# Medically unexplained symptoms in later life

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CHAPTER 6

# Impact of medically unexplained symptoms on health related quality of life: A comparison with medically explained symptoms and age-effects.

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## Abstract

*Objective:* We aimed to clarify whether medically unexplained symptoms (MUS) cause the same degree reduction in health-related quality of life (HRQoL) as medically explained symptoms (MES). Secondary aim is to describe the effects of aging on this impact.

*Method:* In a population based cohort (n=946, aged 28-75 years), MUS and MES were measured using the Composite International Diagnostic Interview (CIDI) and HRQoL using the EuroQol-5 Dimensions (EQ-5D). Using multiple linear regression, we regressed MUS, MES and their interaction with age on HRQoL, first adjusted for socio-demographic variables and subsequently adjusted for psychiatric comorbidity. In case of significant interaction terms, age-stratified results will be presented.

*Results:* Overall the association between MUS and HRQoL was stronger (B=-.247, SE =.021, p<.001) than between MES and HRQoL (B=-. 188, SE=.022, p<.001). Adjusted for psychiatric co-morbidity, these associations became almost equal (for MES: B=-.183, SE=.021, p<.001; for MUS: B=-.194, SE=.020, p<.001). Age significantly interacted with number of MUS in explaining variance in HRQoL, but not with the number of MES. The impact of MUS on HRQoL is much larger in people aged below 65 years (B=-.272, SE=.023, p<.001) versus those aged 65 years and over (B=-.149, SE=.046, p=.002). Only in the older age group, this association lost significance when adjusted for psychiatric co-morbidity (B=-.085, SE=.045, p=.062).

*Conclusion:* In an adult population the impact of MUS on HRQoL is larger than the impact of MES. However in later life the impact of MUS decreases suggesting that older persons cope better with MUS than younger persons.

## Introduction

Physical symptoms account for the majority of consultation in primary care and at least a third of these complaints remain medically unexplained [1]. While it is recognized that physical symptoms are an important cause of illness burden in patients, it is not clear whether medically unexplained symptoms (MUS) cause the same degree of morbidity and reduction in health-related quality of life (HRQoL) as medically explained symptoms (MES). HRQol is defined as those aspects of self-perceived well-being that are related to or affected by the presence of disease or its treatment [2]. The impact of MES and MUS on HRQoL may further differ across the lifespan, taken into account that the number of MES clearly increases with age, while no or only a very weak correlation has been found between the prevalence of MUS and age [3-5].

Because of higher numbers of MES in older persons, one would expect lower HRQoL. Nonetheless, two-thirds of hospitalised older patients report good HRQoL. In this group, lower physical and psychological HRQoL was significantly associated with impaired personal activities of daily living, impaired cognition, depression, anxiety and a higher medication use [6].

MUS are defined as physical symptoms of which presence, severity or consequences cannot be explained by any detectable physical disorder [7]. Although clinicians are almost daily faced with MUS throughout the lifespan, almost no empirical data are available for MUS in later life [8]. A recent review suggests that prevalence rates of MUS are stable until the age of 65 years and decrease thereafter [9]. This might be an artefact caused by diagnostic issues differentiating between MES and MUS in later life as well as by conceptual difficulties. The concept of MUS has been criticized as it is dualistic, and its measurement is time consuming and unreliable [10, 11]. Therefore, it has been suggested that the total number of physical symptoms, including both medically explained and unexplained symptoms, is more informative in estimating health related quality of life [12-15]. Cross-sectional clinical studies indeed found a significant correlation between a high somatic symptom count, including both medically explained and unexplained symptoms, and impaired health status [1, 16]. Furthermore, one prospective cohort study showed that total somatic symptom counts predicted impaired health status over time [17]. The impact of MUS on the HRQoL in old age populations, however, has not been reported yet.

In adult populations some have suggested that MES and MUS are associated with similar levels of disability [18, 19], while others have suggested that MUS are associated with greater disability [20, 21]. In a Dutch primary care population, Quality of Life (QoL) of patients suffering from MUS was lower than that of the overall primary care population, but higher compared to depressed patients in primary care [21]. A proposed explanation for a differential impact on HRQoL between MES and MUS is the increased prevalence of affective disorders in patients suffering from MUS as compared to patients with MES as well as the fact that patients with MUS on average do have higher numbers of somatic symptoms [22]. In a predominant South Asian primary care population, patients with MUS had significantly more physical symptoms, higher levels of anxiety and depression, and lower HRQoL compared with patients with MES.

Health-related quality of life in patients was independently predicted by occupational status, educational status, anxiety, depression, and the number of physical symptoms reported. Whether symptoms were medically explained or not did not add significantly to the model after adjusting for other variables [22].

The primary aim of the present study is to examine the effect of age on the impact of MUS and MES on health-related quality of life. We hypothesize that 1) MUS are more strongly associated with impaired HRQoL than MES, 2) the differential impact of MUS and MES on HRQoL can be explained by an increased prevalence of psychiatric comorbidity in patients with MUS as compared to patients with MES, and 3) the impact of MES on HRQoL decreases with age in contrast to the impact of MUS.

## Method

*Population*

This study has been performed in a cohort derived from Prevention of Renal and Vascular End Stage Disease (PREVEND), a population cohort study investigating micro-albuminuria as a risk factor for renal and cardiovascular disease. The recruitment of participants is described elsewhere [23], but will be summarised below. All inhabitants of the city of Groningen between the ages of 28 and 75 years (85 421 subjects) were asked to send in a morning urine sample and to fill out a short questionnaire on demographics and cardiovascular history. A total of 40 856 subjects (47.8%) responded. After exclusion of subjects with insulin-dependent diabetes mellitus and pregnant women, all subjects with a urinary albumin concentration of >10 mg/l (n=7768), together with a randomly selected control group with a urinary albumin concentration of <10 mg/l (n=3395), were invited for further investigations (total n=11 163). Finally, 8592 subjects completed the total screening program making up the PREVEND study cohort. Because the PREVEND study population was enriched for albuminuria, this oversampling for albuminuria was counterbalanced in the current substudy. Albuminuria-negative participants and a random sample of albuminuria-positive participants were combined so that a population representative ratio of albuminuria-positive participants was achieved. Research assistants handed over invitations in the 2001–2002 wave to 2554 subjects to participate in a substudy, for which additional psychiatric and psychosocial data were collected. Of these 2554 subjects, 1094 (43%) completed the additional measurements.

Follow-up measurements in the 2003–2004 wave were completed by a total of 964 participants (89% of the cohort) with additional psychiatric and psychosocial data (see below). The recruitment of these participants that formed the cohort for the current study has been extensively described elsewhere [24]. The study was approved by the local medical ethics committee and all subjects gave written informed consent to participate.

*Physical symptom count:*

Physical symptom count was based on the somatization section of the Composite International Diagnostic Interview (CIDI), a fully structured psychiatric interview assessment with adequate test–retest reliability and validity [25]. A fully computerized version of the CIDI 2.1 12-month

was applied, suitable for self-administration. Trained interviewers were present for questions and for participants who needed computer help. The probing scheme of the self-administered version is completely identical to the interviewer-administered version; the difference between both versions is that the questions are not read out loud by the interviewer but instead are read on the screen by the participant him/herself.
In short, the CIDI somatization section surveys the occurrence of 43 symptoms in the past year. Symptoms are considered present when they meet severity criteria, i.e. provoke a healthcare visit. If these criteria are met, the interview assesses in a hierarchical fashion whether a medical doctor diagnosed a symptom as due to physical illness or injury, or whether a symptom was caused by the use of medication, drugs or alcohol. If these inquiries are negative for these medical explanations, the symptom is scored as a functional symptom. In those cases in which the diagnosis involved a functional syndrome (such as irritable bowel syndrome, chronic fatigue syndrome or fibromyalgia), the symptom was recoded as a functional symptom.

*Health related quality of life:*
Self-rated health-related quality of life was measured using the descriptive section of the EuroQol-5 Dimensions (EQ-5D) [26]. The EQ-5D consists of a descriptive system that records the level of self-reported problems on each of the five dimensions of the classification (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). For each dimension the respondent is asked to choose between three options: no problem, some/moderate problems, or extreme problems/unable. Health states defined by the five-dimensional descriptive system, can be converted into a weighted health state index by applying scores from value sets elicited from general population samples which leads to a mean weighted health index ranging from 0 (dead) to 1(optimal health) [27, 28].

*Covariates:*
Age, sex, educational level (operationalized as the number of years of education beyond the age of 12), marital status (married or not married) and psychological distress (measured with the Dutch translation of the 12-item General Health Questionnaire [GHQ-12])[29]. The presence of depression and anxiety disorders was assessed by the corresponding sections of the CIDI 2.1, 12 month version. For depression, all diagnoses of single or recurrent depression and dysthymia were included. For anxiety disorder, panic disorder with and without agoraphobia, social phobia and generalised anxiety disorder were included.

*Statistical analyses:*
Demographics and clinical characteristics will be described for participants with and without MUS and/or MES as well as for older and younger patients based on an age cut-off at 65 years [9]. Differences between groups were examined using independent samples t-tests or ANOVA for normally distributed, continuous variables, nonparametric Mann Whitney U tests or Krusskall Wallis for skewed continuous variables, and $\chi^2$ tests for categorical variables.
The impact of the number of MUS and number of MES on HRQoL was assessed with multiple linear regression models with HRQoL as the dependent variable and adjusted for

socio-demographic variables (age, sex, educational level, marital status). In case of a significant interaction term between age and the number of MUS or age and the number of MES, analyses were separately presented for participants aged below 65 years and those aged 65 years and older based on previous found differences in prevalence rates for MUS between these age groups.

In model 1, the impact of the number of MES on HRQoL was examined. In model 2, the impact of the number of MUS on HRQoL was examined. In model 3, the number of MES and number of MUS were simultaneously entered, together with their interaction. In case of a non-significant interaction term, the interaction term was removed from the final model. In order to examine the impact of psychiatric comorbidity, all models were subsequently adjusted for the presence of any depressive or anxiety disorder within the past 12 months. In case the B decreased by 10% or more after adjustment for psychiatric comorbidity, it was considered an explanatory factor.

All analyses were conducted in SPSS version 18 (Chicago, Ill.) with p-values <.05 considered statistically significant.

## Results

For 946/964 (98.1%) of the eligible participants, the EQ-5D and the CIDI physical symptom scores were available. Mean age of these participants was 55.2 (SD 11.1) years, 51.8% was female, and 55.5% was married. The mean number of years of education beyond the age of 12 years was 8.1 (SD= 4.5) years. Overall, 7.1% of the participants suffered from a depressive disorder and 5.1% from an anxiety disorder.

Table 1 presents the characteristics separately for participants without physical symptoms, for participants suffering from MES, for participants suffering from MUS, and finally for participants suffering from both MES and MUS within the past year. MES were associated with older age, while MUS were not. Psychological distress differed significantly between the four groups, with highest levels in participants with MUS and MES, followed by those with MUS alone, those with MES alone, and finally lowest levels in participants without physical symptoms.

The number of physical symptoms for MUS were highest in the group of participants suffering from both type of symptoms. HRQoL also differed across the four groups, although post-hoc tests did not show any difference between persons with only MES versus those with only MUS. HRQoL was highest in the group with neither MUS nor MES, followed by the group with MUS only and MES only, whereas it was lowest in participants suffering from both, MES and MUS.

**Table 1.** Characteristics of people with no somatic symptoms, MES, MUS or MES and MUS together.

| Variables | No MES or MUS (n=284) | MES (n=162) | MUS (n=270) | MES and MUS (n=230) | Statistics |
|---|---|---|---|---|---|
| *Socio-demographics:* | | | | | |
| • Age (mean (SD)) [1,3,4,6] | 53.1 (10.6) | 57.9 (11.5) | 53.7 (10.0) | 57.5 (11.7) | F=12, df=3, p<.001 |
| • Female sex (n (%)) | 106 (37.3) | 86 (53.1) | 153 (56.7) | 145 (63.0) | $x^2$=38.2 df=3, p<.001 |
| • Married (n (%)) | 156 (54.9) | 94 (58.0) | 144 (53.3) | 131 (57.0) | $x^2$=1.7, df=3, p=.76 |
| • Years education (mean (SD)) [1,3,4,6] | 8.8 (4.5) | 7.3 (4.3) | 8.7 (4.5) | 6.7 (4.5) | F=12, df=3, p<.001 |
| *Psychiatric morbidity* | | | | | |
| • Depressive disorder (n (%)) | 7 (2.5) | 8 (4.9) | 26 (9.6) | 26 (11.3) | $x^2$= 19.2, df=3, p<.001 |
| • Anxiety disorder (n (%)) | 4 (1.4) | 5 (3.1) | 19 (7.0) | 20 (8.7) | $x^2$=17.7, df=3, p<.001 |
| • GHQ (mean (SD))[1,2,3,4,5] | 0.9 (1.9) | 1.8 (3.0) | 2.5 (3.3) | 2.7 (3.5) | F=20, df=3, p<.001 |
| *Physical symptoms* | | | | | |
| • Number of MES (median (IQR)) [1,3,4,5,6] | n.a | 1,0 (2.0) | n.a | 2.0 (2.0)2.4 (2.2) | $x^2$=3.1 df=1 p=.077 |
| • Number of MUS (median (IQR)) [2,3,4,5,6] | n.a | n.a | 1.0 (1.0) | 2.0 (2.0) | $x^2$=11.5, df=1, p<.001 |
| *Health related Quality of Life* | | | | | |
| • Dutch EQ-5D (mean (SD)) [1,2,3,5,6] | 0.95 (0.09) | 0.83 (0.21) | 0.84 (0.19) | 0.77 (0.22) | F=45, df=3, p<.001 |

[1] Significant difference post-hoc test (p<.05) between no MES or MUS versus MES

[2] Significant difference post-hoc test (p<.05) between no MES or MUS versus MUS

[3] Significant difference post-hoc test (p<.05) between no MES or MUS versus MES and MUS

[4] Significant difference post-hoc test (p<.05) between MES versus MUS

[5] Significant difference post-hoc test (p<.05) between MES versus MES and MUS

[6] Significant difference post-hoc test (p<.05) between MUS versus MES and MUS

**Abbreviations:** MUS, medically unexplained symptoms; MES, medically explained symptoms; p, p-value; GHQ, General Health Questionnaire; EQ5-D, EuroQol-5 Dimensions; n, number; SD, standard deviation; IQR, Interquartile Range; n.a, not applicable.

Table 2 presents characteristics of participants by age (<65 versus 65 years and over). Older participants were more often married, lower educated and had lower prevalence rates of anxiety disorders compared to their younger counterparts. The proportion of persons with MES was significantly higher in the older age group, as well as the mean number of MES. However, no differences between age groups were found for MUS in both the prevalence of participants with MUS as well as the mean number of MUS.

**Table 2** Comparison between participants under the age of 65, and 65 and over.

| Variables | Age <65 (n=734) | | Age ≥65 (n=212) | | Statistics |
|---|---|---|---|---|---|
| *Demographics:* | | | | | |
| • Female sex | n (%) | 393 (53.5) | 97 | (45.8) | $x^2$=4.0 df=1 p=.046 |
| • Years education | mean (SD) | 8.79 (4.46) | 5.53 | (3.91) | t=10, df =379 p<.001 |
| • Married | n (%) | 389 (53.0) | 136 | (64.2) | $x^2$=8.2 df=1 p<.001 |
| *Psychiatric morbidity* | | | | | |
| • Depressive disorder | n (%) | 58 (7.9) | 9 | (4.2) | $x^2$=3.3 df=1 p=.068 |
| • Anxiety disorder | n (%) | 46 (6.3) | 2 | (0.9) | $x^2$=9.7 df=1 p=.002 |
| • GHQscore | mean (SD) | 2.1 (3.1) | 1.6 | (2.7) | t= 2.3 df=388 p=.019 |
| Health related Quality of Life: | | | | | |
| • Dutch EQ-5D | mean (SD) | .86 (.19) | .84 | (.19) | t=1.7 df=944 p=.10 |
| *Medical symptoms* | | | | | |
| • One year number MES | mean (SD) | .80 (1.6) | 1.4 | (1.8) | t=-4.5 df=316 p<.001 |
| • One year number MUS | mean (SD) | 1.2 (2.0) | 1.2 | (1.9) | t=.37 df=944 p=.75 |
| • Number persons with MES | n (%) | 270 (36.8) | 122 | (57.5) | $x^2$=29.2 df=1 p<.001 |
| • Number persons with MUS | n (%) | 385 (52.5) | 115 | (54.2) | $x^2$=.21 df=1 p=.65 |

**Abbreviations:** MUS, medically unexplained symptoms; MES, medically explained symptoms; n,number; SD standard deviation. GHQ, General Health Questionnaire EQ5-D EuroQol-5 Dimensions.

Within the whole study population, linear regression analyses adjusted for socio-demographic characteristics, showed that the association between MUS and HRQoL was stronger (B=-.247; p<.001) than that between MES and HRQoL (B=-. 188; p<.001). When additionally adjusted for presence of depression and anxiety disorders, the strength of the association of MES and MUS with HRQoL became almost equal: for MES: B=-.183 (p<.001); for MUS: B=-.194 (p<.001). Age significantly interacted with number of MUS in explaining variance in HRQoL (interaction term: β=.405, t=2.7, p<.01), but not with the number of MES (Interaction term: β=-.14, t=-.96, p=.34).

When additionally adjusted for presence of depression and anxiety disorders, this interaction term remains significant for MUS ( interaction term: β=.31, t=2.1, p=.04) and not significant for MES (interaction term β=-.16, t=-1.1, p=.27). Based on the significant interaction term between age and MUS, analyses will be presented separately for younger and older patients.

**Table 3** Association between MES / MUS and health related quality of life by multiple linear regression analysis*

| | Adjusted for socio-demographic characteristics | | | | Adjusted for socio-demographic characteristics &psychopathology | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **B (SE)** | **ß** | **p-value** | **$R^2$** | **B (SE)** | **ß** | **p-value** | **$R^2$** | **∆B** |
| **Age lower than 65 years (n=738)** | | | | | | | | | |
| Model 1 | | | | .11 | | | | .23 | |
| • No. of MES | -.229 (.028) | -.29 | <.001 | | -.211 (.026) | -.27 | <.001 | | 7.9 % |
| Model 2 | | | | .20 | | | | .26 | |
| • No. of MUS | -.293 (.024) | -.42 | <.001 | | -.238 (.024) | -.34 | <.001 | | 19.5 % |
| Model 3** | | | | .25 | | | | .32 | |
| • No. of MES | -.191 (.026) | -.24 | <.001 | | -.185 (.025) | -.24 | <.001 | | 3.1 % |
| • No. of MUS | -.272 (.023) | -.39 | <.001 | | -.220 (.023) | -.32 | <.001 | | 19.1 % |
| **Age 65 years or over (n=217)** | | | | | | | | | |
| Model 1 | | | | .20 | | | | .33 | |
| • No. of MES | -227 (.044) | -.34 | <.001 | | -.194 (.041) | -.29 | | | 14.5 % |
| Model 2 | | | | .17 | | | | .28 | |
| • No. of MUS | -.195 (.047) | -.28 | <.001 | | -.126 (.046) | -.18 | .007 | | 35.4 % |
| Model 3** | | | | .24 | | | | .34 | |
| • No. of MES | -.194 (.045) | -.29 | <.001 | | -.177 (.042) | -.27 | <.001 | | 10.3 % |
| • No. of MUS | -.149 (.046) | -.21 | .002 | | -.085 (.045) | -.12 | .062 | | 42.9 % |

* Linear regression analyses with health related quality of life (EQ-5D) as the dependent variable and adjusted for age, sex, educational level, marital status; separately presented with and without adjustment for depression (CIDI) and anxiety (CIDI).

**Abbreviations:** MUS, medically unexplained symptoms; MES, medically explained symptoms; SE, standard error

Table 3 summarizes the associations between the health related quality of life and the number of MES and the number of MUS in the past 12 months for younger (age < 65 years) and older participants separately.

Model 1 and 2 present the association of MES and MUS with HRQoL without additional adjustment for each other, whereas in model 3 both the number of MES and number of MUS are included. The beta's found in model 1 and 2 hardly differ from those found in model 3, indicating no mutual confounding for MES and MUS.

As indicated by the significant interaction term described above, the results in table 3 clearly

show that the impact of MUS on HRQoL is lower in the older age group compared to the younger age group, whereas no difference is noted with respect to MES.
Overall, the effect size B for MES or MUS was reduced in each model when adjusting for the presence of depression and anxiety. In the younger age group, only the effect size B for MUS decreased with more than 10%, whereas in the older age groups the effect size B for both MES and MUS decreased by more than 10%. Furthermore, the explanatory effect of depression and anxiety in the older age groups were twice as large for MUS as compared to MES.

## Discussion

This study demonstrated that the impact of MUS on the HRQoL is larger than the impact of MES on the HRQoL and becomes nearly equal when adjusted for psychiatric co-morbidity. In contrast to our hypothesis, the impact of MES on HRQoL was not dependent on age, whereas MUS had relatively less impact on HRQoL in later life compared to younger persons. Interestingly, in people aged below 65 years, the impact of MUS on HRQoL is larger than the impact of MES, whereas opposite findings were found in the older age group. The presence of anxiety and depressive disorders partly explained the association between MUS and HRQoL and in the older age group the impact of MUS on the HRQoL even lost significance. In later life, comorbid affective disorders also partly explained the association between MES and HRQoL albeit to a lower extent. Differences between MES and MUS across age groups remained similar when adjusted for psychiatric co-morbidity,

The stable prevalence rates of MUS across the lifespan we found in our study, contrast with many studies reporting on decreasing levels of MUS with increasing age [9, 30, 31]. Nonetheless, the only study describing prevalence rates for MUS above the age of 65 that applied similar methodology by using the CIDI, reported only a mild decrease of MUS above the age of 65 [32]. Interestingly, the impact of MUS on HRQoL decreases with increasing age. This is in line with findings in patients with chronic pain. For example, in a Norwegian community-based study, older persons more often suffered from chronic pain compared to younger and middle aged persons, but they showed better adjustment to their pain and reported higher quality of life scores [33]. Comparably, an outpatient clinical sample of patients suffering from non-malignant chronic pain showed that older patients displayed less disability and preoccupation with somatic symptoms, despite longer duration of pain and multiple medical illnesses compared to their younger counterparts [34]. In a tertiary care pain clinic older patients were more likely to present with identifiable biomedical pathology for their chronic pain, and were less likely to have discernible psychological factors contributing to their complaints compared with younger patients [35]. Several explanations may account for the decrease in impact of MUS with increasing age. Firstly, it could be survivor bias due to a higher mortality rate of MUS patients with poor HRQoL, possibly reflecting unidentified organic causes. This explanation seems unlikely, although data on mortality within MUS patients because of "missed organic causes" are scarce. In a neurological study with a 18-month follow up, missed diagnoses were found in 0.4% [36]. Moreover, mortality rates in MUS patients in a liaison psychiatry practice were even

lower than mortality rates in control group of patients referred for other reasons [37]. Another explanation would be a cohort effect, in which differences between generations explain the reduced effect of MUS on HRQoL in older persons. For example, people that were exposed by World War II and less welfare in the early 20th century might have lower expectations of their health and well-being than the younger generations of babyboomers and following generations [38]. Longitudinal studies are needed to examine possibly cohort effects. The fact that we do not see the same difference in impact of MES on HRQoL between age groups makes a cohort effect less likely.

Another and more plausible explanation is better adaptation and better acceptance of medical symptoms with increasing age. Literature focusing on the perspective of pain in the elderly suggests that older patients have a tendency to expect and accept pain, are more reluctant to complain, and have a stronger will to "keep on going"[39, 40]. For example, the majority of older people with chronic peripheral joint pain do not consult a doctor, because they see joint pain and stiffness as an inevitable part of ageing. They view themselves as healthy despite painful joints [41]. Similarly, in oncology patients with comparable pain intensity and interference, older and younger cancer patients described different adaptations to cancer pain. Older patients adapted by employing accommodative strategies. Younger patients less often used such strategies and more often struggled with accepting the losses associated with cancer pain [42]. Several studies have shown that better acceptance is directly related with a higher level of HRQoL. For example, in hemophilia-related joint pain patients, pain acceptance and HRQoL were correlated and increased pain acceptance was related with higher HRQoL at follow-up [43]. Also, in people with diabetes, HRQoL was strongly related to their levels of illness acceptance [44]. Finally, we found a large explanatory role for comorbid affective disorders in the older age group. This supports the commonly accepted view of a higher level of somatisation and of affective-somatic symptoms in depressed older patients compared to their younger counterparts [45-47]. It is hard to differentiate whether these somatic symptoms originate from somatization or because of accentuation of symptoms of concomitant physical illness [48].

*Methodological considerations*

A major strength of the present study is the large age-range, which enables the study of age-effects applying similar methodology. Nonetheless, for proper interpretations, some methodological issues should be taken into account. Firstly, generalizability of our results is complex. On the one hand, one may consider the attrition rate of the different recruitment steps in our study at least moderate. On the other hand, a population-based approach is valuable with respect to research on MUS and somatisation. In clinical practice, patients with MUS and/or somatoform disorders present in different echelons and different settings in the health care system, which is largely dependent on the local situation. Therefore, studies on clinical samples of patients with somatisation are even more difficult to generalise. Secondly, the prevalence of depression and anxiety disorders was low in the older age group and significantly lower compared to the younger age group. Therefore, the conclusion that depression and anxiety almost fully accounts for the variation in HRQoL of MUS in later life is based on the effects of depression and anxiety in a few older persons. Thirdly, we measured

both MUS and MES using the same instrument, enabling comparisons between both types of symptoms and their associations with HRQoL. The fact that MUS and MES were assessed with a computerized interview might be seen as a limitation. However, symptoms were only counted if participants had visited a medical doctor and only classified as being functional if it was reported that a medical doctor had indicated that all enquiries were negative for medical explanations. Moreover, we collected detailed information on a large number of MUS and performed our analyses on a continuous variable for the number of MUS instead of using an arbitrary cut-off score. Finally, recall bias may have attenuated the reliability of the CIDI to measure MUS and MES and this recall bias is likely to be associated with age [49]. We limited our analyses to symptoms that occurred in the last 12 months by which we have limited the effect of recall bias.

*Conclusion*

In an adult population, the impact of MUS on HRQoL is larger than the impact of MES. This difference is not explained by co-morbid depression and anxiety. However, with increasing age the impact of MUS decreases and in older persons becomes even lower than the effect of MES on HRQoL. Further research has to reveal why the impact of MUS on HRQoL decreases with age in contrast to the impact of MES on HRQol.

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