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

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# Chapter VI

## Frailty and somatic comorbidity in older patients with medically unexplained symptoms

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## Abstract

*Objectives* - To examine the level of frailty and somatic comorbidity in older patients with medically unexplained symptoms (MUS) and compare this to patients with medically explained symptoms (MES).

*Design* - Cross-sectional, comparative study.

*Setting* - Community, primary care, and secondary health care to recruit MUS-patients in various developmental and severity stages and primary care to recruit MES-patients.

*Participants* - 118 patients with MUS and 154 patients with MES, all aged ≥60 years.

*Methods* - Frailty was assessed according to Fried's criteria (gait speed, handgrip strength, unintentional weight loss, exhaustion, and low physical activity), somatic comorbidity according to the self-report Charlson Comorbidity Index and the number of prescribed medications.

*Results* - Although MUS-patients had less physical comorbidity compared to MES-patients, they were prescribed the same number of medications. Moreover, MUS-patients were more often frail compared to MES-patients. Among MUS-patients, physical frailty was associated with the severity of unexplained symptoms, the level of hypochondriacal beliefs, and the level of somatisation.

*Conclusion and implications* - Despite a lower prevalence of overt somatic diseases, MUS-patients are more frail compared to older MES-patients. These results suggest that at least in some patients age-related phenomena might be erroneously classified as MUS, which may affect treatment strategy.

## Introduction

Reported prevalence rates of medically unexplained symptoms (MUS) in people aged ≥65 years range between 1.5 and 18% (Hilderink et al., 2013). People with MUS often describe a low quality of life and frequently suffer from co-morbid anxiety and depressive disorders (De Waal et al., 2004). Furthermore, MUS itself gives rise to high levels of health care consumption in the search for an organic origin of complaints and places especially older persons at risk for iatrogenesis (Smith et al., 2005).

When people persist in seeking medical help, while no organic explanation for these somatic symptoms can be found, it is assumed that these symptoms occur as a result of social or psychological factors, also referred to as somatisation (Lipowski, 1988). Studies also suggest that (the interaction with) physicians plays a role in the persistence of these symptoms (Salmon et al., 2008). Persistence of MUS and somatisation are classified as somatoform disorders and somatic symptom disorders in the DSM-IV-TR and DSM-5, respectively.

Most etiological models for MUS are built from a bio-psycho-social perspective (Mayou et al., 1995; Kirmayer & Taillefer,1997; Kolk et al., 2003; Deary et al., 2005; Henningsen et al., 2007). Nonetheless, biological processes are uniquely included as precipitating factors, whereas psychological and social processes can be either precipitating factors, but also predisposing or perpetuating factors. Most models describe biological processes as bodily sensations, which may originate from normal physiological processes (e.g. bowel peristalsis), from pathophysiological processes due to sub-threshold medical conditions (e.g. elevated blood-glucose levels without actual diabetes), as well as overt diseases, accompanied by a misinterpretation by the patient regarding their origin. Furthermore, in the case of DSM-IV defined somatoform disorders, biological processes play a role by definition as the core diagnostic criteria are the presence of somatic complaints that are more severe than can be explained by the underlying somatic condition. Therefore, we might expect

that somatisation problems increase parallel to an increase in somatic disease burden. Besides a small pilot study of our group (Benraad et al., 2013), no studies have been conducted on the physical performance of older patients with MUS. The somatic disease burden can be distinguished in overt (e.g. number of chronic somatic diseases) and covert (e.g. frailty) somatic conditions. Frailty is 'a condition in which the individual is in a vulnerable state at increased risk of adverse health outcomes and/or dying when exposed to a stressor' (Morley et al., 2013). The prevalence of frailty is estimated at 9.9% among community-dwelling older persons (Collard et al., 2012). In our pilot study on older patients with MUS, the level of somatic comorbidity as well as frailty parameters were significantly higher among patients with MUS which was partially explained by a somatic origin compared to patients with MUS for which no explanation at all was found (Benraad et al., 2013).
The objective of the present study was to compare the level of frailty and somatic comorbidity between a well-characterised and representative cohort of older patients with MUS and older patients with Medically Explained Symptoms (MES). Subsequently, we will explore the association between the severity of MUS and frailty as well as somatic comorbidity.

## Methods

The present study is embedded within the Older Persons with medically Unexplained Symptoms (OPUS) study, a comparative study including 118 patients suffering from MUS and 154 patients suffering from MES. Data of the OPUS study were collected between September 2011 and March 2014. The OPUS study has been described before (Hanssen et al., 2016; Van Dijk et al., 2016), but will be summarized below.
To recruit MUS-patients in various developmental and severity stages, recruitment took place in the community by advertisements in local newspapers, in primary care, and in secondary healthcare. To assist general practitioners (GPs), we preselected the top 20% of older frequent attending patients in their own practice from the GP

Information System. The list of frequent attenders had to be checked by the GP for older MUS-patients. This pre-selection method was chosen, based on previous research projects on MUS in primary care (Katon et al., 2001; Smits et al., 2009). MES-patients were selected from the same frequent attenders list to strive for a comparison group with current physical symptoms with a severity comparable to those of the MUS-patients. As selection bias is inevitable and may especially play a role in older and/or vulnerable population (Gaertner et al., 2016), adding a comparison group of MES patients enables interpretation of the absolute level of the somatic disease burden.

Inclusion criteria for MUS-patients were 1) age of ≥60 years, 2) MUS ≥3 months according to their general practitioner (GP), 3) meeting the definition for MUS of the Dutch College of GPs, i.e. physical symptoms that have existed for more than several weeks and for which adequate medical examination has not revealed any condition that sufficiently explains the symptoms (Olde Hartman et al., 2013). Patients suffering from functional syndromes like fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome or a whiplash-syndrome, were also included as MUS-patients (Wessely et al., 1999). The unexplained nature of the MUS was checked by either a comprehensive assessment conducted by geriatrician (n=70) or an additional chart review of the GP for patients who refused this geriatric assessment (n=48) but agreed with the other study procedures.

Exclusion criteria for MUS- and MES-patients were 1) a primary psychotic disorder; 2) established or suspected diagnosis of dementia; 3) suffering from terminal illness; 4) insufficient mastery of the Dutch language; 5) auditory or visual impairment interfering with reliable data collection; and 6) a physical symptom than can be explained by a psychiatric disorder other than a somatoform disorder.

All participants of the OPUS study gave written informed consent. The local Medical Ethical Committee of the Radboud University Nijmegen Medical Center has approved the OPUS-study.

*Procedures OPUS-study* - All participating MUS-patients were offered a multidisciplinary diagnostic procedure, consisting of a Comprehensive Geriatric Assessment and semi-structured psychiatric diagnostic interview. Subsequently, the participant filled out a number of questionnaires. After the diagnostic procedure, a researcher (D.H.) visited the patient at home to examine social and cognitive functioning in more depth.

If MUS-patients refused to participate in the multidisciplinary diagnostic procedure or were physically not able to visit the clinic, but nevertheless agreed to participate in the OPUS-study, the researcher (D.H., supervised by P.N.) performed two home-visits (40.7%; N=48). The MES-patients always received two home-visits in which all research instruments were administered.

*Measures*

*Physical functioning* - Several aspects of physical functioning were assessed, i.e. somatic comorbidity, the number of prescribed medications, and physical frailty.

We assessed somatic comorbidity using a self-report version of the Charlson Index (Charlson et al., 1987; Katz et al., 1996). In this questionnaire sixteen categories of possible somatic comorbidities were assessed with yes/no answering categories. Since we were interested in differences in somatic comorbidity and not in mortality risk, we did not include age as a factor in the total score.

The number of prescribed medications was based on self-report and checked by the researcher at the patients' home by collecting all medication containers.

The physical frailty phenotype was assessed according to Fried's criteria (Fried et al., 2001), i.e. the presence of ≥3 of the following five criteria: weight loss, weakness, exhaustion, slowness and low physical activity. The operationalization and/or cut-off used for the dichotomized criteria have been described before (Collard et al., 2014). In addition to the syndromal definition of frailty based on the Fried criteria, we also included two unidimensional proxies for frailty based on previous research into

physical frailty, i.e. muscle weakness (Syddall et al., 2003) and gait speed (Cesari et al., 2005). These proxies are based on the maximum handgrip strength, i.e. the best of two squeezes using their dominant hand (in kg) and the time to walk six meters as described above.

*MUS severity indicators* - Several indicators of the severity of MUS have been measured, i.e. 1) the severity of the primary physical complaint using a 10-cm visual analogue scale (VAS), 2) the level of somatisation with the 7-item somatization subscale of the Brief Symptom Inventory (BSI-53) (Derogatis, 1975; Derogatis, 1993), 3) the presence of hypochondriac cognitions with the Whiteley-Index (WI) (Pilowsky, 1967), 4) the presence of a DSM-IV diagnosis of a somatoform disorder, and finally 5) comorbid psychiatric disorders according to the DSM-IV.

All psychiatric disorders were diagnosed with a semi-structured psychiatric interview, i.e. the Mini International Neuropsychiatric Interview (MINI), version 5.0 (Lecrubier et al., 1997; Sheehan et al., 1998).

The somatization subscale of the BSI-53 (Derogatis, 1975; Derogatis, 1993) consists of seven items that have to be rated on a 5-point Likert scale referring to the severity of physical symptoms in younger persons associated with functional syndromes, i.e. dizziness, chest pain/discomfort, nausea, shortness of breath, hot flushes, paresthesias, and faintness/general weakness. The somatization subscale of the BSI-53 is considered the best self-report somatization scale for usage in large-scale epidemiological studies (Derogatis, 1993). In our study, the subscale had a Cronbach's alpha of .77.

The WI consists of 14 statements that have to be rated as yes/no, with higher scores being indicative of a greater severity of hypochondriasis (Pilowsky, 1967).

*Covariates* - Demographic and lifestyle characteristics were included as covariates. As demographic characteristics, we included age, sex, and the highest level of

completed education (low, middle or high) as the basic covariates when comparing MUS- and MES-patients (Lutomski et al., 2013).

As lifestyle characteristics, we included smoking, use of alcohol and BMI ($kg/m^2$). Smoking was based on self-report questions and dichotomized as currently smoking (yes/no). Alcohol use was measured with the first two questions of the Alcohol Use Disorder Identification Test (AUDIT) (Babor et al., 1989). Based on these two questions, i.e. number of days drinking and number of drinks on a typical day, we categorized patients in completely abstinent, severe users defined as >14 drinks a week for women and >21 drinks a weeks for men, and finally moderate use for those in between fully abstinent and severe use.

*Analyses* - First, all variables of interest were checked for significant differences between patients with MUS and MES by either Student t-tests (normally distributed continuous variables) or chi-square tests in case of categorical variables. The variables comorbidity (Charlson Index) and gait speed had a skewed distribution which achieved normality after ln-transformation. For interpretation, the mean values, standard deviations and standard errors presented in tables were back-transformed.

Subsequently, the parameters reflecting physical functioning were compared between patients with MUS and MES by analysis of covariance (ANCOVA) adjusted for age, sex, level of education (as dummies), smoking (yes/no) and BMI. Physical frailty was examined both as a continuous variable (number of components met) and dichotomized (present yes/no). Logistic regression was applied in order to calculate the odds of being frail (dependent variable) with group status (MUS- versus MES-patients) as the independent variables and adjusted for covariates described above.

Finally, within the subgroup of patients with MUS, linear regression models adjusted for the same covariates were conducted to examine the association between each

severity index of MUS as the independent variable of interest and each physical functioning parameter as the dependent variable of interest.

P-values <.05 were considered statistically significant. Analyses were conducted in SPSS, version 24.

## Results

Comparison of the demographic and lifestyle characteristics revealed that MUS-patients were significantly younger, more often female, and had a higher BMI compared to MES-patients (see table 1). The two groups did not differ with respect to level of education, cognitive functioning, smoking, and alcohol usage.

**Table 1** Characteristics of the study population

| Characteristics | | MUS patients* (n=118) | MES patients (n=154) | Statistics |
|---|---|---|---|---|
| *Socio-demographics* | | | | |
| • Age | mean (SD) | 70.5 (6.7) | 73.4 (7.7) | T=-3.2, df=270, p=.001 |
| • Female sex | n (%) | 76 (64.4) | 67 (43.5) | $\chi^2$=11.7, df=1, p=.001 |
| • Level of education | | | | |
| o Lower | n (%) | 29 (26.9) | 27 (17.8) | |
| o Middle | n (%) | 49 (45.4) | 80 (52.6) | $\chi^2$=3.2, df=1, p=.205 |
| o Higher | n (%) | 30 (27.8) | 45 (29.6) | |
| *Lifestyle characteristics* | | | | |
| • Smoking (yes) | n (%) | 17 (15.6) | 22 (14.5) | $\chi^2$=0.1, df=1, p=.802 |
| • Alcohol use: | | | | |
| o None | n (%) | 33 (30.3) | 32 (21.1) | |
| o Moderate | n (%) | 63 (57.8) | 105 (69.1) | $\chi^2$=3.7, df=2, p=.159 |
| o Severe | n (%) | 13 (11.9) | 15 (9.9) | |
| • Body Mass Index | mean (SD) | 28.8 (5.9) | 27.3 (4.2) | t=2.4, df=251, p=.017 |
| *Somatic & physical functioning* | | | | |
| • Somatic comorbidity (Charlson Index)* | mean (SD) | 1.8 (1.9) | 2.2 (1.9) | t=-2.4, df=258, p=.017 |
| • Number of prescribed medications | mean (SD) | 6.1 (4.5) | 5.5 (3.4) | t=1.0, df=229, p=.310 |

| Characteristics | | MUS patients* (n=118) | MES patients (n=154) | Statistics |
|---|---|---|---|---|
| *Somatic & physical functioning (continued)* | | | | |
| • Fried Frailty Index (positive) | n (%) | 13 (12.6) | 9 (6.1) | $\chi^2$=3.2, df=1 p=.071 |
| • Unintentional weight loss | n (%) | 15 (14.2) | 21 (14.3) | $\chi^2$<0.01, df=1 p=.976 |
| • Weakness | n (%) | 41 (39.0) | 30 (20.3) | $\chi^2$=10.7, df=1 p=.001 |
| • Exhaustion | n (%) | 31 (29.2) | 20 (13.4) | $\chi^2$=9.7, df=1 p=.002 |
| • Slow gait | n (%) | 23 (23.5) | 43 (30.1) | $\chi^2$=1.3, df=1 p=.259 |
| • Low physical activity | n (%) | 23 (21.9) | 20 (13.4) | $\chi^2$=3.2, df=1 p=.076 |
| • No of frailty components (sum score) | mean (SD) | 1.2 (1.1) | 0.9 (1.0) | t=2.4, df=237, p=.016 |
| • Gait speed (m/s)* | mean (SD) | 1.05 (1.41) | 1.05 (1.37) | T<0.1, df=240, p=.999 |
| • Hand grip strength (kg) | mean (SD) | 27.2 (12.7) | 32.9 (12.7) | t=-2.5, df=252, p<.001 |

Abbreviations: MUS, medically unexplained physical symptoms; MES, medically explained physical symptoms; SD, standard deviation.
* Student t-test on ln-transformed values, presented values are back transformed for interpretation.

*Physical functioning in MUS- versus MES-patients* - Table 2 compares the two groups with respect to parameters of physical functioning adjusted for covariates. Due to the level of disability, performance-based frailty components were significantly more often missing for patients with MUS compared to patients with MES (gait speed: 20 versus 11; $\chi$2=6.4, df=1, p=.012; handgrip strength: 13 vs. 6, $\chi$2=5.2, df=1, p=.022).

Patients with MUS had significantly lower Charlson Index, a lower maximum handgrip strength and a higher number of frailty components compared to patients with MES. The number of prescribed medications did not differ between the two groups. Logistic regression revealed that the odds of being frail was three times higher for patients with MUS compared to those with MES when adjusted for covariates (OR=3.0 [95% CI:1.1–8.4], p=.035).

Table 2 Somatic and physical functioning of MUS versus MES patients by ANCOVA*

| Characteristics | | MUS patients* (n=118) | MES patients (n=154) | Statistics |
|---|---|---|---|---|
| *Somatic & physical functioning* | | | | |
| • Somatic comorbidity (Charlson Index)** | EMM (SEM) | 1.83 (1.06) | 2.15 (1.05) | F=4.0, df=1,238, p=.045 |
| • Number of prescribed medications | EMM (SEM) | 5.8 (0.4) | 5.5 (0.3) | F=0.3, df=1,209, p=.591 |
| • No of frailty components (sum score) | EMM (SEM) | 1.25 (0.11) | 0.87 (0.09) | F=7.2, df=1,225, p=.008 |
| • Gait speed (m/s)** | EMM (SEM) | 1.07 (1.03) | 1.04 (1.02) | F=0.4, df=1,227, p=.526 |
| • Hand grip strength (kg) | EMM (SEM) | 28.4 (0.8) | 32.1 (0.7) | F=10.3, df=1,239, p=.002 |

* adjusted for age, sex, level of education, smoking, alcohol use, and BMI
** ANCOVA with ln-transformed values, presented values are back transformed for interpretation.
Abbreviations: EMM, estimated marginal means; SEM, standard error of the mean; kg, kilogram.



*Association between physical functioning and MUS-severity indicators in MUS-patients* - Of the 118 patients with MUS, 63 (53.4%) had a somatoform disorder according to DSM-IV criteria and 39 (33.1%) suffered from a comorbid mood-, anxiety or substance use disorder. The mean (standard deviation) item-score (range 0–4) on the BSI-53 somatisation scales was 0.81 (0.65), on the Whitely-Index was 4.3 (2.9), and the severity of the primary complaint was rated at 6.3 (2.1) cm on the 10-cm VAS.

As shown in table 3, a higher number of physical frailty components was associated with a higher severity level of the unexplained symptoms, with stronger hypochondriacal beliefs and a higher level of somatisation. The higher level of somatisation according to the BSI-53 subscale, however, was associated with nearly all physical functioning parameters, i.e. a higher score on the Charlson Index, a higher number of prescribed medications, more frailty parameters and a lower handgrip strength.

**Table 3** Associations between severity measures of MUS and parameters of somatic and physical functioning in MUS patients (n=118) *

| Severity measures of MUS | Charlson Index | | No. of prescribed medications | | Frailty sum score (Fried) | | Gait speed (s) | | Handgrip strength (kg) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | β | p | β | p | β | p | β | p | β | p |
| • Severity of primary complaint (VAS) | .13 | .204 | .07 | .516 | **.23** | **.038** | .12 | .250 | -.11 | .112 |
| • Primary somatoform disorders (yes) | .08 | .421 | -.01 | .941 | <-.01 | .965 | -.04 | .651 | <.01 | .989 |
| • Comorbid psychiatric disorder (yes) | .12 | .207 | .12 | .245 | .14 | .181 | .06 | .576 | -.09 | .221 |
| • Hypochon-driacal beliefs (Whitely Index) | .09 | .339 | **.22** | **.030** | **.22** | **.027** | .09 | .337 | -.08 | .259 |
| • Level of somatisation (BSI subscale) | **.42** | **<.001** | **.36** | **.002** | **.44** | **<.001** | .16 | .146 | **-.21** | **.011** |

* Linear regression models adjusted for age, sex, level of education, smoking, use of alcohol, BMI

As this may question whether the somatisation scale indeed measures somatisation and not somatic disease burden, we post-hoc tested the associations between this scale and the other MUS-severity indicators (with linear regression adjusted for the same covariates). This revealed that the BSI-53 somatisation subscale was significantly associated with the severity of hypochondriacal beliefs (β=0.45, p<.001) and the presence of comorbid psychiatric disorder (β=0.35, p=.001), but neither with the presence of a somatoform disorder (β=0.01, p=.900), nor with the severity of the MUS (β=0.09, p=.419).

## Discussion

Two important findings have emerged from our study. First, older patients with MUS had a significantly lower somatic disease burden compared to their counterparts with MES, whereas they were prescribed the same number of medications. Secondly, patients with MUS were significantly more frail compared to patients with MES and thus can be considered to have a "higher biological age" compared to patients of the same chronological age who suffer from MES.

While the overt somatic disease burden was significantly higher among patients with MES, both patient groups were prescribed a similar number of medications. An explanation might be sought in the higher level of medical consumption generally associated with MUS (Duddu et al., 2008). In up to 18% of hospital outpatient consultations no somatic explanation can be found for symptoms like abdominal pain, back pain, chest pain, and headache (Reid et al., 2001; Hilderink et al., 2013). Physicians are generally inclined to help these patients and easily prescribe some drugs even though they might not be convinced of its benefit (Jackson et al., 2006; Salmon et al., 2008; Nunes et al., 2013). On the other hand, studies mentioned above do not analyse older persons separately, while many somatic symptoms are common in older people and occur in the context of chronic somatic diseases. Higher co-morbidity rates as well as higher a priori chances of underlying physical illnesses as explanation for physical complaints makes it more difficult to distinguish explained from unexplained symptoms in older people.

To our knowledge, physical frailty has never been related to medically unexplained physical symptoms. Previously, it has been consistently shown that physical frailty differs from comorbidity and disability (Fried et al., 2001; Morley et al., 2013) and should be regarded as indicative of lack of resilience to internal and external stressors. Even mild stressors can disturb the "frail" homeostasis of physiological systems in a body and provoke a cascade of negative health outcomes (Morley et al., 2013). Our findings suggest that this frail level of homeostasis might provoke

some physical sensations or non-specific physical symptoms which can not be attributed to overt somatic diseases, but trigger these patients to seek help. Based on the theoretical framework of the "frailty identity crisis", denial of frailty may lead to excess health seeking behavior ("doctor shopping" syndrome) and polypharmacy (Fillit & Butler, 2009). Our empirical findings fits in this framework and if true, at least in some patients, MUS may be a symptom of frailty and thus reflect the aging process.

Being a cross-sectional study, an alternative explanation might be that the presence of MUS is a causative factor of accelerated aging. Affective disorders, primarily depressive disorders, have been postulated as a cause of accelerated aging (Verhoeven et al., 2014). Proposed mediating pathways for which some evidence has been found include inflammatory-metabolic dysregulation and an unhealthy lifestyle (Révész et al., 2016). Nonetheless, the impact of affective disorders on accelerated aging is generally small and seems particularly relevant in middle-aged but not older depressed persons (Schaakxs et al., 2015). We are not aware of studies that have examined lifestyle changes among patients suffering from MUS. As patients with MUS are generally concerned about their health, it may seem unlikely that their lifestyle worsens due to the occurrence of MUS. Nonetheless, we all know patients with a high level of somatization who "protect" themselves against worsening of their symptoms by a self-inflicted reduction in exercise, socialization or participation in meaningful activities. Therefore, the association between MUS and frailty is probably bidirectional and may involve different mechanisms in different subgroups. Longitudinal studies should therefore address potential mediating mechanisms in order to deepen our understanding of this association.

Albeit not a primary aim of the present study, the somatization subscale of the 53-item BSI appeared to be associated with parameters of physical functioning as well as severity parameters of MUS. This can be explained by the fact that this scale consists of common somatic symptoms usually associated with functional

syndromes in younger age groups. In older age groups, these symptoms do not necessarily reflect unexplained symptoms anymore but also reflect the increase in somatic disease burden with age, as mentioned above. Although this problem has been identified before, a systematic review of assessment scales suggests that it still is one of the best options we have to assess the level of somatisation in population-based studies of older people (Van Driel et al., 2018).

For proper interpretation, some methodological issues need to be addressed. A first strength of the present study is the well-characterised and representative sample of older patients with MUS and MES. The fact that patients with MUS were examined by different professionals can be seen as a strength of the study design, since the diagnosis of MUS is difficult to distinguish from common mental disorders and chronic somatic illnesses (Hanssen et al., 2016). However, some limitations should also be acknowledged. First of all, the cross-sectional study design precludes causal interpretations. Therefore, we do not know the direction of the associations presented. Secondly, our sample size is relatively small. Nonetheless, the number of patients with MUS and MES is comparable to previous studies in this field of research (Reid et al., 2001; Klaus et al., 2013). Secondly, the overall prevalence of frailty of 8.8% was quite low in our population, but in line with estimates in the general population (Collard et al., 2012). Moreover, differences with respect to frailty between the two groups are probably underestimated, as significantly more patients with MUS were too disabled to test gait speed or handgrip strength. Nonetheless, the low prevalence rate increases the risk of chance findings, which argues for replication.



## Conclusions and implications

The key findings of this study are that older patients with MUS have a significantly lower somatic disease burden, are significantly more frail, and thus can be considered to have a “higher biological age” compared to patients with MES.

Therefore, MUS is a challenging problem for physicians and this seems to even increase in older patients where MUS and MES can be intermingled. Based on our findings, two advices can be given. The first advice is to consider the presence of frailty as a potential explanation for non-specific complaints before classifying these symptoms as MUS and thus to ensure access to geriatric care models for these patients. Albeit these symptoms may be explained by physical frailty, they still may need a psychological approach as frailty itself is associated with low levels of well-being (Andrew et al., 2012) and decreases quality of life over time (Kojima et al., 2016). The second advice is to be very careful with prescribing new medications, especially as older patients are at increased risk for side-effects, interactions due to polypharmacy, and worsening of frailty (Maher et al., 2014; Wastesson et al., 2018). Although treatment strategies to reverse or slow down the progression of frailty (which is considered a dynamic state) are scarce, physical exercise programmes and protein-enriched diets have been proven efficacious (Loranzo-López et al., 2017; Rogers et al., 2017).

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# Part III

## Adverse health outcomes of physical frailty in late-life depression

### Chapter 7

### The impact of frailty on depressive disorder in later life: Findings from the Netherlands Study of depression in older persons

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### Chapter 8

### Frailty predicts mortality in late-life depression

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