Increasing use of cognitive measures in the operational definition of frailty-A systematic review

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Increasing use of cognitive measures in the operational definition of frailty – a systematic review.

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Abstract

Ageing is associated both with frailty and cognitive decline. The quest for a unifying approach has led to a new concept: cognitive frailty. This systematic review explores the contribution of cognitive assessment in frailty operationalization.

PubMed, Web of Knowledge and PsycINFO were searched until December 2016 using the keywords *aged; frail elderly*; *aged, 80 and over*; *frailty*; *diagnosis*; *risk assessment* and *classification*, yielding 2,863 hits. Seventy-nine articles were included, describing 94 frailty instruments. Two instruments were not sufficiently specified and excluded. 46% of the identified frailty instruments included cognition. Of these, 85% were published after 2010, with a significant difference for publication date ($X^2 = 8.45$, $p < 0.05$), indicating increasing awareness of the contribution of cognitive deficits to functional decline. This review identified 7 methods of cognitive assessment: dementia as co-morbidity; objective cognitive-screening instruments; self-reported; specific signs and symptoms; delirium/clouding of consciousness; non-specific cognitive terms and mixed assessments.

Although cognitive assessment has been increasingly integrated in recently published frailty instruments, this has been heterogeneously operationalized. Once the domains most strongly linked to functional decline will have been identified and operationalized, this will be the groundwork for the identification of reversible components, and for the development of preventive interventional strategies.

Keywords
Cognition; frailty operationalization; elderly; dementia; cognitive frailty; aged

1. Introduction

Worldwide the proportion of the oldest old (80 years and over) is growing faster than that of any other age group. Moreover, their proportion is expected to triple between 2015 and 2050. (United Nations, 2015) (United Nations, 2015) (United Nations, 2015) This demographic tendency has medical, social, economic and political implications, which need to be addressed as soon as possible in order to prevent future imperilments (United Nations, 2015). In this context, research on physical frailty has become a popular topic in recent years. The concept of physical frailty refers to a dynamic, age-related condition characterized by a decline beyond a certain threshold in the reserve capacity of multiple inter-related physiological systems leading to decreased resistance to stressors and an increased risk for adverse health outcomes such as diminished mobility, falls, functional decline, institutionalization, hospitalization and death (Fried et al., 2001; Fulop et al., 2010; Gobbens et al., 2010a). Furthermore, with an increasingly aged population, cognitive decline and its costly personal and societal consequences are also a cause for concern. As people age, a decline is noted in their executive functions, speed of information processing, reasoning, and certain aspects of memory, which threatens their independent functioning (Deary et al., 2009). Since advancing age is associated with both physical frailty and cognitive decline their co-existence in an individual might be related to a common underlying ageing-related process (Morley, 2015) which amongst others targets the central nervous, metabolic, endocrine and cardiovascular systems in addition to inflammation.

From a scientific, clinical, public health and economical points of view, the first step in frailty management is its identification. To date, there is a myriad of conceptual definitions and operationalization of frailty (Azzopardi et al., 2016). However, there are two leading yet contrasting models of frailty operationalization. The *first* model, the Fried's Frailty Phenotype, perceives frailty as a geriatric syndrome consisting of signs and symptoms pertaining exclusively to the physical domain. It is based on 5 criteria, i.e. unintentional weight loss, self-reported exhaustion, slowness (walking speed), muscle strength (hand grip strength) and physical activity. The absence of such criteria indicates robustness, the pre-frail (subclinical) state is defined by the presence of 1 or 2 criteria and ultimately frailty is determined by the presence of 3 or

more criteria. Furthermore, according to the founder of this model, multimorbidity – the co-existence of 2 or more chronic conditions – is a potential risk factor for the development of pre-frailty and frailty due to common underlying pathophysiology (Fried et al., 2001) as well as due to enhanced decline in the reserve capacity of multiple physiological systems (Ruan et al., 2015). Akin to frailty, the prevalence of multimorbidity rises markedly with advancing age from 62.4% in the 65-74 years age group to 76.2% in the over 85 years age group (Rocca et al., 2014). In a study involving senior adults aged 70 years and older, the prevalence of frailty was higher in older men with cardiovascular disease and diabetes (Bartley et al., 2016). Furthermore, in frail older adults, the prevalence of multimorbidity increases dramatically over time (Chamberlain et al., 2016). This highlights the importance of managing underlying conditions, particularly cardiovascular disease, as well as preventing the development of further comorbidities when considering interventions to delay the onset of frailty.

The *second* leading model of frailty operationalization is the Rockwood frailty index, a mathematical model characterized by an accumulation of health deficits across multiple domains including medical, functional, and psychosocial aspects (Rockwood et al., 2005). As long as the health deficits include variables associated with the health status, cover a spectrum of bio-physiological systems, have prevalence increasing with age and do not saturate easily, then, it is the number of deficits rather than their nature which counts. The frailty status is determined by calculating the ratio of health deficits present to the total potential health deficits such that the total score is a continuum between 0 and 1 and a score of 0.2 is suggestive of approaching the frail state (Searle et al., 2008).

Focusing solely on the physical aspects of frailty has negative implications as holistic care may be jeopardized (Gobbens et al., 2010a). In the quest for a resolution of the consequences of this issue, a group of experts consensually developed an integral operational definition of frailty which in addition to physical aspects - such as strength, balance, endurance, mobility and physical activity- also includes nutrition and cognition (Gobbens et al., 2010b). Moreover, in a systematic review published in 2011, the authors corroborate that cognition is one of the most important elements in the identification of frailty (Sternberg et al., 2011). As shown below, the relationship between cognitive impairments and physical frailty has been evaluated in studies of

criterion validity (concurrent and predictive). In a relatively recently published review, the authors analyzed the association between physical frailty and cognitive impairment in both cross-sectional and longitudinal studies (Robertson et al., 2014). In the French Three-City Study involving community-dwelling participants aged 65 years and older, the authors demonstrated that using Fried's frailty criteria (Fried et al., 2001), the percentage of individuals identified with cognitive impairment (defined by the lowest quartile on the Mini Mental State Examination and Isaacs Set Test) was 22% in frail subjects, compared to 12% and 10% in pre-frail and robust individuals respectively. Furthermore, in the same study it was shown that subjects with coexisting cognitive impairment and physical frailty were at an increased risk for the development of adverse health outcomes, implying that cognitive impairment improves the predictive validity of Fried's Frailty Phenotype (Avila-Funes et al., 2009). In the Brazilian FIBRA study it was shown that subjects identified as frail using Fried's model performed worse on the MMSE and the authors suggested the inclusion of cognitive assessment into frailty operationalization (Macuco et al., 2012). This association has also been demonstrated using Rockwood's cumulative health deficit model: frail participants were less subject to stabilization or improvement of cognitive deficits (assessed using the modified MMSE score). Cognitive improvement was observed in 23.9% of non-frail individuals compared to 13.4% in frail individuals (Mitnitski et al., 2011). In a cross-sectional study focusing on older females in Korea, it was reported that subjects with slower walking speed and weakened hand grip strength had lower scores on the Korean version of the Montreal Cognitive Assessment test (Kang et al., 2016). In addition, several longitudinal studies have shown the predictive effect of physical frailty measures on cognitive decline or incident dementia and vice versa (Auyeung et al., 2011; Boyle et al., 2010; Clouston et al., 2013; Robertson et al., 2014; Samper-Ternent et al., 2008; Shim et al., 2011). In contrast, a study analyzing the relationship among seven frailty domains (methodology replicated in three different studies involving elderly populations for consistency), showed that the cognitive domain might not belong to this multi-dimensional frailty concept. Alternatively it could be that in these studies global cognitive impairment was assessed rather than specific cognitive domains such as executive function and processing speed necessary for frailty identification (Sourial et al., 2010). Recent studies have focused on cognitive frailty operationalisation. The findings from a systematic review analyzing the psychometric properties of the

measurements of cognitive frailty (published from 2013 onwards) reflect that an association exists between physical frailty and cognitive decline but currently a valid and reliable operational definition of cognitive frailty is lacking (Sargent and Brown, 2017). Going a step further, a recent study analysed the prediction of different cognitive frailty models to the development of several cognitive outcomes such as late-life cognitive decline, Alzheimer dementia and vascular dementia and noted several discrepancies potentially due to diversity in their operationalisation (Panza et al., 2017). Challenging the cognitive frailty construct is the *Motor Cognitive Risk* syndrome whereby slow gait (a single component of the frailty phenotype) in the presence of cognitive complaints is associated with an advanced risk of progression to dementia (Verghese et al., 2014). In the Gait and Brain study the risk of progression to dementia in three distinct groups - physical frailty alone versus classical cognitive frailty versus the combination of slow gait and objective cognitive impairment – was assessed and it was concluded that the risk is superior in the latter group. This may suggest that physical frailty and cognitive impairment rather than being a unique phenotype known as the cognitive frailty construct, represent two outcomes of a fundamental pathogenic mechanism possibly affecting neural network related to executive function (Montero-Odasso et al., 2016).

The emerging concept of cognitive frailty has gone through various stages in recent years. In 2013, an international consensus group (International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics) suggested an initial definition for the evolving concept of cognitive frailty. It is an umbrella term for the co-occurrence of physical frailty and mild cognitive impairment (defined by a score equal to 0.5 on the clinical dementia rating (CDR)) in the absence of Alzheimer dementia (AD) or other dementias. Cognitive frailty, in parallel with physical frailty has the potential to be reversible (Kelaiditi et al., 2013). Although this concept may allow for the study of aggregate risk, the drawback is that it may hamper the investigation of potentially distinct sources of impairment. More recently this definition has been further elaborated. In 2014, pre-physical frailty was added as a criterion to the definition of cognitive frailty (Dartigues and Amieva, 2014). In addition, in 2015, other authors stated that there are two subtypes of cognitive frailty (Ruan et al., 2015), namely the *reversible* and the *potentially reversible* subtypes. The *reversible* type refers to subjective cognitive decline (SCD) whereby older adults have altered subjective cognitive function but normal performance on cognitive tests.

These individuals have a CDR score of <0.5 (Jessen et al., 2014). The *potentially reversible* type refers to the classical mild cognitive impairment (MCI) stage with a CDR score of 0.5. Pre-physical frailty and subjective cognitive decline being reversible play a significant role in the prevention of frailty. This is a strong argument for the inclusion of cognitive assessment in frailty instruments. Furthermore, in a recent paper the authors highlighted the importance of the chronological development of physical frailty followed by cognitive decline to distinguish the entity of cognitive frailty from other cognitive deteriorations independent of physical dysfunction (Canevelli and Cesari, 2015).

The purpose of this systematic review is to compile an itinerary of the role of cognitive dysfunction in the operationalization of frailty and then to analyze the way in which cognition is evaluated in the related instruments. This is to determine if there has been a shift in recent years in the weight of cognitive measures in frailty operationalization. Although recently several systematic reviews have explored the relationship between cognition and frailty (Canevelli et al., 2015) (Brigola et al., 2015), to the best of the authors' knowledge, this study, which focuses specifically on cognitive inclusion and operationalization in the available frailty instruments is unprecedented.

2. Methodology

2.1 Literature search

The following combination of keywords ("Aged"[Mesh] OR "Frail Elderly"[Mesh] OR "Aged, 80 and over"[Mesh]) AND Frailty AND ("Diagnosis"[Mesh] OR "Risk Assessment"[Mesh] OR "Classification"[Mesh]) was used to search for articles related to frailty instruments in the electronic databases PubMed, Web of Knowledge and PsycINFO. The search was performed for articles published until December 2016. Articles written in English, Dutch, French or German; studies involving participants who are 65 years and older at baseline, independent of their ethnicity or living circumstances; articles describing the development and clinimetric properties of original and modified frailty instruments and articles comparing frailty instruments were included. Comments to other articles, letters to editors, reviews and systematic

reviews were excluded. Two independent researchers assessed the eligibility of articles for inclusion in this systematic review - in case of disagreement a third researcher was involved and the article included only if consensual agreement was achieved.

2.2 Data analysis

The statistical package of SPSS (version 24.0) was used. The relationship between inclusion of cognition in frailty operationalization and date of article publication was analyzed using the Chi square test of independence.

3. Results

3.1 Literature search

The literature search generated 2,863 potential articles: 1,407 in PubMed, 1,424 in Web of Knowledge and 32 in PsycINFO out of which 37 articles were found to be duplicate and thus eliminated. Three hundred and thirty-two potential articles were retained based on their titles and abstracts. Ultimately, based on the full-text, 79 articles were included in this systematic review.

The literature search identified an itinerary of 94 original or modified frailty instruments. The characteristics of the individual frailty instruments, published till 2014 (including study populations, domains assessed in frailty identification, scoring systems applied, objective versus self-reported methods of frailty identification and reported prevalence of frailty) have been laboriously described in a systematic review published in 2016 by our research group-the Gerontopole Brussels Study group (Azzopardi et al., 2016).

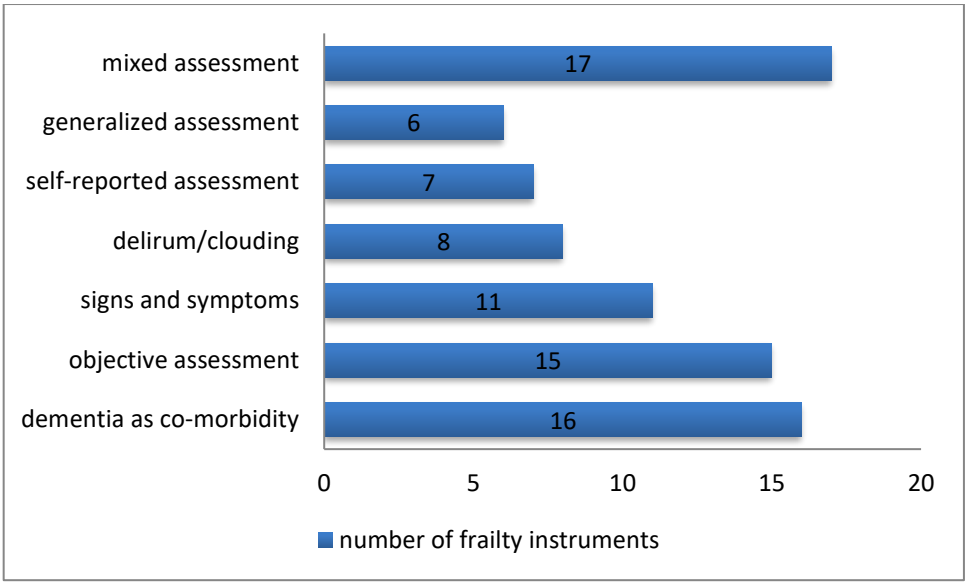
An overview of these frailty instruments is present in Table A.1 (in Appendix). Two of these instruments had items which were not sufficiently specified and thus were not included further in the results section: 38-item Burden model/ Health and Retirement Study HRS (Cigolle et al., 2009) and 43-item Frailty Index/ Conselice Study of Brain Aging (Lucicesare et al., 2010).

3.2 Data analysis

Out of the remaining 92 instruments, 46% (n=42) included a cognitive component in the operationalization of frailty while 54% (n=50) did not. Taking into account those frailty instruments excluding a cognitive domain, 42% (n=22) were published in ≤ 2010 and 58% (n=29) were published after 2010. On the other hand the majority of frailty instruments inclusive of a cognitive domain, 86% (n=36), were published after 2010. The year 2010 has been used as a benchmark for two main reasons - first, in 2010 an integral conceptual frailty definition including the cognitive domain was consensually developed by a group of experts (Gobbens et al., 2010a, b) and secondly, a systematic review of the frailty instruments carried out in 2011 showed that cognition is one of the important domains for frailty identification (Sternberg et al., 2011). Based on the result of the chi square test of independence, the relation between inclusion of cognitive domain in frailty operationalization and study publication date was significant, $X^2 = 8.45$, $p < 0.05$.

Noteworthy, when considering the publication date of modified frailty instruments, we acknowledged the date of the retrieved and included study rather than that of the original paper. Since the objective of this paper is to explore the current state of the inclusion of cognitive assessment in frailty identification the latest modified versions of the original scales were taken into account.

Various ways have been used to evaluate cognitive functioning in the frailty instruments (see Appendix Table A.1 for an overview). This review has identified 7 main sub-groups of cognitive assessment (see Figure 1). The most commonly used way of cognitive evaluation, 38% (n=16), is the presence of dementia or Alzheimer's disease as co-morbidity. The subsequent sub-group consists of objective cognitive-evaluative instruments, 36% (n=15), whereby 8 different cognitive tests have been identified (see Table 1 for more details concerning the cognitive domains assessed). Next sub-group of cognitive evaluation, 26% (n=11), involves the presence of signs and symptoms of cognitive dysfunction. The ensuing cognitive sub-group, 19% (n=8), demands for the presence of clouding or delirium. Penultimately, 17% (n=7) use self-reported cognitiveassessments. Ultimately, the least frequent way to assess cognition, 14% (n=6), involves the use of generalized cognitive dysfunction terms. Interestingly, in 40% (n=17) of the frailty instruments, which evaluate cognition, multiple methods of cognitive assessments have been used.



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239 **Figure 1**: Methods of cognitive assessment in the identified frailty instruments

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Objective assessment of cognition	**Frequency of cognitive test used**	**Cognitive functions evaluated**
MMSE (Folstein et al., 1975)	8	Orientation, registration, attention and calculation, recall, language, copying
Mini-Cog (Borson et al., 2003)	1	Recall, clock-drawing
CAPE (Pattie and Gilleard, 1976)	1	Orientation to time and place, remote and recent memory
TICS (Brandt et al., 1988)	1	Orientation, attention (counting backwards and serial sevens), recall, memory, calculation, abstraction (finding opposites), language, praxis
SPMSQ (Pfeiffer, 1975)	1	Short and long term memory, orientation, calculation
CSID (Chan et al., 2003)	1	Short and long term memory, language, attention, speed of processing, cultural experience, visual processing/visual context, orientation

Date	1	Orientation to time
6-CIT (Brooke and Bullock, 1999)	1	Orientation to time, recall, counting backwards, months of the year in reverse

Table 1: Objective methods of cognitive assessment

Mini-mental state examination *MMSE*; *Mini-cog*; Clifton Assessment Procedures for the Elderly (information/orientation subscale) *CAPE*; Telephone Interview for Cognitive status *TICS*; Short portable mental status questionnaire *SPMSQ*; Cognitive screening instrument for dementia *CSID*; 6-item cognitive impairment test *6-CIT*.

4. Discussion

4.1 Cognitive frailty

This systematic review aims to put into perspective the trend of assessing the cognitive domain within the identified frailty instruments.

The results of this review clearly show that the number of frailty instruments excluding a cognitive domain outnumber those, which include a cognitive domain. Notwithstanding the apparent conflict with the available evidence, which supports the association between physical frailty and cognitive decline, more detailed analysis shows that frailty instruments including cognitive assessment are the most recent ones and have been published after 2010. This seems to fit within the more novel vision that physical frailty and cognitive impairment might co-occur (Arts et al., 2016; Gross et al., 2016; Kelaiditi et al., 2013). This groundwork might point to the fact that physical frailty scores may predict cognitive evolution - an argument in favor of the frailty instruments, which exclude specific cognitive assessment in frailty identification. This is counter-acted by the evidence from longitudinal studies, which demonstrate that the addition of cognitive assessment in frailty operationalization improves its predictive validity for adverse health outcomes (Avila-Funes et al., 2009; Jha et al., 2016).

4.1.1 Definition of concept

Although publications related to the operationalization of physical frailty have started in the 1980s it is only in the 21st century that this tendency has picked up momentum. Despite the vast array of frailty instruments proposed in the literature and consensual expert meetings, a gold standard frailty instrument is regretfully still lacking (Azzopardi et al., 2016).

Even more enigmatic and yet evolving is the recently introduced concept of cognitive frailty. Fundamentally, it is characterized by the co-occurrence or incidence of physical frailty and cognitive impairment in individuals without dementia (Kelaiditi et al., 2013). More recently adaptations have been proposed to this initial framework mainly to include pre-physical frailty and subjective cognitive decline (SCD), which may precede (Ruan et al., 2015) and may be more readily reversible, which is a fundamental aspect of frailty. In clinical practice this parallel association has two very important implications: first, older adults identified with physical frailty may be at an increased risk for the development of cognitive impairment and vice-versa; and second, considering that there are potential common underlying pathophysiological mechanisms (as described below), interventions aimed at managing physical frailty may be successful in managing the cognitive aspect as well (Robertson et al., 2014). On the other hand, although geriatric interventions are usually multi-disciplinary, unsuccessful interventions in older individuals might be due to unrecognized cognitive frailty which increases their vulnerability (i.e. due to non-adherence to proposed healthy life-styles and treatment or less flexible coping mechanisms in relation to stressors (Canevelli et al., 2015)) - and at the same time underlines the unquestionable need to be managed holistically (Buchman and Bennett, 2013).

4.1.2 Pathogenesis

Several reviews have explored the potential multi-factorial pathways or mechanisms linking purely physical frailty with cognitive decline (Halil et al., 2015; Morley, 2015; Robertson et al., 2014). Physical frailty may precede or else be an outcome of cognitive impairment (Godin et al., 2017) suggesting that the latter may either be an independent risk factor for the development of physical frailty or may share a common underlying causal pathway. Deficits in a range of bio-physiological systems as well as inflammation constitute a key part in the pathogenesis of physical frailty as well as cognitive decline.

303 *First*, the contribution of the central nervous system to the development of cognitive
304 frailty is well documented. In the Rush memory and Aging project, the authors found
305 a link between Alzheimer dementia pathology (neurofibrillary tangles and plaques)
306 and the presence of physical frailty (identified by using grip strength, fatigue, walking
307 speed and body composition) 6 months before death in individuals with and without
308 dementia (Buchman et al., 2008).
309 *Second*, the endocrine system also features in this complex framework involving
310 decrease of several hormones with age and so has been implicated in the link between
311 physical frailty and cognitive decline. Testosterone offers protective cognitive effects
312 by increasing synapse plasticity at the hippocampus and by controlling the
313 accumulation of amyloid beta protein (Gouras et al., 2000; Maggio et al., 2012).
314 Furthermore low testosterone is associated with sarcopenia which is a key factor in
315 the development of physical frailty (Muller et al.). Similarly, low levels of growth
316 hormone have been associated with increasing physical frailty (Nass and Thorner,
317 2002) and cognitive decline (Leng et al., 2004; Nass and Thorner, 2002; Nyberg and
318 Hallberg, 2013). On the contrary, a positive correlation has been documented between
319 high levels of cortisol - a stress hormone - and physical frailty (Varadhan et al., 2008)
320 as well as with cognitive decline (Lee et al., 2007). Along the same lines, insulin
321 resistance and diabetes mellitus have been linked to neuronal damage (Neumann et
322 al., 2008). In a study assessing the relationship between hyperinsulinism and cognitive
323 dysfunction in an older cohort, an association was found between insulin resistance
324 and delayed memory (Zhong et al., 2012). Insulin resistance has also been associated
325 with incident frailty (Barzilay et al., 2007).
326 *Another* proposed mechanism underlying the parallel relationship between physical
327 frailty and cognitive decline involves cardiovascular risk factors. Cardiovascular
328 disease is a risk factor for the development of physical frailty (Afilalo et al., 2009;
329 Fried et al., 2001) as well as for cerebrovascular diseases, which in turn lead to
330 cognitive decline. The common denominator is that atherosclerotic disease or embolic
331 events lead to reduced blood flow to the brain, skeletal muscle, the heart and the
332 kidneys leading to cognitive decline and frailty (Halil et al., 2015).
333 *Additionally*, nutrition plays an essential part in this complex interplay involving
334 several physiological systems. This is not surprising considering that unintentional
335 weight loss is one of the 5 prime components of Fried's frailty phenotype (Fried et al.,
336 2001). A diet rich in anti-oxidants such as the Mediterranean diet has been linked to

lower frailty states and better cognitive functions (Mulero et al., 2011). Moreover, female individuals with cognitive impairment may have behavioral changes in relation to nutrition in the sense that they will forget to eat and have increased apathy, which may lead to reduced fat mass and weight loss (Wirth et al., 2011).

Ultimately, an important process affiliated to the pathogenesis of cognitive frailty is inflammation. Older age is associated with chronic inflammation also known as inflammaging. The prolonged exposure of the brain to circulating inflammatory markers is associated with cognitive decline (Aktas et al., 2007; Baune et al., 2008; Rosano et al., 2012). Likewise, inflammation has also been identified as a determinant of physical frailty (Hubbard and Woodhouse, 2010). In a study focusing only on females, inflammation was identified as a potential underlying cause for the association between sarcopenia and cognitive decline (Canon and Crimmins, 2011).

4.1.3 Operationalization

The frailty instruments inclusive of a cognitive evaluation have been studied in various cohorts aged 65 years and older including community-dwellers, nursing home residents, medical in-patients, emergency departments and surgical patients. Although, as discussed previously, there seems to be a general agreement on the correlation between physical frailty and cognitive impairment, the same cannot be said about the operationalization of the cognitive domain. Our systematic review identified 7 different groups of cognitive assessment – dementia as co-morbidity, objective cognitive evaluativeinstruments, presence of signs and symptoms, self-reported cognitive-tests, presence of delirium/clouding of consciousness, generalized cognitive assessment and finally a combination of the previously mentioned assessments. Interestingly, more than one-third of the frailty instruments make use of a combination of cognitive assessments. This latter category of frailty instruments is composed solely of health deficit accumulation indexes.

In this review, consideration has been given to the content validity of cognitive frailty measures. When comparing the cognitive battery, which forms part of the available frailty instruments to the concept of cognitive frailty, several setbacks are noted implying that as yet cognitive frailty operationalization fails to meet the benchmark set by the concept of cognitive frailty.

First, despite the fact that the definition of cognitive frailty excludes the presence of cognitive co-morbidities such as dementia, our review shows that several of the

available frailty instruments operationalize cognitive decline by asking for the presence of established dementia or Alzheimer's disease which are irreversible conditions thus contradicting the foundations of the construct of cognitive frailty itself. Although less straightforward, the other forms of cognitive evaluations identified in this review, such as, the presence of signs or symptoms of cognitive decline and self-reported cognitive complaints vary in their potential to pick up cognitive deficits, which may be reversible.

Second point of interest is the inclusion of delirium/acute state of altered consciousness as a form of cognitive assessment. On the one hand, delirium may be a risk factor for the development of frailty since delirium and frailty share a common concept whereby physiological systems (more specifically the brain in the case of delirium) are unable to reach homeostasis in the event of acute systemic stressors (Quinlan et al., 2011); this may occur in previously cognitively intact individuals and a diagnosis of delirium will rule out dementia. On the other hand, individuals with existing cognitive impairment or established dementia are at an increased risk of delirium (Davis et al., 2015). Last but not least, cognitively intact individuals, who present with a delirium, are at increased risk of subsequently developing dementia (Davis et al., 2012; Setters and Solberg, 2017). Further research should aim to determine whether these three situations with respect to delirium have different predictive values. Therefore the inclusion of Alzheimer's disease and acute conditions such as delirium might dilute their utility as assessment tools for the evaluation of cognitive frailty and its outcomes such as disability.

Third, the temporal occurrence of cognitive deficits in relationship to physical frailty, that is, pre-existing (prevalent) versus acute concurrent (incident) cognitive deficits on a background of physical frailty should be considered. For example, the item 'history relevant to cognitive impairment or loss' from the Rockwood Frailty Index (Rockwood et al., 2005) implies pre-existing cognitive impairment whereas the item 'changes in general mental functions' from the same frailty instrument implies current cognitive changes. To be in harmony with the concept of cognitive frailty (proposed by the International Academy on Nutrition and Aging (I.A.N.A.) and the International Association of Gerontology and Geriatrics (I.A.G.G.), the presence of incident cognitive alterations should prevail in its operationalization.

An important finding in this review relates to the construct validity of the available frailty instruments. When it comes to deciding which cognitive assessment should be

included in the operationalization of cognitive frailty one should first consider the age-related changes that occur in certain cognitive domains. Processing speed, selective attention (the ability to focus on target information while ignoring distracting information) as well as divided attention (the ability to focus on several tasks at the same time) and executive function abilities are the most remarkably affected cognitive functions (Harada et al., 2013). It is understood that there is variability in the age-related changes that occur across all cognitive domains. A challenge posed by the cognitive criteria in the current frailty instruments is that certain objective cognitive assessments, such as the MMSE, evaluate global cognitive function, rather than cognitive domains specifically affected in cognitive frailty, and – for example – many times do not evaluate executive function. Another cognitive function, reduced sustained attention, has been linked to pre-frailty and frailty in community dwellers aged 50 years and older. It has been shown to be the mediator between executive function and pre/frailty (O'Halloran et al., 2014). On the other hand, some instruments focus on specific cognitive functions such as orientation, yet their contribution to cognitive frailty has not been explored. In a study comparing decline in specific cognitive domains in frail and non-frail elderly, the frail participants were found to perform worse in selective cognitive measures, namely executive function and processing speed (Langlois et al., 2012). This was also confirmed in a more recent study showing the association between impaired executive function (identified using Trail Making Test part B) and the development of physical frailty (Gross et al., 2016). There is substantial evidence pointing to deterioration in executive function as the prime underlying factor for these cognitive changes (Glisky, 2007). In a recent paper on the present limitations concerning the cognitive frailty construct, the authors propose the assessment of executive function in an attempt to distinguish cognitive frailty from purely neurological conditions such as Alzheimer's disease (Canevelli and Cesari, 2015). In a study involving community-dwellers aged 70 years and older the cognitive profiles of physically pre-frail or frail individuals (≥1 Fried frailty criteria and CDR=0); physically robust but cognitively impaired individuals (no Fried frailty criteria and CDR=0.5) and physically pre-frail or frail *and* cognitively impaired individuals also known as cognitively frail individuals (≥1 Fried frailty criteria and CDR=0.5) were compared to those of physically and cognitively robust individuals (no Fried frailty criteria and CDR=0). Older adults with cognitive frailty, in contrast to those with cognitive impairment without physical

frailty, showed impairments in several executive functions including processing speed, selective attention and mental flexibility. The authors noted that in cognitive frailty the neuropsychological profile is consistent with a subcortico-frontal cognitive pattern, which can be distinguished from the cortical neurodegenerative pattern attributable to Alzheimer's disease. This has led to the proposal (Delrieu et al., 2016) of several cognitive screening assessments in physically frail individuals such as the Frontal Assessment battery (Dubois et al., 2000), 5 words test (Dubois et al., 2002) as well as cognitive diagnostic tests such as Trail making Test A and B (Reitan, 1958), FCRST (free and cued selective reminding tests)(Grober et al., 1988), Digit Symbol Substitution subtest of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) and verbal fluencies (Cardebat et al., 1990).

4.2 Strengths and limitations

One of the limitations of our study is that some frailty instruments might have been missed given the fact that one of the eligibility criteria for inclusion in this systematic review was an age limit of 65 years and older. However, the main scope of this study was to evaluate the representation of cognitive dysfunction in operationalization of frailty specifically in older people.

A strength of this study is that our literature search identified frailty instruments published until December 2016. Consequently, our results reflect the present situation regarding the role of cognitive assessment in the identification of frailty.

Conclusion

The concept of cognitive frailty is a complex multi-factorial phenotype characterized by the co-occurrence of physical pre-frailty and subclinical cognitive impairment and so is potentially reversible. Our review shows that only 46% of the identified frailty instruments include a cognitive measure in the operationalization of frailty, however, recent instruments, published after 2010, include cognitive assessment in 86% of the scales. However, in the assessment of cognitive decline, a heterogeneous array of cognitive tests has been identified. It appears that unlike the physical frailty measures, cognitive measures included in the available frailty instruments do not adequately address the concept of cognitive frailty. Only one of the identified frailty instruments

(Simple Frailty Score) measures executive dysfunction (by using the Mini-cog) even though it is believed to precede decline in all other cognitive functions. Based on this review, the authors propose that cognitive frailty operationalization, in addition to the identification of physical frailty (using Fried's or Rockwood's model), should also target cognitive impairment by including evaluation of subtle cognitive deficits in executive function, memory and attention whilst omitting the cognitive criterion of established dementia. Furthermore the predictive effect of acute changes such as delirium require further investigation as to their added value in predicting cognitive frailty.

We suggest that future studies focus their research on the practicality of this novel concept – first by identifying the cognitive domain/s affected in cognitive frailty followed by the standardization of the operationalization of cognitive frailty.

In conclusion the standardized operationalization of cognitive frailty - a unifying clinical entity which may holistically portray the trajectories involved in the ageing process - will be the groundwork for the development of preventive interventional strategies for late-life functional decline.

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Appendix

***Table A.1*: The identified frailty instruments and their cognitive components.**

Full Name of Frailty Instruments	Cognition related items **present** in frailty instruments	Sub-groups of cognitive assessment	Cognition related items **absent** in frailty instruments
1. 70-item Frailty Index/Canadian Study of Health and Aging CSHA (Rockwood et al., 2007a; Rockwood et al., 2006; Rockwood et al., 2005)	***Presence of palmomental reflex*** ***Presence of snout reflex*** ***Paranoid features*** ***Restlessness*** ***Changes in general mental functions*** ***Memory changes*** Clouding or delirium *History relevant to cognitive impairment or loss* *Family history relevant to cognitive impairment and loss*	***1.Signs and symptoms*** 2. Delirium *3. Non-specified*	
2. 40-item Frailty Index/CSHA (Rockwood et al., 2006)			X
3. 50-variable Frailty Index derived from Canadian Study of Health and Aging CSHA-FI (Joseph et al., 2014)	*Dementia* ***Memory loss***	*1. Co-morbidity* ***2. Signs and symptoms***	
4. Modified Frailty Index mFI (Hodari et al., 2013)	*History relevant to cognitive impairment or loss* Clouding or delirium	*1. Non-specified* 2. Delirium	
5. 38-item Burden model/ Health and Retirement Study HRS (Cigolle et al., 2009)	Information available is insufficient to conclude about cognitive domain		
6. 40- item Rockwood Frailty Index RFI/ Newcastle 85+ study (Collerton et al., 2012)	*Dementia* **Cognitive function**	*1. Co-morbidity* **2.**	

	using MMSE with a cut-off of ≤ 25	**Objective** (MMSE)	
7. 51-variable / Gothenburg H-70 study (Rockwood et al., 2006)**; original** (Steen and Djurfeldt, 1993)			X
8. Modified 43-item Armstrong Index (Hogan et al., 2012); **original** (Armstrong et al., 2010)	*Alzheimer's disease/dementia* ***Sad, pained worried facial expressions*** ***Persistent anger*** ***Withdrawal from activities of interest*** ***Reduced social interactions***	*1. Co-morbidity* ***2. Signs and symptoms***	
9. 83-item Full Frailty Index (Hogan et al., 2012)	*Alzheimer's disease/dementia* ***Delusions*** ***Hallucinations*** ***Abnormal thought process*** ***Episodes of disorganized speech*** ***Situational memory problems*** ***Procedural memory problems*** ***Short-term memory problems*** ***Easily distracted*** ***Withdrawal from activities of interest*** ***Persistent anger*** ***Repetitive anxiety*** ***Crying/tearfulness***	*1. Co-morbidity* ***2. Signs and symptoms***	
10. 48-item Deficits index DI (Kulminski et al., 2008)			X
11. 32-item Frailty Index – Cumulative Deficits FI-CD (Ensrud et al., 2009; Pilotto et al., 2012)	*Dementia*	*1. Co-morbidity*	
12. 62-item Frailty Index (Woo et al., 2006)	*Past medical history of dementia*	*1. Co-morbidity*	

	Clifton Assessment Procedures for the Elderly CAPE (information/orientation subscale) with a cut-off of ≤7)	**2. Objective** (CAPE)	
13. 47-item Frailty Index FI (Woo et al., 2012)	**Cognitive impairment using CSID (cognitive screening instrument for dementia) with a cut-off of 28.4**	**1. Objective** (CSID)	
14. 44- item Deficit Accumulation Index DAI (Hastings et al., 2008)	*Alzheimer's disease* ***Memory loss interferes with activity*** ***Trouble concentrating***	*1. Co-morbidity* ***2. Signs and symptoms***	
15. 43-item Frailty Index/ Conselice Study of Brain Aging (Lucicesare et al., 2010); **original** (Jones et al., 2004)	Consists of non-specified health deficits so insufficient available information		
16. CSHA rules-based definition of frailty/ Composite B/ Deficit Accumulation Index (Purser et al., 2006; Salvi et al., 2012); **original** (Rockwood et al., 1999)	*Cognitive impairment (categorized as no cognitive impairment; cognitive impairment without dementia; and dementia)*	*1. Non-specified* *2. Co-morbidity*	
17. Canadian Study of health and Aging Clinical Frailty Scale CSHA – CFS (Rockwood et al., 2007a; Rockwood et al., 2005)			X
18. Chinese-Canadian Study of Health and Aging Clinical Frailty Scale Telephone Version CSHA-CFS TV (Chan et al., 2010)			X
19. Frailty Index Comprehensive Geriatric Assessment FI CGA (Pilotto et al., 2012**); original** (Jones et al., 2004)	*No cognitive impairment – implying no problem* *Cognitive impairment, no dementia – implying no problem* Delirium or *dementia* –	*1. Non-specified* *2. Co-*	

	implying severe problem	*morbidity* 3. Delirium	
20. Multidimensional Prognostic Index MPI based on CGA (Pilotto et al., 2012); **original** (Pilotto et al., 2008)	**Cognitive status based on SPMSQ (Short Portable Mental Status Questionnaire 0-2/10 errors – intact intellectual functioning; 3-4/10 errors – mild intellectual impairment; 5-7/10 errors - moderate intellectual impairment; 8-10/10 errors – severe intellectual impairment)**	**1. Objective** (SPMSQ)	
21.Adjusted Clinical Groups-diagnoses based computerized predictive model frailty tag ACG frail/outpatient CGA study at Israeli Health Maintenance Organization (Sternberg et al., 2012)	*Dementia as a co-morbidity*	*1. Co-morbidity*	
22. CGA-frailty (Kristjansson et al., 2012); **original** (Balducci and Extermann, 2000)	**MMSE <24**	**1. Objective** (MMSE)	
23. HUBBARD scale/Chinese cohort (Woo et al., 2012) **; original** (Hubbard et al., 2010)			X
24. Functional domains model/Health and Retirement Study HRS (Cigolle et al., 2009); **original** (Strawbridge et al., 1998)	**Mild to severe cognitive impairment based on TICS (telephone interview for cognitive status: ≤7/35 moderate to severe impairment; 8-10/35 mild impairment)**	**1. Objective** (TICS)	
25. Onco-Geriatric Screening Tool OGS (Valéro et al., 2011)	**Is the patient unable to say what the date is?** ***Does the patient suffer from memory loss?***	**1. Objective** (date) ***2. Signs and symptoms***	
26. Reference test to the Onco-geriatric	**MMSE <26**	**1. Objective**	

screening tool (Valéro et al., 2011)		(MMSE)	
27. Simple Frailty Score (Robinson et al., 2013)	**Mini-Cog ≤ 3**	**1. Objective** (Mini-Cog)	
28. Expanded Frailty Model (Amrock et al., 2014)	Cognitive dysfunction (impaired sensorium on IMPSENS, that is, acute mental status changes)	1. Delirium	
29. Electronic Frailty Model (Amrock et al., 2014)			X
30. 15 variable Trauma-Specific Frailty Index TSFI (Joseph et al., 2014)	*Dementia as a co-morbidity (none, mild, moderate, severe)*	*1. Co-morbidity*	
31. CSBA index /Easy Prognostic Indicator (Forti et al., 2012) **; original** (Ravaglia et al., 2008)			X
32. Conselice Study of Brain Aging Score/Modified easy prognostic score (Lucicesare et al., 2010); **original (**Ravaglia et al., 2008)			X
33. Kihon checklist (Fukutomi et al., 2013)	**Do you sometimes not know what the date is? Do others point out your forgetfulness or tell you "you always ask the same thing"?**	**1. Self-reported**	
34. Barber Questionnaire (Molina-Garrido and Guillen-Ponce, 2011) **; original** (Barber et al., 1980)			X
35. Sherbrooke Postal Questionnaire (Daniels et al., 2012; Metzelthin et al., 2010); **original** (Hebert et al., 1996)	**Do you have problems with your memory? (Yes or no)**	**1. Self-reported**	
36. INTER-FRAIL (Di Bari et al., 2014)	**Memory problems**	**1. Self-reported**	
37. Vulnerable Elders Scale VES-13/Acove Frailty (Kellen et al.,			X

2010; Molina-Garrido and Guillen-Ponce, 2011; Smets et al., 2014; Sternberg et al., 2012); **original** (Saliba et al., 2001)			
38. Modified VES-13/Modified Scoring (Ma et al., 2009)			X
39. Groningen Frailty Indicator (GFI) (Daniels et al., 2012; Kellen et al., 2010; Metzelthin et al., 2010; Olaroiu et al., 2014; Smets et al., 2014); **original** (Steverink et al., 2001)	**Do you have complaints about your memory? (Yes, sometimes, no)**	**1. Self-reported**	
40. Self-assessment version of GFI (Peters et al., 2012)	**Do you have complaints about your memory? (Yes, sometimes, no)**	**1. Self-reported**	
41. Tilburg Frailty Indicator (Daniels et al., 2012; Gobbens et al., 2012; Metzelthin et al., 2010); **original** (Gobbens et al., 2010c)	**Do you have problems with your memory? (Yes, sometimes, no)**	**1. Self-reported**	
42. Modified Short Emergency Geriatric Assessment (SEGAm) instrument (Oubaya et al., 2014) **; original** (Schoevaerdts et al., 2004)	**Cognitive function based on MMSE**	**1. Objective** (MMSE)	
43. Identification of Seniors At Risk ISAR (Salvi et al., 2012); **original** (McCusker et al., 1999)			X
44. Modified Changes in Health, End-Stage Disease and Symptoms and Signs of medical problems CHESS (Hogan et al., 2012); **original** (Hirdes et al., 2003)			X
45. Comprehensive Geriatric Assessment (Smets et al., 2014); **original** (Solomon, 1988)	**Cognitive status based on MMSE (cut off ≤ 23)**	**1. Objective** (MMSE)	

46. Abbreviated CGA (Smets et al., 2014); **original** (Overcash et al., 2005)	**Cognitive status based on 4 questions of the MMSE (attention and calculation; reading; writing and copying)**	**1. Objective** (MMSE)	
47. G8 (Smets et al., 2014); **original** (Soubeyran et al., 2008)	*Mild or severe dementia*	*1.Co-morbidity*	
48. Frailty Index for Elders FIFE (Tocchi et al., 2014)			X
49. Multidimensional Frailty Score MFS (Kim et al., 2014b)	**Mild cognitive impairment or Dementia based on MMSE** Delirium based on the nursing delirium scale	**1. Objective** (MMSE) 2. Delirium	
50. The Frailty Trait Scale FTS (Garcia-Garcia et al., 2014)			X
51. Physical frailty score (Carriere et al., 2005)			X
52. Modified Physical Performance Test + VO_2peak + ADL(Villareal et al., 2004)			X
53. Modified FRAIL Scale/ Chinese cohort (Woo et al., 2012) **; original** (Abellan van Kan et al., 2008)			X
54. Seven potential frailty criteria (Rothman et al., 2008)	**MMSE <24**	**1. Objective** (MMSE)	
55. Marigliano-Cacciafesta polypathology scale MCPS (Martocchia et al., 2013)**; original** (Amici et al., 2008)	Cognitive state and mood - *compromised cognition* *- dementia*	*1. Non-specified* *2. Co-morbidity*	
56. Frailty based on sensor data (Greene et al., 2014)			X
57. Phenotype of frailty/Cardiovascular Health Study CHS (Collerton et al., 2012;			X

Fried et al., 2001; Kim et al., 2014a; Kulminski et al., 2008; Makary et al., 2010; Nemoto et al., 2012); **original** (Fried et al., 2001)			
58. Modified Phenotype of frailty (Hogan et al., 2012)			X
59. Composite A/ Modified Phenotype of frailty (Purser et al., 2006)			X
60. Modified Phenotype of frailty (Woo et al., 2012)			X
61. Modified Phenotype of frailty (Kristjansson et al., 2012)			X
62a. Modified Phenotype of frailty (Ensrud et al., 2007)			X
62b. Modified Phenotype of frailty (Ensrud et al., 2009)			X
63. Modified Phenotype of frailty (Avila-Funes et al., 2009)			X
64. Modified Phenotype of frailty /Mobilise Boston Study MBS (Kiely et al., 2009)			X
65. Phenotype of frailty (Savva et al., 2013)			X
66. Modified Phenotype of frailty/MacArthur Study of Successful Aging MSSA (Gruenewald et al., 2009)			X
67. Modified Phenotype of frailty (Woods et al., 2005)			X
68. Modified Phenotype of frailty/Rush Memory and Aging project (Buchman et al., 2011)			X
69. Modified Phenotype of frailty/Hispanic Established Populations for the Epidemiologic			X

Studies of the Elderly EPESE (Graham et al., 2009)			
70. Modified Phenotype of frailty/ Frail-CHS (Rockwood et al., 2007b; Rockwood et al., 2006)			X
71. Biologic syndrome Model/Health and Retirement Study (Cigolle et al., 2009)			X
72. Adapted Fried using questionnaire data from RAND-36/SF-36/ Helsinki Businessmen Study (Sirola et al., 2011)			X
73. Gill Frailty Index (Kim et al., 2014a)**; original (**Gill et al., 2002)			X
74. Zutphen Elderly Study (Chin et al., 1999)			X
75. Modified Physical Performance Test (Brown et al., 2000)**; original** (Reuben and Siu, 1990)			X
76. Short Physical Performance Battery (Chang et al., 2014)			X
77. Timed Up and Go (Savva et al., 2013)**; original** (Podsiadlo and Richardson, 1991)			X
78. Study of Osteoporotic fractures (Bilotta et al., 2010; Ensrud et al., 2009; Kiely et al., 2009); **original** (Ensrud et al., 2009)			X
79. Modified Study of Osteoporotic fractures index (Forti et al., 2012)			X
80. Frail-NH scale (Kaehr et al.)			X
81. Triage Risk Screening tool (TRST) (Kenig et al., 2015); **original** (Meldon et al., 2003)	***History or evidence of cognitive impairment (poor recall or not oriented)***	***1. Signs and symptoms***	
82. Balducci (Kenig et	*Dementia*	*1. Co-*	

al., 2015); **original** (Balducci and Beghe)	Delirium	*morbidity* 2. Delirium	
83. Frailty based on clinical data and biomarkers (Sanchis et al., 2015)			X
84. EASY-Care Two step Older people Screening Procedure (EASY-Care TOS) (van Kempen et al., 2015)	Step 1 Cognition assessment is based on *1. No cognitive problem,* *2. Mild cognitive problems* *3. Dementia (diagnosed),* *4. Unknown* Step 2 **Do you have any concerns about memory loss or forgetfulness (no, some, yes); do you have problems with brain functions such as memory, attention and thinking (no, some, severe)** **Memory test (6-CIT) – year, month, time, count backwards, months of the year in reverse, repeat memory question (a score of ≥ 10 is indicative of cognitive problems)**	*Non-specified* *Co-morbidity* *Non-specified* **Self-reported** **Objective** (6-CIT)	
85. Expanded timed Up and go Test (ETUG) using inertial sensors (Galan-Mercant and Cuesta-Vargas, 2015)			X
86. Upper extremity frailty (UEF) (Toosizadeh et al., 2016)			X
87. Gait analysis based on trunk acceleration signals (Martinez-Ramirez et al., 2015)			X

88. Care partner derived FI based on CGA (CP-FI-CGA) (Goldstein et al., 2015)	***Memory problem***	***1. Signs and symptoms***	
89. Frailty Index for Acute Care based on the Inter-RAI (FI-AC) (Hubbard et al., 2015)	***Acute change in mental status from the person's usual functioning (restlessness, lethargy, difficult to arouse, displaying altered environmental perception); being easily distracted.***	***1. Signs and symptoms***	
90. Self reported assessment of frailty syndrome (Nunes et al., 2015)			X
91. Modified 15-variable emergency general surgery specific -frailty index (EGSFI) (Jokar et al., 2016)	*Dementia*	*1.co-morbidity*	
92. 23- item FI-Lab (Rockwood et al., 2015); **original** (Howlett et al., 2014)			X
93. 58- item FI-Clinical Long term Care (FI-Clinical-LTC) (Rockwood et al., 2015)	***Short term memory loss*** ***Long term memory loss*** ***Memory changes*** ***Difficulty in mental functioning*** ***Paranoid features*** ***Palmomental reflex*** ***Snout reflex*** ***Suck reflex*** ***Restlessness at night*** Clouding or delirium	***Signs and symptoms*** Delirium	
94. 81-item FI-Combined (Rockwood et al., 2015)	***Short term memory loss*** ***Long term memory loss*** ***Memory changes*** ***Difficulty in mental functioning*** ***Paranoid features*** ***Palmomental reflex*** ***Snout reflex*** ***Suck reflex*** ***Restlessness at night*** Clouding or delirium	***Signs and symptoms*** Delirium	

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