discovered predictors) a new prediction model was beyond the scope of this study. In addition, a previous systematic review and meta-analysis found

no strong evidence of a relationship between AUROCs and the number of predictors used in prediction models.[16] It seems more important that the predictors can be applied in clinical practice, when time is often short. However, given the relative scarcity of external validations, it seems reasonable to prioritize the study of existing prediction models (as opposed to developing new ones) and realize how this might be optimized for clinical use.[21]

Conclusions

Risk prediction models play an important role in current cardiac surgical practice. The study authors herein have provided an independent external validation of a previously developed preoperative prognostic model for incident POD in patients who underwent cardiac surgery in Switzerland. The evaluated prognostic model showed only poor discriminative capacity but fair calibration. However, poor performance in a single validation cohort does not reliably forecast performance on subsequent validations. Therefore, it is worth implementing further rigorous studies to evaluate the generalizability and the clinical validity of this prognostic model to realize how this might be optimized for clinical use.

Conflict of Interest

None.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2022.11.038.

References

1 Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. N Engl J Med 2012;367:30–9.
2 Aitken SJ, Blyth FM, Naganathan V. Incidence, prognostic factors and impact of postoperative delirium after major vascular surgery: A meta-analysis and systematic review. Vasc Med 2017;22:387–97.
3 Goettel N, Steiner LA. Postoperatives delirium: Früherkennung, prävention und therapie. Swiss Medical Forum 2013;13:522–6.
4 Story DA, Leslie K, Myles PS, et al. Complications and mortality in older surgical patients in Australia and New Zealand (the REASON study): A multicentre, prospective, observational study. Anaesthesia 2010;65:1022–30.
5 Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. Anesthesiology 2018;129:872–9.
6 Menzenbach J, Guttenthaler V, Kirfel A, et al. Estimating patients' risk for postoperative delirium from preoperative routine data - Trial design of the PRe-Operative prediction of postoperative DElirium by appropriate SCreening (PROPDESC) study - A monocentre prospective observational trial. Contemp Clin Trials Commun 2019;17:100501.
7 Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. Eur J Anaesthesiol 2017;34:192–214;Erratum in: Eur J Anaesthesiol. 2018;35:718-9.
8 Lin Y, Chen J, Wang Z. Meta-analysis of factors which influence delirium following cardiac surgery. J Card Surg 2012;27:481–92.
9 Hollinger A, Siegemund M, Goettel N, et al. Postoperative delirium in cardiac surgery – an unavoidable menace? J Cardiothorac Vasc Anesth 2015;29:1677–87.
10 Cereghetti C, Siegemund M, Schaedelin S, et al. Independent predictors of the duration and overall burden of postoperative delirium after cardiac surgery in adults: An observational cohort study. J Cardiothorac Vasc Anesth 2017;31:1966–73.
11 Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999;340:669–76.
12 Salvi F, Young J, Lucarelli M, et al. Non-pharmacological approaches in the prevention of delirium. Eur Geriatr Med 2020;11:71–81.
13 Hshieh TT, Yue J, Oh E, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: A meta-analysis. JAMA Intern Med 2015;175:512–20;Erratum in: JAMA Intern Med 2015;175:659.
14 Gosselt AN, Slooter AJ, Boere PR, et al. Risk factors for delirium after on-pump cardiac surgery: A systematic review. Crit Care 2015;19:346.
15 Rudolph JL, Jones RN, Levkoff SE, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. Circulation 2009;119:229–36.
16 van Meenen LC, van Meenen DM, de Rooij SE, et al. Risk prediction models for postoperative delirium: A systematic review and meta-analysis. J Am Geriatr Soc 2014;62:2383–90.
17 Lee A, Mu JL, Joynt GM, et al. Risk prediction models for delirium in the intensive care unit after cardiac surgery: A systematic review and independent external validation. Br J Anaesth 2017;118:391–9.
18 Adibi A, Sadatsafavi M, Ioannidis JPA. Validation and utility testing of clinical prediction models: Time to change the approach. JAMA 2020;324:235–6.
19 Bouwmeester W, Zuithoff NP, Mallett S, et al. Reporting and methods in clinical prediction research: A systematic review. PLoS Med 2012;9:1–12.
20 Siontis GC, Tzoulaki I, Castaldi PJ, et al. External validation of new risk prediction models is infrequent and reveals worse prognostic discrimination. J Clin Epidemiol 2015;68:25–34.
21 Wessler BS, Nelson J, Park JG, et al. External validations of cardiovascular clinical prediction models: A large-scale review of the literature. Circ Cardiovasc Qual Outcomes 2021;14:e007858.
22 Moons KG, Kengne AP, Woodward M, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart 2012;98:683–90.
23 Debray TP, Vergouwe Y, Koffijberg H, et al. A new framework to enhance the interpretation of external validation studies of clinical prediction models. J Clin Epidemiol 2015;68:279–89.
24 Toll DB, Janssen KJ, Vergouwe Y, et al. Validation, updating and impact of clinical prediction rules: A review. J Clin Epidemiol 2008;61:1085–94.
25 Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): Explanation and elaboration. Ann Intern Med 2015;162:W1–73.
26 Devlin JW, Fong JJ, Schumaker G, et al. Use of a validated delirium assessment tool improves the ability of physicians to identify delirium in medical intensive care unit patients. Crit Care Med 2007;35:2721–4;quiz 2725.
27 Bergeron N, Dubois MJ, Dumont M, et al. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med 2001;27:859–64.
28 Copas JB. Using regression models for prediction: Shrinkage and regression to the mean. Stat Methods Med Res 1997;6:167–83.
29 Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement. The TRIPOD Group. Circulation 2015;131:211–9.

30 Damen JA, Hooft L, Schuit E, et al. Prediction models for cardiovascular disease risk in the general population: Systematic review. BMJ 2016;353:i2416.
31 Siregar S, Nieboer D, Versteegh MIM, et al. Methods for updating a risk prediction model for cardiac surgery: A statistical primer. Interact Cardiovasc Thorac Surg 2019;28:333–8.
32 Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;11:941–8.
33 Neto AS, Nassar AP Jr, Cardoso SO, et al. Delirium screening in critically ill patients: A systematic review and meta-analysis. Crit Care Med 2012;40:1946–51.
34 Gusmao-Flores D, Salluh JI, Chalhub RÁ, et al. The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: A systematic review and meta-analysis of clinical studies. Crit Care 2012;16:R115.
35 Albert MS, Levkoff SE, Reilly C, et al. The delirium symptom interview: An interview for the detection of delirium symptoms in hospitalized patients. J Geriatr Psychiatry Neurol 1992;5:14–21.
36 Breitbart W, Rosenfeld B, Roth A, et al. The Memorial Delirium Assessment Scale. J Pain Symptom Manage 1997;13:128–37.
37 Vasilevskis EE, Han JH, Hughes CG, et al. Epidemiology and risk factors for delirium across hospital settings. Best Pract Res Clin Anaesthesiol 2012;26:277–87.
38 van der Sluis FJ, Buisman PL, Meerdink M, et al. Risk factors for postoperative delirium after colorectal operation. Surgery 2017;161:704–11.
39 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
40 Crum RM, Anthony JC, Bassett SS, et al. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993;269:2386–91.
41 Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med 2018;46:e825–73.
42 Monsch RJ, Burckhardt AC, Berres M, et al. Development of a novel self-administered cognitive assessment tool and normative data for older adults. J Neurosurg Anesthesiol 2019;31:218–26.
43 Wong CK, van Munster BC, Hatseras A, et al. Head-to-head comparison of 14 prediction models for postoperative delirium in elderly non-ICU patients: An external validation study. BMJ Open 2022;12:e054023.
44 Austin PC, White IR, Lee DS, et al. Missing data in clinical research: A tutorial on multiple imputation. Can J Cardiol 2021;37:1322–31.
45 Vlisides PE, Vogt KM, Pal D, et al. Roadmap for conducting neuroscience research in the COVID-19 era and beyond: Recommendations from the SNACC research committee. J Neurosurg Anesthesiol 2021;33:100–6.

SUPPLEMENTAL MATERIAL

Table S1. Logistic regression model for the prediction of postoperative delirium (POD) based on 4 preoperative characteristics of Rudolph and colleagues[15]

	Pooled dataset (20 multiple imputed sets) (n=348)			**Original dataset (complete cases) (n=280)**		
Predictor	**Model β Coefficient**	**OR (95% CI)**	**P Value**	**Model β Coefficient**	**OR (95% CI)**	**P Value**
TIA/stroke						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.509	1.664 (0.816 to 3.397)	0.162	0.602	1.826 (0.889 to 3.751)	0.101
Albuminconcentration, g/dL						
Normal value	Ref	Ref	Ref	Ref	Ref	Ref
Abnormal value*	0.313	1.367 (0.702 to 2.662)	0.357	0.267	1.306 (0.651 to 2.618)	0.453
GDS						
	0.147	1.159 (0.997 to 1.346)	0.054	0.105	1.111 (0.939 to 1.313)	0.219
MMSE						
	-0.106	0.899 (0.756 to 1.070)	0.231	-0.066	0.936 (0.772 to 1.135)	0.500

OR >1: in favour of postoperative delirium. *Abnormal value: ≤ 3.5 or ≥4.5 g/dL.

CI indicates confidence Interval; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; OR, odds ratio; Ref, Reference; TIA, transient ischemic attack.

TRIPOD Checklist

TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	see Title page
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	see Abstract
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	1-2
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	2
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	3
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	3
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	3
	5b	Describe eligibility criteria for participants.	3
	5c	Give details of treatments received, if relevant.	—
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	4
	6b	Report any actions to blind assessment of the outcome to be predicted.	4
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	3
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	—
Sample size	8	Explain how the study size was arrived at.	4-5
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	5
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	5-6
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	4
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	4
Risk groups	11	Provide details on how risk groups were created, if done.	—
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	7 + see Fig. 1
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	7 + see Tab. 1
Model development	14a	Specify the number of participants and outcome events in each analysis.	—
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	—
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	—
	15b	Explain how to the use the prediction model.	—
Model performance	16	Report performance measures (with CIs) for the prediction model.	8
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	12-13
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	8-12
Implications	20	Discuss the potential clinical use of the model and implications for future research.	13
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	20
Funding	22	Give the source of funding and the role of the funders for the present study.	see Title page

We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

6. General discussion

In the three presented independent studies in elderly adults, we could replicate previous findings of existing conversion tables of MMSE-MoCA and vice versa (study I). Moreover, we could extend these findings in the sense of providing an easy-to-use table based on all currently available MMSE-MoCA (and vice versa) conversion studies covering the full score range of both tools encompassing a wide range of neurodegenerative and neurological diseases.

Longitudinal changes in cognitive functions in association with AF-type (non-paroxysmal versus paroxysmal) and comorbidities were investigated in a prospective, multicenter national observational Swiss-AF cohort (study II).

Furthermore, we have provided insights on the validity of a preexisting preoperative delirium prediction model after cardiac surgery (study III).

Finally, we have discussed important implications of the three independent studies for clinical practice and future research.

6.1 Conversion tables between MMSE-MoCA

In study I we defined corresponding scores for MMSE-MoCA (and vice versa) using a simple and reliable conversion method which was used in most previous studies in a German-speaking outpatient Memory Clinic sample encompassing a wide range of mild and major neurocognitive disorders. We found a positive correlation with a strong effect of MoCA and MMSE score points in this Memory Clinic sample. This suggests that both tests measure similar aspects of cognitive performance. Moreover, we also found a non-linear relationship between the two tests and consistently lower MoCA scores than MMSE scores. However, this is not surprising as the MMSE allocates more points for orientation (10 of 30 points) compared to only 6 of 30 points in the MoCA. In contrast, the MoCA places greater emphasis on visuospatial domains (4 of 30 points) compared to only 1 of 30 points with the MMSE (Damian et al., 2011). Despite identical range

of values and significant correlation, MoCA and MMSE scores cannot be judged as equivalent since the MoCA includes more demanding tasks (Bergeron et al., 2017). Moreover, both tests were initially developed for different target populations and vary in their psychometric properties. The MMSE discriminates well between cognitively healthy individuals and those with dementia, but it exhibits a ceiling effect which can be explained by the low complexity of the individual tasks. However, this increases the likelihood that individuals in predementia stages score within the normal range which decreases sensitivity. Additionally, the MMSE does not assess executive functions. Furthermore, a copyright restriction since 2001 has made the MMSE less feasible for daily clinical use. Therefore, due to its superior diagnostic utility in identifying MCI in different patient populations (Dong et al., 2010; Freitas et al., 2013; Ozer, Young, Champ, & Burke, 2016; Pendlebury et al., 2010) the MoCA has gained popularity in recent years (Ozer et al., 2016). Nevertheless, verifying MMSE scores in clinical practice is very important as the initiation of prescription of cholinesterase inhibitors and/or memantine and their reimbursement by health insurances are still based on the MMSE scores. However, administering both tests in the same assessment might put unnecessary burden on the patients and might not be feasible in busy clinical settings. Furthermore, test selection often depends on clinicians' preference and may therefore vary in different clinical settings. This makes it difficult to directly compare cognitive scores in screening examinations and over the course of neurocognitive disorders.

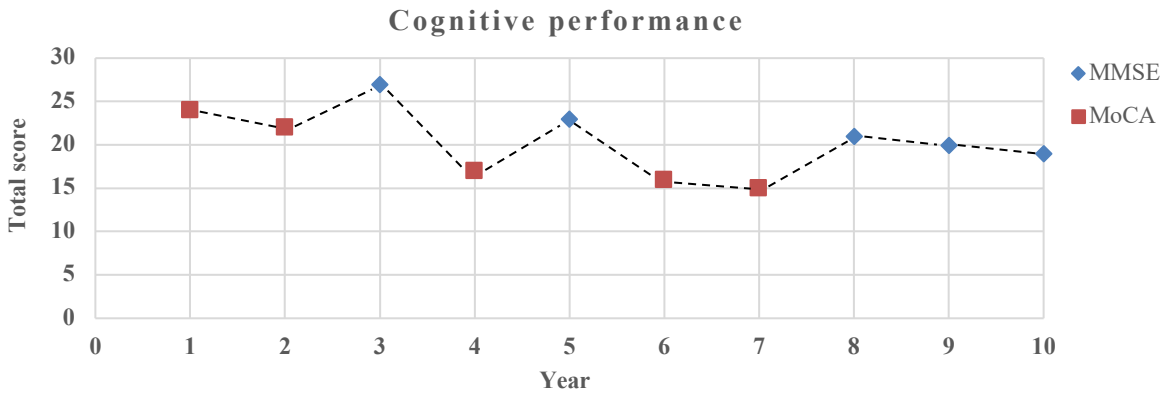
Conversion algorithms and especially conversion tables, which can easily translate one score into another could be very helpful and may facilitate the comparison and synthesis of cognitive data, enhance collaboration between clinicians, and inform clinical and policy decisions in the context of dementia. Consequently, various authors have already provided such scale conversions in recent years. While previous studies have not adequately reflected the heterogeneity of patients encountered in daily clinical practice, such as the unclear cause of cognitive impairment at screening and that comorbid diseases and conditions are often present (Bergeron et al., 2017), our study extended these findings by replicating existing MMSE-MoCA conversion tables and vice versa in a broader range of causes of neurodegenerative and neurological disorders. Additionally, we conducted a systematic review to compile a comprehensive bi-directional MoCA-MMSE conversion based on all currently available conversion studies.

We revealed a very high level of agreement for the higher score range. In the lower score range both conversions showed a larger difference in the equivalent scores of the individual studies. Therefore, conversions in the lower part of the tests must be used with caution and the range should serve as a measure of uncertainty. For the use in clinical practice, we recommend using the weighted mean where each data point contributes equally to the final mean. Nonetheless, this easy-to-use table enables a direct comparison of cognitive scores at screening examinations and over the course of neurocognitive disorders. Moreover, it may be considered to provide this comprehensive table as a pocket card to clinicians which can serve as a reference to continue clinical care using the MoCA in patients who were previously provided with MMSE screenings and vice versa (illustrated in Figure 3).

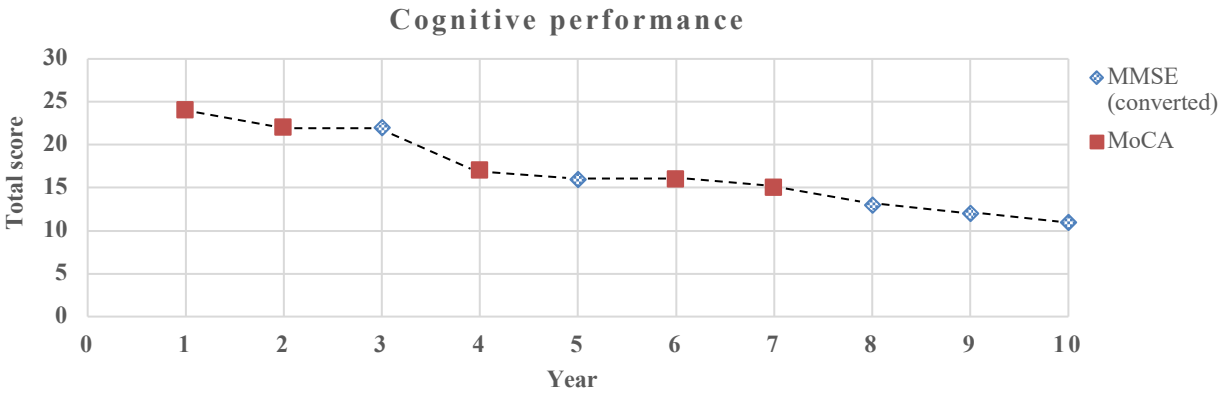
Figure 3

Test results of a fictive patient examined with either the MMSE or the MoCA over 10 years

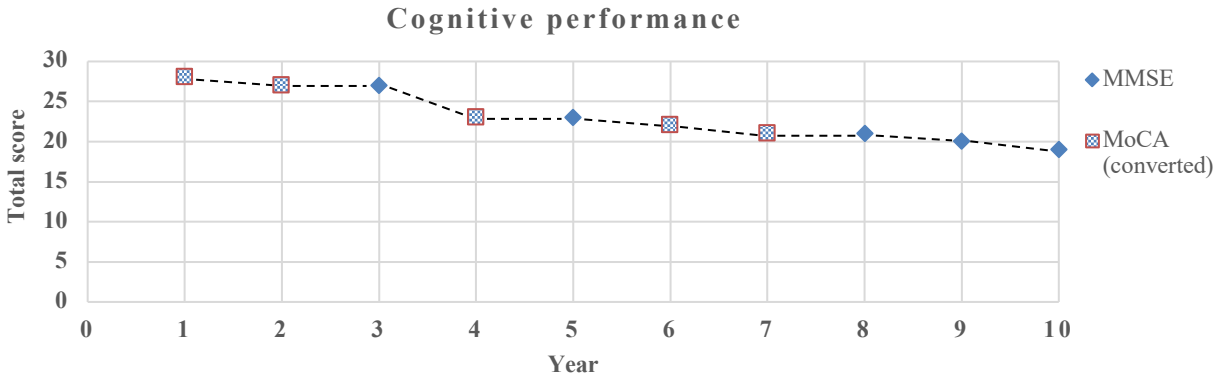
A



B



C



Note. (A) The patient was administered the MoCA at the first two testing sessions as well as at follow-up 4, 6 and 7. In between, the MMSE was used at follow-up 3 and 5. At follow-ups 8, 9 and 10, the MMSE was administered too because the patients cognitive functioning had declined. (B) Course of cognitive performance with converted MMSE to MoCA scores. (C) Course of cognitive performance with converted MoCA to MMSE scores.

Of course, these findings are preliminary. Future studies are required to validate and examine its diagnostic accuracy in detecting cognitive impairment as the included studies for the bi-directional comprehensive MMSE-MoCA table differed in the demographic and diagnostic composition of the patient cohort. For example, it is not clear whether conversion tables generated from individuals with high education levels can be applied to individuals with lower education levels. Hence, individuals with low education usually display

a steeper cognitive decline early in the process of aging compared to those with high education level. Therefore, age, ethnicity, and cultural background as well as considering potential learning effects or other comorbidities and laboratory parameters are also important confounding factors that may influence cognitive performance. Furthermore, because both cognitive screening tests were administered in a specific language and in a specific version the generalizability of the score conversion to other languages and versions also needs further investigation. Thus, it is important to examine the applicability of the existing easy-to-use comprehensive conversion table in other patient populations and settings. As the cognitive profile of patients with different causes of dementia differs, this may contribute to different patterns in conversion. This can be caused by the fact that the MMSE primarily assesses memory and language skills, whereas the MoCA assesses a broader range of cognitive domains including executive and visuospatial functions (Roalf et al., 2013). Therefore, it is imaginable that etiology-specific conversion tables (e.g., for Alzheimer`s disease, Parkinson`s disease etc.) are more reliable when the cause of the cognitive disorder is known.

6.2 Cognitive functions in underlying atrial fibrillation

Previous findings reported no important differences between AF patients and controls in terms of cognitive function either at baseline (Park et al., 2007; Rastas et al., 2007) or during the follow-up period (12 months to 9 years) (Marengoni et al., 2011; Park et al., 2007; Peters et al., 2009; Rastas et al., 2007), some others reported a positive relationship (Bilato et al., 2009; Bunch et al., 2010; Debette et al., 2007; Elias et al., 2006; Forti et al., 2007; Knecht et al., 2008; Koh et al., 2022; Tilvis et al., 2004) between AF and cognitive impairment (Shamloo et al., 2020). Factors such as sample size, statistical methods, assessment of cognitive performance and length of follow-up and attrition bias can underestimate change. The latter one indicating that participants who are most likely to remain in the study tend to be the healthiest, best educated, wealthiest, and have the highest scores on cognitive tests whereas ill participants are less likely to return for study visits (Van Beijsterveldt et al., 2002). However, to describe change and investigating the causal

linkages between atrial fibrillation and cognitive performance as well as their precursors and consequences longitudinal studies are in this context the most powerful designs.

In study II we found a small, constant increase in cognitive functioning over a median duration of 3.97 years in AF patients. Although we aimed to take attrition bias as well as practice effect into account, we cannot completely rule out the possibility that these have led to an increase in cognitive performance over time in AF patients. However, while practice effects are typically considered as biases or error when analyzing data on cognition from repeated administration of cognitive tests, their use as markers of cognitive performance has gained interest (Jutten et al., 2020; Zehnder, Bläsi, Berres, Spiegel, & Monsch, 2007). As based on their literature review, Jutten et al. (2020) concluded that there is accumulating evidence that a deficiency in practice effects may be an early indicator of future cognitive decline and lower practice effects are associated with specific Alzheimer's disease biomarkers. Interestingly among patients with non-paroxysmal (i.e., persistent or permanent) AF we found a less pronounced practice effect in cognitive tests on processing speed, executive functioning and general cognitive functioning compared to patients with paroxysmal AF. Moreover, our results indicated no difference between AF groups in accumulating cases of cognitive drop defined as a threshold of > 1 SD in all cognitive measures. This suggests that lower practice effect in patients with non-paroxysmal AF may reflect a cognitive (e.g., learning) deficit, which could serve as a potential early clinical marker of interest. Using a conventional threshold as an outcome based on clinical standards (e.g., test performance 1–2 SD below the normative mean) (APA, 2013; Weissberger et al., 2017) does not account for potential practice effects. Therefore, comparing practice effects taken as the ability to learn over time might act as a more reliable marker of cognitive change in longitudinal studies. Moreover, it is conceivable that this *lack of practice effect* on cognitive tests of processing speed, executive and general cognitive functioning as we have seen in patients with non-paroxysmal AF (characterized as persistent or permanent and with increased symptom severity) could be of practical interest to physicians or cardiologists in particular to identify high-risk patients and allow for prioritization targeted therapy (e.g., anticoagulation initiation for stroke prevention, MRI screening of the brain) (Ruff et al., 2014).

Although we used five validated and widely used cognitive measures, only derived measures on global cognitive functioning as well as tests on executive functioning and processing speed seem to be most

sensitive in detecting subtle changes in cognition in AF patients even after considering practice effects. However, the generalizability of our results to other populations and settings remains unclear. Thus, not only methodological aspects but also cultural changes (e.g., cohort effects) can influence results. Future studies should investigate the role of practice effects as a marker of cognitive decline by designing follow-up measurements at different time points. Likewise, to gauge the full impact of AF-type on cognitive decline longer follow-up may be required. Since in a disease like cognitive dysfunction (e.g., dementia) there is a slow development over a very long time. In addition, some evidence suggests diabetes, history of stroke/TIA and depression being associated with faster cognitive decline in AF patients. This highlights the importance to investigate in further studies whether early modification addressing these comorbidities may prevent AF-related disease progression and will also result in a reduction in the incidence and advancement of cognitive decline. In this context, studies with a control group are needed to explore the interplay between AF-type and other cardiovascular risk factors and comorbidities in relation to cognitive drop over time. The Swiss-AF CONTROL cohort is currently being recruited with the aim to make this analysis possible.

6.3 External validation of an existing preoperative delirium prediction model

In study III we investigated the validity of the predictive performance of a previously published clinical prediction model for POD (Rudolph et al., 2009) in an independent cohort of cardiac surgery patients in Switzerland. Compared to the original model of Rudolph et al. (2009) we have found poorer discriminative capacity (area under the receiver operating characteristic curve; [AUROC] = 0.60 vs 0.74) but fair calibration in the prediction of POD after cardiac surgery in our contemporary patient cohort. However, poor performance in a single validation cohort does not reliably forecast performance on subsequent validations. Further studies are necessary to evaluate the generalizability and the clinical validity before rejecting the original model completely. Especially multicenter studies are required since analysis of a single region's result may not represent national and international practice and the gained results may not be completely representative. For example, there is wide variation in the assessment of postoperative delirium

across institutions, with over 40 different delirium assessment tools developed to date (Helfand et al., 2021), as well as in the use of multicomponent, pharmacologic and nonpharmacologic interventions to reduce delirium. Moreover, given the aging of the population undergoing cardiac surgery this population has acceptable survival rates thanks to medical advances but nonetheless, elderly individuals appear to have a low tolerance for complications due to advanced age and concomitant medical conditions (Story et al., 2010). Additionally, it is well recognized that frailty is associated with an increased risk of developing POD (Brown et al., 2016; Jung et al., 2015; Li et al., 2021; Persico et al., 2018), as well as being much more common in patients undergoing cardiac surgery, with a reported prevalence of 20% to 46% (Afilalo et al., 2012). To assess frailty, numerous instruments have been developed to identify and quantitate its characteristics. One example is the well-validated Frailty Phenotype Scale (Fried et al., 2001) using gait speed, grip strength, exhaustion, physical activity, and weight loss. Accordingly, it may be worthwhile to recalibrate or extend the Rudolph et al. (2009) clinical prediction model by adding other predictors such as frailty or newly discovered predictors.

As time is often a limited resource in clinical practice, it seems important to facilitate clinical implementation of the prediction model so that the predictors can be applied in clinical practice. Although the Rudolph et al. (2009) prognostic model consists of only four predictors, assessing depression and cognition can still be time-consuming. This is because these measurements often cannot be obtained from the medical record and require the input of a clinician. However, especially cognitive impairment is a known risk factor for delirium development and therefore many guidelines recommend the preoperative evaluation of cognitive function in elderly patients (Lock et al., 2019; Mahanna-Gabrielli et al., 2019). The administration of brief and reliable screening tests is usually a first step in the process of assessing cognitive impairment (Ehrensperger et al., 2014). Furthermore, prior research has demonstrated that individuals with MCI are at a significantly higher risk to develop delirium (Kazmierski et al., 2014; Veliz-Reissmüller, Torres, van der Linden, Lindblom, & Jönhagen, 2007). While the MMSE has been criticized for its low sensitivity in patients with mild dementia or mild cognitive impairment (Nasreddine et al., 2005) the MoCA, which was developed to identify patients with MCI, is better suited in this context (APA, 2013). A future study should investigate whether the performance of the prediction model in study III could be improved by

transferring MMSE scores into corresponding MoCA scores using the comprehensive conversion table from Study I. Besides the fact that most cognitive screening tools available to date are not specifically intended for preoperative use in surgical patients (Long, Shapiro, & Leung, 2012) objective evaluation of cognitive performance is time consuming and usually requires trained personnel. Considering these difficulties, further exploration of cognitive tests that are feasible to administer in clinical settings and that are sensitive to cognitive impairment may enhance delirium prediction. Conserving valuable human resources as well as respecting the time constraint computerized cognitive assessments may increase the efficiency of cognitive evaluation (through e.g., direct availability of the results without manual evaluation, etc.). Thus, in collaboration with the Department of Anesthesia of the University Hospital Basel and the Memory Clinic, University Department of Geriatric Medicine FELIX PLATTER, Basel, a new self-administered tablet-based computer program (CogCheck) was developed in 2014 with the aim of measuring the individual`s cognition and risk of POD. In addition, the self-administrative character of CogCheck and the possibility of remote and parallel testing may reduce personnel and resource costs. Moreover, the composition of different cognitive tests may result in a more adequate assessment as cognitive impairment and dementia may affect different domains of cognition (Monsch et al., 2019). User-friendliness and applicability of CogCheck was demonstrated in a previous pilot study in cognitively healthy and cognitively impaired subjects (Burckhardt, 2014). Additionally, normative data for the CogCheck tool have been generated in a previous study with 283 healthy volunteers (Monsch et al., 2019). The reliability and validity of CogCheck is investigated in ongoing studies at the University Hospital Basel for cardiac surgery patients since April 2018 as well as at the Memory Clinic, University Department of Geriatric Medicine FELIX PLATTER, Basel for patients with mild or major NCD predominantly due to Alzheimer's disease since July 2021, before it can be implemented in a clinical setting.

While the diagnosis of delirium today is still based on clinical skills, there is growing interest in the use of objective parameters for reliable assessment of cerebral damage caused by cardiac surgery. In this context, the detection of elevated or lowered levels of biomarkers seems very promising. Since biomarkers are measurable indicators in the blood, cerebrospinal fluid or brain imaging that can provide insight into the underlying mechanisms and risk factors associated with POD (Majewski et al., 2020; Su et al., 2023). Hence,

it is necessary to look for useful biomarkers such as for example inflammation-related biomarkers (e.g., C-reactive protein [CRP], tumor necrosis factor-alpha [TNF-α], interleukin [IL]-2 etc.) for the detection of POD after cardiac surgery which could potentially be integrated into existing predictive models in future studies.

Another promising approach to improve existing POD risk prediction models is artificial intelligence (AI), particularly the use of machine learning methods (Bishara et al., 2022; Mufti, Hirsch, Abidi, & Abidi, 2019; Weng, Reps, Kai, Garibaldi, & Qureshi, 2017). Current delirium prediction models tend to rely on a range of well-known delirium risk factors such as cognitive impairment (van Meenen et al., 2014). These risk factors are applied to conventional statistical methods like logistic regression (LR), providing a simplified, linearly weighted representation of statistically significant risk factors for predicting delirium (Mufti et al., 2019). However, after cardiac surgery the prediction of delirium is quite complex. In addition to patient-related factors, other elements (e.g., the complexity of the surgical procedure, including aortic clamping, and the choice between the on-pump and off-pump techniques) could also contribute to increasing the risk of postoperative delirium and overlap with the occurrence of patient-related factors. Therefore, to discover such underlying patterns and correlations, machine learning methods offer a powerful way to facilitate the identification of higher-order interactions between risk factors and adapt to changing patient conditions (Lindroth et al., 2018; Weng et al., 2017). Finally, future studies should consider developing dynamic predictive models using advanced statistical methods such as Bayesian networks, AI, and machine learning, as these methods have been shown to improve models built using traditional regression approaches (Bishara et al., 2022; Kim et al., 2011; Lindroth et al., 2018; Mufti et al., 2019; Weng et al., 2017).

7. Outlook

The aging population is increasing rapidly, leading to a higher incidence and prevalence of cognitive difficulties and other age-related pathologies such as cardiovascular and neurological diseases. In this context, atrial fibrillation and delirium are of great clinical relevance due their important role in the development of cognitive dysfunction. Elderly adults are particularly vulnerable to factors that influence cognitive function due to age-related conditions such as frailty and chronic disease. Additionally, the underlying pathomechanisms of atrial fibrillation and postoperative delirium, especially after cardiac surgery, are complex and require further understanding to identify patients at risk and develop potential interventions to prevent or mitigate cognitive impairment in this vulnerable population. Early signs of cognitive impairment can be subtle and often go undiagnosed. Thus, brief and reliable screening tests are usually used as the first step in the assessment. However, traditional screening tools have limitations in terms of sensitivity and specificity, and clinicians may differ in their preferences regarding test selection, making comparisons in clinical routine complicated. By providing a conversion table of two widely used cognitive screening tests (MMSE and MoCA) encompassing a wide range of neurocognitive disease which allows comparison and synthesis of cognitive data from multicenter and longitudinal cohort research this thesis aimed to enhance communication between clinical and research settings. Moreover, the study investigating the longitudinal changes in cognitive function associated with AF-type (non-paroxysmal vs paroxysmal) and comorbidities in a Swiss-AF cohort was conducted to gain a better understanding of the underlying mechanisms of AF and its impact on cognitive changes. Additionally, the validation of an existing prediction model for postoperative delirium after cardiac surgery attempted to get closer to the applicability of a simple prediction model for clinical practice to better identify high-risk patients as early as possible. In particular, the results found on cognitive changes in elderly adults associated with atrial fibrillation and the low discriminatory capacity of the validated prognostic model for postoperative delirium after cardiac surgery highlighted the need for further investigation.

Advancing our understanding and management of AF and POD one potential promising direction for research is to elucidate the still not fully understood underlying mechanisms that link these conditions

to cognitive dysfunction by involving neuroimaging techniques like functional MRI and positron emission tomography (PET) scans to examine changes in brain structure and function as well as molecular and genetic studies to identify key pathways involved. Another promising direction, especially in predicting postoperative delirium is the identification of specific biomarkers that can then serve as early indicators for high-risk patients. However, there are several challenges that must be addressed before identifying such an ideal marker for example POD. The marker should be detected earlier than the occurrence of POD, should be highly sensitive, correlate with the severity of the disease, should be stable, translational, easy to obtain, independent of physiological variables, low in cost, readily available, and should exhibit high validity and specificity in detecting postoperative delirium (Gailiušas et al., 2019).

As precision medicine advances, integrating various factors into a comprehensive risk assessment model, such as age, comorbidities related to AF (e.g., diabetes, stroke/TIA, and depression), as well as potential other factors, like lifestyle factors or the consideration of practice effects in cognitive testing, could allow more personalized approaches to identify an individual's risk for cognitive decline. In terms of POD, it could therefore be worthwhile to recalibrate or refine the already existing risk model. Additionally, by employing advanced machine learning algorithms, including artificial neural networks and deep learning models large amounts of data could be analyzed and thereby complex patterns that may not be apparent with traditional statistical methods could be identified. This could enable even better identification of individuals at higher risk and adjust interventions accordingly. A next possible step would then be to develop tailored interventions, guidelines and protocols that address the complex interplay between AF and postoperative delirium and its role in the development of cognitive dysfunction. For this, multidisciplinary collaboration between neuropsychologists, cardiologists, geriatricians, and other medical professionals is critical. This could allow for comprehensive and holistic approaches to be developed and improve outcomes in this vulnerable group of elderly patients.

Advances in technology including digital tools and wearable devices may open up new possibilities for cognitive assessment and interventions in elderly adults. Computerized cognitive assessment tools like the CogCheck (Monsch et al., 2019) are a potential future alternative to address some barriers to cognitive screening in clinical practice. These tools offer the advantage of covering several

cognitive domains while saving resources at the same time. Patients can perform these assessments independently, which facilitates standardisation and allows for automated scoring. In addition, digital wearables such as smartwatches may lead to earlier diagnosis in the context of AF (Ranganathan & Cheung, 2023), which holds promise for preventing associated cognitive decline as well.

In conclusion, all these further efforts have the potential to improve our understanding, detection, monitoring, and treatment of postoperative delirium and cognitive changes in AF patients, ultimately leading to better health outcomes.

8. References

Abner, E. L., Dennis, B. C., Mathews, M. J., Mendiondo, M. S., Caban-Holt, A., Kryscio, R. J., ... & Crowley, J. J. (2012). Practice effects in a longitudinal, multi-center Alzheimer's disease prevention clinical trial. *Trials, 13*(1), 1-7. doi: 10.1186/1745-6215-13-217

Adams, S. T., & Leveson, S. H. (2012). Clinical prediction rules. *Bmj, 344*. doi:10.1136/bmj.d8312

Adibi, A., Sadatsafavi, M., & Ioannidis, J. P. (2020). Validation and utility testing of clinical prediction models: time to change the approach. *Jama, 324*(3), 235-236. doi: 10.1001/jama.2020.1230

Afilalo, J., Mottillo, S., Eisenberg, M. J., Alexander, K. P., Noiseux, N., Perrault, L. P., ... & Bergman, H. (2012). Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. *Circulation: Cardiovascular Quality and Outcomes*, *5*(2), 222-228. doi: 10.1161/CIRCOUTCOMES.111.963157

Afiune, F. G., Rassi, S., & Afiune Neto, A. (2022). Cognitive Alterations in Elderly Patients with Heart Failure'. *International Journal of Cardiovascular Sciences, 35*, 364-372.

Aiello, E. N., Pasotti, F., Appollonio, I., & Bolognini, N. (2022). Equating Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores: conversion norms from a healthy Italian population sample. *Aging Clinical and Experimental Research, 34*(7), 1721-1724. doi: 10.1007/s40520-022-02089-w

Aitken, S. J., Blyth, F. M., & Naganathan, V. (2017). Incidence, prognostic factors and impact of postoperative delirium after major vascular surgery: a meta-analysis and systematic review. *Vascular Medicine, 22*(5), 387-397. doi: 10.1177/1358863X17721639

Al-Makhamreh, H., Alrabadi, N., Haikal, L., Krishan, M., Al-Badaineh, N., Odeh, O., ... & Hammoudeh, A. (2022). Paroxysmal and Non-Paroxysmal Atrial Fibrillation in Middle Eastern Patients: Clinical Features and the Use of Medications. Analysis of the Jordan Atrial Fibrillation (JoFib)

Study. *International Journal of Environmental Research and Public Health*, *19*(10), 6173. doi: 10.3390/ijerph19106173

Albano, A. D. (2016). equate: An R package for observed-score linking and equating. *Journal of Statistical Software, 74*, 1-36.

Albert, M. S., Levkoff, S. E., Reilly, C., Liptzin, B., Pilgrim, D., Cleary, P. D., ... & Rowe, J. W.(1992). The delirium symptom interview: an interview for the detection of delirium symptoms in hospitalized patients. *Journal of geriatric psychiatry and neurology, 5*(1), 14-21. doi: 10.1177/002383099200500103

Aldecoa, C., Bettelli, G., Bilotta, F., Sanders, R. D., Audisio, R., Borozdina, A., ... & Spies, C. D. (2017). European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. *European Journal of Anaesthesiology EJA, 34*(4), 192-214. doi: 10.1097/EJA.0000000000000594

Aldrugh, S., Sardana, M., Henninger, N., Saczynski, J. S., & McManus, D. D. (2017). Atrial fibrillation, cognition and dementia: a review. *Journal of cardiovascular electrophysiology, 28*(8), 958-965. doi: 10.1111/jce.13261

Alexander, M., Perera, G., Ford, L., Arrighi, H. M., Foskett, N., Debove, C., ... & Gordon, M. F. (2015). Age-stratified prevalence of mild cognitive impairment and dementia in European populations: a systematic review. *Journal of Alzheimer's Disease, 48*(2), 355-359. doi: 10.3233/JAD-150168

Algameel, M. M., Hawash, M., Abd Elrahman, S., & Wafik, W. (2021). Predicting cognitive impairment among geriatric patients at Asir central hospital, Saudi Arabia. *Saudi Journal of Biological Sciences, 28*(10), 5781-5785. doi: 10.1016/j.sjbs.2021.06.023

Alonso, A., & de Larriva, A. P. A. (2016). Atrial fibrillation, cognitive decline and dementia. *European Cardiology Review, 11*(1), 49. doi: 10.15420/ecr.2016:13:2

American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. (2015). American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. *Journal of the American Geriatrics Society*, *63*(1), 142-150. doi: 10.1111/jgs.13281

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. (2013). Arlington, VA: American Psychiatric Association.

Army Individual Test Battery: *Manual of Directions and Scoring*. (1944). Washington, D.C: War Department Adjutant General's Office.

Austin, P. C., White, I. R., Lee, D. S., & van Buuren, S. (2021). Missing data in clinical research: a tutorial on multiple imputation. *Canadian Journal of Cardiology, 37*(9), 1322-1331. doi: 10.1016/j.cjca.2020.11.010

Bano, A., Rodondi, N., Beer, J. H., Moschovitis, G., Kobza, R., Aeschbacher, S., ... & Swiss-Investigators. (2021). Association of diabetes with atrial fibrillation phenotype and cardiac and neurological comorbidities: Insights from the Swiss-AF study. *Journal of the American Heart Association, 10*(22), e021800. doi: 10.1161/JAHA.121.021800

Barr, J., Fraser, G. L., Puntillo, K., Ely, E. W., Gélinas, C., Dasta, J. F., ... & Jaeschke, R. (2013). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical care medicine, 41*(1), 263-306. doi: 10.1097/CCM.0b013e3182783b72

Bartels, C., Wegrzyn, M., Wiedl, A., Ackermann, V., & Ehrenreich, H. (2010). Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. *BMC neuroscience, 11*, 1-12. doi: 10.1186/1471-2202-11-118

Benjamin, E. J., Wolf, P. A., D'Agostino, R. B., Silbershatz, H., Kannel, W. B., & Levy, D. (1998). Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation, 98*(10), 946-952. doi: 10.1161/01.cir.98.10.946

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J, Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 945-950. doi: 10.1001/archpsyc.1961.01710120031004

Beck, I. R., Schmid, N. S., Berres, M., & Monsch, A. U. (2014). Establishing robust cognitive dimensions for characterization and differentiation of patients with Alzheimer's disease, mild cognitive impairment, frontotemporal dementia and depression. *International journal of geriatric psychiatry, 29*(6), 624-634. doi: 10.1002/gps.4045

Bergeron, N., Dubois, M. J., Dumont, M., Dial, S., & Skrobik, Y. (2001). Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive care medicine, 27*, 859-864. doi: 10.1007/s001340100909

Bergeron, D., Flynn, K., Verret, L., Poulin, S., Bouchard, R. W., Bocti, C., ... & Laforce, R. J. (2017). Multicenter validation of an MMSE-Mo CA conversion table. *Journal of the American Geriatrics Society, 65*(5), 1067-1072. doi: 10.1111/jgs.14779

Bilato, C., Corti, M. C., Baggio, G., Rampazzo, D., Cutolo, A., Iliceto, S., & Crepaldi, G. (2009). Prevalence, functional impact, and mortality of atrial fibrillation in an older Italian population (from the Pro. VA study). *The American journal of cardiology*, *104*(8), 1092-1097. doi: 10.1016/j.amjcard.2009.05.058

Bishara, A., Chiu, C., Whitlock, E. L., Douglas, V. C., Lee, S., Butte, A. J., ... & Donovan, A. L. (2022). Postoperative delirium prediction using machine learning models and preoperative electronic health record data. *BMC anesthesiology, 22*(1), 1-12. doi: 10.1186/s12871-021-01543-y

Block, C. K., Johnson-Greene, D., Pliskin, N., & Boake, C. (2017). Discriminating cognitive screening and cognitive testing from neuropsychological assessment: implications for professional practice. *The Clinical Neuropsychologist, 31*(3), 487-500. doi: 10.1080/13854046.2016.1267803

Blum, S., & Conen, D. (2023). Mechanisms and clinical manifestations of cognitive decline in atrial fibrillation patients: potential implications for preventing dementia. *Canadian Journal of Cardiology*, *39*(2), 159-171. doi: 10.1016/j.cjca.2022.10.013

Borson, S., Scanlan, J. M., Chen, P., & Ganguli, M. (2003). The Mini-Cog as a screen for dementia: validation in a population-based sample. *Journal of the American Geriatrics Society, 51*(10), 1451-1454. doi: 10.1046/j.1532-5415.2003.51465.x.

Bouwmeester, W., Zuithoff, N. P., Mallett, S., Geerlings, M. I., Vergouwe, Y., Steyerberg, E.W., ... & Moons, K. G. (2012). Reporting and methods in clinical prediction research: a systematic review. *PLoS medicine, 9*(5), e1001221. doi: 10.1371/journal.pmed.1001221

Breitbart, W., Rosenfeld, B., Roth, A., Smith, M. J., Cohen, K., & Passik, S. (1997). The memorial delirium assessment scale. *Journal of pain and symptom management, 13*(3), 128-137. doi: 10.1016/s0885-3924(96)00316-8

Brown IV, C. H., Max, L., LaFlam, A., Kirk, L., Gross, A., Arora, R., ... & Pustavoitau, A. (2016). The association between preoperative frailty and postoperative delirium after cardiac surgery. *Anesthesia and analgesia, 123*(2), 430-435. doi: 10.1213/ANE.0000000000001271

Brown IV, C. H., Probert, J., Healy, R., Parish, M., Nomura, Y., Yamaguchi, A., ... & Hogue, C. W. (2018). Cognitive decline after delirium in patients undergoing cardiac surgery. *Anesthesiology, 129*(3), 406-416. doi: 10.1097/ALN.0000000000002253

Buchan, T. A., Sadeghirad, B., Schmutz, N., Goettel, N., Foroutan, F., Couban, R., ... & Dodsworth, B. T. (2020). Preoperative prognostic factors associated with postoperative delirium in older people undergoing surgery: protocol for a systematic review and individual patient data meta-analysis. *Systematic reviews*, *9*, 1-5. doi: 10.1186/s13643-020-01518-z

Bunch, T. J., Weiss, J. P., Crandall, B. G., May, H. T., Bair, T. L., Osborn, J. S., ... & Day, J. D. (2010). Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart rhythm, 7*(4), 433-437. doi: 10.1016/j.hrthm.2009.12.004

Burckhardt, A. C. (2014). *Das Delir Risiko Profil: Ein computerisiertes Untersuchungsinstrument zur präoperativen Erfassung des postoperativen Delir-Risikos*. (MD), University of Basel, Basel, Switzerland.

Camm, A. J., Kirchhof, P., Lip, G. Y., ... & Zupan, I. (2010). Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *European heart journal, 31*(19), 2369-2429. doi: 10.1093/eurheartj/ehq278

Caplan, G. (2011). Managing delirium in older patients.

Cereghetti, C., Siegemund, M., Schaedelin, S., Fassl, J., Seeberger, M. D., Eckstein, F. S., ... & Goettel, N. (2017). Independent predictors of the duration and overall burden of postoperative delirium after cardiac surgery in adults: an observational cohort study. *Journal of cardiothoracic and vascular anesthesia, 31*(6), 1966-1973. doi: 10.1053/j.jvca.2017.03.042

Chen, L. Y., Sotoodehnia, N., Bůžková, P., Lopez, F. L., Yee, L. M., Heckbert, S. R., ... & Alonso, A. (2013). Atrial fibrillation and the risk of sudden cardiac death: the atherosclerosis risk in communities study and cardiovascular health study. *JAMA internal medicine, 173*(1), 29-35. doi: 10.1001/2013.jamainternmed.744

Chen, L. Y., Norby, F. L., Gottesman, R. F., Mosley, T. H., Soliman, E. Z., Agarwal, S. K., ... & Alonso, A. (2018). Association of atrial fibrillation with cognitive decline and dementia over 20 years: the ARIC-NCS (atherosclerosis risk in communities neurocognitive study). *Journal of the American Heart Association, 7*(6), e007301. doi: 10.1161/JAHA.117.007301

Chen, X., Wen, H., Wang, J., Yi, Y., Wu, J., & Liao, X. (2021). Conversion between Mini-Mental State Examination and Montreal Cognitive Assessment scores in older adults undergoing selective

surgery using Rasch analysis. *Journal of Advanced Nursing, 77*(2), 729-741. doi: 10.1111/jan.14638

Cheng, G., Huang, C., Deng, H., & Wang, H. (2012). Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Internal medicine journal, 42*(5), 484-491. doi: 10.1111/j.1445-5994.2012.02758.x

Chiang, C. E., Naditch-Brûlé, L., Murin, J., Goethals, M., Inoue, H., O'Neill, J., ... & Steg, P. G. (2012). Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the real-life global survey evaluating patients with atrial fibrillation international registry. *Circulation: Arrhythmia and Electrophysiology, 5*(4), 632-639. doi: 10.1161/CIRCEP.112.970749

Chugh, S. S., Blackshear, J. L., Shen, W. K., Hammill, S. C., & Gersh, B. J. (2001). Epidemiology and natural history of atrial fibrillation: clinical implications. *Journal of the American College of Cardiology, 37*(2), 371-378. doi: 10.1016/s0735-1097(00)01107-4

Chugh, S. S., Havmoeller, R., Narayanan, K., Singh, D., Rienstra, M., Benjamin, E. J., ... & Murray, C. J. (2014). Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation, 129*(8), 837-847. doi: 10.1161/CIRCULATIONAHA.113.005119

Collins, G. S., Reitsma, J. B., Altman, D. G., & Moons, K. G. (2015). Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *Annals of internal medicine, 162*(1), 55-63. doi: 10.7326/M14-0697

Conen, D., Rodondi, N., Mueller, A., Beer, J., Auricchio, A., Ammann, P., ... & Schwenkglenks, M. (2017). Design of the Swiss Atrial Fibrillation Cohort Study (Swiss-AF): structural brain damage and cognitive decline among patients with atrial fibrillation. *Swiss medical weekly, 147*, w14467. doi: 10.4414/smw.2017.14467

Conen, D., Rodondi, N., Müller, A., Beer, J. H., Ammann, P., Moschovitis, G., ... & Swiss-AF Study Investigators. (2019). Relationships of overt and silent brain lesions with cognitive function in patients with atrial fibrillation. *Journal of the American College of Cardiology, 73*(9), 989-999. doi: 10.1016/j.jacc.2018.12.039

Copas, J. B. (1997). Using regression models for prediction: shrinkage and regression to the mean. *Statistical Methods in Medical Research, 6*(2), 167-183. doi: 10.1177/096228029700600206

Crum, R. M., Anthony, J. C., Bassett, S. S., & Folstein, M. F. (1993). Population-based norms for the Mini-Mental State Examination by age and educational level. *Jama, 269*(18), 2386-2391.

Dagres, N., Chao, T. F., Fenelon, G., Aguinaga, L., Benhayon, D., Benjamin, E. J., ... & Chung, M. K. (2018). European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on arrhythmias and cognitive function: what is the best practice?. *EP Europace, 20*(9), 1399-1421. doi: 10.1093/europace/euy046

Damen, J. A., Hooft, L., Schuit, E., Debray, T. P., Collins, G. S., Tzoulaki, I., ... & Moons, K. G. (2016). Prediction models for cardiovascular disease risk in the general population: systematic review. *bmj*, *353*. doi: 10.1136/bmj.i2416

Damian, A. M., Jacobson, S. A., Hentz, J. G., Belden, C. M., Shill, H. A., Sabbagh, M. N., ... & Adler, C. H. (2011). The Montreal Cognitive Assessment and the mini-mental state examination as screening instruments for cognitive impairment: item analyses and threshold scores. *Dementia and geriatric cognitive disorders, 31*(2), 126-131. doi: 10.1159/000323867

Davis, D. H., Muniz Terrera, G., Keage, H., Rahkonen, T., Oinas, M., Matthews, F. E., ... & Brayne, C. (2012). Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study. *Brain, 135*(9), 2809-2816. doi: 10.1093/brain/aws190

Davis, D. H., Muniz-Terrera, G., Keage, H. A., Stephan, B. C., Fleming, J., Ince, P. G., ... & Brayne, C. (2017). Association of delirium with cognitive decline in late life: a neuropathologic study of 3 population-based cohort studies. *JAMA psychiatry, 74*(3), 244-251. doi: 10.1001/jamapsychiatry.2016.3423

de Bruijn, R. F., Heeringa, J., Wolters, F. J., Franco, O. H., Stricker, B. H., Hofman, A., ... & Ikram, M. A. (2015). Association between atrial fibrillation and dementia in the general population. *JAMA neurology, 72*(11), 1288-1294. doi: 10.1001/jamaneurol.2015.2161

Debette, S., Bauters, C., Leys, D., Lamblin, N., Pasquier, F., & Groote, P. D. (2007). Prevalence and determinants of cognitive impairment in chronic heart failure patients. *Congestive heart failure*, *13*(4), 205-208. doi: 10.1111/j.1527-5299.2007.06612.x

Debray, T. P., Moons, K. G., Ahmed, I., Koffijberg, H., & Riley, R. D. (2013). A framework for developing, implementing, and evaluating clinical prediction models in an individual participant data meta-analysis. *Statistics in medicine, 32*(18), 3158-3180. doi: 10.1002/sim.5732

Debray, T. P., Vergouwe, Y., Koffijberg, H., Nieboer, D., Steyerberg, E. W., & Moons, K. G. (2015). A new framework to enhance the interpretation of external validation studies of clinical prediction models. *Journal of clinical epidemiology, 68*(3), 279-289. doi: 10.1016/j.jclinepi.2014.06.018

Devlin, J. W., Fong, J. J., Schumaker, G., O'Connor, H., Ruthazer, R., & Garpestad, E. (2007). Use of a validated delirium assessment tool improves the ability of physicians to identify delirium in medical intensive care unit patients. *Critical care medicine, 35*(12), 2721-2724. doi: 10.1097/01.ccm.0000292011.93074.82

Devlin, J. W., Skrobik, Y., Gélinas, C., Needham, D. M., Slooter, A. J., Pandharipande, P. P., ... & Alhazzani, W. (2018). Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Critical care medicine, 46*(9), e825-e873. doi: 10.1097/CCM.0000000000003299

Diener, H. C., Hart, R. G., Koudstaal, P. J., Lane, D. A., & Lip, G. Y. (2019). Atrial fibrillation and cognitive function: JACC review topic of the week. *Journal of the American College of Cardiology*, *73*(5), 612-619. doi: 10.1016/j.jacc.2018.10.077

Dietzel, J., Haeusler, K. G., & Endres, M. (2018). Does atrial fibrillation cause cognitive decline and dementia?. *EP Europace, 20*(3), 408-419. doi: 10.1093/europace/eux031

Ding, M., & Qiu, C. (2018). Atrial fibrillation, cognitive decline, and dementia: an epidemiologic review. *Current Epidemiology Reports, 5*(3), 252-261. doi: 10.1007/s40471-018-0159-7

Dong, Y., Sharma, V. K., Chan, B. P.-L., Venketasubramanian, N., Teoh, H. L., Seet, R. C. S., … Chen, C. (2010). The montreal cognitive assessment (moca) is superior to the mini-mental state examination (mmse) for the detection of vascular cognitive impairment after acute stroke. *Journal of the Neurological Sciences, 299*(1–2), 15–18. doi: 10.1016/J.JNS.2010.08.051

Doroszkiewicz, H. (2022). How the Cognitive Status of Older People Affects Their Care Dependency Level and Needs: A Cross-Sectional Study. *International Journal of Environmental Research and Public Health, 19*(16), 10257. doi: 10.3390/ijerph191610257

Dublin, S., Anderson, M. L., Haneuse, S. J., Heckbert, S. R., Crane, P. K., Breitner, J. C., ... & Larson, E. B. (2011). Atrial fibrillation and risk of dementia: a prospective cohort study. *Journal of the American Geriatrics Society, 59*(8), 1369-1375. doi: 10.1111/j.1532-5415.2011.03508.x

Ehrensperger, M. M., Taylor, K. I., Berres, M., Foldi, N. S., Dellenbach, M., Bopp, I., ... & Monsch, A. U. (2014). BrainCheck-a very brief tool to detect incipient cognitive decline: optimized case-finding combining patient-and informant-based data. *Alzheimer's research & therapy, 6*(9), 1-12. doi: 10.1186/s13195-014-0069-y

Elias, M. F., Wolf, P. A., D'Agostino, R. B., Cobb, J., & White, L. R. (1993). Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. *American journal of epidemiology, 138*(6), 353-364. doi: 10.1093/oxfordjournals.aje.a116868

Elias, M. F., Sullivan, L. M., Elias, P. K., Vasan, R. S., D'Agostino Sr, R. B., Seshadri, S., ... & Benjamin, E. J. (2006). Atrial fibrillation is associated with lower cognitive performance in the Framingham offspring men. *Journal of Stroke and Cerebrovascular Diseases, 15*(5), 214-222. doi: 10.1016/j.jstrokecerebrovasdis.2006.05.009

Evered, L., Silbert, B., Knopman, D. S., Scott, D. A., DeKosky, S. T., Rasmussen, L. S., ... & Nomenclature Consensus Working Group. (2018). Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery—2018. *Anesthesiology, 129*(5), 872-879. doi: 10.1097/ALN.0000000000002334

Fasnacht, J. S., Wueest, A. S., Berres, M., Thomann, A. E., Krumm, S., Gutbrod, K., ... & Monsch, A. U. (2022). Conversion between the Montreal Cognitive Assessment and the Mini-Mental Status Examination. *Journal of the American Geriatrics Society, 71*(3), 869-879. doi:10.1111/jgs.18124

Feldman, R., & Newman, J. (2013). Copyright at the bedside: should we stop the spread?. *Stanford technology law review: STLR: an online high-technology law journal from Stanford Law School, 16*(3), 623-655.

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. doi: 10.1016/0022-3956(75)90026-6

Fong, T. G., Jones, R. N., Shi, P., Marcantonio, E. R., Yap, L., Rudolph, J. L., ... & Inouye, S. K. (2009). Delirium accelerates cognitive decline in Alzheimer disease. *Neurology, 72*(18), 1570-1575. doi: 10.1212/WNL.0b013e3181a4129a

Forti, P., Maioli, F., Pisacane, N., Rietti, E., Montesi, F., & Ravaglia, G. (2007). Atrial fibrillation and risk of dementia in non-demented elderly subjects with and without mild cognitive impairment (MCI). *Archives of gerontology and geriatrics*, *44*, 155-165. doi: 10.1016/j.archger.2007.01.023

Freitas, S., Simões, M. R., Alves, L., & Santana, I. (2013). Montreal cognitive assessment: validation study for mild cognitive impairment and Alzheimer disease. *Alzheimer Disease & Associated Disorders, 27*(1), 37-43. doi: 10.1097/WAD.0b013e3182420bfe

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., ... & McBurnie, M. A. (2001). Frailty in older adults: evidence for a phenotype. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 56*(3), M146-M157. doi: 10.1093/gerona/56.3.m146

Gailiušas, M., Andrejaitienė, J., Širvinskas, E., Krasauskas, D., Švagždienė, M., & Kumpaitienė, B. (2019). Association between serum biomarkers and postoperative delirium after cardiac surgery. *Acta Medica Lituanica, 26*(1), 8. doi: 10.6001/actamedica.v26i1.3949

Gaita, F., Corsinovi, L., Anselmino, M., Raimondo, C., Pianelli, M., Toso, E., ... & Scaglione, M. (2013). Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. *Journal of the American College of Cardiology, 62*(21), 1990-1997. doi: 10.1016/j.jacc.2013.05.074

Gallinoro, E., D'Elia, S., Prozzo, D., Lioncino, M., Natale, F., Golino, P., & Cimmino, G. (2019). Cognitive function and atrial fibrillation: from the strength of relationship to the dark side of prevention. Is there a contribution from sinus rhythm restoration and maintenance?. *Medicina 55*(9), 587. doi: 10.3390/medicina55090587

Giannone, M. E., Filippini, T., Whelton, P. K., Chiari, A., Vitolo, M., Boriani, G., & Vinceti, M. (2022). Atrial Fibrillation and the Risk of Early-Onset Dementia: A Systematic Review and Meta-Analysis. *Journal of the American Heart Association, 11*(14), e025653. doi:10.1161/JAHA.122.025653

Gibbons, L. E., Carle, A. C., Mackin, R. S., Harvey, D., Mukherjee, S., Insel, P., ... & Alzheimer's Disease Neuroimaging Initiative. (2012). A composite score for executive functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment. *Brain imaging and behavior*, *6*, 517-527. doi: 10.1007/s11682-012-9176-1

Goettel, N., & Steiner, L. A. (2013). Postoperatives delirium: Früherkennung, prävention und therapie. *In Swiss Medical Forum* (Vol. 13, No. 26, pp. 522-526). EMH Media.

Goldberg, T. E., Chen, C., Wang, Y., Jung, E., Swanson, A., Ing, C., ... & Moitra, V. (2020). Association of delirium with long-term cognitive decline: a meta-analysis. *JAMA neurology, 77*(11), 1373-1381. doi: 10.1001/jamaneurol.2020.2273

Gosselt, A. N., Slooter, A. J., Boere, P. R., & Zaal, I. J. (2015). Risk factors for delirium after on-pump cardiac surgery: a systematic review. *Critical Care, 19*, 1-8. doi: 10.1186/s13054-015-1060-0

Gottesman, R. F., Grega, M. A., Bailey, M. M., Pham, L. D., Zeger, S. L., Baumgartner, W. A., ... & McKhann, G. M. (2010). Delirium after coronary artery bypass graft surgery and late mortality. *Annals of neurology, 67*(3), 338-344. doi: 10.1002/ana.21899

Gross, A. F., & Stern, T. A. (2013). The cognitive impact of atrial fibrillation. *The primary care companion for CNS disorders, 15(*1), PCC.12f01471. doi.org/10.4088/PCC.12f01471

Grover, S., & Kate, N. (2012). Assessment scales for delirium: A review. *World journal of psychiatry, 2*(4), 58-70. doi: 10.5498/wjp.v2.i4.58

Gurlit, S., & Möllmann, M. (2008). How to prevent perioperative delirium in the elderly?. *Zeitschrift für Gerontologie und Geriatrie, 41*(6), 447-452. doi: 10.1007/s00391-008-0020-6

Gusmao-Flores, D., Salluh, J. I. F., Chalhub, R. Á., & Quarantini, L. C. (2012). The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. *Critical care, 16*, 1-10. doi: 10.1186/cc11407

Hartley, P., Gibbins, N., Saunders, A., Alexander, K., Conroy, E., Dixon, R., ... & Romero-Ortuno, R. (2017). The association between cognitive impairment and functional outcome in hospitalised

older patients: a systematic review and meta-analysis. *Age and ageing, 46*(4), 559-567. doi: 10.1093/ageing/afx007

Heeringa, J., van der Kuip, D. A., Hofman, A., Kors, J. A., van Herpen, G., Stricker, B. H. C., ... & Witteman, J. C. (2006). Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *European heart journal, 27*(8), 949-953. doi: 10.1093/eurheartj/ehi825

Helfand, B. K., D'Aquila, M. L., Tabloski, P., Erickson, K., Yue, J., Fong, T. G., ... & Jones, R. N. (2021). Detecting delirium: a systematic review of identification instruments for non-ICU settings. *Journal of the American Geriatrics Society, 69*(2), 547-555. doi: 10.1111/jgs.16879

Helmi, L., Meagher, D., O'Mahony, E., O'Neill, D., Mulligan, O., Murthy, S., ... & Adamis, D. (2016). Agreement and conversion formula between mini-mental state examination and montreal cognitive assessment in an outpatient sample. *World Journal of Psychiatry,6*(3), 358-364. doi: 10.5498/wjp.v6.i3.358

Hlavka, J. P., Kinoshita, A. T., Fang, S., & Hunt, A. (2021). Clinical outcome measure crosswalks in Alzheimer's disease: a systematic review. *Journal of Alzheimer's Disease, 83*(2), 591-608. doi: 10.3233/JAD-210060

Hollinger, A., Siegemund, M., Goettel, N., & Steiner, L. A. (2015). Postoperative delirium in cardiac surgery: an unavoidable menace?. *Journal of cardiothoracic and vascular anesthesia, 29*(6), 1677-1687. doi: 10.1053/j.jvca.2014.08.021

Holsinger, T., Deveau, J., Boustani, M., & Williams, J. W. (2007). Does this patient have dementia?. *Jama, 297*(21), 2391-2404. doi: 10.1001/jama.297.21.2391

Hshieh, T. T., Yue, J., Oh, E., Puelle, M., Dowal, S., Travison, T., & Inouye, S. K. (2015). Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. *JAMA internal medicine, 175*(4), 512-520. doi: 10.1001/jamainternmed.2014.7779

Inouye, S. K., van Dyck, C. H., Alessi, C. A., Balkin, S., Siegal, A. P., & Horwitz, R. I. (1990). Clarifying confusion: the confusion assessment method: a new method for detection of delirium. *Annals of internal medicine, 113*(12), 941-948. doi: 10.7326/0003-4819-113-12-941

Inouye, S. K., & Charpentier, P. A. (1996). Precipitating factors for delirium in hospitalized elderly persons: predictive model and interrelationship with baseline vulnerability. *Jama, 275*(11), 852-857.

Inouye, S. K., Bogardus Jr, S. T., Charpentier, P. A., Leo-Summers, L., Acampora, D., Holford, T. R., & Cooney Jr, L. M. (1999). A multicomponent intervention to prevent delirium in hospitalized older patients. *New England journal of medicine, 340*(9), 669-676. doi: 10.1056/NEJM199903043400901

Inouye, S. K. (2006). Delirium in older persons. *New England journal of medicine, 354*(11), 1157-1165. doi: 10.1056/NEJMra052321

Inouye, S. K., Westendorp, R. G., & Saczynski, J. S. (2014). Delirium in elderly people. The *Lancet, 383*(9920), 911-922. doi: 10.1016/S0140-6736(13)60688-1

Inouye, S. K., Marcantonio, E. R., Kosar, C. M., Tommet, D., Schmitt, E. M., Travison, T. G., ... & Jones, R. N. (2016). The short-term and long-term relationship between delirium and cognitive trajectory in older surgical patients. *Alzheimer's & Dementia, 12*(7), 766-775. doi: 10.1016/j.jalz.2016.03.005

January, C. T., Wann, L. S., Alpert, J. S., Calkins, H., Cigarroa, J. E., Cleveland Jr, J. C., ... & Yancy, C. W. (2014). 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation, 130*(23), 2071-2104. doi: 10.1161/CIR.0000000000000040

Jin, J. (2020). Screening for cognitive impairment in older adults. *JAMA, 323*(8), 800. doi: 10.1001/jama.2020.0583

Jung, P., Pereira, M. A., Hiebert, B., Song, X., Rockwood, K., Tangri, N., & Arora, R. C. (2015). The impact of frailty on postoperative delirium in cardiac surgery patients. *The Journal of thoracic and cardiovascular surgery, 149*(3), 869-875. doi: 10.1016/j.jtcvs.2014.10.118

Jung, Y. I., Jeong, E. H., Lee, H., Seo, J., Yu, H. J., Hong, J. Y., & Sunwoo, M. K. (2018). Validation of MoCA-MMSE conversion scales in Korean patients with cognitive impairments. *Dementia and Neurocognitive Disorders, 17*(4), 148-155. doi: 10.12779/dnd.2018.17.4.148

Jutten, R. J., Grandoit, E., Foldi, N. S., Sikkes, S. A., Jones, R. N., Choi, S. E., ... & Rabin, L. A. (2020). Lower practice effects as a marker of cognitive performance and dementia risk: a literature review. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 12*(1), e12055. doi: 10.1002/dad2.12055

Kalantarian, S., Stern, T. A., Mansour, M., & Ruskin, J. N. (2013). Cognitive impairment associated with atrial fibrillation: a meta-analysis. *Annals of internal medicine, 158*(5_Part_1), 338-346. doi: 10.7326/0003-4819-158-5-201303050-00007

Kalantarian, S., & Ruskin, J. N. (2016). Atrial fibrillation and cognitive decline: phenomenon or epiphenomenon?. *Cardiology clinics, 34*(2), 279-285. doi: 10.1016/j.ccl.2015.12.011

Kalbe, E., Kessler, J., Calabrese, P., Smith, R., Passmore, A. P., Brand, M. A., & Bullock, R. (2004). DemTect: a new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. *International journal of geriatric psychiatry, 19*(2), 136-143. doi: 10.1002/gps.1042

Kallenberg, M. H., Kleinveld, H. A., Dekker, F. W., van Munster, B. C., Rabelink, T. J., van Buren, M., & Mooijaart, S. P. (2016). Functional and cognitive impairment, frailty, and adverse health

outcomes in older patients reaching ESRD—a systematic review. *Clinical Journal of the American Society of Nephrology, 11*(9), 1624-1639. doi: 10.2215/CJN.13611215

Kapoor, P., Chen, L., Saripella, A., Waseem, R., Nagappa, M., Wong, J., ... & Chung, F. (2022). Prevalence of preoperative cognitive impairment in older surgical patients.: A systematic review and meta-analysis. *Journal of Clinical Anesthesia, 76*, 110574. doi: 10.1016/j.jclinane.2021.110574

Kazmierski, J., Banys, A., Latek, J., Bourke, J., Jaszewski, R., Sobow, T., & Kloszewska, I. (2014). Mild cognitive impairment with associated inflammatory and cortisol alterations as independent risk factor for postoperative delirium. *Dementia and geriatric cognitive disorders, 38*(1-2), 65-78. doi: 10.1159/000357454

Kim, S. Y., Moon, S. K., Jung, D. C., Hwang, S. I., Sung, C. K., Cho, J. Y., ... & Lee, H. J. (2011). Pre-operative prediction of advanced prostatic cancer using clinical decision support systems: accuracy comparison between support vector machine and artificial neural network. *Korean journal of radiology, 12*(5), 588-594. doi: 10.3348/kjr.2011.12.5.588

Kim, D., Yang, P. S., Yu, H. T., Kim, T. H., Jang, E., Sung, J. H., ... & Joung, B. (2019). Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a population-based cohort. *European heart journal, 40*(28), 2313-2323. doi: 10.1093/eurheartj/ehz386

Kirchhof, P., Benussi, S., Kotecha, D., Ahlsson, A., Atar, D., Casadei, B., ... & Vardas, P. (2016). 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Kardiologia Polska (Polish Heart Journal), 74*(12), 1359-1469. doi: 10.5603/KP.2016.0172

Knecht, S., Oelschläger, C., Duning, T., Lohmann, H., Albers, J., Stehling, C., ... & Wersching, H. (2008). Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. *European heart journal*, *29*(17), 2125-2132. doi: 10.1093/eurheartj/ehn341

Koh, Y. H., Lew, L. Z., Franke, K. B., Elliott, A. D., Lau, D. H., Thiyagarajah, A., ... & Mahajan, R. (2022). Predictive role of atrial fibrillation in cognitive decline: a systematic review and meta-analysis of 2.8 million individuals. *EP Europace*, *24*(8), 1229-1239. doi: 10.1093/europace/euac003

Kolen, M. J., & Brennan, R. L. (2004). Test equating, scaling, and linking.

Koster, S., Hensens, A. G., Schuurmans, M. J., & van der Palen, J. (2013). Prediction of delirium after cardiac surgery and the use of a risk checklist. *European journal of cardiovascular nursing, 12*(3), 284-292. doi: 10.1177/1474515112450244

Kopecek, M., Stepankova, H., Lukavsky, J., Ripova, D., Nikolai, T., & Bezdicek, O. (2017). Montreal cognitive assessment (MoCA): Normative data for old and very old Czech adults. *Applied Neuropsychology: Adult, 24*(1), 23-29. doi: 10.1080/23279095.2015.1065261

Krijthe, B. P., Kunst, A., Benjamin, E. J., Lip, G. Y., Franco, O. H., Hofman, A., ... & Heeringa, J. (2013). Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *European heart journal, 34*(35), 2746-2751. doi: 10.1093/eurheartj/eht280

Kumar, C., Salzman, B., & Colburn, J. L. (2018). Preoperative assessment in older adults: a comprehensive approach. *American family physician, 98*(4), 214-220.

Lancu, I., & Olmer, A. (2006). The minimental state examination--an up-to-date review. *Harefuah, 145*(9), 687-90.

Larner, A. J. (2017). Converting cognitive screening instrument test scores to MMSE scores: regression equations. *International journal of geriatric psychiatry, 32*(3), 351-352. doi: 10.1002/gps.462

Lawton, M., Kasten, M., May, M. T., Mollenhauer, B., Schaumburg, M., Liepelt-Scarfone, I., ... & Ben-Shlomo, Y. (2016). Validation of conversion between mini–mental state examination and montreal cognitive assessment. *Movement Disorders, 31*(4), 593-596. doi: 10.1002/mds.26498

Lee, A., Mu, J. L., Joynt, G. M., Chiu, C. H., Lai, V. K. W., Gin, T., & Underwood, M. J. (2017). Risk prediction models for delirium in the intensive care unit after cardiac surgery: a systematic review and independent external validation. *BJA: British Journal of Anaesthesia, 118*(3), 391-399. doi: 10.1093/bja/aew476

Li, H. C., Wei, Y. C., Hsu, R. B., Chi, N. H., Wang, S. S., Chen, Y. S., ... & Inouye, S. K. (2021). Surviving and thriving 1 year after cardiac surgery: frailty and delirium matter. *The Annals of thoracic surgery, 111*(5), 1578-1584. doi: 10.1016/j.athoracsur.2020.07.015

Lin, Y., Chen, J., & Wang, Z. (2012). Meta-analysis of factors which influence delirium following cardiac surgery. *Journal of cardiac surgery, 27*(4), 481-492. doi: 10.1111/j.1540-8191.2012.01472.x

Lindroth, H., Bratzke, L., Purvis, S., Brown, R., Coburn, M., Mrkobrada, M., ... & Sanders, R. D. (2018). Systematic review of prediction models for delirium in the older adult inpatient. *BMJ open, 8*(4), e019223. doi: 10.1136/bmjopen-2017-019223

Lock, S., Chura, L. R., Barraccca, N., Barracca, N., Olivari, B., Baumgart, M., & Mcguire, L. C. (2019). Globa l COUNCIL on BRAIN health lifestyle RECOMMENDATIONS for adults 50+. *Alzheimers Dement, 15*(7), P892.

Long, L. S., Shapiro, W. A., & Leung, J. M. (2012). A brief review of practical preoperative cognitive screening tools. *Canadian journal of anaesthesia= Journal canadien d'anesthesie, 59*(8), 798-804. doi: 10.1007/s12630-012-9737-1

Madhavan, M., Graff-Radford, J., Piccini, J. P., & Gersh, B. J. (2018). Cognitive dysfunction in atrial fibrillation. *Nature Reviews Cardiology, 15*(12), 744-756. doi: 10.1038/s41569-018-0075-z

Mahanna-Gabrielli, E., Schenning, K. J., Eriksson, L. I., Browndyke, J. N., Wright, C. B., Evered, L., ... & Deiner, S. (2019). State of the clinical science of perioperative brain health: report from the American Society of Anesthesiologists Brain Health Initiative Summit 2018. *British journal of anaesthesia, 123*(4), 464-478. doi: 10.1016/j.bja.2019.07.004

Majewski, P., Zegan-Barańska, M., Karolak, I., Kaim, K., Żukowski, M., & Kotfis, K. (2020). Current Evidence Regarding Biomarkers Used to Aid Postoperative Delirium Diagnosis in the Field of Cardiac Surgery. *Medicina, 56*(10), 493. doi: 10.3390/medicina56100493

Marcantonio, E. R., Flacker, J. M., Wright, R. J., & Resnick, N. M. (2001). Reducing delirium after hip fracture: a randomized trial. *Journal of the American Geriatrics Society, 49*(5), 516-522. doi: 10.1046/j.1532-5415.2001.49108.x

Marcantonio, E. R., Kiely, D. K., Simon, S. E., John Orav, E., Jones, R. N., Murphy, K. M., & Bergmann, M. A. (2005). Outcomes of older people admitted to postacute facilities with delirium. *Journal of the American Geriatrics Society, 53*(6), 963-969. doi: 10.1111/j.1532-5415.2005.53305.x

Marengoni, A., Qiu, C., Winblad, B., & Fratiglioni, L. (2011). Atrial fibrillation, stroke and dementia in the very old: a population-based study. *Neurobiology of aging, 32*(7), 1336-1337. doi: 10.1016/j.neurobiolaging.2009.08.002

Martin, B. J., Buth, K. J., Arora, R. C., & Baskett, R. J. (2010). Delirium as a predictor of sepsis in post-coronary artery bypass grafting patients: a retrospective cohort study. *Critical Care, 14*, 1-6. doi: 10.1186/cc9273

Martin, B. J., Buth, K. J., Arora, R. C., & Baskett, R. J. (2012). Delirium: a cause for concern beyond the immediate postoperative period. *The Annals of thoracic surgery, 93*(4), 1114-1120. doi: 10.1016/j.athoracsur.2011.09.011

Marzona, I., O'Donnell, M., Teo, K., Gao, P., Anderson, C., Bosch, J., & Yusuf, S. (2012). Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. *Cmaj, 184*(6), E329-E336. doi: 10.1503/cmaj.111173

Matarazzo, J. D., & Herman, D. O. (1984). Base rate data for the WAIS-R: Test-retest stability and VIQ-PIQ differences. *Journal of Clinical and Experimental Neuropsychology, 6*(4), 351-366. doi: 10.1080/01688638408401227

McCusker, J., Cole, M. G., Dendukuri, N., & Belzile, E. (2003). Does delirium increase hospital stay?. *Journal of the American Geriatrics Society, 51*(11), 1539-1546. doi: 10.1046/j.1532-5415.2003.51509.x

Menzenbach, J., Guttenthaler, V., Kirfel, A., Ricchiuto, A., Neumann, C., Adler, L., ... & Toma, O. (2020). Estimating patients' risk for postoperative delirium from preoperative routine data-Trial design of the PRe-Operative prediction of postoperative DElirium by appropriate SCreening (PROPDESC) study-a monocentre prospective observational trial. *Contemporary Clinical Trials Communications, 17*, 100501. doi: 10.1016/j.conctc.2019.100501

Melikyan, Z. A., Malek-Ahmadi, M., O'Connor, K., Atri, A., Kawas, C. H., & Corrada, M. M. (2021). Norms and equivalences for MoCA-30, MoCA-22, and MMSE in the oldest-old. *Aging clinical and experimental research, 33*(12), 3303-3311. doi: 10.1007/s40520-021-01886-z

Mistarz, R., Eliott, S., Whitfield, A., & Ernest, D. (2011). Bedside nurse–patient interactions do not reliably detect delirium: An observational study. *Australian Critical Care, 24*(2), 126-132. doi: 10.1016/j.aucc.2011.01.002

Mooney, C. Z., Mooney, C. F., Duval, R. D., Mooney, C. L., & Duvall, R. (1993). Bootstrapping: *A nonparametric approach to statistical inference* (No. 95). sage.

Moons, K. G., Kengne, A. P., Woodward, M., Royston, P., Vergouwe, Y., Altman, D. G., & Grobbee, D. E. (2012a). Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio) marker. *Heart, 98*(9), 683-690. doi: 10.1136/heartjnl-2011-301246

Moons, K. G., Kengne, A. P., Grobbee, D. E., Royston, P., Vergouwe, Y., Altman, D. G., & Woodward, M. (2012b). Risk prediction models: II. External validation, model updating, and impact assessment. *Heart, 98*(9), 691-698. doi: 10.1136/heartjnl-2011-301247

Moons, K. G., Altman, D. G., Reitsma, J. B., Ioannidis, J. P., Macaskill, P., Steyerberg, E. W., ... & Collins, G. S. (2015). Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Annals of internal medicine, 162*(1), W1-W73. doi: 10.7326/M14-0698

Monsch, A. U., & Kressig, R. W. (2010). Specific care program for the older adults: memory clinics. *European Geriatric Medicine, 1*(2), 128-131.

Monsch, R. J., Burckhardt, A. C., Berres, M., Thomann, A. E., Ehrensperger, M. M., Steiner, L. A., & Goettel, N. (2019). Development of a novel self-administered cognitive assessment tool and normative data for older adults. *Journal of neurosurgical anesthesiology, 31*(2), 218-226. doi: 10.1097/ANA.0000000000000510

Monsell, S. E., Dodge, H. H., Zhou, X. H., Bu, Y., Besser, L. M., Mock, C., ... & Weintraub, S. (2016). Results from the NACC uniform data set neuropsychological battery crosswalk study running head: neuropsychological battery crosswalk study results. *Alzheimer disease and associated disorders, 30*(2), 134-139. doi: 10.1097/WAD.0000000000000111

Morris, J. C., Mohs, R. C., & Rogers, H. (1989). Consortium to establish a registry for Alzheimer's Disease (CERAD) clinical and neuropsychological. *Psychopharmacology bulletin, 24*(3-4), 641.

Mossie, A., Regasa, T., Neme, D., Awoke, Z., Zemedkun, A., & Hailu, S. (2022). Evidence-based guideline on management of postoperative delirium in older people for low resource setting: systematic review article. *International Journal of General Medicine*, 4053-4065. doi: 10.2147/IJGM.S349232

Mufti, H. N., Hirsch, G. M., Abidi, S. R., & Abidi, S. S. R. (2019). Exploiting machine learning algorithms and methods for the prediction of agitated delirium after cardiac surgery: models development and validation study. *JMIR medical informatics, 7*(4), e14993. doi: 10.2196/14993

Mufti, H. N., & Hirsch, G. M. (2017). Perioperative prediction of agitated (hyperactive) delirium after cardiac surgery in adults–The development of a practical scorecard. *Journal of Critical Care, 42*, 192-199. doi: 10.1016/j.jcrc.2017.07.045

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., ... & 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. doi: 10.1111/j.1532-5415.2005.53221.x

National Institute for Health and Care Excellence. (2023). Delirium: prevention, diagnosis and management in hospital and long-term care. Retrieved March 16, 2023, from https://www.nice.org.uk/guidance/cg103

National Institute on Aging. (2023). Assessing Cognitive Impairment in Older Patients. Retrieved March 01, 2023, from https://www.nia.nih.gov/health/assessing-cognitive impairment-older-patients

Nishtala, A., Piers, R. J., Himali, J. J., Beiser, A. S., Davis-Plourde, K. L., Saczynski, J. S., ... & Au, R. (2018). Atrial fibrillation and cognitive decline in the Framingham Heart Study. *Heart Rhythm, 15*(2), 166-172. doi: 10.1016/j.hrthm.2017.09.036

Olin, J. T., & Zelinski, E. M. (1991). The 12-month reliability of the Mini-Mental State Examination. Psychological Assessment: *A Journal of Consulting and Clinical Psychology, 3*(3), 427-432.

Ormseth, C. H., LaHue, S. C., Oldham, M. A., Josephson, S. A., Whitaker, E., & Douglas, V. C. (2023). Predisposing and Precipitating Factors Associated With Delirium: A Systematic Review. *JAMA Network Open, 6*(1), e2249950-e2249950. doi: 10.1001/jamanetworkopen.2022.49950

Ott, A., Breteler, M. M., De Bruyne, M. C., Van Harskamp, F., Grobbee, D. E., & Hofman, A. (1997). Atrial fibrillation and dementia in a population-based study: the Rotterdam Study. *Stroke, 28*(2), 316-321. doi: 10.1161/01.str.28.2.316

Owens, D. K., Davidson, K. W., Krist, A. H., Barry, M. J., Cabana, M., Caughey, A. B., ... & US Preventive Services Task Force. (2020). Screening for cognitive impairment in older adults: US preventive services task force recommendation statement. *Jama, 323*(8), 757-763. doi: 10.1001/jama.2020.0435

Ozer, S., Young, J., Champ, C., & Burke, M. (2016). A systematic review of the diagnostic test accuracy of brief cognitive tests to detect amnestic mild cognitive impairment. *International Journal of Geriatric Psychiatry, 31*(11), 1139–1150. doi. 10.1002/gps.4444

Palmer, K., Fratiglioni, L., & Winblad, B. (2003). What is mild cognitive impairment? Variations in definitions and evolution of nondemented persons with cognitive impairment. *Acta Neurologica Scandinavica, 107*, 14-20. doi: 10.1034/j.1600-0404.107.s179.2.x

Pas, M. T., Olde Rikkert, M., Bouwman, A., Kessels, R., & Buise, M. (2022). Screening for mild cognitive impairment in the preoperative setting: A narrative review. In *Healthcare* (Vol. 10, No. 6, p. 1112). MDPI. doi: 10.3390/healthcare10061112

Park, H., Hildreth, A., Thomson, R., & O'Connell, J. (2007). Non-valvular atrial fibrillation and cognitive decline: a longitudinal cohort study. *Age and ageing, 36*(2), 157-163. doi: 10.1093/ageing/afl164.

Partridge, J. S., Crichton, S., Biswell, E., Harari, D., Martin, F. C., & Dhesi, J. K. (2019). Measuring the distress related to delirium in older surgical patients and their relatives. *International Journal of Geriatric Psychiatry, 34*(7), 1070-1077. doi: 10.1002/gps.5110

Pendlebury, Sarah T, Cuthbertson, F. C., Welch, S. J. V, Mehta, Z., & Rothwell, P. M. (2010). Underestimation of cognitive impairment by mini-mental state examination versus the montreal cognitive assessment in patients with transient ischemic attack and stroke. A population-based study. *Stroke, 41*(6), 1290–1293. doi: 10.1161/STROKEAHA.110.579888

Perry, W., Lacritz, L., Roebuck-Spencer, T., Silver, C., Denney, R. L., Meyers, J., ... & Golden, T. (2018). Population health solutions for assessing cognitive impairment in geriatric patients. *Innovation in aging, 2*(2), igy025. doi: 10.1093/geroni/igy025

Persico, I., Cesari, M., Morandi, A., Haas, J., Mazzola, P., Zambon, A., ... & Bellelli, G. (2018). Frailty and delirium in older adults: a systematic review and meta-analysis of the literature. *Journal of the American Geriatrics Society, 66*(10), 2022-2030. doi: 10.1111/jgs.15503

Peters, R., Poulter, R., Beckett, N., Forette, F., Fagard, R., Potter, J., ... & Bulpitt, C. J. (2009). Cardiovascular and biochemical risk factors for incident dementia in the Hypertension in the Very Elderly Trial. *Journal of hypertension*, *27*(10), 2055-2062. doi: 10.1097/HJH.0b013e32832f4f02

Petersen, R. C., Caracciolo, B., Brayne, C., Gauthier, S., Jelic, V., & Fratiglioni, L. (2014). Mild cognitive impairment: a concept in evolution. *Journal of internal medicine, 275*(3), 214-228. doi: 10.1111/joim.12190

Pottie, K., Rahal, R., Jaramillo, A., Birtwhistle, R., Thombs, B. D., Singh, H., ... & Canadian Task Force on Preventive Health Care. (2016). Recommendations on screening for cognitive impairment in older adults. *Cmaj, 188*(1), 37-46. doi: 10.1503/cmaj.141165

Price, C. C., Garvan, C., Hizel, L. P., Lopez, M. G., & Billings IV, F. T. (2017). Delayed recall and working memory MMSE domains predict delirium following cardiac surgery. *Journal of Alzheimer's Disease, 59*(3), 1027-1035. doi: 10.3233/JAD-170380

Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M. World Alzheimer report 2016. Improving Healthcare for People Living with Dementia: Coverage, Quality and Costs Now and in the Future 2016. Retrieved January 16, 2023, from https://www.alzint.org/resource/world-alzheimer-report-2016/

Puccio, D., Vizzini, M. C., Baiamonte, V., Lunetta, M., Evola, S., Galassi, A. R., & Novo, G. (2020). Atrial fibrillation and cognitive disorders: An overview on possible correlation. *Mechanisms of Ageing and Development, 191*, 111326. doi: 10.1016/j.mad.2020.111326

Ramineni, A., & Dangayach, N. (2021). Delirium. *Mount Sinai Expert Guides: Critical Care*, 241-249.

Ranganathan, D., & Cheung, C. C. (2023). 'Wear'Are We? Digital Health Tools in the Detection and Management of Atrial Fibrillation. *EP Lab Digest, 23*(1).

Rastas, S., Verkkoniemi, A., Polvikoski, T., Juva, K., Niinistö, L., Mattila, K., ... & Sulkava, R. (2007). Atrial fibrillation, stroke, and cognition: a longitudinal population-based study of people aged 85 and older. *Stroke*,*38*(5), 1454-1460. doi: 10.1161/STROKEAHA.106.477299

Reilly, B. M., & Evans, A. T. (2006). Translating clinical research into clinical practice: impact of using prediction rules to make decisions. *Annals of internal medicine, 144*(3), 201-209. doi: 10.7326/0003-4819-144-3-200602070-00009

Rengel, K. F., Pandharipande, P. P., & Hughes, C. G. (2018). Postoperative delirium. *La Presse Médicale, 47*(4), e53-e64. doi: 10.1016/j.lpm.2018.03.012

Rivard, L., & Khairy, P. (2017). Mechanisms, clinical significance, and prevention of cognitive impairment in patients with atrial fibrillation. *Canadian Journal of Cardiology, 33*(12), 1556-1564. doi: 10.1016/j.cjca.2017.09.024

Roalf, D. R., Moberg, P. J., Xie, S. X., Wolk, D. A., Moelter, S. T., & Arnold, S. E. (2013). Comparative accuracies of two common screening instruments for classification of Alzheimer's disease, mild cognitive impairment, and healthy aging. *Alzheimer's & Dementia, 9*(5), 529-537. doi: 10.1016/j.jalz.2012.10.001

Robertson, K., Larson, E. B., Crane, P. K., Cholerton, B., Craft, S., McCormick, W. C., ... & Trittschuh, E. H. (2019). Using varying diagnostic criteria to examine mild cognitive impairment prevalence

and predict dementia incidence in a community-based sample. *Journal of Alzheimer's Disease, 68*(4), 1439-1451. doi: 10.3233/JAD-180746

Rockwood, K., Cosway, S., Carver, D., Jarrett, P., Stadnyk, K., & Fisk, J. (1999). The risk of dementia and death after delirium. *Age and ageing, 28*(6), 551-556. doi: 10.1093/ageing/28.6.551

Roheger, M., Xu, H., Hoang, M. T., Eriksdotter, M., & Garcia-Ptacek, S. (2022). Conversion between the mini-mental state examination and the Montreal cognitive assessment for patients with different forms of dementia. *Journal of the American Medical Directors Association, 23*(12), 1986-1989. doi: 10.1016/j.jamda.2022.03.018

Rudolph, J. L., Jones, R. N., Levkoff, S. E., Rockett, C., Inouye, S. K., Sellke, F. W., ... & Marcantonio, E. R. (2009). Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation, 119*(2), 229-236. doi: 10.1161/CIRCULATIONAHA.108.795260

Ruff, C. T., Giugliano, R. P., Braunwald, E., Hoffman, E. B., Deenadayalu, N., Ezekowitz, M. D., ... & Antman, E. M. (2014). Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *The Lancet, 383*(9921), 955-962. doi: 10.1016/S0140-6736(13)62343-0

Sachdev, P. S., Blacker, D., Blazer, D. G., Ganguli, M., Jeste, D. V., Paulsen, J. S., & Petersen, R. C. (2014). Classifying neurocognitive disorders: the DSM-5 approach. *Nature Reviews Neurology, 10*(11), 634-642. doi: 10.1038/nrneurol.2014.181

Saczynski, J. S., Marcantonio, E. R., Quach, L., Fong, T. G., Gross, A., Inouye, S. K., & Jones, R. N. (2012). Cognitive trajectories after postoperative delirium. New England *Journal of Medicine, 367*(1), 30-39. doi: 10.1056/NEJMoa1112923

Saczynski, J. S., Inouye, S. K., Guess, J., Jones, R. N., Fong, T. G., Nemeth, E., ... & Marcantonio, E. R. (2015). The Montreal cognitive assessment: Creating a crosswalk with the mini-mental state

examination. *Journal of the American Geriatrics Society, 63*(11), 2370-2374. doi: 10.1111/jgs.13710

Salthouse, T. A. (2010). Influence of age on practice effects in longitudinal neurocognitive change. *Neuropsychology, 24*(5), 563-572. doi: 10.1037/a0019026

Salvi, F., Young, J., Lucarelli, M., Aquilano, A., Luzi, R., Dell'Aquila, G., & Cherubini, A. (2020). Non-pharmacological approaches in the prevention of delirium. *European Geriatric Medicine, 11*, 71-81. doi: 10.1007/s41999-019-00260-7

Safavynia, S. A., Goldstein, P. A., & Evered, L. A. (2022). Mitigation of perioperative neurocognitive disorders: A holistic approach. *Frontiers in Aging Neuroscience*, *14*. doi: 10.3389/fnagi.2022.949148

Sauer, W. H., & Olchansky, B. (2008). Normal sinus rhythm and sinus arrhythmia. Retrieved April 11, 2023 from https://www.uptodate.com/contents/normal-sinus-rhythm-and-sinus-arrhythmia

Scheffels, J. F., Kräling, H., Kalbe, E., & Kessler, J. (2018). Conversions of cognitive screenings: mini-mental state examination vs. Montreal cognitive assessment vs. DemTect. *Der Nervenarzt, 89*, 1371-1377. doi: 10.1007/s00115-018-0583-4

Schubert, M., Schürch, R., Boettger, S., Garcia Nuñez, D., Schwarz, U., Bettex, D., ... & Rudiger, A. (2018). A hospital-wide evaluation of delirium prevalence and outcomes in acute care patients-a cohort study. *BMC Health Services Research, 18*(1), 1-12. doi: 10.1186/s12913-018-3345-x

Serpa Neto, A., Nassar Júnior, A. P., Cardoso, S. O., Manetta, J. A., Pereira, V. G., Espósito, D. C., ... & Slooter, A. J. (2012). Delirium screening in critically ill patients: a systematic review and meta-analysis. *Crit Care Med, 40*(6), 1946-1951. doi: 10.1097/CCM.0b013e31824e16c9

Shamloo, A. S., Dagres, N., Müssigbrodt, A., Stauber, A., Kircher, S., Richter, S., ... & Arya, A. (2020). Atrial fibrillation and cognitive impairment: new insights and future directions. *Heart, Lung and Circulation, 29*(1), 69-85. doi: 10.1016/j.hlc.2019.05.185

Sheikh, J. I., & Yesavage, J. A. (1986). Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clinical Gerontologist: *The Journal of Aging and Mental Health*, 165-173.

Shining, C. A. I., Jingjing, L. I., Jian, G. A. O., Wenyan, P. A. N., & Zhang, Y. (2022). Prediction models for postoperative delirium after cardiac surgery: systematic review and critical appraisal. *International Journal of Nursing Studies*, 104340. doi: 10.1016/j.ijnurstu.2022.104340

Siddiqi, N., Harrison, J. K., Clegg, A., Teale, E. A., Young, J., Taylor, J., & Simpkins, S. A. (2016). Interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database of Systematic Reviews*, (3). doi: 10.1002/14651858.CD005563.pub3

Singh-Manoux, A., Fayosse, A., Sabia, S., Canonico, M., Bobak, M., Elbaz, A., ... & Dugravot, A. (2017). Atrial fibrillation as a risk factor for cognitive decline and dementia. *European Heart Journal, 38*(34), 2612-2618. doi: 10.1093/eurheartj/ehx208

Siontis, G. C., Tzoulaki, I., Castaldi, P. J., & Ioannidis, J. P. (2015). External validation of new risk prediction models is infrequent and reveals worse prognostic discrimination. *Journal of clinical epidemiology, 68*(1), 25-34. doi: 10.1016/j.jclinepi.2014.09.007

Siregar, S., Nieboer, D., Versteegh, M. I., Steyerberg, E. W., & Takkenberg, J. J. (2019). Methods for updating a risk prediction model for cardiac surgery: a statistical primer. *Interactive cardiovascular and thoracic surgery, 28*(3), 333-338. doi: 10.1093/icvts/ivy338.

Sleeper, T. L. (2021). Cognitive Function, Aging, and the Community Dwelling Elderly Living Alone: Implications for Nursing Practice. *J Comp Nurs Res Care,6*(2), 176.

Small, B. J., Dixon, R. A., McArdle, J. J., & Grimm, K. J. (2012). Do changes in lifestyle engagement moderate cognitive decline in normal aging? Evidence from the Victoria Longitudinal Study. *Neuropsychology, 26*(2), 144-155. doi: 10.1037/a0026579

Smith, S. R., Servesco, A. M., Edwards, J. W., Rahban, R., Barazani, S., Nowinski, L. A., ... & Green, J. G. (2008). Exploring the validity of the comprehensive trail making test. *The Clinical Neuropsychologist, 22*(3), 507-518. doi: 10.1080/13854040701399269

Solomon, T. M., deBros, G. B., Budson, A. E., Mirkovic, N., Murphy, C. A., & Solomon, P. R. (2014). Correlational analysis of 5 commonly used measures of cognitive functioning and mental status: an update. *American Journal of Alzheimer's Disease & Other Dementias®, 29*(8), 718-722. doi: 10.1177/1533317514534761

Springer, A., Monsch, A. U., Dutilh, G., Coslovsky, M., Kievit, R. A., Bonati, L. H., ... & Swiss-AF Study Investigators. (2020). A factor score reflecting cognitive functioning in patients from the Swiss Atrial Fibrillation Cohort Study (Swiss-AF). *Plos one, 15*(10), e0240167. doi: 10.1371/journal.pone.0240167

Sprung, J., Roberts, R. O., Knopman, D. S., Petersen, R. C., Weingarten, T. N., Schroeder, D. R., & Warner, D. O. (2016). Perioperative delirium and mild cognitive impairment. In *Mayo Clinic Proceedings* (Vol. 91, No. 2, pp. 273-274). Elsevier. doi: 10.1016/j.mayocp.2015.12.008

Staerk, L., Wang, B., Preis, S. R., Larson, M. G., Lubitz, S. A., Ellinor, P. T., ... & Trinquart, L. (2018). Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *Bmj, 361*. doi: 10.1136/bmj.k1453

Story, D. A., Leslie, K., Myles, P. S., Fink, M., Poustie, S. J., Forbes, A., ... & REASON Investigators, Australian and New Zealand College of Anaesthetists Trials Group. (2010). Complications and mortality in older surgical patients in Australia and New Zealand (the REASON study): a multicentre, prospective, observational study. *Anaesthesia, 65*(10), 1022-1030. doi: 10.1111/j.1365-2044.2010.06478.x

Strydom, A., Fleisher, M. H., Deb, S., Ring, H., Esralew, L., Dodd, K., ... & Whitwham, S. L. (2016). Neurocognitive disorders. *Diagnostic manual-intellectual disability 2nd edition (DMID-2)*, 573-597.

Su, L. J., Chen, M. J., Yang, R., Zou, H., Chen, T. T., Li, S. L., ... & Hu, R. F. (2023). Plasma biomarkers and delirium in critically ill patients after cardiac surgery: A prospective observational cohort study. *Heart & Lung, 59*, 139-145. doi: 10.1016/j.hrtlng.2023.02.010

Swarbrick, C. J., & Partridge, J. S. L. (2022). Evidence-based strategies to reduce the incidence of postoperative delirium: a narrative review. *Anaesthesia, 77*, 92-101. doi: 10.1111/anae.15607

Thacker, E. L., McKnight, B., Psaty, B. M., Longstreth, W. T., Sitlani, C. M., Dublin, S., ... & Heckbert, S. R. (2013). Atrial fibrillation and cognitive decline: a longitudinal cohort study. *Neurology, 81*(2), 119-125. doi: 10.1212/WNL.0b013e31829a33d1

Thalmann, B., Spiegel, R., Stähelin, H. B., Brubacher, D., Ermini-Fünfschilling, D., Bläsi, S., & Monsch, A. U. (2002). Dementia screening in general practice: optimised scoring for the clock drawing test. *Brain aging*, *2*(2), 36-43.

Thom, R. P., Levy-Carrick, N. C., Bui, M., & Silbersweig, D. (2019). Delirium. *American Journal of Psychiatry, 176*(10), 785-793. doi: 10.1176/appi.ajp.2018.18070893

Tilvis, R. S., Kähönen-Väre, M. H., Jolkkonen, J., Valvanne, J., Pitkala, K. H., & Strandberg, T. E. (2004). Predictors of cognitive decline and mortality of aged people over a 10-year period. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 59*(3), M268-M274. doi: 10.1093/gerona/59.3.m268

Toll, D. B., Janssen, K. J. M., Vergouwe, Y., & Moons, K. G. M. (2008). Validation, updating and impact of clinical prediction rules: a review. *Journal of clinical epidemiology, 61*(11), 1085-1094. doi: 10.1016/j.jclinepi.2008.04.008

Trzepacz, P. T., Hochstetler, H., Wang, S., Walker, B., & Saykin, A. J. (2015). Alzheimer's Disease Neuroimaging I. Relationship between the Montreal Cognitive Assessment and Mini-mental State Examination for assessment of mild cognitive impairment in older adults. *BMC Geriatr, 15*(107), 1-9. doi: 10.1186/s12877-015-0103-3

Van Beijsterveldt, C. E. M., Van Boxtel, M. P. J., Bosma, H., Houx, P. J., Buntinx, F. J. V. M., & Jolles, J. (2002). Predictors of attrition in a longitudinal cognitive aging study: The Maastricht Aging Study (MAAS). *Journal of clinical epidemiology, 55*(3), 216-223. doi: 10.1016/s0895-4356(01)00473-5

van der Sluis, F. J., Buisman, P. L., Meerdink, M., Wouter, B., van Etten, B., de Bock, G. H., ... & Pol, R. A. (2017). Risk factors for postoperative delirium after colorectal operation. *Surgery, 161*(3), 704-711. doi: 10.1016/j.surg.2016.09.010

van Meenen, L. C., van Meenen, D. M., de Rooij, S. E., & ter Riet, G. (2014). Risk prediction models for postoperative delirium: a systematic review and meta-analysis. *Journal of the American Geriatrics Society, 62*(12), 2383-2390. doi: 10.1111/jgs.13138

van Steenoven, I., Aarsland, D., Hurtig, H., Chen-Plotkin, A., Duda, J. E., Rick, J., ... & Weintraub, D. (2014). Conversion between mini-mental state examination, montreal cognitive assessment, and dementia rating scale-2 scores in Parkinson's disease. *Movement Disorders, 29*(14), 1809-1815. doi: 10.1002/mds.26062

Vasilevskis, E. E., Morandi, A., Boehm, L., Pandharipande, P. P., Girard, T. D., Jackson, J. C., ... & Wesley Ely, E. (2011). Delirium and sedation recognition using validated instruments: reliability of bedside intensive care unit nursing assessments from 2007 to 2010. *Journal of the American Geriatrics Society, 59*, S249-S255. doi: 10.1111/j.1532-5415.2011.03673.x

Vasilevskis, E. E., Han, J. H., Hughes, C. G., & Ely, E. W. (2012). Epidemiology and risk factors for delirium across hospital settings. *Best practice & research Clinical anaesthesiology, 26*(3), 277-287. doi: 10.1016/j.bpa.2012.07.003

Veliz-Reissmüller, G., Torres, H. A., van der Linden, J., Lindblom, D., & Jönhagen, M. E. (2007). Pre-operative mild cognitive dysfunction predicts risk for post-operative delirium after elective cardiac surgery. *Aging clinical and experimental research, 19*, 172-177. doi: 10.1007/BF03324686.

Vlisides, P. E., Vogt, K. M., Pal, D., Schnell, E., Armstead, W. M., Brambrink, A. M., ... & Koerner, I. P. (2021). Roadmap for conducting neuroscience research in the COVID-19 era and beyond: recommendations from the SNACC Research Committee. *Journal of neurosurgical anesthesiology, 33*(2), 100-106. doi: 10.1097/ANA.0000000000000758

Vogels, R. L., Scheltens, P., Schroeder-Tanka, J. M., & Weinstein, H. C. (2007). Cognitive impairment in heart failure: a systematic review of the literature. *European journal of heart failure, 9*(5), 440-449. doi: 10.1016/j.ejheart.2006.11.001

Wang, T. J., Larson, M. G., Levy, D., Vasan, R. S., Leip, E. P., Wolf, P. A., ... & Benjamin, E. J. (2003). Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation, 107*(23), 2920-2925. doi: 10.1161/01.CIR.0000072767.89944.6E

Wang, Y. Y., Yue, J. R., Xie, D. M., Carter, P., Li, Q. L., Gartaganis, S. L., ... & Inouye, S. K. (2020). Effect of the tailored, family-involved hospital elder life program on postoperative delirium and function in older adults: a randomized clinical trial. *JAMA internal medicine, 180*(1), 17-25. doi: 10.1001/jamainternmed.2019.4446

Wechsler D. *Wechsler Adult Intelligence Scale–Revised Manual.* (1981). New York, NY: Psychological Corporation.

Weissberger, G. H., Strong, J. V., Stefanidis, K. B., Summers, M. J., Bondi, M. W., & Stricker, N. H. (2017). Diagnostic accuracy of memory measures in Alzheimer's dementia and mild cognitive impairment: a systematic review and meta-analysis. *Neuropsychology review, 27*, 354-388. doi: 10.1007/s11065-017-9360-6

Weng, S. F., Reps, J., Kai, J., Garibaldi, J. M., & Qureshi, N. (2017). Can machine-learning improve cardiovascular risk prediction using routine clinical data?. *PloS one, 12*(4), e0174944. doi: 10.1371/journal.pone.0174944

Wessler, B. S., Nelson, J., Park, J. G., McGinnes, H., Gulati, G., Brazil, R., ... & Kent, D. M. (2021). External validations of cardiovascular clinical prediction models: a large-scale review of the literature. *Circulation: Cardiovascular Quality and Outcomes, 14*(8), e007858. doi: 10.1161/CIRCOUTCOMES.121.007858

Whitlock, E. L., Vannucci, A., & Avidan, M. S. (2011). Postoperative delirium. *Minerva anestesiologica, 77*(4), 448-456.

Wiggins, M., Arias, F., Urman, R. D., Richman, D. C., Sweitzer, B. J., Edwards, A. F., ... & Price, C. (2020). Common neurodegenerative disorders in the perioperative setting: recommendations for screening from the Society for Perioperative Assessment and Quality Improvement (SPAQI). *Perioperative care and operating room management, 20*, 100092. doi: 10.1016/j.pcorm.2020.100092

Williams, S. T., Dhesi, J. K., & Partridge, J. S. (2020). Distress in delirium: causes, assessment and management. *European Geriatric Medicine, 11*(1), 63-70. doi: 10.1007/s41999-019-00276-z

Wilson, J. E., Mart, M. F., Cunningham, C., Shehabi, Y., Girard, T. D., MacLullich, A. M., ... & Ely, E. (2020). Delirium. *Nature Reviews Disease Primers, 6*(1), 1-26. doi: 10.1038/s41572-020-00223-4

Wong, A., Black, S. E., Yiu, S. Y., Au, L. W., Lau, A. Y., Soo, Y. O., ... & Mok, V. C. (2018). Converting MMSE to MoCA and MoCA 5-minute protocol in an educationally heterogeneous sample with stroke or transient ischemic attack. *International journal of geriatric psychiatry, 33*(5), 729-734. doi: 10.1002/gps.4846

Wong, C. K., van Munster, B. C., Hatseras, A., van Leeuwen, B. L., de Rooij, S. E., & Pleijhuis, R. G. (2022). Head-to-head comparison of 14 prediction models for postoperative delirium in elderly non-ICU patients: an external validation study. *BMJ open, 12*(4), e054023. doi: 10.1136/bmjopen-2021-054023

Wolf, P. A., D'Agostino, R. B., Belanger, A. J., & Kannel, W. B. (1991). Probability of stroke: a risk profile from the Framingham Study. *Stroke, 22*(3), 312-318. doi: 10.1161/01.str.22.3.312

World Health Organization. (2023). Ageing and health. Retrieved March 16, 2023, from https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

Wueest, A. S., Zuber, P., Coslovsky, M., Rommers, N., Rodondi, N., Gencer, B., Moschovitis, G., De Perna, M. L., Beer, J. H., Reichlin, T., Krisai, P., Springer, A., Conen, D., Stauber, A., Mueller, A. S., Paladini, R. E., Kuehne, M., Osswald, S., Monsch, A. U., Bonati, L. H., & Swiss-AF Study Investigators. (2023). Mid-term Changes in Cognitive Functions in Patients with Atrial Fibrillation: A Longitudinal Analysis of the Swiss-AF Cohort. *Frontiers in Cardiovascular Medicine*, (under review)

Wueest, A. S., Berres, M., Bettex, D. A., Steiner, L. A., Monsch, A. U., & Goettel, N. (2023). Independent External Validation of a Preoperative Prediction Model for Delirium After Cardiac Surgery: A Prospective Observational Cohort Study. Journal of Cardiothoracic and Vascular Anesthesia, 37(3), 415-422.

Yaffe, K. (2017). Modifiable risk factors and prevention of dementia: what is the latest evidence? *JAMA Intern Med.; 178*(2), 281-282. doi: 10.1001/jamainternmed.2017.7299

Yang, H., Yim, D., & Park, M. H. (2021). Converting from the Montreal cognitive assessment to the Mini-mental state Examination-2. *PLoS One, 16*(7), e0254055. doi: 10.1371/journal.pone.0254055

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1982). Development and validation of a geriatric depression screening scale: a preliminary report. *Journal of psychiatric research, 17*(1), 37-49. doi: 10.1016/0022-3956(82)90033-4

Yu, R. L., Lee, W. J., Li, J. Y., Chang, Y. Y., Chen, C. C., Lin, J. J., ... & Fuh, J. L. (2020). Evaluating mild cognitive dysfunction in patients with Parkinson's disease in clinical practice in Taiwan. *Scientific reports, 10*(1), 1-9. doi: 10.1038/s41598-020-58042-2

Zehnder, A. E., Bläsi, S., Berres, M., Spiegel, R., & Monsch, A. U. (2007). Lack of practice effects on neuropsychological tests as early cognitive markers of Alzheimer disease?. *American Journal of Alzheimer's Disease & Other Dementias®*, *22*(5), 416-426. doi: 10.1177/1533317507302448

Zuin, M., Roncon, L., Passaro, A., Bosi, C., Cervellati, C., & Zuliani, G. (2021). Risk of dementia in patients with atrial fibrillation: Short versus long follow-up. A systematic review and meta-analysis. *International journal of geriatric psychiatry, 36*(10), 1488-1500. doi: 10.1002/gps.5582

Curriculum vitae

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Professional Experience

Since 06/2020	**PhD Student in Neuropsychology** Memory Clinic, University Department of Geriatric Medicine FELIX PLATTER, Basel Department of Anesthesia, University Hospital Basel
09/2017-05/2020	**PhD Student in Clinical Psychology and Psychotherapy Research** University of Zurich
03/2017-09/2017	**Assistant Psychologist** Klinik Wysshölzli, Bern
06/2016-07/2016	**Clinical Internship** Department of Psychosomatic Medicine, Charité Campus Benjamin Franklin, Berlin
01/2016-03/2016	**Clinical Internship** Klinik Schützen, Rheinfelden
03/2015-05/2016	**Research Assistant** Department of Clinical Psychology and Epidemiology, Faculty of Psychology, University of Basel
01/2014-04/2014	**Research and Clinical Internship** Department of Gynecological Social Medicine and Psychosomatics, University Hospital Basel

Education

09/2020-10/2022	**Diploma of Advanced Studies (DAS) in Neuropsychology** University of Zurich, Switzerland
08/2016-N/A	**Master of advanced studies (MAS) in psychotherapy with a cognitive-behavioral focus** University of Basel, Switzerland
08/2014-07/2016	**Master of Science in Psychology** University of Basel, Switzerland Clinical Psychology and Cognitive Neuroscience
08/2011-07/2014	**Bachelor of Science in Psychology** University of Basel, Switzerland

Project work

- Validation study in patients with mild or major neurocognitive disorder predominantly due to Alzheimer`s disease using of a novel self-administered cognitive assessment tool (CogCheck)
- Validation studies on delirium-risk-prediction after cardiac surgery (Rudolph et al. Score, 2009 and CogCheck)
- European prospective one day cohort study of frailty incidence in surgical European patients (FRAGILE)
- Advisory role in the following two projects:
    - Impact of personalised cardiac anaesthesia and cerebral autoregulation on neurological outcomes in patients undergoing cardiac surgery (PRECISION) (Project leader: Dr. Nuno V. Gomes, MD)
    - Association of intraoperative blood pressure excursions below cerebral autoregulatory boundaries with organ injury following major noncardiac surgery (Project leader: Dr. Patrick M. Wanner, MD)
- Assist in writing a book chapter (Delir-Scores) in an upcoming book (in: Carsten Hermes (Hrsg.), Delir, Deutschland: Elsevier))
- Assist with writing a review article (Diagnosing delirium in perioperative and intensive care medicine) in current opinion in anesthesiology

Publication

- Rickenbacher, M., Reinbold, C. S., Herms, S., Hoffmann, P., Cichon, S., **Wueest, A. S.**, ... & Goettel, N. (2022). Genome-wide association study of postoperative cognitive dysfunction in older surgical patients. *Journal of neurosurgical anesthesiology*, *34*(2), 248-250.

Conference Poster

- **Wueest, A. S.**, Fasnacht, J. S., Berres, M., Thomann, A. E., Krumm, S., Gutbrod, K., Steiner, L. A., Goettel, N., Monsch, A. U. *Conversion between the Montreal Cognitive Assessment and the Mini-Mental Status Examination.* German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN) Annual Meeting 2022, Berlin, Germany.

Presentations

05/2023: *Vorhofflimmern und Kognition*, Memory Clinic Seminars; University Department of Geriatric Medicine FELIX PLATTER, Basel

02/2023: *Postopoeratives Delir*; Forschung Neuroanästhesie; Department of Anesthesia, University Hospital Basel

05/2022: *CogCheck- eine Zwischenevaluation*; Memory Clinic Seminars; University Department of Geriatric Medicine FELIX PLATTER, Basel

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