Physical frailty in late-life depression: evidence for a depression-frailty subtype?

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Chapter IX

Summary and general discussion

Humans are inevitably exposed to ageing processes, but the rate of ageing markedly differs between individuals. One of the most challenging aspects of geriatric medicine is to explain the heterogeneity in biological ageing among individuals of the same chronological age. To this end, several markers of biological aging have been proposed, including molecular markers as well as clinical phenotypes like physical frailty. The main aim of this thesis was to study the concept and clinical relevance of physical frailty as a clinical phenotype of accelerated ageing in the context of geriatric psychiatry, with a particular emphasis on late-life depression. This chapter first summarises the results of my thesis. Subsequently, main findings will be discussed, as well as methodological issues, implications for clinical practice, and recommendations for future studies in geriatric psychiatry.

Summary of the findings

In **part I**, we have examined the association between ageing-related biomarkers and physical frailty among depressed older patients who have participated in the Netherlands Study of Depression in Older persons (NESDO). We studied the association with inflammatory markers in **chapter 2**, with leucocyte telomere length in **chapter 3**, and with vitamin D levels in **chapter 4**.

In **Chapter 2** we studied the association between high-sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6) and Neutrophil-Gelatinose-Associated Lipocalin (NGAL or Lipocalin 2) and physical frailty. In general, the average level of pro-inflammatory cytokines as well as hsCRP increase with increasing age, also called “inflamm-ageing” (Grolleau-Julius et al., 2010). These inflammatory markers, however, were neither associated with the presence of frailty, nor with the number of frailty components in our sample of depressed older patients. However, when examining the individual frailty components, we found that gait speed (slowness) was associated with NGAL and handgrip strength (muscle weakness) with both hsCRP and IL-6. Since the

criteria of the Fried Frailty Phenotype may partly overlap with depressive disorder and may not be a unidimensional construct in a sample of depressed patients, we performed a principal component analysis on the frailty components (PCA). This PCA revealed that physical frailty represents two dimensions in our population. The first dimension could be labelled as 'performance-based physical frailty' and was based on the components of slowness, weakness, and low activity level. These components can be considered as indicators of sarcopenia and do not overlap with the criteria of late-life depression (although a low activity level might be a direct consequence of a depressed state). The second dimension, 'vitality-based physical frailty', consisting of the frailty components weight loss and exhaustion, are more likely symptoms of late-life depression. Interestingly, only 'performance-based physical frailty' was associated with low-grade inflammation markers. Based on these results one may hypothesized that low-grade inflammation in late-life depression depends on the level of frailty and difference between depressed and non-depressed persons largely depends on the proportion of frail persons included in either the depressed group versus the comparison group. This finding can also explain why the association between low graded inflammation and depression becomes less consistent with increasing age (Stewart et al., 2009; Matsushima et al., 2015). Moreover, our data also suggest that the physical frailty phenotype may not be a unidimensional construct in late-life depression.

In chapter 3, we have examined the cross-sectional and longitudinal association between leucocyte telomere length and the physical frailty phenotype in late-life depression. Telomere length decreases with each cell division and is considered a molecular marker of ageing. In our sample of depressed older adults, leucocyte telomere length was only cross-sectionally associated with the number of frailty components, but not with the presence of frailty as a syndrome or its individual components. Moreover, leucocyte telomere length at baseline was not associated

with any change in frailty (parameters) over a two-year follow-up. These findings are in line with an increasing number of cross-sectional and longitudinal studies in non-depressed samples that could also not detect any association between physical frailty and leucocyte telomere length (Woo et al., 2008; Collerton et al., 2012; Yu et al, 2015; Breitling et al., 2016). In younger patients the association between leucocyte telomere length and depression has been consistently reported (e.g. Epel et al., 2004; Damjanovic et al., 2007; Tyrka et al., 2010; Garcia-Rizo et al., 2013), whereas this association is less consistent and mostly negative in older samples (Philips et al., 2013; Schaakxs et al., 2015). We hypothesized that the chronological age of the participants is an important source for variation in the association between depression and leucocyte telomere length. A possible source of confounding that may increase with age is the presence of chronic somatic diseases, as in population-based studies or psychiatric cohort studies the severity and chronicity of somatic conditions are usually not taken into account. As Wolkowitz and colleagues stated that the biological age of depressed adults is at least 10 years older compared to their chronological age (Wolkowitz et al., 2010), frailty might be a confounding factor. The small association between the severity of frailty and leucocyte telomere length we found should be replicated, as the NESDO study is rather small for detecting clinical correlates of telomere length shortening. In light of these small effects, we concluded that physical frailty and leucocyte telomere length should be considered as two different, probably complementary markers of the aging process.

A previous study embedded in NESDO showed that depressed patients had significantly lower levels of vitamin D compared to their non-depressed counterparts (Oude Voshaar et al., 2014). Moreover, baseline vitamin D levels did not predict the prognosis of late-life depression, but lower vitamin D levels were associated with a significantly higher mortality rate (Van den Berg et al., 2016). These results might

suggest that vitamin D deficiency is a marker for poor somatic health status or frailty. In chapter 4, we therefore examined the association between vitamin D levels and frailty, its components and its course in a depressed sample. Logistic regression analyses revealed a cross-sectional association between higher vitamin D levels and lower prevalence of frailty with an odds ratio of 0.64 (95%-CI: 0.45 – 0.90, p=.010). Among non-frail depressed patients, higher vitamin D levels were protective for the onset of frailty.

Although the associations between low graded inflammatory markers, leucocyte telomere length and vitamin D are rather small and only present when confined to a specific subset of frailty markers (e.g. performance physical frailty), collectively these findings show that physical frailty is a valid concept in late life depression. Moreover, frailty might point to a specific subgroup of depressed patients in which ageing characteristics are more prominent (Rutherford et al., 2017). Whether a specific ageing-related subtype exists should therefore deserve more attention in future research.

In part II we examined the association between physical frailty and common neuropsychiatric symptoms, particularly cognitive impairment and medically unexplained symptoms.

In chapter 5, we explored the cross-sectional association of physical frailty with four domains of cognitive functioning, i.e. verbal memory, working memory, interference control and processing speed. Linear regression analyses adjusted for confounders, showed that the severity of physical frailty was associated with poorer verbal memory (ß=-0.13, p=.050), slower processing speed (ß=-0.20, p=.001), and decreased working memory (ß=-.18, p=.006), but not with interference control (ß=0.04, p=.56). We concluded that consistent with the concept of cognitive frailty,

stating that a substantial proportion physically frail persons suffers from 'cognitive impairment, no dementia (CIND)', physical frailty is associated with poorer cognitive functioning in late-life depression. Nonetheless, as a depressive disorder itself is associated with a state-effect on cognitive functioning, it still remains to be determined whether cognitive impairment is a relevant concept to identify a specific subgroup of depressed older patients. In contrast to our findings, a recent study did not find any association between frailty markers and neuropsychological dysfunction among depressed older patients (Brown et al., 2019). A recent meta-analysis showed that cognitive deficits in depression persist after remission irrespective of age (Semkovska et al., 2019). Within the NESDO study, latent class analyses did not identify subgroups of frail-depressed patients without cognitive impairment (Lugtenburg et al., accepted for revision). This suggests that cognitive impairment is a trait-effect associated with depression and in case of late-life depression, points to the frail-depressed phenotype.

In chapter 6 we examined the level of frailty and somatic comorbidity among 118 older patients with medically unexplained symptoms (MUS) in comparison to 154 patients with medically explained symptoms (MES) aged 60 years and over. In contrast to previous (and further) studies in this thesis, data were derived from the OPUS study (Older Persons with medically Unexplained physical Symptoms). In the OPUS study, frailty was assessed according to the Fried criteria and similarly operationalised as in the NESDO study. We found that patients with MUS had less physical comorbidity compared with patients with MES, but were prescribed the same number of medications. Moreover, patients with MUS were more often frail compared with patients with MES. Among patients with MUS, physical frailty was associated with a higher severity of unexplained symptoms, higher level of hypochondriacal beliefs, and higher level of somatisation. Collectively, these findings suggest that despite a lower prevalence of overt somatic diseases, patients with

MUS are more frail compared with older patients with MES. These results may suggest that at least in some patients age-related phenomena might be erroneously classified as MUS, which may affect treatment strategy.

In part III we focussed on the clinical relevance of frailty in late-life depression, i.e. the course of late-life depression as well as the ultimate negative health outcome: death.

At a population level, meta-analyses point to a reciprocal association between frailty and depressive disorder (Soysal et al., 2017). Nonetheless, nearly all studies were based on depressive symptom severity scales. Therefore, we examined in chapter 7 whether physical frailty predicts the course of late-life depressive disorder according to DSM-criteria. We showed that an increased level of physical frailty was associated with non-remission of a depressive disorder at two-year follow-up. Interestingly, the previously identified dimensions of physical frailty had opposite effects. A higher level of performance-based physical frailty was associated with non-remission of depression at two-year follow-up, whereas a higher level of vitality-based physical frailty was associated with a higher chance on remission. These findings fit with our idea that vitality-based physical frailty overlap with depression itself for which patients were treated.

Linear mixed models analysing the course of depressive symptoms over time showed that motivational and somatic symptoms of depression improve faster with increasing frailty, while the mood symptoms of depression did not. Despite this faster improvement, motivational and somatic symptoms of depression remained (significantly) higher at the two- year follow-up among frail-depressed patients. This finding has clinical relevance, since these remaining symptoms will trigger patients and physicians for further treatment. When these symptoms are considered as

residual depressive symptoms, patients might be placed at risk for psychiatric overtreatment, especially antidepressant drug treatment and associated side effects. When these symptoms are considered as frailty these patients might profit from geriatric rehabilitation to improve their physical condition.

In chapter 8 we examined whether frailty predicts mortality over a 6-year follow-up among depressed older patients who had participated in the NESDO study. During follow-up, 27/103 (26.2%) frail depressed patients died compared to 35/275 (12.7%) non-frail depressed patients (p<.001). Using Cox-regression analyses, the number of frailty components predicted mortality with a hazard rate (HR) of 1.38 (95%CI: 1.06–1.78, p=.015) adjusted for relevant confounders. The ageing-related biomarkers associated with frailty (see part I) also predicted mortality during follow-up, i.e. hsCRP (HR=1.41 [95%CI : 1.08–1.83], p=.011), lipocalin-2 (HR=1.30 [95%CI: 1.00–1.68], p=.048), and vitamin D (HR=0.60 [95%CI: 0.43–0.85], p=.004). These ageing-related biomarkers partly explained the association between frailty and mortality. Therefore, also these results suggest that treatment of late-life depression might benefit from geriatric care models and/or interventions targeting frailty.

General Conclusions

The prevalence of physical frailty in depressed older adults from the NESDO study was 27.2%. This is lower than prevalence rates identified by a meta-analysis (Soysal et al., 2017) and most likely explained by the fact that in most studies depression is based on self-report depressive symptom scales.

In part I of this thesis we show the validity of the concept of physical frailty when applied to depressed patients, since we found small, but significant associations with different biomarkers of ageing. The low strength of these associations can be explained by the fact that physical frailty is a multifactorial condition with each mechanism only explaining a (small) part.

Based on this thesis as a whole, but especially on part II of this thesis, one may even argue that psychopathology should be part of the concept of frailty (as done by some researchers). Nonetheless, by incorporating mental health in the concept of frailty, the concept may become useless in geriatric psychiatry. This would have negative consequences for geriatric mental health care, as in part III we describe that physical frailty seems to be a relevant concept in late-life depression. Physical frailty has a negative impact on the prognosis of depression, both from a mental health perspective (non-remission) as well as general medicine perspective (predicting mortality). The 'depression-frailty subtype' seems to be a valid concept to identify depressed older patients at risk of adverse negative health outcomes. Seeing the difficulty disentangling depression and frailty among the oldest old, one may even argue for better integrated care in later life.

Methodological considerations

In the previous chapters, strengths and limitations of the individual studies were discussed. Here, we will discuss some overarching methodological issues.

Methodological issues of the NESDO study

Diagnosis of late-life depression – Hitherto, in most studies on the association between frailty and depression, depression is based on self-report depressive symptom scales (see Soysal et al., 2017). This may bias results as this may lead underreporting depression as well as overreporting of depressive symptoms. Underrecognition of depressive symptoms is possible since depression in later life can have a different presentation compared to depression earlier in life (Hegeman et al., 2012; Balsamo et al., 2018). Older adults are less inclined to express a depressed mood (Sözeri-Varma, 2012). They also tend to attribute depressive symptoms, including loss of interest or loss of pleasure, anhedonia or dysphoria, to the normal aging process (Balsamo et al., 2018). Older adults are also less likely to

endorse a decrease in sexual functioning (Hegeman et al., 2012; Balsamo et al., 2018). In contrast, overreporting of depressive symptoms might be due to underlying somatic diseases. It is known that somatically ill patients report elevated depressive symptom scores without being depressed (Thombs et al., 2010). A strength of the NESDO study was the assessment of depressive disorder according to DSM-IV criteria using a structured and well-validated psychiatric interview (Comijs et al., 2011).

Non-depressed control group - Within the NESDO study the control group was recruited among non-depressed visitors of general practitioners. Since these persons visit their general practitioner, it can be assumed that they have more medical complaints or chronic somatic diseases compared to community-dwelling elderly. Therefore, the lack of any differences found between the depressed and non-depressed group might be explained by an overrepresentation of ageing-related disorders in the control group. If true, this might explain why depressive disorder itself was not associated with low-graded inflammation or shortened telomere length (Vogelzangs et al., 2014; Schaakxs et al., 2015; Teunissen et al., 2016; Rozing et al., 2019). However, in case this explanation indeed explains the null-findings in the NESDO study, the associations between these biomarkers and frailty among depressed patients we found simply point to an interaction between frailty and depression on explaining variance in these ageing-related biomarkers and our findings would still bear the same clinical relevance (in this case, the validation of the concept of frailty within late life depression).

Correction for treatment - In Chapter 3, 4, 7, and 8 we used longitudinal data. Although these analyses have been adjusted for potential confounders, we had no detailed information about the specific treatment patients received other than antidepressant drug treatment. Therefore, results may be confounded by indication,

i.e. frail-depressed patients have received a different treatment regimen than non-frail-depressed patients. This may have biased our results in several ways. For example, in case treatment resistant (more frail) patients have received more rigorous psychopharmacological treatment, the treatment itself may have led to increased mortality rates. In another way, frail-depressed patients may have received more often nutritional advice or support by physiotherapists in case the level of frailty has been recognized by their physicians. If true, the real effect of frailty on depression outcome or mortality might be even larger. Nonetheless, as physical frailty is largely neglected in geriatric psychiatry and is not incorporated in clinical guidelines in the Netherlands, we expect that this effect would have been minimal in our studies.

Sample size – Since the studies in this thesis were conducted on pre-existent datasets, we did not a priori perform power analyses. Insufficient statistical power could have resulted in both type I and II errors. Since we report positive results in nearly all chapters, the chance of finding (type I error) cannot be excluded. Furthermore, some inconsistent effects across the different frailty parameters and its components may also simply reflect a type II error. Nonetheless, despite the sample size of both NESDO and OPUS study was small, both studies are comparable to other studies in this field of research. Moreover, the findings were largely in line with a priori set hypotheses based on earlier studies.

Frailty definition

As mentioned earlier, several definitions of frailty are available varying from pure physical phenotypes to broader, multidimensional phenotypes (Rockwood et al., 2005; Roppolo et al., 2015). We considered a syndrome diagnosis, based on the physical frailty phenotype of Fried and colleagues, most appropriate to study frailty within a psychiatric setting to prevent symptom overlap and confounding with

psychiatric disorders. Nonetheless, direct comparisons with other frailty operationalisations have not been made. Future research should address the relevance of the Frailty Index by the group of Rockwood in geriatric psychiatry. A comparison with multidimensional models like the Groningen Frailty Indicator (Peters et al., 2012) or the Tilburg Frailty Index (Gobbens et al., 2010), however may less relevant, as psychiatric patients by definition are frail regarding the psychosocial dimensions addressed within these models. These multidimensional frailty models seems particularly relevant for primary care to target treatment and/or guide referral to specific higher echelons of the health care system.

Unfortunately, the Fried Frailty Phenotype still overlaps with depressive disorder. Firstly, weight loss and slowness are criteria for both disorders albeit the operationalisation differs slightly. Weight loss with respect to frailty refers to unintentional weight loss over the last year, which cannot be explained by a specific disorder, whereas in depression weight loss is related to the loss of appetite during the depressive episode. Secondly, slowness in frailty is operationalised as slow gait speed. Slow gait speed might be partly explained by motivational issues in depression. Moreover, psychomotor retardation in depression is generally associated with severely depressed states or limited to a reduced level of postural and facial expression. Future studies on this topic, therefore, should not only address the course of the depression, but also take the course of frailty parameters into account.

Lack of intervention trials

Both NESDO and OPUS offer the possibility for adjustment of potential confounders. Though, it cannot be excluded that associations studied were confounded by any unknown factors. To exclude the possibility of residual confounding, randomised controlled trials should be conducted. In this field of research, particularly testing interventions targeted at physical frailty during treatment of late-life depression

would be relevant (see future research). While physical frailty is for long completely ignored in pharmacological treatment trials on late-life depression (Benraad et al., 2016), a recent pilot study shows that targeting pharmacological treatment to a frailty status of depressed older patients improves outcome (Rutherford et al., 2019).

Implications for clinical practice

An important goal is to raise more awareness to the importance of frailty in geriatric mental health care and to translate the findings of this dissertation to clinical practice. The concept of frailty is relevant in the care of older patients to direct attention from organ-specific diagnoses towards a more holistic viewpoint of the patient. In geriatric medicine the relevance of frailty is increasingly recognized (Clegg et al., 2013; Hoogendijk et al., 2019), especially the need of adapting treatment strategies to prevent iatrogenic damage. In geriatric mental health care, additional impact may be achieved by a better distinction between psychopathology and physical frailty since criteria overlap and both give specific, but sometimes opposite directions to treatment. When depression and frailty co-exists, one may, for example, prefer a psychological approach to target depression in order to prevent polypharmacy (and side-effects). Furthermore, the past decades complex (multimodal) interventions have been developed aimed to treat frailty symptoms. The core components of interventions for frailty, i.e. reduction of polypharmacy, physical exercises, and dietary interventions (Morley et al., 2013), can all be considered to also have direct benefit for late-life depression, as discussed below.

Polypharmacy

Prescribing medication appropriately in older adults requires a delicate trade-off between benefits and risks (Yong et al., 2015) as frail older adults are more prone to adverse drug events (Yong et al., 2015). However, the number of prescribed

medications is much higher among frail older adults compared to robust (non-frail) older adults (Gnjidic et al., 2012; Yong et al., 2012; Hilmer & Gnjidic, 2017). Reported difference in the prevalence of polypharmacy (≥5 medication classes) has been as large as 65% versus 27% in frail and non-frail persons respectively (Gnjidic et al., 2012). Polypharmacy itself is associated with decreased cognitive, physical and social functioning and increased risk of falls, hospitalization and death (Yong et al., 2015; Hilmer & Gnjidic, 2017). The estimated risk of adverse drug events is 13% in case of two medicines, 38% in case of four medicines, and up to 82% in case of 7 or more medicines (Atkin et al., 1999; Yong et al., 2015). Although the possibility of confounding by indication cannot be excluded, each additional prescribed drug is associated with a 22% higher risk of death in robust community-dwelling elderly (Jamsen et al., 2016). Interestingly, antidepressant medication use increased from 7.7% in 1999 to 12.7% in 2014, an increase of 64,9% (Pratt et al., 2017). Similar to frailty, this increase of antidepressant use is also associated with an increased chronological age and more common among females than males. Studies disentangling frailty and depression are urgently needed, especially as most psychotropic drugs have anticholinergic and sedative effects, which independently may contribute to adverse health outcomes (Yong et al., 2015; Hilmer et al., 2017). A recent systematic review on the association between medication and the risk for falls reported that in a depressed older population, especially antidepressants including selective serotonin reuptake inhibitors, tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, hypnotics and sedatives, are related with a higher risk of falls in older adults (Park et al., 2015). Interestingly, a study that specifically explored the independent effect of depression, frailty and SSRI usage, showed that the fall-risk associated with SSRIs exponentially increases in the presence of frailty (Lin et al., 2019).

In sum, we can postulate that under detection of frailty in an (depressed) older population may lead to overtreatment with antidepressants and/or polypharmacy.

Physical exercise

Increased physical activity is an important strategy in the prevention of frailty in older adults (Savela et al., 2013; Marzetti et al., 2017). Unfortunately, a sedentary lifestyle becomes more common with increasing age (López-Torres Hidalgo et al., 2019). Several studies have shown a positive impact of physical activity on musculo-skeletal parameters (Goodpaster et al., 2008; Snyder et al., 2011; Yamada et al., 2015). A randomized controlled trial showed that physical activity can prevent the occurrence of frailty among older adults with sedentary lifestyle over a one-year period (Cesari et al., 2015). Adding resistance training to physical activity seems particularly relevant to reverse an age-related decline in muscle mass and muscle strength (Morley et al., 2014; Churchward-Venne et al., 2015). Therefore, combined interventions of physical activity and resistance training are recommended in (frail) older adults (Sparling et al., 2015).

Late-life depression is often associated with low physical activity and several randomised controlled trials have shown that increasing physical activity is effective in improving depression (Tsutsumi et al., 1998; Barbour & Blumenthal, 2005; Sjösten & Kivelä, 2006; Mortazavi et al., 2012). However, conflicting results have been reported and methodological weaknesses like inadequate concealed randomization, small sample sizes, short follow-up duration, and poor quality of data analysis argue for replication studies (López-Torres Hidalgo et al., 2019). In this respect, future studies should specifically include frail-depressed older persons.

Nutritional interventions in frailty and depression

Several studies have highlighted the association between malnutrition and an increased risk of frailty development (Jayanama et al., 2018; Hernández-Morante et al., 2019). Malnutrition is considered an important and modifiable risk factor in the development of frailty (Lang et al., 2009; Bonnefoy et al., 2015; Valentini et al.,

2018). An international consensus conference in 2013 on physical frailty agreed that nutritional interventions should in particular focus on supplementation of calories (energy), proteins, and vitamin D (Morley et al., 2013).

Caloric supplementation: A systematic review of 62 randomized controlled trials including a total 10,187 randomized older adults showed that calorie supplementation decreased mortality risk in undernourished older adults (Milne et al., 2009). Caloric supplementation can therefore have a valuable contribution to the treatment of physical frailty. Many depressed patients suffer from malnutrition due to loss of appetite, and thus may profit from calorie supplementation. In this respect, we argue to focus on malnutrition instead of frailty as a syndrome, as overweight may result in metabolic dysregulation, which is in itself associated with a protracted course of depressed symptoms (Vogelzangs et al., 2011; Marijnissen et al., 2017).

Protein supplementation: Inadequate protein intake appears to play a prominent role in the development of the frailty process (Bartali et al., 2006; Coelho-Júnior et al., 2018; Jayanama et al., 2018). Malnutrition with inadequate protein intake causes an imbalance in muscle protein turnover and leads to decreased protein synthesis, resulting in muscle catabolism and sarcopenia (Coelho-Júnior et al., 2018; Cruz-Jentoft et al., 2019). A recent meta-analysis on the association between physical frailty and protein intake in older adults confirmed that adequate protein consumption is inversely related with physical frailty (Coelho-Júnior et al., 2018). The few studies on protein supplementation seem to indicate a protective role against physical frailty (Hernández-Morante et al., 2019).

Vitamin D supplementation: Both frail older persons as well as depressed older persons more often have hypovitaminosis D compared to their non-frail and non-depressed counterparts (Anglin et al., 2013). Although there is lack of large-scale

nutritional intervention studies that report the preventive or curative effect of vitamin D in physical frailty, vitamin D supplementation is generally considered as a potential treatment strategy for physical frailty (Morley et al., 2013). Nonetheless, the effectiveness of vitamin D supplementation trials for the treatment of depression is not yet convincing (Shaffer et al., 2014; Jamilian et al., 2019). Future trials should especially include frail-depressed older persons.

Research shows that nutritional interventions not only might delay or reverse physical frailty, but also hold promise as a unique treatment for the prevention or treatment of (late-life) depression (Lang et al., 2009; Firth et al., 2019). In recent years nutritional interventions are also gaining attention as a low-risk approach in geriatric psychiatry since changing to a well-balanced nutritious diet is unlikely to be harmful. A healthy diet might be protective against depression, while depression might negatively affect food intake (Cabout et al., 2017). Recent studies suggest that a healthy or high-quality diet (heavily loaded by fish, fruit, and vegetables), such as a Mediterranean diet, is protective for developing depression (Akbaraly et al., 2009; Sanchez-Villegas et al., 2009; Rienks et al., 2013). A recent meta-analysis of randomized controlled trials confirmed the inverse association between omega-3 supplementation and the prevalence of depression (Liao et al., 2019). Conversely, consumption of low-quality diets, including diets high in fat, sugar, nutrient-poor, and processed foods, have been associated with increased risk to develop depression (Akbaraly et al., 2009; Jacka et al., 2010).

Psychotherapeutic approach

Although 80% of depressed older patients receive antidepressants in specialised mental health care (van Marwijk et al., 2001; Baldwin et al., 2012; Trevino et al., 2017), guidelines advocate shared decision-making and stress the fact that in case of mild to moderate depression, pharmacotherapy and psychotherapy are equally

effective (Casacalenda et al., 2002). Physical ageing, the process from a robust health state and independency to frailty and dependency, is often accompanied with a psychological transition that can evolve into a so-called "frailty identity crisis", which is characterized inter alia by social isolation, loneliness, loss of purpose, and depression. (Woo et al., 2005; Fillet & Butler, 2009). Early recognition of these negative sequelae might lead to better psychological well-being and possible partial reversibility of the frailty process (Fillet & Butler, 2009). In this respect, the movement of positive psychology, including Acceptance and Commitment therapy (ACT), life review or mindfulness based stress reduction, might be particularly relevant for these patients.

ACT for example is considered a promising psychotherapeutic treatment modality for older adults suffering from physical and mental illness (Petkus & Wetherell, 2013). It focuses on supporting acceptance of internal experiences related to loss and may offer a useful strategy for flexible responding to profound life events in older adults (Karlin et al., 2013; Petkus & Wetherell, 2013). ACT might thus be especially beneficial for enhancing resilience and well-being and reducing distress (Petkus & Wetherell, 2013). While meta-analyses reveal that ACT significantly reduces depressive symptoms in patients with mild depression and improves quality of life (Bai et al., 2019), studies in later life are scarce (Karlin et al., 2013).

Frailty is often characterized as the absence of resilience in the older adult (Holland et al., 2015). Several studies reported that in older age low (social, psychological, and/or biological) resilience is often positively associated with frailty due to increased vulnerability to stressors (White et al., 2010; Rybarczyk et al., 2012; Rebagliati et al., 2016). On the other hand, high resilience at old age is associated with improved mental health, increased quality of life, lower mortality risk and increased longevity (White et al., 2010; Rybarczyk et al., 2012; Rebagliati et al., 2016). Although it has hardly been researched, it is plausible that traumatic life events are positively associated with frailty in later life (Freitag & Schmidt, 2016).

One study among geriatric inpatients found several psychosocial factors modifying the association of frailty with adverse outcomes, including high anxiety levels, and low levels of sense of control (mastery), wellbeing, social activities, and home/neighbourhood satisfaction (Dent & Hoogendijk, 2014). From the literature it can be concluded that high resilience scores seem to be positively associated with physical health or functional independence and negatively associated with late-life depression (Wagnild & Young, 1993).

Collectively, these studies argue for future studies to explore the feasibility and effectiveness of different psychotherapeutic approaches aimed to improve well-being of frail older persons. This is especially important as meta-analyses show that interventions, mainly based on physical exercise or diet, to prevent or reduce frailty have yielded disappointing results thus far (Frost et al, 2017; Van der Elst et al, 2018).

Future directions for research in geriatric psychiatry

From a clinical perspective, we can claim that frailty and depression in later life are interrelated and that physical frailty appears to promote a more severe and more difficult to treat subtype of late-life depression. Specific treatment modalities to decrease both frailty and depression in the older adult should be further investigated in future intervention studies. In addition, studies should also focus on testing the possible benefits produced by multidomain interventions on the 'depression-frailty' phenotype as a subtype of late-life depression. As argued above, such interventions should include reduction of polypharmacy (or a critical medication review), physical exercise (including resistance training), nutritional interventions and psychotherapy.

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